Heterocycles

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Zinc-Catalyzed Alkyne Oxidation/C–H Functionalization: Highly Site-Selective Synthesis of Versatile Isoquinolones and β-Carbolines**

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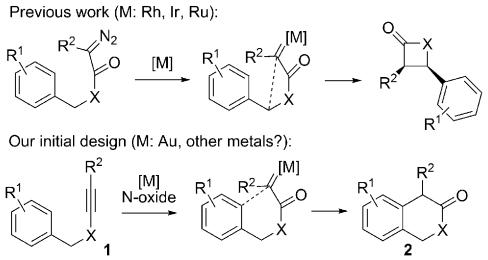
Abstract: *An efficient zinc(II)-catalyzed alkyne oxidation/C–H functionalization sequence was developed, thus leading to highly site-selective synthesis of a variety of isoquinolones and β-carbolines. Importantly, in contrast to the well-established gold-catalyzed intermolecular alkyne oxidation, over-oxidation can be completely suppressed in this system and the reaction most likely proceeds by a Friedel–Crafts-type pathway. Mechanistic studies and theoretical calculations are described.*

During the past decade, transition-metal-catalyzed direct functionalization of C–H bonds has proven to be an extremely powerful and highly versatile synthetic tool for the construction of natural products and pharmaceuticals.[1] Because of the presence of different types of C–H bonds in complex molecules, it still presents particular challenges in achieving highly site-selective C–H functionalization with practical interest. For example, the insertion of metal carbenes into saturated C–H bonds invariably favors the related C(sp^2)–H insertion for transition-metal-catalyzed C–-H insertion of α-diazo compounds (Scheme 1).[2] Reversing this site selectivity not only represents an attractive method to build six-membered heterocycles, but also complements the conventional metal carbene insertion reaction. Therefore, it is highly desirable to develop a direct C–H functionalization method that specifically targets such a C(sp^2)–H bond.

In recent years, gold-catalyzed intermolecular alkyne oxidation by an N-oxide oxidant, a process which presumably involves an α-oxo gold carbenoid intermediate, has attracted significant research attention because it avoids the use of hazardous α-diazo ketones as starting materials for carbene generation.[3,4] Recently, the groups of Tang and Li reported that rhodium could also catalyze such an intermolecular alkyne oxidation.[5] Despite these findings,[6] synthetic application of N-oxide-mediated oxidation of alkynes faces two major technical hurdles: 1) The carbene intermediate, particularly when generated from an internal alkyne such as ynamide,[7] can undergo over-oxidation which generates unwanted byproducts.[8,4c] 2) A noble transition-metal catalyst usually is required for optimal reaction efficiency, and may severely limit the practical application of this approach because of the high cost and toxicity of the catalyst. Herein, we report the first zinc-catalyzed alkyne oxidation/C(sp^2)–H functionalization sequence,[9,8b] thus providing practical access to synthetically useful isoquinolones and β-carbolines. In particular, the undesired over-oxidation could be dramatically suppressed in such an oxidative zinc catalysis.[10] Most importantly, mechanistic studies and theoretical calculations revealed that the reaction presumably proceeds by a Friedel–Crafts-type pathway, which is distinctively different from the related gold-catalyzed oxidative cyclization.



Scheme 1. Initial design.

Our initial investigation[11] focused on the reaction of the ynamide substrate **1a** with 2-bromopyridine *N*-oxide (**3a**) in DCE at 80 °C in the presence of a gold catalyst (5 mol %; Table 1). However, in most cases, only the diketone **2aa** was obtained through the gold-catalyzed over-oxidation of **1a**.[12] We then sought to use other metal catalysts, hoping to circumvent the competing over-oxidation process. Surprisingly, other metal catalysts, especially the non-noble metals, also promoted such an oxidative cyclization (entries 1–3). Importantly, no diketone formation was observed in the presence of either $Fe(OTf)_2$ or $Zn(OTf)_2$ (entries 2 and 3), and the reaction could afford the oxidatively cyclized product **2a** in 47% yield by using 10 mol % of $Zn(OTf)_2$ as the catalyst, albeit along with the hydration product **2ab** in 25% yield (entry 3). Of note, HOTf could also catalyze this reaction in 16% yield.[12,13] In addition, the use of PhCl as the solvent at 100 °C gave a slightly improved yield (entry 4). The yield of product **2a** was further increased to 61% by using 2,6-dibromopyridine *N*-oxide (**3b**) as the oxidant (entry 5). Pleasingly, the use of 4 Å molecular sieve minimized the formation of the hydration byproduct and 86% yield of **2a**

