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Toward a Protecting-Group-Free Halogen−Metal Exchange Reaction: Practical, Chemoselective Metalation of Functionalized Aromatic Halides Using Dianion-type Zincate, $^{t}\text{Bu}_4\text{ZnLi}_2$

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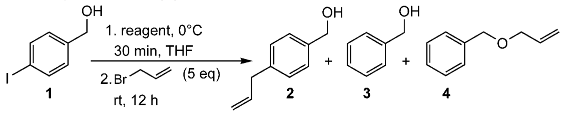
Since the pioneering work by Gilman,[1] the halogen−metal interconversion reaction with the use of alkyllithiums or Grignard reagents has been considered to be an intriguing approach to C−C, C−X, and C−Metal bond formation on aromatic rings in organic synthesis because of the easy procedure, high reactivity, and high regiocontrolability (regioisomeric products are not formed). However, the application of this reaction to the elaboration of complex organic structures is generally limited by low functional group tolerance, significant formation of byproducts, and severe restrictions regarding reaction conditions, particularly, the extremely low temperature and strict exclusion of acidic protons typically required for such reactions. These limitations arise because general organometallics have not only halogen−metal exchange ability but also high nucleophilicity and basicity, and these features have been regarded as difficult or impossible to separate. Thus, the development of a protecting-group-free halogen−metal exchange reaction with high functional group and acidic proton compatibility remains a tremendous challenge in organic and organometallic chemistry.[2]

Our approach capitalizes on the high chemoselectivity of organozincate reagents, which allows flexible design and fine-tuning by modifying the ligation environment.[3] In the initial screening of suitable zincates, *p*-iodobenzyl alcohol (**1**) was selected as a model substrate because it bears an alcoholic proton at the *para* position to the iodine atom, and this proton is well-known to be involved in protonative quenching of the metalation/C−C bond-forming processes even at extremely low temperature.[4] After extensive experimentation, we found that $^{t}\text{Bu}_4\text{ZnLi}_2$ (Table 1, entry 10) metalated **1** smoothly at room temperature. The resultant arylzincate was treated with allyl bromide to give *p*-allylbenzyl alcohol (**2**) in quantitative yield. Stepwise treatments of **1** with alkyllithiums followed by the addition of zinc reagents were examined, but all were ineffective for the formation of the arylzincates. These observations suggest that the complexation of Bu_2Zn and 2 BuLi to form the mixed-metal complex Bu_4ZnLi_2 is a prerequisite for successful metalation.[5] Exchange reactions with the use of other zincates, dialkyl zincs, or alkyllithiums did not proceed selectively, but instead undesired reactions occurred (entries 1−8).

We next confirmed, as shown in Chart 1, that the arylzincate intermediate (**1a**) can be utilized as an aryl anion equivalent without any protection of the OH moiety. The intermediate **1a**, generated by the exchange reaction of **1** with $^{t}\text{Bu}_4\text{ZnLi}_2$, was treated with D_2O or benzaldehyde to give the corresponding product **5** or **6** quantitatively and in 66% yield, respectively. The intermediate **1a** also undergoes copper- and palladium-catalyzed C−C bond-forming reactions, such as alkylation (**7**) and phenylation (**8**), in modest to good yields and with high chemoselectivity. Importantly, extremely low temperature and protection/deprotection processes for the OH moiety are not required in any of these transformations. Consequently, this represents an exceedingly practical method for chemoselective halogen−metal exchange and is an attractive alternative to more traditional metalation/C−C bond-formation procedures.

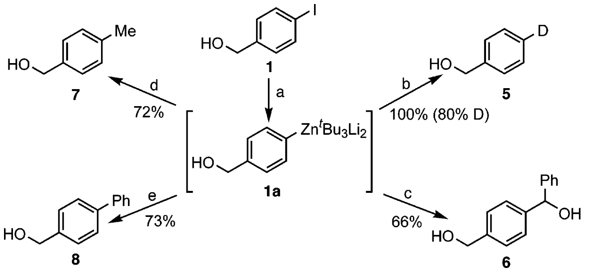
Table 1. Screening of Reagents for Chemoselective Metalation of *p*-Iodobenzyl Alcohol (**1**)



Entry	Reagent (eq)	Yield (%)[a]	Products (%)[b]			Recovery (%)[b]
			2	**3**	**4**	**1**
1/2	^{n}BuLi (1.1/2.2)	67/96	– / –	50/71	17/25	33/4
3/4	^{t}BuLi (1.1/2.2)	54/94	– / –	40/76	14/18	44/3
5	$^{t}\text{Bu}_2\text{Zn}$ (1.1)	0	–	–	–	100
6	Me_3ZnLi (1.1)	0	–	–	–	89
7	Me_4ZnLi_2 (1.1)	13[d]	13	–	–	42
8	$^{n}\text{Bu}_4\text{ZnLi}_2$ (1.1)	93	77	23	–	–
9/10[c]	$^{t}\text{Bu}_4\text{ZnLi}_2$ (1.1/1.1)	70/100	70/100	– / –	– / –	30/ –
11[c]	$^{t}\text{Bu}_3\text{ZnLi}$ (1.1)	64	64	–	–	36

[a] Isolated yield. [b] Determined by ^{1}H NMR. −: Not detected. [c] Performed at room temperature for 2 h. [d] *p*-Methylbenzyl alcohol was also obtained in 29% yield.

