Organic & Biomolecular Chemistry

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2016, **14**, 5233

Received 18th April 2016,
Accepted 14th May 2016

DOI: 10.1039/c6ob00825a

www.rsc.org/obc

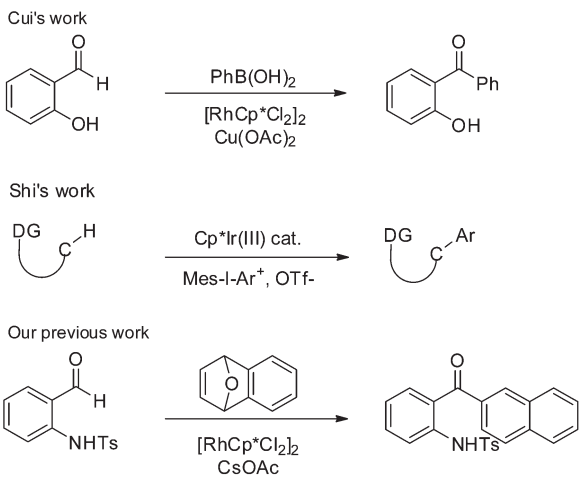
Iridium- and rhodium-catalyzed C–H activation and formyl arylation of benzaldehydes under chelation-assistance†

Xifa Yang, He Wang, Xukai Zhou and Xingwei Li*

Mild and efficient synthesis of benzophenones *via* Ir(III)- and Rh(III)-catalyzed, directing group-assisted formyl C–H arylation of benzaldehydes has been achieved using diaryliodonium salts, in which Rh(III) and Ir(III) catalysts exhibited a complementary substrate scope.

Benzophenones are important and versatile structure motifs in synthetic chemistry owing to their biological activities such as COX-1/COX-2 inhibiting, anti-inflammatory, and neuroprotective properties.[1] As a result, tremendous synthetic efforts have been directed to the construction of benzophenones. Classical protocols to access 2-(aryloxy)benzaldehydes often relied on the Fries rearrangement of phenyl benzoate and the acylation of benzoquinone.[2] On the other hand, traditional synthetic routes to *N*-(2-benzoylphenyl)benzenesulfonamides started from (2-aminophenyl)(phenyl)methanones or 2-aminobenzoic acids.[3] Despite such methods, these reactions generally suffered from the formation of undesired products, low atom-economy, or the requirement of multistep synthesis. Recently, transition metal catalysis has emerged as an increasingly important approach in the preparation of *ortho*-substituted benzophenones.[4] In particular, the strategy of C–H activation represents a desirable and attractive strategy to deliver those products. Several novel methods have been developed by Rao, Dong, Ackermann, Chen, Xu, and others for the synthesis of 2-hydroxybenzophenones using Pd(II), Ni(II), or Ru(II) catalysts.[5] In addition, only a few reports on the synthesis of *N*-(2-benzoylphenyl)benzenesulfonamides have been documented in the literature, which relied on Pd- and Ru-catalyzed directed *ortho* C–H amidation of aromatic ketones.[6] Most of these protocols have one or more drawbacks, such as the requirement of stoichiometric amounts of oxidants, harsh reaction conditions, or limited substrate scopes. Therefore, development of simple, mild, and environmentally benign methods is still highly desirable.

The half-sandwich Cp*Rh(III) catalysts have stood out with high activity, a broad substrate scope, mild conditions, and functional group compatibility,[7] and Rh(III)-catalyzed C–H functionalization of aldehydes has attracted much attention owing to their wide applications in the construction of complex structures (Scheme 1).[8] We recently reported the synthesis of ketones using 7-oxabenzonorbornadienes as an arylating reagent, however the reaction was limited in scope.[9] Very recently, Cui described a Rh(III)-catalyzed arylation of salicylaldehydes using arylboronic acids to afford 2-hydroxybenzophenones, but a stoichiometric amount of $Cu(OAc)_2$ was necessary as an oxidant.[10] Hypervalent iodine reagents have attracted our attention with appealing combination of high reactivity, stability, and environmental friendliness.[11] Thus, Daugulis, Sanford, Gaunt, and others have successfully applied diaryliodonium salts as arylating reagents.[12] In particular, Shi recently reported Cp*Ir(III)-catalyzed arylation of both sp^2 and sp^3 C–H bonds under mild conditions.[12f] As a

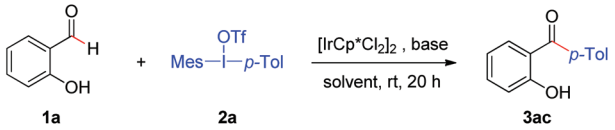


Scheme 1 Rh(III) or Ir(III)-catalyzed C–H arylation of salicylaldehyde.

