

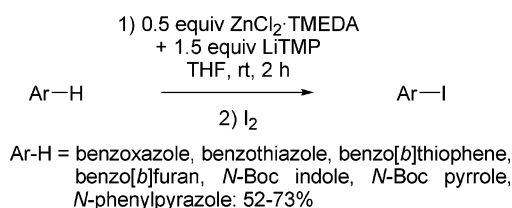
## Deprotonative Metalation of Five-Membered Aromatic Heterocycles Using Mixed Lithium–Zinc Species

Jean-Martial L'Helgoual'ch,<sup>†</sup> Anne Seggio,<sup>†</sup> Floris Chevallier,<sup>†</sup> Mitsuhiro Yonehara,<sup>‡</sup>  
Erwann Jeanneau,<sup>§</sup> Masanobu Uchiyama,<sup>\*,‡</sup> and Florence Mongin<sup>\*,†</sup>

*Synthèse et ElectroSynthèse Organiques, UMR 6510 CNRS, Université de Rennes 1, Bâtiment 10A, Case 1003, Campus Scientifique de Beaulieu, 35042 Rennes, France, The Institute of Physical and Chemical Research, RIKEN, 2-1 Hirosawa, Wako-shi, Saitama 351-0198, Japan, and Centre de Diffraction Henri Longchambon, Université Claude Bernard Lyon 1, 69622 Villeurbanne, France*

florence.mongin@univ-rennes1.fr; uchi\_yama@riken.jp

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Deprotonation of benzoxazole, benzothiazole, benzo[*b*]thiophene, benzo[*b*]furan, *N*-Boc-protected indole and pyrrole, and *N*-phenylpyrazole using an in situ mixture of ZnCl<sub>2</sub>·TMEDA (0.5 equiv) and lithium 2,2,6,6-tetramethylpiperidide (1.5 equiv) in THF at room temperature is described. The reaction was evidenced by trapping with iodine, regioselectively giving the expected functionalized derivatives in 52–73% yields. A mixture of mono- and disubstituted derivatives was obtained starting from thiazole. Cross-coupling reactions of 2-metalated benzo[*b*]thiophene and benzo[*b*]furan with heteroaromatic chlorides proved possible under palladium catalysis. A reaction pathway where the lithium amide and zinc diamide present in solution behave synergically was proposed for the deprotonation reaction, taking account of NMR and DFT studies carried out on the basic mixture.

### Introduction

Substituted five-membered aromatic heterocycles are structural units present in many natural products and pharmaceutical synthetic intermediates.<sup>1</sup> Among the methods used to functionalize them,<sup>1</sup> deprotonation reactions using lithiated bases have been developed.<sup>2</sup> This methodology often requires low temperatures and cannot be used when reactive functional groups are present. In addition, unlike organoboron, organotin, organozinc, and organomagnesium compounds, organolithiums can hardly be involved in cross-coupling reactions.<sup>3</sup> Organomagnesium compounds have been prepared by deprotonation at higher

temperatures.<sup>4</sup> Nevertheless, because of the limited reactivity of the magnesium amide or diamide used to deprotonate functionalized substrates, an excess has, in general, to be employed to ensure good yields.<sup>5</sup> In addition, even if the use of mixed lithium–magnesium amides seems more promising,<sup>6</sup> it is still not extendable to very sensitive substrates.

The deprotonation reactions of sensitive aromatics such as alkyl benzoates, ethyl thiophenecarboxylates, ethyl 2-furancarboxylate, pyridine, quinoline, and isoquinoline using <sup>t</sup>Bu<sub>2</sub>Zn-

<sup>†</sup> Université de Rennes 1.

<sup>‡</sup> RIKEN.

<sup>§</sup> Université Claude Bernard Lyon 1.

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(TMP)Li (TMP = 2,2,6,6-tetramethylpiperidino) as a base were first described in 1999.<sup>7</sup> More recently, the use of the aluminum ate base <sup>t</sup>Bu<sub>3</sub>Al(TMP)Li and the copper ate bases R(TMP)Cu-(CN)Li<sub>2</sub> (R = alkyl, aryl, or TMP) has been developed in order to generate functionalized aromatic compounds including heterocycles.<sup>8</sup> The reactions performed in tetrahydrofuran (THF) proved to be chemoselective, but require 1 or 2 equiv of base.<sup>9</sup>

Several examples of deprotonation using lithium amidozincates in hexane have been reported by Mulvey since 2005.<sup>10</sup> The term *alkali-metal-mediated zincation* has been introduced to depict these reactions because the reactivity (“synergy”) exhibited by the zincates cannot be attained by the homometallic compounds on their own.<sup>11</sup>

Herein, we report a new chemoselective deprotonation tool for regiocontrolled functionalization of five-membered aromatic heterocycles using a basic mixture obtained from a lithium base and TMEDA-chelated zinc chloride.

