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Citation	Tetrahedron, 64(22), 4967-4971 https://doi.org/10.1016/j.tet.2008.03.102
Issue Date	2008-05-26
Doc URL	https://hdl.handle.net/2115/56361
Type	journal article
File Information	(48) Ar-Ar (B-B + H-Ar) (Full).pdf



Practical Synthesis of Pinacolborane for One-pot Synthesis of Unsymmetrical Biaryls *via* Aromatic C-H Borylation–Cross-Coupling Sequence

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Abstract

A method for practical preparation of pinacolborane from borane-diethylaniline and pinacol was newly developed. Aromatic C-H borylation of arenes with pinacolborane or bis(pinacolato)diboron catalyzed by $1/2[\text{Ir}(\text{OMe})(\text{COD})]_2$ -(4,4'-di-*tert*-butyl-2,2'-bipyridine) at 25 °C in hexane to give arylboronic esters was directly followed by cross-coupling with aromatic bromides at 60 °C in the presence of $\text{PdCl}_2(\text{dppf})$ (3.0 mol%) and K_3PO_4 in DMF. This one-pot, two-step procedures provided a variety of unsymmetrical biaryls in high yields.

Keywords: pinacolborane; biaryls; boron; C-H activation; cross-coupling

1. Introduction

Unsymmetrical biaryls are an important class of compounds due to the frequent occurrence of these fragments in natural products, pharmaceuticals, agrochemicals, and functional organic materials.¹ Transition metal-catalyzed cross-coupling of arylmetal compounds with aryl halides or triflates has been proved to be a general method applicable for preparation of such unsymmetrical biaryls.^{1d,1f} Among them, much attention has been focused on the use of arylboronic acids or esters in laboratories and industries since they are nontoxic, thermally stable, and inert to water and oxygen. A traditional method for preparations of such arylboron compounds is alkylation of $\text{B}(\text{OR})_3$ with aromatic lithium or magnesium reagents.² Alternative synthesis based on palladium-catalyzed cross-couplings of aryl halides and triflates with bis(pinacolato)diboron (B_2pin_2 , $\text{pin}=\text{Me}_4\text{C}_2\text{O}_2$)³ or pinacolborane (HBpin)⁴ are milder variants displayed high functional group compatibility. Another economical and environmentally benign process is transition metal-catalyzed direct C-H borylation of arenes developed by Hartwig⁵ and Smith⁶. Among the catalysts developed to date,⁷ a

combination of $[\text{Ir}(\text{OMe})(\text{COD})]_2$ and 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy) was recognized to be the best catalyst which allowed stoichiometric borylation of arenes with B_2pin_2 or HBpin at room temperature.⁸ Pinacolborane necessary for these coupling reactions is available from pinacol and borane-THF or borane-methyl sulfide complex (BMS).⁹ However, the protocol using $\text{BH}_3 \cdot \text{THF}$ and $\text{BH}_3 \cdot \text{SMe}_2$ is not suited for large-scale preparation due to certain inconveniences, e.g., the low concentration of and instability of $\text{BH}_3 \cdot \text{THF}$ and high volatility, flammability and unpleasant odor of dimethyl sulfide from $\text{BH}_3 \cdot \text{SMe}_2$. Because of growing importance of pinacolborane for the syntheses of boron compounds, a practical method for its large-scale preparation can be desirable. Here, we disclose a method for synthesizing pinacolborane from amine-borane complexes and its use for a sequence of the iridium-catalyzed aromatic C-H borylation and the palladium-catalyzed cross-coupling with aryl bromides to create convenient, one-pot procedure for the synthesis of unsymmetrical biaryls.

