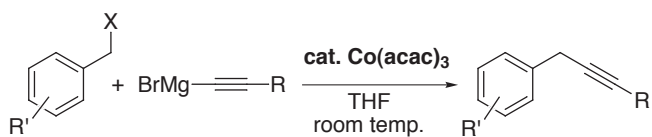


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Cobalt-catalyzed benzyl-alkynyl coupling

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Benzylic halides coupled with 1-alkynyl Grignard reagents in the presence of Co-catalyst.

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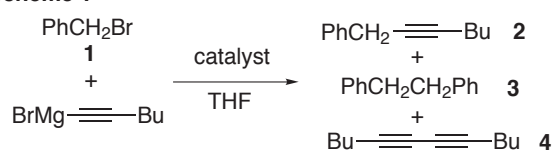
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Abstract—Benzylic halides coupled with 1-alkynylmagnesium halides in the presence of a catalytic amount of $\text{Co}(\text{acac})_3$ to provide 1-aryl-2-alkynes in moderate to good yield. © 2011 Elsevier Science. All rights reserved

Reactions mediated or catalyzed by organometallic compounds have enabled efficient carbon-carbon bond formations between a variety of nucleophiles and electrophiles.¹ However, it is somewhat surprising that coupling between benzylic sp^3 electrophiles (ArCH_2X) and alkynyl sp carbanion ($\text{RC}\equiv\text{C}^-$) has not been necessarily easy and has been limited to a few methods: the reaction of alkyllithium compounds in the presence of DMPU,² the CuX -catalyzed reaction with $\text{RC}\equiv\text{CMgX}$ or $\text{RC}\equiv\text{CLi}$ under high concentration and/or high temperature conditions,^{3,4} Pd-catalyzed coupling with $(\text{RC}\equiv\text{C})_3\text{In}^4$ or $\text{RC}\equiv\text{CZnBr}^5$ and several reactions providing such coupling compounds as a side product have been reported. Herein described is a novel method for benzyl-alkynyl coupling which is catalyzed by cobalt compounds under mild conditions.^{6,7}

Scheme 1



First, we surveyed the possibility of several metallic compounds as a catalyst for benzyl-alkynyl coupling (Scheme 1). Thus, in the presence of 2 mol% of a metallic compound benzyl bromide (**1**) (1.5 mmol) was treated with 1-hexynylmagnesium bromide (2 mmol), prepared from 1-hexyne and EtMgBr , in THF for 2 h at 0 °C to room temperature. The results summarized in Table 1 revealed that $\text{Co}(\text{acac})_3$ [acac = acetylacetonato] could catalyze the coupling to give 39% of 1-phenyl-2-heptyne (**2**) with

production of a small amount of dibenzyl (**3**) and diyne **4** as by-products. The reaction with other metal complexes gave **3** and/or **4** but not the desired **2** at all.

Table 1^a

catalyst (2 mol%)	2	3 ^b	4 ^c	recovered 1
$\text{PdCl}_2(\text{PPh}_3)_2$	trace	4%	trace	96%
CuCN	trace	trace	trace	98%
$\text{Ni}(\text{acac})_2$	0%	6%	7%	94%
$\text{Co}(\text{acac})_3$	39%	2%	5%	59%
$\text{Fe}(\text{acac})_3^d$	0%	10%	15%	90%
$(\text{AcO})_2\text{Mn}(\text{H}_2\text{O})_4$	trace	trace	trace	99%

^aAfter addition of water to the reaction mixture, the organic phase was subjected to GC analysis using an internal standard. ^bBased on consumption of **1** for formation of **3**. ^cBased on 1-hexyne used. ^dThe reaction was performed overnight.

With the results in hand, we investigated the reaction of Scheme 1 with various Co-catalyst precursors to find the better conditions for the production of **2** and the results are summarized in Table 2. CoCl_2 and $\text{CpCo}(\text{CO})_2$ as well as $\text{Co}(\text{acac})_3$ could exhibit similar catalytic activity (entries 1, 7 and 11). Regarding the catalysis with $\text{Co}(\text{acac})_3$, elongation of reaction time (entry 2), increase of temperature (entry 3) or a two-shot addition of the Grignard reagent (entry 4) improved the yield of **2**. A bidentate ligand such as dppp, dppb and bipyridinyl inhibited the formation of **2**. Addition of a monodentate ligand such as

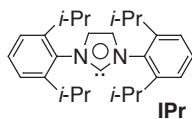
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imidazolium carbene⁸ **IPr** (to CoCl₂) and PPh₃ (to CpCo(CO)₂) had little effect (entries 9,10 and 12). The reaction was specific for benzylic halides: the reaction of *n*-BuC≡CMgBr with other organic halides such as cyclohexyl bromide, allyl bromide and PhCH₂CH₂Br did not proceed (data not shown).