## Results and Discussion

To develop new chemoselective deprotonation reactions of five-membered aromatic heterocycles, our approach capitalizes on the high chemoselectivity of organozincate reagents, which allows flexible design and fine-tuning by modifying the ligation environment. In the initial screening of suitable zincates, benzoxazole (**1**) was selected as a model substrate because this substrate can be readily metalated by alkyllithiums, but the 2-lithiated species is well-known to be in equilibrium with the

corresponding lithium phenolate, even at extremely low temperature.<sup>12</sup> We therefore focused on the stability of intermediary aromatic zincates (relative to their lithium analogues), which is well-known to prevent subsequent rearrangement<sup>13</sup> or side reactions.<sup>14</sup> We assumed that it might allow the regioselective zincation of five-membered aromatic heterocycles and the isolation of 2-zincate intermediates without any successive side reactions.

Previous NMR studies on 2-metallobenzoxazole have shown the equilibrium was completely on the side of the open isomer with lithium, whereas transmetalation to the organozinc derivative favored the ring closure.<sup>15</sup> Then, we performed a preliminary DFT study on the stability of 2-metallobenzoxazoles and their rearrangement pathways by means of the B3LYP/6-31+G\* method. Figure 1 shows the energy changes for each path and the geometries of the transition states, intermediates, and products. While the transition state (TS) and the product (PD) of 2-lithio derivatives were kinetically and thermodynamically stable, those of the 2-zincio compounds were found to be more unstable compared with 2-zincio reactant (RT), which was consistent with the experimental observations. These big energetic changes by the difference of metal species prompted us to further survey whether the zincate bases could be used for chemoselective metalation of aromatic heterocycles.

The deprotonation reaction of **1** was then examined using various zincate reagents (Table 1). The addition of 1 molar equiv (per lithium) of TMEDA or THF to a bulk nonpolar hydrocarbon in order to increase the opportunity for crystal growth proved to favor the deprotonation reactions of *N,N*-diisopropylcarboxamide<sup>10b,c</sup> and anisole<sup>10d</sup> using lithium amidozincates. We therefore decided to prepare bases from ZnCl<sub>2</sub>·TMEDA,<sup>16</sup> much less hygroscopic than ZnCl<sub>2</sub>, and 3 (or 4) equiv of alkyllithium or lithium dialkylamide and to study their ability to deprotonate benzoxazole (**1**) (Table 1).

The first experiments were carried out with bases obtained by mixing 1 equiv of ZnCl<sub>2</sub>·TMEDA and 3 equiv of methyl- or butyllithium and were assumed to be lithium trimethylzincate and lithium tributylzincate, respectively.<sup>17</sup> When used in THF at room temperature for 2 h, these mixed Li–Zn compounds hardly metalated benzoxazole (**1**), giving the 2-substituted derivative **2** in low yields of 28 and 10%, respectively, after trapping with iodine (entries 1 and 2). Since dilithium tetraalkylzincates have been shown to exhibit a reactivity higher than that of lithium trialkylzincates in various reactions including halogen–metal exchange,<sup>18</sup> we decided to use 4 equiv of

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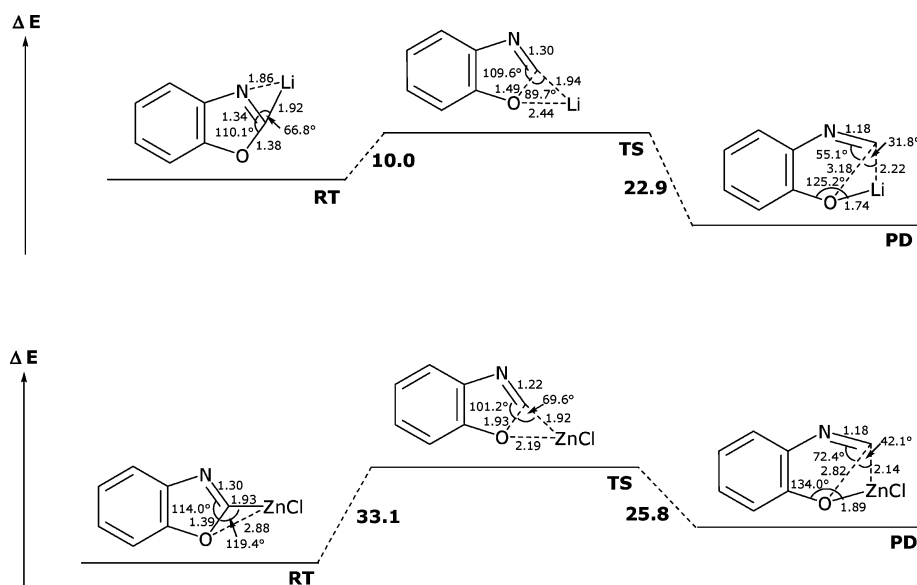
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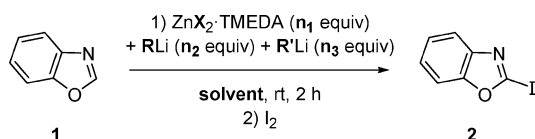
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**FIGURE 1.** Calculated structures for the reactants, transition states and products, and energy changes. Bond lengths and energy changes at the B3LYP/6-31+G\* level are shown in Å and kcal/mol, respectively.

