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Synthesis of 1-Amino-2*H*-quinolizin-2-one Scaffolds by Tandem Silver Catalysis

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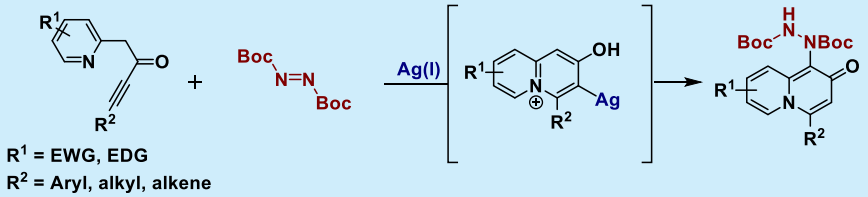
Supporting Information



ABSTRACT: An efficient tandem cycloisomerization−amination reaction catalyzed by silver is described. This rapid and atom-economic reaction delivered 1-amino-2*H*-quinolizin-2-one scaffolds in high yields under mild conditions. The reaction could be extended to an asymmetric version albeit with moderate enantioselective excess of the products. In addition, the products can be easily reduced into various azabicycles containing 4-pyridones, which are important building blocks in organic synthesis.

N-Heterocycles are among the most significant structural components of pharmaceuticals, and more than half of the FDA approved small-molecule drugs contain at least one *N*-heterocyclic ring.[1] Quinolizidines, as one family of *N*-heterocycles, are extremely important components of modern pharmaceuticals and serve as versatile building blocks in organic synthesis.[2] Meanwhile, quinolizidine derivatives are also the indispensable frameworks of numerous natural products, as shown in Figure 1.[3] Inspired by their intriguing

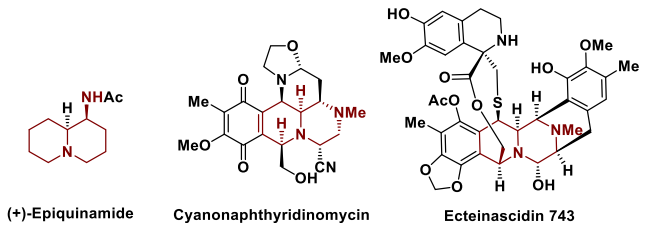
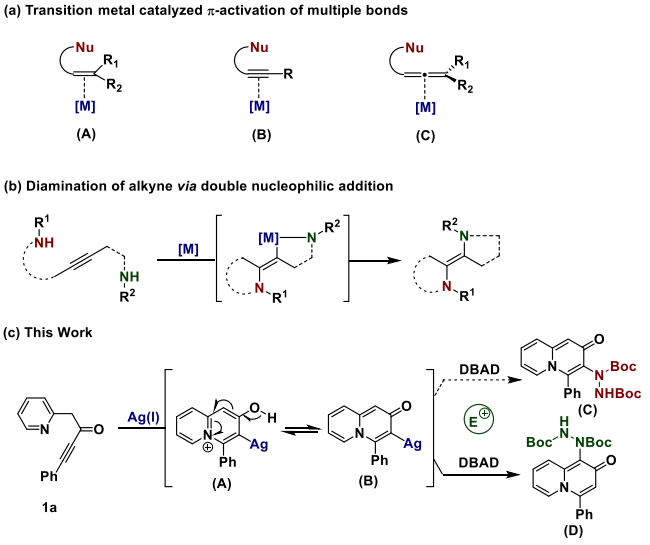


Figure 1. Natural products containing quinolizidine amine/amide frameworks.

structures and biological significance, the construction of quinolizidine frameworks has propagated much research effort to develop novel and efficient methodologies.[4]

Alkynes are very reactive compounds, and the triple bond participates in a number of organic reactions. Along this line, Lewis acids promoted cyclizations of alkyne to generate heterocycle have emerged as an area of great interest.[5] Early work in this area revealed that the potent soft Lewis acidities of transition metals, such as gold, silver, and copper, play a role in activating alkenes, allenes, and alkynes (Scheme 1a).[6] As such, they could activate the multiple bonds, followed by the attack of various nucleophiles affording the alkenyl-metal intermediates, which undergo protonation to obtain the desired product.

