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ortho-Lithiations Reassessed: the Advantages of Deficiency Catalysis in Hydrocarbon Media

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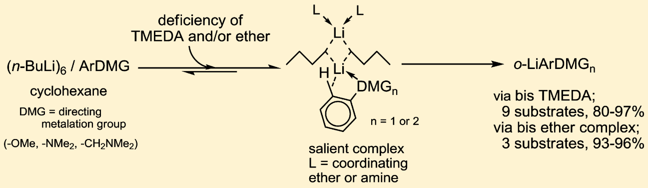
ABSTRACT: Hydrocarbon media based metalation procedures involving "deficiency catalysis" are described for the ortho-lithiation of anisole (A), *p*-chloroanisole (*p*-ClA), *o*-, *m*-, *p*-methylanisoles (*o*-, *m*-, *p*-MA), the three dimethoxybenzenes (DMB's), dimethylaniline (DMA), dimethybenzylamine (DMBA), *m*-methoxydimethylaniline (*m*-MeODMA), and tetramethyl-*p*-phenylenediamine (*p*-TMPDA). These procedures involve certain mechanistic considerations, which must be fine-tuned to maximize the extent of metalation (EoM). Our working hypothesis is that a controlled deoligomerization of the *n*-BuLi hexamer found in hydrocarbon media will afford a "sweet spot" of deoligomerization such that a maximally efficient metalation medium can be formed. In many cases, a substoichiometric ratio of equivalent TMEDA to *n*-BuLi is 0.1−0.2:1.0, but certain substrates suffer multiple sites of metalation under these conditions, so different promoted hydrocarbon media systems incorporating measured equivalents of an ether have been formulated. This paper represents the summary of our successful efforts to render ortho-lithiations safer, greener, and more atom-economical by use of hydrocarbon solvent media. EoM's of 11 of the 12 substrates under these atom-economical conditions range from 87 to 97%.



INTRODUCTION

Over the past two decades, our research program has focused on making strong base chemistry, and in particular the directed ortho-metalation (DoM) reaction,[1] safer, more efficient, atom-economical and, for want of a better notation, "greener."[2] Our approach has been to incorporate the use of bulk hydrocarbon media for these reactions. In so doing, we minimize the principal problem of strong base chemistry, the dependence on ethers as solvents. Ethers offer a greater breadth of solubility of substrates for such reactions, but suffer from several pronounced drawbacks (1) their hydroscopic nature and overall water solubility, (2) their tendency to form explosive peroxides, and (3) their reactivity with strong base reagents,[3] in particular alkyllithium reagents, the strong base reagent of choice for ortho-lithiations.

Use of hydrocarbon solvents has its own set of drawbacks for use with alkyllithium reagents. The most pronounced of these is that alkyllithium reagents in hydrocarbon solvents are highly associated, that is, are in their least reactive state.[4] Hydrocarbon solvents possess a lower ability to dissolve many substrates so preparatory metalations tend to be more dilute than those run in ether. An advantage of hydrocarbon solvents, in addition to their not suffering from the general drawbacks of ethers, is that they require relatively little maintenance or treatments for use in metalation chemistry.

How then to get around the lack of solubility and the lack of the necessary reactivity of alkyllithium reagents in hydrocarbon solvents? The answer is to promote the disassociation of these reagents in such media by the addition of measured amounts of ethers, notably THF, or *bis*-chelating amines such as tetramethylethylenediamine (TMEDA). Both types of agents have long been known to activate alkyllithium reagents by facilitating their disassociation to lower oligomeric forms. These reagents sufficiently activate alkyllithium reagents for DoM chemistry to be realized, ethers from the beginning of ortho-lithiation chemistry and TMEDA, the principal *bis*-chelating amine utilized, from the late 1960s.[5] Indeed, our group was among the first to maintain that DoM could be catalyzed by use of TMEDA.[6] Up to the time of our current investigations, it was customary to use ethers as bulk solvents and TMEDA in ratios amounting to full equiv. relative to the alkyllithium reagent. That fractional equiv. of TMEDA could be effective in catalyzing ortho-lithiations was first demonstrated by our group in 1994[2a] and the effectiveness of measured equiv. of THF in bulk hydrocarbon solvent was illustrated two years later.[2b] The promise of all these discoveries was that not only could DoM chemistry be made safer and greener, but also the potential existed that atom-economy could be achieved upon further parameter and condition refinements. This paper represents the summary of these successful efforts.

Our reasoning began with the fundamental insight provided by W. Bauer and P.v.R. Schleyer[7] that a coordinately unsaturated *n*-BuLi dimer was involved in the transition state

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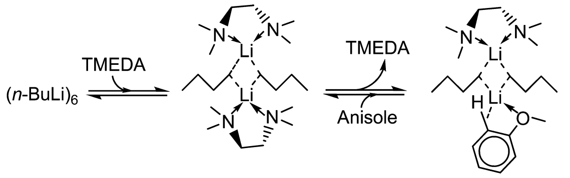
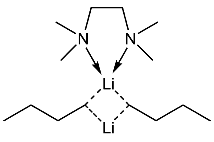
for ortho-lithiation (eq 1).In their view, the n-BuLi hexamer was converted by the bis-chelating amine to a fully saturated n-BuLi dimer stabilized by two amine ligands. Disassociation of one of these amine ligands afforded a coordinately unsaturated n-BuLi dimer **1**, to which an unshared pair of electrons of anisole (A), *N,N*-dimethylaniline (DMA), *etc.* could initially coordinate leaving one vacant orbital on lithium to interact and eventually insert into the aryl-H bond at the ortho-position. Subsequent analyses for the transition state of ortho-lithiation have been published by Schleyer and by others,[8] but none afford the clear predictive potential as the series of intermediates put forward in 1989 by Bauer and Schleyer.[7]



(1)

In our view, the unsaturated mono TMEDA dimer in **1** is a seminal proposal. Additional insight suggests that in ether media (e) (DEE, THF, MTBE, etc.), coordinately deficient dimers **2** and **3** would be formed. Complex **3** can exist in three forms. The ability of substoichiometric amounts of TMEDA to catalyze the ortho-lithiation of various aryl substrates we have termed "deficiency catalysis". We are unsure that equiv. of THF or other ethers in bulk hydrocarbon media can be called catalysis in the same regard, but the effect of 1.0, 2.0, and 3.0 equiv. of THF in bulk hydrocarbon media is certainly profound as we will later demonstrate.

The proposed unsaturated TMEDA dimer possessed the *bis*-coordinated structure **1**. Additional insight by our group suggested that a similar *bis*-coordinated intermediate **2** contributed to metalations in an ether as well. However, the prevailing bis-coordinated n-BuLi dimer ether(e) media intermediate would be **3**. It is likely that **2**, the THF version of the Bauer and Schleyer intermediate,[7] would be present in relatively minor amounts. This may, at least in part, explain n-BuLi's much greater reactivity enhancement when complexed by TMEDA compared to THF. It occurred to us that if **1** were an intermediate in the course of a TMEDA-catalyzed metalation reaction, addition of increasing increments of TMEDA would deoligomerize the n-BuLi hexamer and move the known equilibrium toward the coordinately deficient dimer **1** to an increasing extent. A similar statement can be made regarding THF except that to generate intermediate **2**, stoichiometric quantities of THF would be required to reach effective concentrations of intermediate **2**. It was further realized that too much TMEDA or THF would increase the population of saturated forms of the dimer which would be counterproductive! It is the generation of the coordinately unsaturated intermediates **1** and **2** that must be maximized in our doped hydrocarbon media to achieve the greatest metalation efficiency.



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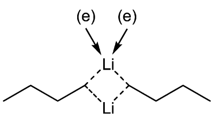

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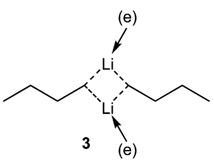

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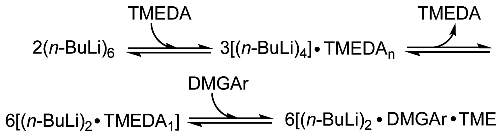
These considerations led to the concept of a "sweet spot" for our hydrocarbon media promoted solutions. Manifestation of this "sweet spot" was to be found by plotting extents-of-metalation (EoM's) vs a range of equiv. of ether or TMEDA additive to the hydrocarbon media and observation of a maximum. Moreover, it was realized that the maximum EoM for any system should be temperature dependent with the maximum EoM at higher temperatures requiring fewer equiv. of additive. Evidence for the truth of this statement is contained herein.