**TABLE 1.** Deprotonation of Benzoxazole (**1**) Using in situ Prepared Mixtures of  $\text{ZnX}_2 \cdot \text{TMEDA}$  and 3 (or 4) equiv of Alkylolithium or Lithium Dialkylamide



entry	X	$n_1$	R	$n_2$	R'	$n_3$	solvent	yield (%)
1	Cl	1.0	Me	3.0			THF	28
2	Cl	1.0	Bu	3.0			THF	10
3	Cl	1.0	Bu	4.0			THF	32
4	Cl	1.0	Bu	2.0	TMP	1.0	THF	35
5	Cl	1.0	<sup>t</sup> Bu	2.0	TMP	1.0	THF	38
6	Cl	1.0	Me	2.0	TMP	1.0	THF	44
7	Cl	0.50	TMP	1.5			THF	57
8	Cl	0.33	TMP	1.0			THF	60
9	Cl	0.40	TMP	1.2			THF	55
10	Cl	0.40	TMP	1.2			hexane	55
11	Br	0.33	TMP	1.0			THF	58

butyllithium instead of 3. Admittedly, the yield was higher using 4 equiv (32%, entry 3) instead of 3 but was still low. Considering the preference for dialkylamino over alkyl transfer in THF,<sup>7d</sup> we then decided to replace one of the butyl groups with a TMP. The heteroleptic base was prepared by successively adding 2 equiv of butyllithium and 1 equiv of LiTMP to a solution of  $\text{ZnCl}_2 \cdot \text{TMEDA}$ . Since the base prepared similarly by successively adding 2 equiv of *tert*-butyllithium and 1 equiv of LiTMP to a solution of  $\text{ZnCl}_2$  in THF proved to be  ${}^t\text{Bu}_2\text{Zn}(\text{TMP})\text{Li}$ ,<sup>7d</sup> we assumed the base we prepared was a zincate.<sup>19</sup> Using the latter (1 equiv) in THF at room temperature for 2 h to metalate benzoxazole (**1**) resulted in a moderate 35% yield of the iodide **2** after interception with iodine (entry 4). Similar bases were prepared by replacing butyllithium with either *sec*-butyllithium (entry 5) or methylolithium (entry 6).<sup>20</sup> Metalation

(19) The base prepared by successively adding 1 equiv of LiTMP and 1 equiv of TMEDA to a solution of dibutylzinc in hexane proved to be  $\text{Bu}_2\text{Zn}(\text{TMP})\text{Li}(\text{TMEDA})$ .<sup>10a</sup>

attempts resulted in slightly improved yields of 38 and 44%, respectively. The moderate 44% yield obtained by employing  $\text{Me}_2\text{Zn}(\text{TMP})\text{Li}$  was partly attributed to the conversion step to the iodo compound **2** and its isolation;<sup>21</sup> indeed, monitoring the reaction by <sup>1</sup>H NMR indicated a complete conversion after 2 h.<sup>22</sup> This result was not satisfying, however, since 1 equiv of zincate is required. It was therefore decided to replace all the alkyl groups with TMP in order to reduce the amount of base. The experiment carried out with 0.5 equiv of  $\text{ZnCl}_2 \cdot \text{TMEDA}$  and 1.5 equiv of LiTMP under the reaction conditions used before furnished the iodide **2** in 57% yield (entry 7). A similar result was obtained using 1/3 equiv of  $\text{ZnCl}_2 \cdot \text{TMEDA}$  and 1 equiv of LiTMP (entry 8, 60% yield), with a <sup>1</sup>H NMR spectrum indicating a 90% conversion after 2 h.<sup>23</sup> Since examples of efficient deprotonation using lithium zincates in hexane have been reported,<sup>10b-d</sup> experiments using hexane instead of THF were performed and ended in similar yields (entries 9 and 10). It was finally decided to see the influence of the zinc source on the result of the reaction. It was found that zinc bromide (entry 11, 58%) and zinc chloride (entry 8, 60%) could be equally employed.

