Silver-catalyzed Alkyl–Alkyl Homo-coupling of Grignard Reagents

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Oxidative homo-coupling of alkyl Grignard reagents possessing β-hydrogens proceeded with high selectivity in the presence of silver tosylate (AgOTs) as a catalyst (1 mol %) and 1,2-dibromoethane as a reoxidant.

Oxidative homo-coupling of organometallics is an important transformation in organic synthesis, and increasing attention has been recently paid to catalytic systems consisting of a catalytic amount of transition metal complex and a stoichiometric amount of oxidizing agent for this transformation.[1] Although the catalytic homo-coupling of arylmetal reagents producing symmetric biaryls has recently made considerable progress,[2] that of alkylmetals, especially those bearing β-hydrogens, has not been developed well[3,4] due to the difficulty of alkyl–alkyl coupling by transition metal catalysis.[5] It has been known for a long time that a silver(I) salt works as a stoichiometric oxidant for the homo-coupling of alkyl Grignard reagents,[6] but its use as a catalyst remains unsolved and challenging.[7] In the course of our studies on the iron-catalyzed homo-coupling of aryl Grignard reagents,[8] we found that a silver(I) salt efficiently catalyzes the homo-coupling of alkyl Grignard reagents in the presence of 1,2-dibromoethane to give symmetrical alkanes in high yields, which is to be reported in this communication.

Table 1 summarizes the results obtained for the reaction of 1-octylmagnesium bromide (**1a**) with 1,2-dihaloethanes in the presence of a catalytic amount (1 mol %) of transition metal salts in THF at ambient temperature for 30 min. The highest yield (98%) of the homo-coupling product, hexadecane (**3a**), was obtained with the combination of silver tosylate (AgOTs) as a catalyst and 1,2-dibromoethane (**2**) as a reoxidant (Entry 1). The silver-catalyzed homo-coupling giving **3a** is much slower with 1,2-dichloroethane in place of 1,2-dibromoethane (**2**), the yield of **3a** being very low even after a prolonged reaction time (Entry 2). Use of $FeCl_3$ as a catalyst, which has been shown to be an effective catalyst for the homo-coupling of aryl Grignard reagents using a 1,2-dihaloethane,[8] gave a low yield (34%) of **3a** together with 31% yield of 1-octene (Entry 3). The formation of 1-octene in a considerable amount was also observed in the reaction catalyzed by $CoCl_2$, $NiCl_2$, and $CuCl_2$ (Entries 4–6). These results may indicate that octyl–metal intermediates, formed by transmetallation of the octyl group from magnesium to the catalyst metals, Fe, Co, Ni, and Cu, are all prone to undergo β-hydrogen elimination, while the alkyl–silver intermediate is not.

Table 1. Oxidative homo-coupling of 1-octylmagnesium bromide (**1a**)[a]

$$\underset{\mathbf{1a}}{C_8H_{17}MgBr} \xrightarrow[\text{THF, rt, 30 min then } H_2O]{\text{oxidant (1.2 equiv) catalyst (1 mol \%)}} \underset{\mathbf{3a}}{C_8H_{17}{-}C_8H_{17}}$$

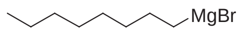
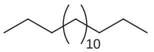
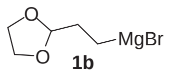
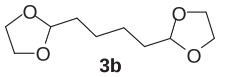
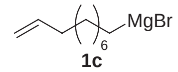
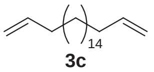
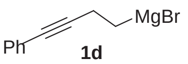
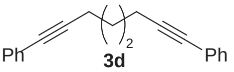
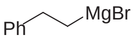
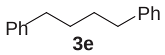
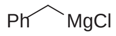
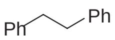
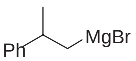
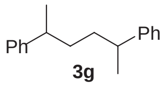
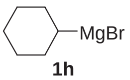
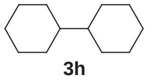
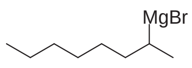
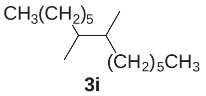
			Yield/%[b]		
Entry	cat	Oxidant	Octane	1-Octene	**3a**
1	AgOTs	$Br(CH_2)_2Br$ (**2**)	3	trace	98
2[c]	AgOTs	$Cl(CH_2)_2Cl$	80	trace	12
3	$FeCl_3$	**2**	33	31	34
4	$CoCl_2$	**2**	35	59	9
5	$NiCl_2$	**2**	37	34	32
6	$CuCl_2$	**2**	22	11	56

