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Pd^{II}-Porphyrin Complexes – the First Use as Safer and Efficient Catalysts for Miyaura Borylation

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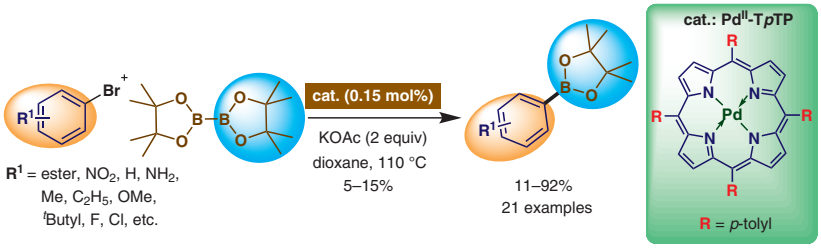

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Abstract We have developed a simple and convenient procedure for the preparation of pinacol arylboronates from aryl/heteroaryl bromides and bis(pinacolato)diborane using a Pd^{II}-porphyrin complex as a catalyst. Seven different Pd^{II}-porphyrin complexes (Pd^{II}-T*m*HPP, Pd^{II}-T*m*CPP, Pd^{II}-TPP, Pd^{II}-TST*p*SPP, Pd^{II}-T*p*CPP, Pd^{II}-T*p*TP, and Pd^{II}-T*p*AP) have been synthesized and investigated for their catalytic influence in the Miyaura borylation.

Key words Miyaura borylation, Pd^{II}-porphyrin complex, pinacol arylboronates

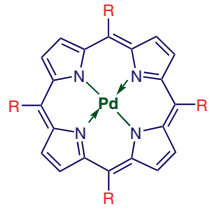
Arylboronic acids and their derivatives, especially, arylboronate esters of diols [pinacol arylboronates (PABs)] have become ubiquitously important synthetic building blocks because of their broad availability and ease of handling due to their air, moisture, and thermal stability.[1] The utility of PABs is exemplified by transition-metal-catalyzed C–X (X = C, N, O, CN, COOH) bond-formation reactions.[2] The most common procedures to access pinacol organoboronates involve hydroboration of C–C multiple bonds,[3] borylation of organic halides with bis(pinacolato)diborane (B_2pin_2) (Miyaura borylation)[4] or pinacolborane (Bpin),[5] Sandmeyer-type reaction of amines with B_2pin_2,[6] direct aryl C–H borylation,[7] and borylation of organomagnesium or organolithium compounds.[8] Of these, the Miyaura borylation is widely employed as it is convenient, utilizes readily available starting materials, and shows high functional group tolerance.[1,4] PABs have the advantages of broad substrate scope, ease of purification, resistance to oligomerization, as well as hydrolytic and thermal stability.[1c,9]

Most of the reports for the Miyaura borylation involve transition-metal catalysis, with palladium being superior.[1,4e–g,10] Many of these palladium-based procedures involve phosphine-based ligands,[4f–g,10] which are highly toxic, difficult to handle, expensive, and moisture and air sensitive.[11] In this context a few reports are based on less toxic, moisture, and thermally stable nitrogen ligands to avoid the difficulties of phosphorus ligands.[4c–e,12]

In continuation of our work on the development of methodologies based on Pd^{II}-porphyrin complexes as catalysts,[13] we report a straightforward method for the formation of PABs from aryl/heteroaryl bromides and B_2pin_2 using Pd^{II}-porphyrin complexes under aerobic conditions. To the best of our knowledge, this is the first report of using porphyrin-based complexes for the Miyaura borylation. Moreover, the metalloporphyrins are inert to air and moisture and are photostable.[14] All the porphyrins and their Pd^{II} complexes used for this methodology are synthesized and characterized as described in our recent reports.[13]

