## Efficient Borylation of Reactive Aryl Halides with MPBH (4,4,6-Trimethyl-1,3,2-dioxaborinane)

Nageswaran PraveenGanesh, Emilien Demory, Christine Gamon, Véronique Blandin, Pierre Y. Chavant\*

Département de Chimie Moléculaire, UMR-5250, ICMG FR-2607, CNRS, Université Joseph Fourier,

BP 53, 38041 Grenoble Cedex 09, France

Fax +33(4)76635983; E-mail: Pierre-Yves.Chavant@ujf-grenoble.fr

Received 27 April 2010

**Abstract:** The combination of 4,4,6-trimethyl-1,3,2-dioxaborinane, a particularly stable and inexpensive borylation reagent, and Buchwald's palladium catalyst provides a simple, fast, cost-effective borylation of electron-rich, reactive iodides, bromides, and triflates to produce stable, easily purified boronic esters.

Key words: boron, palladium, catalysis, arylboronic, Suzuki

The increasing number of applications of the Suzuki-Miyaura coupling prompts the design of efficient and cost-effective methods for the preparation of the arylboronic precursors. Among these, the borylation of aryl halides or triflates with pinacolborane<sup>1</sup> (PinBH) is an excellent alternate to the more classical addition of organometallics to trialkoxyborane. Murata's team<sup>2</sup> and ours<sup>3</sup> proposed the replacement of PinBH in this reaction by the easily accessible, much less expensive, and more conveprepared **MPBH** [4,4,6-trimethyl-1,3,2niently dioxaborinane<sup>4</sup> (1)]. In addition, Billingsley and Buchwald<sup>1i</sup> completed in 2008 the original study of Baudoin et al.<sup>1c</sup> on the very positive role of bulky phosphine ligands in the borylation with PinBH. We wondered if the advantages of both implementations could be combined to provide a convenient and cost-effective access to aryl boronic esters from aryl halides; we discuss herein the advantages and limitations of this system.



Scheme 1 Preparation of MPBH 1. *Reagents and conditions*: dioxane, 20 °C, 30 min.

MPBH is a particularly stable dioxaborinane,<sup>4</sup> readily accessible from hexyleneglycol and borane. We described earlier<sup>2,3</sup> convenient preparations using BH<sub>3</sub>–DMS or B<sub>2</sub>H<sub>6</sub> generated from NaBH<sub>4</sub> and MeSO<sub>3</sub>H. We considered the use of *N*,*N*-diethylaniline-borane, a safe<sup>5</sup> source of borane for large-scale applications, but the reaction of hexylene glycol with this reagent was sluggish. Pd/C is

SYNLETT 2010, No. 16, pp 2403–2406 Advanced online publication: 19.08.2010 DOI: 10.1055/s-0030-1258059; Art ID: D10810ST © Georg Thieme Verlag Stuttgart · New York known<sup>6</sup> to accelerate the decomplexation and solvolysis of amine-boranes in methanol. In an analogous manner (Scheme 1), we found that reacting *N*,*N*-diethylaniline-borane and hexyleneglycol in the presence of Pd/C (5% by weight of 10% Pd/C reagent) resulted in the complete consumption of the diol in 30 min at room temperature. Distillation of the reaction mixture in vacuo provided neat MPBH in 75% yield.<sup>7,8</sup>



Scheme 2 Borylation of aryl halides and triflates

Then we studied the palladium-catalyzed borylation of various aryl halides and triflates with MPBH and a catalyst prepared from Pd<sub>2</sub>(dba)<sub>3</sub> and CyJohnPhos<sup>9</sup> according to Baudoin's procedure<sup>1c</sup> (Scheme 2, Table 1).<sup>10</sup> In preliminary experiments, we found that toluene and dioxane were equally suitable solvents.

With PinBH, a dramatic feature of this catalyst system compared to others<sup>1–3</sup> is the extreme rapidity of the process, when applied to electron-rich aryl iodides<sup>11</sup> or bromides.<sup>12</sup> The same is true with MPBH. This high reactivity allows complete conversion of reactive aryl iodides and bromides (entries 1–4, 7, 8) between 20–40 °C within a few hours. To our knowledge, operating at 20 °C has not been described for this reaction yet.<sup>13</sup>

The process remained efficient at low levels of catalyst: the boronate ester was produced from *p*-bromo-N,N-dimethylaniline in 90% yield in six hours at 20 °C when 0.3 mol% Pd was used (10 mmol run, entry 7).

