Heterogeneous Catalysis

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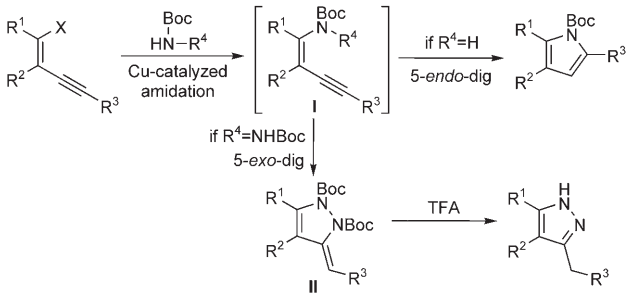
Domino Cu-Catalyzed C–N Coupling/Hydroamidation: A Highly Efficient Synthesis of Nitrogen Heterocycles**

*Rubén Martín, Marta Rodríguez Rivero, and Stephen L. Buchwald**

Heterocyclic compounds are of great chemical and biological significance.[1] In particular, nitrogen-containing heterocycles are structural constituents of many bioactive natural products, medicinally important compounds, and organic materials.[2] Recent strategies for the synthesis of heterocycles based on metal-catalyzed reactions nicely complement the classical synthetic approaches. Among their advantages is that harsh conditions are frequently avoided and readily available starting materials can be utilized.[3] Despite the advances realized, more flexible and general routes to a variety of heterocycles are needed. In particular, techniques that can readily give access to heterocyclic cores with a diverse and easily manipulated set of substituents are still of critical importance.

In the last decade, metal-catalyzed C–N bond-forming reactions[4] have become important methods for the preparation of nitrogen-containing compounds in both academic and pharmaceutical laboratories.[5] In recent years, Cu-promoted processes have evolved into viable alternatives to the more widely practiced Pd-catalyzed reactions.[6,7] The Cu-based methods are distinguished by their broad scope, high efficiency, and mild reaction conditions, thus making them attractive vehicles for further applications.[8]

The development of a method for generating multiple classes of nitrogen-containing heterocycles from common building blocks is a highly desirable goal. Previously, Ackermann showed that substrates for the Cacchi indole synthesis[9] can be prepared by Pd- or Cu-catalyzed amination of *o*-alkynyl aryl halides.[10] Under the conditions of these coupling processes, cyclization to the *N*-benzyl or *N*-aryl indoles takes place in an efficient manner.[11] We wondered whether it would be possible to effect a related transformation as a means to access other important nitrogen heterocycles, particularly pyrroles and pyrazoles. Herein, we describe our study of this approach, which combines an initial Cu-catalyzed amidation of a haloenyne followed by an intramolecular hydroamidation of the latent alkyne in situ[12,13] (Scheme 1). We also demonstrate that cyclization of the initially formed C–N coupling product **I**, which can be readily isolated, requires the presence of both a base and copper catalyst.



Scheme 1. Synthesis of heterocycles through a domino copper-catalyzed amidation/hydroamidation sequence. TFA = trifluoroacetic acid.

We envisioned that an array of heterocycles could be synthesized through 5-*exo*-dig and 5-*endo*-dig pathways involving intermediate **I**. This objective could be achieved both by varying the nature of the nucleophile as well as the substitution pattern on the haloenyne precursor. We focused our attention on the synthesis of pyrroles[14] and pyrazoles[15] as applications of the Cu-catalyzed vinylation methodology.[16] A series of ligands were examined for the reaction of the model substrate (*Z*)-4-iododec-4-en-6-yne (**1**) with *tert*-butyl carbamate and bis(*tert*-butyloxycarbonyl)hydrazine (bis(Boc)hydrazine; Figure 1). The reaction was carried out in THF with CuI as the precatalyst and Cs_2CO_3 as the base at 80 °C for 12 h. Among those examined, 1,2-diamine ligands show the highest activity, with 20 mol % *N,N′*-dimethylethylenediamine (ligand **g**) giving exclusively the desired cascade products in excellent overall yield. We note that the successful preparation of **2** represents, to the best of our knowledge, the first metal-catalyzed coupling of vinyl halides with a hydrazide.[17]

