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Letter

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Potassium Trimethylsilanolate Enables Rapid, Homogeneous Suzuki−Miyaura Cross-Coupling of Boronic Esters

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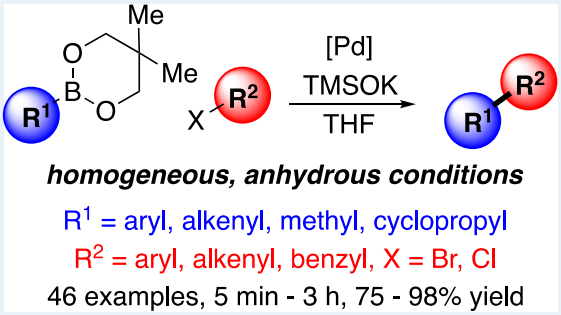
Supporting Information

ABSTRACT: Herein, a mild and operationally simple method for the Suzuki−Miyaura cross-coupling of boronic esters is described. Central to this advance is the use of the organic-soluble base, potassium trimethylsilanolate, which allows for a homogeneous, anhydrous cross-coupling. The coupling proceeds at a rapid rate, often furnishing products in quantitative yield in less than 5 min. By applying this method, a >10-fold decrease in reaction time was observed for three published reactions which required >48 h to reach satisfactory conversion.



KEYWORDS: *cross-coupling, Suzuki−Miyaura reaction, homogeneous catalysis, synthetic methods, palladium*

The Suzuki−Miyaura reaction[1−4] is one of the premier methods for the formation of carbon−carbon bonds. Advances in ligand design have allowed for successful cross-coupling at room-temperature,[5−9] cross-coupling of substrates bearing a poor nucleofuge,[9,10] as well as those involving sterically hindered partners.[11,12] However, competitive protodeboronation often necessitates the use of the organometallic coupling partner in excess,[13−15] and multiple strategies have been developed to mitigate this issue. Most common is the use of masked boronic acids such as BF_3K salts,[16−18] MIDA boronates,[19,20] and triolboronate salts[11,21] which slowly release the boronic acid *in situ*. In other cases, the reaction rate is increased such that the desired cross-coupling outpaces the protodeboronation reaction, either by ligand design[6] or use of a secondary transmetalation agent.[12,19,22] The most robust solution is to run Suzuki−Miyaura reactions anhydrously to minimize protodeboronation using an insoluble, inorganic base, as protodeboronation cannot occur in the absence of a proton source.[23−25] Although occasionally effective, this modification introduces a new set of problems, as the particle size, stir rate, and flask shape/size become relevant factors in heterogeneous reactions.

Pioneering work from this laboratory demonstrated that boronic esters are competent transmetalation partners without the need for hydrolysis to the parent boronic acid and that the structure of the boronic ester (in particular dimethyl and glycol esters) has a significant effect on the rate of transmetalation.[26] We sought to demonstrate this effect in catalytic systems to illustrate that the identity of boron reagent used in the Suzuki−Miyaura coupling can increase the rate of sluggish reactions, thereby demonstrating the value of these reagents beyond their use as protecting groups.

To qualify as a superior alternative to existing procedures, this new method must satisfy several criteria: (1) all reagents used must be inexpensive, simple to prepare, and stable, (2) the reaction conditions must be anhydrous to avoid ester hydrolysis and mitigate protodeboronation, (3) the procedure must be operationally simple and robust enough to compete with the state of the art, and (4) the conditions should effect rapid cross-coupling at room-temperature. The first point of optimization was the identification of a boronic ester that best fulfills these criteria.

Although glycol boronic esters were attractive from a kinetic standpoint, they were labile to column chromatography. Furthermore, we observed competitive reduction of the aryl halide when they were employed, likely arising from Pd-mediated β-hydride elimination of the glycol backbone. Thus, a search for a more stable ester that maintained the enhanced reaction rate was initiated by comparing new boronic esters alongside the nucleophiles we previously investigated (acid, pin, neop, gly)[26c] in the stoichiometric model of transmetalation rate (Figure 1). Boronic esters derived from *cis*-tetrahydrofuran-3,4-diol **5a**, *cis*-cyclopentane-1,2-diol **6a**, and neopentyl glycol[27] **7a** appeared most favorable of those examined. Each possessed transmetalation rates significantly higher than the parent boronic acid **3a** as well as improved stability when compared to the glycol ester **4a**. Esters **6a**, **7a**, and **8a** exhibited non-first-order kinetics; as a result, a numerical comparison of transmetalation rate could not be established between these esters and **3a**. However, it is clear that they transmetalate faster than **3a**. Furthermore, when

