Organic & Biomolecular Chemistry

COMMUNICATION

View Article Online
View Journal | View Issue





Cite this: *Org. Biomol. Chem.*, 2018, **16**, 9147

Received 17th October 2018,
Accepted 14th November 2018

DOI: 10.1039/c8ob02582g

rsc.li/obc

# A gold-catalyzed cycloisomerization/aerobic oxidation cascade strategy for 2-aryl indenones from 1,5-enynes†

Jia Guo,‡[a,b] Xiaoshi Peng,‡[a,b] Xiaoyu Wang,[a,b] Fukai Xie,[a,b,c] Xinhang Zhang,[a,b,c] Guoduan Liang,[a,b,c] Zenghui Sun,[a,b,c] Yongxiang Liu,[a,b,c] Maosheng Cheng[a,b] and Yang Liu *[a]

**A unique gold(I)-catalyzed 5-*endo*-dig cyclization/aerobic oxidation cascade strategy from 1,5-enyne substrates with molecular oxygen as the oxidant to yield the indenone was described. The reaction mechanism was studied by heavy atom labelling and some related experiments. This method was applied to the formal total synthesis of isoprekinamycin.**

Indenones or their corresponding reductive derivatives indanones are important carbocycles that serve as valuable skeletons in many biologically active compounds and synthetic drugs,[1] such as donepezil, mukagolactone, indacrinone, MJ-II-38, pauciflorol F and isoprekinamycin (Fig. 1). Furthermore, indenone derivatives are useful synthetic precursors to steroids and some drugs.[2] Therefore, the preparation of indenones has received considerable attention. Different metal-catalyzed routes for efficient preparation of indenones from various starting materials have been developed in the past decades.[3] Recently, Hashmi and co-workers developed a gold-catalyzed unprecedented oxidative cyclization of diynes to give this type of product.[4]

Gold-catalyzed cycloisomerization of 1,5- and 1,6-enynes is one of the most important strategies for forming functionalized carbocyclic frameworks.[5] However, in the presence of organic oxidants, most enynes failed to produce oxidative products. Recently a new type of gold(I)-catalyzed oxidative cyclization of 1,5-enynes to indanones and indenes mediated by 8-methylquinoline *N*-oxide was discovered by Liu's group.[6] As an ideal oxidant in transition metal-catalyzed oxidation, dioxygen had drawn much attention,[7] and the range of transition-metal catalysts compatible with aerobic oxidation were extended to gold. Recently some exciting breakthroughs in the combination of gold catalysts and dioxygen have been discovered, such as the oxidation of vinyl–gold complexes into aldehydes by synergistic Au/Fe catalysts and dioxygen,[8] the autoxidation of electron-rich alkenes into aldehydes by gold(I) catalysts and dioxygen[9] and the reaction of Au-bound cationic bicyclo[3.2.0]-heptane with a triplet oxygen to form a metalloradical through a single electron transfer from Au(I) to $O_2$.[10]

During the course of our research in developing a gold-catalyzed cascade cyclization strategy to carbocycles,[11] we observed different cyclization paths of the substituted 1,5-enynes with an electron-rich enol ether. In previous studies, we disclosed a gold(I)-catalyzed alkyne alkoxylation/tandem cyclization strategy of 1,5-enynes to afford naphthalenes.[11a] Herein, we report a distinct pathway of the same 1,5-enynes to produce indenones *via* a gold-catalyzed 5-*endo*-dig cyclization/aerobic oxidation cascade strategy (Scheme 1).

