ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: S. Mai, C. Rao, M. Chen, J. Su, J. Du and Q. Song, *Chem. Commun.*, 2017, DOI: 10.1039/C7CC05746F.

This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the author guidelines.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the ethical guidelines, outlined in our author and reviewer resource centre, still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

Journal Name

View Article Online
DOI: 10.1039/C7CC05746F

COMMUNICATION

Merging gold catalysis, organocatalytic oxidation, and lewis acid catalysis for chemodivergent synthesis of functionalized oxazoles from *N*-propargylamides

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

DOI: 10.1039/x0xx00000x

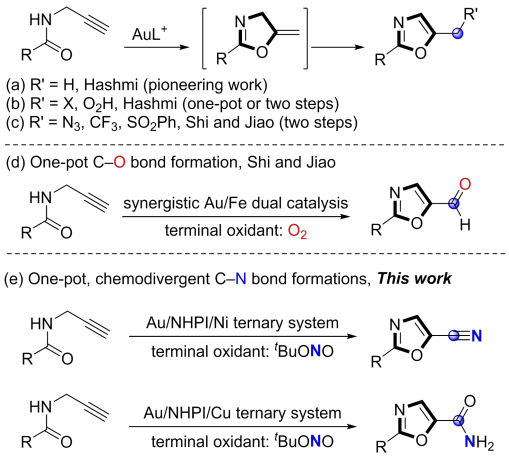
www.rsc.org/

Shaoyu Mai,[a] Changqing Rao,[a] Ming Chen,[b] Jihu Su,[b] Jiangfeng Du,[b] and Qiuling Song*[a]

Novel catalytic systems consisted of cationic gold complex, *N*-hydroxyphthalimide (NHPI), and transition-metal-based Lewis acids have been developed for the one-pot synthesis of functionalized oxazoles from *N*-propargylamides with excellent functional group tolerance. These transformations demonstrated the excellent compatibility of homogeneous gold catalysis with organocatalytic oxidative carbon–nitrogen bond formations using *tert*-butyl nitrite as the terminal oxidant. Moreover, oxazolecarbonitriles or carboxamides can be easily synthesized in a one-pot protocol according to the different synthetic requirements.

Oxazole derivatives are widely found in natural products and pharmaceuticals with impressive biological properties, such as antiviral, antibacterial, antileukemia, and antitumor activities.[1] Tremendous efforts have been devoted to the development of new methodologies and strategies to construct the oxazole ring,[2] such as condensations,[2c] cyclizations,[2d] transition-metal-catalyzed addition of diazo compounds to nitriles,[2e] and rearrangements.[2f] However, most of these reactions require harsh reaction conditions, limiting the wide application of these classical oxazole synthetic methods in organic synthesis.

Homogeneous gold catalysis provides a practical solution to address this challenge.[3–5] In 2004, Hashmi group developed a gold-catalyzed 5-*exo*-dig cyclization of *N*-propargylamide to synthesize functionalized 5-methyloxazoles (Scheme 1a).[4a] In their pioneering work, the catalytic cycle was furnished by a protodeauration step, leading to a methyleneoxazoline intermediate. Thereafter, the same group attempted to react the *in situ* generated methyleneoxazoline with electrophilic halogenating reagents[4c] or dioxygen[4e] for the formation of carbon–halogen and carbon–oxygen bonds, respectively (Scheme 1b). However, the reaction yield is generally not satisfactory unless the gold-catalyzed cyclization and the oxidation reaction were conducted in two seperated operations.



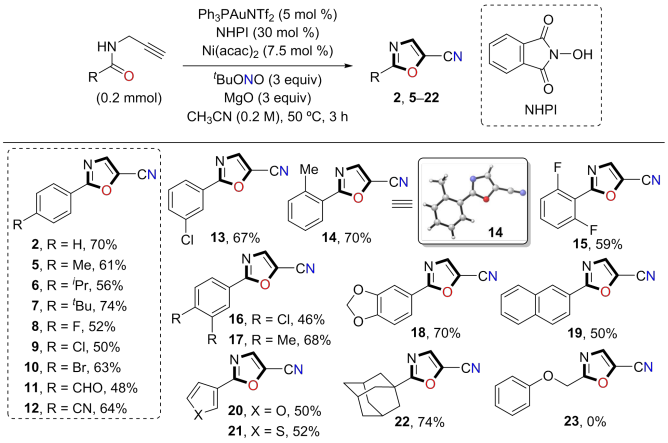
Scheme 1 Gold-catalyzed cyclizations of *N*-propargylamides for functionalized oxazole synthesis.

