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Ligand-Activated Lithium-Mediated Zincation of *N*-Phenylpyrrole

Anne Seggio,[a] Marie-Isabelle Lannou,[a] Floris Chevallier,[a] Daisuke Nobuto,[b] Masanobu Uchiyama,*[b] Stéphane Golhen,[c] Thierry Roisnel,[c] and Florence Mongin*[a]

Abstract: Metalation of *N*-phenylpyrrole by using an in situ mixture of $ZnCl_2$·TMEDA (0.5 equiv; TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) and LiTMP (1.5 equiv; TMP = 2,2,6,6-tetramethylpiperidino) was optimized. The reaction carried out at room temperature in THF resulted in incomplete metalation (56% conversion) and selectivity (mixture of 2-iodo and 2,2′-diiodo derivatives in an 86:14 ratio after trapping with iodine). By using diethyl ether (DEE), toluene, or hexane instead of THF, low conversions of 17, 38, or 23% were observed, respectively, but the formation of the diiodide was avoided. When hexane was used as solvent, strong lithium-complexing ligands such as [12]crown-4 and *N*,*N*′-dimethylpropylideneurea (DMPU) inhibited the reaction whereas more (hemi)labile ligands (TMEDA > THF ≈ DME) favored it. This result shows that a temporary accessibility of lithium to interact with the rest of the base and/or the substrate is a prerequisite for an efficient metalation. A 75% yield of 2-iodo-*N*-phenylpyrrole was obtained after reaction with the base in the presence of five equivalents of TMEDA for two hours at room temperature, and subsequent trapping with iodine. We were able to successfully replace the spare TMP with a less expensive butyl group.

Keywords: heterocycles · ligand effects · lithium · metalation · zincates

Introduction

Substituted pyrroles are structural units present in many natural products and pharmaceutical synthetic intermediates.[1] Among the methods used to functionalize pyrroles,[1] metalation reactions with lithium bases have been developed.[2] These methods often require low temperatures and cannot be used when reactive functional groups are present.

Starting from *N*-phenylpyrrole (**1**), two sites (2 and 2′) can be attacked depending on the reaction conditions. Whereas 2,2′-dimetalation occurs by using *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA)-activated butyllithium in diethyl ether (DEE) under kinetic conditions,[3] 2-monometalation is observed employing either the same base under thermodynamic conditions[3b,4] (in DEE at room temperature after long reaction times, or in refluxing hexane) or potassium *tert*-butoxide-activated butyllithium (LIC-KOR) in tetrahydrofuran (THF) at −75 °C.[3b,5]

The metalation reactions of functionalized aromatics such as alkyl benzoates, ethyl thiophenecarboxylates, ethyl 2-furancarboxylate, pyridine, quinoline, and isoquinoline by using lithium di-*tert*-butyl(2,2,6,6-tetramethylpiperidino)zincate ("TMP-zincate") as a base were first described in 1999.[6] The reactions performed in THF at room temperature proved to be chemoselective, but required one or two equivalents of base, only TMP (TMP = 2,2,6,6-tetramethylpiperidino) participating in the reaction.

Several examples of efficient metalation by using lithium or sodium amidozincates have been reported by Mulvey and co-workers since 2005.[7] The term *alkali-metal-mediated zincation* has been introduced to depict these reactions because

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[a] A. Seggio, Dr. M.-I. Lannou, Dr. F. Chevallier, Prof. F. Mongin
Synthèse et ElectroSynthèse Organiques
UMR 6510 CNRS, Université de Rennes 1
Bâtiment 10A Case 1003, Campus Scientifique de Beaulieu
35042 Rennes Cedex (France)
Fax: (+33) 2-2323-6955
E-mail: florence.mongin@univ-rennes1.fr

[b] D. Nobuto, Prof. M. Uchiyama
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

[c] Dr. S. Golhen, Dr. T. Roisnel
Sciences Chimiques de Rennes, UMR 6226 CNRS
Université de Rennes 1
Bâtiment 10B, Campus Scientifique de Beaulieu
35042 Rennes Cedex (France)

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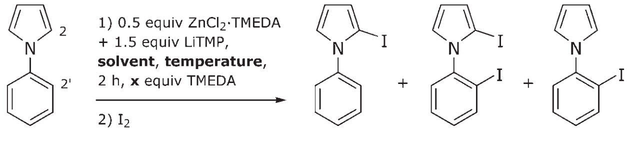
the reactivity (“synergy”) exhibited by the zincates cannot be replicated by the homometallic compounds on their own.[8] Reactions were performed by adding a one-molar equivalent (per lithium) of TMEDA or THF to bulk apolar hydrocarbon to increase the opportunity for crystal growth; these conditions thus proved to favor the metalation reactions of *N*,*N*-diisopropylcarboxamide[7c,d] and anisole[7g] by using lithium amidozincates.

Herein, we describe the optimized metalation reaction of *N*-phenylpyrrole by using zinc diamide-lithium base mixtures (reaction time and temperature, solvent, amount and nature of base, concentration, and so on). The effect of a variety of lithium ligands on the outcome of the reaction was also examined, and the reaction pathway and mechanism were discussed on the basis of second-order Møller–Plesset perturbation (MP2) calculations.

