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Cobalt-Catalyzed Cross-Coupling Reactions of Arylboronic Esters and Aryl Halides

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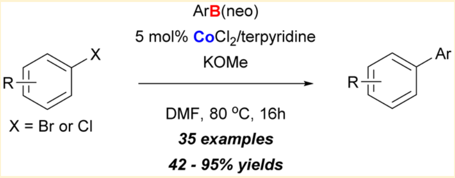
Supporting Information

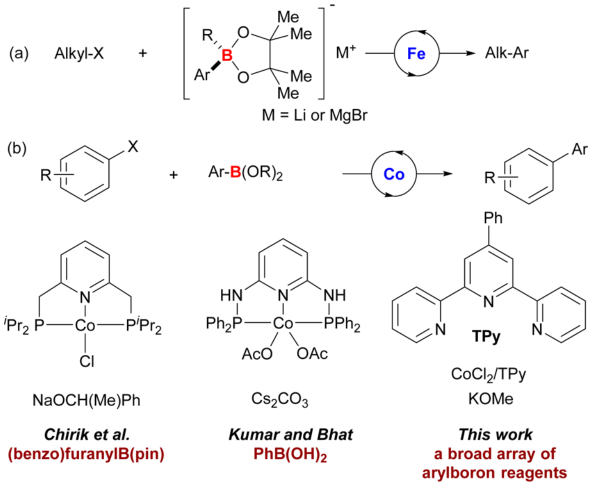
ABSTRACT: An efficient cobalt catalyst system for the Suzuki–Miyaura cross-coupling reaction of arylboronic esters and aryl halides has been identified. In the presence of cobalt(II)/terpyridine catalyst and potassium methoxide, a diverse array of (hetero)biaryls have been prepared in moderate to excellent yields.



The Suzuki–Miyaura cross-coupling reaction is currently one of the most frequently employed methods for carbon–carbon bond formation in organic synthesis, including the manufacture of complex small-molecule intermediates and active pharmaceutical ingredients (APIs) on a commercial scale.[1] Catalysts based on palladium are predominantly used for this purpose. Palladium, however, is a precious metal with high price volatility and is prohibitively expensive when required in large quantities. Thus, the search for alternative catalytic processes employing inexpensive and highly abundant first-row transition metals such as iron and cobalt represents an important approach toward sustainable chemistry.

In comparison to nickel and copper,[2,3] much less has been achieved with iron and cobalt as catalyst in the Suzuki–Miyaura reaction, presumably due to the difficulty associated with transmetalation from boron to these earlier transition metals.[4] Indeed, iron- and cobalt-catalyzed cross-coupling reactions are generally accomplished with more reactive organometals in Kumada- and Negishi-type reactions.[5,6] To facilitate transmetalation, organoboron compounds can be activated by highly reactive organolithium and organomagnesium reagents for cross-coupling reactions under iron catalysis (Scheme 1a).[7] Recently, Chirik et al. developed a bis(phosphino)pyridine cobalt catalyst for the cross-coupling of aryl triflates and (benzo)furanylboronic esters in the presence of an alkaline alkoxide (Scheme 1b).[8] Presumably, transmetalation was enabled through initial coordination of the oxygen lone pair in the heteroarylboron nucleophile to the metal center. Concurrently, Kumar and Bhat reported an *N*,*N*′-bis(phosphino)-2,6-diaminopyridine pincer cobalt acetate complex as catalyst for the cross-coupling of phenylboronic acid and aryl halides (Scheme 1b).[9] Notably, the scope of the organoboron nucleophile was not described beyond phenylboronic acid. We report herein a cobalt catalyst system capable of cross-coupling a wide range of organoboronic esters with (hetero)aryl halides, leading to a diverse array of (hetero)biaryl products (Scheme 1b).