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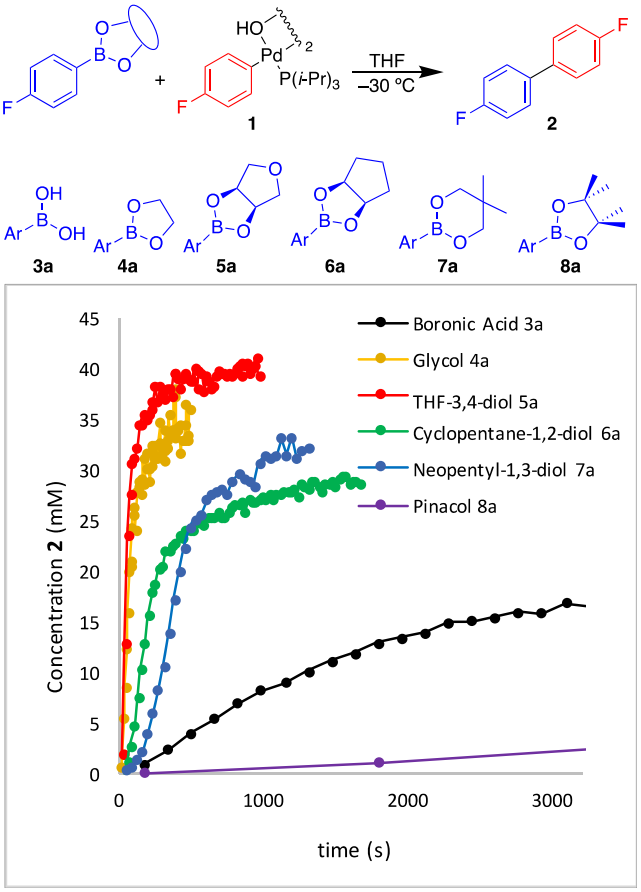
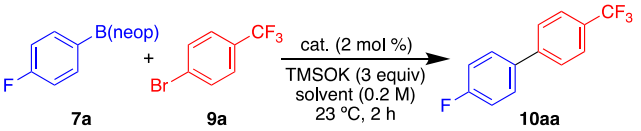


Figure 1. Relative rates of transmetalation for various boronic esters. Reactions were run with 1 equiv of ester with respect to Pd and monitored by ^{19}F NMR against an internal standard. See the Supporting Information for details.

Table 1. Survey of Catalyst and Solvent for the Coupling of 7a with 9a



	yield of **10aa** (%)[a]		
	THF	dioxane	DME
Pd-XPhos-G3	<5	<5	0
Pd-P(*t*-Bu)$_3$-G3	100	50	<5
PEPPSI IPr	0	0	0
Pd[P(*t*-Bu)$_3$]$_2$	0	0	0

[a]Yield of **10aa** obtained by ^{19}F NMR against an internal standard. Reactions run on 0.10 mmol scale using 1.20 equiv of boronic ester **7a**.

neopentyl and pinacol esters **7a** and **8a** were combined with palladium hydroxide dimer **1**, the rate of transmetalation was substantially faster in the presence of excess ester. On the basis of these data, the neopentyl, cyclopentanediol, and THF-diol esters were selected for further investigation. Additional details on the stoichiometric studies using these esters are available in the Supporting Information.

Next, a search for an optimal base was conducted. Guided by the previously reported results,[26] CsOH·H$_2$O was tested; however, the reactions were plagued by irreproducibility owing to insolubility. An appropriate soluble base was sought to address this issue; such a base would also be of considerable interest in systems that utilize anhydrous conditions to attenuate protodeboronation.

Extensive investigations on silicon-based, cross-coupling reactions from this laboratory[28−32] suggested the use of potassium trimethylsilanolate (TMSOK) because of its low cost and high solubility in ethereal solvents.[33] Initial results were encouraging; in a survey of three solvents and four catalysts for the coupling of 4-bromobenzotrifluoride (**9a**) with neopentyl 4-fluorophenylboronic ester (**7a**), the combination of Pd−P(*t*-Bu)$_3$-G3 and THF was uniquely effective (Table 1).[34]

Initial experiments combining the three 4-fluorophenylboronic esters **5a**, **6a**, and **7a** with **9a** (Table 2) revealed a striking dependence on stoichiometry.[35] Optimal results were obtained with 1.4 equiv of base; two of three esters furnished **10aa** in quantitative yield within 5 min at room temperature. Excesses of TMSOK (2.0 or 3.0 equiv) resulted in reaction stalling at low conversion.