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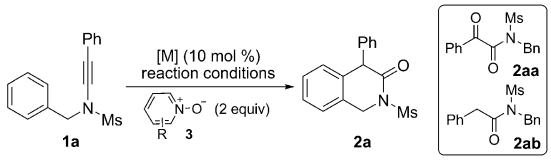
Table 1: Optimization of reaction conditions.[a]

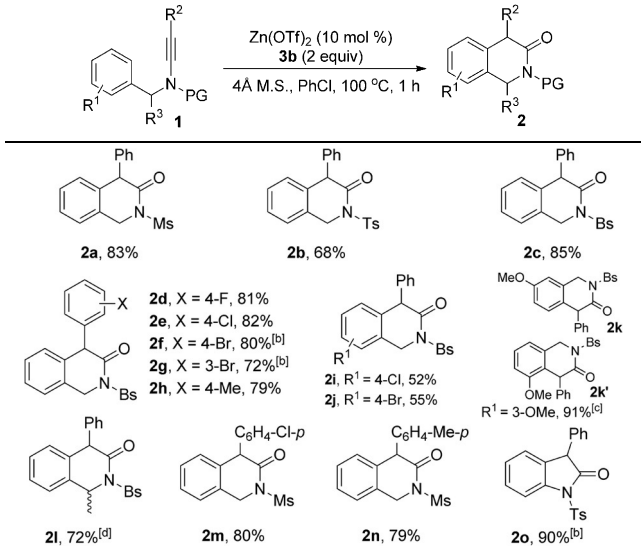


Entry	Metal catalyst	**3** (R)	Reaction conditions	Yield [%][b] **2a**	**2aa**	**2ab**
1	$Cu(OTf)_2$	**3a** (2-Br)	DCE, 80 °C, 3 h	23	12	< 1
2	$Fe(OTf)_2$	**3a** (2-Br)	DCE, 80 °C, 3 h	29	< 1	5
3	$Zn(OTf)_2$	**3a** (2-Br)	DCE, 80 °C, 3 h	47	< 1	25
4	$Zn(OTf)_2$	**3a** (2-Br)	PhCl, 100 °C, 1 h	50	< 1	20
5	$Zn(OTf)_2$	**3b** (2,6-Br_2)	PhCl, 100 °C, 1 h	61	< 1	18
6[c]	$Zn(OTf)_2$	**3b** (2,6-Br_2)	PhCl, 100 °C, 1 h	86	< 1	< 5
7[c]	$Sc(OTf)_3$	**3b** (2,6-Br_2)	PhCl, 100 °C, 1 h	81	< 1	< 5
8[c]	$Sm(OTf)_3$	**3b** (2,6-Br_2)	PhCl, 100 °C, 1 h	64	< 1	< 5
9[c]	$Yb(OTf)_3$	**3b** (2,6-Br_2)	PhCl, 100 °C, 5 h	81	< 1	< 5
10[c]	$Y(OTf)_3$	**3b** (2,6-Br_2)	PhCl, 100 °C, 1 h	66	< 1	< 5
11[c]	$Dy(OTf)_3$	**3b** (2,6-Br_2)	PhCl, 100 °C, 5 h	79	< 1	6
12[c]	$In(OTf)_3$	**3b** (2,6-Br_2)	PhCl, 100 °C, 1 h	77	< 1	< 5

[a] Reaction conditions: [**1a**] = 0.05 M. [b] Measured by ^{1}H NMR spectroscopy using diethyl phthalate as the internal standard. [c] Using 4 Å molecular sieves (20 mg) as the additive. Ms = methanesulfonyl, Tf = trifluoromethanesulfonyl.

could be achieved (entry 6). Notably, it was found that a variety of other Lewis acids could also catalyze such an oxidative cyclization to deliver the desired **2a** in 64–81% yields (entries 7–12), thus indicating that the reaction is proposed to occur by an electrophilic aromatic substitution pathway. Without the zinc catalyst or the oxidant, the reaction failed to afford any of **2a**, and only **2ab** was formed (96% yield) in the latter case.

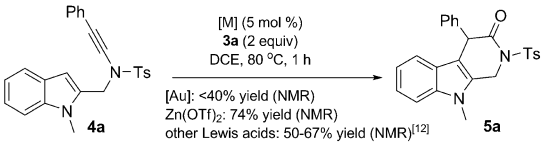
Table 2: Reaction scope study.[a]



[a] Reactions run in vials. Yields are those for the isolated products. [b] 3 equiv of **3b** was used. [c] **2k**/**2k′** = 3:1. [d] *trans*/*cis* = 5.6:1. Bs = 4-bromobenzenesulfonyl, M.S. = molecular sieves, PG = protecting group, Ts = 4-toluenesulfonyl.

