ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: Y. Zhao, C. Wang, Y. Hu and B. Wan, *Chem. Commun.*, 2018, DOI: 10.1039/C8CC00881G.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

View Article Online
DOI: 10.1039/C8CC00881G

Journal Name

Communication

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

Received 00th January 20xx,
Accepted 00th January 20xx

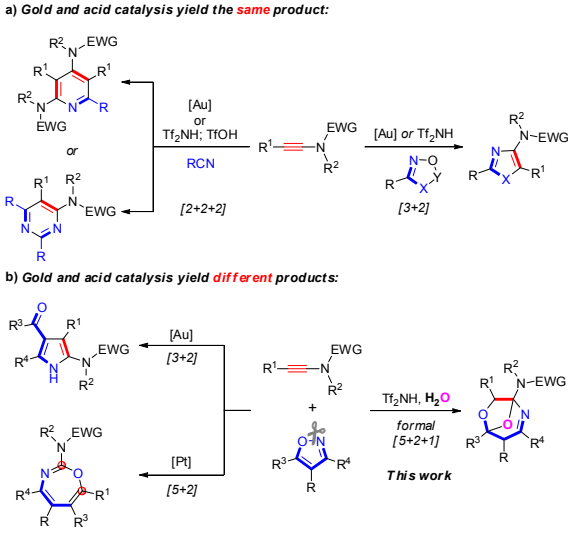
DOI: 10.1039/x0xx00000x

www.rsc.org/

Yingying Zhao,[a,b] Chunxiang Wang,[a] Yancheng Hu,*[a] and Boshun Wan*[a]

A Brønsted acid-catalyzed formal [5+2+1] cycloaddition of ynamides and isoxazoles with water is described. This process provides an atom-economical access to oxygen-bridged tetrahydro-1,4-oxazepines, where the bridged oxygen atom is originated from water. The unique property of 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 the 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 cycloaddtions 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 an easy access to oxazoles and imidazoles (Scheme 1a, right). All of these transformations yielded the same products as that of 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 cycloaddition 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, upper left).[10a,b] Very recently, the same group reported a platinum-catalyzed formal [5+2] cycloaddition of isoxazoles with ynamide 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 small amount of

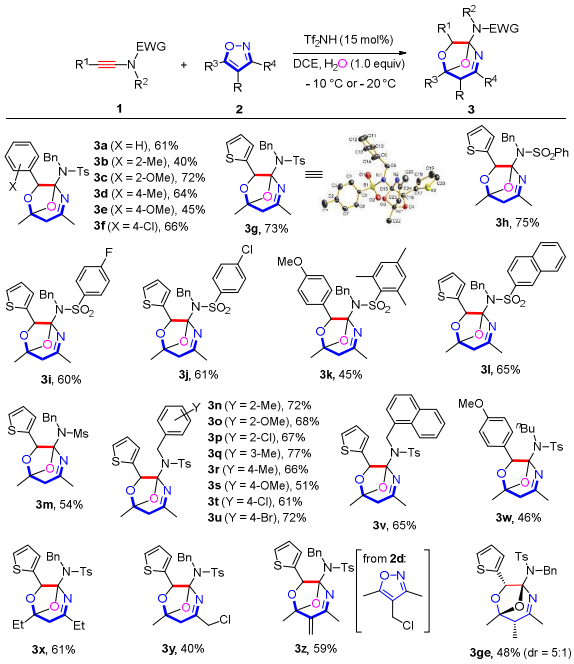
[a] Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian 116023, China
E-mail: ychu@dicp.ac.cn; bswan@dicp.ac.cn
[b] University of Chinese Academy of Sciences, Beijing 10049, China

† Electronic Supplementary Information (ESI) available: Experimental details, characterization data of the reactants and products, and copies of NMR spectroscopy. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C8CC00881G