Recently, the incompatibility between gold catalysis and transition-metal-catalyzed oxidations has also been observed by Shi and Jiao groups (Scheme 1c).[5] For example, due to the poor compatibility and the orthogonal reactivity of the two catalytic systems, the carbon–nitrogen (C–N_3) bond formation can only be achieved in a two-step approach. To solve this problem, Shi, Jiao, and co-workers[5] developed an elegant synergistic gold and iron dual catalysis[6] for the synthesis of 5-formyloxazoles (Scheme 1d). Such reaction efficiently constructed the oxazole skeleton with an additional carbon–oxygen double bond. To the best of our knowledge, no other successful examples for the synthesis of valuable oxazole derivatives have been achieved to solve the incompatibility between gold catalysis and oxidation reactions. Therefore, it becomes highly desirable yet very challenging to develop new catalytic reactions by the combination of gold-catalyzed cyclization and oxidation processes. We envisioned that organocatalytic oxidations,[7] which appear to be milder compared to traditional oxidation processes, may be compatible with gold catalysis, and thus may promote new

[a] Institute of Next Generation Matter Transformation, College of Chemical Engineering, College of Material Sciences, Huaqiao University, Xiamen, Fujian 361021, China.
E-mail: qsong@hqu.edu.cn
[b] CAS Key Laboratory of Microscale Magnetic Resonance, Department of Modern Physics, University of Science and Technology of China, Hefei, Anhui 230026, China
Electronic Supplementary Information (ESI) available. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x

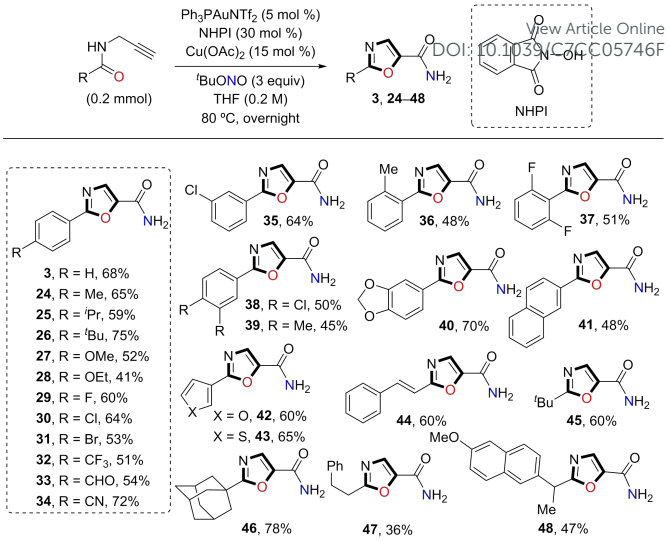
transformations of significant interest. Considering that metal-based Lewis acid (LA) additives are known to improve the efficiency of aerobic oxidations catalyzed by *N*-hydroxyphthalimide (NHPI) and other organocatalysts,[7] we also expected that the introduction of Lewis acids and suitable solvents may help to blend homogeneous gold catalysts and redox-active organocatalysts together.

Herein, we report two novel Au/NHPI/LA ternary catalytic systems for the practical synthesis of highly functionalized oxazoles from easily prepared *N*-propargylamide substrates (Scheme 1e). To the best of our knowledge, the one-pot generation of these C–N bond formation products by merging gold catalysis and catalytic oxidations has never been reported before.