We tested our proposal as shown in Scheme 1 by subjecting 1,5-enyne substrate **1** (Table 1) with $Ph_3PAuCl/AgBF_4$ in toluene under an $N_2$ atmosphere. The 5-*endo*-dig cyclization product **2** could be isolated with excellent yield. Then indene **2** was exposed to air to observe the oxidation. To our delight,

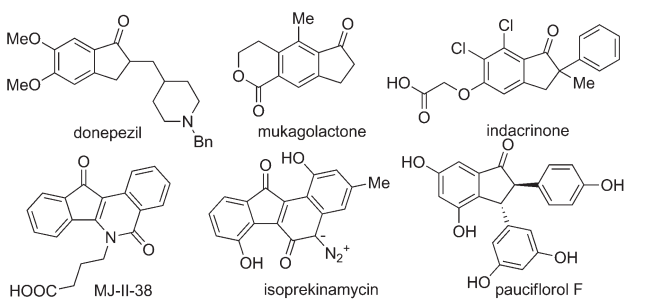
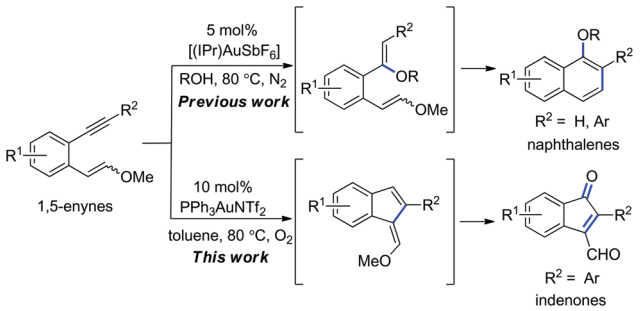



**Fig. 1** Indenone and indanone-containing biologically active molecules and drugs.

[a]*Key Laboratory of Structure-Based Drug Design and Discovery (Shenyang Pharmaceutical University), Ministry of Education, Shenyang 110016, P. R. China. E-mail: yongxiang.liu@syphu.edu.cn, mscheng@syphu.edu.cn*
[b]*Institute of Drug Research in Medicine Capital of China, Benxi, 117000, P. R. China*
[c]*Wuya College of Innovation, Shenyang Pharmaceutical University, Shenyang 110016, P. R. China*

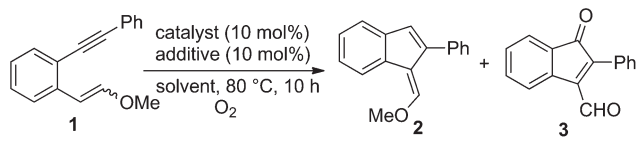
†Electronic supplementary information (ESI) available: Detailed condition screening, experimental procedures and spectra. CCDC 1451285. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8ob02582g

‡These authors contributed equally.




