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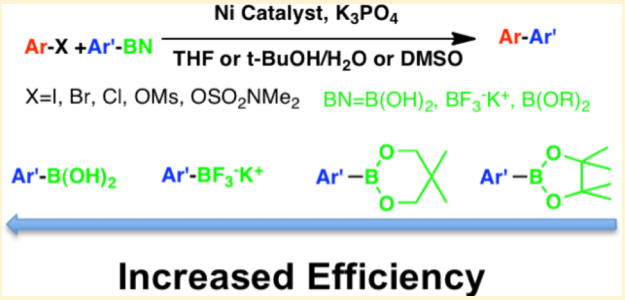
Comparison of Arylboron-Based Nucleophiles in Ni-Catalyzed Suzuki−Miyaura Cross-Coupling with Aryl Mesylates and Sulfamates

Na Zhang, David J. Hoffman, Nicholas Gutsche, Jayesh Gupta, and Virgil Percec*

Roy & Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323, United States

Supporting Information

ABSTRACT: The efficiency of arylboron-based nucleophiles, boronic acid, potassium trifluoroborate, neopentylglycolboronate, and pinacol boronate in nickel-catalyzed Suzuki−Miyaura cross-coupling reactions with the two C−O electrophiles, mesylates, and sulfamates was compared. Arylboronic acid is the most reactive and most atom-economic of the four boron species studied. Arylpotassium trifluoroborate cross-couples efficiently only in the presence of water. In the absence of water, aryl neopentylglycolboronate is more efficient, less expensive, and more atom-economic than aryl pinacolboronate.



INTRODUCTION

The Suzuki−Miyaura cross-coupling reaction represents one of the most important transformations in organic chemistry. This cross-coupling reaction is frequently used in the construction of functional biaryl architectures in organic, polymer, and supramolecular chemistry.[1−11] Recent developments of the Suzuki−Miyaura cross-coupling reaction involve the replacement of Pd with less expensive metals, such as Ni,[11] the development of new electrophiles including C−O-based electrophiles,[11−13] the elaboration of reaction conditions for the cross-coupling of steric hindered substrates,[14] and the development of new nucleophiles as alternative to boronic acid.[10] Arylboron-based nucleophiles are important cross-coupling partners for the Suzuki−Miyaura cross-coupling reaction. Currently, arylboronic acids,[3] aryl trifluoroborates,[9,10] aryl neopentylglycolboronates,[11] and aryl pinacolboronates[10] are the four major classes of boron-based nucleophiles employed in the nickel-catalyzed Suzuki−Miyaura cross-coupling reaction. Great progresses have been achieved in employing C−O-based electrophiles in the nickel-catalyzed cross-coupling with arylboronic acids, boronates, and trifluoroborates. Aryl C−O-based electrophiles such as sulfonates,[15−23] ethers,[24] esters,[18,25,26] sulfamates,[20,21,27−29] carbamates,[27−31] and phosphates[32] have been successfully cross-coupled in good to excellent yields under various conditions with a diversity of arylboron-based nucleophiles. Recently, a comparative study of all aryl C−O electrophiles in the cross-coupling with arylboronates was reported.[33] While these progresses have been mainly focused on developing the electrophiles, arylboron-based nucleophiles are also important partners in the Suzuki−Miyaura cross-coupling reactions.[10] Progress on the development of boron-based nucleophiles has mainly focused on applying aryl trifluoroborates and boronates in the cross-coupling reactions. The reactivity,[20,34] stability, and atom economy[10] of the boron-based nucleophiles in the Suzuki−Miyaura cross-coupling depend on the structure of the aryl C−O electrophile employed. For example, the reaction conditions optimized for arylboronic acids are not necessarily applicable to aryl trifluoroborates and boronates. The cross-coupling reactions involving aryl trifluoroborates requires different conditions due to the low solubility of aryl trifluoroborates in solvents used for the cross-coupling of arylboronic acids. Moreover, it is necessary to cleave the trifluoroborates in situ.[9] Catalytic systems for the cross-coupling of aryl methyl ethers with aryl neopentylglycolboronates have been developed.[24] Our laboratory has been involved in the development of one-pot, two-step neopentylglycolborylation reactions[35−38] and in the cross-coupling reactions of aryl neopentylglycolboronates with aryl halides[35] and C−O-based electrophiles.[20,21] Recently, our laboratory reported two efficient catalytic systems for the cross-coupling of aryl neopentylglycolboronates with aryl sulfonates and sulfamates at room temperature.[20,21] A reactivity difference between arylboronic acid and aryl neopentylglycolboronate was observed during cross-coupling reactions with aryl mesylates catalyzed by $Ni(COD)_2/PCy_3/K_3PO_4$ in THF.[20] Cross-coupling of aryl neopentylglycolboronates with aryl esters, carbamates, and carbonates is less efficient but more selective than reactions carried out with arylboronic acids.[33] Other research groups also observed the reactivity difference between arylboronic acids, arylboronates, and trifluoroborates in the cross-coupling reactions.[39] Pinacolboronates[40] and neopentylglycolboronates[20,21,24,33] are the most commonly employed boronate nucleophiles. However, the difference between the efficiency of these two aryl boronates in the Suzuki−Miyaura cross-coupling reactions is not elucidated. Here, we report a comparative study of the efficiency of arylboron-based nucleophiles, boronic acid, potassium trifluoroborate,

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neopentylglycolboronate, and pinacolboronate in Ni-catalyzed cross-coupling with two aryl C−O based electrophiles, mesylates, and sulfamates.

RESULTS AND DISCUSSION

A Brief Discussion of the Atom Economy and of the Synthesis of Aryl Boronic Acids, Aryl Trifluoroborates, Aryl Neopentylglycolboronates, and Aryl Pinacolboroantes. Because of their high reactivity and commercial and preparative availability, arylboronic acids are the most widely used arylboron based nucleophiles in the Suzuki−Miyaura cross-coupling reaction. Arylboronic acid is also the most atom economic[41] from all arylboron-based nucleophiles (Table 1).

Table 1. Economy of Boron-Based Nucleophiles in the Suzuki−Miyaura Cross-Coupling Reactions

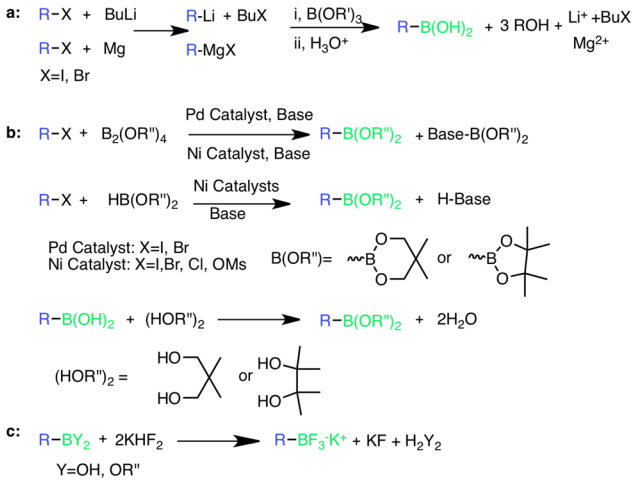
	R−B(OH)$_2$	R−BF$_3^-$K$^+$		
Formula	BH_2O_2	BF_3K	$C_5H_{10}BO_2$	$C_6H_{12}BO_2$
M.W.	44.8257	106.9045	112.9427	126.9693
Price in $ per mole of boron nucl.[a]		7.63[b]	2.62	85.20

[a]Commercial souce.[42] [b]Two equivalents of KHF_2 is consumed per boronic acid.