2. Results and discussion

2-1. Synthesis of pinacolborane

The first synthesis of HBpin (**1**) in 63% yield reported by Knochel involves reaction between $\text{BH}_3 \cdot \text{SMe}_2$ (BMS) and pinacol (Eq. 1).⁹ We adopted the use of amine-borane complexes as a borane source due to their advantage in large-scale preparation because of high thermal stability, low vapor pressure, inflammability and unpleasant odor.¹⁰ Borane-amine complexes are accessible by a reaction between metal borohydride and HNR_3Cl ¹¹ or by treatment of $\text{BH}_3 \cdot \text{THF}$ or $\text{BH}_3 \cdot \text{SMe}_2$ with amines.¹⁰ To investigate their reaction with pinacol to give HBpin, representative borane-amine complexes (**2**) were synthesized by treatment of $\text{BH}_3 \cdot \text{SMe}$ with amines in THF.¹⁰ Evaporation of the solvent and dimethyl sulfide in *vacuo* gave pure **2** in quantitative yields for NH_3 , 2,6-diisopropylaniline, N,N-dimethylaniline, N,N-diethylaniline, N-ethyl-N-isopropylaniline and diisopropylaniline (Eq 2). Sodium borohydride is an economical borane source that has been utilized for the preparation of BH_3 -THF or other borane-base adducts by treatment with $\text{BF}_3 \cdot \text{OEt}_2$.^{12,13} Thus, we utilized this protocol for preparation of $\text{BH}_3 \cdot \text{N}(\text{Ph})\text{Et}_2$ (**2d**) (Eq. 3). The reaction took place smoothly in the presence of N,N-diethylaniline in THF. Filtration of NaBF_4 through a Celite pad and evaporation of THF in *vacuo* afford **2d** in 89% yield. The preparation of **2d** suffered from some contamination of fluoroborane species. This byproduct was completely eliminated when NaBH_4 was used in slightly excess (1.07 eq) of the required stoichiometry for $\text{BF}_4 \cdot \text{OEt}_2$. By this method, 0.42 mol of pure **2d** was obtained from 0.5 mol of NaBH_4 .

Reaction of pinacol with these borane-amines complexes in tetraglyme yielded HBpin (**1**) and B₂pin₃ (**3**)¹⁴ with various molar ratios (Table 1). The conversions of borane-amine complexes (**2**, δ -21 – -6 ppm) and ratios of **1** (δ 28 ppm) and **3** (δ 20 – 22 ppm) were determined by ¹¹B NMR. The reaction was very slow for stable, small amine complexes such as NH₃ and dimethylaniline complex (entries 1 and 3) and fast for much sterically hindered 2,6-diisopropylaniline and diethylaniline complex (entries 2 and 4). Further increase in steric hindrance by N-substituents resulted in no reaction (entries 6 and 7). Selectivities giving HBpin toward **3** were parallel to these reaction rates. Thus, 100% selectivity was achieved by diethylamine complex which exhibited the fastest reaction rate among six complexes examined (entry 4). However, isolation of HBpin suffered from low yields (ca. 50%) because of formation of non volatile **3** during distillation in vacuo. It was difficult to prevent this equilibration when stoichiometric amount of **2d** and pinacol were used,¹⁵ but the yield was improved to 75% in the presence of 50% excess of BH₃ · N(Ph)Et₂ toward pinacol (entry 5).

2-2. One-pot synthesis of biaryls

Aromatic C-H borylation with HBpin (**1**) or B₂pin₂ takes place at room temperature in the presence of an iridium(I)-dtbpy catalyst. The preparation of 1.1 equivalents of arylboronate (**5**) was directly followed by cross-coupling with bromoarenes for one-pot synthesis of biaryls (**6**) (Scheme 1).

Previous studies on the aromatic C-H borylation of aromatic compounds reported by Smith's group⁶ and by us^{7,8} are summarized in Scheme 2. Functional group tolerance of the borylation is very high. The reaction selectively occurs at the C-H bond for substrates possessing Cl, Br, I, CF₃, OMe, CO₂Me, and CN groups. The reaction occurs only at the aromatic C-H bonds even when the substrate has weaker benzylic C-H bonds.^{16,17} The regiochemistry of the borylation of arenes is primarily controlled by the steric effects of substituents. The reaction occurs at C-H bonds located meta or para to a substituent in preference to those located ortho. Thus, 1,2-disubstituted arenes bearing identical substituents yield arylboronates as single isomers. The borylation of 1,3-disubstituted arenes proceeds at the common meta position; therefore, isomerically pure products are obtained even for two distinct substituents on the arenes.⁷ In the case of five-membered heteroarenes such as furans, thiophenes and pyrroles, the electronegative heteroatom causes the C-H bonds at the α -positions to be active so that the borylation occurs at the α -positions.¹⁸ Thus, the regioselective monoborylation of benzo-fused substrates can be possible. In this study, we employed such arenes that produce single arylboronic ester (**5**).

