

## Direct Cobalt-Catalyzed Cross-Coupling Between Aryl and Alkyl Halides

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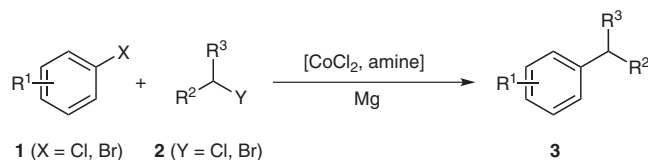
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**Abstract:** An operationally simple cross-coupling reaction between aryl halides and alkyl halides with high selectivity has been developed. The underlying domino process utilizes  $\text{CoCl}_2/\text{Me}_4\text{-DACH}$  as a catalyst system. The methodology exhibits high sustainability as it obviates the need for the pre-formation and handling of stoichiometric amounts of hazardous Grignard compounds.

**Keywords:** cobalt, cross-coupling, aryl halides, domino reactions

Transition-metal catalyzed cross-coupling reactions have matured to play a commanding role as carbon–carbon bond forming reactions in organic synthesis.<sup>1</sup> Especially, palladium and nickel complexes have exhibited high catalytic activity for a wide range of substrates and, thus, prompted several industrial applications in the manufacture of pharmaceuticals and materials.<sup>2</sup> However, the high costs<sup>3</sup> of palladium catalysts have constricted a more general use of such protocols in large scale productions, while nickel catalysts are highly controversial due to their allergenic and cancerogenic toxicity.<sup>4</sup> Furthermore, both metals usually require the presence of air-sensitive phosphine ligands of high molecular weight. The nucleophilic component in most cross-coupling protocols is a moisture-sensitive organometallic species ( $M = \text{Mg}, \text{B}, \text{Zn}, \text{Sn}$ ) that must be prepared from organohalides in a separate, upstream operation. From an economic standpoint, there is clearly a demand for more efficient cross-coupling methodologies that obviate the need for complex and toxic catalyst systems as well as sensitive and hazardous reactants.<sup>5</sup>

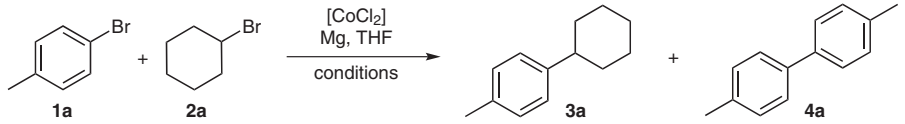
Recent developments of cobalt-catalyzed cross-coupling protocols have addressed some of these sustainability issues. Oshima et al.<sup>6</sup> and Cahiez et al.<sup>7</sup> have reported on highly active cobalt/amine catalyst systems that facilitate cross-coupling between various organohalides and Grignard reagents under mild conditions.<sup>8</sup> However, we especially wanted to devise a protocol that obviates the need for the pre-formation and handling of stoichiometric Grignard reagents. In view of industrial applications, the employment of highly sensitive Grignard compounds still imposes stringent and costly safety arrangements.<sup>9</sup> Here we report on an operationally simple one-pot protocol for the *direct* cobalt-catalyzed cross-coupling of aryl halides (**1**) and alkyl halides (**2**) to give substituted arenes (**3**) (Scheme 1).



**Scheme 1** Direct cobalt-catalyzed aryl–alkyl cross-coupling

Metal salts have been known to promote the formation of Grignard species from the reaction of magnesium and an organohalide.<sup>10</sup> A sequential combination with a transition-metal catalyzed cross-coupling reaction would allow a domino process to transform two electrophilic organohalides into their cross-coupling product. Based on this concept, Gosmini et al. have recently reported on direct cross-coupling reactions between  $\text{sp}^2$ -hybridized organohalides.<sup>11</sup> We set out to investigate the potential of various metal salts to act as catalysts for the direct  $\text{sp}^2$ – $\text{sp}^3$  cross-coupling of an aryl halide ( $\text{sp}^2$ ) with an alkyl halide ( $\text{sp}^3$ ) in the presence of stoichiometric amounts of magnesium as the reductant. Although electronically differentiated,<sup>12</sup> metathesis [from Alkyl– $\text{MgX}$  (kinetic) to  $\text{ArMgX}$  (thermodynamic)], competitive biaryl coupling,  $\beta$ -hydride elimination, or hydrodehalogenation could reduce the selectivity for the cross-coupling product. Gratifyingly, we discovered that  $\text{CoCl}_2$  displays good activity and selectivity in such domino magnesiation–cross-coupling reactions (Scheme 1), complementing our recent iron-catalyzed procedure.<sup>13</sup>

