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Catalytic Ring Expansion of Activated Heteroarenes Enabled by Regioselective Dearomatization

Jiyoung Kim and Eun Jeong Yoo*

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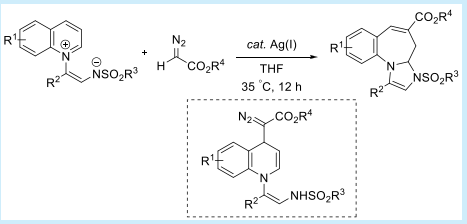
ABSTRACT: Catalytic ring expansion of activated heteroarenes through 1,4-dearomative addition of diazoacetates was established for the construction of various fused azepines by an elaborate control of the reaction kinetics at each step. The use of a silver catalyst was essential to drive the overall reaction for generating the desired seven-membered azepines. Because of the excellent substrate scope and selectivity, the developed methodology presents an innovative approach for the synthesis of multifused azepines, which are biologically relevant molecules.



Seven-membered heterocyclic compounds, especially azepines or diazepines, are privileged structures in natural products and potent pharmacophores.[1] In particular, azepine frameworks fused with another heterocycle are frequently responsible for outstanding biological activities in humans and livestock.[2] Hence, synthetic methods that provide easy access to azepine derivatives or their precursors have received significant attention in fields such as organic synthesis, pharmaceutical chemistry, and the animal feed industry.

To construct medium-sized azepine derivatives, ring expansion via ring opening of fused cyclic systems is considered an effective approach. In particular, methods for the introduction of cyclopropane-containing intermediates by employing diazo compounds, which are thermodynamically driven by releasing nitrogen gas, have received considerable attention (Scheme 1A). In the early stages, unsafe diazomethane or its Grignard form was used as a source of C1 from quinolinium salts to induce the formation of reactive cyclopropane intermediates, followed by ring expansion.[3] The use of TMS-diazomethane is effective in synthesizing azepines from quinoline derivatives;[4] however, the developed method could not be used to prepare diverse derivatives. Although various other strategies such as the use of diazoacetate have also been employed,[5] all previous studies essentially extend the 1,2-addition reaction of diazo compounds to imine compounds,[6] i.e., ring expansion via 1,2-dearomative addition. Herein, for the first time, we describe the regioselective 1,4-dearomative ring expansion of quinolinium zwitterions which provides access to a variety of azepine derivatives that are otherwise difficult to synthesize (Scheme 1B, (a)).

As a part of our ongoing study on the regiodivergent reactions of N-aromatic compounds,[7] we focused on the ring expansions of quinolinium derivatives via a 1,4-dearomative reaction, which has not been investigated to date. However, undesired but plausible reaction pathways were anticipated, and careful preliminary consideration was required before initiating the investigation.

1,2-Dearomative ring expansion of a quinolinium zwitterion, as reported previously (Scheme 1B, (b)), and the cycloaddition of quinolinium zwitterions and diazo compounds were considered as the predominant pathways (Scheme 1B, (c)). It was already observed that the nucleophilicity of quinolinium zwitterions was sufficient to attack the pregenerated carbenoid species.[7b] Hence, it was crucial to establish the reaction conditions that could regulate the kinetics of each step. In other words, it was necessary to establish reaction conditions, especially a catalyst, in the presence of which the 1,4-dearomative addition of diazoacetates preceded the release of nitrogen gas ($r_1 > r_2$).