Table 2^a

entry	catalyst (2 mol%)	conditions	yield, % ^b			
			2	3^c	4^d	1
1	Co(acac) ₃	r.t., 2 h	38	2	7	60
2	"	r.t., 12 h	76	24	9	0
3	"	40 °C, 2 h	53	6	11	40
4	"	r.t., 4 h ^e	70	18	18	12
5	Co(acac) ₃ + dppp ^f	r.t., 2 h	4	28	14	68
6	Co(acac) ₃ + bipyridinyl ^g	r.t., 2 h	8	14	7	78
7	CoCl ₂	r.t., 2 h	31	12	12	57
8	CoCl ₂ + dppb ^h	r.t., 2 h	0	18	14	82
9	CoCl ₂ + IPr	r.t., 21 h	63	6	10	31
10	"	45 °C, 21 h	60	16	7	24
11	CpCo(CO) ₂	r.t., 24 h	34	12	11	54
12	CpCo(CO) ₂ + 2PPh ₃	r.t., 24 h	33	8	24	59

^aTo a mixture of **1** (1.0 mmol) and catalyst precursor (2 mol%) in THF (2 mL) was added a solution of *n*-BuC≡CMgBr (1.5 mmol) in THF (5 mL) at 0 °C and the mixture was stirred under given conditions. ^bDetermined by GC analysis using an internal standard. ^cBased on consumption of **1** for formation of **3**. ^dBased on 1-hexyne used. ^eThe reaction was started with 1.0 equiv of *n*-BuC≡CMgBr. After 2h, an additional 0.8 equiv of *n*-BuC≡CMgBr was added and the mixture was stirred for an additional 2 h. ^f2 mol% of Co(acac)₃ + 3 mol% of dppp [1,3-bis(diphenylphosphino)propane]. ^g2,2'-dipyridyl. ^h2 mol% of CoCl₂ + 3 mol% of dppb [1,4-bis(diphenylphosphino)butane].



The better reaction conditions thus found (entry 2 or 4 in Table 2) were subsequently utilized for the benzyl-alkynyl coupling reaction of a series of representative benzylic halides depicted in Table 3.⁹ As revealed from the table, the reaction with Me₃SiC≡CMgBr afforded the corresponding benzyl-alkynyl coupling product in good to excellent yield, except for the reaction of 1-bromo-2-chloromethylbenzene (entry 6). Whereas the coupling of benzyl bromide with *n*-BuC≡CMgBr proceeded in a synthetically useful yield, the reaction with other benzylic halides gave poor yield. The substituent of the substrate halides affected the reaction electronically (entries 2-5) but, interestingly, opposite trends were observed for the reactions with Me₃SiC≡CMgBr and *n*-BuC≡CMgBr.

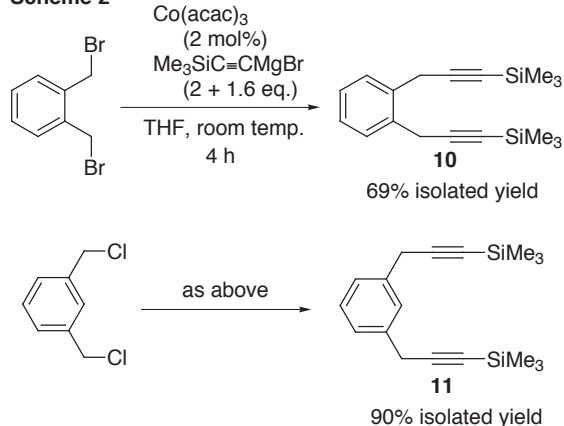
Table 3^a

entry	ArCH ₂ X	isolated yield, % ^b	
		R = <i>n</i> -Bu	R = SiMe ₃
1		2a : 70	2b : 71
2		2a : (21)	2b : 82
3		5a : (14)	5b : 98
4		6a : (25)	6b : 80
5		7a : (38)	7b : 63
6		8a : (31)	8b : (40)
7		— ^c	9a : 93

^aThe reaction was performed under the conditions indicated in entry 2 or 4 of Table 2.

