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Cobalt-Catalyzed Intramolecular Heck-Type Reaction of 6-Halo-1-hexene Derivatives

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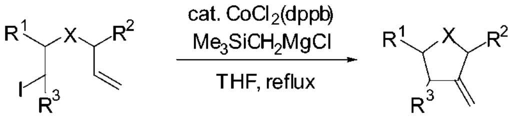
ABSTRACT



Treatment of 6-iodo-1-hexene derivatives with trimethylsilylmethyl Grignard reagent in the presence of $CoCl_2$(dppb) in refluxing THF affords Heck-type products, methylenecyclopentanes, in good yields.

The Heck reaction has become one of the most useful carbon−carbon bond-forming reactions in organic synthesis.[1,2] However, the organic halide moiety employed in the reaction is limited to aryl or vinyl halides. Palladium-catalyzed Heck-type cyclization of 6-halo-1-hexene derivatives has not been reported.[3] One reason is that oxidative addition of alkyl halide to palladium is more difficult than that of aryl and vinyl halides. The other problematic issue is β-hydride elimination prior to cyclization, which yields the corresponding diene.

Heck-type conversion of 6-halo-1-hexenes into methylenecyclopentanes has alternatively been accomplished by cobaloxime-mediated cyclization.[4] In each case, a stoichiometric amount of cobaloxime and irradiation are required, and no reports of cobaloxime-catalyzed Heck-type cyclization are known.[5,6]

Very recently, we reported a complementary method to the palladium-catalyzed intermolecular Heck reaction, in which a cobalt complex proved to catalyze intermolecular Heck-type reaction of alkyl halides with styrenes.[7] Herein we disclose the cobalt-catalyzed cyclization of 6-halo-1-hexenes into methylenecyclopentanes.

Iodo acetal **1a** was selected as a model substrate. Trimethylsilylmethylmagnesium chloride (1.0 M THF solution, 1.5 mmol) was added to a mixture of cobalt(II) chloride (0.05 mmol) and 1,4-bis(diphenylphosphino)butane (0.06 mmol) in THF. The resulting mixture was stirred for 5 min, and iodo acetal **1a** (0.50 mmol) was added at 0 °C. The mixture was heated at reflux for 5 min. Aqueous workup followed

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(1) (a) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581. (b) Heck, R. F.; Nolley, Jr., J. P. *J. Org. Chem.* **1972**, *37*, 2320−2322.

(2) (a) Bräse, S.; de Meijere, A. In *Metal-catalyzed Cross-coupling Reactions*, Diederich, F.; Stang, P. J. Ed., Wiley-VCH: Weinheim, 1998; Chapter 3. (b) Link, J. T.; Overman, L. E. In *Metal-catalyzed Cross-coupling Reactions*, Diederich, F.; Stang, P. J. Ed., Wiley-VCH: Weinheim, 1998; Chapter 6. (c) Heck, R. F. *Org. React.* **1982**, *27*, 345−390. (d) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066. (e) Beller, M.; Riermeier, T. H.; Stark, G. In *Transition Metals for Organic Synthesis*; Beller, M.; Bolm, C., Ed., Wiley-VCH: Weinheim, 1998; Volume 1, Chapter 2.13. (f) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: New York, 1996; Chapter 31.

(3) Intramolecular carbopalladation in which the carbon is sp^3-hybridized was reported. However, in most cases, there are no hydrogens that are involved in β-hydride elimination. See ref 2f. An exception was the following: Oppolzer, W.; De Vita, R. J. *J. Org. Chem.* **1991**, *56*, 6256−6257.

(4) (a) Pattenden, G. *Chem. Soc. Rev.* **1988**, *17*, 361−382. (b) Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519−564. (c) Tada, M. *J. Synth. Org. Chem. Jpn.* **1998**, *56*, 544−556.

(5) Cobaloxime-catalyzed intermolecular Heck-type reaction was reported: Branchaud, B. P.; Detlefsen, W. D. *Tetrahedron Lett.* **1991**, *32*, 6273−6276.

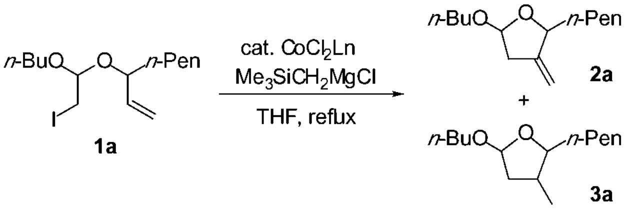
(6) Sodium telluride-induced reaction was reported: Bell, W.; McQueen, E. D.; Walton, J. C.; Foster, D. F.; Cole-Hamilton, D. J.; Hails, J. E. *J. Cryst. Growth* **1992**, *117*, 58−66.

(7) Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2002**, *124*, ASAP (JA026296L).

10.1021/ol0261128 CCC: $22.00

by silica gel column purification afforded the desired product **2a** in 84% yield along with saturated analogue **3a** (Scheme 1).

Scheme 1



1a

2a

3a

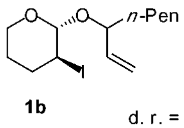
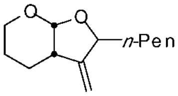
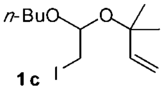
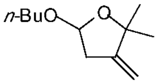
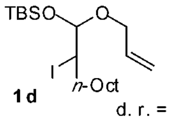
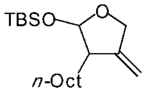
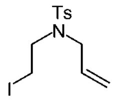
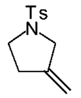
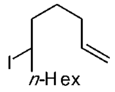
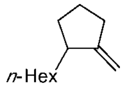
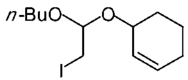
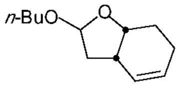
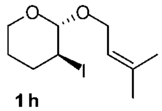
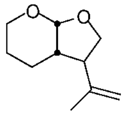
Ln	DPPM	DPPE	DPPP	DPPB	DPPPEN	DPPH	DPPF
2a/%	58	8	68	84	78	69	81
3a/%	28	74	20	9	8	8	11

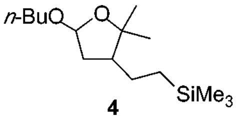
The choice of the ligand was important. Use of DPPM, DPPE, DPPP, DPPPEN,[8] DPPH,[8] and DPPF furnished **2a** in 58, 8, 68, 78, 69, and 81% yields, respectively. Surprisingly, **3a** was obtained in 74% yield when DPPE was employed. No deuterium incorporation into **3a** was observed when the reactions were quenched with DCl/D_2O. The formation of **3a** suggests a radical cyclization pathway where the corresponding oxacyclopentylmethyl radical abstracts a hydrogen from THF. We assume that product **2a** was also produced via a radical intermediate as suggested in the previous report.[7] Use of a trialkylsilylmethyl Grignard reagent was essential for the successful reaction. For example, Me_3CCH_2MgBr was inferior to Me_3SiCH_2MgCl and afforded **2a** and **3a** in 18% and 60% yields, respectively. Other alkyl Grignard reagents such as *n*-BuMgBr also yielded **3a** as a major product. In the absence of $CoCl_2$(dppb), starting material **1a** was completely recovered.

The present conditions were slightly different from the conditions of the intermolecular reaction.[7] The reaction at ambient temperature was slow and yielded a complicated crude mixture compared with the reaction in refluxing THF. The reaction in ether at reflux resulted in a lower yield of **2a**. The corresponding bromide of **1a** was a poorer substrate than **1a**, leading to a lower yield of **2a** (59% with contamination by 20% of **3a**).

Examples of cobalt-catalyzed intramolecular Heck-type reaction are summarized in Table 1. Substrates with terminal alkenes **1b−f** underwent cyclization to provide the corresponding products in good yields. For instance, the reaction of **1d** proceeded smoothly to give **2d** in 94% yield. Substrates bearing unsubstituted allyloxy groups were not suitable for the cobalt-catalyzed tandem cyclization/phenylation reaction.[9] The standard heated conditions provided anticipated product **2c** in 79% yield. Interestingly, the Me_3SiCH_2 group was incorporated to give **4** in 20% yield upon treatment of **1c** at 25 °C. In addition to oxacycles, the reaction effectively constructed aza- and carbocycles **2e** and **2f**. In each case of **2b−f**, its saturated analogue was detected in less than 9% yield. Exposure of **1g** to Me_3SiCH_2MgCl in the presence of $CoCl_2$(dppb) afforded bicyclic product **2g** possessing a disubstituted olefin. Cyclization onto a trisubstituted alkene resulted in a moderate yield of the expected Heck-type product. Use of DPPP instead of DPPB slightly increased the yield of **2h** to 66%. Considerable amounts of isopropyl-substituted product were obtained in both cases (DPPB: 13%, DPPP: 14%).

Table 1. Cobalt-Catalyzed Intramolecular Heck-Type Conversion.

substrate	product	yield
 **1b** d. r. = 1/1		**2b:** 74% d. r. = 67/33
 **1c**		**2c:** 79%
 **1d** d. r. = 1/1		**2d:** 94% d. r. = 62/38
 **1e**		**2e:** 91%
 **1f**		**2f:** 82%
 **1g** d. r. = 1/1		**2g:** 82% d. r. = 50/50
 **1h**		**2h:** 58% (DPPB) 66% (DPPP) d. r. = 63/37



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We also examined substrates **5** and **7**, which undergo usual oxidative addition to palladium (Scheme 2).[10] The prenyl

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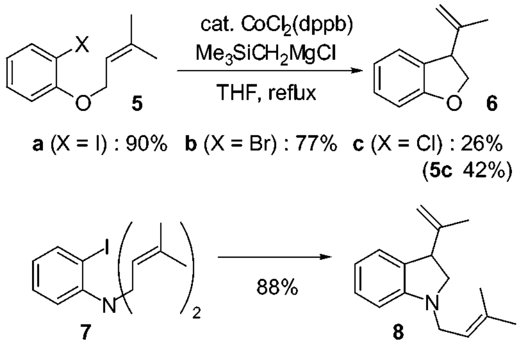
(8) DPPPEN = 1,5-bis(diphenylphosphino)pentane. DPPH = 1,6-bis-(diphenylphosphino)hexane.

(9) Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 5374−5375.

(10) For example, Larock reported palladium-catalyzed cyclization reaction of **5** leading to isopropyl-substituted benzofuran. Larock, R. C.; Stinn, D. E. *Tetrahedron Lett.* **1988**, *29*, 4687−4690.

Scheme 2



ether of iodophenol **5a** and *N*,*N*-diprenyl-2-iodoaniline (**7**) were cleanly converted to isopropenyl-substituted heterocycles **6** and **8**, respectively.[11] Notably, no trace of isopropyl-substituted product was obtained, which is different from the reaction of **1a**. This indicates that aryl halides **5** and **7** may undergo oxidative addition to form aryl−cobalt bonds. Namely, the path may be similar to that of the palladium-catalyzed reaction. Substrate **5b** was less reactive. The yield was decreased to 26% upon treatment of aryl chloride **5c**. Starting material (42%) was also recovered, and chlorophenol was obtained in 20% yield.

In summary, the combination of CoCl$_2$(dppb) catalyst and Me$_3$SiCH$_2$MgCl in refluxing THF induced intramolecular Heck-type reaction of 6-halo-1-hexenes. The present reaction broadens the scope of the substrates for Heck-type conversion.

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Supporting Information Available: Detailed experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0261128

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[11] Manganese- and iron-catalyzed similar conversions were reported: (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. (c) Hayashi, Y.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1998**, *39*, 63−66.