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Copper-catalyzed intramolecular hydroamination of allenylamines to 3-pyrrolines or 2-alkenylpyrrolidines

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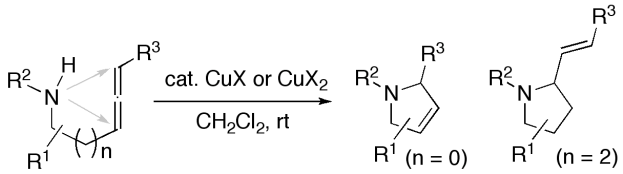

Copper salts, such as CuCl, CuI, $CuCl_2$ and $Cu(OTf)_2$, were used to catalyze the intramolecular hydroamination of allenylamines to provide the corresponding 3-pyrrolines or 2-alkenylpyrrolidines.

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Copper-catalyzed intramolecular hydroamination of allenylamines to 3-pyrrolines or 2-alkenylpyrrolidines

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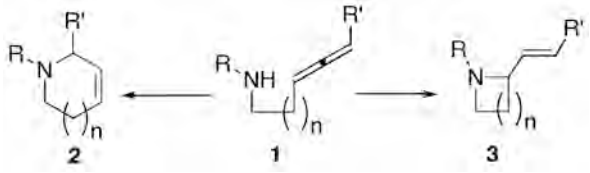
Abstract—Copper salts, such as CuCl, CuI, $CuCl_2$ and $Cu(OTf)_2$, were used to catalyze the intramolecular hydroamination of allenylamines to provide the corresponding 3-pyrrolines or 2-alkenylpyrrolidines.

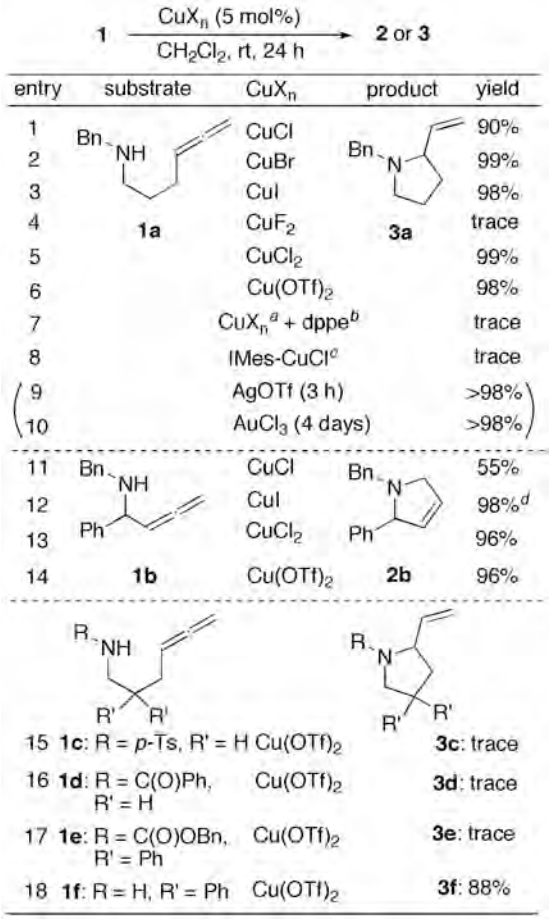
Cyclization of allenylamines **1** gives *N*-heteocycles **2**, *via* an *endo*-hydroamination pathway, or **3**, *via* an *exo*-hydroamination pathway.[1] Many means to catalyze these transformations have been developed with metal salts or complexes of Ti, Zr,[3] lanthanides,[3] Pd,[4] Ag,[5] Au[6] and Hg[7] (Scheme 1).[8] Herein disclosed is our finding that copper (I) and (II) salts, such as CuCl, CuBr, CuI, $CuCl_2$, $Cu(OTf)_2$ [OTf = OSO_2CF_3], can effectively catalyze the transformation of **1** to 3-pyrrolines **2** (n = 0) or 2-alkenylpyrrolidines **3** (n = 2).[9]



Scheme 1. Transformation of allenylamines to *N*-heterocycles.

The results for the reaction of γ-allenylamine **1a** and α-allenylamine **1b** with various copper salts are summarized in entries 1-14 of Table 1. Entries 1-6 show that, except for CuF_2, a variety of copper (I) and (II) salts catalyzed the intramolecular hydroamination of **1a** in an *exo*-cyclization fashion to provide 2-vinylpyrrolidine **3a** in excellent yields. Similarly, **1b** was effectively cyclized, but in an *endo*-fashion, to 3-pyrroline **2b** in good to excellent yields (entries 11-14). The reaction with copper catalysts was faster than that with $AuCl_3$ but slower than that with AgOTf under the same conditions (entries 9 and 10). Introduction of a ligand, such as diphosphine (dppe) and *N*-hetrocyclic carbene, to the reaction with copper salts did not result in any conversion of the substrate (entries 7 and 8). Among the copper salts effective to the reaction, $Cu(OTf)_2$ catalyzed at the fastest rate. As revealed by entries 15-18, secondary as well as primary amines (**1f**) were smoothly cyclized in the presence of copper salts,

Table 1. Copper-catalyzed intramolecular hydroamination of allenylamines.



