Mechanistic Studies

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Origin of Chemoselectivity of TMP Zincate Bases and Differences between TMP Zincate and Alkyl Lithium Reagents: A DFT Study on Model Systems**

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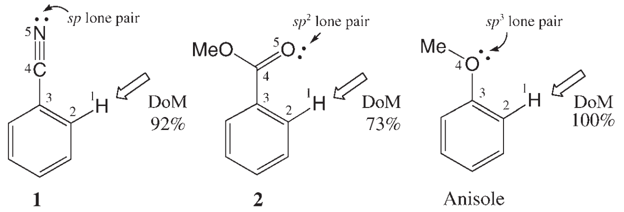
Since the discovery of the directed *ortho* metalation (DoM) reaction of aromatic compounds over 65 years ago by Gilman, Wittig, and co-workers,[1] DoM has been one of the most effective tools for the regioselective construction of functionalized arenes and aryl metal building blocks. Strong bases, such as organolithium reagents, have been used for this transformation, as one naturally expects for the deprotonation of an aromatic C–H bond.[2] Therefore, the application of these reactions to the elaboration of complex organic structures has been limited by low functional-group tolerance, strict requirements for the reaction conditions, and the extremely low temperature typically required for such reactions. Recently, one of our research groups developed TMP zincates[3] ($R_2Zn(TMP)Li$; R = Me, *t*Bu; TMP = 2,2,6,6-tetramethylpiperidide) and a TMP aluminate[4] ($i$$Bu_3Al(TMP)Li$), which promote highly chemoselective DoM reactions of multifunctionalized arenes under mild conditions. In particular, when ate bases are used, not only an alkoxy group (sp^3-hybrid structure), but also a cyano (sp-hybrid structure) or methyl ester group (sp^2-hybrid structure) on an aromatic ring can be used as a metalation-directing group and is tolerated in the deprotonative metalation for the first time (Scheme 1). It would be of great interest to uncover the reasons for the excellent chemoselectivity and the extensive substrate compatibility of ate bases. Herein, we report a density functional study on the mechanism of DoM reactions with TMP zincates, and we address the question of the origin of the unique chemoselectivity.



Scheme 1. Substrates for DoM reactions with $tBu_2Zn(TMP)Li$.

In the present computational/theoretical studies, we focused on the reactions of benzonitrile (**1**) and methyl benzoate (**2**) with TMP zincates as compared to the equivalent reactions with alkyl lithium reagents (Scheme 1). Substrates **1** and **2** were selected on the basis of the experimental observation that TMP zincates react smoothly with these compounds, as well as with anisole, to mediate the DoM reaction selectively, whereas alkyl lithium reagents react vigorously with the cyano or methyl ester functional group to give 1,2-adducts. DFT calculations (B3LYP/631SVP) were performed to investigate these reaction pathways. We employed $Me_2Zn(NMe_2)Li$[5] and $(MeLi)_2$ as the simplest possible chemical models of TMP zincate bases and alkyl lithium reagents, with a molecule of Me_2O (as a model of THF) coordinated to the Li atoms.[6] Although we must keep in mind that the simplification of these models may lead to an underestimation of the steric interactions, these structures provide a valuable starting point for our consideration of the differences between the TMP zincate bases and alkyl lithium bases.[6b]

The reactions of **1** with alkyl lithium reagents are discussed first (Scheme 2). These reagents initially form a Lewis acid–Lewis base complex **CP1** with a moderate

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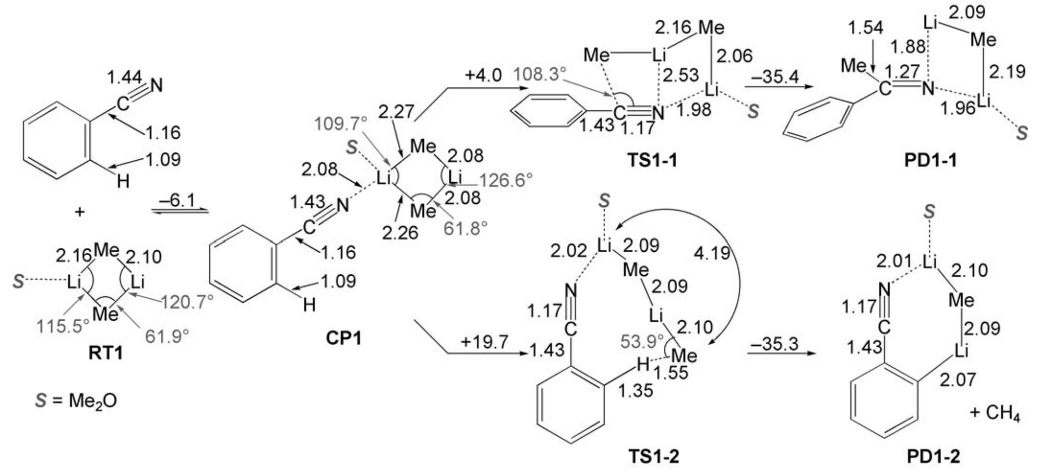