When less reactive iodides were used, some hydrodehalogenation was observed. This side reaction is always met in analogous borylation with PinBH and is favored by electron-withdrawing substituents on the aryl ring. In the present work as well as in the literature,<sup>1</sup> it is the only side reaction: the homocoupling product was never observed. We indicate whenever available the ArB(OR)<sub>2</sub>/ArH ratio, but low-boiling arenes were seldom accurately measurable. Note that all reactions of Table 1 were run to complete conversion of the starting material. Thus, lower

 Table 1
 Borylation of Various Aryl Halides and Triflates with MPBH Catalyzed by Pd/CyJohnPhos<sup>a,10</sup>

Entry	Substrate	Conditions	ArB(OR) <sub>2</sub> /ArH <sup>b</sup>	Product yield (%) <sup>c</sup>
1	Me <sub>2</sub> N	Pd (3 mol%), 20 °C, <0.5 h	>99:1	<b>2a</b> 90
2	MeO	Pd (1 mol%), 20 °C, 1 h	>95:5	<b>2b</b> 91
3	H <sub>2</sub> N	Pd (0.5 mol%), 20 °C, 0.5 h	>97:3	<b>2c</b> 79
4	NH <sub>2</sub>	Pd (1 mol%), 20 °C, 3 h	>97:3	<b>2d</b> 88
5	MeOOC	Pd (1 mol%), 80 °C, 3 h	70:30	<b>2e</b> 69
6	O <sub>2</sub> N	Pd (1 mol%), 40 °C, 16 h	n.d. <sup>d</sup>	<b>2f</b> 60
7	Me <sub>2</sub> N	Pd (0.3 mol%), 20 °C, 6 h	>99:1	<b>2a</b> 90 <sup>e</sup>
8	MeO	Pd (0.5 mol%), 40 °C, 6 h	>95:5	<b>2b</b> 81
9 10	Br	MPBH (3 equiv), Pd (1 mol%), 100 °C, toluene, <sup>f</sup> 30 h PinBH (3 equiv), Pd (1 mol%), 100 °C, toluene, <sup>f</sup> 15 h	30:70 92:8	2g - 3g
11 12	Ph	MPBH, Pd (1 mol%), 150 °C, toluene, <sup>f</sup> 15 min <sup>g</sup> PinBH, Pd (1 mol%), 150 °C, toluene, <sup>f</sup> 15 min <sup>g</sup>	29:71 70:30	2h - 3h 70 <sup>1i</sup>
13	OTF	Pd (1 mol%), 80 °C, 6 h	n.d.	<b>2i</b> 82
14	OUTI	Pd (1 mol%), 80 °C, 16 h	n.d.	<b>2j</b> 73
15	MeO	Pd (1 mol%), 100 °C, 16 h	>95:5	<b>2b</b> 90
16	OMe	Pd (2 mol%), 80 °C, 16 h	51:49	<b>2k</b> 45
17	CI	Pd (1 mol%), 80 °C, 24 h	n.d.	<b>2i</b> 62

<sup>a</sup> Unless otherwise stated: MPBH (1.5 equiv), Et<sub>3</sub>N (3 equiv), Pd [as Pd<sub>2</sub>(dba)<sub>3</sub>], CyJohnPhos (2 equiv per Pd), in dioxane.

<sup>b</sup> Measured by GC, except entries 3 and 4: <sup>1</sup>H NMR.

<sup>c</sup> Isolated yields after chromatography.

<sup>d</sup> n.d.: not determined.

<sup>e</sup> 10 mmol bromide.

<sup>f</sup> Run in toluene.

<sup>g</sup> Sealed vessel, microwaves heating.

Synlett 2010, No. 16, 2403-2406 © Thieme Stuttgart · New York

isolated yields reflect a higher level of hydrodehalogenation. With the reactive substrates of entries 1–4, 7, and 8, the reduced product was below detection. In all cases, it was found to be less present than with the  $PdCl_2(TPP)_2$ catalyst in our former work.<sup>3</sup> It can be concluded that in the case of reactive, electron-rich aryl iodides and bromides, MPBH is a cost-effective substitute to pinacolborane in a fast and efficient palladium-catalyzed borylation.

Disappointingly, with less reactive aryl halides, a clearcut difference in reactivity between PinBH and MPBH appeared, with MPBH favoring the unwanted hydrodehalogenation. The difference remained limited with electrondepleted iodides (entries 5 and 6). Entry 5 (69% yield) should be compared with Masuda's<sup>1b</sup> result: borylation of ethyl 4-iodobenzoate with PinBH in the presence of PdCl<sub>2</sub>dppf yielded 79% ArPin (hydrodehalogenated product 17%). More dramatic differences appeared with electron-depleted bromides, for which hydrodehalogenation became deleterious (entries 9–12). In the same conditions, PinBH was much more efficient (compare entries 9 and 10, 11 and 12).

