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TECHNICAL NOTE

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Noncryogenic Preparation of Functionalized Arylboronic Esters through a Magnesium−Iodine Exchange with in Situ Quench

Emilien Demory, Véronique Blandin, Jacques Einhorn, and Pierre Y. Chavant*

Département de Chimie Moléculaire, UMR-5250, ICMG FR-2607, CNRS, Université Joseph Fourier, BP 53, 38041 Grenoble Cedex 09, France.

Supporting Information

ABSTRACT: Various functionalized aryl boronic esters derived from hexylene glycol and pinacol were prepared in excellent yields according to a simple, safe procedure. The metal−halogen exchange reaction between ^{i}PrMgCl·LiCl and aryl iodides is performed at 0 °C in the presence of a cyclic borate ester (MPBO^{i}Pr or PinBO^{i}Pr); the organomagnesium intermediate is immediately trapped in situ so that no accumulation of hazardous reactive species can occur. The reaction is very selective, and particularly clean crude products are obtained. The scope of the procedure and the tuning of reaction parameters are investigated.

INTRODUCTION

Arylboronic acids and esters have found a prominent place in the synthetic chemist's toolbox, the latter being often preferred for convenience in their purification and characterization and for their ability to be observed via gas or liquid chromatography.[1] Despite the recent developments in transition metal-catalyzed borylation,[1−4] the cheapest and most common way of synthesizing arylboronic acids and esters remains the reaction of an organolithium or organomagnesium intermediate with a trialkylborate at low temperature, typically −78 °C (Li) up to −10 °C (Mg).[1,5] An attractive method in this context is the generation of the aryl Grignard reagent by metal−halogen exchange using reagents such as ^{i}PrMgBr or ^{i}PrMgCl·LiCl.[6] Compared to the historic Grignard synthesis from Mg^{0}, this procedure, introduced by Knochel and Cahiez,[7] allows the preparation of the reagent at milder temperatures (−40 °C to room temperature), which broadly enlarges the functional group compatibility: for instance, arylmagnesium halides bearing ester or nitrile substituents become accessible. The exchange reaction is generally completed within hours, and the organomagnesium species can then be reacted with an electrophile at temperatures below 0 °C, typically −30 to −10 °C in the case of a trialkylborate.[8]

The functionalized Grignard reagents are intrinsically unstable, even if they can be kept for several hours at low temperature.[6a] Furthermore, with the expanding use of this magnesium−halogen method for the preparation of arylmagnesium reagents, some concerns have been raised regarding the stability of the reaction mixture. Process safety evaluation studies[9] revealed that an exothermic decomposition of the solution is possible—even for phenylmagnesium chloride—and that onset temperatures as low as 55 °C can be found. The structure of the aromatic ring and the concentration of the solution have a strong influence on the severity of the event, fluorine substituents and concentrated media being detrimental. A solution to avoid the prolonged coexistence of the aryl Grignard reagent, reactive functional groups, and ^{i}PrX, the byproduct of the magnesium−halogen exchange, would be to directly trap the reactive species by the electrophile in situ. Such a procedure has proven efficient in some cases with organolithium species and triisopropyl borate, but yields are still inadequate for challenging substrates such as ethyl *p*-bromobenzoate.[10] Regarding the magnesium−halogen exchange reaction, scarce examples of in situ trapping with trialkylborates can be found, with varying degrees of success.[11]

Among boronic acid derivatives, arylboronic hexylene glycol esters emerged as interesting compounds. Murata's team[12] and ours[13] have shown that they exhibit excellent stability toward air, water, and chromatography,[14] and undergo Suzuki−Miyaura reactions with aryl iodides, bromides, and triflates in excellent yields. Advantageously, hexylene glycol—a solvent—is much less expensive than pinacol.[15] We thus wondered whether 2-isopropoxy-4,4,6-trimethyl-1,3,2-dioxaborinane[16] (MPBO^{i}Pr, **1**) could be an efficient in situ trapping agent for arylmagnesium species issuing from a magnesium−halogen exchange.

RESULTS AND DISCUSSION

Reagent **1** was easily prepared from boric acid, hexylene glycol, and isopropanol by azeotropic removal of water (see Experimental Section),[17] and methyl 4-iodobenzoate **2a** was chosen as the first substrate. The magnesium−iodine exchange reaction was carried out with in situ quench, at 0 °C, through gradual addition of a THF solution of ^{i}PrMgCl·LiCl to the mixture of **1** and **2a** in THF (Scheme 1).[18] Monitoring the reaction by GC analysis showed that the transformation of **2a** into arylboronic ester **3a** was complete by the end of the addition. Hydrolysis of the reaction mixture led to a dramatically clean crude product[19] and to the corresponding boronic ester in 77% isolated yield after a simple filtration over silica gel.

This first result was very promising, given the competitive reactions at stake (Scheme 2): magnesium−iodine exchange, nucleophilic addition of the organomagnesium species onto the electrophilic MPBO^{i}Pr[20] or onto the carboxylic ester.[6b] Once the exchange has occurred, the aryl Grignard reagent does not accumulate but instantaneously reacts with **1** to give the

