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Highly Efficient Cu(I)-Catalyzed Synthesis of *N*-Heterocycles through a Cyclization-Triggered Addition of Alkynes

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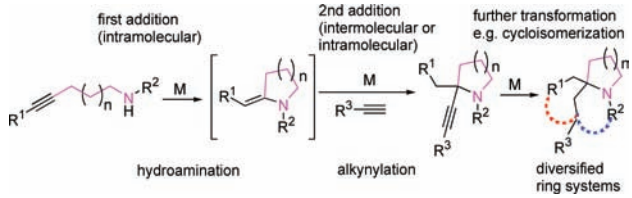
N-Heterocycles containing five-, six-, or seven-membered rings and various substitution patterns are indisputably important as building blocks and targets.[1,2] In this regard, the transition metal catalyzed hydroamination of alkynes has played a preponderant role in their synthesis.[2,3] Depending on the substitution pattern of the starting material and of the catalyst used, the hydroamination of alkynes can yield an enamine or imine (in the case of primary amines). The reported methodologies have focused mostly on hydroamination using primary amines. The addition of a terminal alkyne to an activated enamine is the methodology of choice for the synthesis of racemic or chiral propargyl amines.[4] We conceived an alternative approach: if a secondary amine attacks an electrophilically activated alkyne, the resulting activated enamine intermediate then becomes a new electrophilic precursor capable of reacting with a second nucleophile, such as a terminal alkyne, to give a new addition product. This essentially corresponds to a double addition to a triple bond. If the first step is an intramolecular cyclization using an aminoalkyne (Scheme 1), then the second step adds a second alkynyl group (C≡C—R^3), which can then interact with R^1 or R^2 and spur further transformations (e.g., cycloisomerization). We call this strategy a cyclization-triggered addition and are now pleased to report its proof of concept, namely, a highly efficient and atom-economical synthesis of functionalized five-, six-, and seven-membered *N*-heterocycles, via a Cu(I)-catalyzed, one-pot, tandem hydroamination/alkynylation.

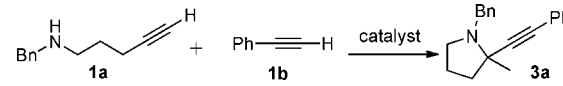
Scheme 1. Cyclization-Triggered Alkynylation



Che and co-workers have reported a gold(I) catalyzed tandem synthesis of pyrrolo[1,2-*a*]quinolines;[5a] their reaction requires aromatic amines and terminal alkynes. On the other hand, Li and co-workers reported the tandem addition of an amine and alkyne to α,β-unsaturated esters through an iminium intermediate.[6] We envisioned a broader scope for a tandem hydroamination/alkynylation process, namely, the amination of inactive alkynes (terminal or internal) in the presence of a single metal catalyst operating on the hydroamination and alkynylation steps. The reaction of aminoalkyne **1a**, readily prepared from alkynyl alcohol by a tosylation/amination sequence, with phenylacetylene **2a** was used as a model (Table 1).

Among the various coinage metal catalysts screened, copper was the best, and Cu(I) was better than Cu(II) (Table 1, entries 1−5). Copper's excellent performance may be due to its higher tolerance toward basic amines and the fact that it is a superior catalyst for

Table 1. Screening of Conditions[a]



entry	catalyst	**1b**/equiv	solvent	temp/time	yield%
1	AuCl	4	dioxane	MW[b]/100 °C/0.5 h	15
2	$Cu(OTf)_2$	4	dioxane	MW/100 °C/0.5 h	50
3	$PdCl_2$	4	dioxane	MW/100 °C/0.5 h	15
4	$AgNO_3$	4	dioxane	MW/100 °C/0.5 h	42
5	CuI	4	dioxane	MW/100 °C/0.5 h	95
6	CuBr	4	dioxane	MW/100 °C/0.5 h	99
7	CuBr	4	dioxane	MW/60 °C/0.5 h	65
8	CuBr	4	dioxane	heat/100 °C/12 h	99
9	CuBr	4	toluene	MW/100 °C/0.5 h	98
10	CuBr	4	CH_3CN	MW/100 °C/0.5 h	98
11	CuBr	1.5	dioxane	MW/100 °C/0.5 h	99
12[c]	CuBr	1.5	dioxane	MW/100 °C/0.5 h	99

[a] The reactions were conducted on a 0.25 mmol scale. [b] MW = microwave. [c] The reaction was conducted on a 3 mmol scale.

alkynylation (Sonogashira-type reactions). Under microwave conditions, this reaction is very fast and gives excellent yields, but conventional heating also works very well if longer reaction times are employed (Table 1, entry 8). This reaction was initially conducted in dioxane; however, toluene and acetonitrile also give excellent results (Table 1, entries 9 and 10). At first, we used a large excess of terminal alkyne **2a** to avert a potential competition between the two terminal alkynes, but to our surprise, even when the number of equivalents of **2a** was reduced from 4.0 to 1.5, the reaction still furnished **3a** in excellent yields (Table 1, entry 11). Operating on a larger scale did not reduce the yield of product (Table 1, entry 12).

