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Gold-catalyzed formation of indole derivatives from 2-alkynyl arylazides and oxygen-containing heterocycles†

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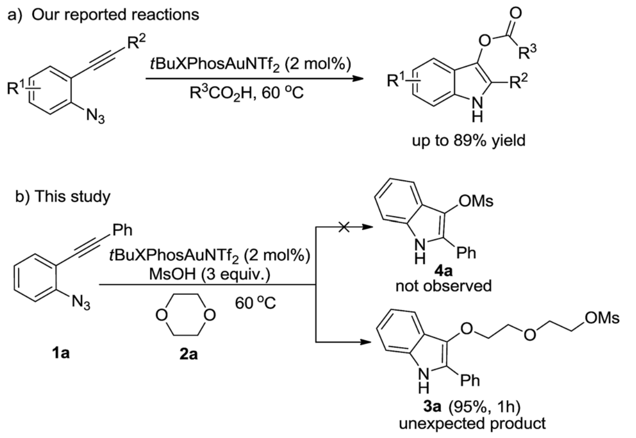
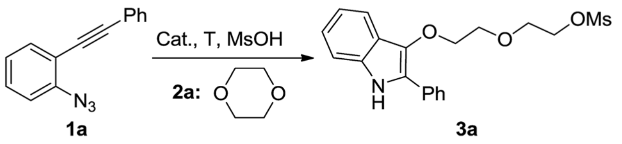
A novel method for the formation of indole derivatives *via* gold-catalyzed tandem reactions of 2-alkynyl arylazides and oxygen-containing heterocycles has been developed. A variety of indole derivatives were prepared under mild reaction conditions.

Indoles are very important core structures in organic chemistry, which can be found in many natural products and bioactive compounds.[1] They are also serve as versatile building blocks for functional materials.[2] For this reason, the development of a novel synthetic methodology to this class of N-containing heterocycles still remains highly active.[3,4] Recently, an increasing number of studies have demonstrated the use of 2-alkynyl arylazides as efficient substrates in gold-catalyzed indole formation strategies.[5] In our continuing studies on gold-catalyzed tandem reactions,[6] we recently reported an efficient and convenient synthetic method to 1*H*-indol-3-yl esters *via* gold-catalyzed tandem reactions of 2-alkynyl arylazides with carboxylic acids (Scheme 1a).[7] Based on these earlier studies, we reasoned 1-azido-2-(phenylethynyl)benzene **1a** might also undergo a similar intermolecular trapping of putative α-imino



Scheme 1 Our design for indole synthesis.

Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	*T* (°C)	*t* (h)	Yield[b] (%)
1	*t*BuXPhosAuNTf$_2$	60	1	95
2	PPh$_3$AuNTf$_2$	60	1	92
3	XPhosAuNTf$_2$	60	1	93
4	IPrAuNTf$_2$	60	1	86
5	AuCl$_3$	60	1	—[c]
6	JohnPhosAuCl	60	1	n.r.[d]
7	AgNTf$_2$	60	1	n.r.[d]
8	—[e]	60	1	n.r.[d]
9	PPh$_3$AuNTf$_2$	r.t.	24	59
10	PPh$_3$AuNTf$_2$	80	1	71
11	*t*BuXPhosAuNTf$_2$	60	1	—[c,f]
12	*t*BuXPhosAuNTf$_2$	60	1	61[g]
13	*t*BuXPhosAuNTf$_2$	60	4	n.r.[d,h]
14	*t*BuXPhosAuNTf$_2$	60	1	—[c,i]

[a] Unless stated otherwise, all reactions were performed in 0.5 mL 1,4-dioxane with a catalyst/**1a**/MsOH ratio of 0.02 : 1 : 3. [b] Isolated yield. [c] Mixture of unknown side products afforded based on ^{1}H NMR analysis of the crude mixture. [d] No reaction was observed. Only starting material left. [e] Reaction conducted without catalyst. [f] Reaction conducted without MsOH. [g] *p*-TsOH·H$_2$O used as acid additive. [h] TFA used as acid additive. [i] TfOH used as acid additive.