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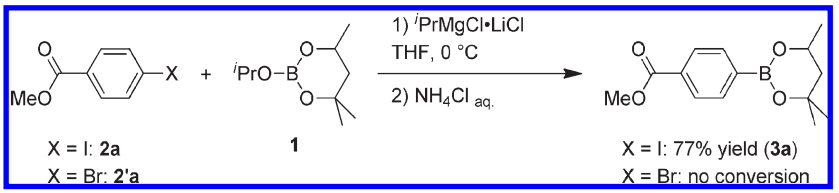
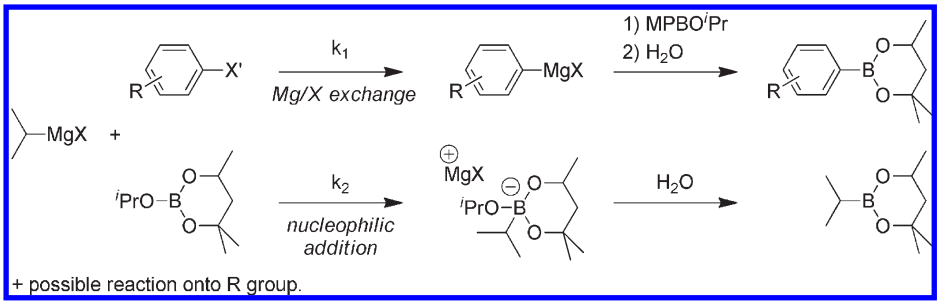
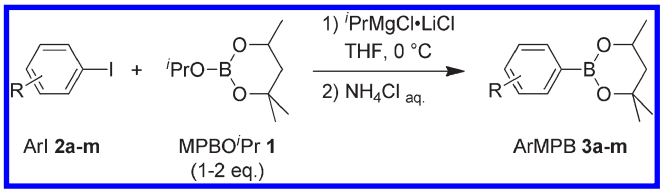
Scheme 1. First result for the in situ borylation of methyl 4-halobenzoate with MPBO^{i}Pr through a magnesium−halide exchange



Scheme 2. Competitive reactions for the in situ borylation with 1 through a magnesium−halide exchange



Scheme 3. In situ borylation of aryl iodides with MPBO^{i}Pr in the presence of ^{i}PrMgCl·LiCl



arylboronic ester. Indeed, we did not detect any methyl benzoate by GC analysis of hydrolyzed aliquots sampled during the addition of ^{i}PrMgCl·LiCl. The selectivity in the case of **2a** can be partly explained by the presence of the electron-withdrawing substituent, known to strongly accelerate the magnesium−halogen exchange.[21] However, the nature of the halogen is crucial. Indeed, in the case of aryl bromide **2′a**, the exchange proved too slow[22] compared to the nucleophilic addition onto **1**, and methyl 4-bromobenzoate **2′a** was recovered unchanged when submitted to the protocol from Scheme 1.

We then investigated the nature of the aryl iodides that could undergo the magnesium−iodine exchange in the presence of MPBO^{i}Pr **1** (Scheme 3 and Table 1). The reaction proceeds smoothly with aryl iodides bearing electron-withdrawing reactive substituents such as ester and nitrile groups, leading to arylboronic hexylene glycol esters **3a**−**c** in high yields (Table 1, entries 1−3). The use of ^{i}PrMgCl·LiCl was not suitable for a nitro group and led to a complex mixture. PhMgCl is known to allow magnesium−iodine exchange in the presence of an *o*-nitro group, but to react on a nitro group in meta- or para- position.[23] In the present system, the only reaction that takes place is between PhMgCl and MPBO^{i}Pr: a mixture of unreacted 1-iodo-3-nitrobenzene **2d** and phenylboronic ester was obtained (Table 1, entry 4).

Starting from diiodobenzenes, the monoborylated products **3e**−**f** are selectively obtained (Table 1, entries 5−6); traces (∼1%) of the diborylated compound were detected only in the case of the para-disubstituted **2e**, by ^{1}H NMR and GC analysis of the crude material.[24] The borylation of *o*-halo iodobenzene occurs at the iodine position, and no product resulting from aryne formation[25] could be detected (Table 1, entries 6−8). Running the reaction at lower temperature slightly improved the yield in arylboronic ester **3f** (Table 1, entry 6). The *o*-trifluoromethyl arylboronic ester **3i** was prepared in quantitative yield up to a 100 mmol scale using only a slight excess (10 mol %) of reagents (Table 1, entry 9). This excellent result is particularly interesting as the corresponding aryl Grignard reagent is reported to be prone to a highly exothermic decomposition.[9b] The very clean crude product was engaged without further purification in a Suzuki−Miyaura coupling leading to biaryl **5** bearing electron-withdrawing substituents on both aryl rings in 80% unoptimised yield (Scheme 4).[26] 2-Pyridyl boronic acids are notoriously unstable, and ester derivatives are therefore attractive compounds;[27] we were thus pleased to obtain 6-bromopyridin-2-yl boronic ester **3j** in excellent yield (Table 1, entry 10).

Electron-donating substituents proved detrimental to the reaction: the slower rate of the magnesium−iodine exchange[28] (constant k_1 in Scheme 2) made the nucleophilic addition of the alkylmagnesium species onto **1** competitive. ^{i}PrMgCl·LiCl was consumed to give MPB^{i}Pr and the conversion of aryl iodide **2** was therefore incomplete; no synthetically useful yield of arylboronic ester **3** could be obtained at 0 °C (Table 1, entries 11−13).

As we can see from the above results, the electronic nature of the aryl iodide plays an important part in the outcome of the borylation, by modifying the rate constant k_1 in Scheme 2. For a given aryl iodide, other parameters can favor the exchange reaction over the nucleophilic addition, by changing either the rate constants (k_1, k_2) or the reaction rates. To test the influence of the reaction conditions, we chose 2-iodoanisole as a borderline substrate for which k_1 is close to k_2;[29] some aryl iodide remained unreacted, and we used the conversion of **2m** into arylboronic ester **3m** as a measure of effectiveness (Scheme 5 and Table 2).