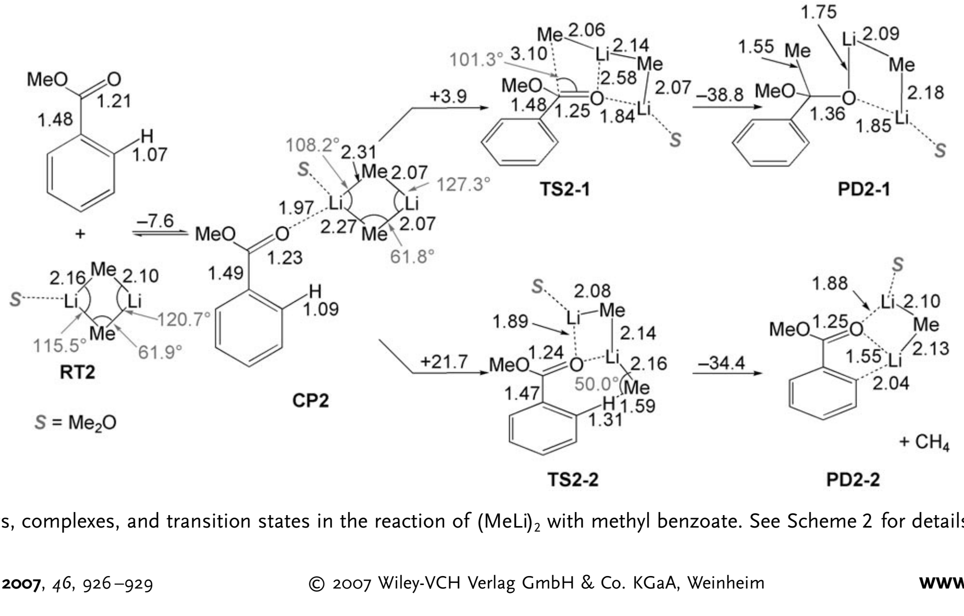
Scheme 2. Reactants, complexes, and transition states in the reaction of $(MeLi)_2$ with benzonitrile. Bond lengths [Å] and angles at the B3LYP/631SVP level are shown. Energy changes [kcal mol^{-1}] at the B3LYP/631SVP level are presented on the arrows.

stabilization energy. For the Me ligand to reach the *ortho* hydrogen atom of **1** without loss of the CN···Li coordination, the bimetallic rhombic structure of $(MeLi)_2$ needs to change to an "open form".[7] The Me–Li electrostatic bond cleaves with an overall energy loss of 19.7 kcal mol^{-1}. This high value suggests that the reaction would be slow. However, the transition state (TS) for the 1,2-addition of the Me ligand to the cyano group (**TS1-1** in Scheme 2) is only 4.0 kcal mol^{-1} higher in energy than **CP1**, and therefore more favorable than **TS1-2** by 15.7 kcal mol^{-1}, because of double activation[8] of the nitrogen atom of the cyano group by both lithium atoms of the alkyl lithium dimer. These values are much lower than the barrier to DoM, in accordance with experimental results.[9] The cylindrical symmetry of the CN group prevents the DoM reaction of the alkyl lithium reagent.

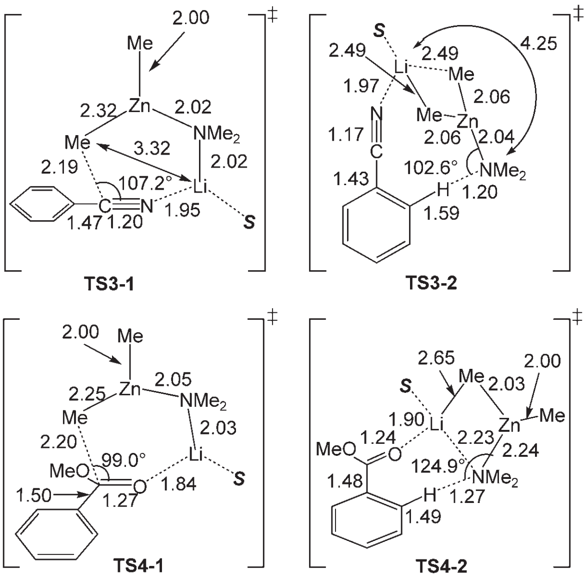
Next, a search for transition structures corresponding to the reaction of **2** also afforded two TSs: **TS2-1** for 1,2-addition and **TS2-2** for DoM (Scheme 3). **TS2-1** is analogous to **TS1-1**, the double-activation TS for **1. TS2-2** is fundamentally different from that obtained for **1**. Judging from the Li–O and C=O bond lengths in **TS2-2**, the doubly activated form of the carbonyl oxygen atom is maintained when the Me ligand reacts with the arene hydrogen atom. However, the activation barrier to DoM is still high, which indicates that the double activation of the carbonyl group does not effectively raise the acidity of the aromatic C–H bond through an inductive effect.

