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Cu(I)-Catalyzed Intramolecular Hydroamination of Unactivated Alkenes Bearing a Primary or Secondary Amino Group in Alcoholic Solvents

Hirohisa Ohmiya, Toshimitsu Moriya, and Masaya Sawamura*

Department of Chemistry, Faculty of Science, Hokkaido University,
Sapporo 060-0810, Japan

sawamura@sci.hokudai.ac.jp

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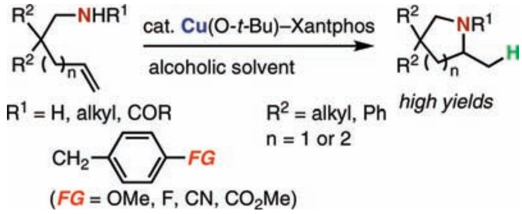
ABSTRACT



The Cu-Xantphos system [Cu(O-*t*-Bu)-Xantphos, 10−15 mol %] catalyzes the intramolecular hydroamination of unactivated terminal alkenes bearing an unprotected aminoalkyl substituent in alcoholic solvents, giving pyrrolidine and piperidine derivatives in excellent yields. This system is applicable to both primary and secondary amines and tolerates a variety of functional groups.

Metal-catalyzed intramolecular hydroamination of alkenes is one of the simplest methods for the preparation of nitrogen heterocycles.[1] Recent research in the intramolecular hydroamination of alkenes has pursued the establishment of a universal hydroamination methodology. However, the development of a catalytic system applicable to the addition of primary or secondary amines to unactivated alkenes remains an interesting challenge. Various catalysts that involve different metals have been developed. Lanthanide and group 4 metal complexes catalyze the hydroamination with superb efficiency.[2] However, the poor functional group compatibility and high air- and moisture-sensitivity of these metal complexes have limited their synthetic utility. Recently, some complexes incorporating precious metals such as Rh,[3a,e] Pt,[3b,c] and Ir[3d,e] have been introduced as catalysts for the intramolecular hydroamination of unactivated alkenes bearing an amino group. Although these catalysts exhibited excellent

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(1) For reviews on the hydroamination of alkenes and alkynes, see: (a) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675–703. (b) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795–3892.

(2) For selected papers on intramolecular hydroaminations of alkenes catalyzed by lanthanide and group 4 metal complexes, see: (a) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673–686. (b) Stubbert, B. D.; Marks, T. J. *J. Am. Chem. Soc.* **2007**, *129*, 4253–4271. (c) Bexrud, J. A.; Beard, J. D.; Leitch, D. C.; Schafer, L. L. *Org. Lett.* **2005**, *7*, 1959–1962. (d) Gribkov, D. V.; Hultzsch, K. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 5542–5546. See also ref 1.

(3) For late transition metal catalyzed intramolecular hydroamination of unactivated alkenes with alkylamines, see the following. Rh: (a) Liu, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 1570–1571. Pt: (b) Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 1070–1071. (c) Bender, C. F.; Hudson, W. B.; Widenhoefer, R. A. *Organometallics* **2008**, *27*, 2356–2358. Ir: (d) Hesp, K. D.; Stradiotto, M. *Org. Lett.* **2009**, *11*, 1449–1452. Ir and Rh: (e) Bauer, E. B.; Andavan, G. T. S.; Hollis, T. K.; Rubio, R. J.; Cho, J.; Kuchenbeiser, G. R.; Helgert, T. R.; Letko, C. S.; Tham, F. S. *Org. Lett.* **2008**, *10*, 1175–1178.

(4) For hydroaminations and hydroamidations of (activated) alkenes catalyzed by Cu or Fe, see the following. Cu: (a) Taylor, J. G.; Whittall, N.; Hii, K. K. *Org. Lett.* **2006**, *8*, 3561–3564. (b) Munro-Leighton, C.; Delp, S. A.; Blue, E. D.; Gunnoe, T. B. *Organometallics* **2007**, *26*, 1483–1493. (c) Munro-Leighton, C.; Delp, S. A.; Alsop, N. M.; Blue, E. D.; Gunnoe, T. B. *Chem. Commun.* **2008**, 111–113. Fe: (d) Komeyama, K.; Morimoto, T.; Takaki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2938–2941.

