



Cite this: *Chem. Commun.*, 2018, 54, 6911

Received 30th March 2018,  
Accepted 18th May 2018

DOI: 10.1039/c8cc02570c

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Herein, we demonstrate a new catalytic cycloaddition of quinolinium zwitterions involving a gold-bound allylic cation intermediate. This ligand-free higher-order cycloaddition efficiently affords a variety of fused 1,4-diazepine derivatives in a stereospecific manner at room temperature.

Polycyclic heterocycles are one of the most common skeletons found in natural products, biologically active compounds, and functional materials. Among these polycycles, fused 1,4-diazepine derivatives are of particular significance in pharmaceutical chemistry and can be found in Alprazolam, Flumazenil, and related drugs,<sup>1</sup> as well as in bioactive natural products such as sclerotigenin, benzomalvins (A–C), asperlicins, and circumdatin analogues (A–G)<sup>2–5</sup> (Fig. 1).

Higher-order cycloaddition is one of the most powerful and widely used synthetic methods for the construction of medium-sized heterocyclic skeletons.<sup>6</sup> Although the application of dipolar cycloaddition to the synthesis of five- and six-membered heterocycles is well documented, examples of higher-order cycloadditions employing well-established 1, *n*-dipoles are still rare. One of the few examples includes the utilization of [4+3] cycloadditions of 1,3-dipoles to access seven-membered heterocycles.<sup>7</sup> In comparison to the above-mentioned case, [5+2] cycloadditions have been under-explored because of the absence of practical 1,5-dipoles, *e.g.*, most catalytic [5+2] cycloadditions employ vinylcyclopropanes and their derivatives as five-carbon synthons.<sup>8</sup> Although we have previously reported the synthesis of seven- and eight-membered heterocycles using a unique isolable pyridinium zwitterion as a 1,5-dipole,<sup>9</sup> the development of the respective cycloadditions is still in its infancy.

Activated allene substrates,<sup>10</sup> especially allenamides, have been proved to be versatile and useful substrates in organic synthesis and have recently been used as two-carbon synthons

## Gold-catalyzed [5+2] cycloaddition of quinolinium zwitterions and allenamides as an efficient route to fused 1,4-diazepines†

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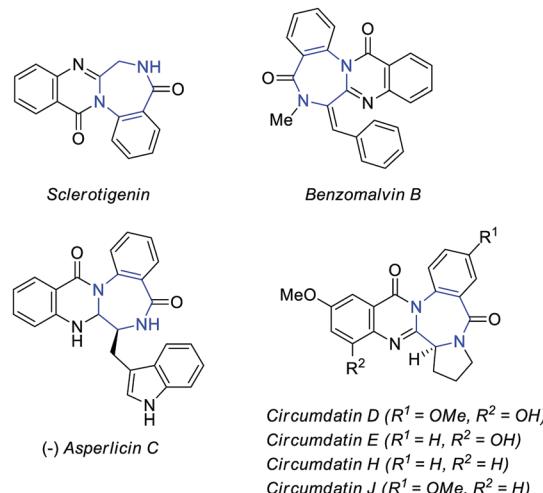


Fig. 1 Fused N-heterocycles possessing a 1,4-diazepine moiety.

in gold(i)-catalyzed cycloadditions. Since the first suggestion of the involvement of Au-bound allylic cation intermediates in these reactions, formal [2+2], [4+2], and [2+2+2] cycloadditions of allenamides with different types of  $2\pi$ -dipolarophiles, such as indoles (Scheme 1a), olefins (1b), dienes (1c), and carbonyl compounds (1d) to afford four- or six-membered cyclic compounds have been established.<sup>10–12</sup> Interestingly, in contrast to  $2\pi$ -dipolarophiles, 1, *n*-dipoles have never been explored as allenamide partners in gold-catalyzed cycloadditions.

Herein, we describe a new gold(i)-catalyzed [5+2] cycloaddition of quinoline-based 1,5-dipoles and allenamides that furnishes fused 1,4-diazepine derivatives. Compared to the first and only example of gold(i)-catalyzed [5+2] cycloaddition of phenylpropargyl acetals (Scheme 1e),<sup>13</sup> the developed cycloaddition is a very simple, mild, and efficient route to fused N-heterocyclic compounds.

