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Metalation in hydrocarbon solvents: the mechanistic aspects of substrate-promoted *ortho*-metalations

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Abstract—The methoxy-substituted aromatic reagents 1,2- and 1,3-dimethoxybenzene (1,2-DMB and 1,3-DMB) and 1,2,4-trimethoxybenzene (1,2,4-TMB) each undergo directed *ortho*-metalation in high yield in *n*-BuLi/hydrocarbon media without the aid of a catalyst. These reactions, coined 'substrate-promoted *ortho*-metalations', proceed with the methoxy aromatic substrate functioning as both the directing metalation group (DMG) and as the deoligomerization agent. Evidence that the substrates themselves serve to deoligomerize *n*-BuLi comes from ^{13}C NMR. The relative extent of metalated product formed as a function of time for each of the three aromatics directly correlates with the substrate's time-dependent ability to coordinate to *n*-BuLi as measured by ^{13}C NMR. The interpretation of NMR results from experiments involving 1,2,4-TMB is consistent with the metalation proceeding via the activated complex [(1,2,4-TMB)$_2$·(*n*-BuLi)$_2$]. Finally, conclusions from solubility experiments are that for every substrate-promoted metalation investigated, a precipitate forms in the hydrocarbon solvent, and this precipitate mostly contains the *ortho*-lithiated aryl intermediate.

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1. Introduction

Ethers are the predominant solvents utilized for directed *ortho*-metalation (DoM) reactions because they are sufficiently polar to deoligomerize alkyllithium reagents and also readily dissolve arene substrates. The disadvantages of ethers as solvents in these applications are, however, manifold. Ethers tend to react with alkyllithium reagents under various metalation conditions, particularly when agents such as tetramethylethylenediamine (TMEDA) are present.[1] Moreover, care must be taken to remove both peroxides and water contaminants from ether solvents, a concern that necessitates pre-reaction treatments of such solvents or the use of excess alkyllithium reagent. As a result of these instability and safety concerns, ether solvents are seldom considered for large-scale industrial synthetic applications.

Hydrocarbons such as *n*-pentane, *n*-hexane, cyclohexane, and toluene can also serve as solvents for metalation reactions. These solvents are inert towards alkyllithium reagents and peroxide and water contamination are non-issues. Further, in industrial applications, hydrocarbon solvents do not present as significant environmental or safety problems as do bulk quantities of ethers. However, hydrocarbon solvents are nonpolar and therefore cannot deoligomerize alkyllithium reagents, hence deoligomerizing agents must be utilized. The main drawback of using such agents in ether media is that their presence accelerates media decomposition. Our efforts to prevent such occurrences initially involved use of fractional equivalents of TMEDA in ether solvent[2] and, more recently, equivalents of THF in hydrocarbon solvent[3] as well as fractional equivalents of TMEDA in hydrocarbon solvent.[4] These metalation systems are noteworthy in that they afford greater regiospecificity of and extents of metalation of the various arene substrates than have been previously reported.[5]

Our interest here lies in the monometalation of the dimethoxybenzenes (DMB's) and the trimethoxybenzenes (TMB's), arenes whose metalations are well documented. In the 1979 review by Gschwend and Rodriguez, some 50 metalations of 1,3-DMB are reported;[6] in every case an ether solvent was utilized. Only three metalation studies of 1,2-DMB are listed in the Gschwend and Rodriguez review.[6] No studies of 1,4-DMB are cited. Relatively numerous studies of these species have been undertaken in the ensuing 24 years with the vast majority of these being undertaken in ether solvents.[7–9] Monometalations of 1,2,3-, 1,2,4-, and 1,3,5-TMB have received some

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literature attention.[10] In two instances, dimetalation of the trimethoxybenzenes has been reported.[10a,d] Again, ethers were the principal component of the reaction media utilized.

We have recently reported initial observations with 1,2- and 1,3-DMB in which significant metalations in a hydrocarbon solvent were achieved but with no conventional deoligomerization agent present.[11] Ostensibly, the substrate molecules themselves must sufficiently coordinate to the alkyllithium reagent that deoligomerization occurs. This assumption is reasonable in that *n*-BuLi in the hydrocarbon solvent cannot deoligomerize without a ‘catalyst’ present. The substrate is assumed to function as both the directing metalation group (DMG) and as the deoligomerization agent. To our knowledge, our work represents the first ‘substrate-promoted’ metalation recorded in the literature.[11]

The principal goals of this paper are (1) to further the mechanistic understanding of ‘substrate-promoted’ metalations in hydrocarbon solvents, (2) to extend the range of arenes investigated over the two reported in our initial publication[11] and (3) to investigate the constitution of the copious quantities of solids formed during the reactions. The mechanistic goal is addressed by utilizing ^{13}C NMR methods for evaluating the extent of complexation between the substrate and *n*-BuLi in these metalations. The emphasis of the NMR work is to test the assumption that substrates capable of undergoing metalation in hydrocarbon media do so via coordination with and deoligomerization of *n*-BuLi. The second goal is achieved by extending the protocol of substrate-promoted metalation to include the three isomeric trimethoxybenzenes. The total array of substrates investigated include anisole, 1,2-dimethoxybenzene, 1,3-dimethoxybenzene, 1,2,4-trimethoxybenzene, 1,2,3-trimethoxybenzene, 1,3,5-trimethoxybenzene and 3-methoxydimethylaniline. Lastly, to attain the third goal, the constitution of the isolated solid material is investigated resulting in a relationship between the extent of complexation (as determined by ^{13}C NMR) and the extent of metalation being proposed.

2. Discussion and results

2.1. Background

Existing views hold that there are two general limiting mechanisms for directed *ortho*-metalation (DoM) reactions and that most DMG’s direct by a combination of these two limiting mechanisms (Fig. 1). One of these limiting mechanisms involves a prior-coordination complex between the alkyllithium reagent and the DMG of the aromatic substrate. This prior coordination complex is paramount to involvement of the ‘complexed-induced proximity effect’ (CIPE).[12] Facilitated by the proximity of the lithium atom to an *ortho*-hydrogen on the substrate, a lithium/*ortho*-H exchange occurs. The energetics of this exchange have been computationally determined to be ‘kinetically enhanced’,[13] but there is little experimental evidence to corroborate the predictions. In the second limiting mechanism,[6] the acidity of the *ortho*-hydrogen(s) is the controlling factor (Fig. 1). The acidic *ortho*-hydrogen is more readily removed by the basic *n*-BuLi, thereby promoting a high rate of regiospecific metalation of the aromatic ring at the *ortho*-position. In this mechanism, herein coined the ‘overriding-base mechanism’, no prior-coordination complex is involved.