Chart 1. Trapping of the Intermediate (**1a**) with Various Electrophiles[a]



[a] Reagents and conditions: (a) $^{t}\text{Bu}_4\text{ZnLi}_2$, THF, rt, 2 h; (b) D_2O, rt, 5 min; (c) PhCHO, rt, 12 h; (d) (2-Thienyl)Cu(CN)Li, MeI, rt, 20 h; (e) 2.5 mol % of $\text{Pd(PPh}_3)_4$, PhI, rt, 18 h.

With optimized conditions in hand, and having confirmed the applicability of the reagent for C−C bond-forming reactions, we studied the scope of this unique metalation reaction. As summarized in Table 2, the protecting-group-free halogen−metal exchange reaction can be extended to a wide variety of substrates. Not only suitably protected alcohols and acetylene, but also a variety of acidic protons (C−H, N−H or O−H), such as a glycerol C2 proton, an amide N−H, and a phenolic OH, are compatible with the reaction (entries 3, 5, and 6).[6] No epimerization at all was observed in entry 3, although epimerization to give racemic mixtures often occurs in base-catalyzed reactions of glycerol derivatives. Moreover, the functional group compatibility of this metalation is also very high because of an organozincate-mediated reaction, and substrates containing polar functional groups, including esters, amides, and TMS, can also be utilized when $^{t}\text{Bu}_4\text{ZnLi}_2$ is employed. Although a methyl ester is generally inconsistent with the halogen−metal exchange

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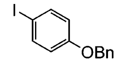
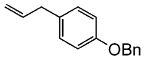
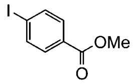
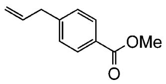
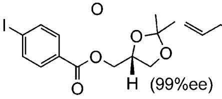
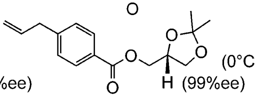
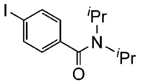
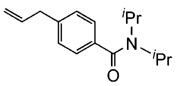
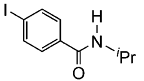
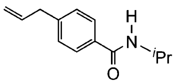
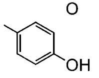
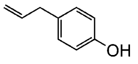
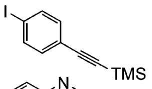
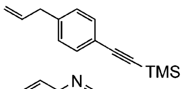
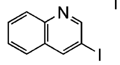
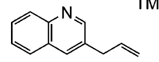
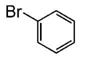
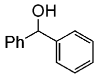
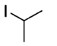
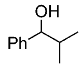
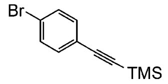
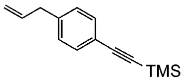
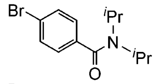
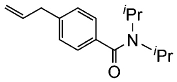
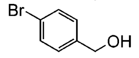
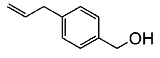
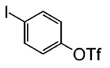
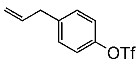
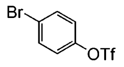
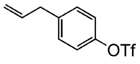
Table 2. Metalation of Various Functionalized Organic Halides[a]

Entry	Substrate	Product	Yield (%)[b] (temp, time, E$^+$)
1			86 (0°C, 2 h, allyl bromide)
2			90 (0°C, 2 h, allyl bromide)
3			74 (0°C, 2 h, allyl bromide)
4			79 (0°C, 2 h, allyl bromide)
5[c]			62 (0°C, 2 h, allyl bromide)
6[c]			79 (40°C, 2 h, allyl bromide)
7			94 (0°C, 2 h, allyl bromide)
8			77 (0°C, 2 h, allyl bromide)
9			72 (60°C, 2 h, PhCHO)
10			62 (0°C, 2 h, PhCHO)
11			98 (60°C, 2 h, allyl bromide)
12			87 (60°C, 2 h, allyl bromide)
13[d]			0 (60°C, 2 h, allyl bromide)
14			87 (0°C, 2 h, allyl bromide)
15			71 (60°C, 2 h, allyl bromide)

[a] Unless otherwise noted, the metalation was carried out using ^{t}Bu$_4$ZnLi$_2$ (1.1 equiv) and substrate (1.0 equiv) in THF under the given conditions, and the resultant metalated intermediate was treated with E$^+$ (allyl bromide or benzaldehyde). [b] Isolated yield. [c] Zincate (2.2 equiv) was used. [d] Benzyl alcohol was obtained as a major product.

reaction,[3f] essentially no side reaction was observed under our reaction conditions, due to the high chemoselectivity of this reagent. A π-deficient heteroaromatic moiety also caused no problem (entry 8).