The transformation outlined above merits some further discussion: 1) two different heterocycles could be obtained from a common starting material; 2) no 6-*endo*-dig cyclization was observed using bis(Boc)hydrazine as the nucleophile; 3) although the *trans* arrangement of the hydrogen and iodide species in **1** suggests a potential for dehydrohalogenation, only traces of the undesired bisalkyne were detected.[18]

Encouraged by our initial results, we sought to examine the scope and the generality of the method. The domino Cu-catalyzed amidation/hydroamidation of haloenynes[19] with *tert*-butyl carbamate shows excellent chemoselectivity, and its wide scope is evident from the results compiled in Table 1. As summarized below, different combinations of substituents on the alkyne and alkene can be used to allow the synthesis of di- and trisubstituted pyrroles, including those bearing alkene, ester, silyl ether, and alkyl halide substituents.

[*] Dr. R. Martín, Dr. M. Rodríguez Rivero, Prof. Dr. S. L. Buchwald
Department of Chemistry, Room 18–490
Massachusetts Institute of Technology
Cambridge, MA 02139 (USA)
Fax: (+1) 617-253-3297
E-mail: sbuchwal@mit.edu

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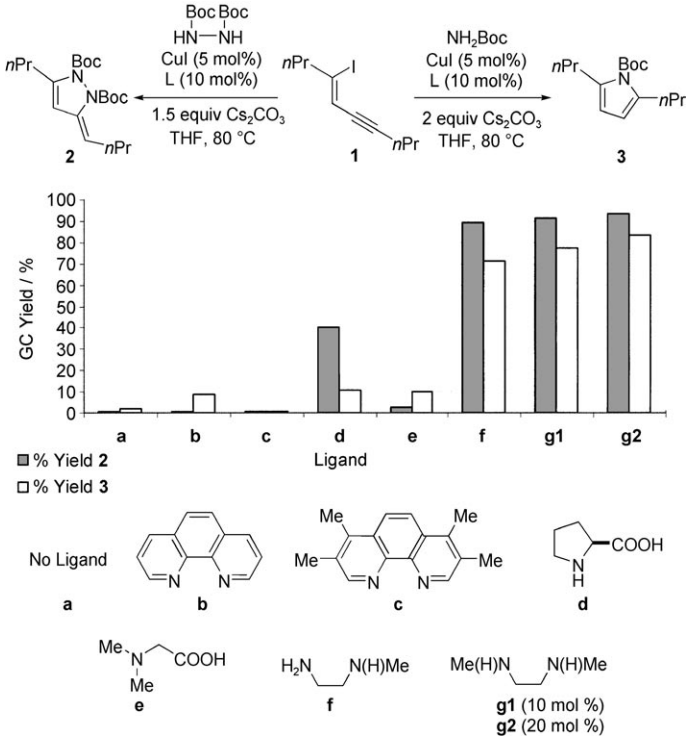
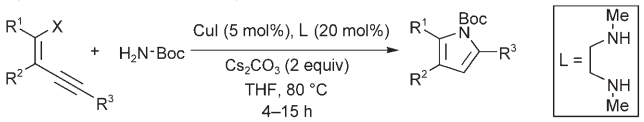
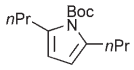
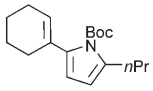
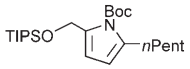
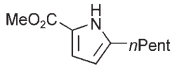
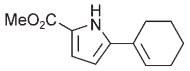
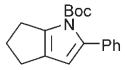
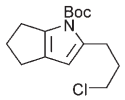
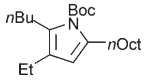
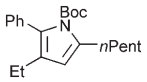
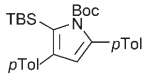
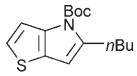
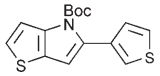
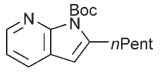


Figure 1. Ligand screening in the domino Cu-catalyzed amidation/hydroamidation of haloenyne **1**.