Measured doping of hydrocarbon solvents, that is, the addition of increments of THF, TMEDA, etc. to bulk hydrocarbon solvents containing an alkyllithium, in particular n-BuLi, has revealed maximally effective metalating solutions for a variety of substrates (*vide infra*). Such solutions drive the oligomer equilibrium to favor the unsaturated dimers (structures **1** and **2**), the putative reactive intermediate in alkyllithium metalation chemistry. Just as would bulk ether solvents or media containing a full equiv. of TMEDA, hydrocarbon media promoted metalation solutions will contain some concentration of a coordinately unsaturated dimer. This unsaturated dimer must exist so that the more weakly coordinating DMG (directing metalation group) of the aryl substrate can associate with the dimer. The association to be sure also takes place in bulk ether solvents and in the presence of a full equiv. of TMEDA, but the dimer concentration, presumably larger than in our doped media, is either coordinatively saturated or nearly so. This makes it more difficult for the ArDMG reacting substrate to achieve the prior coordination necessary to proceed through the transition state. Only by supplying a measured amount of deoligomerizing agent(s) to the hydrocarbon solution can the balance between dimer formation and ArDMG coordination be made most efficient. This equilibrium is illustrated in eq 2 for TMEDA complexation. We are uncertain of the number of TMEDA's in the n-BuLi tetramer, but we hypothesize that among the dimer complex population, some percentage would possess structure **1**. A similar set of "deficiency catalysis" equilibria applies to metalations in THF/hydrocarbon media.



$$2(n\text{-BuLi})_6 \xrightleftharpoons{\text{TMEDA}} 3[(n\text{-BuLi})_4]\bullet\text{TMEDA}_n \xrightleftharpoons{\text{TMEDA}}$$
$$6[(n\text{-BuLi})_2\bullet\text{TMEDA}_1] \xrightleftharpoons{\text{DMGAr}} 6[(n\text{-BuLi})_2\bullet\text{DMGAr}\bullet\text{TMEDA}_1] \qquad (2)$$

■ RESULTS AND DISCUSSION

Anisole (A). ortho-Lithiation chemistry began with the seminal observations of Gilman[9] and Wittig[10] that anisole, upon treatment with n-BuLi in ether and subsequently derivatized, afforded ortho-substituted products. Since that time countless papers have appeared detailing efforts to determine the mechanism of the ortho-lithiation process.[8] Anisole has served as the benchmark for virtually all of these studies. Numerous other reports of the utilization of ortho-lithioanisole (*o*-LiA) in synthesis have also been published with modest to good product yields being reported in most cases.[11] We attribute most of these modest yields to initial incomplete ortho-lithiation of anisole. Yields approaching 100% have been realized by the expedient of using the halogen/lithium exchange on *o*-bromoanisole at −78 °C.[12]

Utilizing this benchmark substrate, we have studied EoM's in three time-honored media: (1) DEE, (2) DEE/TMEDA, and

(3) THF. Over the course of these reactions, it is clear that high EoM's can be achieved in TMEDA/ether and in THF (Table 1). Our studies emphasize a 1:1 ratio of anisole to *n*-BuLi whereas many of the examples found in the literature employ an excess of the alkyllithium reagent. All of the EoM vs time plots recorded herein involve derivatization of the generated ortho-lithio intermediate with chlorotrimethylsilane (ClTMS) and subsequent GC analysis as a measure of EoM. EoM is a GC percentage defined simply as the areas of TMSAr / (TMSAr + ArH) × 100. In that the efficient reactions afforded EoM's >87%, no correction factor was applied. These transformations are very clean for the anisole metalation with no other material besides the unreacted starting material and the product being detected under all conditions.

Table 1. Summary of Preliminary Anisole Metalation Studies

medium	equiv. amine/ether	*T* (°C)	time (h)[a]	EoM (%)
DEE[b]	0	22	6	57
DEE[b]	1.0 TMEDA	22	4	83
THF[b]	0	22	3	89
Cyclohexane[c]	1.0 THF	22	8	62
Cyclohexane[c]	2.0 THF	22	6	78
Cyclohexane[c]	3.0 THF	22	6	84
Cyclohexane[c]	1.0 THF	45	8	85
Cyclohexane[c]	2.0 THF	45	6	86
Cyclohexane[c]	3.0 THF	45	6	90
Cyclohexane[c]	0.2 PMDTA[d]	22	6	94
Cyclohexane[c]	0.2 (−)-sparteine	22	6	92

[a] Period at which a maximum EoM was observed. [b] Reactants 1.3 M. [c] Reactants 1.0 M. [d] Pentamethyldiethylenetriamine.

Our earliest study of metalation in hydrocarbon solvents revealed that a maximum EoM of anisole at room temperature could be achieved by the addition of 3 equiv. of THF to the bulk hexane solvent.[2b] A repeat of this study using cyclohexane as solvent instead of hexane (Table 1) illustrates that in 8 h an 85% EoM of anisole is obtained at ambient temperature using 3 equiv. of THF. Lesser EoM's are obtained using 1.0 or 2.0 equiv. of THF. We since have observed that higher EoM's for this system can be obtained at elevated temperatures, explicitly 45 °C (Table 1) and 60 °C (Figure 1) with about a 95% EoM being realized at 60 °C. Moreover, at 60 °C, the system containing just 2.0 equiv. of THF afforded nearly the same EoM when comparing the 4 h points. As elevated temperatures are not normally associated with ortho-lithiations, these results provided initial impetus for our further study of the effect of elevated temperatures on metalation procedures. Under these same conditions and over the same period, but without the presence of THF, that is, in pure hydrocarbon media, metalation of anisole could be effected in only about an 8−10% EoM at 22 °C and about a 40% EoM at 60 °C.

Further investigation involved the use of TMEDA instead of THF to enhance EoM in cyclohexane. Varying the equiv. of TMEDA vs equiv. of anisole and *n*-BuLi from 0.05:1:1 to 2:1:1 provided significantly different EoM's, but data points exhibited unacceptable scatter for plotting. The solutions over all equiv. ratios of TMEDA were heterogeneous with copious amounts of a white flocculant precipitate being produced. This situation made reproducible repeated sampling difficult. Nevertheless, it became apparent that a maximum EoM was possible for this system with a catalyst: reactant equiv. ratio of 0.1−0.2:1.0:1.0. Larger ratios of TMEDA than 0.2 equiv. were counterproductive in that the EoM was observed to decrease. Study of the effect of temperature for the 0.1:1:1 system exhibited a significant variation (Figure 2). This study was performed on more dilute systems (0.67 M vs the usual 1.0 or 1.3 M), which allowed reproducible samples to be obtained, but with slightly lower EoM's.

Subsequent investigation maintaining the 0.1:1:1 ratio of TMEDA and the two reactants each 2 M in cyclohexane afforded reproducible 93−95% EoM's (Figure 3). Further enhancement of the purity of this solution was possible by centrifugation, syringing off the supernate and replacing same with an equal volume of cyclohexane. This procedure was sufficient to remove the few remaining percent of anisole such that the residual *o*-LiA approached a purity of 99%. As *o*-LiA is insoluble in hydrocarbon solvents, minimal loss of intermediate was experienced and so the remaining amount of *o*-LiA could be determined by simply allowing for the 2−4% loss of unmetalated anisole upon washing and transfer. This is a defining example since all the other ortho-lithio intermediates possess greater solubility in hydrocarbon media.

Interestingly, both PMDTA and (−)-sparteine were found to catalyze the ortho-lithiation of anisole at 22 °C (Table 1). Both studies were performed in a 1.0 M cyclohexane solution of the reactants with 0.2 equiv. of catalyst and must be regarded as preliminary at the present time. The (−)-sparteine studies afforded no increase in EoM with an increase in temperature.

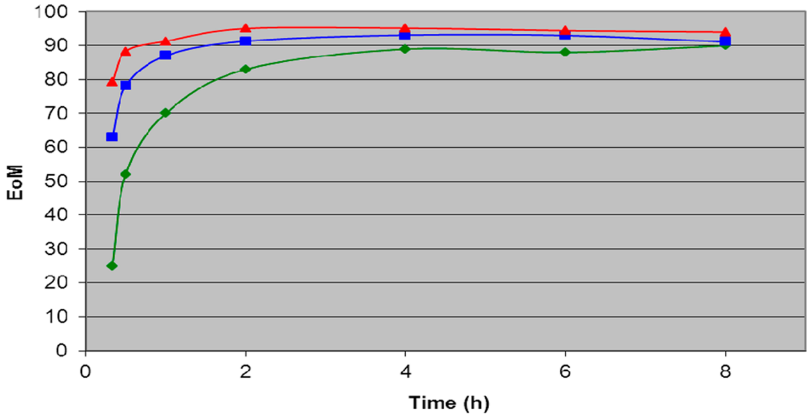


Figure 1. EoM vs time utilizing a 1.0 M solution of anisole/*n*-BuLi at 60 °C in cyclohexane containing (green) 1.0 equiv. THF, (blue) 2.0 equiv. THF, and (red) 3.0 equiv. THF.