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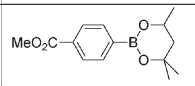
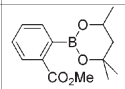
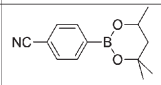
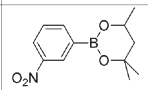
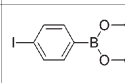
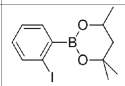
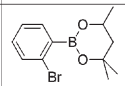
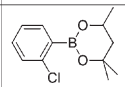
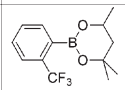
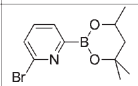
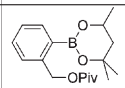
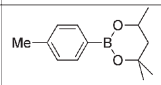
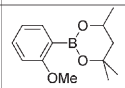
Table 1. Borylation of aryl iodides 2 with MPBO^{i}Pr in the presence of ^{i}PrMgCl·LiCl[a]

Entry	Arylboronic ester ArMPB		Isolated yield (%)	Additional informations
1		**3a**	79	5 mmol scale[b]
2		**3b**	89	—
3		**3c**	87	—
4		**3d**	n.d.[c]	complex mixture
			0[d]	PhMgCl; no conversion of **2d**
5		**3e**	87	—
			> 95	5 mmol scale[b]
6		**3f**	82	—
			90	reaction run at -15 °C
7		**3g**	86[e]	—
8		**3h**	76	—
9		**3i**	> 95	10 mmol scale[b]
			> 95	100 mmol scale[f]
10		**3j**	92	—
11		**3k**	n.d.[g]	55% conversion of **2k**
12		**3l**	n.d.[g]	37% conversion of **2l**
13		**3m**	n.d.[g]	25% conversion of **2m**

[a] Reaction conditions, unless otherwise stated: ^{i}PrMgCl·LiCl (1.1−1.2 equiv, 1.3 M in THF (addition rate: 0.2 mL/min)) was added at 0 °C to a solution of aryl iodide **2** (1 mmol) and MPBO^{i}Pr **1** (1.9 equiv) in THF ([ArI] = 0.5 M). [b] 1.1 equiv MPBO^{i}Pr, ^{i}PrMgCl·LiCl (addition rate: 0.2−0.5 mL/min). [c] 1.1 equiv MPBO^{i}Pr; isolated yield not determined. [d] PhMgCl (1.7 M in THF, 1.1 equiv, addition rate: 0.2 mL/min) was employed; 1.5 equiv MPBO^{i}Pr. [e] 1.4 equiv ^{i}PrMgCl·LiCl. [f] 1.1 equiv MPBO^{i}Pr, ^{i}PrMgCl·LiCl (0.8 M in THF, addition rate: 4.8 mL/min). [g] Isolated yield not determined; conversion of **2** determined on the basis of the ^{1}H NMR spectrum of the crude product.

The conversion reached 25% when conditions from Table 1 were applied (Table 2, entry 1). Running the reaction at lower temperature was again beneficial (Table 2, entry 3). As stressed by Knochel, LiCl accelerates the magnesium−halogen exchange (higher k_1);[6b] we observed in our case that ^{i}PrMgCl·LiCl significantly improved the conversion of **2m** into **3m** (compare Table 2, entries 1, 4, and 6). Decreasing the amount of MPBO^{i}Pr **1** (1.1 equiv vs 1.9 equiv) slows down the rate of the direct addition of ^{i}PrMgCl·LiCl onto **1**. As a result, a better, albeit still low, conversion of the aryl iodide was achieved (compare Table 2, entries 2 vs 1 and 5 vs 4). More generally, decreasing the amount of MPBO^{i}Pr **1** has a practical consequence: crude materials even cleaner than usual are obtained and can be directly engaged in further transformation (Scheme 4).[30]

With the rate constant k_2 being directly correlated to the structure of the trapping agent, we wondered whether our procedure for the preparation of functionalized arylboronic esters could be applied to the corresponding pinacol derivative 2-isopropoxy-4,4,5,5-tetramethyl[1,3,2]dioxaborolane (PinBO^{i}Pr, **6**).[31] Indeed, pinacol esters are the best-known arylboronic esters for Suzuki−Miyaura reactions.[1] We chose *o*-iodo trifluoromethylbenzene **2i** and *o*-iodo anisole **2m** as representative substrates (Scheme 6 and Table 3). In the case of the aryl iodide bearing an electron-withdrawing substituent, an excellent 93% yield in the pinacol ester **7i** was obtained (Table 3, entry 1). In the borderline case of substrate **2m**, PinBO^{i}Pr **6** gave better results than MPBO^{i}Pr **1**, whichever alkyl Grignard reagent was used (compare Table 3, entries 3 vs 2 and 5 vs 4). The extent of nucleophilic addition of the isopropylmagnesium species onto **6** is probably lessened by the increased steric hindrance around the boron atom compared to **1**. Finally, as seen in Table 2, the effect of the borate ester stoichiometry proved significant (compare Table 3, entries 6 vs 5).