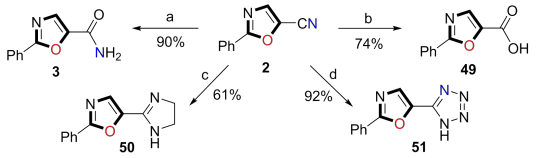
Scheme 2 5-Oxazolecarbonitrile synthesis catalyzed by Au/NHPI/Ni ternary system.

We commenced our investigations with *N*-propargylbenzamide (**1**) as the standard substrate by examining various conditions.[8] It was observed that Conditions A (Table S1, entry 4) afforded the 5-oxazolecarbonitrile **2** in 70% yield, whereas 5-oxazolecarboxamide **3** was obtained in 68% yield under Conditions B (Table S1, entry 14). The generation of 5-oxazolecarbonitriles was first tested (Scheme 2). Gratifyingly, a variety of *N*-propargylamide substrates bearing aryl substituents with different electronic effects and functional groups were well tolerated in this transformation, affording the desired products in moderate to good yields (**2**, **5**–**21**). Notably, the *ortho* substituents on the phenyl ring did not affect the reaction yields (**14** and **15**). Moreover, the structure of **14** was unambiguously confirmed by X-ray crystallographic analysis.[9] 2-Naphthyl substrate was also well tolerated under the standard conditions (**19**). Substrates with heteroaromatic substituents, such as 3-furanyl and 3-thiophenyl groups, were compatible as well, giving the desired products **20** and **21** in 50% and 52% yields, respectively. It is noteworthy that substrate with the steric-demanding 1-adamantanyl substituent was also suitable in this transformation, generating the corresponding nitrile product **22** in 74% yield. Unfortunately, phenoxylmethyl substrate did not give the desired product **23** under the standard conditions.



Scheme 3 5-Oxazolecarboxamide synthesis catalyzed by Au/NHPI/Cu ternary system.

Then we investigated the substrate scope for the synthesis of 5-oxazolecarboxamides (Scheme 3). The reaction worked well with *para*-substituted arylamide substrates. Alkyl (**24**–**26**), alkoxy (**27** and **28**), halo (**29**–**31**), trifluoromethyl (**32**), formyl (**33**), and cyano (**34**) groups were all compatible under the standard conditions, leading to the desired products in moderate to good yields. Meanwhile, *meta*-, *ortho*-, and disubstituted arylamide substrates also showed good tolerance with the target transformation (**35**–**40**). Other substrates with aromatic substituents, including 2-naphthyl as well as the heteroaromatic 3-furanyl and 3-thiophenyl groups, were also good candidates for this protocol, rendering the corresponding products in reasonable yields (**41**–**43**). Gratifyingly, alkenyl- and alkylamides demonstrated good reactivity as well and the desired products were obtained in decent yields (**44**–**48**), which underscores the great potential and the broad spectrum of this novel catalytic system.

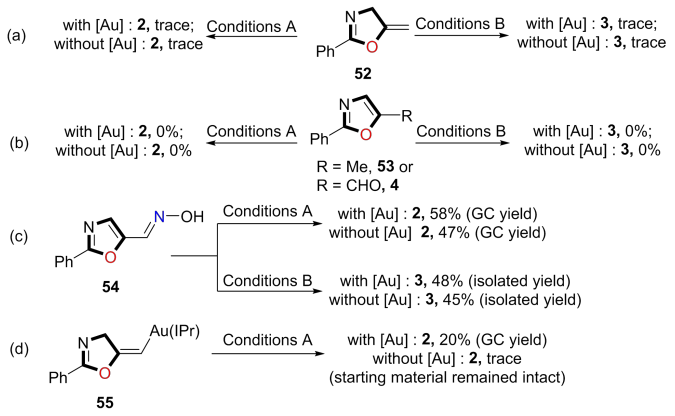


(a) **2** (0.2 mmol), ^{t}BuOK (3 equiv), ^{t}BuOH (3 mL), rt, 12 h; (b) **2** (0.2 mmol), KOH (3 equiv), EtOH (3 mL), reflux, 12 h; (c) **2** (0.2 mmol), *p*-TsOH·H_2O (1.5 equiv), $(CH_2NH_2)_2$ (3.5 mL), reflux, 5 h; (d) **2** (0.2 mmol), NaN_3 (2 equiv), NH_4Cl (2 equiv), DMF (2 mL), 120 °C, 14 h.

