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Cross-Coupling of Diarylborinic Acids and Anhydrides with Arylhalides Catalyzed by a Phosphite/N-Heterocyclic Carbene Co-supported Palladium Catalyst System

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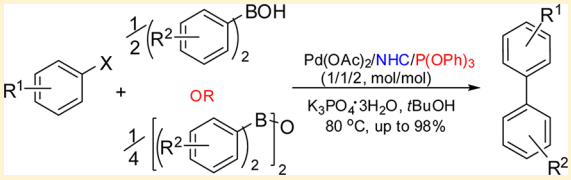
Supporting Information

ABSTRACT: A highly efficient cross-coupling of diarylborinic acids and anhydrides with aryl chlorides and bromides has been effected by using a palladium catalyst system co-supported by a strong σ-donor N-heterocyclic carbene (NHC), *N*,*N*′-bis(2,6-diisopropylphenyl) imidazol-2-ylidene, and a strong π-acceptor phosphite, triphenylphosphite, in *tert*-BuOH in the presence of $K_3PO_4 \cdot 3H_2O$. Unsymmetrical biaryls with a variety of functional groups could be obtained in good to excellent yields using as low as 0.01, 0.2−0.5, and 1 mol % palladium loadings for aryl bromides and activated and deactivated aryl chlorides, respectively, under mild conditions. A ligand synergy between the σ-donor NHC and the π-acceptor phosphite in the Pd/NHC/$P(OPh)_3$ catalytic system has been proposed to be responsible for the high efficacy to arylchlorides in the cross-coupling. A scalable and economical process has therefore been developed for synthesis of Sartan biphenyl from the Pd/NHC/$P(OPh)_3$ catalyzed cross-coupling of di(4-methylphenyl)borinic acid with 2-chlorobenzonitrile.



INTRODUCTION

The advantages of Suzuki coupling over the other transition-metal-catalyzed cross-coupling reactions are mainly attributed to the friendly properties of organoboronic acids, e.g., nontoxicity, air/moisture stability, and tolerance of a variety of functional groups.[1] Innumerable improvements on the original protocol have been reported with respect to catalyst/ligand systems, solvents, additives, and experimental conditions,[1,2] among which a couple of breakthroughs include the conquest of inert arylchlorides by developing highly active catalyst systems of palladium supported by bulky electron-rich phosphines[3] or sterically demanding N-heterocyclic carbene (NHC) ligands[4] and use of organotrifluoroborates to improve reaction stoichiometry as well as compatibility to reaction conditions.[5] Comparatively, few advances have been made on the utility of high-order arylborons,[6] e.g., diarylborinic acids, triarylboranes, and tetraarylborates, in Suzuki coupling. High-order arylborons not only have higher atom economy but also could be more readily prepared by reaction of aryl magnesium halides with boronates, the most traditional and economical way for preparation of arylboronic acids albeit less functional group compatible compared with the transition-metal-catalyzed protocols.[7] In fact, synthesis of arylboronic acids by reaction of aryl magnesium halides with alkylboronates would always generate diarylborinic acids and triarylboranes as major byproducts unless harsh cryogenic conditions or extra additives were used,[7,8] while high-order arylborons could be prepared from almost equivalent arylmagnesium halides and boronates under noncryogenic conditions, even by one-pot procedures from aryl halides, boronates, and magnesium.[9]

The air sensitivity of triarylboranes and poor solubility of tetraarylborates in organic solvents as well as their reluctance in Suzuki coupling make them less competitive with arylboronic acids. Diarylborinic acids, except for slow crystallization,[10] not only have higher atom economy but also share most of the friendly features of arylboronic acids. Therefore, it is surprising that diarylborinic acids and derivatives have been rarely applied in transition-metal-catalyzed cross-coupling reactions.[11] In fact, to the best of our knowledge, except for our pending patent,[12] Winkle et al. described the only example of a Suzuki coupling reaction of diarylborinic acids, in situ generated bis(3,5-dimethylphenyl)borinic acid with a highly reactive vinyl triflate, in developing a process for synthesis of a potent endothelin A antagonist PD 0182783.[11c] More recently, Knochel et al. reported the use of a mixture of magnesium mono-, di-, and triorganoboronates generated in situ from arylbromides, boronates, magnesium, and lithium chloride, although a formula of $Ar_2B(OBu)_2MgX$ was used to reflect the stoichiometry, in Suzuki coupling with active arylhalides and pseudohalides.[13] Herein, we report a highly efficient cross-coupling of diarylborinic acids and anhydrides with arylhalides catalyzed by a σ-donor NHC and π-acceptor phosphite co-supported palladium catalyst system.

