Organic LETTERS
Letter
pubs.acs.org/OrgLett

Copper-Catalyzed Hydroamination of Terminal Allenes

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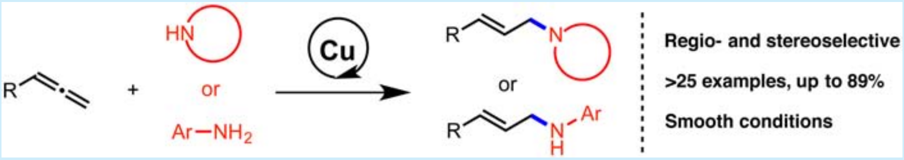
Supporting Information

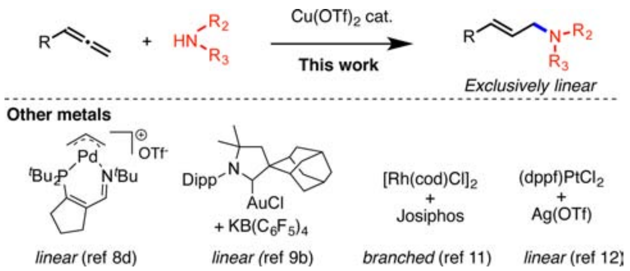


ABSTRACT: The ligand-free copper-catalyzed hydroamination of allenes has been accomplished in the presence of cyclic secondary amines or anilines derivatives. This novel methodology undergoes the selective generation of (*E*)-allylamines under smooth conditions with total regio- and stereoselectivity.

Currently, hydroamination reactions constitute the most direct and atom-economical synthetic approach starting from a molecule containing an unsaturated C−C bond to generate amines and derivatives. Over 15 years, a bountiful number of reports have described novel catalysts for this efficient transformation. Among them, late transition metals appeared to be the most efficient, and numerous precursors of catalyst for hydroamination of alkenes, alkynes, and allenes have been reported.[1] However, most of the used d-block metals are expensive and need an association with a complex ligand. On the other hand, iron and copper do not suffer from these practical and economical drawbacks. Fe-catalyzed cyclohydroamination of aminoalkenes was recently developed by Hannedouche thanks to a well-defined iron-catalyst.[2] The Lalic,[3] Miura,[4] and Buchwald[5] groups quasi simultaneously reported a formal hydroamination of alkenes catalyzed by a copper system in the presence of electrophilic amines. In 2014, Yang et al. reported the first Fe-catalyzed hydroamination with the use of electrophilic aminating reagents.[6] Though these original methods are efficient in terms of reactivity, they suffer from the necessary prefunctionalization of the amines. In our group, we studied cross-coupling and hydroamination reactions catalyzed by simple, cheap, and easy to handle catalysts based on copper or iron.[7] In 2015, we were able to describe two copper-based catalytic systems enabled to perform the regio- and stereoselective hydroamination of terminal alkynes with nonmodified secondary amines.[7l,m]

To pursue our efforts for the development of simple methods to create C−N bonds, we focused our attention on the addition of amines on terminal allenes catalyzed by copper systems. To the best of our knowledge, there are no examples in the literature of intermolecular hydroamination of allenes promoted by a copper catalyst.

Scheme 1. Representative Examples with Metal-Catalyzed Hydroamination of Cyclic Secondary Amines or Anilines



The intermolecular hydrofunctionalization of allenes with secondary amines and anilines has been described with different metal-based catalysts such as Pd,[8] Au,[9] Ag,[10] Rh,[11] Pt,[12] Zr,[13] and Ti[14] (Scheme 1). Palladium-based catalysts were the most described metallic system for the hydroamination of terminal allenes. It is noteworthy that well-defined Au-based catalysts associated with complex ligands (NHC, diaryl phosphines) were also efficient for these transformations. To date, only one example catalyzed by a copper-based system has been reported in intramolecular reaction for the cyclization of aminoallenes.[15]

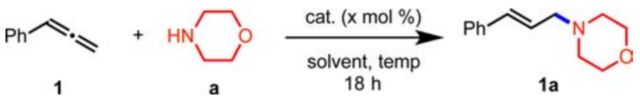
Herein, we report the first example of intermolecular hydroamination of allenes catalyzed by a copper system. This ligand-free, copper-catalyzed strategy offers cheap and smooth synthetic access to (*E*)-allylamines from simple and easy-accessible substrates.

