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Gold-catalyzed synthesis of oxazoles from alkynyl triazenes and dioxazoles†

Zhenjun Mao ^a and Hao Zeng ^b

A gold-catalyzed regioselective [3 + 2] cycloaddition of alkynyl triazenes with 1,2,4-dioxazoles was developed. The triazene group in the products could be replaced to obtain iodo-oxazoles, providing potential transformations to diverse oxazole structures. This protocol features readily available starting materials, mild reaction conditions and scalability. A plausible mechanism involving a nitrene transfer process was proposed.

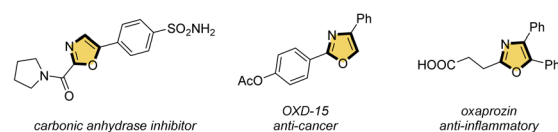
Introduction

Oxazoles are a ubiquitous structural motif, which is widely found in a broad range of drugs, natural products, functional materials, agrochemicals and ligands (Scheme 1a).¹ The presence of the oxazole moiety in these molecules plays important roles in respective processes. For example, the oxazole structures in drug molecules could mimic biological interactions, providing increased metabolic stability.² Considering the significance of this type of aromatic five-membered nitrogen-containing heterocycle, the construction of oxazole skeletons has attracted considerable attention.³ Typically, amine and carbonyl analogs are classical synthons for the construction of oxazoles,⁴ and these methods mostly rely on bimolecular cycloaddition processes. Despite recent advances, the exploration of modular and practical routes to trisubstituted oxazoles with structural diversity is less explored,⁵ and thus remains understudied.

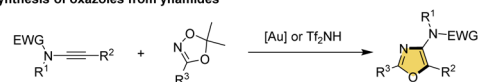
The alkynyl triazene is a novel type of electron-rich alkynes, whose structure bears a triazenyl group attached to the triple bond directly. Originally prepared and demonstrated as ynamide analogs by Severin and co-workers,⁶ the alkynyl triazenes have received considerable attentions in organic synthesis, especially in the construction of heterocycles and biologically valuable skeletons.⁷ Typically, a variety of elegant works have been successively reported by Severin and Cramer,⁸ and Cui.⁹ The versatility of triazenyl group was subsequently realized by the diverse transformations of products in these reactions, thus representing modular, efficient and practical methods toward promising structures. However, compared to the ynamide,¹⁰ the

flagship of electron-rich alkynes, alkynyl triazenes show vast space to be explored. In this context, we presented intense interests in the development of novel reactions based on alkynyl triazenes. Previously, Liu and Wan independently revealed an Au-catalyzed and a Tf₂NH-promoted synthesis of oxazoles from ynamides and dioxazoles (Scheme 1b).¹¹ Based on these studies, we envisioned that alkynyl triazenes and dioxazoles might undergo a regioselective [3 + 2] cycloaddition to assemble oxazoles as well, and more importantly, the electron-donating and transformable properties of triazenyl group could realize the further derivations of products for accessing diverse fully substituted oxazoles. To this end, we attempt to explore the reaction under gold-catalysis, due to the multi-advantages, such as high efficiency and excellent reactive selectivity.¹² Herein, we report a gold-catalyzed synthesis of oxazoles from alkynyl triazenes and dioxazoles (Scheme 1c). It is noteworthy that the expected transformations of triazenyl group in the oxazole products are difficult. To our delight, iodination of the oxazole product could be successfully realized, demonstrating the

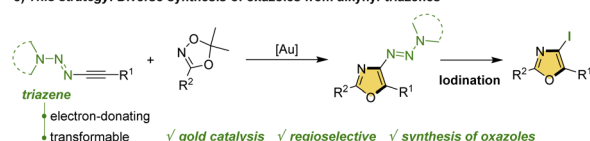
a) Representative biological oxazoles



b) Synthesis of oxazoles from ynamides



c) This strategy: Diverse synthesis of oxazoles from alkynyl triazenes



Scheme 1 Representative biological oxazoles and synthesis of oxazoles.

