Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201401153

Amine–Borane Complexes: Air- and Moisture-Stable Partners for Palladium-Catalyzed Borylation of Aryl Bromides and Chlorides

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Received: December 12, 2014; Revised: February 16, 2015; Published online: March 24, 2015

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201401153.

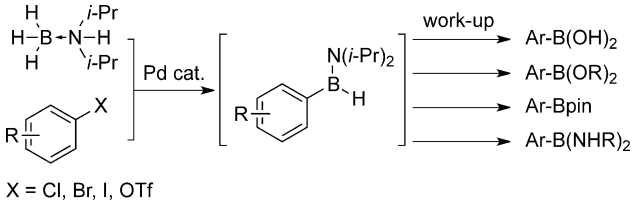
Abstract: A method for using amine–borane complexes directly in palladium catalyzed borylation has been developed. The reaction proceeds through the sequential formation of a boronium species followed by deprotonation leading to the aminoborane. This reagent is then directly used in the borylation process leading, after work-up, to various boronic acid derivatives. The reaction was applied to (hetero)aryl triflates, iodides, bromides and chlorides.

Keywords: amine–borane complexes; aryl halides; boron; C–B bond formation; homogeneous catalysis

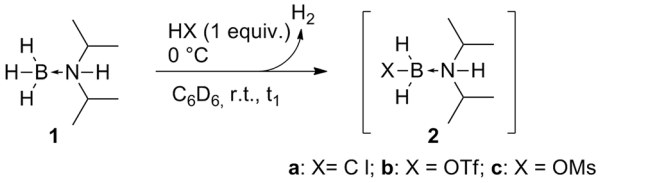
Arylboronic acids and their derivatives are very important compounds in organic chemistry, as chemical intermediates or building blocks. Their use in transition metal-catalyzed cross-coupling reactions can lead, for example, to carbon–carbon and carbon–heteroatom bond formation. Traditionally arylboronic acids and boronates are obtained from aryl halides (I, Br) after metal-halogen exchange with lithium or magnesium and subsequent reaction with trialkoxyboranes.[1] Although efficient, such conditions are not compatible with many functional groups (e.g., reactive carbonyl, nitrile, etc.…) eventually requiring tedious additional protection–deprotection steps. Since the late 1990s, transition metal-catalyzed borylation reactions have been developed considerably. Direct C–H borylations[2] of aromatics catalyzed mainly by Rh[3] and Ir[3a,4] have been reported using bispinacolatodiboron and pinacolborane as borylating agents.[2–5] Mostly, mixture of regioisomers are obtained[5h,j] except in the case of 1,3-disubstituted benzenes,[5a,b] or where sterically hindered groups[5c] and chelating groups[5d–g,i] are used to orientate the borylation.

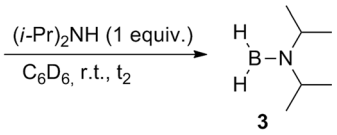
Alternatively, Pd-,[6] Ni-,[7] Cu-,[8] or Zn[9]-catalyzed borylations of aryl halides (I, Br) or sulfonates have been described.[10] Few publications deal with the metal-catalyzed borylation of aryl chlorides,[6c–j,n,o,q,u,7a,c–f,h,11] in particular of electron-poor unreactive aryl chlorides.[7e,f] Rh-catalyzed borylation of nitriles[12] and Ni-catalyzed borylation of amides and carbamates[13] through the cleavage of C–CN, C–N and C–O bonds have also been described. Very recently, transition metal-free borylation of aryl iodides[14] and metal-free borylation of amines,[15] *via in situ* diazotization, have been studied. An elegant metal-free borylation of aryl bromides using silylborane was published by Ito et al.[16] Unfortunately low yields were obtained from relative inexpensive and broadly available aryl chlorides.

