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Base-Controlled Cu-Catalyzed Tandem Cyclization/Alkynylation for the Synthesis of Indolizines

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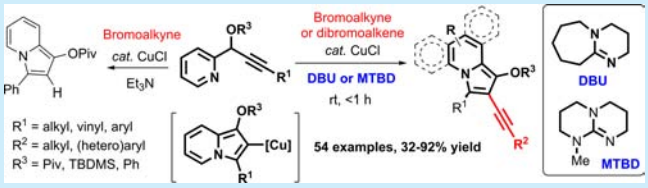
Supporting Information

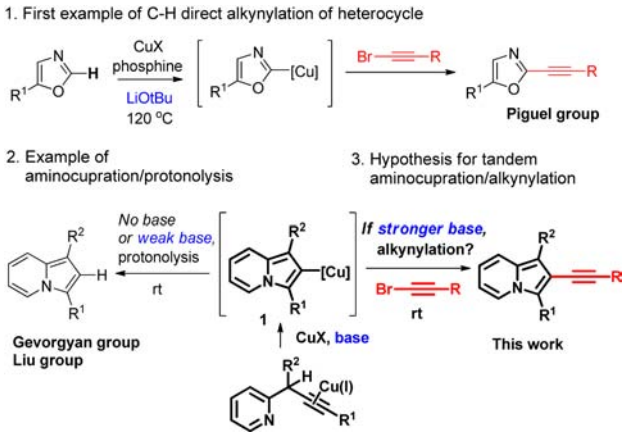
ABSTRACT: A base-controlled Cu-catalyzed tandem cyclization/alkynylation of propargylic amines provides rapid access to functionalized indolizine derivatives under mild reaction conditions. The reaction first proceeded via a 5-*endo-dig* aminocupration, followed by a coupling between the copper-bound intermediate and alkynyl bromide, to afford the products in good to excellent yields. The successful tandem reaction is attributed to the unique property of the bases, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and MTBD (7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene used).



The synthesis of fused *N*-heterocycles has attracted a great deal of attention owing to its broad application in medicinal[1] and material chemistry.[2] In particular, *N*-heterocycles are utilized in the development of potent bioactive compounds[3] and highly efficient electronic materials.[4] Over the past decade, transition-metal-catalyzed aminometalation[5] of alkynes has been widely used for the synthesis of heterocycles such as indolizines.[6] A tandem reaction strategy has been used to access diversely functionalized indolizines as well, utilizing a metal-bound intermediate generated *in situ* for the subsequent C−C coupling reaction with prechosen reagents.[7] The procedure benefits from good atom and step economy, offers flexibility in constructing the organic backbone, and has excellent selectivity in the C−C bond forming reaction. To date, most examples are limited to Pd catalysis for the synthesis of indolizine involving cycloisomerization, followed by C−C coupling reactions such as addition reaction,[7a] arylation,[7b,c] carbonylative carbonylation,[7d] and oxidative arylation.[7e] These methods, however, require harsh reaction conditions and expensive metal and ligand. Interestingly, the copper-catalyzed tandem C−C coupling reaction has rarely been explored despite copper metal's natural abundance and cheap price.[8]

With regard to the C−C bond formation for tandem reaction, we initially focused on the metal-catalyzed C−H direct alkynylation of heterocycles using bromoalkyne.[9] There are limited examples of copper-catalyzed reactions, typically involving a direct deprotonation by a strong base to generate a heterocycle-bound σ-copper(I) intermediate (Scheme 1-1).[9d,e] We surmised that if the copper(I) intermediate is produced via mild cycloisomerization[6f,10] instead of a harsh, direct deprotonation process as described above, it can be subsequently utilized for alkynylations. Recently, the simple cyclizations of propargylic pyridine with Et_3N or without base, in the presence of Cu(I), to indolizines were reported by Liu[6f] and Gevorgyan.[6h] Liu proposed that the cyclization reaction was accomplished by a sequential process of aminocupration,

Scheme 1. Working Hypothesis of a Base-Controlled Copper-Catalyzed Annulative Direct Alkynylation



followed by protonolysis of the copper(I) intermediate, **1**. (Scheme 1-2).

