

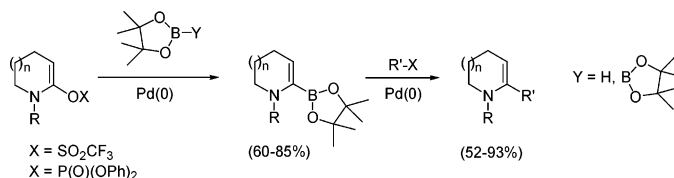
Preparation and Suzuki–Miyaura Coupling Reactions of Tetrahydropyridine-2-boronic Acid Pinacol Esters

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A study on the conversion of lactam-derived vinyl triflates and phosphates into the corresponding vinyl boronates was carried out. While δ -valerolactam-derived vinyl triflates were successfully converted into 1,4,5,6-tetrahydropyridine-2-boronic acid pinacol ester derivatives by Pd-catalyzed coupling reaction with both bis(pinacolato)diboron and pinacolborane, pyrrolidinone and ϵ -caprolactam derivatives either did not react or were readily reduced. The δ -valerolactam-derived vinyl boronates are thermally stable compounds that efficiently coupled, under Pd catalysis, with structurally diverse aryl and heteroaryl bromides and triflates, vinyl iodides and bromides, and aromatic acid chlorides, to give the corresponding 2-substituted piperidines in good to excellent yields. The number of electrophiles that can virtually be coupled with these new boronic esters makes them very useful reagents for the synthesis of N-heterocyclic compounds.

Introduction

Boronic acids and esters have emerged as two of the most useful classes of organoboron compounds in organic synthesis, particularly in Pd-catalyzed cross-coupling reactions with organic halides and triflates (the Suzuki–Miyaura reaction).¹ Over the past few years, in particular, there has been an increased availability of heteroaromatic boronic acids and esters.² By contrast, there are only a few examples of preparation of nonaromatic heterocyclic boronic acids (or esters) to be employed in metal-catalyzed reactions for the formation of new C–C bonds.^{2b,3} Among a number of methods for the preparation of boronic esters, the Pd-catalyzed borylation of alkenyl halides and triflates by bis(pinacolato)diboron⁴ or pinacolborane⁵ has recently been reported. Vinyl triflates and phosphates **2** obtained from lactams **1**

(Scheme 1) have frequently been used as key intermediates in the synthesis of heterocyclic compounds through diverse palladium-catalyzed coupling reactions.^{6,7} The

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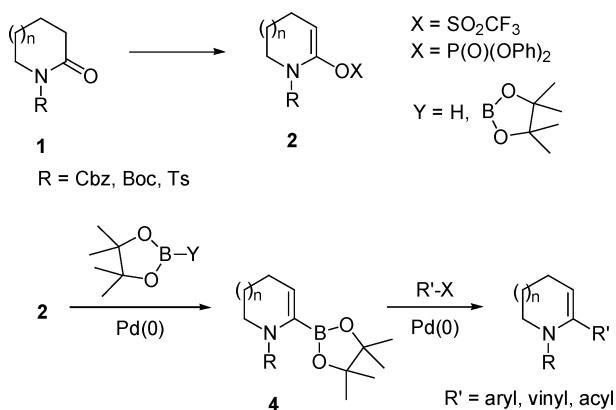
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SCHEME 1



scope of vinyl triflates **2** would certainly be expanded if an umpolung of these electrophiles is realized by α -borylation of the heterocycle (Scheme 1), thus producing a new class of nonaromatic heterocyclic boronates **4** potentially useful for Suzuki–Miyaura cross-coupling reactions. The overall procedure should, in principle, be of wider applicability than the direct use of the lactam-derived vinyl triflates because of the vast availability of the electrophiles (e.g., alkenyl and aryl halides, triflates, acid chlorides, etc.) that can be used as partners in metal-catalyzed coupling reactions. Moreover, boronates **4** should hopefully be compounds of greater stability than the corresponding triflates, which instead, depending on the ring size and substitution pattern, are often prone to rapid degradation.⁶ With this in mind, we first evaluated the feasibility of the transformation of various lactam-derived vinyl triflates and phosphates into the corresponding boronates. The heterocycle ring size, the electron-withdrawing group on the N atom, and the leaving group in **2** were the parameters we decided to modify to this end. This was followed by a study on the Pd-catalyzed coupling reactions of boronates **4** with diverse electrophiles to assess the scope of these new reagents in the synthesis of α -substituted N-heterocycles.⁸

