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Efficient borylation of reactive aryl halides with MPBH (4,4,6-trimethyl-1,3,2-dioxaborinane).

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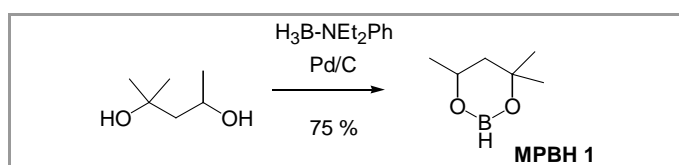
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Abstract: The combination of 4,4,6-trimethyl-1,3,2-dioxaborinane, a particularly stable and inexpensive borylation reagent, and Buchwald's palladium catalyst provides a simple, fast, cost-effective borylation of electron-rich, reactive iodides, bromides,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

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

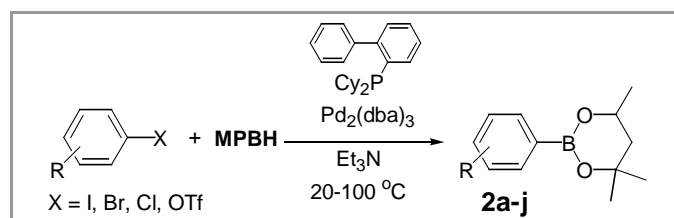
The increasing number of applications of the Suzuki-Miyaura coupling prompts the design of efficient and cost-effective methods for the preparation of the arylboronic precursors. Among these, the borylation of aryl halides or triflates with pinacolborane¹ (PinBH) is an excellent alternate to the more classical addition of organometallics to trialkoxyborane. Murata's team² and ours³ proposed the replacement of PinBH in this reaction by the easily accessible, much less expensive and more conveniently prepared MPBH (4,4,6-trimethyl-1,3,2-dioxaborinane⁴ **1**). In addition, Billingsley and Buchwald¹¹ completed in 2008 the original study of Baudoin *et al.*^{1c} 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,⁴ readily accessible from hexyleneglycol and borane. We described earlier^{2,3} convenient preparations using BH₃-DMS or B₂H₆ generated from NaBH₄ and MeSO₃H. We considered the use of *N,N*-diethylaniline-borane, a safe⁵ source of borane for large-scale applications, but the reaction of hexylene glycol with this reagent was sluggish. Pd/C is known⁶ 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.^{7,8}



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 Pd₂(dba)₃ and CyJohnPhos⁹ according to Baudoin's procedure^{1c} (Scheme 2, Table 1).¹⁰ In preliminary experiments, we found that toluene and dioxane were equally suitable solvents.

With PinBH, a dramatic feature of this catalyst system compared to others¹⁻³ is the extreme rapidity of the process, when applied to electron-rich aryl iodides¹¹ or bromides.¹² 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 and 40°C within a few hours. To our knowledge, operating at 20°C has not been described for this reaction yet.¹³

The process remained efficient at low levels of catalyst: the boronate ester was produced from *p*-bromo-*N,N*-dimethylaniline in 90% yield in 6 h 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 electro-withdrawing substituents on the aryl ring. In the present work as well as in the literature,¹ it is the only side-reaction: the homocoupling product was never observed. We indicate whenever available the Ar-B(OR)₂/Ar-H 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 isolated yields reflect a higher level of hydrodehalogenation. With the reactive substrates of entries 1-4, 7 and 8, the reduced product was below detec-

tion. In all cases, it was found to be less present than with the PdCl₂(TPP)₂ catalyst in our former work.³ 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 clear-cut difference in reactivity between PinBH and MPBH appeared, with MPBH favouring the unwanted hydrodehalogenation. The difference remained limited with electron-depleted iodides (entries 5 and 6). Entry 5 (69% yield) should be compared with Masuda's^{1b} result: borylation of ethyl 4-iodobenzoate with PinBH in the presence of PdCl₂dppf yielded 79% Ar-Pin (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).¹⁴ Remarkably, aryl triflates^{1b,15} were borylated efficiently (entries 13-14). The extent of the hydrodetriflation seemed less dependent of the electro-donating (entry 13) or electro-withdrawing nature of the substituents (entry 14, compare also with entry 11).

