Deprotonative cadmation of functionalized aromatics†

Jean-Martial L'Helgoual'ch,[a] Ghenia Bentabed-Ababsa,[ab] Floris Chevallier,[a] Mitsuhiro Yonehara,[c] Masanobu Uchiyama,*[c] Aïcha Derdour[b] and Florence Mongin*[a]

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This communication describes the deproto-metalation of a large range of aromatics including heterocycles using a newly developed lithium–cadmium base; the reaction proceeds at room temperature with an excellent chemoselectivity and efficiency, and proved to be regioselective in most cases.

The deprotonative metalation of aromatic rings has been widely used as a powerful method for regioselective functionalization.[1] Various strong bases such as alkyllithiums and lithium dialkylamides have been largely employed for this purpose because of their solubility in ethers and alkanes, and also because many of them are commercially available. However, the use of alkyllithiums on their own as bases has been limited to substrates with C–H acidity enhanced by directing groups. In addition, recourse to simple lithium dialkylamides for aromatics bearing reactive functions (*e.g.* ester or cyano groups) or sensitive π-deficient heterocycles required strictly controlled conditions (extremely low reaction temperatures, *in situ* trapping. . .) due to the high reactivity of the corresponding aryllithiums. The use of additives for lithium compounds in order to get more efficient or more chemoselective bases, or else to modify the deprotonation site, is a challenging area. Representative activation ways are the formation of chelates between alkyllithiums and *N*,*N*,*N′*,*N′*-tetramethylethylenediamine (TMEDA), as well as the formation of complexes between alkyllithiums and potassium *tert*-butoxide (*e.g.* LIC-KOR superbase).

By combining soft organometallic compounds with alkali additives (*e.g.* LiTMP, TMP = 2,2,6,6-tetramethylpiperidino, or LiCl), bases such as $^t\mathrm{Bu_2Zn(TMP)Li}$,[2] $^i\mathrm{Bu_3Al(TMP)Li}$,[3] $\mathrm{(Me_3SiCH_2)_2Mn(TMP)Li{\cdot}TMEDA}$,[4] $\mathrm{MeCu(TMP)(CN)Li_2}$[5] and $\mathrm{(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl}$[6] have been prepared and used to generate functionalized aromatic compounds.

Mulvey introduced the term *alkali metal-mediated metalation* to depict the reactions of ate bases because the reactivity ("synergy") they exhibit cannot be attained by the homometallic compounds on their own.[7] When performed in tetrahydrofuran (THF), the reactions proved to be chemoselective, but require 1 or 2 equiv of base.

Herein we report an efficient regio- and chemoselective direct cadmation on functionalized aromatics including very sensitive heterocycles using a newly designed lithium cadmate base. Among organometallics, organocadmium reagents have been mainly prepared by reaction of organic halides with cadmium metal or by transmetalation, and used as soft nucleophilic reagents in organic synthesis.[8] Wittig *et al.* documented in 1951 the synthesis of $\mathrm{Ph_3ZnLi}$ and $\mathrm{Ph_3CdLi}$, and their efficiency to deprotonate fluorene in diethyl ether.[9] Quenching with CO_2 and subsequent acidic work-up afforded diphenyleneacetic acid in a low yield of 16% after 10 days reaction time using $\mathrm{Ph_3ZnLi}$ whereas a satisfying 64% yield was obtained after 3 days using $\mathrm{Ph_3CdLi}$, a result attributed to the size of the central metal. This prompted us to study the use of lithium cadmates for the deproto-metalation of sensitive aromatic substrates.

A recent study showed LiTMP and $\mathrm{(TMP)_2Zn}$, even if not associated in the form of a zincate, could behave synergistically, combining both the efficiency of LiTMP and the chemoselectivity of $\mathrm{(TMP)_2Zn}$.[10] In order to seek more efficient and direct methods for introducing functionalities into heteroaromatic rings, we focused the deprotonative metalation using the corresponding mixture with cadmium instead of zinc on the difference of metal size. First attempts using anisole (**1a**) as substrate indicated that an *in situ* prepared mixture of $\mathrm{CdCl_2{\cdot}TMEDA}$[11] (0.5 equiv.) and LiTMP (1.5 equiv.) was suitable for an efficient reaction, when used in THF at room temperature. Indeed, subsequent trapping with iodine after 2 h afforded the expected derivate **2a** in 74% yield, against 30% yield using $\mathrm{CdCl_2{\cdot}TMEDA}$ (0.5 equiv.) and LiTMP (1.5 equiv.). Since $\mathrm{(TMP)_2Cd}$ (1 equiv.) and LiTMP (1 equiv.) give much lower conversions when used separately under the same reaction conditions, both of them play a role in the reaction mechanism. In order to obtain additional information about the active species of a basic mixture obtained from a THF solution of LiTMP and $\mathrm{CdCl_2{\cdot}TMEDA}$ (0.33 equiv.), NMR and DFT studies were carried out. The analysis of the ^{13}C NMR spectra revealed that LiTMP was not present in solution, suggesting the formation of a lithium cadmate. This was confirmed by the B3LYP-calculated equilibrium between LiTMP and $\mathrm{(TMP)_2Cd}$ on one side and $\mathrm{(TMP)_3CdLi}$ on the other side, which is in sharp contrast to the corresponding zinc–lithium mixture obtained from LiTMP and $\mathrm{ZnCl_2{\cdot}TMEDA}$ (Scheme 1).[10]