Our study began with the model reaction of phenylallene **1** with morpholine **a** in the presence of different copper sources (see the Supporting Information (SI)) under various conditions of temperature and time (Table 1). Without any ligand or solvent, results showed that 20 mol % of $Cu(OTf)_2$ appeared to be the most effective catalyst for the formation of the expected (*E*)-allyl amine **1a** when the reaction was performed at 120 °C for 18 h (Table 1, entry 1, and SI). Blank experiments confirmed the absolute necessity of the copper presence and also showed that triflic acid is not responsible for this

Received: February 16, 2016
Published: March 9, 2016

DOI: 10.1021/acs.orglett.6b00452
Org. Lett. 2016, 18, 1482−1485

Table 1. Hydroamination of Phenylallene with Morpholine: Selected Data for Reaction Development[a,b]



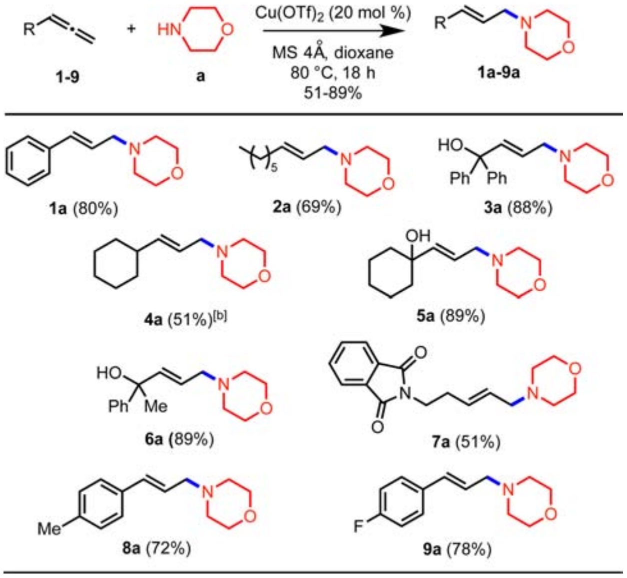
entry	cat. (mol %)	solvent	temp (°C)	yield[b] (%)
1	$Cu(OTf)_2$ (20)		120	46
2			120	nd
3	HOTf (40)		120	nd
4	$Cu(OTf)_2$ (40)		120	60
5	$Cu(OTf)_2$ (40)		80	68
6	$Cu(OTf)_2$ (40)		50	78
7	$Cu(OTf)_2$ (40)		rt	9
8	$Cu(OTf)_2$ (20)		50 (80)	29 (61)[c]
9	$Cu(OTf)_2$ (40)	DMF	50 (80)	46 (68)[c]
10	$Cu(OTf)_2$ (40)	NMP	50 (80)	49 (69)[c]
11	$Cu(OTf)_2$ (40)	DMSO	50 (80)	47 (59)[c]
12	$Cu(OTf)_2$ (40)	dioxane	50 (80)	42 (79)[c]
13	$Cu(OTf)_2$ (40)	dioxane MS 4 Å	80	85
14	$Cu(OTf)_2$ (20)	dioxane MS 4 Å	80	84 (72)[d]

[a] Reaction conditions: **1** (0.5 mmol), **a** (2.0 mmol) and catalyst (0.1 to 0.2 mmol) were placed in a screw tube under argon with or without solvent (0.5 mL) for 18 h at indicated temperature. [b] NMR yields using 1,3,5-trimethoxybenzene as internal standard. [c] 80 °C. [d] Reaction conducted with 3 equiv of amine.

