

Co-Catalyzed Cross-Coupling of Alkyl Halides with Tertiary Alkyl Grignard Reagents Using a 1,3-Butadiene Additive

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S Supporting Information

ABSTRACT: The cobalt-catalyzed cross-coupling of alkyl (pseudo)halides with alkyl Grignard reagents in the presence of 1,3-butadiene as a ligand precursor and LiI is described. Sterically congested quaternary carbon centers could be constructed by using tertiary alkyl Grignard reagents. This reaction proceeds via an ionic mechanism with inversion of stereochemistry at the reacting site of the alkyl halide and is compatible with various functional groups. The use of both 1,3-butadiene and LiI was essential for achieving high yields and high selectivities.


Transition-metal-catalyzed cross-coupling is one of the most fundamental routes to the construction of carbon skeletons. In the past decade, various efficient catalytic systems have been developed for cross-coupling at sp³-hybridized carbon centers.¹ Although cross-coupling at the tertiary alkyl carbons is a promising route for constructing quaternary carbon centers, only limited examples are available using congested tertiary alkyl nucleophiles,^{2–4} and the reactions often result in low yields due to steric hindrance, facile β-hydrogen elimination, and ease of isomerization of tertiary alkylmetals.⁵ In pioneering work by Kumada et al., the cross-coupling of *t*-BuMgCl with β-bromostyrene catalyzed by a nickel complex bearing a dppf ligand was demonstrated to proceed efficiently, although undesired isomerization of the tertiary alkyl group as well as the hydrodehalogenation of β-bromostyrene occurred concomitantly.² After this discovery, several examples of the cross-coupling of sp²-hybridized organo halides with tertiary alkylmetal reagents using various transition metals were reported,³ however isomerization of alkylmetal reagents as well as β-hydrogen elimination remains a serious problem to be controlled.^{3g,h} In contrast to the progress achieved using sp²-hybridized organic halides, to the best of our knowledge, the catalytic cross-coupling of alkyl halides with tertiary alkylmetals has been attained only by Cu catalysts employing *tert*-butyl Grignard reagent and continues to be a challenging issue in organic synthesis.⁴


Previously we reported on the development of the Ni-, Pd-, and Cu-catalyzed cross-coupling reaction of alkyl (pseudo)-halides with alkyl Grignard reagents utilizing unsaturated hydrocarbon additives.^{4d,e,6} Here we report a Co/LiI/1,3-butadiene catalytic system as a new route to alkyl–alkyl cross-coupling reactions,^{7,8} in which alkyl halides are successfully

coupled with tertiary alkyl Grignard reagents to afford branched alkanes including quaternary carbon centers.

When 2 mol % of CoCl₂ was added to a THF solution of *n*-OctBr, *t*-BuMgCl (1.2 equiv), 1,3-butadiene (2 equiv), and LiI (4 mol %) at –78 °C, followed by stirring at 50 °C for 5 h, the cross-coupling product **3a** was obtained in 84% yield without any detectable byproducts arising from the isomerization of the *t*-Bu group (Table 1, entry 1).⁹ In contrast, the use of NiCl₂ and

Table 1. Cross-Coupling of *n*-OctBr and *t*-BuMgCl^a

entry	<i>n</i> -Oct–Br + <i>t</i> -Bu–MgCl		2 mol % MCl ₂ 4 mol % additive 2 equiv 		
	1	2a (1.2 equiv)	THF, T (°C), 5 h	<i>n</i> -Oct– <i>t</i> -Bu 3a	Octane + Octenes 4 5
	MCl ₂	T (°C)	additive	3a (%) ^b	4 (%) ^b 5 (%) ^b
1	CoCl ₂	50	LiI	84	1 1
2	NiCl ₂	50	LiI	7	<1 1
3	PdCl ₂	50	LiI	<1	11 3
4 ^c	CuCl ₂	50	LiI	19	2 <1
5	CoCl ₂	rt	LiI	nd	6 1
6	CoCl ₂	0	LiI	nd	2 <1
7	CoCl ₂	50	none	18	4 <1
8	CoCl ₂	50	LiCl	27	7 2
9	CoCl ₂	50	LiBr	31	10 5
10	CoCl ₂	50	MgI ₂	60	3 2
11 ^d	CoCl ₂	50	LiI	<1	16 <1
12 ^e	CoCl ₂	50	LiI	92	<1 1

