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Cobalt-Mediated Cross-Coupling Reactions of Primary and Secondary Alkyl Halides with 1-(Trimethylsilyl)ethenyl- and 2-Trimethylsilylethynylmagnesium Reagents

Hirohisa Ohmiya, Hideki Yorimitsu,* and Koichiro Oshima*

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

yori@orgrxn.mbox.media.kyoto-u.ac.jp; oshima@orgrxn.mbox.media.kyoto-u.ac.jp

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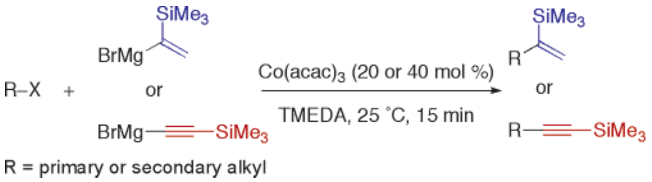
ABSTRACT



This paper describes cobalt-mediated cross-coupling reactions of alkyl halides with 1-(trimethylsilyl)ethenylmagnesium bromide and 2-(trimethylsilyl)ethynylmagnesium bromide, respectively. The cobalt system allows for employing secondary as well as primary alkyl halides as the substrates. The reactions offer facile formations of alkyl–alkenyl and alkyl–alkynyl bonds. The reaction mechanism would include single-electron transfer from a cobalt complex to alkyl halide to generate the corresponding alkyl radical. The cobalt system thus enables sequential radical cyclization/alkenylation and cyclization/alkynylation reactions of 6-halo-1-hexene derivatives.

In organic synthesis, conventional nucleophilic substitution of alkyl halides with very reactive organometallic reagents (Mg and Li, for instance) is one of the most straightforward methods of carbon−carbon bond formation.[1] Contrary to the seeming simplicity of this reaction, however, its synthetic utility is quite limited. In particular, nucleophilic substitution reactions of secondary alkyl halides do not proceed smoothly, leaving most of the starting material untouched or suffering from E2 elimination. Organocopper reagents are also known as being highly reactive in the nucleophilic substitution.[2] However, it seems very difficult to perform the reactions of unactivated secondary alkyl halides with organometalic reagents in the presence of stoichiometric or catalytic amounts of copper compounds. Among them, there are very few copper-mediated alkenylations of secondary alkyl halides.[3] Similar reactions with alkynylcopper reagents have not been reported so far. As an alternative to the copper systems, the development of transition-metal-catalyzed cross-coupling reactions (Ni, Pd, Fe, Co, etc.) of alkyl halides has been achieving remarkable progress.[4] To date, nearly all of the investigations on the cross-coupling reactions of alkyl halides have focused on the use of alkyl and arylmetal nucleophiles. As for the coupling reaction of secondary alkyl

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(1) Wakefield, B. J. *Organolithium Methods*; Academic Press: London, 1988; Chapter 8. (b) Wakefield, B. J. *Organomagnesium Methods in Organic Synthesis*; Academic Press: London, 1995; Chapter 8.

(2) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135−631.

(3) Coupling reaction of 2-iodooctane with 1,3-butadien-2-ylmagnesium chloride: Nunomoto, S.; Kawakami, Y.; Yamashita, Y. *J. Org. Chem.* **1983**, *48*, 1912−1914.

(4) For reviews: (a) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674−688. (b) Terao, J.; Kambe, N. *J. Synth. Org. Chem. Jpn.* **2004**, *62*, 1192−1204. (c) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525−1532. (d) Fürstner, A.; Martin, R. *Chem. Lett.* **2005**, *34*, 624−629. (e) Terao, J.; Kambe, N. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 663−672.

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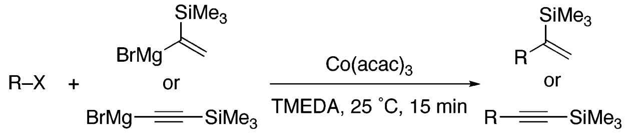
halide,[5] reports of transition-metal-catalyzed coupling reactions with alkenyl nucleophiles are rare.[3,5g,6] There are very few reports on the alkynylation of secondary alkyl halides.[7] The transition-metal-mediated alkenylation and alkynylation of secondary alkyl halides remain as interesting challenges in the field of carbon−carbon bond formation.