The scope of this zinc-catalyzed oxidative cyclization was then studied. Initial investigation of N-protecting groups demonstrated that the Bs-protected substrate **1c** gave a slightly improved yield (Table 2). Then, various aryl-substituted ynamides were investigated and the reaction furnished the corresponding isoquinolones **2d–h** in 72–82% yields. However, with an alkyl-substituted (R^2 = alkyl) substrate, the reaction failed to give the desired isoquinolone and an α,β-unsaturated amide was isolated in 85% yield instead.[12] In addition, reducing the electron density of the benzyl group decreased product formation (**2i,j**, 52–55% yield), which was similar to that observed by Zhang and co-workers and Gagosz and co-workers.[9a,b] In the case of the substrate bearing an electron-donating methoxy substituent at the *meta*-position, a 3:1 regioselectivity and 91% combined yield of **2k** and **2k′** could be obtained. For the methyl-substituted ynamide **1l**, the reaction still led to a respectable 72% yield with a *trans*/*cis* ratio of 5.6:1. Other Ms-protected ynamides were also suitable substrates for this reaction to furnish the desired **2m**,**n** in good yields. Notably, *N*-phenyl ynamide, which only forms diketone in gold-catalyzed alkyne oxidation,[8b] also showed outstanding performance (**2o**). Finally, it should be mentioned that in some cases slightly improved yields could be achieved by using 3 equivalents of **3b** to prohibit the background hydration reaction (**2f**, **2g**, and **2o**). These results demonstrated that this zinc-catalyzed oxidative cyclization provides a highly efficient and practical route for the construction of the isoquinolone scaffold, which can be found in various bioactive alkaloids,[14] without over-oxidation or β-lactam formation.

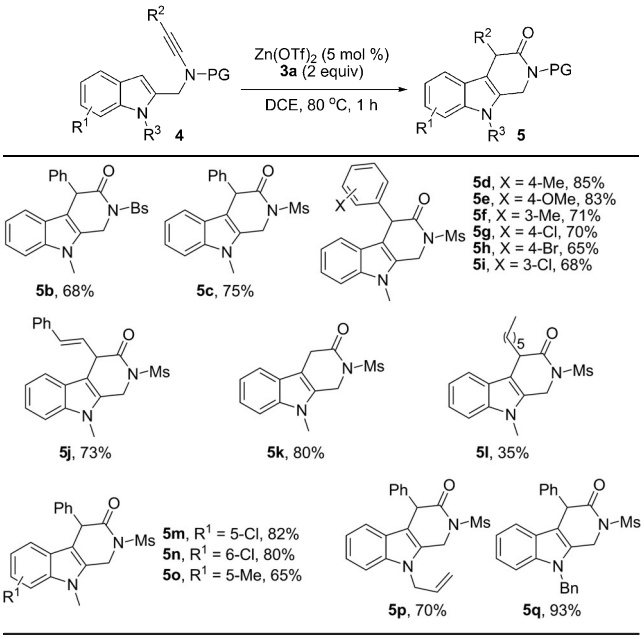
We next considered the possibility of extending the reaction to other electron-rich heterocycle-substituted ynamides. Gratifyingly, in the presence of $Zn(OTf)_2$ as the catalyst, the desired β-carboline **5a** could be achieved in 74% yield as determined by NMR spectroscopy (isolated yield: 66%), whereas less than 40% yield was obtained by using gold catalysts [Eq. (1); DCE = 1,2-dichloroethane].[12]



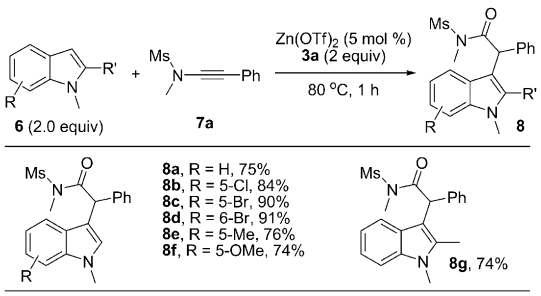
(1)

