

## TMP–Zincate as Highly Chemoselective Base for Directed Ortho Metalation

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Since the pioneering work by Gilman and Wittig,<sup>1</sup> the directed ortho metalation reaction has been widely used as a powerful and efficient method for regioselective functionalization of aromatic compounds.<sup>2</sup> Various directing groups have been employed for facilitating the deprotonation of arenes, and various strong bases such as alkyllithiums or lithium dialkylamides have been employed. The ester group has been regarded as an important and attractive directing group; however, use has been limited because the deprotonation requires strictly controlled reaction conditions due to the instability of intermediary aryllithium species with the ester functionality. To develop a new chemoselective deprotonation of functionalized arenes, we investigated the chemoselective formation of arylzincates using newly developed lithium di-*tert*-butyltetramethylpiperidinozincate (TMP–zincate) as a base. The ortho metalation of alkyl benzoates and direct  $\alpha$ -metalation of  $\pi$ -deficient aza-aromatics proceeded smoothly at room temperature to give the corresponding arylzincates and heteroarylzincates which reacted with electrophiles.

Among various organometallics, organozinc reagents have been widely used as soft nucleophilic reagents in organic synthesis, and organozinc reagents with functional groups were successfully prepared by oxidative addition of organic halides to zinc metal activated by various methods.<sup>3</sup> We recently reported that lithium trialkylzincates<sup>4</sup> can be used as chemoselective metalating reagents for the halogen–metal exchange reaction of aryl halides with electrophilic functional groups.<sup>5</sup> The arylzincates with ester groups are considered to be more stable than ester-containing aryllithiums, and self-condensation of the arylmetal species can be minimized. Especially, lithium tri-*tert*-butylzincate was found to be the practically useful metalating agent because the *tert*-butyl group in the triorganozincates was found to be behind any other organic groups in the migratory preference.<sup>5b</sup>

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Lithium tetramethylpiperidine has been used for directed ortho lithiation of arylcarboxylic esters; however, unwanted condensation reactions between the aryllithium and electrophilic directing groups have been known to occur during the metalation.<sup>6</sup> In situ trapping of the aryllithium by electrophiles during the deprotonation of the arylcarboxylic esters has been reported; however, the bulkiness of the ester group is essential for the successful deprotonation—in situ trapping.<sup>7</sup>

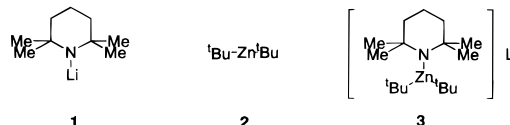
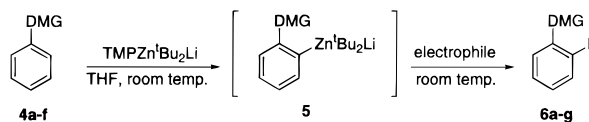


Figure 1.

To develop a new chemoselective metalating reagent, we investigated the novel deprotonative zincation of functionalized aromatics and heteroaromatics using TMP–zincate. TMP–zincate **3** was prepared by adding di-*tert*-butylzinc **2** to the solution of lithium tetramethylpiperidine **1** in THF at  $-78$  °C, and the complex solution was allowed to warm to room temperature (Figure 1). From our preliminary <sup>13</sup>C NMR study, the complex **3** showed different signals in the spectra from that of lithium tetramethylpiperidine **1** or di-*tert*-butylzinc **2** (*t*-BuLi + ZnCl<sub>2</sub>), suggesting the formation of the new ate complex.<sup>8</sup> No decomposition was observed judging from the spectra after several hours at room temperature.