Table 1. Effect of solvent on the metalation of **1** by using an in situ mixture of $ZnCl_2$·TMEDA (0.5 equiv) and LiTMP (1.5 equiv).



1 **2** **3** **4**

Entry	Solvent	Temperature	*x*	**1**/**2**/**3**/**4**[a] (Conversion)
1	THF	RT	0	44/48/8/0 (56 %)
2	THF	reflux	0	30/41/27/2[b] (70 %)
3	DEE	RT	0	83/16/0/1 (17 %)
4	toluene	RT	0	62/35/2/1 (38 %)
5	hexane	RT	0	77/23/0/0 (23 %)
6	THF	RT	1.5	56/40/4/0 (44 %)
7	DEE	RT	1.5	98/1/0/1 (2 %)
8	toluene	RT	1.5	62/38/0/0 (38 %)
9	hexane	RT	1.5	46/54/0/0 (54 %)

[a] Ratios determined from the integration values of the ^1H NMR spectra of the crude reaction mixtures. [b] 13/55/30/2 by using an in situ mixture of $ZnCl_2$·TMEDA (1.0 equiv) and LiTMP (3.0 equiv).

Results

The observation by Mulvey and co-workers of the beneficial effect of a stoichiometric amount of TMEDA on the efficiency of lithium-mediated zincation in hexane[7c,d,g] led us to prepare bases from $ZnCl_2$·TMEDA,[9] which is much less hygroscopic than $ZnCl_2$, and to study their metalation ability. The metalation of *N*-phenylpyrrole (**1**) was attempted by using an in situ prepared mixture of $ZnCl_2$·TMEDA (0.5 equiv) and LiTMP (1.5 equiv), and the influence of the solvent on the reaction was examined initially.

Solvent has an important impact on the reactivity of organometallics involved in reactions. In addition to its direct dissolving effect, the ability of the solvent to chelate Lewis acidic metals modifies the aggregation state of organometallics species. For example, butyllithium, which is available as hexameric aggregates in hydrocarbons,[10] is shifted to entropically favored tetrameric[11] or temperature-dependant equilibrium of dimeric and tetrameric aggregates[12] in DEE and THF, respectively. Improved reactivities observed in polar solvents are partly attributed to lower aggregation states of alkyllithium species.[2,13]

Diamines such as TMEDA and *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine (PMDTA) are also able to deaggregate classical bases including alkyllithium bases when employed as additives. Butyllithium is, for example, present as dimers in TMEDA[13] and can be monomeric in the presence of PMDTA, because the nonbonding pairs of the three nitrogen atoms all coordinate the lithium atom of the base.[12b]

The effect of different media (THF, DEE, toluene, and hexane) on the course of the reaction was therefore studied (Table 1). The use of the in situ prepared mixture of $ZnCl_2$·TMEDA (0.5 equiv) and LiTMP (1.5 equiv) in THF at room temperature resulted in incomplete metalation and a lack of selectivity: After the products had been trapped with iodine, NMR analysis of the crude reaction mixture showed that 2-iodo-*N*-phenylpyrrole (**2**) was present together with the substrate (**1**) and 2-iodo-*N*-(2-iodophenyl)pyrrole (**3**) (Table 1, entry 1). Refluxing in THF increased the relative amount of the diiodide **3**; negligible amounts of *N*-(2-iodophenyl)pyrrole (**4**) were detected too. This result is unexpected if one considers that by using TMEDA-activated butyllithium,[3b] the thermodynamic aryl metal is 2-lithio-*N*-phenylpyrrole and the kinetic one 2,2′-dilithio-*N*-phenylpyrrole. Reversion of the 2,2′-dimetalated *N*-phenylpyrrole to the 2-metalated *N*-phenylpyrrole could be prevented when the metal was zinc. The use of a larger amount of base reduced the recovery of substrate (**1**), but had no appreciable effect on the selectivity (Table 1, entry 2).

DEE, which is less coordinating than THF, gave a poor 17 % conversion (Table 1, entry 3). In toluene (Table 1, entry 4), a solvent able to solvate the alkali-metal cation electrostatically through its π system, as well as in hexane (Table 1, entry 5), the conversion proved to be low (38 and 23 %, respectively), probably connected with the poor solubility observed, but the reaction occurred selectively at the 2 position.

Examples in the literature show that hexane containing TMEDA is a better solvent than THF for performing metalation reactions.[14] We therefore decided to attempt the reaction in the four solvents previously tested in the presence of additional equivalents of TMEDA.

As expected,[13] adding 1.5-molar equivalents of TMEDA to the base dissolved in polar THF or DEE did not improve conversions or selectivities (Table 1, entries 6 and 7). TMEDA also had no beneficial effect on the reaction in toluene (Table 1, entry 8), but in contrast, it was found to make the reaction in hexane easier (Table 1, entry 9).

