Copper-Catalyzed Allylation of Alkyl Halides with Allylic Grignard Reagents

Masahiro Sai, Hideki Yorimitsu,* and Koichiro Oshima*

Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto-daigaku
Katsura, Nishikyo-ku, Kyoto 615-8510

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E-mail: yori@orgrxn.mbox.media.kyoto-u.ac.jp, oshima@orgrxn.mbox.media.kyoto-u.ac.jp

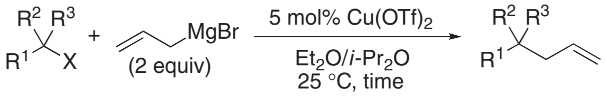
Treatment of alkyl halides, including secondary and tertiary alkyl bromides, with allylic Grignard reagents in the presence of a catalytic amount of copper(II) triflate in diisopropyl ether at 25 °C yielded the corresponding allylated products in high yields. The coupling reactions of tertiary alkyl halides lead to construction of allylated quaternary carbon centers. The active species is likely to be allylcuprate.

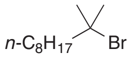
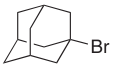
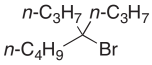
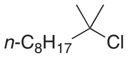
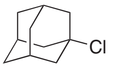
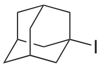
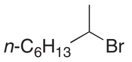
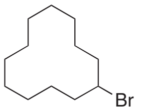
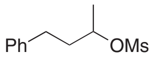
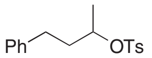
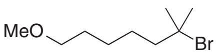
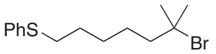
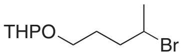
Recently, we have been interested in the metal-catalyzed reactions of alkyl halides, including secondary and tertiary substrates, with allylic Grignard reagents.[1] Cobalt[1a,1b] and silver[1c] proved to be effective for the reactions. However, the cobalt-catalyzed reaction requires fine tuning of reaction conditions in accordance with substrates used. Very recently, we found that copper(II) triflate (=trifluoromethanesulfonate) [$Cu(OTf)_2$] catalyzes the reaction of secondary and tertiary alkyl halides with an allylic metal reagent, a cyclopentadienylmagnesium reagent.[2,3] Here we report that similar reaction conditions are applicable to the reactions with other allylic magnesium reagents. The efficiency and generality of the copper catalysis proved to be comparable to those of silver catalysis.[1c] Notably, copper-catalyzed reactions of secondary and tertiary alkyl halides have been rarely reported.[2,3e,4]

Treatment of 2-bromo-2-methyldecane (**1a**) with 2 equiv of allylmagnesium bromide in the presence of 5 mol % of $Cu(OTf)_2$ in diisopropyl ether at 25 °C provided the corresponding allylated product **2a** in high yield (Table 1, Entry 1). 1-Bromoadamantane (**1b**) also underwent allylation smoothly (Entry 2). The reaction of sterically congested **1c** was less efficient probably because of limited accessibility to the tertiary carbon (Entry 3). Tertiary alkyl chlorides **1a**-Cl and **1b**-Cl were less reactive and required an elevated temperature and a prolonged reaction time (Entries 4 and 5). In contrast, 1-iodoadamantane (**1b**-I) reacted more smoothly within 30 min (Entry 6).

Secondary alkyl bromides **1d** and **1e** also participated in the allylation reaction (Entries 7 and 8). The reaction of primary alkyl bromide, 1-bromodecane (**1f**), should be performed in refluxing diisopropyl ether to achieve full conversion (Entry 9). Secondary alkyl mesylate **1g**-Ms and tosylate **1g**-Ts reacted to yield the corresponding allylated product **2g** in good yields (Entries 10 and 11). It is worth noting that secondary alkyl mesylates and tosylates resisted allylation under cobalt or silver catalysis.[1] Functional groups including a strongly coordinating sulfide moiety were tolerant under the reaction conditions (Entries 12–14).