Inspired by the well-studied Au-bound allylic cation intermediate **I** generated by the nucleophilic addition of the Au catalyst to allenamides (**2**),<sup>10d,e,11a</sup> we envisioned that the above-mentioned intermediate might be nucleophilically attacked by a zwitterionic

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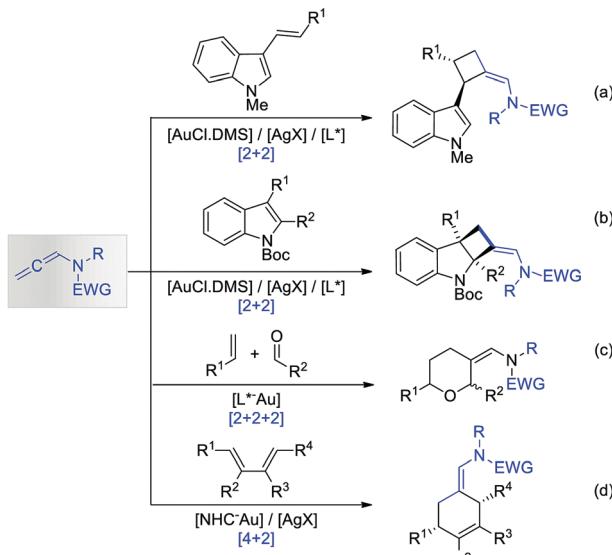
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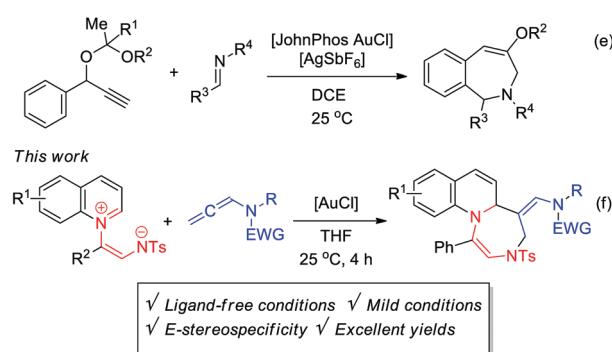
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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c8cc02570c

## A. Gold-Catalyzed Cycloadditions of Allenamide

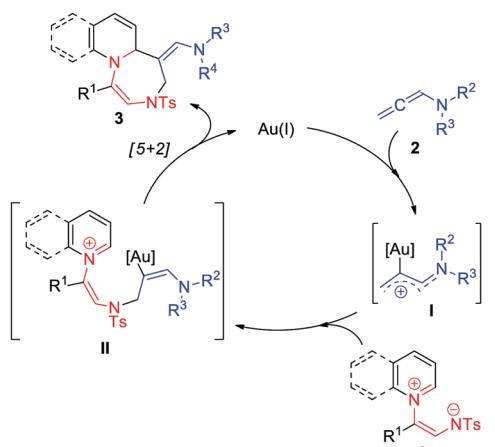


## B. Gold-Catalyzed [5+2] Cycloadditions



Scheme 1 [A] Au-Catalyzed [m+2] cycloadditions of allenamides. [B] Au-catalyzed [5+2] cycloadditions.

1,5-dipole (**1**) and could thus undergo [5+2] cycloaddition. As illustrated in Scheme 2, the gold catalyst is thought to initially activate the allenamide (**2**) to afford a Au-bound allylic cation (**I**), which is nucleophilically attacked by the nitrogen of **1** to generate a tethered intermediate **II**. Subsequently, the intramolecular

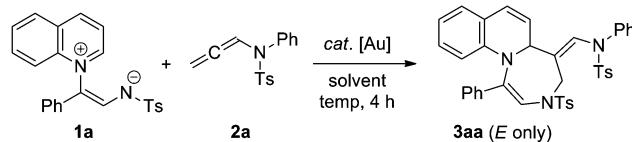


Scheme 2 Plausible mechanism of gold-catalyzed [5+2] cycloaddition.

cyclization of **II** affords seven-membered 1,4-diazepines (**3**) and leads to catalyst regeneration.