**Scheme 1** Competitive cyclization paths of 1,5-enynes.

**Table 1** The screening of reaction conditions



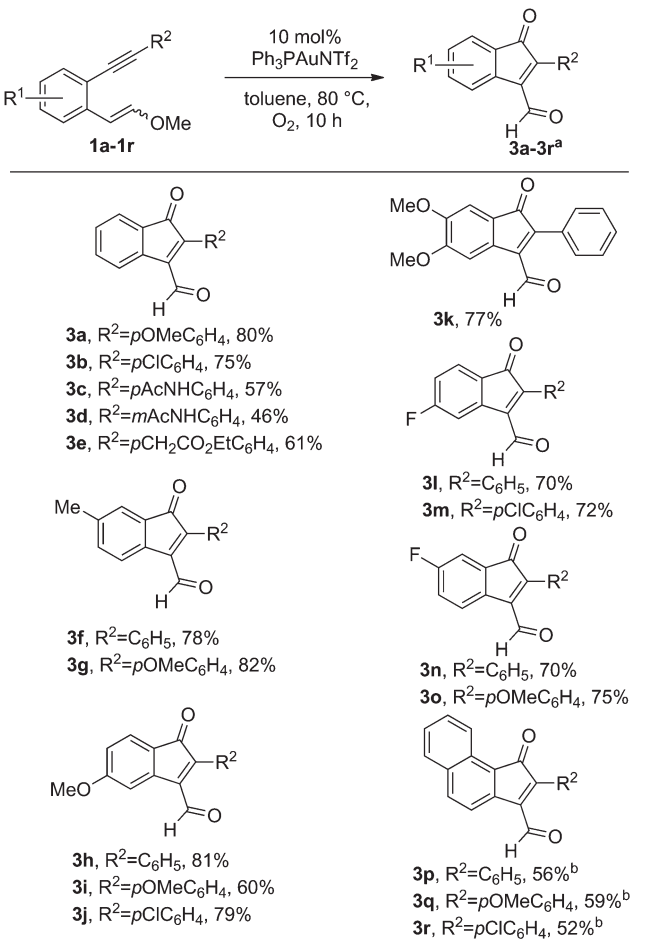

| Entry | Catalyst | Additive | Solvent | Yield[a] (%) |
|---|---|---|---|---|
| 1 | $Ph_3PAuBF_4$ | — | Dioxane | **2** (65) |
| 2 | $Ph_3PAuBF_4$ | — | DCE | **2** (80) |
| 3 | $Ph_3PAuBF_4$ | — | THF | **2** (86) |
| 4 | $Ph_3PAuBF_4$ | — | Toluene | **3** (65) |
| 5 | $Ph_3PAuCl$ | — | Toluene | — |
| 6 | $Ph_3PAuCl$ | $AgSbF_6$ | Toluene | **3** (51) |
| 7 | $Ph_3PAuCl$ | AgOTf | Toluene | **3** (60) |
| **8** | **$Ph_3PAuNTf_2$** | — | **Toluene** | **3 (75)** |
| 9 | [(IPr)AuCl] | $AgNTf_2$ | Toluene | **3** (72) |
| 10 | $Ph_3PAuNTf_2$ | — | Toluene | **3** (55)[b] |
| 11 | $HAuCl_4$ | — | Toluene | **2** (10) |
| 12 | $HNTf_2$ | — | Toluene | **3** (15) |

[a] Average isolated yield of at least two runs. [b] Performed with 5 mol% $Ph_3PAuNTf_2$.

indenone **3** was detected in 30% yield with 60% of indene **2** remaining after one week.

In order to improve the yield of indenone **3**, we performed an intensive screening of optimal conditions to realize these two transformations in one pot (Table 1). First we set about investigating solvent effects. Among the tested solvents, only toluene allowed for the formation of indenone **3**. The rest of the solvents would result in indene **2** in high yield even under an $O_2$ atmosphere (Table 1, entries 1–4). The influences of counterions on the catalyst were examined by combining $Ph_3PAuCl$ with several silver salts or using commercially available catalysts (Table 1, entries 5–8) and $Ph_3PAuNTf_2$ afforded the best yield. Then a screening of different ligands at the Au-center was carried out. Interestingly, a slight decrease in yield was observed when mixing [(IPr)AuCl] with silver salts resulting in the discovery that the combination of the [(IPr)AuCl] precatalyst [IPr = 1,3-bis(diisopropylphenyl)imidazole-2-ylidene] (10 mol%) and silver trifluoromethanesulfonate (10 mol%) was almost the same as $Ph_3PAuNTf_2$, yielding the product in 72% isolated yield (Table 1, entry 9). Decreasing the catalyst loading to 5 mol% reduced the yield by 20% (Table 1, entry 10). $HAuCl_4$ could catalyze the cascade cyclization with a yield of 10%, which was very messy (Table 1, entry 11). In order to exclude the possibility that a trace amount of acid catalyzed the reactions, the same amount of $HNTf_2$ itself was tested and a smaller amount of product **3** was produced with a messy reaction profile (Table 1, entry 12).

Next the scope of the transformation was investigated under the optimized conditions (Scheme 2). The reaction with the substrates bearing both electron-donating and withdrawing groups on both aryl rings proceeded smoothly in moderate to good yields (Scheme 2, **3a–3o**). However, naphthalene-containing products could only be obtained with lower yields (Scheme 2, **3p–3r**). Terminal alkyne and alkyl and silyl substituted alkyne substrates could not participate in this reaction under the standard conditions. Interestingly, Liu and coworkers reported a copper-catalyzed oxidative cyclization of 1,5-enynes and C–C bond cleavage to generate 3-formyl-1-indenones,[3f] whose structures were similar to our products. The structures of our products were determined by comparing our products with these reported compounds and further confirmed by a single crystal X-ray diffraction of **3l** (Fig. 2).