^aDepartment of Chemistry, Zhejiang University, Hangzhou 310058, China. E-mail: maozhenjun@zju.edu.cn

^bCollege of Biosystems Engineering and Food Science, Zhejiang University, Hangzhou 310058, China

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potential for the further derivatization. This protocol features readily available starting materials, high regioselectivity, mild reaction conditions.

Results and discussion

We successfully prepared the alkynyl triazene **1a** and dioxane **2a** as the model substrates to investigate our hypothesis. The optimizations were listed as Table 1. Initially, numerous gold catalysts, such as AuCl, PPh₃AuCl, IPrAuCl and XPhosAuCl, were tested, and no distinct products formed, due to scarce consumption of both starting materials (entries 1–4). Then we tried to replace the chlorine in these catalysts to other anions. For PPh₃AuCl, adding AgOTf or AgNTf₂ could yield a new product successfully, albeit in low yields (entries 5–6). NMR spectroscopy, mass spectrometry as well as the X-ray crystal analysis¹³ showed that **3a** was a 3-triazenyl-2,5-diphenyloxazole, indicating that a regioselective [3 + 2] cycloaddition occurred. The similar replacement was used in IPrAuCl, XPhosAuCl and JohnPhosAuCl, and to our delight, the yields of **3a** were significantly increased (entries 7–12). Of note, using JohnPhosAuCl in combination of AgOTf could furnish **3a** in a satisfactory 81% yield (entry 11).

The utilize of AgOTf or Zn(OTf)₂, or without any catalyst could suppress the reaction completely (entries 13–15). Subsequently, a solvent survey showed that the DCE was effective as well, giving the corresponding **3a** in 66% yield (entry 16), whilst the use of THF, MeCN or toluene led to the inefficient reactions (entries 17–19).

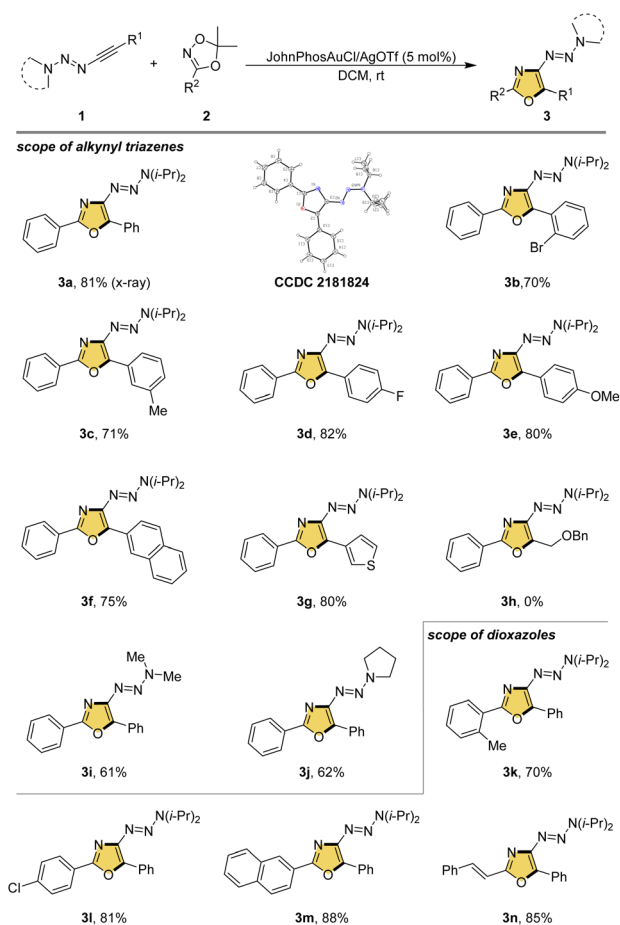
Finally, when replaced **2a** with **2b** or **2c**, the reaction would completely suppressed (entries 20–21), demonstrating the exclusive reactivity of **2a** in this oxazole synthesis process.