Considering the plausible reaction pathways, we attempted to develop a ring-expansion reaction via regioselective dearomatization with a quinolinium zwitterion (**1a**) and ethyl diazoacetate (**2a**) as the starting materials (Table 1). First, rhodium(II), gold(I), and copper(I) catalysts were employed for the generation of a carbenoid species,[8] a key intermediate, from the diazo compound (**2a**) (entries 1−3). However, the desired product was not obtained, presumably due to the extremely rapid generation of the corresponding carbenoid. Interestingly, in the presence of silver catalysts, hardly known to generate carbenoids of diazoacetates,[9] the reaction produced azepine derivative **3a**. The structure of the obtained azepine (**3a**) was confirmed by NMR and X-ray analyses of its single-molecule crystal. $AgPF_6$, AgOTf, and AgOBz catalyzed the reaction of the quinolinium zwitterion

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Scheme 1. Strategies to Synthesize Azepines

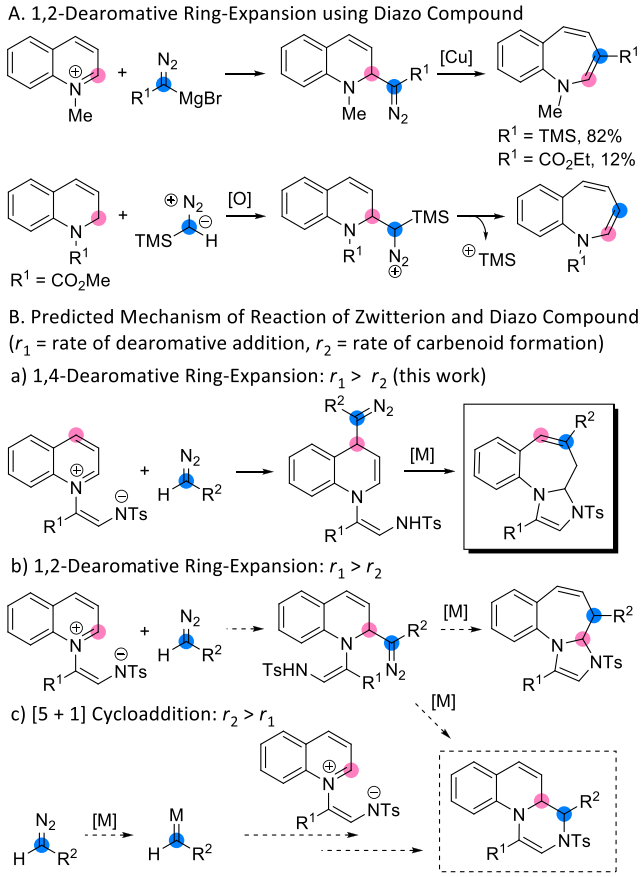
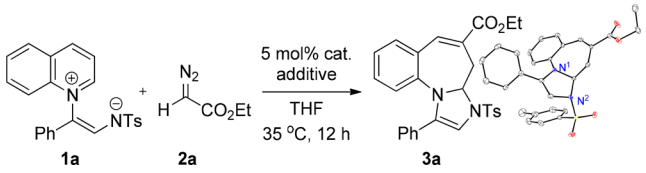


Table 1. Optimization of the Ring-Expansion Reaction[a]



entry	catalyst	additive	yield (%)[b]
1	$Rh_2(OPiv)_4$		<1
2	IPrAuCl		<1
3	CuCl		<1
4	$AgPF_6$		48
5	AgOTf		58
6	AgOBz		49
7	$Ag[O_2C(4\text{-}FC_6H_4)]$		78
8	$Ag[O_2C(4\text{-}NO_2C_6H_4)]$		80
9	$Ag[O_2C(3,5\text{-}(NO_2)_2C_6H_3)]$		83
10		NaOBz	<1
11		DBU	<1

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (3.0 equiv), catalyst (5 mol %), additive (1.3 equiv), and THF (4 mL) at 35 °C for 12 h. [b]Isolated yields.

(**1a**) with ethyl diazoacetate (**2a**) to afford the desired product (**3a**) in ~50% yield; slight differences in the yields were observed with these catalysts (entries 4−6). To improve the yield of the desired product (**3a**), several silver salts derived from silver benzoate were synthesized and employed in the reaction (entries 7−9).