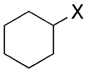
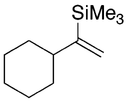
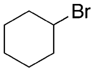
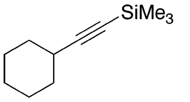
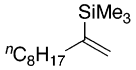
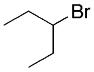
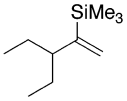
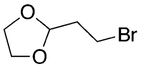
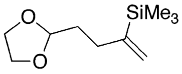
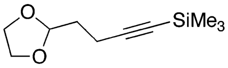
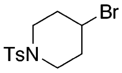
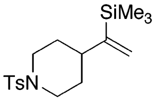
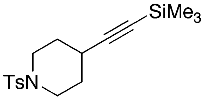
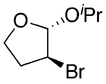
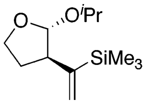
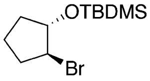
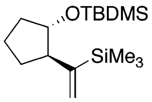
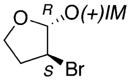
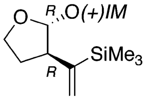
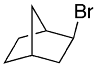
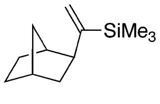
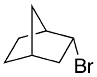
Along the lines of our studies on cobalt-mediated coupling reactions,[8] here we wish to report cobalt-mediated cross-coupling reactions of alkyl halides with 1-(trimethylsilyl)-ethenylmagnesium bromide and 2-(trimethylsilyl)ethynylmagnesium bromide.[9] The cobalt-mediated coupling reactions utilize radical oxidative addition that begins with single-electron transfer from a cobalt complex to alkyl halide.[5n,8a,b,e,f] The single-electron transfer enables the use of unactivated secondary alkyl halide in the cross-coupling reaction.

Substrate (0.5 mmol) was added to a suspension of $Co(acac)_3$ (0.2 mmol) in TMEDA (1 mL). Then, a Grignard reagent, 1-(trimethylsilyl)ethenylmagnesium bromide or 2-(trimethylsilyl)ethynylmagnesium bromide (2.0 mmol, a suspension in 1.5 mL of TMEDA), was added over 3 s at 25 °C. An exothermic reaction immediately took place. After the mixture was stirred at 25 °C for 15 min, usual workup followed by silica gel column purification afforded the corresponding coupling product.

The cobalt-mediated alkenylation and alkynylation of a variety of alkyl halides proceeded smoothly (Table 1). Not

Table 1. Cobalt-mediated Alkenylation and Alkynylation[a]



entry	R-X		product		yield %
1 2 3		**1-I** **1-Br** **1-Cl**		**10**	87 (X=I) 85 (X=Br) 26 (X=Cl)[b]
4		**1-Br**		**11**	71[b]
5 6	$^{n}C_8H_{17}$–X	**2-I** **2-Br**		**12**	90 (X=I)[c] 90 (X=Br)[c]
7 8	**2-I** **2-Br**		$^{n}C_8H_{17}C{\equiv}CSiMe_3$	**13**	74 (X=I)[b,c] 70 (X=Br)[c]
9		**3**		**14**	64
10		**4**		**15**	80[c]
11	**4**			**16**	54
12		**5**		**17**	82
13	**5**			**18**	67
14		**6**		**19**	81[d]
15		**7**		**20**	70[d]
16		**8**		**21**	87[e]
17		**9-*exo***		**22**	73[f]
18		**9-*endo***			69[f]

[a] Conditions: R−X (0.50 mmol), $Co(acac)_3$ (40 mol %), and Grignard reagent (2.0 mmol) were used. [b] The yield was determined by ^1H NMR. [c] Conditions: R−X (0.50 mmol), $Co(acac)_3$ (20 mol %), and Grignard reagent (1.5 mmol) were used. [d] The *trans* isomer was exclusively detected. [e] (+)*IM* = (+)-isomenthyl; the (*R*,*R*)-product was obtained with 98% de. [f] *Exo*/*endo* = 93:7.

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(5) Alkylation of unactivated secondary alkyl electrophiles: (a) Burns, D. H.; Miller, J. D.; Chan, H.-K.; Delaney, M. O. *J. Am. Chem. Soc.* **1997**, *119*, 2125−2133. (b) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726−14727. (c) Fisher, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594−4595. (d) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482−10483. Arylation of unactivated secondary alkyl halides: (e) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340−1341. (f) Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 7788−7789. (g) Powell, D. A.; Maki, T.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 510−511. (h) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686−3687. (i) Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297−1299. (j) Fürstner, A.; Martin, R.; *Angew. Chem., Int. Ed.* **2004**, *43*, 3955−3957. (k) Nakamura, M.; Ito, S.; Matsuo, K.; Nakamura, E. *Synlett* **2005**, 1794−1798. (l) Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Goodby, J. W.; Hird, M. *Chem. Commun.* **2004**, 2822−2823. (m) Bedford, R. B.; Betham, M.; Bruce, D. W.; Danopoulos, A. A.; Frost, R. M.; Hird, M. *J. Org. Chem.* **2006**, *71*, 1104−1110. (n) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 1886−1889.