Scheme 4 Derivatizations of carbonitrile **2**.

Boger and co-workers have found that 5-substituted oxazoles are potent inhibitors of fatty acid amide hydrolase.[10] Therefore, we investigated the derivatizations of nitrile **2** mainly at the C5-position to demonstrate the synthetic value of our methodologies (Scheme 4). **2** can be easily converted into either amide **3**[11] or carboxylic acid **49** under different basic conditions in good yields. 2-Imidazoline **50** containing two heterocycles was prepared in 61% yield by mixing **2** and ethylenediamine up with *p*-TsOH·H_2O (*p*-toluenesulfonic acid)

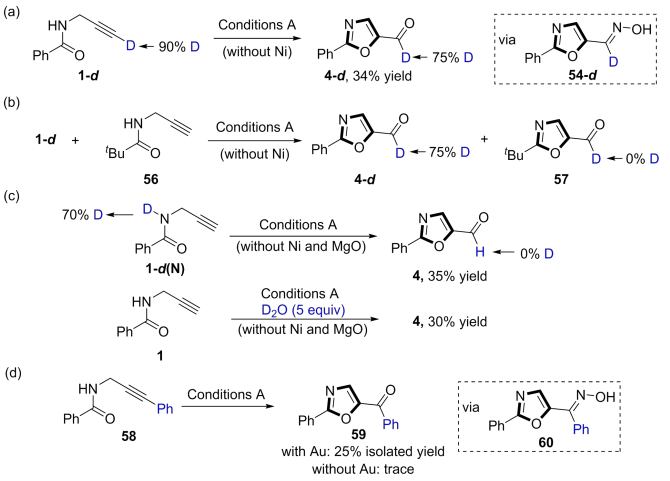
under reflux conditions.[12] Tetrazole **51** can also be easily prepared from **2** with sodium azide in 92% yield.[13]



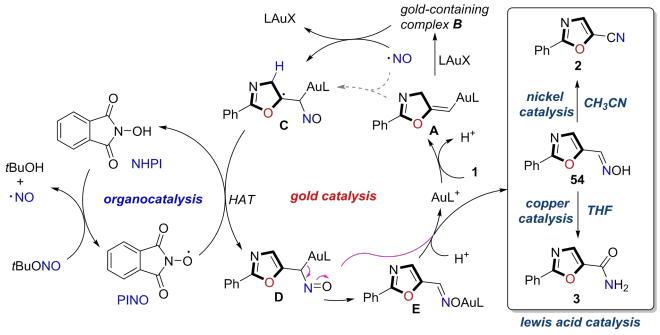
Scheme 5 Control experiments to explore the possible intermediates in our catalytic transformations

To gain insights into the reaction mechanism, we started to explore the possible intermediates in our catalytic systems. The intermediacy of methyleneoxazoline **52** has been previously proposed by Hashmi group.[4a] To verify whether the same intermediate exists in our reactions, we synthesized **52** and subjected it to both Conditions A and B in the presence or absence of the gold catalyst (Scheme 5a). In all cases, only traces amount of the desired products were detected, suggesting that **52** should not be an intermediate in our transformations. Similar results were found when 5-methyl-2-phenyloxazole **53** and aldehyde **4** were employed (Scheme 5b), indicating that **53** and **4** may also not be involved in the catalytic cycle. Inspired by previous work,[14a, 14d] we prepared aldoxime **54** and treated it under both Conditions A and B (Scheme 5c). To our delight, the desired products **2** and **3** were obtained in reasonable yields. These results are consistent with the previous reports by Lu[15a] and Williams groups,[15b] showing that nickel and copper complexes are efficient catalysts for aldoxime dehydration and rearrangement, respectively. These control experiments indicated that aldoxime **54** may indeed be the key intermediate in our Au/NHPI/LA ternary catalytic system. Moreover, to further explore possible gold-containing intermediates, we prepared a stable vinyl–Au–IPr complex **55** according to the literature[16] and subjected it to the NHPI/Ni catalytic system (Scheme 5d). Surprisingly, the corresponding product **2** was not formed in the absence of Au, however, it was obtained in 20% yield under Conditions A (with Au catalyst). We speculate that another active complex generated from vinyl–Au–L complex and gold catalyst maybe involved in the catalytic cycle.[17, 18]