To better differentiate the three esters, the ability of each to transfer two different arenes, one heterocyclic (**5b**−**7b**), and one electron deficient (**5c**−**7c**) with several aryl halides was examined. In addition, the stability of each ester to silica gel column chromatography and storage was evaluated, along with their physical properties (Table 3). Esters derived from *cis*-3,4-tetrahydrofurandiol and neopentyl glycol were crystalline solids, whereas the esters derived from *cis*-1,2-cyclopentanediol were oils. Of the six esters prepared, all were indefinitely bench stable save for the cyclopentanediol ester of furan-2-boronic acid. When combined with **9a** or **11a**, esters **6b** and **7b** each afforded the product **10ba** in quantitative yield. When these aryl halides were combined with **5b**, the product yield was slightly diminished. However, yields of **10cb** were significantly lower, likely owing to the lesser migratory aptitude of the 3,5-bis(trifluoromethyl)phenyl unit. In reactions with **11b**, neopentyl ester **7c** afforded the highest yield followed by **6c** and then ester **5c**. In reactions with **9b** little variation in yield was observed. From these comparisons, neopentyl glycol boronic esters were deemed only marginally superior; however, in view of their price[36] and familiarity, these esters were selected for development.

The foregoing preliminary studies revealed that some reactions afforded quantitative yield in <5 min, but those that did not proceeded in low yield or failed to react altogether. A working hypothesis identifies three factors: (1) the previous observation that ≥2.0 equiv of TMSOK was detrimental (Table 2), (2) the failure of substrates with lesser migratory aptitude (Table 3), and (3) the extraordinary rate of reaction (Figure 2). It appears the reaction stalls when the base is present in excess of boronic ester; however, for many substrates, a substantial quantity of base is consumed by the time the entire portion is added owing to the rate of reaction. To support this hypothesis, the rate at which the room-temperature cross-coupling of **7a** and **9a** occurs under these conditions was determined (Figure 2). We employed our rapid-injection NMR apparatus (RI-NMR)[37] to obtain a kinetic profile of the reaction. After 6 s (the minimum time required to adequately mix the sample), the reaction was observed to be >50% complete, with full conversion achieved in under 60 s (Figure 2). Thus, to retain reactivity for sluggish

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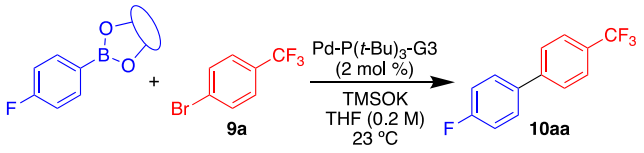
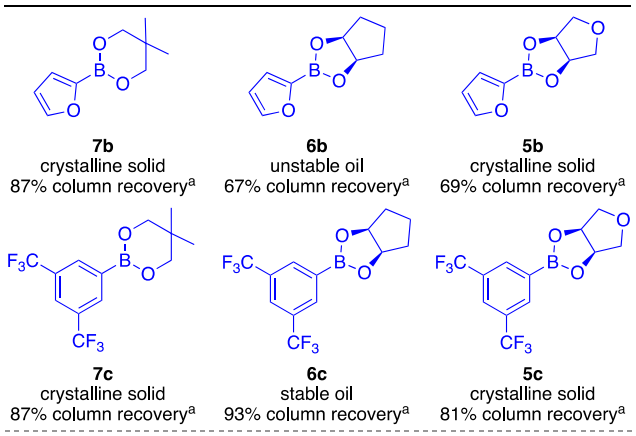
Table 2. Study of TMSOK Stoichiometry

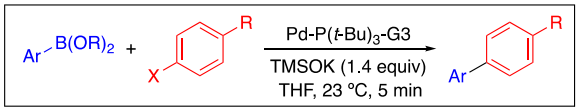


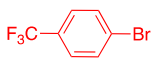
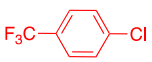
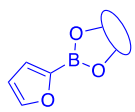
			yield of **10aa** (%)[a]			
boronic ester	base source	time	1.2 equiv	1.4 equiv	2.0 equiv	3.0 equiv
7a	Oakwood[35]	5 min	96	100	100	23
7a	Gelest	5 min	96	100	25	31
7a	Gelest	1 h	100	100	21	38
6a	Gelest	5 min	88	100	8	8
5a	Gelest	5 min	54	12	<5	20

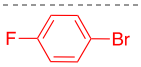
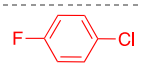
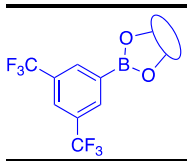
[a]See footnote *a* in Table 1. Reactions run on 0.25 mmol scale using 1.20 equiv of boronic ester.