Scheme 1. Transition Metal Catalyzed π-Activation of Multiple Bonds



Consequently, a few examples of diamination of alkynes as a new strategy for the construction of *N*-heterocycle skeletons have been reported.[7] However, they are generally prepared via the double nucleophilic addition with assistance of a stoichiometric oxidant (Scheme 1b). As an alternative methodology, we sought to explore this regime through the use of an electrophile to trap the vinyl-metal intermediates instead of the protonation step during the catalytic cycle. In

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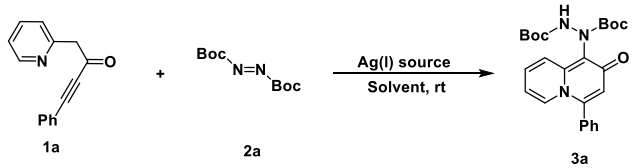
this case, the diamination of an alkyne would be achieved which provides the ability to synthesize *N*-heterocycles.

We started our proposal by using 4-phenyl-1-(pyridin-2-yl)but-3-yn-2-one (**1a**) as the model substrate. Ideally, the reaction would proceed via silver-catalyzed cyclization using a pyridine moiety as a nucleophile, and then intermediate **A** would prefer to transfer to the nucleophilic intermediate **B**. At last, the intermediate **B** would be trapped by an electrophile di-*tert*-butyl azodicarboxylate (DBAD) which afforded the desired product **C** (Scheme 1c). However, to our surprise, product **D** was obtained exclusively, and the product derived from the vicinal diamination of alkynes was not observed. Encouraged by this discovery, we set out to further optimize the reaction conditions.

We initiated our optimization by examining the reaction condition paramters such as solvent, catalyst, and reaction time, using **1a** and DBAD as the model reaction (Table 1). As

Table 1. Optimized Conditions for the Reaction[a]



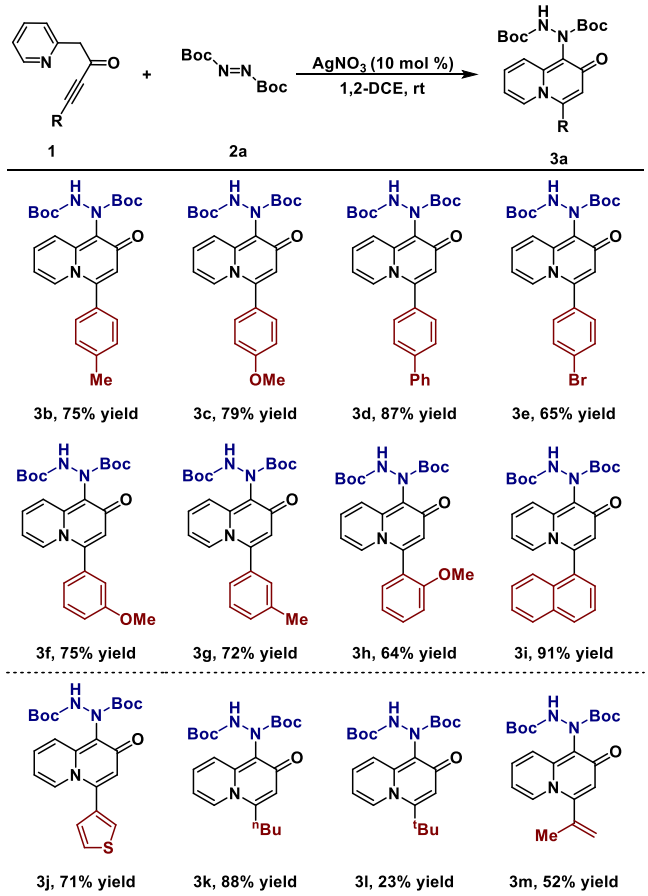
entry	cat.	time (h)	solvent	yield (%)[b]
1	$AgNO_3$	1.5	DCM	80
2	$AgNO_3$	1.0	1,2-DCE	85
3	$AgNO_3$	12	Toluene	36
4	$AgNO_3$	0.5	MeCN	76
5	$AgNO_3$	0.5	DMF	trace
6	$AgNO_3$	1.5	MeOH	76
7	$AgNO_3$	1.2	THF	38
8	AgOAc	4.0	1,2-DCE	58
9	$AgBF_4$	1.0	1,2-DCE	85
10	AgOTf	1.5	1,2-DCE	72
11	Ag_2CO_3	6.0	1,2-DCE	41
12	$AgSbf_6$	2.0	1,2-DCE	75
13	$AgNTf_2$	1.0	1,2-DCE	74

[a]Reaction conditions: **1a** (0.1 mmol), DBAD (0.2 mmol), cat. (10 mol %), solvent (1.0 mL), rt. [b]Yield of isolated product.

could be seen in Scheme 2, 1,2-DCE was found to be effective in the presence of $AgNO_3$, and an 85% yield of product was obtained (Table 1, entry 2). Toluene and THF were not compatible for the reaction owing to the low solubility of substrate **1a** (Table 1, entries 3 and 7). A trace amount of product was obtained when the reaction was performed in DMF (Table 1, entry 5). Other solvents such as DCM, MeCN, and MeOH gave us slightly lower yields of 76%−80% (Table 1, entries 1, 4, and 6). Most silver catalysts shown in Table 1 led to the desired products in good yields except for Ag_2CO_3 and AgOAc (Table 1, entries 8−13). While $AgBF_4$ was found to be comparable in efficiency (Table 1, entry 9), $AgNO_3$ was more economical and stable in air which was used as the best catalyst.