In 2003, Vaultier et al. reported the Pd-catalyzed borylation of iodides and bromides using dialkylaminoboranes[17] as boron source. Recently, we extended the scope of this reaction with sequential aminoborylation/Suzuki–Miyaura cross-coupling reaction leading to non-symmetrical biaryl compounds.[18] and with the borylation of unactivated aryl chlorides in the presence of potassium iodide as additive.[19] Aryldiazonium tetrafluoroborates can also participate in the borylation process with aminoborane through the formation of the aryl radical.[20] Overall, dialkylaminoboranes appeared to be very efficient reagents in borylation reactions. Indeed, resulting aminoarylboranes are easily transformable in boronic acids, boronates or trifluoroborate salts, depending on reaction work-up.[19,21] Only monomeric aminoboranes, typically $(i\text{-Pr})_2NBH_2$, participate in the catalyzed borylation process. They are usually prepared by thermal decomposition of the corresponding amine–borane complexes or by trimethylsilyl chloride treatment of lithium dialkylaminoborohydrides.[22] Metal-catalyzed dehydro-



Scheme 1. Catalytic borylation with amine–borane complexes.





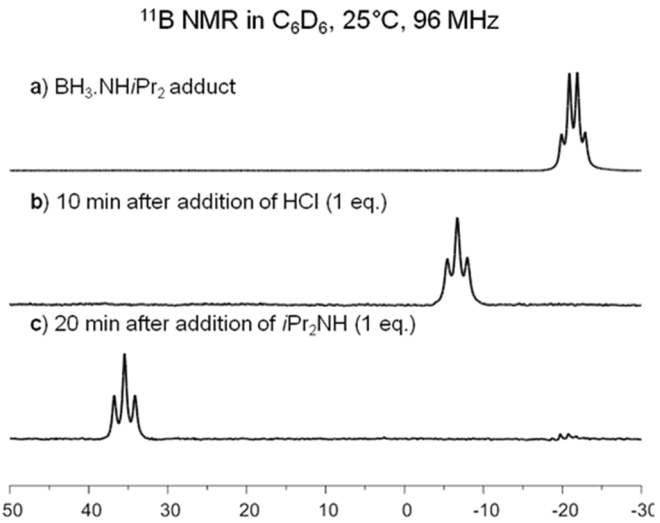


Figure 1. Preparation of diisopropylaminoborane: ^{11}B NMR monitoring (C_6D_6, 25 °C).

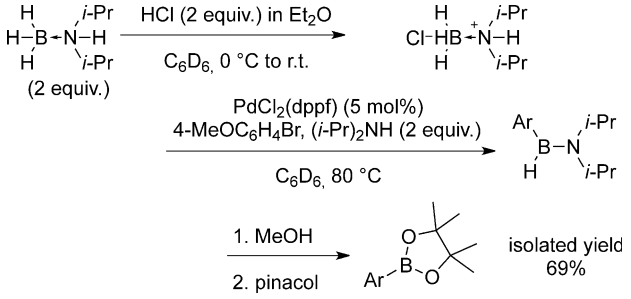
genation of these complexes can also be used but remains inefficient on sterically hindered amine–borane complexes.[23] In all cases, the prepared aminoborane is recovered before further use.

One of the downsides of this methodology stands in the relative instability of the aminoborane. Indeed, similarly to trialkoxyborane or dialkoxyborane, these reagents are prone to fast hydrolysis and require distillation before use. On the contrary, amine–borane complexes are obtained directly from dialkylamines and a BH_3 source[17b] or $NaBH_4$[17b,24] and are relatively air- and moisture-stable. As a precursor of aminoboranes, we tentatively used them in a dehydrogenation–coupling sequence, but the efficiency was fairly low with isolated yields limited to 50%.[24] Herein, we wish to report our recent results concerning a practical, economic and efficient Pd-catalyzed borylation of aryl halides using diisopropylamine–borane[25] as reagent (Scheme 1).