Fortunately, silver catalysts with a counteranion of a benzoate derivative bearing an electron-withdrawing group (e.g., F, Cl, or NO_2) significantly improved the reaction efficiency and afforded product **3a** in high yields. When 5 mol % of silver 3,5-dinitrobenzoate was added to the THF solution of the quinolinium zwitterion and ethyl diazoacetate, product **3a** was obtained in 83% yield (entry 9). The reaction did not proceed in the presence of an inorganic base (entry 10) or organic base (entry 11).[10] Hence, it was already evident that silver played a crucial role in this reaction.

With the optimized reaction conditions in hand, we explored the scope of both reactants for synthesizing the azepine derivatives (Scheme 2). First, electronic and steric variations (R^1) were introduced on the quinolinium moiety of the zwitterion to understand their effect on silver catalysis. The 5-bromoquinolinium zwitterion, which could be used for further transformations, participated in this catalytic reaction to give the desired product (**3b**) in 58% yield. The 6-methoxyquinolinium zwitterion smoothly reacted with ethyl diazoacetate to afford the corresponding product (**3c**) in 62% yield. In contrast to an electron-rich substituent, the quinolinium zwitterion bearing the electron-deficient fluoro group on an identical position required 10 mol % of silver catalyst and 4.0 equiv of the reacting partner (**2a**) to afford a similar yield of product **3d**. The 8-methoxyquinolinium zwitterion also afforded the desired product **3e** in a satisfying yield, although the product was too unstable to be isolated by silica gel column chromatography. Addition of 1.5 equiv of K_2CO_3 after the completion of catalysis afforded the detosylated compound (**3e′**) in 46% yield.[10] It was also noteworthy that the zwitterion derived from 1,7-phenanthroline transformed into the fused seven-membered azepine derivative **3f** in 66% yield, albeit requiring a higher amount of the catalyst. Compounds with modification (R^2) on the enamine moiety of the zwitterions were also tolerated. *Para-tert*-butylphenyl- and *para*-trifluoromethylphenyl groups on R^2 of the zwitterions did not influence the efficiency of this silver-catalyzed reaction, and the desired products **3g** and **3h** were obtained in 65% and 73% yields, respectively. Comparing products **3i** and **3j**, it was observed that the electronic feature of the meta-substituted phenyl group on R^2 slightly affected product yields, and the zwitterion with the electron-deficient fluoro substituent was readily converted into the desired product **3j** in 83% yield. In addition, *ortho*-fluoro and 3,5-difluoro substituents were well tolerated under the optimized reaction conditions. Conversely, electronic variations of the sulfonyl group on the quinolinium zwitterions dramatically influenced the overall yield. Consequently, products (**3m** and **3n**) with neutral- or electron-rich sulfonyl groups on the nitrogen atom were obtained in acceptable yields.

Evidently, the scope of the diazoacetates in this reaction is quite broad. Primary, secondary, and even tertiary alkyl diazoacetates could be employed as substrates for the ring-expansion reaction to afford the desired products (**3p**−**3t**) in high yields under the optimized reaction conditions. The compatibility of the diazo compounds is an outstanding feature of this reaction and is distinct from previously reported strategies. Further, *para*-methoxyphenyl diazoacetate was reacted with the quinolinium zwitterion (**1a**) to furnish the desired product (**3u**) in 50% yield under slightly modified reaction conditions.

To verify further synthetic utility of the developed methodology, general transformations were examined. As