Scheme 1. Iron- and Cobalt-Catalyzed Suzuki–Miyaura Cross-Coupling Reactions



To probe any potential reactivity of organoboron compounds under cobalt catalysis, we started out to explore the reactions of different arylboron reagents with 2-chloropyridine (**1a**), an activated substrate that had been well-studied in iron- and cobalt-catalyzed Kumada and Negishi cross-coupling reactions (Table 1).[5a,6] After some experimentation with different alkoxides,[10] we realized that **3a** could be formed in a moderate yield in the reaction of **1a** with PhB(neo) (**2a**) in the presence of 12 mol % of $CoCl_2$ and 1.5 equiv of KOMe (Table 1, entry 1). Since bis(phosphino)pyridine, pyridine diimine, and terpyridine pincer ligands are known to support cobalt complexes in $C(sp^2)$–H borylation and cross-coupling reactions,[8,11] we evaluated some easily accessible or commercially available ligands belonging to these families (entries 3–5). 4′-Phenyl-2,2′:6′,2-terpyridine (TPy) was found to serve as

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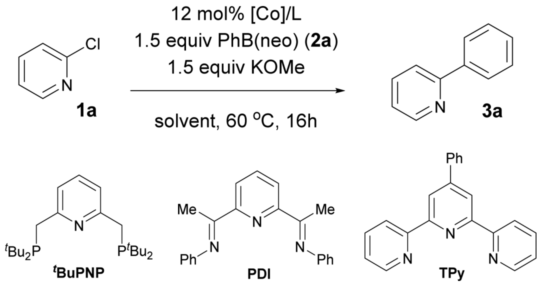
Organometallics XXXX, XXX, XXX–XXX

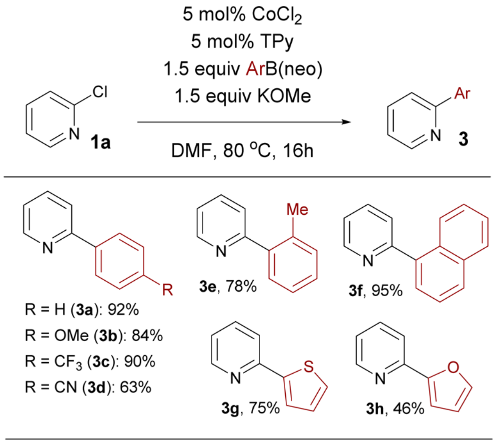
Table 1. Optimizations of the Co-Catalyzed Cross-Coupling of 1a and 2a



entry	[Co]	L	solvent	conversn (%)[a]	yield (%)[a]
1	CoCl$_2$	none	THF	61	38
2	CoCl$_2$	bipy	THF	87	41
3	CoCl$_2$	^{t}BuPNP	THF	51	31
4	CoCl$_2$	PDI	THF	16	2
5	CoCl$_2$	TPy	THF	100	90
6	CoCl$_2$	TPy	DMF	100	94
7[b]	CoCl$_2$	TPy	DMF	100	93
8[c]	CoCl$_2$	TPy	DMF	47	46
9[d]	CoCl$_2$	TPy	DMF	8	7
10[e]	CoCl$_2$	TPy	DMF	100	92
11	none	TPy	DMF	16	0
12	PdCl$_2$	TPy	DMF	80	12
13	NiCl$_2$	TPy	DMF	15	8
14	CuCl	TPy	DMF	9	0
15	FeCl$_2$	TPy	DMF	0	0
16[f]	CoCl$_2$	TPy	DMF	85	75
17[g]	CoCl$_2$	TPy	DMF	52	40

[a] Determined by GC using dodecane as an internal standard. [b] 5 mol % CoCl$_2$ and 5 mol % TP were used, and the reaction was run at 80 °C. [c] 0.5 equiv of KOMe was employed. [d] KO^{t}Bu was employed instead of KOMe. [e] KOEt was employed instead of KOMe. [f] PhB(OH)$_2$ was employed instead of PhB(neo). [g] PhB(pin) was employed instead of PhB(neo).

Table 2. Scope of Arylboronic Esters in the Co-Catalyzed Reaction[a]



[a] Conditions: 5 mol % of CoCl$_2$, 5 mol % of TPy, 1.5 equiv of ArB(neo), 1.5 equiv of KOMe, DMF, 80 °C, 16 h.