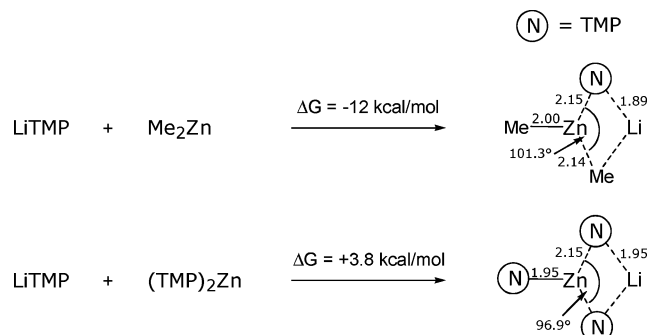
In order to obtain additional information about the active species of a basic mixture obtained from a THF solution of 1/3 equiv of  $\text{ZnCl}_2 \cdot \text{TMEDA}$  and 1 equiv of LiTMP, NMR and DFT studies were then carried out. Since  $(\text{TMP})_2\text{Zn}$  (1 equiv) and LiTMP (1 equiv) give lower conversions when used separately under the same reaction conditions, both of them play a role in the deprotonation mechanism. However, even if alkali-metal triamidozincates have been evidenced,<sup>24</sup> sterically hindered lithium dialkylamide and diamidozinc (e.g.,  $\text{LiN}(\text{SiMe}_3)_2$  and

(20) The use of *tert*-butyllithium was not attempted. Indeed, it has been shown that methyl and *tert*-butyl groups in  $\text{R}_2\text{Zn}(\text{TMP})\text{Li}$  behave similarly when deprotonation is concerned, with the nature of these dummy ligands on Zn only influencing the stability of the generated metalated substrates.<sup>7c</sup>

(21) Compound **2** rapidly decomposes at room temperature.

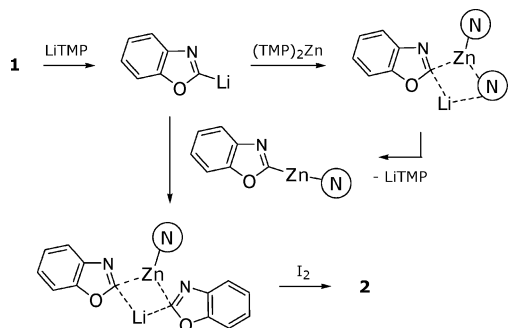
(22) A 90% yield of lithium 2-(isocyno)phenolate was estimated from the NMR spectrum using 1,2-dimethoxyethane as internal standard.

(23) Fifteen and 5% yields of lithium 2-(isocyno)phenolate and benzoxazole, respectively, were estimated from the NMR spectrum using 1,2-dimethoxyethane as internal standard. The 2-zincated species of benzoxazole which form (about 80% yield) are insoluble in the reaction mixture.

**SCHEME 1.** Bond Lengths at the B3LYP/6-31G\* Level are Shown in Angstroms

$\text{Zn}[\text{N}(\text{SiMe}_3)_2]_2$  rarely stabilize as a lithium triamidozincate.<sup>25</sup> In addition, the in situ prepared 1:3 mixture of  $\text{ZnCl}_2 \cdot \text{TMEDA}$  and LiTMP in THF was studied by NMR, and the analysis of the  $^{13}\text{C}$  spectra revealed that the main species in solution were LiTMP and  $(\text{TMP})_2\text{Zn}$ .<sup>26</sup> This was confirmed by the B3LYP-calculated equilibrium between LiTMP and  $(\text{TMP})_2\text{Zn}$  on one side and  $(\text{TMP})_3\text{ZnLi}$  on the other side (Scheme 1), which is interestingly in sharp contrast to dialkylamidozincate (TMP-zincates).<sup>7a,d,10a,b</sup>

On this basis, one can assume a reaction pathway where the deprotonation proceeds with LiTMP, and the resultant aryl-lithium intermediate converts smoothly and quickly by in situ trapping with  $(\text{TMP})_2\text{Zn}$  (or  $\text{ArZnTMP}$ ) to the more stabilized arylzinc species, as depicted in Scheme 2. Further studies on a structural study of this basic mixture and a mechanistic investigation of this novel metalation are in progress with the help of ab initio calculations and spectroscopies.<sup>27</sup>

**SCHEME 2.** Proposed Pathway for the Metalation of Benzoxazole (1) Using an in situ Prepared 1:3 Mixture of  $\text{ZnCl}_2 \cdot \text{TMEDA}$  and LiTMP

Having obtained the active species and mechanism that is likely to be experimentally relevant, metalation of other substrates using the in situ prepared mixture of 0.5 equiv of  $\text{ZnCl}_2 \cdot \text{TMEDA}$  and 1.5 equiv of LiTMP was attempted to