Consideration of alkyllithium dimer structure(s) must be taken into account in the understanding of DoM reactivity. The most commonly used alkyllithium, *n*-BuLi, has the ability to equilibrate among three different olgimeric structures: dimer, tetramer, and hexamer.[14] Both the nature of the solvent, as well as that of the deoligomerization agent, affect oligomeric structure. In non-polar hydrocarbon solvents a hexameric structure exists, which permits little, if any, metalation of aromatic substrates. In diethylether *n*-BuLi exists in a tetrameric form, whereas in THF a mixture of the dimeric and tetrameric structures exist. Moderate to high metalation yields can be achieved in these ether solvents. While the tetramer may be reactive in some

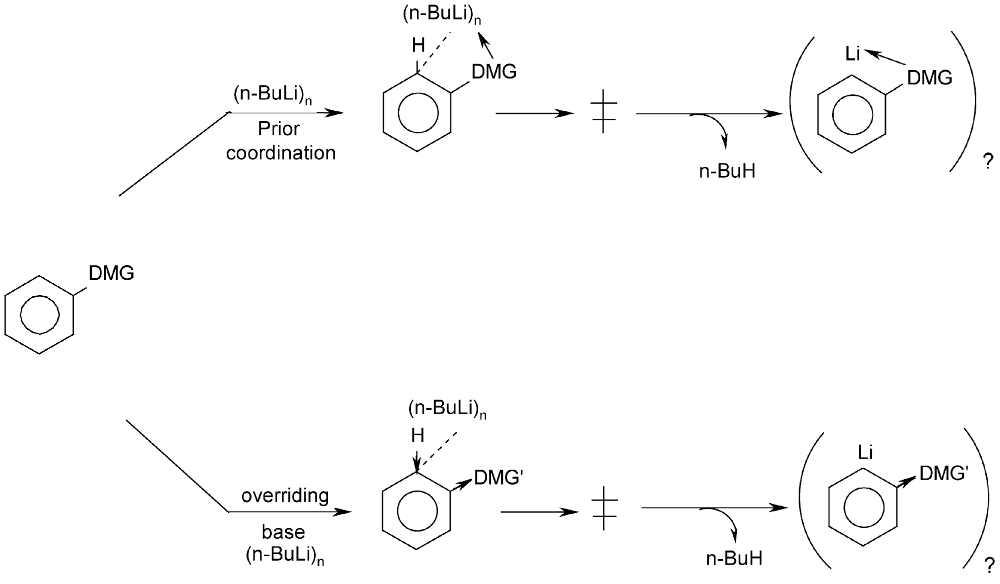

Figure 1. The two limiting mechanisms for directed *ortho*-metalation.

cases, the dimer is considered the most reactive of the *n*-BuLi oligomeric forms.[15]

When catalysts such as THF and TMEDA are added to non-polar hydrocarbon solvents in low concentration, significant metalation yields result.[3,4] Recently, low temperature NMR studies have shown formation of a symmetrical dimeric *n*-BuLi–TMEDA complex in the presence of stoichiometric amounts of TMEDA in toluene-d_8 under extreme dilution (Fig. 2).[16] Subsequently, Collum has shown that the dimer is formed in a >20:1 ratio over any other oligomer structure in toluene-d_8 when TMEDA is added.[17] Through kinetics studies, Collum has also found that the transition state stoichiometry for the metalation of anisole is [anisole·(*n*-BuLi)$_2$·(TMEDA)$_2$].[18]

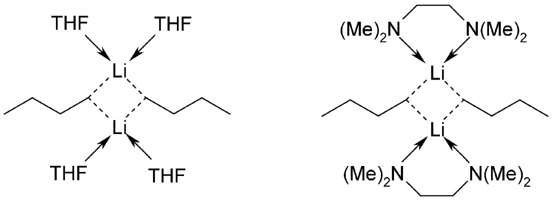

Figure 2. *n*-BuLi dimer formation facilitated by THF (monodentate) and TMEDA (bidentate) coordination.

It can be envisioned that an aromatic species possessing DMG's sufficiently able to complex and thereby deoligomerize *n*-BuLi could simultaneously function as both the substrate and as the 'catalyst'. That is, the substrate itself would first deoligomerize the alkyllithium reagent to a reactive dimer, and then, once in this reactive form, the substrate can react to generate a lithiated aromatic intermediate. A potential species to affect such chemistry is 1,2-dimethoxybenzene (1,2-DMB). Heretofore, this substrate would be considered to undergo 3-metalation by a combination of the two limiting mechanisms (Fig. 1). It is our hypothesis that the 1,2-situation of the methoxy groups will bis-coordinate to a lithium within a dimeric complex (Fig. 3b). Calculations at the ab initio density functional level (B3LYP 6-311+G**) support a 1,2-DMB bis-coordinated dimer structure (Fig. 3b) in that (1) the through space distance between the oxygens of 1,2-DMB is 2.63 Å, which compares to 2.98 Å for the N–N distance in TMEDA, (2) a favorable 5-membered ring chelation interaction is formed in both cases and (3) a stable local minimum structure corresponding to Figure 3b is found whose geometry is reasonable.[19] For the 1,3-arrangement of methoxy groups as in 1,3-DMB, a computationally realized minimum involving the bridged complex in Figure 3a has been proposed.[20]

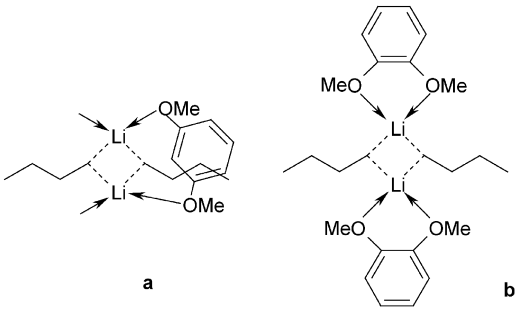

Figure 3. (a) The bidentate complexation of 1,3-DMB proposed by Saa[20] and (b) an envisioned complex between 1,2-DMB and the *n*-BuLi dimer. The second 1,3-DMB ligand in (a) has been omitted for clarity.

