



HAL
open science

Deprotonative Cadmation of Functionalized Aromatics

J.M. L'Helgoual'Ch, Ghenia Bentabed-Ababsa, Floris Chevallier, M. Yonehara,
Masanobu Uchiyama, Aïcha Derdour, Florence Mongin

► **To cite this version:**

J.M. L'Helgoual'Ch, Ghenia Bentabed-Ababsa, Floris Chevallier, M. Yonehara, Masanobu Uchiyama, et al..
Deprotonative Cadmation of Functionalized Aromatics. *Chemical Communications*, 2008, 42, pp.5375-5377.
<10.1039/b809543d>. <hal-00783743>

HAL Id: hal-00783743

<https://hal.science/hal-00783743v1>

Submitted on 4 Feb 2014

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization

Deprotonative Cadmation of Functionalized Aromatics.

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

Received (in XXX, XXX) 1st January 2007, Accepted 1st January 2007

First published on the web 1st January 2007

DOI: 10.1039/b000000x

This communication describes the deprotonation 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 superbases).

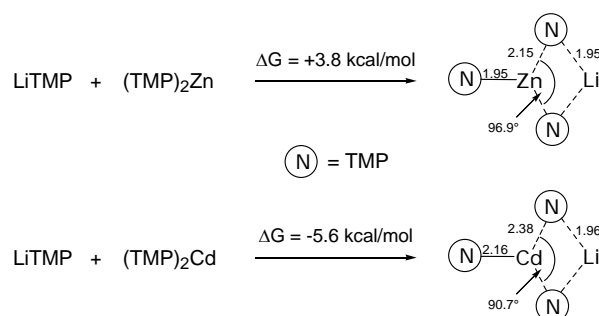
By combining soft organometallic compounds with alkali additives (*e.g.* LiTMP, TMP = 2,2,6,6-tetramethylpiperidino, or LiCl), bases such as ^tBu₂Zn(TMP)Li,² ^tBu₃Al(TMP)Li,³ (Me₃SiCH₂)₂Mn(TMP)Li·TMEDA,⁴ MeCu(TMP)(CN)Li₂⁵ and (TMP)₂Zn·2 MgCl₂·2 LiCl⁶ have been prepared and used to generate functionalized 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 and co-workers documented in 1951 the synthesis of Ph₃ZnLi and

Ph₃CdLi, and their efficiency to deprotonate fluorene in diethyl ether.⁹ Quenching with CO₂ and subsequent acidic work-up afforded diphenyleneacetic acid in a low yield of 16% after 10 days reaction time using Ph₃ZnLi whereas a satisfying 64% yield was obtained after 3 days using Ph₃CdLi, a result attributed to the size of the central metal. This prompted us to study the use of lithium cadmates for the deprotonation of sensitive aromatic substrates.

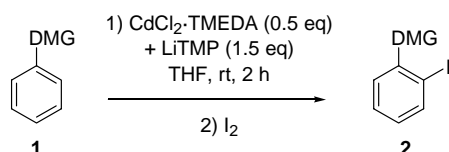
A recent study showed LiTMP and (TMP)₂Zn, even if not associated in the form of a zincate, could behave synergically, combining both the efficiency of LiTMP and the chemoselectivity of (TMP)₂Zn.¹⁰ In order to seek more efficient and direct methods for introducing functionalities into heteroaromatic rings, 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 CdCl₂·TMEDA¹¹ (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 hours afforded the expected derivated **2a** in 74% yield, against 30% yield using ZnCl₂·TMEDA (0.5 equiv) and LiTMP (1.5 equiv). Since (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 CdCl₂·TMEDA (1/3 equiv), NMR and DFT studies were carried out. The analysis of the ¹³C 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 (TMP)₂Cd on one side and (TMP)₃CdLi on the other side, which is in sharp contrast to the corresponding zinc-lithium mixture obtained from LiTMP and ZnCl₂·TMEDA (Scheme 1).¹⁰



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

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 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**.

Table 1 Deprotonative cadmation of functionalized benzenes



Entry	Substrate (1)	Product (2)	Yield
1			74% (30%) ^a
2			79%
3			91%
4			62%
5			68%
6			66%
7			97%
8			83%
9			60%

^a Using ZnCl₂·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 RT. 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**).

Table 2 Deprotonative cadmation of aromatic heterocycles^a

Entry	Substrate (1)	Product (2)	Yield (%)
1			97 (73) ^b
2			84 (69) ^b
3			68 (68) ^b
4			97 (52) ^b
5			63 (57) ^b
6			41 ^c
			55 ^c
7			71 (57) ^b
8			63 ^d (59) ^b

²⁵ ^a Reactions carried out using CdCl₂·TMEDA (0.5 eq) and LiTMP (1.5 eq). ^b Using ZnCl₂·TMEDA (0.5 eq) and LiTMP (1.5 eq). ^{10,12} ^c Using CdCl₂·TMEDA (1 eq) and LiTMP (3 eq). ^d Using CdCl₂·TMEDA (0.33 eq) and LiTMP (1 eq).