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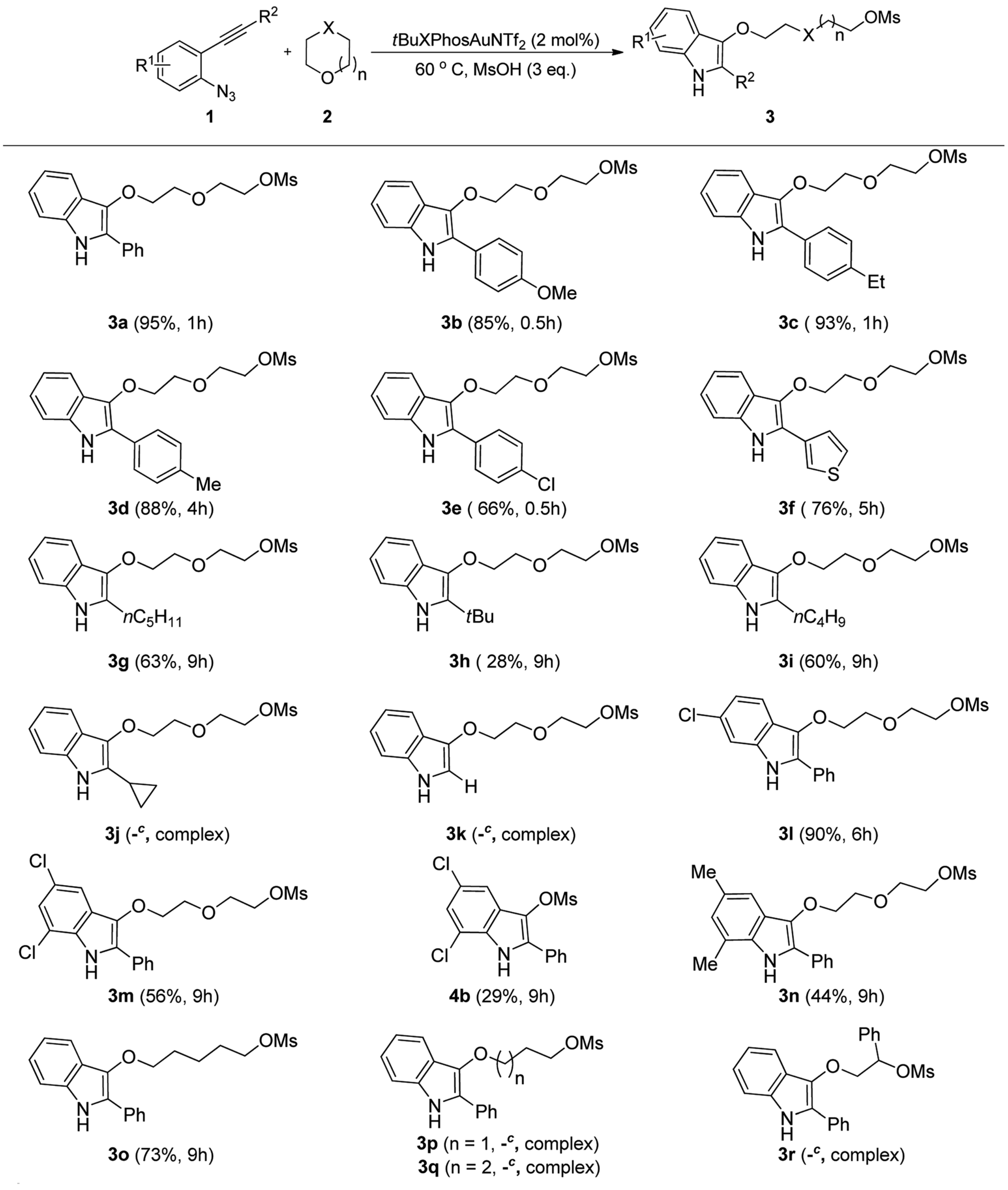
Table 2 Gold-catalyzed ring-opening reactions of 2-alkynyl arylazides **1** with **2**[a,b]



