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Copper-Catalyzed Hydroamination of *N*-Allenylazoles: Access to Amino-Substituted *N*-Vinylazoles

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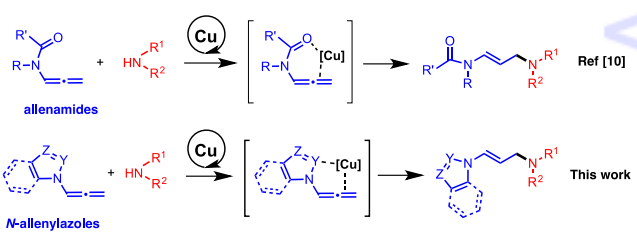
Abstract. Building on mechanistic studies, the innate capability of azoles to act as a directing group has been exploited to design an efficient and simple procedure for the hydroamination of *N*-allenylazoles with secondary amines. The reaction proceeds under mild conditions by copper(I) catalysis yielding the corresponding and original linear *E* allylic amines with total regio- and stereoselectivity. Density Functional Theory (DFT) calculations offer a mechanistic explanation of the significantly higher reactivity of *N*-allenyl-(1,2)-azoles compared to their 1,3-analogues as a result of the reaction-enhancing coordination of the pyridine-like nitrogen to the copper center.

Keywords: Allenes; copper; hydroamination; homogeneous catalysis; reaction mechanisms

Currently, hydroamination of unsaturated compounds is one of the most straightforward and atom-economical pathways to generate amines from simple substrates. Due to its high activation barrier, hydroamination reactions require a catalyst, often based on early- or late-transition metals, or alkali earth metals.[1] Among the numerous reports describing hydroamination, allenes are used much less often than alkynes and alkenes, even if some of them are readily available.[2] Catalytic systems based on Pd,[3] Pt,[4] Au,[5] Rh[6], Ni[7] or Ag[8] are able to perform intermolecular hydroamination of allenes with the selective formation of linear or branched allylic amines. In 2016, our group reported the first copper-catalyzed intermolecular hydroamination of aliphatic and aromatic terminal allenes with $Cu(OTf)_2$ at 80 °C.[9] In a recent study, mechanistic investigations revealed the prominent role of the *in situ*-formed Cu(I) as catalytically active species and spurred the extension of this reaction to allenamides under mild conditions at room temperature with a cationic Cu(I) catalyst.[10] One of the key factors for the success of this reaction under milder conditions was the effect of the coordination of copper by the oxygen atom of the allenamide (Scheme 1).
Capitalizing on this concept of anchimeric assistance, we decided to explore the latter by testing others directing groups anchored on the allene. Thus we aimed to extend this chelating-assisted catalysis to other classes of substrates having a built-in nitrogen coordinating moiety, and namely *N*-allenylazoles (Scheme 1).



Scheme 1. Hydroamination of allenes derivatives featuring innate directing groups.

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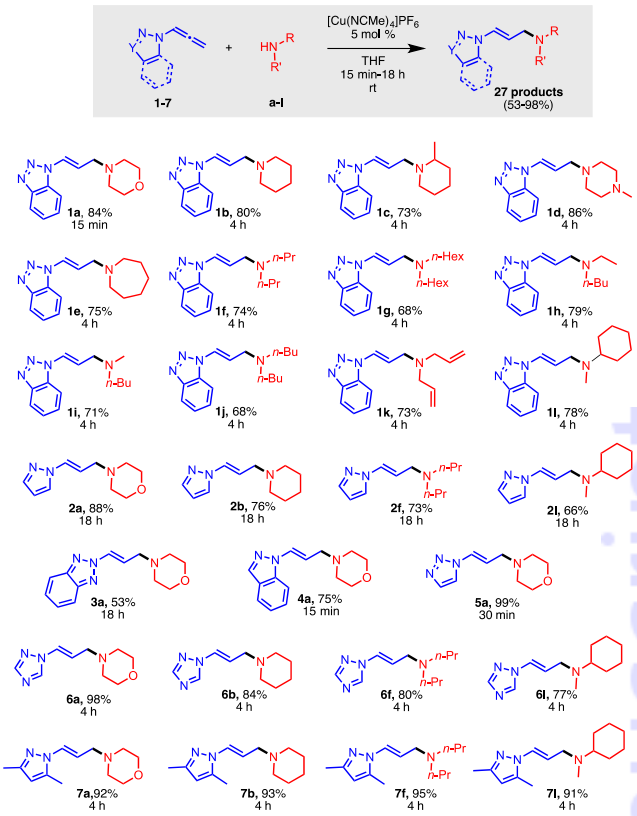
Herein we report the hydroamination of *N*-allenylazoles catalyzed by Cu(I) under smooth conditions. This powerful methodology allows the synthesis of original *N*-vinylazoles bearing an amino substituent at the allylic position, with excellent regio- and *E* stereoselectivities.