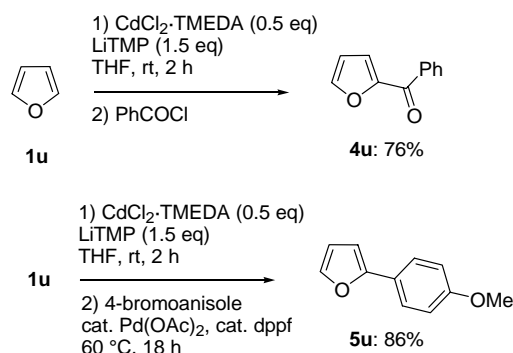
Starting from pyrazine (**1q**), the 2,5-diiodo derivative **3q** was isolated concomitantly in 20% yield using 0.5 equiv of TMP-cadmate, probably through dideprotonation, whereas it was avoided using 1/3 equiv. The formation of dimetalated derivatives being described using zincate¹³ or manganate^{4,14} 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).

Table 3 Deprotonative dicadmation of aromatic heterocycles^a

Entry	Substrate (1)	Product (3)	Yield (%)
1			58
2			50
3			74
4			81
5			60

⁴⁰ ^a Reactions carried out using CdCl₂·TMEDA (1 eq) and LiTMP (3 eq).

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 the furylcadmate was attempted using other electrophiles: benzoyl chloride^{8b} to afford the ketone **4u**, and 4-bromoanisole to give the expected coupling¹⁶ 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 Mn⁴ and Cu⁵ 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 actually try hard to develop basic mixtures containing cadmium salts as catalysts. In addition, works in order to develop new mixed lithium-metal bases of ate type still efficient and chemoselective but less toxic are in parallel under investigation, profiting from the present study.

The authors gratefully acknowledge the financial support of Région Bretagne (to J.M.L.), MESRS of Algeria (to G.B.), and Hoansha and KAKENHI (Young Scientist (A), Houga, and Priority Area No. 452 and 459) (to M.U.). The calculations were performed on the RIKEN Super Combined Cluster (RSCC).

Notes and references

^a *Chimie et Photonique Moléculaires, UMR 6510 CNRS, Université de Rennes 1, Bâtiment 10A, Case 1003, Campus Scientifique de Beaulieu, 35042 Rennes, France. Fax: +33-2-2323-6955; E-mail: florence.mongin@univ-rennes1.fr*

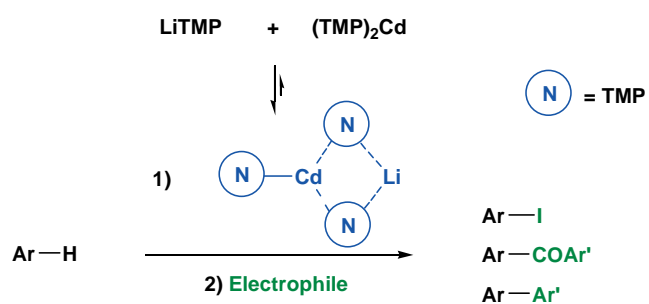
^b *Laboratoire de Synthèse Organique Appliquée, Faculté des Sciences de l'Université, BP 1524 Es-Senia, Oran 31000, Algeria*

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

† Electronic Supplementary Information (ESI) available: Experimental procedures and characterizations (¹H and ¹³C NMR spectra for all compounds), and theoretical data (details of computational methods, cartesian coordinates and Gibbs free energies). See DOI: 10.1039/b000000x/