Having the optimized reaction conditions in hand, we next set out to study the substrate scope of alkynyl triazenes and dioxazoles (Scheme 2). For the alkynyl triazene component, the substitution at the β-position of the alkyne was first screened. Benzene rings bearing the bromo, methyl, fluoro or methoxy in different positions were compatible with this reaction, resulting in corresponding oxazole products in good yields (**3b–3e**). The functional groups and substituted position did not show significant influence to the yield. Furthermore, terminal 2-naphthyl and 3-thiophenyl substituted alkynyl triazenes were proved suitable to access oxazole **3f** and **3g** in 75% and 80% yields, respectively. Unfortunately, aliphatic substituted alkynyl

Table 1 Reaction optimizations^a

Entry	2	Catalyst	Solvent	Yield ^b (%)
1	2a	AuCl	DCM	0
2	2a	PPh ₃ AuCl	DCM	0
3	2a	IPrAuCl	DCM	Trace
4	2a	XPhosAuCl	DCM	0
5	2a	PPh ₃ AuCl/AgOTf	DCM	24
6	2a	PPh ₃ AuCl/AgNTf ₂	DCM	22
7	2a	IPrAuCl/AgOTf	DCM	72
8	2a	IPrAuCl/AgNTf ₂	DCM	67
9	2a	XPhosAuCl/AgOTf	DCM	76
10	2a	XPhosAuCl/AgNTf ₂	DCM	76
11	2a	JohnPhosAuCl/AgOTf	DCM	81
12	2a	JohnPhosAuCl/AgNTf ₂	DCM	78
13	2a	AgOTf	DCM	Trace
14	2a	ZnOTf	DCM	Trace
15	2a	None	DCM	0
16	2a	JohnPhosAuCl/AgOTf	DCE	66
17	2a	JohnPhosAuCl/AgOTf	THF	19
18	2a	JohnPhosAuCl/AgOTf	MeCN	20
19	2a	JohnPhosAuCl/AgOTf	Toluene	23
20	2b	JohnPhosAuCl/AgOTf	DCM	0
21	2c	JohnPhosAuCl/AgOTf	DCM	0

^a Reaction conditions: **1a** (0.2 mmol), **2** (0.24 mmol), catalyst (5 mol%), solvent (2 mL), rt, 24 h, argon. ^b Yield refers to isolated product. DCM, dichloromethane; DCE, 1,2-dichloroethane; THF, tetrahydrofuran.



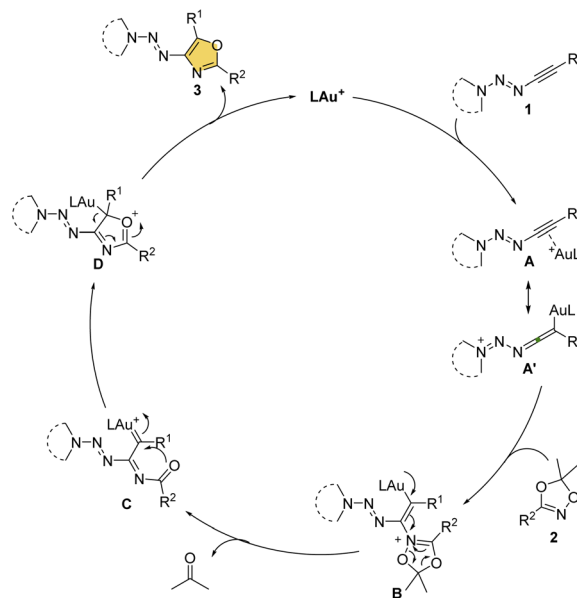
Scheme 2 Substrate scope. a reaction conditions: JohnPhosAuCl (5 mol%) and AgOTf (5 mol%) were mixed in DCM (1 mL) for 15 min. Then **1a** (0.2 mmol) and **2** (0.24 mmol) in DCM (1 mL) were added at rt under argon. Yield refers to isolated product.



triazene was not compatible under the current reaction conditions (**3h**). The variation of triazenyl group was also studied. For example, dimethyl amine derived and tetrahydropyrrole derived alkynyl triazenes were participated well in this cycloaddition, leading to the products in slightly lower yields (**3i** and **3j**). The oxazoles derived from several aromatic acids including 2-methyl benzoic acid, 4-chlorobenzoic acid and 2-naphthoic acid provided the corresponding oxazole products in satisfactory yields (**3k–3m**). Notably, cinnamic acid derived dioxazole was well tolerated with this process to furnish oxazole **3n** in 85% yield.