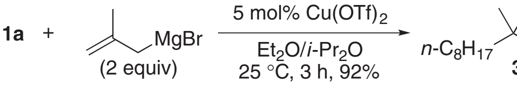
Table 1. Scope of Alkyl Halides and Pseudohalides



Entry	Alkyl halides	Time/h	2	Yield/%
1	 **1a**	3	**2a**	92
2	 **1b**	3	**2b**	88
3	 **1c**	3	**2c**	49
4	 **1a**-Cl	6	**2a**	$54^{a)}$
5	 **1b**-Cl	6	**2b**	$69^{a)}$
6	 **1b**-I	0.5	**2b**	78
7	 **1d**	6	**2d**	68
8	 **1e**	6	**2e**	89
9	$n\text{-}C_{10}H_{21}\text{–}Br$ **1f**	3	**2f**	$86^{a)}$
10	 **1g**-Ms	4	**2g**	64
11	 **1g**-Ts	4	**2g**	77
12	 **1h**	3	**2h**	75
13	 **1i**	3	**2i**	98
14	 **1j**	3	**2j**	63

a) Reflux. b) THP: Tetrahydropyranyl.

The reaction of **1a** with methallylmagnesium bromide proceeded efficiently (eq 1). Unfortunately, the reaction with 2-butenyl- or prenylmagnesium chloride resulted in formation of regioisomeric mixtures as well as moderate yields (eqs 2 and 3). The reaction of **1a** with butyl- or phenylmagnesium bromide led to the recovery of **1a**.



(1)

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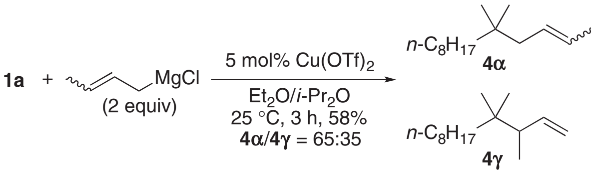
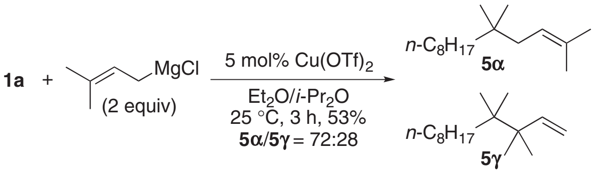


(2)



(3)

The reaction proceeds in the presence of copper(I) catalyst as well as copper(II). The reaction of **1a** with allylmagnesium bromide in the presence of Cu(OTf) afforded **2a** in 80% yield. This suggests that reduction of Cu(OTf)$_2$ would take place in situ upon addition of allylic Grignard reagent.[5,6] To investigate the reaction mechanism, the reaction of **1a** with a stoichiometric copper reagent was examined with varying amounts of allylmagnesium bromide (Table 2). Treatment of **1a** (0.50 mmol) with a copper reagent that was prepared from 0.50 mmol of Cu(OTf)$_2$ and 0.50 mmol of CH$_2$=CHCH$_2$MgBr led to no conversion of **1a**. A copper reagent obtained by mixing 0.50 mmol of Cu(OTf)$_2$ and 1.0 mmol of CH$_2$=CHCH$_2$MgBr effected allylation in 24% yield. Use of three equivalents of CH$_2$=CHCH$_2$MgBr gave **2a** in 63% yield. This implies that the actual copper species would be magnesium diallylcuprate(I).[7] The exact reaction mechanism is not clear.

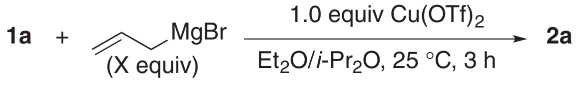
In summary, we have developed an additional protocol for the efficient reaction of secondary and tertiary alkyl halides with allylic Grignard reagents by using a copper catalyst.

Experimental

Instrumentation and Chemicals. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were taken on a Varian Mercury 300 spectrometer and were obtained in CDCl$_3$ with tetramethylsilane as an internal standard. IR spectra were determined on a SHIMADZU FTIR-8200PC spectrometer. Elemental analyses were carried out at the Elemental Analysis Center of Kyoto University. TLC analyses were performed on commercial glass plates bearing a 0.25-mm layer of Merck Silica gel 60F$_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Cu(OTf)$_2$ was purchased from Aldrich. Allylic Grignard reagents were prepared from magnesium turnings (Nacalai Tesque, Inc.) and the corresponding allylic halides in ether. Ether was purchased from Kanto Chemical Co., stored under nitrogen, and used as is. Diisopropyl ether was purchased from Nacalai Tesque. Tertiary alkyl halides were commercially available or prepared from the corresponding alcohol in concentrated hydrobromic or -chloric acid.