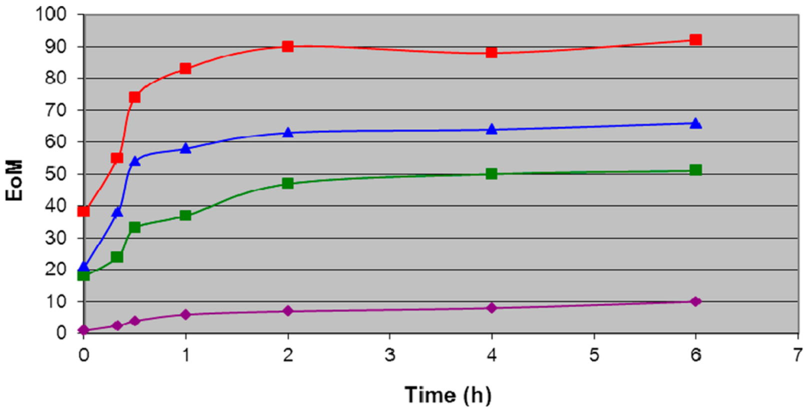
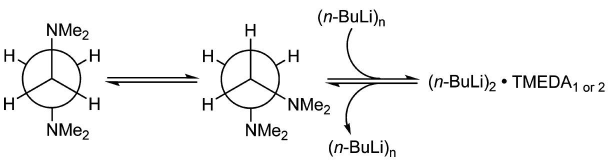


Figure 2. EoM vs time for a 0.67 M solution of anisole/*n*-BuLi in cyclohexane containing 0.1 equiv. TMEDA at various temperatures: (purple) 0 °C, (green) 22 °C, (blue) 45 °C, and (red) 60 °C.

Figure 3. Typical product solution from the treatment of anisole (2 M) with *n*-BuLi (2 M) with the addition of 0.15 equiv. of TMEDA. The top layer is the supernate and the bottom layer is associated *o*-LiA precipitate.

This is a provocative observation suggesting that TMEDA experiences conformational benefit from *bis*-chelation with increasing temperature (eq 3).With increasing temperature the



(3)

staggered/eclipsed Newman projection form on the right would increase in population causing enhanced complexing ability with *n*-BuLi and as a consequence enhanced ortho-metalation. (−)-Sparteine possesses a locked conformation, which is essentially eclipsed. Therefore it significantly outperforms TMEDA at 22 °C, but with no *bis*-chelating enhancement with increasing temperature, trails TMEDA at 60 °C in EoM. These arguments obviate whether or not TMEDA simultaneously *bis*-chelates a lithium in the oligomer or first becomes monodentate and then conformational interconverts to become *bis*-chelated.

***p*-Chloroanisole (*p*−ClA).** The EoM enhancement with increase of temperature of anisole prompted us to reexamine the ortho-lithiation of *p*-chloroanisole (*p*-ClA).[2e,13] The initial hydrocarbon media based studies were carried out in hexanes media at ambient temperature. Using the same conditions as were employed in the high yield ortho-lithiation of anisole (1.0 M substrate and *n*-BuLi, cyclohexane, equiv. THF, 60 °C), enhanced EoM's compared to the original results were realized (Figure 4).

Metalation experiments utilizing TMEDA were attempted. *p*-ClA in the presence of TMEDA brought immediate formation of a benzyne intermediate due to a competing lithiation ortho to the −Cl substituent.[2h] For *p*-ClA, as little as 0.5 equiv. of THF in cyclohexane at 60 °C after 6 h afforded EoM's >95%.

***o*-, *m*- and *p*- Methylanisole (*o*-, *m*-, *p*-MA).** The continuing interest in calixarenes, cavitands, carcarands and similar constructs suggests that synthetic routes to specifically substituted alkylanisoles and alkylphenols will be useful. Our program has long been involved with the study of metalation of the methylanisoles. Already reported are our results for *p*-methylanisole (*p*-MA)[2b,c] and *o*-methylanisole (*o*-MA).[2i] Herein we document our results for improved ortho-metalation of *o*-MA and *p*-MA. Successful ortho-metalation of *m*-MA in hydrocarbon media is reported for the first time.

Several previous studies of the methylanisoles have appeared in the literature with some contentious results having been reported. Early studies by Shirley and co-workers of the metalation and carboxylation of the *o*-MA system resulted in isolation of a benzoic acid, which was the product of ortho-lithiation and an acetic acid, the product of lateral lithiation.[14a] These products were obtained in modest yields and in various ratios. An earlier work had provided the same mixture of products in low yields.[14b] The papers by Shirley and co-workers first agreed with and then disputed the concept that the ortho-methyl group caused a conformational steric bias of the methoxy group that would retard the ortho-lithiation process in this system. This was in response to the significant retardation observed for the metalation of *o*-*t*-butylanisole observed under various conditions.[11j] Further intrigue relative to the course of this metalation is to be found in assessments of these observations in the literature. Anisoles, among them alkylanisoles, have been observed in superbase solution at

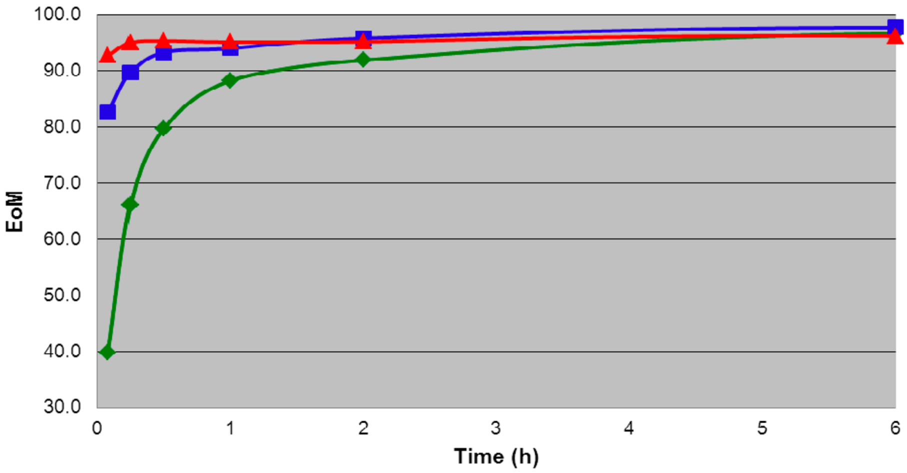


Figure 4. EoM vs time for a 1.0 M solution of *p*-ClA/*n*-BuLi in cyclohexane at 60 °C containing (green) 0.5 equiv. THF, (blue) 1.0 equiv. THF, and (red) 2.0 equiv. THF.

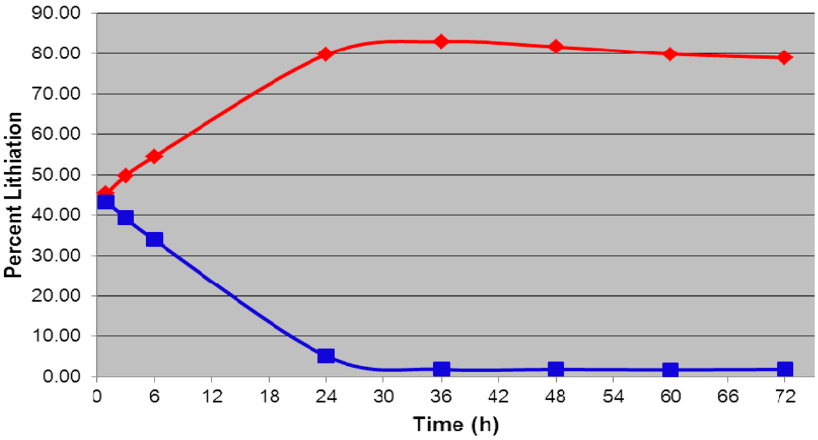


Figure 5. EoM vs time for a 3-MeA/*n*-BuLi in cyclohexane containing 0.1 equiv. of TMEDA and 1.0 equiv. of THF at 60 °C; (red) 6-TMS-3-MA and (blue) 2-TMS-3-MA.

reflux to undergo a methyl migration from the oxygen atom to adjacent positions.[15] An authoritative review, which has examined these metalations in light of the previous studies, concludes that metalation of *o*-MA cannot be regiospecifically accomplished.[16] Likewise, a computational treatment of the *o*-MA systems concludes in line with the experimental observations that regiospecific lithiation at either position cannot be achieved.[17]