However, the decomposition of arylboronic acid by proto-deborylation and oxidation proceeds readily both during storage and its cross-coupling.[6,43,44] Most arylboronic acids are waxy solids, making their purification difficult. Moreover, the presence of dimeric or trimeric species of arylboronic acids makes it difficult to calculate their reaction stoichiometry. Finally, the boronic acid is hard to incorporate in multiple-step syntheses.[10] The most common preparation of arylboronic acid is through electrophilic trapping of organolithium or Grignard reagents followed by cleavage of the ester bond in aqueous acid. The metal and alkyl groups are lost during this reaction. This method does not tolerate electrophilic functional groups sensitive to organolithium or Grignard reagents and sometimes suffers from regioselectivity problems.[44] (Scheme 1, a)

An alternative way to introduce the boron-containing group is through transition-metal-catalyzed borylation.[44] Miyaura discovered the Pd-catalyzed borylation with tetraalkoxydiboron reagents.[5] Recently, Ni has been applied as an inexpensive catalyst for borylation reactions of aryl iodides, bromides,[35,38] chlorides,[37,38] sulfonates,[36] and carbamates.[45] Borylation of sterically hindered aryl halides using tetraalkoxydiboron was reported in good to excellent yields using both nickel[46] and palladium catalysts.[47] Moreover, applying nickel catalysts can replace the need of expensive and nonatom economic tetraalkoxydiboron reagents by the easily prepared, even in situ formed borane reagents (Scheme 1, b).[35] Aryl boronates can also be synthesized via esterification of arylboronic acids with the corresponding diols.[24,44] Most of the arylboronates are crystalline solids and can be purified by column chromatography. The transition-metal-catalyzed borylation reaction tolerates sensitive functional groups. Aryl boronates exist in monomeric form and have a higher molecular weight than the corresponding arylboronic acids and hence lower atom economy. However, for some applications such as stepwise polymerizations, it is important to have a perfect control of the reaction stoichiometry. Therefore, arylboronates are also important cross-coupling partners in polymerization reactions. Two arylboronates are most frequently employed in cross-coupling reactions, namely pinacolboronates[48] and neopentylglycolboronates.[20,21,24,33,35] Neopentyglycolboronates are more atom-economic than pinacolboronates and less expensive (Table 1). Pinacol is about six times more expensive than potassium hydrofluoride, while the price of neopentylglycol is only one-sixth of the price of potassium hydrofluoride (Table 1, columns 3 and 4).

Scheme 1. Synthesis of Arylboron-Based Nucleophiles



Aryl trifluoroborates are also synthesized as a protecting form of arylboronic acids. They are synthesized by reacting other boron-based nucleophiles with KHF_2.[9] Aryl trifluoroborates are shelf-stable for several years.[6] They also exist in monomeric form, and therefore, their reaction stoichiometry can be calculated. The molecular weight of aryl trifluoroborate is higher than that of arylboronic acid but lower than that of arylboronates (Table 1). Therefore, the atom economy of aryl trifluoroborates is lower than that of arylboronic acids but higher than that of arylboronates (Table 1, column 3). Considering the price of the protecting group, aryl trifluoroborate is about six times less expensive than aryl pinacolboronate but about six times more expensive than neopentylglycolboronates (Table 1).

A Comparison of the Competitive and Kinetic Experiments of Aryl Boron-Based Nucleophiles. The turnover number (TON) and the turnover frequency (TOF) are two important characters for catalytic reactions. The efficiency of catalysts are best represented by TON or TOF of the reaction.[49,50] The TON of nickel-catalyzed coupling reactions[51,52] is generally lower than that of palladium-catalyzed coupling reactions.[53] In order to compare aryl neopentylglycolboronates with aryl pinacolboronates, the TON of cross-coupling of 4-methoxyphenyl neopentylglycolboronate and 4-methoxyphenyl pinacolboronate with methyl 4-((methylsulfonyl)-oxy)benzoate were determined (Table 2).

The TON and TOF of cross-coupling using 4-methoxyphenyl neopentylglycolboronate are higher than those of cross-coupling using 4-methoxyphenyl pinacolboronate. This shows that 4-methoxyphenyl neopentylglycolboronate is more effective than 4-methoxyphenyl pinacolboronate.

The reactivity of both aryl neopentylglycolboronate and pinacolboronate in cross-coupling reactions was estimated from kinetic experiments. Competitive experiments provide also an alternative method that can be used to determine the efficiency difference of two boron-based nucleophiles in cross-coupling

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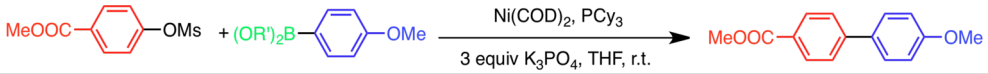
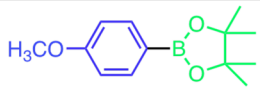
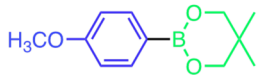
Table 2. Turnover Number (TON) and Turnover Frequency (TOF) for the Cross-Coupling of Methyl 4-((Methylsulfonyl)oxy)benzoate with 4-Methoxyphenyl Neopentylglycolboronate and 4-Methoxyphenyl Pinacolboronate[a]



Boronate[a]	$Ni(COD)_2$ (%)	PCy_3 (%)	Time (h)	Yield[b] (%)	TON ($mol_{mesylate}$ /mol_{nickel})	TOF ($mol_{mesylate}$/ (mol_{nickel}•h))
	1	2	60	60	60	1
	1	2	60	96	96	1.6

[a]Reaction conditions: Ar-X (0.3 mmol) arylboronate (0.3 mmol), $Ni(COD)_2$ (0.003 mmol), PCy_3 (0.006 mmol), K_3PO_4 (0.9 mmol), THF (1 mL). [b]Reaction yield determined by NMR.