RESULTS AND DISCUSSION

Diarylborinic acids could be readily prepared by reaction of aryl magnesium halides with an equivalent amount of alkylboronates at room temperature or by a one-pot procedure from arylbromides, tributylboronate, and magnesium in THF at 30−40 °C.[9c] However, purification of diarylborinic acids proved

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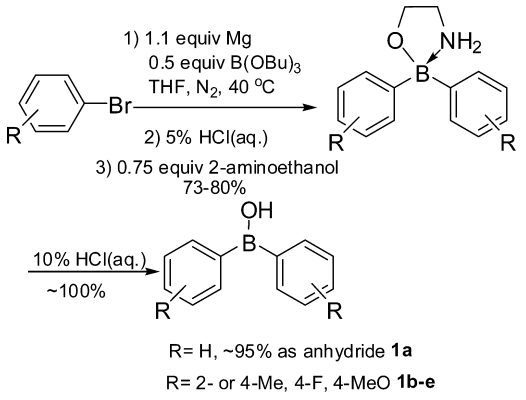
tedious, especially for those that have low melting points. Fortunately, treatment of the crude products with 2-aminoethanol afforded crystalline solid materials of 2-aminoethoxy diarylborates, which could be readily purified by recrystallization in ethanol and converted back into diarylborinic acids in almost quantitative yields by simple acidification with aqueous HCl (10%) (Scheme 1). Diphenylborinic acid was further converted to anhydride for convenience in reaction stoichiometry due to its ease to dehydration.

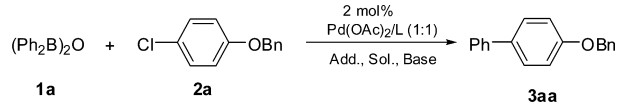
Scheme 1. Scalable Process for Preparation of Diarylborinic Acids



Electron-rich arylchlorides belong to difficult electrophile counterparts in Suzuki coupling, especially with a low catalyst loading. Therefore, reaction of diphenylborinic anhydride **1a** with 4-(benzyloxy)phenyl chloride **2a** was used as the model reaction to screen catalyst systems. Almost no reaction was observed for both diphenylborinic anhydride and $Ar_2B(OBu)_2MgBr$ generated in situ with the catalyst system of $[Pd(dppf)Cl_2]/Cs_2CO_3$ in DMF that was reported to work for active arylhalides.[13] Using the well-established catalyst systems for arylchlorides in Suzuki coupling, such as $[Pd/P(Cy)_3)]$, $[Pd/P(tBu)_3)]$[3] and [Pd/(IPr)] (IPr = *N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidene,[4] the desired cross-coupling product **3aa** was obtained in 32−78% yields depending on the structure of supporting ligands for palladium and strongly on reaction conditions (Table 1, entries 1−10).

The $Pd(OAc)_2$/IPr·HCl combination was selected for further optimization of the reaction parameters considering that Pd/NHC systems have proven not only more practical than the air-sensitive $Pd/P(tBu)_3$ but also more tunable in catalytic activity as pioneered by Nolan[4] and Organ[14] groups. For example, NHC palladium complexes used along with a secondary weakly coordinating ligand, such as pyridines,[4d,14] phosphites,[15] NEt_3,[16] etc., have been reported to show significantly higher catalytic activity in cross-coupling through either speeding formation of active species or trapping and conserving the active species in solution.[14b] Unfortunately, the yields of **3aa** decreased when pyridine, $P(OMe)_3$, $P(OiPr)_3$, or NEt_3 was added to the catalyst system (Table 1, entries 11−14). However, when $P(OPh)_3$ was used in the range of 2−20 equiv to palladium, the yields of **3aa** remarkably increased to 92−95% from 68−78%, although 1 equiv of $P(OPh)_3$ showed little effect (Table 1, entries 15−19), possibly benefiting from a ligand synergy between the σ-donor NHC and the strong π-acceptor triphenylphosphite.[17] A control experiment in the absence of NHC showed that almost no reaction occurred under the otherwise identical conditions (Table 1, entry 20),

Table 1. Cross-Coupling of Diphenylborinic Anhydride with 4-(Benzyloxy)phenyl Chloride[a]



