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Noncryogenic I/Br−Mg Exchange of Aromatic Halides Bearing Sensitive Functional Groups Using *i*-PrMgCl−Bis[2-(*N*,*N*-dimethylamino)ethyl] Ether Complexes

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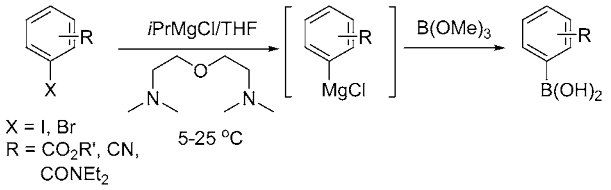
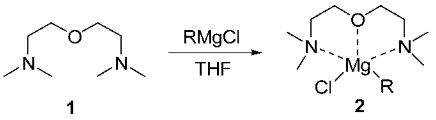
ABSTRACT



Iodo- and bromoaromatics bearing sensitive carboxylic ester and cyano groups underwent a selective halide−magnesium exchange with isopropylmagnesium chloride at ambient temperature in the presence of bis[2-(*N*,*N*-dimethylamino)ethyl] ether to afford the corresponding Grignard reagents. The newly formed reactive Grignard reagents were allowed to react with electrophiles such as trimethylborate to afford arylboronic acids in good to excellent yields.

The halogen−magnesium exchange has provided a general and chemoselective method for the preparation of functionalized arylmagnesium reagents of considerable synthetic utility.[1] This method tolerates a wide range of sensitive functional groups such as ester and cyano groups.[2] However, most iodine−magnesium exchanges are performed under cryogenic conditions (≤20 °C) to suppress the competing side reactions of sensitive functional groups.[3] Recently, we disclosed an efficient synthesis of aryl ketones from aryl acid chlorides and Grignard reagents that involved moderating the reactivity of the organomagnesium reagents by complexation with a simple organic ligand, bis[2-(*N*,*N*-dimethylaminoethyl)] ether (**1**).[4] A possible formation of complex **2** (Scheme 1) by the tridentate interaction between **1** and Grignard reagents deactivates Grignard reagents, therefore, preventing the resulting ketone functionality from attack by

Scheme 1



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[1] For a review, see: Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302.

[2] (a) Knochel, P.; Krasovskiy, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333. (b) Yang, X.; Rotter, T.; Piazza, C.; Knochel, P. *Org. Lett.* **2003**, *5*, 1229. (c) Abarbri, M.; Thibonnet, J.; Bérillon, L.; Dehmel, F.; Rottlander, M.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 4618.

[3] For example, see: (a) Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P.; Krasovskiy, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1701. (b) Jensen, A. E.; Dohle, W.; Sapountzis, I.; Lindsay, D. M.; Vu, V. A.; Knochel, P. *Synthesis* **2002**, 565. (c) Varchi, G.; Ricci, A.; Cahiez, G.; Knochel, P. *Tetrahedron* **2000**, *56*, 2727.

[4] Wang, X.-j.; Zhang, L.; Sun, X.; Xu, Y.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2005**, *7*, 5593.

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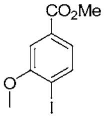
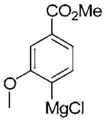
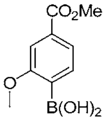
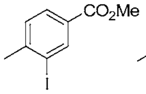
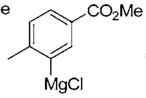
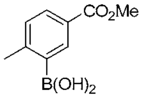
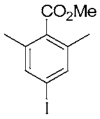
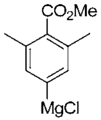
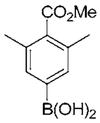
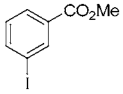
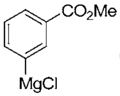
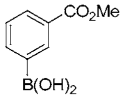
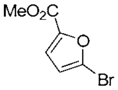
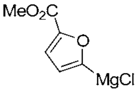
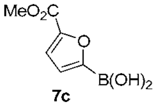
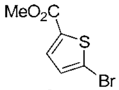
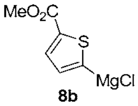
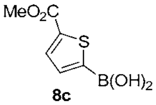
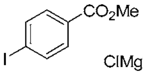
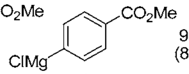
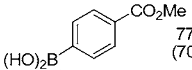
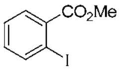
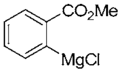
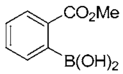
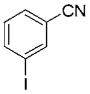
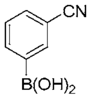
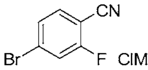
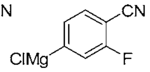
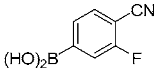
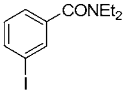
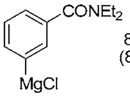
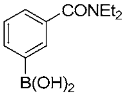
organomagnesium species. Diamines and polyethers have been used to complex Grignard reagents, and the resulting complexes, where Mg coordination ranged from four to six, were characterized spectroscopically and by X-ray crystallography.[5]