We began our search with screening the catalysts for Miyaura borylation using methyl 4-bromobenzoate (**1a**) and B_2pin_2 (**2**) at 110 °C (identified as effective temperature). We evaluated the influence of seven Pd^{II}-porphyrin complexes; Pd^{II}-5,10,15,20-*meso*-tetra(*m*-hydroxyphenyl)-porphyrin (**Pd^{II}-T*m*HPP**), Pd^{II}-5,10,15,20-*meso*-tetra(*m*-carboxyphenyl)porphyrin (**Pd^{II}-T*m*CPP**), Pd^{II}-5,10,15,20-*meso*-tetraphenylporphyrin (**Pd^{II}-TPP**), Pd^{II}-tetrasodium-5,10,15,20-*meso*-tetra(*p*-sulfonatophenyl)porphyrin (**Pd^{II}-TST*p*SPP**), Pd^{II}-5,10,15,20-*meso*-tetra(*p*-cyanophenyl)porphyrin (**Pd^{II}-T*p*CPP**), Pd^{II}-5,10,15,20-*meso*-tetra(*p*-tolyl)-porphyrin (**Pd^{II}-T*p*TP**), and Pd^{II}-5,10,15,20-*meso*-tetra(*p*-anisyl)-porphyrin (**Pd^{II}-T*p*AP**) (Figure 1). The results are listed in Table 1 and revealed that the complex, **Pd^{II}-T*p*TP** shows a very good yield of **3a** with a catalyst load of 0.15 mol% (Table 1, entry 6). The increase in the catalyst load (0.2 mol% and 0.3 mol%) does not show any improvement in yield (Table 1, entries 7 and 8). **Pd^{II}-T*p*AP** also displays high yield of PBA (**3a**) but the reaction is slow and with slightly low yields when compared with **Pd^{II}-T*p*TP** (Table 1, entries 9 and 10).

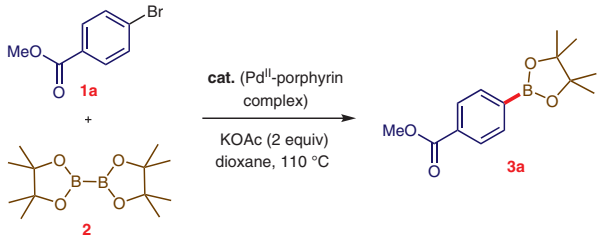
The complexes, **Pd^{II}-T*m*HPP**, **Pd^{II}-T*m*CPP** and **Pd^{II}-TST*p*SPP** gave good to moderate yield of **3a** (Table 1, entries 1, 2, 4). **Pd^{II}-T*p*CPP** displays low yield (Table 1, entry 5) and no catalysis was found for **Pd^{II}-TPP** (Table 1, entry 3).



Pd^{II}-T*m*HPP: R = *m*-HO-C_6H_4
Pd^{II}-T*m*CPP: R = *m*-HO_2C-C_6H_4
Pd^{II}-TPP: R = C_6H_5
Pd^{II}-TST*p*SPP: R = *p*-NaO_3S-C_6H_4
Pd^{II}-T*p*CPP: R = *p*-NC-C_6H_4
Pd^{II}-T*p*TP: R = *p*-Me-C_6H_4
Pd^{II}-T*p*AP: R = *p*-MeO-C_6H_4

Figure 1 Structures of Pd^{II}-porphyrin complexes

Table 1 Search for the Catalyst[a]

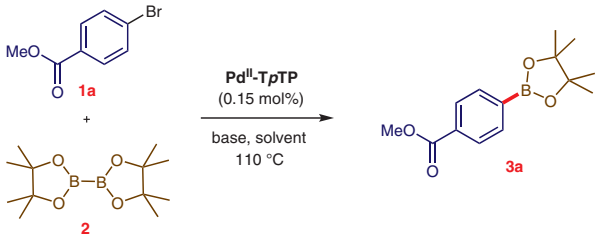


Entry	Catalyst (mol%)	Time (h)	Isolated yield (%)
1	**Pd^{II}-T*m*HPP** (0.15)	8.5	68
2	**Pd^{II}-T*m*CPP** (0.15)	6.0	79
3	**Pd^{II}-TPP** (0.30)	16	–
4	**Pd^{II}-TST*p*SPP** (0.15)	8.0	52
5	**Pd^{II}-T*p*CPP** (0.30)	12.0	29
6	**Pd^{II}-T*p*TP** (0.15)	5.5	88
7	**Pd^{II}-T*p*TP** (0.20)	6.0	86
8	**Pd^{II}-T*p*TP** (0.30)	7.0	86
9	**Pd^{II}-T*p*AP** (0.15)	6.0	82
10	**Pd^{II}-T*p*AP** (0.30)	8.0	82

[a] Reaction conditions: Methyl 4-bromobenzoate (1 mmol), B_2pin_2 (1.2 mmol), KOAc (2 mmol), and dioxane (5 mL) at 110 °C.