Results and Discussion

The conversion of *N*-Cbz vinyl triflate **2a**^{7,9} into the corresponding boronate **4a** (Table 1) was first realized

TABLE 1. Pd-Catalyzed Borylation of Lactam-Derived Vinyl Triflates **2a–c**

entry	substrate	R	conditions	time (h)	4 (%) ^a	5 (%) ^b
1	2a	Cbz	5% $(\text{Ph}_3\text{P})_2\text{PdCl}_2$, 2 M Na_2CO_3 , 3 (1.5 equiv), THF, 50 °C	3	39 ^b	6
2			3% $(\text{Ph}_3\text{P})_2\text{PdCl}_2$, 6% Ph_3P , K_2CO_3 (1.5 equiv), 3 (1.5 equiv), dioxane, 90 °C	7	85	8
3	2b	Boc	as in entry 2	5	81	<5
4	2c	Ts	as in entry 2	5	82	<5

^a Isolated yield after chromatography. ^b Conversion determined by ¹H NMR analysis of the crude reaction mixture.

by the Pd-catalyzed coupling with commercial bis(pinacolato)diboron **3**,¹⁰ a reagent successfully employed for the preparation of boronates from diverse vinyl triflates.⁴ The best protocol (entry 2) was that which uses $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ (3%) as a catalyst, in the presence of Ph_3P and with finely powdered K_2CO_3 as a base, in anhydrous dioxane at 90 °C.^{4a} The reaction was complete in 7 h, furnishing vinyl boronate **4a** in 85% yield after chromatographic purification. Although K_2CO_3 , if compared to weaker bases, is reported to induce further coupling between the boronate and the triflate during the borylation reaction,^{4a} in situ coupling of **2a** with boronate **4a** to give dimer **5a**¹¹ was almost completely suppressed (about 8% by ¹H NMR analysis of the crude reaction mixture) by employing 1.5 equiv of bis(pinacolato)diboron. The same procedure, when applied to *N*-Ts and *N*-Boc vinyl triflates **2b** and **2c**, provided boronates **4b** and **4c** in 81 and 82% yield, respectively, after chromatography.

Compared to pinacolborane, bis(pinacolato)diboron **3** is quite an expensive reagent; moreover, only one of its two dioxaborolanyl fragments is transmetalated to form the boronate.^{4e} Therefore, we evaluated the use of pinacolborane for the preparation of **4a–c** (Table 2), although with this reagent the reduction of the triflates to tetrahydropyridines **7**¹² is a possible concurrent reaction. In analogy to the work of Baudoin, who employed sterically hindered phosphine ligands for the borylation of ortho-substituted phenyl halides,¹³ we initially used tricyclohexylphosphine and Buchwald's phosphine **8**¹⁴ (Figure 1) as ligands, as reported in entries 2–4. However, we only observed the formation of a modest amount of **4a** in the presence of Cy_3P , the main reaction pathway being the reduction to **7a**, whereas with Buchwald's

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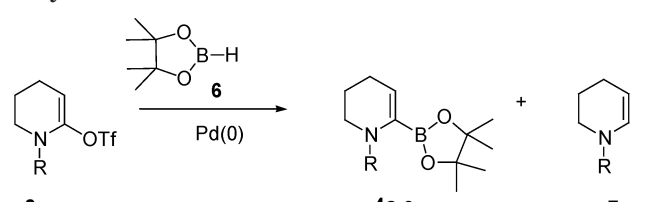
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(11) ¹H NMR (200 MHz, CDCl_3) spectrum of **5a**: δ 7.35–7.25 (m, 10 H), 5.33 (br t, 2 H), 5.07 (s, 4 H), 3.50–3.10 (m, 4 H), 2.10–1.95 (m, 4 H), 1.75–1.50 (m, 4 H).