These results on the reactivity and selectivity of alkyl lithium reagents are fully consistent with the results of experiments with conventional DoM reagents, such as alkyl lithium reagents, and a cyano group or ester group as a metalation-directing group.

It has been established experimentally that DoM occurs selectively in the reactions of **1** or **2** with TMP zincates or the TMP aluminate; therefore these bases are regarded as "chemoselective".[2,3] To address the origin of the chemoselectivity of these ate bases, we investigated the DoM reactions of **1** and **2**, in comparison with the 1,2-addition reactions, by using $Me_2Zn(NMe_2)Li$ as a model of the zincate. The B3LYP/631SVP-optimized transition structures for the 1,2-addition and DoM reactions are shown in Scheme 4. The



Scheme 3. Reactants, complexes, and transition states in the reaction of $(MeLi)_2$ with methyl benzoate. See Scheme 2 for details.



Scheme 4. Four transition states in the reactions of $Me_2Zn(NMe_2)Li$ with **1** and **2**. See Scheme 2 for details.

activation energies from the prereaction complexes for **TS3-1**, **TS3-2**, **TS4-1**, and **TS4-2** are 29.8, 27.0, 27.7, and 25.7 kcal mol^{-1}, respectively.[10]

Although the energy differences between the TSs for 1,2-addition and DoM are only a few kcal mol^{-1}, these results are consistent with the experimentally derived knowledge that the barriers to the DoM reactions are lower than those to the 1,2-addition reactions. Moreover, some characteristic aspects of the reaction pathway with $Me_2Zn(NMe_2)Li$ follow from the results shown in Scheme 4: 1) The broad substrate compatibility in DoM reactions with zincate bases: As seen in **TS3-2**, in the reaction of **1**, the rearrangement of the Li position in the zincate proceeds smoothly so that the Me_2N ligand can interact with the *ortho* hydrogen atom. On the other hand, in the reaction of **2**, the deprotonation occurs with retention of the "closed-form" structure of the zincate base. We found no other energetically plausible transition states. These two pathways with very different transition states apparently suggest that the zincate bases can change their transition-state structures flexibly to adapt to various substrates—that is, they show high substrate compatibility (Scheme 1). 2) Deactivation of the 1,2-addition pathway: The pathways of 1,2-addition for $Me_2Zn(NMe_2)Li$ are very different from those for $(MeLi)_2$. The most important difference is the spread of Lewis acidity in homo- or heterobimetallic species. Alkyl lithium dimers are homodimers in which Lewis acidity is shared equally on the two Li atoms, and hence extremely low activation barriers for 1,2-addition are possible through the double coordination of both Li atoms to C–X multiple bonds. However, in the case of zincates, which are heterobimetallic species, the LUMO components are localized completely on the Li atom. Therefore, the central Zn atom can not be involved in the activation of the carbonyl or cyano group, and hence the barrier to 1,2-addition is high—higher than the barrier to DoM. For this reason, DoM is favored over 1,2-addition with zincate bases.

In summary, the present study has revealed the mechanisms and origin of chemoselectivity of the DoM reaction of functionalized arenes with TMP zincate bases and alkyl lithium reagents. The theoretical analysis delineated herein should contribute to the rational design of synthetic transformations. Further theoretical studies on the nature of other standard synthetic reactions of organozincate species, including conjugate addition and transmetalation, are in progress.

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[10] The Gibbs and MP2/6-311++G**(single-point) energies of activation (298.15 K) are as follows: **TS3-1**: 31.6 kcal mol^{-1} (Gibbs), 32.9 kcal mol^{-1} (MP2); **TS3-2**: 26.0 kcal mol^{-1} (Gibbs), 24.9 kcal mol^{-1} (MP2); **TS4-1**: 31.0 kcal mol^{-1} (Gibbs); **TS4-2**: 26.8 kcal mol^{-1} (Gibbs). Although the differences between the energy of activation for 1,2-addition and DoM tend to be greater than the equivalent differences in the B3LYP/631SVP electric energies, these calculations do not change the conclusion of the above analysis.