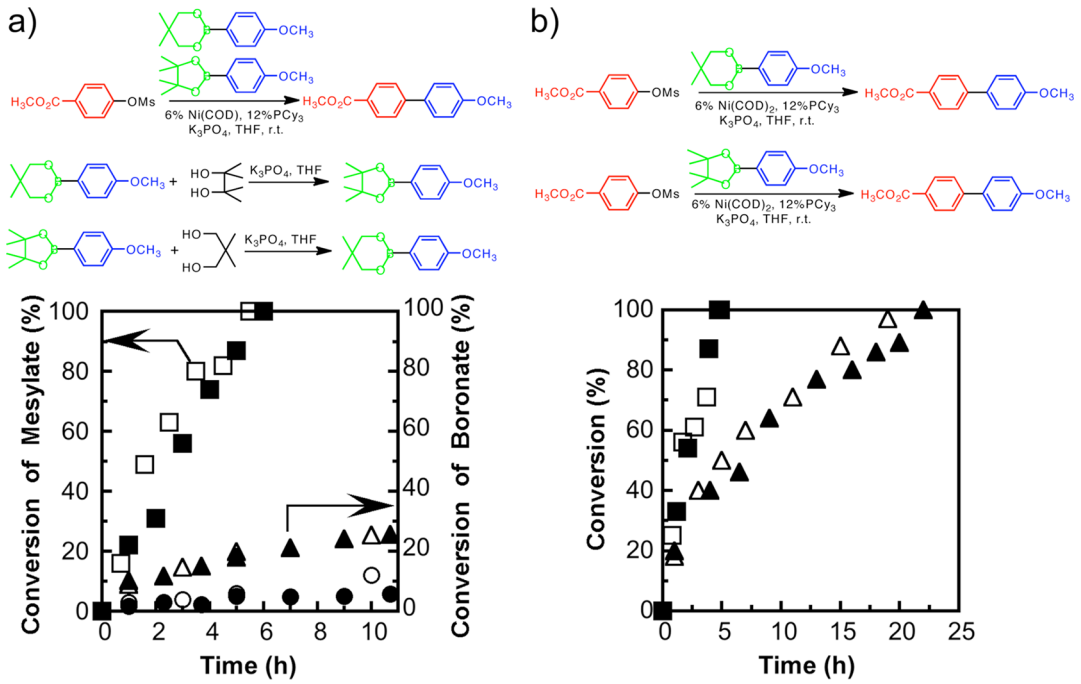


Figure 1. (a) Comparison of the rate of the competitive cross-coupling of 4-methoxyphenyl pinacolboronate and 4-methoxyphenyl neopentylglycolboronate (■, □), diol exchange rate of 4-methoxyphenyl neopentylglycolboronate with pinacol (▲, △), and diol exchange rate of 4-methoxyphenyl pinacolboronate with neopentylglycol (●, ○). (b) Comparison of the rate of the cross-coupling of 4-methoxyphenyl neopentylglycolboronate (■, □) and 4-methoxyphenyl pinacolboronate (▲, △) with methyl 4-((methylsulfonyl)oxy)benzoate. In all kinetic experiments, two sets of experimental data, plotted in solid and open symbols, were used.

reactions. However, competitive experiments are valid only when the rate of diol exchange is much smaller than the rate of the competitive cross-coupling reaction. Two sets of kinetic experiments were performed. The first one was used to compare the reactivity of two arylboronates and the second one to compare the rate of competitive experiments with the rate of diol exchange experiments. In order to slow the reaction and decease the impact of sampling process to reaction progress, these kinetic experiments were carried out at half of the concentration of the rest of the experiments to be discussed in this report (Figure 1).

As can be seen clearly from Figure 1a, the overall rate of the competitive experiments is 8 times faster than the rate of diol exchange of 4-methoxyphenyl neopentylglycolboronate with pinacol and 10 times faster than the rate of diol exchange of 4-methoxyphenyl pinacolboronate with neopentylglycol when the concentration of boronates are the same. Therefore, the diol-exchange reaction will not impact significantly the conclusion obtained from competitive experiments. The overall reactivity of 4-methoxyphenyl neopentylglycolboronate is 5 times higher than that of 4-methoxyphenyl pinacolboronate in cross-coupling with methyl 4-((methylsulfonyl)oxy)benzoate (Figure 1b). This is in agreement with the results obtained from the competitive experiments. On the basis of this set of experiments, the rest of the reactivity studies will be carried out by competitive experiments.

Competitive Experiments of Arylboron Based Nucleophiles. In order to compare the efficiency of arylboron based nucleophiles, competitive experiments were carried with different catalytic systems. The comparison of the reactivity of different boron nucleophiles should be carried out under conditions optimized for different boron nucleophiles.[10] For the comparison of 4-methoxyphenylboronic acid with

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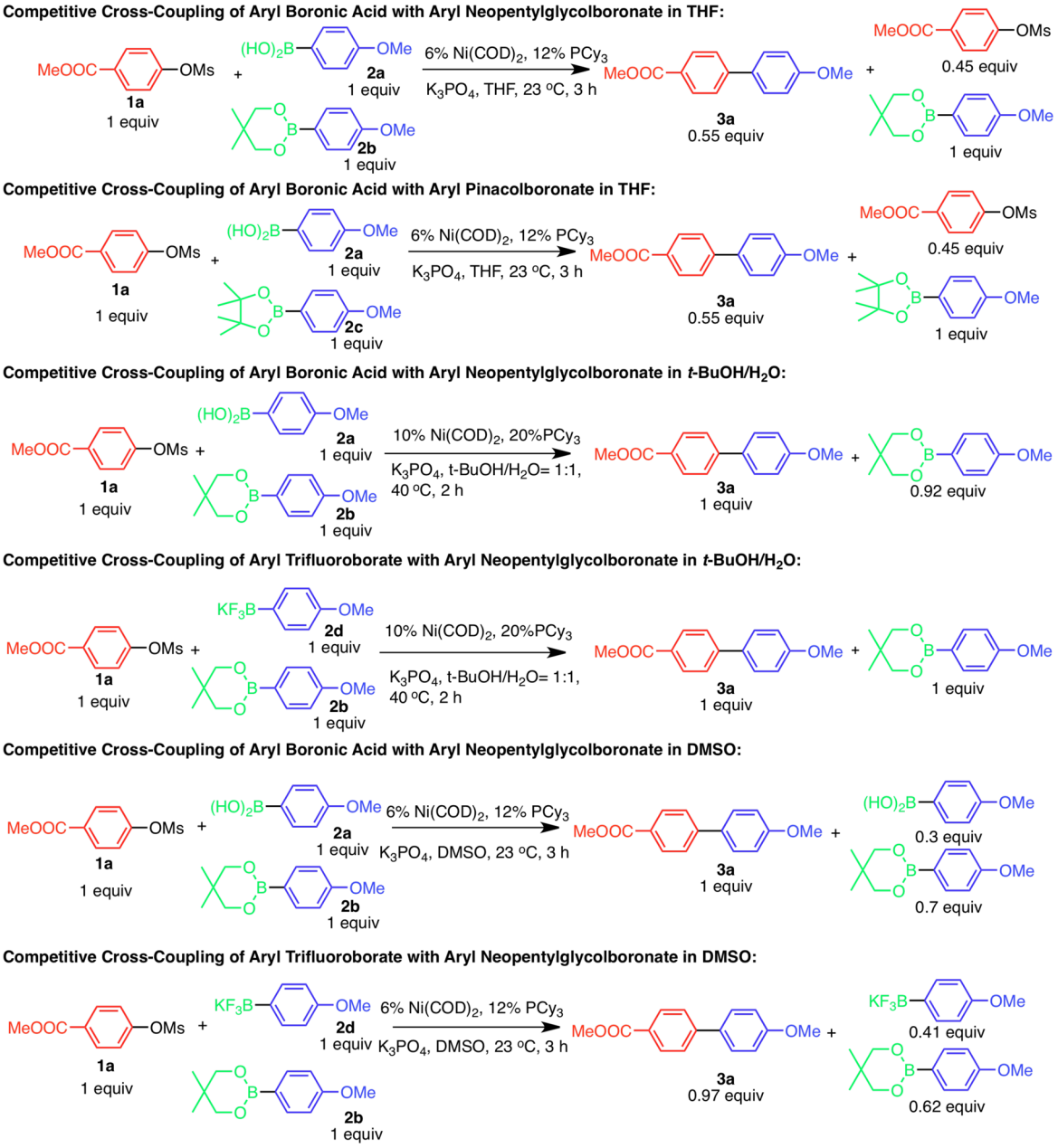
Scheme 2. Competitive Cross-Coupling of Aryl Boron Based Nucleophiles