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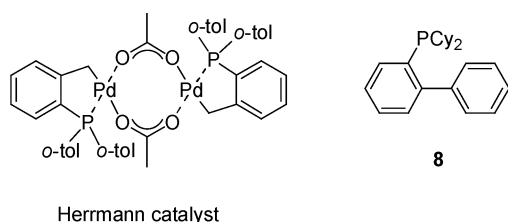
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TABLE 2. Pd-Catalyzed Borylation of Lactam-Derived Vinyl Triflates **2a–c**^a


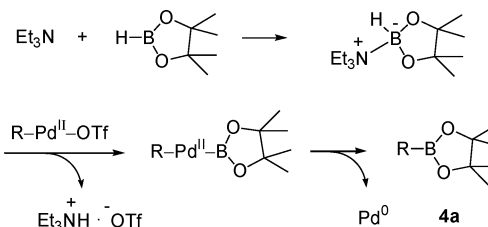
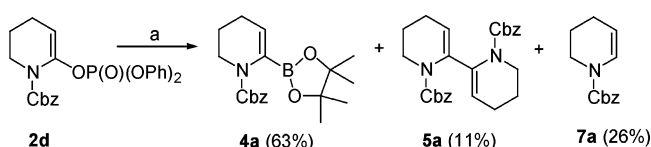
entry	substrate	R	catalyst	T (°C)	4 (%) ^b	7 (%) ^b
1	2a	Cbz	3% (Ph ₃ P)PdCl ₂	50	0	26
2			3% Pd(OAc) ₂ , 12% Cy ₃ P	50	19	81
3			3% Pd ₂ (dba) ₃ , 12% Cy ₃ P	50	21	70
4			3% Pd(OAc) ₂ , 12% 8	90	14	86
5			3% (dppf)PdCl ₂	20	0	52
6				50	83 (71) ^c	17
7				90	66	34
8			3% (dppf)PdCl ₂ , 12% Ph ₃ As	50	85	15
9			3% (dppf)PdCl ₂ , 12% Ph ₃ As	90	43	57
10	2b	Boc	3% (dppf)PdCl ₂	50	67 (60) ^c	33
11	2c	Ts	3% (dppf)PdCl ₂	50	0	<10
12			3% (dppf)PdCl ₂	90	95 (83) ^c	5

^a Conditions: **6** (1.5 equiv), Et₃N (3 equiv), dioxane, 2 h.
^b Conversion determined by ¹H NMR analysis of the crude reaction mixture. ^c Isolated yield after chromatography.

**FIGURE 1.** Structures of the Herrmann catalyst and Buchwald's phosphine **8**.

ligand the reaction occurred at 90 °C, yielding, again, mainly **7a** (entry 4). The highest yields of **4a–c** (up to 83%, after chromatography) were obtained when the couplings were performed in the presence of 3% (dppf)-PdCl₂ as a catalyst and Et₃N (3 equiv) as a base, in dioxane at 50 °C (entries 6 and 10) or 90 °C (entry 12).^{5a} The presence of Ph₃As as an additional ligand appears to be unnecessary in these reactions (compare entries 6 and 8), as instead reported by Masuda for the transformation of cyclic alkenyl triflates into the corresponding boronates with pinacolborane.^{5b} When the reaction was carried out at room temperature (entry 5), only the partial reduction of the substrate to **7a** (52%) was observed. This reduction process must be Pd-catalyzed because the starting material (**2a**) was recovered unreacted after 4 h of heating without the catalyst under the conditions of entry 6. The transmetalation of the hydride from pinacolborane, which occurred at room temperature to form a R–Pd–H species (which in turn undergoes reductive elimination delivering R–H, i.e., **7a**), is remarkable on the basis of the low nucleophilicity of this hydride. However, quaternization of the B atom by Et₃N (Figure 2) could play a role in this.¹⁵ The transfer of the

(15) Masuda has proposed a mechanism for the borylation in which Et₃N deprotonates pinacolborane forming a boryl anion that then is transferred to the R–Pd–OTf complex to form the R–Pd–B(OR')₂ intermediate. Please see ref 5a.