1 **2** **3**

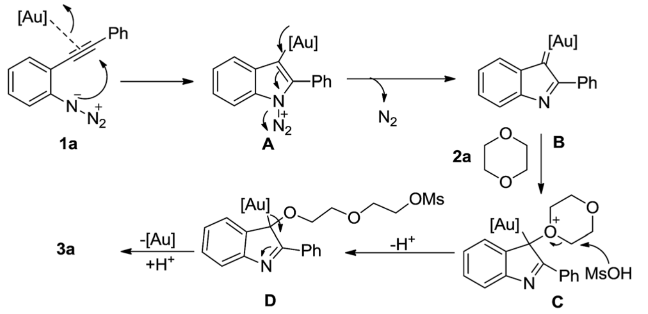
3a (95%, 1h)
3b (85%, 0.5h)
3c (93%, 1h)
3d (88%, 4h)
3e (66%, 0.5h)
3f (76%, 5h)
3g (63%, 9h)
3h (28%, 9h)
3i (60%, 9h)
3j (-[c], complex)
3k (-[c], complex)
3l (90%, 6h)
3m (56%, 9h)
4b (29%, 9h)
3n (44%, 9h)
3o (73%, 9h)
3p (n = 1, -[c], complex)
3q (n = 2, -[c], complex)
3r (-[c], complex)

[a] Unless stated otherwise, all reactions were performed at 60 °C in 0.5 mL 1,4-dioxane with a catalyst/**1**/MsOH ratio of 0.02 : 1 : 3. [b] Values noted in parentheses denote isolated product yields and reaction times. [c] Unknown compounds based on ^{1}H NMR spectroscopic analysis of the crude mixture.

gold carbene species[5,8,9] generarated *in situ* by methanesulfonic acid. We anticipated the desired 2-phenyl-1*H*-indol-3-yl methanesulfonate **4a** would be afforded under the similar gold-catalyzed reaction conditions, which could be a potential aryl mesylate cross-coupling reagent.[10] In this reaction, 1,4-dioxane was used as solvent to dilute the methanesulfonic acid due to its highly activity. To our surprising, we did not detect the desired product **4a** by analyzing the TLC and crud ^{1}H NMR spectrum. However, only the unexpected ring-opening product 2-(2-((2-phenyl-1*H*-indol-3-yl)oxy)ethoxy)ethyl methanesulfonate **3a** was obtained in 95% yield (Scheme 1b).[11] Herein, we disclose the details of this efficient gold-catalyzed ring-opening reactions of 2-alkynyl arylazides with oxygen-containing heterocycles in the presence of methanesulfonic acid for the synthesis of novel indole derivatives.

Initially, we chose to focus our attention on ring-opening reaction of 1-azido-2-(phenylethynyl)benzene **1a** and 1,4-dioxane in the presence of 3 equivalents of methanesulfonic acid by a variety of gold catalysts to establish the reaction conditions (Table 1). This revealed treating a solution of reaction containing **1a** (1 equiv.) and **2a** (0.5 mL) with 2 mol% *t*BuXPhosAuNTf$_2$ in the presence of 3 equivalents of MsOH at 60 °C for 1 h gave the best result (entry 1). Under these conditions, 2-(2-((2-phenyl-1*H*-indol-3-yl)oxy)ethoxy)ethyl methanesulfonate **3a** was obtained in 95% yield. On the other hand, a slightly lower product yields were observed when the gold catalyst was changed from *t*BuXPhosAuNTf$_2$ to PPh$_3$AuNTf$_2$, XPhosAuNTf$_2$ and IPrAuNTf$_2$ (entries 2–4). In contrast, the use of AuCl$_3$ as the catalyst led to a mixture of side products that could not be identified by ^{1}H NMR analysis (entry 5). Notably, only the starting material was recovered when JohnPhosAuCl or AgNTf$_2$ used as catalyst (entries 6–7). Similar result was obtained when this reaction was repeated in the absence of any gold catalyst (entry 8). The reaction temperature was also checked. High or low temperature led to a markedly lower yields of 59–71% (entries 9–10). Additional control experiment without MsOH led to a mixture of unknown products that could not be identified by TLC and ^{1}H NMR analysis (entry 11). In contrast, other acid additives were also examined. The corresponding product 2-(2-((2-phenyl-1*H*-indol-3-yl)oxy)ethoxy)ethyl 4-methylbenzenesulfonate **5** was obtained in 61% yield where the MsOH was replaced with *p*-TsOH·H$_2$O as the acid additive (entry 12). However, either no reaction or a mixture of unknown compounds were observed when TFA or TfOH was used as acid additive (entries 13–14).