Table 1 shows selected optimization experiments for the model reaction of *p*-tolyl bromide (**1a**) with cyclohexyl bromide (**2a**) to give 1-cyclohexyl-4-methylbenzene (**3a**).<sup>14</sup> The reaction seemed to be highly dependent on the structure of the amine ligand. Generally, monodentate amines exhibited poor selectivity, while pyridine gave moderate cross-coupling selectivity. Biaryl formation was dominant with 1,10-phenanthroline. The employment of TMEDA and  $\text{Me}_4\text{-DACH}$  resulted in comparable reactivities, with the latter being more selective for the cross-coupling product and giving less biaryl. The generation of ate complexes by addition of LiI did not lead to a superior catalyst system.<sup>7c</sup> Unlike its iron counterpart,<sup>13</sup> the cobalt-catalyzed reaction requires only catalytic amounts of ligand. With catalytic  $\text{FeCl}_3$ , the presence of stoichiometric amounts of TMEDA assured a slow formation of the intermediate Grignard species. Our observation that the initiating Grignard formation is much slower in the presence of  $\text{CoCl}_2$  thus obviates the need for stoichiometric amine addition.<sup>14,15</sup> The optimized set of conditions in-

**Table 1** Selected Optimization Experiments of the Model Reaction<sup>a</sup>


Temp (°C)	Ligand (mol%) <sup>a</sup>	CoCl <sub>2</sub> (mol%)	1a/2a	Yield 3a (4a) (%) <sup>b</sup>
0	–	5	1:1	6 (15)
	Et <sub>3</sub> N (5)			3 (22)
	DABCO (5)			23 (18)
	py (5)			41 (17)
	phen (5)			3 (50)
	TMEDA (5)			53 (12)
	Me <sub>4</sub> -DACH (5)			57 (5)
0	(1)	1	1:1	5
	Me <sub>4</sub> -DACH (2.5)	2.5		62
	(10)	10		55
–10	Me <sub>4</sub> -DACH (10)	5	1:1	2
0				69
10				56
<b>0</b>	<b>Me<sub>4</sub>-DACH (10)</b>	<b>5</b>	1:1.5	45
			1:1.2	64
			<b>1.2:1</b>	<b>73</b>
			1.5:1	58
<b>0</b>	<b>Me<sub>4</sub>-DACH (10)</b>	<b>5</b>	1:1	54 <sup>c</sup>
0	TMEDA (20)	5	1.2:1	56 (14) <sup>d</sup>

<sup>a</sup> DABCO = 1,4-diazabicyclo[2.2.2]octane, py = pyridine, phen = 1,10-phenanthroline, TMEDA = *N,N,N',N'*-tetramethylethylenediamine, Me<sub>4</sub>-DACH = *N,N,N',N'*-tetramethyl-1,2-diaminocyclohexane.

<sup>b</sup> GC yields.

<sup>c</sup> Mg powder (1.2 equiv).

<sup>d</sup> LiI (10 mol%) added.<sup>7c</sup>

volve reaction at 0 °C in THF solution with 5 mol% CoCl<sub>2</sub>, 10 mol% Me<sub>4</sub>-DACH and stoichiometric amounts of magnesium turnings. A slight excess of the aryl bromide (1.2 equiv) proved beneficial.<sup>14</sup>

Table 2 shows a series of fifteen aryl halides and one alkyl bromide that were subjected to direct cross-coupling conditions in the presence of alkyl halides without resorting to a laborious and costly pre-formation of the sensitive Grignard compounds. Bromoarenes with alkyl, alkoxy, amino, and fluoro substituents showed good reactivity with both primary and secondary alkyl bromides. In all cases, formation of the homocoupling products (biaryl, bialkyl) was marginal (<15%). Isomerization of primary alkyl bromides to the more stable secondary isomer was not observed. With fluoro-substituted aryl bromides (see **3k,l**), activation of the Ar–F bond was observed in minor quantities (<10%).<sup>16</sup> β-Bromostyrene, as a vinylic substrate, exhibited moderate selectivity (**3n**). Low conversions (<5%) were attained with ester and cyano moieties in the arene or alkane component. Here, consumption of the magnesium was largely inhibited, probably due to surficial deactivation.<sup>17</sup> The employment of alkyl chlorides and aryl chlorides resulted in low conversions.

We postulate a mechanism based upon the 17e<sup>–</sup> biarylcobalt(0) catalyst species **I** that can be formed via an initial reduction of the employed CoCl<sub>2</sub> with arylmagnesium ha-

lide and collateral biaryl formation (Scheme 2).<sup>6c,8d,18</sup> Reactions with pre-formed Grignard species suggest the operation of an ArMgBr–RBr coupling.<sup>18b</sup> The oxidative addition is likely to adopt a single electron transfer (SET) pathway via carbon-centered free radical R<sup>•</sup> and complex **II**. The 17e<sup>–</sup> species **III** undergoes reductive elimination of the cross-coupling product and, upon further transmetalation (from ArMgBr), regenerates catalyst **I**. The rather slow magnesiation of ArBr at 0 °C impedes the accumulation of ArMgX and hence reduces the amount of homobiaryl formation (Ar<sub>2</sub>). Consistently, quenching experiments have documented a constantly low concentration of ArMgX over the course of the reaction (steady-state).<sup>14</sup>