Inspired by these results, we also examined the scope of this zinc-catalyzed oxidative cyclization of indolyl ynamides **4**. As shown in Table 3, the reaction took place smoothly and the desired tricyclic lactams **5** were obtained in mostly good to excellent yields. Besides the Ts-protected ynamide **4a**, it was found that ynamides with a Bs or a Ms group also worked well (**5b,c**). Then, a variety of Ms-protected ynamides were investigated. The reaction worked satisfactorily with various aryl-substituted ynamides, thus providing the desired **5d–i** in 65–85% yields. In addition, the reactions also proceeded with

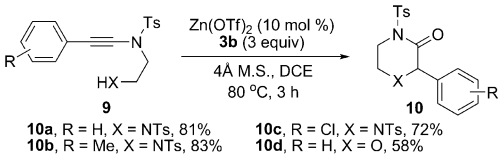
Table 3: Reaction scope study.[a]



[a] Reactions run in vials. Yields are those for the isolated products.



Scheme 2. Intermolecular reaction of the indoles **6** with the ynamide **7a** through oxidative zinc catalysis.



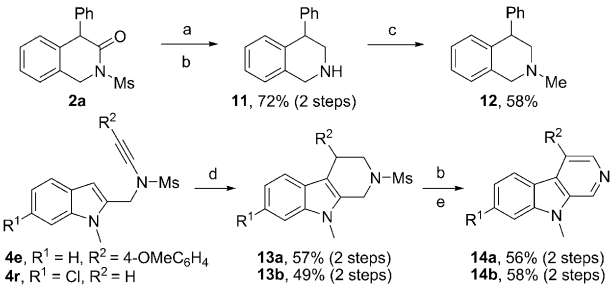
(2)

a styryl-substituted ynamide and even terminal ynamide, thus delivering **5j** (73%) and **5k** (80%), respectively. Notably, this chemistry also worked with an alkyl-substituted ynamide to produce the desired **5l**, albeit less efficiently, and no α,β-unsaturated imide product was formed. Subsequent investigation demonstrated that the ynamides with an electron-withdrawing substituent on the indole gave significantly better yields (**5m–o**). To our delight, N-substituted indolyl ynamides containing an allyl or benzyl group were also suitable substrates for this cyclization, thus furnishing the anticipated **5p** (70%) and **5q** (93%), respectively. The molecular structure of **5c** was further confirmed by X-ray diffraction.[15] Significantly, this zinc-catalyzed oxidative cyclization is highly site-selective in comparison with the related diazo approach, which often suffers from problems in control of the chemoselectivity of the C–H insertion.[16]

We then wondered whether this oxidative zinc catalysis is applicable to the intermolecular reaction of indoles with ynamides. Gratifyingly, it was found that the reaction of the indoles **6**, ynamide **7a**, and oxidant **3a** in the presence of 5 mol% $Zn(OTf)_2$ under solvent-free conditions could afford the corresponding products **8a–g** in good to excellent yields (Scheme 2). Once again, no diketone formation was observed in all cases.

We discovered that the zinc-catalyzed oxidation could also be used to promote facile formal N–H and O–H insertions, thus generating useful piperazin-2-one and morpholin-3-one structures, respectively [Eq. (2)]. To our best knowledge, this is the first example of a catalytic alkyne oxidation/X–H insertion reaction for the preparation of a six-membered ring.[17,11c,d] Notably, hydration products were obtained as the main product under gold catalysis conditions.

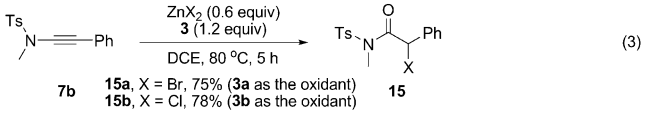
The utility of this chemistry is additionally demonstrated through the total synthesis of several biologically active compounds and the natural product bauerine A. As summarized in Scheme 3, reduction of the cyclization product **2a** with B_2H_6, followed by deprotection could furnish 4-phenyl 1,2,3,4-tetrahydroisoquinoline (THIQ; **11**) which displays high affinity to the PCP binding site.[18f] Moreover, THIQ is an important structural motif in many alkaloids.[18] Further N-methylation of **11** gave the THIQ **12**, an agonist of dopamine receptors.[19] In addition, the synthesis of the Ca^{+2} influx and IL-2 production inhibitor **14a**[20] and the natural product bauerine A (**14b**)[21] could be achieved in 31.9 and 28.4% overall yields (4 steps), respectively, by a zinc-catalyzed oxidative cyclization and diborane reduction in a one-pot process, and subsequent deprotection and dehydrogenative oxidation.