In 2006, Baker et al. described the use of acids to catalyze the dehydrocoupling of ammonia–borane in aminoborane *via* the boryl–ammonium intermediate $[H_2B\text{-}NH_3]^+$.[26] Later, cyclotriborazane $[(NH_2\text{-}BH_2)_3]$ was prepared by basic treatment of $[BH_2\text{-}NH_3]Cl$.[27] Thus we planned to generate the boryldiisopropylammonium salt from the corresponding amine–borane complex. Upon base addition, the aminoborane would be generated in the reaction mixture. During our study, our strategy was validated by Manners who reported the formation of methyl- and dimethylaminoborane, as polymer and dimer, respectively, from borylammonium salts $[RR'NH\text{-}BH_2]^+X^-$ [X = $B(C_6F_5)_3$, OTf] or amine–chloroborane complexes $RR'NH\text{-}BH_2X$.[28] Formation of $MeNH{=}BH_2$ was proven by ^{11}B NMR spectroscopy monitoring of the reaction at low temperature.

In our case, diisopropylamine (DIPA) was chosen as base to avoid refunctionalization of boron derivatives often occurring when amine mixtures are used. We investigated a series of acids (HCl, TFA, $MeSO_3H$ and H_2SO_4) and monitored the reaction using ^{11}B NMR spectroscopy. Hence, to a solution of diisopropylamine–borane complex (q at −20.4 ppm, Figure 1a) was added one equivalent of the studied acid. All acids were added in pure form, except HCl which was used in Et_2O. Upon reaction, a triplet (Figure 1b), characteristic of borylammonium intermediate, is observed between −7 and −3 ppm depending on the counter-anion (Cl, −6.7 ppm; OTf, −3.7 ppm; OMs, −4.1 ppm; SO_4, −3.7 ppm as broad signal). These results are consistent with those of Manners who observed in ^{11}B NMR, a downfield shift from −6.8 ppm to −2.2 ppm when the chloride substituent was replaced by triflate anion in borylmethylammonium.[28] Complete disappearance of the amine–borane complex proceeded within 15 min except for CH_3SO_3H for which 5 h were required to obtained a complete conversion. Then, addition of one equivalent of diisopropylamine led to the expected diisopropylaminoborane (triplet at 35.5 ppm, Figure 1c) through deprotonation of the borylammonium. In the case of H_2SO_4, despite the formation of the borylammonium, no $(i\text{-}Pr)_2NBH_2$ was observed upon DIPA addition and only a broad signal at 28 ppm was observed and attributed to the formation of trivalent borane–sulfate oligomers.

The borylammonium counter-anion influences the acidity of the intermediate **2** resulting in strong variation of the deprotonation efficiency. As mentioned by Manners,[28] the pK_a is lowered by poorly coordinating



Scheme 2. One-pot dehydrogenation/arylation of diisopropylamine–borane with 4-bromoanisole.

substituents. As chloride has weaker interactions with boron than oxygenated anions, the proton on the NH group of **2a** is the most acidic and leads to fast deprotonation (20 min). Similarly, the reactivity difference observed between triflate (5 h) **2b** and methylsulfonate **2c** (16 h) is directly related to the decreased binding of the oxygen atom induced by the trifluoromethyl group.

After having generated *in situ* the boryldiisopropylammonium by HCl addition, we successively added diisopropylamine, 4-methoxybenzyl bromide, and a catalytic amount of $PdCl_2$(dppf) (Scheme 2). The mixture was heated to 80 °C and the reaction monitored by ^{1}H and ^{11}B NMR (see the Supporting Information). After 2 h 30 min, the characteristic triplet at 35.5 ppm, in the ^{11}B NMR spectrum, was replaced by a broad signal at 39 ppm indicating the formation of the aminoarylborane **4**. The reaction was quenched with deuterated methanol. After 1 h, the signal at 39 ppm wholely disappeared leading unsurprisingly to a mixture of corresponding methyl boronate [Ar-B$(OCD_3)_2$, 28.1 ppm] and boroxine (20.7 ppm). After transesterification with pinacol, the boronate **5a** was isolated in 69% yield.

