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Lithium Cadmate-Mediated Deprotonative Metalation of Anisole: Experimental and Computational Study

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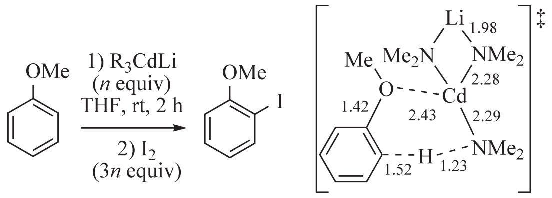
Received January 28, 2010



Cd-assisted TS

Lithium cadmates bearing different ligands were compared with efficient (TMP)$_3$CdLi (TMP = 2,2,6,6-tetramethylpiperidino) for their ability to deprotometalate anisole. The generated arylcadmates were evidenced using I$_2$. The results show that it is possible to replace only one of the TMP (with a piperidino, a diisopropylamino, a butyl, or a *sec*-butyl) without important yield drop. In the light of DFT calculations, reaction pathways were proposed for the deprotocadmations of anisole using a triamino, an alkyldiamino, and an aminodialkyl cadmate.

The deprotonative metalation has been widely used as a powerful method for the regioselective functionalization of aromatic compounds.[1] Organolithiums and hindered lithium amides have been largely employed for this purpose because they are either commercially available or can be readily prepared in ethers and alkanes. However, their compatibility with sensitive substrates and functional groups is low. In addition, in the absence of polar solvents such as tetrahydrofuran (THF), activating agents such as N,N,N',N'-tetramethylethylenediamine (TMEDA), or directing groups able to disaggregate the base, the efficiency of reactions using lithium compounds on their own as bases is limited.

The use of metal additives in order to modify the behavior of bases is a challenging field. Various (R)$_n$(R$'$)$_{n'}$MLi (M = metal, R, R$'$ = alkyl, amino, chloro...)-type compounds already prepared behave as superbases since such species exhibit behaviors that cannot be reproduced by the monometallic compounds on their own. Well-known examples of powerful RR$'$MLi mixtures of organolithiums and M alkali metal alkoxides BuLi$-{}^t$BuOK first described by Schlosser[2] and Lochmann,[3] and BuLi$-$Me$_2$N(CH$_2$)$_2$OLi developed in the pyridine series by Gros and Fort.[4] (R)$_n$(R$'$)$_{n'}$MLi-type bases with M different from an alkali metal have also been described since then by different groups.[5] Among them, examples are the mixed Li$-$Zn bases R$_2$Zn(TMP)Li($\cdot$TMEDA) (R = ^{t}Bu, Bu) described by the groups of Kondo, Uchiyama, Mulvey and Hevia[6] and (TMP)$_2$Zn$\cdot$2MgCl$_2\cdot$2LiCl[7] and TMPZnCl$\cdot$LiCl[8] developed by the group of Knochel.

We recently developed a mixed Li$-$Cd base, (TMP)$_3$CdLi, which allowed efficient and chemoselective reactions.[9] This base was easily prepared by mixing CdCl$_2\cdot$TMEDA with 3 equiv of LiTMP, and its ate structure has been shown on the basis of NMR spectroscopy and DFT calculation studies. In order to identify the structural requirements to meet in order to get an efficient metalation, the deprotonation ability of different (R)$_n$(R$'$)$_{(3-n)}$CdLi compounds was investigated.

The metalation of anisole by (TMP)$_3$CdLi (0.5 equiv of CdCl$_2\cdot$TMEDA and 1.5 equiv of LiTMP) in THF at room

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DOI: 10.1021/jo100150s

TABLE 1. **Metalation of Anisole Using Different Homo- and Heteroleptic Li−Cd Bases Followed by Trapping with I_2**