Scheme 3. Synthetic applications. Reagents and conditions: a) B_2H_6·THF (4 equiv), THF, reflux; b) Red-Al (5 equiv), toluene, 110°C; c) HCHO, $NaBH_4$, MeOH, RT; d) $Zn(OTf)_2$ (5 mol%), **3a** (2.0 equiv), DCE, 80°C, 1 h; B_2H_6·THF (4 equiv), THF, reflux, 6 h; e) for **13a**: Pd/C, *p*-xylene, 135°C; for **13b**: MnO_2 (2 equiv), toluene, 100°C. THF = tetrahydrofuran.

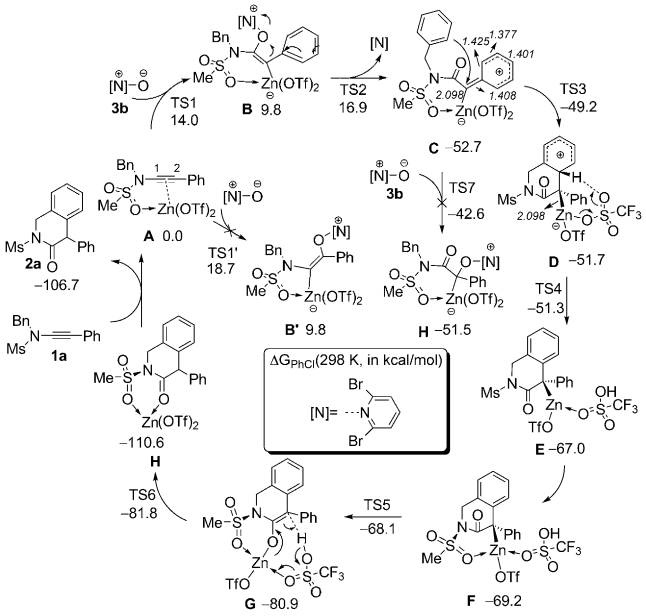
To probe the reaction mechanism, we first performed kinetic isotopic effect (KIE) studies. The absence of an intramolecular and intermolecular isotope effect suggests that the oxidative cyclization is most likely to involve an electrophilic aromatic substitution process.[12] In addition, it was found that the ynamide **7b** could undergo oxidative bromination or chlorination smoothly to afford the corresponding

α-bromo amide **15a** and α-chloro amide **15b** in 75 and 78% yields, respectively [Eq. (3)], and not only represents the first tandem alkyne oxidation/halogenation, but also indicates that the metal carbene pathway is less likely.[12]



(3)

On the basis of the above experimental observations and density functional theory (DFT) computations,[12] a plausible mechanism to rationalize the formation of **2** is presented in Scheme 4. First, nucleophilic attack of the N-oxide **3b** occurs



Scheme 4. Plausible mechanism. Theoretical investigations on the reaction pathways for the formation of **2a**: relative free energies (ΔG_{PhCl}, in kcal mol^{-1}) of key intermediates and transition states were computed at the M06/6-31G(d,p)/LanL2DZ level of theory in PhCl at 298 K.

regioselectively at C1 of the zinc-activated alkyne **A** to form the zinc-substituted alkene **B**, from which facile release of pyridine gives the phenyl-stabilized carbocation intermediate **C**. Subsequent intramolecular nucleophilic addition of N-benzyl to the carbocation site produces the intermediate **D** with no change in the Zn–C bond (2.098 Å). Thus this cyclization step is more like a Friedel–Crafts alkylation than a metal–carbene insertion.[22,23] Finally, the intermediate **D** underwent aromatization, enolization, protonation,[24] and ligand exchange to furnish the final product **2a**. These steps are predicted to be nearly barrierless and highly exothermic. Notably, besides intramolecular cyclization, **C** could also be attacked by another **3b** leading to over-oxidation, but the barrier was 6.6 kcal mol^{-1} higher, thus predicting good chemoselectivity. This might be attributed to steric repulsion between the incoming **3b** and the OTf anions ligated onto Zn^{II}.[12]

In summary, we report herein the first example of non-noble metal catalyzed intermolecular alkyne oxidation, thus leading to the highly site-selective synthesis of versatile isoquinolones and β-carbolines. This methodology proves to be a very general method, applicable both intramolecularly and intermolecularly, for both C–H functionalization and X–H insertion. Importantly, it was revealed that this oxidative zinc catalysis could significantly inhibit the undesired diketone formation, which might serve as a general solution to the problem of over-oxidation in such an oxidative catalysis. Moreover, the reaction is proposed to occur by a Lewis acid catalyzed Friedel–Crafts-type pathway on the basis of both mechanistic studies and DFT calculations. Further application of this Lewis acid catalyzed alkyne oxidation will be pursued in our laboratory.

