

Cobalt-catalyzed Cross-coupling Reactions of Aryl Bromides with Alkyl Grignard Reagents

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Aryl bromides react with primary alkyl Grignard reagents in the presence of *N,N,N',N'*-tetramethyl-1,3-propanediamine and catalytic amounts of cobalt(II) chloride and an N-heterocyclic carbene to yield the corresponding cross-coupling products in high yields.

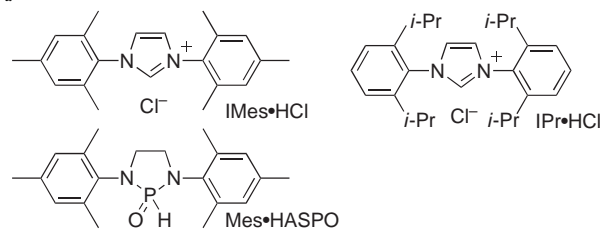
Palladium- and nickel-catalyzed cross-coupling reactions are powerful tools for carbon-carbon bond formation. Recently, cross-coupling reactions catalyzed by transition metals other than palladium and nickel have attracted increasing attention.¹ We have been interested in cobalt-catalyzed cross-coupling reactions.² To expand the scope of cobalt-catalyzed cross-coupling reactions, we report herein cobalt-catalyzed cross-coupling reactions of aryl bromides with alkyl Grignard reagents.

Treatment of *p*-bromoanisole (**1a**) with octylmagnesium chloride in the presence of catalytic amounts of cobalt(II) chloride and a precursor of an N-heterocyclic carbene (NHC), IMes·HCl,³ and 1.5 equiv of *N,N,N',N'*-tetramethyl-1,3-propanediamine (TMPDA) in diethyl ether afforded *p*-octylanisole (**2a**) in 91% yield (Table 1, Entry 1).⁴ In this reaction, IMes·HCl and TMPDA played key roles. In the absence of either IMes·HCl or TMPDA, no **2a** was obtained (Entries 2 and 8). The use of phosphine ligands also failed to afford **2a** (Entries 3–5).⁵ In contrast, the bulkier NHC precursor, IPr·HCl,³ served as an effective ligand in the cross-coupling reaction (Entry 6). Mes·HASPO⁶ did not work (Entry 7). The use of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) instead of TMPDA provided **2a** in good yield (Entry 9). No **2a** was obtained when 1,3-propanediamine, 2,2'-bipyridyl, and triethylamine were employed as an additive (Entries 10–12). The stoichiometric amount of TMPDA was essential: the reaction in the presence of 10 mol % of TMPDA led to no formation of **2a** (Entry 13). This result suggests that TMPDA coordinates to magnesium to promote the reaction. Diethyl ether was the best solvent. The reactions in THF, 1,4-dioxane, and 1,2-dimethoxyethane afforded **2a** in 60%, 57%, and 68% yields, respectively.

The scope of aryl bromides in the cobalt-catalyzed cross-coupling reaction is summarized in Table 2. Acetals (Entries 2 and 4) and silyl ether (Entry 3) were compatible under the reaction conditions. The coupling reaction occurred at the brominated carbon exclusively to yield **2f**, leaving the chloro moiety untouched (Entry 5). Dimethylamino-substituted aryl bromide **1g** underwent the coupling reaction smoothly (Entry 6). The reaction of **1h** having an electron-withdrawing trifluoromethyl group resulted in moderate yield (Entry 7). Not only *p*-bromoanisole (**1a**) but also *m*- and *o*-bromoanisole were efficiently converted to the corresponding products (Entries 8 and 9). Sterically demanding **1k** and **1n** were also octylated in good yields

Table 1. Cobalt-catalyzed reaction of *p*-bromoanisole (**1a**) with octylmagnesium chloride

Entry	Ligand ^a	Additive	2a /%	1a /%
1	IMes·HCl	TMPDA	91	0
2	None	TMPDA	0	85
3	PPh ₃	TMPDA	0	55
4	P(<i>c</i> -C ₆ H ₁₁) ₃	TMPDA	0	57
5	Pr-Bu ₃	TMPDA	0	77
6	IPr·HCl	TMPDA	75	0
7	Mes·HASPO	TMPDA	0	81
8	IMes·HCl	None	0	50
9	IMes·HCl	TMEDA	72	0
10	IMes·HCl	H ₂ N(CH ₂) ₃ NH ₂	0	83
11	IMes·HCl	Et ₃ N ^b	0	69
12	IMes·HCl	2,2'-Bipyridyl	0	79
13	IMes·HCl	TMPDA ^c	0	61

^a^b3.0 equiv. ^c10 mol %.

(Entries 10 and 13). However, the reaction of *o*-bromotrifluoromethylbenzene (**1m**) led to low yield, albeit with full conversion (Entry 12). *p*-Iodoanisole, generally the more reactive than **1a**, was converted to **2a** in only 28% yield, and a significant amount of anisole was obtained. The reaction of *p*-chloroanisole suffered from low conversion as well as formation of a trace amount of **2a**. The effect of the leaving groups is not clear at this stage.