We also performed an asymmetric reaction in the presence of enantiopure (*R,R*)-Me<sub>4</sub>-DACH as ligand (Scheme 3).<sup>14</sup> Employment of racemic 3-bromobutylbenzene<sup>19</sup> and 2-bromoanisole gave the cross-coupling product **3q** with an enantiomeric excess of 20%.<sup>20</sup>

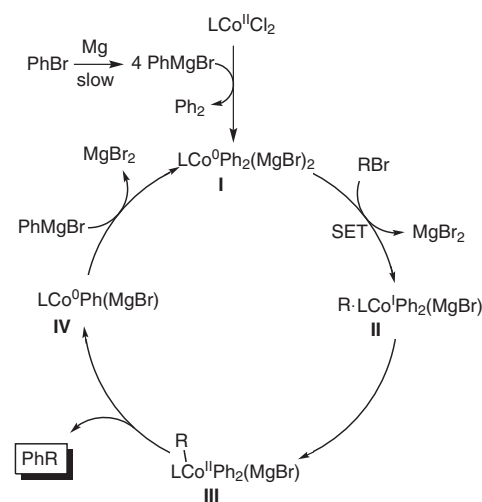
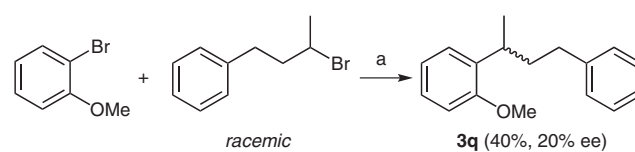
In summary, we have developed a new protocol for the direct cross-coupling of aryl bromides and alkyl bromides under mild conditions. The reaction is highly sustainable as it obviates the pre-formation and handling of stoichiometric amounts of sensitive Grignard compounds. Despite direct employment of two electrophilic organohalides, the one-pot methodology leads to unexpectedly high selectivity for the cross-coupling product.

**Table 2** Substrate Scope<sup>14</sup>

X	Y	Product	Yield of <b>3</b> (%)
Br	Br		69
Cl	Br		42
Br	Cl		8
Br	Br		79
Cl	Br		9
Br	Br		85
Br	Br		68
Br	Br		64
Br	Br		65
Br	Br		76
Br	Br		68
Br	Br		52
Br	Br		75
Br	Br		62
Br	Br		59

**Table 2** Substrate Scope (continued)<sup>14</sup>

X	Y	Product	Yield of <b>3</b> (%)
Br	Br		53
Br	Br		39
Br	Br		<5
Br	Br		<5

**Scheme 2** Postulated mechanism**Scheme 3** Asymmetric cross-coupling: Reaction conditions: (a)  $\text{CoCl}_2$  (5 mol%), (*R,R*)- $\text{Me}_4\text{-DACH}$  (10 mol%), Mg (1.2 equiv), THF, 3 h, 0 °C.

**Supporting Information** for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synlett>.

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- (12) (a) C(sp<sup>3</sup>)–Br and C(sp<sup>2</sup>)–Br bond strengths at 298 K: EtBr (68 kcal mol<sup>–1</sup>); PhBr (80 kcal mol<sup>–1</sup>). Taken from: *CRC Handbook of Chemistry and Physics*; Weast, R. C.; Astle, M. J., Eds.; CRC Press: Boca Raton, **1981**. (b) The single electron transfer (SET) into the π\* orbital of the ArBr is reversible, and the π\*–σ\* transition required for dissociation of the C–Br bond is slow.
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- (14) (a) For further details, see Supporting Information. (b) General procedure: A 10 mL flask was placed in a water bath (r.t.), charged with Mg turnings (63 mg, 2.6 mmol), fitted with a rubber septum, and purged with argon (1 min). A solution of CoCl<sub>2</sub> (13 mg, 0.1 mmol, 5 mol%) and Me<sub>4</sub>-DACH (35 μL, 0.2 mmol, 10 mol%) in anhydrous THF (4 mL) was added via syringe. The mixture was stirred at r.t. for 15 min, then the reaction was cooled to 0 °C and aryl bromide (2.4 mmol) and alkyl bromide (2.0 mmol) were added. After 6 h at 0 °C, the reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (5 mL) and aqueous HCl (10%, 2 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuo, and subjected to flash chromatography (SiO<sub>2</sub>; cyclohexane–ethyl acetate).
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- (20) Reactions with (–)-sparteine and quinine as chiral ligands instead of Me<sub>4</sub>-DACH each afforded **3q** in <7% yield (ee was not determined).

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