5374 *J. Am. Chem. Soc.* **2001,** *123,* 5374−5375

Cobalt-Catalyzed Tandem Radical Cyclization and Cross-Coupling Reaction: Its Application to Benzyl-Substituted Heterocycles

Katsuyu Wakabayashi, Hideki Yorimitsu, and
Koichiro Oshima*

Department of Material Chemistry
Graduate School of Engineering, Kyoto University
Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

Received January 4, 2001

Radical reaction mediated by group 14 metal hydrides, mainly tin hydrides, has been extensively investigated and widely used in organic synthesis.[1] Accordingly, radical reaction with other metallic reagents is a fascinating and developing area in synthetic radical chemistry.[2−9] The most attractive feature of this strategy is the generation of a new carbon−metal bond by the capture of a carbon-centered radical, derived from a certain radical transformation, with a metallic reagent. Sequential ionic reaction offers multibond-forming events, that is, a heterogenerative process[10] (Scheme 1). However, further carbon−carbon bond formation is not always easy because of the low stability or reactivity of the resulting organometallics. Electrophiles used for elongating a carbon chain are allyl halides and reactive carbonyl compounds such as acid chloride, aldehyde, and ketone. In a few cases, activated carbon−carbon multiple bonds[4] and alkyl halides[6] could be employed as electrophiles. On the other hand, cross-coupling reaction with alkenyl or aryl halides seems difficult. Although we have also developed radical cyclization of 6-halo-1-hexene derivatives mediated by organomagnesium,[11] -manganese,[12] and -iron[13] reagents, the following carbon−carbon bond formation was quite limited. Attempts to combine a cyclopentylmethylmetallic species with iodobenzene resulted in very poor yields of the cross-coupling product. Here we wish to report a new route to phenylation of a cyclopentylmethy group. Cobalt-catalyzed coupling reaction of halo acetal with a phenyl Grignard reagent proceeded smoothly, involving radical cyclization prior to coupling. Coupling reaction under cobalt catalysis is rare[14,15] compared with nickel, palladium, and copper catalysts,[16] and remains to be studied.

Scheme 1

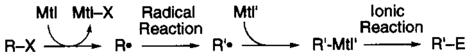
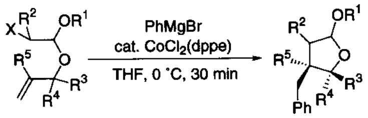


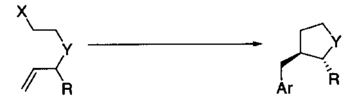
Table 1. Cobalt-Catalyzed Phenylative Radical Cyclization[a]



substrate	X	R^1	R^2	R^3	R^4	R^5	product	yield[b]
1a	Br	*n*-C_4H_9	H	H	*n*-C_5H_{11}	H	**2**	80% (55/45)
1b	I	*n*-C_4H_9	H	H	*n*-C_5H_{11}	H	**2**	78% (55/45)
1c	Cl	*n*-C_4H_9	H	H	*n*-C_5H_{11}	H	**2**	N.R.
1d	Br	$(CH_2)_3$		H	*n*-C_5H_{11}	H	**3**	71% (51/49)
1e	Br	$(CH_2)_3$		Me	Me	H	**4**	84% (62/38)
1f	I	$(CH_2)_3$		Me	Me	H	**4**	84% (60/40)
1g	Br	$(CH_2)_3$		H	H	Me	**5**	51% (single)
1h	I	$(CH_2)_3$		H	H	H	**6**	22% (91/9)

[a] Substrate (0.5 mmol), $CoCl_2$(dppe) (0.05 mmol), PhMgBr (1.1 mmol), and THF (1 mL) were employed. [b] Isolated yield. Diastereomer ratios are in parentheses.

Scheme 2



7a: R = H, X = I, Y = 4-Me-C_6H_4N **8a**: 81% (Ar = Ph)
7b: R = *n*-C_5H_{11}, X = Br, Y = O **8b**: 59% (Ar = Ph)
7c: R = H, X = I, Y = CH_2 **8c**: 59% (Ar = 4-MeO-C_6H_4)

Bromo acetal **1a** was treated with phenylmagnesium bromide in THF at 0 °C in the presence of $CoCl_2$(dppe)[17,18] under argon. After being stirred for 30 min, the reaction mixture was quenched with saturated ammonium chloride solution. Usual workup followed by silica gel column purification provided phenylated cyclic acetal **2** in 80% yield (Table 1, entry 1).

