ORGANIC LETTERS

2011
Vol. 13, No. 17
4479–4481

Highly Efficient One-Pot Access to Functionalized Arylboronic Acids via Noncryogenic Bromine/Magnesium Exchanges

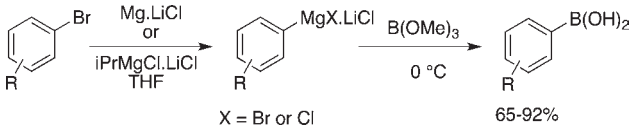
Timo Leermann, Frédéric R. Leroux,* and Françoise Colobert*

Laboratoire de Stéréochimie (UMR CNRS 7509), CNRS/Université de Strasbourg (ECPM), 25 Rue Becquerel, F-67087 Strasbourg, France

francoise.colobert@unistra.fr; frederic.leroux@unistra.fr

Received June 16, 2011

ABSTRACT



A general and convenient protocol for the electrophilic borylation of aryl Grignard reagents prepared from arylbromides by direct insertion of magnesium in the presence of LiCl or by Mg/Br exchange with ^{i}PrMgCl·LiCl has been developed. Various aryl boronic acids were synthesized in a straightforward manner in excellent yields at 0 °C.

The popularity of arylboronic acids in modern synthetic organic chemistry mostly results from their role as cross-coupling partners in a wide range of transition-metal-catalyzed coupling reactions. One of the first and, probably, still the cheapest and most common synthetic methods for the preparation of arylboronic acids remains the reaction of an aryllithium or arylmagnesium intermediate with a trialkylborate at low temperature (typically −78 °C (Li) and up to −10 °C (Mg) followed by an acidic aqueous workup.[1] However, this method has several limitations. The major drawback of the standard reaction protocols is, first, the need for cryogenic conditions[2] during the reaction of the organometallic intermediate with the trialkylborate. The use of cryogenic conditions usually minimizes the formation of borinic acid and borane byproducts, which arise from second and third additions of the aryl metal reagent onto the borate ester. Second, it is difficult to apply this method to substrates bearing functional groups not compatible with organolithium or organomagnesium reagents such as esters and nitriles. Third, some aryllithium intermediates are unstable under noncryogenic conditions, as in the case of many aromatic heterocycles.[3] Alternately, arylboronic esters can be prepared from aryl halides or aryl triflates *via* the more recently developed $PdCl_2$(dppf)-catalyzed borylation with tetra(alkoxy)diboron[4] or with dialkoxyboranes such as pinacolborane.[5] The latter method possesses several advantages. The borylation using pinacolborane is an atom economical approach, tolerating various functional groups, being sensitive to air, moisture, and temperature and mostly chromatography stable.[6] However, they are not suitable for large-scale synthesis because tetraalkoxydiboron and dialkoxyhydroborane are expensive.

In 2006 Senanayake et al. reported on a concept of moderating the reactivity of Grignard reagents, prepared according to a procedure developed by Krasovskiy and

(1) *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine*; Wiley-VCH: Weinheim, 2005.

(2) Brown, H. C.; Cole, T. E. *Organometallics* **1983**, *2*, 1316–1319.

(3) Gilman, H.; Spatz, S. M. *J. Org. Chem.* **1951**, *16*, 1485–1494.

(4) (a) Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447–3450. (b) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508–7510.

(5) (a) Broutin, P.-E.; Cerna, I.; Campaniello, M.; Leroux, F.; Colobert, F. *Org. Lett.* **2004**, *6*, 4419–4422. (b) Baudoin, O.; Guénard, D.; Guéritte, F. *J. Org. Chem.* **2000**, *65*, 9268–9271. (c) Murata, M.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 6458–6459.

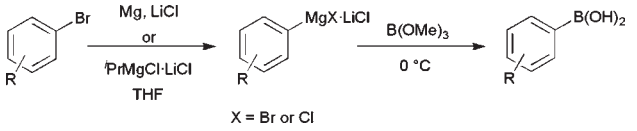
(6) (a) Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 3482–3485. (b) Pereira, S.; Srebnik, M. *Organometallics* **1995**, *14*, 3127–3128. (c) Pereira, S.; Srebnik, M. *J. Am. Chem. Soc.* **1996**, *118*, 909–910. (d) Pereira, S.; Srebnik, M. *Tetrahedron Lett.* **1996**, *37*, 3283–3286. (e) Murata, M.; Watanabe, S.; Masuda, Y. *Tetrahedron Lett.* **1999**, *40*, 2585–2588.