This encouraging result prompted us to study the impact of increasing the amounts of this metal-complexing agent on the reaction (Table 2). Varying the additional number of equivalents of TMEDA from zero to five resulted in increasing conversions of *N*-phenylpyrrole (**1**) from 23 to 92 % when the reaction was conducted in hexane. Very small amounts of the iodides **3** and **4** were detected (< 5 %), and

Table 2. Metalation of **1** by using an in situ mixture of $ZnCl_2$·TMEDA (0.5 equiv) and LiTMP (1.5 equiv) in hexanes at about 0.3 M[a] and about 1.0 M[a] in the presence of different amounts of TMEDA.

$$\mathbf{1}\ \xrightarrow[\text{2) } I_2]{\text{1) 0.5 equiv } ZnCl_2\cdot\text{TMEDA} + \text{1.5 equiv LiTMP, } \mathbf{x} \text{ equiv TMEDA, hexanes, RT, 2 h}}\ \mathbf{2} + \mathbf{3} + \mathbf{4}$$

Entry	x	**1/2/3/4**[b] at 0.3 M[a]	**1/2/3/4**[b] at 1.0 M[a]
1	0	77/23/0/0	52/46/0/2
2	0.5	50/48/2/0	–
3	1	46/53/1/0	–
4	1.5	46/54/0/0	26/70/0/4
5	3	–	18/81/0/1
6	5	8/88/0/4 (**2**: 75 % yield)	8/89/0/3 (**2**: 65 % yield)

[a] Initial molar amount of **1**/total volume of hexanes. [b] Ratios determined from the integration values of the ^{1}H NMR spectra of the crude reaction mixtures.

the iodide **2** was isolated in 75 % yield by using five equivalents of TMEDA. To simplify the procedure, reactions were attempted without adding extra solvent to butyllithium hexanes (1.0 M instead of 0.3 M concentration); under these conditions, the iodide **2** was successfully obtained in good yield and selectivity. Nevertheless, solubility problems were encountered by using only butyllithium hexanes (1.0 M concentration) because lithium chloride is only partially soluble in the reaction mixture and the arylzincate progressively precipitates as it forms.

For this reason, the reaction time was then optimized at room temperature by using 1.5 equivalents of TMEDA in hexane (0.3 M concentration) (Table 3). The results show that two days are required to obtain almost complete and selective metalation of *N*-phenylpyrrole (**1**), yielding the iodide **2** in 72 % yield. The metalated pyrrole exhibits a good stability at room temperature under these conditions.

Table 3. Effect of reaction time on the metalation of **1** by using an in situ mixture of $ZnCl_2$·TMEDA (0.5 equiv) and LiTMP (1.5 equiv) in hexane containing 1.5 equivalents of TMEDA.

$$\mathbf{1}\ \xrightarrow[\text{2) } I_2]{\text{1) 0.5 equiv } ZnCl_2\cdot\text{TMEDA} + \text{1.5 equiv LiTMP, 1.5 equiv TMEDA, RT hexane, } \textbf{reaction time}}\ \mathbf{2} + \mathbf{3} + \mathbf{4}$$

Entry	Reaction time	**1/2/3/4**[a]
1	10 min	88/12/0/0
2	40 min	62/38/0/0
3	2 h	46/54/0/0
4	6 h	28/72/0/0
5	24 h	18/81/0/1
6	48 h	8/89/2/1 (**2**: 72 % yield)
7	72 h	4/90/1/5

[a] Ratios determined from the integration values of the ^{1}H NMR spectra of the crude reaction mixtures.

Finally, reactions conducted at different temperatures[15] (Table 4) showed that competitive dimetalation only occurred above a temperature of 40 °C.

Table 4. Effect of reaction temperature on the metalation of **1** by using an in situ mixture of $ZnCl_2$·TMEDA (0.5 equiv) and LiTMP (1.5 equiv) in hexane containing 1.5 equivalents of TMEDA.

$$\mathbf{1}\ \xrightarrow[\text{2) } I_2]{\text{1) 0.5 equiv } ZnCl_2\cdot\text{TMEDA} + \text{1.5 equiv LiTMP 1.5 equiv TMEDA, hexane } \textbf{temperature}\text{, 2 h}}\ \mathbf{2} + \mathbf{3} + \mathbf{4}$$

Entry	Temperature	**1/2/3/4**[a]
1	0 °C	74/26/0/0
2	20 °C	67/33/0/0
3	40 °C	20/73/5/2 (17/80/2/1)[b]
4	reflux	26/61/11/2

[a] Ratios determined from the integration values of the ^{1}H NMR spectra of the crude reaction mixtures. [b] By using 5 equivalents of TMEDA.

The beneficial effect of TMEDA on the efficiency of the reaction challenged us to consider other amine-, but also, ether-type donors (Table 5). Indeed, dialkyl ethers have already been used as co-solvents of hydrocarbons for metalation purposes[14,16] to circumvent side reactions occurring in neat ethers.