2.2. Metalation studies

The assertion that such substrate/*n*-BuLi complexes could facilitate metalation is unprecedented. In fact, two recent articles speculate that two methoxy groups *ortho* to each other on the aromatic ring will either sterically interfere with one another and thereby decrease the rate of *ortho*-metalation[10f] or form a bidentate complex similar to that in Figure 3b which is speculated to be *less* reactive.[8k] This is contrary to what we have observed. Metalation of 1,2-DMB in *n*-hexane at 25°C without the presence of a catalyst affords a maximum 78% corrected GC yield of the mono-trimethylsilyl (TMS) product (Fig. 4). Interestingly, there are slight solvent effects when the hydrocarbon solvent is changed from hexane to toluene and then to cyclohexane. As a function of time, the percent 3-TMS product in cyclohexane tracks that in toluene, each yielding 72% product after 6 h. However, in *n*-hexane solvent the yield of 3-TMS product approaches 80%. In all three hydrocarbon solvent systems, copious amounts of precipitate are formed with no trace of the product from dimetalation being detected.[21] The latter may be attributed to the relative insolubility of the 3-lithio intermediate such that it is removed from solution before a second metalation, known to take place at the 6-position,[10a] can occur.

A competitive metalation of 1 equiv. of a system made up of 1,2-DMB and 1 equiv. of anisole was performed in cyclohexane at 25°C using 1 equiv. of *n*-BuLi. After 6 h, 54% metalation of the 1,2-DMB occurred along with 15% metalation of anisole. This demonstrated, in a manner different from that in our preliminary publication,[11] that the rate of metalation of 1,2-DMB is greater than that of anisole.[10k] It is curious, however, that the ratio of time-dependent yields for this in situ competition is no better than 4:1 whereas comparison of separate experimentally determined time-dependent metalation yields, as reported in our preliminary publication, resulted in a ratio of 24:1.[11] The relatively high extent of metalation of anisole (15%) observed under the in situ conditions is the cause of this discrepancy since the extent of anisole metalation in hydrocarbon solvent is recorded as being only 3% in 6 h.[3a] This suggested that the presence of 1,2-DMB was accelerating the rate of metalation of anisole. To test this hypothesis, experiments were set up where 0.2 equiv. of 1,2-DMB and 1.0 equiv. of anisole in cyclohexane were treated with 1.0 equiv. of *n*-BuLi. After 6 h at 25°C, the 0.2 equiv. of 1,2-DMB was about 90% metalated and the full equiv. of anisole was over 50% metalated. In other words, 1,2-DMB promoted the metalation of anisole. This remarkable observation reinforces our contention that *n*-BuLi in the presence of 1,2-DMB can form the dimer intermediate as in Figure 3b and that this dimer intermediate can be intercepted by anisole in a manner similar to which the *n*-BuLi·TMEDA dimer is intercepted by anisole.

Several reactions were examined where ether was used with or without added TMEDA as the media for metalating 1,2-DMB so that a direct comparison could be made with

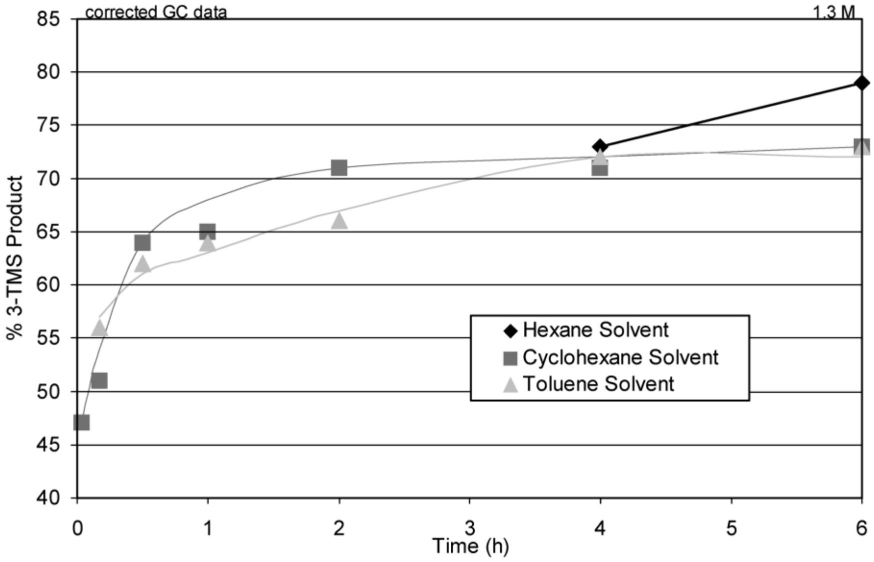

Figure 4. Substrate-promoted metalation of 1,2-DMB in common hydrocarbon solvents.

our metalation results in hydrocarbon media. No conditions were found where the metalation of 1,2-DMB proceeded as well in ether solvent as it did in hydrocarbon solvent. The best reported results for the metalation of 1,2-DMB are from the laboratories of Crowther and Sundberg[10a] who report an ultimate yield of 86% monometalated product in *n*-BuLi/ether with TMEDA as catalyst. However, a 10% excess of the 1:1 *n*-BuLi/TMEDA reagent and a two day reaction period were utilized. When run for shorter periods under similar conditions, but with no excess of *n*-BuLi and utilizing fractional equivalents of TMEDA,[4] lower extents of metalation were observed (Fig. 5).

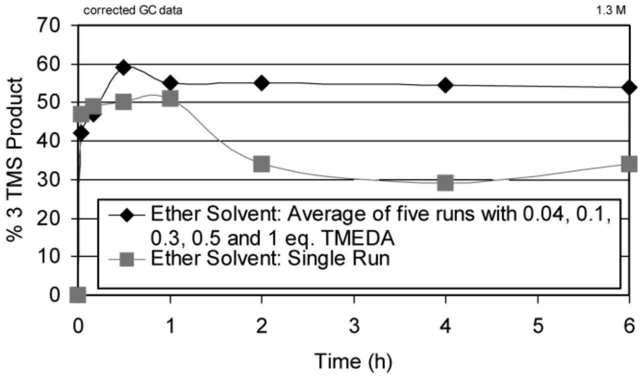

Figure 5. Metalation of 1,2-DMB in diethylether.

