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Copper-Catalyzed Reaction of Alkyl Halides with Cyclopentadienylmagnesium Reagent

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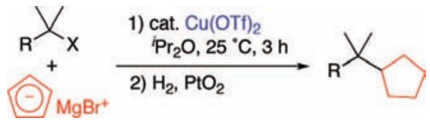
ABSTRACT



Treatment of alkyl halides, including tertiary alkyl bromides, with cyclopentadienylmagnesium bromide in the presence of a catalytic amount of copper(II) triflate yielded the corresponding cyclopentadienylated products in high yields. The following hydrogenation of the products provided alkyl-substituted cyclopentanes.

Copper-catalyzed reactions of alkyl halides with organometallic reagents are among the most useful carbon−carbon bond forming reactions in organic synthesis.[1] Whereas copper-catalyzed reactions of primary alkyl halides have been well-established, there are few examples of copper-catalyzed reactions of secondary[1d] and tertiary alkyl halides with organometallic reagents that create tertiary quaternary carbons.[2] Here we report such a rare example. The cyclopentadienyl Grignard reagent proved to react with tertiary alkyl halides under copper catalysis to afford the corresponding coupling products.

Treatment of 2-methyl-2-bromodecane (**1a**) with cyclopentadienylmagnesium bromide in the presence of a catalytic amount of copper(II) triflate in diisopropyl ether afforded a mixture of the corresponding coupling products **3a** and **3a′** in high combined yield (Scheme 1).[3] Initially formed **2a** would undergo isomerization into **3a** and **3a′** because of the high acidity of the hydrogen on the cyclopentadienyl ring. In order to simplify the analysis of the products,[4] the products were subjected to hydrogenation with the aid of platinum oxide in boiling acetic acid.[5] Cyclopentyl-substituted product **4a** was obtained in 85% overall yield.

The choice of solvent is crucial to attain high yield (Table 1). Bulky ethers such as diisopropyl ether and *t*-butyl methyl

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(1) (a) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 149–631. (b) Terao, J.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2003**, *125*, 5646–5647. (c) Terao, J.; Todo, H.; Begum, S. A.; Kuniyasu, H.; Kambe, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 2086–2089. (d) Burns, D. H.; Miller, J. D.; Chan, H. K.; Delaney, M. O. *J. Am. Chem. Soc.* **1997**, *119*, 2125–2133. (e) Cahiez, G.; Chaboche, C.; Jezequel, M. *Tetrahedron* **2000**, *56*, 2733–2737. (f) Herber, C.; Breit, B. *Eur. J. Org. Chem.* **2007**, 3512–3519.

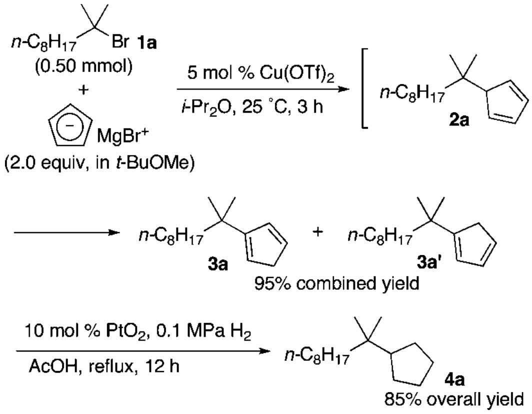
(2) Cobalt and silver are known to catalyze the reactions of tertiary alkyl halides with allyl- or benzylmagnesium reagents: (a) Tsuji, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 4137–4139. (b) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Chem.—Eur. J.* **2004**, *10*, 5640–5648. (c) Someya, H.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2008**, *10*, 969–971.

(3) **General procedure**: Copper(II) triflate (9.0 mg, 0.0025 mmol) was placed in a 30 mL reaction flask under argon. A solution of cyclopentadienylmagnesium bromide (0.86 M in *t*-butyl methyl ether, prepared from cyclopentadiene and butylmagnesium bromide, 1.16 mL, 1.0 mmol) was then added to the flask. Substrate **1a** (118 mg, 0.50 mmol) in diisopropyl ether (4.0 mL) was added. After being stirred for 3 h at 25 °C, the reaction mixture was poured into a saturated ammonium chloride solution (10 mL). The products were extracted with hexane (10 mL × 3). The combined organic layer was dried over Na_2SO_4 and concentrated. Silica gel column purification (hexane) of the crude product provided a mixture of **3a** and **3a′** (105 mg, 0.47 mmol) in 95% combined yield. Platinum oxide (11 mg, 0.047 mmol) was placed in a 30 mL reaction flask. The flask was filled with argon first, and then with hydrogen. The mixture of **3a** and **3a′** (105 mg, 0.47 mmol) in acetic acid (10 mL) was added, and the resulting mixture was heated for 12 h. After being cooled to room temperature, the mixture was filtered through a pad of Celite. After evaporation, the crude product was chromatographed on silica gel (hexane) to afford **4a** (96 mg, 0.43 mmol) in 85% overall yield.