Other organic halides, including *bromo*benzenes and an *alkyl*-iodide, can be also utilized in the halogen−zinc exchange reaction. Importantly, an iodine moiety is preferable for high chemoselectivity and mild conditions. In the case of bromobenzene derivatives, higher reaction temperatures were required for the exchange reactions to proceed completely. Therefore, in the reaction of *p*-bromobenzyl alcohol with ^{t}Bu$_4$ZnLi$_2$, deprotonation reaction took place prior to bromine−zinc exchange, and the desired C−C bond formation was not observed at all (entry 13).

Finally, to investigate the chemoselectivity of this interconversion, the reactivities of ^{t}Bu$_4$ZnLi$_2$ with aromatic chloride, triflate, and halogen−triflate mixed substrates were examined: aromatic chloride or triflate did not react at all (not shown), and the halogen−zinc exchange reactions turned out to proceed with complete selectivity in iodine(bromine)−triflate mixed substrates (entries 14 and 15).

In conclusion, this report describes a new and highly chemoselective procedure for the halogen−metal exchange reaction of functionalized benzene derivatives containing an ester, amide, or acidic proton. A wide variety of substrates could be readily metalated under mild and operationally simple reaction conditions, and the metalated aromatic intermediates could be utilized effectively for C−C bond formation or transmetalation without any protection. We are continuing work to expand the scope and synthetic utility of this methodology and to elucidate the reaction mechanism and the origin of the unique selectivity with the help of theoretical and spectroscopic studies.

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Supporting Information Available: Experimental procedures and characterizations (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(2) Increasing attention has been devoted to the protecting-group-free synthesis driven by the development of powerful and chemoselective transformations. For example, see: (a) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 15394. (b) Kopp, F.; Krasovskiy, A.; Knochel, P. *Chem. Commun.* **2004**, 2288. (c) Jackson, R. F. W.; Rilatt, I.; Murray, P. J. *Org. Biomol. Chem.* **2004**, *2*, 110.

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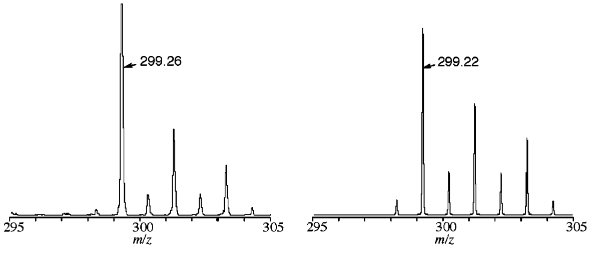
(5) The ^{1}H, ^{13}C, and ^{7}Li NMR spectra of ca. 1.0 M ^{t}Bu$_4$ZnLi$_2$ (prepared by mixing ^{t}Bu$_2$Zn and ^{t}BuLi (2 equiv) in THF) in THF at −100 °C each show only singlets (Supporting Information), indicative of a single species. In all the NMR spectra of ca. 1.0 M ^{t}Bu$_4$ZnLi$_2$ in THF at −100 °C, no signals corresponding to free ^{t}BuLi or ^{t}Bu$_2$Zn were detected. The addition of 1 more equiv of ^{t}BuLi to the ^{t}Bu$_4$ZnLi$_2$ solution showed two signals corresponding to the signal of ^{t}BuLi and that of ^{t}Bu$_4$ZnLi$_2$ at −100 °C. Furthermore, we measured the ESI-MS spectrum of ca. 1.0 M THF solution of the zincate, and the peak ($M^- = 299.26$), which could be attributed to [^{t}Bu$_4$ZnLi]$^-$ (C$_{16}$H$_{27}$ZnLi = 299.22), was clearly observed. The isotopic pattern of this peak was fully consistent with that of [^{t}Bu$_4$ZnLi]$^-$ (C$_{16}$H$_{27}$ZnLi) (see below). In addition, our preliminary density functional theory (DFT) study also suggested that the ate complexation reaction of two molecules of ^{t}BuLi and one molecule of ^{t}Bu$_2$Zn to give ^{t}Bu$_4$ZnLi$_2$ is energetically favored, that is, highly exothermic (38.4 kcal/mol; B3LYP/6-31+G(d) and SVP for Zn).


(a) Observed ESI-MS spectra **(b) Calculated isotropic pattern of [^{t}Bu$_4$ZnLi$_2$]$^-$**

(6) The C−C bond-forming reaction with the use of other zincates or alkyllithiums did not proceed under the same reaction conditions, but instead undesired reactions occurred.

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