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(27) An alternative mechanism is to assume that  $(\text{TMP})_2\text{ZnLi} \cdot \text{TMEDA}$  is the catalytic deprotonating species.<sup>26</sup>

**TABLE 2.** Deprotonation of Five-Membered Aromatic Heterocycles Using the 1:3 in situ Prepared Mixture of  $\text{ZnCl}_2 \cdot \text{TMEDA}$  and LiTMP

Ar—H	1) $\text{ZnCl}_2 \cdot \text{TMEDA}$ (0.5 equiv) + LiTMP (1.5 equiv)		Ar—I
	THF, rt, 2 h		
	2) $\text{I}_2$		
entry	substrate	product(s)	yield (%)
1	1:	2:	57
2	3:	4:	52
3	5:	6:	73
4	7:	8:	69 (64) <sup>a,b</sup>
5	9:	10:	67
6	11:	12:	68
7	13:	14:	56
8	15:	16:	22 (30) <sup>a</sup>
		17:	17 (9) <sup>a</sup>

<sup>a</sup> Using 1/3 equiv of  $\text{ZnCl}_2 \cdot \text{TMEDA}$  and 1 equiv of LiTMP. <sup>b</sup> Lower conversions of 10 and 20% were obtained using  $(\text{TMP})_2\text{Zn}$  (1 equiv) and LiTMP (1 equiv), respectively, under the same reaction conditions.

evaluate the scope of the reaction under the reaction conditions used before (Table 2).

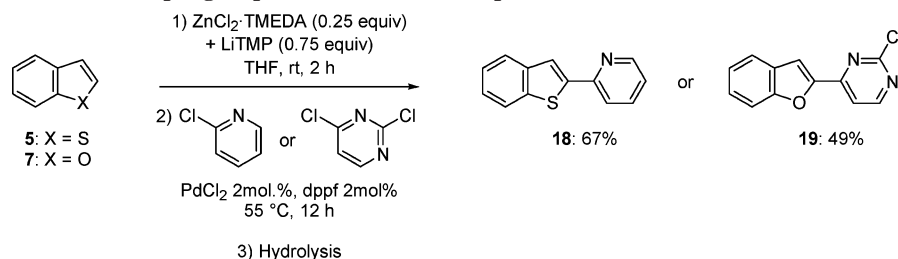
Lithiation of benzothiazole (3) has been reported using phenyl- and butyllithium in ethers at very low temperatures.<sup>28</sup> When treated with the in situ prepared mixture of 0.5 equiv of  $\text{ZnCl}_2 \cdot \text{TMEDA}$  and 1.5 equiv of LiTMP, metalation also occurred at the 2 position, as demonstrated by quenching with iodine to afford the iodide 4 in a medium 52% yield (entry 2).

Benzo[*b*]thiophene (5) can be easily metalated using butyllithium in THF at 0 °C.<sup>29</sup> Our basic mixture furnished after trapping with iodine the expected derivative 6 in 73% yield. A similar result was observed from benzo[*b*]furan (7). The latter has previously been deprotonated using *tert*-butyllithium in diethyl ether at  $-78$  °C.<sup>30</sup> The metalation with the in situ

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SCHEME 3. Metalation/Cross-Coupling Sequences of Benzo[*b*]thiophene (5) and Benzo[*b*]furan (7)

prepared basic mixture was attempted using both 0.5 equiv of  $\text{ZnCl}_2 \cdot \text{TMEDA}$  and 1.5 equiv of LiTMP, and 1/3 equiv of  $\text{ZnCl}_2 \cdot \text{TMEDA}$  and 1 equiv of LiTMP without any important change (69 and 64% yields of **8**, respectively).

We next turned to *N*-Boc-indole (**9**). The lithiation of the latter has been described using *tert*-butyllithium in THF at  $-75$  °C.<sup>31</sup> Our method allowed the metalation to take place at room temperature, with the iodide **10** being isolated in 67% yield. Whereas *tert*-butyllithium proved not suitable, LiTMP can be used at  $-80$  °C in THF for the deprotonation of *N*-Boc-pyrrole (**11**).<sup>31</sup> No degradation was observed using our procedure, and the iodide **12** was given in 68% yield.

1-Phenylpyrazole (**13**) has been metalated using butyllithium at  $-65$  °C.<sup>32</sup> In diethyl ether, substitution occurs in the 5 and 2' positions in a ratio of about 4:1. Reaction carried out at room temperature using 0.5 equiv of  $\text{ZnCl}_2 \cdot \text{TMEDA}$  and 1.5 equiv of LiTMP provided the iodide **14** in 56% yield after electrophilic trapping.