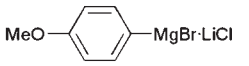
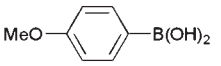
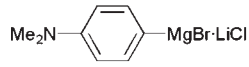
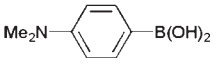
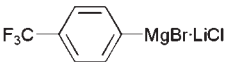
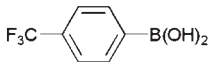
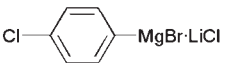
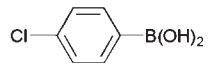
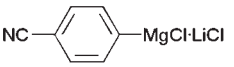
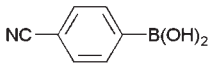
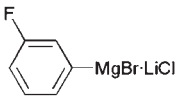
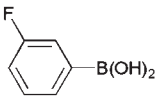
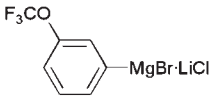
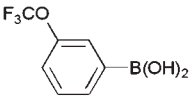
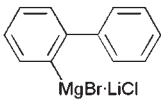
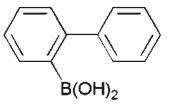
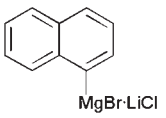
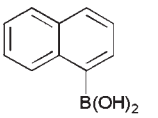
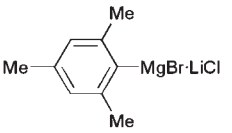
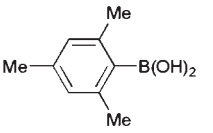
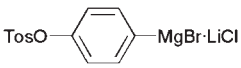
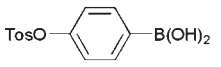
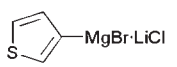
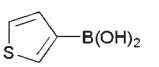
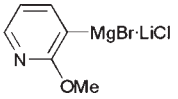
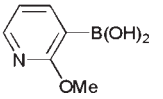
10.1021/ol2016252
Published on Web 08/11/2011

Knochel,[7] using bis[2-(*N*,*N*-dimethylamino)ethyl]ether as a ligand which allowed the reaction of aryl Grignards with trimethylborate at 0 °C to deliver the desired boronic acids after aqueous acidic workup in high yields.[8] However, in most cases the use of expensive aryl iodides has been necessary. In recent years, elegant examples dealing with the development of the LiCl-mediated preparation of Grignard reagents by Knochel and co-workers has been reported[9] where this additive considerably facilitates the insertion of magnesium into various aromatic and heterocyclic bromides. However, its use in the synthesis of aryl or hetaryl boron reagents has, to the best of our knowledge, only once been reported by Kalvins when he improved the synthesis of 3-(1-adamantyl)-4-methoxyphenyl-boronic acid.[10] They observed that the presence of lithium chloride allowed the performance of the reaction between the organomagnesium intermediate and trimethylborate at a temperature between 0 and 5 °C. This result prompted us to investigate the preparation of aryl Grignard reagents starting from cheaper aryl bromides by direct insertion of magnesium into the C–Br bond in the presence of lithium chloride or by Br/Mg exchange with ^{i}PrMgCl·LiCl.

In a first experiment, we converted 1-bromo-4-methoxybenzene by means of a Br–Mg exchange with Mg in the presence of LiCl in THF into the corresponding Grignard reagent. The subsequent addition of 2 equiv of trimethylborate at 0 °C followed by acidic aqueous workup resulted in the formation of the desired boronic acid in 92% yield (Table 1, entry 1). To further investigate the scope of the procedure we have chosen a couple of aryl bromides bearing different electron-donating and -withdrawing substituents. If possible arylmagnesium compounds were prepared by direct insertion of magnesium into the C–Br bond in the presence of LiCl in THF (method A). As shown in Table 1, the reaction of aryl Grignard reagents with trimethylborate in the presence of LiCl at 0 °C gives the desired boronic acids in good yields and therefore has substantial scope. Sterically unhindered substrates such as 4-dimethylamino- (Table 1, entry 2), 4-trifluoromethyl- (Table 1, entry 3), 4-chloro- (Table 1, entry 4), and 4-cyanophenyl magnesium bromides (Table 1, entry 5) were converted with excellent yields into the boronic acids without increased hydrolysis of the Grignard reagents. Only the 4-cyano derivative was converted into the

Table 1. Borylation of Aryl Grignard Reagents in the Presence of LiCl



entry	ArMgX·LiCl	product	yield [%]
1[a]			92
2[a]			82
3[a]			91
4[a]			81
5[b]			72
6[a]			83
7[a]			85
8[a]			89
9[a]			86
10[a]			91
11[a]			74
12[b]			87
13[a]			65

[a] Method A: Direct insertion of Mg into the C–Br bond in the presence of LiCl. [b] Method B: Br/Mg exchange with ^{i}PrMgCl·LiCl.