Herein, we wish to report application of the concept of moderating the reactivity of Grignard reagents to the halogen−magnesium exchange. Aryl and heteroaryl iodides/bromides containing sensitive ester and cyano groups underwent a mild and selective halogen−magnesium exchange with *i*-PrMgCl in the presence of **1** at ambient temperature, and addition of the newly formed arylmagnesium species to trimethylborate afforded boronic acids in good to excellent yields.

In an initial experiment, 4-iodo-3-methoxybenzoate **3a** was treated with a mixture of isopropylmagnesium chloride (1.2 equiv) and **1** (1.2 equiv) in THF at 22 °C (Table 1). Within 15 min, a complete I−Mg exchange was observed to give arylmagnesium chloride **3b** in a remarkable 95% yield, as indicated by quantitative HPLC analysis of the reaction mixture for the protonated product, ethyl 3-methoxybenzoate. In contrast to this excellent result, in the absence of **1**, the same exchange of **3a** with *i*-PrMgCl (1.2 equiv) at 10−22 °C proceeded to completion in less than 5 min and gave rise to **3b** in only 43% yield, as indicated by quantitative HPLC analysis, along with many unidentified byproducts. In both cases, the resulting arylmagnesium chloride was quenched with trimethylborate to afford boronic acid **3c** in 86% and 28% isolated yields, respectively.[6] Significant improvement was also observed for the I−Mg exchange of other iodobenzoates **4−6a** with *i*-PrMgCl at ambient temperature (Table 1). Generally, the presence of **1** for I−Mg exchange minimized side reactions to give arylmagnesium reagents and subsequent addition products, exemplified as boronic acids in Table 1, in good to excellent yields. The absence of **1** usually gave a moderate yield of arylmagnesium intermediates and a poor isolated yield of the corresponding boronic acids. A similar result was obtained for Br−Mg exchange of electron-deficient bromides **7−8a**. Interestingly, it was found that the absence of **1** for I−Mg exchange of *o*-iodobenzoate **10a** with *i*-PrMgCl at 22 °C afforded arylmagnesium chloride **10b** in 90% yield, a result very similar to the one in the presence of **1**. This excellent chemoselectivity can be explained by a chelation effect of the *ortho*-carbonyl group that facilitates the formation of **10b** and possibly stabilizes it.[7] On the other hand, the absence of **1** for I−Mg exchange of *para*-iodobenzoate **9a**, benzonitriles **11−12a**, and iodobenzamide **13a** gave **9b** and **11−13b** and subsequent boronic acids **9c** and **11−13c** in good to excellent yields, whereas the presence of **1** gave a slightly better or similar result.[8,9]

Table 1. Br or I/Mg Exchange at 10−25 °C in THF Followed by Addition of $B(OMe)_3$

substrate	Grignard[a]	yield[b] (yield)[c]	boronic acid	yield[d] (yield)[e]
 **3a**	 **3b**	95% (43%)	 **3c**	86% (28%)
 **4a**	 **4b**[f]	90% (57%)	 **4c**	71% (42%)
 **5a**	 **5b**[f]	84% (65%)	 **5c**	73% (44%)
 **6a**	 **6b**	87% (61%)	 **6c**	81% (39%)
 **7a**	 **7b**	93% (57%)	 **7c**	77% (28%)
 **8a**	 **8b**	95% (85%)	 **8c**	86% (72%)
 **9a**	 **9b**	96% (87%)	 **9c**	77% (70%)
 **10a**	 **10b**	91% (90%)	 **10c**	75% (74%)
 **11a**	 **11b**	93% (87%)	 **11c**	85% (82%)
 **12a**	 **12b**[f]	90% (87%)	 **12c**	78% (75%)
 **13a**	 **13b**	87% (82%)	 **13c**	76% (69%)

[a] >97% conversion in 15−30 min. Because of the deactivation of *i*-PrMgCl and I/Br−Mg, exchange in the presence of **1** was slower than that in the absence of **1**. [b] Wt % assay of protonated product by HPLC. [c] In the absence of **1**. [d] Isolated yield by crystallization. [e] In the absence of **1**. [f] Reaction run for 2−3 hours in the presence of **1**.

We next studied the stability of magnesium reagents **3b** and **7b** (Table 2). After a complete I/Br−Mg exchange of

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(5) Uhm, H. L. In *Handbook of Grignard Reagents*; Silverman, G. S., Rakita, P. E., Eds.; Marcel Dekker: New York, 1996; p 117.