Dalian Institute of Chemical Physics, Chinese Academy of Science, Dalian 116023, China. E-mail: xwli@dicp.ac.cn

† Electronic supplementary information (ESI) available: Experimental procedures and characterization of new compounds. See DOI: 10.1039/c6ob00825a

Table 1 Optimization studies[a]



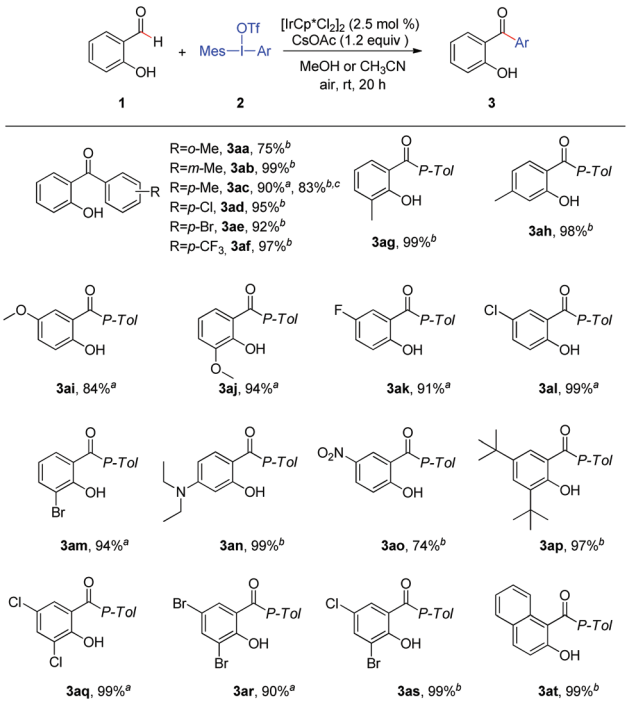
Entry	Catalyst (mol%)	Base (equiv.)	Solvent	Yield[b]
1	2.5	CsOAc (1.2)	DCE	92%
2	2.5	CsOAc (1.2)	MeOH	99%
3	2.5	CsOAc (1.2)	CH_3CN	99%
4[c]	2.5	CsOAc (1.2)	MeOH	96%
5	1.0	CsOAc (1.2)	MeOH	91%
6	2.5	CsOAc (1.0)	MeOH	92%
7[d]	2.5	CsOAc (1.2)	MeOH	Trace

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.22 mmol), $[Cp^*IrCl_2]_2$, base, solvent (2.0 mL), under air at rt for 20 h. [b] Isolated yield after column chromatography. [c] Under N_2. [d] $[Cp^*RhCl_2]_2$ as a catalyst.

continuation of our interest in the Rh(III)-catalyzed coupling of arenes with a hypervalent iodine reagent,[8f,13] we now report rhodium- and iridium-catalyzed complementary C–H arylation of aldehydes with diaryliodonium salts.

We embarked on our studies with the screening of the reaction conditions for the coupling between salicylaldehyde and *p*-tolyl(mesityl)iodonium triflate (Table 1). We initially applied $[IrCp^*Cl_2]_2$ as a catalyst in the presence of CsOAc without exclusion of air in DCE. Gratifyingly, the desired coupling did occur. Subsequently, various solvents were investigated, and the best yield was obtained in MeOH or CH_3CN, and product **3ac** was isolated in 99% yield in both cases (entries 2 and 3). The yield decreased slightly when the reaction was performed under N_2 (entry 4), and this result agrees with our previous report.[8f] Notably when the catalyst loading (1 mol%, entry 5) or the amount of CsOAc was lowered (1 equiv., entry 6), the efficiency of this transformation was slightly affected. Therefore, the optimal reaction conditions were identified as $[IrCp^*Cl_2]_2$ (2.5 mol%), CsOAc (1.2 equiv.) at rt in MeOH or CH_3CN for 20 h.