We then screened various solvents and bases for the effective catalysis of **Pd^{II}-T*p*TP** (Table 2) using **1a** and **2** as model reactants. From this screening, we identified dioxane as effective solvent in the presence of KOAc (Table 2, entry 1). Toluene was also suitable for this conversion, but it provides less yield of **3a** than dioxane (Table 2, entry 2). The solvents such as DME, DMF, 2-methyl THF, DMA, xylene, and NMP display moderate to low yield of **3a** in the presence of KOAc. In 10% aq. dioxane the reaction did not proceed (Table 2, entry 9). The base, tetrabutylammonium acetate offers a comparable yield to KOAc (Table 2, entry 10). Bases such as K_2CO_3, Cs_2CO_3, NaOAc, K_3PO_4 tribasic, and KO^{t}Bu shows low yield of **3a** in dioxane (Table 2, entries 11–16) and observed no reaction, when triethylamine, Hünig's base, and DBU are the bases (Table 2, entries 17–19). These results disclosed that the solvent, dioxane, bases, KOAc, and tetrabutylammonium acetate are appropriate for the present conversion. We have chosen KOAc instead of tetrabutylammonium acetate in dioxane for further investigations depending on their relative cost.

Table 2 Solvent and Base Screening[a]

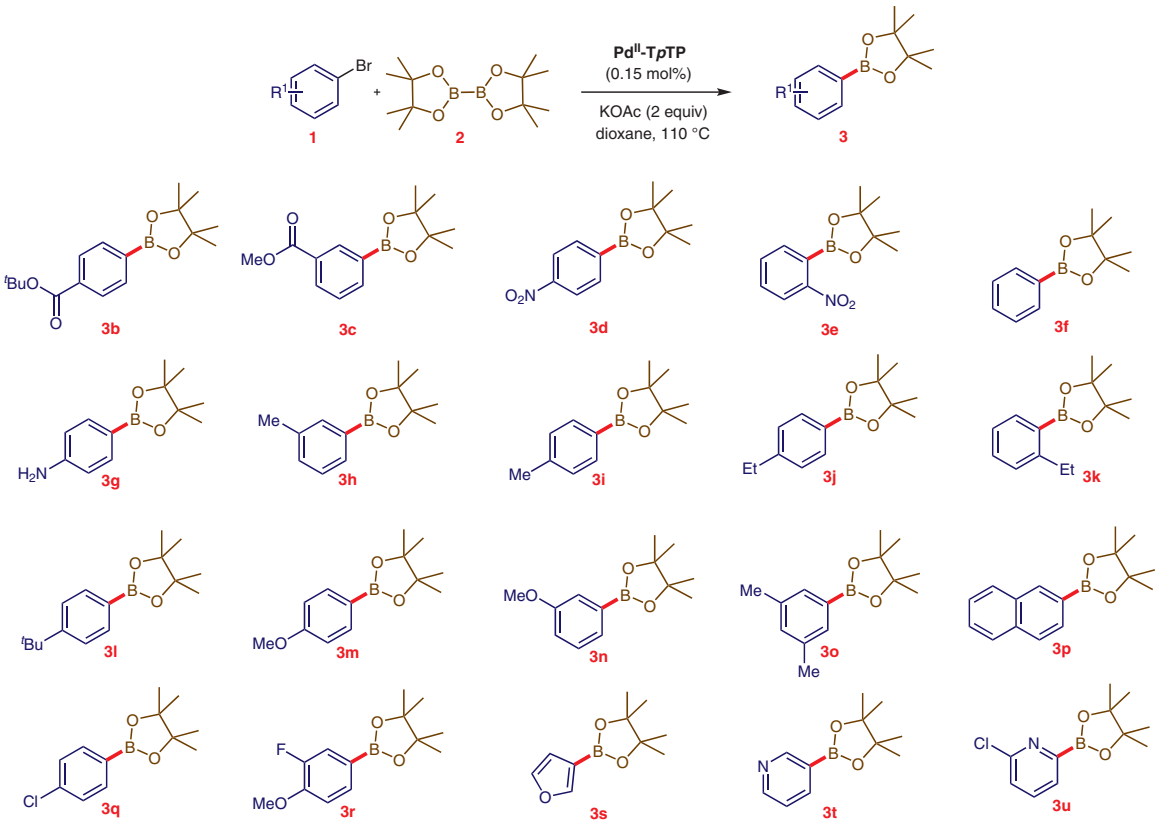


Entry	Solvent	Base	Time (h)	Isolated yield (%)
1	dioxane	KOAc	5.5	88
2	toluene	KOAc	6.0	75
3	xylene	KOAc	8.0	16
4	DMF	KOAc	12.0	21
5	NMP	KOAc	12.0	9
6	2-methyl THF	KOAc	12.0	19
7	DME	KOAc	12.0	52
8	DMA	KOAc	16.0	17
9	10% aq. dioxane	KOAc	16.0	–
10	dioxane	tetrabutylammonium acetate	6.0	88
11	dioxane	NaOAc	8.0	32
12	dioxane	K_2CO_3	12.0	41
13	dioxane	NaOH	12.0	18
14	dioxane	Cs_2CO_3	12.0	37
15	dioxane	K_3PO_4 tribasic	12.0	32
16	dioxane	KO^{t}Bu	16.0	21
17	dioxane	triethylamine	16.0	–
18	dioxane	Hünig's base	16.0	–
19	dioxane	DBU	16.0	–

