

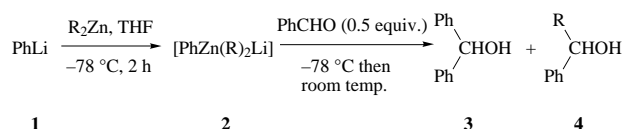
# Lithium tri-*tert*-butylzincate as a chemoselective metallating reagent for functionalized organic halides

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Chemoselective metallation of functionalized organic halides has been performed under mild reaction conditions using a halogen–zinc exchange with lithium tri-*tert*-butylzincate and subsequent transformation of the zincates has been investigated.

Organozinc derivatives have been used as soft and chemoselective reagents in organic synthesis.<sup>1</sup> As a new type of organozinc reagent, organozincates have been regarded as attractive intermediates for carbon–carbon bond formation.<sup>2</sup> We recently reported a novel preparation of functionalized lithium aryldimethylzincates, using a halogen–metal exchange of aryl halides with lithium trimethylzincate, and their reactions with some electrophiles.<sup>3</sup> In connection with our recent studies on chemoselective metallation of functionalized aromatic compounds,<sup>4</sup> we were interested in designing new chemoselective metallating reagents. In order to evaluate the non-transfer ability of alkyl groups, we investigated the migratory aptitude of various alkyl groups from lithium aryldialkylzincates. The *tert*-butyl group turned out to be the best non-transfer group<sup>5</sup> and lithium tri-*tert*-butylzincate<sup>6</sup> (LTBZ) was found to be an effective reagent for the chemoselective halogen–zinc exchange<sup>7</sup> of functionalized organic halides. First, the migratory aptitude of lithium dialkylphenylzincates was investigated as illustrated in Scheme 1. Aryllithium **1** was treated with dialkylzinc to form an ‘ate’



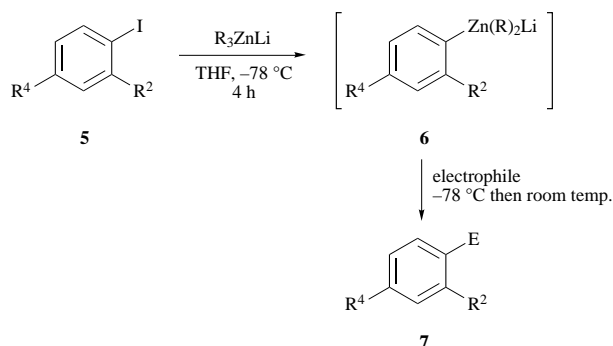
Scheme 1

Table 1 Migratory aptitude of aryldialkylzincates

R	Ratio 3:4
Me	93:7
Bu	21:79
Bu <sup>t</sup>	100:0

complex **2** which was treated with 0.5 equiv. benzaldehyde. The crude mixture of products **3** and **4** was analysed by 300 MHz <sup>1</sup>H NMR spectroscopy to estimate the ratio of **3**:**4**.

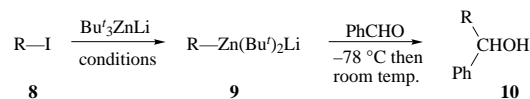
Since the *tert*-butyl group turned out to be the most effective non-transfer alkyl group, the halogen–zinc exchange of functionalized aryl halides with lithium tri-*tert*-butylzincate (LTBZ) was examined. As shown in Scheme 2, the halogen–zinc exchange reaction generally proceeded smoothly and reaction of the arylyzincates with electrophiles also proceeded without transferring the *tert*-butyl group. To demonstrate the compatibility of this reaction with an electrophilic substituent, methyl-4-iodobenzoate **5c** was treated with LTBZ and the zincate was then treated with some electrophiles. 1,2-Addition to benzalde-



Scheme 2

hyde, alkylation with methyl iodide and allylation with allyl iodide gave the expected products **7c,d** and **e** respectively, and acylation with benzoyl chloride proceeded smoothly without a palladium catalyst to give **7f**. Zincation of 2-iodoanisole **5d** with LTBZ followed by treatment with benzaldehyde gave the corresponding alcohol **7g** in excellent yield, whereas the corresponding reaction using lithium trimethylzincate gave **7g** in low yield.

We then investigated the metallation of functionalized alkyl halides to confirm the generality of metallation with LTBZ. Halogen–zinc exchange of primary and secondary alkyl iodides **8a** and **b** with LTBZ proceeded smoothly and the subsequent reaction with benzaldehyde gave the expected alcohols **10a** and **b**. Metallation of alkyl iodides possessing an electrophilic functional group with LTBZ was also shown to be possible through the reaction of iodoacetonitrile **8d** and ethyl iodoacetate **8c** with LTBZ. These functionalized alkylzincates are considered to be synthetically valuable as new entries to Reformatsky<sup>8</sup> type organozinc derivatives.