Keywords: heterocycles · homogeneous catalysis · nitrogen oxides · synthetic methods · zinc

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Angew. Chem. **2015**, *127*, 8363–8367

[1] For recent selected reviews, see: a) M. P. Doyle in *Modern Rhodium-Catalyzed Transformations* (Ed.: P. A. Evans), Wiley-VCH, Weinheim, **2005**, chap. 15; b) M. P. Doyle in *Topics in Organometallic Chemistry, Vol. 10* (Ed.: K.-H. Dotz), Springer, Berlin, Germany, **2004**, p. 203; c) H. M. L. Davies, Y. Lian, *Acc. Chem. Res.* **2012**, *45*, 923; d) H. M. L. Davies, D. Morton, *Chem. Soc. Rev.* **2011**, *40*, 1857; e) M. P. Doyle, R. Duffy, M. Ratnikov, L. Zhou, *Chem. Rev.* **2010**, *110*, 704; f) H. M. L. Davies, J. R. Denton, *Chem. Soc. Rev.* **2009**, *38*, 3061.

[2] For recent examples, see: a) L. Fu, H. Wang, H. M. L. Davies, *Org. Lett.* **2014**, *16*, 3036; b) J.-C. Wang, Y. Zhang, Z.-J. Xu, V. K.-Y. Lo, C.-M. Che, *ACS Catal.* **2013**, *3*, 1144; c) M. K.-W. Choi, W.-Y. Yu, C.-M. Che, *Org. Lett.* **2005**, *7*, 1081; for a review, see: d) P. M. P. Gois, C. A. M. Afonso, *Eur. J. Org. Chem.* **2004**, 3773.

[3] For reviews, see: a) H.-S. Yeom, S. Shin, *Acc. Chem. Res.* **2014**, *47*, 966; b) L. Zhang, *Acc. Chem. Res.* **2014**, *47*, 877; c) J. Xiao, X. Li, *Angew. Chem. Int. Ed.* **2011**, *50*, 7226; *Angew. Chem.* **2011**, *123*, 7364; for pioneer work, see: d) N. D. Shapiro, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 4160; e) G. Li, L. Zhang, *Angew. Chem. Int. Ed.* **2007**, *46*, 5156; *Angew. Chem.* **2007**, *119*, 5248.

[4] For recent selected examples, see: a) J. Schulz, L. Škríba, A. JaŠíková, J. Roithová, *J. Am. Chem. Soc.* **2014**, *136*, 11513; b) S. N. Karad, R.-S. Liu, *Angew. Chem. Int. Ed.* **2014**, *53*, 5444; *Angew. Chem.* **2014**, *126*, 5548; c) T. Wang, S. Shi, M. M. Hansmann, E. Rettenmeier, M. Rudolph, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2014**, *53*, 3715; *Angew. Chem.* **2014**, *126*, 3789; d) M. D. Santos, P. W. Davies, *Chem. Commun.* **2014**, *50*, 6001; e) J. Li, K. Ji, R. Zheng, J. Nelson, L. Zhang, *Chem. Commun.* **2014**, *50*, 4130; f) E. P. A. Talbot, M. Richardson, J. M. McKenna, F. D. Toste, *Adv. Synth. Catal.* **2014**, *356*, 687; g) P. Nösel, N. L. dos Santos Comprido, T. Lauterbach, M. Rudolph, F. Rominger, A. S. K. Hashmi, *J. Am. Chem. Soc.* **2013**, *135*, 15662; h) L. Wang, X. Xie, Y. Liu, *Angew. Chem. Int. Ed.* **2013**, *52*, 13302; *Angew. Chem.* **2013**, *125*, 13544; i) S. K. Pawar, C.-D. Wang, S. Bhunia, A. M. Jadhav, R.-S. Liu, *Angew. Chem. Int. Ed.* **2013**, *52*, 7559; *Angew. Chem.* **2013**, *125*, 7707; j) K. Ji, Y. Zhao, L. Zhang, *Angew. Chem. Int. Ed.* **2013**, *52*, 6508; *Angew. Chem.* **2013**, *125*, 6636; k) S. Ghorpade, M.-D. Su, R.-S. Liu, *Angew. Chem. Int. Ed.* **2013**, *52*, 4229; *Angew. Chem.* **2013**, *125*, 4323.