[a] Reaction conditions: Methyl 4-bromobenzoate (1 mmol), B_2pin_2 (1.2 mmol), **Pd^{II}-T*p*TP** (0.15 mol%), base (2 mmol) and solvent (5 mL) at 110 °C.

With the optimized conditions, we extended the scope of the procedure to a variety of aryl bromides with both the electron-withdrawing and electron-donating groups or heteroaryl bromides, and the results are illustrated in Table 3.[15] The aryl bromides with electron-withdrawing groups such as ester, chloro, nitro, and fluoro show very good to excellent yields of products (Table 3, entries 1–4, 16, 17), and 1-bromo-4-nitrobenzene (**1d**) was observed to be the best substrate. The electron-rich substrates such as **1g–o** display

Table 3 Miyaura Borylation of Aryl/Heteroaryl Bromides[a]



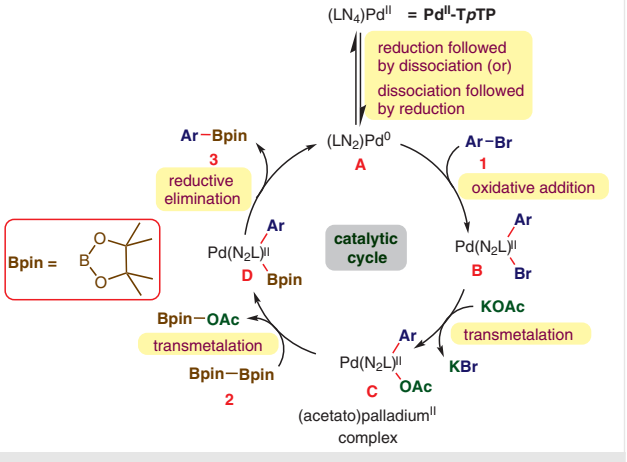
Entry	Aryl/heteroaryl bromide **1**	Time (h)	Product **3**	Isolated yield (%)
1	*tert*-butyl 4-bromobenzoate (**1b**)	6.0	**3b**	85
2	methyl 3-bromobenzoate (**1c**)	7.0	**3c**	83
3	1-bromo-4-nitrobenzene (**1d**)	5.0	**3d**	92
4	1-bromo-2-nitrobenzene (**1e**)	6.5	**3e**	85
5	bromobenzene (**1f**)	8.0	**3f**	84
6	4-bromoaniline (**1g**)	8.0	**3g**	68
7	3-bromotoluene (**1h**)	8.0	**3h**	75
8	4-bromotoluene (**1i**)	8.0	**3i**	78
9	1-bromo-4-ethylbenzene (**1j**)	10.0	**3j**	73
10	1-bromo-2-ethylbenzene (**1k**)	10.0	**3k**	43
11	1-bromo-4-*tert*-butylbenzene (**1l**)	10.0	**3l**	73
12	4-bromoanisole (**1m**)	8.0	**3m**	80
13	3-bromoanisole (**1n**)	8.0	**3n**	75
14	5-bromo-*m*-xylene (**1o**)	8.0	**3o**	75
15	2-bromonaphthalene (**1p**)	6.0	**3p**	83
16	1-bromo-4-chlorobenzene (**1q**)	8.0	**3q**	82
17	4-bromo-2-fluoroanisole (**1r**)	8.0	**3r**	70
18	3-bromofuran (**1s**)	15	**3s**	11
19	3-bromopyridine (**1t**)	12	**3t**	35
20	2-bromo-6-chloropyridine (**1u**)	12	**3u**	31