Table 5. Metalation of **1** by using an in situ mixture of $ZnCl_2$·TMEDA (0.5 equiv) and LiTMP (1.5 equiv) in hexane containing different co-solvents.

$$\mathbf{1}\ \xrightarrow[\text{2) } I_2]{\text{1) 0.5 equiv } ZnCl_2\cdot\text{TMEDA} + \text{1.5 equiv LiTMP, } \mathbf{x} \text{ equiv } \textbf{cosolvent}\text{, hexane, RT, 2 h}}\ \mathbf{2} + \mathbf{3} + \mathbf{4}$$

Entry	Co-solvent (x equiv)	**1/2/3/4** ratio[a]
1	–	77/23/0/0
2	triethylamine (3)	88/12/0/0
3	TMEDA (1.5)	46/54/0/0
4	PMDTA (1.5)	75/19/5/1
5	PMDTA (5)	75/17/8/0
6	DABCO (1.5)	93/6/0/1
7	THF (3)	53/45/0/2
8	DME (1.5)	56/43/0/1
9	[12]crown-4 (1.5)	97/3/0/0
10	DMPU (3)	100/0/0/0

[a] Ratios determined from the integration values of the ^{1}H NMR spectra of the crude reaction mixtures.

In the amine series, triethylamine (Table 5, entry 2), TMEDA (Table 5, entry 3), PMDTA (Table 5, entries 4 and 5), and diazabicyclo[2.2.2]octane (DABCO, Table 5, entry 6) were tested as additives. Compared to the control reaction without co-solvent, the conversion only increased when using TMEDA. In the ether series, THF (Table 5, entry 7), 1,2-dimethoxyethane (DME, Table 5, entry 8), and [12]crown-4 (Table 5, entry 9) were tested. Whereas [12]crown-4 completely inhibited the reaction, the conversion increased by using THF and DME. To detect a possible cooperative effect,[17] the use of THF (2 equiv)/TMEDA (0.5 equiv) and DME (1 equiv)/TMEDA (0.5 equiv) mixtures as co-solvents was found to be unsuccessful, giving low conversions of 18 and 4 %, respectively.

For stoichiometry efficiency, it was important to check that the reaction could not occur by using an in situ prepared mixture of $ZnCl_2$·TMEDA (1/3 equiv) and LiTMP (1.0 equiv). The reaction attempted in hexane containing 1.5 equivalents of TMEDA gave a lower conversion; in addition, lower selectivities were noted along with increased reaction times.

The replacement of excess TMP by a less expensive ligand was attempted. Conducting the reaction by using a mixture that was prepared in situ by adding successively LiTMP (1.0 equiv) and BuLi (0.5 equiv) to $ZnCl_2$·TMEDA (0.5 equiv), in hexane in the presence of five equivalents of TMEDA, gave the expected iodide **2** in 83% yield after stirring for 24 h and subsequent trapping with iodine. However, replacing extra TMP by butyl groups (that is, by using heteroleptic $Bu_2Zn(TMP)Li$·TMEDA or Bu_3ZnLi·TMEDA) resulted in low conversions.

In addition, the use of either 0.5 equivalents of the zinc diamide (prepared by mixing $ZnCl_2$·TMEDA with 2 equiv of LiTMP) or one equivalent of LiTMP gave lower conversions (0 and 20%, respectively) under the same reaction conditions.

Discussion

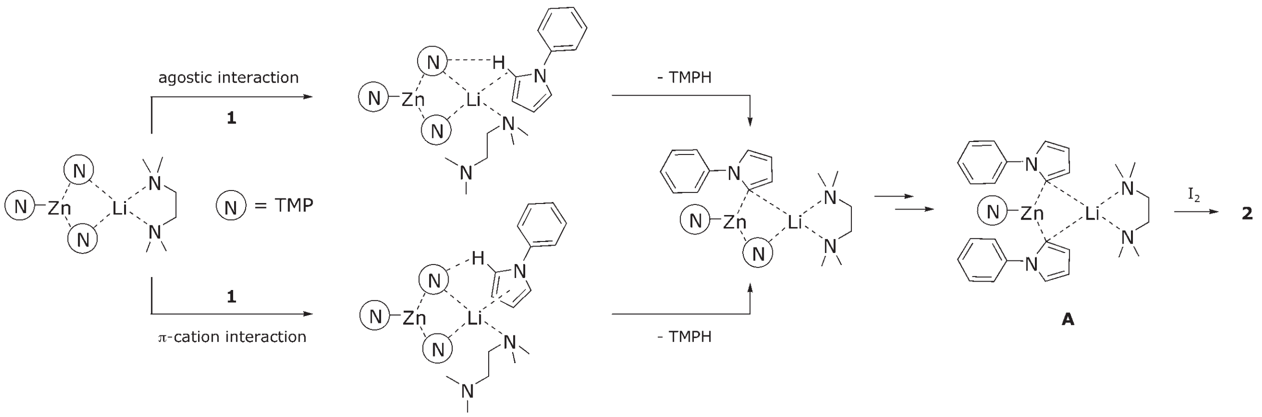
As sterically hindered alkali-metal (including lithium) triamidozincates have already been observed,[18] and also because bis(2,2,6,6-tetramethylpiperidino)zinc and LiTMP give lower conversions when used separately, we assumed that the metalating species was $(TMP)_3ZnLi$·TMEDA when an in situ mixture of $ZnCl_2$·TMEDA and LiTMP (3 equiv) was used.