In one-pot, two-step reactions where each step is catalyzed by different metal complexes, a catalyst used at first step often inhibits second step. Thus, our initial efforts were focused on finding effective reaction conditions for the second cross-coupling step (Table 2). Pinacol 3,5-dichlorophenylborate (ca. 1.1 mmol) was prepared *in situ* by the C-H borylation of 1,3-dichlorobenzene (1.36 mmol) with pin₂B₂ **2** (0.65 mmol) in the presence of the 1/2[Ir(OMe)(COD)]₂-dtbpy catalyst (0.020 mmol) in hexane (2 mL) at 25 °C for 4 h. This solution was directly allowed to react with bromobenzene (1.0 mmol) at 60 °C for 2 h by using a variety of palladium catalysts (0.03 mmol), bases (3 mmol), and solvents (4 mL). Fortunately, it was found that a combination of PdCl₂(dppf), K₃PO₄•nH₂O, and DMF works well to form the desired 3,5-dichlorobiphenyl in 96% yield (entry 1). Use of PdCl₂(PPh₃)₂ (entry 2) or Pd(dba)₂ (entry 3) resulted in low yield due to formation of inactive palladium-black. As for bases, K₃PO₄ in DMF gave the best results among four bases employed (entries 1 and 4-6). The reactions were faster in polar DMF (Entry 7) than in less-polar dioxane and hexane (entries 7 and 8). The C-H borylation of 1,3-dichlorobenzene (1.30 mmol) with HBpin (1.43 mmol) at 25 °C for 8 h yielded pinacol 3,5-dichlorophenylboronate (ca. 1.1 mmol). Its cross-coupling with bromobenzene (1.0 mmol) with PdCl₂(dppf), K₃PO₄•nH₂O in DMF was also effective for synthesis of 3,5-dichlorobiphenyl in 93% yield (entries 9).

Representative results of one-pot synthesis of unsymmetrical biaryls (**6**) *via* the sequential reactions involving the aromatic C-H borylation of arenes with B₂pin₂ (Method A) or that by HBpin (**1**) (Method B) and the cross-coupling with bromoarenes under the conditions optimized in Table 2 are summarized in Table 3. The method provides a convenient and efficient route for preparing a variety of **6**. Representative bromoarenes possessing an electron-withdrawing group, donating group, and an *ortho*-substituent afforded **6** in high yields (entries 1-7), while electron-rich (entry 3) or sterically hindered bromoarene (entry 4) required longer reaction times to complete the cross-coupling. The C-H borylation of 1,3-disubstituted arenes having two distinct substituents (entries 5 and 6) and 1,2-disubstituted arenes bearing identical substituents (entry 7) generated isomerically pure arylboronates and biaryls. Although α -heteroarylboronic acids such as 2-pyridineboronic acid and 2-pyrroleboronic acid are highly susceptible to hydrolytic protodeboration, the corresponding pinacol esters are much stable for such B-C bond cleavage in the presence of a base. Thus, 2-indoleboronate generated from indole smoothly coupled with 2-bromothiophene (entry 8). There were no significant differences in the yields and reaction rates between method A and B, but high stability of B₂pin₂ to air and water can be convenient for

handling and economical HBpin can be much suited for large-scale preparation of arylboronates and biaryls.

3. Experimental

3.1. Synthesis of borane-amine complexes (**2**)

Borane/amine complexes (**2**) were synthesized by the methods of Vaultier and Brown.¹⁰ The synthesis of **2d** from NaBH₄, BF₃ · OEt₂ and PhNEt₂ is followed.