[5] a) R. Liu, G. N. Winston-McPherson, Z.-Y. Yang, X. Zhou, W. Song, I. A. Guzei, X. Xu, W. Tang, *J. Am. Chem. Soc.* **2013**, *135*, 8201; b) X. Zhang, Z. Qi, X. Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 10794; *Angew. Chem.* **2014**, *126*, 10970; for an iridium-catalyzed alkyne oxidation, see: c) G. Song, D. Chen, Y. Su, K. Han, C.-L. Pan, A. Jia, X. Li, *Angew. Chem. Int. Ed.* **2011**, *50*, 7791; *Angew. Chem.* **2011**, *123*, 7937.

[6] For rhodium-catalyzed metallonitrene-initiated alkyne oxidation cascades, see: a) N. Mace, A. R. Thornton, S. B. Blakey, *Angew. Chem. Int. Ed.* **2013**, *52*, 5836; *Angew. Chem.* **2013**, *125*, 5948; b) A. R. Thornton, V. I. Martin, S. B. Blakey, *J. Am. Chem. Soc.* **2009**, *131*, 2434; c) A. R. Thornton, S. B. Blakey, *J. Am. Chem. Soc.* **2008**, *130*, 5020.

[7] For recent reviews on ynamide reactivity, see: a) X.-N. Wang, H.-S. Yeom, L.-C. Fang, S. He, Z.-X. Ma, B. L. Kedrowski, R. P. Hsung, *Acc. Chem. Res.* **2014**, *47*, 560; b) K. A. DeKorver, H. Li, A. G. Lohse, R. Hayashi, Z. Lu, Y. Zhang, R. P. Hsung, *Chem. Rev.* **2010**, *110*, 5064; c) G. Evano, A. Coste, K. Jouvin, *Angew. Chem. Int. Ed.* **2010**, *49*, 2840; *Angew. Chem.* **2010**, *122*, 2902.

[8] a) K.-B. Wang, R.-Q. Ran, S.-D. Xiu, C.-Y. Li, *Org. Lett.* **2013**, *15*, 2374; b) L.-Q. Yang, K.-B. Wang, C.-Y. Li, *Eur. J. Org. Chem.* **2013**, 2775; c) R. B. Dateer, K. Pati, R.-S. Liu, *Chem. Commun.* **2012**, *48*, 7200; d) A. Mukherjee, R. B. Dateer, R. Chaudhuri, S. Bhunia, S. N. Karad, R.-S. Liu, *J. Am. Chem. Soc.* **2011**, *133*, 15372; e) D. Vasu, H.-H. Hung, S. Bhunia, S. A. Gawade, A. Das, R.-S. Liu, *Angew. Chem. Int. Ed.* **2011**, *50*, 6911; *Angew. Chem.* **2011**, *123*, 7043; f) C.-W. Li, K. Pati, G.-Y. Lin, S. M. A. Sohel, H.-H. Hung, R.-S. Liu, *Angew. Chem. Int. Ed.* **2010**, *49*, 9891; *Angew. Chem.* **2010**, *122*, 10087.

[9] For such a gold-catalyzed oxidative cyclization, which is limited to terminal alkynes or electron-deficient internal alkynes, see: a) G. Henrion, T. E. J. Chava, X. Le Goff, F. Gagosz, *Angew. Chem. Int. Ed.* **2013**, *52*, 6277; *Angew. Chem.* **2013**, *125*, 6397; b) Y. Wang, K. Ji, S. Lan, L. Zhang, *Angew. Chem. Int. Ed.* **2012**, *51*, 1915; *Angew. Chem.* **2012**, *124*, 1951; c) D. Qian, J. Zhang, *Chem. Commun.* **2012**, *48*, 7082.

[10] For recent reviews on zinc catalysis, see: a) S. Enthaler, *ACS Catal.* **2013**, *3*, 150; b) X.-F. Wu, H. Neumann, *Adv. Synth. Catal.* **2012**, *354*, 3141.

[11] For our efforts on the gold-catalyzed intermolecular alkyne oxidation, see: a) L. Li, C. Shu, B. Zhou, Y.-F. Yu, X.-Y. Xiao, L.-W. Ye, *Chem. Sci.* **2014**, *5*, 4057; b) F. Pan, S. Liu, C. Shu, R.-K. Lin, Y.-F. Yu, J.-M. Zhou, L.-W. Ye, *Chem. Commun.* **2014**, *50*, 10726; c) C. Shu, L. Li, X.-Y. Xiao, Y.-F. Yu, Y.-F. Ping, J.-M. Zhou, L.-W. Ye, *Chem. Commun.* **2014**, *50*, 8689; d) C. Shu, L. Li, Y.-F. Yu, S. Jiang, L.-W. Ye, *Chem. Commun.* **2014**, *50*, 2522.