With the optimized conditions in hand, we then explored the scope and limitations of the reaction. The results were summarized in Schemes 2 and 3. To our delight, a wide range of alkynes were tolerated and all the reactions delivered the desired products in good to excellent yields. Arylacetylene bearing a series of *para*-substituents including the −Me,

Scheme 2. Substrate Scope of the R Group[a]



[a]Reaction conditions: **1** (0.1 mmol), DBAD (0.2 mmol), $AgNO_3$ (10 mol %), 1,2-DCE (1.0 mL), rt. Yield of isolated product.

−MeO, and −Ph group reacted smoothly (Scheme 2, compounds **3b**−**3d**). However, the yield of the desired product was decreased when *para*-substitution included an electron-withdrawing group such as a halogen (Scheme 2, compound **3e**).[8] The *meta*- and *ortho*-substituents on the phenyl ring were also tested which provided the desired products in good to excellent yields (Scheme 2, compounds **3f**−**3h**). In addition, the phenyl group was amenable to bulky and heterocycle groups, affording the products in 91% and 71% yield, respectively (Scheme 2, compounds **3i** and **3j**). The alkyl groups were also tolerated in the reaction, albeit with a 23% yield of **3l** (Scheme 2, compounds **3k** and **3l**). Finally, we noticed that the reaction was compatible with an alkene, leaving the double bond intact for further transformations (Scheme 2, compound **3m**).

With respect to the pyridine analogues, substituted groups on pyridine ring were then tested (Scheme 3). A variety of functional groups at the C3 position such as −Me, −OMe, −Ph, and −C≡CPh were tolerated, affording the desired products in moderate to excellent yields (Scheme 3, compounds **3n**−**3q**). However, the group at the C6 position affected the reaction significantly, and no desired product was obtained (Scheme 3, compound **3t**).[9] The substitutions at the C4 and C5 positions were tolerated, forming the desired products in 53% and 87% yields, respectively (Scheme 3, compounds **3r** and **3s**). Notably, the pyridine ring in the substrate **1** could be changed to other heterocycles such as

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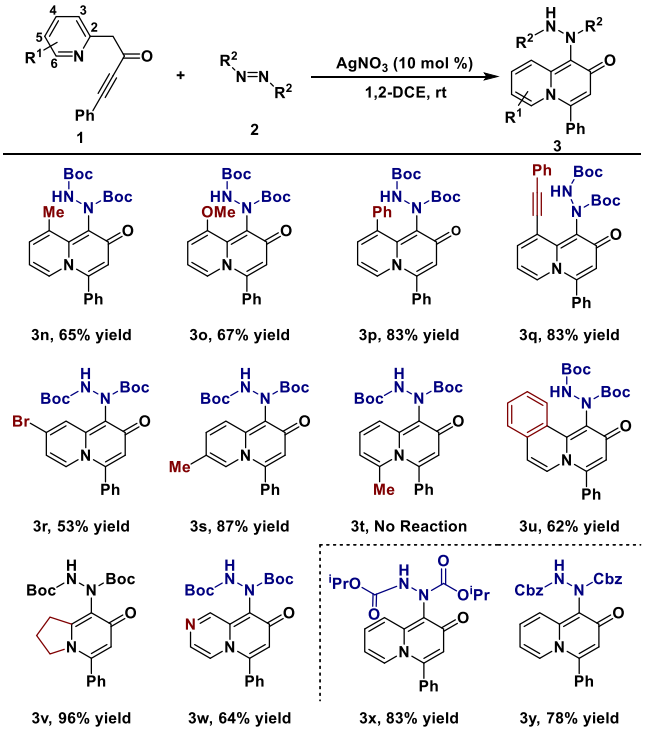
Scheme 3. Substrate Scope of Pyridine Ring and Diazenes[a]