The scope of this tandem amination/alkynylation reaction is outlined in Table 2. The reaction worked extremely well in all cases giving near quantitative chemical yields of five-, six-, and seven-membered rings. Complete regioselectivity was observed. When *N*-methyliminodiacetic acid (MIDA) boronate[7] alkyne **2f** was used, the terminal alkyne product **3k** was obtained (Table 2, entry 11); this may be due to cleavage of MIDA boronate during the reaction. When a chiral aminoalkyne was used (**1g**), a small chiral induction was observed (*dr* = 1:1.3, Table 2, entry 12), probably because the existing chiral center is relatively far away from the newly generated chiral center. The sterically encumbered TMS-substituted aminoalkyne **1h** did not give the desired product (Table 2, entry 13). And the reaction of proline derivative **1i** gave a fused ring product (Table 2, entry 14). The regioselectivity obeyed Baldwin's rules.[8] The cyclization of 3-yn-amine **1b** and **1a** gave five-membered ring products through *5-endodig* and *5-exodig* processes. And the reactions of 5-yn-amine (e.g., **1c**) and 6-yn-amine (e.g., **1e**) give six-membered and seven-membered rings, through *6-exodig* and *7-exodig* processes, respectively.

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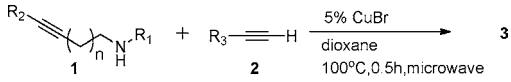
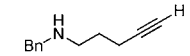
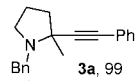
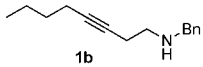
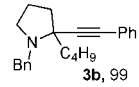
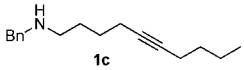
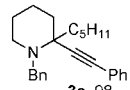
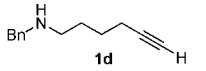
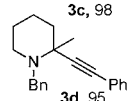
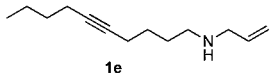
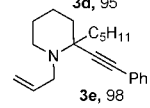
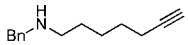
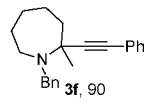
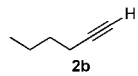
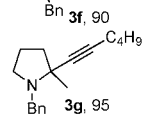
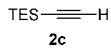
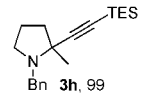
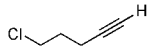
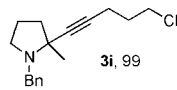
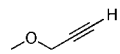
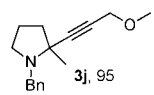
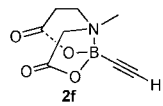
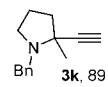
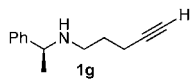
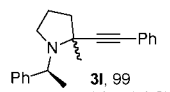
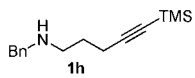
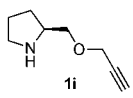
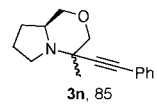
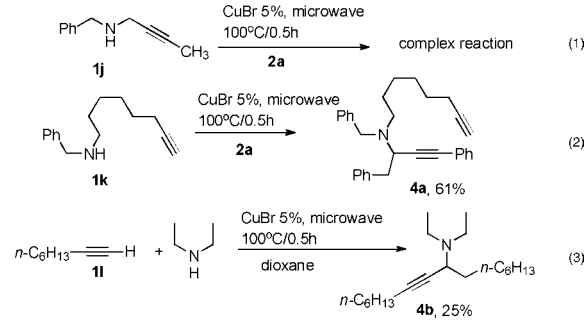
Table 2. Scope of Tandem Amination/Alkynylation Reaction[a]



entry	1	2	3 (yield %)
1	 **1a**	**2a**	 **3a**, 99
2	 **1b**	**2a**	 **3b**, 99
3	 **1c**	**2a**	 **3c**, 98
4	 **1d**	**2a**	 **3d**, 95
5	 **1e**	**2a**	 **3e**, 98
6	 **1f**	**2a**	 **3f**, 90
7	**1a**	 **2b**	 **3g**, 95
8	**1a**	 **2c**	 **3h**, 99
9	**1a**	 **2d**	 **3i**, 99
10	**1a**	 **2e**	 **3j**, 95
11	**1a**	 **2f**	 **3k**, 89
12	 **1g**	**2a**	 **3l**, 99 (*dr* = 1:1.3)
13	 **1h**	**2a**	**3m**, 0
14	 **1i**	**2a**	 **3n**, 85 (*dr* = 1:7.0)

[a] **1** (0.5 mmol), **2** (2.0 mmol), 1 mL dioxane.

Attempts to form three- or four-membered rings under similar conditions, using **1j**, were unsuccessful (eq 1). Surprisingly, the reaction of 7-yn-amine **1k** led to the intermolecular hydroamination/alkynylation product **4a** in good yield, through a double addition to phenyl acetylene, rather than the corresponding eight-membered ring (eq 2). Taking this as a cue for a possible intermolecular variant, we then reacted an unfunctionalized alkyne **1l** with a simple secondary amine, using similar conditions (eq 3). This reaction gave the desired product **4b**, albeit in lower chemical yield. We have not yet conducted optimization studies for this intermolecular version.



The cycloisomerization of 1,*n*-enynes and 1,*n*-diynes is currently a highly competitive field in organic synthetic chemistry.[9] Our newly found method provides direct entry to functionalized 1,*n*-enynes, as showcased by the synthesis of 1,6-enyne (**3e**) in high yield in a single step (Table 2, entry 5). Our reaction is also capable of furnishing fused ring systems, if a cyclic secondary amine is present (Table 2, entry 14).

In conclusion, we have developed a powerful strategy to access *N*-heterocycles of the most common ring sizes (5, 6, and 7) through a tandem hydroamination/alkynylation sequence catalyzed by a cheap and environmentally friendly copper catalyst. The broader implications of this reaction, including an asymmetrical version, and its application to natural product synthesis, are currently under investigation.

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Supporting Information Available: Experimental procedures, characterization, spectroscopic spectra for **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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