CONCLUSION

Combining the generation, at 0 °C, of the aryl Grignard reagent by magnesium−iodine exchange with its in situ trapping by a cyclic borate ester proved to be a very simple, safe, and selective procedure for the preparation, in excellent yields and crude purity, of functionalized arylboronic esters from electron-deficient aryl iodides. Regarding arylboronic hexylene glycol esters, the present procedure is complementary to the Pd-catalyzed borylation of electron-rich aryl halides with 4,4,6-trimethyl-1,3,2-dioxaborinane (methyl pentanediol borane).[12,13]

EXPERIMENTAL SECTION

General Experimental Methods. THF was freshly distilled from sodium benzophenone ketyl. Reagents and solvents were purchased from commercial sources and were used as received. Alkylmagnesium reagents were titrated according to literature.[32] GC analyses were performed on a Shimadzu C17 apparatus equipped with a flame ionization detector and a BPX1 column (15 m × 0.25 mm, SGE; 2.5 min at 150 °C, then 150 to 250 at 15 °C per min; He). Infrared spectra (IR) were recorded on a Nicolet iS10 spectrometer using attenuated total reflection (ATR), and the data are reported as absorption maxima in cm^{-1}. Unless otherwise stated, ^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz), ^{11}B NMR (128 MHz) and ^{19}F NMR (282 MHz) spectra were recorded on a Varian 400MR spectrometer in $CDCl_3$ (δ_C 77.2 ppm; standard for ^{1}H spectra: tetramethylsilane δ_H 0.0 ppm). Data for ^{1}H NMR are presented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quadruplet, hept = heptuplet, m = multiplet), coupling constant *J* (Hz) and integration. Data for ^{13}C NMR are reported in terms of chemical

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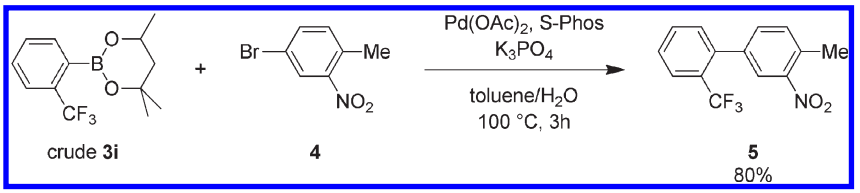
Scheme 4. Suzuki−Miyaura coupling of *o*-trifluoromethyl arylboronic ester 3i



Scheme 5. Borylation of 2-iodoanisole with MPBO^{i}Pr

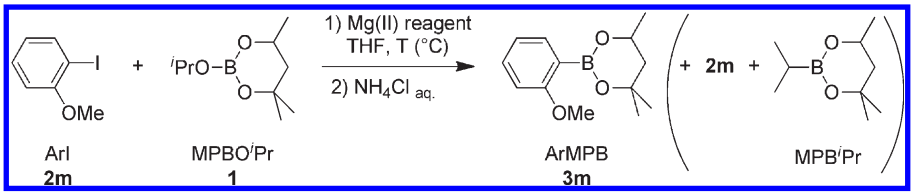


Table 2. Influence of reaction conditions on the borylation of 2-iodoanisole 2m with MPBO^{i}Pr[a]

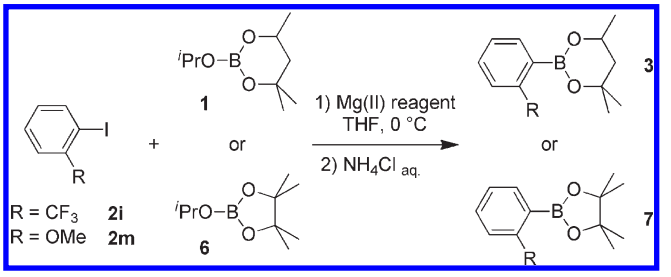
entry	MPBO^{i}Pr (equiv)	Mg(II) reagent	T (°C)	conversion of **2m** (%) [b]
1	1.9	^{i}PrMgCl·LiCl	0	25
2	1	^{i}PrMgCl·LiCl	0	30
3	1.9	^{i}PrMgCl·LiCl	−20	65
4	1.9	^{i}PrMgCl	0	11
5	1.1	^{i}PrMgCl	0	24
6	1.9	^{i}PrMgBr	0	10

[a] Reaction conditions: aryl iodide **2m** (1 mmol), MPBO^{i}Pr, THF ([**2m**] = 0.5 M), T (°C), Mg(II) reagent (1.1−1.2 equiv, [^{i}PrMgCl·LiCl] = 1.3 M in THF (addition rate: 0.2 mL/min) or [^{i}PrMgCl] = 2 M in THF (addition rate: 0.1 mL/min) or [^{i}PrMgBr] = 0.9 M in THF (addition rate: 0.2 mL/min)). [b] Determined on the basis of the ^{1}H NMR spectrum of the crude product.

shifts (ppm), and multiplicity (as above) followed by coupling constant (Hz) for fluorine-containing compounds. Note that the ^{13}C NMR signals of the boron-bound carbon atoms are very broad and remain undetected. Mass spectra (LRMS) were recorded on a ThermoFinnigan PolarisQ EI/CI ion-trap spectrometer (DCI: methane) or an Esquire 300 Plus Bruker Daltonics spectrometer (ESI). The isotopic distribution of the base peak is reported.

