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# Dioxazoles, a new mild nitrene transfer reagent in gold catalysis: highly efficient synthesis of functionalized oxazoles†

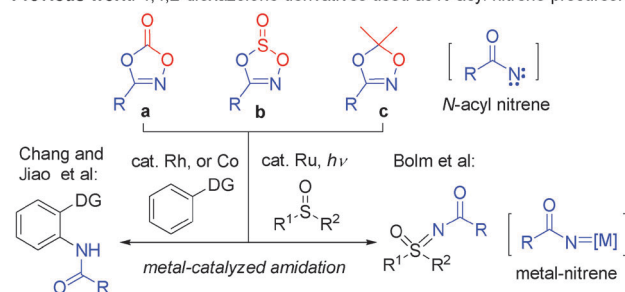
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**A gold-catalyzed regioselective [3+2] cycloaddition of ynamides with 1,4,2-dioxazoles was developed and offers a novel approach to obtain highly functionalized oxazoles under mild reaction conditions. 1,4,2-Dioxazole was found to act as an efficient *N*-acyl nitrene equivalent to trigger a facile generation of  $\alpha$ -imino gold-carbene intermediate through the elimination of a ketone.**

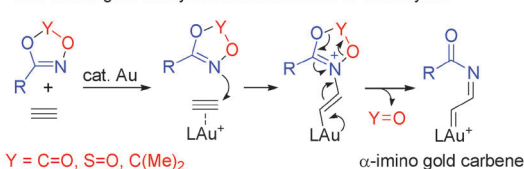
In recent years, gold-carbene-mediated reactions have attracted considerable attention since they serve as promising intermediates in the synthesis of various types of carbo- or heterocycles.<sup>1</sup> Compared with  $\alpha$ -carbonyl gold carbenes,<sup>2</sup> the generation and reactions of  $\alpha$ -imino gold carbenes have been less explored.<sup>3</sup> These highly reactive gold-species are mainly accessed through gold-catalyzed nitrene transfer to alkynes using azides as the nitrene equivalent, as reported by Toste,<sup>4a</sup> Gagosz,<sup>4b</sup> Zhang<sup>4c-e</sup> and others.<sup>4</sup> Recently, 2*H*-azirines,<sup>5</sup> *N*-iminopyridium ylides,<sup>6</sup> isoxazoles,<sup>7</sup> benzoisoxazoles<sup>8</sup> and triazapentalene<sup>9</sup> have also been used as nitrene equivalents. Despite the impressive progress made so far, the development of new methods for the generation of  $\alpha$ -imino gold carbenes involving the utilization of less reactive/sensitive nitrene transfer reagents with high chemo- and regioselectivities under milder reaction conditions is still highly desired. 1,4,2-Dioxazol-5-one **a**, a cyclic carbonate of hydroxamic acids, and its derivative 1,4,2-dioxazol-5-thione **b**, were found in 1968 to undergo thermal or photo-induced decomposition leading to highly reactive *N*-acyl nitrene intermediates *via* the elimination of CO<sub>2</sub> or SO<sub>2</sub>.<sup>10</sup> 1,4,2-Dioxazole **c** decomposed similarly at elevated temperatures (above 150 °C) into isocyanates and ketones.<sup>11</sup> These attractive and easily accessible heterocyclic compounds are potentially useful as *N*-acyl nitrene precursors in place of hazardous acyl azides, and could produce the *N*-acyl nitrene or

*N*-acyl nitrenoid intermediates under mild reaction conditions, such as in the presence of a metal catalyst. Recently, Bolm *et al.* described an elegant light-induced ruthenium-catalyzed synthesis of *N*-acyl sulfoximines and sulfimides at room temperature *via* a ruthenium *N*-acyl nitrene intermediate using dioxazolone **a** as the nitrene precursor.<sup>12</sup> More recently, Chang and others<sup>13</sup> revealed that the substrates **a–c** could also be used as amidating reagents in metal-catalyzed C–H amidation reactions, in which a metal–nitrene complex is proposed to be involved (Scheme 1). During our continuous work on gold-catalyzed oxidative reactions, we hypothesized that these five-membered heterocycles could be employed as a nucleophilic nitrene equivalent to trigger an efficient generation of  $\alpha$ -imino gold-carbene species through nucleophilic attack of the gold-activated alkyne followed by expulsion of a leaving group. In this design, no metal–nitrene complex is formed, which is different from the other metal-catalyzed reactions shown above. Herein, we describe a novel

Previous work: 1,4,2-dioxazolone derivatives used as *N*-acyl nitrene precursors



This work: gold-catalyzed nitrene transfer to the alkynes



**Scheme 1** Metal-catalyzed reactions involving nitrene equivalents of 1,4,2-dioxazolone derivatives and the design of gold-catalyzed nitrene transfer reactions.