entry	putative base (*n*)	yield (%)	entry	putative base (*n*)	yield (%)
1	$(TMP)_3CdLi$ (0.5)	75	12	$Bu_2Cd(TMP)Li$ (0.5)	7
2	$(P)_3CdLi$ (1)	0	13	$Bu_2Cd(TMP)Li$ (1)	28
3	$(HMDS)_3CdLi$ (1)	0	14	Bu_3CdLi (0.5)	9
4	$(DA)_3CdLi$ (1)	42	15	$^sBuCd(TMP)_2Li$ (1)	75
5	$(P)Cd(TMP)_2Li$ (1)	75	16	$^sBu_2Cd(TMP)Li$ (1)	8
6	$(HMDS)Cd(TMP)_2Li$ (1)	21	17	$^tBuCd(TMP)_2Li$ (1)	39
7	$(TMP)Cd(HMDS)_2Li$ (1)	3	18	$^tBu_2Cd(TMP)Li$ (1)	3
8	$(DA)Cd(TMP)_2Li$ (1)	84	19	$TMSCH_2Cd(TMP)_2Li$ (1)	51
9	$(TMP)Cd(DA)_2Li$ (1)	39	20	$(TMSCH_2)_2Cd(TMP)Li$ (1)	13
10	$BuCd(TMP)_2Li$ (0.5)	34	21	$(TMSCH_2)_3CdLi$ (1)	0
11	$BuCd(TMP)_2Li$ (1)	78			

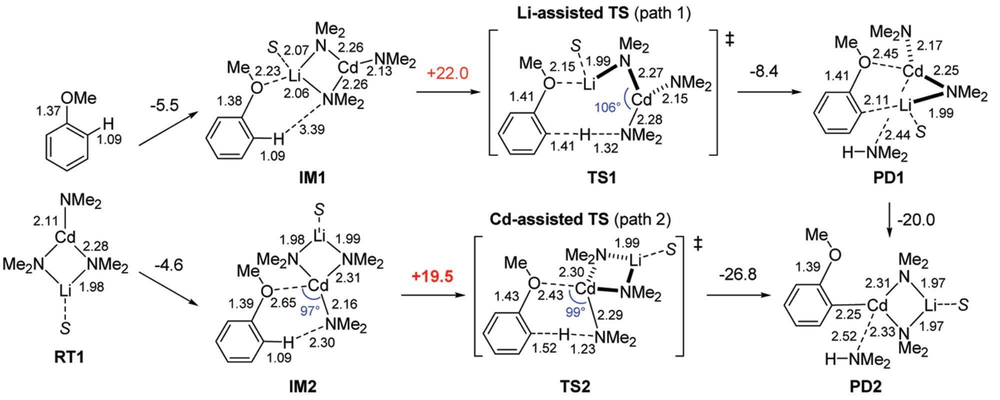

FIGURE 1. Reactants, intermediates, complexes, and TSs in the deprotonation reaction of anisole with $(Me_2N)_3CdLi$. Bond lengths and energy changes at the B3LYP/631SVPs level are shown in Å and kcal/mol, respectively.

temperature for 2 h, followed by subsequent trapping with I_2, proceeds in 75% yield (Table 1, entry 1).[10] Amines such as piperidine, diisopropylamine, and even 1,1,1,3,3,3-hexamethyldisilazane are less expensive than HTMP, and the use of the corresponding amino groups in homo- and heteroleptic bases was considered. Putative $(P)_3CdLi$ (P = piperidino) and $(HMDS)_3CdLi$ (HMDS = $N(SiMe_3)_2$) failed in metalating anisole (entries 2,3). In contrast, the expected 2-iodoanisole was isolated in 42% yield with $(DA)_3CdLi$ (DA = N^iPr_2), provided that 1 equiv was used (entry 4).[11]

The use of heteroleptic Li−Cd amides bearing one or two TMP ligand(s) was then attempted. It was found possible to replace one of the three TMP groups of $(TMP)_3CdLi$ with a P group without altering the efficiency of the reaction (entry 5). In contrast, the use of one or two HMDS groups resulted in low yields (entries 6,7). As observed by replacing one TMP with a P, the use of one DA group for two remaining TMP proved efficient, affording the iodide in 84% yield (entry 8). The replacement of a second TMP led to a low conversion of anisole; the 39% yield obtained with $(TMP)Cd(DA)_2Li$ (entry 9) is similar to that of 42% observed using $(DA)_3CdLi$.

$(TMP)_3CdLi$ was next compared with $RCd(TMP)_2Li$ and $R_2Cd(TMP)Li$ (R = alkyl). By replacing one TMP group with one Bu, the metalation of anisole still took place efficiently, provided that 1 equiv of base was used (entries 10,11).[11] Decidedly lower yields, decreasing with the number of TMP groups, were obtained employing $Bu_2Cd(TMP)Li$ and Bu_3CdLi (entries 12−14). Similar results were observed by replacing TMP groups of $(TMP)_3CdLi$ with ^{s}Bu groups (entries 15,16). With ^{t}Bu (entries 17,18) and Me_3SiCH_2 (entries 19−21) groups, yields still decrease with increasing numbers of alkyl groups but, in these cases, the reaction efficiency is poorer than observed with Bu and ^{s}Bu groups.