[a]The reaction was carried out with 1.00 mmol of **1a** in THF at room temperature for 30 min. [b]Determined by GC analysis using dodecane as an internal standard. [c]Reaction for 12 h.

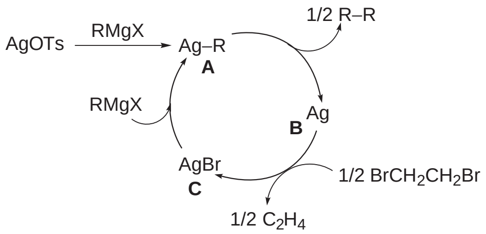
As illustrated in Table 2, the present silver-catalyzed homo-coupling is applicable to a broad range of alkyl Grignard reagents. In the presence of 1 mol % of silver tosylate as a catalyst and 1,2-dibromoethane (**2**) at room temperature for 30 min, high yields of the corresponding symmetric alkanes were produced from primary alkyl Grignard reagents substituted with acetal (**1b**), alkene (**1c**), and alkyne (**1d**) functionality (Entries 2–4). It is remarkable that 2-phenylethylmagnesium bromide (**1e**),

Table 2. Silver-catalyzed oxidative homo-coupling of alkyl Grignard reagents **1**[a]

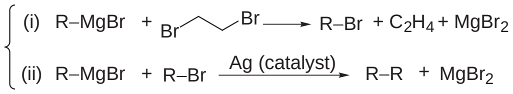
$$\underset{\mathbf{1}}{R_{alkyl}{-}MgX} \xrightarrow[\text{THF, rt, 30 min}]{\text{BrCH}_2\text{CH}_2\text{Br } (\mathbf{2}) \text{ (1.2 equiv) AgOTs (1 mol \%)}} \underset{\mathbf{3}}{R_{alkyl}{-}R_{alkyl}}$$

Entry	R–MgX (**1**)	R–R(**3**)	Yield/%[b]
1	 **1a**	 **3a**	97
2	 **1b**	 **3b**	80
3	 **1c**	 **3c**	99
4	 **1d**	 **3d**	95
5	 **1e**	 **3e**	90
6	 **1f**	 **3f**	99
7 8[c,d]	 **1g**	 **3g**	40[e] 66[e]
9 10[c]	 **1h**	 **3h**	46 70
11 12[c]	 **1i**	 **3i**	68[e] 78[e]

[a]The reaction was carried out with **1** (1.00 mmol), **2** (1.20 mmol), and AgOTs (0.01 mmol). [b]Isolated yield after column chromatography. [c]With **2** (0.55 mmol) in THF at 50 °C. [d]For 12 h. [e]A mixture of *meso*- and *dl*-isomers.



Scheme 1. Plausible mechanism for silver-catalyzed homo-coupling.

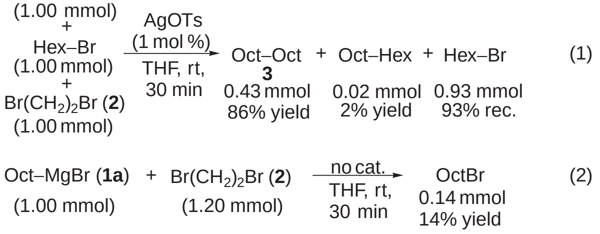


Scheme 2. Alternative mechanism for silver-catalyzed homo-coupling.