- For excellent reviews, see: (a) H. W. Gschwend and H. R. Rodriguez, *Org. React.*, 1979, **26**, 1–360; (b) V. Snieckus, *Chem. Rev.*, 1990, **90**, 879–933.
- (a) Y. Kondo, M. Shilai, M. Uchiyama and T. Sakamoto, *J. Am. Chem. Soc.*, 1999, **121**, 3539–3540; (b) M. Uchiyama, T. Miyoshi, Y. Kajihara, T. Sakamoto, Y. Otani, T. Ohwada and Y. Kondo, *J. Am. Chem. Soc.*, 2002, **124**, 8514–8515; (c) H. R. L. Barley, W. Clegg, S. H. Dale, E. Hevia, G. W. Honeyman, A. R. Kennedy and R. E. Mulvey, *Angew. Chem.* 2005, **117**, 6172–6175 (*Angew. Chem. Int. Ed.*, 2005, **44**, 6018–6021); (d) W. Clegg, S. H. Dale, E. Hevia, G. W. Honeyman and R. E. Mulvey, *Angew. Chem.*, 2006, **118**, 2430–2434 (*Angew. Chem. Int. Ed.*, 2006, **45**, 2370–2374); (e) W. Clegg, S. H. Dale, R. W. Harrington, E. Hevia, G. W. Honeyman and R. E. Mulvey, *Angew. Chem.*, 2006, **118**, 2434–2437 (*Angew. Chem. Int. Ed.*, 2006, **45**, 2374–2377); (f) W. Clegg, S. H. Dale, A. M. Drummond, E. Hevia, G. W. Honeyman and R. E. Mulvey, *J. Am. Chem. Soc.*, 2006, **128**, 7434–7435; (g) M. Uchiyama, Y. Matsumoto, D. Nobuto, T. Furuyama, K. Yamaguchi and K. Morokuma, *J. Am. Chem. Soc.*, 2006, **128**, 8748–8750; (h) M. Uchiyama, Y. Kobayashi, T. Furuyama, S. Nakamura, Y. Kajihara, T. Miyoshi, T. Sakamoto, Y. Kondo and K. Morokuma, *J. Am. Chem. Soc.*, 2008, **130**, 472–480.
- (a) M. Uchiyama, H. Naka, Y. Matsumoto and T. Ohwada, *J. Am. Chem. Soc.*, 2004, **126**, 10526–10527; (b) J. Garcia-Alvarez, D. V. Graham, A. R. Kennedy, R. E. Mulvey and S. Weatherstone, *Chem. Commun.*, 2006, **30**, 3208–3210; (c) J. Garcia-Alvarez, E. Hevia, A. R. Kennedy, J. Klett and R. E. Mulvey, *Chem. Commun.*, 2007, **23**, 2402–2404; (d) H. Naka, M. Uchiyama, Y. Matsumoto, A. E. H. Wheatley, M. McPartlin, J. V. Morey and Y. Kondo, *J. Am. Chem. Soc.*, 2007, **129**, 1921–1930.
- J. Garcia-Alvarez, A. R. Kennedy, J. Klett and R. E. Mulvey, *Angew. Chem.*, 2007, **119**, 1123–1126 (*Angew. Chem. Int. Ed.*, 2007, **46**, 1105–1108).
- S. Usui, Y. Hashimoto, J. V. Morey, A. E. H. Wheatley and M. Uchiyama, *J. Am. Chem. Soc.*, 2007, **129**, 15102–15103.
- S. H. Wunderlich and P. Knochel, *Angew. Chem.*, 2007, **119**, 7829–7832 (*Angew. Chem. Int. Ed.* 2007, **46**, 7685–7688).
- For reviews, see: (a) R. E. Mulvey, *Organometallics*, 2006, **25**, 1060–1075; (b) R. E. Mulvey, F. Mongin, M. Uchiyama and Y. Kondo, *Angew. Chem.*, 2007, **119**, 3876–3899 (*Angew. Chem. Int. Ed.*, 2007, **46**, 3802–3824).
- (a) P. R. Jones and P. J. Desio, *Chem. Rev.*, 1978, **78**, 491–516; (b) P. O'Brien and M. A. Malik, *Science of Synthesis*, 2004, **3**, 91–131.
- G. Wittig, F. J. Meyer and G. Lange, *Liebigs Ann. Chem.*, 1951, **571**, 167–201.
- J.-M. L'Helgoual'ch, A. Seggio, F. Chevallier, M. Yonehara, E. Jeanneau, M. Uchiyama and F. Mongin, *J. Org. Chem.*, 2008, **73**, 177–183.
- G. Kedarnath, L. B. Kumbhare, V. K. Jain, P. P. Phadnis and M. Nethaji, *Dalton Trans.*, 2006, 2714–2718.
- A. Seggio, F. Chevallier, M. Vaultier and F. Mongin, *J. Org. Chem.*, 2007, **72**, 6602–6605.
- (a) W. Clegg, S. H. Dale, E. Hevia, L. M. Hogg, G. W. Honeyman, R. E. Mulvey and C. T. O'Hara, *Angew. Chem.*, 2006, **118**, 6698–6700 (*Angew. Chem. Int. Ed.*, 2006, **45**, 6548–6550); (b) D. R. Armstrong, W. Clegg, S. H. Dale, D. V. Graham, E. Hevia, L. M. Hogg, G. W. Honeyman, A. R. Kennedy and R. E. Mulvey, *Chem. Commun.*, 2007, 598–600.
- L. M. Carrella, W. Clegg, D. V. Graham, L. M. Hogg, A. L. Kennedy, J. Klett, R. E. Mulvey, E. Rentschler and L. Russo, *Angew. Chem.*, 2007, **119**, 4746–4750 (*Angew. Chem. Int. Ed.*, 2007, **46**, 4662–4666).
- N. Plé, A. Turck, K. Couture and G. Quéguiner, *J. Org. Chem.*, 1995, **60**, 3781–3786.
- To our knowledge, cross-coupling reactions using cadmium compounds have only been described starting from organocadmium chlorides: (a) E.-i. Negishi, T. Takahashi, S. Baba, D. E. Van Horn and N. Okukado, *J. Am. Chem. Soc.*, 1987, **109**, 2393–2401; (b) N. Bumagin, A. B. Ponomarev and I. P. Beletskaya, *Zh. Org. Khim.*, 1987, **23**, 1345–1353. See also: (c) J. A. Miller and R. P. Farrell, *Tetrahedron Lett.*, 1998, **39**, 7275–7278.

Graphical and textual abstract for the contents pages.



⁵ The deprotonation of a large range of aromatics including heterocycles is described using a newly developed lithium-cadmium base. The reaction proceeds at room temperature with excellent chemoselectivity and efficiency, and proved to be
¹⁰ regioselective in most cases.