1a 2a 3aa

entry	L	Add. (mol %)	Sol.	Base	yield (%)[b]
1[c]	PCy_3		DMF	$K_3PO_4·3H_2O$	32
2[c]	$P(tBu)_3$		DMF	$K_3PO_4·3H_2O$	70
3[c]	IPr		DMF	$K_3PO_4·3H_2O$	45
4	IPr		*t*BuOH	$K_3PO_4·3H_2O$	68
5	IPr		*t*BuOH	NaOH	78
6	IPr		*i*PrOH	NaOH	18
7	IPr		EtOH	NaOH	trace
8	IPr		THF	NaOH	55
9	IPr		dioxane	NaOH	43
10	IPr		THF	*t*BuOK	55
11	IPr	Et_3N (40)	*t*BuOH	NaOH	40
12	IPr	pyridine (40)	*t*BuOH	NaOH	53
13	IPr	$P(OMe)_3$ (40)	*t*BuOH	NaOH	10
14	IPr	$P(OiPr)_3$ (40)	*t*BuOH	NaOH	17
15	IPr	$P(OPh)_3$ (40)	*t*BuOH	NaOH	95
16	IPr	$P(OPh)_3$ (20)	*t*BuOH	NaOH	95
17	IPr	$P(OPh)_3$ (8)	*t*BuOH	NaOH	93
18	IPr	$P(OPh)_3$ (4)	*t*BuOH	NaOH	92
19	IPr	$P(OPh)_3$ (2)	*t*BuOH	NaOH	76
20		$P(OPh)_3$ (2)	*t*BuOH	NaOH	trace
21[d]	IPr	$P(OPh)_3$ (2)	*t*BuOH	NaOH	95
22[e]	IPr	$P(OPh)_3$ (1)	*t*BuOH	NaOH	90
23[d]	IPr	$P(OPh)_3$ (2)	*t*BuOH	K_2CO_3	30
24[d]	IPr	$P(OPh)_3$ (2)	*t*BuOH	$K_3PO_4·3H_2O$	98
25[d]	IPr	$P(OPh)_3$ (2)	*t*BuOH	$Ba(OH)_2·8H_2O$	65
26[d]	IPr	$P(OPh)_3$ (2)	*t*BuOH	Cs_2CO_3	74
27[e]	IPr	$P(OPh)_3$ (1)	*t*BuOH	$K_3PO_4·3H_2O$	81
28[d]	IMes	$P(OPh)_3$ (2)	*t*BuOH	$K_3PO_4·3H_2O$	18
29[d]	SIPr	$P(OPh)_3$ (2)	*t*BuOH	$K_3PO_4·3H_2O$	86
30[f]	IPr	$P(OPh)_3$ (2)	*t*BuOH	$K_3PO_4·3H_2O$	71

[a]Reaction conditions: $(Ph_2B)_2O$ (0.55 mmol), 4-(benzyloxy)phenyl chloride (2.0 mmol), base (4.0 mmol), solvent (5 mL), N_2, 80 °C, 12 h; $P(tBu)_3$ and IPr used in form of $P(tBu)_3·HBF_4$ and IPr·HCl, respectively; [b]Isolated yields. [c]At 110 °C. [d]1 mol % $Pd(OAc)_2$ used. [e]0.5 mol % $Pd(OAc)_2$ used. [f]1 mol % $Pd(OAc)_2$ and 2 mol % IPr·HCl used.

excluding the possibility of a catalysis of Pd species supported by $P(OPh)_3$ alone. This result and the fact that the catalyst system has worked well in the presence of large excess (20 equiv) of $P(OPh)_3$ support the ligand synergy, namely, at least one $P(OPh)_3$ molecule remains coordinated to the catalytic active NHC palladium(0) species,[15] e.g., $[(NHC)Pd\{P(OPh)_3\}_n]$, during the catalytic cycle.

The model reaction still proceeded smoothly to offer the cross-coupling product **3aa** in 90−95% yields even when the palladium catalyst loading was decreased to 0.5−1 mol % from 2 mol % (Table 1, entries 18, 21, and 22). Considering the possible problems of functional group compatibility of NaOH, a couple of weak bases such as K_2CO_3, $K_3PO_4·3H_2O$, $Ba(OH)_2·8H_2O$, and Cs_2CO_3 were investigated, and $K_3PO_4·3H_2O$ was found to work even slightly better than NaOH with 1 mol % palladium catalyst loading (Table 1, entries 23−26). The structure of NHCs also affected the activity of the corresponding NHC/phosphite palladium

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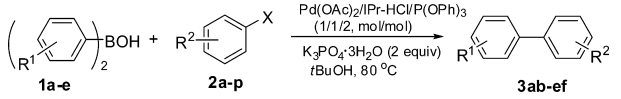
catalyst system. The saturated analogue of IPr, *N*,*N*′-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene (SIPr), also worked in the system, while the less sterically demanding NHC, *N*,*N*′-dimestylimidazol-2-ylidene (IMes), provided product **3aa** in only 18% yield (Table 1, entries 28 and 29). The catalysis efficiency decreased remarkably when the mole ratio of NHC to Pd was increased to 2:1 from 1:1 (Table 1, entry 30), indicating that bis(NHC) palladium complexes [Pd(NHC)$_2$] would be less catalytically active than the species co-supported by a NHC and phosphites, [Pd(NHC){P(OPh)$_3$}$_n$]. No reaction occurred when 2-aminoethoxy diphenylborate was used in the model reaction under the otherwise identical conditions.