### Scheme 1



The ortho metalation of arenes with directed metalating groups was examined using this complex solution. First, the reaction of various alkyl benzoates with TMP–zincate **3** was investigated, the metalation was found to proceed smoothly at room temperature, and the arylzincates thus prepared were treated with I<sub>2</sub> to give iodobenzoates **6a–d** in excellent yields respectively (Table 1, entry 1–4). Stepwise treatment of alkyl benzoates with lithium tetramethylpiperidine **1** followed by the addition of di-*tert*-butylzinc **2** was examined to be ineffective for the formation of the arylzincates, and the precomplexation of the reactants **1** and **2** is essential for the successful metalation. *N,N*-Diisopropyl benzamide **4e** was also metalated, and the subsequent treatment with I<sub>2</sub> gave the iodide **6e** (Table 1, entry 5). The cyano group also worked well as an excellent directing group, and the metalation proceeded smoothly. The arylzincate was trapped with I<sub>2</sub> or benzaldehyde to give iodide **6f** or alcohol **6g** in excellent yield respectively (Table 1, entry 6,7).

The arylzincate derived from ethyl benzoate **4b** and TMP–zincate was reacted with iodobenzene and 3-iodopyridine in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> at room temperature for 24 h to give biarylcarboxylates **7a,b** respectively (Scheme 2).

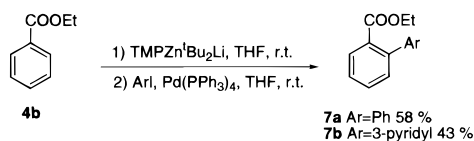
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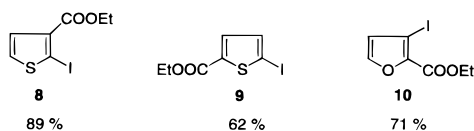
(8) <sup>13</sup>C NMR spectrum of TMP–zincate **3** in THF showed the signal of  $\beta$ -C (<sup>t</sup>Bu) at 36.209 ppm, while the signal of <sup>t</sup>Bu<sub>2</sub>Zn appeared at 31.908 ppm (lit.  $\delta$   $\beta$ -C for <sup>t</sup>Bu<sub>2</sub>Zn 31.03 ppm: Muller, H.; Rosch, L.; Erb, W. *J. Organomet. Chem.* **1977**, *140*, C17–C20.). No shift of the signal was observed by changing the ratio of the reactants.

**Table 1.** Hydrogen–Zinc Exchange Reaction with TMP–Zn<sup>t</sup>Bu<sub>2</sub>Li

entry	substrate	DMG	TMP–Zn <sup>t</sup> Bu <sub>2</sub> Li (equiv)	electrophile	E	product	yield (%)
1	<b>4a</b>	COOMe	2.0	I <sub>2</sub>	I	<b>6a</b>	73
2	<b>4b</b>	COOEt	2.0	I <sub>2</sub>	I	<b>6b</b>	94
3	<b>4c</b>	COO <sup>t</sup> Pr	2.0	I <sub>2</sub>	I	<b>6c</b>	98
4	<b>4d</b>	COO <sup>t</sup> Bu	2.0	I <sub>2</sub>	I	<b>6d</b>	99
5	<b>4e</b>	CON <sup>t</sup> Pr <sub>2</sub>	2.0	I <sub>2</sub>	I	<b>6e</b>	95
6	<b>4f</b>	CN	1.0	I <sub>2</sub>	I	<b>6f</b>	92
7	<b>4f</b>	CN	1.0	PhCHO	CH(OH)Ph	<b>6g</b>	96

**Scheme 2**

Intrigued by the high chemoselectivity of TMP–zincate **3**, we turned our focus to the metalation of various heteroaromatic compounds at diverse positions. Ethyl 3-thiophenecarboxylate was easily metalated at the 2-position with TMP–zincate at room temperature, followed by treatment with I<sub>2</sub> to give 2-iodo derivative **8** in 89% yield, and the similar reaction using ethyl 2-thiophenecarboxylate gave 5-iodo derivative **9** in 62% yield. Ethyl 2-furancarboxylate showed different regioselectivity from that of ethyl 2-thiophenecarboxylate, and 3-iodo derivative **10** was obtained in 71% yield (Figure 2).