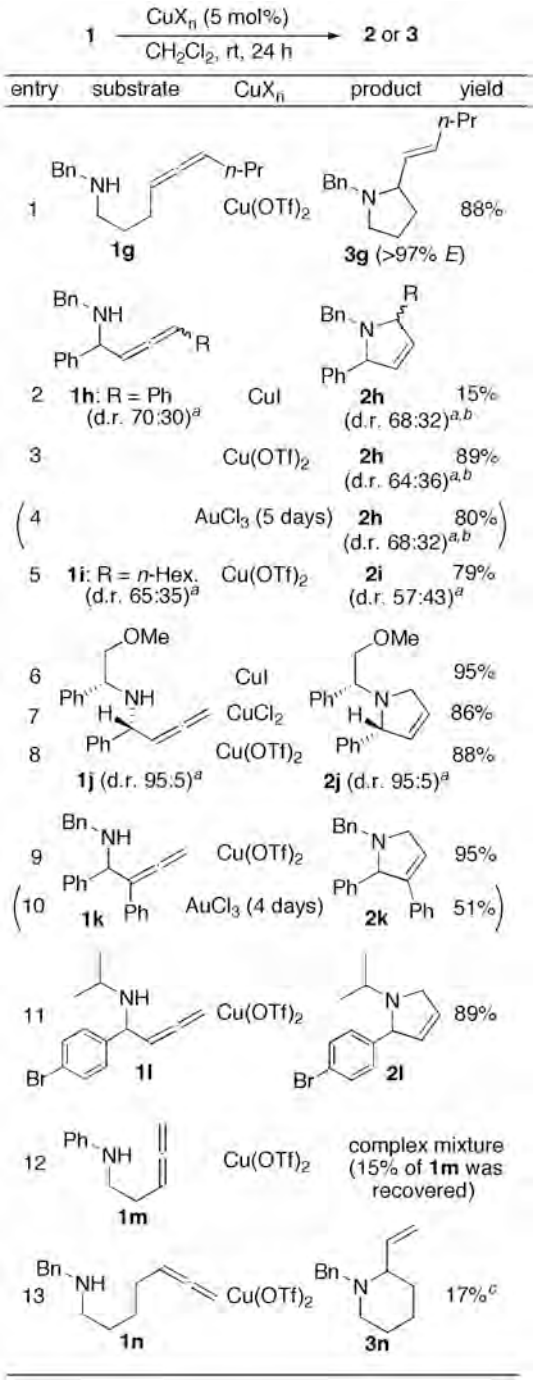
entry	substrate	CuX_n	product	yield
1	**1a**	CuCl	**3a**	90%
2		CuBr		99%
3		CuI		98%
4		CuF_2		trace
5		$CuCl_2$		99%
6		$Cu(OTf)_2$		98%
7		CuX_n[a] + dppe[b]		trace
8		IMes-CuCl[c]		trace
9		AgOTf (3 h)		>98%
10		$AuCl_3$ (4 days)		>98%
11	**1b**	CuCl	**2b**	55%
12		CuI		98%[d]
13		$CuCl_2$		96%
14		$Cu(OTf)_2$		96%
15	**1c**: R = *p*-Ts, R' = H	$Cu(OTf)_2$		**3c**: trace
16	**1d**: R = C(O)Ph, R' = H	$Cu(OTf)_2$		**3d**: trace
17	**1e**: R = C(O)OBn, R' = Ph	$Cu(OTf)_2$		**3e**: trace
18	**1f**: R = H, R' = Ph	$Cu(OTf)_2$		**3f**: 88%

[a]CuI, CuCl or $Cu(OTf)_2$. [b]1,2-Bis(diphenylphosphino)ethane. [c]*N*,*N*'-Di(2,4,6-trimethylphenyl)imidazol-2-ylidene copper (I) chloride. [d]15 h.

whereas all amides tested (**1c**, **1d** and **1e**) did not react in this system at all.