Scope of the cross-coupling of diarylborinic acids with arylhalides was explored briefly (Table 2). A wide range of functional groups such as aldehyde, ester, nitrile, and acetyl survived the reaction (Table 2, entries 1−5). Electron-deficient arylchlorides, such as 4-$CH_3COC_6H_4Cl$, 4-CNC_6H_4Cl, and 2-CNC_6H_4Cl, reacted faster than electron-neutral or -rich analogues, e.g., 4-$CH_3C_6H_4Cl$ and 4-$CH_3OC_6H_4Cl$, even with a lower catalyst loading (0.5 mol % Pd(OAc)$_2$).

It has been observed that the presence of pyridine or triethylamine in the system led to a yield decrease in the model reaction (Table 1, entries 11 and 12). Therefore, it is interesting to investigate if the ligand synergy between NHC and P(OPh)$_3$ in [(NHC)Pd{P(OPh)$_3$}$_n$] could possibly be disturbed by competitive coordination to Pd(NHC) of N groups in substrates, such as 4-$Me_2NC_6H_4Cl$ and 3-chloropyridine (Table 2, entries 8−12). When 4-$Me_2NC_6H_4Cl$ or 3-chloropyridine was subjected to the standard conditions, the desired reaction did take place but in obviously slower rates (49% and 86%, respectively, 10 h). To confirm the depression of the competitive coordination from N groups of substrates to Pd(NHC) catalytic species on the reaction rates, control experiments without use of P(OPh)$_3$ and with a high loading of P(OPh)$_3$ (20 equiv to Pd) were conducted (Table 2, entries 9, 10, and 12). For the deactivated chloride, 4-$Me_2NC_6H_4Cl$, no reaction was detected after 10 h in the absence of P(OPh)$_3$, although the cross-coupling product **3aj** was isolated in 24% yield for 3-chloropyridine. In contrast, 63% and 98% yields of **3ai** and **3aj** were obtained for the reactions of 4-$Me_2NC_6H_4Cl$ and 3-chloropyridine, respectively, with 20 equiv P(OPh)$_3$ to palladium. These results are obviously consistent with the existence of competitive coordination of N-containing groups in substrates to catalytic palladium species in the NHC and phosphite co-supported catalyst system.

An electronic effect similar to that observed in the reaction of aryl chlorides was also found for bromides. However, only 0.01 mol % palladium loading proved to be enough for the reaction of arylbromides to complete within reasonable time (4−10 h) regardless of the substitutents on benzene ring (Table 2, entries 13−18). It is noteworthy to point out that the competitive depression by coordination of the Me_2N- group in the reaction of 4-dimethylaminophenyl chloride (49% yield, 1 mol % Pd(OAc)$_2$) was not observed for 4-dimethylaminophenyl bromide (94% yield, 0.01 mol % Pd(OAc)$_2$) due to the high activity of the NHC/phosphite palladium catalyst system to arylbromides (Table 2, entries 8 and 14). Electronic properties of diarylborinic acids showed a negligible influence on the coupling reaction (Table 2, entries 19−26). All of the investigated examples gave the desired products in excellent yields, although bis(4-methoxyphenyl)borinic acid **1e**, (4-$MeOC_6H_4)_2BOH$, suffered from the common side reaction in Suzuki coupling, proton deboronation.

Table 2. Scope of the Cross-Coupling of Diarylborinic Acids with Arylhalides[a]



entry	R^1	R^2 or ArX	X	Pd (mol %)	T (h)	product	yield (%)[b]
1	H (**1a**)	4-CHO (**2b**)	Cl	0.5	4	**3ab**	95
2	H (**1a**)	4-CO_2Me (**2c**)	Cl	0.5	3	**3ac**	94
3	H (**1a**)	2-CN (**2d**)	Cl	0.5	4	**3ad**	91
4	H (**1a**)	4-CN (**2e**)	Cl	0.5	4	**3ae**	97
5	H (**1a**)	4-COMe (**2f**)	Cl	0.5	6	**3af**	90
6[c]	H (**1a**)	4-Me (**2g**)	Cl	0.5	10	**3ag**	91
7[c]	H (**1a**)	4-OMe (**2h**)	Cl	1.0	10	**3ah**	92
8	H (**1a**)	4-NMe_2 (**2i**)	Cl	1.0	10	**3ai**	49
9	H (**1a**)	4-NMe_2 (**2i**)	Cl	1.0	10	**3ai**	63[d]
10	H (**1a**)	3-Cl-Py (**2j**)	Cl	0.5	10	**3aj**	24[e]
11	H (**1a**)	3-Cl-Py (**2j**)	Cl	0.5	10	**3aj**	86
12	H (**1a**)	3-Cl-Py (**2j**)	Cl	0.5	6	**3aj**	98[d]
13[c]	H (**1a**)	4-OMe (**2k**)	Br	0.01	10	**3ah**	96
14	H (**1a**)	4-NMe_2 (**2l**)	Br	0.01	10	**3ai**	94
15[c]	H (**1a**)	4-Me (**2m**)	Br	0.01	10	**3ag**	90
16[c]	H (**1a**)	2,5-dimethyl (**2n**)	Br	0.01	10	**3an**	90
17	H (**1a**)	4-COMe (**2o**)	Br	0.01	6	**3af**	93
18	H (**1a**)	4-CN (**2p**)	Br	0.01	4	**3ae**	94
19	4-Me (**1b**)	4-OBn (**2a**)	Cl	1.0	10	**3ba**	96
20	2-Me (**1c**)	4-OBn (**2a**)	Cl	1.0	10	**3ca**	88
21	4-F (**1d**)	4-OBn (**2a**)	Cl	1.0	10	**3da**	98
22	4-OMe (**1e**)	4-OBn (**2a**)	Cl	1.0	10	**3ea**	92
23	4-Me (**1b**)	4-COMe (**2f**)	Cl	0.5	6	**3bf**	95
24	2-Me (**1c**)	4-COMe (**2f**)	Cl	0.5	6	**3cf**	90
25	4-F (**1d**)	4-COMe (**2f**)	Cl	0.5	6	**3df**	93
26	4-OMe (**1e**)	4-COMe (**2f**)	Cl	0.5	6	**3ef**	82 (98)[f]