4-methoxyphenyl boronate, reaction conditions developed for the room-temperature nickel-catalyzed cross-coupling reactions of boronic acids[15,22] and boronic esters[20,21] with aryl sulfonates were applied. A mixture of equal equivalence of aryl mesylate, 4-methoxyphenylboronic acid, and 4-methoxyphenyl boronates were added at the beginning of the reaction. After 3 h, the reaction was worked up, and the crude mixture was examined by 500 MHz, ^{1}H NMR. The mesylate (0.45 equiv), the product (0.55 equiv), and the 4-methoxyphenyl boronate (1 equiv) were detected by NMR (Scheme 2, part a).

It is reasonable to conclude that the product was produced solely from 4-methoxyphenylboronic acids. Neither aryl neopentylglycolboronate nor aryl pinacolboronate was consumed in the reaction. Comparison of aryl trifluoroborates with other boron nucleophiles cannot be carried out in THF because arylpotassium trifluoroborates are not soluble in dry THF.

In order to compare aryl trifluoroborates with aryl boronates, the catalytic system developed by Molander's laboratory for cross-coupling of aryl mesylates and pivalates with aryl and heteroaryl trifluoroborates[18] was applied with the only modification that a lower reaction temperature was used. In 2 h, arylboronic acid and aryl trifluoroborate were fully consumed, while the aryl boronates remained almost unconsumed, as determined by NMR from the composition of the crude mixture. In the case of arylboronic acid, protodeborylation was detected by NMR, and 0.08 equiv boronic ester was consumed to compensate the difference. In the presence of water and base, potassium trifluoroborate hydrolyzed and was completely consumed, while 4-methoxyphenyl neopentylglycolboronate remained unconsumed (Scheme 2, part b).

To study the impact of the amount of water to the efficiency of arylboron-based nucleophiles, anhydrous DMSO and K_3PO_4 dried at 40 °C under vacuum overnight were employed.

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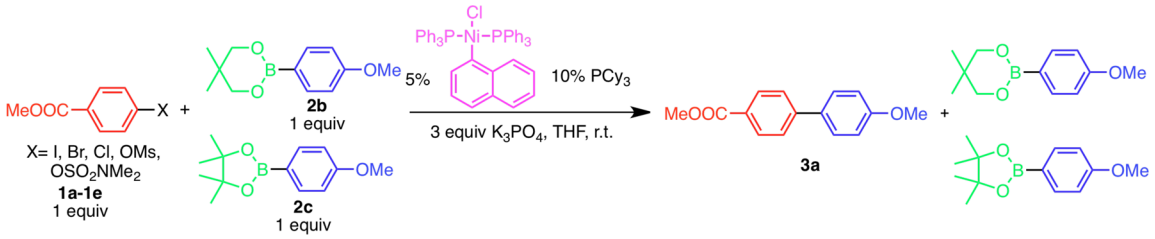
Table 3. Competitive Cross-Coupling of 4-Methoxyphenyl Pinacolboronate and 4-Methoxyphenyl Neopentylglycolboronate in Reaction Catalyzed by Ni(II)Cl(1-Naphthyl)$(PPh_3)_2$/PCy_3/K_3PO_4 in THF[a]



entry	X	time (h)	equiv of 3a[b]	equiv of 2b[b]	equiv of 2c[b]	2b/2c[c]
1	I (**1b**)	1.7	1	0.26	0.74	2.8
2	Br (**1c**)	3	0.64	0.45	0.86	3.9
3	Cl (**1d**)	4	0.79	0.28	0.64	2.0
4	OMs (**1a**)	3	1	0.15	0.85	5.7
5	OSO_2NMe_2 (**1e**)	12	1	0.28	0.72	2.6

[a]Reaction conditions: Ar-X (0.3 mmol), arylboronic ester (0.3 mmol) each, Ni(II)Cl(1-naphthyl)$(PPh_3)_2$ (0.015 mmol), PCy_3 (0.03 mmol), K_3PO_4 (0.9 mmol), THF (1 mL). [b]Equivalence determined by NMR. [c]Ratio refers to consumption of **2b** to **2c** in reaction.

Interestingly, the efficiency difference of arylboron based nucleophiles decreases dramatically when DMSO was used as solvent. Taking the amount of boron species consumed in reaction as efficiency, arylboronic acid was only 2.3 times more efficient than neopentylglycolboronate and aryl trifluoroborate was only 1.55 times more efficient than neopentylglycolboronate respectively (Scheme 2, part c). It is noteworthy to mention that the efficiency difference of aryl trifluoroborates and arylboronates is highly dependent on the amount of water involved in the reaction. When the reaction was carried out in the absence of water (flame-dried K_3PO_4), no cross-coupling product was observed when aryl trifluoroborate was employed.

Above all, the efficiency of arylboronic acid is the highest of the four arylboron-based nucleophiles studied. Aryl trifluoroborates are more efficient than arylboronates when sufficient water for cleavage of C−F bond is present in the reaction. When reactions are carried out in the absence of water, aryl trifluoroborates are inefficient. The difference between the efficiency of aryl neopentylglycolboronates and pinacolboronates will be discussed in more detail in the following subchapter.