an excellent ligand, as **3a** was obtained in 90% yield (entry 5). Running the reaction in DMF at 80 °C allowed the catalyst loading to be lowered to 5 mol % without any erosion in yield (entries 6 and 7). A reduction of KOMe to 0.5 equiv led to an incomplete conversion of **1a** (entry 8). Regarding the base additive, the activity of KOEt was similar to that of KOMe, whereas sterically hindered *tert*-butoxide performed poorly in the reaction (entries 9 and 10).[12] While the reaction with 99.998% CoCl$_2$ exhibited a comparable level of activity, no product was observed in the absence of a cobalt salt (entry 11). Other metal catalysts (i.e., Pd, Ni, Cu, and Fe) resulted in poor yields of **3a** under similar conditions (entries 12–15). These results confirmed cobalt as the active catalyst in this reaction. Reactions employing PhB(OH)$_2$ or PhB(pin) as the organoboron nucleophile were less efficient, resulting in an incomplete conversion of **1a** after heating at 80 °C for 16 h (entries 16 and 17).[13]

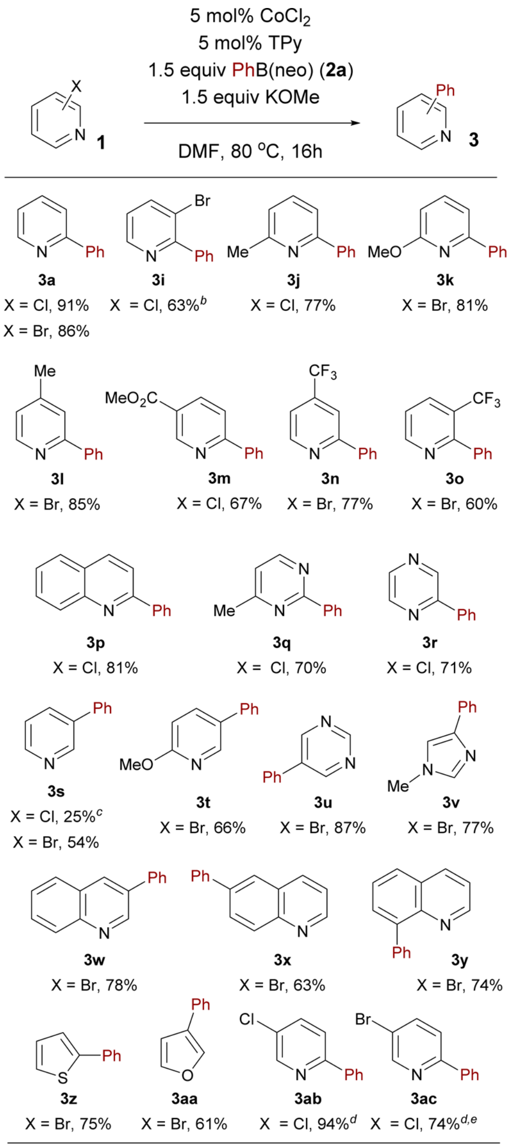
The developed conditions were amenable to the cross-coupling of a range of boronic esters with **1a** (Table 2). Both electron-rich and electron-deficient arylboronic esters were efficiently coupled with **1a** to give **3b**,**c** in 84% and 90% yields, respectively. A moderate yield of **3d** was obtained in the reaction of electronically deactivated 4-cyanophenylboronic ester. Sterically hindered 2-methylphenylboronic ester reacted with **1a** to give **3e** in 78% yield. The reaction of 2-naphthylboronic ester proceeded under cobalt catalysis to give **3f** in an excellent yield of 95%. 2-Thienylboronic ester underwent the coupling reaction in 75% yield, whereas the reaction of 2-furanylboronic ester resulted in only 46% of **3h** with full consumption of **1a**. We suspected that the latter could be due to the instability of the heteroarylboron reagent. However, an increase of 2-furanylboronic ester to 3.0 equiv (in the presence of 1.5 or 3.0 equiv of KOMe) did not help improve the reaction yield.

A variety of 2-chloro- and 2-bromopyridines can be coupled with **2a** in moderate to excellent yields (Table 3). In comparison to 2-chloropyridine, 2-bromopyridine gave a slightly lower yield in the coupling with **2a** to afford **3a** in 86% isolated yield. 2-Halopyridines featuring electron-donating and electron-withdrawing groups all gave the arylated products in good yields (**3j**–**l**,**n**). Lower yields were obtained with the highly activated ester **3m**, and those featuring a β-substituent (**3i**,**o**), presumably due to reduced steric accessibility. Other *N*-heteroaryl chlorides, including 2-chloroquinoline (**3p**), 2-chloropyrimidine (**3q**), and 2-chloropyrazine (**3r**), could be coupled with **2a** in good yields.