**Scheme 2** Scope of gold-catalyzed cascade cyclization. [a] Isolated yields. [b] Performed for 20 h.

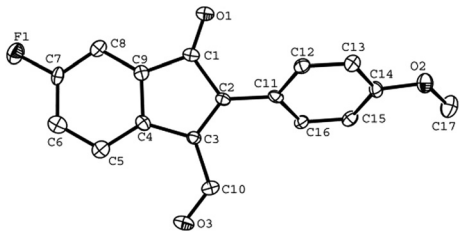
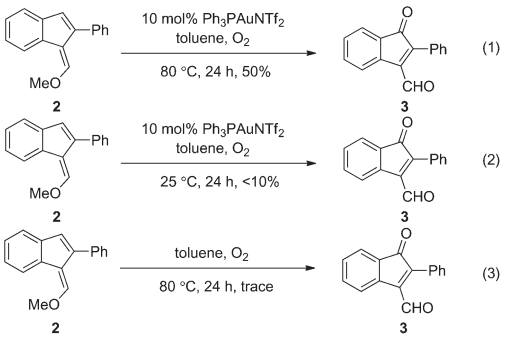



Fig. 2 Single crystal X-ray diffraction of **3o**.

To investigate the source of O atoms in carbonyl groups, we performed the reaction in the presence of $^{18}O_2$ or $^{18}O_2/H_2O$,[12] employing **1i** as a substrate (Scheme 3). Interestingly, the products **3i-1** (89%) and **3i-2** (11%) were detected under an $^{18}O_2$ atmosphere assisted with LC-MS. A control experiment by subjecting the isolated intermediate **2i** to the standard conditions under an $^{18}O_2$ atmosphere resulting in the isolation of the products **3i-1** and **3i-2** ruled out the possibility of incorporation of the $^{18}O$ into an aldehyde after cycloisomerization. However, in the presence of $^{18}O_2/H_2O$ or $H_2O$, no $^{18}O$ atom was incorporated into the product, and only the product **4i** derived from the hydrolysis and isomerization of the corresponding cycloisomerization product was isolated. However, **4i** could not be transformed into the desired product **3i** under the standard conditions. These results suggested that the ketone group in **3i** was not derived from the oxidation of the benzylic C–H bond of **4i**.

To gain more insight into the reaction mechanism, the isolated indene intermediate **2** in the screening of conditions was subjected to the optimal conditions and the isolation of indenone **3** indicated that the indene **2** was possibly the key intermediate in the transformation (Scheme 4, eqn (1)). A decrease in the temperature to 25 °C would result in lower yield (Scheme 4, eqn (2)) and the control experiment without gold was also performed, whose results verified the significance of

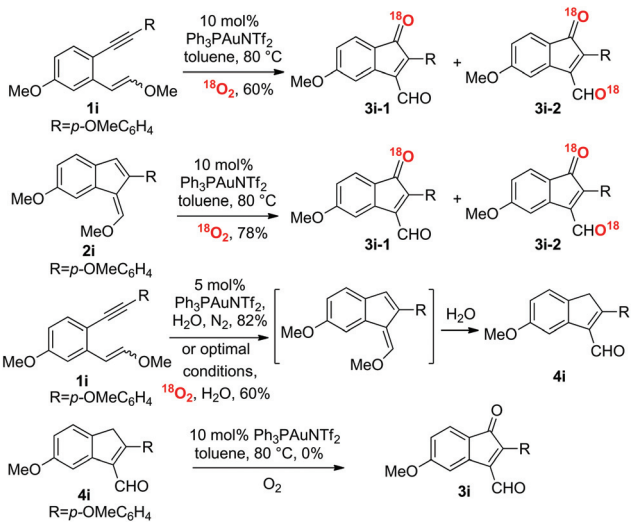



Scheme 4 Control experiments using indene intermediate **2**.