Lithiation of thiazole (**15**) has been reported using butyllithium in diethyl ether at very low temperatures.<sup>28a,33</sup> When treated with a mixture of 0.5 equiv of  $\text{ZnCl}_2 \cdot \text{TMEDA}$  and 1.5 equiv of LiTMP in THF at room temperature for 2 h, both the monoiodide **16** and the diiodide **17** were obtained after interception with iodine (22 and 17%, respectively). Reducing the amount of base to 1/3 equiv of  $\text{ZnCl}_2 \cdot \text{TMEDA}$  and 1 equiv of LiTMP favored formation of the monoiodo derivative **16** (30%) over the diiodo **17** (9%).<sup>34</sup> The formation of dizincated arenes has been recently reported in the course of deprotonation reactions using a zincate: naphthalene was dimetalated at both 2 and 6 positions,<sup>35</sup> and benzene at both 1 and 4 positions,<sup>36</sup> when treated with  ${}^t\text{Bu}_2\text{Zn}(\text{TMP})\text{Na} \cdot \text{TMEDA}$  in hexane. Whereas the generation of dilithiums and disodiums is generally precluded by using a stoichiometric amount of base in a solvent of sufficient polarity such as THF,<sup>37</sup> the dizincated derivatives are still present after long reaction times, a result that could be attributed to their relative stability compared to that of the corresponding bis(alkali metal) compounds.

Subsequent cross-coupling of 2-metalated substrates was then considered in order to get bis(heterocycles). Reactions of

2-deprotonated benzo[*b*]thiophene and benzo[*b*]furan were attempted under palladium catalysis using 1,1'-bis(diphenylphosphino)ferrocene (dppe) as ligand.<sup>38</sup> When the intermediates were subjected to reaction with 2-chloropyridine and 2,4-dichloropyrimidine, respectively, in THF at 55 °C, the bis(heterocycles) **18** and **19** were isolated in 67 and 49% yields (Scheme 3).

## Conclusion

Activation of organometallic compounds in order to get more efficient and chemoselective bases for the deprotonation of sensitive substrates such as aromatic heterocycles is a challenging area. Our approach is based on the synergy exhibited by a mixture of  $(\text{TMP})_2\text{Zn}$  (0.5 equiv) and LiTMP (0.5 equiv), in situ prepared from LiTMP and  $\text{ZnCl}_2 \cdot \text{TMEDA}$  in a 3:1 ratio. The reaction could proceed by metalation with LiTMP, stabilization of the deprotonated aromatic by trapping with  $(\text{TMP})_2\text{Zn}$  (or  $\text{ArZnTMP}$ ), and regeneration of the deprotonating species from sterically congested zincate intermediates. The main advantage of the method developed is the relative stability of the organometallic species formed, allowing cross-coupling reactions to be performed without transmetalation to more stable organometallics. Indeed, whereas hydrogen–lithium exchange of aromatic heterocycles often has to be performed at low temperature in order to prevent side nucleophilic addition, the protocol described here can be conducted at room temperature. The method could find synthetic applications in the deprotonation of aromatic heterocycles including sensitive substrates.<sup>39</sup>

## Experimental Section

**General Procedure 1 for the Deprotonation–Iodination of Heterocycles.** To a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (1.1 mL, 6.0 mmol) in THF (5 mL) were successively added BuLi (about 1.6 M hexanes solution, 6.0 mmol) and, 5 min later,  $\text{ZnCl}_2 \cdot \text{TMEDA}$ <sup>17</sup> (0.50 g, 2.0 mmol). The mixture was stirred for 15 min at 0 °C before introduction of the substrate (4.0 mmol) at 10 °C. After 2 h at room temperature, a solution of  $\text{I}_2$  (1.5 g, 6.0 mmol) in THF (10 mL) was added. The mixture was stirred overnight before addition of an aqueous saturated solution of  $\text{Na}_2\text{S}_2\text{O}_3$  (4 mL) and extraction with EtOAc (3 × 20 mL). The combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure.

**2-Iodobenzoxazole (2).** **2** was obtained according to the general procedure 1 from benzoxazole (**1**, 0.48 g) and isolated after purification by chromatography on silica gel (eluent: heptane/AcOEt 90/10) as a pale yellow powder, which rapidly turns brown upon standing (0.56 g, 57%): mp 86–90 °C (dec); <sup>1</sup>H NMR

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(CDCl<sub>3</sub>)  $\delta$  7.26–7.31 (m, 2H), 7.49–7.53 (m, 1H), 7.65–7.69 (m, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  109.2, 109.9, 118.9, 124.4, 125.1, 142.3, 153.7. These values are consistent with the literature.<sup>40</sup>