To obtain more mechanistic information, we conducted several deuterium labeling experiments (Schemes 6a-c). These control experiments indicated that the σ-activation should not be the major reaction pathway. Furthermore, these results have also excluded the involvement of protodeauration steps in our reaction systems, otherwise a certain amount of deuterium incorporation should be observed when excess D_2O was added (Scheme 6c). Then, we prepared an internal alkyne substrate **58** and subjected it to Conditions A. To our delight, the desired product ketone **59** (generating from hydrolysis of oxime **60**) was obtained in 25% isolated yield in the presence of gold catalyst, yet only a trace amount of **59** was observed without the cationic gold complex (Scheme 6d). This experimental observation supported our previous hypothesis that the σ-activation should not be the major reaction pathway.[19]



Scheme 6 Isotopic labeling experiments and reaction of internal alkyne **58**.



Scheme 7 Plausible reaction mechanism.

According to the above-mentioned mechanistic experiments EPR experiments (see ESI for details) and precedented reports,[5, 14, 17] a plausible reaction mechanism is proposed in Scheme 7. First, cyclization of propargyl amide **1** initiated by cationic Au(I) leads to the vinyl-Au intermediate **A**. Based on our control experiments (Scheme 5d), we speculate that intermediate **A** itself could react with LAuX to give complex **B**, which might compete with protodeauration giving the good affinity of π bond to NO radical. Radical addition of complex **B** with NO then takes place to give intermediate **C** with a newly formed carbon–nitrogen bond. The subsequent hydrogen atom transfer (HAT) from the intermediate **C** to PINO occurs, generating NHPI and an aromatized intermediate **D**. Finally, this intermediate would be expected to rapidly isomerize or proton transfer to aldoxime **54**, which undergoes further Lewis acids catalyzed transformations to give the final products **2** and **3** by choosing appropriate solvents. This hypothesis

combines radical reactions, gold catalysis and Lewis acid catalysis which are unusual in homogeneous gold catalyzed reactions.[5-7] Further detailed studies are underway to clarify this intriguing point.

In conclusion, we have disclosed a novel ternary catalytic system consisted of gold catalyst, redox-active NHPI catalyst, and transition-metal catalysts for the pratical and chemodivergent synthesis of functionalized 2,5-disubstituted oxazoles in a one-pot fashion. This protocol is an efficient and robust method to construct oxazole scaffolds with excellent functionality tolerance. *Tert*-butyl nitrite was used as the terminal oxidant and the nitrogen source, leading to C–N bond formation products in good yields. The excellent compatibility of homogeneous gold catalysis with organocatalytic oxidation process is crucial in the success of our transformations. Further mechanistic studies are ongoing in our laboratory.

Financial support from the Recruitment Program of Global Experts (1000 Talents Plan), the Natural Science Foundation of Fujian Province (2016J01064), the National Key Basic Research Program of China (973 Program, 2013CB921802), Fujian Hundred Talents Plan, and Program of Innovative Research Team of Huaqiao University (Z14X0047) are gratefully acknowledged. We also thank Instrumental Analysis Center of Huaqiao University for analysis support. S.M. thanks the Subsidized Project for Cultivating Postgraduates' Innovative Ability in Scientific Research of Huaqiao University.