Acidifying effects of substituents,[19] substrate–metal agostic contacts,[20] and base deliveries by the substituent–metal complex-induced proximity effect (CIPE)[21] have been proposed to justify hydrogen/lithium permutations on aromatic substrates. More recently, a mechanism in which reactive intermediates and transition structures are based upon triple ions (lithium ate compounds) was inferred from ab initio computational studies for BuLi/TMEDA-mediated metalations of substituted benzenes in apolar solvents; according to the authors, inductive effects play a greater role than precomplexation during these reactions.[22]

Efforts to investigate the mechanistic origins of the metalation by using alkali-metal zincates have been recently documented by Mulvey and co-workers. Three types of substrate–base interactions have been evidenced by X-ray crystallography: 1) interactions between substrate substituent and zincate alkali metal;[7c] 2) interactions between substrate π cloud and zincate alkali metal[23] and; 3) agostic interactions between C−H bond and zincate alkali metal.[23] If such interactions exist in the rate-limiting transition structure, they could stabilize it and lower the entropy of the metalation reaction, reducing the activation energy. Starting from *N*-phenylpyrrole (**1**) as substrate, only Li–π and agostic C−H/Li contacts are possible.

When either [12]crown-4, or *N,N′*-dimethylpropylideneurea (DMPU,[24] Table 5, entry 10), which strongly solvates lithium cations and converts contacted ion-pairs into separated ones,[25] or DABCO (which is a stronger lithium complexing agent than TMEDA)[26] were used, the reaction did not proceed. Inhibition of the reaction caused by strong lithium ligands shows that accessibility of lithium is a prerequisite for efficient metalation. Schlosser and Masson showed that the coordination of a metal cation to an arene electron sextet can only manifest itself if no better donor components are available.[27] Good ligands such as [12]crown-4, DMPU, PMDTA, and DABCO could then prevent or impede lithium–substrate and lithium–TMP interactions.

In contrast, more labile ligands such as TMEDA, THF, and DME could enable the alkali metal to interact with the TMP ligands and/or the substrate (Li–π and/or C−H/Li interactions), and then regain its position on lithium,[7c] as depicted in Scheme 1. According to the pathways proposed in Scheme 1 for the metalation of *N*-phenylpyrrole (**1**), only two thirds of the TMP groups participate in the reaction. Indeed, attempts to use an in situ prepared mixture of $ZnCl_2$·TMEDA (1/3 equiv) and LiTMP (1.0 equiv) resulted in low yields.



Scheme 1. Proposed pathways for the metalation of *N*-phenylpyrrole (**1**) by using an in situ prepared mixture of $ZnCl_2$·TMEDA (0.5 equiv) and LiTMP (1.5 equiv).

Second-order Møller–Plesset perturbation (MP2)[28] studies were then performed to understand the present metalation reaction. $(NH_2)_3ZnLi{\cdot}EDA$ and *N*-methylpyrrole were employed as chemical models for $(TMP)_3ZnLi{\cdot}TMEDA$ and *N*-phenylpyrrole, respectively.

The directed *ortho*-metalation (DoM) reaction by using the *N* ligand of the zincate seems to proceed through an "open form" transition state (**TS**) without the premetalation complex with an activation energy of 19.1 kcal mol^{-1} to give a 2-pyrryl cyclic zincate complex (**CP**) (energy gain: 16.2 kcal mol^{-1}). The zincation reaction is thus endothermic by 2.9 kcal mol^{-1}. We confirmed the nonexistence of cation/π complexes in the reaction pathway by making an artificial Li^+/π complex between $(NH_2)_3ZnLi{\cdot}EDA$ and *N*-methylpyrrole by first placing *N*-methylpyrrole $2\approx2.5$ Å above the lithium atom. Geometry optimization then caused smooth collapse of the Li^+/π complex structure without an energy barrier. Similarly, other energetically plausible premetalation complexes (e.g., the agostic interaction complex) were not found (Figure 1).

However, as judged from the Li–C2(pyrrole) bond length (2.44 Å) in **TS**, the DoM reaction seems to proceed with assistance from the Li^+/π complex. The coordination of the pyrrole ring on the Li atom in **TS** could decrease the Li–N-(NH_3) bond strength so that the bond breaks more easily. Therefore, the appropriate coordination of the (bidentate) ligand to the Li counter cation plays a critical role for the metalation through activation of the basicity of the *N* ligand. Strong ligands, such as [12]crown-4 and DMPU, could inhibit the metalation reaction by preventing favorable access of the substrate to the organometallic reagent through competitive coordination onto the Li atom.

Elucidation of the structure of the zincate intermediate formed in the deprotonating lithium-mediated zincation process was attempted to increase our understanding of zincate chemistry. The solid that precipitated from the reaction mixture after storage for several days at 4 °C was characterized by X-ray diffraction crystallography. As previously observed by Mulvey and co-workers,[7a] the intermediate metallo product is not a lithium zincate (in contrast to the case with "TMP-zincate" and related reagents), but the lithium-free neutral TMEDA-chelated bis(*N*-phenyl-2-pyrryl) zinc complex **5** (Figure 2).