2-Isopropoxy-4,4,6-trimethyl-1,3,2-dioxaborinane (MPBO^{i}Pr) 1. A 500 mL Erlenmeyer flask equipped with a magnetic stirrer was charged with boric acid (25 g, 0.40 mol) and 2-methylpentan-2,4-diol (48 g, 0.40 mol). Pentane was then added (q.s. 250 mL), and the heterogeneous reaction mixture was stirred overnight at room temperature. The solid was filtered and dried under reduce pressure, then transferred into a 250 mL round-bottomed flask equipped with a magnetic stirrer. Isopropanol (100 g) was added, and the mixture was stirred overnight at room temperature. The reaction flask was equipped with a Cadiot distillation system, and water was removed azeotropically with isopropanol (2 × 100 g) under atmospheric pressure. The residue was finally distilled under reduced pressure to afford MPBO^{i}Pr as a colorless liquid (41 g, 0.22 mol, 55% yield). MPBO^{i}Pr can be stored for months under exclusion of air and moisture. Bp: 92 °C, 24 Torr (lit.[16] 47 °C, 0.6 Torr). IR: 2972 (CH), 2933 and 2908 (CH_3), 1304 and 1126 (B−O). ^{1}H NMR δ 4.34 (hept, J = 6.2, 1H), 4.23 (dqd, J = 11.7, 6.2 and 2.8, 1H), 1.73 (dd, J = 13.9 and 2.8, 1H), 1.46 (dd, J = 13.9 and 11.7, 1H), 1.29 (s, 3H), 1.27 (s, 3H), 1.24 (d, J = 6.2, 3H), 1.16 (d, J = 6.2, 6H). ^{13}C NMR δ 71.6 (C_q), 65.5 (CH), 64.9 (CH), 45.9 (CH_2), 31.2 (CH_3), 27.8 (CH_3), 24.4 (CH_3), 24.3 (CH_3), 23.1 (CH_3). ^{11}B NMR δ 17.8.

Scheme 6. Influence of the trapping agent



General Procedure for Borylation via Magnesium−Iodine Exchange. A dry and nitrogen-flushed 10-mL flask equipped with a magnetic stirrer and a septum was charged with iodoaryl **2** (1 mmol) and MPBO^{i}Pr **1** (353 mg, 1.9 mmol). THF was then added (2 mL). The reaction mixture was cooled to 0 °C (water−ice bath), and ^{i}PrMgCl·LiCl (0.85 mL, 1.3 M in THF, 1.1 mmol) was added portionwise over 5 min. At the end of addition, the conversion was verified by GC analysis of a hydrolyzed reaction aliquot. The reaction mixture was quenched with a saturated aqueous NH_4Cl solution (20 mL), diluted with ethyl acetate (30 mL), and the two phases were separated. The organic layer was washed with a saturated aqueous NH_4Cl solution (20 mL). The combined aqueous phases were extracted with ethyl acetate (20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was filtered through a thin pad of silica gel (Macherey Nagel silica gel 60 M (230−400 mesh), eluent DCM) to afford the desired product **3**. Compounds **3a,c,l**[13a] and **3m**[12a] have been previously described.

Methyl 2-(4,4,6-trimethyl-1,3,2-dioxaborinan-2-yl)benzoate 3b. 3b was prepared according to general procedure starting

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Table 3. Influence of the trapping agent[a]

entry	ArI	borate ester	Nb. equiv borate ester	Mg(II) reagent	ArMPB	conversion of ArI (%)[b]
1	**2i**	**6**	1.8	^{i}PrMgCl·LiCl	**7i**	100 (93)[c]
2	**2m**	**1**	1.8	^{i}PrMgCl	**3m**	13
3	**2m**	**6**	1.8	^{i}PrMgCl	**7m**	38
4	**2m**	**1**	2	^{i}PrMgCl·LiCl	**3m**	25
5	**2m**	**6**	2	^{i}PrMgCl·LiCl	**7m**	53
6	**2m**	**6**	1.5	^{i}PrMgCl·LiCl	**7m**	71

[a] Reaction conditions: aryl iodide (1 mmol), borate ester, THF ([ArI] = 0.5 M), 0 °C, Mg(II) reagent (1.1−1.2 equiv, [^{i}PrMgCl·LiCl] = 1.3 M in THF (addition rate: 0.2 mL/min) or [^{i}PrMgCl] = 2 M in THF (addition rate: 0.1 mL/min)). [b] Determined on the basis of the ^{1}H NMR spectrum of the crude product. [c] Isolated yield.

from methyl 2-iodobenzoate (262 mg, 1 mmol): yellow oil (236 mg, 89%). IR: 3057 and 3016 (CH ar.), 3973 (CH_3), 1716 (C═O), 1598 and 1566 (C═C ar.), 1391 (B−C), 1301 (B−O asym.), 1166 (B−O sym.). ^{1}H NMR δ 7.90 (dt, J = 7.9 and 0.8, 1H), 7.50−7.43 (m, 2H), 7.34 (ddd, J = 7.9, 5.4 and 3.5, 1H), 4.38 (dqd, J = 11.5, 6.2 and 3.2, 1H), 3.88 (s, 3H), 1.85 (dd, J = 13.8 and 3.2, 1H), 1.76 (dd, J = 13.8 and 11.5, 1H), 1.43 (s, 3H), 1.34 (s, 3H), 1.30 (d, J = 6.2, 3H). ^{13}C NMR δ 168.7 (C_q), 132.9 (C_q), 131.8 (CH), 131.5 (CH), 128.8 (CH), 128.2 (CH), 71.5 (C_q), 65.4 (CH), 52.0 (CH_3), 45.8 (CH_2), 31.2 (CH_3), 27.8 (CH_3), 23.1 (CH_3). ^{11}B NMR δ 28.2. LRMS (CI) m/z: 262.9 ($[M + H]^+$, 100).