Representative results from the metalation-trapping sequences of benzenes bearing various directing metalation groups (DMG) using lithium tris(2,2,6,6-tetramethylpiperidino)cadmate (TMP-cadmate) are summarized in Table 1. Veratrole (**1b**) was similarly regioselectively deprotonated. Polar functional groups including

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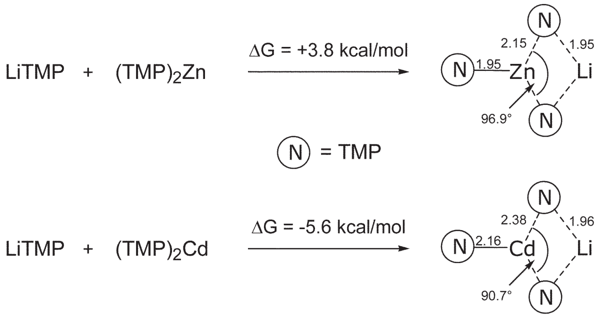
[a] *Chimie et Photonique Moléculaires, UMR 6510 CNRS, Université de Rennes 1, Bâtiment 10A, Case 1003, Campus Scientifique de Beaulieu, F-35042 Rennes Cedex, France. E-mail: florence.mongin@univ-rennes1.fr; Fax: +33-2-23-23-69-55; Tel: +33-2-23-23-69-31*

[b] *Laboratoire de Synthèse Organique Appliquée, Faculté des Sciences de l'Université, BP 1524 Es-Senia, Oran, 31000, Algeria*

[c] *The Institute of Physical and Chemical Research, RIKEN, 2-1 Hirosawa, Wako-shi, Saitama, 351-0198, Japan. E-mail: uchi_yama@riken.jp; Fax: +81-48-467-2879*

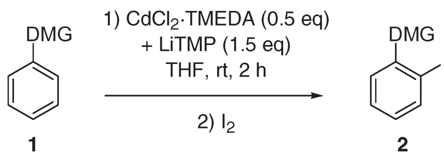
† Electronic supplementary information (ESI) available: Experimental procedures and characterizations (^{1}H and ^{13}C NMR spectra for all compounds), and theoretical data (details of computational methods, cartesian coordinates and Gibbs free energies). See DOI: 10.1039/b809543d

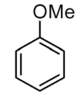
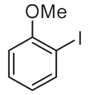
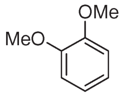
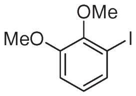
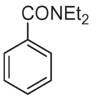
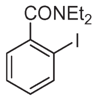
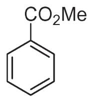
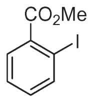
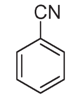
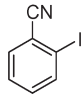
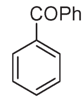
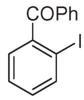
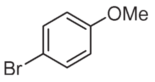
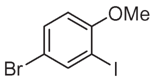
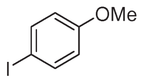
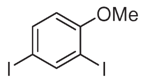
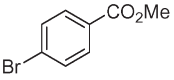
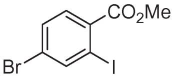
amide, ester, nitrile and even ketone (substrates **1c**, **1d**, **1e** and **1f**, respectively) are tolerated in the reaction. Aromatic halides **1g** and **1h** are chemoselectively converted to the metalated derivatives, with a complete regioselectivity for the position far from the heavy halogen atom. Bromo ester **1i** behaved similarly to give after trapping the iodide **2i**.



Scheme 1 Bond lengths at the B3LYP/6-31G*&SVP(Zn) level in Å.

Table 1 Deprotonative cadmation of functionalized benzenes



Entry	Substrate (**1**)		Product (**2**)		Yield (%)
1		**1a**		**2a**	74 (30)[a]
2		**1b**		**2b**	79
3		**1c**		**2c**	91
4		**1d**		**2d**	62
5		**1e**		**2e**	68
6		**1f**		**2f**	66
7		**1g**		**2g**	97
8		**1h**		**2h**	83
9		**1i**		**2i**	60

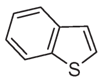
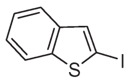
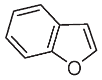
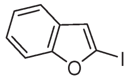
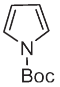
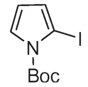
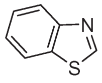
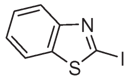
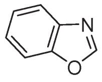
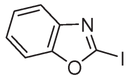
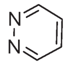
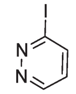
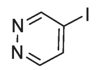
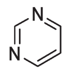
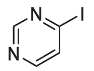
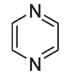
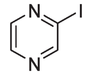
[a] Using ZnCl$_2$·TMEDA (0.5 eq.) and LiTMP (1.5 eq.).