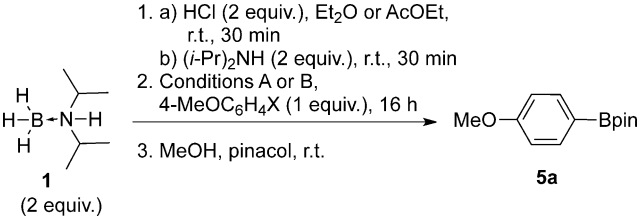
Encouraged by this result, we carried on with the borylation of anisoles substituted with various leaving groups (X = I, Br, Cl, OTf) in the *para* position. Previously, aminoborane borylation conditions had been optimized, and varied slightly depending on the halide carried by the aromatic ring. Consequently, borylations of 4-iodoanisole,[18] 4-anisyl triflate and 4-bromoanisole were carried out using $PdCl_2$(dppp) as catalyst in toluene at 110 °C.[17a,b] Diisopropylamine was preferred to triethylamine in order to keep the same base for the whole reaction sequence. Borylation of 4-chloroanisole was carried out with $Pd(OAc)_2$, XPhos as ligand and potassium iodide as additive, in ethyl acetate at 50 °C, according to our recent results on the borylation of aryl chlorides.[19a] Triethylamine was kept as base since it has been proved to be more efficient than diisopropylamine. A solution of hydrochloric acid in ethyl acetate was used to generate the amine boronium.

The one-pot dehydrogenation/arylation of diisopropylamine–borane complex proceeds smoothly with the aromatic iodide and triflate. In both cases, after work-up and treatment with pinacol, the borylated compound was isolated in 99% yield (entries 1 and 2, Table 1). In case of bromo- and chloroanisoles, yields in isolated products were lower, 70% and 64% respectively (entries 3 and 5, Table 1). The presence of diisopropylammonium chloride resulting from the formation of aminoborane is detrimental in the coupling process as it reacts with the DIPA. A simple filtration before adding catalysts and substrate improved the yields to 99% and 97%, respectively (entries 4 and 6, Table 1).

With the optimized conditions in hand, the substrate scope of this reaction was examined with a variety of aryl bromides (Table 2). Obvious improvements in yields were observed *via* this methodology compared to our previous results *via* sequential dehydrogenation arylation of $(i\text{-Pr})_2$NH–BH_3 with Pd nanoparticles[24] (Table 2). In general, the borylation of various aryl bromides occurred in good to excellent yields from **1**. Aryl bromides bearing an electron-donating group, such as methoxy, methyl or phenyl, afforded the corresponding pinacolboronate esters in high yields (Table 2 entries 1–4, 7 and 8).

The borylation of 2-bromothiophene afforded 81% of **5f** (Table 2, entry 6) while the less reactive 3-regioisomer has been borylated with an acceptable yield of 69% (Table 2, entry 5). Other heteroaromatics such as 3- and 5-bromobenzo[*b*]thiophenes were also borylated efficiently (Table 2, entries 9 and 10) showing that potential coordination of the boron center to the sulfur atom of these substrates was not detrimental.

Table 1. Sequential dehydrogenation–arylation of diisopropylamine–borane **1**.