(5) For Pd, see: (a) Michael, F. E.; Cochran, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 4246–4247. For Au, see: (b) Zhang, J.; Yang, C.-G.; Chuan, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798–1799. See also ref 1.

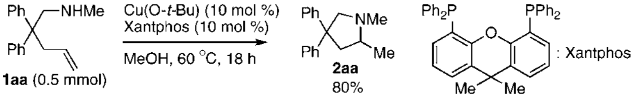
10.1021/ol9007712 CCC: $40.75

functional group compatibility, there still remains room for further investigation. Specifically, the development of hydroamination using a cheap and environmentally benign metal catalyst is greatly anticipated.[4] To date, most of the investigations on the intramolecular *hydroamination* of alkenes catalyzed by late transition metals have focused on the use of amides or carbamates bearing electron-withdrawing *N*-substituents such as Ts, Cbz, Boc, or Ac groups instead of free amines.[5]

Here we report the intramolecular hydroamination of unactivated alkenes catalyzed by a Cu-phosphine system.[4,6−8] Several aspects of this transformation are noteworthy: (i) Cu, which is a relatively abundant metal in the earth crust and hence cheap and environmentally benign, is used as the metal; (ii) alcoholic solvents are used;[7] (iii) both secondary and primary amines can be used; (iv) not only pyrrolidine but also piperidine derivatives are obtained; (v) a variety of functional groups are tolerated; and (vi) olefinic side products due to β-hydride elimination or alkene isomerization are not formed, and the yields are generally high.

The reaction of ω-alkenic secondary amine **1aa** in the presence of Cu(O-*t*-Bu) (10 mol %) and Xantphos (10 mol %) in MeOH (1 mL) proceeded at 60 °C and afforded the pyrrolidine derivative **2aa** in 80% yield (97% NMR yield) after 18 h reaction time (Scheme 1).

Scheme 1. Cu(I)-Catalyzed Intramolecular Hydroamination of Aminoalkene **1aa**

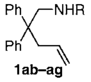
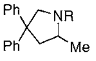
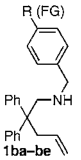
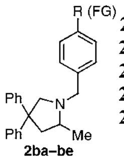
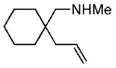
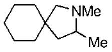
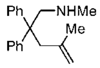
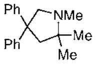
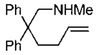
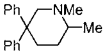
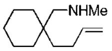
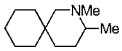


The employment of the alcoholic solvent MeOH had a significant impact on the yield of **2aa**.[9] The use of other solvents such as toluene, hexane, THF, dioxane, CH_3CN, acetone, DMF, and DMSO resulted in lower yields of **2aa** (0−19% NMR yields). The effectiveness of the protic solvent would imply a tolerance of this reaction toward a wide variety of functional groups. Furthermore, its crucial role in the rate acceleration is of considerable interest from a mechanistic viewpoint.[7,8,10]

Our ligand screening has identified Xantphos, which features an extraordinary large bite-angle, to be the best, while the ligand effect was moderate.[11] Even without the ligand, the hydroamination of **1aa** proceeded in 49% NMR yield under essentially the same conditions. Nitrogen-based ligands such as 1,10-phenanthroline reduced the activity of the catalyst (20% NMR yield).

Analogues (**1ab**−**ag**, **1ba**−**be**) of aminopentene **1aa** bearing different *N*-substituents were transformed into the corresponding pyrrolidine derivatives (**2ab**−**ag**, **2ba**−**be**) smoothly at higher temperatures (100 or 140 °C) in a mixed solvent (MeOH/toluene or MeOH/*o*-xylene) (Table 1, entries 1−11). Thus, alkyl substituents such as Et, *n*-Pr, *i*-Bu, and 2-phenethyl groups were tolerated at the nitrogen atom (entries 1−4). Amide substrates **1af** and **1ag**, bearing electron-withdrawing *N*-substituents such as acetyl or benzoyl groups, also underwent hydroamidation in high yields (entries 5 and 6). Although the aminopentene (**1ba**) with an *N*-benzyl group was less reactive than **1aa**−**ae**, the reaction of this substrate also proceeded smoothly and led to completion with 15 mol % catalyst loading (entry 7). Notably, functionalities such as methoxy, fluoro, cyano, and ester were tolerated on the aromatic ring of the *N*-benzyl group (reactions of **1bb**−**be**, entries 8−11).