In 1974, studies of the metalation of *m*-MA afforded mixtures of products from metalation at both ortho positions.[14] Schlosser et al were later able to efficiently provide lateral metalation of *m*-MA in 71% GC yield (carbonation, diazomethane) using *n*-BuLi/NaO*t*-Bu.[18] Utilizing a different metalating mixture, *t*-BuLi/pentamethyldiethylenetriamine (PMDTA), nearly regiospecific ortho-lithiation at the unhindered ortho-position was achieved.[18]

In an early study, Letsinger and Schnizer found that ortho-lithiation and carbonation of *p*-MA using *n*-BuLi/KO*t*-Bu and subsequent carbonation afforded 59% of the ortho-product along with 10% of the product from metalation of the *p*-methyl group.[19] A few years later, Schlosser utilized the same metalating system in THF followed by carbonation, treatment with diazomethane and GC analysis to attain a 78% GC yield of the ortho-lithiation product of *p*-MA.[20] An attempt by Schlosser to selectively laterally metalate the *p*-methyl group of *p*-MA resulted in a mixture of ortho- and lateral metalation products. Our own group's previous contribution to these studies was the realization by GC analysis of >90% EoM using 2 equiv. of *n*-BuLi/0.2 equiv. TMEDA in DEE contaminated with 2–3% of the laterally metalated product[2c] and essentially regiospecific ortho-lithiation using increments of THF/*n*-hexane in a GC analyzed 80% EoM.[2b]

All these earlier background observations have been contradicted by the results of the thorough examination of the metalation of all the MA's by Schlosser and co-workers. For ortho-lithiation of *o*-MA a 52% yield was attained using the base combination of *n*-BuLi/NaO*t*-Bu.[18] Lateral metalation was regiospecifically accomplished in 67% yield using a different base combination, that is, LDA/KO*t*-Bu. Other base combinations, *t*-BuLi/PMDTA and *t*-BuLi/KO*t*-Bu were utilized to regiospecificially metalate *m*-MA (64%) and *p*-MA (78%). All of the results recorded by Schlosser et al. are based on carboxylation, treatment with diazomethane followed by CG analysis.

Satisfactory discrimination between the ortho-metalated intermediated and lateral (*α*-) metalated intermediate was observed by our group.[2i] ortho-Lithiation was achieved using the original procedure of Harmon and Shirley,[13] which utilized a full equiv. of TMEDA. These authors reported about a 4:1 bias toward ortho-metalation at ambient temperature after 10 h.

Repeating these conditions, we achieved a 7.5:1 preponderance of the ortho-metalation intermediate in 1h.[2i] Further tweaking of these conditions has resulted in a significant improvement in the selectivity to a realized ortho-product preponderance of 11:1. These new conditions involved merely reducing the TMEDA/*n*-BuLi ratio to 0.92:1 and heating the solution to 60 °C. Alternatively, DEE can be used to effect ortho-lithiation of *o*-MA.[21]

A completely different metalation profile was realized for *m*-MA. After metalation for at least 48 h at 60 °C, 6-position EoM reached 70% (Figure 5). Further equilibration for another 24 h brought a maximized EoM of 80%. Nearly negligible amounts of the 2-lithio intermediate were detected after 48 h, the remaining contaminant being starting material. In unpublished work, a number of derivatives of the 6-metalated intermediate have been prepared and isolated in yields from 41 to 84%.

p-MA was efficiently ortho-metalated using the same conditions as those used for 95% EoM of anisole, 3 equiv. THF/cyclohexane, 60 °C. An EoM comparable to that for anisole was realized. A slightly retarding effect of the *p*-methyl substituent on the rate and EoM was noted.[22]

Dimethoxybenzenes (*o*-, *m*-, *p*-DMB). Utilization of the "deficiency catalysis" concept with the dimethoxybenzenes (DMB's) brought quick reward with little fine-tuning of the equiv. of TMEDA. Only 0.1 and 0.3 equiv. of TMEDA were investigated with 1,2-DMB requiring 0.3 equiv. and the other two isomers requiring only 0.1 equiv. For 1,2- and 1,4-DMB, the principal compromising effect for a high EoM of monometalation of these two aryl substrates was the tendency to afford the dimetalated intermediate. In the case of 1,2-DMB, this was the 3,6-dilithio intermediate and for the 1,4-DMB, the 2,5-dilithio intermediate. High EoM's (88−90%) of these substrates were attained in short periods of time at ambient temperature. Each was contaminated with a small quantity of the respective dilithiated intermediate. For 1,2-DMB, trituration with pentane afforded 95% pure 3-lithio 1,2-DMB free of the dilithio intermediate. This procedure proved impractical for the 1,4-isomer as the lithio intermediate was too soluble in pentane. The EoM of 1,3-DMB was so high (97%) that no attempt was made to further upgrade its purity.

There are questions regarding the relative reactivity of the DMB's in comparison to that of anisole. Certainly, 1,3-DMB is more reactive than anisole in all cases. The origin of this increased reactivity has had some varying insights ranging from the "tweezer effect" articulated by Saa and co-workers[23] to the monocoordinated, second methoxy group acidifying effect described by Collum et al.[24] A hydrocarbon medium only ortho-lithiation has been described for each of the DMB's.[2g] However, none of these procedures are what we would consider to approach atom-economy(≥90% ortho-lithiation). In hydrocarbon media, all three DMB's are more reactive than anisole with the order of reactivity being 1,2- > 1,3- > 1,4- > A.[2f] This is not the order found in ether media. The hydrocarbon media activation has been attributed to the substrate itself providing the necessary deoligomerizative activation of *n*-BuLi to effect ortho-lithiation. Thus the order observed reflects the relative *bis*-chelating ability of the substrate with 1,2- being greater than 1,3-. That 1,4-DMB is less reactive than either of the other two DMB's reflects its inability to *bis*-chelate, but its greater reactivity compared to anisole to a different effect, the opposing-π-resonance effect.[25] Here the normal delocalization of the unshared pairs on the methoxy group's oxygens is opposed by the delocalization of the *p*-oriented methoxy group. The results is that e-density is more localized on the oxygens of 1,4-DMB than that in A, making the coordinating ability of the oxygens in 1,4-DMB greater than the oxygen in A. Stated differently, this would result in an enhanced complex-induced-proximity-effect (CIPE).[8a,b] This activation toward ortho-lithiation takes precedent in spite of the fact that the overall e-density of the aromatic ring is higher in 1,4-DMB than it is in A.

However, our goal here is to activate the already described regiospecific metalations in hydrocarbon media sufficient to render these metalations atom-economical. Numbers of procedures for the metalation of all the DMB's have been described in the literature.[26−28] Most utilize either ether or THF as the reaction medium and a few use a combination of both ethers. Only for 1,4-DMB were several instances described where the 2-Li-1,4-DMB intermediate was accessed via the halogen/lithium exchange of 2-Br-1,4-DMB.[29] Room temperature metalations are the norm, with a significant number of such metalations having been effected at lower temperatures. Virtually all of these metalations have been accomplished with *n*-BuLi with other organolithiums being utilized only rarely. Extents of metalation (EoM's) have in general been modest as judged by isolated yields. In certain cases, metalation yields have been quite high, but these yields are based on use of an excess of metalating agent.

Dimethylaniline (DMA). ortho-Lithiation of DMA to produce *o*-LiDMA has proven to be somewhat problematical over the years. First described by Art Lepley and co-workers in the 1960s,[30] subsequent papers describe varying success with this ortho-lithiation. Notable among these, although not atom-economical, is the procedure recorded by Brandsma and Verkruijse.[1h] This procedure relied on significant excess of DMA. Other papers report product yields from the metalation of DMA that are extremely varied.[31] As with anisole and 1,4-DMB, some researchers preferred to prepare *o*-LiDMA through the ortho-bromo derivative via the halogen/metal exchange.[32]

Surprisingly, several of the systems found successful for promoting high yields of *ortho*-lithiation in anisole failed when applied to DMA. A study of equiv. of THF in cyclohexane at 25 °C afforded no better than a 15% EoM of DMA. Similar results were achieved with fractional equiv. of (−)-sparteine. One is tempted to ascribe steric congestion to the (−)-sparteine●*n*-BuLi complex's interaction with the dimethylamino group of DMA as the cause for the failure of the (−)-sparteine metalation system. A rationale for the failure of the THF-promoted hydrocarbon media system is puzzling and requires, in all likelihood, a more subtle explanation.

Further exploration turned to the system of fractional equiv. of TMEDA in cyclohexane, the system so successful for the ortho-lithiation of anisole. For this system reproducible sampling data was attainable such that a plot of EoM vs equiv. of TMEDA at various temperatures could be achieved (Figure 6). The data supports our contention that there is a competition between the dimer complexed with two TMEDA's and that with just one TMEDA and the substrate. Clearly, at 45 and 60 °C a deficiency of TMEDA provides superior results.