To define the scope of the present procedure, we next turned our attentions to the reactions of a variety of 2-alkynyl arylazides **1** with oxygen-containing heterocycles **2** (Table 2). These experiments showed that with *t*BuXPhosAuNTf$_2$, 2-alkynyl arylazides bearing *para*-substituted electron-donating or electron-withdrawing substituents on the phenyl ring or thienyl group **1b–f** efficiently underwent the tandem ring-opening process and gave the corresponding products **3b–f** in good to excellent yields. We also tested the effect of an aliphatic substituent on the alkyne carbon and found that, for substrates where R^2 = *n*C$_5$H$_{11}$ or *n*C$_4$H$_9$, lower yields 63% and 60% were obtained for **3g** and **3i**, respectively. Under the standard reaction conditions, the desired ring-opening indole 3 h was also provided with the sterically hindered substrate 1 h However, the substrate with cyclopropyl group **1j** or terminal alkyne moiety **1k** only gave a mixture of unknown side products that could not be identified by TLC and ^{1}H NMR analysis. Next, arylazides with Cl or Me group on the phenyl ring **3l–n** also can provide the desired indole derivatives in moderate to excellent yields. Notably, the 5,7-dichloro-2-phenyl-1*H*-indol-3-yl methanesulfonate **4b** was obtained in 29% yield as a side product when the substrate with disubstituted group on the aromatic ring was employed. Next, other oxygen-containing heterocycles were also examined under the optimal reaction conditions. When dioxane was changed to tetrahydro-2*H*-pyran, we found that the corresponding ring-opening indole product **3o** was afforded in 73% yield. Very interesting, the reaction of **1a** with oxetane **2c**, tetrahydrofuran **2d**, or 2-phenyloxirane **2e** only gave a mixture of unknown side products that could not be identified by TLC and ^{1}H NMR analysis.



Scheme 2 Proposed mechanism for the formation of **3a**.

We tentatively propose the present *t*BuXPhosAuNTf$_2$ catalyzed ring-opening indole-forming reaction to proceed by the mechanism outlined in Scheme 2, although it is highly speculative. This could involve activation of 1-azido-2-(phenylethynyl)benzene **1a** through coordination of the gold catalyst with the alkyne, which would be attacked by the azide to deliver intermediate **A**. Subsequently, the α-imino gold carbene **B** was formed after the expulsion of N$_2$ with the assist of gold catalyst, which was further attacked by 1,4-dioxane to release the intermediate **C**. Ring opening of **C** with methanesulfonic acid would provide the complex **D**, which undergo a final protodemetalation step to deliver the 2-(2-((2-phenyl-1*H*-indol-3-yl)oxy)ethoxy)ethyl methanesulfonate **3a**.

In summary, an unexpected gold-catalyzed synthetic method to indole derivatives based on the ring-opening reaction of 2-alkynyl arylazides with oxygen-containing heterocycles in the presence of methanesulfonic acid has been reported. These results show that the reaction tolerates a structurally diverse set of 2-alkynyl arylazides substrates that can be prepared easily in two steps from commercially available materials. Moreover, the gold-catalyzed tandem reactions were also shown to be practical since inert and moisture-free conditions were not required. Further studies on the applications of this synthetic method are currently underway in our laboratory.

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Program Development of Jiangsu Higher Education Institutions (PAPD).