^aReaction conditions: *n*-OctBr (1 mmol), *t*-BuMgCl (in THF, 1.2 mmol), MCl₂ (2 mol %), additive (4 mol %), 1,3-butadiene (2 equiv) at 50 °C for 5 h. ^bDetermined by GC analysis. ^c58% of **6** was obtained. ^dIn the absence of 1,3-butadiene. ^eIsoprene was used instead of 1,3-butadiene. **6**: *n*-Oct 

PdCl₂, which are efficient catalysts for the coupling reaction of alkyl halides with primary and secondary alkyl Grignard reagents,^{6c} resulted in the formation of **3a** in poor yields (entries 2 and 3). Under the present conditions using CuCl₂, **3a** was obtained only in 19% yield accompanied by a 58% yield of 2,2-dimethyl-4-tetradecene (**6**), which was formed by the carbomagnesiation of *t*-BuMgCl to 1,3-butadiene and subsequent cross-coupling.^{9,10} We next optimized the reaction conditions using CoCl₂ as a catalyst. When the reaction temperature was decreased to room temperature or 0 °C, no










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reaction took place. Both LiI and 1,3-butadiene played important roles in achieving efficient cross-coupling. For example, the reduction of *n*-OctBr took place in the absence of 1,3-butadiene (entry 11).¹¹ When LiCl or LiBr was used instead of LiI, the yield of the coupling product decreased to 27% and 31%, respectively (entries 8 and 9), though the mechanistic roles of LiI in this catalytic system are not clear at this time.^{12,13} The use of MgI₂ also resulted in an improvement, but only moderately, with **3a** being produced in 60% yield (entry 10). The addition of N or P based ligands failed to improve the reaction and sometimes resulted in inhibition.^{11,13} We conducted further investigations on the Co-catalyzed cross-coupling using various unsaturated hydrocarbon additives including substituted dienes, styrene, and phenylpropyne¹³ and found isoprene to be the best additive (92%, entry 12).

Under optimized reaction conditions, we investigated the scope and limitations of Grignard reagents (Table 2). The

Table 2. Co-Catalyzed Cross-Coupling of *n*-OctBr with Various Grignard Reagents





















<i>n</i> -Oct-Br 1	R-MgX 2 (1.2 equiv)	yield (%) ^a	entry	R-MgX 2	yield (%) ^a
1 ^b		2b 91	6	<i>s</i> -BuMgCl	2g 93
2 ^b		2c 85(82)	7 ^c		2g 80
3 ^b		2d 81(80)	8		2h 89(83)
4		82(80)	9 ^b		2i 90(86)
5		2e <1	10	<i>n</i> -BuMgCl	2j 92
		2f <1	11	<i>i</i> -BuMgCl	2k 77
			12	MeMgCl	2l 4
			13	PhMgBr	2m <1

^aDetermined by GC. Isolation yields are in parentheses. ^b*n*-DecBr instead of *n*-OctBr. ^c0.1 mol % of CoCl₂ was used.

reaction of *n*-OctBr with acyclic tertiary alkyl Grignard reagents afforded the cross-coupling products in high yields. In all cases, no isomerization was observed (entries 1–4). No reaction took place when an adamantyl Grignard reagent was used (entry 5). Acyclic and cyclic secondary alkyl Grignard reagents smoothly coupled with *n*-OctBr in 89–93% yields (entries 6, 8, 9). When the catalyst loading was reduced to 0.1 mol %, **3g** was obtained in 80% yield, where the TON reached 800 (entry 7). Primary alkyl Grignard reagents were also applicable to the present catalytic system, giving good yields of products (entries 10, 11), however the use of MeMgCl and PhMgBr that contain no β -hydrogens resulted in very poor results (entries 12 and 13, *vide infra*). Substituents at the β -position of the Grignard reagent had a slight effect on the yield (entry 11).