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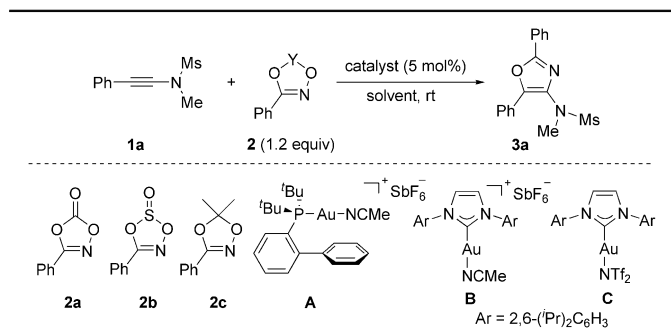
reaction of dioxazole derivatives, which act as a new type of nitrene transfer reagents and undergo gold-catalyzed [3+2] cycloaddition with ynamides, leading to a facile synthesis of highly functionalized oxazoles.<sup>6b-d</sup>

To test our hypothesis, we initially investigated the reactions of mesylamide-derived ynamide **1a** with three different types of dioxazole derivatives **2a–2c** in the presence of 5 mol% Johnphos(MeCN)AuSbF<sub>6</sub> (catalyst **A**) in DCE at room temperature. However, in the case of dioxazolone **2a**, a non-clean reaction mixture resulted with significant remaining **2a**, possibly as the rapid self-reaction of ynamide had occurred under gold-catalyzed conditions.<sup>14</sup> No desired cyclization product was observed also in the case of dioxathiazole **2b** (Table 1, entries 1 and 2). Considering the lower nucleophilicity of **2a** and **2b**, we reasoned that employing more nucleophilic dioxazole might be feasible for the successful transformation. Gratifyingly, employing dioxazole **2c** led to the desired 4-amino-oxazole **3a** in a 92% yield within 2 h (entry 3). The results implied that an efficient [3+2] cycloaddition of ynamide with dioxazole had taken place, and that the self-reaction of ynamide was mostly suppressed. A similar reaction outcome was found when *N*-heterocyclic carbene gold(i) complex **B** (IPrAu(MeCN)SbF<sub>6</sub>) or **C** (IPrAuNTf<sub>2</sub>)<sup>15</sup> was used as the catalyst (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) (entries 4 and 5). Various commonly used gold catalysts also catalyze the desired cyclization efficiently, furnishing **3a** in lower yields of 72–87% (entries 6–8). The reaction could also be performed smoothly in the DCM, THF, toluene or CH<sub>3</sub>CN solvents (entries 9–12). No reaction was observed catalyzed by

IPrAuCl or AgNTf<sub>2</sub> alone or in the absence of any catalyst (entries 13–15).

Encouraged by these results, we next investigated the substrate scope of the reaction. The scope of ynamides was first investigated using dioxazole **2c** as the reaction partner under the reaction conditions given in Table 1, entry 5. The results are shown in Table 2. The effects of the electron-withdrawing groups on nitrogen were first examined. The reactions proceeded very well with tosyl, *para*-bromobenzenesulfonyl (Bs) and a stronger electron-withdrawing *para*-nitrobenzenesulfonyl (*p*-Ns) moiety, furnishing **3c–3e** in 72–86% yields. The more electron-rich ynamide with an oxazolidine group also afforded the corresponding oxazole **3f** in an 89% yield. *N*-Aryl mesylamide, whenever bearing an electron-neutral, electron-deficient CF<sub>3</sub>, or electron-rich MeO substituent on its aromatic ring, was tolerated well in this reaction, leading to **3b** and **3g–3h** in 96–99% yields. *N*-Benzyl mesylamide was also suitable, providing **3i** in an 85% yield. Next, the effect of the R<sup>1</sup> group on the alkyne terminus was examined. For aryl substituted alkynes, a wide range of functionalities, such as F, Cl, CF<sub>3</sub>, Me and MeO, on aromatic rings were compatible, furnishing **3j–3n** in good to high yields. It was noted that when *p*-MeO-substituted aryl alkyne was used, part of the product precipitated during the reaction process at room temperature, which appeared to interfere with the reaction process.