Scheme 3

In order to investigate further the synthetic potential of this halogen–zinc exchange with LTBZ, transmetalation of lithium di-*tert*-butylphenylzincate with thienylcyanocuprate was examined.<sup>9</sup> As shown in Scheme 4, the phenyl group smoothly underwent 1,4-addition to cyclohex-2-enone to give **11** in the presence of lithium thienylcyanocuprate, while the reaction in the absence of the cuprate was very sluggish.

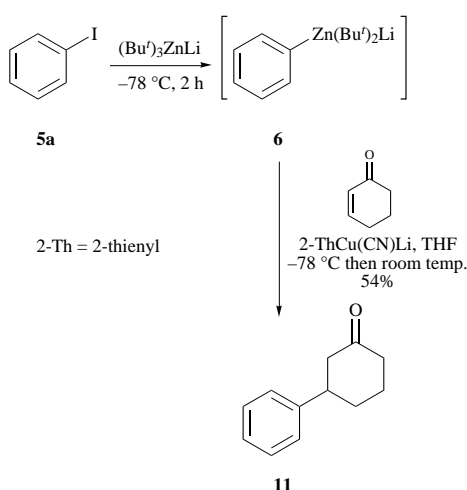
This halogen–zinc exchange is also applicable to the metallation of the corresponding bromides depending to a certain extent on the structure of the substrates and the reaction conditions. Further applications of the metallation with LTBZ for organic synthesis are being developed.

**Table 2** Halogen–zinc exchange of iodobenzenes

Substrate	R <sup>2</sup>	R <sup>4</sup>	R	Electrophile	Product	E	Yield (%)
<b>5a</b>	H	H	Bu <sup>t</sup>	PhCHO	<b>7a</b>	CH(OH)Ph	70
<b>5b</b>	H	OMe	Bu <sup>t</sup>	PhCHO	<b>7b</b>	CH(OH)Ph	67
<b>5c</b>	H	CO <sub>2</sub> Me	Bu <sup>t</sup>	PhCHO	<b>7c</b>	CH(OH)Ph	53
<b>5c</b>	H	CO <sub>2</sub> Me	Bu <sup>t</sup>	MeI	<b>7d</b>	Me	41
<b>5c</b>	H	CO <sub>2</sub> Me	Bu <sup>t</sup>	CH <sub>2</sub> =CHCH <sub>2</sub> I	<b>7e</b>	CH <sub>2</sub> CH=CH <sub>2</sub>	54
<b>5c</b>	H	CO <sub>2</sub> Me	Bu <sup>t</sup>	PhCOCl	<b>7f</b>	COPh	56
<b>5d</b>	OMe	H	Me	PhCHO	<b>7g</b>	CH(OH)Ph	29
<b>5d</b>	OMe	H	Bu <sup>t</sup>	PhCHO	<b>7g</b>	CH(OH)Ph	83

**Table 3** Halogen–zinc exchange of alkyl halides

Substrate	R	Conditions	Product	Yield (%)
<b>8a</b>	Bu	THF, room temp., 3 h	<b>10a</b>	86
<b>8b</b>	Pr <sup>i</sup>	THF, room temp., 3 h	<b>10b</b>	48
<b>8c</b>	CH <sub>2</sub> CO <sub>2</sub> Et	Et <sub>2</sub> O, –78 °C, 3 h	<b>10c</b>	50
<b>8d</b>	CH <sub>2</sub> CN	THF, –78 °C, 3 h	<b>10d</b>	77

**Scheme 4**

## Experimental

### Reaction of methyl 4-iodobenzoate **5c** with LTBZ followed by reaction with benzoyl chloride

Bu<sup>t</sup>Li (1.37 M pentane solution, 3.3 ml, 4.5 mmol) was added to a mixture of dry THF (6 ml) and a solution of ZnCl<sub>2</sub> in dry THF (1 M solution, 1.5 ml, 1.5 mmol) at 0 °C, and the mixture was stirred at 0 °C for 30 min. The mixture was cooled to –78 °C, methyl 4-iodobenzoate (393 mg, 1.5 mmol) was added and the mixture was stirred at –78 °C for 4 h. Benzoyl chloride (633 mg, 4.5 mmol) was added at –78 °C. The mixture was allowed to warm to room temperature gradually during 12 h. The reaction was quenched with aq. NH<sub>4</sub>Cl (2 ml) and then the THF was evaporated *in vacuo*. The residue was diluted with H<sub>2</sub>O (30 ml), and the mixture was extracted with CHCl<sub>3</sub> (30 ml × 3). The organic layer was dried over anhydrous MgSO<sub>4</sub>. After purification on silica gel column chromatography (AcOEt–hexane 1:14), the crude material was recrystallized from AcOEt–hexane to give colourless scales of **7f** (202 mg, 56%); mp 106 °C; δ<sub>H</sub>(300 MHz, CDCl<sub>3</sub>) 8.16 (d, 2 H, *J* 8.0 Hz), 7.79–7.86 (m, 4 H), 7.63 (m, 1 H), 7.51 (m, 2 H), 3.97 (s, 3 H).

## Acknowledgements

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