Results for the cross-coupling of various alkyl electrophiles are shown in Table 3. Alkyl fluorides, which have the strongest single bond (C–F) in organic compounds,¹⁴ coupled with *t*-BuMgCl to give **3a** in a moderate yield. Although the reaction of *n*-OctCl was sluggish and only a 2% yield of coupling product was obtained, octyl iodide and tosylate reacted with *t*-BuMgCl to good yields. Alkyl bromides carrying an arene, olefin, alkyne, trifluoromethyl, THP, or silyl ether unit coupled with *t*-BuMgCl in good to excellent yields (entries **8a–f**). Amide, *N*-Boc and *N*-tosyl protecting groups were also well tolerated (entries **8g–m**), where a secondary alkyl Grignard reagent gave slightly better results than a tertiary one (*vide*

Table 3. Co-Catalyzed Alkylation of Various Alkyl Halides^a

Alkyl-Br 7	R ¹ R ² R ³	2 mol % CoCl ₂ , 4 mol % Lil 2 equiv isoprene	THF, 50 °C, 5 h	Alkyl 3 or 8
<i>n</i> -Oct	X = F	62% (24 h)		3a from <i>n</i> -Oct-X
	X = Cl	2%		
	X = I	71%		
	X = OTs	58%		
		95%		8a : 95%
		86%		8b : 86%
		88% (86%)		8c : 88% (86%)
		80% (76%)		8d : 80% (76%)
		84% (80%)		8e : 84% (80%)
		95% (91%)		8f : 95% (91%)
		69% (67%)		8g : 69% (67%) from Alkyl-I
		79% (73%)		8h : 79% (73%)
		81% (76%)		8i : 81% (76%)
		61% (60%)		8j : 61% (60%)
		76% (74%)		8k : 76% (74%)
		58% (55%)		8l : 58% (55%)
		79% (74%)		8m : 79% (74%)
		78% (72%)		8n : 78% (72%)
		80% (78%)		8o : 80% (78%)
		92% (88%)		8p : 92% (88%)
		74% (71%) (12 h)		8q : 74% (71%) (12 h)
		86% (12 h)		8r : 86% (12 h)
		71%		8s : 71%
		94%		8t : 94%

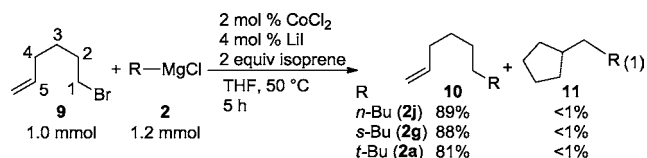
^aReaction conditions: see Table 1, entry 12. Yields were determined by GC. Isolation yields are in parentheses.

infra). The reaction of ethyl 6-bromohexanoate (**7n**) gave the corresponding product in 78% yield without affecting the ethyl ester group that could react with Grignard reagents (entry **8n**). Thiophene moiety also survived under the reaction conditions (entry **8o**). We then attempted the chemoselective coupling of dihaloalkanes. An alkyl bromide having a chloro substituent selectively coupled with *t*-BuMgCl in 92% yield to afford the corresponding alkyl chloride **8p**. When dibromides were used as the substrate, site selective coupling was observed at the primary alkylbromo moiety to give the corresponding secondary alkyl bromides in 74% and 86% yields as the sole coupling products (entries **8q,r**). The reaction occurred exclusively at the sp³C–Br bond even in the presence of the sp²C–Br bond (entries **8s,t**).