Other representative examples for the transformation are illustrated in Table 2.[10,11] Substrates having an allene-substituent, **1g**, **1h** and **1i**, were cyclized in the presence of $Cu(OTf)_2$ to the corresponding pyrrolidine **3g** and 3-pyrrolines **2h** and **2i**, respectively, in good yields (entries 1-5). Thus, the reaction of **1g** gave 88% of 2-penten-1-ylpyrrolidine **3g** with >97% *E* of olefin geometry. Cyclization of **1h** and **1i** with CuI or $Cu(OTf)_2$ catalyst afforded the corresponding 2,5-disubstituted pyrrolidines with similar diastereomeric ratios to those of the substrates (entries 2-5). The results for the cyclization of **1j** (entries 6-8) indicate that no epimerization at the amine α position(s) occurred under the reaction conditions. β-Substituted α-allenylamine **1k** also smoothly reacted to give 2,3-disubstituted 3-pyrroline **2k** in excellent yield (entry 9). It was observed again that the $Cu(OTf)_2$-catalyzed reaction was much faster than the reaction with $AuCl_3$ (entries 4 and 10). The catalysis could be applied to the cyclization of α-allenylamine having a secondary *N*-substituent (entry 11). The reaction of δ-allenylamines **1n** with $Cu(OTf)_2$ catalyst proceeded slowly to provide 6-*exo*-cyclization product piperidine **3n** in 17% yield after 24 h, where 83% of **1n** was recovered. Meanwhile, β-allenylamine **1m** reacted faster than **1n** but resulted in the formation of a complex mixture.

Table 2. Other representative examples.



[a]Determined by ^{1}H NMR analysis. [b]*Anti(dl)* product was major. [c]After the reaction for 2 days, 81% of **1n** was recovered.

Based on the alkene geometry of the product, reaction mechanisms for the *exo*-cyclization, *via* the metal-catalyzed intramolecular hydroamination of allenylamines, have been proposed in the literatures involving an *anti*-aminometallation pathway through a metal-coordinated allenic species **a** or **b** [Figure 1, (i), in which **a** is disfavor due to steric repulsion between R and NHR' groups] and an *syn*-aminometallation process through a metal amide intermediate **c** [Figure 1, (ii)].[1-8] As revealed from the results of the transformation of **1g**, the present copper-catalyzed reaction gave **3g** with high selectivity for the *E*-olefin geometry and, therefore, an *anti*-aminometallation pathway (i) may be postulated for the mechanism.[12]

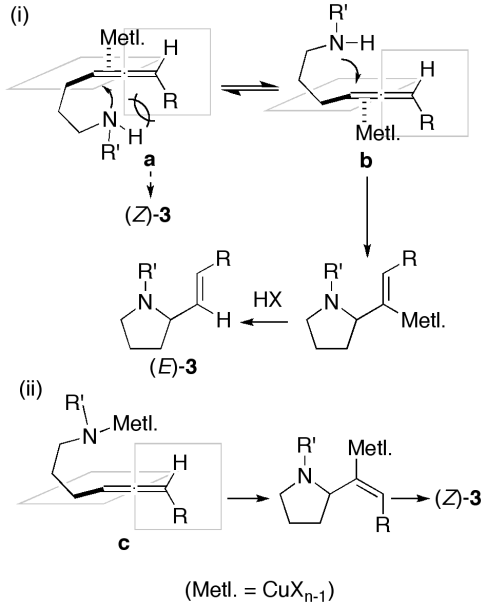


Figure 1. Possibility for the reaction mechanism.

In summary, we have demonstrated that the intramolecular hydroamination of allenylamines to 3-pyrolines or 2-alkenylpyrrolidines is effectively catalyzed by various copper salts. These salts, which exhibited good catalytic reactivity, are inexpensive and relatively less-toxic, both of which are characteristics that should be synthetically useful especially for application to a large-scale process. More details concerning the stereospecificity of the reaction and its application to asymmetric processes are underway.