[12] For details, please see the Supporting Information.

[13] For acid-promoted oxidative cyclizations, see: a) K. Graf, C. L. Rühl, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2013**, *52*, 12727; *Angew. Chem.* **2013**, *125*, 12960; b) D.-F. Chen, Z.-Y. Han, Y.-P. He, J. Yu, L.-Z. Gong, *Angew. Chem. Int. Ed.* **2012**, *51*, 12307; *Angew. Chem.* **2012**, *124*, 12473.

[14] K. W. Bentley, *The Isoquinoline Alkaloids*, *Vol. 1*, Hardwood Academic, Amsterdam, The Netherlands, **1998**.

[15] CCDC 1032701 (**5c**) 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.

[16] a) B. Zhang, A. G. H. Wee, *Chem. Commun.* **2008**, *44*, 4837; b) E. Cuevas-Yañez, J. M. Muchowski, R. Cruz-Almanza, *Tetrahedron* **2004**, *60*, 1505; c) M. E. Jung, F. Slowinski, *Tetrahedron Lett.* **2001**, *42*, 6835; d) M. Salim, A. Capretta, *Tetrahedron* **2000**, *56*, 8063.

[17] a) L. Ye, W. He, L. Zhang, *Angew. Chem. Int. Ed.* **2011**, *50*, 3236; *Angew. Chem.* **2011**, *123*, 3294; b) L. Ye, W. He, L. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 8550; c) L. Ye, L. Cui, G. Zhang, L. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 3258.

[18] For reviews, see: a) M. Chrzanowska, M. D. Rozwadowska, *Chem. Rev.* **2004**, *104*, 3341; b) J. D. Scott, R. M. Williams, *Chem. Rev.* **2002**, *102*, 1669; c) P. S. Charifson, *Drugs Future* **1989**, *14*, 1179; for recent examples, see: d) S. Wang, M. B. Onaran, C. T. Seto, *Org. Lett.* **2010**, *12*, 2690; e) S. J. Coote, S. G. Davies, A. M. Fletcher, P. M. Roberts, J. E. Thomson, *Chem. Asian J.* **2010**, *5*, 589; f) M. Ludwig, C. E. Hoesl, G. Höfner, K. T. Wanner, *Eur. J. Med. Chem.* **2006**, *41*, 1003.

[19] P. A. Dandridge, C. Kaiser, M. Brenner, D. Gaitanopoulos, L. D. Davis, R. L. Webb, J. J. Foley, H. M. Sarau, *J. Med. Chem.* **1984**, *27*, 28.

[20] K. D. Hargrave, C. K. Miao, T. P. Parks, I. F. Potocki, R. J. Snow, PCT Int. Appl. WO 9806719A1, **1998**.

[21] a) S. W. Dantale, B. C. G. Söderberg, *Tetrahedron* **2003**, *59*, 5507; b) L. K. Larsen, R. E. Moore, G. M. L. Patterson, *J. Nat. Prod.* **1994**, *57*, 419.

[22] For the generation of zinc carbenoids from alkynes, see: a) M. J. González, L. A. López, R. Vicente, *Org. Lett.* **2014**, *16*, 5780; b) J. González, L. A. López, R. Vicente, *Chem. Commun.* **2014**, *50*, 8536; c) B. Song, L.-H. Li, X.-R. Song, Y.-F. Qiu, M.-J. Zhong, P.-X. Zhou, Y.-M. Liang, *Chem. Eur. J.* **2014**, *20*, 5910; d) R. Vicente, J. González, L. Riesgo, J. González, L. A. López, *Angew. Chem. Int. Ed.* **2012**, *51*, 8063; *Angew. Chem.* **2012**, *124*, 8187.

[23] For relevant examples of gold-catalyzed alkyne oxidations which do not involve gold carbene intermediates, see: a) D. Qian, H. Hu, F. Liu, B. Tang, W. Ye, Y. Wang, J. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 13751; *Angew. Chem.* **2014**, *126*, 13971; b) M. Chen, Y. Chen, N. Sun, J. Zhao, Y. Liu, Y. Li, *Angew. Chem. Int. Ed.* **2015**, *54*, 1200; *Angew. Chem.* **2015**, *127*, 1216.

[24] When the reaction was performed in the presence of 5 equiv of D_2O, >85% deuterium incorporation at the α-position was observed, and further supports our proposed mechanism. Please see the Supporting Information for full details.

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