Table 1. % Complex formation between methoxyarenes and *n*-BuLi via ^{13}C NMR

Substrate	Time (h)	Solid (%)	Complex in solution (%)	Total complexed (%)[a]
Anisole 1 M	0	0	0	0
	1	0	0	0
	3	0	<1	<1
	24	0	7	7
1,3-DMB 1 M	0	8	26	32
	1	49	43	71
	3	51	68	84
1,2-DMB 1 M	0	87	29	91
	1	95	52	97
	3	>98	–	>98
1,2,4-TMB 1 M	0	100	–	100
	1	100	–	100
	3	100	–	100
1,2,4-TMB 0.1 M	0	>98	–	>98
	1	>98	–	>98
	3	>98	–	>98

[a] It is assumed that the lithiated material that has precipitated has passed through the soluble complex stage. The % total complexed=% solid+(100−% solid)×% complex in solution.

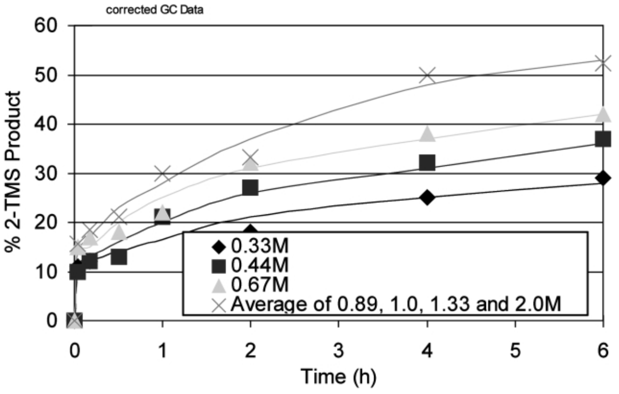

Figure 6. Substrate-promoted metalation of 1,3-DMB in *n*-hexane at various concentrations.

A second potential candidate for substrate-promoted metalation is 1,3-dimethoxybenzene (1,3-DMB). NMR data mandate that 1,3-DMB forms a complex with *n*-BuLi (Table 1), the nature of which is still open to investigation.[19,20] Nevertheless, an analogous CIPE mechanism can be envisioned in which the 1,3-DMB serves as both the substrate and as the catalyst (Fig. 3a). When we conducted the reaction of 1,3-DMB in pure hydrocarbon solvent at 25°C at various concentrations, greater than 50% yield of the 2-metalated product was achieved (Fig. 6). Significantly less precipitate formation for this system was observed than for any of the other substrate systems. The range of concentration of reactants that exhibited the highest yields was from 0.9 to 2.0 M. To test for temperature effects on the overall yield of derivatized product, the reaction in cyclohexane was performed at 25, 45, and 60°C (Fig. 7).

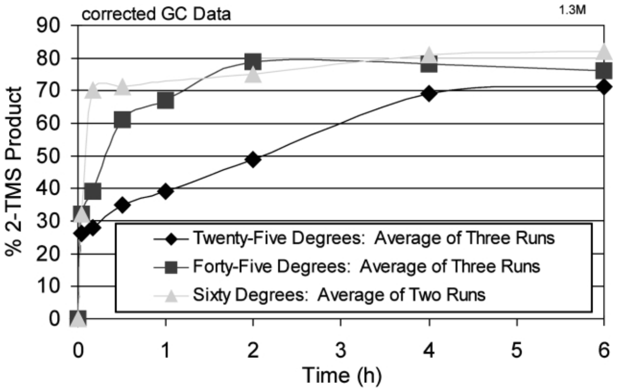

Figure 7. Substrate-promoted metalation of 1,3-DMB in cyclohexane at various temperatures.

The yield improved with increasing temperature to provide over 82% derivatized product, which equals the best reported yields for metalation of this substrate in the literature.[22]

Extension of the substrate-promoted concept to the TMB's revealed further surprises. 1,3,5-TMB did not undergo significant metalation in any of the hydrocarbon solvents. This may be attributable to a relative lack of solubility of 1,3,5-TMB in hydrocarbon solvents, but it also could be caused by some subtle electronic factor.[10k] In direct contrast, 1,2,4-TMB underwent immediate substrate-promoted metalation in cyclohexane and toluene with an 84% yield being achieved in cyclohexane in just 10 min (Fig. 8). Rapid solidification of the reaction mixture was also observed. That 1,2,4-TMB undergoes metalation in the 3-position has been documented in the literature,[10a] but the extraordinary rapid rate of metalation under these conditions is unprecedented. A combination of the bridging intermediates proposed for the 1,2- and 1,3-DMB system (Fig. 3) can be envisioned. The extraordinary rapid rate of metalation of 1,2,4-TMB may be attributable to the relative greater acidity of the 3-position proton in this arene.

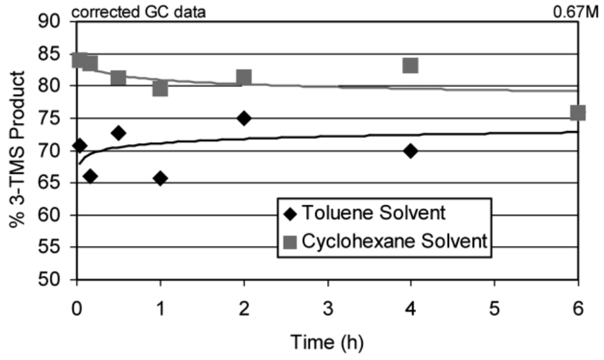

Figure 8. Substrate-promoted metalation of 1,2,4-TMB in common hydrocarbon solvents.