Notes and references

1 For selected examples, see: (a) W. Crow and J. Hodgkin, *Aust. J. Chem.*, 1968, **21**, 3075; (b) M. Debono, R. M. Molloy, J. L. Occolowitz, J. W. Paschal, A. H. Hunt, K. H. Michel and J. W. Martin, *J. Org. Chem.*, 1992, **57**, 5200; (c) A. Rudi, Z. Stein, S. Green, I. Goldberg, Y. Kashman, Y. Benayahu and M. Schleyer, *Tetrahedron*, 1994, **35**, 2589; (d) S. L. McGovern, E. Caselli, N. Grigorieff and B. K. Shoichet, *J. Med. Chem.*, 2002, **45**, 1712.

2 For selected reviews/books, see: (a) P. Wipf, *Chem. Rev.*, 1995, **95**, 2115; (b) D. C. Palmer, Ed. *Oxazoles: Synthesis, reactions, and spectroscopy, Part A;* J. Wiley & Sons: Hoboken, NJ, 2003; Vol. 60; For selected examples, see: (c) H. H. Wasserman and F. J. Vinick, *J. Org. Chem.*, 1973, **38**, 2407; (d) P.-Y. Coqueron, C. Didier and M. A. Ciufolini, *Angew. Chem., Int. Ed.*, 2003, **42**, 1411; (e) T. Ibata, and K. Fukushima, *Chem. Lett.*, **1992**, 2197; (f) S. R. Shah, S. S. Navathe, A. G. R. Dikundwar and A. T. Vasella, *Eur. J. Org. Chem.*, **2013**, 264; (g) W. He, C. Li and L. Zhang, *J. Am. Chem. Soc.*, 2011, **133**, 8482; (h) D. Haas, M. Mosrin and P. Knochel, *Org. Lett.*, 2013, **15**, 6162.

3 For recent reviews on homogeneous gold catalysis, see: (a) A. S. K. Hashmi, *Acc. Chem. Res.*, 2014, **47**, 864; (b) L. Zhang, *Acc. Chem. Res.*, 2014, **47**, 877; (c) Y.-M. Wang, A. D. Lackner and F. D. Toste, *Acc. Chem. Res.*, 2014, **47**, 889; (d) C. Obradors and A. M. Echavarren, *Acc. Chem. Res.*, 2014, **47**, 902; (e) A. Fürstner, *Acc. Chem. Res.*, 2014, **47**, 925; (f) R. Dorel and A. M. Echavarren, *Chem. Rev.*, 2015, **115**, 9028; (g) D. Pflästerer and A. S. K. Hashmi, *Chem. Soc. Rev.*, 2016, **45**, 1331; (h) D. B. Huple, S. Ghorpade and R.-S. Liu, *Adv. Synth. Catal.*, 2016, **358**, 1348.

4 (a) A. S. K. Hashmi, J. P. Weyrauch, W. Frey and J. W. Bats, *Org. Lett.*, 2004, **6**, 4391; (b) A. S. K. Hashmi, M. Rudolph, S. Schymura, J. Visus and W. Frey, *Eur. J. Org. Chem.*, **2006**, 4905; (c) J. P. Weyrauch, A. S. K. Hashmi, A. Schuster, T. Hengst, S. Schetter, A. Littmann, M. Rudolph, M. Hamzic, J. Visus, F. Rominger, W. Frey and J. W. Bats, *Chem. – Eur. J.*, 2010, **16**, 956; (d) A. S. K. Hashmi, A. M. Schuster, M. Schmuck and F. Rominger, *Eur. J. Org. Chem.*, **2011**, 4595; (e) A. S. K. Hashmi, M. C. Blanco Jaimes, A. M. Schuster and F. Rominger, *J. Org. Chem.*, 2012, **77**, 6394.

5 H. Peng, N. G. Akhmedov, Y.-F. Liang, N. Jiao, and X. Shi, *J. Am. Chem. Soc.*, 2015, **137**, 8912.

6 (a) Y. Shi, S. M. Peterson, W. W. Haberaecker III, S. A. Blum, *J. Am. Chem. Soc*., 2008, **130**, 2168; (b) J. delPozo, D. Carrasco, M. H. P. Temprano, M. G. Melchor, R. Álvarez, J. A. Casares and P. Espinet, *Angew. Chem., Int. Ed*., 2013, **52**, 2189; (c) P. García-Domínguez, C. Nevado, *J. Am. Chem. Soc.*, 2016, **138,** 3266.