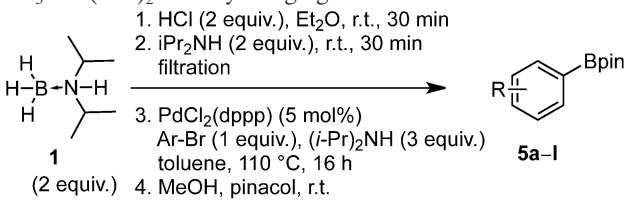


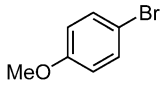
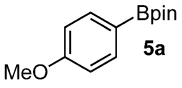
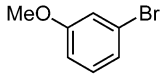
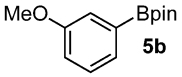
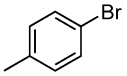
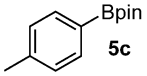
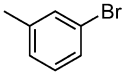
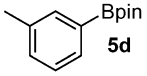
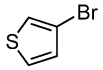
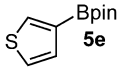
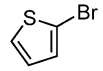
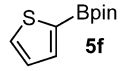
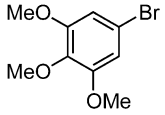
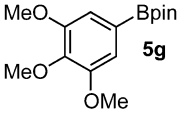
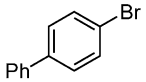
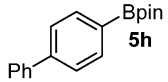
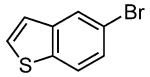
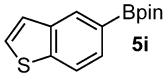
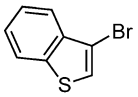
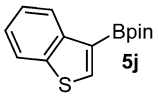
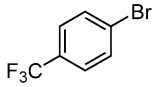
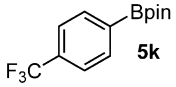
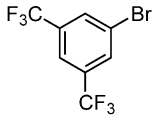
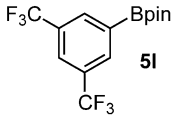
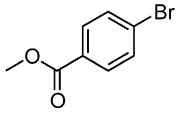
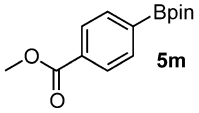
Entry	X	Procedure[a]	Yield [%]
1	I	A	99
2	OTf	A	99
3	Br	A	70
4	Br	A	99[b]
5	Cl	B	64
6	Cl	B	97[b]

[a] Procedure A: $PdCl_2$(dppp) (5 mol%), $(i\text{-Pr})_2$NH, toluene, 110 °C. Procedure B: $Pd(OAc)_2$ (2 mol%), XPhos (6 mol%), Et_3N, KI (2 mol%) AcOEt, 50 °C.

[b] With filtration of $(i\text{-Pr})_2NH_2Cl$.

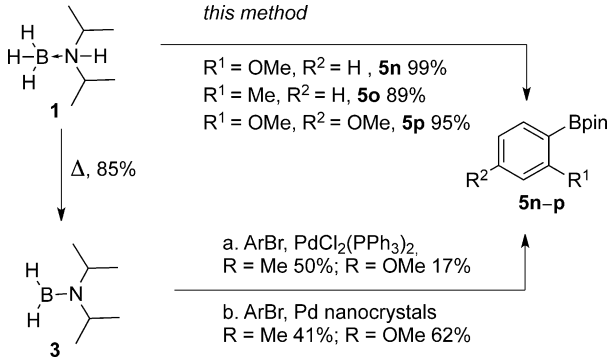
Table 2. Synthesis of boronates from aryl bromides using $BH_3{\cdot}NH(i\text{-}Pr)_2$ as borylating agent.



Entry	Ar-Br	Ar-Bpin	Yield [%]	Yield [%][24]
1		 **5a**	99	50
2		 **5b**	94	40
3		 **5c**	78	45
4		 **5d**	87	37
5		 **5e**	69	n.d.
6		 **5f**	81	35
7		 **5g**	89	26
8		 **5h**	95	33
9		 **5i**	73	n.d.
10		 **5j**	83	n.d.
11		 **5k**	99[a]	26
12		 **5l**	68[a]	n.d.
13		 **5m**	38	n.d.

[a] 0.5 equiv. of KI were used.

With electron-withdrawing groups, as aforementioned, yields decreased sharply. 1-Bromo-4-trifluoromethylbenzene **5k** and 1-bromo-3,5-bis(trifluoromethyl)benzene **5l** have been synthesized in 65% and 40% yields, respectively. Nevertheless, the very low reactivity of electron-poor substrates can be compensated by addition of potassium iodide. With 0.5 equivalent of KI, 1-bromo-4-trifluoromethylbenzene led to 99% of **5k** and a 68% yield was reached when the aromatic bears two withdrawing trifluoromethyl substituents (Table 2, entries 11 and 12). Methyl 4-bromobenzoate led to the formation of 75% of the desired product with 25% of methyl benzoate (38% yield after purification Table 2, entries 13).