**2-Iodobenzothiazole (4).** **4** was obtained according to the general procedure 1 from benzothiazole (**3**, 0.54 g, 0.44 mL) and isolated after purification by chromatography on silica gel (eluent: heptane/AcOEt 80/20) as a yellow powder (0.54 g, 52%): mp 78–82 °C (dec); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.35–7.49 (m, 2H), 7.83–7.87 (m, 1H), 8.01–8.06 (m, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  105.8, 120.6, 122.7, 125.8, 126.5, 139.3, 154.4. These values are consistent with the literature.<sup>41</sup>

**2-Iodobenzo[*b*]thiophene (6).** **6** was obtained according to the general procedure 1 from benzo[*b*]thiophene (**5**, 0.54 g) and isolated after purification by chromatography on silica gel (eluent: heptane) as a pale yellow powder (0.76 g, 73%): mp 64 °C (lit.<sup>42</sup> 64–65 °C); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.41–7.45 (m, 2H), 7.64 (s, 1H), 7.81–7.92 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  79.3, 121.3, 122.4, 124.5, 124.6, 133.9, 140.9, 144.5. These values are consistent with the literature.<sup>43</sup> HRMS: calcd for C<sub>8</sub>H<sub>5</sub>IS (M<sup>+</sup>) 259.9157, found 259.9165. Anal. Calcd for C<sub>8</sub>H<sub>5</sub>IS (260.09): C, 36.94; H, 1.94; S, 12.33. Found: C, 36.90; H, 1.95; S, 12.28.

**2-Iodobenzo[*b*]furan (8).** **8** was obtained according to the general procedure 1 from benzo[*b*]furan (**7**, 0.47 g, 0.44 mL) and isolated after purification by chromatography on silica gel (eluent: heptane) as a yellow oil (0.67 g, 69%): <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  6.96 (s, 1H), 7.20–7.24 (m, 2H), 7.46–7.54 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  96.0, 110.9, 117.3, 119.8, 123.2, 124.3, 129.3, 158.3. These values are consistent with the literature.<sup>44</sup> HRMS: calcd for C<sub>8</sub>H<sub>5</sub>IO (M<sup>+</sup>) 243.9385, found 243.9370.

***N*-Boc-2-iodoindole (10).** **10** was obtained according to the general procedure 1 from *N*-Boc-indole (**9**, 0.87 g, 0.81 mL) and isolated after purification by chromatography on silica gel (eluent: heptane/CH<sub>2</sub>Cl<sub>2</sub> 30/70) as a pale yellow oil (0.94 g, 68%): <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.77 (s, 9H), 7.01 (s, 1H), 7.22–7.30 (m, 2H), 7.48 (dd, 1H, *J* = 7.8 and 2.0 Hz), 8.17 (d, 1H, *J* = 7.2 Hz). These values are consistent with the literature.<sup>45</sup> <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  28.3 (3C), 74.9, 85.2, 115.4, 119.4, 121.9, 122.8, 124.2, 131.1, 137.5, 149.2. HRMS: calcd for C<sub>13</sub>H<sub>14</sub>INO<sub>2</sub> (M<sup>+</sup>) 343.0069, found 343.0070. Anal. Calcd for C<sub>13</sub>H<sub>14</sub>INO<sub>2</sub> (343.16): C, 45.50; H, 4.11; N, 4.08. Found: C, 45.47; H, 4.10; N, 4.16.

***N*-Boc-2-iodopyrrole (12).** **12** was obtained according to the general procedure 1 from *N*-Boc-pyrrole (**11**, 0.67 g, 0.67 mL) and isolated after purification by chromatography on silica gel (eluent: heptane/CH<sub>2</sub>Cl<sub>2</sub> 80/20 to 30/70) as a pale yellow oil (0.79 g, 67%): <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.52 (s, 9H), 6.08 (t, 1H, *J* = 3.4 Hz), 6.43 (dd, 1H, *J* = 3.4 and 1.8 Hz), 7.30 (dd, 1H, *J* = 3.6 and 2.0 Hz). These values are consistent with the literature.<sup>46</sup> <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  27.9 (3C), 63.1, 84.6, 113.5, 124.8, 125.4, 147.9.

**5-Iodo-1-phenylpyrazole (14).**<sup>47</sup> **14** was obtained according to the general procedure 1 from 1-phenylpyrazole (**13**, 0.58 g, 0.53 mL) and isolated after purification by chromatography on silica gel (eluent: heptane) as a pale brown powder (0.60 g, 56%): mp 82–88 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  6.63 (d, 1H, *J* = 1.6 Hz), 7.46–7.51 (m, 5H), 7.69 (d, 1H, *J* = 1.4 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  80.8, 117.6, 126.4 (2C), 128.8, 129.0 (2C), 140.3, 142.8.