We initially began our study by selecting 1-allenyl-1*H*-benzotriazole **1** and morpholine **a** as the model substrates. First we wanted to confirm the feasibility of the reaction under the previously reported conditions.[10-11] The use of 5 mol % of $[Cu(NCMe)_4]PF_6$ at room temperature using only 1.2 equivalents of the amine partner provided the desired hydroaminated product **1a** with 84% yield in only 15 min (Scheme 2).

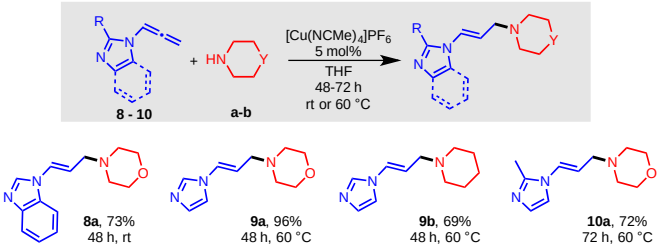
With these smooth conditions in hand, we then explored the scope and limitations of this novel reaction. A set of seven different *N*-allenyl-(1,2)-azoles (**1-7**) was tested as summarized in scheme 2. In all the cases, the corresponding *E* allylic amines were isolated in good yields. No detectable amounts of the *Z* amine or other isomeric products were formed, as assessed by ^{1}H NMR spectroscopic analysis of the crude reaction mixtures. Allenes substituted by benzotriazole **1** and **3**, pyrazole **2** and **7**, indazole **4**, triazoles **5** and **6** are suitable partners for this reaction. Hydroaminated products **1a**, **4a** and **5a** containing morpholine were obtained in very short reaction times with good yields. Allenylpyrazoles **2** required a longer reaction time to obtain similar results (Scheme 2, **2a**). It is worth noting that these reaction conditions are efficient after 4 h for a large array of amine partners such as cyclic (**a-e**), open-chain (**f-j**), bis(allylic) **k**, and sterically hindered amines (**c** and **l**). Unfortunately, no reaction took place when primary amines were employed as substrates.



[a]Reaction conditions: 1-7 (1 equiv), a-l (1.2 equiv), $[Cu(NCMe)_4]PF_6$ (5 mol %), THF, argon. Isolated yields.

Scheme 2. Cu-catalyzed hydroamination of *N*-allenyl-(1,2)-azoles.[a]

In a second set of experiments, we decided to extend the methodology to *N*-allenyl-(1,3)-azoles and their benzo-fused analogues (Scheme 3), unable to provide anchimeric assistance (Scheme 1). Within this class of substrates, the reactivity is strikingly variable.[8] When *N*-allenylbenzimidazole **8** was reacted with morpholine in the presence of $[Cu(NCMe)_4]PF_6$, (5 mol%), it took 48 h of reaction to obtain the desired product **8a** in 73% yield. On the other hand, *N*-allenylimidazoles **9** and **10** are significantly less reactive. Almost no reaction takes place at room temperature and heating the reaction mixture at 60 °C for longer time is needed to obtain the corresponding products **9a-b** and **10a**. Irrespective of reaction rate, yields are good to excellent.



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[a]Reaction conditions: allene **8-10** (1.0 equiv), **a-b** (1.2 equiv), 5 mol % of $[Cu(NCMe)_4]PF_6$, THF, argon. Isolated yields.

Scheme 3. Cu-catalyzed hydroamination of *N*-allenyl-(1,3)-azoles.[a]

The trends in the reactivity of the heterocyclic substrates considered herein are summarized in Figure 1. Generally speaking, *N*-allenyl-substituted azoles featuring a second nitrogen atom at position 2 are more reactive than imidazoles and benzimidazole is more reactive than imidazole.

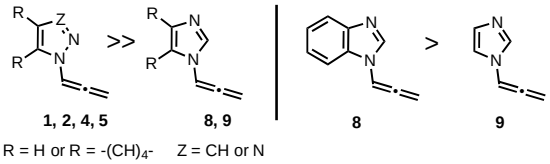
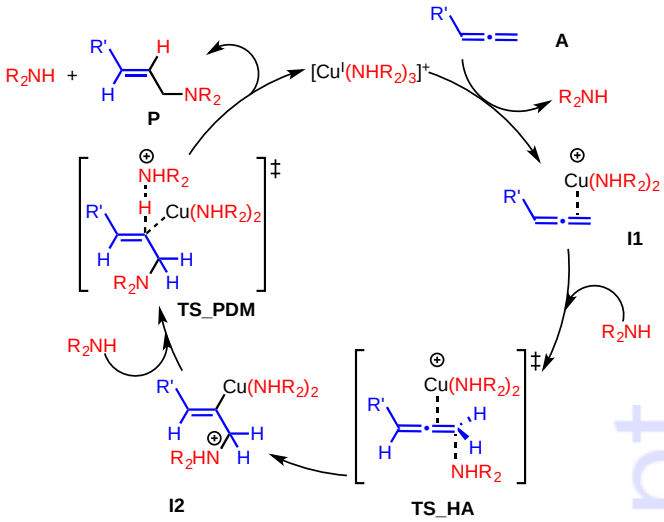


Figure 1. Reactivity trends for the hydroamination of different *N*-allenylazoles.