Based on the two examples (Scheme 1-1 and 1-2), we hypothesized that if the base is strong enough to trap the acid generated during the intramolecular nucleophilic attack of pyridine to the copper-activated π-bond and could stabilize the copper(I) as a ligand, the copper(I) intermediate, **1**, would survive the protonolysis step and react with a bromoalkyne species to give an alkynylated indolizine (Scheme 1-3). Stepwise synthesis of an alkynylated indolizine has been reported by the Kim group.[6m] Herein, we describe a mild base-controlled Cu-catalyzed *in situ* oxidative alkynylation reaction, which occurs after an intramolecular aminocupration of *N*-heterocycles to copper-bound alkyne, to give indolizine derivatives using bicyclic bases.

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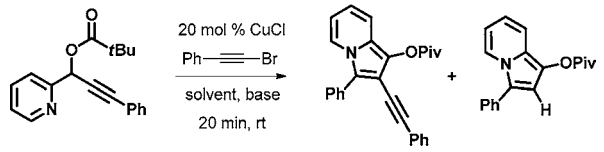
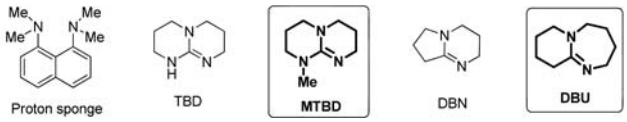
To test our hypothesis, we experimented using the known cycloisomerization conditions,[6f] which employed Et_3N in CH_3CN (Table 1, entry 1). Unsurprisingly, we observed only

Table 1. Optimization of Reaction Conditions[a]



2 3a 3a'

entry	base[b]	solvent	conversion (%)	yield of 3a:3a' (%)[c]
1	Et_3N	CH_3CN	>99	6:92
2	2,6-Lutidine	CH_3CN	49	10:37
3	DABCO	CH_3CN	>99	14:80
4	Proton sponge	CH_3CN	>99	16:37
5	Hünig base	CH_3CN	>99	58:39
6	TBD	CH_3CN	>99	4:19
7	MTBD	CH_3CN	>99	54:0
8	DBN	CH_3CN	>99	18:9
9	DBU	CH_3CN	>99	78:12
10	DBU	EtOH	>99	86:3
11	DBU	MeOH	>99	25:21
12	DBU	*n*-PrOH	>99	81:0
13[d]	DBU	*i*-PrOH	>99	93:0
14	DBU	*n*-BuOH	>99	97:0
15	MTBD	*i*-PrOH	>99	94:0
16	Et_3N	*i*-PrOH	>99	7:90



[a]Reaction conditions: **2** (1.0 equiv), bromoalkyne (1.5 equiv), CuCl (20 mol %), base (1.2 equiv), solvent (0.3 M), rt, 20 min. [b]pK_a of the conjugate acid of amine in acetonitrile:[11] Et_3N (18.82), 2,6-lutidine (14.13), proton sponge (18.62), Hünig base (−), DABCO (−), TBD (25.98), MTBD (25.44), DBN (23.89), DBU (24.33). [c]NMR yield based upon internal standard (dibromomethane). [d]CuBr and CuI gave the same results.

6% of the desired product, **3a**, based on the crude NMR analysis. Next, we tested other bases while maintaining the use of CH_3CN, and the yields of the desired product increased accordingly: from 10% to 58% with bases such as 2,6-lutidine, DABCO (1,4-diazabicyclo[2.2.2]octane), proton sponge (1,8-bis(dimethylamino)naphthalene), and Hünig base (*N*,*N*-diisopropylethylamine) (entries 2−5). We then proceeded to test bicyclic amine bases (Table 1, entries 6−9), which include TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene), MTBD (7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene), DBN (1,5-diazabicyclo-[4.3.0]non-5-ene), and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene). TBD, a secondary amine, was incompatible as most of **2a** disappeared during the reaction, giving a minimal amount of the product (entry 6). Surprisingly, only the desired product was formed (at a moderate yield) when MTBD was used, showing the absence of the cyclized product, **3a**′ (entry 7). DBU gave the highest yield (78%) in CH_3CN while employing DBN led to a significant drop in yield (18%) (entries 8−9). Finally, the screening of alcoholic solvents revealed that *n*-BuOH was better than EtOH, MeOH, *n*-PrOH, and *i*-PrOH, giving a 97% yield of **3a** and an undetectable amount of the simple cyclization product, **3a**′, in *n*-PrOH, *i*-PrOH, and *n*-BuOH (entries 10−14). Despite a slightly lower yield, *i*-PrOH was chosen as the reaction solvent because *n*-BuOH has a higher boiling point and an unpleasant odor. The optimum base in *i*-PrOH was also MTBD, giving a 94% yield of **3a** (entry 15). In order to investigate the effect of solvent on the formation of **3a**, the reaction was performed in *i*-PrOH with Et_3N but minimal alkynylation was observed (entry 1 vs 16).