The borylation of chlorides was practically limited to the most reactive, electron-rich ones (entries 15–17).<sup>14</sup> Remarkably, aryl triflates<sup>1b,15</sup> were borylated efficiently (entries 13 and 14). The extent of the hydrodetriflation seemed less dependent of the electron-donating (entry 13) or electron-withdrawing nature of the substituents (entry 14, compare also with entry 11).

So far, all reported optimizations of this reaction were carried out with electron-rich substrates.<sup>1-3</sup> We decided to check the influence of reaction parameters on the borylation/hydrodehalogenation ratio when the substrate was electron withdrawn; 2-bromonaphthalene was our model of such an 'unreactive' substrate.<sup>16</sup> Reactions were monitored by GC with an internal standard. Although we could not increase the yield in boronic ester 2g above 50%, some interesting trends became apparent. Higher temperatures favored borylation over hydrodehalogenation (37% yield in 2g at 80 °C, 50% at 150 °C), making this reaction a good candidate for closed-vessel, microwaves-heated conditions. Nevertheless, at identical temperatures, microwave heating did not lead to significantly faster reaction than conventional heating. With 2-bromonaphthalene and MPBH, other ligand systems (dppf,1a,b dpePhos,1f  $TPP,^3$ N-(dicyclohexylphosphino)-2-(2'excess tolyl)indole<sup>17</sup> or di-tert-butylbipyridyl) led to slower reactions and increased hydrodehalogenation.

Monitoring the course of the reaction showed that the borylation/hydrodehalogenation ratio is lower at early stages of the reaction. Examples have been reported with PinBH<sup>18</sup> where prolonged heating of the reaction mixtures caused an increase of the hydrodehalogenation. In the present conditions, both reactions are concurrent. Prolonged heating after the end of the conversion of the bromide never caused any significant loss of borylated product. A larger excess of MPBH (3 equiv) slightly favored hydrodehalogenation and best results were obtained with only 1.5 equivalents dialkoxyborane.

Our hypothesis is that MPBH is more prone than PinBH to some disproportionation<sup>19</sup> under the reaction conditions, releasing small amounts of BH<sub>3</sub> that would favor Pd-catalyzed reduction of the substrate. Indeed, replacing MPBH by  $BH_3$ -Et<sub>3</sub>N caused extensive hydrodehalogenation.

In conclusion, the combination of MPBH, a particularly stable and inexpensive reagent, and Buchwald's palladium catalyst provides a simple, very fast, cost-effective borylation of reactive, electron-rich aryl iodides, bromides, and triflates, to produce stable, easily purified boronic esters, that can be readily used as such in Suzuki couplings.<sup>1,2</sup>

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

## Acknowledgment

We gratefully thank the Université J. Fourier and the CNRS for financial support.

## **References and Notes**

- (1) (a) Murata, M.; Watanabe, S.; Masuda, Y. J. Org. Chem. 1997, 62, 6458. (b) Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. J. Org. Chem. 2000, 65, 164. (c) Baudoin, O.; Guenard, D.; Gueritte, F. J. Org. Chem. 2000, 65, 9268. (d) Melaimi, M.; Mathey, F.; Le Floch, P. J. Organomet. Chem. 2001, 640, 197. (e) Doux, M.; Mezailles, N.; Melaimi, M.; Ricard, L.; Le Floch, P. Chem. Commun. 2002, 1566. (f) Broutin, P. E.; Cerna, I.; Campaniello, M.; Leroux, F.; Colobert, F. Org. Lett. 2004, 6, 4419. (g) Murata, M.; Sambommatsu, T.; Watanabe, S.; Masuda, Y. Synlett 2006, 1867. (h) Miller, W. D.; Fray, A. H.; Quatroche, J. T.; Sturgill, C. D. Org. Process Res. Dev. 2007, 11, 359. (i) Billingsley, K. L.; Buchwald, S. L. J. Org. Chem. 2008, 73, 5589. Mechanism: (j) Lam, K. C.; Marder, T. B.; Lin, Z. Organometallics 2010, 29, 1849. (k) Dang, L.; Lin, Z.; Marder, T. B. Chem. Commun. 2009, 3987. For borylation with aminoborane reagent, see: (1) Euzenat, L.; Horhant, D.; Ribourdouille, Y.; Duriez, C.; Alcaraz, G.; Vaultier, M. Chem. Commun. 2003, 2280. For a related Cu-catalyzed borylation, see: (m) Zhu, W.; Ma, D. Org. Lett. 2006, 8, 261. For a related Ni-catalyzed borylation with in situ prepared 5,5-dimethyl-1,3,2-dioxaborinane, see: (n) Rosen, B. M.; Huang, C.; Percec, V. Org. Lett. 2008, 10, 2597. (o) Moldoveanu, C.; Wilson, D. A.; Wilson, C. J.; Corcoran, P.; Rosen, B. M.; Percec, V. Org. Lett. 2009, 11, 4974. (p) Wilson, D. A.; Wilson, C. J.; Moldoveanu, C.; Resmerita, A.-M.; Corcoran, P.; Hoang, L. M.; Rosen, B. M.; Percec, V. J. Am. Chem. Soc. 2010, 1800. (q) Morgan, A. B.; Jurs, J. L.; Tour, J. M. J. Appl. Polym. Sci. 2000, 76, 1257. Arene C-H borylation has been recently reviewed: (r) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. Chem. Rev. 2010, 110, 890.
- (2) Murata, M.; Oda, T.; Watanabe, S.; Masuda, Y. *Synthesis* **2007**, 351.
- (3) PraveenGanesh, N.; Chavant, P. Y. *Eur. J. Org. Chem.* **2008**, 4690.

