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N-Heterocyclic Carbene Ligands in Cobalt-Catalyzed Sequential Cyclization/Cross-Coupling Reactions of 6-Halo-1-hexene Derivatives with Grignard Reagents

Hidenori Someya, 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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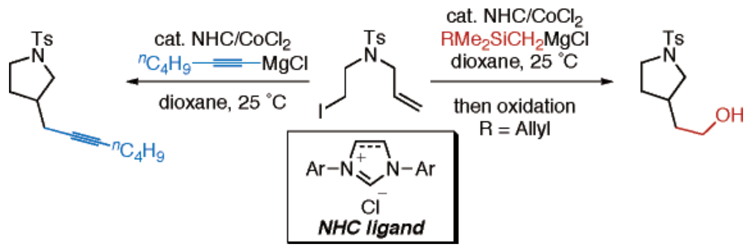
ABSTRACT



N-Heterocyclic carbene/cobalt systems effectively catalyze sequential cyclization/cross-coupling reactions of 6-halo-1-hexene derivatives with trialkylsilylmethyl and 1-alkynyl Grignard reagents, which phosphine and amine ligands did not promote.

N-Heterocyclic carbenes (NHCs) have been attracting increasing attention in various fields of organic chemistry. From a viewpoint of transition-metal-catalyzed reactions, they are widely used as two-electron σ-donor ligands for a number of reactions including carbon−carbon bond formations, carbon−heteroatom formations, and C−H activation.[1] Among these reactions, NHC ligands display excellent performance in the palladium-catalyzed cross-coupling reactions.[2] In contrast to the development of the NHC/palladium system, there are few examples of the use of NHC ligands in cobalt-catalyzed cross-coupling reactions.[3,4] In this context, we have been exploring the possibility of NHCs in the cobalt-catalyzed carbon−carbon bond-forming process. Herein, we present cobalt-catalyzed cross-coupling reactions of alkyl halides with Grignard reagents that involve intramolecular cyclizations,[5−7] which proceed only with the aid of NHC ligands (Figure 1).

In light of the importance of silyl groups as a hydroxy equivalent, NHC/cobalt-catalyzed sequential cyclization/cross-coupling reaction with allyldimethylsilylmethylmagnesium chloride was first investigated. SIEt·HCl (**1**, 0.025 mmol) and substrate **5** (0.5 mmol) were added to a suspension of CoCl$_2$ (0.025 mmol) in dioxane (2 mL). Then allyldimethylsilylmethylmagnesium chloride (1.5 mmol, 1 M ether solution) was added over 5 s at 25 °C. An

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(1) (a) N-Heterocyclic Carbenes in Transition Metal Catalysis. In *Topics in Organometallic Chemistry*; Glorius, F., Ed.; Springer: Heidelberg, 2007; Vol. 21. (b) *N-Heterocyclic Carbenes in Synthesis*; Nolan, S. P., Ed.; Wiley-VCH: Weinheim, 2006. (c) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290−1309. (d) Bourissou, D.; Guerret, O.; Gabbaï, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39−91.

(2) For reviews on the use of NHC ligands in palladium-catalyzed cross-coupling reactions, see: (a) Hillier, A. C.; Grasa, G. A.; Viciu, M. S.; Lee, H. M.; Yang, C.; Nolan, S. P. *J. Organomet. Chem.* **2002**, *653*, 69−82. (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211.

(3) Kuno, A.; Saino, N.; Kamachi, T.; Okamoto, S. *Tetrahedron Lett.* **2006**, *47*, 2591−2594. In this report, a NHC/CoCl$_2$ system served as effectively as a Co(acac)$_3$ catalyst without any additional ligands. No significant advantage of NHC in cobalt-catalyzed cross-coupling reactions was observed.

(4) Intramolecular cyclotrimerization of triynes catalyzed by an NHC/cobalt system was reported. See: Saino, N.; Kogure, D.; Okamoto, S. *Org. Lett.* **2005**, *7*, 3065−3067.

10.1021/ol070392f CCC: $37.00

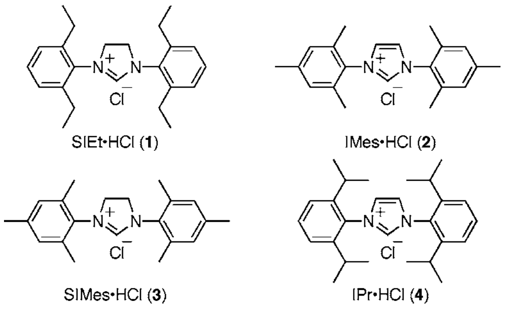
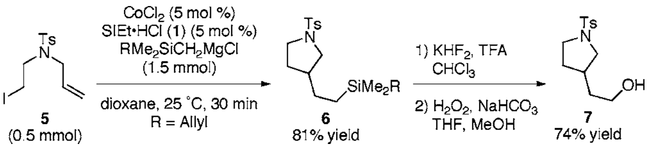


Figure 1. N-Heterocyclic carbenes.