Comparison of Aryl Neopentylglycolboronates and Aryl Pinacolboronates. Aryl boronates are important cross-coupling partners for the Suzuki−Miyaura cross-coupling reactions. For stepwise polymerizations,[54] aryl boronates are more preferred than arylboronic acids, because boronates exist only in monomeric form. Pinacolboronates are presently widely used.[40] However, pinacol is a relatively expensive diol and has a higher molecular weight than neopentylglycol (Table 1). It is reasonable to replace aryl pinacolboronates with aryl neopentylglycolboronates if the reactivities of both boronates are similar. However, the reactivity difference of neopentylglycolboronate and pinacolboronate in nickel-catalyzed Suzuki−Miyaura cross-coupling reaction of C−O electrophiles is not known. The control experiments (Figure 1a) demonstrated that the diol exchange reactions are much slower than the competitive cross-coupling experiments. Competitive cross-coupling experiments of aryl neopentylglycolboronates and pinacolboronates catalyzed by Ni$(COD)_2$/PCy_3/K_3PO_4[20] and Ni(II)Cl(1-naphthyl)$(PPh_3)_2$/PCy_3/K_3PO_4[21] in THF were carried out to study the efficiency difference of these two aryl boronates. These reaction conditions were optimized by our laboratory for the cross-coupling of aryl and heteroaryl mesylates and sulfamates with aryl and heteroaryl neopentylglycolboronates.[20,21] Aryl iodides, bromides, chlorides, mesylates, and sulfamates were employed as electrophiles. Equal equivalence of electrophile and of the two boronates were added at the beginning of the reaction, and the crude reactions were examined by NMR. Blank experiments were carried out to exclude the possibility of consumption of boronates by protodeborylation. It was observed that less 4-methoxyphenyl neopentylglycolboronate than pinacolboronates was left unconsumed in the crude reaction mixture in all cases, indicating that more neopentylglycolboronate than pinacolboronate was consumed in this reaction (Tables 3 and 4).

The equivalence of product and boronates left in the crude reaction mixture was calculated from the NMR spectrum of the crude mixture. The ratios between the consumption of 4-methoxyphenyl neopentylglycolboronates to pinacolboronates were calculated and listed in Tables 3 and 4. The efficiency difference was best presented when aryl mesylate was used as an electrophile. The efficiency of neopentylglycolboronate is nearly six times higher than that of aryl pinacolboronate when cross-coupled with aryl mesylates (Table 3, entry 4, and Table 4, entry 4). Competitive experiments of electron-deficient aryl boronates were also carried out. The efficiency trend was similar (Supporting Information).

Competitive experiments showed the reactivity difference of these two boronates. However, it also might be possible that one boronate was deactivating the other one. Hence, Ni$(COD)_2$/PCy_3/K_3PO_4[20] and Ni(II)Cl(1-naphthyl)$(PPh_3)_2$/PCy_3/K_3PO_4[21] catalyzed cross-coupling reactions of aryl mesylates and sulfamates bearing electron-withdrawing and electron-rich substituents were carried out in THF. After the same reaction time, lower GC yields and isolated yields were observed for the cross-coupling reactions carried out with 4-methoxylphenyl pinacolboronates than with neopentylglycolboronates in the presence of both catalytic systems. The reactivity difference was best observed for electron-rich substrates. For example, after 4 h, methyl 4-((methylsulfonyl)oxy)benzoate was completely consumed when cross-coupled with 4-methoxyphenyl neopentylglycolboronate, while only 75% of the mesylate was consumed when cross-coupled with 4-methoxylphenyl neopentylglycolboronate (Table 5, entry 1).

The efficiency difference was even larger when the Ni$(COD)_2$/PCy_3/K_3PO_4 catalytic system was employed. Only 31% of methyl 4-((methylsulfonyl)oxy)benzoate was cross-coupled

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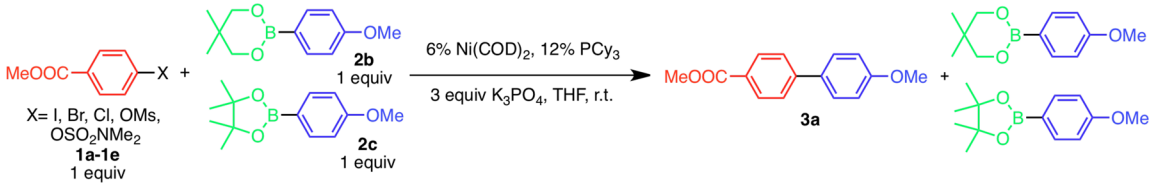
Table 4. Competitive Cross-Coupling of 4-Methoxyphenyl Pinacolboronate and 4-Methoxyphenyl Neopentylglycolboronate Catalyzed by $Ni(COD)_2/PCy_3/K_3PO_4$ in THF[a]



entry	X	time (h)	equiv of 3a[b]	equiv of 2b[b]	equiv of 2c[b]	2b/2c[c]
1	I (**1b**)	1	1	0.23	0.77	3.3
2	Br (**1c**)	3	0.44	0.61	0.98	4.8
3	Cl (**1d**)	3	0.34	0.74	0.98	3.3
4	OMs (**1a**)	2.5	1	0.15	0.85	5.7
5	OSO_2NMe_2 (**1e**)	12	1	0.33	0.67	2.0

[a]Reaction conditions: Ar-X (0.3 mmol), arylboronic ester (0.3 mmol) each, $Ni(COD)_2$ (0.018 mmol), PCy_3 (0.036 mmol), K_3PO_4 (0.9 mmol), THF (1 mL). [b]Ratio determined by NMR. [c]Ratio refers to consumption of **2b** to **2c** in reaction.

after 4 h when 4-methoxyphenylboronate was used (Table 6, entry 1). With results from both competitive and comparison experiments (Table 3−6), it is reasonable to conclude that aryl neopentylglycolboronate is more efficient, less expensive, and more atom economic than aryl pinacolboronate in nickel-catalyzed cross-coupling reactions with aryl C−O-based electrophiles.

Comparison of the Efficiency of Different Boron-Based Nucleophiles in Nickel-Catalyzed Cross-Coupling Reactions in Different Solvents. A summary of the efficiency trend for boron-based nucleophiles in nickel-catalyzed Suzuki−Miyaura cross-coupling reactions with C−O electrophiles is presented in Table 7. The consumption of boron-based nucleophiles in the cross-coupling with methyl 4-((methylsulfonyl)oxy)benzoate was considered as the measurement of the efficiency. Arylboronic acid is the most reactive of all boron based nucleophiles. In the presence of water, aryl trifluoroborates will cleave and form in situ the corresponding arylboronic acid. Hence, aryl trifluoroborates were much more efficient in cross-coupling with aryl C−O-based electrophiles than arylboronates in a *t*-BuOH/water mixture. However, in DMSO, all boron-based nucleophiles showed a comparable reactivity. The efficiency of arylboronic acid and boronate decreased when DMSO was used as solvent. Nevertheless, the reactivity trend remains: arylboronic acid > aryl trifluoroborates > arylboronates. Aryl neopentylglycolboronates were more efficient than aryl pinacolboronates in THF by a factor of 6 (Table 7, entry 3).