- (4) (a) Chavant, P. Y.; PraveenGanesh, N. In *Electronic Encyclopaedia of Reagents for Organic Synthesis (e-EROS)*; Paquette, L. A., Ed.; John Wiley and Sons: New York, **2008**. (b) Woods, W. G.; Strong, P. L. *J. Am. Chem. Soc.* **1966**, 88, 4667. (c) Fish, R. H.; Newsom, H. C. FR 1536699, **1968**. (d) Fish, R. H.; Newsom, H. C. US 19670427, **1968**.
  (e) Kono, H.; Ito, K.; Nagai, Y. *Chem. Lett.* **1975**, 1095.
  (f) Männig, D.; Nöth, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 878. (g) PraveenGanesh, N.; d'Hondt, S.; Chavant, P. Y. *J. Org. Chem.* **2007**, *72*, 4510.
- (5) Wilkinson, H. S.; Tanoury, G. J.; Wald, S. A.; Senanayake, C. H. Org. Process Res. Dev. 2002, 6, 146.
- (6) (a) Couturier, M.; Tucker, J. L.; Andresen, B. M.; Dube, P.; Negri, J. T. Org. Lett. 2001, 3, 465. (b) Couturier, M.; Tucker, J. L.; Andresen, B. M.; Dube, P.; Brenek, S. J.; Negri, J. T. Tetrahedron Lett. 2001, 42, 2285.
- (7) Preparation of MPBH
  - Under a well-ventilated fume hood ( $H_2$  evolution), a 100 mL flask equipped with a Claisen distillation head was charged with 10% Pd/C (320 mg) and anhyd dioxane (10 mL). The flask was flushed with nitrogen and freshly distilled 2-methyl-2,4-pentanediol (50 mmol, 6.4 g) in dioxane (10 mL) was added. A solution of *N*,*N*-diethylaniline-borane (60 mmol, 9.78 g) in dioxane (10 mL) was added at 20 °C over 30 min. The reaction mixture was stirred for an additional 30 min at 20 °C. Low pressure distillation gave neat MPBH (4.8 g, 75%, bp 45 °C/0.05 bar).
- (8) Our attempts to use *N*,*N*-diethylaniline as the base in subsequent borylations failed.
- (9) [1,1'-Biphenyl]-2-yl-dicyclohexylphosphine: Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. J. Am. Chem. Soc. 1999, 121, 9550.
- (10) Typical Procedure for the Borylation An oven-dried Schlenk vessel (or a 10 mL microwaves vial) was charged with Pd<sub>2</sub>(dba)<sub>3</sub> (2.3 mg, 2.5 µmol, described as 0.5% in Table 1) and CyJohnPhos (3.5 mg, 10 µmol, always 2 equiv/Pd) and placed under an atmosphere of Argon. Anhydrous dioxane (0.6 mL), the aryl halide (0.5 mmol), Et<sub>3</sub>N (152 mg, 1.5 mmol) and MPBH (96 mg, 0.75 mmol) were introduced (solid aryl halides were added along with the other solid reagents). The reaction mixture was then heated at the indicated temperature until the aryl halide has been completely consumed as determined by gas chromatography. The reaction was allowed to cool to r.t., and filtered through a short pad of Celite (eluent Et<sub>2</sub>O). The eluate was concentrated and the crude material purified by flash chromatography on silica gel. Products **2a-j**<sup>2,3</sup>, **3g**<sup>1b</sup> and **3h**<sup>1i</sup> have been previously described.