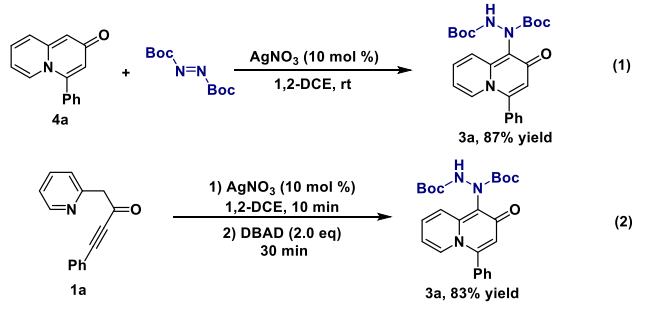


[a]Reaction conditions: **1** (0.1 mmol), diazene (0.2 mmol), $AgNO_3$ (10 mol %), 1,2-DCE (1.0 mL), rt. Yield of isolated product.

isoquinoline, pyrroline, and pyrazine which gave us the products in good to high yields (Scheme 3, compounds **3u**–**3w**). This result extended our methodology to potential useful building blocks in the synthesis of other nitrogen containing pharmaceuticals. Last, different protecting groups of diazenes were also tested which furnished the desired products in excellent yields (Scheme 3, compounds **3x** and **3y**).[10]

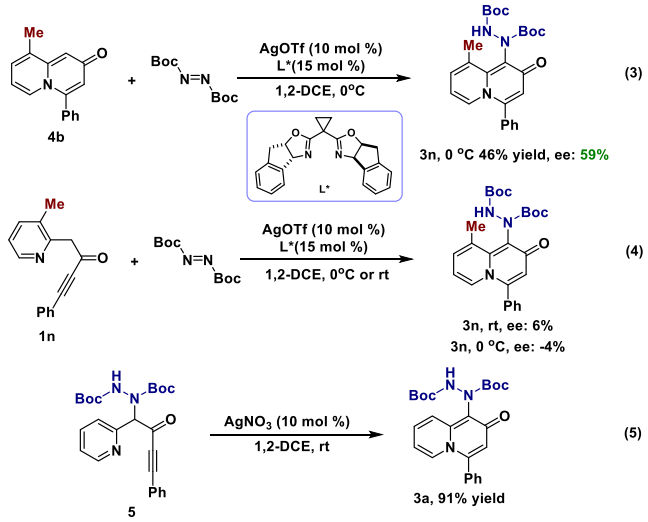
In an effort to gain more insight into the cascade reaction, the mechanism studies and control experiments were carried out. First, the compound **4a** was synthesized and subjected into our reaction system. To our delight, the reaction proceeded smoothly, affording **3a** in 87% yield (Scheme 4, eq 1), and no desired product was obtained in the absence of the silver catalyst. This result suggests the rare direct C–N bond formation of **4a** by a silver catalyst. Second, the reaction could also occur by stepwise operation which further indicated the tandem cycloisomerization–amination process (Scheme 4, eq 2).

Scheme 4. Silver Catalyzed Direct C–H Amination and Stepwise Cycloisomerization–Amination



In light of the axial chirality properties of the products **3**, we investigated the enantioselective version of the reaction. To simplify the studies of the enantioselectivities, compound **4b** was used as the substrate for the reaction. A series of silver salts and chiral ligands were surveyed (see Supporting Information (SI) for the details). Finally, **3n** could be obtained in 59% ee with 46% yield in the presence of AgOTf (Scheme 5, eq 3).[11]

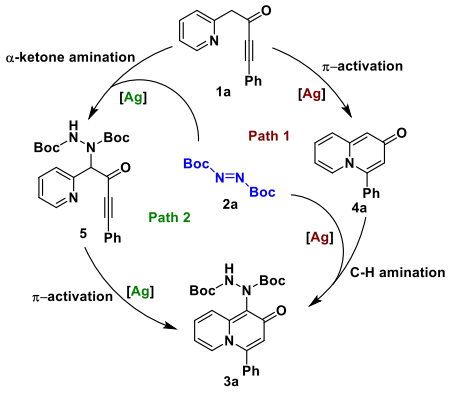
Scheme 5. Enantioselective Silver-Catalyzed C–H Amination, Cycloisomerization–Amination, and Cycloaddition Reaction



Interestingly, a different configuration of the product was obtained when the reaction was conducted at different temperatures using **1n** as the substrate (Scheme 5, eq 4). This outcome convinced us that the reaction proceeded by multiple pathways. In order to test our hypothesis, the compound **5** was synthesized and its homocoupling reaction was carried out. As a result, the reaction proceeded smoothly and a 91% yield of **3a** was obtained (Scheme 5, eq 5).[12]

Presumably, two competitive reactions may occur during the catalytic process. For the first pathway, the Ag(I) complex first activated the carbon–carbon triple bonds, followed by the attack of pyridine to form **4a**. The reason why no product resulting from the vicinal diamination of **1a** is obtained is believed to the result of the fast protonation of intermediate **B** (Scheme 1c). The silver-catalyzed C–H amination then occurred to afford the desired product (Scheme 6, path 1).