**Figure 2.**

$\alpha$ -Metalation of  $\pi$ -deficient heteroaromatic compounds has been investigated in order to seek a more efficient, direct method for introducing functionalities into heteroaromatic rings;<sup>9</sup> however, controlling the reactivity of metal species has been one of the most important and essential issues in this approach.<sup>10</sup> Thus, the direct  $\alpha$ -metalation of  $\pi$ -deficient heteroaromatics using TMP–zincate **3** was considered to be a challenging subject.<sup>11</sup> The  $\alpha$ -metalation of pyridine was found to proceed smoothly at room temperature, and the resulting pyridinylzincate was treated with

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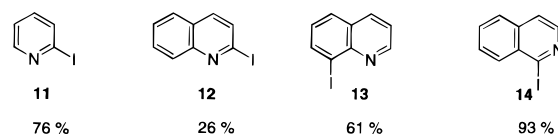
(11) Direct  $\alpha$ -metalation of  $\pi$ -deficient aza-aromatics has been carried out by the activation of substrates using in situ complexation. (a) Taylor, S. L.; Lee, D. Y.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4158–4159. (b) Kessar, S. V.; Singh, P.; Singh, K. N.; Dutt, M. *J. Chem. Soc., Chem. Commun.* **1991**, 570–571. (c) Kessar, S. V.; Singh, P. *Chem. Rev.* **1997**, *97*, 721–737. (d) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1996**, *118*, 1809–1810. (e) Vedejs, E.; Monahan, S. *J. Org. Chem.* **1996**, *61*, 5192–5193.

(12) For the preferential 8-position metalation, see: ref 1 (c) p 265 and ref 9 (b) p 232.

(13) See Supporting Information for in situ FT-IR spectrum of the metalation of **4e** using mesityllithium and TMP–zincate. **4e**:  $\nu$  (C=O) 1636 cm<sup>-1</sup>; Ar–Li:  $\nu$  (C=O) 1578 cm<sup>-1</sup>; Ar–Zn<sup>t</sup>Bu<sub>2</sub>Li:  $\nu$  (C=O) 1594 cm<sup>-1</sup>.

(14) See Supporting Information for <sup>13</sup>C NMR data of the metalated benzamides. Deprotonative zincation of **4e** using TMP–zincate **3** and the halogen–metal exchange reaction of 2-iodo-*N,N*-diisopropylbenzamide using <sup>t</sup>Bu<sub>3</sub>ZnLi gave the similar <sup>13</sup>C NMR spectra.

I<sub>2</sub> to give 2-iodopyridine **11** in 76% yield. Interestingly, quinoline was metalated preferentially at the 8-position, and the treatment with I<sub>2</sub> gave 8-iodoquinoline **13** in 61% yield together with  $\alpha$ -metalated 2-iodoquinoline **12** in 26% yield.<sup>12</sup> Isoquinoline was also easily metalated at the 1-position, and 1-iodoisoquinoline **14** was obtained in 93% yield (Figure 3). To the best of our knowledge, no successful example for the direct  $\alpha$ -lithiation of isoquinoline has been reported due to the formation of the isoquinoline dimer.<sup>10a</sup>

**Figure 3.**

An in situ FT-IR study was performed by using **4e** as the substrate for monitoring the metalation. The zincation of **4e** using TMP–zincate **3** and the lithiation of **4e** using mesityllithium were monitored, and in both cases the absorption due to the carbonyl group gradually decreased and the newly generated red-shifted absorption increased during the course of the metalation.<sup>13</sup> The two metalations showed the different red-shifted values in the spectrum. <sup>13</sup>C NMR data of the metalated benzamides suggest the metal species formed by the deprotonation with TMP–zincate to be the arylzincate.<sup>14</sup> The mechanism for this ortho zincation using TMP–zincate is considered to be more complex than that of the conventional ortho lithiation;<sup>15</sup> however, complex-induced proximity effects<sup>16</sup> should play an important role, and the bimetallic system of TMP–zincate is considered to form an effectively complexed transition state for efficient agostic hydrogen activation.

In summary, the highly chemoselective deprotonative zincation of functionalized aromatic and heteroaromatic compounds was realized using TMP–zincate as a base. Further studies for revealing the scope and limitation of the metalation using TMP–zincate are underway, together with the structural study of TMP–zincate and the mechanistic investigation of the novel metalation.

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**Supporting Information Available:** Representative experimental procedure, spectral data and ATR FT-IR spectra (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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