## 4,4,6-Trimethyl-2-naphthalen-2-yl[1,3,2]dioxaborinane (2g)

 $^{1}$ H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.34 (s, 1 H), 7.89–7.85 (m,

- 2 H), 7.82–7.76 (m, 2 H), 7.48–7.40 (m, 2 H), 4.38 (dqd, J = 11.8, 6.2, 2.9 Hz, 1 H), 1.87 (dd, J = 13.7, 2.9 Hz, 1 H), 1.62 (dd, J = 13.7, 11.8 Hz, 1 H), 1.41 (s, 3 H), 1.39 (s, 3 H), 1.38 (d, J = 6.2 Hz, 3 H) ppm. <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>):  $\delta = 134.8$  (2×), 132.99, 130.14, 128.68, 127.67, 129.5 (v br, CB), 126.62, 126.39, 125.44, 71.16, 65.14, 46.15, 31.38, 28.27, 23.30 ppm. <sup>11</sup>B NMR (128 MHz, CDCl<sub>3</sub>):  $\delta = 27.10$ . IR (neat): 3053, 2972, 2932, 2911, 1630, 1598, 1503, 861, 823, 765, 746, 685 cm<sup>-1</sup>. MS (EI, 70 eV): m/z (%) = 255 (26), 254 (100), 253 (28).
- (11) (a) Baudoin, O.; Decor, A.; Cesario, M.; Gueritte, F. *Synlett* 2003, 2009. (b) Joncour, A.; Decor, A.; Thoret, S.; Chiaroni, A.; Baudoin, O. *Angew. Chem. Int. Ed.* 2006, *45*, 4149. (c) Poriel, C.; Lachia, M.; Wilson, C.; Davies, J. R.; Moody, C. J. *J. Org. Chem.* 2007, *72*, 2978.
- (12) (a) Combs, A.; Zhu, W.; Crawley, M.; Glass, B.; Polam, P.; Sparks, R. B.; Modi, D.; Takvorian, A.; McLaughlin, E.; Yue, E.; Wasserman, Z.; Bower, M.; Wei, M.; Rupar, M.; Ala, P. J.; Reid, B. M.; Ellis, D.; Gonneville, L.; Emm, T.; Taylor, N.; Yeleswaram, S.; Li, Y.; Wynn, R.; Burn, T. C.; Hollis, G.; Liu, P. C. C.; Metcalf, B. *J. Med. Chem.* **2006**, *49*, 3774. (b) Mentzel, U. V.; Tanner, D.; Tonder, J. E. *J. Org. Chem.* **2006**, *71*, 5807.
- (13) For related room-temperature Suzuki couplings, see:
  (a) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* 2000, 65, 1158.
  (b) Billingsley, K. L.; Barder, T. E.; Buchwald, S. L. Angew. Chem. Int. Ed. 2007, 46, 5359.
- (14) Very recently, Murata et al. borylated aryl chlorides with both PinBH and MPBH in the presence of excess Bu<sub>4</sub>NI: Murata, M.; Sambommatsu, T.; Oda, T.; Watanabe, S.; Masuda, Y. *Heterocycles* **2010**, *80*, 213.
- (15) (a) Wakim, S.; Bouchard, J.; Simard, M.; Drolet, N.; Tao, Y.; Leclerc, M. *Chem. Mater.* 2004, *16*, 4386. (b) Ahmed, V.; Liu, Y.; Silvestro, C.; Taylor, S. D. *Bioorg. Med. Chem.* 2006, *14*, 8564. (c) Tam, V. K.; Liu, Q.; Tor, Y. *Chem. Commun.* 2006, 2684.
- (16) See Supporting Information for a detailed table of these experiments.
- (17) So, C. M.; Lau, C. P.; Kwong, F. Y. Org. Lett. 2007, 9, 2795.
- (18) (a) Altemoeller, M.; Podlech, J.; Fenske, D. *Eur. J. Org. Chem.* 2006, 1678. (b) Suzuki, A. *Proc. Jpn. Acad.* 2004, 80, 359.
- (19) The disproportionation of dialkoxyboranes yields trialkoxyboranes and BH<sub>3</sub>. See: (a) Rose, S. H.; Shore, S. G. *Inorg. Chem.* **1962**, *1*, 744. (b) Pasto, D. J.; Balasubramaniyan, V.; Wojtkowski, P. W. *Inorg. Chem.* **1969**, *8*, 594. The reaction is influenced by phosphines and/ or metal species: (c) Hadebe, S. W.; Robinson, R. S. *Eur. J. Org. Chem.* **2006**, 4898; and references cited therein.