[a] Reaction conditions: Aryl/heteroaryl bromide (1 mmol), B_2pin_2 (1.2 mmol), **Pd^{II}-*Tp*TP** (0.15 mol%), KOAc (2 mmol), and dioxane (5 mL) at 110 °C.

moderate to good yields of PABs (Table 3, entries 6–14), but 1-bromo-2-ethylbenzene (**1j**) shows low yield (Table 3, entry 10) of its corresponding product **3j**. It may be due to the steric hindrance of the ethyl group in *o*-position. Bromobenzene and 2-bromonaphthalene are proved to be good substrates for the present conversion and gave very good yields of PABs (Table 3, entries 5, 15). Heteroaryl bromides (**1s–u**) were found poorly reactive and provided very low to moderate yields of the products (Table 3, entries 18–20).

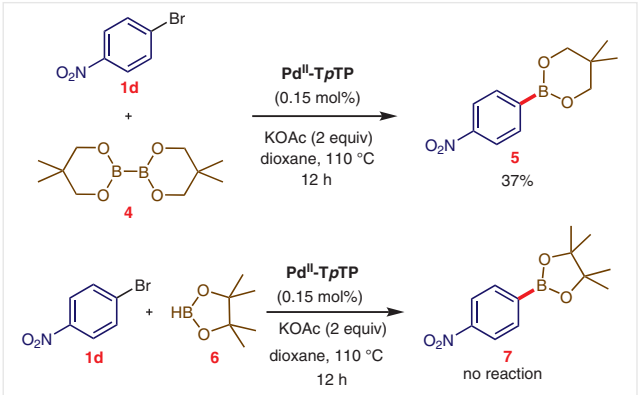
The present conversion shows chemoselectivity, i.e., the priority for the bromine over chlorine or fluorine was found in the case of aryl di(mixed)halides, 1-bromo-4-chlorobenzene (**1q**), 4-bromo-2-fluoroanisole (**1r**), and 2-bromo-6-chloropyridine (**1u**) (Table 3, entries 16, 17, 20). However, the reaction proceeds at slower rate for **1s** and **1u** to give moderate yield of borylated products, **3s** and **3u** (Table 3, entries 18, 20). The present finding shows tolerance to ester, nitro, amino, and chloro functional groups.

The following scheme (Scheme 1) represents the plausible mechanism of **Pd^{II}-T*p*TP**-catalyzed Miyaura borylation, and the catalytic cycle is analogous to our recent report on **Pd^{II}-TST*p*SPP**-catalyzed Mizoroki–Heck coupling[13b] and palladium-catalyzed Miyaura borylation, described by Ishiyamaet al.[16] A Pd^0 species (**A**) may be formed initially by the reduction followed by dissociation or reverse[13b,16] and it involves in oxidative insertion to aryl bromide (**1**). The intermediate **B** formed in this step may involve in transmetalation with KOAc to give (acetato)palladium^{II} complex (**C**), which is involved in further transmetalation reaction with B_2pin_2 (**2**) to form intermediate **D**. Finally, the intermediate **D** participates in reductive elimination to form PBA (**3**) and catalytically active species **A**.