Notes and references

1 (*a*) X.-H. Cai, Z.-Z. Du and X.-D. Luo, *Org. Lett.*, 2007, **9**, 1817; (*b*) X.-H. Cai, Q.-G. Tan, Y.-P. Liu, T. Feng, Z.-Z. Du, W.-Q. Li and X.-D. Luo, *Org. Lett.*, 2008, **10**, 577; (*c*) T. Feng, X.-H. Cai, P.-J. Zhao, Z.-Z. Du, W.-Q. Li and X.-D. Luo, *Planta Med.*, 2009, **75**, 1537; (*d*) X.-H. Cai, Y.-P. Liu, T. Feng and X.-D. Luo, *Chin. J. Nat. Med.*, 2008, **6**, 20; (*e*) X.-H. Cai, J.-H. Shang, T. Feng, X.-D. Z. Naturforsch and B. J. Luo, *Chem. Sci.*, 2010, **65**, 1164; (*f*) X.-J. Qin, Y.-L. Zhao, P.-K. Lunga, X.-W. Yang, C.-W. Song, G.-G. Cheng, L. Liu, Y.-Y. Chen, Y.-P. Liu and X.-D. Luo, *Tetrahedron*, 2015, **71**, 4372; (*g*) L. Liu, Y.-Y. Chen, X.-J. Qin, B. Wang, Q. Jin, Y.-P. Liu and X.-D. Luo, *Fitoterapia*, 2015, **105**, 160; (*h*) X.-J. Qin, Y.-L. Zhao, C.-W. Song, B. Wang, Y.-Y. Chen, L. Liu, Q. Li, D. Li, Y.-P. Liu and X.-D. Luo, *Nat. Prod. Bioprospect.*, 2015, **5**, 185; (*i*) H. Zhou, H.-P. He, X.-D. Luo, Y.-H. Wang, X.-W. Yang, Y.-T. Di and X.-J. Hao, *Helv. Chim. Acta*, 2005, **88**, 2508; (*j*) L. Zhang, *Acc. Chem. Res.*, 2014, **47**, 877; (*k*) A. S. K. Hashmi, *Acc. Chem. Res.*, 2014, **47**, 864; (*l*) C. Obradors and A. M. Echavarren, *Chem. Commun.*, 2014, **50**, 16; (*m*) J. Xiao and X. Li, *Angew. Chem., Int. Ed.*, 2011, **50**, 7226; (*n*) A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2010, **49**, 5232.

2 G. Nie, Z. Bai, J. Chen and W. Yu, *ACS Macro Lett.*, 2012, **1**, 1304.

3 For recent reviews on the synthesis of indoles, see: (*a*) S. Cacchi and G. Fabrizi, *Chem. Rev.*, 2011, **111**, 215; (*b*) R. Vicente, *Org. Biomol. Chem.*, 2011, **9**, 6469; (*c*) S. Cacchi, G. Fabrizi and A. Goggiamani, *Org. Biomol. Chem.*, 2011, **9**, 641; (*d*) M. Bandini and A. Eichholzer, *Angew. Chem., Int. Ed.*, 2009, **48**, 9608; (*e*) I. V. Seregin and V. Gevorgyan, *Chem. Soc. Rev.*, 2007, **36**, 1173; (*f*) G. R. Humphrey and J. T. Kuethe, *Chem. Rev.*, 2006, **106**, 2875; (*g*) S. Cacchi and G. Fabrizi, *Chem. Rev.*, 2005, **105**, 2873; (*h*) G. Zeni and R. C. Larock, *Chem. Rev.*, 2004, **104**, 2285; (*i*) G. Balme, D. Bouyssi, T. Lomberget and N. Monteiro, *Synthesis*, 2003, 2115.

4 For recent selected examples on the synthesis of indoles, see: (*a*) J. Barluenga, F. Rodríguez and F. J. Fańanás, *Chem.–Asian J.*, 2009, **4**, 1036; (*b*) O. Miyata, N. Takeda and T. Naito, *Heterocycles*, 2009, **78**, 843; (*c*) K. Krüger, A. Tillack and M. Beller, *Adv. Synth. Catal.*, 2008, **350**, 2153.

5 (*a*) N. Li, T.-Y. Wang, L.-Z. Gong and L. Zhang, *Chem.–Eur. J.*, 2015, **21**, 1; (*b*) B. Lu, Y. Luo, L. Liu, L. Ye, Y. Wang and L. Zhang, *Angew. Chem., Int. Ed.*, 2011, **50**, 8358.

6 For our recent studies on the gold-catalyzed tandem reactions, see: (*a*) W. Rao, D. Susanti, B. J. Ayers and P. W. H. Chan, *J. Am. Chem. Soc.*, 2015, **137**, 6350; (*b*) W. Rao, M. J. Koh, D. Li, H. Hirao and P. W. H. Chan, *J. Am. Chem. Soc.*, 2013, **135**, 7926; (*c*) W. Rao, Sally, M. J. Koh and P. W. H. Chan, *J. Org. Chem.*, 2013, **78**, 3183; (*d*) W. Rao, M. J. Koh, P. Kothandaraman and P. W. H. Chan, *J. Am. Chem. Soc.*, 2012, **134**, 10811; (*e*) W. Rao, D. Susanti and P. W. H. Chan, *J. Am. Chem. Soc.*, 2011, **133**, 15248.

