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Non-cryogenic metalation of aryl bromides bearing proton donating groups: formation of a stable magnesio-intermediate

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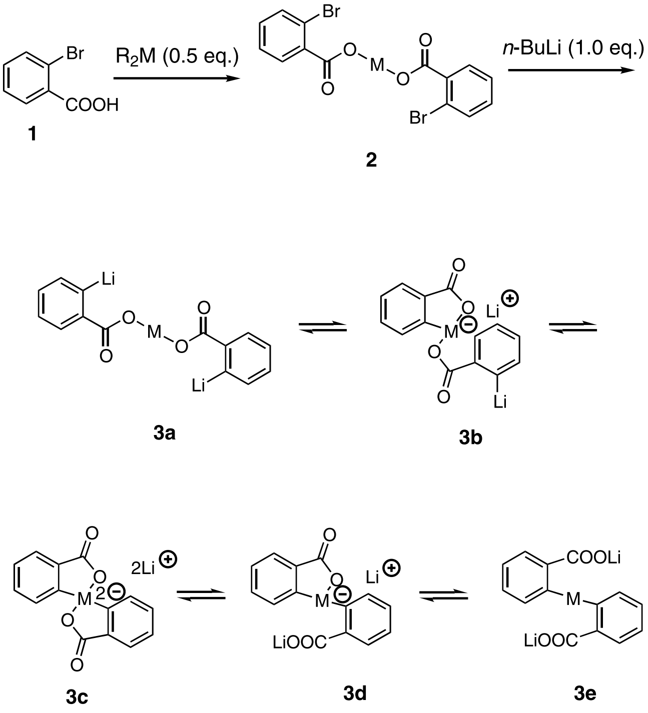
Abstract—Bromine–metal exchange of *o*-bromobenzoic acid (**1**) with Bu_2Mg followed by *n*-BuLi was successfully carried out at non-cryogenic temperature (>–20°C), and gave a stabilized metal species which smoothly reacted with several electrophiles. This methodology expanded to several other bromides bearing proton donating groups (PDGs). © 2002 Elsevier Science Ltd. All rights reserved.

The halogen–metal exchange reaction is a valuable transformation for carbon–carbon bond formation in synthetic organic chemistry.[1] However, this reaction is normally conducted with an alkyllithium reagent at cryogenic temperatures (–78°C) which limits its practicality and economic feasibility for industrial scale operation. Recently, halogen–metal exchange reactions at higher temperature ranges have been developed.[2] (We have also reported that magnesium ate complexes are quite effective for this purpose.[3]) During the course of our ongoing process development efforts, we required a non-cryogenic metalation of *o*-bromobenzoic acid (**1**).[4,5] Although halogen–metal exchange reactions on aryl halides bearing proton donating groups (PDGs) have been successfully conducted with alkyllithiums at –78°C, considerable amounts of the corresponding protonated products are also formed due to intermolecular quenching.[6] Hence, development of new methodology which can simultaneously address these issues was quite desirable. In this article, we wish to report a non-cryogenic metalation of aryl bromides bearing PDGs (which involves formation of a stable magnesium species) and their subsequent reactions with several electrophiles under non-cryogenic temperature (>–20°C).

Our initial concept involved quenching the carboxylic acid with a base to prevent proton transfer and subsequent generation of a stable metalated intermediate that would also have the appropriate reactivity to effect a clean reaction in a higher temperature range.[7]

In this regard, magnesium and zinc organometallic compounds appeared to be the most attractive candidates.[8] Knochel and co-workers have reported that halogen–magnesium exchange reactions are mediated by *i*-PrMgBr or *i*-Pr_2Mg. However, these reagents have been thus far limited to relatively reactive aryl halides such as aryl iodides or electron deficient aryl bromides



Scheme 1.

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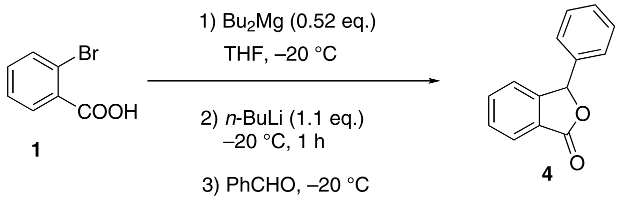
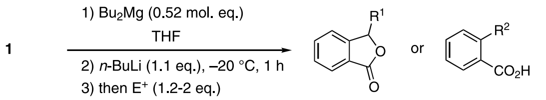
due to sluggish exchange reactions with non-activated aryl halides.[1c] Accordingly, the high reactivity of alkyllithiums is fascinating although the resulting aryllithiums are generally unstable at >–20°C. We envisioned that immediate conversion of an unstable aryllithium, under non-cryogenic conditions, to a stable aryl metal species might address these problems. More specifically, we proposed that treatment of **1** with 0.5 equiv. of a dialkyl metal (M = Mg or Zn) would afford metal dibenzoate **2**, which would then undergo bromine–metal exchange reaction directly with an alkyllithium (or indirectly via an intramolecular ate complex) to immediately form the more stable ate complexes **3b** (via **3a**). Consequently, two C–Mg bonds might be formed via these ate complexes to favorably generate a stable diaryl metal bis-(lithium carboxylate) **3e** (via **3d**) in an equilibrium under non-cryogenic temperatures (or **3b**, **3d** and **3e** might exist as an equilibrium mixture (Scheme 1)).