To test this hypothesis, we reacted quinolinium zwitterion **1a**, which is more reactive than the previously reported pyridinium zwitterion, with allenamide **2a** under various conditions (Table 1). To our delight, in the presence of  $\text{AuCl}_3$ , the desired seven-membered ring **3aa** was obtained in 62% yield in dichloromethane

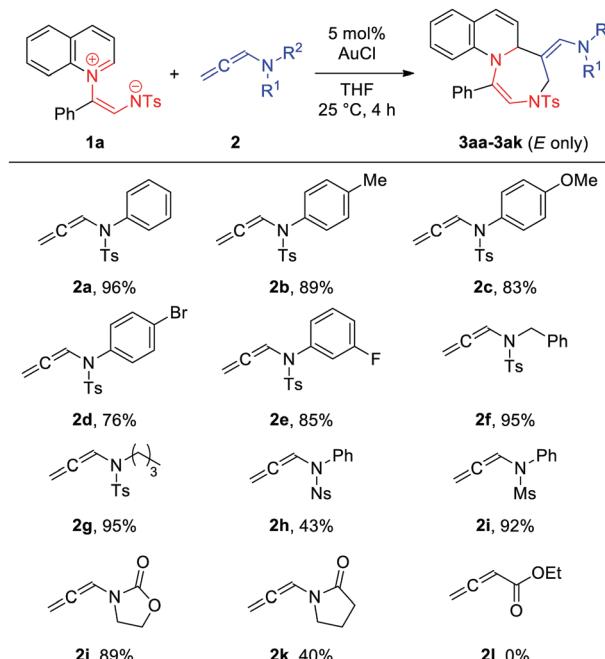
Table 1 Optimization of the conditions<sup>a</sup>



| Entry | Au catalyst                 | Solvent     | Temp. (°C) | Yield <sup>b</sup> (%) |
|-------|-----------------------------|-------------|------------|------------------------|
| 1     | $\text{AuCl}_3$             | DCM         | 40         | 62                     |
| 2     | $\text{AuPy-cat}^c$         | DCM         | 40         | 86                     |
| 3     | $\text{PPh}_3\text{AuCl}^d$ | DCM         | 25         | 0                      |
| 4     | $\text{AuCl}$               | DCM         | 25         | 88                     |
| 5     | $\text{AuCl}$               | DCE         | 25         | 90                     |
| 6     | $\text{AuCl}$               | THF         | 25         | 99 (96) <sup>e</sup>   |
| 7     | $\text{AuCl}^f$             | THF         | 25         | 87                     |
| 8     | $\text{AuCl}$               | Toluene     | 25         | 24                     |
| 9     | $\text{AuCl}$               | 1,4-Dioxane | 25         | 92                     |
| 10    | $\text{AuCl}$               | THF         | 25         | 87                     |
| 11    | —                           | THF         | 25 → 80    | 0                      |

<sup>a</sup> Reaction conditions: quinolinium zwitterion **1a** (0.1 mmol), allenamide **2a** (1.3 equiv.), gold catalyst (5 mol%), and solvent (2.0 mL) for 4 h. <sup>b</sup> NMR yield of **3aa** using  $\text{CH}_2\text{Br}_2$  as an internal standard. <sup>c</sup>  $\text{AuPy-cat}$ : dichloro-(2-pyridinecarboxylato)gold. <sup>d</sup> 60% product (**3aa**) was formed when  $\text{AgSbF}_6$  (5 mol%) was additionally added. <sup>e</sup> Isolated yield. <sup>f</sup> 2.5 mol%  $\text{AuCl}$  was used.