Table 3. Comparison of Coupling Efficiency, Stability, and Physical State of Six Boronic Esters





		reaction with  **9a**	reaction with  **11a**
arene	boronic ester	yield of **10ba** (%)[b]	yield of **10ba** (%)[b]
	**7b**	100	100
	6b	100	100
	5b	92	80

		9b 	**11b** 
arene	boronic ester	yield of **10cb** (%)[b]	yield of **10cb** (%)[b]
	**7c**	15	41
	6c	10	29
	5c	18	9

[a]Recovery determined by subjecting 150 mg of each ester to silica gel column chromatography (3.0 cm column, 30 g silica gel). [b]Yield of **10ba** and **10cb** obtained by ^{19}F NMR against an internal standard. Reactions run on a 0.25 mmol scale using 1.20 equiv of boronic ester.

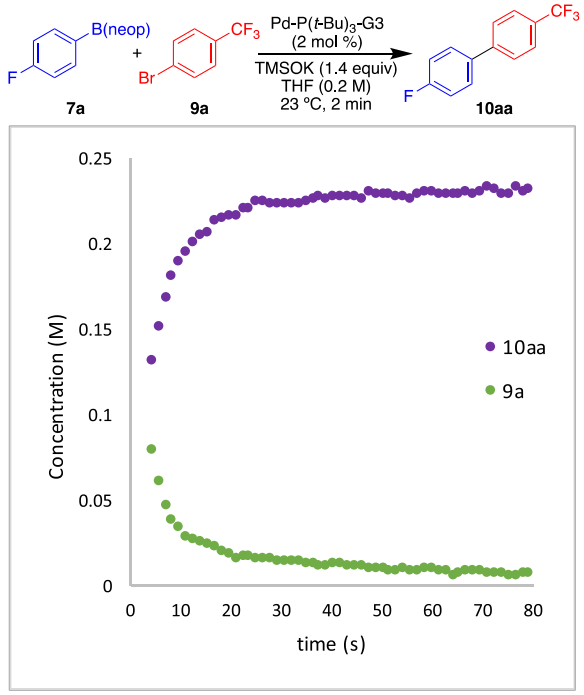
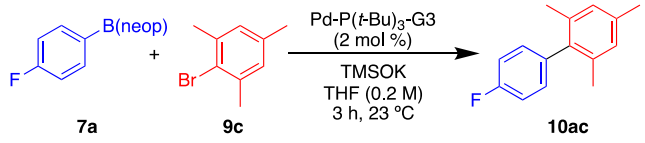


Figure 2. Rapid-injection NMR reaction profile. Concentration of **10aa** obtained by ^{19}F NMR against an internal standard. Reaction run on 0.16 mmol scale using 1.20 equiv of boronic ester.

Table 4. Development of a Portionwise Addition Protocol for Challenging Substrates[a,b]



entry	base addition method	yield (%)
1	1.4 equiv added in one portion	52 ± 31
2	1.4 equiv added dropwise over 15 s	45 ± 39
3	1.0 equiv added in one portion	80 ± 1
4	1.0 equiv, followed by 0.4 equiv at 45 min	98 ± 0
5	0.9 equiv, followed by 0.5 equiv at 45 min	98 ± 1

[a]Reactions run in triplicate on 0.25 mmol scale using 1.20 equiv of boronic ester **7a**. [b]Yield of **10ac** obtained by ^{19}F NMR against an internal standard.

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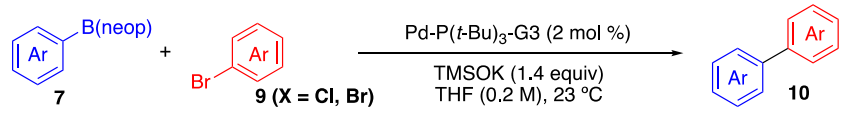
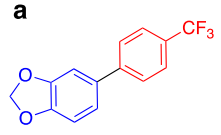
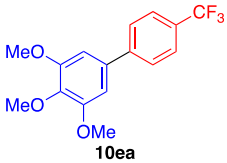
Table 5. Reaction Scope of Neopentylboronic Esters[a]



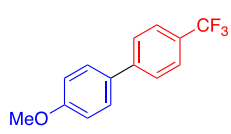
a



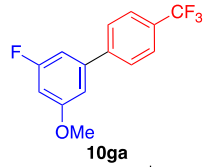
10da
5 min, 95%



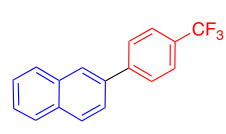
10ea
5 min, 100%[b]