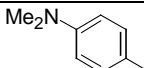
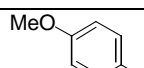
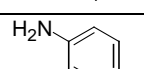
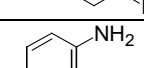
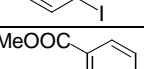
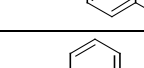
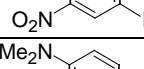
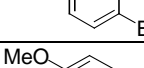
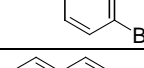
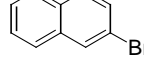
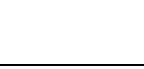
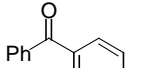
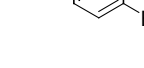
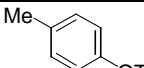
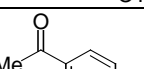
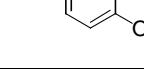
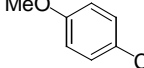
So far, all reported optimizations of this reaction were done with electron-rich substrates.¹⁻³ We decided to check the influence of reaction parameters on the borylation-hydrodehalogenation ratio when the substrate is electron-depleted; 2-bromonaphtalene was our model of "unreactive" substrate.¹⁶ Reactions were monitored by GC with internal standard. Although we could not increase the yield in boronic ester **2g** above 50%, some interesting trends appeared. Higher temperatures favor 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 reactions. Nevertheless, at identical temperatures, microwaves heating did not lead to significantly faster reaction than conventional heating. With 2-bromonaphtalene and MPBH, other ligand systems (dppf,^{1a,b} dpePhos,^{1f} excess TPP,³ *N*-(dicyclohexylphosphino)-2-(2'-tolyl)indole¹⁷ 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 PinBH¹⁸ 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 eq.) slightly favored hydrodehalogenation: best results were obtained with only 1.5 eq. dialkoxyborane.

Our hypothesis is that MPBH is more prone than PinBH to some disproportionation¹⁹ in the reaction conditions, releasing small amounts of BH₃ (that would favor Pd-

catalyzed reduction of the substrate. Indeed, replacing MPBH by BH₃:Et₃N caused extensive hydrodehalogenation.

Table 1 Borylation of various aryl halides and triflates with MPBH catalyzed by Pd/CyJohnPhos.^{a,10}

Entry	substrate	conditions	ArB(O R) ₂ /Ar H ^b	Product yield (%) ^c
1		3% Pd, 20°C, <0.5 h	> 99:1	2a 90
2		1% Pd, 20°C, 1 h	> 95:5	2b 91
3		0.5% Pd, 20°C, 0.5 h	> 97:3	2c 79
4		1% Pd, 20°C, 3 h	> 97:3	2d 88
5		1% Pd, 80°C, 3 h	70:30	2e 69
6		1% Pd, 40°C, 16 h	n.d. ^d	2f 60
7		0.3% Pd, 20°C, 6 h	> 99:1	2a 90 ^e
8		0.5% Pd, 40°C, 6 h	>95:5	2b 81
9		MPBH (3 eq.) 1% Pd, 100°C Tol. ^f , 30 h	30:70	2g –
10		PinBH (3 eq.) 1% Pd, 100°C Tol. ^f , 15 h	92:8	3g –
11		MPBH 1% Pd, 150°C Tol. ^f , 15min ^g	29:71	2h –
12		PinBH 1% Pd, 150°C Tol. ^f , 15min ^g	70:30	3h litt. ¹¹ 70
13		1% Pd, 80°C, 6 h	n.d.	2i 82
14		1% Pd, 80°C, 16h	n.d.	2i 73
15		1% Pd, 100°C, 16h	>95:5	2b 90
16		2% Pd, 80°C, 16 h	51:49	2j 45
17		1 % Pd, 80°C, 24 h	n.d.	2i 62

^a Unless otherwise stated: MPBH 1.5 eq., Et₃N 3 eq., Pd (as Pd₂(dba)₃), CyJohnPhos 2 eq. per Pd, in dioxane.

^b Measured by GC, except entries 3 and 4: ¹H-NMR.

^c Isolated yields after chromatography.

^d n.d.: not determined.

^c 10 mmol bromide.
^f run in toluene.
^g sealed vessel, microwaves heating.