Table 1: Synthesis of pyrroles through Cu-catalyzed domino amidation/hydroamidation of haloenynes.[a]



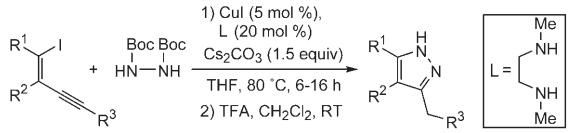
Entry	Product	X	Yield [%][b]
1[c]		Br	70
2		I	74
3		I	84
4		I	83
5[c]		Br	82
6[c]		Br	81
7[d]		I	68
8		I	52
9		I	78
10		I	85
11		I	91
12		I	95
13[c]		Br	83
14[c]		Br	74
15		I	71

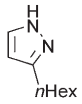
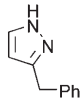
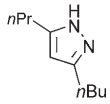
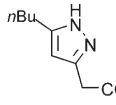
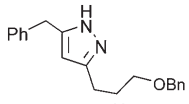
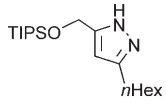
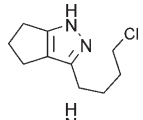
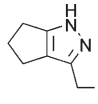
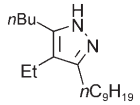
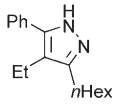
[a] Reaction conditions: haloenyne (1.0 equiv), NH_2Boc (1.2 equiv), CuI (5 mol%), *N*,*N*′-dimethylethylenediamine (20 mol%), Cs_2CO_3 (2.0 equiv), THF (0.5 M). [b] Yields of the isolated products are the average of two runs and are estimated to be over 95% pure by ^{1}H NMR spectroscopic and GC analysis. [c] Using K_2CO_3 (2.0 equiv) and toluene (0.5 M) at 110 °C. [d] R^3 = TMS. TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.

Although the reaction of a substrate bearing a terminal alkyne led to decomposition, the synthetic equivalent of this transformation can be accomplished by the use of a trimethylsilyl (TMS) group, which masks the terminal acetylene and is deprotected in situ (Table 1, entry 7).[20] Thus, not only 2,5- but also 2,3-disubstitution on the pyrrole core can be achieved, albeit in lower yield. Although the Cu-catalyzed coupling of primary amides with vinyl halides bearing an α-electron-withdrawing group has little precedent,[21] we were pleased to find that the cascade reaction took place, with cleavage of the carbamate group, thus providing the deprotected pyrroles in excellent overall yield (Table 1, entries 5 and 6). Although this study focused on the use of iodoenynes, we also demonstrated that bromoenynes could be used if the reaction was carried out in toluene at 110 °C (Table 1, entries 1, 5, 6, 13, and 14). Polyheterocylic compounds could also be prepared in high yields by introducing a heterocyclic moiety either in the alkene or alkyne counterpart (Table 1, entries 13–15).

To extend the scope of this methodology to the synthesis of pyrazoles, the reaction of several iodoenynes was evaluated under the optimized conditions using bis(Boc)hydrazine as the nucleophilic component (Table 2). In this case, simple treatment of the intermediate **II** with trifluoroacetic acid (Scheme 1), with no need for isolation, afforded the free pyrazoles (for simplicity, represented as one tautomer) in good-to-excellent overall yields. Although the hydroamidation reaction could theoretically proceed through two possible pathways, 5-*exo*-dig or 6-*endo*-dig, exclusive formation of the five-membered ring was observed in all cases. It is worth noting that mono-, di- and trisubstituted pyrazoles can be accessed through this route. As in the case of pyrroles, alkenes and alkynes with a wide variety of substituents are viable reaction components. Moreover, despite acidic treatment of **II**, many functional groups, such as alkyl halides, esters, benzyl ethers, and even silyl ethers, are well tolerated in the reaction. In this manner, this protocol provides rapid and modular access to a variety of nitrogen-containing heterocycles with different substitution patterns.