**FIGURE 2.** Possible mechanism of borylation with pinacolborane.**SCHEME 2^a**

^a Key: **3** (1.5 equiv), 3% (Ph₃P)₂PdCl₂, 6% Ph₃P, K₂CO₃ (1.5 equiv), dioxane, 90 °C, 5 h.

boryl moiety to the R–Pd–OTf complex to generate the R–Pd–B(OR')₂ intermediate turns out to be significant only when the temperature is increased (entries 6 and 8), although the reduction process becomes again not marginal if the reaction is carried out at 90 °C (entries 7 and 9).

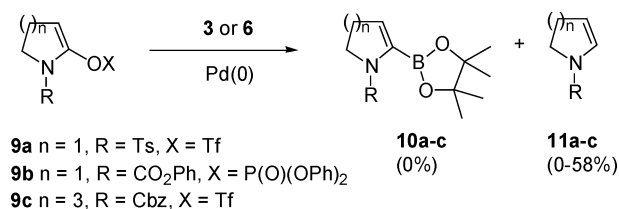
Interestingly, *N*-Ts derivative **2c** proved to be less reactive than **2a,b** toward both the borylation and reduction reactions: conversion to **4c** was observed only at 90 °C (entry 12), whereas at lower temperature only less than 10% (by ¹H NMR) of the substrate was reduced to **7c** (entry 11).

As already observed in other cases,^{5,13} pinacolborane showed a greater reactivity than bis(pinacolato)diboron toward lactam-derived vinyl triflates **2a–c**, as the borylations with the former reagent were complete in 2 h at 50–90 °C. To further lower the cost of these transformations, we considered the possibility of using lactam-derived vinyl phosphates in place of the triflates, which are similarly prepared by trapping the lactam-derived potassium enolate with the very cheap diphenyl phosphoryl chloride.^{6,7k,16} We tried a series of conditions with *N*-Cbz derivative **2d** (Scheme 2), but the reductive process was predominant under various conditions in the presence of pinacolborane. Although a certain conversion to boronate **4a** (63%) was observed by carrying out the reaction with bis(pinacolato)diboron (1.5 equiv) in the presence of 3% (Ph₃P)₂PdCl₂ in dioxane at 90 °C (Scheme 2), the results obtained with vinyl triflate **2a** are superior.

Disappointingly, while the δ-valerolactam derivatives **2a–c** were successfully converted into boronates by Pd-catalyzed coupling reaction with both bis(pinacolato)diboron and pinacolborane, pyrrolidinone and ε-caprolactam derivatives **9a–c** either did not react or were readily reduced to **11** (Scheme 3) under the optimized conditions reported above for the six-membered derivatives. In particular, **9a**^{7g} (R = Ts, X = Tf) decomposed during the reaction, and **9b**¹⁶ [R = CO₂Ph, X = P(O)(OPh)₂] did not react with bis(pinacolato)diboron. Phosphate **9b** was completely reduced to pyrroline **11b** with

(16) Nicolaou, K. C.; Shi, G.-Q.; Namoto, K.; Bernal, F. *Chem. Commun.* **1998**, 1757.

SCHEME 3



pinacolborane. Similar results were obtained with the seven-membered derivative **9c**.^{7j} These results are indeed not surprising given the thermal instability of pyrrolidinone- and ϵ -caprolactam-derived vinyl triflates, which decompose on standing or during the coupling reaction.^{6,7j,17}