The deprotonative metalation using cadmate bases was theoretically investigated using DFT calculations. To this purpose, $(Me_2N)_3CdLi$, $MeCd(NMe_2)_2Li$, and $Me_2Cd(NMe_2)Li$ were, respectively, employed as models for $(TMP)_3CdLi$, $RCd(TMP)_2Li$, and $R_2Cd(TMP)Li$. A molecule of Me_2O (instead of THF) was incorporated to complete lithium atom coordination. Although the choice of this simplified model system may lead to an underestimation of the steric effects of bulky groups, the essential character of the reaction should still be observable using this model system.

Reaction Pathway of Deprotonation of Anisole with Lithium Tris(dimethylamino)cadmate (Figure 1). Among several possibilities for the deprotonation reaction using $(Me_2N)_3CdLi$, we identified two plausible reaction pathways through Li-assisted and Cd-assisted deprotonation TSs (**TS1** and **TS2**). In both cases, the reaction coordinates started with formation of a relatively stable initial complex (**IM1** or **IM2**) between anisole oxygen and the countercation Li or the central Cd metal. This indicated that the regioselectivity of the *ortho* cadmation reaction can be explained by a coordinative approximation effect between functional group and the Li or Cd metal, enabling initial complex formation and orienting the ate base ligand exclusively toward aromatic

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(10) The synergy of the reaction was demonstrated using either LiTMP or $(TMP)_2Cd$; see ref 9.

(11) The 75% yield obtained using 0.5 equiv of $(TMP)_3CdLi$ was not equaled using 0.5 equiv of any of the other Li−Cd combinations. Similar results were obtained in some cases provided that 1 equiv of base was used.

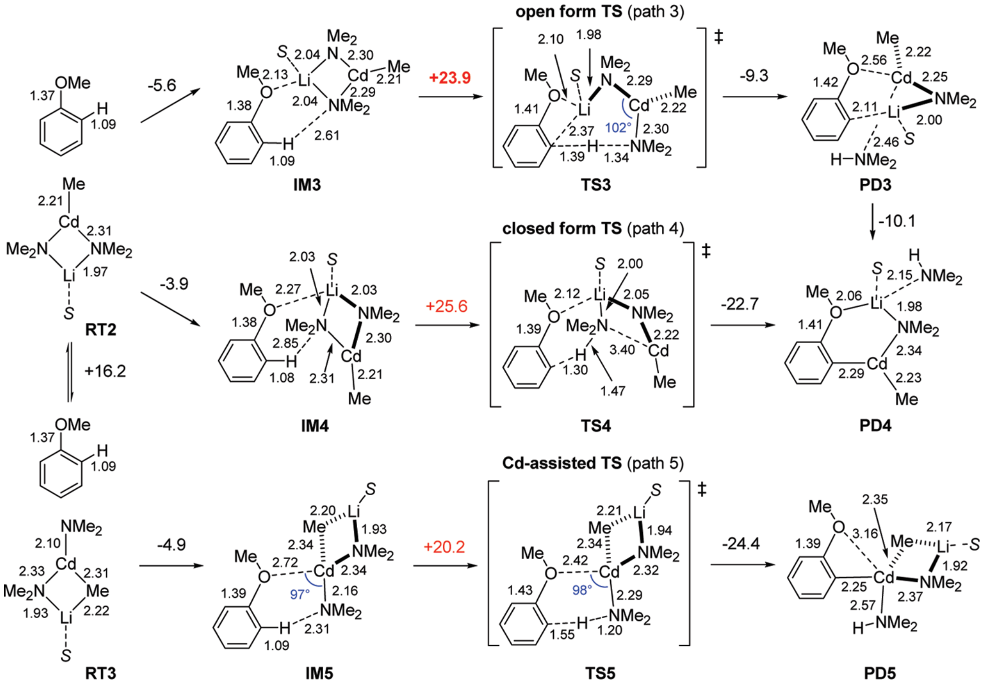

FIGURE 2. Reactants, intermediates, complexes, and TSs in the deprotonation reaction of anisole with $MeCd(NMe_2)_2Li$. See Figure 1 for details.

