

Graphical Abstract

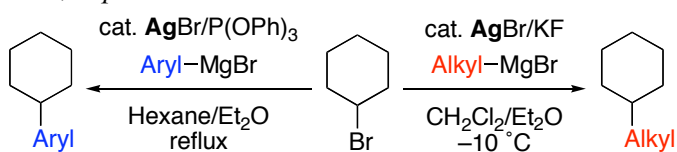
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Silver-catalyzed cross-coupling reactions of alkyl bromides with alkyl or aryl Grignard reagents

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Silver-catalyzed cross-coupling reactions of alkyl bromides with alkyl or aryl Grignard reagents

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Abstract—Treatment of secondary or tertiary alkyl bromides with alkyl Grignard reagents in the presence of catalytic amounts of silver bromide and potassium fluoride in CH₂Cl₂ afforded the corresponding cross-coupling products in reasonable yields. Moreover, silver showed catalytic activity for the cross-coupling reactions of alkyl bromides with aryl Grignard reagents. © 2010 Elsevier Science. All rights reserved

Transition-metal-catalyzed cross-coupling reactions of alkyl halides with Grignard reagents are very useful methods for carbon-carbon bond formation in organic synthesis.¹ Among them, the use of unactivated secondary or tertiary alkyl halides as substrates is more difficult than that of primary alkyl halides, due to the faster β -hydride elimination from the corresponding alkyl transition-metal intermediates. Recently, the cross-coupling reactions of unactivated secondary alkyl halides with aryl,² alkenyl,³ or alkynyl^{3a} Grignard reagents have been achieved. However, the cross-coupling reactions of unactivated secondary alkyl halides with alkyl Grignard reagents are still rare, and have to be established.^{1,4}

Recently, we have reported silver-catalyzed coupling reactions of alkyl halides with benzyl and allyl Grignard reagents.⁵ In these reactions, secondary and tertiary alkyl halides can be employed as substrates. Along the line of our studies on silver-catalyzed coupling reactions, here we wish to report silver-catalyzed cross-coupling reactions of alkyl bromides with alkyl or aryl Grignard reagents.⁶

Treatment of 2-bromooctane (**1a**) with 3-phenylpropylmagnesium bromide in the presence of a catalytic amount of AgCl in Et₂O afforded the cross-coupling product **2a** in 34% yield (Table 1, entry 1). When we used PdCl₂, NiCl₂, FeCl₃, or CuCl without any ligands instead of AgCl, only trace amounts of **2a** were detected. After optimizing reaction conditions, we found that AgBr

was the most effective catalyst (entry 2). Using CH₂Cl₂ as a solvent improved the yield slightly (entry 3).⁷ We thought that the low yields were due to the decomposition of alkylsilver intermediates at room temperature, because octane, propylbenzene, and allylbenzene were mainly produced.^{8,9} Indeed, the better yield was achieved at –10 °C (entry 4). The reaction in entry 4 showed poor reproducibility. When 10 mol % KF was added, we could reproduce the result and obtain the corresponding coupling product **2a** in 68% yield (entry 5). AgF was not effective (entry 6).¹⁰ Even though both AgF and LiBr were added, the product **2a** was obtained in only 23% yield (entry 7). Although the role of KF is not clear at this stage, KF would dissociate the aggregation of AgBr or stabilize alkylsilver intermediates by coordination to the silver metal.¹¹

The silver-catalyzed alkylation reactions (10 mol % AgBr/KF) of various substrates are summarized in Table 2.¹² Both cyclic and acyclic secondary alkyl bromides underwent the alkylation reactions (Table 2, entries 1–4). The reaction of tertiary alkyl halide **1e** suffered from a moderate yield (entry 5). In this case, 2-methyldecane was mainly obtained. Although the reaction of 1-bromoadamantane (**1f**) was slow, it resulted in a reasonable yield of **2f** (entry 6). It is quite interesting that tertiary alkyl bromides can be used as reaction partners.¹ The substrates having functional groups such as THP ether and sulfonamide could be also employed (entries 7 and 8). The

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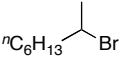
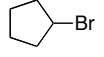
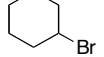
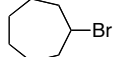
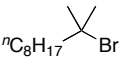
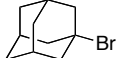
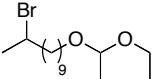
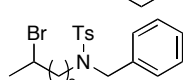
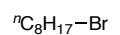
reaction of 1-bromooctane (**1i**) resulted in low yield (entry 9).

Table 1. Optimization of conditions

$^n\text{C}_6\text{H}_{13}\text{CH}_2\text{Br} + \text{BrMg}(\text{CH}_2)_3\text{Ph} \xrightarrow[15\text{ h}]{\text{Mtl (10 mol \%)}} ^n\text{C}_6\text{H}_{13}\text{CH}_2(\text{CH}_2)_3\text{Ph}$				
	1a	2.0 equiv		2a
entry	Mtl	solvent	temp.	yield ^a / %
1	AgCl	Et ₂ O	25 °C	34 ^b
2	AgBr	Et ₂ O	25 °C	45
3	AgBr	CH ₂ Cl ₂	25 °C	47
4	AgBr	CH ₂ Cl ₂	−10 °C	44–62
5	AgBr/KF	CH ₂ Cl ₂	−10 °C	68
6	AgF	CH ₂ Cl ₂	−10 °C	< 5 ^c
7	AgF/LiBr	CH ₂ Cl ₂	−10 °C	23 ^d

^aBased on NMR analysis. ^b3% of **1a** was recovered. ^c26% of **1a** was recovered. ^d11% of **1a** was recovered.

Table 2. Silver-catalyzed alkylation of alkyl bromides^a

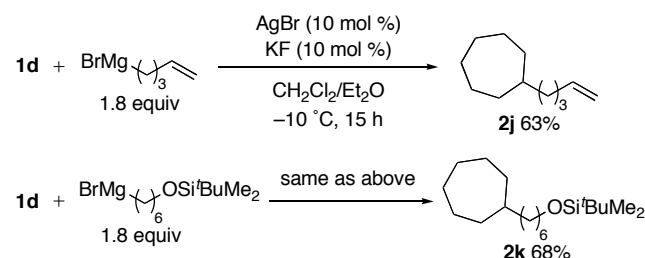
$\text{Alkyl-Br} + \text{BrMg}(\text{CH}_2)_3\text{Ph} \xrightarrow[1.8\text{ equiv}]{\text{AgBr (10 mol \%)}, \text{KF (10 mol \%)}, \text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}, -10\text{ °C}, 15\text{ h}} \text{Alkyl}(\text{CH}_2)_3\text{Ph}$				
	1		2	
entry	Alkyl-Br	2	yield ^b / %	
1		1a → 2a	62	
2		1b → 2b	57	
3		1c → 2c	66	
4		1d → 2d	69	
5		1e → 2e	36	
6		1f → 2f	69 ^c	
7		1g → 2g	58	
8		1h → 2h	44	
9		1i → 2i	20	

^aThe Grignard reagent was 2.0 M Et₂O solution. ^bIsolated yields. ^cPerformed with 3.0 equiv of the Grignard reagent at 25 °C for 64 h.

An alkyl Grignard reagent bearing a terminal alkene moiety reacted with secondary alkyl bromide **1d** smoothly to afford **2j** in 63% yield (Scheme 1). Although KF was added in this alkylation reaction, the reaction conditions were compatible with a *tert*-butyldimethylsiloxy group.

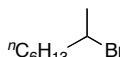
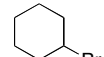
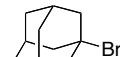
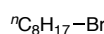
Unfortunately, the reactions with secondary and tertiary alkyl Grignard reagents afforded only trace amounts of the corresponding coupling products under these reaction conditions.¹³

Scheme 1. Scope of alkyl Grignard reagents



Next, we applied the silver catalysis to the cross-coupling reactions with phenyl Grignard reagent. Under the conditions with KF, we could not obtain the phenylated product and the starting material was recovered. After reoptimization of reaction conditions, we found that treatment of bromocyclohexane (**1c**) with phenylmagnesium bromide in the presence of 10 mol % AgBr/P(OPh)₃ in refluxing hexane afforded the cross-coupling product **3c** in 81% yield (Table 3, entry 2).^{14,15} Acyclic alkyl bromides as well as cyclic ones underwent the reactions (entry 1). The reaction of 1-bromoadamantane (**1f**) took 10 h for completion (entry 3). Primary alkyl bromide **1i** underwent the phenylation to give **3i** in high yield (entry 4).