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**2-Iodothiazole (16).** **16** was obtained according to the general procedure 1 from thiazole (**15**, 0.34 g, 0.28 mL) and isolated after purification by chromatography on silica gel (eluent: heptane/AcOEt 90/10) as a yellow-orange oil (0.19 g, 22%): <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.34 (d, 1H, *J* = 3.4 Hz), 7.62 (d, 1H, *J* = 3.4 Hz). These values are consistent with the literature.<sup>5f</sup> <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  100.0, 124.8, 144.3. 2,5-Diiodothiazole **17** was isolated similarly as a yellow powder (0.23 g, 17%): mp 106–110 °C (lit.<sup>48</sup> 103–105 °C); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.61 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  74.8, 104.0, 152.9.

**General Procedure 2 for the Deprotonation–Cross-Coupling of Heterocycles.** To a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (1.1 mL, 6.0 mmol) in THF (5 mL) were successively added BuLi (about 1.6 M hexanes solution, 6.0 mmol) and, 5 min later, ZnCl<sub>2</sub>·TMEDA<sup>17</sup> (0.50 g, 2.0 mmol). The mixture was stirred for 15 min at 0 °C before introduction of the substrate (8.0 mmol) at 10 °C. After 2 h at room temperature, the heterocyclic chloride (6.0 mmol), PdCl<sub>2</sub> (28 mg, 0.16 mmol), and dppf (89 mg, 0.16 mmol) were added to the mixture, which was stirred for 12 h at 55 °C. The mixture was cooled before addition of water (0.5 mL) and AcOEt (100 mL), dried over MgSO<sub>4</sub>, and the solvents were removed under reduced pressure.

**2-(2-Benzo[*b*]thienyl)pyridine (18).** **18** was obtained according to the general procedure 2 from benzo[*b*]thiophene (**5**, 1.1 g) and 2-chloropyridine (0.68 g, 0.57 mL) and isolated after purification by chromatography on silica gel (eluent: heptane/CH<sub>2</sub>Cl<sub>2</sub> 50/50 to 30/70) as a white powder (0.85 g, 67%): mp 126 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.21 (m, 1H), 7.36 (m, 2H), 7.73 (td, 1H, *J* = 8.0 and 1.6 Hz), 7.81 (m, 4H), 8.64 (d, 1H, *J* = 5.0 Hz). These values are consistent with the literature.<sup>49</sup> <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  119.6, 121.1, 122.6 (2C), 124.1, 124.5, 125.0, 136.6, 140.5, 140.6, 144.8, 149.7, 152.5.

**4-(2-Benzo[*b*]furyl)-2-chloropyrimidine (19).** **19** was obtained according to the general procedure 2 from benzo[*b*]furan (**7**, 0.95 g, 0.88 mL) and 2,4-dichloropyrimidine (0.89 g) and isolated after purification by chromatography on silica gel (eluent: CH<sub>2</sub>Cl<sub>2</sub>/MeOH 100/0 to 80/20) as a pale yellow powder (0.68 g, 49%): mp 186 °C; <sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>)  $\delta$  7.37 (br t, 1H, *J* = 7.8 Hz), 7.51 (br t, 1H, *J* = 7.8 Hz), 7.69 (br d, 1H, *J* = 7.8 Hz), 7.82 (br d, 1H, *J* = 7.8 Hz), 7.90 (s, 1H), 7.97 (d, 1H, *J* = 5.2 Hz), 8.86 (d, 1H, *J* = 5.2 Hz). These values are consistent with the literature.<sup>50</sup> <sup>13</sup>C NMR (CD<sub>3</sub>COCD<sub>3</sub>):  $\delta$  110.9, 112.4, 115.4, 123.5, 124.7, 128.1, 128.7, 152.2, 156.5, 158.6, 161.8, 162.1.

**Computations:** All calculations were carried out with the Gaussian 03 program package.<sup>51</sup> The molecular structures and harmonic vibrational frequencies were obtained at the B3LYP<sup>52</sup> level with the basis set of Ahlrichs' SVP all-electron basis set<sup>53</sup>

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for Zn<sup>54</sup> and 6-31+G\*/6-31G\* for the other atoms. 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 (the number of imaginary frequencies, NIMAG, was 0 for minima and 1 for TSs). All of the transition state structures and the reaction coordinates (Hessian eigenvectors with negative eigenvalues) were examined visually. The intrinsic

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reaction coordinate (IRC) method<sup>55</sup> was used to track minimum energy paths from transition structures to the corresponding local minima.

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**Supporting Information Available:** General procedures, Cartesian coordinates, and total electron energies, copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra for compounds **2**, **4**, **6**, **8**, **10**, **12**, **14**, **16**, **17**, **18**, and **19**, as well as X-ray diffraction analysis of compound **17** including ORTEP figure and CIF file. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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