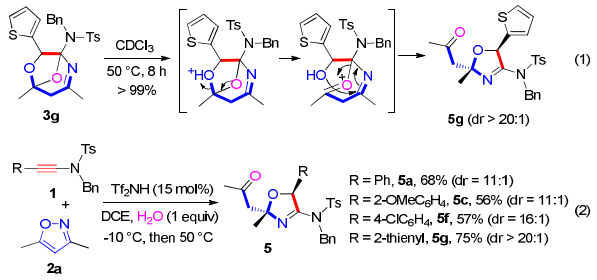
water, an unexpected formation of oxygen-bridged 1,4-oxazepine derivative was observed (Scheme 1b, right), in which isoxazole acts as a five-atom building unit to construct the seven-membered ring and water acts as the bridged oxygen atom source. To the best of knowledge, transition-metal-free catalytic 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 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 ESI† for full details). The optimized reaction conditions were found to be Tf_2NH as 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]



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 were given in the ESI†. Isolated yields are reported.

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 ynamide were well tolerated regardless of their steric and electronic properties, leading to the desired products **3a–3f** in 40–72% yield. The reaction could also be extended to 2-thienyl-derived substrate **1g**, which was transformed into the 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** with 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 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 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 in 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. Disappointedly, 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 in R^3 and R^4 to 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.

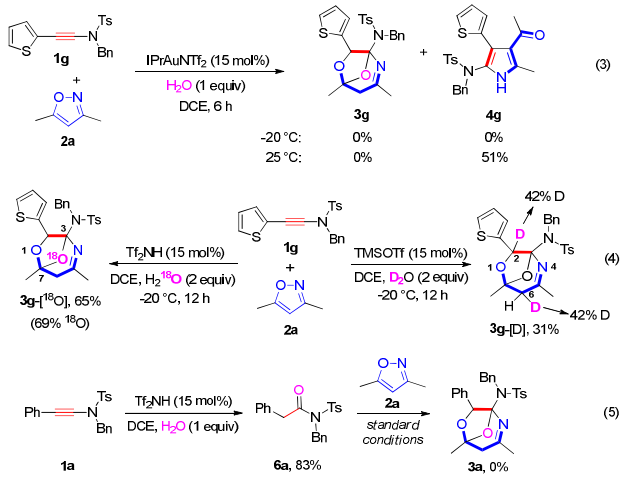


Scheme 3. Further transformations.

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**

View Article Online
DOI: 10.1039/C8CC00881G

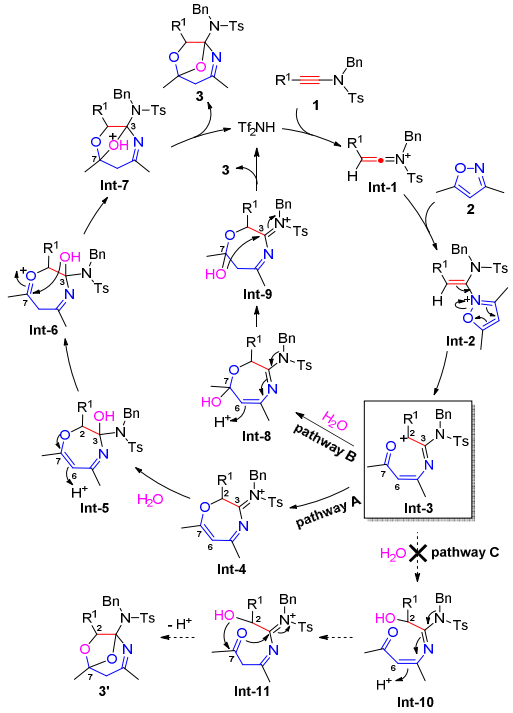
can be directly synthesized from ynamides and isoxazole via a one-pot two-step process [Scheme 3, eqn (2)].



Scheme 4. Mechanistic investigations.

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 Brønsted acid gives a distinct reaction pathway from that of 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 H/D exchange between Brønsted acid and D_2O, the deuterium atom was partially incorporated into **3g** (42% D) at C2 and C6 positions respectively [Scheme 4, eqn (4), right]. Additionally, when the reaction was carried out with $H_2{}^{18}O$, ^{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 (C3, Δδ = 0.025 ppm) and 103.8 ppm (C7, Δδ = 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 ynamide can easily undergo hydrolysis to produce amide in the presence of water and acid,[19] we then speculated that 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 ynamide,[5,6] a plausible mechanism was proposed in Scheme 5. Ynamide **1** is first protonated by Tf_2NH to generate 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 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 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 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 the 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 alkyl-substituted carbocation (R^1 = alkyl) in **Int-3** is less stable than the aryl analogue (R^1 = aryl).