In contrast to aromatic 2-pyridylboronic esters and, generally, to boronic acids and esters adjacent to a heteroatom, which are reported to be highly susceptible to hydrolytic protodeboronation,¹⁸ 1,4,5,6-tetrahydro-2-pyridylboronic ester derivatives **4a–c** are compounds indefinitely stable at room temperature that can be purified by chromatography on silica gel. An initial study of reaction conditions for the coupling of **4a** with bromobenzene resulted in three optimized protocols: one employs 2 mol % Herrmann catalyst¹⁹ (Figure 1) in anhydrous toluene at 110 °C with K_2CO_3 as a base; using this procedure, a certain amount of 3,4-dihydro-2H-pyridine **7a** (16% by 1H NMR analysis of the crude reaction mixture) was formed. The second procedure employs the $Pd(OAc)_2$ (10 mol %)/ Ph_3P (20 mol %) catalytic system in the presence of $K_3PO_4 \cdot H_2O$ (2 equiv) as a base in dioxane at 100 °C. The third protocol employs aqueous conditions [5% $(Ph_3P)_2PdCl_2$, 2 M Na_2CO_3 (aq), THF, 50 °C]. All of the three procedures were applied to a series of commercial electron-rich and electron-deficient aryl bromides, and the best result for each substrate is reported in Table 3. Good to excellent yields were obtained with all of the bromoarenes (entries 1–10). Only 2-bromoacetophenone did not react at all under any of the conditions, presumably because of steric impediment. It is interesting to note that we always observed the formation of **7a** as a secondary product when we used the Herrmann catalyst, to an extent exclusively dependent on the nature of the aryl bromide: for example, with 2-bromotoluene, the amount of this byproduct produced after 4 h at 110 °C was higher (42% by 1H NMR analysis of the crude reaction mixture) than that produced with 4-methoxybromobenzene (20%) after 8 h at the same temperature. Also, the reaction of **4a** with bromobenzene took place at lower temperature (90 °C) with the Herrmann catalyst; however, it was much slower (15% conversion after 3.5 h), and in practice, the ratio between **12** and byproduct **7a** did not change.

With aryl triflates (entries 11 and 12), the highest yields were instead obtained under aqueous conditions, which provided phenyl and naphthyl derivatives **12** and **16** in 82 and 81% yield, respectively, after chromatography. As expected boronate **4a** does not undergo hydrolysis to the corresponding boronic acid under these aqueous conditions, as we recovered the boronate unaltered when a THF solution of **4a** was heated at 50 °C for 2 h in the presence of the aqueous base.

The coupling reactions with heteroaryl bromides (Table 4) were generally slower than with aryl bromides and in some cases did not reach completion even after prolonged heating, as in the case of 2-bromopyridine (entry 1). In one case only, conditions employing the palladacycle as the catalyst were superior (entry 3), allowing for the synthesis of 2-thienyl derivative **24** in 81% yield. 3-Bromofuran reacted only under aqueous conditions (entry 5) as did various alkenyl halides and triflates (Table 5, entries 1–4) to give 2-(1-alkenyl)-substituted piperidines, which are useful dienes in Diels–Alder reactions.²⁰

The coupling of boronic acids or boronates with acid chlorides has been described in a few cases.²¹ We attempted several of the reported reaction conditions²¹ in order to couple vinyl boronate **4a** with aromatic acid chlorides. The coupling reaction with benzoyl chloride, carried out under various anhydrous conditions [for example, with $(Ph_3P)_2PdCl_2$ in dioxane and K_2CO_3 as a base or in toluene with K_3PO_4 ; with $(Ph_3P)_4Pd$ in toluene and Cs_2CO_3 as a base],^{21a,c} did not occur at all, unless 1–2 equiv of water was added. In this case, a low conversion was observed after prolonged heating. An appreciable conversion to the desired product **31** was observed under Bumagin's conditions (Table 5, entry 5),^{21d} although the highest yield was obtained when we moved to our standard aqueous conditions (entry 6). Reasonably, the quaternization of the boron atom by an HO^- ion [or the coordination of the latter to the acyl– $Pd(II)$ complex]²² is needed to render the transmetalation step possible, which is further accelerated by increasing the concentration (4 M) of the aqueous base. However, only electron-rich benzoyl chlorides, as in entry 7, reacted under these conditions to give the coupling products without undergoing hydrolysis, and the protocol was inapplicable to aliphatic acid chlorides.