Table 2. Allylation by Means of a Stoichiometric Amount of Cu(OTf)$_2$



X/equiv	Yield/%
1.0	0
2.0	24
3.0	63

Typical Procedure for Copper-Catalyzed Reactions. The reaction of **1a** with allylmagnesium bromide (Table 1, Entry 1) is described as a representative procedure. Copper(II) triflate (9.0 mg, 0.025 mmol) was placed in a 30-mL reaction flask under argon. Substrate **1a** (118 mg, 0.50 mmol) in diisopropyl ether (3.0 mL) was added to the flask. A solution of allylmagnesium bromide (0.70 M in diethyl ether, 1.43 mL, 1.0 mmol) was then 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$_2$SO$_4$ and concentrated. Silica gel column purification (hexane) of the crude product provided the corresponding allylated product **2a** (90.5 mg, 0.46 mmol) in 92% isolated yield.

Characterization of New Compounds: Compounds **1a**,[1b] **1a-Cl**,[1b] **2a**,[1b] **2b**,[1c] **2d**,[1c] **3**,[1b] **4**,[1b] and **5**[1b] showed spectra identical with those reported in the literature.

4-Bromo-4-propyloctane (1c): IR (neat): 2961, 2874, 2360, 1684, 1559, 1457, 1128, 668 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 0.92 (t, $J = 7.0$ Hz, 3H), 0.93 (t, $J = 7.3$ Hz, 6H), 1.28–1.49 (m, 8H), 1.79–1.84 (m, 6H); ^{13}C NMR (CDCl$_3$): δ 14.22, 14.37, 18.78, 23.02, 27.63, 42.48, 45.02, 79.91. Found: C, 56.45; H, 10.04%. Calcd for C$_{11}$H$_{23}$Br: C, 56.17; H, 9.86%.

1-Methyl-3-phenylpropyl Methanesulfonate (1g-Ms): IR (neat): 3028, 2983, 2939, 1456, 1340, 1174, 972, 910, 751, 701 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.46 (d, $J = 6.0$ Hz, 3H), 1.89–1.96 (m, 1H), 2.02–2.10 (m, 1H), 2.67–2.80 (m, 2H), 2.99 (s, 3H), 4.81–4.87 (m, 1H), 7.19–7.21 (m, 3H), 7.28–7.32 (m, 2H); ^{13}C NMR (CDCl$_3$): δ 21.43, 31.59, 38.45, 38.88, 79.68, 126.36, 128.51, 128.73, 140.89. Found: C, 58.06; H, 6.83%. Calcd for C$_{11}$H$_{16}$O$_3$S: C, 57.87; H, 7.06%.

1-Methyl-3-phenylpropyl *p*-Toluenesulfonate (1g-Ts): IR (neat): 3028, 2937, 1599, 1456, 1363, 1189, 1176, 893, 816, 750, 664 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.30 (d, $J = 6.5$ Hz, 3H), 1.77–1.84 (m, 1H), 1.89–1.97 (m, 1H), 2.45 (s, 3H), 2.47–2.51 (m, 1H), 2.58–2.64 (m, 1H), 4.62–4.68 (m, 1H), 7.05–7.07 (m, 2H), 7.16–7.19 (m, 1H), 7.23–7.27 (m, 2H), 7.32–7.34 (m, 2H), 7.78–7.81 (m, 2H); ^{13}C NMR (CDCl$_3$): δ 21.03, 21.82, 31.34, 38.33, 80.06, 126.23, 127.92, 128.44, 128.62, 129.96, 134.64, 141.01, 144.69. Found: C, 67.20; H, 6.47%. Calcd for C$_{17}$H$_{20}$O$_3$S: C, 67.08; H, 6.62%.

6-Bromo-1-methoxy-6-methylheptane (1h): IR (neat): 2939, 2862, 1653, 1558, 1507, 1457, 1387, 1369, 1121 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.35–1.42 (m, 2H), 1.50–1.63 (m, 4H), 1.75 (s, 6H), 1.78–1.81 (m, 2H), 3.34 (s, 3H), 3.38 (t, $J = 6.8$ Hz, 2H); ^{13}C NMR (CDCl$_3$): δ 26.32, 26.34, 29.71, 34.43, 47.69, 58.76, 68.64, 72.91. Found: C, 48.71; H, 8.62%. Calcd for C$_9$H$_{19}$BrO: C, 48.44; H, 8.58%.