This system exhibited somewhat greater component solubility than that of anisole allowing more reproducible sampling data points to be obtained. It is clear from the plot that ca. 90% *o*-LiDMA can be obtained at 60 °C using 0.1−0.2 equiv. (we have settled on 0.15 equiv.) of TMEDA with the same 2 M concentration of reactants as was so successful for the metalation of anisole. As with *o*-LiA, metalation slurry's of

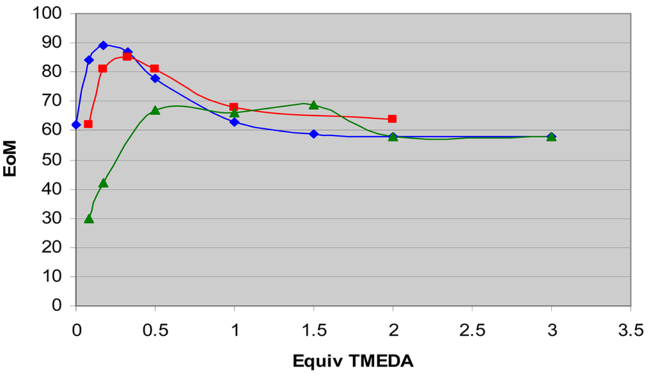


Figure 6. EoM vs Equiv. TMEDA for 1.3 M DMA/1.3 M *n*-BuLi in cyclohexane at various temperatures: (blue) 60 °C, (red) 45 °C, and (green) 22 °C.

this system could be upgraded by centrifugation, removal and replacement of the supernate with pure hydrocarbon solvent. However, for the DMA system to achieve purities of 95% or greater two such washings were needed. Unfortunately, the *o*-LiDMA is somewhat more soluble than *o*-LiA in cyclohexane/hexanes and so more intermediate is lost in the washings. It is estimated that ca. 15% of the DMA (as DMA and *o*-LiDMA) is lost during such washings. Therefore working titers of this reactive intermediate are assessed to be 85% of the original 2 M solutions, that is, 1.7 M.

Dimethylbenzylamine (DMBA). Initial examination of THF-doped and TMEDA-doped hydrocarbon solutions for the metalation of DMBA were a disappointment. All additive increments examined afforded percentages of the well-known α-(lateral) metalation product (Figure 7).

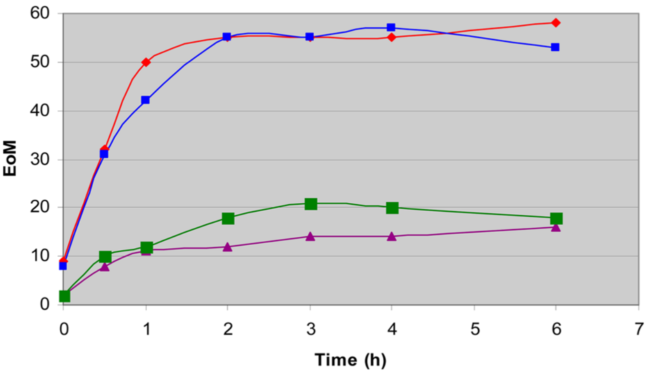


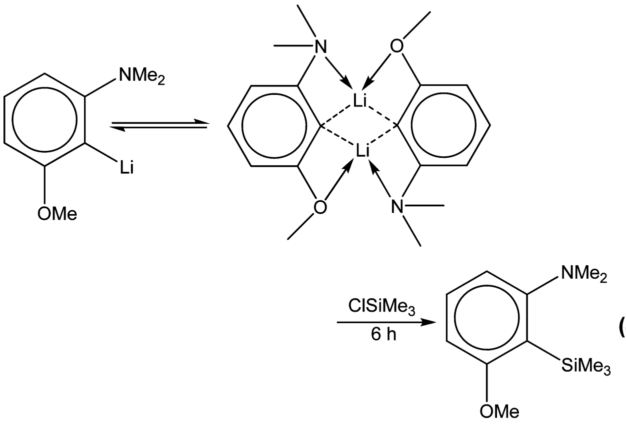
Figure 7. EoM vs time for the system 1.3 M DMBA/1.3 M *n*-BuLi at 22 °C containing 0.3 equiv. of TMEDA: (1) ortho-lithio intermediate in (red) hexanes, (blue) cyclohexane and (2) α-intermediate in (purple) hexanes, (green) cyclohexane.

C. R. Hauser, who discovered the directing properties of the $-CH_2NMe_2$ group,[33] also identified the α-lithio intermediate. In an elegant study, he and his students demonstrated the rearrangement of the α- to the *o*-lithio intermediate over time.[34] Numbers of papers over the years have utilized the various potentials of metalation of the DMBA system.[35]

With the failure of our standby regimens to affect regiospecific ortho-lithiation, a working observation that MTBE was useful in promoting efficient EoM's was put to the test. Earlier studies had shown that increments of MTBE, usually about 1.0 equiv, promoted the ortho-lithiation of several substrates, but that it was not as effective as THF. Since the $-CH_2NMe_2$ group was a relatively strong director, it was reasoned that a more weakly activating promoter might provide a more selective metalation, and avoid α-metalation. A series of cyclohexane solutions were doped with MTBE with the gratifying results plotted in Figure 8. Not only was 1.0 equiv. of MTBE found to provide enhanced and accelerated ortho-lithiation, but also significant regioselectivity. At 60 °C reproducible atom-economical yields of *o*-LiDMBA in the 95−97% range could be attained. At 60 °C, ca. 2% of the α-intermediate is generated which essentially disappears after 6 h resulting in a two-phase system of the *ortho*-lithio intermediate (Figure 9) similar in appearance to that obtained for *o*-LiA (Figure 3).

***m*-Methoxydimethylaniline(*m*-MeODMA) and *p*-Tetramethylphenylenediamine (*p*-TMPDA).** Few metalations of these substrates are to be found in the literature. Our earlier work denoting the metalation of *m*-MeODMA in ether at ambient temperature achieved an EoM of 80%.[6c] That procedure utilized a 1:1 *n*-BuLi/TMEDA ratio each about 0.5 M with results determined by NMR analysis. In the present study, our GC determined EoM of 88% using deficiency catalysis at 60 °C surpasses this. Interestingly, the maximum EoM is realized after 3 h which is much more rapid than those noted for A and DMA (*vide supra*). However, 0.5 equiv. of TMEDA was found necessary to achieve this EoM. In contrast, 1,3-DMB is metalated to an EoM of 97% in 1.5 h at ambient temperature using a deficiency catalyzing TMEDA concentration of only 0.1 equiv.

A cooperative effect of the 1,3-oriented DMG's appears likely. Originally, this effect was called the "tweezer effect" by Saa,[23] but has more recently been attributed to an additional acidifying effect of the second methoxy group by Collum.[24] A relevant observation made during our studies is that derivatization with ClTMS must gestate at least 6 h in order for an accurate EoM to be observed. This suggests that the 1,3-DMG dimer proposed by Saa et al.[23] might not only possess some generality, but also some stability (eq 4). Only one of the several possible bridged dimers is depicted. It is likely that a mixture of these dimers exists as they do for *o*-LiDMBA as determined by Reich and co-workers.[35t,u]



(4)

In contrast, metalation of *p*-TMPDA using deficiency catalysis achieved results (ca. 95% EoM) slightly better than that for DMA. A higher ratio of *n*-BuLi to TMEDA (1: 0.25) was utilized but the reaction was run at ambient temperature. Most importantly, barely detectable amounts (ca. 0.1%) of a product from dimetalation (presumably the 2-,5-product) was observed. This is much more of a problem with the metalation

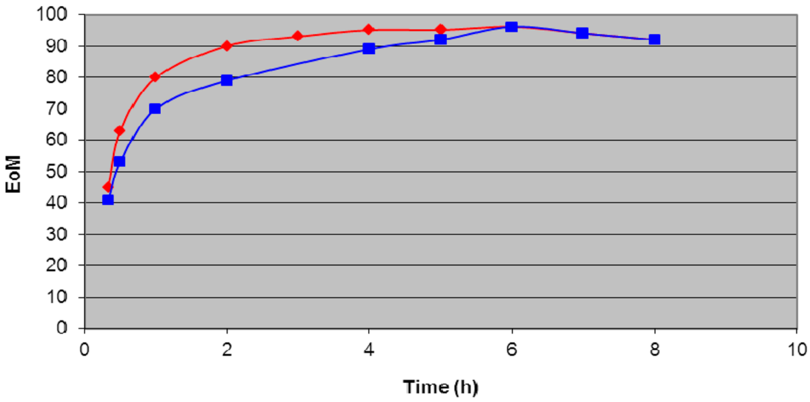


Figure 8. EoM vs time for the system 1.3 M DMBA/1.3 M *n*-BuLi in cyclohexane containing (blue) 0.7 equiv. and (red) 1.0 equiv. MTBE in hexanes at 60 °C.