To demonstrate the scalability of this cycloaddition, a 5 mol scale reaction was performed to give the oxazole **3a** in 78% yield (Scheme 3a). Next, we studied the synthetic transformation of triazenyl group. According to the reported methods, we attempted to use acid to remove the triazenyl group to form the cation, which could be captured by various nucleophilic reagents.^{8,9} Unfortunately, all these attempts were failed, probably due to the instability of 3-oxazole cation to trigger the ring opening. To our delight, heating **3a** in CH₃I at high temperature could obtain a 3-iodo oxazole in moderate yield, which provide an opportunity to further derivation *via* coupling reactions.¹⁴

On the basis of the reaction results and literature,^{8a,11a} a plausible reaction mechanism was depicted in Scheme 4. First, the gold catalyst coordinates to alkynyl triazenes **1** to form the complex **A** or **A'**, which is regioselectively attacked by dioxazole **2** at the carbon adjacent to the triazenyl group due to the polarity of the triple bond, resulting in the intermediate **B**. Subsequently, **B** transforms to the gold carbene species **C** along with the elimination of acetone *via* a ring fragmentation. Next an intramolecular nucleophilic cyclization occurs between acyl oxygen and gold carbene to form the intermediate **D**, which collapses to the product **3** and the gold catalyst, thus completing the catalytic cycle.



Scheme 4 Proposed mechanism.

Conclusions

In conclusion, we have developed a gold-catalyzed synthesis of fully-substituted oxazoles from alkynyl triazenes and dioxazoles. This protocol features readily available starting materials, mild reaction conditions and scalability. The triazene moiety in products could be transformed to iodo-oxazole derivative. A plausible mechanism involving a nitrene transfer process was proposed.

Author contributions

Z. M. conceived the project, Z. M. and H. Z. performed the experiments, analysed the data, and wrote the manuscript.

Conflicts of interest

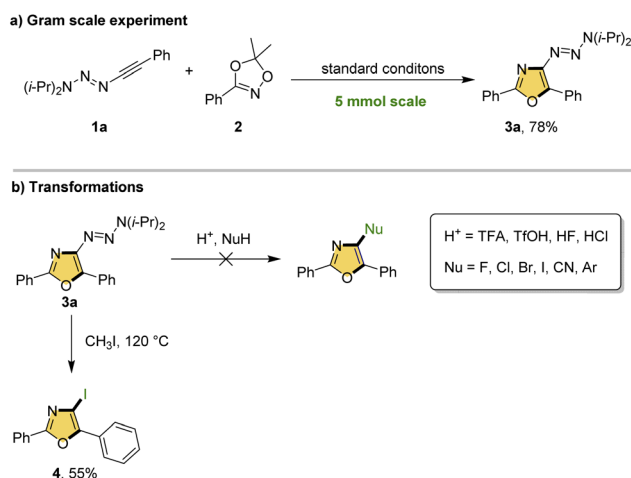
There are no conflicts to declare.

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Notes and references

- For selective reviews and examples, see: (a) N. David, R. Pasceri, R. R. A. Kitson, A. Pradal and C. J. Moody, *Chem.-Eur. J.*, 2016, **22**, 10867–10876; (b) J. R. Davies, P. D. Kane, C. J. Moody and A. M. Z. Slawin, *J. Org. Chem.*, 2005, **70**, 5840–5851; (c) M. D. Delost, D. T. Smith, B. J. Anderson and J. T. Njardarson, *J. Med. Chem.*, 2018, **61**, 10996–11020; (d) F. Grundmann, V. Dill, A. Dowling, A. Thanwisai, E. Bode, N. Chantratita, R. Ffrench-Constant



Scheme 3 Gram scale experiment and transformations.