Scheme 6. Proposed Mechanism of the Reaction



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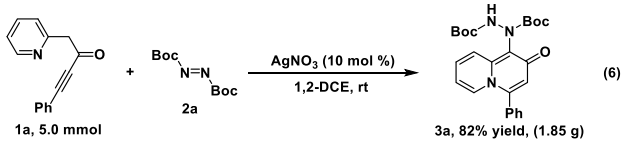
Alternatively, **1a** was first activated by a silver catalyst to react with DBAD, yielding the intermediate **5**. Afterward, the cycloisomerization proceeded to generate the desired product (Scheme 6, path 2). Although we could not clearly distinguish the two pathways, we surmised path 1 might be slightly more competitive than path 2 based on the asymmetric induction of **3n** in eqs 3 and 4.

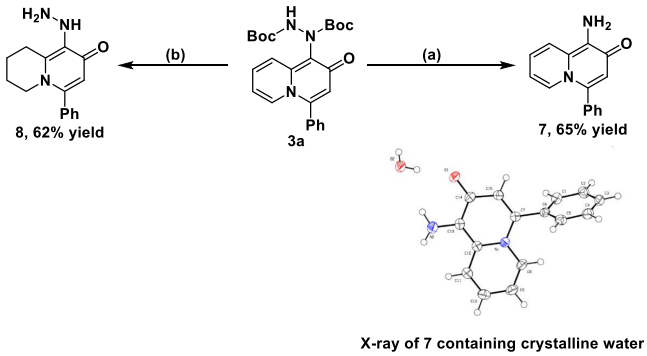
To test the practicality of the synthesis of 1-amino-2*H*-quinolizin-2-one derivatives, a gram-scale reaction of **1a** with DBAD was carried out. As expected, **3a** was isolated in 82% yield under the optimized conditions (Scheme 7, eq 6).

Scheme 7. Gram-Scale Reaction



Finally, the selective reductions were carried out to obtain versatile heterocyclic rings. The removal of Boc groups with TFA and DCM, followed by treatment with the Zn/AcOH system, afforded the amino derivative **7** (CCDC 1875492) in 65% isolated yield. A Pd/C-catalyzed hydrogenation that also promoted the deprotection of the Boc groups converted **3a** to **8** in 62% yield (Scheme 8).

Scheme 8. Selective Reductions of 3a[a]



[a]TFA/DCM, 50 °C overnight; then Zn, AcOH, 10 h. (b) TFA/DCM, 50 °C overnight; then Pd/C, H_2 (1 atm), MeOH, rt for 3 h.

In conclusion, we have developed a novel strategy to 1-amino-2*H*-quinolizin-2-one scaffolds by silver catalysis. The tandem cycloisomerization/amination process is attractive due to a wide substrate scope. The preliminary mechanistic studies indicated two possible pathways of the reaction. Moreover, the rare direct site-selective C−H amination of the 2*H*-quinolizin-2-one core was developed and extended to be an asymmetric transformation. Large-scale reaction and selective reductions were achieved, demonstrating the usefulness of the methodology to access a diversity of *N*-heterocyclic molecules. Detailed mechanistic studies including the DFT calculations and efforts to achieve high enantioselectivities of the C−H amination are currently in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03935.

Experimental procedures, detail reaction optimizations, HPLC traces, and characterization details (PDF)

Accession Codes

CCDC 1875492 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(8) No desired product was obtained when R was H or a strong electron-withdrawing group.

(9) The reason for no desired product may be attributed to the methyl group at the C6 position which prohibits the cyclo-isomerization.

(10) No desired products were obtained using (*E*)-1,2-diphenyldiazene and methyl (*E*)-2-(naphthalen-2-yl)diazene-1-carboxylate as the electrophiles for the reaction. A trace amount of product was obtained when using a strong electron-withdrawing group in a pyridine ring such as −CN in the C3 position.

(11) Syntheses of products such as **3n**−**3p** and **3t** were also attempted by asymmetric transformation. However, all of them were obtained with low enantioselectivities.

(12) The homocoupling for the synthesis of **3m** was also carried out, and −4% ee of product was obtained. The consistency with the reaction from **1m** to **3m** further indicated the existence of the path 2 of the reaction. See SI for the details.

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