^bYield in the parentheses was determined by GC analysis. ^cNot carried out.

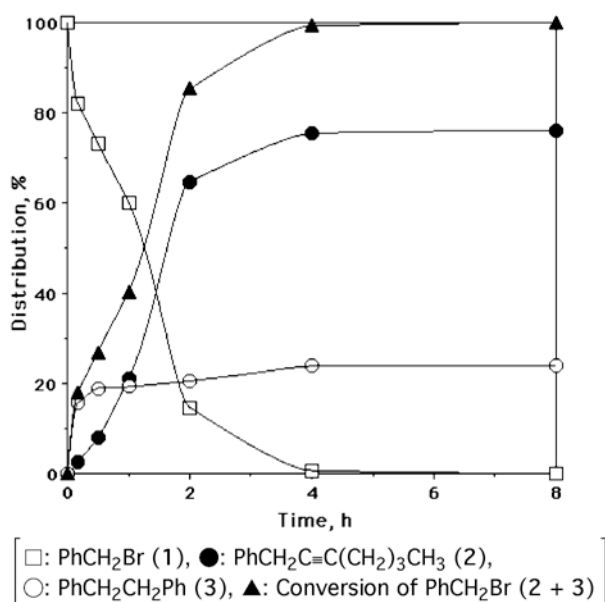
Scheme 2 illustrates additional successful examples which are double-alkynylation of dibromide or dichloride. Thus, *o*- or *m*-di(halomethyl)benzene could smoothly couple with Me₃SiC≡CMgBr in the presence of 2 mol% of Co(acac)₃ at room temperature to provide di-propargylated benzenes **10** and **11** in good yield, respectively.

Scheme 2^a

^aThe reactions were performed under the conditions indicated in entry 4 of Table 2.

To discuss the reaction mechanism, we investigated the time course of the present coupling reaction, which was traced by GC analyses. Thus, PhCH₂Br was treated with *n*-BuC≡CMgBr (1.5 equiv) in the presence of 2 mol% of Co(acac)₃ and the time-course of the distribution of **1**, **2** and **3** is summarized in Figure 1. As revealed from the figure, PhCH₂CH₂Ph (**3**) was rapidly produced in the beginning 0.5~1 h and then it increased no longer. In the period, the production of **2** was relatively slow and, after this initiation time, the reaction rate of formation of **2** increased and yield of **2** reached >70% within 4 h. Although this switch of the reaction course from formation of **3** to production of **2** at around 0.5~1 h of reaction time is currently difficult to explain, probably an active catalyst for the formation of **2** would gradually be generated *via* the reaction(s) affording **3** in the beginning 0.5~1 h. Since CpCo(CO)₂ could catalyze the coupling similarly to Co(acac)₃- and CoCl₂-based catalysis (entries 11 and 12 in Table 1), it is likely that the reaction may involve the Co(I) species. Therefore, Co(II) and Co(III) complexes may initially be reduced by the reaction with R-C≡CMgBr through the formation of di- and/or tri-alkynyl cobalt complex(es) and the following elimination of diyne **4**. Then, the reaction may proceed *via* the oxidative addition¹⁰ with benzylic halide and the following substitution with the alkynyl anion and the reductive elimination of the coupling compound to give a Co(I) compound(s) again.

Figure 1 Time course of coupling reaction of PhCH₂Br with *n*-BuC≡CMgBr



In summary, we have demonstrated that cobalt complexes such as Co(acac)₃ could catalyze coupling of benzylic halides with alkynyl Grignard reagents under mild reaction conditions. Although generality of the reaction is not necessarily high at this time, the several cases presented here are synthetically useful and further study for generalization of the reaction is under way in our laboratory.

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9. Typical procedure: To a mixture of Co(acac)₃ (7.13 mg, 0.02 mmol) and 4-methylbenzyl chloride (140 mg, 1.0 mmol) in THF (0.5 mL) was added dropwise a solution of Me₃SiC≡CMgBr (1.5 mmol) in THF (3.5 mL) at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred for 10 h. After addition of sat. aq. NH₄Cl, usual extractive work-up gave a residue which was purified by column chromatography on silica gel to provide **6b** (162 mg) in 80% yield.
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