Conclusion

In conclusion, we have demonstrated that δ -valerolactam-derived vinyl triflates can be converted into the corresponding tetrahydropyridine-2-boronic acid pinacol ester derivatives, which results in an umpolung. Conditions were optimized for the Pd-catalyzed borylation carried out with both bis(pinacolato)diboron and pinacolborane. Instead, this was not possible for pyrro-

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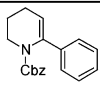
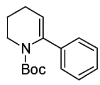
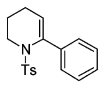
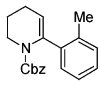
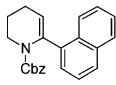
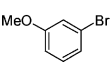
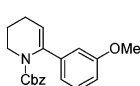
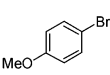
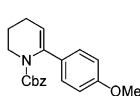
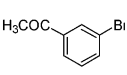
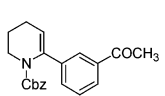
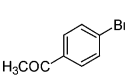
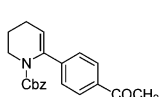
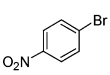
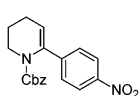
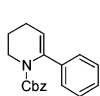
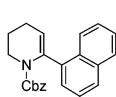
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TABLE 3. Pd-Catalyzed Cross-Coupling Reaction of 4a–c with Arylbromides and Aryltriflates^a

entry	R-X	substrate	conditions	time (h)	product	yield (%) ^b
1		4a	Method A ^c at 100 °C	1.5		12 88
2		4b	Method A at 90 °C	6		13 90
3		4c	Method A at 90 °C	6		14 85
4		4a	Method A at 100 °C	2.5		15 87
5		4a	Method A at 100 °C	2		16 91
6		4a	Method A at 100 °C	2		17 93
7		4a	Method B ^d at 110 °C	8		18 73
8		4a	Method A at 100 °C	2		19 89
9		4a	Method A at 100 °C	2		20 87
10		4a	Method A at 100 °C	1.5		21 83
11		4a	Method C ^e at 50 °C	1.5		12 82
12		4a	Method C at 50 °C	2		16 81

^a Reactions carried out with 1.5 equiv of RX and stopped when TLC showed total consumption of **4**. ^b Isolated yield after chromatography. ^c Method A: 10% Pd(OAc)₂, 20% Ph₃P, K₃PO₄·H₂O (2 equiv), dioxane. ^d Method B: 2% Herrmann catalyst, K₂CO₃ (2 equiv), toluene. ^e Method C: 5% (Ph₃P)₂PdCl₂, 2 M Na₂CO₃–THF (volume ratio 1.5:2).

lidinone and ϵ -caprolactam derivatives, which did not react or were reduced during the Pd-catalyzed coupling reactions. These δ -valerolactam-derived vinyl boronates efficiently coupled under Pd catalysis with aryl and heteroaryl bromides and triflates, alkenyl triflates and halides, and aromatic acid chlorides to give the corresponding 2-substituted piperidines, which are useful intermediates in organic synthesis. The overall

methodology has two advantages compared to the direct use of the lactam-derived vinyl triflates in coupling processes: first, these vinyl boronates are indefinitely stable on standing. Second, the procedure is of wide applicability due to the vast range of commercially available electrophiles for the cross-coupling reactions. The conversion of the lactam-derived vinyl boronates into the corresponding boronic acids and trifluoroborates is

TABLE 4. Pd-Catalyzed Cross-Coupling Reaction of 4a with Heteroaryl bromides^a

entry	R-Br	conditions	time (h)	product	yield (%) ^b
1		Method A ^c at 100 °C	5		22 45 ^d
2		Method A at 100 °C	4		23 77
3		Method B ^e at 110 °C	7		24 81
4		Method A at 100 °C	2		25 62
5		Method C ^f at 50 °C	3		26 71

^a Reactions carried out with 1.5 equiv of RBr and stopped when TLC showed complete consumption of **4a**. ^b Isolated yield after chromatography. ^c Method A: 10% Pd(OAc)₂, 20% Ph₃P, K₃PO₄·H₂O (2 equiv), dioxane. ^d Conversion determined by ¹H NMR analysis of the crude reaction mixture. ^e Method B: 2% Herrmann catalyst, K₂CO₃ (2 equiv), toluene. ^f Method C: 5% (Ph₃P)₂PdCl₂, 2 M Na₂CO₃–THF (volume ratio 1.5:2).

TABLE 5. Other Pd-Catalyzed Cross-Coupling Reactions of 4a^a

entry	R-X	conditions	time (h)	product	yield (%) ^b
1		Method C ^c at 55 °C	1		27 67
2		Method C at 50 °C	2		28 78
3		Method C at 50 °C	5		29 78
4		Method C at 50 °C	2		30 75
5		Method D ^d at 20 °C	24		31 21
6		Method C at 55 °C ^e	3		31 52
7		Method C at 55 °C ^f	2.5		32 76

^a Reactions carried out with 1.5 equiv of RX and stopped when TLC showed complete consumption of **4**. ^b Isolated yield after chromatography. ^c Method C: 5% (Ph₃P)₂PdCl₂, 2 M Na₂CO₃, THF. ^d Method D: 0.1 M PdCl₂, 1.63 M Na₂CO₃, acetone–water (volume ratio 3:1). ^e Performed with 4 M Na₂CO₃ and 2 equiv of acid chloride. ^f Performed with 2 equiv of acid chloride.

currently under study in our laboratory to further extend their application to other metal-catalyzed C–C bond forming reactions such as the 1,2- and 1,4-addition to

carbonyl compounds and the addition to alkenes and alkynes. The results of these studies will be reported in due course.

Experimental Section

Procedures for the Preparation of Boronate **4a**:

Method A. *N*-Cbz triflate **2a** (780 mg, 2.14 mmol) was dissolved in anhydrous dioxane (14 mL) in a two-necked flask under a nitrogen atmosphere. To the solution were added, in the following order, bis(pinacolato)diboron **3** (816 mg, 3.21 mmol), (Ph₃P)₂PdCl₂ (46 mg, 0.066 mmol), Ph₃P (34 mg, 0.13 mmol), and anhydrous K₂CO₃ (444 mg, 3.21 mmol). The mixture was heated with an oil bath to 90 °C and left under stirring for 7 h, after which time the reaction was complete (by TLC). After cooling to room temperature, the mixture was diluted with Et₂O (60 mL) and washed with water (3 × 40 mL). The organic phase was dried over Na₂SO₄, filtered, and concentrated. The crude oil was chromatographed (EtOAc–petroleum ether, 1:8, *R*_f 0.20), affording pure **4a** (623 mg, 85%) as a white solid.

Method B. *N*-Cbz triflate **2a** (183 mg, 0.5 mmol) was dissolved in anhydrous dioxane (2.5 mL) in a Schlenk flask under a nitrogen atmosphere. To the solution were added, in the following order, (dppf)PdCl₂ (11 mg, 0.015 mmol), pinacolborane **6** (109 μL, 0.75 mmol), and Et₃N (206 μL, 1.5 mmol). The mixture was heated with an oil bath to 50 °C and left under stirring for 2 h, after which time the reaction was complete (by TLC). After cooling to room temperature, the mixture was diluted with Et₂O (15 mL) and washed with water (3 × 5 mL). The organic phase was dried over Na₂SO₄, filtered, and concentrated. The crude oil was chromatographed (EtOAc–petroleum ether, 1:8, *R*_f 0.20), affording pure **4a** (122 mg, 71%) as a white solid: mp 65–66 °C; ¹H NMR (200 MHz, CDCl₃) δ 7.35–7.20 (m, 5 H), 5.28 (br s, 1 H), 5.20 (s, 2 H), 3.59–3.50 (m, 2 H), 2.09–2.02 (m, 2 H), 1.81–1.66 (m, 2 H), 1.31 (s, 12 H); ¹³C NMR (50.33 MHz, CDCl₃) δ 155.6 (s), 135.5 (s), 133.0 (br), 128.2 (d, 2 C), 127.9 (d, 2 C), 127.6 (d), 114.5 (d), 82.8 (s, 2 C), 68.2 (t), 41.5 (t), 24.6 (q, 4 C), 21.7 (t), 21.2 (t); MS *m/z* (%) 343 (M⁺, 0.1), 194 (20), 152 (31), 91 (100). Anal. Calcd for C₁₉H₂₆BN₂O₄: C, 66.49; H, 7.64; N, 4.08. Found: C, 66.84; H, 7.74; N, 4.01.