Various substrates were examined, and the results are summarized in Table 1, Scheme 2 and Scheme 3. Halo acetal bearing a terminal alkene moiety underwent phenylative cyclization to give the corresponding benzyl-substituted tetrahydrofuran derivative in good to excellent yield (Table 1). It is worth noting that the stereochemistry of the products was quite similar to that in the previous reports of radical reaction.[4,11−13,19] This observation is highly suggestive of the same transition state of the cyclization

---

[1] (a) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH Verlagsgesellschaft mbH.; Weinheim, 1996. (b) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301−856.

[2] SmI_2: Curran, D. P.; Totleben, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 6050−6058 and references therein.

[3] PhLi: Bailey, W. F.; Carson, M. W. *J. Org. Chem.* **1998**, *63*, 9960−9967.

[4] Et_2Zn-mediated reaction with Pd or Ni catalyst. Further carbon−carbon bond formation was carried out after converting a zinc species into organocopper: (a) Knochel, P. *Synlett* **1995**, 393−403. (b) Stadtmüller, H.; Vaupel, A.; Tucker, C. E.; Stüdemann, T.; Knochel, P. *Chem. Eur. J.* **1996**, *2*, 1204−1220.

[5] Cobaloxime and related cobalt complexes: (a) Pattenden, G. *Chem. Soc. Rev.* **1988**, *17*, 361−382. (b) Ali, A.; Harrowven, D. C.; Pattenden, G. *Tetrahedron Lett.* **1992**, *33*, 2851−2854. (c) Torii, S.; Inokuchi, T.; Yukawa, T. *J. Org. Chem.* **1985**, *50*, 5875−5877. (d) Okabe, M.; Tada, M. *J. Org. Chem.* **1982**, *47*, 5382−5384.

[6] Catalytic Cp_2TiCl_2 with Grignard reagent: (a) Terao, J.; Saito, K.; Nii, S.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1998**, *120*, 11822−11823. (b) Nii, S.; Terao, J.; Kambe, N. *J. Org. Chem.* **2000**, *65*, 5291−5297.

[7] $CrCl_2$: Takai, K.; Matsukawa, N.; Takahashi, A.; Fujii, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 152−155.

[8] Cp_2TiCl: (a) Gansäuer, A. *Synlett* **1998**, 801−809. (b) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986−987.

[9] Mn: Takai, K.; Ueda, T.; Ikeda, N.; Moriwake, T. *J. Org. Chem.* **1996**, *61*, 7990−7991.

[10] Wender, P. A. *Chem. Rev.* **1996**, *96*, 1−2.

[11] Inoue, A.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2000**, *2*, 651−653.

[12] (a) Inoue, R.; Nakao, J.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2039−2049. (b) Nakao, J.; Inoue, R.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1997**, *62*, 1910−1911.

[13] Hayashi, Y.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1998**, *39*, 63−66.

[14] (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) Kharasch, M. S.; Fields, E. K. *J. Am. Chem. Soc.* **1941**, *63*, 2316−2320. (e) Elsom, L. F.; Hunt, J. D.; McKillop, A. *Organomet. Chem. Rev. A* **1972**, *8*, 135−152.

[15] Coupling reaction of organic halides with stoichiometric cobalt-ate complexes, such as Me_4CoLi_2, was reviewed: Kauffmann, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 386-403.

[16] *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: New York, 1991; Vol. 3, Chapter 2.1−2.5.

[17] The catalyst $CoCl_2$[1,2-bis(diphenylphosphino)ethane] was prepared by mixing THF solutions of $CoCl_2$ and of dppe. It is crucial for success that even a trace of water should be removed. When hygroscopic $CoCl_2$ was insufficiently dried, the nonphenylated cyclic product was the major product, probably because an active cobalt catalyst for phenylation was not formed in the presence of water. In each experiment, $CoCl_2$ and dppe were dried carefully under reduced pressure (0.5 Torr) by heating with a hair-dryer for 30 min immediately before use. Also see Supporting Information.