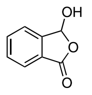
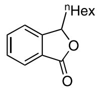
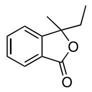
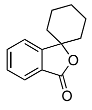
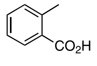
Based on the above hypothesis, **1** was treated with 0.52 equiv. of Bu_2Mg in THF at –20°C to give **2** as colorless precipitates.[9] At this stage, benzoic acid was not detected. To this slurry was added 1.1 equiv. of *n*-BuLi at –20°C and the mixture was aged for 1 h. Finally, addition of benzaldehyde to the resulting yellowish slurry followed by treatment of 2 M hydrochloric acid afforded 3-phenylphthalide (**4**) in 88% yield (Scheme 2). Only a few percent of benzoic acid was observed while a similar reaction with *n*-BuLi (2 equiv.) produced a significant amount of benzoic acid. The metalated intermediate was fairly stable, giving **4** in 70–80% yield even at 0°C or even after aging for 5 h. In contrast, the reaction with 2.2 equiv. of *n*-BuLi in THF at –20°C for 1 h gave **4** in only 11% yield after subsequent addition reaction and lactonization.[4] The halogen–metal exchange with *i*-PrMgCl was not completed even when 3 equiv. of the reagents were used at 20°C.[10] It has not yet been clarified whether some species exist in equilibrium, or not, since all intermediates formed existed as a slurry in THF throughout the reaction. However, it is apparent that this protocol provides a stability–reactivity balanced magnesium species under non-cryogenic conditions.



Scheme 2.

Table 1. Extension to several electrophiles



entry	E$^+$	temp / time[a]	product		yield (%)
1	Me_2NCHO	–20 °C, 2 h		5	72
2	^nHexCHO	–20°C, 1 h		6	89
3	MeCOEt[b]	–20 °C, 2 h		7	65
4	cyclohexanone[b]	–20 °C, 2 h		8	60
5	MeI	20 °C, 5 h		9	69

[a] Temperatures and aging times in reactions with electrophiles.

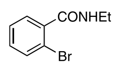
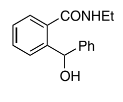
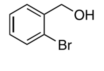
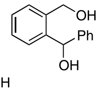
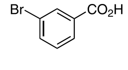
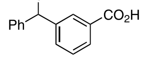
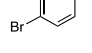
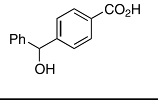
[b] 1.2 equiv. of ketones were used.

Reactions of the magnesio-intermediate generated above with other electrophiles were next examined. The results are summarized in Table 1. Reaction with *N*,*N*-dimethylformamide (entry 1), aldehydes (entry 2) or ketones at –20°C gave the corresponding phthalides in good yields. Slightly lower yields were obtained with 2-butanone and cyclohexanone, probably due to α-proton abstraction of the ketones (entries 3 and 4). Also, considerable amounts (22 and 21% yields) of benzoic acid were produced. Reaction with alkyl halide needed higher temperature. With methyl iodide, *o*-toluic acid was obtained in reasonable yield (entry 5).

We next examined the extension of this protocol to aryl bromides bearing other PDGs. The results are summarized in Table 2. Bromine–metal exchange of *N*-ethyl-*o*-bromobenzamide (**10**) smoothly proceeded at –20°C without any complications (as reported by Beak and co-workers),[6] to furnish the corresponding diaryl-

Table 2. Extension to other aryl bromides bearing proton donating group

$$\text{PDG-Ar-Br} \xrightarrow[\text{2) } n\text{-BuLi (1.1 eq.)} \quad \text{3) then PhCHO (1.5-2.0 eq.), 1 h}]{\text{1) Bu}_2\text{Mg (0.52 mol eq.)} \quad \text{THF}} \text{PDG-Ar-CH(OH)Ph}$$

entry	substrates		temp / time[a]	product		yield (%)
1		10	–20 °C, 1 h		14	58
2		11	0 °C, 2 h		15	89
3		12	–20 °C, 1 h		16	68
4		13	–20 °C, 1 h		17	71

[a] Temperatures and aging times in metalation reactions.

methanol **14** in 58% yield after reaction with benzaldehyde (entry 1).[11] *o*-Bromobenzyl alcohol (**11**), lacking electron withdrawing functionality, also showed good result, but required higher reaction temperature in order to complete the bromine–metal exchange (entry 2). Furthermore, we tried bromine–metal exchanges of *m*- and *p*-bromobenzoic acids (**12** and **13**). Interestingly, both bromine–metal exchanges were successfully carried out at −20°C, giving **16** and **17** in 68 and 71% yields, respectively. Intermolecular stabilization might also be involved in these examples, but would probably be less effective than intramolecular stabilization in comparison with **1**.