Figure 9. Product solution from treatment of 1.3 M DMBA/1.3 M *n*-BuLi in cyclohexane containing 1.0 equiv. of MTBE. The top layer is the supernate and the bottom layer is associated *o*-LiDMBA.

of *p*-DMB where 2−3% of a product from dimetalation was routinely found. This product from several studies is known to possess a 2-,5-orientation. The EoM for *p*-TMPDA recorded here is much higher than from any other reported metalation of this substrate.[36]

CONCLUSIONS

These hydrocarbon media metalations emphasize atom-economy. For the most part, the Li/H exchange (ortho-lithiation) of *n*-BuLi and an activated aryl's ortho-position is effected in a 1:1 ratio of the reactants. Moreover, minimum quantities of catalyst/promoter are utilized resulting in heterogeneous product solutions of nearly pure ortho-lithio intermediates. No other alkyl-/aryl-lithium or other metal-containing reagents are utilized. The fact that these transformations can be efficiently accomplished in promoted hydrocarbon media provides safety, sustainability, green and control factors to these procedures, which are advantageous compared to those for ether media.

Table 2 summarizes the details of the 12 procedures. Seven of the 12 substrates were successfully metalated using a deficiency of TMEDA between 0.1 and 0.5 equiv. For three of the remaining substrates, *p*-ClA, *p*-MA and DMBA, increments of TMEDA proved too aggressive and so promotion of the metalation utilized equiv. of an ether. Uniquely, for 3-MA, a combination of TMEDA and THF provided the maximum EoM. Lastly, 2-MA, the only substrate containing a sterically impacted directing group, required a more aggressive metalating system, which was found using 0.92 equiv. of TMEDA.

Table 2. Summary of Hydrocarbon Media ortho-Lithiations

substrate	analyzed ortho-deriv.	equiv. amine/ether	time (h)	EoM%	purified
A	-TMS	0.15 TMEDA	18−24	93−96	96−98
p-ClA	-TMS (**4**)[a]	0.5 THF	4	96	N/A
2-MA	-CPh_2OH	0.92 TMEDA	1	86−88	N/A
3-MA	-CPh_2OH (**5**)[a]	0.1 TMEDA/1.0 THF	36	78−83	N/A
4-MA	-TMS	3.0 THF	24	94−96	N/A
1,2-DMB	-TMS	0.3 TMEDA	0.63	89−90	94−95
1,3-DMB	-TMS	0.1 TMEDA	1.5	96−97	N/A
1,4-DMB	-TMS	0.1 TMEDA	0.33	87−88	N/A
DMA	-TMS	0.15 TMEDA	18−24	85−91	98−99
DMBA	-TMS	1.5 MTBE	18−24	91−96	97−98
3-MeODMA	-CPh_2OH (**6**)[a]	0.5 TMEDA	3	86−88	N/A
1,4-TMPDA	-TMS (**7**)[a]	0.25 TMEDA	19	93−95	N/A

[a] New compound.

Consideration of the reactivity of these ArLi's generated in hydrocarbon media has caused us to begin dilution/dissolution studies. At present we have focused on these studies using THF and MTBE. Some scattered but significant alterations/improvements in nucleophilic reactions have been noted which are highly dependent on the ArLi being studied. There is literature evidence that these ortho-lithio aryl intermediates exhibit some of the same equilibria as *n*-BuLi, that is, dimer, tetramer, etc.[11e,35t,u] As our deficiency catalysis approach and subsequent purification procedures (when applicable) allow relatively unadulterated ortho-lithio intermediates to be prepared, the study of additives/promoters on derivatization of these intermediates is anticipated to be both insightful and fruitful.

Much progress has been made in ortho-metalations using other metalation agents which incorporate a variety of metal/base combinations. In this current study, we have shown that highly selective, efficient ortho-lithiation can be achieved by deficiency catalysis using *n*-BuLi as the only base. We believe that media manipulation can complement metal manipulation in the enhancement of ortho-metalations. It is a logical extrapolation that investigation of additive/promoters will enhance derivatization procedures as it has for the metalation protocols described herein. Our preliminary studies indicate that this is so; the literature has already provided a few provocative examples.[8i,11u,37]

■ EXPERIMENTAL SECTION

General. All reagents including anhydrous reaction solvents were purchased from Aldrich Chemical Co. and used without further purification unless otherwise noted. Usually, reactions were run with a 1:1 ratio of substrate and *n*-BuLi (2 M in cyclohexane or 10 M in hexanes) at concentrations ranging from 1.0 to 2.0 M in cyclohexane at the temperature indicated. Lower concentration runs were occasionally utilized to provide smoother reaction sampling/profiling. Reactions were conducted in 25, 50, or 100 mL one-neck septum sealed flasks (fitted with a condenser if heated) that was purged and maintained at a slight positive pressure with N_2 or Ar. Typically, the substrate was introduced into the flask, followed by hydrocarbon solvent, and an additive [*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), THF, etc.]. *n*-BuLi was then introduced to the septum-fitted flask via syringe, the syringe having been filled to the requisite volume under a slight positive pressure of N_2 or Ar. Exotherms were controlled with a water bath or ice bath. The plots of extents-of-metalation (EoM) vs time were made by extracting via syringe ca. 0.4 mL samples from the reaction mixture. Many of these reacting solutions form flocculent precipitates. From such heterogeneous mixtures, representative samples could be extracted utilizing a syringe fitted with a 14 gauge needle, which allowed both particulate matter and solution to be taken up. The sample aliquots were injected into a modest excess of a 2 M chlorotrimethylsilane (ClTMS) solution in cyclohexane and allowed to sit for >30 min unless otherwise indicated. After dilution with 2−3 mL of MTBE and aqueous Na_2CO_3 (2−3 mL) work up, each sample was analyzed by GC equipped with a BP-10 capillary column (25 m × 0.22 mm, 0.25 μm film and FID). Identities of products were confirmed by GC/MS analysis (30 m × 0.32 mm, 0.25 μm film) on an instrument equipped with a quadrupole mass detector and separate FID. GC yields were not corrected since TMS-derivative GC yields were, with one exception, 87% or greater resulting in minimal change upon correction. Each plot represents the average of at least three runs. In several cases where the *o*-lithio intermediate had some solubility in cyclohexane, hexane or pentane was used for the wash. NMR data was attained using an ECA-500 MHz instrument. Combustion analysis was performed on a CHN analyzer. Previously unknown compounds **4**−**7** were purified by column chromatography using silica gel (60 Å, 65 × 250 mesh, 500−600 m^2/g) available from Sorbent Technologies. TLC analysis was performed using identical silica plates also available from Sorbent Technologies.

***o*-Lithioanisole (*o*-LiA) Method 1 (Standard Procedure).** To a clean, dry round-bottom flask equipped with a large stir bar was added anisole (4.35 mL, 40.0 mmol) and cyclohexane (4.74 mL) via syringe. Next, *n*-BuLi (2 M in cyclohexane) (20.0 mL, 40.0 mmol) followed by TMEDA (0.91 mL, 6.0 mmol) (0.15 equiv.) were added slowly via syringe to attain an overall reaction molarity of 1.33 M. The reaction mixture was stirred at 60 °C for 18−24 h under nitrogen atmosphere. At this point the EoM of *o*-LiA was found to be 93−96% by ClTMS derivatization followed by GC analysis. If TMEDA removal and further purification is desired, the reaction, now containing a copious amount of precipitate, was allowed to cool and the stirred slurry was transferred via syringe fitted with a 14 gauge needle to clean, dry nitrogen-purged, graduated centrifuge tubes, which were each sealed with a septum and centrifuged for 2 min. The resulting supernate was removed via syringe and discarded. The settled solid was agitated with a volume of anhydrous cyclohexane equal to the amount previously removed in order to retain the approximate molarity of 1.33 M (i.e., total volume remained 30 mL). The tube was centrifuged again and the supernate removed to afford 96−98% pure *o*-LiA, as demonstrated by ClTMS treatment and GC analysis. The supernate contained no *o*-LiA using the same analytical procedure as above, only minute amounts of anisole. If desired, the generated pure *o*-LiA precipitate can be dissolved in THF or other ether media for subsequent homogeneous derivatization. At this scale minute losses are incurred during transfer and purification providing a routinely overall recoverable yield of solid *o*-LiA of ca. 85%.