[a]Reaction conditions: **1a** (0.55 mmol) as anhydride or diarylborinic acids **1b−e** (1.1 mmol), arylhalides (2.0 mmol), $K_3PO_4{\cdot}3H_2O$ (4.0 mmol), *t*BuOH (5 mL), N_2, 80 °C. [b]Isolated yields. [c]3 equiv of arylhalide according to diarylborinic acids due to its low bp. [d]20 equiv of P(OPh)$_3$ with respect to Pd(OAc)$_2$ used. [e]No P(OPh)$_3$ added. [f]0.65 equiv of di(4-methoxyphenyl)borinic acid **1e** used.

To demonstrate potential of the cross-coupling of diarylborinic acids with arylchlorides in practical applications, we performed a synthesis of 4′-methyl-2-cyanobiphenyl, the so-called Sartan biphenyl, as an example. Sartan biphenyl is a key

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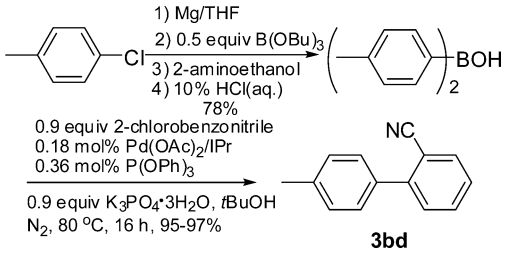
intermediate for the synthesis of a family of angiotensin II receptor antagonists, Sartans, for treatment of hypertension[18] and represents one of the most important fine chemicals that have been produced by using transition-metal-catalyzed cross-coupling reactions in industry. Currently, Sartan biphenyl has to be produced by Kumada or Negishi coupling of 2-chlorobenzonitrile with 4-methylphenyl magnesium or zinc halide instead of Suzuki coupling due to the high cost of 4-methylphenylboronic acid.[19] Although there are a couple of transition-metal-catalyzed borylations of aromatics with catecholborane or bis(pinacolato)diboron for synthesis of 4-methylphenylboronic acid,[7] because of the high cost of these boron reagents, none has advantages over the reaction of 4-methylphenyl magnesium chloride with an excess amount of trimethylboronate even under cryogenic conditions. Since di(4-methylphenyl)borinic acid could be more economically prepared by reaction of 4-methylphenyl magnesium chloride with almost equivalent boronates at room temperature, we anticipated that a more practical process for the synthesis of Sartan biphenyl would be possible by using the cross-coupling of diarylborinic acids with arylhalides (Scheme 2).

Scheme 2. Scalable Synthesis of Sartan Biphenyl by Cross-Coupling of Di(4-methylphenyl)borinic Acid with 2-Chlorobenzonitrile



3bd

In fact, di(4-methylphenyl)borinic acid was readily prepared from 4-methylphenyl chloride, Mg, and $B(OBu)_3$ in 78% overall yield in mole scale. Tributylboronate $B(OBu)_3$ was used instead of atom-economical $B(OMe)_3$ considering that the former is more readily prepared by just refluxing $B(OH)_3$ in BuOH with Dean–Stark and that the byproduct BuOH could be more easily recovered and reused than MeOH. It was found that 0.2 mol % palladium loading and 1 equiv of $K_3PO_4{\cdot}3H_2O$ with respect to 2-chlorobenzonitrile was enough for the coupling reaction to complete within 16 h and provide 4′-methyl-2-cyanobiphenyl **3bd** in excellent yields (95–97%) in repeated experiments.