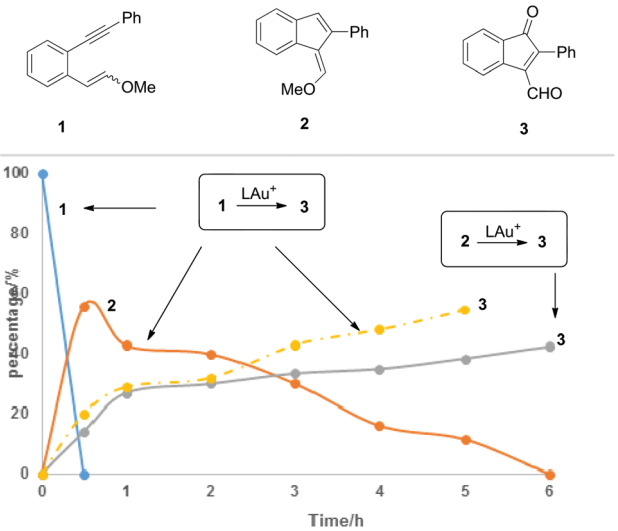
the catalyst in the oxidation step, which was consistent with the first attempt at the very beginning (Scheme 4, eqn (3)).

To confirm that indene **2** was the true intermediate of the oxidation, the reaction kinetic profiles under various conditions were performed as shown in Scheme 5. A very faster rate from substrate **1** to indene **2** was observed, which indicated that indene **2** could be generated easily under the reaction conditions. In the transformation from substrate **1** to indenone **3**, it was found that the yield of product **3** would increase gradually accompanied by the slow consumption of indene **2**. And the similar kinetic profiles observed from the oxidations of **1** to **3** and **2** to **3** strongly supported that indene **2** should be the active intermediate in the oxidation process.

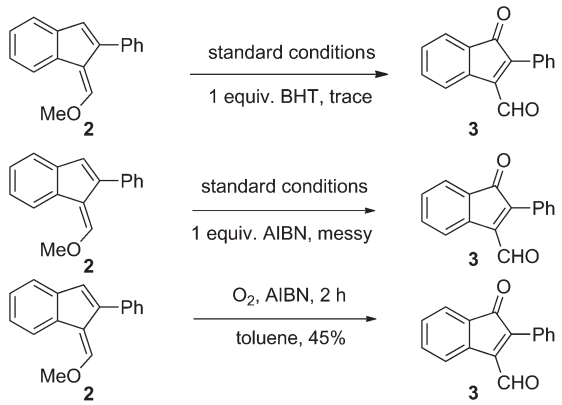
According to the precedent study, a radical mechanism may be involved in this transformation.[8–10] The verification experiments using the radical inhibitor butylated hydroxytoluene (BHT) are summarized in Scheme 6. The formation of indenone **3** from indene **2** was completely blocked in the presence of 1 equivalent amount of BHT. However, the treatment of intermediate **2** with the combination of a gold catalyst and the radical initiator azodiisobutyronitrile (AIBN) gave a messy reac-




Scheme 3 Control experiments under an $^{18}O_2$ atmosphere.