To evaluate the synthetic scope of this method, we tested different types of bromoalkynes to ascertain whether the reaction conditions can accommodate a wide range of functionalities (condition A). gem-Dibromo alkenes were also tested as an equivalent of bromoalkyne, and the reaction conditions were further optimized in one pot (condition B). Most product yields obtained with gem-dibromo alkenes were slightly lower than those with 1-bromoalkynes, presumably owing to a loss in yield during the first elimination step (Scheme 2). Aromatic rings bearing ortho-, meta-, and para-electron-withdrawing, as well as electron-donating, substituents were well tolerated to give the desired products (**3a**−**n**) in 76−91% yields except for the nitro substituent, which gave **3o**−**p** in 32−64% yields. In addition, 1- and 2-naphthyl substrates gave the desired compounds, **3q**−**r** in 69−88% yields, whereas heterocyclic substrates gave **3s**−**t** in 69−90% yields. In order to expand the scope of the pyridine moiety, we attempted to prepare the product, **3u**−**y**. Using fused pyridine substrates, pyrrolo[1,2-*a*]quinolone, **3u**, and pyrrolo[2,1-*a*]isoquinoline, **3v**, were successfully prepared in good yields (74−81%). The methyl group at C-6 of pyridine did not decrease the yield of **3w** (90%). Electron-withdrawing bromine at C-5 gave a 52% yield of **3x**, and fluorine at C-3 had almost no influence on the yield of **3y** (91%). When we attempted to synthesize the hexyl ethynyl product **3z**, it was found that bromooctyne reacted readily to give an 85% yield but the reaction was unsuccessful with gem-dibromooctene.[12] This could be caused by an absence of an elimination reaction of the gem-dibromooctene under the reaction conditions. TBDMS ether and phenyl ether were also tolerated to afford the desired products, **3aa** and **3ab**, in 60% and 81% yields. It is valuable to note that most substrates gave almost no detectable simple cyclization products with bromoalkynes and dibromoalkenes in crude ^1H NMR.

The alkyne moiety in propargylic pyridines bearing the alkyl and alkenyl groups, **4a** and **4b**, reacted well with 1-bromo-2-phenylacetylene (Scheme 3). In the case of hexyl propargylic pyridine, **4a**, MTBD was an optimal base to afford 82% of the product in 2 h. Meanwhile, vinyl propargylic pyridine, **4b**, gave an 83% yield under the standard reaction conditions. Unfortunately, the alkynyl-substituted propargylic pyridine, **4c**, was not successful in affording the desired product, **5c**.

Recently, fluorescent indolizines[13] have been applied for the use of biological imaging. The Park group[13a] and You and Lan group[13b] have developed full-color-tuned fluorescent probes for cell assay, independently. In order to show functional group compatibility, easy access to coupling with complex molecules, and potent bioapplications of indolizine as imaging units, we attempted to a combination with bioactive steroids, such as ethisterone and ethynylestradiol, and the reaction proceeded

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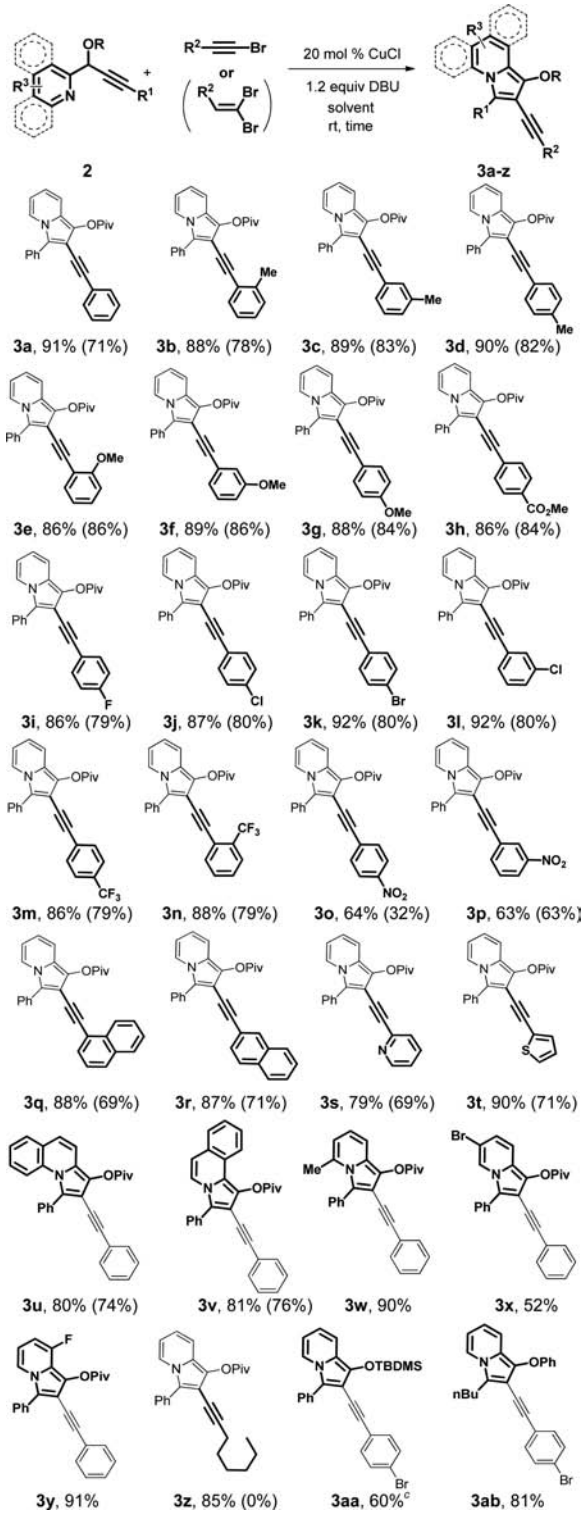
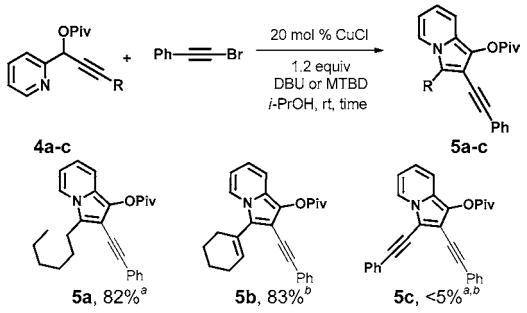
Scheme 2. Synthesis of Indolizines from 2 with 1-Bromoalkynes or gem-Dibromoalkenes[a,b]



[a]Isolated yield under condition A [**2** (1.0 equiv), bromoalkyne (1.5 equiv), CuCl (20 mol %), DBU (1.2 equiv), *i*-PrOH (0.3 M), rt, 20 min]. [b]Isolated yield was shown in the parentheses under condition B [**2** (1.0 equiv), dibromoalkene (1.5 equiv), DBU (3.0 equiv), DMSO (0.6 M), rt, 30 min; CuCl (20 mol %), *n*-BuOH (0.2 M), rt, 20 min]. [c]MTBD was used at 30 °C for 2 h.

smoothly to afford **6** and **7** in 72% and 75% yields under the standard conditions (Figure 1).

Scheme 3. Synthesis of Indolizines from Alkyl, Alkenyl, and Alkynyl Propargylic Pyridines



[a]MTBD was used for 2 h. [b]DBU was used for 20 min.

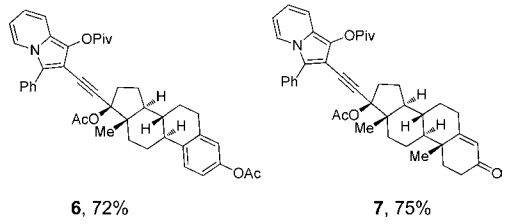
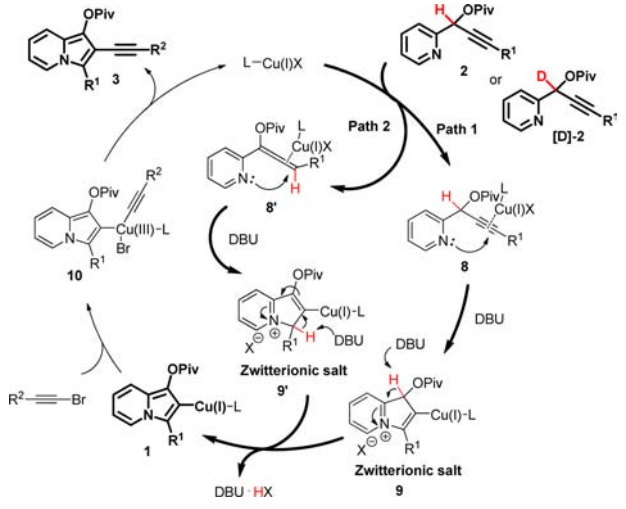


Figure 1. Synthesis of indolizine, **6** and **7** from bromo ethylestradiol acetate and bromo ethisterone.

For a mechanistic explanation, there are two possible reaction pathways (Scheme 4). In path 1, Cu(I) is first

Scheme 4. Proposed Mechanism



coordinated by the alkyne, followed by a nucleophilic attack of the alkyne by the pyridine nitrogen via a 5-*endo-dig* cyclization, as reported in the literature.[6d−f] Next, DBU (or MTBD) deprotonates the cyclized zwitterionic salt, **9**. As for path 2, the same cyclized zwitterionic salt, **9′**, could be produced via a propargyl-allenyl isomerization, followed by an intramolecular amine attack of the Cu-bound allenyl double bond. It is presumed that the basicity of DBU (or MTBD) is strong enough to prevent the copper intermediate, **1**, from undergoing protonolysis;[11] thus, **1** readily associates with the bromoalkyne to generate **10**, which then undergoes reductive elimination to form the desired product, **3**. At the same time, bulky DBU (or MTBD) may serve as a good ligand to inhibit the copper intermediate from protonolysis and to facilitate the oxidative

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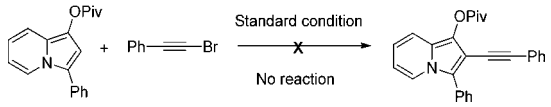
alkynylation reaction. Investigation of the kinetic isotope effect using [**D**]-**2** revealed that the rate-determining step involves cleavage of the C−H bond (k_H/k_D = 4.48)[14] which may occur in propargyl-allenyl isomerization[15] and/or deprotonation of the zwitterionic salt.[16] An unsuccessful C−H direct alkynylation under the standard reaction conditions used supports our proposed mechanism (Scheme 5).

Scheme 5. Unsuccessful Attempt of C−H Direct Alkynylation



In summary, we have developed a base-controlled Cu(I)-catalyzed tandem cyclization/alkynylation of propargylic pyridines which provides rapid and functional group tolerant access to indolizines. Halide-substituted propargylic pyridines and bromoalkynes are also compatible with the reaction conditions, which might be challenging substrates if used in the case of a Sonogashira reaction. The reaction proceeds via a 5-*endo-dig* aminocupration of propargylic ester, followed by a copper-catalyzed coupling reaction with alkynyl bromide or alkenyl dibromide. This method was also successfully applied to the synthesis of steroid-substituted indolizines. This work demonstrates that the tandem C−C coupling reaction could be realized with an inexpensive copper catalyst with the proper choice of bases.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00821.

Experimental procedures, full characterization of products, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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