CONCLUSION

In summary, a highly efficient cross-coupling of diarylborinic acids and anhydrides with aryl chlorides and bromides has been effected by using a palladium catalyst system co-supported by a strong σ-donor NHC, *N*,*N*′-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene, and a strong π-acceptor phosphite, triphenyl phosphite. The Pd/NHC/phosphite catalyst system worked well for both active and inert aryl halides, providing the desired unsymmetrical biphenyl products in good to excellent yields under mild conditions and within reasonable reaction time. The high efficacy of the catalyst system for deactivated arylchlorides has been attributed to a ligand synergy between NHC and phosphite in Pd/NHC/phosphite catalytic species generated in situ. The higher process and atom economies of diarylborinic acids promise a potential of this technique as a cost-effective version of Suzuki coupling. Using this technique, a scalable and economical process has been developed for synthesis of Sartan biphenyl, a key intermediate for production of a family of angiotensin II receptor antagonists. These results also imply that utility of diarylborinic acids in other transition-metal-catalyzed coupling reactions of organoboronic acids would be possible.

EXPERIMENTAL SECTION

General Information. All reactions were carried out under a nitrogen atmosphere unless otherwise stated. Commercially available chemicals were used as received. IPr·HCl,[20] IMes·HCl,[20] and SIPr·HBr[21] were prepared according to previously reported procedures. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at ambient temperature. Chemical shifts in NMR were reported in ppm (δ), relative to the internal standard of tetramethylsilane (TMS). The signals observed were described as s (singlet), d (doublet), t (triplet), dd(double doublet), m (multiplets), b (broad). The number of protons (n) for a given resonance was indicated as nH. Coupling constants were reported as J in Hz. The high resolution mass spectra (HRMS) were performed on an electron ionization mass spectrometer with a quadrupole analyzer.

Typical Procedure for Synthesis of Diarylborinic Acids. Under a N_2 atmosphere, a mixture of $B(OBu)_3$ (11.51 g, 50 mmol) and bromobenzene (15.70 g, 100 mmol) in 50 mL of THF was added dropwise to a stirred mixture of magnesium turnings (2.64 g, 110 mmol) and a small crystal of I_2 in THF (50 mL) at 40 °C over a period of 30 min. The reaction was maintained at 40 °C for an additional 2 h and then hydrolyzed by the addition of 100 mL of 5% HCl (aq) after being cooled to room temperature. The mixture was extracted with EtOAc and then concentrated to 20 mL before 2-ethanolamine (4.58 g, 75 mmol) was added. The resulting solution was stirred at room temperature for 2 h and then washed with water. The organic layer was concentrated under vacuum to obtain the crude product of 2-aminoethoxydiphenyl borate, which was recrystallized in ethanol and then acidified with 50 mL of 10% HCl (aq). The mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum to afford diphenylborinic acid, which was further converted into anhydride by heating at 80 °C for 2 h under vacuum.

Diphenylborinic Anhydride 1a.[22] White solid (6.75 g, 78%); mp 120–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89–7.61 (m, 8H), 7.53–7.36 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 131.4, 128.1. HRMS (EI) m/z (M^+) calcd for $C_{24}H_{20}B_2O$: 346.1700, found 346.1704.

Bis(4-methylphenyl)borinic Acid 1b.[23] White solid (8.18 g, 78%); mp 42–44 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.0 Hz, 4H), 7.26 (d, J = 8.4 Hz, 4H), 5.75 (bs, 1H), 2.41 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 136.2, 135.0, 128.9, 21.8.

Bis(2-methylphenyl)borinic Acid 1c. White solid (7.67 g, 73%); mp 66–67 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 7.2 Hz, 2H), 7.35–7.30 (m, 2H), 7.20–7.16 (m, 4H), 5.96 (s, 1H), 2.39 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 134.5, 130.2, 130.0, 125.2, 22.7. HRMS (EI) m/z (M^+) calcd for $C_{14}H_{15}BO$ 210.1216, found 210.1218.

Bis(4-fluorophenyl)borinic Acid 1d. White solid (8.72 g, 80%); mp 78–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79–7.75 (m, 4H), 7.15–7.10 (m, 4H), 5.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2 (dd, J = 22.0, 251.0 Hz,), 137.6 (dd, J = 8.0, 109.0 Hz), 115.3 (dd, J = 15.0, 20.0 Hz). HRMS (EI) m/z (M^+) calcd for $C_{12}H_9BOF_2$ 218.0715, found 218.0710.

Bis(4-methoxyphenyl)borinic Acid 1e.[24] White solid (9.18 g, 76%); mp 96–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.8 Hz, 4H), 6.96 (d, J = 8.8 Hz, 4H), 5.75 (s, 1H), 3.85 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 137.9, 136.8, 113.5, 55.2.