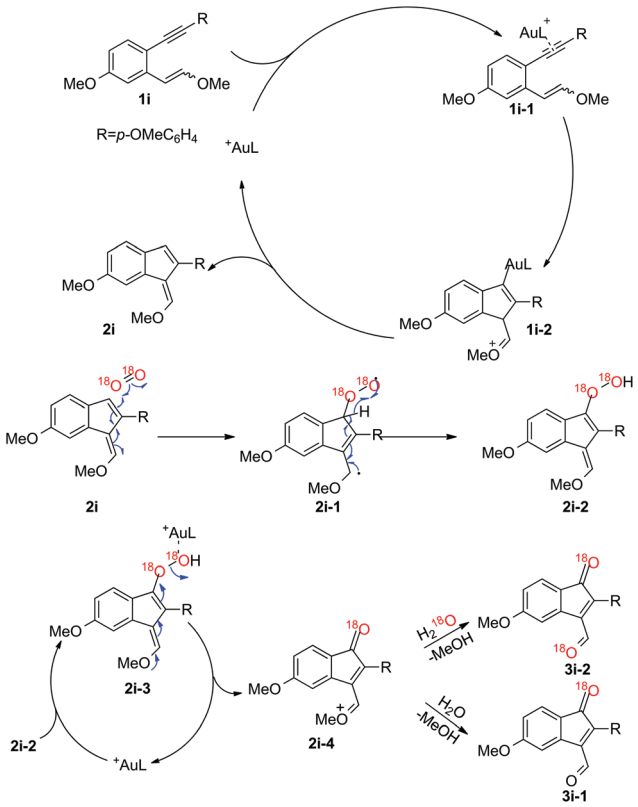

Scheme 5 Reaction kinetic profiles under various conditions.



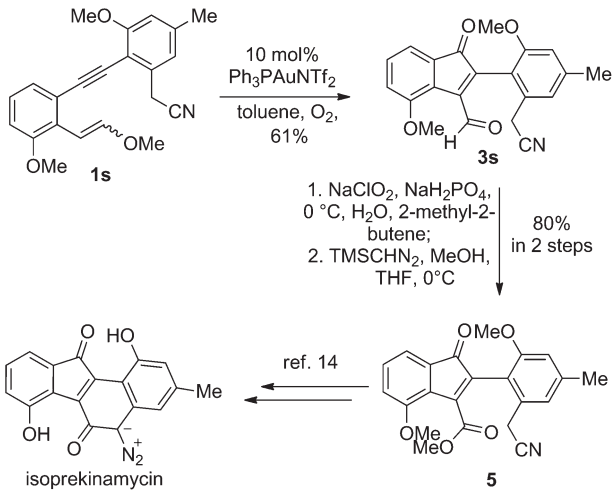

Scheme 6 Radical verification experiments.

tion profile. It indicated that the gold catalyst and radical conditions were incompatible, which had been described in the precedent literature.[8] Then a following experiment by treating the substrate **2** with AIBN itself and $O_2$ led to the generation of the desired product **3** in a much shorter time. These results suggested that the oxidation by $O_2$ might happen *via* some radical intermediates.[13]

Based on the experimental results, a plausible mechanism was proposed as depicted in Scheme 7. Activation of the alkyne in **1i** promoted a 5-*endo*-dig cyclization of enol ether to




Scheme 7 The proposed mechanism.




Scheme 8 The formal total synthesis of isoprekinamycin.

produce the indene **2i** after protodeauration. A following radical addition of $^{18}O_2$ to intermediate **2i** resulted in the formation of **2i-1**, which underwent an isomerization to give **2i-2**. Coordination of cationic Au species with the oxygen atom initiated the cleavage of the $^{18}O$–$^{18}O$ bond to provide the oxonium intermediate **2i-3**, which could be captured by $H_2{}^{18}O$ or $H_2O$ to generate the indenone **3i-1** or **3i-2** after removing the methoxyl group.

Significantly, the assembly of highly functionalized indenones with this unique method allowed the rapid preparation of structurally diverse molecules by functional group manipulations. In order to expand the utility of this method further, isoprekinamycin, a cytotoxic benzo[*a*]fluorene natural product was chosen as our target. Retrosynthetically, isoprekinamycin could be disconnected into indenone intermediate **5**, which was the key intermediate in Dmitrienko's total synthesis of this molecule.[14] Our synthesis started from gold(I)-catalyzed tandem cyclization reaction of **1s** to give indenone **3s** in 61% yield under the optimal conditions. The transformation from **3s** to ester **5** by Pinnick oxidation and esterification achieved the formal total synthesis of isoprekinamycin by providing the Dmitrienko's key intermediate (Scheme 8).