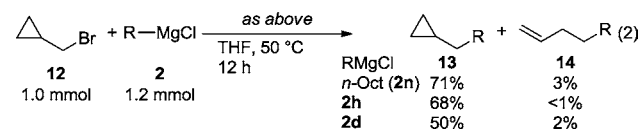
To estimate the relative reactivity of alkyl halides, we performed competition reactions using an alkyl fluoride, bromide, and tosylate and found that *n*-HepOTs reacted faster with *s*-BuMgCl than *n*-NonBr and *n*-OctF. From the initial reaction ratio of each substrate, the relative reactivity was estimated to be OTs:Br:F = 1:0.3:<0.06.¹³ Unfortunately, a similar experiment using an alkyl iodide and tosylate afforded complicated results due to the OTs-I exchange reaction that competed with the coupling. We thus estimated the relative reactivity of iodide and tosylate to be I:OTs = >6:1 by comparing the independent reactions of *n*-OctI and *n*-HepOTs. Based on these results, the relative reactivities of (pseudo)-halides were determined to be I > OTs > Br > F ≫ Cl. Interestingly this is in large contrast to the Ni/1,3-butadiene^{6c} and Cu/alkyne^{4c} catalytic systems reported by us, where, for example, alkyl bromides reacted with primary alkyl Grignard reagents ~50 times faster than alkyl tosylates in the former case.^{6h}

It is well-known that alkyl radical intermediates generated by a single electron transfer (SET) from transition metals to alkyl halides play important roles in Co-catalyzed cross-coupling reactions of alkyl halides.^{7,8} We thus examined the reaction using 6-bromo-1-hexene (**9**)¹⁵ and confirmed that no cyclized

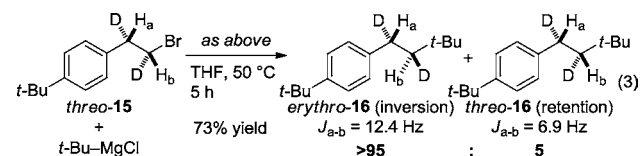
products **11** were formed in any cases with primary, secondary, and tertiary alkyl Grignard reagents under optimized conditions (eq 1). Furthermore, when bromide **12** was used,¹⁵ only 3%,



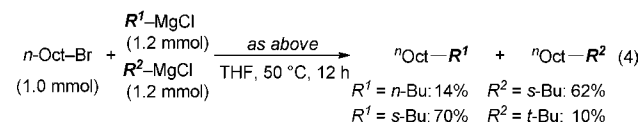
<1%, and 2% of the ring-opened products **14** were observed in the reactions with octyl, 3-heptyl, and 2,5-dimethyl-2-hexyl Grignard reagents, respectively (eq 2). These results indicate that radicals are not produced from alkyl bromides as intermediates in this catalytic reaction.



To gain insights into the stereochemistry of the C–C bond forming step, we conducted the cross-coupling reaction using a diastereomerically pure deuterated substrate *threo*-**15** and *t*-BuMgCl under optimized conditions and obtained the coupling product **16** in 73% yield. ¹H NMR analysis of the product revealed that the reaction proceeded with inversion of stereochemistry at the alkyl halide carbon (*erythro*:*threo* = >95:5). This result clearly suggests that the present reaction proceeds by an S_N2 mechanism, which is consistent with the evidence for a nonradical mechanism as shown in eqs 1 and 2.



The present reaction worked well with all primary, secondary, and tertiary alkyl Grignard reagents. We thus estimated the relative reactivity of these Grignard reagents (eq 4). A competition experiment using an equimolar amount of *n*-

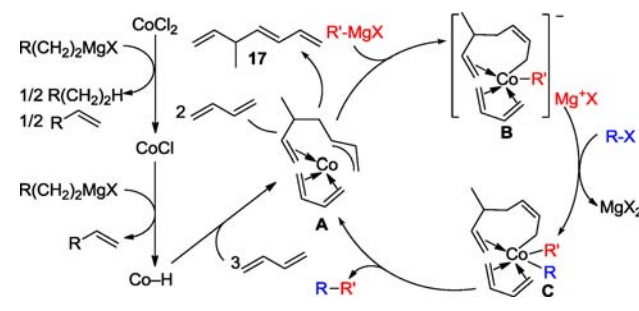


and *s*-BuMgCl under optimized conditions gave the corresponding coupling products in 14% and 62% yield, respectively. A similar experiment using a 1:1 mixture of *s*- and *t*-BuMgCl afforded the coupling products in 70% and 10% yields, respectively. From these experiments, the relative reactivity of alkyl Grignard reagents was roughly estimated to be *n*:-*s*:-*t*-BuMgCl = 1:4:0.6.¹⁶