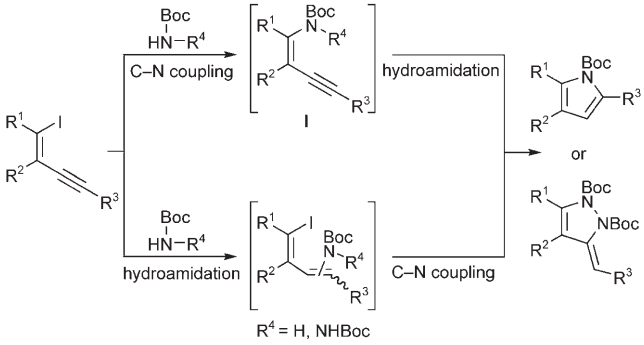
Table 2: Synthesis of pyrazoles through Cu-catalyzed domino amidation-hydroamidation of iodoenynes.[a]



Entry	Product	Yield [%][b]
1		92
2		93
3		83
4		81
5		72
6		78
7		89
8		86
9[c]		66
10		72

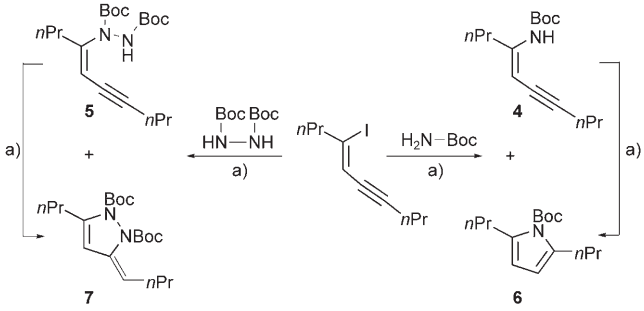
[a] Reaction conditions: iodoenyne (1.0 equiv), NHBoc–NHBoc (1.2 equiv), CuI (5 mol%), *N,N′*-dimethylethylenediamine (20 mol%), Cs_2CO_3 (1.5 equiv), THF (0.5 M). [b] Yields of the isolated products are the average of two runs and are estimated to be over 95% pure by ^{1}H NMR spectroscopic and GC analysis. [c] Ligand: *trans*-1,2-cyclohexanediamine (20 mol%).

In principle, two different mechanisms can be envisioned for these domino processes: 1) initial C–N coupling followed by intramolecular hydroamidation of the alkyne portion of **I** or 2) intermolecular hydroamidation and subsequent intramolecular amidation (Scheme 2). Experiments performed by Ackermann in his synthesis of indoles indicated that a mechanism consisting of an intermolecular hydroamination and a subsequent intramolecular metal-catalyzed C–N bond-forming process was predominantly operative, although no isolation of the proposed intermediate was reported.[10]



Scheme 2. Possible mechanisms for the domino reaction.

To probe the reaction mechanism of our method, the reaction of vinyl iodide **1** with *tert*-butyl carbamate and bis(Boc)hydrazine was stopped after 4 h at 80 °C (Scheme 3).



Scheme 3. Mechanistic insight by trapping the intermediates in the Cu-catalyzed domino process. a) CuI (5 mol%), *N,N′*-dimethylethylenediamine (20 mol%), Cs_2CO_3 (1.5 equiv), THF (0.5 M), 80 °C, 4 h.

As shown below, the only compounds detected by NMR spectroscopy of the crude reaction mixture were the corresponding C–N coupling intermediates **4** and **5** along with significant amounts of the final cascade product.[22] Remarkably, **4** and **5** could be obtained in analytically pure form by carrying out the reactions at room temperature and 40 °C in 59 and 48% yields of the isolated products, respectively. Full conversion into the desired cascade products was observed by resubjecting **4** and **5** to the reaction conditions for an additional 4 h. Interestingly, the treatment of **4** and **5** with either CuI (5 mol%) or Cs_2CO_3 (1.5 equiv) under otherwise identical conditions resulted in reisolated starting materials; not even traces of the final cascade products were observed. Only the combination of catalyst with base was effective, thus suggesting that the intramolecular hydroamidation is both a copper-catalyzed[23] and base-assisted process. These results strongly support a mechanism involving an initial C–N coupling followed by intramolecular hydroamidation of the latent alkyne (top pathway, Scheme 2).[24]

In conclusion, a general, highly flexible, and efficient Cu-catalyzed domino C–N coupling/hydroamidation reaction has been developed. The transformation constitutes a straightforward alternative to the existing methodology for the prepa-

ration of pyrroles and pyrazoles. A mechanism in which the metal acts with dual roles, thus facilitating both amidation and hydroamidation reactions is proposed. Further studies on synthetic applications of these important and related transformations are currently in progress.

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Keywords: amidation · copper · domino reactions · heterocycles · hydroamidation

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