A 500-mL flask charged with NaBH₄ (0.4 mol) and PhNEt₂ (0.5 mol) in THF (100 mL) was dropwise added BF₃ · OEt₂ (0.5 mol) at -78 °C. The mixture was allowed slowly warm to room temperature and stirred for 1-4 h. The complete disappearance of B-F species was checked by ¹¹B NMR. The mixture was diluted with pentane (100 mL) to precipitate NaBF₄. Filtration of solid residue through a Celite pad was followed by evaporation of solvent and other volatiles. Further evaporation of trace of volatiles in high vacuo (10⁻² mmHg) for 16 h gave 72.5 g (89%) of **2d**. ¹H NMR (400 MHz, CDCl₃) δ 1.06 (t, *J*=7.16 Hz, 6H), 1.84 (q, *J*=90.3 Hz, 3H, BH₃), 3.29-3.40 (m, 4H), 7.27 (t, *J*=7.34 Hz, 1H), 7.38 (t, *J*=7.94 Hz, 2H), 7.65 (d, *J*=8.48 Hz, 2H); ¹¹B NMR (128 MHz, CDCl₃) δ -12.0.

3.2. Synthesis of pinacolborane

A 100 mL-flask, assembled a Claisen-head distillation apparatus, was charged with BH₃ · N(Ph)Et₂ (**2d**, 75 mmol) and tetraglyme (20 mL). A solution of pinacol (50 mmol) in tetraglyme (5M solution, 10 mL) was dropwise added over 30 min to the flask cooled by a water bath (25 °C). The mixture was stirred for 30 min at room temperature. Distillation in vacuo gave pinacolborane (4.8 g, 75%). Bp 36 °C/42 mmHg. ¹H NMR (400 MHz, CDCl₃) δ 1.27 (s, 12H), 4.10 (q, *J*=168 Hz, 1H); ¹¹B NMR (128 MHz, CDCl₃) δ 28.1.

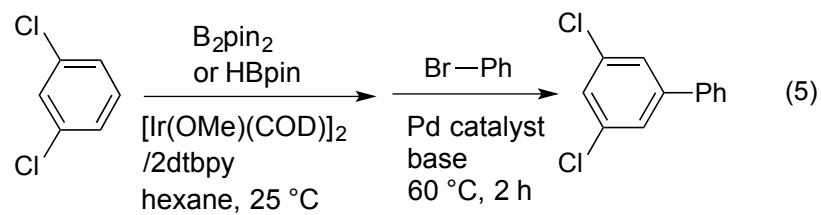
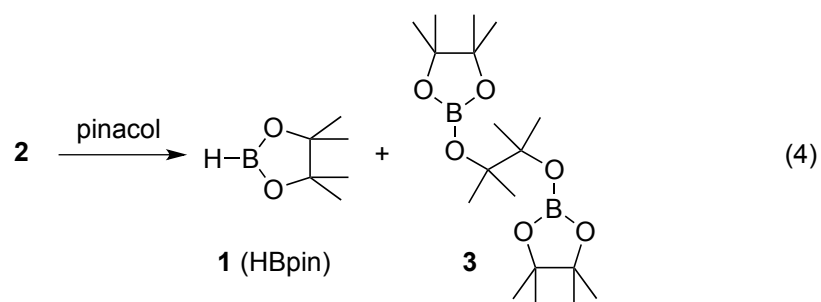
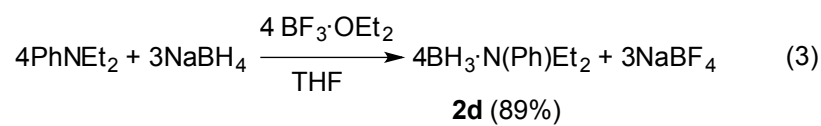
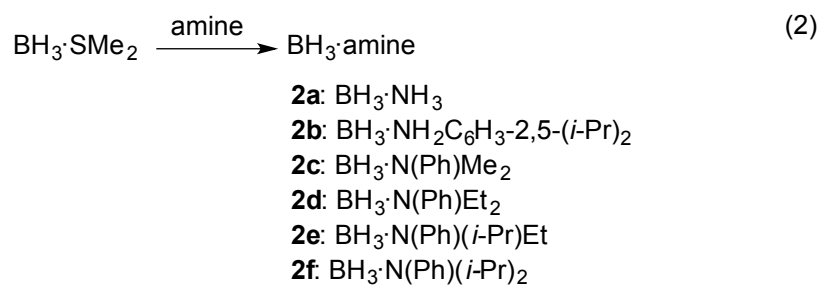
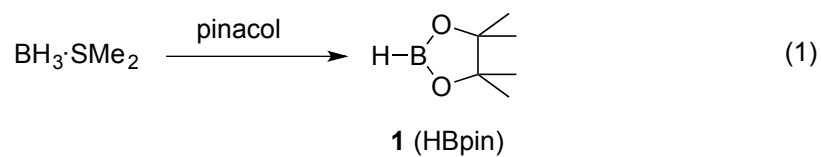
3.3. Procedure for one-pot biaryl cross-coupling using B₂pin₂ (Method A)