In order to explain these trends and confirm our initial working hypothesis on the role of the second N atom as an additional coordination site for the catalyst, we engaged in theoretical mechanistic studies, which were performed at Density Functional Theory (DFT) level. Four model substrates were chosen: *N*-allenyl-1*H*-pyrazole (**2**), *N*-allenyl-1*H*-imidazole (**9**), *N*-allenyl-1*H*-indazole (**4**), *N*-allenyl-1*H*-benzimidazole (**8**). Compounds **2** and **4** are representative of 1,2-azoles, **8** and **9** of 1,3-azoles; **4** and **8** are benzo-fused, while **2** and **9** are not.
Consistently with what we have demonstrated in our previous study concerning the hydroamination of allenamides,[10] the reaction takes place by a rate-limiting *antiperiplanar* attack (with respect to copper, Scheme 4) of the amine on the cationic allene/Cu(I) complex **I1** *via* transition state **TS_HA**.[12] This process leads to the *Z* alkenylcopper intermediate **I2**, which in turn gives the *trans* alkene **P** after stereospecific proto-demetallation with retention of configuration *via* **TS_PDM**.



Scheme 4. Catalytic cycle for the Cu-catalyzed hydroamination of allenes. [10]

With reference to the heterocyclic moiety, two conformers of the relevant transition state are possible, featuring a *proximal* or a *distal* relationship between Cu and the YZ moiety of the heteroaromatic ring (Figure 2). If Y=N, complexation to the copper center is possible only in the *proximal* configuration, and it can stabilize the transition state, similarly to what happens for the oxygen atom of the amide in the case of allenamides (cf. Scheme 1). [10]

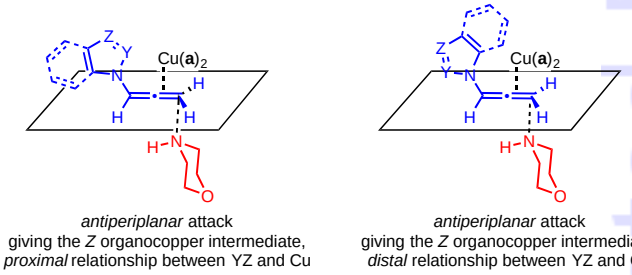


Figure 2. Schematic representation of the two possible conformers of the transition state for the hydroamination of *N*-allenylazoles.

The transition states depicted in figure 2 have been located by DFT calculations for all four model compounds (**2**, **4**, **8** and **9**), so that the energetics of the rate-limiting step of the catalytic reaction could be assessed (Figure 3, see the Supporting Information for computational details and additional data).

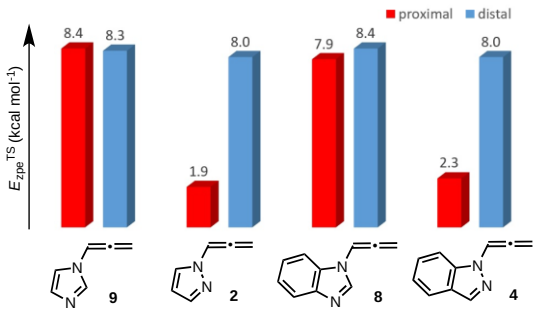


Figure 3. Energetics of the transition states for the hydroamination of model substrates with morpholine. Gibbs free energies calculated at the DFT level are reported in kcal mol^{-1} for both proximal and distal conformers, with reference to the uncoordinated allene, amine *a* and the complex [Cu(*a*)$_2$]$^+$, which have been set to zero.

From the transition state energies shown in Figure 3, it is clear that in the *proximal* conformation the activation barrier for the case of 1,2-azoles (**2** and **4**) is significantly lower than the one of their 1,3-analogues (**9** and **8**). Inspection of the geometries of the transition state confirms the anticipated coordination of the pyridine-like nitrogen of pyrazole **2** in the *proximal*-type transition state, while this is not possible for imidazole **9** (Figure 4). Moreover, the transition state for **2** is significantly more *product-like* than that of **9**, as can be inferred by comparing the length of the newly forming C-N bond (2.05 Å vs 2.20 Å, respectively).