Table 1. Cu(I)-Catalyzed Hydroamination of Unactivated Alkenes Bearing Secondary Amino or Amido Groups[a]

entry	aminoalkene		product		temp (°C)	time (h)	yield[b] (%)
1	 1ab–ag	R = Et (**1ab**)	 2ab–ag	**2ab**	100	48	87
2		R = *n*-Pr (**1ac**)		**2ac**	100	48	93
3		R = *i*-Bu (**1ad**)		**2ad**	100	48	88
4		R = $(CH_2)_2Ph$ (**1ae**)		**2ae**	100	48	87
5		R = $COCH_3$ (**1af**)		**2af**	100	48	96[d]
6		R = COPh (**1ag**)		**2ag**	140	48	94
7[c]	 1ba–be	R = H (**1ba**)	 2ba–be	**2ba**	100	48	99
8[c]		FG = OMe (**1bb**)		**2bb**	100	48	94
9[c]		FG = F (**1bc**)		**2bc**	100	48	98
10[c]		FG = CN (**1bd**)		**2bd**	100	48	86
11[c]		FG = CO_2Me (**1be**)		**2be**	100	48	86
12		**1c**		**2c**	100	4	91
13[c]		**1d**		**2d**	140	48	89
14		**1e**		**2e**	100	24	92
15		**1f**		**2f**	100	24	94

[a] Conditions: Cu(O-*t*-Bu)-Xantphos (10 mol %), **1** (0.5 mmol), MeOH/toluene (1:1, 1.0 mL), 100 °C or MeOH/*o*-xylene (1:1, 1.0 mL), 140 °C. [b] Isolated yield. [c] Conditions: Cu(O-*t*-Bu)-Xantphos (15 mol %), **1** (0.5 mmol), MeOH/toluene (1:1, 1.0 mL), 100 °C or MeOH/*o*-xylene (1:1, 1.0 mL), 140 °C. [d] The isolated product was contaminated with a small amount of **1af** (5%).

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(6) For Cu-catalyzed enantioselective intramolecular carboamination and aminooxygenation of unactivated alkenes, see: (a) Zeng, W.; Chemler, S. R. *J. Am. Chem. Soc.* **2007**, *129*, 12948–12949. (b) Fuller, P. H.; Kim, J.-W.; Chemler, S. R. *J. Am. Chem. Soc.* **2008**, *130*, 17638–17639.

(7) For Cu-catalyzed addition of terminal alkynes to aldehydes with alcoholic solvents, see: (a) Asano, Y.; Hara, K.; Ito, H.; Sawamura, M. *Org. Lett.* **2007**, *9*, 3901–3904. (b) Asano, Y.; Hara, K.; Ito, H.; Sawamura, M. *Organometallics* **2008**, *27*, 5984–5996.

(8) For related studies from our group, see: (a) Ito, H.; Watanabe, A.; Sawamura, M. *Org. Lett.* **2005**, *7*, 1869–1871. (b) Ito, H.; Kawakami, C.; Sawamura, M. *J. Am. Chem. Soc.* **2005**, *127*, 16034–16035. (c) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 14856–14857. (d) Ito, H.; Kosaka, Y.; Nonoyama, K.; Sasaki, Y.; Sawamura, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7424–7427. (e) Ito, H.; Sasaki, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2008**, *130*, 15774–15775.

(9) For details of the solvent effect, see Supporting Information.

(10) Yamamoto, Y.; Kirai, N.; Harada, Y. *Chem. Commun.* **2008**, 2010–2012.

(11) DPPF was as effective as Xantphos at 60 °C, while slightly less effective at 40 °C. For details of the ligand effect, see Supporting Information.

