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Substrate-promoted *ortho*-metallation in hydrocarbon solvents[†]

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Abstract—Certain *o*- and *m*-disubstituted aromatics where both substituents are directing metallation groups (DMG's) should, in contrast to singly substituted DMG-containing arenes, undergo metallation in hydrocarbon solvents. It is proposed that the activation of such systems towards *ortho*-metallation is a synergistic generation of the appropriate bis-chelated alkyllithium dimer structure as well as complexed stabilization of the transition state. © 2002 Elsevier Science Ltd. All rights reserved.

Directed *ortho*-metallation (DoM) is a prime example of a reaction that requires self-assembly before the transition state can be accessed. For the metallation of anisole Bauer and Schleyer's[1] original proposal of an anisole-associated alkyllithium dimer intermediate (Fig. 1) now must be considered a pre-equilibrium intermediate complex[2] on the pathway to the ultimate transition state.[3] Recently, Collum and co-workers have deduced that the stoichiometry of the transition state for the TMEDA-catalyzed metallation of anisole is $(n\text{-BuLi})_2(\text{TMEDA})_2(\text{anisole})$.[4] Clearly, alkyllithium dimer formation must take place before the ultimate Li/H transfer can occur. However, because of the complexity of alkyllithium oligomer structures in various solvents,[5] facilitation of the formation of the alkyllithium dimer often must be effected before the ultimate Li/H transfer can be made to efficiently occur.

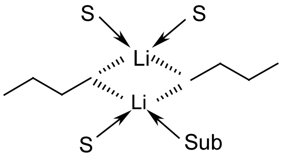

Figure 1. S = coordinating ether or amine. Sub = substrate coordinated through its directing metallation group (DMG), e.g., anisole.

To establish procedures for *ortho*-metallations in hydrocarbon solvents, our investigations have revealed catalytic systems appropriate for use in hydrocarbon media; (1) equivalent(s) of THF[6,7] and (2) fractional equivalents of TMEDA.[8] Such hydrocarbon systems lessen the moisture, stability and peroxide problems of the classical ether media in which metallations are usually and more easily performed. For all the numerous known directing groups (DMG's) for DoM, none are known to afford significant metallation in hydrocarbon solvents without the addition of an *n*-BuLi-deoligomerizing catalyst.

An extension of this paradigm suggested that two DMG's acting in concert would simultaneously activate *n*-BuLi and direct *ortho*-metallation, i.e. the substrate itself would effect all coordinating contributions depicted in Fig. 1. In support of this hypothesis, we now report that appropriate arene substrates can be metallated in hydrocarbon solvents *without the addition of any catalytic agents*. Such metallations we term 'substrate-promoted *ortho*-metallations.'

m-DMB was smoothly metallated in neat *n*-hexane at 25°C in over 50% GC yield of the ClTMS quench product[9] using a 1.0 or 1.3 M solution of 1:1 *n*-BuLi/*m*-DMB (Fig. 2).[10,11] These solutions were essentially homogeneous over the first 2–4 h of reaction. Intermolecular *n*-BuLi activation by the complex was precluded by an experiment wherein a mixture of 1 equiv. of anisole and 1 equiv. of *m*-DMB was metallated using 1 equiv. of *n*-BuLi. No acceleration of the known rate of metallation of anisole under these conditions[6] was observed. These results suggest that *m*-DMB facilitates the dimer structure by formation of the bidentately complexed *n*-BuLi dimer intermediate, (*m*-

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[†] This paper is dedicated to Professor A. I. 'Al' Meyers upon his retirement from the faculty of Colorado State University. His contributions and service to the profession are gratefully acknowledged.