In summary, we have developed a novel halogen–metal exchange reaction of aryl bromide bearing PDGs under non-cryogenic conditions. This protocol obviates both intermolecular quenching, observed in reactions with alkyllithiums, and the necessity of cryogenic temperature ranges by providing a stable magnesio-intermediate. In addition, the appropriate reactivity of the metalated intermediate allows one to effect clean subsequent transformations with several electrophiles. This new methodology[12] offers a significant advantage for practical and large-scale synthesis of *ortho*-substituted aryls bearing PDGs.

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2. (a) Trécourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F.; Quéguiner, G. *Tetrahedron Lett.* **1999**, *40*, 4339–4342; (b) Abarbi, M.; Dahmel, F.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 7449–7453; (c) Kitagawa, K.; Inoue, A.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2481–2483; (d) Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 4333–4339.
3. Iida, T.; Wada, T.; Tomimoto, K.; Mase, T. *Tetrahedron Lett.* **2001**, *42*, 4841–4844.
4. Bromine–lithium exchange of **1** with *n*-BuLi at lower temperature than −75°C was well studied by Parham and co-workers, see: Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300–305.
5. *ortho*-Metalation of benzamide with alkyllithium has been conducted at −78°C. This protocol practically has some drawbacks such as tedious amidation/deamidation process and use of *sec*- or *tert*-BuLi (with handling difficulties). Direct metalation of benzoic acid with *sec*-BuLi/TMEDA at −90 to −78°C was also reported, see: Mortier, J.; Moyroud, J.; Bennetau, B.; Cain, P. A. *J. Org. Chem.* **1994**, *59*, 4042–4044. Direct method in a higher temperature range is still to be challenged.
6. (a) Beak, P.; Musick, T. J.; Chen, C.-W. *J. Am. Chem. Soc.* **1988**, *110*, 3538–3542; (b) Beak, P.; Musick, T. J.; Liu, C.; Cooper, T.; Gallagher, D. J. *J. Org. Chem.* **1993**, *58*, 7330–7335.
7. Simple application of our ate complex protocol (Bu_3MgLi) for this case did not work well.
8. $CrCl_3$-mediated additions of the arylzinc compound prepared from methyl *o*-iodobenzoate to aldehydes at room temperature were reported, see: Ogawa, Y.; Saiga, A.; Mori, M.; Shibata, T.; Takagi, K. *J. Org. Chem.* **2000**, *65*, 1031–1036.
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10. 9% of the substrate **1** remained unreacted although 51% of the desired product **4** was obtained.
11. Considerable amount of protonated product (ca. 30%) was formed probably due to incomplete formation of the magnesium salt.
12. Typical experimental procedure: A solution of *o*-bromobenzoic acid (**1**, 1 g, 4.97 mmol) in THF (10 mL) was cooled below −15°C under nitrogen atmosphere, and 1.0 M Bu_2Mg in heptane (2.6 mL, 2.6 mmol, 0.52 equiv.) was slowly added to the solution below −5°C. Then 1.56 M of *n*-BuLi in hexane (3.4 mL, 5.30 mmol, 1.07 equiv.) was slowly added to the slurry below −15°C over 20 min under effective stirring. The solution became viscous slurry during addition of Bu_2Mg and then changed to less viscous yellowish slurry gradually during addition of *n*-BuLi. After stirring below −15°C for 1 h, a solution of benzaldehyde (1.0 mL, 9.84 mmol, 2 equiv.) in heptane (3 mL) was added to the mixture below −15°C. After stirring below −15°C for 1 h, the reaction was quenched with 2 M HCl (10 mL). The resulting mixture was stirred at room temperature overnight. EtOAc (20 mL) was added to the resulting mixture and the mixture was stirred for a few minutes. The organic layer was separated and washed with H_2O (5 mL), 5% aqueous $NaHCO_3$ (10 mL), H_2O (5 mL) and saturated aqueous NaCl (5 mL) successively. After drying over anhydrous Na_2SO_4, the solvent was removed under reduced pressure, and the crude solid thus obtained was purified with silica gel chromatography (Wako gel™ C-300, EtOAc–heptane) to afford 3-phenylphthalide (**4**, 919 mg) as colorless crystals in 88% yield.