To shed some light on the nature of the active catalytic species, control reactions were conducted. When $CoCl_2$ (0.1 mmol) was treated with *n*-OctMgCl (0.4 mmol) in the presence of LiI (0.2 mmol) and 1,3-butadiene (10 mmol) at 50 °C for 1 h, ~1.5 equiv of octene and 10.8 equiv of 5-methyl-1,3,6-heptatriene (**17**), based on the Co used, were obtained.¹³ The formation of octene can be attributed to the reaction of $CoCl_2$ with the octyl Grignard reagent via transmetalation

followed by β -hydrogen elimination with the concomitant formation of a Co–H species, which is known to catalyze the dimerization of 1,3-butadiene.¹⁷ The addition of *s*-BuMgCl to the mixture completely suppressed the dimerization of 1,3-butadiene leading to **17**. Based on these results along with the studies shown in SI,¹³ the catalytic pathway shown in Scheme 1

Scheme 1. A Plausible Mechanism



is proposed. The reduction of $CoCl_2$ by the alkyl Grignard reagent gives 0.5 equiv of alkane and alkene and a $Co(I)$ species, which then undergoes transmetalation and β -hydrogen elimination to give a $Co-H$ species. The cobalt hydride reacts with 3 molecules of 1,3-butadiene to form complex A.¹⁷ Although complex A has catalytic activity for the dimerization of 1,3-butadiene to give triene **17**, it also readily reacts with Grignard reagents ($R'-MgX$) to form an anionic complex B under the catalytic conditions used. This anionic complex would possess enhanced nucleophilicity and attacks alkyl halides ($R-X$) to give product and complex A directly or through complex C via an S_N2 mechanism. It is noteworthy that hitherto known Co -catalyzed cross-coupling involves alkyl radical intermediates generated by facile SET from the Co center to alkyl halides,^{7,8} however, this is not the case of the present catalyst due to the specific features of the anionic intermediate B.

The evidence that no reaction took place with Grignard reagents having no β -hydrogen (Table 2, entries 12 and 13) supports the intermediacy of $Co-H$ species generated at the initiation step, as shown in Scheme 1. Indeed, the $MeMgCl$ coupled with *n*-OctBr to give nonane in 56% yield accompanied by 21% yield of dodecane when $MeMgCl$ (1.2 mmol) was added to the reaction mixture of *n*-OctBr (1.0 mmol) and *n*-BuMgCl (0.3 mmol) catalyzed by Co after 30 min.¹³

In conclusion, we report on the development of a Co -catalyzed cross-coupling reaction of alkyl halides and tertiary alkyl Grignard reagents that is promoted by 2 mol % of $CoCl_2$ in the presence of 4 mol % LiI and isoprene. This is the first example of the construction of quaternary carbon centers by cross-coupling between sp^3 -carbon centers, except for the case of Cu catalysts. The present catalytic system also catalyzed the coupling of secondary and primary alkyl Grignard reagents and tolerates various functionalities well. The reaction is efficient and can be run using only 0.1 mol % of $CoCl_2$. In the present reaction, C–C bond formation proceeded with stereoinversion via an ionic mechanism without involving the formation of radical intermediates. Relative reactivities of primary, secondary, and tertiary alkyl Grignard reagents as well as alkyl halides were roughly estimated as *n*:-*s*:-*t*-BuMgCl = 1:4:0.6 and I:OTs:Br:F = >6:1:0.3:<0.06, respectively.

■ ASSOCIATED CONTENT

■ Supporting Information

Additional experimental results and procedures and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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