hydroamination reaction (Table 1, entries 2 and 3). In a second experiment, we tested various amounts of $Cu(OTf)_2$ at different temperatures, and we observed that 40 mol % of the latter at 50 °C allowed the formation of 78% of the allyl amine **1a** (Table 1, entries 4–8). At this stage of development, we tested a series of solvents and showed that the reaction carried out in dioxane also afforded a good yield (79%) of **1a** but at higher temperature (80 °C) (Table 1, entries 9–12). However, we demonstrated that under these conditions addition of molecular sieves (4 Å) increased the formation rate of **1a** and allowed the use of only 20 mol % of catalyst (Table 1, entries 13 and 14). Finally, we showed that 4 equiv of morpholine is necessary to obtain the best formation yield in **1a** (Table 1, entry 14). Nevertheless, we were able to recover 75% of remaining **a** at the end of the reaction (see the SI) and then to engage them in a new reaction. To resume this reaction development, we set up the reaction conditions as follows: in a solution of dioxane at 80 °C with molecular sieves 4 Å in the presence of 20 mol % of $Cu(OTf)_2$, the reaction of 0.5 mmol of phenylallene **1** with 2 mmol of morpholine **a** undergoes the formation of 84% of the desired amine **1a** in 18 h.

With this efficient catalytic system in hand, we undertook studies of the scope and limitations of the hydroamination reaction by first varying the nature of the allene substrate (Scheme 2). Both aromatic and alkyl terminal allenes are suitable substrates for this reaction. We were pleased to obtain the corresponding hydroaminated products (**1a**–**9a**) in fair to excellent yields. Furthermore, allenic alcohols engaged under optimized conditions selectively provided the desired molecules (**3a**, **5a**, **6a**) in greater than 88% yield. All of the obtained products are formed by the formal addition of the morpholine **a** on the terminal carbon of the allenes **1**–**9** and present a *E* double bond. We also observed that both electron-withdrawing and electron-donating groups with *para*-substitution on the aromatic ring of the starting allene allowed the formation of aminated molecules **8a** and **9a**, respectively, in 72% and 78% yields. It is worth noting that hydroamination of internal or 1,1-disubstituted allenes under these conditions did not provide the expected aminated molecules.

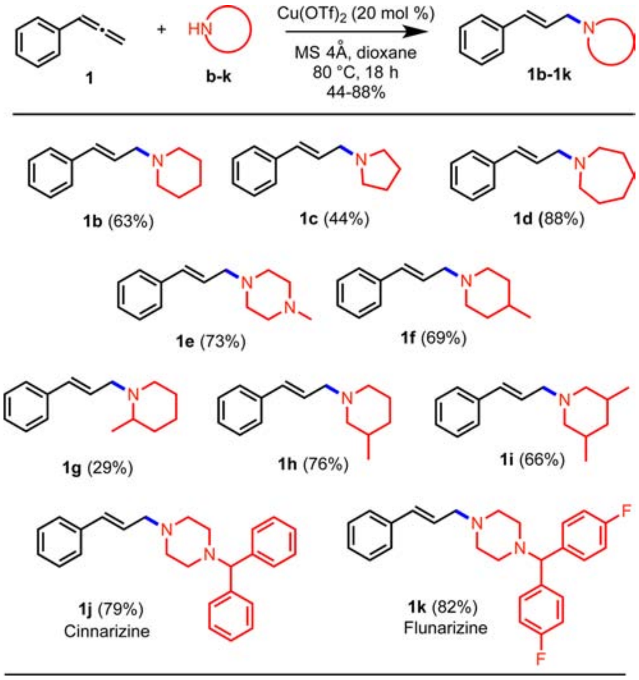
Scheme 2. Cu-Catalyzed Hydroamination of Different Allenes[a]



[a] Reaction conditions: **1**–**9** (0.5 mmol), **a** (2 mmol), $Cu(OTf)_2$ (0.1 mmol), molecular sieves 4 Å (100 mg), dioxane (0.5 mL), argon, 80 °C, 18 h. Isolated yields.