Acknowledgement

This study was partially supported by the Scientific Frontier Research Project from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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10. *General Procedure*: To a solution of allenylamine **1** (0.50 mmol) in CH_2Cl_2 (1.0 mL) was added a copper salt (0.0025 mmol, 5.0 mol%) and then the mixture was stirred at ambient temperature. After addition of aqueous saturated Na_2CO_3, the mixture was extarcted with ether (2 x 10 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography. Spectroscopic data of **3a** and **3n** (^1H, ^{13}C NMR) were in good agreement with those reported (Katrizky, A. R.; Yao, J.; Yang, B. *J. Org. Chem.* **1999**, *64*, 6066). ^1H NMR data of other products (500 or 600 MHz, $CDCl_3$) δ: **2b**, 7.10-7.95 (m, 10H), 5.85 (d, *J* = 4.5 Hz, 1H), 5.72 (d, *J* = 4.5 Hz, 1H), 4.61 (br s, 1H), 3.97 (d, *J* = 13.5 Hz, 1H), 3.75 (dd, *J* = 4.5, 14.0 Hz, 1H), 3.55 (d, *J* = 13.5 Hz, 1H), 3.31 (dd, *J* = 5.5, 14.0 Hz, 1H); **2h** 6.90-7.50 (m, 15H), (for *anit, dl*) 5.97 (br s, 1H), 4.98 (br s, 1H), 3.73 (d, *J* = 14.5 Hz, 1H), 3.25 (d, *J* = 14.5 Hz, 1H), (for *syn, meso*) 5.68 (br s, 1H), 4.85 (br s, 1H), 3.82 (s, 2H); **2i** 7.10-7.50 (m, 10H), 1.10-1.70 (m, 10H), 0.88 (t, *J* =7.2 Hz, 3H), (for major) 5.72 (br d, *J* = 6.0 Hz, 1H), 5.58 (br d, *J* = 5.4 Hz, 1H), 4.68 (dt, *J* = 4.8, 2.4 Hz, 1H), 3.92 (d, *J* = 13.8 Hz, 1H), 3.82 (m, 1H), 3.80 (d, *J* = 13.8 Hz, 1H), (for minor), 5.97 (br d, *J* = 6.6 Hz, 1H), 5.81 (br s, *J* = 6.0 Hz, 1H), 4.79 (d, *J* = 5.4 Hz, 1H), 3.69 (m, 1H), 3.81 (d, *J* = 14.4 Hz, 1H), 3.49 (d, *J* = 14.4 Hz, 1H); **2j**, 6.90-7.40 (m, 10H), 5.73 (br s, 1H), 5.52 (br s, 1H), 4.80 (br s, 1H), 3.91 (t, *J* = 5.5 Hz, 1H), 3.61-3.83 (m, 3H), 3.58 (dd, *J* = 6.8, 9.6 Hz, 1H), 3.15 (s, 3H); **2k**, 7.10-7.45 (m, 15H), 6.31 (dd, *J* = 2.5, 4.0 Hz, 1H), 5.04 (br s, 1H), 3.83 (d, *J* = 13.0 Hz, 1H), 3.82 (ddd, *J* = 1.5, 5.5, 14.0 Hz, 1H), 3.62 (d, *J* = 13.0 Hz, 1H), 3.55 (ddd, *J* = 1.5, 4.0, 14.0 Hz, 1H); **2l**, 7.41 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 5.80 (d, *J* = 3.5 Hz, 1H), 5.56 (d, *J* = 3.5 Hz,

1H), 4.66 (br s, 1H), 3.84 (dd, J = 5.5, 14.5 Hz, 1H), 3.57 (dt, J = 14.5, 3.0 Hz, 1H), 2.86 (hept, J = 6.0 Hz, 1H), 0.99 (d, J = 6.5 Hz, 3H), 0.96 (d, J = 6.0 Hz, 3H); **3f**, 7.04-7.42 (m, 10H), 5.86 (ddd, J = 6.9, 10.3, 17.2 Hz, 1H), 5.12 (d, J = 17.2 Hz, 1H), 4.97 (d, J = 10.3 Hz, 1H), 3.76 (d, J = 10.9 Hz, 1H), 3.74 (m, 1H), 3.45 (d, J = 10.9 Hz, 1H), 2.75 (ddd, J = 1.7, 6.9, 12.6 Hz, 1H), 2.25 (dd, J = 9.2, 12.6 Hz, 1H); **3g**, 7.18-7.34 (m, 5H), 5.61 (dt, J = 14.9, 6.9 Hz, 1H), 5.38 (dd, J = 8.0, 14.5 Hz, 1H), 4.04 (d, J = 13.2 Hz, 1H), 3.02 (d, J = 13.2 Hz, 1H), 2.92 (t, J = 8.1 Hz, 1H), 2.72 (q, J = 8.0 Hz, 1H), 2.02-2.10 (m, 3H), 1.93 (m, 1H), 1.57-1.80 (m, 3H), 1.36-1.47 (m, 2H), 0.91 (t, J = 7.5 Hz, 3H).

11. *Preparation of allenylamines*: Allenylamines **1a**, **1c-f**, **1m** and **1n** were prepared from the corresponding terminal alkynes by treatment with $(CH_2O)_n$, $(i\text{-Pr})_2NH$, CuI. See refs 2-6. Compounds **1b** and **1h-le** were synthesized from imines through the reaction of the corresponding (η^2-imine)Ti(O-*i*-Pr)$_2$ complexes with propargyl compounds. See: Fukuhara, K.; Okamoto, S.; Sato, F. *Org. Lett.* **2003**, *5*, 2145. For synthesis of **1g**, see ref 2b.
12. Production of **2b** from **1b** by the reaction with 5 mol% of CuI in the presence of CaH_2 (10 mol%) as a proton scavenger could rule out the possibility of the role of a proton as an actual catalyst.