1,2,3-TMB undergoes substrate-promoted metalation, but with a complicating feature. In both hydrocarbon and ether media a second product was detected. Precipitate formation was observed in both media, with that in hydrocarbon media being quite significant. This second product, produced to the extent of 5–20% in both media, has now been isolated and identified as 2-*n*-butyl-1,3-DMB by a combination of MS and NMR data. Nucleophilic displacement of a methoxy group from an aromatic ring is not unprecedented. In appropriate arenes, methoxy group displacement has been used in synthesis.[23] However, this secondary reaction pathway has gone unrecognized in previous reports of the metalation of the 1,2,3-TMB system.[10a,c]

Lastly, 3-methoxydimethylaniline (3-MDMA) has been briefly examined. At 60°C in cyclohexane about 4% metalation was achieved. As 3-MDMA is quite soluble in cyclohexane, unlike 1,3,5-TMB, and is relatively polar as compared to 1,3,5-TMB, the reason(s) for the lack of reactivity of 3-MDMA is puzzling. These systems, as well as related analogs, are still under investigation.

Examination of the precipitates produced by metalations under substrate-promoted conditions revealed that they are chiefly comprised of the appropriate *ortho*-lithio intermediates. The data presented in Figures 4–8 arise from experiments in which the *ortho*-lithiated aryl ion of the substrate was quenched by reaction with ClTMS. The extent of TMS derivative formed was then plotted against time. In the generation of such data, a wide bore syringe was utilized to remove, from a rapidly stirred suspension, a representative aliquot containing both solid and liquid, which is added to a second vial with the quenching agent, ClTMS. We modified this approach for the purpose of determining the identity of the solid material. In one type of experiment, the reaction media was allowed to settle without stirring and a syringe needle with a filter was utilized so as to ensure that the liquid phase aliquot taken contained no solid. When this liquid phase aliquot was quenched with ClTMS in the usual manner and the resulting mixture was analyzed, no derivitized product was observed for any of the DMG substrates investigated. In each case, unreacted starting material was detected. In a second type of experiment, the majority of the liquid from the unstirred reaction vessel was removed so that what remained was almost pure solid material. This solid was then transferred via a wide bore syringe and added to a second vessel containing ClTMS. The resulting mixture, when analyzed, contained a high yield of TMS derivative and little or no unreacted starting material. The conclusion from these experiments is that for every substrate investigated, the solid formed is constituted primarily of the *ortho*-lithiated aryl intermediate. Therefore, since the *ortho*-lithiated species are relatively insoluble, no direct evidence for such species in our NMR data can be anticipated.

2.3. NMR studies

Having established that the solids produced during these metalations were the respective *ortho*-lithio intermediates, the proposed bis-coordinated intermediates (Fig. 3) were inferred to remain in solution. To demonstrate the presence of the proposed soluble bis-coordinated species, NMR examination of reaction solutions was instigated. ^{7}Li spectra, insightful in other of our investigations, provided no information regarding substrate complexation. In contrast, ^{13}C spectra proved particularly rewarding as separate signals for complexed and uncomplexed methoxy groups could be discerned in all spectra. Specifically, we analyzed anisole, 1,2-DMB, 1,3-DMB, and two isomeric trimethoxybenzenes, 1,2,4-TMB and 1,2,3-TMB. As stated previously, the 1,2,3-TMB exhibited a complicating secondary metalation which confused interpretation of the ^{13}C spectra. In each case, the data was analyzed with an emphasis on measuring the extent of substrate/*n*-BuLi complex formed as a function of time and then comparing that evidence against the degree of substrate-promoted metalation that occurred for the same substrate and *n*-BuLi under reaction conditions.

In order for any species to be observed by the NMR methods employed here, it is necessary for that species to be soluble in the solvent media utilized. If the complex or the aryl metalated (*ortho*-lithiated) ion that comes from the complex is insoluble and falls out of solution, direct evidence for that species is lost, in that the line widths of the solid material broaden into the baseline and, therefore, their signals do not appear in the spectrum. Since some solid forms in every substrate-promoted reaction performed, we endeavored to determine the identity of the insoluble solid material prior to the NMR investigations enabling proper assignments in the ^{13}C spectra once that data was collected.

2.3.1. Anisole.

Anisole is not efficiently metalated in hydrocarbon media. Without addition of THF or TMEDA,[3,4] the extent of metalation of anisole in hydrocarbon solvents at 25°C never exceeds 10%, even after 24 h. The reason that anisole cannot undergo substrate-promoted metalation is its relative inability to complex to and deoligomerize *n*-BuLi. Because anisole possesses only a single methoxy group, it cannot undergo what seemingly is required for high efficiency substrate-promoted deoligomerization—bidentate complexation.

When the ^{13}C NMR spectra of anisole in cyclohexane is compared to a similar spectrum of a 1:1 mixture of anisole:*n*-BuLi that has been allowed to equilibrate at room temperature for 1, 3, and 24 h, several observations are noted (Table 1). The NMR signals for the anisole carbons do not change in the first 3 h of equilibration time. After 24 h, a set of minor signals have emerged. The signals correspond to a new form of anisole, the most tractable signal being the one at ca. 53.9 ppm which is assigned to the complexed methoxy group. This signal, after 24 h, has grown to roughly 7% of the intensity of the original methoxy signal at 54.9 ppm. Because we have demonstrated that these *ortho*-lithiated aryl intermediates fall out of solution and become transparent to NMR observation, the new set of signals are assigned to a soluble anisole-complexed *n*-BuLi oligomer. Hence, as expected, and consistent with metalation results, anisole does not complex to an *n*-BuLi oligomer (tetramer or dimer) until after 24 h of room temperature equilibration, and then only to a small degree.

2.3.2. 1,3-DMB.

There exists one methoxy carbon signal at 54.7 ppm in the ^{13}C NMR spectrum of 1,3-DMB in cyclohexane. When sufficient *n*-BuLi in cyclohexane is added to the 1,3-DMB to generate a mixture with a 1:1 molar ratio of *n*-BuLi to 1,3-DMB, a second methoxy carbon signal at 53.5 ppm begins to emerge with increasing time. The new signal represents an additional methoxy group environment with a single symmetry. We assign this signal to a methoxy group from a 1,3-DMB that is complexed to an *n*-BuLi oligomer. Because there is only one symmetry type for the methoxy group, it is certain that both methoxy groups of the 1,3-DMB must be complexed in a bidentate fashion. Saa[20] would suggest it to be the bidentate structure incorporating 1,3-DMB shown in Figure 3a. It should be noted that new aromatic signals also emerge with time, consistent with condensed-phase complexed species. The amount of the complexed form of 1,3-DMB versus uncomplexed 1,3-DMB increases dramatically faster than that for anisole (Table 1). At time zero, defined as the time in which the *n*-BuLi was added to substrate plus the analysis time for the NMR spectrum (ca. 45 min), the amount of total complexed 1,3-DMB corresponds to 32%. After 1 h reaction time, this mixture constitutes 71% and increases to roughly 84% after 3 h. Interestingly, after 3 h, the extent of solid formation is 51%, closely approximating the yield of 2-TMS product after the same period (Fig. 6). Therefore, direct evidence for 1,3-DMB substrate-promoted complexation to *n*-BuLi is provided with the amount of complex formed as a function of time tracking the time-dependant yield of metalated product.