CONCLUSIONS

The efficiency and atom economy of arylboron-based nucleophiles in nickel-catalyzed cross-coupling reactions with aryl C−O-based electrophiles were investigated. Arylboronic acids have both the highest atom economy and reactivity in cross-coupling reactions. However, the decomposition and the presence of dimers and trimers of boronic acids limit their applicability. In the presence of water, aryl trifluoroborates are more efficient in the cross-coupling reactions than aryl boronates. Aryl trifluoroborates are also shelf stable, less expensive than pinacolboronates, and easier to synthesize than other boron nucleophiles. However, the extra step in the preparation and the requirement of polar solvents and water for their cross-coupling reactions limits the use of aryl trifluoroborates in synthetic organic, material, and polymer chemistry. Aryl neopentylglycolboronates, with higher atom-economy, lower price, and higher efficiency than aryl pinacolboronates, accompanied by the two-step, one-pot nickel-catalyzed neopentylglycolborylation, are expected to play an important role in Suzuki−Miyaura cross-coupling reactions with aryl C−O electrophiles. Moreover, the reactivity difference of arylboronic acids in THF and trifluoroborates in *t*-BuOH/H_2O mixture with aryl boronates made it possible to apply orthogonal cross-coupling of arylboronic acids or trifluoroboratess with aryl boronates in organic synthesis.

EXPERIMENTAL SECTION

General Experimental Methods. Ni(II)Cl(1-naphthyl)$(PPh_3)_2$[55] and (4-methoxyphenyl)boronic acid were prepared according to literature methods.[56] 2-(4-Methoxyphenyl)-5,5-dimethyl-1,3,2-dioxaborinane and 2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane were synthesized by the esterification of (4-methoxyphenyl)boronic acid with the corresponding diol. (4-Methoxyphenyl)trifluoroborate was synthesized according to a literature procedure.[38] K_3PO_4 from a commercial source was dried at 40 °C under vacuum overnight prior to use. THF was distilled over sodium/benzophenone. *t*-BuOH and water were degassed by bubbling with N_2 overnight. DMSO was distilled from calcium hydride. Aryl mesylates and aryl sulfamates were synthesized according to literature procedures.[20] All other reagents were used as received from commercial sources. General procedure for the cross-coupling reactions were carried out according to a literature procedure elaborated in our laboratory.[20,21] ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded using TMS as internal standard. High-resolution mass spectra of new compounds were obtained on a high-resolution double focusing chemical ionization mass spectrometer. A GC coupled with an FID detector and column HP 19091J-413 (5% phenyl)methylpolysiloxane 30 m length 0.32 mm internal diameter was used to follow the reaction conversions and to assess the purity of the final compounds. This method is complementary to the NMR technique. The crude reaction mixtures were dissolved in THF and analyzed by GC as reported in the previous publications from our laboratory.[38]

General Procedure for Competitive Experiments in THF. To an oven-dried test tube (15 × 85 mm) were added the aryl mesylate (69 mg, 0.3 mmol), the two arylboron-based nucleophiles (0.30 mmol each), Ni(II)Cl(1-naphthyl)$(PPh_3)_2$ (11 mg, 0.015 mmol) when indicated, and K_3PO_4 (191 mg, 0.9 mmol). The tube was taken into a glovebox. $Ni(COD)_2$ when indicated and PCy_3 (0.030 mmol) were added. Dried THF (1.0 mL) was then added, and the tube was capped with a rubber septum. The reaction was stirred at room temperature under nitrogen in the glovebox for 1−12 h (see Scheme 2, part a; Tables 3, 4). A sample was taken via syringe inside the glovebox. The sample was dissolved in distilled THF and was filtered through a short column of silica gel. The solvent was evaporated, and the NMR spectrum of the crude was examined.

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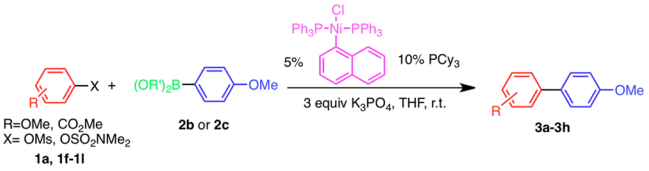
Table 5. Comparison of the Efficiency of 4-Methoxyphenyl Neopentylglycolboronate and 4-Methoxyphenyl Pinacolboronate in the Cross-Coupling with Aryl Mesylates and Sulfamates Catalyzed by Ni(II)Cl(1-Naphthyl)(PPh_3)$_2$/PCy_3/K_3PO_4 in THF[a]



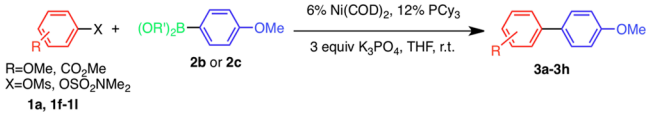
1a, 1f-1l	2b time (h)	2b Convn[b]/Yield[c] (%)	2c time (h)	2c Convn[b]/Yield[c] (%)
1a	4	100/99	4	75/57
1f	12	100/94	12	50/50
1g	14	100/89	14	100/77
1h	14	100/87	14	70/44
1i	10	100/81	20	97/86
1j	24	83/80	24	51/46
1k	14	100/93	14	95/90
1l	60	100/94	74	96/88

[a]Reaction conditions: Ar-X (0.3 mmol), arylboronate (0.3 mmol) each, Ni(II)Cl(1-naphthyl)(PPh_3)$_2$ (0.015 mmol), PCy_3 (0.03 mmol), K_3PO_4 (0.9 mmol), THF (1 mL). [b]Conversion determined by GC. The GC yield has always the same value as the conversion. [c]Isolated yield.

General Procedure for Competitive Experiments in *t*-BuOH/H_2O = 1:1. To an oven-dried test tube (15 × 85 mm) were added the aryl mesylate (69 mg, 0.3 mmol), the two arylboron-based nucleophiles (0.30 mmol each), and K_3PO_4 (191 mg, 0.9 mmol). The tube was taken into a glovebox, Ni(COD)$_2$ (8.3 mg, 0.03 mmol) and PCy_3 (16.7 mg, 0.060 mmol) was added. The tube was capped and taken out of the glovebox. Degassed *t*-BuOH (0.5 mL) and degassed deionized water (0.5 mL) were added via a syringe. The reaction was stirred at 40 °C for 2 h (see Scheme 2, part b). The mixture was extracted with ethyl acetate three times and dried over anhydrous magnesium sulfate. The solvent was evaporated via rotary evaporator and characterized by NMR.