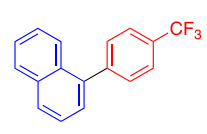
10fa
5 min, 98%



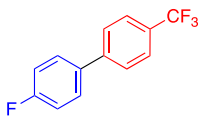
10ga
5 min, 89%[b]



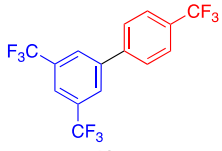
10ha
5 min, 92%



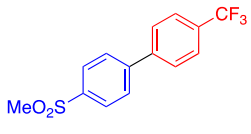
10ia
5 min, 98%



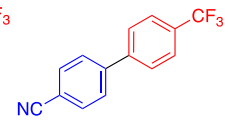
10aa
5 min, 95%



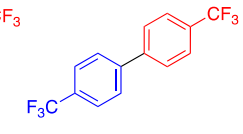
10ca
15 min, 95%



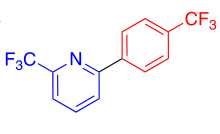
10ja
15 min, 89%[b]



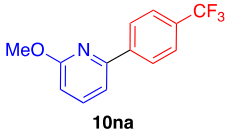
10ka
15 min, 96%



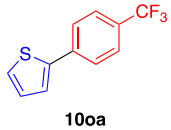
10la
5 min, 95%



10ma
2 h, 50 °C, 96%[c]



10na
12 h, 50 °C, 78%[c]



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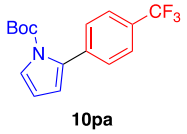
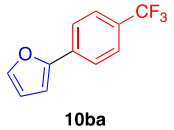
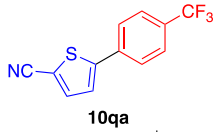
5 min, 100%



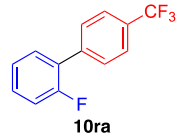
10pa
5 min, 99%



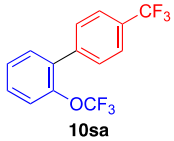
10ba
5 min, 93%



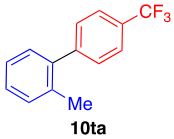
10qa
15 min, 89%[b]



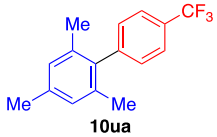
10ra
5 min, 92%



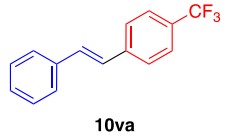
10sa
30 min, 94%



10ta
30 min, 93%

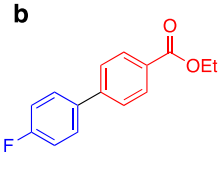


10ua
3 h, 40%[d,e]

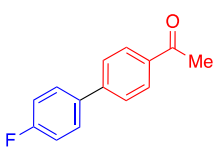


10va
15 min, 98%[f]

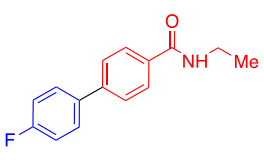
b



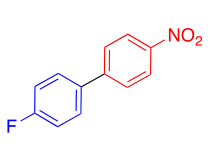
10ad
5 min, 92%



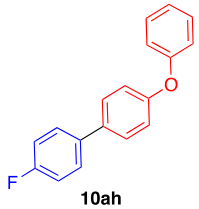
10ae
5 min, 100%



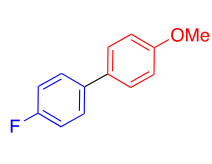
10af
5 min, 98%[b]



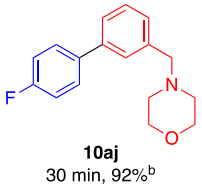
10ag
5 min, 95%



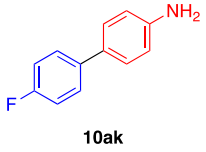
10ah
5 min, 98%



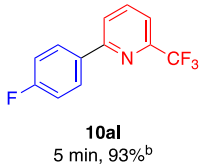
10ai
5 min, 100%



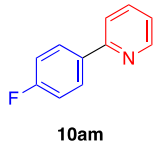
10aj
30 min, 92%[b]



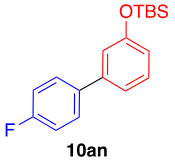
10ak
15 min, 50 °C, 88%



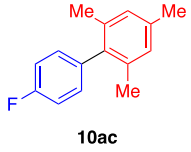
10al
5 min, 93%[b]