As a 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.^{1,2}

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

Acknowledgment

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- (7) **Preparation of MPBH:** under a well-ventilated fume hood (H₂ evolution), a 100-mL flask equipped with a Claisen distillation head was charged with 320 mg of 10 % Pd/C and anhydrous 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%, b.p. 45 °C / 35 Torr).
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- (10) **Typical procedure for the borylation:** an oven-dried Schlenk vessel (or a 10-mL microwaves vial) was charged with Pd₂(dba)₃ (2.3 mg, 2.5 μmol, described as 0.5 % in Table 1) and CyJohnPhos (3.5 mg, 10 μmol, always 2 eq./Pd) and placed under an atmosphere of Argon. Anhydrous dioxane (0.6 mL), the aryl halide (0.5 mmol), triethylamine (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 room temperature, and filtered through a thin pad of Celite (eluent ether). The eluate was concentrated and the crude material purified via flash chromatography on silica gel. Products **2a**-**j**^{2,3}, **3g**^{1b} and **3h**¹ⁱ have been previously described. 4,4,6-trimethyl-2-naphthalen-2-yl-[1,3,2]dioxaborinane **2g**: ¹H NMR (400 MHz, CDCl₃) δ ppm 8.34 (s, 1H), 7.89-7.85 (m, 2H), 7.82-7.76 (m, 2H), 7.48-7.40 (m, 2H), 4.38 (dq, *J* = 11.8, 6.2, 2.9 Hz, 1H), 1.87 (dd, *J* = 13.7, 2.9 Hz, 1H), 1.62 (dd, *J* = 13.7, 11.8 Hz, 1H), 1.41 (s, 3H), 1.39 (s, 3H), 1.38 (d, *J* = 6.2 Hz, 3H); ¹³C NMR (75.5 MHz, CDCl₃) δ ppm 134.8 (x2), 132.99, 130.14, 128.68, 127.67, 129.5 (very broad, C-B), 126.62, 126.39, 125.44, 71.16, 65.14, 46.15, 31.38, 28.27, 23.30; ¹¹B NMR (128 MHz, CDCl₃) δ ppm 27.10; IR (neat, cm⁻¹): 3053, 2972, 2932, 2911, 1630, 1598, 1503, 861, 823, 765, 746, 685; MS (EI, 70eV) 255 (26), 254 (100), 253 (28).
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Supporting Information to

Efficient borylation of reactive aryl halides with MPBH (4,4,6-trimethyl-1,3,2-dioxaborinane).

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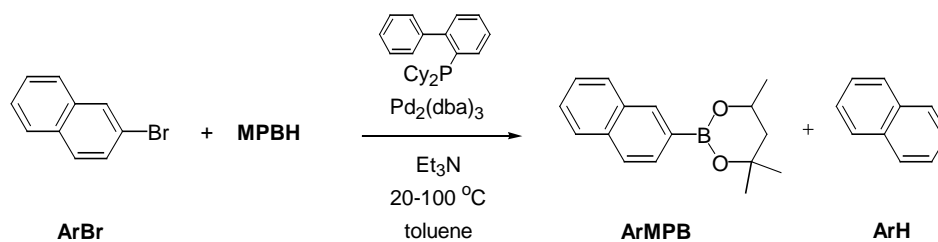
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This article describes our study on borylation of aryl halides and triflates with 4,4,6-trimethyl-1,3,2-dioxaborinane (**MPBH**), a stable and easily available reagent. The combination of MPBH and Buchwald's palladium catalyst provides a simple, fast, cost-effective borylation of electron-rich, reactive aryl iodides, bromides, and triflates, to produce stable, easily purified boronic esters.

In the course of this work we found that the desired borylation can be hampered by a concurrent hydrodehalogenation of the substrate. We studied the influence of various parameters on the extent of this side-reaction in the case of 2-bromonaphtalene as the model. The results of this study are summarized in the table below.

Standard procedure for the borylation of 2-bromonaphtalene

An oven-dried Schlenk vessel (or a 10-mL microwaves vial) was charged with 2-bromonaphtalene (0.5 mmol), Pd₂(dba)₃ (2.3 mg, 0.5 %) and CyJohnPhos (3.5 mg, 2 %) and placed under an atmosphere of Argon. Anhydrous toluene (1 mL), triethylamine (152 mg, 1.5 mmol), MPBH (96 mg, 0.75 mmol) and tetradecane (as an internal standard) were introduced with a syringe. The reaction mixture was then heated at the indicated temperature for the indicated time. When microwaves were used the reaction was hydrolysed after this time and analyzed by GC (relative response factors of the components were determined from mixtures of pure samples). Reactions performed in an oil bath at atmospheric pressure were monitored by repeated analysis of small aliquots.