(4) Products **3a** and **3a′** underwent smooth dimerization by the Diels−Alder reaction even at room temperature overnight. The following hydrogenation should be performed immediately.

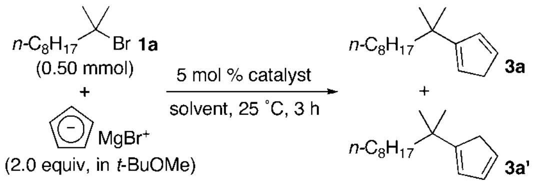
10.1021/ol800814k CCC: $40.75

Scheme 1. Copper-Catalyzed Cyclopentadienylation of Tertiary Alkyl Bromide **1a** Followed by Hydrogenation



ether were suitable solvents (entries 1 and 2). Toluene that had no heteroatoms was comparable to diisopropyl ether (entry 3). The reactions in widely used diethyl ether, THF, and dioxane were sluggish (entries 4−6). Cyclopentyl methyl ether and dibutyl ether also failed to serve as the solvent (entries 7 and 8). Thus, less coordinating solvents afforded higher combined yields of **3a** and **3a′**.

Table 1. Solvent Effect and Catalyst Screening



entry	solvent	catalyst	combined yield/%[a]
1	*i*-Pr$_2$O	Cu(OTf)$_2$	96 (95)[b]
2	*t*-BuOMe	Cu(OTf)$_2$	68
3	toluene	Cu(OTf)$_2$	90
4	diethyl ether	Cu(OTf)$_2$	16
5	dioxane	Cu(OTf)$_2$	12
6	THF	Cu(OTf)$_2$	15
7	*c*-C$_5$H$_{11}$OMe	Cu(OTf)$_2$	13
8	Bu$_2$O	Cu(OTf)$_2$	22
9	*i*-Pr$_2$O	CuF$_2$	77
10	*i*-Pr$_2$O	CuCl$_2$	59
11	*i*-Pr$_2$O	CuCl	44
12	*i*-Pr$_2$O	CuBr	57
13	*i*-Pr$_2$O	CuI	31
14	*i*-Pr$_2$O	CuOAc	30
15	*i*-Pr$_2$O	CuCN	26
16	*i*-Pr$_2$O	CuOTf•0.5 C$_6$H$_6$	27
17	*i*-Pr$_2$O	AgNO$_3$	26

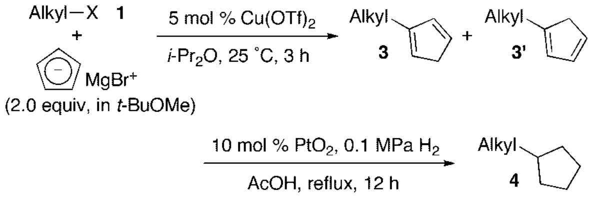
[a] NMR yield. [b] Isolated yield.

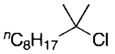
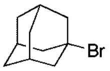
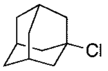
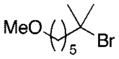
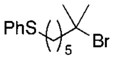
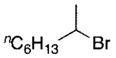
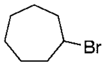
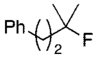
It is worth noting that cyclopentadienylmagnesium bromide should be prepared by deprotonation of cyclopentadiene with butylmagnesium bromide in *t*-butyl methyl ether. The reagent in THF or diethyl ether was far less reactive. Attempts to prepare the reagent in diisopropyl ether failed, resulting in incomplete deprotonation.

A variety of copper salts showed the catalytic activity (Table 1, entries 1 and 9−15). Copper(II) fluoride is an alternative catalyst, albeit with lower efficiency (entry 9). Copper(II) chloride was less efficient (entry 10). Not only copper(II) halides but also copper(I) halides exhibited modest catalytic activity (entries 11−13). Other copper salts such as copper(I) acetate and cyanide exhibited low catalytic activity (entries 14 and 15). Silver(I) nitrate, which was effective in the cross-coupling reaction of tertiary alkyl halides with allyl or benzyl Grignard reagent,[2c] was less effective than copper(II) triflate (entry 17).