7 X. Zhang, X. Sun, H. Zhang, X. Cui and M. Ma, *Chin. J. Inorg. Chem.*, 2015, **35**, 1469.

8 For recent selected reviews on the generation of gold carbenes, see: (*a*) R. Dorel and A. M. Echavarren, *Chem. Rev.*, 2015, **115**, 9028; (*b*) D. Qian and J. Zhang, *Chem. Soc. Rev.*, 2015, **44**, 677; (*c*) Y. Wang, M. E. Muratore and A. M. Echavarren, *Chem.–Eur. J.*, 2015, **21**, 7332; (*d*) F. Wei, C. Song, Y. Ma, L. Zhou, C.-H. Tung and Z. Xu, *Sci. Bull.*, 2015, **60**, 1479; (*e*) H.-S. Yeom and S. Shin, *Acc. Chem. Res.*, 2014, **47**, 966; (*f*) L. Fensterbank and M. Malacria, *Acc. Chem. Res.*, 2014, **47**, 953; (*g*) C. Obradors and A. M. Echavarren, *Acc. Chem. Res.*, 2014, **47**, 902.

9 For recent selected a review on the generation of α-imino gold carbenes, see: P. W. Davies and M. Garzûn, *Asian J. Org. Chem.*, 2015, **4**, 694; for recent selected examples, see: **5a**, **5b** and (*a*) Y. Pan, G.-W. Chen, C.-H. Shen, W. He and L.-W. Ye, *Org. Chem. Front.*, 2016, **3**, 491; (*b*) H. Jin, L. Huang, J. Xie, M. Rudolph, F. Rominger and A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2016, **55**, 794; (*c*) 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; (*d*) 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; (*e*) L. Zhu, Y. Yu, Z. Mao and X. Huang, *Org. Lett.*, 2015, **17**, 30; (*f*) S. K. Pawar, R. L. Sahani and R.-S. Liu, *Chem.–Eur. J.*, 2015, **21**, 10843; (*g*) A. Prechter, G. Henrion, P. F. dit Bel and F. Gagosz, *Angew. Chem., Int. Ed.*, 2014, **53**, 4959; (*h*) M. Garzón and P. W. Davies, *Org. Lett.*, 2014, **16**, 4850; (*i*) Y. Tokimizu, S. Oishi, N. Fujii and H. Ohno, *Org. Lett.*, 2014, **16**, 3138; (*j*) E. Chatzopoulou and P. W. Davies, *Chem. Commun.*, 2013, **49**, 8617; (*k*) Z.-Y. Yan, Y. Xiao and L. Zhang, *Angew. Chem., Int. Ed.*, 2012, **51**, 8624; (*l*) Y. Xiao and L. Zhang, *Org. Lett.*, 2012, **14**, 4662; (*m*) P. W. Davies, A. Cremonesand and L. Dumitrescu, *Angew. Chem., Int. Ed.*, 2011, **50**, 8931; (*n*) A. Wetzel and F. Gagosz, *Angew. Chem., Int. Ed.*, 2011, **50**, 7354; (*o*) C. Li and L. Zhang, *Org. Lett.*, 2011, **13**, 1738; (*p*) D. J. Gorin, N. R. Davis and F. D. Toste, *J. Am. Chem. Soc.*, 2005, **127**, 11260.

10 (*a*) C. F. Wai, M. S. Chau and Y. K. Fuk, *Org. Lett.*, 2015, **17**, 5906; (*b*) C. M. So and F. Y. Kwong, *Chem. Soc. Rev.*, 2011, **40**, 4963; (*c*) S. I. Kozhushkov, H. K. Potukuchi and L. Ackermann, *Catal. Sci. Technol.*, 2013, **3**, 562; (*d*) M. C. Wilkinson, *Org. Lett.*, 2011, **13**, 2232; (*e*) G. A. Molander and I. Shin, *Org. Lett.*, 2012, **14**, 3138.

11 For a gold-catalyzed ring-opening reaction of tetrahydrofuran, see: W. Huang, J. Xiang and W. He, *Chem. Lett.*, 2014, **43**, 893.