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Homogeneous Ruthenium Precatalyst for Suzuki–Miyaura Coupling Reaction

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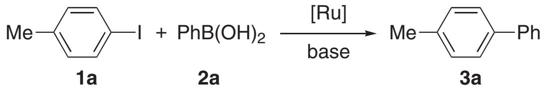
Ru(cod)(2-methylallyl)$_2$ was found to catalyze the Suzuki–Miyaura cross-coupling reaction of aryl bromides and aryl iodides with arylboronic acids. The reaction was catalyzed by 10 mol % Ru(cod)(2-methylallyl)$_2$ at 60 °C, and afforded the biaryls in moderate to good yields.

The Suzuki–Miyaura cross-coupling reaction is one of the most versatile synthetic methods for the construction of carbon–carbon bonds and has been used for the synthesis of biaryls.[1] Originally, the reaction used a palladium catalyst, and several highly active palladium–ligand catalysts have been developed in the last decade.[2] Alternatively, the cross-coupling of aryl halides with arylboronic acids has also been accomplished using other metal catalysts such as nickel,[3] copper,[4] platinum,[5] or rhodium.[6] Ruthenium is also known to catalyze the coupling reaction, but its use is limited to heterogeneous systems.[7,8] For example, Rothenberg reported in 2002 that ruthenium nanocolloid catalyzed the Suzuki–Miyaura cross-coupling.[7] Two years later, Chang et al. succeeded in demonstrating that supported ruthenium on alumina (Ru/Al$_2$O$_3$) effectively catalyzed the coupling reaction, and they also mentioned that a homogeneous ruthenium precursor is much less effective.[8] However, we understand they suggested that the homogeneous ruthenium catalyst system is potentially capable of promoting cross-coupling, therefore, we initiated a study to realize a practical homogeneous ruthenium-catalyzed Suzuki–Miyaura cross-coupling reaction. We now report the homogeneous ruthenium precatalyst [Ru(cod)(2-methylallyl)$_2$] catalyzed Suzuki–Miyaura reaction of aryl iodides and bromides with arylboronic acid.

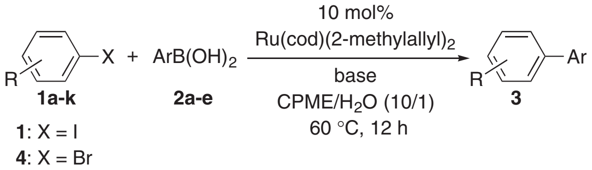
As shown in Table 1, a series of commercially available ruthenium precursors were screened for the reaction of 4-iodotoluene (**1a**) with phenylboronic acid (**2a**). The reaction using RuCl$_3$, Ru$_3$(CO)$_{12}$, and [RuCl$_2$(*p*-cymene)]$_2$ ([Ru-1]) resulted in less than 5% yield (Entries 1–3). The reaction with RuCl$_2$(cod) gave the desired biaryl compound in moderate yield (Entry 4). To our delight, Ru(cod)(2-methylallyl)$_2$ ([Ru-2]) effectively catalyzed the reaction at 60 °C in THF/H$_2$O solvent, and a 71% yield of **3a** was obtained (Entry 5). Optimization of the reaction conditions for the Ru(cod)(2-methylallyl)$_2$ catalyzed reaction of **1a** with **2a** revealed that the cyclopentyl methyl ether (CPME) is the best solvent for the reaction (Entries 5–7). The choice of base is also important in order to realize a high yield, and we concluded that NaO^{t}Bu or CsOH is a promising base to produce a good yield (Entries 7–10).

Table 1. Optimization of the ruthenium-catalyzed Suzuki–Miyaura coupling of **1a** with **2a**[a]



Entry	[Ru][b]	Base	Solvent	Yield /%[c]
1	RuCl$_3$•xH$_2$O	KOH	THF/H$_2$O (10/1)	0
2	Ru$_3$(CO)$_{12}$	KOH	THF/H$_2$O (10/1)	0
3	[Ru-1]	KOH	THF/H$_2$O (10/1)	5
4	[RuCl$_2$(cod)]$_n$	KOH	THF/H$_2$O (10/1)	56
5	[Ru-2]	KOH	THF/H$_2$O (10/1)	71
6	[Ru-2]	KOH	dioxane/H$_2$O (10/1)	11
7	[Ru-2]	KOH	CPME/H$_2$O (10/1)	79
8	[Ru-2]	NaOH	CPME/H$_2$O (10/1)	52
9	[Ru-2]	CsOH	CPME/H$_2$O (10/1)	86
10	[Ru-2]	NaO^{t}Bu	CPME/H$_2$O (10/1)	90

[a] All reactions were carried out with **1a** (0.35 mmol), **2a** (1.06 mmol), ruthenium (0.035 mmol for RuCl$_3$, RuCl$_2$(cod), and [Ru-2]. 0.018 mmol for [Ru-1]. 0.012 mmol for Ru$_3$(CO)$_{12}$), and base (0.88 mmol) in solvent (2.0 mL) under nitrogen at 60 °C for 12 h. [b] [Ru-1]: [RuCl$_2$(*p*-cymeme)]$_2$. [Ru-2]: Ru(cod)(2-methylallyl)$_2$. [c] Determined by HPLC analysis.



Scheme 1.