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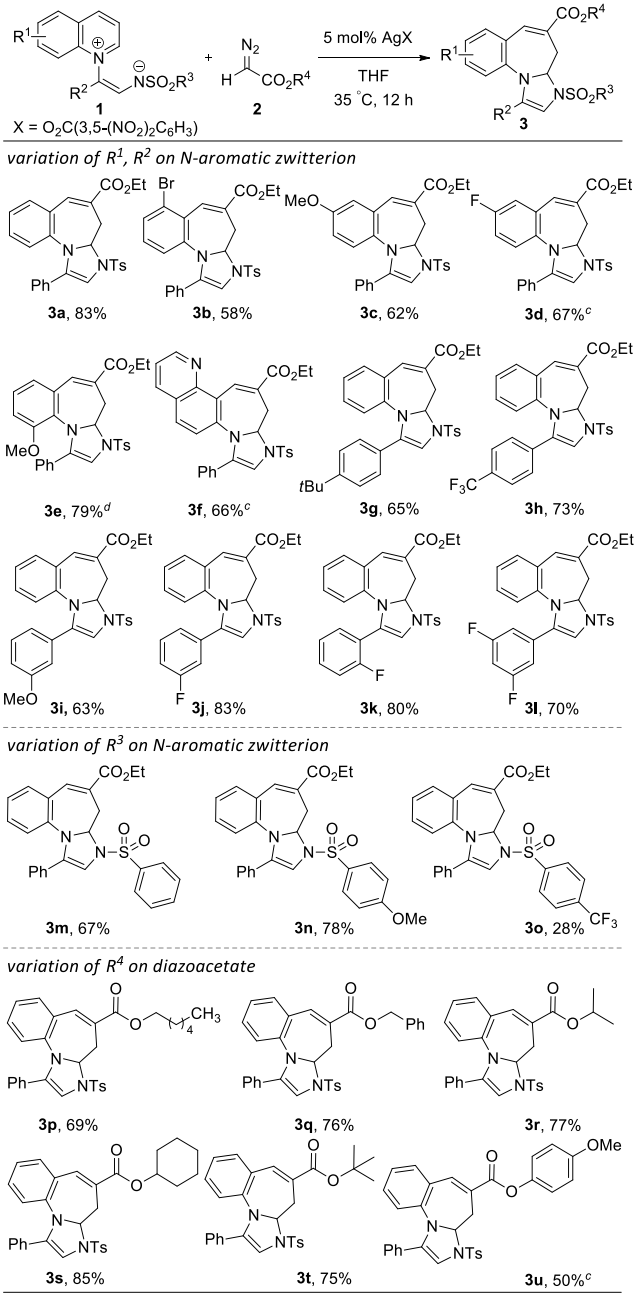
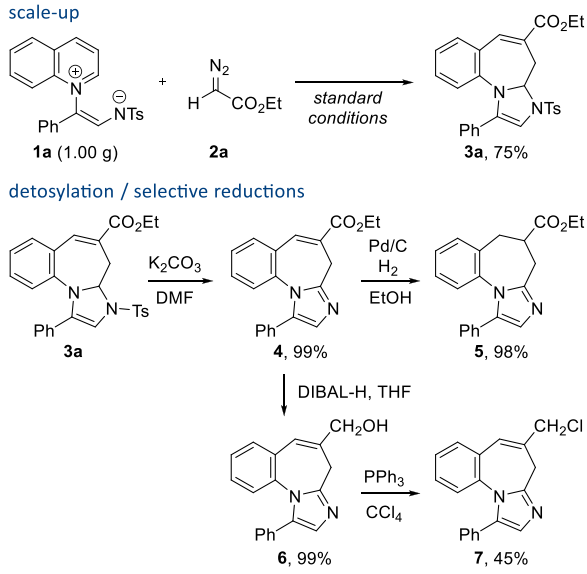
Scheme 2. Silver-Catalyzed Ring-Expansion Reactions of N-Aromatic Zwitterions and Diazoacetates[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2** (3.0 equiv), silver catalyst (5 mol %), and THF (4 mL) at 35 °C for 12 h. [b]Isolated yields. [c]4.0 equiv of **2** and 10 mol % of silver catalyst were used. [d]^{1}H NMR yield based on the dibromomethane internal standard.