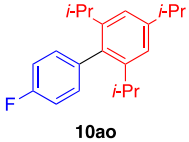
10am
15 min, 94%



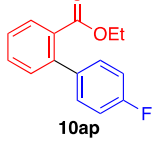
10an
5 min, 93%



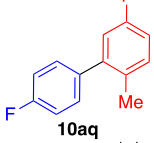
10ac
3 h, 93%



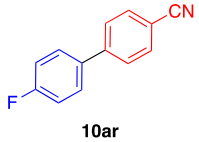
10ao
3 h, 78%[d]



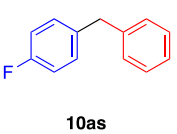
10ap
15 min, 92%



10aq
30 min, 75%[b,d]
(X=Cl)



10ar
15 min, 91%
(X = Cl)



10as
2 h, 85%[d,e]
(X = Cl)

[a]Reactions with 1.00 mmol of aryl halide with 1.2 equiv of boronic ester. Yields of isolated product after column chromatography. [b]Product was further purified to analytical purity, see the Supporting Information. [c]Pinacol ester used. [d]Concentration was 0.4 M. [e]4 mol % catalyst used. [f]1.04 equiv of boronic ester used.

reaction partners, the slow or portionwise addition of base was investigated (Table 4).

In the reaction of mesityl bromide with **7a**, addition of a THF solution of TMSOK, either in a single bolus or dropwise

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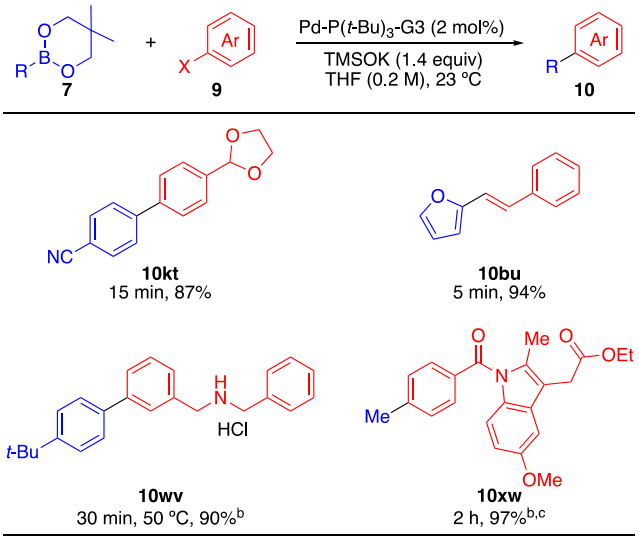
Table 6. Cross-Coupling of Nonfluorinated Arenes[a]