2.3.3. 1,2-DMB.

There exists one methoxy carbon signal at 54.8 ppm in the ^{13}C NMR spectrum of 1,2-DMB in cyclohexane. When *n*-BuLi in cyclohexane is added to the 1,2-DMB to generate a mixture with a 1:1 molar ratio of *n*-BuLi:1,2-DMB, a second methoxy carbon signal at 53.9 ppm begins to emerge with increasing time. The new signal represents the methoxy groups from a 1,2-DMB that is complexed to some *n*-BuLi oligomer. Again, there is only one symmetry type for the methoxy group, and therefore both methoxy groups of the 1,2-DMB are asserted to be complexed in a bidentate fashion, presumably as in Figure 3b. The amount of the complexed form of 1,2-DMB versus uncomplexed 1,2-DMB increases with time more markedly than that for 1,3-DMB. At time zero, 91% total complexation is observed (Table 1). After 1 h reaction time, the total complexed form is approximately 97%. After 3 h, the NMR sample tube containing the 1,2-DMB/*n*-BuLi/cyclohexane is nearly entirely solid, corresponding to better than 98% total complexation. The NMR spectrum after 3 h showed almost no uncomplexed species remaining, and the soluble complexed species was barely above the noise level (though much larger than the signal for the uncomplexed species). Here it is assumed that, as the concentration of the complex increases, it becomes insoluble and, as such, becomes transparent to the NMR observation methods employed. Interestingly, after 1 h reaction time, only 32% of 1,3-DMB had complexed to *n*-BuLi whereas, after the same period, 1,2-DMB had almost completely complexed. This is quite consistent with the observed relative metalation chemistry, where the time-dependent yield of metalated product for 1,2-DMB (Fig. 4), is over twice that for 1,3-DMB (Fig. 6). Therefore, the increased extent of metalation product formed as a function of time for 1,2-DMB over 1,3-DMB directly correlates with the increased ability that 1,2-DMB has over 1,3-DMB to complex to *n*-BuLi.

In view of these findings, a reasonable question arises: why does 1,2-DMB complex to, and therefore deoligomerize, *n*-BuLi better than does 1,3-DMB? If it is asserted that the complex involves an *n*-BuLi dimer, then it could be argued that 1,2-bidentate complexation is more favorable than 1,3-bidentate complexation. The investigations with the trimethoxybenzenes (TMB's) discussed below shed some light on this issue.

2.3.4. 1,2,4-TMB. The ^{13}C NMR spectrum of 1,2,4-TMB possesses three distinct signals between 54 and 56 ppm that correspond to the three different methoxy groups of the unsymmetric substrate (Fig. 9). When *n*-BuLi in cyclohexane is added to the 1,2,4-TMB to generate a mixture with a 1:1 molar ratio of *n*-BuLi to 1,2,4-TMB (1 M concentration of *n*-BuLi), complete solidification of the system in the NMR tube occurs and solution NMR spectroscopy is not possible (Table 1). In an effort to gain more insight, the sample tube was again prepared at a 1:1 molar ratio of *n*-BuLi to 1,2,4-TMB, but this time at 0.1 M in *n*-BuLi. The lower concentration still resulted in some solid formation, but an NMR spectrum could be obtained (Fig. 9, middle spectrum). No evidence for either 1,2,4-TMB or *n*-BuLi exists in the spectrum (the only observable signals were from cyclohexane and toluene-d$_8$). The two species apparently formed a complex and/or reacted and fell out of solution. To test this, excess 1,2,4-TMB was added and a new spectrum was obtained (Fig. 9, top spectrum). This spectrum clearly shows the added, uncomplexed 1,2,4-TMB. If more *n*-BuLi is added so as to again return to a 1:1 ratio, once more evidence for the substrate and for *n*-BuLi vanishes from the spectrum (and additional solid falls out of solution). It is possible to see NMR evidence for the 1,2,4-TMB substrate only when it exists in greater than a 1:1 molar ratio with respect to *n*-BuLi. The *n*-BuLi signals are present only when excess alkyllithium exists. Whenever a 1:1 molar ratio of 1,2,4-TMB:*n*-BuLi is achieved, neither species survives in solution and hence the solution is transparent to the NMR measurements made under the conditions of the experiment.

The most reasonable conclusion that can be drawn from these observations is that about 75% lithiation of the 1,2,4-TMB instantaneously occurs (Fig. 8) generating the 3-lithio intermediate which immediately precipitates from solution. In so doing, it includes the remaining 25% of substrate and *n*-BuLi. It may be fortuitous that the ratio of the *n*-BuLi to substrate that disappears from solution is 1:1, but we infer that rapid complex formation has taken place to form a bidentate complex analogous to those in Figure 3, i.e. [(1,2,4-TMB)$_2$·(*n*-BuLi)$_2$]. Moreover, we contend, this complex is occluded and/or coprecipitated with the rapidly formed 3-lithio-1,2,4-TMB intermediate. This conclusion is reached as follows: since the time-dependent extent of substrate complexation by NMR (Table 1) and the time-dependent extent of metalation (Figs. 4–8) track each other in the order anisole <1,3-DMB<1,2-DMB for both variables, the observation that the metalation of 1,2,4-TMB