- and H. B. Bode, *Beilstein J. Org. Chem.*, 2012, **8**, 749–752; (e) V. T. T. Huong, T. B. Tai and M. T. Nguyen, *J. Phys. Chem. A*, 2014, **118**, 3335–3343; (f) Z. Jin, *Nat. Prod. Rep.*, 2013, **30**, 869–915; (g) P. Wipf and S. Venkatraman, *J. Org. Chem.*, 1996, **61**, 6517–6522; (h) V. S. C. Yeh, *Tetrahedron*, 2004, **60**, 11995–12042; (i) X. X. Zhang, X. P. Sun, H. Fan, C. Lyu, P. Li, H. F. Zhang and W. D. Rao, *RSC Adv.*, 2016, **6**, 56319–56322; (j) Q. Zhao, S. Liu, Y. Li and Q. Wang, *J. Agric. Food Chem.*, 2009, **57**, 2849–2855.
- 2 For selective examples, see: (a) D. J. S. Jean and C. Fotsch, *J. Med. Chem.*, 2012, **55**, 10315; (b) D. J. St Jean and C. Fotsch, *J. Med. Chem.*, 2012, **55**, 6002–6020; (c) R. N. Gaykar, S. Deswal, A. Guin, S. Bhattacharjee and A. T. Biju, *Org. Lett.*, 2022, **24**, 4145–4150; (d) Y. Liu, K. Zhu, Y. Kong, X. Li, J. Cui, Y. Xia, J. Zhao, S. Duan and P. Li, *J. Org. Chem.*, 2021, **86**, 18247–18256; (e) S. Mai, C. Rao, M. Chen, J. Su, J. Du and Q. Song, *Chem. Commun.*, 2017, **53**, 10366–10369; (f) W. Rodphon, K. Jaithum, S. Linkhum, C. Thongsornkleeb, J. Tummatorn and S. Ruchirawat, *J. Org. Chem.*, 2022, DOI: [10.1021/acs.joc.2c00940](https://doi.org/10.1021/acs.joc.2c00940); (g) Z. Tu, B. Zhao, J. Wan, C. Wang and Y. Liu, *Chin. J. Org. Chem.*, 2021, **41**, 4780–4788.
- 3 For selective reviews and examples, see: (a) A. V. Gulevich, A. S. Dudnik, N. Chernyak and V. Gevorgyan, *Chem. Rev.*, 2013, **113**, 3084–3213; (b) A. S. K. Hashmi, *Chem. Rev.*, 2007, **107**, 3180–3211; (c) Y. Hu, X. Xin and B. Wan, *Tetrahedron Lett.*, 2015, **56**, 32–52.
- 4 For selective reviews and examples, see: (a) O. Possel and A. M. Vanleusen, *Heterocycles*, 1977, **7**, 77–80; (b) R. H. Prager, J. A. Smith, B. Weber and C. M. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2665–2672; (c) I. J. Turchi and M. J. S. Dewar, *Chem. Rev.*, 1975, **75**, 389–437; (d) R. H. Wiley, *Chem. Rev.*, 1945, **37**, 401–442.
- 5 (a) S. Bresciani and N. C. O. Tomkinson, *Heterocycles*, 2014, **89**, 2479–2543; (b) P. Querard, S. A. Girard, N. Uhlig and C. J. Li, *Chem. Sci.*, 2015, **6**, 7332–7335; (c) T. T. Zeng, J. Xuan, W. Ding, K. Wang, L. Q. Lu and W. J. Xiao, *Org. Lett.*, 2015, **17**, 4070–4073; (d) Z. Qi and S. Wang, *Org. Lett.*, 2021, **23**, 8549–8553.
- 6 (a) G. Kiefer, T. Riedel, P. J. Dyson, R. Scopelliti and K. Severin, *Angew. Chem., Int. Ed.*, 2015, **54**, 302–305; (b) F. G. Perrin, G. Kiefer, L. Jeanbourquin, S. Racine, D. Perrotta, J. Waser, R. Scopelliti and K. Severin, *Angew. Chem., Int. Ed.*, 2015, **54**, 13393–13396.
- 7 A. A. Suleymanov and K. Severin, *Angew. Chem., Int. Ed.*, 2021, **60**, 6879–6889.