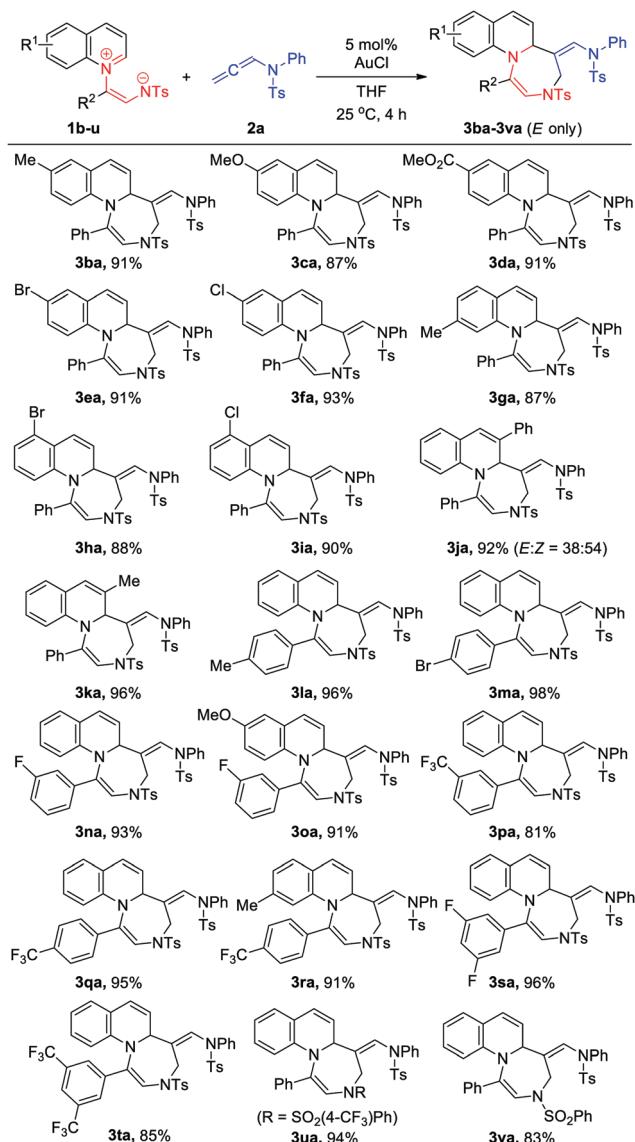
Table 2 Scope of allenamides<sup>a,b</sup>



<sup>a</sup> Reaction conditions: quinolinium zwitterion **1a** (0.1 mmol), allenamide **2** (1.3 equiv.),  $\text{AuCl}$  (5 mol%), and THF (2.0 mL) at room temperature for 4 h. <sup>b</sup> Isolated yield of **3**.

(DCM) at 40 °C (entry 1). Notably, this reaction stereospecifically furnished *E*-cycloadduct **3aa**, as confirmed by 2D NMR and NOE experiments.<sup>14</sup> Another Au(III) catalyst, dichloro(2-pyridinecarboxylato)-gold, provided a better result under identical reaction conditions (entry 2). Although phosphine-chelated  $\text{PPh}_3\text{AuCl}$  was completely ineffective in the absence of an Ag additive (entry 3), the sole use of AuCl afforded the best results even at room temperature (entry 4). Subsequently, diverse solvents were screened to optimize the reaction conditions (entries 5–10). The best results were observed with the relatively non-polar THF, which allowed for the desired products to be exclusively obtained within 4 h (entry 6). The role of the Au catalyst was confirmed by performing a control experiment under catalyst-free conditions (entry 11), which afforded intramolecular cyclized product **1a** at high temperatures.<sup>14</sup> Additionally,

Table 3 Scope of quinolinium zwitterions<sup>a,b</sup>



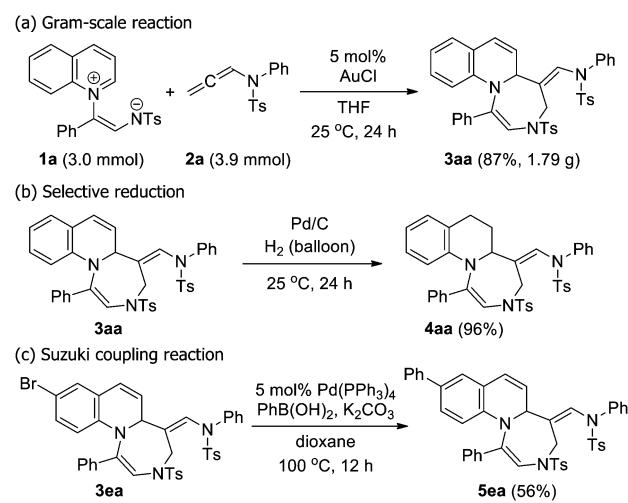
<sup>a</sup> Reaction conditions: quinolinium zwitterion **1b-u** (0.1 mmol), allenamide **2a** (1.3 equiv.), AuCl (5 mol%), and THF (2.0 mL) at room temperature for 4 h. <sup>b</sup> Isolated yield of **3**.