Other primary alkylmagnesium chlorides participated in the cross-coupling reaction (Table 3). Hexyl- and butylmagnesium chloride reacted with **1a** to yield the corresponding *p*-alkylanisoles in good yields (Entries 1 and 2). However, attempted ethylation suffered from low yield, possibly because of the slower transmetalation (Entry 3). Octylmagnesium bromide was as reactive as the corresponding chloride (Entry 4). Methyl and allyl Grignard reagents did not react with **1a** (Entries 5 and 6). Methyl Grignard reagent might undergo transmetalation sluggishly. Allyl Grignard reagent could be too reactive, and the carbene ligand can be decomposed. Silyl-substituted methylmagnesium

Table 2. Scope of aryl bromides

Entry	1	R	2	Yield/%
1	1b	<i>p</i> -Me	2b	84
2	1c	<i>p</i> -CMe(OCH ₂ CH ₂ O)	2c	89
3	1d	<i>p</i> -OSi ^t BuMe ₂	2d	93
4	1e	<i>p</i> -OTHP	2e	93
5	1f	<i>p</i> -Cl	2f	69
6	1g	<i>p</i> -Me ₂ N	2g	88
7	1h	<i>p</i> -CF ₃	2h	56
8	1i	<i>m</i> -MeO	2i	83
9	1j	<i>o</i> -MeO	2j	85
10	1k	<i>o</i> -Me	2k	72
11	1l	H	2l	68
12	1m	<i>o</i> -CF ₃	2m	24
13	1n	(1-Naphthyl)	2n	64

Table 3. Scope of Grignard reagents

Entry	RMgX	3	Yield/%
1	<i>n</i> -C ₆ H ₁₃ MgCl	3a	78
2	<i>n</i> -C ₄ H ₉ MgCl	3b	66
3	EtMgCl	3c	11
4	<i>n</i> -C ₈ H ₁₇ MgBr	3d (=2a)	87
5	MeMgI	3e	0 ^a
6	CH ₂ =CHCH ₂ MgBr	3f	0 ^b
7	Me ₃ SiCH ₂ MgCl	3g	72 ^c
8	<i>i</i> -PrMgCl	3h	9 (34 ^d)
9	<i>c</i> -C ₆ H ₁₁ MgCl	3i	32
10	CH ₂ =CH(CH ₂) ₉ MgCl	3j'	(75 ^e)
11	PhMgBr	3k	21

^a90% of **1a** was recovered. ^b82% of **1a** was recovered. ^cPerformed at reflux for 16 h. ^dYield of *p*-propylanisole (**3h'**). ^eYield of *p*-9-undecylanisole (**3j'**).

reagent reacted in boiling ether (Entry 7). The reaction of **1a** with isopropylmagnesium chloride was sluggish, providing *p*-isopropylanisole (**3h**) in only 9% yield (Entry 8). As a byproduct, aside from anisole, *p*-propylanisole (**3h'**) was obtained in 34% yield. It is probable that isomerization of isopropylcobalt to *n*-propylcobalt would take place through β -hydride elimination followed by the *anti*-Markovnikov hydrocobaltation.⁷ The reaction of cyclohexylmagnesium chloride thus afforded **3i** in 32% yield as the sole alkylated product (Entry 9). Under the reaction conditions, isomerization of terminal to internal olefin occurred (Entry 10).⁸ Unfortunately, the reaction with phenylmagnesium bromide was sluggish, affording a large amount of anisole (Entry 11).

Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday.

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4 **Typical experimental procedure:** Anhydrous cobalt(II) chloride (3.2 mg, 0.025 mmol) and IMes·HCl (10 mg, 0.030 mmol) were placed in a 20-mL reaction flask and were heated with a hair dryer in vacuo for 2 min. After the color of the cobalt salt became blue, substrate **1a** (94 mg, 0.50 mmol) in anhydrous diethyl ether (1.0 mL) and TMPDA (0.13 mL, 0.75 mmol) were added under argon. Octylmagnesium chloride (0.75 mL, 1.0 M ethereal solution, 0.75 mmol) was then added at one push at 25 °C under argon. The resulting mixture was stirred for 1 h at 25 °C. The reaction mixture was poured into a saturated ammonium chloride solution. The product was extracted with ethyl acetate (20 mL \times 2). The combined organic layer was passed through a pad of Florisil, dried over Na₂SO₄, and concentrated to provide an oil. Purification by silica gel column chromatography (hexane/ethyl acetate = 20:1) provided **2a** (100 mg, 0.45 mmol) in 91% isolated yield. Product **2a** showed the identical spectra in the literature: T. Brenstrum, D. A. Gerristma, G. M. Adjabeng, C. S. Frampton, J. Britten, A. J. Robertson, J. McNulty, A. Capretta, *J. Org. Chem.* **2004**, *69*, 7635.

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