Scheme 5. Proposed reaction mechanism.

In summary, we have developed a Brønsted acid-catalyzed formal [5+2+1] cycloaddition of ynamides and isoxazoles with water, providing an 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.

Financial support from the National Natural Science Foundation of China (no. 21572225 and 21772194) is gratefully acknowledged.

Notes and references

1 For examples on rhodium catalysis: (a) D. L. Smith, S. R. Chidipudi, W. R. Goundry and H. W. Lam, *Org. Lett.*, 2012, **14**, 4934; (b) R. N. Straker, Q. Peng, A. Mekareeya, R. S. Paton and E. A. Anderson, *Nat. Commun.*, 2016, **7**, 10109; (c) C.-Z. Zhu, J.-J. Feng and J. Zhang, *Chin. J. Org. Chem.*, 2017, **37**, 1165; (d) Y. Liao, Q. Lu, G. Chen, Y. Yu, C. Li and X. Huang,

View Article Online
DOI: 10.1039/C8CC00881G

ACS Catal., 2017, **7**, 7529; For examples on ruthenium catalysis: (e) C. Schotes and A. Mezzetti, *Angew. Chem. Int. Ed.,* 2011, **50**, 3072; (f) P. R. Walker, C. D. Campbell, A. Suleman, G. Carr and E. A. Anderson, *Angew. Chem. Int. Ed.,* 2013, **52**, 9139; For examples on Lewis-acid catalysis: (g) W. D. Mackay, M. Fistikci, R. M. Carris and J. S. Johnson, *Org. Lett.,* 2014, **16**, 1626; (h) H. Liu, Y. Yang, S. Wang, J. Wu, X.-N. Wang and J. Chang, *Org. Lett.,* 2015, **17**, 4472; (i) Y. Yang, H. Liu, C. Peng, J. Wu, J. Zhang, Y. Qiao, X.-N. Wang and J. Chang, *Org. Lett.,* 2016, **18**, 5022; (j) L. Chen, Y.-M. Cui, Z. Xu, J. Cao, Z.-J. Zheng and L.-W. Xu, *Chem. Commun.,* 2016, **52**, 11131; (k) L. Chen, L. Yu, Y. Deng, Z.-J. Zheng, Z. Xu, J. Cao and L.-W. Xu, *Adv. Synth. Catal.,* 2016, **358**, 480; (l) L. Chen, J. Cao, Z. Xu, Z.-J. Zheng, Y.-M. Cui and L.-W. Xu, *Chem. Commun.,* 2016, **52**, 9574; (m) T. Kuzuguchi, Y. Yabuuchi, T. Yoshimura and J. Matsuo, *Org. Biomol. Chem.,* 2017, **15**, 5268; (n) K. H. Oh, J. G. Kim and J. K. Park, *Org. Lett.,* 2017, **19**, 3994.

