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

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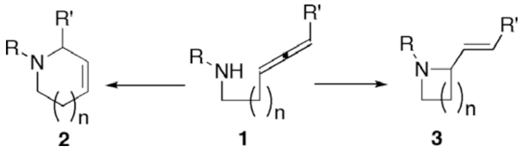
ABSTRACT

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*-heterocycles **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, $CuCl_2$ and $Cu(OTf)_2$ [$OTf = OSO_2CF_3$], can effectively catalyze the transformation of **1** to 3-pyrrolines **2** ($n = 0$) or 2-alkenylpyrrolidines **3** ($n = 2$).[9]

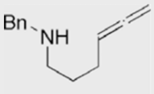
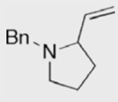
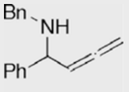
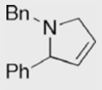
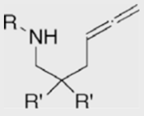
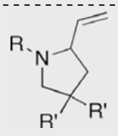
The results for the reaction of γ-allenylamine **1a** and α-allenylamine **1b** with various copper salts are summarized in entries 1–14 of Table 1. Entries 1–6 show that, except for CuF_2, a variety of copper (I) and (II) salts catalyzed the intramolecular hydroamination of **1a** in an *exo*-cyclization 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 ligands, such as diphosphine (dppe) and *N*-heterocyclic carbene, to the reaction with copper salts did not result in any conversion of the substrate (entries 7 and 8). Among the copper salts that were 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, whereas all amides tested (**1c**, **1d** and **1e**) did not react in this system at all.



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

Table 1
Copper-catalyzed intramolecular hydroamination of allenylamines

$$\mathbf{1} \xrightarrow[CH_2Cl_2,\ rt,\ 24\ h]{CuX_n\ (5\ mol\%)} \mathbf{2}\text{ or }\mathbf{3}$$

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.

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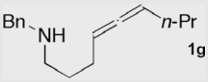
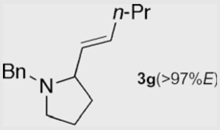
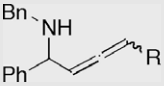
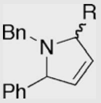
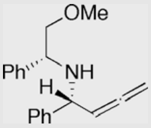
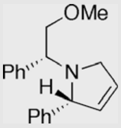
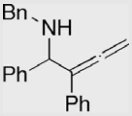
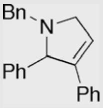
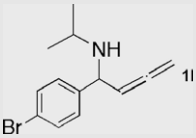
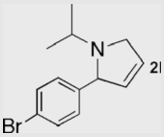
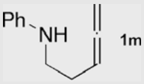
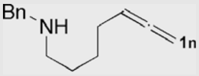
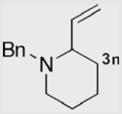
Other representative examples for the transformation are illustrated in Table 2.[10,11] Substrates having an allene-substituent, **1g**, **1h** and **1i**, were cyclized in the presence of Cu(OTf)$_2$ to the corresponding pyrrolidine **3g** and 3-pyrrolines **2h** and **2i**, respectively, in good yields (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

Table 2
Other representative examples

$$\mathbf{1} \xrightarrow[\text{CH}_2\text{Cl}_2\text{, rt, 24 h}]{\text{CuX}_n\text{ (5 mol\%)}} \mathbf{2}\text{ or }\mathbf{3}$$

Entry	Substrate	CuX$_n$	Product	Yield (%)
1	 1g	Cu(OTf)$_2$	 3g(>97%*E*)	88
				
2	**1h**: R = Ph (dr 70:30)[a]	CuI	**2h** (d.r. 68:32)[a,b]	15
3	**1h**: R = Ph (dr 70:30)[a]	Cu(OTf)$_2$	**2h** (d.r. 64:36)[a,b]	89
(4	**1h**: R = Ph (dr 70:30)[a]	AuCl$_3$ (5 days)	**2h** (d.r. 68:32)[a,b]	80)
5	**1i**: R = n-Hex (dr 65:35)[a]	Cu(OTf)$_2$	**2i** (d.r. 57:43)[a]	79
				
6	**1j** (dr 95:5)[a]	CuI	**2j** (dr 95:5)[a]	95
7	**1j** (dr 95:5)[a]	CuCl$_2$	**2j** (dr 95:5)[a]	86
8	**1j** (dr 95:5)[a]	Cu(OTf)$_2$	**2j** (dr 95:5)[a]	88
				
9	**1k**	Cu(OTf)$_2$	**2k**	95
(10	**1k**	AuCl$_3$ (4 days)	**2k**	51)
11	 1l	Cu(OTf)$_2$	 2l	89
12	 1m	Cu(OTf)$_2$	Complex mixture (**15** of **1m** was recovered)	
13	 1n	Cu(OTf)$_2$	 3n	17[c]

[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.

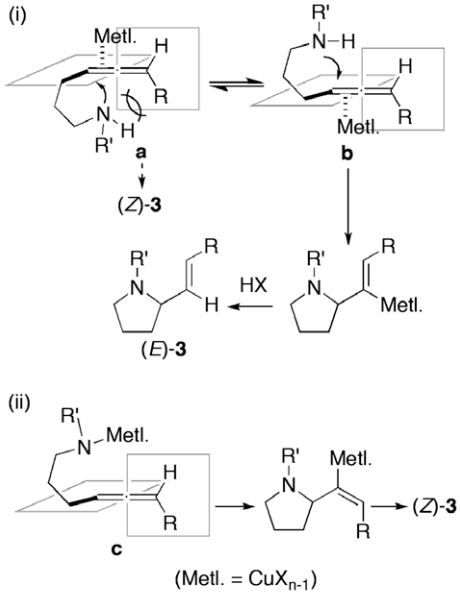


Figure 1. Possibility for the reaction mechanism.

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.

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** (Fig. 1, (i), in which **a** is disfavour due to steric repulsion between R and NHR' groups) and an *syn*-aminometallation process through a metal amide intermediate **c** (Fig. 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]

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 are 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.

Acknowledgements

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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 solution, the mixture was extracted with ether (2 × 10 mL), dried over anhydrous $MgSO_4$ and concentrated in vacuo. The resultant residue was purified by silica gel column chromatography. Spectroscopic data of **3a** and **3n** (^{1}H, ^{13}C NMR) were in good agreement with those reported (Katrizky, A. R.; Yao, J.; Yang, B. *J. Org. Chem.* **1999**, *64*, 6066). ^{1}H 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* = .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, 3 H), 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 $(CH_2O)_n$, $(i\text{-Pr})_2NH$ and CuI. See Refs. 2–6. Compounds **1b** and **1h**–**e** 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.