[18] Several ligands such as tmeda, dppm, dppe, dppp, dppb, PPh_3, and $P(OPh)_3$ were examined. Among them, dppe was extremely efficient. The use of other ligands resulted in lower yields of the phenylated product and gave a nonphenylated byproduct (30−50%). $CoCl_2$ itself and $CoCl(PPh_3)_3$ did not give satisfactory results. Employing $Co(dmgH)_2PyCl$ (see ref 5) resulted in recovery of the starting material.

10.1021/ja0100423 CCC: $20.00

Scheme 3

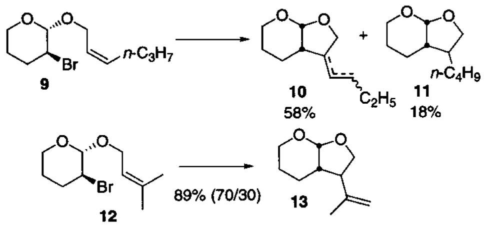
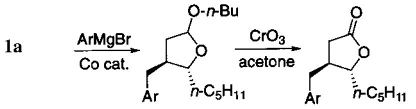


Table 2. Radical Cyclization with Various Arylmagnesium Reagents



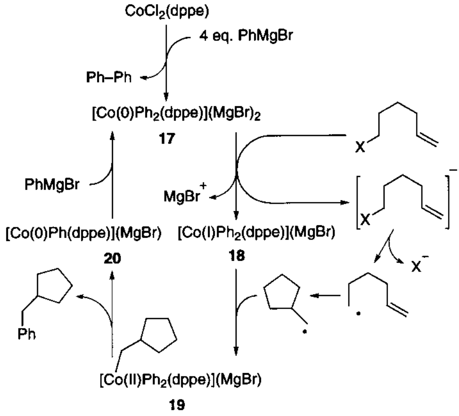
Ar	yield of acetal /%		yield of lactone /%	
C_6H_5	**2**	80	**14**	97
3-CF_3-C_6H_4	**15a**	65	**16a**	83
4-MeO-C_6H_4	**15b**	81	**16b**	95
2-MeO-C_6H_4	**15c**	<5	**16c**	–
2-Me-C_6H_4	**15d**	<15	**16d**	–
2-thienyl	**15e**	63	**16e**	75

step in the present reaction as in the free radical reaction. Allylic alcohols, constituting the substrates, were not detected in the reaction mixture. Thus, β-alkoxy elimination, which could be facilitated by halogen–metal exchange, did not take place. Therefore, a mechanism involving halogen–cobalt exchange followed by intramolecular carbocobaltation might be improbable.[20] Radical reaction is a preferable methodology to construct a quaternary carbon, and this is indeed the case of **1g**. Bicyclic acetal **5** was obtained as a single isomer. However, the reaction of **1h** having a nonsubstituted allyloxy group was sluggish. The expected product **6** was obtained in 22% yield in addition to allylbenzene. Chloro acetal **1c** did not undergo the reaction.

Nitrogen-containing substrate **7a** was also subjected to cyclization in the presence of the cobalt catalyst to yield 3-benzylpyrrolidine derivative **8a** (Scheme 2). Synthesis of carbocycle **8c**, where the Thorpe–Ingold effect does not work, was achieved in good yield.[21] However, in the case of cyclization onto an internal alkene moiety, incorporation of a phenyl group was not successful (Scheme 3). Treatment of **9** with PhMgBr in the presence of CoCl$_2$(dppe) gave a mixture of regio- and stereoisomers in regard to the double bond formed, accompanied with the nonphenylated cyclic acetal **11**. When **12** was employed, the only product obtained was **13** via regioselective β-hydride elimination.

Not only PhMgBr but also a wide range of aryl Grignard reagents, including a 2-thienylmagnesium reagent, could be employed (Table 2). Jones oxidation of the products yielded β-arylmethyl-γ-lactones, which can be useful building blocks of some lignans.[22] Unfortunately, introduction of 2-substituted aryl groups was problematic. Steric effect of the substituents on a metal center is likely to upset the catalytic cycle.

Scheme 4



To get deeper insight into the reaction mechanism, the reaction of **1a** with a stoichiometric cobalt complex was examined with varying amounts of PhMgBr. Treatment of **1a** (1 mmol) with the cobalt complex, prepared from 1 mmol of CoCl$_2$(dppe) and 2 mmol of PhMgBr, provided a trace of **2**. Most of **1a** was recovered, and biphenyl was quantitatively obtained. Accordingly, Co(II)Ph$_2$(dppe) was unstable under the reaction conditions and underwent reductive elimination.[23] Three equivalents of PhMgBr also gave biphenyl (1 mmol), and **1a** remained unchanged. Employing a complex generated by CoCl$_2$(dppe) (1 mmol) and 4 mmol of PhMgBr dramatically changed the outcome. The phenylated product **1a** was obtained in reasonable yield (31%), along with biphenyl (1.2 mmol). Therefore, the cobalt species that is active for this reaction would be the 17-electron-ate complex [Co(0)Ph$_2$(dppe)](MgBr)$_2$, which would potentially exist as an equilibrium mixture of a mono-ate complex and the di-ate complex. Judging from these results, we are tempted to propose a draft mechanism for the catalytic reaction as shown in Scheme 4. The reaction of CoCl$_2$(dppe) with 4 equiv of PhMgBr gives [Co(0)Ph$_2$(dppe)](MgBr)$_2$ (**17**) with concomitant production of 1 equiv of biphenyl. The zero-valent-ate complex undergoes a single electron transfer[24] to a substrate to yield an anion radical of the substrate and cobalt(I) complex **18**. The immediate loss of bromide from the anion radical affords 5-hexenyl radical intermediate, which is transformed into a cyclopentylmethyl radical. Then, the cobalt species **18** would recombine with the carbon-centered radical to form divalent cobalt species **19**. The following reductive elimination provides the product and the Co(0) complex **20**, which is reconverted into **17** by the action of the remaining PhMgBr.

In summary, cobalt-catalyzed sequential radical cyclization and cross-coupling reaction provides a new methodology of multibond formation in a single operation. This method promises high efficiency in the construction of arylmethyl-substituted heterocycles.

Acknowledgment. This work was supported by Grants-in-Aid for Scientific Research (Nos. 12305058 and 10208208) from the Ministry of Education, Culture, Sports, Science and Technology, Government of Japan. H.Y. acknowledges the JSPS Research Fellowship for Young Scientists.

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

JA0100423

---

[19] Procedure for the stereochemical assignments is described in Supporting Information.

[20] Stable β-hydroxy- or β-alkoxyalkylcobalt species are known: (a) Grubb, L. M.; Branchaud, B. P. *J. Org. Chem.* **1997**, *62*, 242–243. (b) Kettschau, G.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 2027–2028 and references therein. These examples seem peculiar to cobaloximes. In our case, electron-rich cobalt complexes would be active species. Therefore, the β-di(alkoxy)alkylcobalt, if formed, probably undergoes fast β-alkoxy elimination. However, there remains a discussion, that is, which is faster, β-alkoxy elimination or intramolecular carbocobaltation.

[21] Cyclic product **8c**, in addition to a small amount of biphenyl, was the only product. No uncyclized product, derived from simple cross coupling, was detected. Methylcyclopentane and 1,5-hexadiene might be major byproducts.

[22] (a) Doyle, M. P.; Protopopova, M. N.; Zhou, Q.-L.; Bode, J. W.; Simonsen, S. H.; Lynch, V. *J. Org. Chem.* **1995**, *60*, 6654–6655. (b) Ward, R. S. *Nat. Prod. Rep.* **1995**, *12*, 183–205.

[23] In the absence of halo acetal, treating CoCl$_2$(dppe) with 2 equiv of PhMgBr in THF at 0 °C for 1 min gave biphenyl in 57% yield. Quenching after 5 min yielded biphenyl quantitatively.

[24] Single-electron transfer from electron-rich-ate complexes to organic halides is reported: Ashby, E. C.; DePriest, R. N.; Tuncay, A.; Srivastava, S. *Tetrahedron Lett.* **1982**, *23*, 5251–5254. Also see refs 12 and 13.