Scheme 3. Synthetic Applications



shown in Scheme 3, the gram-scale reaction conducted with **1a** as the starting material proceeded smoothly to give the desired product (**3a**), without any significant loss of yield. As mentioned before, deprotection of the sulfonyl group of the obtained product (**3a**) was quantitatively achieved by adding 1.5 equiv of K_2CO_3 to give compound **4**, which was stable enough to easily transform into other functionalized products. Regioselective reduction reactions of compound **4** were also accomplished. In the presence of a Pd/C catalyst and hydrogen gas (1 atm), the conjugated carbon−carbon double bond of compound **4** was selectively reduced to a single bond (**5**). When treated with DIBAL-H, the ester group of compound **4** was reduced to an alcohol (**6**) in high yield. Moreover, the alcohol functional group of compound **6** was converted into alkyl chloride (**7**) in appreciable yield under Appel reaction condtions.[11]

Next, we investigated the detailed mechanism of the developed ring-expansion reaction. As shown in Scheme 4, a series of isotope-labeling experiments were conducted. Under the optimized reaction conditions, the deuterium-labeled quinolinium zwitterion (**1a-D**) reacted with ethyl diazoacetate (**2a**) to give the seven-membered product **3a^1-D**, in which deuterium was quantitatively incorporated in the identified position. In contrast, the reaction between the quinolinium zwitterion (**1a**) and ethyl diazoacetate labeled with deuterium (**2a-D**) did not result in deuterium incorporation in the product (**3a**) under identical reaction conditions. Interestingly, when unlabeled reactants were stirred with the silver catalyst in a THF−D_2O (40:1) mixture, the product (**3a^2-D**) with deuterium incorporated at the 3-position was afforded. Applying our previously reported method,[7c] cyclopropane-fused heterocyclic compound **8** was successfully synthesized to examine the ring-opening reaction. However, compound **8** was too stable to be converted to the desired compound under the standard reaction conditions. In fact, we recovered compound **8**, which did not react even when treated with stronger bases. Thus, the reaction pathway in which both cyclopropane and imidazole were formed first, followed by ring expansion, was tentatively ruled out. Other diazo compounds, referred to as acceptor−donor or acceptor−acceptor substituted, did not react with the quinolinium zwitterion (**1a**) under the optimized reaction conditions;[10] only diazoacetates were compatible in this catalysis. In addition, we observed that the diazoacetate anion was formed when diazoacetate was stirred with a stoichiometric amount of silver salt regardless of the presence of the zwitterion.[10] While exploring the substrate scope, we were pleased to isolate side-product **9** with a carbon−carbon double bond at the C4-position of the quinoline moiety. These results strongly suggest that the anion generated from the diazoacetate attacked the C4-