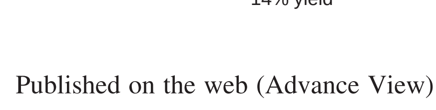
which would be expected to readily undergo β-hydrogen elimination giving styrene, gave a high yield of the homo-coupling product **3e** (Entry 5). The reactions of a β-disubstituted Grignard reagent **1g** and secondary alkyl Grignard reagents **1h** and **1i** are slow at room temperature resulting in low yields of the homo-coupling products, but the yields were improved to some extent by heating the reaction at 50 °C (Entries 7–12).

A plausible mechanism for the present silver-catalyzed homo-coupling is shown in Scheme 1. The reaction of an alkyl Grignard reagent (R–MgX) with the precatalyst AgOTs forms an alkyl–silver species (Ag–R, **A**), which undergoes disproportionation to give homo-coupling product (R–R) and a silver(0) species **B**.[9] Oxidation of **B** with 1,2-dibromoethane[10] giving silver bromide (Ag–Br, **C**) followed by transmetallation of an alkyl group from magnesium to silver regenerates **A** to carry the catalytic cycle.

Based on the report by Kochi[6c] that a silver salt catalyzes the coupling reaction of BuMgBr with BuBr giving octane (79%), one would propose an alternative mechanism where the alkyl Grignard reagent (R–MgBr) is converted into alkyl bromide (R–Br) on reacting with 1,2-dibromoethane and the coupling of R–MgBr with R–Br in the presence of a silver catalyst produces R–R (Scheme 2). This mechanism is ruled out by the control experiments shown in Eqs 1 and 2. Thus, Oct–MgBr (**1a**) was allowed to react with Hex–Br and 1,2-dibromoethane (**2**) in the presence of AgOTs (1 mol %) in THF at room temperature to give a high yield (86%) of Oct–Oct but only a trace amount (2%) of Oct–Hex (Eq 1), indicating that the homo-coupling of alkyl Grignard reagent in the presence of **2** is much faster than the cross-coupling between the Grignard reagent and alkyl bromide. It was also demonstrated by the reaction of Oct–MgBr with 1,2-dibromoethane (**2**) (Eq 2) that the oxidation of alkyl Grignard reagent with **2** giving alkyl bromide is slow.



$$\begin{array}{c}\text{Oct–MgBr }(\mathbf{1a})\\(1.00\text{ mmol})\\+\\\text{Hex–Br}\\(1.00\text{ mmol})\\+\\\text{Br(CH}_2)_2\text{Br }(\mathbf{2})\\(1.00\text{ mmol})\end{array}\xrightarrow[\text{THF, rt, 30 min}]{\text{AgOTs (1 mol \%)}}\underset{\substack{0.43\text{ mmol}\\86\%\text{ yield}}}{\underset{\mathbf{3}}{\text{Oct–Oct}}}+\underset{\substack{0.02\text{ mmol}\\2\%\text{ yield}}}{\text{Oct–Hex}}+\underset{\substack{0.93\text{ mmol}\\93\%\text{ rec.}}}{\text{Hex–Br}}\qquad(1)$$



$$\underset{(1.00\text{ mmol})}{\text{Oct–MgBr }(\mathbf{1a})}+\underset{(1.20\text{ mmol})}{\text{Br(CH}_2)_2\text{Br }(\mathbf{2})}\xrightarrow[\text{THF, rt, 30 min}]{\text{no cat.}}\underset{\substack{0.14\text{ mmol}\\14\%\text{ yield}}}{\text{OctBr}}\qquad(2)$$

In summary, we have developed a new and practical reaction system for oxidative homo-coupling of alkyl Grignard reagents possessing β-hydrogens. The reaction is efficiently catalyzed by 1 mol % of silver tosylate in the presence of inexpensive 1,2-dibromoethane as a stoichiometric oxidant under mild and ligandless conditions.

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