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Halogen–Zinc Exchange Reaction of Haloaromatics with Lithium Trimethylzincate

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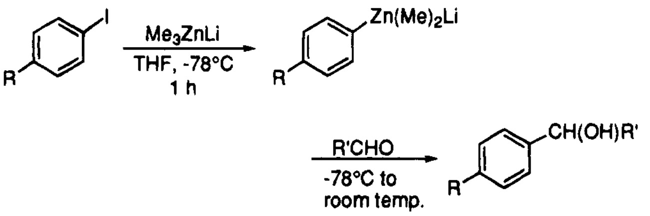
Summary: Lithium aryldimethylzincates were prepared using a halogen–zinc exchange reaction of aromatic halides with lithium trialkylzincates, and the reactions with some electrophiles for the functionalization of aromatic rings were investigated.

Halogen–metal exchange is one of the most useful processes for the preparation of aromatic metal compounds such as lithio[1] and magnesio[2] derivatives. In spite of great potential in synthetic application, use of organometals other than organolithiums and organomagnesiums for the halogen–metal exchange reaction seemed rather limited. In connection with our interest in aromatic and heteroaromatic zinc derivatives,[3] we became interested in the halogen–zinc exchange reaction of aromatic halides with organozinc derivatives. Lithium trialkylzincates (R_3ZnLi) are known as versatile reagents for the 1,4-addition reaction of alkyl groups to α,β-unsaturated ketones;[4] however, lithium aryldimethylzincates are less reactive toward the 1,4-addition reaction[4d] and their synthetic values have been unknown. We wish to report a novel preparation of lithium aryldimethylzincates[5] using halogen–zinc exchange reaction of aromatic halides with lithium trimethylzincate[6] and their reactions with some electrophiles.

First, iodobenzene was treated with lithium trimethylzincate in THF at −78 °C for 1 h followed by the reaction with benzaldehyde to give the 1,2-adduct in 65% yield. Aromatic iodides with a *para*-substituent were examined for the same reaction, and various functional groups were found to be tolarable for the halogen-zinc exchange reaction, and the corresponding 1,2-adducts were obtained in good yields. Especially compatibility with nitro group is noteworthy.[7] The reaction with propionaldehyde was also successful, and the arylzincate from *p*-iodoanisole gave the 1,2-adduct in 66% yield. Aryl bromides were expected to be the substrate for the halogen–zinc exchange reaction; however, the halogen–zinc exchange reaction of methyl *p*-bromobenzoate was sluggish under the same reaction conditions and prolonged reaction time was not effective for the zincate formation.

Scheme 1



R	R'	Yield (%)
H	Ph	65
Me	Ph	62
OMe	Ph	60
OMe	Et	66
COOMe	Ph	74
NO_2	Ph	68

In order to evaluate the reactivity of the lithium aryldimethylzincates prepared by the halogen–zinc exchange reaction, some other electrophiles were allowed to react with the zincate derived from *p*-iodoanisole. The reaction with allyl iodide proceeded to give the allyl derivative in 54% yield. The cross-coupling reaction with iodobenzene in the presence of palladium catalyst also proceeded to give phenylated product in 26% yield, and the details of this coupling reaction are under investigation. The zincate also reacted with benzoyl chloride in the presence of a palladium catalyst to give the ketone in 52% yield.

From the high functional group compatibility in the zincates and the experimental simplicity of this halogen–zinc exchange reaction, the present method seems to have great potential for the selective functionalization of aromatic and heteroaromatic compounds. On the mechanism for this halogen–zinc exchange reaction, similar discussions with halogen–lithium exchange[8] seem to be possible; however, situations might be much more complicated.

Organozinc compounds have been widely used for organic syntheses, and new applications are still the subject of studies by synthetic organic chemists because of their functional group compatibility and chemoselec-

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[5] The methyl group was chosen as the nontransferable group of mixed homozincates because the following reactivity order is known for the 1,4-addition reaction.[4b] $Me_2PhSi \gg CH{=}CH_2 > Et, n\text{-}Bu, i\text{-}Pr > Ph, i\text{-}Bu > t\text{-}Bu, Me \gg t\text{-}BuCH_2$.