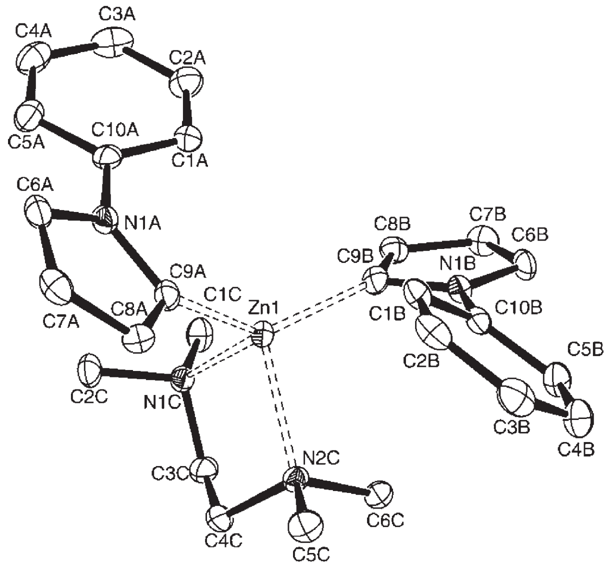


Figure 2. Molecular structure of **5**. The hydrogen atoms are omitted for clarity. Displacement ellipsoids are shown at the 50 % probability level.

Zn1 lies in a distorted tetrahedral coordination sphere which is made up of two nitrogen atoms (N1C, N2C) belonging to one bidentate TMEDA ligand and the carbon adjacent to the nitrogen atom of the pyrrole fragment of two phenylpyrrole molecules labeled A and B. The Zn–C bond lengths are 2.008(3) (C9A) and 2.011(3) Å (C9B), whereas the Zn–N bond lengths are 2.214(2) (N2C) and 2.240(2) Å (N1C). The corresponding angles are 133.25(12) and 82.76(8)° for C9A-Zn1-C9B and N1C-Zn1-N2C, respectively, the four remaining angles range from 103.32(10) to 111.23(10)°. The bond lengths of the two TMEDA molecules are quite similar, but the angles made up of the pyrrole- and the phenyl-ring mean planes are 29.97(17) and 37.84(12)° for A and B, respectively. No significant intermolecular contacts were observed.

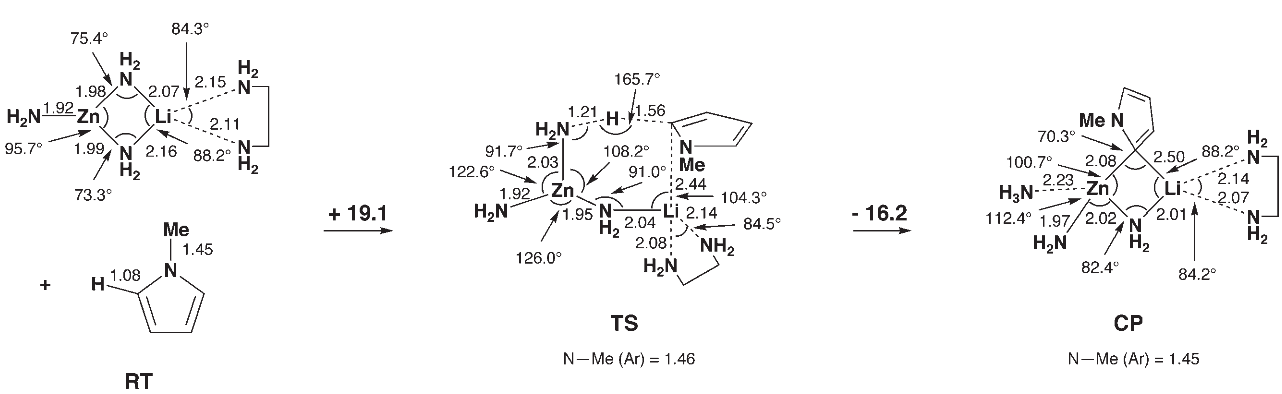


Figure 1. Calculated structures for the reactants, transition states and products, and Gibbs free energy changes. Bond lengths, angles, and energy changes at the MP2/631SVPs level are shown in Å, degrees, and kcal mol^{-1}, respectively.

This compound could result from the release of LiTMP from the expected lithium–zinc mixed intermediate **A** (see Scheme 1). ^{1}H and ^{13}C NMR analysis seem to show that the complex **5** is also the main species in solution.