6-Bromo-6-methyl-1-phenylsulfanylheptane (1i): IR (neat): 2936, 2859, 1700, 1653, 1559, 1507, 1481, 1437, 1369, 1093, 1025 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.43–1.57 (m, 4H), 1.65–1.72 (m, 2H), 1.75 (s, 6H), 1.75–1.80 (m, 2H), 2.93 (t, $J = 7.3$ Hz, 2H), 7.15–7.19 (m, 1H), 7.26–7.34 (m, 4H); ^{13}C NMR (CDCl$_3$): δ 26.04, 28.86, 29.19, 33.69, 34.42, 47.52, 68.50, 125.92, 129.03, 129.15, 137.00. Found: C, 56.05; H, 6.87%. Calcd for C$_{14}$H$_{21}$BrS: C, 55.81; H, 7.03%.

2-(4-Bromopentyloxy)-1-oxacyclohexane (1j, Mixture of Diastereomers): IR (neat): 2924, 2869, 1442, 1379, 1353, 1201, 1121, 1078, 1034, 979, 869, 816 cm^{-1}; ^{1}H NMR (CDCl$_3$) for a mixture of isomers: δ 1.40–1.93 (m, 10H), 1.72 (d, $J = 6.5$ Hz, 3H), 3.38–3.45 (m, 1H), 3.46–3.52 (m, 1H), 3.72–3.79 (m, 1H), 3.82–3.86 (m, 1H), 4.14–4.21 (m, 1H), 4.54–4.59 (m, 1H); ^{13}C NMR ($CDCl_3$) for a mixture of isomers: δ 19.82, 19.84, 25.64 (two signals merged), 26.68 (two signals merged), 28.24, 28.29, 30.90 (two signals merged), 38.13, 38.21, 51.77, 51.82, 62.56, 62.60, 66.85, 66.92, 99.05, 99.07. Found: C, 47.65; H, 7.53%. Calcd for $C_{10}H_{19}BrO_2$: C, 47.82; H, 7.62%.

4,4-Dipropyl-1-octene (2c): IR (neat): 3075, 2958, 2932, 2862, 1639, 1456, 1378, 994, 911, 745 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.85–0.91 (m, 9H), 1.10–1.28 (m, 14H), 1.94 (dt, $J = 7.5$, 1.3 Hz, 2H), 4.96–5.00 (m, 2H), 5.72–5.80 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 14.39, 15.19, 16.41, 23.80, 25.43, 36.48, 38.01, 39.34, 41.37, 116.46, 135.85. Found: C, 85.89; H, 14.42%. Calcd for $C_{14}H_{28}$: C, 85.63; H, 14.37%.

Allylcyclododecane (2e): IR (neat): 2931, 2862, 1640, 1471, 1446, 1346, 992, 909, 719 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.20–1.42 (m, 22H), 1.49–1.55 (m, 1H), 1.96–1.99 (m, 2H), 4.95–5.01 (m, 2H), 5.74–5.83 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 21.91, 23.54, 23.59, 24.28, 24.90, 28.95, 34.13, 39.77, 115.40, 138.49. Found: C, 86.62; H, 13.61%. Calcd for $C_{15}H_{28}$: C, 86.46; H, 13.54%.

(3-Methyl-5-hexenyl)benzene (2g): IR (neat): 3027, 2917, 2858, 1640, 1497, 1454, 994, 911, 745, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.94 (d, $J = 7.0$ Hz, 3H), 1.41–1.48 (m, 1H), 1.51–1.61 (m, 1H), 1.63–1.70 (m, 1H), 1.92–1.98 (m, 1H), 2.09–2.14 (m, 1H), 2.55–2.61 (m, 1H), 2.63–2.69 (m, 1H), 4.98–5.03 (m, 2H), 5.74–5.82 (m, 1H), 7.16–7.19 (m, 3H), 7.25–7.29 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 19.55, 32.58, 33.63, 38.57, 41.45, 115.90, 125.76, 128.46, 128.53, 137.57, 143.14. Found: C, 89.36; H, 10.22%. Calcd for $C_{13}H_{18}$: C, 89.59; H, 10.41%.

9-Methoxy-4,4-dimethyl-1-nonene (2h): IR (neat): 2934, 2862, 2827, 1473, 1457, 1387, 1122, 912 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.84 (s, 6H), 1.15–1.33 (m, 6H), 1.55–1.60 (m, 2H), 1.93 (dt, $J = 7.5$, 1.1 Hz, 2H), 3.33 (s, 3H), 3.36 (t, $J = 6.5$ Hz, 2H), 4.96–5.01 (m, 2H), 5.76–5.84 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 24.00, 27.16, 27.20, 29.88, 33.22, 42.03, 46.64, 58.74, 73.15, 116.66, 126.10. Found: C, 77.98; H, 13.38%. Calcd for $C_{12}H_{24}O$: C, 78.20; H, 13.12%.