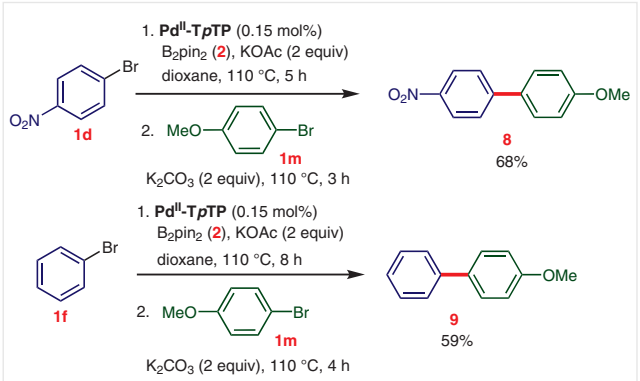
Scheme 1 Plausible mechanism of **Pd^{II}-T*p*TP**-catalyzed Miyaura borylation

Further, we studied the preparation of neopentyl glycolato arylboronate and PAB from aryl bromide, **1d** and bis(neopentylglycolato)diborane (B_2npg_2) (**4**) or Bpin (**6**) (Scheme 2).[15] In this connection, 1-bromo-4-nitrobenzene (**1d**) gave 37% of its corresponding neopentyl glycolato 4-nitrophenylborate (**5**) under the current experimental conditions, but Bpin shows no reactivity.



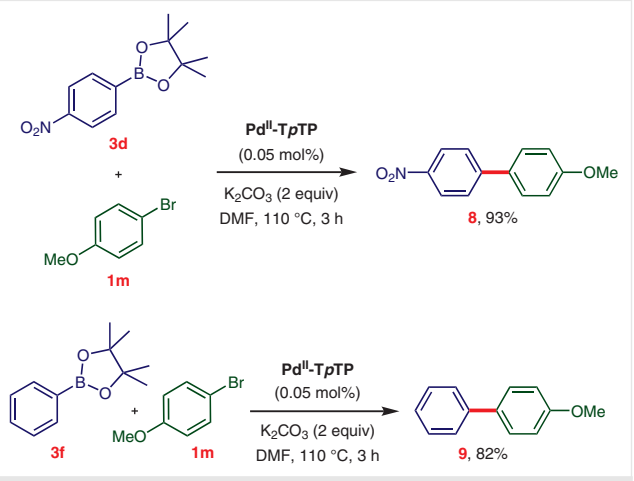
Scheme 2 Miyaura borylation of **1c** with B_2npg_2 and Bpin

Finally, we studied the Suzuki–Miyaura coupling (SMC) of PABs formed, in single pot. It was observed that the formation of SMC products **8** and **9** with moderate overall yields in two steps in one pot (Scheme 3).[17] The SMC was consistent when studied separately for the isolated PABs with aryl bromides and resembles our recent report[13a] (Scheme 4). In this connection PABs **3d** and **3f** offers 93% and 82% of SMC products with 4-bromoanisole (**1m**) in 3 h and 4 h using DMF and K_2CO_3 (2 equiv).



Scheme 3 Miyaura borylation followed by Suzuki–Miyaura coupling

In summary, we developed a Pd^{II}-porphyrin complex catalyzed convenient method for the preparation of pinacol arylboranates from aryl/heteroaryl bromides and B_2pin_2. The reaction proceeds at aerobic conditions by using moisture insensitive, stable, and nontoxic catalysts. The method also offers the one-pot preparation of biaryls by a Miyaura borylation followed by SMC of aryl bromides. The broad substrate scope, high functional group tolerance and chemoselectivity, simple preparation of the catalysts, easy separation of the products, no need of inert reaction atmosphere, and low catalyst load (0.15 mol%) are the remarkable advantages of the present procedure.



Scheme 4 Suzuki–Miyaura coupling of PABs

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591549.