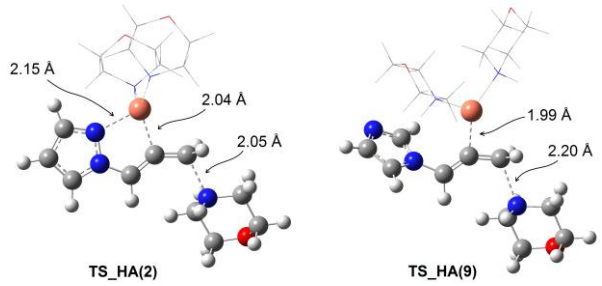


Figure 4. Transition states for the hydroamination of 2 and 9 (*proximal*-type conformer shown), as obtained by DFT modeling.

In the case of 1,3-azoles, coordination of copper by the pyridine-like nitrogen is not a reaction-enhancing event as it is for pyrazoles, but it is a pathway that competes with productive allene π-coordination. Moreover, energetics of the transition state alone may not be the only reason for the enhanced reactivity of benzimidazole **8** compared to imidazole **9**. A possible further contribution to this disparity is that the pyridine-like nitrogen of benzimidazole is less available for coordination than the one of imidazole (in agreement with the observation that the latter is a weaker base),[13] so unproductive *N*-coordination is less favorable for the benzannelated heterocycle. Computed thermodynamic parameters for the isomerization of the Cu/allene complexes support this view, since π-to-*N* isomerization is less favorable for **8** than for **9** (Figure 5).

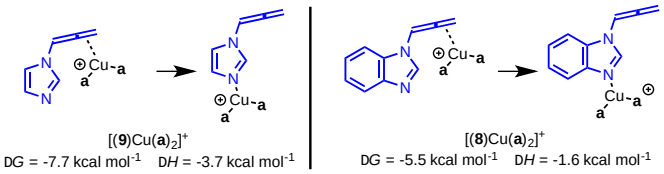


Figure 5. Competition for *N*- and π-coordination for 8 and 9. Computed thermodynamic parameters at the DFT level are reported.

In summary, we demonstrated that the synthesis of unprecedented linear allylic amines bearing *N*-heterocycles (amino-substituted *N*-vinylazoles) can be achieved through copper-catalyzed hydroamination reaction involving *N*-allenylazoles and a large array of aliphatic amines. Smooth conditions and low catalytic loading of a readily available copper(I) complex make this cost-effective strategy very attractive in terms of atom- and step-economy. Insights provided by DFT calculations, showed that the pyridine-like nitrogen of *N*-allenyl-(1,2)-azoles greatly contributes to a more effective catalysis by coordination to the copper atom. Continuous studies to extend the substrate scope of this reaction are ongoing in our laboratory.

Experimental Section

For detailed experimental information, computational details and the full characterization of all new *N*-vinylazoles, see the ESI.

General procedure for Hydroamination of *N*-allenylazoles: An NMR tube (5 mm diameter) or a Schlenk flask of appropriate size was charged with $Cu(NCMe)_4PF_6$ (0.05 equiv) and closed with a rubber septum. After evacuation and back-filling with argon for three times, dry THF (1 mL per mmol of N-allenylheterocycle), the required secondary amine (1.2 equiv) and the *N*-allenylazole (1.0 equiv) were sequentially added. The vessel was shaken until a completely homogeneous solution resulted and the mixture was stirred at room temperature until conversion was complete, as checked by ^{1}H NMR. The vessel was opened to the air, the content was poured into 10 volumes of ethyl acetate and partitioned with 3 volumes of saturated NaCl aqueous solution. The aqueous phase was back-extracted with ethyl acetate (3 x 3 volumes) and the combined organic phases were exsiccated over Na_2SO_4. Volatiles were evaporated under reduced pressure and the residue was purified by flash chromatography on $NaHCO_3$-treated silica gel to afford the required hydroamination product.

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[11] In our previous study,[10] we disclosed that a necessary condition for Cu(I) salts to be effective catalysts for the hydroamination of allenes is to have poorly coordinating anions, such as PF_6^- or TfO^-. Moreover, the addition of ancillary ligands is unnecessary, since the amine substrate itself can serve as a ligand for Cu(I). Commercially available and air-stable $Cu(NCMe)_4PF_6$ was thus adopted also on the grounds of practical considerations.

[12] As in with our previous work,[10] Cu(I) complexes featuring two morpholine molecules as ligands have been considered for all the theoretical calculations. Indeed, the maximum achievable coordination number for cationic Cu(I)/amine complexes may vary between 2 and 4 depending on the nature of the ligands. See ref. [10], note 22 for more details on this point.

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UPDATE

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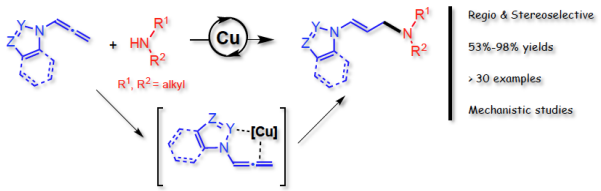

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