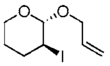
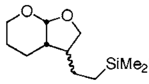
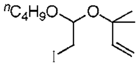
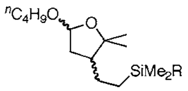
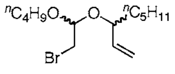
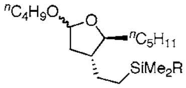
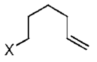
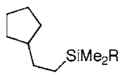
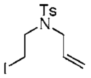
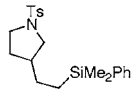
Scheme 1



exothermic reaction immediately took place. The mixture was stirred at 25 °C for 30 min to afford the corresponding cyclization/coupling product **6** in 81% yield (Scheme 1). The 3-(silylethyl)pyrrolidine derivative **6** underwent Tamao−Fleming oxidation to furnish the corresponding alcohol **7**.[8] This reaction mechanism would consist of the following sequence:[6] (1) generation of the corresponding carbon-centered radical from **5** by single-electron transfer from an electron-rich cobalt complex, (2) radical cyclization, (3) capture of the 3-pyrrolidinomethyl radical by a cobalt complex, and (4) reductive elimination.

A variety of imidazolium salts were screened to reveal that SIEt•HCl (**1**) was the best ligand. For example, the use of 1,3-dialkyl-substituted imidazolium salts (not shown in Figure 1) resulted in no more than 5% yields of **6**, and significant amounts of 1-toluenesulfonyl-3-methylenepyrrolidine were instead formed via β-elimination. On the other hand, 1,3-dimesityl-substituted derivative **2** showed modest activity (36% yield), and the use of **3**, the dihydro analogue of **2**, further improved the yield of **6** (54% yield). IPr•HCl (**4**) that bears larger aryl groups than IMes•HCl (**2**) furnished none of the coupling product, leaving most of the starting material. The use of other ligands such as phosphines (PPh$_3$, P^{t}Bu$_3$, and 1,3-bis(diphenylphosphino)propane) and diamines (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine and *N*,*N*,*N*′,*N*′-tetramethyl-1,2-cyclohexanediamine[6g]) resulted in much lower yields (<10%).

Table 1. Representative Examples of NHC/Cobalt-Catalyzed Sequential Cyclization/Cross-Coupling Reaction[a]

entry	substrate		product (R = Allyl)		yield %
1		**8**		**13**	72 (85/15)
2		**9**		**14**	81 (67/33)
3		**10**[b]		**15**	78 (54/46)
4		**11** (X = I)		**16**	67 (X = I)
5		**12** (X = Br)			18 (X =Br)
6[c]		**5**		**17**	78

[a] The reaction conditions are described in Scheme 1 (**5**→**6**). [b] 1:1 mixture of diastereomers. [c] Dimethylphenylsilylmethylmagnesium chloride was employed.

Various substrates were examined,[9] and the results are listed in Table 1. Halo acetals bearing a terminal alkene moiety underwent the cyclization/coupling reactions to give the corresponding silylethyl-substituted tetrahydrofuran derivatives in good yields (entries 1−3). Carbocycle **16** was obtained exclusively in the reaction of 6-iodo-1-hexene (**11**) in 67% yield (entry 4). The corresponding bromide **12** was

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(5) For 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) Gomes, P.; Gosmini, C.; Périchon, J. *Org. Lett.* **2003**, *5*, 1043−1045. (f) Amatore, M.; Gosmini, C.; Périchon, J. *Eur. J. Org. Chem.* **2005**, 989−992.

(6) (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. (g) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 1886−1889. (h) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2006**, *8*, 3093−3096. (i) Yorimitsu, H.; Oshima, K. *Pure Appl. Chem.* **2006**, *78*, 441−449.

(7) Several groups reported the use of NHC ligands in the palladium- and iron-catalyzed cross-coupling reactions of alkyl halides with organometallic reagents. See: (a) Frisch, A. C.; Rataboul, F.; Zapf, A.; Beller, M. *J. Organomet. Chem.* **2003**, *687*, 403−409. (b) Eckhardt, M.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 13642−13643. (c) Arentsen, K.; Caddick, S.; Cloke, F. G. N.; Herring, A. P.; Hitchcock, P. B. *Tetrahedron Lett.* **2004**, *45*, 3511−3515. (d) Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Org. Lett.* **2005**, *7*, 3805−3807. (e) Bedford, R. B.; Betham, M.; Bruce, D. W.; Danopoulos, A. A.; Frost, R. M.; Hird, M. *J. Org. Chem.* **2006**, *71*, 1104−1110. (f) Altenhoff, G.; Würtz, S.; Glorius, F. *Tetrahedron Lett.* **2006**, *47*, 2925−2928.