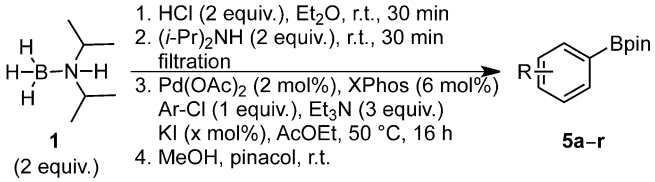


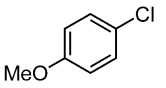
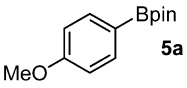
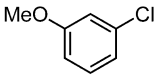
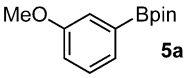
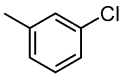
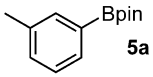
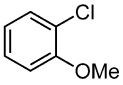
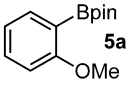
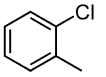
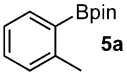
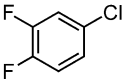
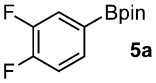
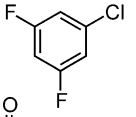
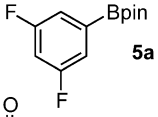
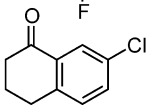
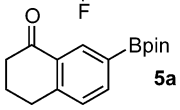
Scheme 3. Comparison with reactivity with isolated $BH_2N(i\text{-}Pr)_2$ on *ortho*-substituted aryl bromides.

Then, we applied these borylation conditions to sterically hindered aryl bromides (Scheme 3). Borylation of *ortho*-substituted bromides was not strongly affected by steric hindrance. Indeed **5n**, **5o** and **5p** were isolated in 99%, 89% and 95% yields, respectively (Scheme 3). This result is in contrast with results observed with isolated $BH_2N(i\text{-}Pr)_2$. For instance, pinacol 2-methylphenylboronate **5o** has never been obtained in yield greater than 50% in the past using aminoborane. In our case, **5o** is isolated in 89% yield. As a comparison, yields previously obtained with identical substrates using diisopropylaminoborane as borylation reagent with $PdCl_2(PPh_3)_2$[17a,22a] or Pd nanocrystals[29] were significantly lower (Scheme 3).

Aryl chlorides remain challenging substrates and only few methods are efficient enough to allow their borylation with limited side product formation, especially *ortho*-substituted or electron-poor ones. The conditions optimized previously (Table 1, entry 6) proved to be efficient for most aryl chlorides bearing donor substituents in *para*- and *meta*-positions (Table 3, entries 1 to 3). More importantly, this method was also applicable to more reluctant aryl chlorides provided that more potassium iodide was used. 2-Chlorotoluene and 2-chloroanisole led to the expected pinacolboronate esters **5o** and **5n** in 75% and 99% yields, respectively (Table 3, entries 4 and 5). Aryl chlorides bearing fluorine reacted smoothly to give **5q** and **5r** in excellent yields exceeding 90% (Table 3, entries 6 and 7) and chlorochromanone was converted to **5s** without ketone reduction (Table 3,

Table 3. Synthesis of boronates from aryl chlorides using $BH_3{\cdot}NH(i\text{-}Pr)_2$ as borylating agent.