Typical Procedure for Cross-Coupling Reaction. Under a N_2 atmosphere, to a 10 mL flask were added 4-benzyloxychlorobenzene (0.44 g, 2.0 mmol), diphenylboronic anhydride (0.19 g, 0.55 mmol),

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$Pd(OAc)_2$ (4.50 mg, 0.02 mmol), IPr·HCl (8.50 mg, 0.02 mmol), $P(OPh)_3$ (12.40 mg, 0.04 mmol), $K_3PO_4·3H_2O$ (1.06 g, 4.0 mmol), and *t*BuOH (5 mL). The mixture was stirred at 80 °C and monitored by TLC until 4-benzyloxychlorobenzene was completely consumed. The reaction mixture was diluted with CH_2Cl_2 (15 mL), followed by washing with H_2O (2 × 10 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give crude product. The pure product was obtained by column chromatography on silica gel with EtOAc/petroleum ether.

4-Benzyloxybiphenyl 3aa.[25] White solid (0.510 g, 98%); mp 131−133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.51 (m, 4H), 7.45−7.37 (m, 6H), 7.34−7.27 (m, 2H), 7.04 (d, J = 8.4 Hz, 2H), 5.07 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 139.7, 135.9, 133.0, 127.7, 127.6, 127.1, 126.9, 126.4, 125.7, 125.6, 114.1, 69.0.

Biphenyl-4-carbaldehyde 3ab.[26] Yellow solid; mp 57−59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (s, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 7.6 Hz, 2H), 7.48 (t, J = 7.4 Hz, 2H), 7.41 (t, J = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 147.2, 139.7, 135.2, 130.3, 129.1, 128.5, 127.7, 127.4.

Methyl Biphenyl-4-carboxylate 3ac.[27] White solid; mp 114−115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.4 Hz, 2H), 7.59−7.54 (m, 4H), 7.39 (t, J = 7.4 Hz, 2H), 7.32 (t, J = 7.4 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 144.5, 138.9, 129.0, 127.9, 127.8, 127.1, 126.2, 126.0, 51.0.

2-Cyanobiphenyl 3ad.[28] White solid; mp 35−37 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 7.6 Hz, 1H), 7.63 (t, J = 7.6 Hz, 1H), 7.65−7.41 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 137.0, 132.6, 131.8, 128.9, 127.6, 126.5, 117.6, 110.1.

4-Cyanobiphenyl 3ae.[28] White solid; mp 86−89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−7.58 (m, 4H), 7.52−7.49 (m, 2H), 7.42−7.32 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 138.0, 131.5, 128.0, 127.6, 126.6, 126.1, 117.9, 109.7.

4-Acetylbiphenyl 3af.[28] White solid; mp 120−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 6.8 Hz, 2H), 7.49−7.45 (m, 2H), 7.42−7.38 (m, 1H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 145.7, 139.8, 135.8, 129.0, 128.9, 128.3, 127.3, 127.2, 26.7.

4-Methylbiphenyl 3ag.[29] White solid; mp 45−48 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 7.6 Hz, 2H), 7.48 (d, J = 7.6 Hz, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.31 (t, J = 7.4 Hz, 1H), 7.24 (d, J = 7.6 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 138.5, 137.1, 129.6, 128.8, 127.1, 21.2.

4-Methoxybiphenyl 3ah.[28] White solid; mp 88−89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (t, J = 8.6 Hz, 4H), 7.40 (t, J = 8.0 Hz, 2H), 7.29 (t, J = 7.4 Hz, 1H), 6.97 (d, J = 8.4 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 140.9, 133.8, 128.8, 128.2, 126.8, 126.7, 114.3, 55.4.

4-*N*,*N*-Dimethylaminobiphenyl 3ai.[30] White solid; mp 121−123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.8 Hz, 2H), 7.31 (t, J = 7.8 Hz, 2H), 7.17 (t, J = 7.4 Hz, 1H), 6.72 (d, J = 8.8 Hz, 2H), 2.90 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 140.1, 128.1, 127.6, 126.6, 125.2, 124.9, 111.7, 39.4.

3-Phenylpyridine 3aj.[31] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.59 (d, J = 4.4 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.47 (t, J = 7.4 Hz, 2H), 7.41−7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 148.1, 137.6, 136.4, 134.1, 129.0, 128.0, 127.0, 123.4.

2,5-Dimethylbiphenyl 3an.[32] White solid; mp 107−109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.37 (m, 2H), 7.32−7.30 (m, 3H), 7.15 (d, J = 7.6 Hz, 1H), 7.07 (d, J = 7.6 Hz, 2H), 2.34 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 141.9, 135.3, 132.3, 130.7, 130.4, 129.3, 128.2, 128.1, 126.8, 21.1, 20.1.

4-Benzyloxy-4′-methylbipheny 3ba.[33] White solid; mp 140−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.36 (m, 6H), 7.32 (t, J = 7.6 Hz, 2H), 7.25 (t, J = 7.0 Hz, 1H), 7.14 (d, J = 8.0 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 5.01 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 138.0, 137.1, 136.4, 134.0, 129.5, 128.7, 128.0, 127.6, 126.7, 115.2, 70.1, 21.2.