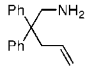
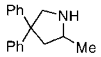
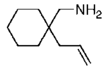
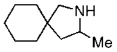
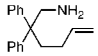
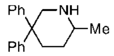
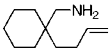
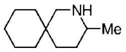
The diphenylmethylene insert of the aminoalkene **1aa** could be replaced with a cyclohexane-1,1-diyl group without affecting the reactivity toward the hydroamination (reaction of **1c**, Table 1, entry 12). Unfortunately, however, the substrate without substituents in the linker chain, where the Thorpe–Ingold effect does not work, resisted the reaction.

The 1,1-disubstituted alkene **1d** also underwent hydroamination under more forcing conditions (15 mol % of Cu, 140 °C) (Table 1, entry 13). Conversely, the addition to a 1,2-disubstituted alkene did not proceed at all.

The extension of the Cu-catalyzed hydroamination from a five- to six-membered ring formation was feasible, as was the case with the other catalyst systems reported previously. Thus, the reaction of 1-amino-5-hexene derivatives **1e** and **1f** occurred within 24 h at 100 °C to give the corresponding piperidine derivatives (**2e** and **2f**) in excellent yields (Table 1, entries 14 and 15).[1]

The Cu catalyst system was also effective for the reaction of *ω*-alkenic primary amines (**1g**–**j**) (Table 2). In fact, the reaction of **1g**–**j** to form five- and six-membered rings in the presence of 10 or 15 mol % of Cu(I)-Xantphos catalyst proceeded at 100 °C, delivering the corresponding NH-free cyclic secondary amines (**2g**–**j**) in high yields. It should be noted that the late transition metal catalyzed intramolecular hydroamination of unactivated alkenes bearing a primary amino group has been achieved in only the cases with the Rh catalyst,[3a] whereas various catalysts have been used for the additions of amides and carbamates, where the nitrogen moieties require installation and removal of the electron-withdrawing group.[4]

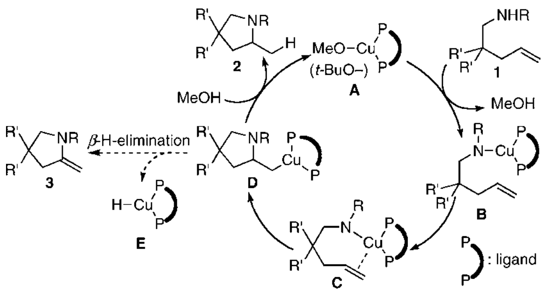
Table 2. Cu(I)-Catalyzed Hydroamination with Primary Aminoalkenes **1g**–**j**[a]

entry	aminoalkene		Cu (mol %)	product		yield (%)[b]
1		**1g**	15		**2g**	92
2		**1h**	15		**2h**	79[c]
3		**1i**	15		**2i**	87
4		**1j**	10		**2j**	91

[a] Conditions: Cu(O-*t*-Bu) (0.05–0.075 mmol), Xantphos (1 equiv to Cu), **1** (0.5 mmol), MeOH/toluene (1:1, 1.0 mL), 100 °C, 72 h. [b] Isolated yield. [c] The isolated yield was reduced by the volatility of the product.

A possible mechanism for the Cu-catalyzed intramolecular hydroamination is proposed in Scheme 2.[7,8] The catalytic cycle would be initiated by *σ*-bond metathesis between alkoxycopper **A** and the H–N bond of the substrate (**1**) to form copper amide **B**. Subsequently, the terminal alkene coordinates to the Cu atom to form Cu-alkene *π*-complex **C**. Next, the addition of the Cu–N bond across the C–C double bond affords alkylcopper intermediate **D** with a nitrogen heterocycle. Finally, protonolysis of the Cu–C bond of **D** with MeOH gives the final product (**2**). According to this mechanism, the protonation of **D** should be much faster than the *β*-hydride elimination to form enamine **3** and copper hydride **E**.

Scheme 2. Proposed Mechanism



In summary, the Cu-Xantphos system catalyzed the intramolecular hydroamination of unactivated terminal alkenes bearing an unprotected aminoalkyl substituent in alcoholic solvents, giving pyrrolidine and piperidine derivatives in excellent yields. This system is applicable to both primary and secondary amines and tolerates a variety of functional groups. We believe that this is a significant step toward economically advantageous and environmentally benign alkene hydroaminations. Further studies to find more efficient catalyst systems based on copper are underway.

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

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