ortho hydrogen. The Li-assisted deprotonation (path 1) is a pathway similar to that seen in TMP-Zn-ate mediated DoM reactions[6g] and takes place via "open form TS" (**TS1**) with a reasonable activation energy (+22.0 kcal/mol). The Cd-assisted deprotonation (path 2), an unique pathway of this Cd-ate base, proceeds smoothly with a smaller activation energy (19.5 kcal/mol). This deprotonation is facilitated by the direct push−pull synergy of the Lewis acidic Cd metal and the negatively charged NMe_2 moiety to generate a stable product (**PD2**). The stabilization energy is very large (−26.8 kcal/mol) because this deprotonation occurs with maintenance of the stable $Me_2N\cdots Li\cdots NMe_2$ coordination.

Reaction Pathway of Deprotonation of Anisole with Lithium Bis(dimethylamino)alkylcadmate (Figure 2). The computational results of deprotonation with $MeCd(NMe_2)_2$-Li indicated that the Li-assisted pathway via the "open form" TS (path 3) is the most probable. In this pathway, the DoM reaction proceeds through **TS3** by using one of the Me_2N ligands of $MeCd(\mu\text{-}NMe_2)_2Li$ (in **RT2**). The activation energy of path 3 is 4.4 kcal/mol higher than that of the Cd-assisted pathway (path 2) in the reaction with $(Me_2N)_3CdLi$. This calculation indicates that the reaction of $RCd(TMP)_2Li$ (Table 1, entry 11) proceeds as well as the reaction of $(TMP)_3$-CdLi. The reaction pathway via the "closed form" **TS4** (path 4) is rather unfavorable. A Cd-assisted deprotonation pathway (path 5) was also identified, and the activation energy (+20.2 kcal/mol) is energetically more favorable than that of the Li-assisted "open form" pathway (path 3) by 3.7 kcal/mol because of direct activation of the Cd−N bond by anisole oxygen. This pathway, however, first requires the reformation of the most stable symmetric cadmate in **RT2** to an unstable unsymmetric one in **RT3**, including the dissociation of the stable $Li\cdots N$ bond, a process leading the 16.2 kcal/mol loss of energy. Therefore, this pathway is much less likely to take place than those of Li-assisted deprotonation shown in Figure 2.

Reaction Pathway of Deprotonation of Anisole with Lithium Dialkyl(dimethylamino)cadmate (Figure 3). Two structures are also a priori possible for $Me_2Cd(NMe_2)Li$, i.e., the unsymmetrical one (in **RT4**) and the symmetrical one (in **RT5**): the former structure is computed to be much more stable, mainly due to the stable $Me_2N\cdots Li$, than the latter one by 17.0 kcal/mol. Initial electrostatic coordination of Li to anisole oxygen occurs, resulting in the formation of a complex (**IM6**) with a stabilization energy of 7.4 kcal/mol. From **IM6**, the DoM reaction using the Me_2N ligand can take two pathways through **TS6** ("closed form" TS, path 6) and **TS7** ("open form" TS, path 7). Although the activation energies are only 0.7 kcal/mol higher than that of the DoM reaction with $MeCd(\mu\text{-}NMe_2)_2Li$ (path 3), the deprotonation occurs with more than 10 kcal/mol endothermicity. This large energy loss is a result of the cleavage of the stable $Me_2N\cdots Li$ bond and of the rather small energy gain to form a $C\cdots Li$ bond at the expense of the $Me_2N\cdots Li$ bond cleavage. These results indicate that path 6 and 7 are kinetically favored but thermodynamically unfavored. The computed predilection accounts for the experimental observation that dialkylamidocadmate complexes are almost inert in the deprotonative cadmation reaction of anisole (Table 1, entries 12,13). Deprotonation by the μ-Me ligand on Cd (path 8) was also found to be kinetically unfavorable, requiring a much higher activation energy of 32.7 kcal/mol.

In summary, among all the homo- and heteroleptic Li−Cd amides tested, $(TMP)_3CdLi$ was the more efficient reagent; by replacing one TMP with a P or a DA group, similar yields were obtained but with a double amount of base, as if P and DA were unable to act as bases. A ligand of $(TMP)_3CdLi$ could be replaced in the same way with a Bu or a ^{s}Bu group.