In summary, we have developed a unique strategy for the synthesis of indenones by a gold(I)-catalyzed cyclization/aerobic oxidation cascade reaction from simple aryl 1,5-enyne substrates. The possible mechanism was probed based on heavy isotope labelling and a series of control experiments. The application of this method to the formal total synthesis of isoprekinamycin was achieved. Notably, molecular oxygen, the most environmentally friendly oxidant, was employed combined with a gold catalyst to provide indenone scaffolds in a single step from acyclic precursors.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

Financial support for this research was provided by the Natural Science Foundation of Liaoning Province of China (Grants 20170540855) and the Liaoning Province Education Administration of China (Grants 2017LQN08 & LR2017043). We thanked the program for innovative research team of the Ministry of Education and program for Liaoning innovative research team in university.

## Notes and references

1 (*a*) B. A. Brooks, A. F. Lant, W. R. McNabb and F. H. Noormohamed, *Br. J. Clin. Pharmacol.*, 1984, **17**, 497; (*b*) R. S. Laufer and G. I. Dmitrienko, *J. Am. Chem. Soc.*, 2002, **124**, 1854; (*c*) B. L. Staker, M. D. Feese, M. Cushman, Y. Pommier, D. Zembower, L. Stewart and A. B. Burgin, *J. Med. Chem.*, 2005, **48**, 2336; (*d*) R. S. Senaiar, J. A. Teske, D. D. Young and A. Deiters, *J. Org. Chem.*, 2007, **72**, 7801; (*e*) Z. Luo, J. Sheng, Y. Sun, C. Lu, J. Yan, A. Liu, H. Luo, L. Huang and X. Li, *J. Med. Chem.*, 2013, **56**, 9089; (*f*) D. J. Kerr, M. Miletic, N. Manchala, J. M. White and B. L. Flynn, *Org. Lett.*, 2013, **15**, 4118.

2 (*a*) J. P. Scott, M. S. Ashwood, K. M. J. Brands, S. E. Brewer, C. J. Cowden, U. Dolling, K. M. Emerson, A. D. Gibb, A. Goodyear, S. F. Oliver, G. W. Stewart and D. J. Wallace, *Org. Process Res. Dev.*, 2008, **12**, 723; (*b*) J. T. Mohr, M. R. Krout and B. M. Stoltz, *Nature*, 2008, **455**, 323.

3 (*a*) T. Miura and M. Murakami, *Org. Lett.*, 2005, **7**, 3339; (*b*) P. A. Wender, T. J. Paxton and T. J. Williams, *J. Am. Chem. Soc.*, 2006, **128**, 14814; (*c*) H. Tsukamoto and Y. Kondo, *Org. Lett.*, 2007, **9**, 4227; (*d*) Y. Harada, J. Nakanishi, H. Fujihara, M. Tobisu, Y. Fukumoto and N. Chatani, *J. Am. Chem. Soc.*, 2007, **129**, 5766; (*e*) Z. Qi, M. Wang and X. Li, *Org. Lett.*, 2013, **15**, 5440; (*f*) J. Zhang, D. Wu, X. Chen, Y. Liu and Z. Xu, *J. Org. Chem.*, 2014, **79**, 4799.

4 P. Nösel, L. N. dos Santos Comprido, T. Lauterbach, M. Rudolph, F. Rominger and A. S. K. Hashmi, *J. Am. Chem. Soc.*, 2013, **135**, 15662.

5 (*a*) A. S. K. Hashmi, T. M. Frost and J. W. Bats, *J. Am. Chem. Soc.*, 2000, **122**, 11553; (*b*) V. Mamane, T. Gress, H. Krause and A. Furstner, *J. Am. Chem. Soc.*, 2004, **126**, 8654; (*c*) M. R. Luzung, J. P. Markham and F. D. Toste, *J. Am. Chem. Soc.*, 2004, **126**, 10858; (*d*) L. M. Zhang and S. A. Kozmin, *J. Am. Chem. Soc.*, 2004, **126**, 11806; (*e*) F. Gagosz, *Org. Lett.*, 2005, **7**, 4129; (*f*) L. M. Zhang and S. A. Kozmin, *J. Am. Chem. Soc.*, 2005, **127**, 6962; (*g*) S. Wang and L. Zhang, *J. Am. Chem. Soc.*, 2006, **128**, 14274; (*h*) A. S. K. Hashmi, *Pure Appl. Chem.*, 2010, **82**, 1517; (*i*) J. Sun, M. P. Conley, L. Zhang and S. A. Kozmin, *J. Am. Chem. Soc.*, 2006, **128**, 9705; (*j*) D. Vasu, H. H. Hung, S. Bhunia, S. A. Gawade, A. Das and R. S. Liu, *Angew. Chem., Int. Ed.*, 2011, **50**, 6911.