2 For representative examples on gold catalysis: (a) P. W. Davies, A. Cremonesi and L. Dumitrescu, *Angew. Chem. Int. Ed.,* 2011, **50**, 8931; (b) R. B. Dateer, B. S. Shaibu and R.-S. Liu, *Angew. Chem. Int. Ed.,* 2012, **51**, 113; (c) S. N. Karad, S. Bhunia and R.-S. Liu, *Angew. Chem. Int. Ed.,* 2012, **51**, 8722; (d) E. Rettenmeier, A. M. Schuster, M. Rudolph, F. Rominger, C. A. Gade and A. S. K. Hashmi, *Angew. Chem. Int. Ed.,* 2013, **52**, 5880; (e) S. K. Pawar, D. Vasu and R.-S. Liu, *Adv. Synth. Catal.,* 2014, **356**, 2411; (f) L. Zhu, Y. Yu, Z. Mao and X. Huang, *Org. Lett.* 2015, **17**, 30; (g) S. K. Pawar, R. L. Sahani and R.-S. Liu, *Chem.–Eur. J.,* 2015, **21**, 10843; (h) Y. Wu, L. Zhu, Y. Yu, X. Luo and X. Huang, *J. Org. Chem.,* 2015, **80**, 11407; (i) C. Shu, Y.-H. Wang, B. Zhou, X.-L. Li, Y.-F. Ping, X. Lu and L.-W. Ye, *J. Am. Chem. Soc.,* 2015, **137**, 9567; (j) Y. Yu, G. Chen, L. Zhu, Y. Liao, Y. Wu and X. Huang, *J. Org. Chem.,* 2016, **81**, 8142; (k) A. D. Gillie, R. J. Reddy and P. W. Davies, *Adv. Synth. Catal.,* 2016, **358**, 226; (l) Z. Zeng, H. Jin, X. Song, Q. Wang, M. Rudolph, F. Rominger and A. S. K. Hashmi, *Chem. Commun.,* 2017, **53**, 4304.

3 (a) S. N. Karad and R.-S. Liu, *Angew. Chem. Int. Ed.,* 2014, **53**, 9072; (b) Y. L. Chen, P. Sharma and R.-S. Liu, *Chem. Commun.,* 2016, **52**, 3187.

4 (a) M. Chen, N. Sun, H. Chen and Y. Liu, *Chem. Commun.,* 2016, **52**, 6324; (b) Z. Zeng, H. Jin, J. Xie, B. Tian, M. Rudolph, F. Rominger and A. S. K. Hashmi, *Org. Lett.,* 2017, **19**, 1020; (c) W. Xu, G. Wang, N. Sun and Y. Liu, *Org. Lett.,* 2017, **19**, 3307.

5 (a) Y. Wang, L.-J. Song, X. Zhang and J. Sun, *Angew. Chem. Int. Ed.,* 2016, **55**, 9704; (b) J. Zhang, Q. Zhang, B. Xia, J. Wu, X.-N. Wang and J. Chang, *Org. Lett.,* 2016, **18**, 3390; (c) L.-G. Xie, S. Shaaban, X. Chen and N. Maulide, *Angew. Chem. Int. Ed.,* 2016, **55**, 12864; (d) L.-G. Xie, S. Niyomchon, A. J. Mota, L. González and N. Maulide, *Nat. Commun.,* 2016, **7**, 10914; (e) P. Chen, C.-X. Song, W.-S. Wang, X.-L. Yu and Y. Tang, *RSC Adv.,* 2016, **6**, 80055.

6 (a) Y. Zhao, Y. Hu, C. Wang, X. Li and B. Wan, *J. Org. Chem.,* 2017, **82**, 3935; (b) Y. Zhao, Y. Hu, X. Li and B. Wan, *Org. Biomol. Chem.,* 2017, **15**, 3413.

7 The prices of $IPrAuNTf_2$, $Ph_3PAuNTf_2$, Tf_2NH and TfOH in Sigma-Aldrich are \$320/mmol, \$267/mmol, \$7.3/mmol and \$0.23/mmol, respectively.

8 For a review see: F. Hu and M. Szostak, *Adv. Synth. Catal.*, 2015, **357**, 2583.

9 For selected examples on the cycloaddition of isoxazoles: (a) J. R. Manning and H. M. L. Davies, *J. Am. Chem. Soc.,* 2008, **130**, 8602; (b) J. R. Manning and H. M. L. Davies, *Tetrahedron,* 2008, **64**, 6901; (c) X. Lei, L. Li, Y.-P. He and Y. Tang, *Org. Lett.,* 2015, **17**, 5224; (d) N. V. Rostovskii, J. O. Ruvinskaya, M. S. Novikov, A. F. Khlebnikov, I. A. Smetanin and A. V. Agafonova, *J. Org. Chem.,* 2017, **82**, 256.