(7) (a) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333–3336. (b) Krasovskiy, A.; Straub, B. F.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 159–162.

(8) Wang, X. J.; Sun, X.; Zhang, L.; Xu, Y.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2006**, *8*, 305–307.

(9) (a) Piller, F. M.; Metzger, A.; Schade, M. A.; Haag, B. A.; Gavryushin, A.; Knochel, P. *Chem.—Eur. J.* **2009**, *15*, 7192–7202. (b) Knochel, P.; Krasovskiy, A.; Sapountzis, I. In *Handbook of Functionalized Organometallics*; Knochel, P., Ed.; Wiley-VCH: Weinheim, 2005. (c) Piller, F. M.; Appukkuttan, P.; Gavryushin, A.; Helm, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 6802–6806. (d) Yamada, S.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 2215–2218. (e) Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2219–2222. (f) Jensen, A. E.; Dohle, W.; Sapountzis, I.; Lindsay, D. M.; Vu, V. A.; Knochel, P. *Synthesis* **2002**, 565–569. (g) Rottländer, M.; Boymond, L.; Bérillon, L.; Leprêtre, A.; Varchi, G.; Avolio, S.; Laaziri, H.; Knochel, P. *Chem.—Eur. J.* **2000**, *6*, 767–770. (h) Abarbri, M.; Dehmel, F.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 7449–7453. (i) Trécourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F.; Quéguiner, G. *Tetrahedron* **2000**, *56*, 1349–1360. (j) Kitagawa, K.; Inoue, A.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2481–2483. (k) Kopp, F.; Krasovskiy, A.; Knochel, P. *Chem. Commun.* **2004**, 2288–2289.

(10) Tribulovich, V. G.; Garabadzhiu, A. V.; Kalvins, I. *Russ. J. Gen. Chem.* **2010**, *80*, 868–869.

Grignard reagent applying method B, *i.e.*, a Br/Mg exchange with ^{i}PrMgCl·LiCl (Table 1, entry 5). In general the conversion of 4-cyanophenyl bromide into the corresponding Grignard reagent was described by Knochel using methods A and B.[7a,9c] In our case method A was not successful. Beller and co-workers observed the same problem when using magnesium in the presence of LiCl to prepare the Grignard reagent from 4-cyanophenyl bromide.[9e]

Next, we studied 3-substituted derivatives such as 3-fluoro and 3-trifluoromethoxy (Table 1, entries 6 and 7) and could show that the boronic acids were obtained in excellent yields.

All attempts to convert substrates bearing an ester group such as *tert*-butyl 4-bromobenzoate or 4-bromophenyl pivalate into the corresponding Grignard reagents at temperatures between 0 °C and room temperature failed. Knochel and co-workers have observed that bromo-substituted aromatic esters also underwent a magnesium insertion in the presence of LiCl, but that the resulting arylmagnesium compounds decomposed rapidly.[9c] However, as the protocol allows the presence of a cyano group, the latter can be converted later on into an ester functional group.

Sterically hindered substrates such as 2-bromobiphenyl (Table 1, entry 8), 1-bromonaphthalene (Table 1, entry 9), and even bromomesitylene (Table 1, entry 10) can be very efficiently converted into the desired boronic acids applying protocol A.

The procedure was also successfully applied to more sensitive substrates such as a tosylate (Table 1, entry 11), 3-bromothiophene (Table 1, entry 12), and a 3-bromopyridine which afforded all the desired boronic acids in high yields of 74%, 87%, and 65%, respectively.

In summary, we developed a simple and convenient one-pot procedure for converting cheap aromatic bromides into the corresponding boronic acids under noncryogenic conditions. Sterically crowded and electron-rich Grignard reagents were very efficiently prepared and transformed into the corresponding boronic acids which are otherwise difficult to prepare because of the hydrolytic deborylation during acidic aqueous workup. The methodology is very tolerant toward many functional groups; aryl moieties with electron-donating and -withdrawing substituents gave the boronic acids in excellent yields. Even an aryl bromide bearing a sensitive cyano group could be converted into the corresponding boronic acid in good yield.

Acknowledgment. We thank the CNRS and the "Ministère de l'Education Nationale et de la Recherche", France for financial support. T.L. is very grateful to the French Embassy in Germany for a postdoctoral grant.

Supporting Information Available. ^{1}H, ^{13}C, ^{11}B, and ^{19}F NMR spectra of all boronic acids shown in Table 1, as well as detailed descriptions of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.