We next demonstrated that TMP-cadmate was suitable for the chemoselective metalation of a large range of aromatic heterocycles, giving in general higher yields than using Zn[10,12] (Table 2). The reaction with both π-excessive (substrates **1j**, **1k** and **1l**) and π-deficient (substrates **1m**, **1n**, **1o**, **1p** and **1q**) heterocycles was found to proceed smoothly at room temp. The expected iodides formed regioselectively, except 3-iodopyridazine (**2o**), which was accompanied by the 4-iodo derivative **2′o** (about 60 : 40 ratio for **2o** : **2′o**).

Starting from pyrazine (**1q**), the 2,5-diodo derivative **3q** was isolated concomitantly in 20% yield using 0.5 equiv. of TMP-cadmate, probably through dideprotonation, whereas it was avoided using 1/3 equiv. The formation of dimetalated derivatives being described using zincate[13] or manganate[4,14] type bases, the use of a larger amount of TMP-cadmate (1 equiv.) was attempted to deprotonate **1q**. Under the same reaction conditions, the diiodide **3q** was isolated in 58% yield. The method was successfully extended to five-membered substrates **1r**, **1s**, **1t** and **1l** (Table 3).

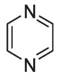
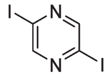
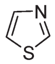
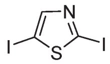
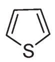
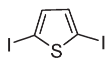
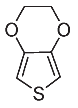
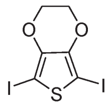
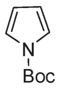
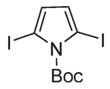
In summary, highly chemo- and regioselective deprotonative cadmation of functionalized aromatics including heterocycles was realized using a newly developed TMP-Cd-ate base. The latter is compatible with very sensitive substrates such as diazines for which classical lithium bases can hardly be used, even at very low temperatures.[15] The aromatic lithium cadmates were evidenced using iodine as electrophile. Trapping of

Table 2 Deprotonative cadmation of aromatic heterocycles[a]

Entry	Substrate (**1**)		Product (**2**)		Yield (%)
1		**1j**		**2j**	97 (73)[b]
2		**1k**		**2k**	84 (69)[b]
3		**1l**		**2l**	68 (68)[b]
4		**1m**		**2m**	97 (52)[b]
5		**1n**		**2n**	63 (57)[b]
6		**1o**		**2o**	55[c]
				**2′o**	41[c]
7		**1p**		**2p**	71 (57)[b]
8		**1q**		**2q**	63[d] (59)[b]

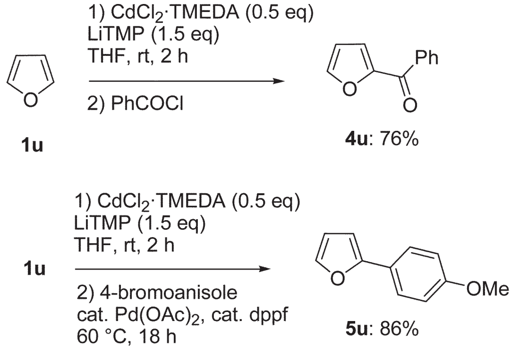
[a] Reactions carried out using CdCl$_2$·TMEDA (0.5 eq.) and LiTMP (1.5 eq.). [b] Using ZnCl$_2$·TMEDA (0.5 eq.) and LiTMP (1.5 eq.).[10,12] [c] Using CdCl$_2$·TMEDA (1 eq.) and LiTMP (3 eq.). [d] Using CdCl$_2$·TMEDA (0.33 eq.) and LiTMP (1 eq.).

Table 3 Deprotonative dicadmation of aromatic heterocycles[a]

Entry	Substrate (**1**)		Product (**3**)		Yield (%)
1		**1q**		**3q**	58
2		**1r**		**3r**	50
3		**1s**		**3s**	74
4		**1t**		**3t**	81
5		**1l**		**3l**	60

[a] Reactions carried out using $CdCl_2 \cdot TMEDA$ (1 eq.) and LiTMP (3 eq.).

the furylcadmate was attempted using other electrophiles: benzoyl chloride[8b] to afford the ketone **4u**, and 4-bromoanisole to give the expected coupling[16] product **5u** under palladium catalysis, as depicted in Scheme 2.



Scheme 2 Other trapping reactions of heterocyclic cadmates.

Comparisons with previously described combinations of LiTMP on the one hand, and Zn,[2] Al,[3] Mn[4] and Cu[5] organometallic compounds on the other hand, showed the basic mixture we here described is both more efficient and/or more chemoselective.

Due to the toxicity of cadmium compounds we are attempting to develop basic mixtures with cadmium salts as catalysts rather than in stoichiometric quantities. In addition, work in order to develop new mixed lithium–metal bases of ate type that are still efficient and chemoselective but less toxic are in parallel under investigation, profiting from the present study.

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