We then showed that this easy-to-handle catalytic reaction is tolerant toward various cyclic secondary amines (Scheme 3). Starting with piperidine **b**, pyrrolidine **c**, and azepane **d**, the

Scheme 3. Cu-Catalyzed Hydroamination of Phenylallene with Various Cyclic Secondary Amines[a]

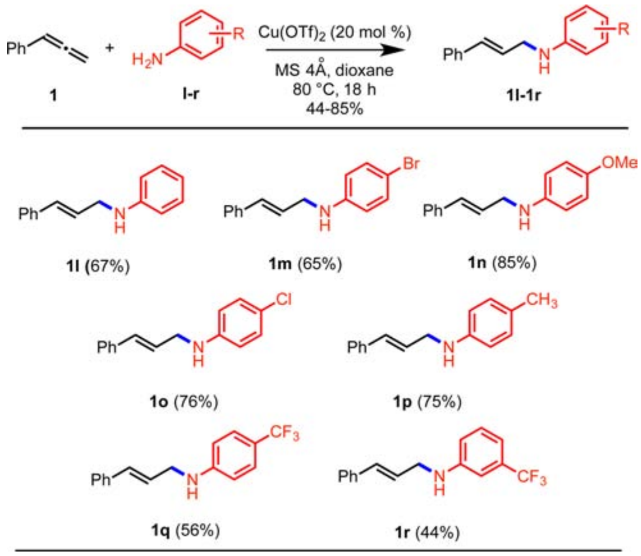


[a] Reaction conditions: **1** (0.5 mmol), **b**–**k** (2 mmol), $Cu(OTf)_2$ (0.1 mmol), molecular sieves 4 Å (100 mg), dioxane (0.5 mL), argon, 80 °C, 18 h. Isolated yields.

corresponding allylic amines **1b–d** were obtained in moderate to excellent yields (63%, 44%, and 88%, respectively). Various substitutions on 6-membered cyclic amines **f–i** also provided the desired products in fair to good yields, except with 2-methylpiperidine **g**, probably due to steric hindrance. Unfortunately, primary aliphatic amines did not constitute suitable substrates for this reaction. We also applied the smooth reaction conditions to the synthesis of two biologically active molecules. We thus obtained cinnarizine[16] **1j** (treatment of problems affecting the inner ear and balance, such as dizziness and sickness) and flunarizine[17] **1k** (treatment of migraine, occlusive peripheral vascular disease, and vertigo of central and peripheral origin), respectively, in 79% and 82% yields. This copper-catalyzed route constitutes a direct, smooth, and efficient pathway for the formation of these drugs.

Finally, we successfully showed that various aniline derivatives **l–r** are also suitable N-nucleophiles for the hydroamination of allenes (Scheme 4). Thus, the reaction of phenylallene **1** with aniline **l** provided the desired molecule **1l** in 67% yield. The reaction could also be efficient with halogenated anilines (with 4-Br and 4-Cl) and afforded **1m** and **1o**, respectively, in 65% and 76% yields. We noticed that electron-donating substituents in the *para*-position on the aromatic ring of aniline allowed the formation of the corresponding allylamines **1n** and **1p** in good yields, whereas the anilines bearing an electron-withdrawing group afforded **1q** and **1r** in modest yields of 56% and 44%.

Scheme 4. Cu-Catalyzed Hydroamination with Various Anilines[a]



[a]Reaction conditions: **1** (0.5 mmol), **l–r** (2 mmol), $Cu(OTf)_2$ (0.1 mmol), molecular sieves 4 Å (100 mg), dioxane (0.5 mL), argon, 80 °C, 18 h. Isolated yields.

In summary, hydroamination of terminal allenes with cyclic secondary amines and anilines can now be effected using a very simple catalytic system based on ligand-free copper(II)triflate. This novel methodology also features a regio- and stereo-selective access to (*E*)-allylamines with fair to excellent yields. A broad range of allenes and amines was tolerated for this valuable catalytic transformation. Ongoing studies of kinetic and theoretical investigations for the elucidation of the mechanism will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00452.

Detailed experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support provided by Région Languedoc-Roussillon (Chercheur d'Avenir fellowship to FM), IUF (Institut Universitaire de France to FM), ANR CD_2I (Agence Nationale de la Recherche), and CNRS is warmly acknowledged.

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