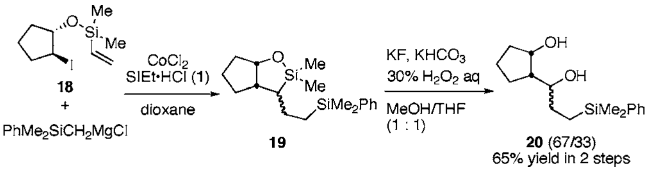
(8) (a) Tamao, K.; Nakajima, T.; Kumada, M. *Organometallics* **1984**, *3*, 1655−1660. (b) Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc., Chem. Commun.* **1984**, 29−31. (c) Klos, A. M.; Heintzelman, G. R.; Weinreb, S. M. *J. Org. Chem.* **1997**, *62*, 3758−3761. For reviews on carbon−silicon bond oxidation, see: (d) Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599−7662.

(9) The NHC/cobalt system could be employed for cross-coupling reactions of primary alkyl halides without a cyclization process. For instance, treatment of isobutyl iodide (0.5 mmol) with allyldimethylsilylmethylmagnesium chloride (1.5 mmol, 1 M ether solution) in dioxane (2 mL) in the presence of SIEt•HCl (**1**, 0.025 mmol) and CoCl$_2$ (0.025 mmol) for 30 min at 25 °C afforded the corresponding coupling product in 79% yield.

less reactive (entry 5). Dimethylphenylsilylmethylmagnesium chloride was also available for this reaction (entry 6).

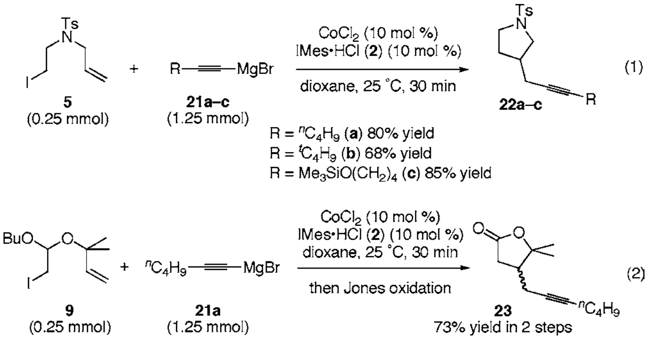
The silicon-tethered 6-iodo-1-hexene derivative **18** was employed for the NHC/cobalt-catalyzed reaction, and the corresponding cyclization/coupling product **19** could be easily transformed to the diol **20** after oxidation with alkaline hydrogen peroxide (Scheme 2).[10]

Scheme 2



We have recently reported TMEDA/cobalt-mediated alkynylation of alkyl halides.[6h] However, the scope of the alkynyl Grignard reagents available for use is limited. Namely, we obtained promising results only with 2-trimethylsilylethynylmagnesium bromide. The previous conditions could not be applied to alkyl-substituted alkynyl Grignard reagents such as 1-hexynylmagnesium bromide. On the other hand, NHC ligand **2** proved to be effective for sequential cyclization/cross-coupling reactions with 1-alkynyl Grignard reagents (Scheme 3). For example, treatment of **5** with 1-hexynylmagnesium bromide (**21a**) in the presence of IMes•HCl (**2**) and CoCl$_2$ provided alkynylated product **22a** in 80% yield (eq 1). The alkynes **21b** and **21c**, bearing a sterically bulky group and a siloxy group, respectively, reacted smoothly. This alkynylation required the 1,3-dimesityl-substituted imidazolium salt **2** to attain satisfactory results.

Scheme 3



The reactions with the aid of SIEt•HCl (**1**), SIMes•HCl (**3**), and IPr•HCl (**4**) gave none of the coupling product and resulted in recovery of the starting material. Treatment of **9** led to a highly effective cyclization/alkynylation followed by Jones oxidation producing lactone **23** in 73% yield (eq 2).

In summary, NHC ligands **1** and **2** have emerged as irreplaceable ligands in fast-growing cobalt-catalyzed cross-coupling reactions.[6] With the aid of the NHC ligands, we have developed new and useful variants of sequential cyclization/coupling reactions of 6-halo-1-hexene derivatives with trialkylsilylmethyl and 1-alkynyl Grignard reagents.

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

OL070392F

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[10] Someya, H.; Kondoh, A.; Sato, A.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Synlett* **2006**, 3061−3064.