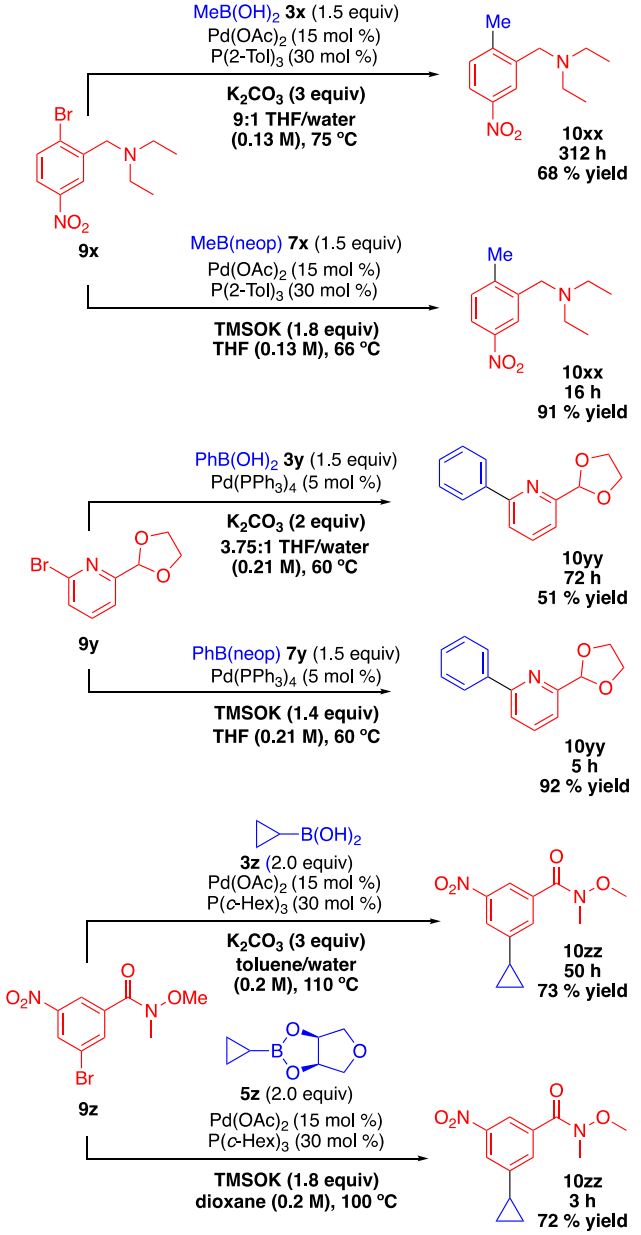


[a]Reactions with 1.00 mmol of aryl halide with 1.2 equiv of boronic ester. Yields of isolated product after column chromatography. [b]Product was further purified to analytical purity, see the Supporting Information. [c]0.44 M concentration.

over 15 s gave variable and unsatisfactory yields (entries 1 and 2). Decreasing the quantity of base to 1.0 equiv restored reaction reproducibility (entry 3) but did not proceed to completion within 3 h. Addition of 1.0 equiv of TMSOK solution followed by an additional 0.4 equiv after 45 min provided sufficient base to achieve full conversion (entry 4). Ultimately, we chose to use 0.9 equiv of TMSOK followed by 0.5 equiv after 45 min (entry 5) to accommodate the possibility of using 1.0 equiv of ester.[38]

With optimized conditions fully developed, the generality of the TMSOK-promoted cross-coupling was explored with a series of neopentyl boronic esters and **9a** (Table 5a). In general, reactions were complete in 5 min affording product in excellent (>90%) yield. Reactions using electron-rich partners such as 4-methoxyphenyl-, 3,4,5-trimethoxyphenyl-, and 3,4-methylenedioxyphenylboronic ester or electronically neutral partners such as 4-fluorophenyl-, 2-naphthyl-, and 1-naphthylboronic ester furnished the respective products in >90% yield in under 5 min. Electron-deficient nucleophiles such as 4-cyano-, 4-trifluoromethyl-, 4-sulfonyl-, and 3,5-bis(trifluoromethyl)phenylboronic esters required slightly extended reaction times to reach completion but also afforded >90% yields. Protodeboronation prone heterocycles such as 2-furyl, 2-thienyl, 2-(4-cyano)thienyl, and *n*-Boc-pyrrolyl-2-boronic ester gave excellent yields as well, with all but **10qa** proceeding to completion in less than 5 min. The neopentyl ester of 2-pyridylboronic acid proved too unstable for effective isolation; however, the pinacol ester of 6-substituted pyridylboronic acids such as 6-trifluoromethyl-2-pyridyl-boronic ester and 6-methoxy-2-pyridylboronic ester were effectively cross-coupled at slightly elevated temperatures and extended reaction times. Boronic esters bearing unobtrusive groups such as 2-fluorophenyl- and 2-trifluoromethoxyphenyl boronic ester reacted in 5 and 30 min, respectively, each in >90% yield. The more encumbered 2-methylphenylboronic ester was successfully cross-coupled in 94% yield after 30 min. However, mesitylboronic ester was cross coupled in only 40% yield after 3 h, using 4.0 mol % catalyst.

Table 7. Improving the Rate of Known Reactions[a]



[a]Reactions with 1.00 mmol of aryl halide. Yields of isolated product after column chromatography.

Next, the electrophile scope and functional group compatibility were examined by combining a series of aryl halides with **7a** (Table 5b). Electron deficient aryl halides were excellent partners, leading to complete reaction in <5 min. 4-Nitrophenyl bromide (**9g**) reacted successfully, and secondary amides were competent without protection, as was 4-bromoacetophenone (**9e**). 4-Ethoxycarboxyphenyl bromide (**9d**) reacted rapidly and did not suffer saponification; however, methyl esters undergo competitive demethylation. Electron rich aryl halides that retard the rate of oxidative addition were equally competent; 4-bromodiphenyl ether (**9h**) and 4-bromoanisole (**9i**) both reacted in quantitative yield in <5 min.

Amines were compatible under these conditions; tertiary amine-containing aryl bromide **9j** gave an excellent yield. Some nitrogen heterocycles were compatible; 6-trifluoromethyl-2-

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bromopyridine reacted quantitatively in <5 min, and 2-bromopyridine reacted quantitatively in 15 min.

Silyl protected phenols (**9n**) and anilines (**9k**) were compatible as well. Highly encumbered aryl bromides underwent cross-coupling readily. Mesityl bromide (**9c**) gave excellent yield in only 3 h, and the extremely encumbered 2,4,6-triisopropyl-bromobenzene was successfully cross-coupled in good yield. Aryl chlorides were also competent; 4-chlorobenzonitrile reacted cleanly, and the 2-substituted aryl chloride **11q** could be cross-coupled in only 30 min, albeit in 75% yield. Finally, benzyl chloride **11s** cross-coupled effectively without ether formation with TMSOK.

Several additional combinations of nonfluorinated substrates were tested (Table 6). Aldehydes were not compatible but the protected aldehyde **9t** did couple with **7k** in 87% yield. Styrenyl bromide **9u** was coupled with **7b** in 94% yield. Neopentyl 4-*tert*-butylphenylboronic ester **7w** was successfully combined with **9v** to furnish **10wv** in 90% yield after crystallization of the product as the HCl salt. Finally, the ethyl ester of indomethacin (**10w**) was methylated in 97% yield using neopentyl methylboronic ester.

To challenge the state of the art, it was deemed crucial to demonstrate that these modifications are applicable to other systems. Several published reactions were identified that take >48 h to proceed to satisfactory conversion which were then executed under the conditions developed herein (Table 7). The reaction of methylboronic acid and bromide **9x** catalyzed by $Pd(OAc)_2/P(2\text{-}Tol)_3$ provides **10xx** in 68% yield after 312 h.[39] By substituting the neopentyl ester for the boronic acid and using TMSOK as the base, **10xx** was produced in 91% yield after only 16 h. The cross-coupling of pyridyl bromide **9y** and phenylboronic acid catalyzed by $Pd(PPh_3)_4$ is run for 72 h to obtain **10yy** in 51% yield.[40] With the modifications described above, the product was obtained in 92% yield after 5 h. Finally, the coupling of bromide **9z** with cyclopropylboronic acid was investigated under catalysis by $Pd(OAc)_2/P(c\text{-}Hex)_3$, which furnished product **10zz** in 73% yield after 50 h.[41] Substituting with TMSOK and neopentyl cyclopropylboronic ester gave a lower yield owing to competitive protodehalogenation. Switching to the THF-3,4-diol ester suppressed this side reaction and afforded **10zz** in 72% yield after 3 h. These examples demonstrate that by simply using a boronic ester in place of the acid, using TMSOK as a base, and a compatible solvent system (ethereal, anhydrous solvents), the rate of cross-coupling is increased in a variety of catalytic systems; the catalyst/ligand for each system has not been changed. As such, we posit that this is a general advance that can provide benefits complementary to other improvements in ligand design.

In conclusion, we have demonstrated that the use of an organic soluble base, TMSOK, allows for a homogeneous, anhydrous reaction that improves reproducibility and ease of use. Additionally, boronic ester structure represents a powerful new point of optimization in the Suzuki–Miyaura reaction which can complement recent advances in ligand and precatalyst design.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.9b04353.

Experimental procedures and characterization data for all new compounds along with copies of the NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(34) Other candidates such as dialkyl phosphates, potassium and sodium alkoxides, and tetraalkylammonium hydroxides, fluorides, and carboxylates were either ineffective or impractical.
(35) The discrepancy between Tables 1 and 2 occurs because samples of TMSOK obtained from Oakwood were contaminated with significant quantities of KOH. Purity was assessed by filtration of 10 mL of a 1.0 M solution of Oakwood TMSOK, see the Supporting Information. Fortunately, TMSOK from Gelest gave only mildly turbid solutions in THF at 1.0 M that became transparent after simple filtration. To assure reproducibility, filtered solutions of Gelest TMSOK were used in the remainder of this study.
(36) Neopentyl glycol (Alfa Aesar): $51/2.5 kg. Pinacol (ABAChemScene): $141/1 kg. *cis*-tetrahydrofuran-2,3-diol: 1 step from erythritol. Erythritol: (Oakwood Chemical) $60/1 kg. *cis*-cyclopentane-1,2-diol: derived from dihydroxylation of cyclopentene, comparatively expensive.
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NOTE ADDED IN PROOF

During the processing of this manuscript, two related papers appeared in *ACS Catalysis* (DOI: 10.1021/acscatal.9b03667 and 10.1021/acscatal.9b03666), which also describe anhydrous, base-activated Suzuki−Miyaura cross-couplings albeit at significantly higher temperatures than we report.

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