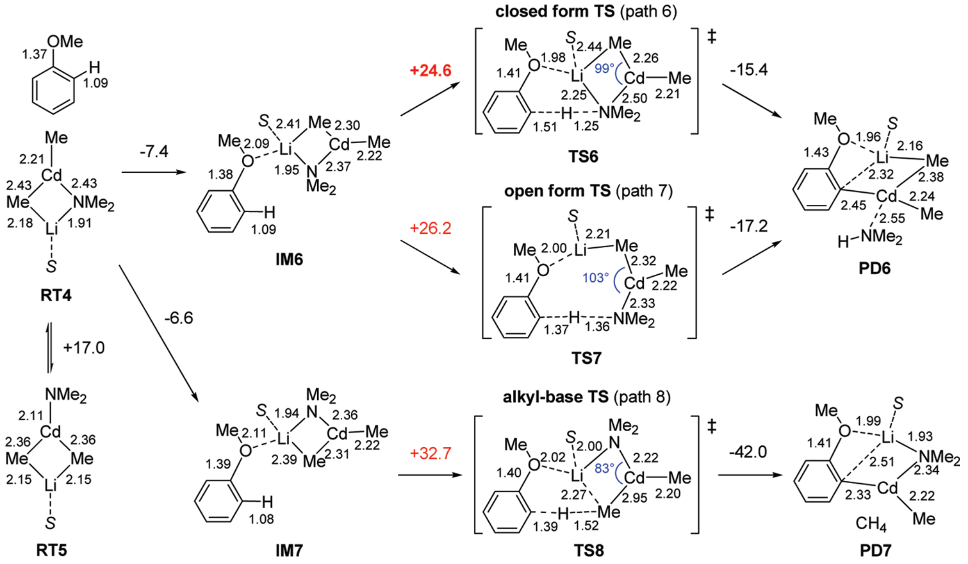

FIGURE 3. Reactants, intermediates, complexes, and TSs in the deprotonation reaction of anisole with Me$_2$Cd(NMe$_2$)Li. See Figure 1 for details.

From a mechanistic point of view, the DFT calculations revealed that the metalation with (TMP)$_3$CdLi proceeds through a Cd-assisted transition state while pathways with higher activation energies and Li-assisted transition states were found with RCd(TMP)$_2$Li and R$_2$Cd(TMP)Li (R = alkyl). The mechanism of the anisole deprotonation using TMP-dialkyl zincates has been the subject of studies.[6g,i] A two-step mechanism has been proposed where the lithium zincate first acts as an amino base, and thus generated HTMP then returns back to zinc through 2-anisyl- or R-mediated deprotonation. Studies will be soon started in order to identify the species present in reaction mixtures coming from metalation steps using Li–Cd combinations and to possibly propose more complete mechanisms.

(TMP)$_3$CdLi proved to allow amazing reactions such as the dideprotonation of sensitive pyrazine[12] and ferrocene esters,[13] which cannot be achieved using other (R)$_n$(R')$_{n'}$MLi-type bases. To overcome concerns about inherent toxicity of cadmium compounds,[14] new mixed Li-metal bases of ate type are under development.

Experimental Section

All bases were synthesized from CdCl$_2$·TMEDA.[15]

Computational Details

All calculations were carried out with the Gaussian 03 program package.[16] The molecular structures and harmonic vibrational frequencies were obtained using the hybrid density functional method based on Becke's three–parameter exchange function and the Lee–Yang–Parr nonlocal correlation functional (B3LYP).[17] We used Ahlrichs' SVP[18] all-electron basis set for the cadmium atom and 6-31G* for the other atoms (denoted as 631SVPs in the text). Geometry optimization and vibrational analysis were performed at the same level. All stationary points were optimized without any symmetry assumptions and characterized by normal coordinate analysis at the same level of theory (number of imaginary frequencies, NIMAG, 0 for minima and 1 for TSs).

Acknowledgment. We gratefully acknowledge the financial support of Région Bretagne (to K.S.) and Agence Nationale de la Recherche (ACTIVATE program) (to K.S. and M.U.). The calculations were performed by using the RIKEN Integrated Cluster of Clusters (RICC) facility.

Supporting Information Available: Experimental procedures, computational methods, Cartesian coordinates, and total electron energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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