7 For selected reviews on organocatalytic oxidations, see: (a) Y. Ishii, S. Sakaguchi and T. Iwahama, *Adv. Synth. Catal.*, 2001, **343**, 393; (b) R. A. Sheldon and I. W. C. E. Arends, *Adv. Synth. Catal.*, 2004, **346**, 1051; (c) F. Recupero and C. Punta, *Chem. Rev.*, 2007, **107**, 3800; (d) C. Galli, P. Gentili and O. Lanzalunga, *Angew. Chem., Int. Ed.*, 2008, **47**, 4790; (e) L. Melone and C. Punta, *Beilstein J. Org. Chem.*, 2013, **9**, 1296; (f) K. Chen, P. Zhang, Y. Wang and H. Li, *Green Chem.*, 2014, **16**, 2344.

8 See Electronic Supplementary Information for details.

9 CCDC 1482206 (**14**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

10 (a) F. A. Romero, W. Du, I. Hwang, T. J. Rayl, F. S. Kimball, D. Leung, H. S. Hoover, R. L. Apodaca, J. G. Breitenbucher, B. F. Cravatt and D. L. Boger, *J. Med. Chem.*, 2007, **50**, 1058; (b) C. Ezzili, M. Mileni, N. McGlinchey, J. Z. Long, S. G. Kinsey, D. G. Hochstatter, R. C. Stevens, A. H. Lichtman, B. F. Cravatt, E. J. Bilsky and D. L. Boger, *J. Med. Chem.*, 2011, **54**, 2805.

11 G. C. Midya, A. Kapat, S. Maiti and J. Dash, *J. Org. Chem.*, 2015, **80**, 4148.

12 M. Nasr-Esfahani, M. Montazerozohori and S. Mehrizi, *J. Heterocycl. Chem.*, 2011, **48**, 249.

13 W. Zhou, L. Zhang and N. Jiao, *Angew. Chem., Int. Ed.*, 2009, **48**, 7094.

14 (a) Z. Shu, Y. Ye, Y. Deng, Y. Zhang and J. Wang, *Angew. Chem., Int. Ed.*, 2013, **52**, 10573; (b) Z. Shu, Y. Zhou, Y. Zhang and J. Wang, *Org. Chem. Front.*, 2014, **1**, 1123; (c) J. Yu and L. Ming, *Org. Biomol. Chem.*, 2015, **13**, 7397; (d) J. Liu, H. Zheng, C. Yao, B. Sun and Y. Kang, *J. Am. Chem. Soc.,* 2016, **138**, 3294.

15 (a) X.-Y. Ma, Y. He, T.-T. Lu and M. Lu, *Tetrahedron*, 2013, **69**, 2560; (b) S. K. Sharma, S. D. Bishopp, C. L. Allen, R. Lawrence, M. J. Bamford, A. A. Lapkin, P. Plucinski, R. J. Watson, J. M. J. Williams, *Tetrahedron Lett.*, 2011, **52**, 4252.

16 A. S. K. Hashmi, A. M. Schuster and F. Rominger, *Angew. Chem., Int. Ed.*, 2009, **48**, 8247.

17 (a) D. Weber, M. A. Tarselli and M. R. Gagné, *Angew. Chem., Int. Ed.*, 2009, **48**, 5733; (b) G. Seidel, C. W. Lehmann and A. Fürstner, *Angew. Chem., Int. Ed.,* 2010, **49**, 8466; (c) T. J. Brown, D. Weber, M. R. Gagné and R. A. Widenhoefer, *J. Am. Chem. Soc.,* 2012, **134**, 9134.

18 According to the ^{31}P NMR data, we speculate another possible pathway maybe involved in the catalytic cycle (see ESI for details).

19 For a review on the regioselectivity of alkyne cyclization, see: Gilmore, K.; Alabugin, I. V. *Chem. Rev.* **2011**, *111*, 6513.

View Article Online
DOI: 10.1039/C7CC05746F

TOC: