

Silver-Catalyzed Benzylation and Allylation Reactions of Tertiary and Secondary Alkyl Halides with Grignard Reagents

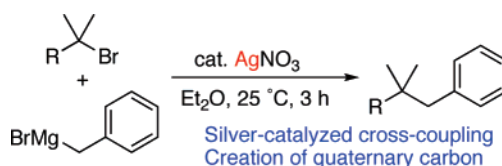
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ABSTRACT



Treatment of alkyl halides, including tertiary alkyl bromides, with benzylic or allylic Grignard reagent in the presence of a catalytic amount of silver nitrate in ether yielded the corresponding cross-coupling products in high yields. The coupling reactions of tertiary alkyl halides provide efficient access to quaternary carbon centers.

Recent researches in transition-metal-catalyzed cross-coupling reactions pursue much wider scope for establishing universal cross-coupling methodology and new catalysts that exhibit extremely high catalytic activity and/or unique reactivity. Among them, replacement of palladium and nickel catalysts by other transition metal catalysts has been attracting increasing attention. The replacement does not only offer economical and environmental advantages but also results in discovery of new reactivity. The success of copper,¹ manganese,² cobalt,³ and iron⁴ catalysts in cross-coupling reactions prompted us to survey other transition metals further, the catalytic performance of which remains unexplored in the field of cross-coupling reactions. Here we report

that silver salts can efficiently catalyze cross-coupling reactions of alkyl halides^{5,6} including tertiary alkyl halides with benzyl or allyl Grignard reagent. Use of tertiary alkyl halides as a coupling partner is still challenging⁷ and has to be established.

Treatment of 2-methyl-2-bromodecane (**1a**) with benzylmagnesium bromide in the presence of a catalytic amount of silver nitrate in ether afforded the cross-coupling product **2a** in high yield (Table 1, entry 1).^{8–11} The silver-catalyzed

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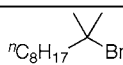
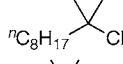
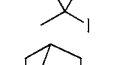
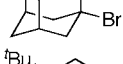
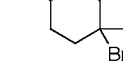
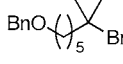
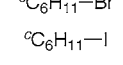
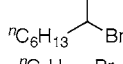
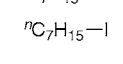
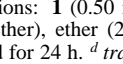
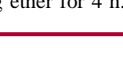
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Table 1. Silver-Catalyzed Benzylation of Alkyl Halides^a

entry	Alkyl-X	1	cat. /mol %	2	yield /%
1		1a	1.0	2a	87
2		1b	1.0	2a	66 ^b
3		1c	1.0	2b	14
4		1d	1.0	2c	80 ^c
5		1e^d	1.0	2d	81 ^e
6		1f	1.0	2e	88
7		1g	2.5	2f	77
8		1h	2.5	2f	67
9		1i	2.5	2g	80
10		1j	2.5	2h	32 ^f
11		1k	2.5	2h	32

^a Conditions: **1** (0.50 mmol), benzylmagnesium bromide (0.65 mmol, 1.0 M in ether), ether (2 mL). ^b Performed in refluxing ether for 10 h. ^c Performed for 24 h. ^d *trans/cis* = 81:19. ^e *trans/cis* = 66:34. ^f Performed in refluxing ether for 4 h.

benzylation features facile creation of quaternary carbon centers (entries 1–6). Tertiary alkyl chloride **1b** reacted smoothly in refluxing ether (entry 2). Tertiary alkyl iodide was likely to be too reactive under the reaction conditions (entry 3). The reaction of 1-bromoadamantane (**1d**) was slow, and the completion of the reaction took 24 h (entry 4). The reaction of **1e** was not stereospecific (entry 5), which is highly suggestive of the existence of an intermediate having an sp²-hybridized carbon center. Proper protective groups such as a benzyloxy group were compatible under the highly basic conditions (entry 6). The conversions of the tertiary alkyl halides were quantitative, and the byproducts were the corresponding alkenes and alkane.

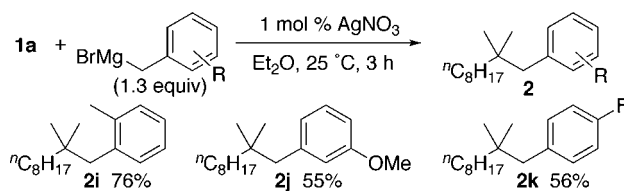
(8) **General procedure for Ag-catalyzed benzylation of tert-alkyl halides:** Silver nitrate (0.8 mg, 0.005 mmol) was placed in a 20-mL reaction flask. Anhydrous diethyl ether (2 mL) and substrate **1a** (117.6 mg, 0.50 mmol) were added under argon. Benzylmagnesium bromide (1.0 M diethyl ether solution, 0.65 mL, 0.65 mmol) was then added to the reaction mixture at 25 °C. While the Grignard reagent was being added, the mixture turned to a black suspension. After the mixture was stirred for 3 h at 25 °C, black precipitations appeared at the bottom of the reaction flask, and the supernatant solution became colorless. Then the reaction mixture was poured into a saturated ammonium chloride solution (20 mL). The products were extracted with hexane (20 mL × 3). The combined organic layer was dried over Na₂SO₄ and concentrated. Silica gel column purification (hexane) of the crude product provided the corresponding benzylated product **2a** (107 mg, 0.44 mmol) in 87% isolated yield.

(9) The reactions in hexane, toluene, and THF resulted in lower yields (ca. 70%).

(10) 1,2-Diphenylethane (0.12 mmol) was detected.

Secondary alkyl bromides and iodide underwent the benzylation, although a higher catalyst loading was necessary (entries 7–9). The reaction of primary alkyl halides suffered from low yields (entries 10 and 11). Secondary and primary alkyl chlorides resisted the reaction.

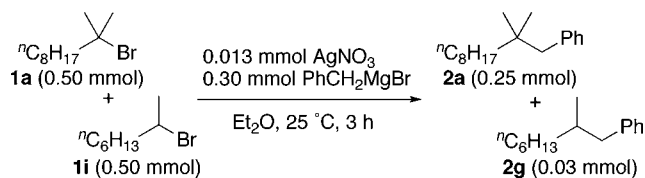
A benzylic Grignard reagent having a methyl group at the ortho position reacted with tertiary alkyl bromide **1a** smoothly to yield **2i** in good yield (Scheme 1). Methoxy and

Scheme 1. Scope of Benzylic Grignard Reagents

fluoro groups did not retard the reaction significantly. The steric as well as electronic factor of the benzylic Grignard reagents is thus moderate. Under similar reaction conditions, attempted phenylation, methylation, and butylation failed to afford the corresponding coupling products.

We reported cobalt-catalyzed benzylation reaction of alkyl halides with benzylmagnesium bromide.^{7b} The present silver-catalyzed reaction is much more efficient in terms of catalyst loading, reactivity, yield, and scope of the substrates. For instance, the cobalt-catalyzed reaction was not useful for benzylation of tertiary alkyl halides.

Treatment of a mixture of tertiary **1a** (0.50 mmol) and secondary **1i** (0.50 mmol) with benzylmagnesium bromide (0.30 mmol) in the presence of silver nitrate afforded 0.25 mmol of **2a** and 0.03 mmol of **2g** (Scheme 2). The

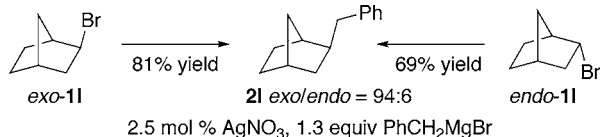
Scheme 2. Comparison of the Reactivity of Secondary and Tertiary Alkyl Bromides

predominant conversion of **1a** suggests that the reaction would include generation of an sp²-hybridized carbon center from **1**. Furthermore, the silver-catalyzed benzylation reactions of *exo*- and *endo*-bromonorbornanes (*exo*- and *endo*-**11**) yielded **2i** with the same *exo/endo* selectivity (Scheme 3), which indicates the existence of a planar carbon center with no original stereochemical information.

When (2-iodocyclohexyloxy)vinylosilane **3** was subjected to the silver-catalyzed benzylation reaction, bicyclic compound **4** was obtained (Scheme 4). Since **4** readily underwent

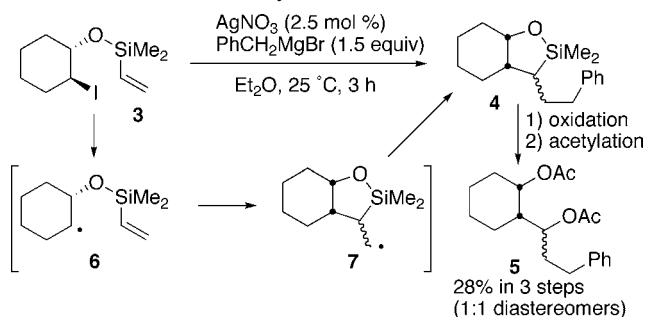
(11) The reaction was slow when performed in the presence of 0.1 mol% of silver nitrate. After 5 h, **2a** was obtained in 79% yield, along with 5% of **1a** and 10% of the dehydrobrominated products.

Scheme 3. Benzylation of Bromonorbornane



hydrolysis and **4** was hence difficult to handle, **4** was converted to diacetate **5** by Tamao–Fleming oxidation

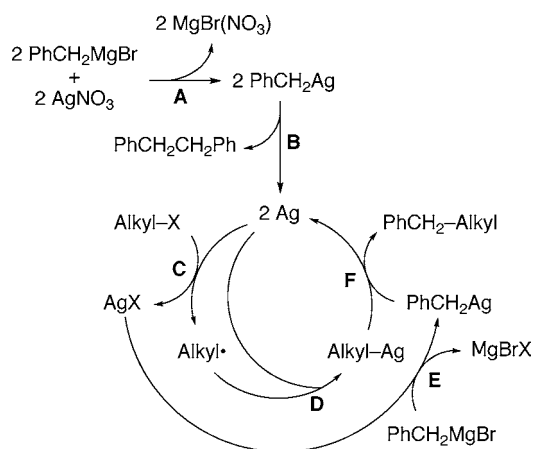
Scheme 4. Cyclization of Iodoacetal **3**



followed by acetylation. Although the yield of **5** was low, the formation of **5** suggests that the silver-catalyzed benzylation reaction would proceed via radical intermediates **6** and **7**,¹² not via cationic ones.¹³

On the basis of the mechanistic study on silver-catalyzed reactions by Tamura and Kochi,^{5a,14} we propose a draft

Scheme 5. Plausible Mechanism



mechanism as outlined in Scheme 5. Benzylmagnesium bromide would first react with silver nitrate to yield zerovalent

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silver¹⁵ and diphenylethane (Steps A and B). The zerovalent silver would effect single electron-transfer to alkyl halide to form the corresponding alkyl radical and silver halide (Step C). The alkyl radical would immediately couple with another zerovalent silver to yield the corresponding alkylsilver (Step D). Silver halide formed by the single electron-transfer would react with benzylmagnesium bromide to generate benzylsilver (Step E). Reductive coupling of the benzylsilver with the alkylsilver affords the benzylated product and regenerates the zerovalent silver (Step F). The details of the reductive coupling, especially the reason for the predominant cross-coupling reaction over possible homocoupling reaction of the benzylsilver, are not clear at this stage.

The silver-catalyzed conditions were applicable not only to the benzylation but also to the coupling reactions with allylic Grignard reagents. Allylation and methylation reactions of tertiary and secondary alkyl bromides proceeded smoothly (Table 2). Unfortunately, silver-catalyzed preny-

Table 2. Allylation and Methylation of Alkyl Halides

entry	1	cat. /mol %	Grignard reagent	8	yield /%
1	1a	1.0	R = H (1.3 equiv)	8a	83
2	1i	2.5	R = H (1.3 equiv)	8b	80
3	1a	1.0	R = Me (1.5 equiv)	8c	80
4	1i	2.5	R = Me (1.5 equiv)	8d	79

lation and crotylation of alkyl halide resulted in poor regioselectivity (Table 3).

Table 3. Reactions with Crotyl and Prenyl Grignard Reagents

entry	1	cat. /mol %	R ¹	R ²	yield /%	9/10
1	1a	1.0	Me	H	77	9a/10a = 65:35
2	1i	2.5	Me	H	76	9b/10b = 70:30
3	1a	1.0	Me	Me	46	9c/10c = 76:24
4	1i	2.5	Me	Me	48	9d/10d = 82:18

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Supporting Information Available: Characterization data of the products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(15) The zero-valent silver can be multi-atomic or clustered and might not be single atom.