Typical Coupling Procedures. 6-Phenyl-3,4-dihydro-2H-pyridine-1-carboxylic Acid Benzyl Ester (12**):**⁷ **Method A.** Pd(OAc)₂ (3.4 mg, 15 μmol), Ph₃P (8 mg, 30 μmol), and boronate **4a** (52 mg, 0.15 mmol) were dissolved in anhydrous dioxane (1.5 mL) in a Schlenk flask under a nitrogen atmosphere. To the solution was added bromobenzene (24 μL, 0.23 mmol), followed by K₃PO₄·H₂O (69 mg, 0.30 mmol), and the resulting mixture was heated at 100 °C. After 1.5 h, the reaction was complete (by TLC) and the mixture was diluted with Et₂O (15 mL) and washed with water (30 mL). The organic phase was dried over Na₂SO₄, filtered, and concentrated. The crude oil was chromatographed (EtOAc–petroleum ether, 1:8, 1% Et₃N, *R*_f 0.42), affording pure **12** (39 mg, 88%) as a colorless oil.

Method C. To a stirred solution of **4a** (52 mg, 0.15 mmol) in THF (2 mL) were added, under a nitrogen atmosphere, 2 M Na₂CO₃(aq) (1.5 mL), (Ph₃P)₂PdCl₂ (5.3 mg, 7.5 μmol), and phenyl trifluoromethanesulfonate (51 mg, 0.23 mmol). The mixture was heated to 50 °C, left under stirring for 1.5 h, and, after cooling, diluted with water (10 mL) and extracted with Et₂O (3 × 10 mL). The organic phase was dried for 30 min over K₂CO₃ and concentrated in vacuo. The crude oil was chromatographed (EtOAc–petroleum ether, 1:8, 1% Et₃N, *R*_f 0.42), affording pure **12** (36 mg, 82%) as a colorless oil: ¹H NMR (200 MHz, CDCl₃) δ 7.29–7.18 (m, 8 H), 6.79 (m, 2 H), 5.42 (t, *J* = 4.0 Hz, 1 H), 4.93 (s, 2 H), 3.83–3.76 (m, 2 H), 2.35–2.23 (m, 2 H), 1.97–1.83 (m, 2 H).

6-(4-Methoxyphenyl)-3,4-dihydro-2H-pyridine-1-carboxylic Acid Benzyl Ester (18**):** **Method B.** Herrmann catalyst (1.4 mg, 1.5 μmol) and boronate **4a** (52 mg, 0.15 mmol) were dissolved in anhydrous toluene (2 mL) in a Schlenk flask under a nitrogen atmosphere. To the solution was added 4-bromoanisole (28 μL, 0.23 mmol), followed by anhydrous K₂CO₃ (41.4 mg, 0.30 mmol), and the resulting mixture was heated at 110 °C. After 8 h, the reaction was complete (by TLC), and the mixture was diluted with Et₂O (15 mL), washed with water (30 mL), and dried over Na₂SO₄. Evaporation of the solvent and chromatography (EtOAc–petroleum ether, 1:8, *R*_f 0.36) gave pure **18** (35 mg, 73%) as a colorless oil: ¹H NMR (200 MHz, CDCl₃) δ 7.22–7.18 (m, 5 H), 6.82–6.76 (m, 4 H), 5.32 (t, *J* = 3.7 Hz, 1 H), 4.92 (s, 2 H), 3.79 (s, 3 H), 3.78–3.73 (m, 2 H), 2.30–2.23 (m, 2 H), 1.92–1.83 (m, 2 H); ¹³C NMR (50.33 MHz, CDCl₃) δ 158.8 (s), 152.8 (s), 139.3 (s), 135.8 (s), 132.1 (d), 128.0 (d, 2 C), 127.5 (d, 2 C), 126.1 (d, 2 C), 115.6 (s), 114.8 (d), 113.4 (d, 2 C), 67.4 (t), 55.2 (q), 45.2 (t), 23.6 (t), 23.5 (t); MS *m/z* (%) 323 (M⁺, 16), 91 (100). Anal. Calcd for C₂₀H₂₁NO₃: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.21; H, 6.49; N, 4.38.

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Supporting Information Available: Full experimental details and compound characterization. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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