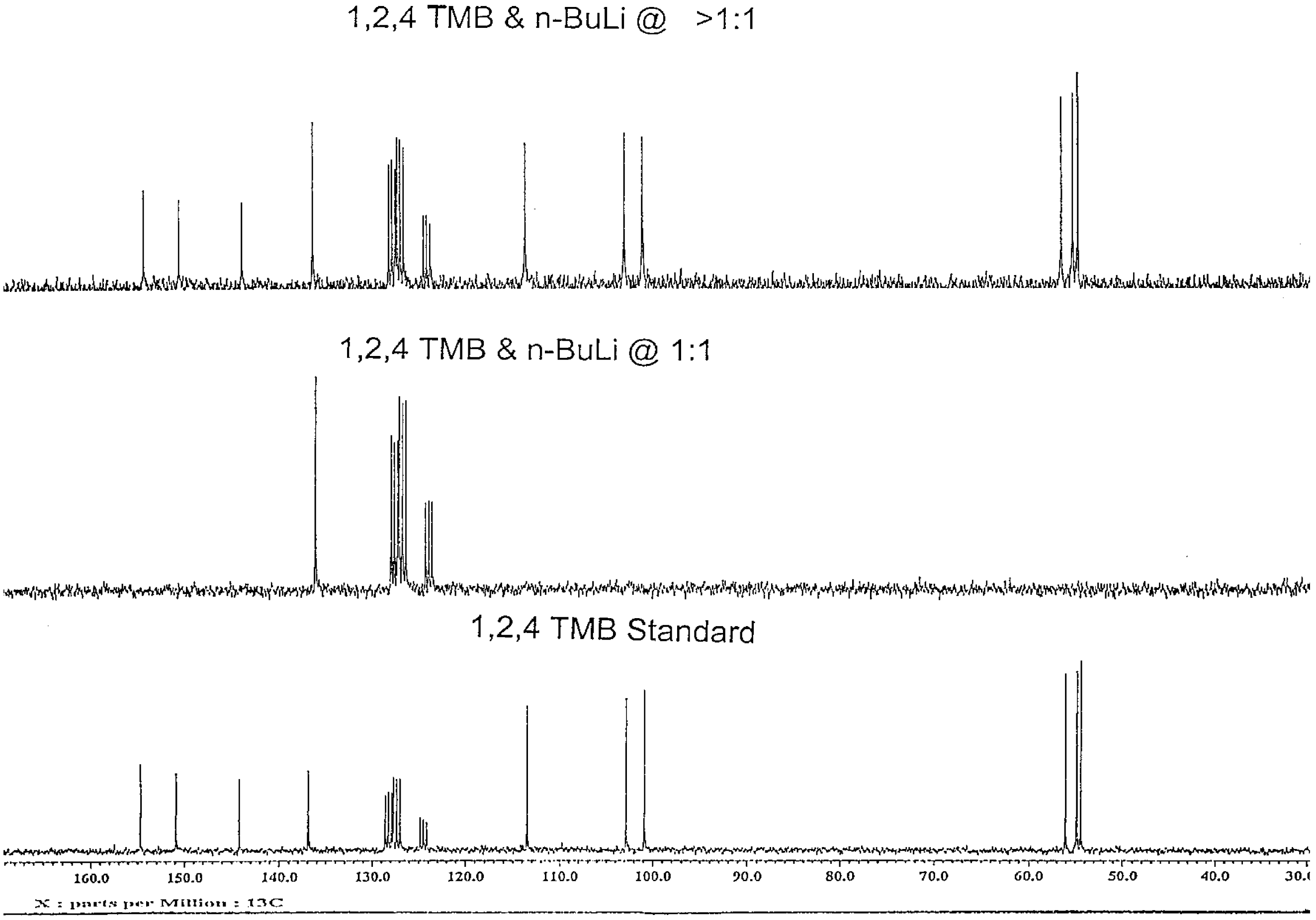

Figure 9. The room temperature ^{13}C NMR spectra of 1,2,4-TMB in cyclohexane (bottom), a 1:1 mixture of 1,2,4-TMB/*n*-BuLi (middle), and a mixture of 1,2,4-TMB/*n*-BuLi with a slight molar excess of 1,2,4-TMB.

is virtually instantaneous suggests that the rate and extent of complexation are both instantaneous. It is not unreasonable to conclude that the unreacted substrate and unreacted *n*-BuLi lost from the solution and therefore present in the solid, is there as the bidentately complexed *n*-BuLi dimer.[24]

3. Conclusions

1,2- and 1,3-DMB as well as 1,2,4-TMB undergo *ortho*-metalation in high yield in an *n*-BuLi/hydrocarbon solvent media without the aid of a catalyst. Since *n*-BuLi is in its least reactive oligomeric form in hydrocarbon solvents and, we believe, does not directly undergo lithium/*ortho*-H exchange from this oligomeric form, the substrate must aid in the deoligomerization of *n*-BuLi by means of complexation. The interpretation of NMR data is consistent with this premise and enables the quantitation of percent complexation for each substrate with *n*-BuLi. This has proven possible because, on the NMR time scale, exchange of the environments between complexed and uncomplexed methoxy groups in solution is slow. In contrast, the TMEDA-catalyzed metalations of similar substrates involve rapid exchange between complexed and uncomplexed TMEDA.[25] The results of the percent complex formation as a function of time correlate directly to the extents of product formation in actual metalation experiments (compare Table 1 and Figures 4, 6 and 8). These complexes are partially soluble in hydrocarbon media, but substantial amounts of the complexes can, and do, fall out of solution. Solubility studies indicate that for each substrate the *ortho*-lithiated intermediates that come from the substrate/*n*-BuLi complex are themselves insoluble in the media utilized. Therefore, under our conditions, when metalation reactions take place, the electrophilic species (in our case, ClTMS) used to quench the reaction reacts in solution with a solid form of the nucleophilic *ortho*-lithiated aryl intermediate.

The interpretation of the reactivity results from experiments involving 1,2,4-TMB suggests that the *n*-BuLi within the complex is in dimeric form. Further, the stoichiometry of this complex supports our contention that all three multi-methoxy substrates engage in bidentate complexation. The ability of the substrate to form a bidentate complex, then, is a prerequisite for substrate-promoted *ortho*-metalation. Anisole, which possesses a single methoxy group, is not metalated well without the aid of a catalyst, substantiating the claim that the key to substrate-promoted *ortho*-metalation lies within a substrate's ability to form a bidentate complex. Two forms of bidentate complexation are proposed. When two methoxy groups are in the 1,2-positions, bidentate complexation as depicted in Figure 3b takes place. Complexation of two methoxy groups situated 1,3- with respect to one another can also occur in a fashion perhaps best represented by Saa[20] as the bridged structure in Figure 3a. The former mode of complexation is apparently more efficient than is the latter.