the [5+2] cycloaddition of the above-mentioned pyridinium zwitterion was unsuccessful because of the occurrence of a competing cascade [5+2]/[2+2] cycloaddition,<sup>14</sup> which was very similar to that observed for the reaction of the same pyridinium zwitterion with benzyne.<sup>9c</sup>

With the optimized conditions in hand, we then explored the scope of [5+2] cycloadditions using different allenamide substrates (Table 2). A wide range of allenamides furnished the desired cycloadducts in good to excellent yields irrespective of the electronic nature of the *N*-substituent in **2a–2e**. Both *N*-benzyl and *N*-alkyl allenamide variants (**2f** and **2g**, respectively) were tolerated. Compared to the reactions of *N*-tosyl- or *N*-mesyl-substituted allenamides, that of *N*-nosyl-substituted allenamide **2h** was rather sluggish. Interestingly, although oxazolidone-based allenamide **2j** was found to efficiently undergo [5+2] cycloaddition, the corresponding pyrrolidone derivative **2k** was less effective under the optimized reaction conditions. Notably, no reaction was observed for allenolate analogue **2l**. Moreover, 1,1- and 1,3-disubstituted allenamides were found to be ineffective in this protocol.

Next, higher-order cycloadditions between quinolinium zwitterions **1** and allenamide **2a** were tested to confirm the generality and stereoselectivity of this method (Table 3). As a result, it was found that, except for **1j**, 1,5-dipoles **1** bearing both electron-donating and electron-withdrawing substituents on the quinoline backbone (**1b–1k**) were well tolerated and exclusively provided (*E*)-cycloadducts. The proximal 3-phenyl group of the quinoline backbone adjacent to the reaction site was believed to significantly impact product stereoselectivity, whereas no considerable change was observed for the corresponding methyl analogues **1k**. Quinoline zwitterions bearing various aryl substituents on the enamide moiety of 1,5-dipoles (**1l–1t**) also provided the desired adducts in excellent yields and stereospecificities.

To further demonstrate the synthetic utility of the developed method, a gram-scale [5+2] cycloaddition was carried out (Scheme 3), and the *E*-cycloadduct was exclusively isolated in



Scheme 3 Gram-scale [5+2] cycloaddition reaction and synthetic diversification.

87% yield (1.79 g), which indicated that the reaction efficiency and stereospecificity were not affected by the scale-up. Additionally, the obtained product underwent smooth reduction or cross-coupling to furnish the corresponding cyclic compounds (**4aa** and **5ea**, respectively) in acceptable yields. However, the attempted exocyclic C=C bond cleavage *via* ozonolysis was unsuccessful, thereby resulting in the decomposition of the obtained 1,4-diazepine.

In conclusion, in this study, we developed a new ligand-free gold-catalyzed [5+2] cycloaddition of quinolinium zwitterions and allenamides that provides stereospecific access to fused 1,4-diazepine derivatives in good to excellent yields. A wide range of substrates were tolerated for both reagents, and a gram-scale feasibility test proved the high potential and versatility of this protocol. The development of an enantioselective [5+2] cycloaddition is currently underway in our laboratory.

This research was supported by the National Research Foundation of Korea (NRF) (NRF-2016R1A2B4015351, NRF-2016R1A4A1011451) funded by the Korea government and the GRRC program of Gyeonggi province (GRRCKyungHee2018-A01).

## Conflicts of interest

There are no conflicts to declare.

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- See the ESI,† for details.