(6) Alkenylation of primary alkyl halides: (a) Menzel, K.; Maki, T.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 3718−3719. (b) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527−12530. (c) Wiskur, S. L.; Korte, A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 82−83. Alkynylation of primary alkyl halides: (d) Eckhardt, M.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 13642−13643. (e) Yang, L.-M.; Huang, L.-F.; Luh, T.-Y. *Org. Lett.* **2004**, *6*, 1461−1463.

(7) Very recently, palladium-catalyzed alkynylation of secondary alkyl halides is reported: Altenhoff, G.; Würtz, S.; Glorius, F. *Tetrahedron Lett.* **2006**, *47*, 2925−2928.

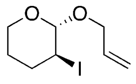
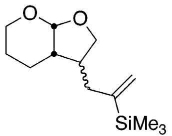
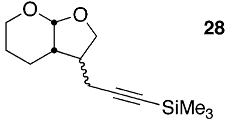
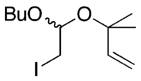
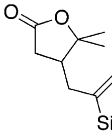
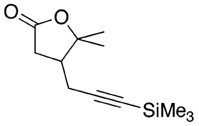
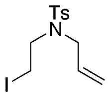
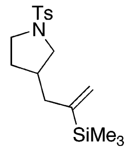
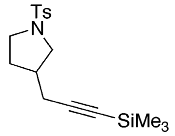
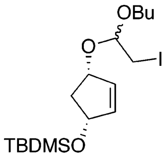
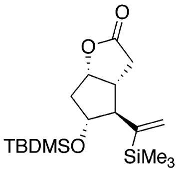
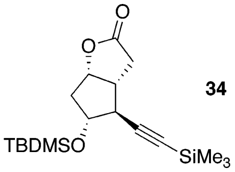
(8) (a) Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 5374−5375. (b) Ohmiya, H.; Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2006**, *62*, 2207−2213. (c) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Chem. Lett.* **2004**, *33*, 1240−1241. (d) Mizutani, K.; Yorimitsu, H.; Oshima, K. *Chem. Lett.* **2004**, *33*, 832−833. (e) Tsuji, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 4137−4139. (f) Ohmiya, H.; Tsuji, T.; Yorimitsu, H.; Oshima, K. *Chem. Eur. J.* **2004**, *10*, 5640−5648.

(9) Recent reports on cobalt-catalyzed coupling reactions, see: (a) Cahiez, G.; Avedissian, H. *Tetrahedron Lett.* **1998**, *39*, 6159−6162. (b) Avedissian, H.; Bérillon, L.; Cahiez, G.; Knochel, P. *Tetrahedron Lett.* **1998**, *39*, 6163−6166. (c) Nishii, Y.; Wakasugi, K.; Tanabe, Y. *Synlett* **1998**, 67−69. (d) Korn, T. J.; Knochel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 2947−2951. (e) Sezen, B.; Sames, D. *Org. Lett.* **2003**, *5*, 3607−3610. (f) Gomes, P.; Gosmini, C.; Périchon, J. *Org. Lett.* **2003**, *5*, 1043−1045. (g) Amatore, M.; Gosmini, C.; Périchon, J. *Eur. J. Org. Chem.* **2005**, 989−992.

only primary alkyl halides but also secondary ones participated in the coupling reaction. Alkyl iodides and bromides are the choice of the coupling partner. The reaction of chlorocyclohexane resulted in poor yield (entry 3). Optically pure bromo acetal **8** underwent diastereoselective alkenylation without suffering from β-alkoxy elimination, furnishing optically pure 2-alkoxy-3-alkenyl-1-oxacyclopentane **21** in good yield (entry 16). Interestingly, the alkenylations of *exo*- and *endo*-**9** provided the *exo*-product **22** predominantly with the same diastereoselectivity, which indicates the existence of a planar carbon center with no original stereochemical information (entry 17, 18). Unfortunately, *tert*-butyl bromide and iodide provided none of the relevant product and gave a mixture of the reduction and the β-elimination products. The reaction of 1-bromoethylbenzene resulted in failure and gave ethylbenzene and styrene.