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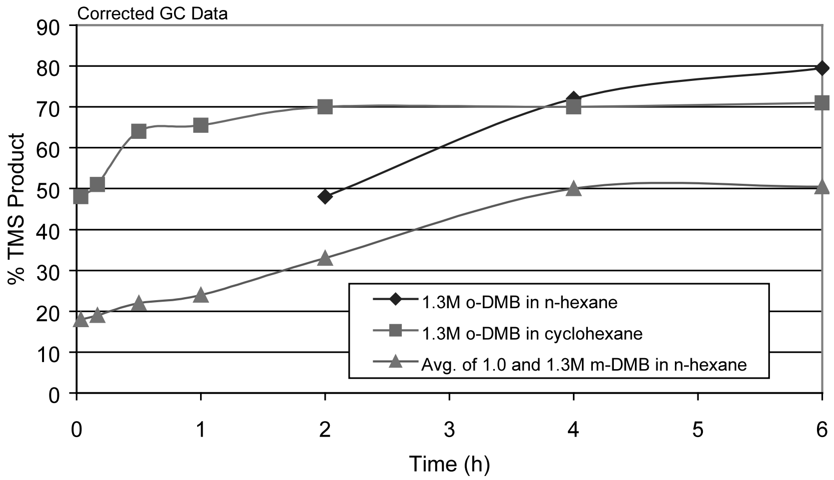

Figure 2. Substrate-catalyzed metallation of *o*- and *m*-DMB at 25°C in hydrocarbon media.

$C_6H_4(OMe)_2 \cdot n\text{-BuLi})_2$.[12] Buildup of this pre-equilibrium complex would dramatically facilitate the formation of the ultimate transition state. Since no crossover metallation of anisole was observed, it is possible that the ultimate metallation step takes place within this complex.

Attempts to effect a hydrocarbon solvent-only metallation of *o*-DMB[11] initially met with failure. Addition of 1.0 equiv. of *n*-BuLi to a 0.67, 1.0 or 1.3 M solution of 1.0 equiv. of *o*-DMB in *n*-hexane at 25°C brought formation of a copious gummy precipitate. Recently, it was discerned that if the precipitate were allowed to digest for approximately 2 h, stirring could be effected and appropriate samples taken. As soon as a representative sample could be taken (the system remains heterogeneous with flocculent particulate matter suspended in the rapidly stirred solvent), the ClTMS quench revealed a nearly 80% GC yield of 3-TMS-1,2-DMB (Fig. 2). To our knowledge this is the highest % monometallation of *o*-DMB reported using a 1:1 ratio of reactants.[13] Remarkably, no evidence of dimetallation is to be found under these conditions, a problem that had plagued previous attempts on our part to metallate *o*-DMB in ether media.[14,15]

These observations strongly suggest the formation of a pre-equilibrium coordination complex between *n*-BuLi and *o*-DMB. This complex most likely takes the form depicted in Fig. 3. Initially, the complex is quite stable and retains little solubility in hydrocarbon solvents.[16] With time this complex reorganizes in such a manner that the formation of the transition state is facilitated. This reorganization appears to be remarkable in its efficiency and permits extents of metallation of *o*-DMB which rival those achieved for anisole using catalytic TMEDA/ether[17] and THF/*n*-hexane,[6,7] systems wherein external additives are inferred to support the dimer structure. We conclude that the metallations of *o*-DMB and *m*-DMB in hydrocarbon solvents are 'self-promoted' in nature in the sense that they, *on their own*, provide the necessary reorganization of the alkyllithium reagent and stabilization of the pre-equilibrium complex depicted for *o*-DMB in Fig. 3. Such complexation, suitably reorganized, would stabilize the transition state as well.[3]

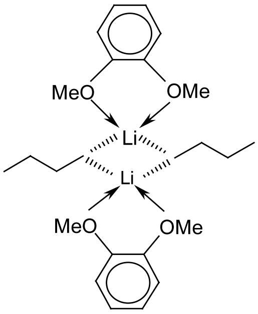

Figure 3.

Our observations contrast with those recently reported for these systems. The extent-of-metallation of *o*-DMB in cyclohexane at 25°C is 72% after 2 h (Fig. 2) while that for anisole in *n*-hexane is about 3% after the same period.[6] This indicates that the ratio of metallation yields of *o*-DMB and anisole is 24:1. A like calculation for *m*-DMB affords a metallation yield ratio in comparison to anisole of 16:1. These results differ from those recently reported wherein anisole was metallated faster than *o*-DMB.[18] This observation was attributed to a new phenomenon of adjacent methoxy group interference in the metallation process. Other investigators attribute this retardation, not to methoxy group interference, but rather to formation of a 'chelated species' between the *o*-DMB substrate and *n*-BuLi.[19] As this is exactly the complex form to which we attribute *activation* of the system, we conclude that further consideration and investigation of these intriguing systems and observations is warranted.