[6] Halogen–zinc exchange reactions of vinyl halides and cyclopropyl halides have been reported. (a) Harada, T.; Hara, D.; Hattori, K.; Oku, A. *Tetrahedron Lett.* **1988,** *29,* 3821–3824. (b) Harada, T.; Hattori, K.; Katsuhira, K.; Oku, A. *Tetrahedron Lett.* **1989,** *30,* 6035–6038. (c) Harada, T.; Katsuhira, K.; Hattori, K.; Oku, A. *Tetrahedron Lett.* **1989,** *30,* 6039–6040. (d) Harada, T.; Kotani, Y.; Katsuhira, K.; Oku, A. *Tetrahedron Lett.* **1991,** *32,* 1573–1576. (e) Harada, T.; Katsuhira, K.; Oku, A. *J. Org. Chem.* **1992,** *57,* 5805–5807. (f) Harada, T.; Katsuhira, K.; Hattori, K.; Oku, A. *J. Org. Chem.* **1993,** *58,* 2958–2965. (g) Harada, T.; Katsuhira, K.; Hara, D.; Kotani, Y.; Maejima, K.; Kaji, R.; Oku, A. *J. Org. Chem.* **1993,** *58,* 4897–4907.

[7] Halogen–lithium exchange reaction of halobenzenes with functional groups has been achieved under strictly controlled conditions (−100 °C). *o*-Bromonitrobenzene has been lithiated under such conditions; however, there is no example for the reactions of *p*-halonitrobenzenes. Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982,** *15,* 300–305. Kobrich, G.; Buck, P. *Chem. Ber.* **1970,** *103,* 1412–1419.

[8] Bailey, W. F.; Patricia, J. J. *J Organomet. Chem.* **1988,** *352,* 1–46.

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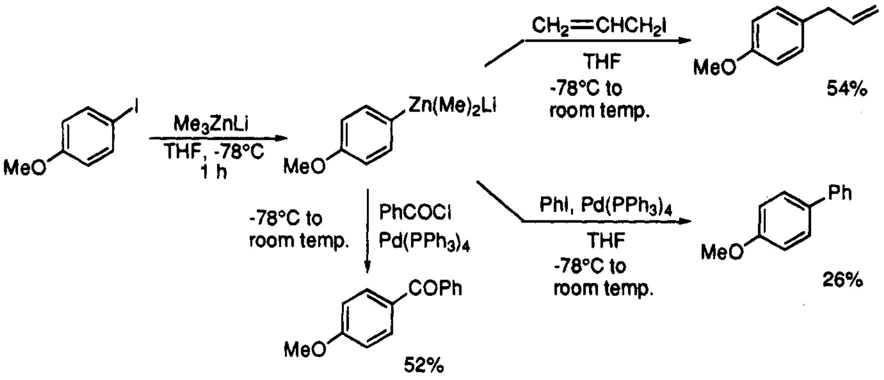
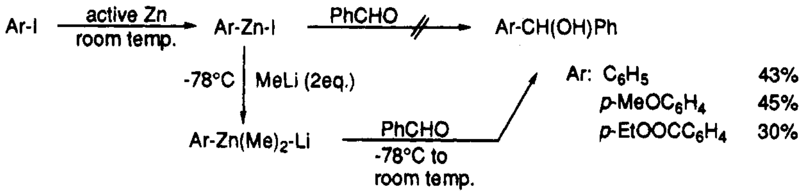
Scheme 2



Scheme 3



tive nature.[9] Knochel[10] and Rieke[11] reported the use of highly active zinc metal for the preparation of arylzinc halides, respectively. Rieke's active zinc allows the preparation of arylzinc halides in mild conditions with the substrates having a functional group such as an alkoxycarbonyl or cyano group. The arylzinc halides have been used for chemoselective carbon–carbon bond formation using transition metals such as Pd or Cu as a mediator;[12] however, examples for the 1,2-addition reaction of arylzinc halides to aldehydes seemed rather limited. During the course of our studies on heteroaromatic zinc derivatives, we realized that the arylzinc halides were unreactive toward 1,2-addition reaction without any additive. We planned the conversion of arylzinc halides into lithium aryldimethylzincates by treating the arylzinc halides with 2 equiv of methyllithium. The zincates showed high reactivity toward 1,2-addition reaction as expected, and alkoxycarbonyl group was compatible in the reaction. However, in comparison with the results of the halogen–zinc exchange reaction using lithium trimethylzincate, yields of 1,2-adducts were not satisfactory and the major problem seemed to be due to the two-step procedure for the preparation of lithium aryldimethylzincates, which involves the uncertain estimation of arylzinc halides formation.

We are continuing our studies for the evaluation of the reactivity of lithium aryldimethylzincates, and further applications for organic syntheses are in progress.

Supplementary Material Available: Representative experimental procedures and spectral data (^{1}H-NMR, mass) (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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