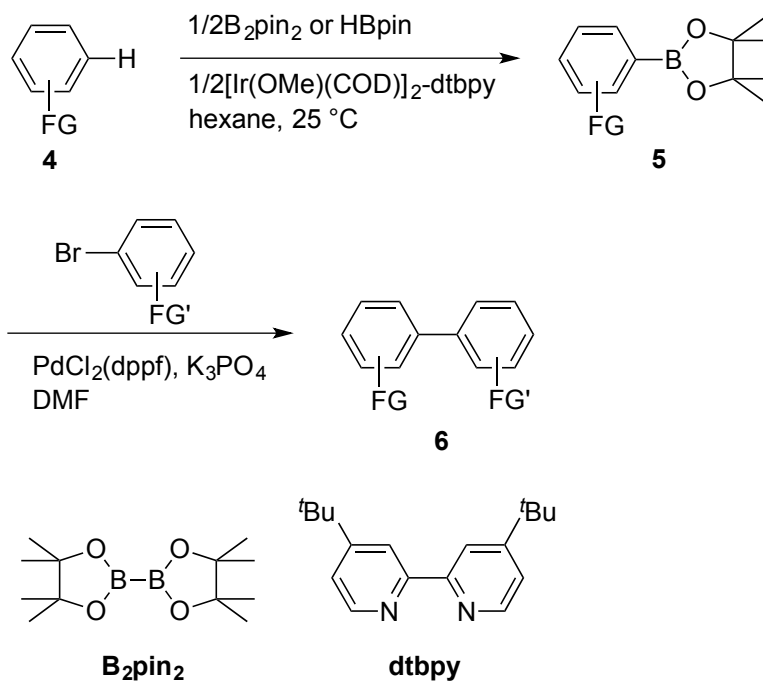
A 25-mL flask assembled a magnetic stirring bar, a septum inlet, and a condenser was charged with [Ir(OMe)(COD)]₂¹⁹ (0.01 mmol), 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy, 0.02 mmol), and bis(pinacolato)diboron (B₂pin₂, 0.65 mmol) and then flushed with nitrogen. Hexane (2 mL) and 1,3-dichlorobenzene (1.36 mmol) were added, and the mixture was then stirred at 25 °C for 4 h to give pinacol 3,5-dichlorophenylboronate (ca. 1.1 mmol). To this solution were added PdCl₂(dppf) (0.030 mmol), K₃PO₄ · nH₂O (3

mmol), and DMF (4 mL), and the mixture was stirred at 60 °C for 2 h. The formation of methyl 4-(3,5-dichlorophenyl)benzoate (**2b**) in 96% yield was analyzed by GC and GC mass spectroscopy. The product was extracted with benzene, washed with brine, and dried over MgSO₄. Chromatography over silica gel (hexane/AcOEt) gave analytically pure **2b**.