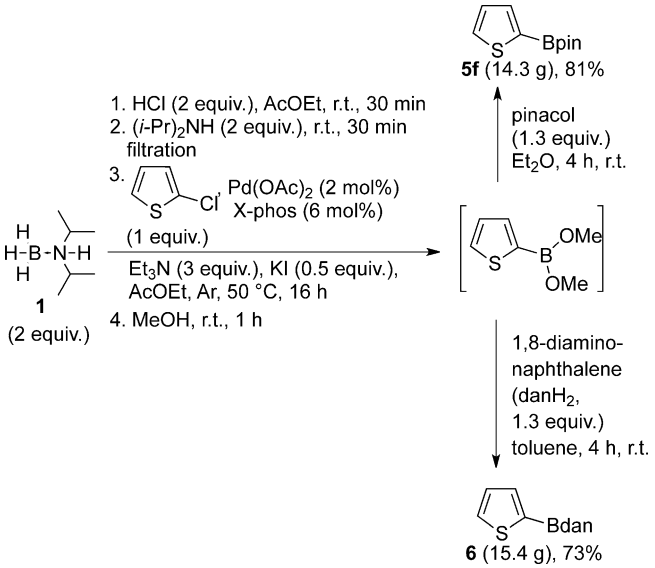
Entry	Ar-Cl	Ar-Bpin	Yield [%]	Yield [%][24]
1		 **5a**	99[a]	50
2		 **5a**	93[a]	97
3		 **5a**	99[a]	88
4		 **5a**	99[b]	88
5		 **5a**	75[b]	62
6		 **5a**	90[b]	n.d.
7		 **5a**	96[b]	59
8		 **5a**	90[b]	89

[a] 2 mol% KI were used.
[b] 50 mol% KI were used.

entry 8). In all cases, the new procedure using directly diisopropylamine–borane as borylating agent affords similar or much better yields than previous methods (Table 3), in particular with deactivated aryl chlorides.

This procedure is not only efficient, but also applicable for the multigram scale preparation of heteroarylboronates. As an example, the borylation of 84 mmol of 2-chlorothiophene led to the isolation of nearly 15 g of the boron derivative (Scheme 4). This multigram scale experiment was performed twice to afford the 1,8-diaminonaphthalene-derived arylborane **6** (Ar-Bdan **6**, 73%), used in iterative cross-coupling reactions,[30] or the aryl pinacolboronate **5f** (Ar-Bpin **5f**, 81%).

In summary, we have developed an efficient and very convenient method for the borylation of aryl and heteroaryl halides using easily accessible and quite stable diisopropylamine–borane. It is noteworthy that



Scheme 4. Borylation of 2-chlorothiophene on multigram scale.

sterically hindered and unreactive aryl or heteroaryl chlorides, known to be very challenging substrates, reacted smoothly, and led to borylated products in good to excellent yields, including on larger scale.

Experimental Section

Techniques

GC-MS analyses were performed with an HP 6890 series GC-system equipped with a J&W Scientific DB-170 capillary column, an HP 5973 mass selective detector (EI) using the following conditions: 70 °C for 1 min then 20 °C·min^{-1} until 230 °C then 6 min at 230 °C. ^{1}H, ^{11}B, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker 300 MHz Avance I and a 400 MHz Avance II spectrometer. The chemical shifts (δ) and coupling constants (J) are expressed in ppm and hertz, respectively. The following abbreviations are used to describe the multiplicities: s: singlet, d: doublet, t: triplet, dd: doublet of doublets, td: triplet of doublets, ddd: doublet of doublets of doublets, m: multiplet.

Chemicals

Pinacol and diisopropylamine were purchased from Sigma–Aldrich and distilled before use. Aryl chlorides, aryl bromides and sodium borohydride were used without further purification. All catalytic reactions were carried out under an argon atmosphere unless otherwise specified. All chemicals were stored under argon. Toluene, THF and diethyl ether were distilled from sodium benzophenone and ethyl acetate from CaH_2. Silica gel (230–400 mesh) purchased from Merck was used for flash chromatography. Analytical TLC aluminium plates covered with silica gel 60 F254 were used.

Preparation of Amine–Borane Complex 1

To a stirred solution of diisopropylamine (70.6 mL, 0.5 mol) and $NaBH_4$ (30 g, 0.79 mol) in THF (500 mL) was added at 0 °C over a period of 45 min sulfuric acid (21.5 mL, 0.6 mol). The mixture was allowed to warm to room temperature and stirred for 3 h. The crude mixture was concentrated under vacuum and the residue was taken up with CH_2Cl_2, and then filtered to eliminate all solid residues. The filtrate was washed with water (4×100 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give the amine–borane complex as colorless oil which solidified upon cooling; yield: 51.8 g (90%).