3-Chloropyridine was less reactive than 3-bromopyridine, affording **3s** in only 25% yield as determined by GC analysis. Further exploration reveals that the cobalt-catalyzed reaction is applicable to both π-electron-rich and π-electron-deficient heteroaryl bromides featuring diverse substitution patterns. Heterobiaryls incorporating pyrimidine, imidazole, quinoline, thiophene, and furan units could be prepared in good yields (**3u**–**3aa**). Reactions of 2,5-dichloropyridine and 2-chloro-5-bromopyridine with a reduced amount of PhB(neo) (1.2 equiv) to minimize diarylation gave the monophenylated products **3ab**,**ac** in 94% and 74% yields, respectively. 2-Chloro-5-phenylpyridine was also obtained in 8% yield in the latter.

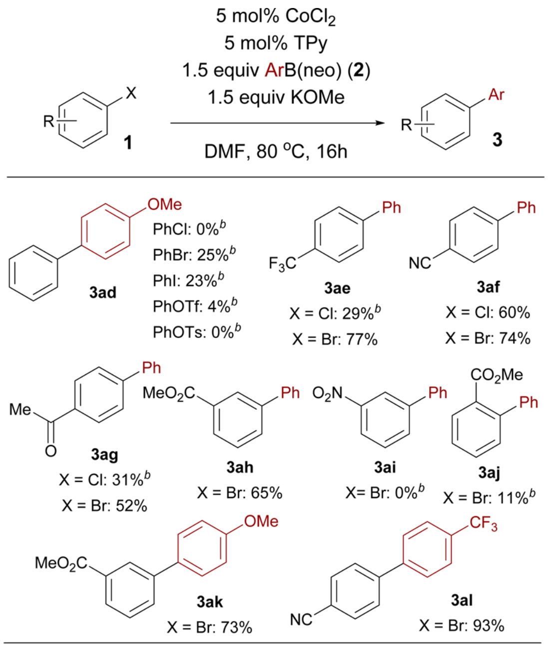
Phenyl (pseudo)halides were poor substrates in the cobalt-catalyzed reaction (Table 4). Chlorobenzene and phenyl tosylate failed to give any trace of **3ad**, while the reactions of iodobenzene, bromobenzene, and phenyl triflate resulted in mainly decomposition, presumably due to protodehalogenation.[14] Running the reactions at a higher temperature (e.g., 100 °C) did not help improve the reaction yield. This is rather surprising, considering the reactivity displayed by π-electron-rich 2-bromothiophene (**3z**) and 2-bromofuran (**3aa**) (Table

Table 3. Scope of Heteroaryl Halides in the Co-Catalyzed Reaction[a]



[a]Conditions: 5 mol % of $CoCl_2$, 5 mol % of TPy, 1.5 equiv of ArB(neo), 1.5 equiv of KOMe, DMF, 80 °C, 16 h. [b]2-Phenylpyridine (**3a**) resulting from protodebromination of **3i** was also obtained in ca. 14% yield. [c]Determined by GC analysis. [d]1.2 equiv of ArB(neo) and 1.2 equiv of KOMe were used. [e]2-Chloro-5-phenylpyridine was also obtained in 8% yield.

Table 4. Scope of Aryl Halides in the Co-Catalyzed Reaction[a]



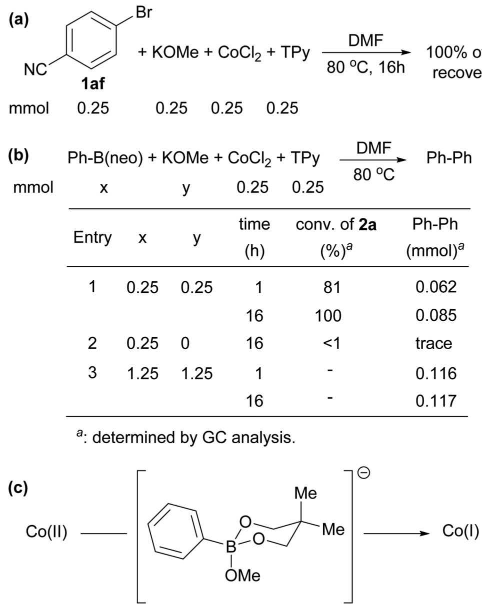
[a]Conditions: 5 mol % of $CoCl_2$, 5 mol % of TPy, 1.5 equiv of ArB(neo), 1.5 equiv of KOMe, DMF, 80 °C, 16 h. [b]Determined by GC/GCMS analysis.