10 (a) A.-H. Zhou, Q. He, C. Shu, Y.-F. Yu, S. Liu, T. Zhao, W. Zhang, X. Lu and L.-W. Ye, *Chem. Sci.,* 2015, **6**, 1265; (b) X.-Y. Xiao, A.-H. Zhou, C. Shu, F. Pan, T. Li and L.-W. Ye, *Chem.–Asian J.,* 2015, **10**, 1854. For platinum-catalyzed annulations of isoxazoles with ynamide by the same group, see: (c) W.-B. Shen, X.-Y. Xiao, Q. Sun, B. Zhou, X.-Q. Zhu, J.-Z. Yan, X. Lu and L.-W. Ye, *Angew. Chem. Int. Ed.,* 2017, **56**, 605.

11 For gold-catalyzed cycloaddition of benzisoxazoles with ynamides, see: (a) H. Jin, L. Huang, J. Xie, M. Rudolph, F. Rominger and A. S. K. Hashmi, *Angew. Chem. Int. Ed.,* 2016, **55**, 794; (b) H. Jin, B. Tian, X. Song, J. Xie, M. Rudolph, F. Rominger and A. S. K. Hashmi, *Angew. Chem. Int. Ed.,* 2016, **55**, 12688.

12 For gold-catalyzed cycloaddition of propiolates with isoxazoles or benzisoxazoles, see: (a) R. L. Sahani and R.-S. Liu, *Angew. Chem. Int. Ed.,* 2017, **56**, 1026; (b) R. L. Sahani and R.-S. Liu, *Angew. Chem. Int. Ed.,* 2017, **56**, 12736.

13 (a) C. Wang, X. Li, F. Wu and B. Wan, *Angew. Chem. Int. Ed.,* 2011, **50**, 7162; (b) C. Wang, D. Wang, H. Yan, H. Wang, B. Pan, X. Xin, X. Li, F. Wu and B. Wan, *Angew. Chem. Int. Ed.,* 2014, **53**, 11940; (c) H. Yan, H. Wang, X. Li, X. Xin, C. Wang and B. Wan, *Angew. Chem. Int. Ed.*, 2015, **54**, 10613; (d) T. Li, F. Xu, X. Li, C. Wang and B. Wan, *Angew. Chem. Int. Ed.,* 2016, **55**, 2861.

14 (a) R. Innocenti, E. Lenci, G. Menchi, A. Pupi and A. Trabocchi, *Bioorg. Med. Chem.,* **2017**, *25*, 5077; (b) A. Trabocchi, C. Mannino, F. Machetti, F. De Bernardis, S. Arancia, R. Cauda, A. Cassone and A. Guarna, *J. Med. Chem.,* **2010**, *53*, 2502.

15 CCDC 1561884 (**3g**) and CCDC 1819934 (**5a**) contain the supplementary crystallographic data for this paper.

16 Butyl- and TIPS-substituted ynamides failed to participate in the cycloaddition, see the ESI† for details.

17 In the cases of **3k** and **3w**, attempts to synthesize the corresponding 2-thienyl-derived ynamides did not succeed. Thus 4-$OMeC_6H_4$ substituted ynamides were employed in the reaction.

18 The configuration of dihydrooxazoles was confirmed by single-crystal X-ray diffraction analysis of **5a** (CCDC 1819934).

19 (a) C. Theunissen, B. Metayer, N. Henry, G. Compain, J. Marrot, A. Martin-Mingot, S. Thibaudeau and G. Evano, *J. Am. Chem. Soc.,* 2014, **136**, 12528; (b) S. Xu, J. Liu, D. Hu and X. Bi, *Green Chem.,* 2015, **17**, 184.

20 For reviews on the reactivity of keteniminium ions: (a) C. Madelaine, V. Valerio and N. Maulide, *Chem.–Asian. J.,* 2011, **6**, 2224; (b) G. Evano, M. Lecomte, P. Thilmany and C. Theunissen, *Synthesis,* 2017, **49**, 3183; For some leading examples: (c) B. Peng, X. Huang, L.-G. Xie and N. Maulide, *Angew. Chem. Int. Ed.,* 2014, **53**, 8718; (d) M. Lecomte and G. Evano, *Angew. Chem. Int. Ed.,* 2016, **55**, 4547.