***o*-LiA Method 2 (Additive Experiments).** To a clean, dry round-bottom flask equipped with a large stir bar was added anisole (1.1 mL, 10 mmol) and cyclohexane (1.8 mL) via syringe. Next, *n*-BuLi (2 M in cyclohexane) (5 mL, 10.0 mmol) immediately followed by the desired ether additive (THF, MTBE, DEE, 2-methyl THF, dibutyl ether, glyme, diglyme, dioxane, or dioxolane) (10 or 20 mmol) (1 or 2 equiv, respectively) were added via syringe to attain an overall reaction molarity of 1.0M. The reaction mixture was stirred at the desired temperature (22, 45, or 65 °C) under nitrogen atmosphere. Aliquots were analyzed by first quenching with a modest excess of a 2 M cyclohexane solution of ClTMS and allowing to sit for >30 min. After aqueous Na_2CO_3 work up, each sample was analyzed by GC and GC/MS to obtain EoM. Some comparative results are shown in Table 1 with the best results, those for THF, plotted in Figure 1.

2-Lithio-4-chloroanisole (2-Li-4-ClA). To a clean, dry round-bottom flask equipped with a large stir bar was added anhydrous cyclohexane (5.1 mL), 4-chloroanisole (1.8 mL, 15 mmol), and THF (0.61 mL, 7.5 mmol) (0.5 equiv.) under a nitrogen atmosphere. Next *n*-BuLi (2 M in hexanes) (7.5 mL, 15 mmol) was carefully added with stirring. The overall reaction concentration was 1.0 M. The reaction mixture was stirred at 60 °C. The EoM was determined to be 96% in 4 h. There was *ca.* 1.0% of what appeared to be a biphenyl product detected after ClTMS derivatization. The EoM was observed to slowly decline after 24 h.

Isolation of (5-Chloro-2-methoxyphenyl)trimethylsilane (4). The entire 2-Li-4-ClA reaction above was slowly quenched with ClTMS (2.85 mL, 22.5 mmol) after 4 h and allowed to stir overnight. Following quenching with aqueous saturated Na_2CO_3 carbonate, the reaction mixture was transferred to a separatory funnel with the aid of 25−30 mL MTBE. The organic layer was separated, washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The crude product was recrystallized with hexanes (3 mL) and filtered to provide 2.83 g, 88% of pure product **4** as clear needles. mp = 43.9−46.0 °C. ^{1}H NMR ($CDCl_3$) δ 0.25 (s, 9H), 3.78 (s, 3H), 6.73−6.75 (dd, *J* = 9.2, 3.5 Hz, 1H), 7.25−7.27 (m, 2H). ^{13}C NMR δ −1.1, 55.5, 110.9, 125.7, 130.2, 130.6, 134.6, 162.8. Anal. Calcd for $C_{10}H_{15}ClOSi$ (214.06): C, 55.93; H, 7.04. Found: C, 55.69; H, 7.13.

6-Lithio-2-methylanisole (6-Li-2-MeA). To a clean, dry, round-bottom flask equipped with a large stir bar was added 2-methylanisole (0.62 mL, 5 mmol), anhydrous cyclohexane (1.2 mL), and TMEDA (0.69 mL, 4.6 mmol) (0.92 equiv.) under nitrogen atmosphere. Next, the flask was carefully charged with *n*-BuLi (2 M in cyclohexane) (2.5

mL, 5 mmol). The overall reaction concentration was 1 M. A very slight exotherm was observed and the reaction was allowed to stir at 60 °C for 1 h. The resulting solution was analyzed by quenching a sample with a slight excess of a cyclohexane solution of benzophenone. After work up with brine and MTBE, an 86% yield of the benzophenone derivative of 2-lithio-5-methylanisole was found by GC analysis. There was 8.2% of α-metalated product observed with the remainder being starting material. Benzophenone was used as the GC derivatizing agent because excellent resolution of the ortho- and lateral derivatives was achieved. The comparable -TMS derivatives could not be resolved by GC.[2i] Isolation of the benzophenone derivative has already been reported.[2i]

6-Lithio-3-methylanisole (6-Li-3-MeA). To a clean, dry, round-bottom flask equipped with a large stir bar was added 3-methylanisole (1.9 mL, 15 mmol), anhydrous cyclohexane (4.2 mL), THF (1.21 mL, 15 mmol) (1.0 equiv.) and TMEDA (0.23 mL, 1.5 mmol) (0.1 equiv.) under a nitrogen atmosphere. Next, the flask was carefully charged with *n*-BuLi (2 M in cyclohexane) (7.5 mL, 15 mmol). The overall reaction concentration was 1 M. A very slight exotherm was observed and the reaction was allowed to stir at 60 °C. The reaction provided a 50:50 mixture of the two possible *ortho*-lithio intermediates (i.e., the 2-lithio-3-methyl anisole and the 6-lithio-3-methyl anisole) within the first several hours as determined by ClTMS derivatization. This mixture equilibrated over 36 h to 83% of the 6-lithio-3-methyl anisole with <1% of the 2-lithio-3-methyl anisole being detected. The only other contaminant was starting material.

Isolation of (2-methoxy-4-methylphenyl)diphenylmethanol (5). The TMS derivative, 6-TMS-3-methylanisole proved difficult to separate from starting material and so the benzophenone derivative was isolated. The entire 6-Li-3-MeA reaction above was slowly quenched with benzophenone (2.54 g, 13.9 mmol) and allowed to stir overnight. Following quenching with water, the reaction mixture was transferred to a separatory funnel with the aid of 25−30 mL MTBE. The aqueous layer was back-extracted with 25 mL MTBE and the combined organic layers were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. Following trituration with cyclohexane (8 mL), the slurry was filtered to provide 2.93 g, 70% of pure **5** as a white powder. mp = 134.8−135.8 °C. ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H), 3.64 (s, 3H), 5.27 (s, OH), 6.36−6.37 (d, J = 7.4 Hz, 1H), 6.61−6.63 (d, J = 7.4 Hz, 1H), 6.76 (s, 1H), 7.22−7.29 (complex m, 10H). ^{13}C NMR δ 21.5, 55.7, 82.0, 113.1, 121.1, 127.0, 127.7, 127.9, 130.2, 132.5, 139.1, 146.9, 157.3. Anal. Calcd for $C_{21}H_{20}O_2$ (304.15): C, 82.86; H, 6.62. Found: C, 82.80; H, 6.55.

2-Lithio-4-methylanisole (2-Li-4-MeA). To a clean, dry round-bottom flask equipped with a large stir bar was added anhydrous cyclohexane (1.6 mL), 4-methylanisole (1.9 mL, 15.0 mmol), and THF (3.65 mL, 45.0 mmol) (3 equiv.) under nitrogen atmosphere. Next *n*-BuLi (2 M in hexanes) (7.9 mL, 15.0 mmol) was carefully added with vigorous stirring. The reaction was allowed to stir at room temperature. The overall reaction concentration was 1.0 M. The EoM was determined to be 94% after 24 h. The only other component observed in the GC spectrum was starting material.

3-Lithio-1,2-dimethoxybenzene (3-Li-1,2-DMB). To a clean, dry round-bottom flask equipped with a large stir bar was added anhydrous cyclohexane (5.59 mL), 1,2-dimethoxybenzene (1,2-DMB) (1.61g, 12.6 mmol), and TMEDA (0.57 mL, 3.78 mmol) (0.3 equiv.) under a nitrogen atmosphere. Next *n*-BuLi (10 M in hexanes) (1.26 mL, 12.6 mmol) was carefully added with vigorous stirring followed immediately by anhydrous pentane (6.5 mL). The overall reaction concentration was 0.81 M. The reaction was highly exothermic during this period so the flask was cooled in a water bath as the reaction mixture went from clumpy to a tractable white suspension. The EoM was determined to be 90% in 40 min; the EoM began to decline after 1−1.5 h. There was 1.2% dimetalated product detected by TMS derivatization, that is, 3,6-bis-TMS-1,2-DMB. To remove TMEDA and purify the lithio intermediate, the reaction mixture was centrifuged and washed with pentane twice and hexane once, removing the supernate each time. Very little lithiated intermediate was lost in these washes (≤1% as evidenced by TMS derivatization/GC analysis); the overall yield of 95% pure 3-lithio-1,2-DMB was 85%.