3). Possibly, initial coordination of the heteroatom in these heterocycles to cobalt promotes the subsequent coupling event.

Electron-deficient aryl bromides were coupled with **2a** under cobalt catalysis to give **3ae,af** in 77% and 74% yields, respectively. **3ag** incorporating a ketone functional group could be synthesized in 52% yield. Methyl 3-bromobenzoate was coupled with **2a** to give **3ah** in 65% yield, whereas **3ai** was not formed in the reaction of 1-bromo-3-nitrobenzene, indicating the incompatibility of the cobalt catalyst with a nitro functional group. The reaction of sterically hindered methyl 2-bromobenzoate led to only an 11% yield of **3aj**, as determined by GC analysis of the reaction mixture. Both electron-rich and electron-deficient arylboronic esters were effective in the coupling reaction, as **3ak,al** were formed in 73% and 93% yields, respectively. 4-Chlorobenzonitrile was coupled with **2a** to give **3af** in 60% yield, whereas less activated 4-chlorobenzotrifluoride (**3ae**) and 4-chloroacetophenone (**3ag**) resulted in a significant decomposition of the aryl chlorides.[14]

To probe whether the aryl halide is involved in catalyst activation, we reacted **1af** with $CoCl_2$ (1 equiv), TPy (1 equiv), and KOMe (1 equiv) (Scheme 2a). **1af** was chosen because the protodebromination product (benzonitrile), if formed, could be monitored by GC/GCMS. However, **1af** was fully recovered after the reaction. On the other hand, a stoichiometric reaction

Scheme 2. Experiments To Probe Catalyst Activation Pathway



Entry	x	y	time (h)	conv. of **2a** (%)[a]	Ph-Ph (mmol)[a]
1	0.25	0.25	1	81	0.062
			16	100	0.085
2	0.25	0	16	<1	trace
3	1.25	1.25	1	-	0.116
			16	-	0.117

[a]: determined by GC analysis.

of PhB(neo) (**2a**), CoCl$_2$ (1 equiv), and TPy (1 equiv) (Scheme 2b) proceeded rapidly in the presence of KOMe (entry 1). No conversion was observed in the absence of the base additive (entry 2). These results indicate that catalyst activation likely involves the reduction of Co(II) by an arylborate species. Notably, Thomas et al. reported that an alkoxide such as NaO^{t}Bu can form an "ate" species with HBpin or silane that then serves as a reducing agent for cobalt and iron complexes.[15] Moreover, a reaction of 0.25 mmol of CoCl$_2$/TPy with excess PhB(neo)/KOMe resulted in only 0.117 mmol of biphenyl even after prolonged heating (Scheme 2b, entry 3). Since the formation of biphenyl from the organoboron is a two-electron process, a stoichiometry close to 0.5 is in agreement with a reduction of Co(II) to Co(I). Thus, it is possible that Co(II) is reduced by phenylborate to a catalytically active Co(I) species (Scheme 2c) and a Co(I)/Co(III) catalytic cycle similar to that proposed by Chirik et al. could be in operation.[8] Further studies are needed to evaluate this hypothesis and to fully elucidate the mechanism of the cobalt-catalyzed reaction.

In conclusion, we have developed an efficient cobalt catalyst system for the Suzuki−Miyaura cross-coupling of arylboron reagents and aryl halides. The substrate scope encompasses a broad array of π-electron-rich and π-electron-deficient heteroaryl halides and electron-deficient aryl halides. Further study is now underway to gain more insights into the mechanism of the cobalt-catalyzed reaction and to extend the chemistry to other classes of substrates.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.7b00726.

Experimental details and NMR spectra of the compounds obtained in this paper (PDF)

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Notes

The authors declare no competing financial interest.

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(10) See the Supporting Information for more details on screening of ligands, boron nucleophiles, solvents, and cobalt sources.

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