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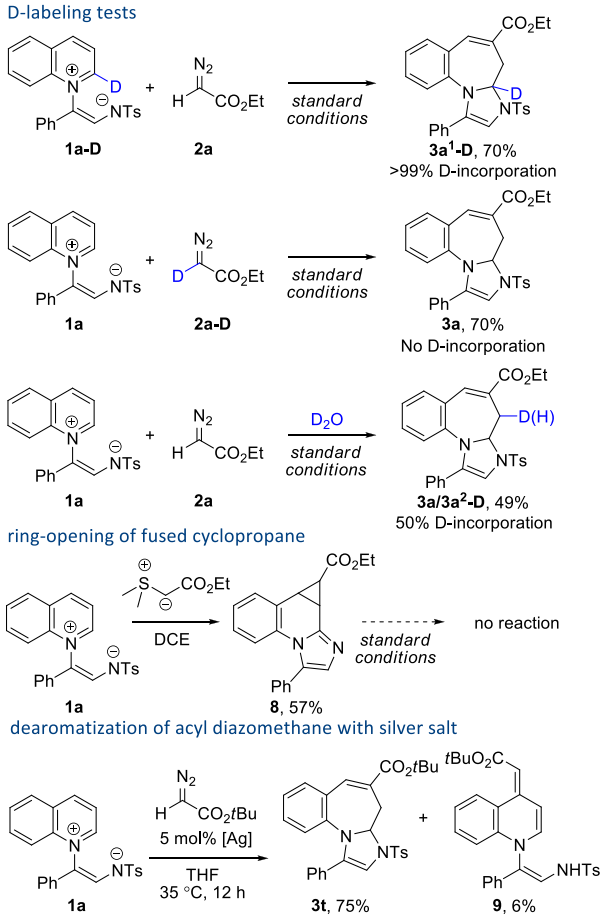
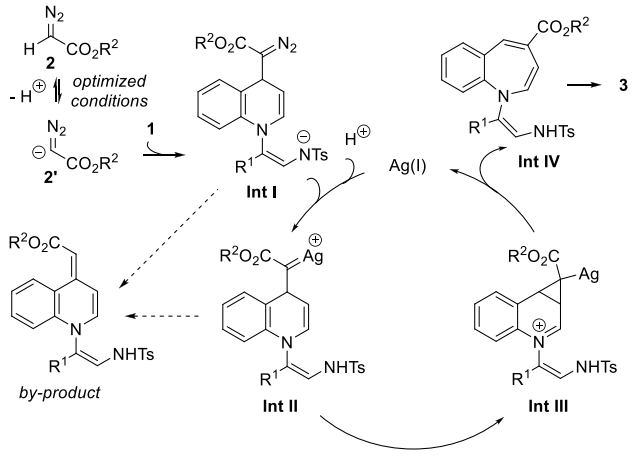
Scheme 4. Investigation of the Plausible Mechanism



position of the quinolinium zwitterion to afford regioselective 1,4-dearomatization.[12]

Based on the experimental results and reported literature,[13] a catalytic mechanism is proposed (Scheme 5). First, diazoacetate (**2**) is converted into the anionic form (**2′**) under the reaction conditions, which regioselectively attacks the N-aromatic zwitterion (**1**) to generate **Int I** possessing the diazo functional group. We also considered the possibility that diazoacetate could act as a 1,2-dipole to directly attack the N-aromatic zwitterions without converting to the anionic form (**2′**). However, this possibility was carefully excluded based on the results of the mechanistic investigations, particularly the results of the reaction employing disubstituted diazo compounds. Following this, the reaction of a silver catalyst accompanied by N_2 release to generate silver-carbenoid **Int II** is proposed (at this point, Int I or Int II can be converted into a separable side product). **Int II** can then be readily transformed into **Int III** through intramolecular cyclopropanation via iminium formation. Afterward, ring expansion proceeds via the neutralization of iminium-type **Int III** along with regeneration of the silver catalyst for another cycle. It is noteworthy that this route is consistent with the good yields obtained using the zwitterions substituted with electron-poor R^2. Finally, **Int IV** undergoes intramolecular hydroamination to afford the final product (**3**).

Scheme 5. Proposed Mechanism



In conclusion, a regioselective silver(I)-catalyzed reaction for easy access to 4-substituted azepine derivatives has been developed. Mechanistic studies revealed that the entire catalytic reaction was driven by the ability of the diazoacetate species to regioselectively undergo 1,4-dearomative addition, which has been witnessed here for the first time. This methodology demonstrates that N-aromatic zwitterions allow access not only to fused six-membered cyclic compounds via simple dearomative strategies but also to their seven-membered analogues via successive ring expansion. Further related studies utilizing N-aromatic zwitterions and their skeletal restructuring are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01173.

Experimental procedures and analytical data (PDF)

Accession Codes

CCDC 2060953 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.

■ AUTHOR INFORMATION

Corresponding Author

Eun Jeong Yoo − *Department of Applied Chemistry, Kyung Hee University, Yongin 17104, Republic of Korea;* orcid.org/0000-0003-4027-2441; Email: ejyoo@khu.ac.kr

Author

Jiyoung Kim − *Department of Applied Chemistry, Kyung Hee University, Yongin 17104, Republic of Korea*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c01173

Notes

The authors declare no competing financial interest.

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