- 8 For selective examples, see: (a) L. N. Jeanbourquin, R. Scopelliti, F. F. Tirani and K. Severin, *Org. Lett.*, 2017, **19**, 2070–2073; (b) D. Kossler, F. G. Perrin, A. A. Suleymanov, G. Kiefer, R. Scopelliti, K. Severin and N. Cramer, *Angew. Chem., Int. Ed.*, 2017, **56**, 11490–11493; (c) I. R. Landman, E. Acuna-Bolomey, R. Scopelliti, F. Fadaei-Tirani and K. Seyerin, *Org. Lett.*, 2019, **21**, 6408–6412; (d) A. A. Suleymanov, M. Doll, A. Ruggi, R. Scopelliti, F. Fadaei-Tirani and K. Severin, *Angew. Chem., Int. Ed.*, 2020, **59**, 9957–9961; (e) A. A. Suleymanov, R. Scopelliti, F. F. Tirani and K. Severin, *Adv. Synth. Catal.*, 2018, **360**, 4178–4183; (f) J. F. Tan, C. T. Bormann, F. G. Perrin, F. M. Chadwick, K. Seyerin and N. Cramer, *J. Am. Chem. Soc.*, 2019, **141**, 10372–10383; (g) J. F. Tan, C. T. Bormann, K. Severin and N. Cramer, *Chem. Sci.*, 2021, **12**, 9140–9145.
- 9 For selective examples, see: (a) C. Wang, Z. Lai, H. Xie and S. Cui, *Angew. Chem., Int. Ed.*, 2021, **60**, 5147–5151; (b) S. Xu, L. Zeng and S. Cui, *Org. Lett.*, 2022, **24**, 2689–2693; (c) L. Zeng, Z. Lai, C. Zhang, H. Xie and S. Cui, *Org. Lett.*, 2020, **22**, 2220–2224.
- 10 For recent reviews of ynamides, see: (a) R. H. Dodd and K. Cariou, *Chem.-Eur. J.*, 2018, **24**, 2297–2304; (b) G. Evano, B. Michelet and C. Zhang, *C. R. Chim.*, 2017, **20**, 648–664; (c) B. Prabagar, N. Ghosh and A. K. Sahoo, *Synlett*, 2017, **28**, 2539–2555; (d) L. Li, T.-D. Tan, Y.-Q. Zhang, X. Liu and L.-W. Ye, *Org. Biomol. Chem.*, 2017, **15**, 8483–8492; (e) F. Pan, C. Shu and L.-W. Ye, *Org. Biomol. Chem.*, 2016, **14**, 9456–9465; (f) G. Evano, C. Theunissen and M. Lecomte, *Aldrichimica Acta*, 2015, **48**, 59–70; (g) X.-N. Wang, H.-S. Yeom, L.-C. Fang, S. He, Z.-X. Ma, B. L. Kedrowski and R. P. Hsung, *Acc. Chem. Res.*, 2014, **47**, 560–578; (h) K. A. DeKorver, H. Li, A. G. Lohse, R. Hayashi, Z. Lu, Y. Zhang and R. P. Hsung, *Chem. Rev.*, 2010, **110**, 5064–5106; (i) G. Evano, A. Coste and K. Jouvin, *Angew. Chem., Int. Ed.*, 2010, **49**, 2840–2859; (j) B. Zhou, T.-D. Tan, X.-Q. Zhu, M.-Z. Shang and L.-W. Ye, *ACS Catal.*, 2019, **9**, 6393–6406.
- 11 (a) M. Chen, N. Sun, H. Chen and Y. Liu, *Chem. Commun.*, 2016, **52**, 6324–6327; (b) Y. Zhao, Y. Hu, C. Wang, X. Li and B. Wan, *J. Org. Chem.*, 2017, **82**, 3935–3942.
- 12 (a) L. Zhang, *Acc. Chem. Res.*, 2014, **47**, 877–888; (b) Z. Zheng, X. Ma, X. Cheng, K. Zhao, K. Gutman, T. Li and L. Zhang, *Chem. Rev.*, 2021, **121**, 8979–9038.
- 13 CCDC 2181824.
- 14 For selective examples of coupling of iodo-oxazoles, see: E. F. Flegeau, M. E. Popkin and M. F. Greaney, *J. Org. Chem.*, 2008, **73**, 3303–3306.