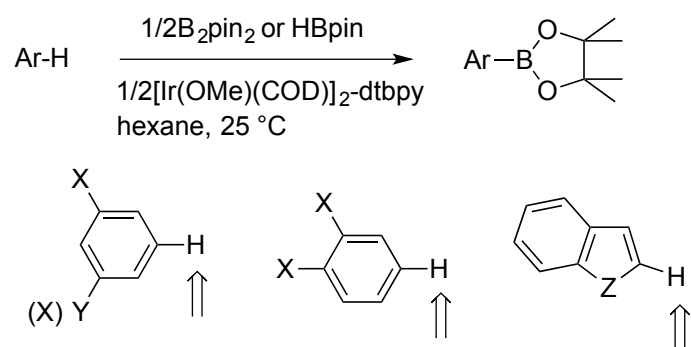
3.4. Procedure for one-pot biaryl cross-coupling using HBpin (Method B)

A 25-mL flask assembled a magnetic stirring bar, a septum inlet, and a condenser was charged with [Ir(OMe)(COD)]₂¹⁹ (0.02 mmol) and 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy, 0.04 mmol) and then flushed with nitrogen. Hexane (2 mL), pinacolborane (HBpin, 1.43 mmol), and 1,3-dichlorobenzene (1.3 mmol) were then added, and the mixture was stirred at 25 °C for 8 h to give pinacol 3,5-dichlorophenylboronate (ca. 1.1 mmol). The solution thus obtained was directly subjected to cross-coupling under conditions same as the above procedures shown in the section 3.3.



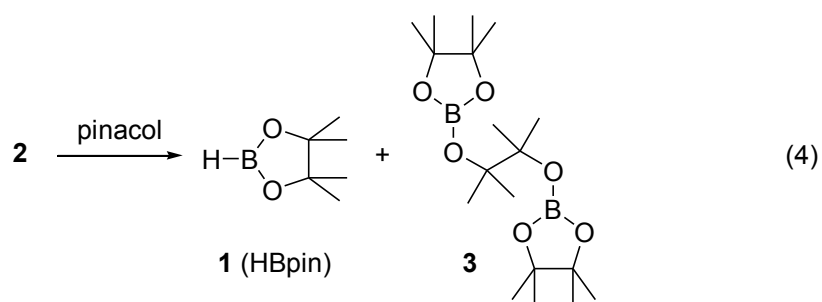


Scheme 1. One-pot synthesis of biaryls *via* aromatic C-H borylation–cross-coupling sequence.



Scheme 2. Orientations of aromatic C-H borylation

Table 1. Synthesis of pinacolborane^a



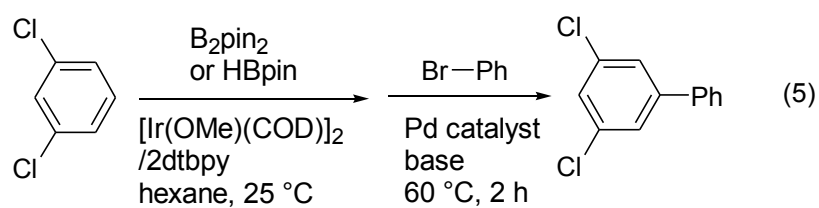
entry	2 (amine=)	conversion/% ^b	1/3	isolated yield/%
1	NH ₃ (2a)	12	42 : 58	
2	2,6-(<i>i</i> -Pr) ₂ C ₆ H ₃ NH ₂ (2b)	82	85 : 15	
3	PhNMe ₂ (2c)	43	60 : 40	
4	PhNEt ₂ (2d)	100	100: 0	(50)
5	PhNEt ₂ (2d) ^c	100	100 : 0	(75)
6	PhN(<i>i</i> -Pr)Et (2e)	0		
7	PhN(<i>i</i> -Pr) ₂ (2f)	0		

^aA mixture of amine-borane complex (50 mmol) and pinacol (50 mmol) in tetraglyme (5 ml) was stirred for 1 h at 20 °C.

^bConversions and ratios determined by ¹¹B NMR.

^c1.5 equivalents of **2d** was used.

Table 2. Reaction conditions for one-pot synthesis of biaryls^a

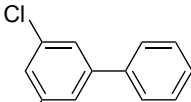
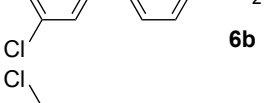
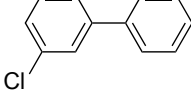
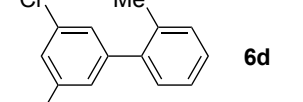
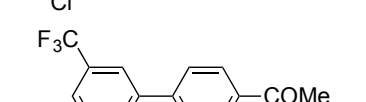
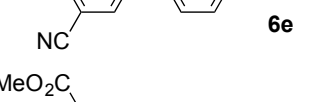
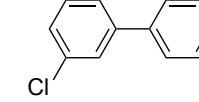


entry	B ₂ pin ₂ or HBpin	Pd catalyst	base	solvent	yield/% ^b
1	B ₂ pin ₂	PdCl ₂ (dppf)	K ₃ PO ₄	DMF	96
2	B ₂ pin ₂	PdCl ₂ (PPh ₃) ₂	K ₃ PO ₄	DMF	55
3	B ₂ pin ₂	Pd(dba) ₂	K ₃ PO ₄	DMF	1
4	B ₂ pin ₂	PdCl ₂ (dppf)	Cs ₂ CO ₃	DMF	88
5	B ₂ pin ₂	PdCl ₂ (dppf)	K ₂ CO ₃	DMF	80
6	B ₂ pin ₂	PdCl ₂ (dppf)	KOAc	DMF	53
7	B ₂ pin ₂	PdCl ₂ (dppf)	K ₃ PO ₄	dioxane	84
8	B ₂ pin ₂	PdCl ₂ (dppf)	K ₃ PO ₄	hexane	9
9	HBpin	PdCl ₂ (dppf)	K ₃ PO ₄	DMF	93

^aC-H borylation of 1,3-dichlorobenzene (1.36 mmol) with B₂pin₂ (0.65 mmol) in hexane (2 mL) at 25 °C for 4 h in the presence of 1/2[Ir(OMe)(COD)]₂-dtbpy (3.0 mol%, 0.020 mmol) was followed by cross-coupling with bromobenzene (1.0 mmol) at 60 °C for 2 h by using Pd catalyst (0.030 mmol), base (3.0 mmol), and solvent (4 mL).

^bGC yields based on bromobenzene.

Table 3. One-pot Synthesis of biaryls via C-H borylation-cross-coupling sequence^a

entry	product 6 ^b	yield /% ^c (time/h) ^d	
		Method A ^e	Method B ^f
1	 6a	96 ^g (2)	93 ^g (2)
2	 6b	96 (2)	91 ^g (2)
3	 6c	87 (4)	81 (4)
4	 6d	88 (4)	84 (8)
5	 6e	93 (2)	91 (2)
6	 6f	93 (2)	87 (2)
7	 6g	96 (2)	86 (2)
8	 6h	93 (2)	87 (2)

^aThe C-H borylation of arenes with B₂pin₂ (Method A) or HBpin (Method B) to give arylboronates (**5**, ca. 1.1 mmol) was followed by cross-coupling with aryl bromides (1.0 mmol) at 60 °C in the presence of PdCl₂(dppf) (0.03 mmol), K₃PO₄ (3 mmol) and DMF (4 mL) ..

^bLeft part of biaryls comes from arenes and right part from boromoarenes. ^cIsolated yields.

^dReaction times at the cross-coupling stage.

^eThe C-H borylation of arene (1.30-1.43 mmol) with B₂pin₂ (0.63-0.69 mmol) was carried out for 0.5-8 h in the presence of 1/2[Ir(OMe)(COD)]₂-dtbpy (3.0 mol%, 0.020 mmol).

^fAromatic C-H borylation of arene (1.12-1.57 mmol) with HBpin (1.23-1.73 mmol) was carried out for 2-8 h in the presence of 1/2[Ir(OMe)(COD)]₂-dtbpy (3.0 mol%, 0.034-0.048 mmol).

^gGC yields.

Graphical Abstract