The reaction was finally conducted by using in situ prepared bis(2,2,6,6-tetramethylpiperidino)zinc (0.5 equiv), and 0.10, 0.25, 0.40, or 0.60 equivalents of LiTMP (Table 6). The results show that the zinc diamide cannot be satisfactorily used in the presence of substoichiometric amounts of LiTMP.[29]

Table 6. Metalation of **1** by using in situ prepared bis(2,2,6,6-tetramethylpiperidino)zinc (0.5 equiv) in the presence of substoichiometric amounts of LiTMP.

$$\mathbf{1}\ \xrightarrow[\text{2) } I_2]{\substack{\text{1) 0.5 equiv } ZnCl_2\cdot\text{TMEDA} \\ +\ (1.0 + \mathbf{x}) \text{ equiv LiTMP,} \\ \text{5 equiv TMEDA, hexane, RT, 2 h}}}\ \mathbf{2}$$

Entry	*x* equiv LiTMP	**1/2**[a] ratio[b]
1	0.10	84/16
2	0.25	50/50
3	0.40	20/80
4	0.60	5/95

[a] Very small amounts of the iodides **3** and **4** were detected (<5%). [b] Ratios determined from the integration values of the ^{1}H NMR spectra of the crude reaction mixtures.

Conclusion

Metalation of *N*-phenylpyrrole by using an in situ mixture of ZnCl$_2$•TMEDA (0.5 equiv) and LiTMP (1.5 equiv) has been optimized. Hexane containing a (hemi)labile lithium ligand proved to be a better solvent than bulk ethers for this lithium-mediated zincation. To save 2,2,6,6-tetramethylpiperidine, an in situ prepared mixture of ZnCl$_2$•TMEDA (0.5 equiv), LiTMP (1.0 equiv), and BuLi (0.5 equiv) was tested with success. When used in hexane containing five equivalents of TMEDA at room temperature, the in situ mixture of ZnCl$_2$•TMEDA (0.5 equiv) and LiTMP (1.5 equiv) gave better results (92% conversion after two hours) than LiTMP (1 equiv, 20% conversion after two hours) and its corresponding zinc diamide (no conversion). In addition to the synergic chemistry it exhibits, the 1:3 in situ mixture of ZnCl$_2$•TMEDA and LiTMP could be useful in synthetic applications in the metalation of sensitive and/or functionalized substrates such as bare diazines,[30] for which reaction with classical lithium amides,[31] or mixed lithium–magnesium amides[32] can hardly be performed due to competitive nucleophilic addition reactions.

Experimental Section

All reactions were performed in Schlenk tubes under argon atmosphere. THF and DEE were distilled over sodium/benzophenone. Hexane and toluene were distilled after drying over P$_4$O$_{10}$. ZnCl$_2$•TMEDA was prepared by using a described procedure.[33] Nuclear magnetic resonance spectra were acquired on a Bruker ARX 200 spectrometer (200 MHz and 50 MHz for ^{1}H and ^{13}C, respectively). Chemical shifts are given in ppm as δ values relative to tetramethylsilane. The ratios were determined from the ^{1}H NMR integration values. High-resolution mass spectral measurements were performed at the CRMPO in Rennes (Centre Régional de Mesures Physiques de l'Ouest) by using a Micromass MS/MS ZABSpec TOF instrument in EI mode.

Metalation procedure by using the in situ prepared mixture of ZnCl$_2$•TMEDA and LiTMP: To a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.53 mL, 3.0 mmol) in hexane (5 mL) were successively added BuLi (1.6 M solution in hexanes, 3.0 mmol), TMEDA (1.5 mL, 10 mmol), and ZnCl$_2$•TMEDA (0.25 g, 1.0 mmol). The mixture was stirred for 15 min at 0 °C before introduction of *N*-phenylpyrrole (**1**, 0.29 g, 2.0 mmol). After 2 h at room temperature, a solution of I$_2$ (0.76 g, 3.0 mmol) in THF (5 mL) was added. The mixture was stirred overnight before addition of an aqueous saturated solution of Na$_2$S$_2$O$_3$ (2 mL) and extraction with EtOAc (3×15 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated under reduced pressure.

2-Iodo-*N*-phenylpyrrole (2): Compound **2** was obtained according to the metalation procedure and was isolated after purification by flash chromatography on silica gel (heptane/CH$_2$Cl$_2$: 80/20) as a colorless oil (0.41 g, 75%) which rapidly turned brown (decomposition by loss of iodine). ^{1}H NMR (CDCl$_3$): δ=6.32 (dd, *J*=3.0 and 3.6 Hz, 1 H), 6.53 (dd, *J*=1.8 and 3.6 Hz, 1 H), 7.02 (dd, *J*=1.8 and 3.0 Hz, 1 H), 7.41 ppm (m, 5 H); ^{13}C NMR (CDCl$_3$): δ=69.1, 111.9, 120.5, 125.9, 127.0 (2 C), 128.0, 128.9 (2 C), 140.9 ppm; HRMS: **1** and I$_2$ were detected instead of **2**, which is unstable. Data for **1**: *m*/*z*: calcd: 143.0735 [M^+]; found: 143.0721.

2-Iodo-*N*-(2-iodophenyl)pyrrole (3): Compound **3** was identified in crude mixtures. ^{1}H NMR (CDCl$_3$): δ=6.28 (dd, *J*=3.2 and 3.4 Hz, 1 H), 6.53 (dd, *J*=1.4 and 3.4 Hz, 1 H), 7.02 (dd, *J*=1.4 and 3.2 Hz, 1 H), 7.08–7.43 (m, 3 H), 7.89 ppm (d, *J*=8.0 Hz, 1 H).