General Procedure for Competitive Experiments in DMSO. To an oven-dried test tube (15 × 85 mm) were added the aryl mesylate (69 mg, 0.3 mmol), the two arylboron-based nucleophiles (0.30 mmol each), and K_3PO_4 (191 mg, 0.9 mmol). The tube was taken into a glovebox. Ni(COD)$_2$ and PCy_3 (10.1 mg, 0.036 mmol) were added. Dry DMSO (1 mL) was added inside the glovebox. The tube was capped and allowed to stir at room temperature. After 3 h, the tube was taken

Table 6. Comparison of the Efficiency of 4-Methoxyphenyl Neopentylglycolboronate and 4-Methoxyphenyl Pinacolboronate in the Cross-Coupling with Aryl Mesylates And Sulfamates Catalyzed by Ni(COD)$_2$/PCy_3/K_3PO_4 in THF[a]



1a, 1f-1l	2b time (h)	2b Convn[b]/Yield[c] (%)	2c time (h)	2c Convn[b]/Yield[c] (%)
1f	4	90/89	4	31/30
1a	4	100/94	4	75/56
1g	9	100/90	9	96/81
1h	8	99/89	12	88/86
1j	12	100/93	12	58/63
1i	8	100/92	8	91/88
1k	12	100/98	12	100/98
1l	12	100/99	12	45/38

[a]Reaction conditions: Ar-X (0.3 mmol), arylboronate (0.36 mmol), Ni(COD)$_2$ (0.018 mmol), PCy_3 (0.036 mmol), K_3PO_4 (0.9 mmol), THF (1 mL). [b]Conversion determined by GC. The GC yield is always the same as the conversion. [c]Isolated yield.

Table 7. Efficiency Trend for Boron-Based Nucleophiles in the Cross-Coupling Reactions[a]

Solvent	R–B(OH)$_2$ [b]	R–$BF_3^-K^+$ [b]	R–B(O)(O)C(C)(C)C(C)(C)O [b]	R–B(O)(O)C(C)(C)C(C)(C)O [b]
t-BuOH /H_2O=1:1[c]	>>1	>>1	1	NA
DMSO[d]	2.3	1.55	1	NA
THF[d]	>>1	N.R. (insoluble)	6	1

[a]Comparison was made based on the cross-coupling with methyl 4-((methylsulfonyl)oxy)benzoate. The least reactive species under each condition was arbitrary set as one. The data was calculated according to the consumption of boron-based nucleophiles. The trend for both aryl boronate is consistent for all electrophiles. [b]R was 4-methoxyphenyl group. [c]10% Ni(COD)$_2$, 20% PCy_3, K_3PO_4 (3 equiv), 40 °C. [d]6% Ni(COD)$_2$, 12% PCy_3, K_3PO_4 (3 equiv), 23 °C.

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out of the glovebox, and the crude reaction mixture was washed with water then extracted with ethyl acetate three times. The organic phase was collected and dried over anhydrous magnesium sulfate. The solvent was evaporated in a rotary evaporator and characterized by NMR.

Procedure for Blank Experiments of Comparison of 4-Methoxyphenyl Neopentylglycolboronate with 4-Methoxylphenyl Pinacolboronate in THF. To an oven-dried test tube (15 × 85 mm) were added two arylboron-based nucleophiles (0.30 mmol each), Ni(II)Cl(1-naphthyl)(PPh_3)$_2$ (11 mg, 0.015 mmol), and K_3PO_4 (191 mg, 0.9 mmol). The tube was taken into a glovebox. PCy_3 (0.030 mmol) was added. Dried THF (1.0 mL) was then added, and the tube was capped with a rubber septum. The reaction was stirred at room temperature under nitrogen in the glovebox for 3 h. A sample was taken via syringe inside the glovebox. The sample was dissolved in distilled THF and was filtered through a short column of silica gel. The solvent was evaporated, and the NMR spectrum of the crude reaction mixture was examined.

General Procedure for Kinetic Studies of the Cross-Coupling Reactions. To an oven-dried test tube (15 × 85 mm) were added the aryl mesylate (69 mg, 0.3 mmol), the aryl boronate (0.30 mmol), and K_3PO_4 (191 mg, 0.9 mmol). The tube was taken into a glovebox. Ni(COD)$_2$ and PCy_3 (10.1 mg, 0.036 mmol) was added. Dry THF (2 mL) was added inside the glovebox. The tube was capped and allowed to stir at room temperature. Samples were taken in the glovebox at predetermined times and then dissolved in THF, passed though a short neutral alumina gel column, and dried under vacuo. The conversion was determined by ^{1}H NMR spectroscopy. A representative example for the determination of conversion is provided in the Supporting Information.

General Procedure for Kinetic Studies of the Diol-Exchange Reactions. To an oven-dried test tube (15 × 85 mm) were added the aryl boronates (0.3 mmol), the diol (0.30 mmol), and K_3PO_4 (191 mg, 0.9 mmol). The tube was taken into a glovebox. Dry THF (2 mL) was added inside the glovebox. The tube was capped and allowed to stir at room temperature. Samples were taken in the glovebox at predetermined times and then dissolved in THF, passed though a short cotton column, and dried under vacuo. The conversion was determined by ^{1}HNMR spectroscopy. A representative example of the determination of conversion is provided in the Supporting Information.

General Procedure for the Turnover Number (TON) Measurement. To an oven-dried test tube (15 × 85 mm) were added the aryl mesylate (69 mg, 0.3 mmol), 4-methoxylphenyl neopentylglycolboronate (0.30 mmol), and K_3PO_4 (191 mg, 0.9 mmol). To another oven-dried test tube were added the aryl mesylate (69 mg, 0.3 mmol), 4-methoxylphenyl pinacolboronate (0.30 mmol), and K_3PO_4 (191 mg, 0.9 mmol). The tubes were taken into a glovebox. A stok solution of Ni(COD)$_2$ (1.7 mg, 0.002 mmol), PCy_3 (3.3 mg, 0.0040 mmol), and dry THF (1 mL) was prepared in the glovebox. Half of the solution (0.5 mL) was added in each tube. Another 1 mL of THF was used to rinse the vial and added evenly to the tubes. The tubes were capped and allowed to stir at room temperature. After 60 h, the conversion was determined by ^{1}H NMR spectroscopy, and the TONs were calculated.

2-(4-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2c): colorless oil (3.48 g, 96%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80−7.71 (m, 2H), 6.93−6.84 (m, 2H), 3.83 (s, 3H), 1.33 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.4, 113.2, 83.5, 55.0, 24.8. NMR spectrum is identical with literature data.[57]

Methyl 4′-methoxy(1,1′-biphenyl)-4-carboxylate (3a): white solid (Table 5: from 4-methoxyphenyl neopentylglycolboronate: 72 mg; 99%; from 4-methoxyphenyl pinacolboronate: 41.0 mg, 57%; Table 6: from 4-methoxyphenyl neopentylglycolboronate: 64.0 mg; 89%; from 4-methoxyphenyl pinacolboronate: 22.0 mg, 30%); mp 173 °C (lit.[21] mp 173−174 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.2, 11H), 7.60 (dd, J = 22.7, 8.3, 23H), 7.26 (s, 17H), 7.00 (d, J = 8.5, 11H), 3.90 (d, J = 35.1, 34H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7, 145.1, 132.3, 130.9, 130.0, 128.3, 128.2, 126.4, 114.3, 55.3, 52.0.

4,4′-Dimethoxy-1,1′-biphenyl (3b): white solid (Table 5: from 4-methoxyphenyl neopentylglycolboronate: 60.0 mg; 94%; from 4-methoxyphenyl pinacolboronate: 32.3 mg, 50%; Table 6: from 4-methoxyphenyl neopentylglycolboronate: 60.2 mg; 94%; from 4-methoxyphenyl pinacolboronate: 36.0 mg, 56%); mp 173 °C (lit.[21] mp 171−172 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, J = 8.5, 1H), 6.96 (d, J = 8.6, 1H), 3.85 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.9, 133.6, 127.9, 114.3, 55.6.

Methyl 4′-Methoxy(1,1′-biphenyl)-2-carboxylate (3c): colorless oil (Table 5: from 4-methoxyphenyl neopentylglycolboronate: 64.0 mg; 89%; from 4-methoxyphenyl pinacolboronate: 56.0 mg, 77%; Table 6: from 4-methoxyphenyl neopentylglycolboronate: 65.0 mg; 90%; from 4-methoxyphenyl pinacolboronate: 58.0 mg, 81%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90−7.70 (m, 1H), 7.51 (td, J = 7.6, 1.4, 1H), 7.41−7.31 (m, 2H), 7.28−7.20 (m, 4H), 6.99−6.88 (m, 2H), 3.85 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (126 MHz, CDCl3) δ 169.5, 159.1, 142.2, 133.8, 131.3, 131.0, 130.9, 129.9, 129.6, 126.9, 113.7, 100.1, 55.4, 52.1. NMR spectrum is identical with the literature data.[21]

2,4′-Dimethoxy-1,1′-biphenyl (3d): white solid (Table 5: from 4-methoxyphenyl neopentylglycolboronate: 56.0 mg; 87%; from 4-methoxyphenyl pinacolboronate: 28.0 mg, 44%; Table 6: from 4-methoxyphenyl neopentylglycolboronate: 57.0 mg; 89%; from 4-methoxyphenyl pinacolboronate: 55.2 mg, 86%); mp 69 °C (lit.[21] mp 64−66 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 − 7.43 (m, 1H), 7.30 (td, J = 7.4, 1.6, 1H), 7.04 − 6.92 (m, 2H), 3.85 (s, 2H), 3.81 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.5, 156.4, 130.8, 130.6, 130.5, 130.2, 128.1, 120.7, 113.4, 111.1, 55.5, 55.2.

Methyl 4′-methoxy(1,1′-biphenyl)-4-carboxylate (3e): white solid (Table 5: from 4-methoxyphenyl neopentylglycolboronate: 58.3 mg; 81%; from 4-methoxyphenyl pinacolboronate: 66 mg, 92%; Table 6: from 4-methoxyphenyl neopentylglycolboronate: 62.0 mg; 86%; from 4-methoxyphenyl pinacolboronate: 63.0 mg, 88%); mp 175 °C (lit.[21] mp 173−174 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, J = 8.2, 1H), 7.63 (d, J = 8.2, 1H), 7.59 (d, J = 8.8, 1H), 7.01 (d, J = 8.8, 1H), 3.95 (s, 2H), 3.87 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.1, 160.0, 145.4, 132.6, 130.3, 128.5, 128.4, 126.6, 114.5, 55.5, 52.2.

4,4′-Dimethoxy-1,1′-biphenyl (3f): white solid (Table 5: from 4-methoxyphenyl neopentylglycolboronate: 51.0 mg; 80%; from 4-methoxyphenyl pinacolboronate: 29.5 mg, 46%; Table 6: from 4-methoxyphenyl neopentylglycolboronate: 53.5 mg; 93%; from 4-methoxyphenyl pinacolboronate: 40.5 mg, 63%); mp 174 °C (lit.[21] mp 171−172 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 − 7.44 (m, 1H), 7.01 − 6.91 (m, 1H), 3.84 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.6, 133.4, 127.6, 114.1, 55.3.

Methyl 4′-methoxy(1,1′-biphenyl)-2-carboxylate (3g): colorless oil (Table 5: from 4-methoxyphenyl neopentylglycolboronate: 67.0 mg; 93%; from 4-methoxyphenyl pinacolboronate: 65.0 mg, 90%; Table 6: from 4-methoxyphenyl neopentylglycolboronate: 70 mg; 98%; from 4-methoxyphenyl pinacolboronate: 70 mg, 98%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 − 7.73 (m, 1H), 7.50 (tt, J = 13.6, 6.8, 1H), 7.43 − 7.31 (m, 2H), 7.31 − 7.19 (m, 4H), 6.99 − 6.89 (m, 2H), 3.85 (s, 3H), 3.67 (s, 3H); ^{13}C (126 MHz, $CDCl_3$) δ 169.3, 158.9, 141.9, 133.6, 131.1, 130.8, 130.6, 129.6, 129.4, 126.7, 113.5, 55.2, 51.9. NMR spectrum matches with literature data.[21]

2,4′-Dimethoxy-1,1′-biphenyl (3h): white solid (Table 5: from 4-methoxyphenyl neopentylglycolboronate: 60.0 mg; 94%; from 4-methoxyphenyl pinacolboronate: 56.0 mg, 88%; Table 6: from 4-methoxyphenyl neopentylglycolboronate: 64 mg; 99%; from 4-methoxyphenyl pinacolboronate: 24.5 mg, 38%); mp 68 °C (lit.[21] mp 64−66 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51−7.45 (m, 2H), 7.29 (td, J = 7.4, 1.6, 2H), 7.02 (td, J = 7.4, 1.1, 1H), 7.00−6.93 (m, 3H), 3.85 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.8, 155.7, 130.0, 129.8, 129.7, 129.5, 127.3, 120.0, 112.6, 110.3, 54.7, 54.4.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H NMR of reaction crude of Scheme 2, Tables 3 and 4; ^{1}H NMR and ^{13}C NMR spectra of compounds **2c**, **3a**−**h**. This information is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: percec@sas.upenn.edu.

Notes

The authors declare no competing financial interest.

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