No coupling product was formed when Co(acac)$_3$ was omitted.[10] The use of CoCl$_2$ or Co(acac)$_2$ slightly lowered the yield by approximately 20% under otherwise identical conditions.[11] The choice of solvent had a significant impact on the yield. TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine) proved to be the best reaction medium. Other solvents such as THF, dioxane, and ether did not promote the reaction at all. The use of TMEDA as an additive (300 mol %) in THF resulted in much lower yield of the corresponding product (20−30%). Several ligands such as *N*,*N*,*N*′,*N*′-tetramethyl-1,2-cyclohexanediamine,[5n] (1*S*,2*S*)-*N*,*N*,*N*′,*N*′-tetramethyl-1,2-diphenylethylenediamine, and 1,3-bis(diphenylphosphino)propane were less effective. Various alkenyl- and alkynylmagnesium reagents were examined. However, we obtained promising results only with trimethylsilyl-substituted Grignard reagents. Triisopropylsilyl-substituted alkenyl- and alkynylmagnesium reagents did not give satisfactory results. Employing phenylethynyl or 1-decynyl Grignard reagent gave the desired adducts in no more than 20% yields. An attempted alkylation reaction resulted in failure. The use of a phenylmagnesium reagent instead of the alkenyl and alkylmagnesium reagents afforded the phenylated product in high yield.[5n]

Table 2. Cobalt-Mediated Sequential Cyclization/Alkenylation or -Alkynylation

entry	R-X		product		yield %
1		**23**		**27**	60 (89/11)[a]
2		**23**		**28**	44 (89/11)[a]
3		**24**		**29**	78[b]
4		**24**		**30**	66[b]
5		**25**		**31**	75
6		**25**		**32**	68
7		**26**		**33**	65[b] (>98%de)
8		**26**		**34**	30[b] (>98%de)

[a] Diastereomeric ratios are shown in parentheses. [b] The products were isolated as lactones after Jones oxidation of the initially formed cyclic acetals.

Taking advantage of the generation of alkyl radical from alkyl halides by means of single-electron transfer, we next turned our attention to the alkenylation and alkynylation that follow radical cyclization. Namely, this reaction mechanism would consist of the following sequence: (1) generation of an alkyl radical from an alkyl halide by single-electron transfer from a cobalt complex, (2) radical cyclization, (3) capture of the alkyl radical by a cobalt complex, and (4) reductive elimination. A series of substrates bearing an alkene moiety were examined, and the results are summarized in Table 2. For example, iodo acetal **23** was converted to the corresponding alkenylated cyclic acetal **27** under the alkenylation conditions (entry 1). Sequential cyclization/alkynylation proceeded similarly (entry 2). It is worth noting that the diastereoselectivity observed in the reaction of iodo acetal **23** was identical with that of free-radical cyclization reaction of **23** with tributyltin hydride.[12] The identity of the diastereoselectivity strongly suggests that both the cobalt-mediated and tin-mediated cyclizations would proceed via the same transition states. The sequence mentioned above is thus most probable. Nitrogen-containing substrate **25** was also

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(10) The use of catalytic amounts of Co(acac)$_3$ was examined (Table 1, entry 2). The conditions were less effective; 52% yield of **10** with 10 mol % of Co(acac)$_3$, 66% with 20 mol %, and 76% with 30 mol %.

(11) The reason Co(III) is more effective than Co(II) in this reaction is not clear.

(12) Mayer, S.; Prandi, J.; Bamhaoud, T.; Bakkas, S.; Guillou, O. *Tetrahedron* **1998**, *54*, 8753−8770.

subjected to the cyclization in the presence of $Co(acac)_3$ to yield pyrrolidine derivatives **31** and **32** (entries 5 and 6). Treatment of an optically pure **26** led to a highly diastereoselective cyclization/alkenylation reaction followed by Jones oxidation to yield an alkenylated lactone **33** (entry 7).[13] An alkynylated analogue **34** was also available, although the yield was modest (entry 8). These lactones, **33** and **34**, can be precursors of prostaglandins and related compounds.[14]

In summary, we have found that cobalt efficiently mediates a cross-coupling reaction of alkyl halides with 1-(trimethylsilyl)ethenyl- and 2-(trimethylsilyl)ethynylmagnesium reagents. The procedure is simple and permits the use of primary and secondary alkyl halides. The cobalt-mediated reaction proceeds via a radical pathway.[15] This cobalt-mediated coupling reaction provides a new tool for carbon−carbon bond formation.

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Supporting Information Available: Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Initially formed cyclic acetals could be isolated before oxidation but showed complex ^{1}H NMR spectra (Table 2, entries 7 and 8).

(14) (a) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; John Wiley & Sons: New York, 1989; Chapter 11. (b) Tanami, T.; Kameo, K.; Ono, N.; Nakagawa, T.; Annou, S.; Tsuboi, M.; Tani, K.; Okamoto, S.; Sato, F. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1507−1510.

(15) The cobalt species that is active for this coupling reaction can be a Co(0)− or Co(I)−ate complex. See ref 8a,b.