(6) For synthetic applications of boronic acids, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (c) Suzuki, A. *Pure Appl. Chem.* **1994**, *66*, 213. (d) Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419.

(7) (a) Sapountzis, I.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 1610. (b) Kneisel, F. F.; Knochel, P. *Synlett* **2002**, *11*, 1799.

(8) Varchi, G.; Kofink, C.; Lindsay, D. M.; Ricci, A.; Knochel, P. *Chem. Commun.* **2003**, 396.

Table 2. Stability of the Resulting Organomagnesium Species after Br or I/Mg Exchange at 10−25 °C in THF

entry	substrate[a]	0.2 h	1 h	2 h
1	**3b-1**[b]	95%	89%	88%
2	**3b**[b]	43%	36%	20%
3	**7b-1**[b]	95%	93%	92%
4	**7b**[b]	61%	50%	39%

[a] >98% conversion after 0.2 h. [b] Wt % assay of protonated product by HPLC.

3a and **7a** in 15 min at 22 °C, quantitative HPLC wt % assay indicated about 95% of the resulting **3b** and **7b** in the presence of **1**. After being kept at 22 °C for 2 h, only a slight degradation was observed for both cases. However, significant decomposition of **3b** and **7b** was observed in the absence of **1**. This result suggests that possible tridentate interaction between the resulting **3b**/**7b** after I/Br−Mg exchange and **1** stabilizes these sensitive arylmagnesium reagents.

It was known that I−Mg exchange of iodide **14a** with *i*-PrMgCl at −30 °C produced magnesiated 1,3-oxazin-4-one **14b**.[10] The stability of **14b** was found to be limited with a half-life of ca. 1 h at −30 °C. To further test our conditions, I−Mg exchange of iodide **14a** with *i*-PrMgCl in the presence of **1** was performed. Treatment of **14a** with a slight excess of *i*-PrMgCl−bis[2-(*N*,*N*-dimethylamino)ethyl] ether (**1**) complex in THF at −5 to 0 °C resulted in complete conversion to the corresponding Grignard **14b** in 10 min (Figure 1). Quantitative HPLC analysis indicated only <10% degradation of **14b** when being kept at −5 °C for 1 h. Clearly, the presence of **1** prevented the resulting Grignard **14b** from fast degradation even at higher temperature. As a result, the reaction of the **14b-1** complex with trimethyl borate and benzaldehyde furnished the expected addition products **14c** (70%) and **14d** (62%), respectively.

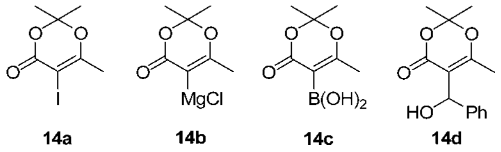

Figure 1.

In summary, we have shown that iodo- and bromoaromatics bearing sensitive ester, cyano, and amide groups can undergo a chemoselective I/Br−Mg exchange with isopropylmagnesium chloride in the presence of bis[2-(*N*,*N*-dimethylaminoethyl)] ether[11] at ambient temperature.[12] Although direct evidence of the interaction between *i*-PrMgCl and **1** postulated here is not yet at hand, this concept of altering the reactivity of Grignard reagents can be utilized in a number of other instances. In this preliminary report, we have shown the application of the new protocol to the preparation of a variety of aryl boronic acids, key reagents for Suzuki coupling reactions.[6]

Supporting Information Available: Spectroscopic data for new compounds **3c**−**8c** and **14c**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL052704P

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(9) The nitro group is generally not compatible under these conditions except for highly electron-deficient aryl iodides such as 2,4-dinitrophenyliodide.[7a]

(10) Vu, V. A.; Bérillon, L.; Knochel, P. *Tetrahedron Lett*. **2001**, *42*, 6847.

(11) Preliminary experiments indicated that TMEDA as an alternative ligand was less effective for this exchange, and *N*-methylmorpholine had no effect at all.

(12) A typical experimental procedure is as follows: To a solution of **1** (0.22 mL, 1.2 mmol) in THF (5 mL) was added isopropylmagnesium chloride (0.60 mL, 1.2 mmol, 2 M solution in THF) at 15 °C. The mixture was stirred at this temperature for 20 min. Methyl 3-methoxy-4-iodobenzoate (290 mg, 1.0 mmol) was added. After the resulting mixture was stirred at 22−25 °C for 10 min, trimethylborate (0.23 mL, 2.0 mmol) was added at 0 °C. The mixture was then quenched with 0.1 N HCl and extracted with EtOAc. The extract was dried over $MgSO_4$ and concentrated. The residue was purified by crystallization in hexane to give **3c** (187 mg, 89%).