Scheme: Borylation of 2-bromonaphtalene

Table. Borylation of 2-bromonaphtalene with MPBH						
Standard conditions: 2-bromonaphtalene, MPBH 1.5 eq., Et ₃ N 3 eq., Pd (as Pd ₂ (dba) ₃) 1 mol%, CyJohnPhos 2 mol%, toluene (2 mL/mmol ArBr)						
Entry	temp.	time	deviation from standard conditions	conversion	Ar-MPB:Ar-H	
18	40°C (thermal)	16 hrs	3 eq. MPBH	99	38:62	
19	80°C (thermal)	6 hrs	–	100	37:63	
20	110°C (thermal)	20 min	3 eq. MPBH	100	35:65	
21	110°C (thermal)	30 min	–	49	39:61	
22	110°C (μW)	30 min	–	55	42:58	
23	110°C (thermal)	16 hrs	–	100	44:56	
24	150°C (μW)	5 min	–	100	45-50:50-55 ¹	
25	180°C (μW)	5 min	–	100	50:50	
26	150°C (μW)	5 hrs	0,1mol% Pd, 0,2 mol% ligand	82	49:51	
27	150°C (μW)	30 min	1 eq Et ₃ N	78	49:51	
28	150°C (μW)	5 min	1.2 eq. MPBH	87	47:53	
29	150°C (μW)	15 min	1.2 eq. MPBH	98	44:56	
30	150°C (μW)	30 min	1.2 eq. MPBH, dioxane	95	43:57	
31	150°C (μW)	30 min	Pd as Pd(AcO) ₂	100	48:52	
32	150°C (μW)	30 min	2 mol% <i>N</i> -(dicyclohexylphosphino)-2-(2'-tolyl)indole	84	46:54	
33	150°C (μW)	30 min	1mol% DPEphos	55	43:57	
34	150°C (μW)	60 min	1mol% dppf	100	39:61	
35	150°C (μW)	30 min	2 mol% TPP	100	33:67	
36	110°C (thermal)	110 min	3 eq. MPBH, 4 mol% TPP, dioxane	100	21:79	
37	150°C (μW)	30 min	1mol% dtbpy ²	61	13:87	
38	150°C (μW)	30 min	Pd/C, no ligand	65	3:97	

¹ run repeated thrice.

² 4,4'-di-tert-butyl-2,2'-dipyridyl

Typical microwaves experiment: heating profiles

The profiles below (entry 31) are typical. This reaction was performed on a 0.5 mmol scale in a 10 mL vessel; solvent was toluene.

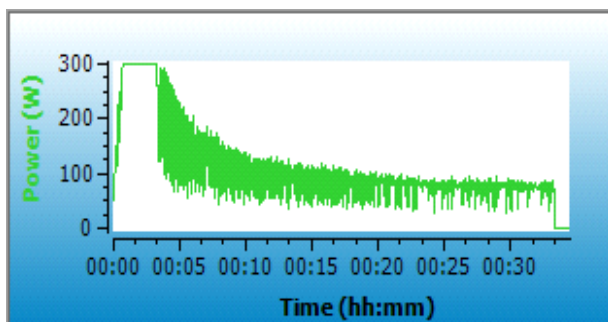
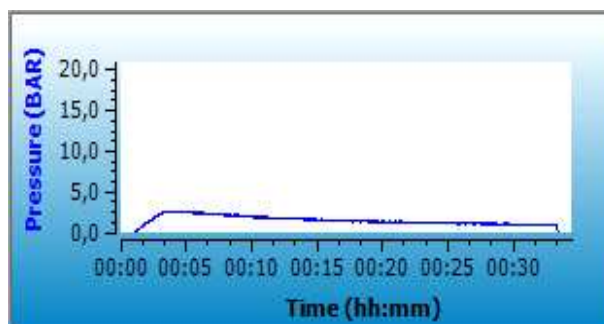
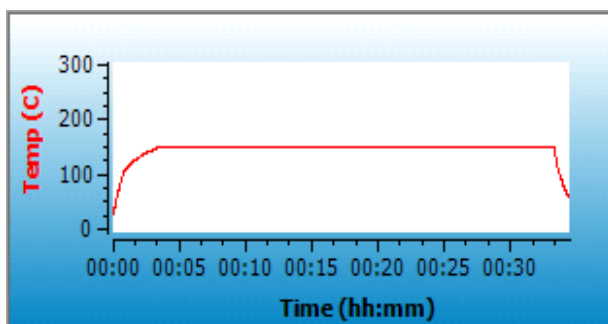
CEM DISCOVER apparatus,

Method Parameters

Prestirring(mm:ss): 00:15

Type:Dynamic	Stage	Temp(C)	Time(mm:ss)	Pressure(BAR)	Power(W)	PowerMAX	Stirring
	1	150	30:00	17,0	300	No	Low

Graphs



Method Summary

Reaction started:	30/10/2009 11:12:40
Temperature setpoint reached:	30/10/2009 11:16:00
Reaction cooling started:	30/10/2009 11:46:01
Cooling/Reaction ended:	30/10/2009 11:47:07

Reaction Completed Successfully!

Maximum temperature:	151 C
Maximum pressure:	3 BAR
Time to obtain setpoint:	03:20 mm:ss
Time at setpoint:	30:01 mm:ss
Time cooling:	01:06 mm:ss