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Brønsted acid-catalyzed formal [5+2+1] cycloaddition of ynamides and isoxazoles with water: access to oxygen-bridged tetrahydro-1,4-oxazepines†

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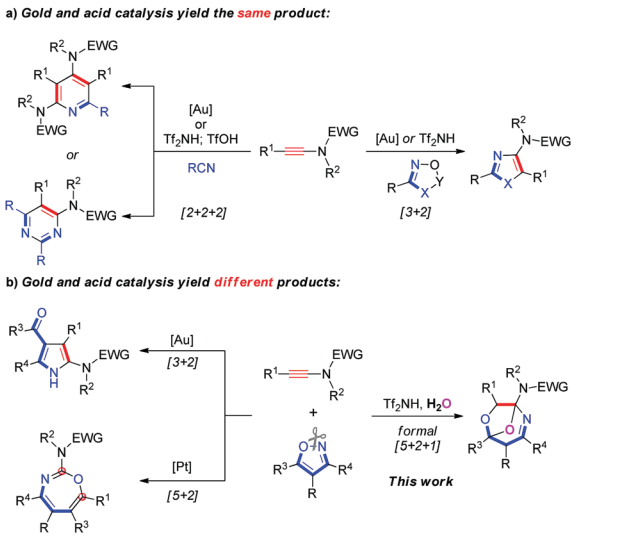
A Brønsted acid-catalyzed formal [5+2+1] cycloaddition of ynamides and isoxazoles with water is described. This process provides atom-economical access to oxygen-bridged tetrahydro-1,4-oxazepines, where the bridged oxygen atom originates from water. The unique property of the Brønsted acid shows distinct chemoselectivity from the corresponding gold-catalyzed cycloadditions.

Over the past decade, the cycloaddition of ynamides with various unsaturated precursors has created remarkable opportunities for the assembly of complex amino-functionalized heterocycles. Much progress has been achieved by transition-metal catalysis, gold catalysis in particular.[1–5] For example, Liu and coworkers described an elegant gold-catalyzed [2+2+2] cycloaddition of ynamides with nitriles for the divergent synthesis of pyrimidines[3a] and pyridines[3b] (Scheme 1a, left). Besides, various unsaturated N–O heterocycles such as 1,4,2-dioxazoles,[4a] 1,2,4-oxadiazoles,[4b] and 4,5-dihydro-1,2,4-oxadiazoles[4c] have also served as three-atom synthons in gold-catalyzed cycloadditions with ynamides, thereby yielding amino-substituted oxazoles and imidazoles (Scheme 1a, right). In comparison with the significant advances achieved in gold catalysis, it was not until very recently that metal-free catalytic cycloadditions of ynamides were disclosed.[5,6] The groups of Sun,[5a] Chang,[5b] Maulide[5c,d] and Tang[5e] independently found that nitriles and ynamides could undergo [2+2+2] cycloadditions in the presence of Tf_2NH or TfOH to generate pyridines and pyrimidines (Scheme 1a, left). Later, we reported the Tf_2NH-catalyzed [3+2] cycloadditions of ynamides with dioxazoles[6a] or oxadiazolones,[6b] enabling easy access to oxazoles and imidazoles (Scheme 1a, right). All of these transformations yielded the same products as gold catalysis, making the Brønsted acid a highly economical alternative[7] for the gold-catalyzed cycloadditions of ynamides. However, despite these advances, the development of acid-catalyzed cycloadditions of ynamides that can show distinct reactivity from that of gold catalysis is still desirable and of great importance.



Scheme 1 Gold *versus* Brønsted acid-catalyzed cycloadditions of ynamides.

Isoxazoles are an important class of heterocycles in organic synthesis[8] and have recently proved to be versatile precursors for the synthesis of other valuable scaffolds.[9–12] In this context, Ye and co-workers discovered that 3,5-dimethylisoxazole could undergo [3+2] cycloaddition with ynamides in the presence of a gold catalyst to deliver 2-aminopyrroles (Scheme 1b, top left).[10a,b] Very recently, the same group also reported a platinum-catalyzed formal [5+2] cycloaddition of isoxazoles with ynamides to afford unexpected 1,3-oxazepines (Scheme 1b, bottom left).[10c] Encouraged by these results and in continuation of our work on the cycloaddition reactions,[6,13] we envisioned that a Brønsted acid-catalyzed intermolecular cycloaddition of ynamides with isoxazoles could provide access to 1,4-oxazepines. Intriguingly, by introducing a

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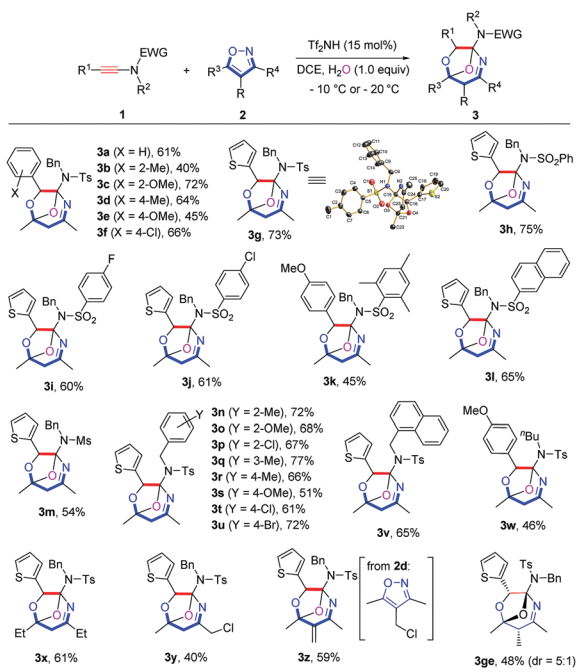
small amount of water, an unexpected formation of the oxygen-bridged 1,4-oxazepine derivative was observed (Scheme 1b, right), in which isoxazole acts as a five-atom building unit to construct the seven-membered ring and water acts as the bridged oxygen atom source. To the best of our knowledge, transition-metal-free catalytic three-component formal cycloaddition to construct bridged skeletons has not been disclosed yet. Herein, we report our results on the Brønsted acid-catalyzed [5+2+1] cycloaddition of ynamides and isoxazoles with water to afford oxygen-bridged tetrahydro-1,4-oxazepines, which are potentially bioactive molecules.[14] The unique property of the Brønsted acid, as well as introducing a small amount of water, shows distinct chemoselectivity from the corresponding gold-catalyzed cycloadditions.[10]

We commenced our investigation with the optimization of the reaction conditions by choosing ynamide **1a** and 3,5-dimethylisoxazole **2a** as the model substrates (see the ESI† for full details). The optimized reaction conditions were found to be Tf_2NH as a catalyst (15 mol%), 1.5 equivalents of **1a**, 1.0 equivalent of H_2O, and −10 °C for 6 h. The structure of **3a** was unambiguously confirmed by single-crystal X-ray diffraction analysis of its analogue **3g**.[15] It is noteworthy that no 2-aminopyrrole was detected during the optimization (including the one in the absence of water), revealing the distinct catalytic activity of acid catalysis from that of gold catalysis.[10]

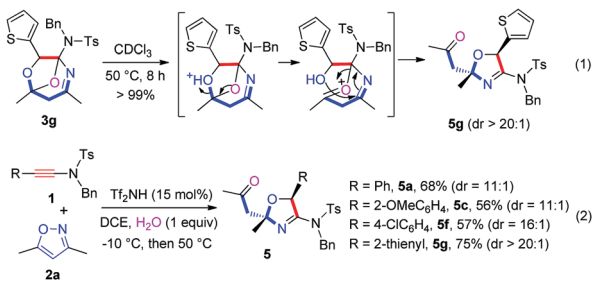
With the optimized conditions in hand, we then examined the generality of this process, and the results are summarized in Scheme 2. A variety of aryl-substituted ynamides were well tolerated regardless of their steric and electronic properties, leading to the desired products **3a–3f** in 40–72% yield.



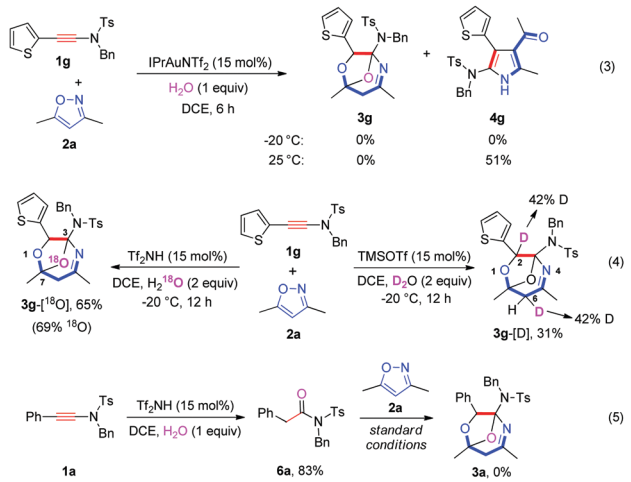
Scheme 2 Substrate scope. The reactions of ynamides **1a–1f** with 3,5-dimethylisoxazole **2a** were conducted at −10 °C, while others were performed at −20 °C. Detailed conditions are given in the ESI.† Isolated yields are reported.

The reaction could also be extended to 2-thienyl-derived substrate **1g**, which was transformed into product **3g** in 73% yield.[15] However, unfortunately, this cycloaddition was not suitable for alkyl-substituted ynamides (see the ESI†).[16] The scope of the electron-withdrawing groups on the nitrogen atom was also investigated. The treatment of *N*-SO_2Ph derived ynamide **1h** under the standard conditions led to the formation of **3h** in 75% yield. Besides, halogen substituents (*e.g.* F, Cl) on the phenylsulfonyl group were also compatible with the process, providing the desired products in moderate yields (**3i**, **3j**). Ynamides possessing sterically hindered 2,4,6-trimethylphenylsulfonyl (**1k**) and 2-naphthylsulfonyl (**1l**) groups proved to be suitable substrates as well.[17] Notably, when an alkyl substituent such as Me was employed in the sulfonyl group (*N*-Ms), the cycloaddition proceeded smoothly to generate the corresponding product **3m** in 54% yield. The substituents on the R^2 group were then screened. It was found that the electronic and steric factors on the benzyl group of the ynamides had no significant impact on the reaction (**3n–3u**), furnishing the corresponding products in 51–77% yield. Similarly, ynamide **1v** bearing a 1-naphthylmethyl group at R^2 underwent the cycloaddition efficiently to deliver **3v** in 65% yield. Pleasingly, this transformation was also applicable to *N*-^{n}Bu ynamide **1w**,[17] thus allowing the assembly of oxygen-bridged heterocycle **3w** in 46% yield. Disappointingly, the more electron-rich oxazolidinone-substituted ynamide failed to participate in the reaction owing to its relatively lower reactivity (see the ESI†). Finally, the feasibility of extending the protocol to other isoxazoles was demonstrated. Replacing the methyl substituents at R^3 and R^4 with ethyl groups generated **3x** in a satisfactory yield. Upon exposure of 3-(chloromethyl)-5-methylisoxazole **2c** to the standard conditions, the target product **3y** was isolated in 40% yield. To our surprise, an unexpected dehydrochlorinated product **3z** was obtained when 4-(chloromethyl)-3,5-dimethylisoxazole **2d** was employed as the reactant. 3,4,5-Trimethylisoxazole was also a suitable substrate, generating product **3ge** (dr = 5 : 1) in 48% yield.

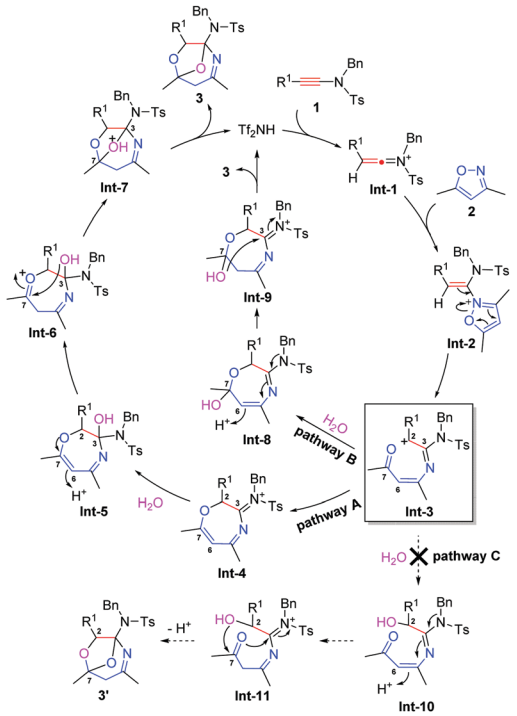
To illustrate the utility of this method, a scale-up experiment (1.36 mmol) was carried out for ynamide **1g** and isoxazole **2a** (see the ESI†). The reaction proceeded smoothly in the presence of 7.5 mol% Tf_2NH, providing **3g** in 58% yield. The resulting product can undergo hydrolysis to give highly functionalized dihydrooxazole **5g** in $CDCl_3$ at 50 °C [Scheme 3, eqn (1)].[18] Besides, we found that various dihydrooxazoles **5** can be directly synthesized from ynamides and isoxazoles *via* a one-pot two-step process [Scheme 3, eqn (2)].



Scheme 3 Further transformations.



Scheme 4 Mechanistic investigations.



Scheme 5 The proposed reaction mechanism.

To shed light on the reaction mechanism, some control experiments were conducted. The gold catalyst ($IPrAuNTf_2$) could not promote this cycloaddition under the optimized conditions [Scheme 4, eqn (3)]. However, when the reaction was performed at 25 °C, the formation of 2-aminopyrrole **4g** instead of **3g** was observed,[10] revealing that the Brønsted acid gives a distinct reaction pathway from that of the gold catalyst in this process [Scheme 4, eqn (3)]. When D_2O was engaged in the reaction in the presence of TMSOTf, which can rule out any H/D exchange between the Brønsted acid and D_2O, the deuterium atom was partially incorporated into **3g** (42% D) at the C2 and C6 positions, respectively [Scheme 4, eqn (4), right]. In addition, when the reaction was carried out with $H_2{}^{18}O$, an ^{18}O-labeled product was obtained in 65% yield with 69% ^{18}O incorporation [Scheme 4, eqn (4), left]. The splitting of the carbon signal at 104.9 ppm (C3, $\Delta\delta$ = 0.025 ppm) and 103.8 ppm (C7, $\Delta\delta$ = 0.023 ppm) was observed in the ^{13}C NMR spectrum of **3g**-[^{18}O], thus explicitly illustrating that the bridged oxygen atom originates from water (see the ESI†). Considering that ynamides can easily undergo hydrolysis to produce an amide in the presence of water and acid,[19] we then speculated that the amide might be the intermediate for this reaction. However, amide **6a**, which was prepared by the Tf_2NH-catalyzed hydrolysis of ynamide **1a**, failed to participate in the cycloaddition under the standard conditions, thus excluding this hypothesis [Scheme 4, eqn (5)].

On the basis of the above experimental observations and the precedents on the chemistry of ynamides,[5,6] a plausible mechanism was proposed in Scheme 5. Ynamide **1** is first protonated by Tf_2NH to generate a keteniminium ion **Int-1**.[20] Then, an N-attack of isoxazole **2** on the α-carbon atom of **Int-1** yields the adduct **Int-2**, which further undergoes ring fragmentation to form carbocation **Int-3** through the cleavage of the N–O bond. A subsequent intramolecular O-attack onto the carbocation of **Int-3** furnishes the seven-membered heterocycle **Int-4**. Eventually, the addition of H_2O to the iminium ion (C3) and subsequent acid-catalyzed ketalization afford the target product **3** (pathway A). Alternatively, H_2O is likely to attack the carbonyl group (C7) of **Int-3** to facilitate the intramolecular cyclization, yielding the seven-membered ring **Int-8**, which then undergoes acid-catalyzed O,O-acetal formation to deliver **3** (pathway B). The ^{18}O-labeling experiment implies that the oxygen atom bridging C3 and C7 in **3** originates from water, thus supporting the possibility of pathways A and B, and ruling out pathway C which involves the attack of H_2O onto the carbocation of **Int-3** to form the oxygen atom bridging C2 and C7 in the product. This cationic-type mechanism is also supported by the failure of alkyl-derived ynamides in the cycloaddition,[16] because the alkyl-substituted carbocation (R^1 = alkyl) in **Int-3** is less stable than the aryl analogue (R^1 = aryl).

In summary, we have developed a Brønsted acid-catalyzed formal [5+2+1] cycloaddition of ynamides and isoxazoles with water, providing atom-economical access to oxygen-bridged tetrahydro-1,4-oxazepines, with the bridged oxygen atom originating from water. This protocol will not only enrich the chemistry of ynamides, but also provide important insights into designing and developing unprecedented acid-catalyzed cycloadditions with distinct selectivity. Studies along this direction are currently underway in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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15 CCDC 1561884 (**3g**) and 1819934 (**5a**)†.

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