2-(4-Iodophenyl)-4,4,6-trimethyl-1,3,2-dioxaborinane 3e. **3e** was prepared according to general procedure starting from 1,4-diiodobenzene (1.65 g, 5 mmol), MPBO^{i}Pr (1.02 g, 5.5 mmol) and ^{i}PrMgCl·LiCl (4.4 mL, 1.3 M in THF, 5.5 mmol): yellow oil (1.66 g, quantitative). IR: 3069 and 3037 (CH ar.), 2972 (CH_3), 1583 (C═C ar.), 1399 (B−C), 1301 (B−O asym.), 1163 (B−O sym.). ^{1}H NMR δ 7.66 (d, J = 8.1, 2H), 7.51 (d, J = 8.1, 2H), 4.30 (dqd, J = 11.8, 6.2 and 2.9, 1H), 1.83 (dd, J = 13.8 and 2.9, 1H), 1.55 (dd, J = 13.8 and 11.8, 1H), 1.35 (s, 3H), 1.33 (s, 3H), 1.32 (d, J = 6.2, 3H). ^{13}C NMR δ 136.7 (CH), 135.7 (CH), 97.9 (C_q), 71.4 (C_q), 65.2 (CH), 46.1 (CH_2), 31.4 (CH_3), 28.3 (CH_3), 23.3 (CH_3). ^{11}B NMR δ 26.8. LRMS (EI) m/z: 329.0 (29), 330.0 (100), 331.0 (14).

2-(2-Iodophenyl)-4,4,6-trimethyl-1,3,2-dioxaborinane 3f. **3f** was prepared according to general procedure starting from 1,2-diiodobenzene (330 mg, 1 mmol): yellow oil (270 mg, 82%). IR: 3062 (CH ar.), 2973 and 2932 (CH_3), 1584 and 1553 (C═C ar.), 1395 (B−C), 1304 (B−O asym.), 1166 (B−O sym.). ^{1}H NMR δ 7.78 (d, J = 7.8, 1H), 7.45 (dd, J = 7.4 and 1.7, 1H), 7.30−7.24 (m, 1H), 6.98 (td, J = 7.8 and 1.7, 1H), 4.37 (dqd, J = 11.9, 6.2 and 3.0, 1H), 1.85 (dd, J = 13.8 and 3.0, 1H), 1.65 (dd, J = 13.8 and 11.9, 1H), 1.40 (s, 3H), 1.39 (s, 3H), 1.35 (d, J = 6.2, 3H). ^{13}C NMR δ 139.3 (CH), 134.8 (CH), 130.9 (CH), 127.1 (CH), 100.2 (C_q), 72.2 (C_q), 65.9 (CH), 46.2 (CH_2), 31.2 (CH_3), 28.3 (CH_3), 23.2 (CH_3). ^{11}B NMR δ 26.9. LRMS (EI) m/z: 329.0 (34), 330.0 (100), 331.0 (15).

2-(2-Bromophenyl)-4,4,6-trimethyl-1,3,2-dioxaborinane 3g. **3g** was prepared according to general procedure starting from 2-iodo-1-bromobenzene (283 mg, 1 mmol): yellow oil (204 mg, 86%). IR: 3063 and 3048 (CH ar.), 2974 and 2932 (CH_3), 1588 and 1557 (C═C ar.), 1396 (B−C), 1305 (B−O asym.), 1167 (B−O sym.). ^{1}H NMR δ 7.52 (dd, J = 7.3 and 1.8, 1H), 7.48 (dd, J = 7.5 and 1.1, 1H), 7.23 (td, J = 7.3 and 1.1, 1H), 7.15 (td, J = 7.5 and 1.8, 1H), 4.36 (dqd, J = 11.8, 6.2 and 3.0, 1H), 1.85 (dd, J = 13.9 and 3.0, 1H), 1.63 (dd, J = 13.9 and 11.8, 1H), 1.39 (s, 3H), 1.37 (s, 3H), 1.34 (d, J = 6.2, 3H). ^{13}C NMR δ 135.1 (CH), 132.6 (CH), 130.8 (CH), 127.3 (C_q), 126.4 (CH), 72.0 (C_q), 65.8 (CH), 46.0 (CH_2), 31.2 (CH_3), 28.2 (CH_3), 23.2 (CH_3). ^{11}B NMR δ 27.0. LRMS (EI) m/z: 281.1 (28), 282.0 (100), 283.0 (35), 284.0 (94), 285.0 (18).

2-(2-Chlorophenyl)-4,4,6-trimethyl-1,3,2-dioxaborinane 3h. **3h** was prepared according to general procedure starting from 2-iodo-1-chlorobenzene (241 mg, 1 mmol): yellow oil (182 mg, 76%). IR: 3063 (CH ar.), 2974 (CH_3), 1592 and 1561 (C═C ar.), 1395 (B−C), 1305 (B−O asym.), 1167 (B−O sym.). ^{1}H NMR δ 7.58 (dd, J = 7.2 and 1.9, 1H), 7.29 (dd, J = 7.8 and 1.3, 1H), 7.23 (td, J = 7.8 and 1.9, 1H), 7.17 (td, J = 7.2 and 1.3, 1H), 4.35 (dqd, J = 11.8, 6.2 and 3.0, 1H), 1.85 (dd, J = 13.9 and 3.0, 1H), 1.61 (dd, J = 13.9 and 11.8, 1H), 1.38 (s, 3H), 1.36 (s, 3H), 1.33 (d, J = 6.2, 3H). ^{13}C NMR δ 138.7 (C_q), 135.3 (CH), 130.8 (CH), 129.4 (CH), 125.8 (CH), 71.9 (C_q), 65.7 (CH), 46.0 (CH_2), 31.2 (CH_3), 28.2 (CH_3), 23.2 (CH_3). ^{11}B NMR δ 26.9. LRMS (EI) m/z: 236.2 (3), 237.1 (25), 238.1 (100), 239.1 (19), 240.1 (46), 241.1 (4).

4,4,6-Trimethyl-2-(2-(trifluoromethyl)phenyl)-1,3,2-dioxaborinane 3i. *The 2.5-g Scale Preparation.* **3i** was prepared according to general procedure starting from 2-iodo-1-trifluoromethylbenzene (2.72 g, 10 mmol), MPBOiPr (2.06 g, 11 mmol), and ^{i}PrMgCl·LiCl (8.7 mL, 1.3 M in THF, 11 mmol): yellow oil (quantitative) that was used without further purification for the synthesis of **5**.