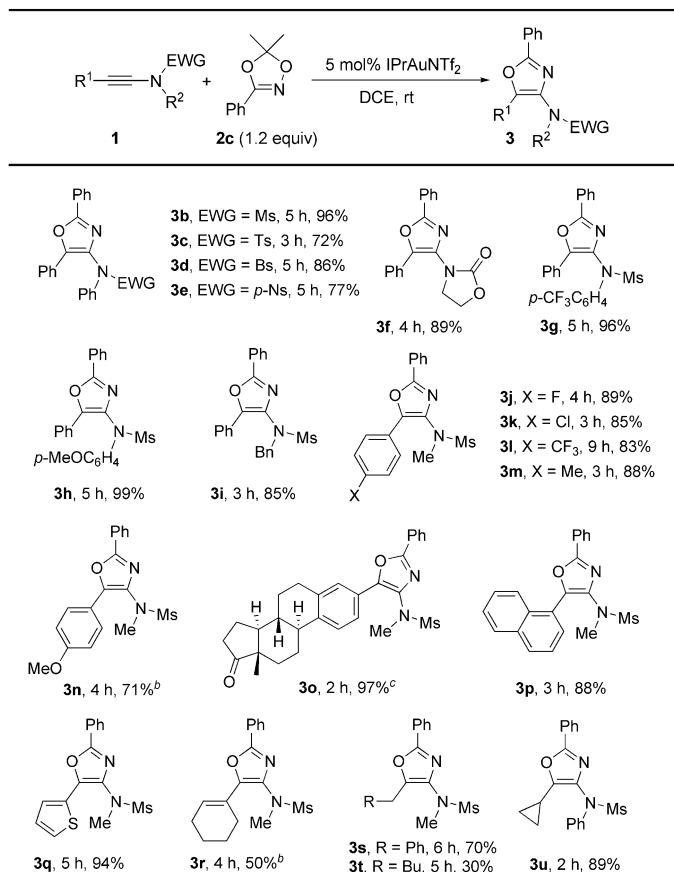
Table 1 Optimization of the reaction conditions



Entry	Substrate	Catalyst	Solvent	Time (h)	Yield <sup>a</sup> (%)
1	<b>2a</b>	<b>A</b>	DCE	3	—
2	<b>2b</b>	<b>A</b>	DCE	3	—
3	<b>2c</b>	<b>A</b>	DCE	2	92
4	<b>2c</b>	<b>B</b>	DCE	2	90
5	<b>2c</b>	<b>C</b>	DCE	2	95
6	<b>2c</b>	PPh <sub>3</sub> AuNTf <sub>2</sub>	DCE	2	85
7	<b>2c</b>	PPh <sub>3</sub> AuSbF <sub>6</sub>	DCE	3	87
8	<b>2c</b>	PPh <sub>3</sub> AuOTf	DCE	3	72
9	<b>2c</b>	<b>C</b>	DCM	3	91
10	<b>2c</b>	<b>C</b>	THF	3	86
11	<b>2c</b>	<b>C</b>	Toluene	3	88
12	<b>2c</b>	<b>C</b>	MeCN	3	92
13	<b>2c</b>	IPrAuCl	DCE	3	—(99)
14	<b>2c</b>	AgNTf <sub>2</sub>	DCE	3	—(98)
15	<b>2c</b>	None	DCE	12	—(99)

<sup>a</sup> Isolated yields. Ms = methanesulfonyl. The yields of recovered **1a** are shown in parentheses.