A variety of alkyl halides were subjected to the cyclopentadienylation (Table 2). Not only alkyl bromide **1a** but also the corresponding chloride **1a-Cl** reacted smoothly with CpMgBr (entry 1). The reactions of 1-haloadamantane

Table 2. Copper-Catalyzed Cyclopentadienylation of Alkyl Halides Followed by Hydrogenation



entry	alkyl-X	**1**	combined yield of **3** and **3'** /%	**4**	overall yield of **4** from **1**/%
1		**1a-Cl**	88	**4a**	80
2		**1b**	94[a]	**4b**	83
3		**1b-Cl**	95[a]	**4b**	83
4		**1c**	90	**4c**	84
5		**1d**	95	**4d**	50
6		**1e**	51[a]	**4e**	49
7		**1f**	77[a]	**4f**	52
8	$^{n}C_9H_{19}$−Br	**1g**	(32)[a,c]	**4g**	25
9		**1h**	69[b]	**4h**	61

[a] Performed at reflux for 6 h. [b] Performed for 6 h. [c] Determined by ^{1}H NMR analysis. Starting material **1g** was recovered in 67% yield.

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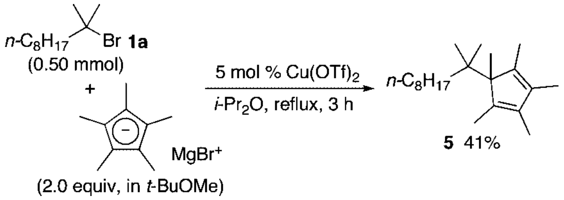
(5) The hydrogenation is not a trivial reaction because of the steric hindrance of the tertiary alkyl group. Initial attempts to reduce the mixture of **3a** and **3a′** in other solvents such as isopropyl alcohol and formic acid under 0.1 MPa of hydrogen failed to attain full conversion.

required a higher temperature and a prolonged reaction time (entries 2 and 3). Gratifyingly, a phenylsulfanyl group as well as a methoxyl group was compatible without deactivating the copper catalyst (entries 4 and 5). Unfortunately, the following hydrogenation of **3d** and **3d′** proceeded inefficiently, although the reaction conditions were not optimized for the sulfur-containing substrate. The reaction of secondary alkyl halides were moderate (entries 6 and 7). The reaction of primary alkyl bromide **1g** was sluggish (entry 8). Interestingly, tertiary alkyl fluoride **1h** participated in the cyclopentadienylation (entry 9).

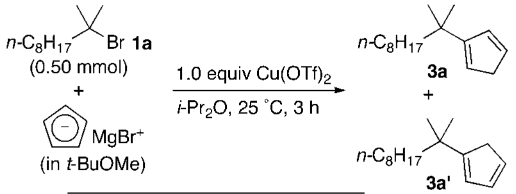
The copper-catalyzed reaction of **1a** with pentamethylcyclopentadienylmagnesium bromide in refluxing diisopropyl ether afforded the corresponding coupling product **5** in 41% yield (Scheme 2). This reaction provides a rare example of construction of two adjacent quaternary carbon centers.

Scheme 2. Copper-Catalyzed Pentamethylcyclopentadienylation of Tertiary Alkyl Bromide **1a**



To gain information about the reaction mechanism, the reactions of **1a** with stoichiometric copper reagents were examined with varying amounts of CpMgBr (Scheme 3). Treatment of **1a** (0.50 mmol) with a copper complex, prepared from 0.50 mmol of Cu(OTf)$_2$ and 0.50 mmol of CpMgBr, did not provide **3a** and **3a′** with complete recovery of **1a**. Most of **1a** remained unchanged when **1a** was treated with a copper reagent, prepared from 0.50 mmol of Cu(OTf)$_2$ and 1.0 mmol of CpMgBr. A reagent generated from 0.50 mmol of Cu(OTf)$_2$ and 1.5 mmol of CpMgBr dramatically changed the outcome. The desired products were obtained in a high combined yield of 86%. Hence, the copper reagent that is active for this reaction might be [Cp$_3$Cu]MgBr[6] or a more complex cuprate.[7]

Scheme 3. Stoichiometric Reactions



amount of Grignard reagent	NMR yield
1.0 equiv	0%
2.0 equiv	15%
3.0 equiv	86%

In summary, Cu(OTf)$_2$ proved to efficiently catalyze the reaction of tertiary alkyl halides with cyclopentadienyl Grignard reagent. Including the following hydrogenation of the cyclopentadienyl ring with hydrogen under Pt$_2$O catalysis, the overall transformation represents formal cyclopentylation of tertiary alkyl halides.

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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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[6] No dicyclopentadienyl (Cp−Cp) was formed upon treatment of Cu(OTf)$_2$ with 2 equiv of CpMgBr in the absence of organic halide. This fact indicates that the active copper species in the reaction mixture is not Cu^{I} or Cu^{0} species but Cu^{II}.

[7] We examined some experiments to assess the intermediacy of alkyl radicals in the reaction, which failed to support the intermediacy. Investigations to reveal the reaction mechanism are underway.