Finally, the percent yields of *ortho*-substituted aromatic product in the metalation of 1,2-DMB, 1,3-DMB, and 1,2,4-TMB in hydrocarbon solvent without the aid of catalyst (78, 82 and 84%, respectively) exceeds that for the same substrates reacted in pure ether solvent. The yields reported here are comparable to the best yields reported for the metalation of these species in ether solvent with added catalyst.[6,8–10]

4. Experimental

4.1. Metalation studies

All reagents were purchased from Aldrich Chemical Company and used without further purification unless otherwise mentioned. 0.04 mol of 1,2-DMB or 1,3-DMB was slurried in 10 mL of dry cyclohexane or other hydrocarbon solvent (dried over molecular sieves, 4 Å, 4–8 mesh) in a one-neck flask sealed with a septum and purged with N_2. For the TMB's, 0.02 mol of the reactants in 30 mL of solvent was utilized. The flask was placed in a water bath maintained at the appropriate temperature. To this solution was added 20 mL (0.04 mol) of 2.0 M *n*-BuLi in cyclohexane to bring the volume of cyclohexane to 30 mL. Runs in hexanes utilized either 1.6 M *n*-BuLi in hexanes (FMC Corp) or 2.5 M *n*-BuLi in hexanes with suitable adjustment to make the final volume 30 mL. Runs in toluene utilized 10 M *n*-BuLi. For 1,2-DMB, most hydrocarbon solutions became pastes upon addition of *n*-BuLi. After 2 h, stirring of the solutions could be effected so that representative samples could be taken with a wide-bore syringe inserted through the septum resulting in particulate matter as well as solution being taken up. The plot of percentage metalation versus time was constructed by extracting 1 mL samples from the slurry after 2, 10, 30 min and 1, 2, 4 and 6 h, or other periods as necessary, and quenching with a solution containing excess ClTMS in *n*-hexane. After aqueous workup each sample was subjected to GC analysis (HP 5890 A with OV-17 packed glass column). Identities of products were checked by GC–MS analysis (Agilent 5973 MSD with 6890N Network GC system). Analysis of corrected spectra of TMS derivative(s) provided an estimate of the extent of metalation as measured by the lithio-intermediate's capture of the TMS moiety. Each plot represents an average of at least three runs, unless otherwise designated.

4.2. NMR studies

All NMR experiments were performed on a 270 MHz JEOL CPF-270 instrument. The ^{13}C NMR spectra, collected at room temperature, were an average of 512 scans, taken with a three second pulse delay, equating to a ca. 43-min acquisition time for each experiment. Thus, for a spectra reported as a 3 h point, the sample was equilibrated at room temperature for 3 h and then the spectra collected between times 3:00 and ca. 3:43 h. In the NMR investigations, each NMR tube contained 8×10^{-4} mol of *n*-BuLi. For the 1 M samples, the total volume of each NMR tube was 800 μL, consisting of 200 μL of toluene-d_8, 400 μL of 2 M *n*-BuLi in cyclohexane and a combination of substrate and cyclohexane equaling 200 μL volume. The particular substrate in each experiment was added in a 1:1 molar ratio with *n*-BuLi. In the investigation of some substrates, minor solid formation was observed in the NMR tubes. Solid formation tended to increase as a function of time. However, no problem was encountered in the successful generation of valid ^{13}C NMR spectra. For other substrates, large quantities of solid were produced and excessive line broadening resulted. In order to reduce solid formation and study these systems, the molarity of the *n*-BuLi in the tube was reduced to 0.1 M. In these cases, we used 8×10^{-5} mol of *n*-BuLi in a total volume of 800 μL (with 200 μL of toluene-d_8, 40 μL of 2 M *n*-BuLi in cyclohexane and a combination of substrate and cyclohexane of 560 μL). 8×10^{-4} mol of substrate was utilized in these experiments at 0.1 M in *n*-BuLi, maintaining a 1:1 molar ratio of *n*-BuLi/substrate.

The quantitation of the percent complex formed between the substrate and *n*-BuLi as reported in Table 1 was determined by the following procedure: the 200 μL of toluene-d_8 in each NMR tube served as both the deuterated lock solvent and as an internal standard by which to compare relative changes in peak height. By comparing the combined integrations of assigned aromatic peaks within the substrate to that for an internal standard of toluene-d_8, the percentage of solid formation was determined. Specifically, the relative ratio of the signals for the aromatic toluene-d_8 and the aromatic peaks from the substrate were determined for a standard solution which consisted of substrate, solvent, internal standard (toluene-d_8) but no *n*-BuLi. The substrate cannot complex to anything in these standard experiments and so the ratio of aromatic signals for the substrate to the toluene-d_8 serve as a benchmark for 0% solid formation (and zero complexation). Then, in separate experiments, NMR tubes containing substrate, solvent, internal standard and *n*-BuLi were analyzed in a similar fashion. In these experiments, the ratio of the aromatic signals were measured at time equals 0, 1, and 3 h. The intensity of the sample signals with respect to the toluene-d_8 progressively decrease as a function of time. Next, the 0, 1 and 3 h ratios were divided by the standard ratio. These numbers, expressed as percentages, represent the amounts of substrate remaining in solution in both complexed and uncomplexed form. Subtractions of these respective percentages from 100 yields the percent solids recorded in Table 1. Next, the integrations of the uncomplexed and the complexed peak were measured in the methoxy region of the NMR spectrum. The height of the complexed peak was divided by the sum of the complexed and uncomplexed peak heights. These numbers, expressed as percentages, represent the amount of complexed substrate remaining in solution. The total complexed substrate, the solid putatively having passed through the soluble complex state, is determined by adding the percent solid to the normalized percent complex remaining in solution.

4.3. Computational studies

All ab initio calculations were carried out by using the Linux Spartan™ '02 suite of programs running on a 1.9 GHz AMD processor with 1 Gb of DDR RAM. Geometry optimizations were performed in stepwise fashion from MM2, to PM3 semi empirical, to Hartree–Fock 6-31G* and then ultimately to density functional theory at the B3LYP 6-311+G** level. We replicated structures for alkyllithium complexes with nitrogen and oxygen species from the literature to ensure proper methodology and results and were able to reproduce reported geometries and energies to within 1% of relative reported values.[13b]

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