9-Phenylsulfanyl-4,4-dimethyl-1-nonene (2i): IR (neat): 2931, 2859, 1586, 1471, 1439, 1365, 1026, 912, 737, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.83 (s, 6H), 1.14–1.42 (m, 6H), 1.63–1.70 (m, 2H), 1.92 (dt, $J = 7.0$, 1.3 Hz, 2H), 2.91 (t, $J = 7.3$ Hz, 2H), 4.95–5.02 (m, 2H), 5.75–5.83 (m, 1H), 7.14–7.18 (m, 1H), 7.25–7.33 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 23.70, 27.14, 29.37, 29.90, 33.22, 33.77, 41.92, 46.63, 116.72, 125.82, 129.00, 129.03, 136.03, 137.21. Found: C, 78.02; H, 10.18%. Calcd for $C_{17}H_{26}S$: C, 77.80; H, 9.99%.

2-(4-Methyl-6-heptenyloxy)-1-oxacyclohexane (2j, Mixture of Diastereomers): IR (neat): 2940, 2871, 1558, 1507, 1457, 1201, 1121, 1079, 1027, 992, 909, 870 cm^{-1}; ^{1}H NMR ($CDCl_3$) for a mixture of isomers: δ 0.88 (d, $J = 6.5$ Hz, 3H), 1.14–2.10 (m, 13H), 3.34–3.40 (m, 1H), 3.47–3.52 (m, 1H), 3.69–3.74 (m, 1H), 3.85–3.89 (m, 1H), 4.56–4.58 (m, 1H), 4.96–5.01 (m, 2H), 5.73–5.82 (m, 1H); ^{13}C NMR ($CDCl_3$) for a mixture of isomers: δ 19.56 (two signals merged), 19.89 (two signals merged), 25.69 (two signals merged), 27.46, 27.48, 30.97 (two signals merged), 32.85 (two signals merged), 33.07 (two signals merged), 41.50 (two signals merged), 62.56 (two signals merged), 68.08, 68.11, 99.02, 99.06, 115.74 (two signals merged), 137.75 (two signals merged). Found: C, 73.29; H, 11.66%. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39%.

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References

1 a) T. Tsuji, H. Yorimitsu, K. Oshima, *Angew. Chem., Int. Ed.* **2002**, *41*, 4137. b) H. Ohmiya, T. Tsuji, H. Yorimitsu, K. Oshima, *Chem.—Eur. J.* **2004**, *10*, 5640. c) H. Someya, H. Ohmiya, H. Yorimitsu, K. Oshima, *Org. Lett.* **2008**, *10*, 969. d) K. Oshima, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1.

2 M. Sai, H. Someya, H. Yorimitsu, K. Oshima, *Org. Lett.* **2008**, *10*, 2545.

3 Reviews and representative recent examples of copper-catalyzed cross-coupling reactions of alkyl halides: a) B. H. Lipshutz, S. Sengupta, *Org. React.* **1992**, *41*, 149. b) H.-Q. Do, O. Daugulis, *J. Am. Chem. Soc.* **2007**, *129*, 12404. c) J. Terao, A. Ikumi, H. Kuniyasu, N. Kambe, *J. Am. Chem. Soc.* **2003**, *125*, 5646. d) J. Terao, H. Todo, S. A. Begum, H. Kuniyasu, N. Kambe, *Angew. Chem., Int. Ed.* **2007**, *46*, 2086. e) D. H. Burns, J. D. Miller, H.-K. Chan, M. O. Delaney, *J. Am. Chem. Soc.* **1997**, *119*, 2125. f) G. Cahiez, C. Chaboche, M. Jézéquel, *Tetrahedron* **2000**, *56*, 2733. g) C. Herber, B. Breit, *Eur. J. Org. Chem.* **2007**, 3512. h) J. Terao, N. Kambe, *Acc. Chem. Res.* **2008**, *41*, 1545.

4 The reaction of secondary alkyl halides with stoichiometric organocuprate was reported: E. C. Ashby, J. J. Lin, *J. Org. Chem.* **1977**, *42*, 2805.

5 H. O. House, W. L. Respess, G. M. Whitesides, *J. Org. Chem.* **1966**, *31*, 3128.

6 Other copper salts were also effective: CuF_2 (64%), $CuCl_2$ (84%), CuBr (91%), and CuCN (85%).

7 A. S. E. Karlström, J.-E. Bäckvall, *Chem.—Eur. J.* **2001**, *7*, 1981.