General Procedure for the Borylation of Aryl Iodides, Aryl Triflates and Aryl Bromides

In a flask A charged with amine–borane complex **1** (0.3 mL, 2 mmol) under an argon atmosphere was added slowly, at 0 °C, HCl in Et_2O (1 mL, 2 M solution, 2 mmol). After stirring for 30 min at room temperature distilled $(i\text{-Pr})_2NH$ (0.28 mL, 2 mmol) was added and the solution was stirred for 30 min. In a flask B charged with $PdCl_2$dppp (30 mg, 0.05 mmol) under an argon atmosphere was added, in the following order: anhydrous toluene (1 mL), distilled $(i\text{-Pr})_2NH$ (0.42 mL, 3 mmol), aryl halide or aryl triflate (1 mmol) (Procedure A). In the case of aryl bromides bearing electron-withdrawing substituents, potassium iodide (83 mg, 0.5 mmol) was also introduced in flask B (Procedure B). Finally, the amine–borane complex obtained in the flask A in Et_2O was filtered and added to flask B. The reaction mixture was heated at 110 °C for 16 h before being cooled at −5 °C, quenched with anhydrous MeOH (2 mL) and stirred for 1 h at room temperature. All volatiles were removed under vacuum before adding pinacol (153 mg, 1.3 mmol) and Et_2O (2 mL), and the mixture was stirred for 4 h at room temperature. Then the reaction mixture was diluted with Et_2O (10 mL), and the organic phase was washed first with a solution of HCl (0.1 N, 2×10 mL), followed by an aqueous solution of $CuCl_2$ (50 g L^{-1}, 3×10 mL);[31] it was then dried over Na_2SO_4, filtered and concentrated under vacuum. The crude oil was passed through a pad of silica gel, eluting with Et_2O. The resulting filtrate was concentrated under vacuum and eventually purified by flash chromatography if some impurities were present in the residue.

General Procedure for the Borylation of Aryl Chlorides

In a flask A charged with amine–borane complex **1** (0.3 mL, 2 mmol) under an argon atmosphere was added slowly at 0 °C, HCl in AcOEt (1 mL, 2 M solution, 2 mmol). After stirring for 30 min at room temperature distilled $(i\text{-Pr})_2NH$ (0.28 mL, 2 mmol) was added and the solution was stirred for 30 min. In a flask B charged with $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), potassium iodide (3.3 mg, 0.02 mmol if procedure C is followed or 83 mg, 0.5 mmol in case of procedure D) and XPhos (28 mg, 0.06 mmol) under an argon atmosphere were added, in the following order: anhydrous EtOAc (1 mL), distilled Et_3N (0.4 mL, 3 mmol), and aryl chloride (1 mmol). Finally, the amine–borane complex obtained in the flask A in EtOAc was filtered and added to flask B. The reaction mixture was heated at 50 °C for 16 h before being cooled at −5 °C, quenched with anhydrous MeOH (2 mL) and stirred for 1 h at room temperature. All volatiles were removed under vacuum before adding pinacol (153 mg, 1.3 mmol) and Et_2O (2 mL), and the mixture was stirred for 4 h at room temperature. Then the reaction mixture was diluted with Et_2O (10 mL), and the organic phase was washed first with a solution of HCl (0.1 N, 2×10 mL), followed by an aqueous solution of $CuCl_2$ (50 g L^{-1}, 3×10 mL);[31] it was then dried over Na_2SO_4, filtered and concentrated under vacuum. The crude oil was passed through a pad of silica gel, eluting with Et_2O. The resulting filtrate was concentrated under vacuum and eventually purified by flash chromatography if some impurities were present in the residue.

Acknowledgements

H.D.S.G. acknowledges AST-Innovation for funding.

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