Acknowledgements

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9. Experimental (runs in *n*-hexane): *o*- or *m*-DMB (0.04 mol) was slurried in 5 mL of dry *n*-hexane (molecular seives, Aldrich, 4 Å, 4–8 mesh) in a one-neck flask purged with N_2 and sealed with a septum. The flask was placed in a water bath maintained at 25°C. To this solution is added 25 mL (0.04 mol) of 1.6 M *n*-BuLi in *n*-hexane (FMC Corp.) to bring the volume of *n*-hexane to 30 mL. For *o*-DMB, the reaction mixture immediately became a paste. After 2 h, stirring of the solution could be effected so that representative samples could be taken with a wide-bore syringe inserted through the septum. The plot of percentage metallation versus time was constructed by extracting 1 mL samples from the slurry after 2, 4 and 6 h, or other periods as necessary as in the case of the *m*-DMB runs, and quenching with a solution containing excess chlorotrimethylsilane (ClTMS) in *n*-hexane. After aqueous work-up each sample was subjected to GC analysis (HP5890 A with OV-17 packed glass column). Identities of products were checked by GC–MS analysis (HP 5890 A gas chromatograph coupled with an HP 5970 series mass selective detector). Analysis of corrected spectra of TMS derivative(s) provided an estimate of the extent of metallation as measured by the lithio-intermediate's capture of the TMS moiety. Each plot represents an average of at least three runs.
10. Preliminary runs of *m*-DMB at 45°C afford extents of 2-metallation of *m*-DMB of >75% with no evidence of decomposition. This is in direct contrast to the results for the *o*-DMB system at 45°C (vide infra).
11. Numerous citations of the metallation of *m*-DMB have appeared in Gschwend, H. W.; Rodriquez, H. R. *Org. React.* **1979**, *26*, 1. Others have appeared since. None mention the metallation of *m*-DMB in hydrocarbon solvent(s); only three references for the metallation of *o*-DMB are provided in Gschwend and Rodriquez.
12. This structure likely involves bis-coordination of the *n*-BuLi dimer by *m*-DMB with each methoxy of one DMB coordinated to a separate lithium atom. Such a structure has been computed to possess an energy minimum. See: Saa, J. M.; Deya, P. M.; Suner, G. A.; Frontera, A. *J. Am. Chem. Soc.* **1992**, *114*, 9093.
13. Raising the temperature for the metallation of the *o*-DMB system brought about decomposition. After a run at 45°C several products were discernable in the GC and GC/MS spectra, including one at $m/z = 196$ indicating the loss of a methyl group.
14. Initially, because of the slurried nature of the reaction mixture, a competitive metallation of anisole and *o*-DMB in cyclohexane led to inconclusive results. By the expedient of diluting the reaction mixture samples with cyclohexane and analyzing as described, significant metallation of anisole has been observed. This suggests that the putative bidentate complex for *o*-DMB and the *n*-BuLi dimer (Fig. 3) possesses a reactivity similar to that of the *n*-BuLi TMEDA dimer. This also suggests that the self-promoted *ortho*-metallation of *o*-DMB is intermolecular in nature.
15. Preliminary results from metallation of 1,2,4-trimethoxybenzene(TMB) in cyclohexane indicate that 80% metallation in the 2-position can be achieved in under 1 h. This is the fastest self-promoted system for metallation to date. Investigation of self-promoted metallation of the other TMB's is in progress.
16. Preliminary evidence has been attained for the 1:1 stoichiometry of these intermediates. NMR experiments involving sequential precipitation of the DMB *n*-BuLi complexes, excess *n*-BuLi or substrate addition, followed by stoichiometry readjustment show that only a 1:1 ratio of reactants provides a solution devoid of signals for *n*-BuLi or the substrate.
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