2-Lithio-1,4-dimethoxybenzene (2-Li-1,4-DMB). To a clean, dry, round-bottom flask equipped with a large stir bar was added 1,4-dimethoxybenzene (1,4-DMB) (2.69 g, 19.5 mmol), anhydrous cyclohexane (9 mL), TMEDA (0.3 mL, 1.95 mmol) (0.1 equiv.) and anhydrous pentane (10 mL) under a nitrogen atmosphere. The mixture was gently heated until all the 1,4-DMB was dissolved. Next *n*-BuLi (10 M in hexanes) (1.95 mL, 19.5 mmol) was carefully added with vigorous stirring. The overall reaction concentration was 0.81 M. After 2−3 min stirring at room temperature an additional amount of anhydrous pentane (2 mL) was added in order to maintain a smoothly stirring mixture. After 5−10 min, the reaction solution became a white suspension. The EoM reached 88% in 20 min. There was 2% dimetalated product by ClTMS derivatization, that is, 2,5-bis-TMS-1,4-DMB. The *o*-lithio intermediate began to degrade after 1 h. It is not recommended to attempt purification of this intermediate.

2-Lithio-1,3-dimethoxybenzene (2-Li-1,3-DMB). To a clean, dry, round-bottom flask equipped with a large stir bar was added anhydrous hexanes (6 mL), *n*-BuLi (2 M in cyclohexane) (7.88 mL, 15.8 mmol) and TMEDA (0.23 mL, 1.52 mmol) (0.1 equiv.) under a nitrogen atmosphere. After vigorous stirring for several minutes, 1,3-dimethoxybenzene (1,3-DMB) (1.96 mL, 15.0 mmol) was added. The overall reaction concentration was 1.1 M. The reaction reached maximum EoM (97%) in 1.5 h, slowly declining in yield when left for longer periods. There was 0.6% dimetalation (2,4-bis-TMS-1,3-DMB) and 0.3% of the desired product that had been demethylated. With such a high initial EoM, there was no attempt to further purify this lithio intermediate.

***o*-Lithiodimethylaniline (*o*-LiDMA).** To a clean, dry round-bottom flask equipped with a large stir bar was added *N*,*N*-dimethylaniline (DMA) (7.6 mL, 60.0 mmol), anhydrous cyclohexane (15.0 mL), TMEDA (1.36 mL, 9.0 mmol) (0.15 equiv.) and *n*-BuLi (10 M in hexanes) (6 mL, 60.0 mmol) under nitrogen atmosphere. The overall reaction concentration was 2 M. The solution was allowed to stir at 60 °C for 18−22 h, whereupon after cooling, a copious precipitate of *o*-LiDMA formed. At this point, the EoM of *o*-LiDMA was 85−91% by ClTMS derivatization/GC analysis and can be used as is if desired. If TMEDA removal and further purification is desired, the reaction, now containing a copious amount of precipitate, was allowed to cool and the stirred slurry was transferred via syringe fitted with a 14 gauge needle to clean, dry nitrogen-purged centrifuge tubes, which were each sealed with a septum and centrifuged for 2 min. The supernate was removed and replaced with an equal volume of anhydrous hexanes. Following centrifugation, removal of the hexane supernate and repeating the hexane washing process, the now 98−99% pure *o*-LiDMA was diluted for subsequent reaction(s). The overall yield was ca. 70% of nearly pure solid *o*-LiDMA. These procedures have been performed on a 15, 30, and 60 mL scale with identical profiles.

***o*-Lithiodimethylbenzylamine (*o*-Li-DMBA).** To a clean, dry, round-bottom flask equipped with a large stir bar was added *N*,*N*-dimethylbenzylamine (DMBA) (3.0 mL, 20 mmol), anhydrous cyclohexane (6.4 mL), MTBE (3.6 mL, 30 mmol) (1.5 equiv.) under a nitrogen atmosphere. Next the flask was carefully charged with *n*-BuLi (10 M in hexanes) (2.0 mL, 20 mmol) with an exotherm being observed. The overall reaction concentration was 1.33 M. The reaction was allowed to continue stirring at room temperature for 18 h. The reaction can be allowed to stir at room temperature for as long as 48 h with minimal product decomposition. A 93−96% EoM as determined by ClTMS quench and GC analysis was found after 18 h. Over the first 6 h, 1−2% of a second intermediate, the product of α-lithiation, was noted. A slightly lower EoM for the *o*-LiDMBA (91−95%) was observed when the reaction was stirred at 60 °C for 6 h. To effect purification, the *o*-lithio intermediate was centrifuged and washed with anhydrous hexanes as described previously to remove MTBE and to obtain product with purity as high as 98%. An estimated 10−15% overall loss of *o*-LiDMBA was incurred using this procedure. Reactions have been performed on a 15, 30, and 60 mL scale with identical EoM profiles.

2-Lithio-3-methoxy-*N*,*N*-dimethylaniline (2-Li-3-MeODMA). To a clean, dry, round-bottom flask equipped with a large stir bar was added anhydrous cyclohexane (0.86 mL), TMEDA (0.51 mL, 3.4 mmol) (0.5 equiv.) and 3-methoxy-*N,N*-dimethylaniline (3-MeODMA) (purchased from Alfa Aeasar) (1.0 mL, 6.8 mmol) under nitrogen atmosphere. Next, the flask was carefully charged with *n*-BuLi (2 M in cyclohexane) (4.43 mL, 8.85 mmol), a 1.3 equiv. excess. The overall reaction concentration was 1 M. An external exotherm was initially observed, after which the reaction was allowed to stir at 60 °C for 3 h. The reaction proceeded to an 88% EoM as determined by ClTMS quench. It was found that the quench solution must be left for at least 6 h to ensure complete ClTMS derivatization.

Isolation of (2-(Dimethylamino)-6-methoxyphenyl)-diphenylmethanol (6). The 2-Li-3-MeODMA procedure was repeated as described above, and was slowly quenched with benzophenone (1.24 g, 6.8 mmol) and allowed to stir overnight. Following quenching with water, the reaction mixture was transferred to a separatory funnel with the aid of 25−30 mL MTBE. The aqueous layer was back-extracted with 25 mL MTBE and the combined organic layers were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. Following trituration with cyclohexane (8 mL), the slurry was filtered to provide 1.39 g, 60% of pure **6** as a white powder. mp = 144.0−146.1 °C (lit.[6c] 142−143 °C). ^{1}H NMR ($CDCl_3$) δ 2.56 (s, 6H), 3.05 (s, 3H), 6.73−6.75 (d, J = 8 Hz, 1H), 7.02−7.04 (d, J = 8 Hz, 1H), 7.16−7.34 (complex m, 11H), 11.2 (s, OH) . ^{13}C NMR δ 45.7, 55.6, 82.2, 111.7, 115.4, 126.2, 127.3, 127.7, 128.9, 132.4, 148.9, 153.5, 157.7.

2-Lithio-*N,N,N′,N′*-tetramethyl-1,4-phenylenediamine (2-Li-1,4-TMPDA). To a clean, dry round-bottom flask equipped with a large stir bar was added *N,N,N′,N′*-tetramethyl-1,4-phenylenediamine (1,4TMPDA) (1.5 g, 9.1 mmol), anhydrous cyclohexane (4.6 mL) and TMEDA (0.35 mL, 2.3 mmol) (0.25 equiv.) and *n*-BuLi (10 M in hexanes) (0.91 mL, 9.1 mmol) under nitrogen atmosphere. The overall reaction concentration was 1.24 M. After 15 min the solution became milky as a copious precipitate of the 2-Li-1,4-TMPDA formed. The solution was allowed to stir at room temperature for 19 h. At this point the EoM of 2-Li-1,4-TMPDA was 95% by ClTMS derivatization/GC analysis with 0.1% product from dimetalation being observed, presumably 2,5-bis-TMS-1,4-TMPDA.

Isolation of *N,N,N′,N′*-Tetramethyl-2-(trimethylsilyl)-benzene-1,4-diamine (7). The entire *o*-Li-*p*-TMPDA reaction above was slowly quenched with ClTMS (1.38 mL, 10.9 mmol) and allowed to stir overnight. Following quenching with aqueous saturated sodium carbonate, the reaction mixture was transferred to a separatory funnel with the aid of 25−30 mL MTBE. The organic layer was washed with brine, dried over sodium sulfate, concentrated *in vacuo* and purified by column chromatography to provide 1.74 g, 81% of pure **7** as a yellow oil. R_f = 0.78 (ethyl acetate). ^{1}H NMR ($CDCl_3$) δ 0.30 (s, 9H), 2.59 (s, 6H), 2.94 (s, 6H), 6.78−6.81 (dd, J = 8.6, 2.9 Hz, 1H), 6.847−6.854 (d, J = 3.4 Hz, 1H), 7.22−7.24 (d, J = 8.6 Hz, 1H). ^{13}C NMR δ −0.038, 41.2, 47.3, 115.0, 118.8, 122.4, 139.0, 148.2, 151.2. Anal. Calcd for $C_{13}H_{24}N_2Si$ (236.43): C, 66.04; H, 10.23, N, 11.85. Found: C, 65.94; H, 10.43; N, 11.66.

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Notes

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