The coupling reactions of several aryl iodides **1a**–**1k** with arylboronic acids **2a**–**2e** were examined using an optimized catalytic system (Scheme 1).[9] Typically, the reaction was carried out as follows: 10 mol % Ru(cod)(2-methylallyl)$_2$, NaO*t*-Bu or CsOH (2.5 equiv), the aryl iodide and arylboronic acid (3 equiv) were mixed in CPME/H$_2$O (10/1) at 60 °C for 12 h. The results are summarized in Table 2. Aryl iodides **1b**–**1d** were coupled with phenylboronic acid (**2a**) to give the corresponding biaryls in good yields (88–95% isolated yield) (Entries 1–5). For the reaction of **1b** and **1c**, NaO*t*-Bu produced a better result than CsOH. On the other hand, CsOH realized higher yields than NaO*t*-Bu for the reactions of **1e**–**1h**, which contained electron-donating or electron-withdrawing groups at the *para*-position

Table 2. Ru(cod)(2-methylallyl)$_2$-catalyzed Suzuki–Miyaura coupling of aryl iodides **1a**–**1k**[a]

Entry	R	Ar	Base	Yield/%[b,c]
1	H (**1b**)	Ph (**2a**)	NaO^{t}Bu	89
2	H (**1b**)	Ph (**2a**)	CsOH	86
3	4-*t*-Bu (**1c**)	Ph (**2a**)	NaO^{t}Bu	95
4	4-*t*-Bu (**1c**)	Ph (**2a**)	CsOH	88
5	4-Ph (**1d**)	Ph (**2a**)	NaO^{t}Bu	88
6	4-OMe (**1e**)	Ph (**2a**)	NaO^{t}Bu	68
7	4-OMe (**1e**)	Ph (**2a**)	CsOH	75 (82)[d]
8	4-F (**1f**)	Ph (**2a**)	NaO^{t}Bu	23
9	4-F (**1f**)	Ph (**2a**)	CsOH	60
10	4-Br (**1g**)	Ph (**2a**)	CsOH	70
11	4-CO$_2$Me (**1h**)	Ph (**2a**)	CsOH	53
12	2-Me (**1i**)	Ph (**2a**)	NaO^{t}Bu	44
13	2-OMe (**1j**)	Ph (**2a**)	NaO^{t}Bu	72
14	4-Ac (**1k**)	Ph (**2a**)	NaO^{t}Bu	(8)[d]
15	4-Ac (**1k**)	Ph (**2a**)	CsOH	(8)[d]
16	4-Me (**1a**)	4-MeOC$_6$H$_4$ (**2b**)	NaO^{t}Bu	52
17	4-Me (**1a**)	4-FC$_6$H$_4$ (**2c**)	NaO^{t}Bu	55
18	4-Me (**1a**)	4-PhC$_6$H$_4$ (**2d**)	NaO^{t}Bu	54
19	4-Me (**1a**)	4-MeC$_6$H$_4$ (**2e**)	NaO^{t}Bu	59

[a]Reaction conditions: **1** (0.35 mmol), **2** (1.06 mmol), [Ru-2] (0.035 mmol), and base (0.88 mmol) in CPME/H$_2$O (10/1) (2.0 mL) under nitrogen at 60 °C for 12 h. [b]Isolated yield by silica gel column chromatography. [c]An average of at least two runs. [d]HPLC yields in parentheses.

(Entries 6–11). For example, when NaO*t*-Bu was used for the reaction of 1-fluoro-4-iodobenzene (**1f**), a biaryl was produced in only 23% yield, but when using CsOH, the yield increased to 60% (Entries 8 and 9). Furthermore, the reaction of 1-bromo-4-iodobenzene (**1g**) proceeded with perfect chemoselectivity, and we observed no trace amounts of *p*-terphenyl and 4-iodobiphenyl (Entry 10). The sterically hindered *ortho*-substituted aryl iodides, such as **1i** and **1j**, also produced the desired biaryls by the combination of Ru(cod)(2-methylallyl)$_2$ and NaO*t*-Bu (Entries 12 and 13). Unfortunately, the reactions of **1k** with **2a** resulted in very poor yields (Entries 14 and 15). We further examined the reactions with other arylboronic acids. Several *para*-substituted arylboronic acids **2b**–**2e** reacted with **1a** under the optimized reaction conditions, producing the desired products in moderate isolated yields (52–59%) (Entries 16–19).

We next attempted the Ru(cod)(2-methylallyl)$_2$ catalyzed Suzuki–Miyaura coupling of aryl bromides **4a**–**4d**. The results are summarized in Table 3. After a small modification[10] of the reaction conditions, the desired coupling reactions of the aryl bromides **4a**–**4d** with arylboronic acids **2a** and **2b** were effectively promoted by the Ru(cod)(2-methylallyl)$_2$ at 60 °C, and the corresponding biaryls were obtained in good yield.

In conclusion, we succeeded in demonstrating the Ru(cod)(2-methylallyl)$_2$-catalyzed Suzuki–Miyaura cross-coupling reaction of aryl iodides and aryl bromides.

Table 3. Ruthenium-catalyzed Suzuki–Miyaura coupling of aryl bromides **4a**–**4d**[a]

Entry	R	**2**	Base	Yield /%[b,c]
1	H (**4a**)	**2a**	NaO^{t}Bu	73
2	4-Me (**4b**)	**2a**	NaO^{t}Bu	88
3	4-Cl (**4c**)	**2a**	CsOH	79
4	4-OMe (**4d**)	**2a**	CsOH	86
5	4-Me (**4b**)	**2b**	NaO^{t}Bu	64

[a]Reaction conditions: **1** (0.35 mmol), **2** (1.06 mmol), [Ru-2] (0.035 mmol), and base (1.05 mmol) in CPME/H$_2$O (10/1) (2.0 mL) under nitrogen at 60 °C for 12 h. [b]Isolated yield by silica gel column chromatography. [c]An average of at least two runs.

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10 The amount of base was changed from 2.5 equiv to 3.0 equiv.