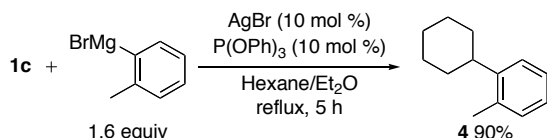
Table 3. Silver-catalyzed phenylation of alkyl bromides^a

$\text{Alkyl-Br} + \text{BrMgPh} \xrightarrow[1.6\text{ equiv}]{\text{AgBr (10 mol \%)}, \text{P(OPh)}_3 (10\text{ mol \%)}, \text{Hexane/Et}_2\text{O}, \text{reflux}, 5\text{ h}} \text{AlkylPh}$				
	1		3	
entry	Alkyl-Br	3	yield ^b / %	
1		1a → 3a	63	
2		1c → 3c	81	
3		1f → 3f	61 ^c	
4		1i → 3i	88	

^aThe Grignard reagent was 1.0 M Et₂O solution. ^bIsolated yields. ^cPerformed for 10 h.

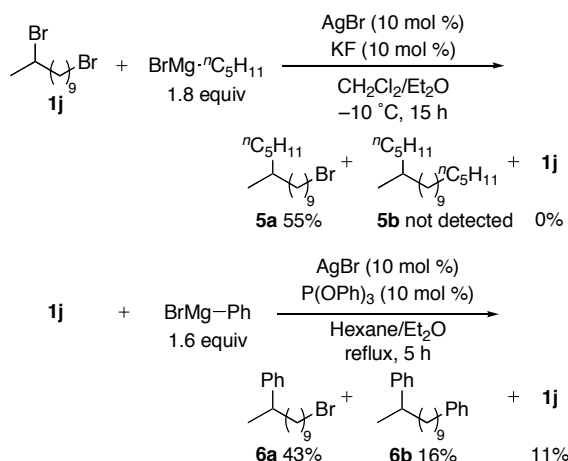
o-Tolyl Grignard reagent can be also employed to afford the corresponding product **4** in 90% yield (Scheme 2).

Scheme 2. Reaction with *o*-tolyl Grignard reagent



Treatment of 1,10-dibromoundecane (**1j**) with pentylmagnesium bromide under the AgBr/KF-catalyzed alkylation conditions afforded monoalkylated product **5a** in 55% yield (Scheme 3). Dialkylated product **5b** was not detected. The reaction of **1j** with phenylmagnesium bromide under the AgBr/P(OPh)₃-catalyzed arylation conditions yielded monophenylated product **6a** and diphenylated product **6b** in 43% and 16% yields, respectively. The fact that secondary alkyl bromide reacted faster than primary one suggested that these reactions would involve the generation of the corresponding carbocation or carbon-centered radical intermediates from alkyl bromides.

Scheme 3. Comparison of the reactivities of primary and secondary alkyl bromides



In summary, we have developed the silver-catalyzed coupling reaction of alkyl bromides with alkyl or aryl Grignard reagents, where secondary and tertiary alkyl bromides can be used as substrates. The present results unveil the new catalytic potential of silver.

Acknowledgments

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- The reactions in CH_2Cl_2 , Et_2O , and THF resulted in lower yields. The reaction in pentane resulted in a similar yield with a prolonged reaction time of 11 h.
- When pyridine, dppe, P(OMe)₃, and KF were used as additives in refluxing hexane, **3c** was obtained in 44%, 16%, 54%, and 56% yield, respectively. When no additive was used, **3c** was obtained in 41% yield.

Supplementary Material

Experimental details, and characterization data of **1g**, **1h**, **1j**, and the products. Supplementary data associated with this article can be found in the online version.