***N*-(2-Iodophenyl)pyrrole (4)**: Compound **4** was identified in crude mixtures. ^{1}H NMR (CDCl$_3$): δ=6.34 (t, *J*=2.1 Hz, 2 H), 6.81 (t, *J*=2.1 Hz, 2 H), 7.10 (ddd, *J*=1.8, 7.8, and 7.8 Hz, 1 H), 7.30 (dd, *J*=1.8 and 7.8 Hz, 1 H), 7.41 (ddd, *J*=1.3, 7.8, and 7.8 Hz, 1 H), 7.94 ppm (dd, *J*=1.3 and 7.8 Hz, 1 H); ^{13}C NMR (CDCl$_3$): δ=96.0, 109.3 (2 C), 122.3 (2 C), 128.2, 129.1, 129.5, 140.1, 144.1 ppm. These values are consistent with the literature.[34]

Bis(2,2,6,6-tetramethylpiperidino)zinc: To a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (1.0 mL, 6.0 mmol) were successively added BuLi (2.0 M solution in cyclohexane, 6.0 mmol) and ZnCl$_2$•TMEDA (0.76 g, 3.0 mmol). After addition of THF (10 mL), the mixture was stirred for 15 min at 0 °C. ^{13}C NMR (C$_6$D$_6$): δ=19.5 (2 C), 36.7 (8 C), 39.5 (4 C), 53.0 ppm (4 C).

Metalation procedure by using LiTMP: To a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.35 mL, 2.0 mmol) in hexane (5 mL) were successively added BuLi (1.6 M hexanes solution, 2.0 mmol) and TMEDA (1.5 mL, 10 mmol). The mixture was stirred for 15 min at 0 °C before introduction of *N*-phenylpyrrole (**1**, 0.29 g, 2.0 mmol). After 2 h at room temperature, a solution of I$_2$ (0.51 g, 2.0 mmol) in THF (5 mL) was added. The mixture was stirred overnight before addition of an aqueous saturated solution of Na$_2$S$_2$O$_3$ (2 mL) and extraction with EtOAc (3×15 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated under reduced pressure. A **1**/**2** ratio of 80:20 was estimated from the integration values of the crude reaction mixture ^{1}H NMR spectrum.

Crystallography: Crystals of **5** were obtained according to the metalation procedure, but by using cyclohexane instead of hexane, and with an additional amount of THF (10 mL). Single crystals suitable for X-ray diffraction were grown after storage for several days at 4 °C. ^{1}H NMR (C$_6$D$_6$): δ=1.90 (brs, 16 H), 6.36 (m, 2 H), 6.50 (t, *J*=2.8 Hz, 2 H), 7.10 (m, 8 H), 7.74 ppm (d, *J*=7.8 Hz, 4 H); ^{13}C NMR (C$_6$D$_6$): δ=111.0 (2 C), 120.4 (2 C), 121.3 (2 C), 124.0 (4 C), 124.5 (2 C), 129.5 (4 C), 140.6 (2 C), 147.0 ppm (2 C).

X-ray diffraction data were collected at $T=100(2)$ K by using an APEX-II Bruker-AXS diffractometer, with $Mo_{K\alpha}$ radiation ($\lambda=0.71073$ Å).

Crystal data for **5**: $C_{26}H_{32}N_4Zn$, $M_r=465.93$, monoclinic, space group $P2_1/n$, $a=9.6568(8)$, $b=11.4667(12)$, $c=21.055(2)$ Å, $\beta=95.030(3)°$, $V=2322.5(4)$ Å^3, $Z=4$, $\rho_{calcd}=1.333\,g\,cm^{-3}$, $\mu=1.078\,mm^{-1}$. The structure was solved by direct methods by using the SIR97 program,[35] and was then refined with full-matrix least-square methods based on F^2 (SHELX-97)[36] with the aid of the WINGX[37] program. All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were finally included in their calculated positions. A final refinement on F^2 with 5251 unique intensities (3372 data $>2\sigma$) and 280 parameters converged at $R(F, F^2>2\sigma(F^2))=0.0478$, $R(F, \text{all data})=0.0911$, $R_w(F^2, F^2>2\sigma(F^2))=0.0833$, $R_w(F^2, \text{all data})=0.0930$, $S=0.952$.

CCDC-643584 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Computations: All the calculations were carried out by using the Gaussian 03 program package.[38] The molecular structures and harmonic vibrational frequencies were obtained by using the second-order Møller–Plesset perturbation theory (MP2).[28] We used the Ahlrichs[39] SVP all-electron basis set for the Zn 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 were characterized by normal coordinate analysis at the same level of theory (the number of imaginary frequencies, NIMAG, was 0 for minima and 1 for TSs). All the transition-state structures and the reaction coordinates (Hessian eigenvectors with negative eigenvalues) were examined visually. The intrinsic reaction coordinate (IRC) method[40] was used to track minimum energy paths from transition structures to the corresponding local minima.

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