6 D. Vasu, H. H. Hung, S. Bhunia, S. A. Gawade, A. Das and R. S. Liu, *Angew. Chem., Int. Ed.*, 2011, **50**, 6911.

7 For selected examples of aerobic oxidation of $sp^2$ C–H bonds, see: (*a*) R. Neumann and M. Dahan, *Nature*, 1997, **388**, 353; (*b*) Y. Ishii, S. Sakaguchi and T. Iwahama, *Adv. Synth. Catal.*, 2001, **343**, 393; (*c*) A. S. K. Hashmi, M. C. Blanco Jaimes, A. M. Schuster and F. Rominger, *J. Org. Chem.*, 2012, **77**, 6394; (*d*) L. Wang, Y. Zhu, J. Wang, F. Liu, J. Huang, X. Meng, J. M. Basset, Y. Han and F. S. Xiao, *Nat. Commun.*, 2015, **6**, 6957; (*e*) A. Gonzalez-de-Castro and J. Xiao, *J. Am. Chem. Soc.*, 2015, **137**, 8206; (*f*) X. Sun, X. Li, S. Song, Y. Zhu, Y. Liang and N. Jiao, *J. Am. Chem. Soc.*, 2015, **137**, 6059; (*g*) A. A. Andia, M. R. Miner and K. A. Woerpel, *Org. Lett.*, 2015, **17**, 2704.

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

9 A. S. K. Hashmi, M. C. Blanco Jaimes, A. M. Schuster and F. Rominger, *J. Org. Chem.*, 2012, **77**, 6394.

10 D. V. Patil, H. S. Park, J. Koo, J. W. Han and S. Shin, *Chem. Commun.*, 2014, **50**, 12722.

11 (*a*) Y. Liu, J. Guo, Y. Liu, X. Wang, Y. Wang, X. Jia, G. Wei, L. Chen, J. Xiao and M. Cheng, *Chem. Commun.*, 2014, **50**, 6243; (*b*) X. Peng, L. Zhu, Y. Hou, Y. Pang, Y. Li, J. Fu, L. Yang, B. Lin, Y. Liu and M. Cheng, *Org. Lett.*, 2017, **19**, 3402; (*c*) Z. Xiong, X. Zhang, Y. Li, X. Peng, J. Fu, J. Guo, F. Xie, C. Jiang, B. Lin, Y. Liu and M. Cheng, *Org. Biomol. Chem.*, 2018, **16**, 7361.

12 (*a*) C. Zhang and N. Jiao, *J. Am. Chem. Soc.*, 2010, **132**, 28; (*b*) T. Wang and N. Jiao, *J. Am. Chem. Soc.*, 2013, **135**, 11692.

13 (*a*) A. Laguna and M. Laguna, *Coord. Chem. Rev.*, 1999, **193**, 837; (*b*) B. Sahoo, M. N. Hopkinson and F. Glorius, *J. Am. Chem. Soc.*, 2013, **135**, 5505; (*c*) X. Shu, M. Zhang, Y. He, H. Frei and F. D. Toste, *J. Am. Chem. Soc.*, 2014, **136**, 5844.

14 W. Liu, M. Buck, N. Chen, M. Shang, N. J. Taylor, J. Asoud, X. Wu, B. B. Hasinoff and G. I. Dmitrienko, *Org. Lett.*, 2007, **9**, 2915.