The 25-g Scale Preparation. A dry and nitrogen-flushed 500-mL three-neck round-bottom flask equipped with a magnetic stirrer, a thermometer, a 250-mL pressure-equalizing dropping funnel, and a septum was charged with 2-iodobenzotrifluoride **2i** (24.7 g, 91 mmol) and MPBO^{i}Pr **1** (18.9 g, 102 mmol). THF was then added (100 mL). ^{i}PrMgCl·LiCl (prepared according to ref 6b, 130 mL, 0.8 M in THF, 104 mmol) was charged in the dropping funnel. The reaction mixture was cooled to −10 °C (NaCl−ice bath), ^{i}PrMgCl·LiCl was added portionwise over 27 min. The internal temperature remained under +1 °C. The dropping funnel was charged with a saturated aqueous NH_4Cl solution (50 mL) that was added to the reaction mixture in two portions; the temperature rose to +15 °C, and a solid precipitated. The mixture was diluted with 50 mL water (dissolution of the solid) and was transferred into a 500-mL separating funnel. The organic phase was separated, and the aqueous phase was extracted with Et_2O (150 mL). The combined organic phases were then washed with a saturated aqueous NH_4Cl solution (20 mL) and a saturated aqueous NaCl solution (40 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure, affording **3i** as a yellow oil (24.7 g, quantitative).

IR: 3063 and 3028 (CH ar.), 2976 (CH_3), 1401 (B−C), 1316 (B−O asym.), 1159 (B−O sym.). ^{1}H NMR δ 7.66−7.57 (m,

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2H), 7.51−7.36 (m, 2H), 4.37 (dqd, J = 11.8, 6.2 and 3.0, 1H), 1.88 (dd, J = 13.9 and 3.0, 1H), 1.65 (dd, J = 13.9 and 11.8, 1H), 1.39 (s, 3H), 1.35 (s, 3H), 1.32 (d, J = 6.2, 3H). ^{13}C NMR δ 133.6 (CH), 133.0 (q, ^{2}J = 31.0, C_q), 130.8 (CH), 129.0 (CH), 125.4 (q, ^{3}J = 4.8, CH), 124.9 (q, ^{1}J = 273.5, C_q), 72.0 (C_q), 65.9 (CH), 46.0 (CH_2), 31.1 (CH_3), 27.9 (CH_3), 23.1 (CH_3). ^{11}B NMR δ 27.8. ^{19}F NMR δ −59.2. LRMS (EI) m/z: 172.1 (28), 173.1 (100), 174.1 (8), 271.2 (3), 272.2 (9), 273.2 (1).

2-Bromo-6-(4,4,6-trimethyl-1,3,2-dioxaborinan-2-yl)pyridine 3j. 3j was prepared according to general procedure starting from 6-iodo-2-bromopyridine (284 mg, 1 mmol): yellow oil (260 mg, 92%). IR: 3044 (CH ar.), 2973 (CH_3), 1575 and 1548 (C═C ar.), 1403 (B−C), 1299 (B−O asym.), 1164 (B−O sym.). ^{1}H NMR δ 8.58 (d, J = 1.7, 1H), 7.80 (dd, J = 7.9 and 1.7, 1H), 7.35 (d, J = 7.9, 1H), 4.28 (dqd, J = 10.8, 6.2 and 3.0, 1H), 1.82 (dd, J = 14.4 and 3.0, 1H), 1.53 (dd, J = 14.4 and 10.8, 1H), 1.31 (s, 3H), 1.30 (s, 3H), 1.27 (d, J = 6.2, 3H). ^{13}C NMR δ 155.5 (CH), 144.5 (C_q), 143.9 (CH), 127.3 (CH), 71.8 (C_q), 65.5 (CH), 46.0 (CH_2), 31.2 (CH_3), 28.2 (CH_3), 23.1 (CH_3). ^{11}B NMR δ 26.4. LRMS (EI) m/z: 282.0 (25), 283.0 (100), 284.0 (25), 285.0 (92), 286.0 (15).

4,4,5,5-Tetramethyl-2-(2-(trifluoromethyl)phenyl)-1,3,2-dioxaborolane 7i. 7i was prepared according to general procedure starting from 2-iodo-1-trifluoromethylbenzene (281 mg, 1 mmol) and PinBO^{i}Pr (335 mg, 1.8 mmol): yellow oil (250 mg, 93%). IR: 3063 (CH ar.), 2981 (CH_3), 1354 (B−C), 1316 (B−Oasym.), 1140 (B−O sym.). ^{1}H NMR δ 7.76−7.69 (m, 1H), 7.68−7.61 (m, 1H), 7.55−7.45 (m, 2H), 1.37 (s, 12H). ^{13}C NMR δ 134.9 (CH), 134.0 (q, ^{2}J = 31.4, C_q), 130.9 (CH), 130.1 (CH), 125.4 (q, ^{3}J = 5.0, CH), 124.6 (q, ^{1}J = 273.4, C_q), 84.6 (C_q), 24.8 (CH_3). ^{11}B NMR δ 31.2. ^{19}F NMR (376 MHz) δ −59.7. LRMS (ESI^{+}) m/z: 295.0 (100, $[M + Na]^{+}$).

Suzuki coupling: Preparation of 4′-Methyl-3′-nitro-2-(trifluoromethyl)-1,1′-biphenyl 5. A dry, nitrogen-flushed 10-mL flask equipped with a magnetic stirrer and a septum was charged with 4-bromo-2-nitrotoluene (216 mg, 1 mmol), **3i** (408 mg, 1.5 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), S-Phos (8.2 mg, 0.02 mmol), and K_3PO_4 (848 mg, 4 mmol). Toluene (2 mL) and water (0.4 mL) were then added, and the reaction mixture was heated at 100 °C. The consumption of the bromide was followed by GC. The completion was obtained after 3 h. The crude mixture was filtered through a thin pad of silica gel. After concentration of the filtrate, purification of the residue by flash chromatography (eluent: cyclohexane/ethyl acetate, 99:1) yielded **5** as a yellow oil (226 mg, 80%). IR: 3069 (CH ar.), 2971 and 2932 (CH_3), 1530 (nitro ar.), 1125 and 1112 (CF_3). ^{1}H NMR δ 7.96 (d, J = 1.5, 1H), 7.78 (d, J = 7.6, 1H), 7.60 (t, J = 7.6, 1H), 7.53 (t, J = 7.6, 1H), 7.50−7.45 (m, 1H), 7.38 (d, J = 7.9, 1H), 7.33 (d, J = 7.6, 1H), 2.66 (s, 3H). ^{13}C NMR δ 148.8 (C_q), 138.9 (C_q), 138.7 (q, ^{3}J = 2.0, C_q), 133.6 (q, ^{4}J = 1.2, CH), 133.1 (C_q), 132.5 (CH), 132.0 (CH), 131.8 (CH), 128.8 (q, ^{2}J = 30.1, C_q), 128.4 (CH), 126.4 (q, ^{3}J = 5.3, CH), 125.2 (q, ^{4}J = 1.4, CH), 124.1 (q, ^{1}J = 273.9, C_q), 20.3 (CH_3). ^{19}F NMR δ −56.8. LRMS (ESI^{+}) m/z: 304.0 ($[M + Na]^{+}$, 100).

■ ASSOCIATED CONTENT

Supporting Information. Copies of NMR spectra for all new compounds; ^{1}H, ^{11}B (and ^{19}F) NMR spectra of the crude products for **3a** and **3i**; ^{1}H NMR spectra of the crude product for the borylation of **2m** (Table 2, entry 3). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

Telephone: (+)33 476635796. Fax: (+)33 476635983. E-mail: Pierre-Yves.Chavant@ujf-grenoble.fr.

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(24) For the preparation of the dimagnesium reagent from *p*-diiodobenzene, see: Krasovskiy, A.; Straub, F.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 159–162.

(25) Formation of an aryne from *o*-halo magnesium species at room temperature, and even at −78 °C, has been hypothesized: (a) Hart, H.; Harada, K.; Du, C.-J. F. *J. Org. Chem.* **1985**, *50*, 3104–3110. (b) Ghosh, T.; Hart, H. *J. Org. Chem* **1988**, *53*, 3555–3558. Formation of 2-halo arylmagnesium species via magnesium−iodine exchange before addition of a trialkylborate was performed at low temperature: −78 °C:(c) Baron, O.; Knochel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 3133–3135. (d) Wegner, H. A.; Reisch, H.; Rauch, K.; Demeter, A.; Zachariasse, K. A.; de Meijere, A.; Scott, L. T. *J. Org. Chem.* **2006**, *71*, 9080–9087. (e) Al-Zoubi, R. M.; Marion, O.; Hall, D. G. *Angew. Chem., Int. Ed.* **2008**, *47*, 2876–2879. (f) Diemer, V.; Leroux, F. R.; Colobert, F.; Eur. *J. Org. Chem* **2011**, 327–340. −30 °C:(g) Huang, H.; Drueckhammer, D. G. *Chem. Commun.* **2006**, 2995–2997. The 2-iodophenylmagnesium species is stable for 30 min at −20°C:(h) Cvengros, J.; Stolz, D.; Togni, A. *Synthesis* **2009**, 2818–2824.

(26) The Suzuki−Miyaura coupling was performed according to Buchwald's procedure: Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696, using 1.5 equiv of boronic ester. Interestingly, 0.3 equiv of unreacted arylboronic ester were recovered after chromatography, indicating that a lower excess could have been used.

(27) (a) Fischer, F. C.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 21–24. Bibliography, see:(b) Campeau, F.-C.; Fagnou, K. *Chem. Soc. Rev.* **2007**, *36*, 1058–1068. (c) Dick, G. R.; Knapp, D. M.; Gillis, A. P.; Burke, M. D. *Org. Lett.* **2010**, *12*, 2314–2317.

(28) See in particular refs 6a and 21c.

(29) It is worth noting that anisyl halides are among the best substrates for all variants of Pd-catalyzed-borylation (which is fast and high-yielding with electron-rich substrates).

(30) On small laboratory scales, a slight excess (10 mol %) of MPBO^{i}Pr **1** should be kept so that accidental excess of isopropylmagnesium halide will be trapped by **1**.

(31) PinBO^{i}Pr (**5**) is commercially available (for instance: 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 98%, 5 mL, Aldrich, €54.10) or can be prepared (see for instance the recent example: Lin, Q.; Meloni, D.; Pan, Y.; Xia, M.; Rodgers, J.; Shepard, S.; Li, M.; Galya, L.; Metcalf, B.; Yue, T.-Y.; Liu, P.; Zhou, J. *Org. Lett.* **2009**, *11*, 1999–2002. Note that MPBO^{i}Pr (**1**) is also commercially available (2-isopropoxy-4,4,6-trimethyl-1,3,2-dioxaborinane, 99%, 5 mL, Aldrich, €20.20).

(32) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165–168.