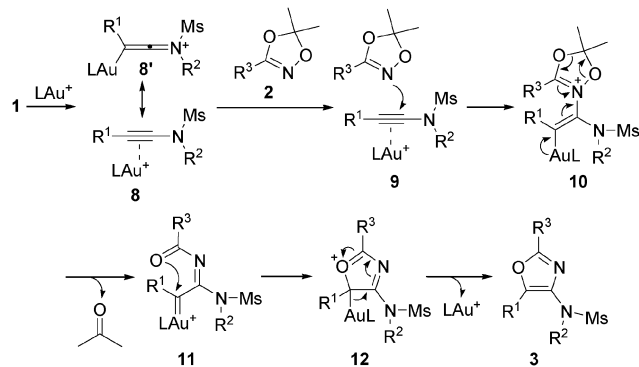
Table 2 Scope of the ynamides<sup>a</sup>



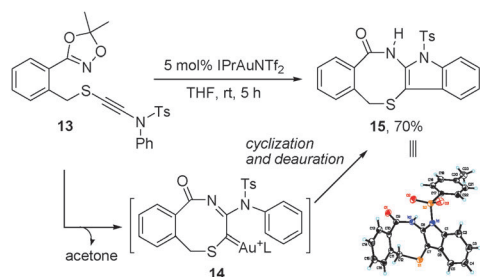
<sup>a</sup> Isolated yields. Ts = toluene-4-sulfonyl, Bs = *para*-bromobenzenesulfonyl. *p*-Ns = *para*-nitrobenzenesulfonyl. <sup>b</sup> 50 °C. <sup>c</sup> 80 °C.







Scheme 4 Possible reaction mechanism.

Scheme 5 Trapping of the  $\alpha$ -imino gold-carbene intermediate.

C=N bond due to the steric repulsion with the R<sup>3</sup> substituent on dioxazole with the amino moiety,<sup>6a</sup> resulting in a *cis* orientation of an *N*-acyl group with gold-carbene. Nucleophilic attack of the acyl oxygen in **11** to gold-carbene<sup>18</sup> is followed by elimination of the gold catalyst, leading to the oxazole products **3**. The reaction pathway involving the formation of *N*-acylaziridine *via* gold-nitrene followed by cyclization is unlikely, since an oxazole with a different regioselectivity would possibly have resulted.<sup>6b,19</sup>

To understand the reaction mechanism, we also tried to trap the  $\alpha$ -imino gold-carbene intermediate *via* an intramolecular cyclization of dioxazole-ynamide **13**, since the C–O bond formation can be avoided in such a case. To our delight, **13** cyclized efficiently to give the fused indole derivative **15**<sup>15</sup> in a 70% yield (Scheme 5). The results indicated that the  $\alpha$ -imino gold-carbene **14** was likely generated in the process, and could be trapped by the *N*-aryl ring, followed by deauration to furnish the cyclized product.

In summary, we disclosed that 1,4,2-dioxazole can be used as an efficient nitrene equivalent in gold-catalyzed nitrene transfer reactions to ynamides. The reaction proceeds under mild reaction conditions to afford highly functionalized oxazoles in good to excellent yields likely *via* the formation of an  $\alpha$ -imino gold-carbene intermediate followed by cyclization. This method offers several advantages, such as easily accessible starting

materials, high regioselectivity, wide functional group compatibility and high efficiency. Further investigations on the detailed reaction mechanism and application of this chemistry are in progress.