4-Benzyloxy-2′-methylbiphenyl 3ca. White solid (0.482 g, 88%); mp 62−63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 7.2 Hz, 2H), 7.40 (t, J = 7.2 Hz, 2H), 7.35−7.31 (m, 1H), 7.26−7.21 (m, 6H), 7.02 (d, J = 8.8 Hz, 2H), 5.09 (s, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 140.4, 135.9, 134.3, 133.5, 129.2, 129.1, 128.8, 127.5, 126.8, 126.4, 125.9, 124.7, 113.3, 68.8, 19.5; HRMS (EI) m/z (M^+) calcd for $C_{20}H_{18}O$ 274.1358, found 274.1360.

4-Benzyloxy-4′-fluorobiphenyl 3da. White solid (0.545 g, 98%); mp 139−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.36 (m, 6H), 7.31 (t, J = 7.4 Hz, 2H), 7.25 (t, J = 7.2 Hz, 1H), 7.00 (t, J = 8.4 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 5.02 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1(d, J = 250 Hz), 157.3, 135.9, 132.0, 127.6, 127.2, 127.1, 127.0, 126.4, 114.5 (d, J = 21 Hz), 114.1, 69.0; HRMS (EI) m/z (M^+) calcd for $C_{19}H_{15}OF$ 278.1107, found 278.1108.

4-Benzyloxy-4′-methoxybiphenyl 3ea.[34] White solid; mp 172−174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.37 (m, 6H), 7.32 (t, J = 7.2 Hz, 2H), 7.25 (t, J = 7.2 Hz, 1H), 6.95 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 5.02 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 156.9, 136.0, 132.7, 132.4, 128.3, 127.6, 126.9, 126.7, 126.5, 114.1, 113.1, 69.1, 54.3.

1-(4′-Methylbiphenyl-4-yl)ethanone 3bf.[35] White solid; mp 118−119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, J = 2.0, 8.4 Hz, 2H), 7.66 (dd, J = 2.0, 8.4 Hz, 2H), 7.53 (dd, J = 2.0, 8.0 Hz, 2H), 7.28 (d, J = 6.4 Hz, 2H), 2.63 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 145.7, 138.3, 136.9, 135.6, 129.7, 129.0, 127.1, 126.9, 26.7, 21.2.

1-(2′-Methylbiphenyl-4-yl)ethanone 3cf.[36] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.31−7.21 (m, 4H), 2.65 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 147.0, 140.8, 135.6, 135.2, 130.6, 129.6, 129.5, 128.3, 128.0, 126.0, 26.7, 20.5.

1-(4′-Fluorobiphenyl-4-yl)ethanone 3df.[37] White solid; mp 108−109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.4 Hz, 2H), 7.65−7.57 (m, 4H), 7.16 (t, J = 8.8 Hz, 2H), 2.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.7, 162.9 (d, J = 247.0 Hz), 144.7, 135.9 (d, J = 3.0 Hz), 135.8, 129.0, 128.9 (d, J = 8.0 Hz), 127.0, 115.9 (d, J = 22.0 Hz), 26.6.

1-(4′-Methoxybiphenyl-4-yl)ethanone 3ef.[38] White solid; mp 156−158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.8 Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 159.9, 145.3, 135.2, 132.2, 129.0, 128.4, 126.6, 114.4, 55.4, 26.7.

Synthesis of Sartan Biphenyl by Cross-Coupling of Di(4-methylphenyl)borinic Acid with 2-Chlorobenzonitrile. Under a N_2 atmosphere, to a 250 mL flask were added 2-chlorobenzonitrile (19.2 g, 140 mmol), di(4-methylphenyl)borinic acid (16.4 g, 78 mmol), $Pd(OAc)_2$ (0.063 g, 0.28 mmol), IPr·HCl (0.119 g, 0.28 mmol), $P(OPh)_3$ (0.174 g, 0.56 mmol), $K_3PO_4·3H_2O$ (37.1 g, 140 mmol), and *t*BuOH (100 mL). The mixture was stirred at 80 °C for 16 h. After removal of *t*BuOH by distillation, the residue was washed with H_2O and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford the crude product, which was purified by distillation under vacuum (154−156 °C, 1 mmHg) to give 4′-methyl-2-cyanobiphenyl **3bd** (26.1 g, 97%), which solidifies at room temperature.

2-Cyano-4′-methylbiphenyl 3bd.[39] White solid; mp 49−50 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.6 Hz, 1H), 7.62 (t, J = 7.2 Hz, 1H), 7.51−7.39 (m, 4H), 7.30 (d, J = 8.0 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 138.7, 135.3, 133.8, 132.9, 130.1, 129.5, 128.7, 127.4, 119.0, 111.1, 21.3.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all compounds reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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