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(15) **General Procedure for Miyaura Borylation**
Aryl/heteroaryl bromide **1** (1 mmol), B_2pin_2(**2**), B_2npg_2(**4**) or Bpin (**6**, 1.2 mmol), and dioxane (5 mL) are taken into a 25 mL round-bottomed flask. KOAc (2 mmol) was added and stirred the resultant mixture at room temperature for 5 min, **Pd^{II}-T*p*TP** (0.15 mol%) was added, and the contents were refluxed on pre-heated oil bath at 110 °C under constant stirring in open-air. The reaction progress was ensured by TLC. After completion of the reaction, the mixture was cooled, dilute with water (20 mL) and extracted with ^{tert}butylmethyl ether (3 × 10 mL). The combined n-hexane layers were concentrated, and the crude product obtained was purified by column chromatography (CC)

on silica gel using a mixture of ethyl acetate and hexane (1:30) as eluent.

The structure of all the products were characterized by their spectral (^{1}H NMR, ^{13}C NMR and mass) analysis and are in good agreement with the literature data. Spectral data of some representative compounds are given below.

Pinacol (^{tert}Butyl 4-carboxyphenyl)boronate (3b)

White color solid; 85% (258 mg) yield. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 7.90 (d, J = 8.4 Hz, 2 H), 7.78 (d, J = 8.4 Hz, 2 H), 1.55 (s, 9 H), 1.31 (s, 12 H) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz): δ = 164.8, 134.5, 133.7, 128.2, 84.1, 81.0, 27.8, 24.7 ppm. GC-MS: *m/z* = 304.2 [M$^{+\cdot}$].

Pinacol 4-Ethylphenylboronate (3j)

Colorless liquid; 73% (169 mg) yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.74 (d, J = 7.8 Hz, 2 H), 7.21 (d, J = 7.8 Hz, 2 H), 2.66 (q, J = 7.5 Hz, 2 H), 1.33 (s, 12 H), 1.23 (t, J = 7.8 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 147.7, 134.9, 127.4, 83.6, 29.1, 24.9, 15.5 ppm. GC-MS: *m/z* = 232.2 [M$^{+\cdot}$].

Pinacol 2-Fluoro-4-anisylboronate (3r)

Colorless solid; 70% (176 mg) yield. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 7.47 (dd, J = 7.8, 1.2 Hz, 1 H), 7.34 (dd, J = 12.0, 1.5 Hz, 1 H), 7.18 (t, J = 8.4 Hz, 1 H), 3.87 (s, 3 H), 1.28 (s, 12 H) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz): δ = 150.9 (d, J = 244.8 Hz), 149.6 (d, J = 10.3 Hz), 131.4 (d, J = 3.4 Hz), 120.4 (d, J = 15.7 Hz), 113.1, 83.4, 55.6, 24.3 ppm. GC-MS: *m/z* = 252.0 [M$^{+\cdot}$].

Pinacol 6-Chloro-2-pyridinylboronate (3r)[18]

Colorless crystalline solid; 31% (74 mg) yield. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 8.48 (dd, J = 4.8, 2.1 Hz, 1 H), 8.04 (dd, J = 7.5, 2.1 Hz, 1 H), 7.42 (dd, J = 7.5, 4.8 Hz, 1 H), 1.33 (s, 12 H) ppm. GC-MS: *m/z* = 239.0 [M$^{+\cdot}$].

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(17) **Procedure for Miyaura Borylation – Suzuki–Miyaura Coupling**

After completion of the progress of the Miyaura borylation reaction (as indicated by the TLC and as given in Table 3) of aryl bromide **1d** or **1f** was added separately to each, **1m** (1.2 mmol) and K_2CO_3 (2 mmol). The reactions are conducted at 110 °C and after completion the reaction mixture was cooled to room temperature, diluted by adding 20 mL water, and extracted with ^{tert}butylmethyl ether (3 × 10 mL). The combined ether portions are evaporated in vacuo, and the crude product obtained was purified by CC by using a mixture of n-hexane and ethyl acetate (19:1) as eluent.

The products were characterized by ^{1}H NMR and ^{13}C NMR spectroscopic, and mass spectrometric data and are in good agreement with our recent report.[13a]

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