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## References

- For reviews, see: (a) Gold Carbenes: L. Zhang, in *Contemporary Carbene Chemistry*, ed. R. A. Moss and M. P. Doyle, Wiley, Hoboken, 2013, p. 526; (b) Y. Wang, M. E. Muratore and A. M. Echavarren, *Chem. – Eur. J.*, 2015, **21**, 7332.
- For reviews, see: (a) J. Xiao and X. Li, *Angew. Chem., Int. Ed.*, 2011, **50**, 7226; (b) L. Zhang, *Acc. Chem. Res.*, 2014, **47**, 877.
- For a review, see: P. W. Davies and M. Garzón, *Asian J. Org. Chem.*, 2015, **4**, 694.
- (a) D. J. Gorin, N. R. Davis and F. D. Toste, *J. Am. Chem. Soc.*, 2005, **127**, 11260; (b) A. Wetzel and F. Gagosz, *Angew. Chem., Int. Ed.*, 2011, **50**, 7354; (c) B. Lu, Y. Luo, L. Liu, L. Ye, Y. Wang and L. Zhang, *Angew. Chem., Int. Ed.*, 2011, **50**, 8358; (d) Y. Xiao and L. Zhang, *Org. Lett.*, 2012, **14**, 4662; (e) Z.-Y. Yan, Y. Xiao and L. Zhang, *Angew. Chem., Int. Ed.*, 2012, **51**, 8624; (f) Y. Tokimizu, S. Oishi, N. Fujii and H. Ohno, *Org. Lett.*, 2014, **16**, 3138; (g) Y. Wu, L. Zhu, Y. Yu, X. Luo and X. Huang, *J. Org. Chem.*, 2015, **80**, 11407.
- (a) A. Prechter, G. Henrion, P. Faudot dit Bel and F. Gagosz, *Angew. Chem., Int. Ed.*, 2014, **53**, 4959; (b) L. Zhu, Y. Yu, Z. Mao and X. Huang, *Org. Lett.*, 2015, **17**, 30.
- (a) C. Li and L. Zhang, *Org. Lett.*, 2011, **13**, 1738; (b) P. W. Davies, A. Cremonesi and L. Dumitrescu, *Angew. Chem., Int. Ed.*, 2011, **50**, 8931; (c) E. Chatzopoulou and P. W. Davies, *Chem. Commun.*, 2013, **49**, 8617; (d) A. D. Gillie, R. J. Redd and P. W. Davies, *Adv. Synth. Catal.*, 2016, **358**, 226. In the reactions of ref. 6b–d, oxazoles were formed *via* gold-catalyzed [3+2] cycloaddition of pyridine-*N*-aminides with ynamides or alkynyl indoles; (e) H.-H. Hung, Y.-C. Liao and R.-S. Liu, *J. Org. Chem.*, 2013, **78**, 7970.
- A. Zhou, Q. He, C. Shu, Y. Yu, S. Liu, T. Zhao, W. Zhang, X. Lu and L. Ye, *Chem. Sci.*, 2015, **6**, 1265.
- H. Jin, L. Huang, J. Xie, M. Rudolph, F. Rominger and A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2016, **55**, 794.
- J. González, J. Santamaría, Á. L. Suárez-Sobrino and A. Ballesterosa, *Adv. Synth. Catal.*, 2016, DOI: 10.1002/adsc.201600022.
- J. Sauer and K. K. Mayer, *Tetrahedron Lett.*, 1968, **9**, 319.
- H. Noura, K. Inoue, H. Hattori, T. Okawa and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 1967, **40**, 664.
- V. Bizet, L. Buglioni and C. Bolm, *Angew. Chem., Int. Ed.*, 2014, **53**, 5639.
- (a) Y. Park, K. T. Park, J. G. Kim and S. Chang, *J. Am. Chem. Soc.*, 2015, **137**, 4534; (b) J. Park and S. Chang, *Angew. Chem., Int. Ed.*, 2015, **54**, 14103; (c) Y. Liang, Y. Liang, C. Tang, Y. Yuan and N. Jiao, *Chem. – Eur. J.*, 2015, **21**, 16395.
- S. Kramer, Y. Odabachian, J. Overgaard, M. Rottländer, F. Gagosz and T. Skrydstrup, *Angew. Chem., Int. Ed.*, 2011, **50**, 5090.
- CCDC 1455247 (IPrAuNTf<sub>2</sub>), 1450076 (**3b**) and 1455246 (**15**).
- For selected papers, see: (a) C. Wan, J. Zhang, S. Wang, J. Fan and Z. Wang, *Org. Lett.*, 2010, **12**, 2338; (b) C. Lalli, J. M. Bouma, D. Bonne, G. Masson and J. Zhu, *Chem. – Eur. J.*, 2011, **17**, 880; (c) W. He, C. Li and L. Zhang, *J. Am. Chem. Soc.*, 2011, **133**, 8482; (d) Y. Luo, K. Ji, Y. Li and L. Zhang, *J. Am. Chem. Soc.*, 2012, **134**, 17412; (e) Ref. 6b–d. For Ru/Cu-catalyzed reaction of 1,4,2-dioxazol-5-ones with terminal alkynes to oxazoles, see: (f) C. Zhong, B. Tang, P. Yin, Y. Chen and L. He, *J. Org. Chem.*, 2012, **77**, 4271.
- See ESI†.
- (a) S. Kramer and T. Skrydstrup, *Angew. Chem., Int. Ed.*, 2012, **51**, 4681; (b) X. Huang, B. Peng, M. Luparia, L. F. R. Gomes, L. F. Veiros and N. Maulide, *Angew. Chem., Int. Ed.*, 2012, **51**, 8886.
- H. Li and R. P. Hsung, *Org. Lett.*, 2009, **11**, 4462.