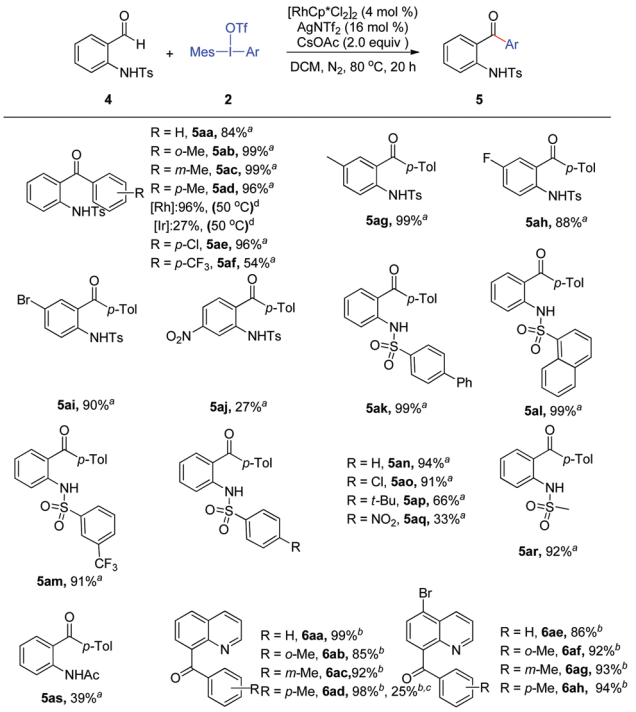
With the optimal reaction conditions in hand, the scope and limitations of this reaction were next investigated (Scheme 2). Diaryliodonium salts bearing both electron-donating (**3ac**) and -withdrawing (**3ad–3af**) groups all reacted in excellent yields, implying that the electronic effect of the diaryliodonium salt is insignificant. Meanwhile, *ortho*- and *meta*-substituted diaryliodonium salts were chosen to examine the steric effect, and the desired products (**3aa** and **3ab**) were obtained in 75% and 99% yields, respectively. Next, the scope of the salicylaldehydes was examined using *p*-tolyl(mesityl) iodonium triflate as a coupling partner. Various alkyl, halide, alkoxyl, and diethylamino substituents at the 3-, 4-, and 5-positions of salicylaldehyde were tolerated (**3ag–3an**), and the expected products were isolated in 84%–99% yields. Even the electron-poor 5-nitrosalicylaldehyde also reacted to afford **3ao** in 74% yield. Furthermore, this reaction was not limited to monosubstituted substrates, disubstituted salicylaldehydes



Scheme 2 Ir(III)-catalyzed C–H arylation of salicylaldehyde. [a] Reaction conditions: salicylaldehyde **1** (0.2 mmol), **2** (0.22 mol), CsOAc (0.24 mmol), $[Cp^*IrCl_2]_2$ (2.5 mol%), CH_3OH (2.0 mL), under air at rt for 20 h. Isolated yield after chromatography. [b] Reaction was performed in CH_3CN. [c] $[Cp^*RhCl_2]_2$ instead of $[Cp^*IrCl_2]_2$.

(**1ap–1as**) coupled to afford the corresponding products in 90%–99% yields. As expected, the naphthaldehyde substrate **1at** was also viable and afforded product **3at** in 99% yield.

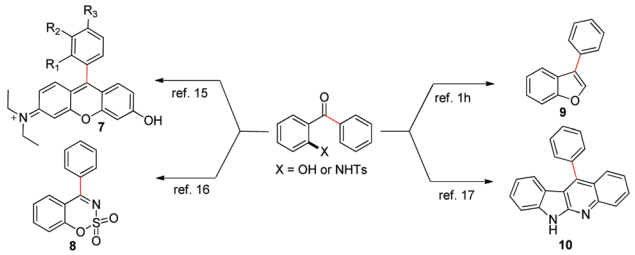
To further explore the applicability of this transformation, we turned our attention to arylation of *N*-sulfonyl-2-aminobenzaldehydes. Although they are isostructural to salicylaldehydes, *N*-sulfonyl-2-aminobenzaldehydes reacted with good efficiency under N_2, and $[Cp^*RhCl_2]_2$ proved to be the active catalyst. Introduction of a methyl to the *ortho*, *meta* and *para* positions (**5ab–5ad**) of the diaryliodonium salts was fully tolerated, indicative of the compatibility with the steric effect. Meanwhile, electron-neutral and -withdrawing substituents at the *para*-position of diaryliodonium triflates were also tolerated, and the desired products **5aa**, **5ae**, and **5af** were isolated in 84%, 96% and 54% yields, respectively. The coupling of *N*-sulfonyl-2-aminobenzaldehydes bearing different substituents (methyl, halogen, and nitro) all proceeded smoothly (**5ag–5aj**), although *N*-(2-formyl-5-nitrophenyl)-4-methylbenzenesulfonamide **4aj** afforded the corresponding product **5aj** in only 27% yield. Next, we extended the sulfonyl group to benzenesulfonyls bearing different electron-donating and -withdrawing groups (**5ak–5aq**) as well as methanesulfonyl (**5ar**). Switching the *N*-tosyl to *N*-acetyl also furnished the desired product **5as** in 39% yield. Encouraged by the above results, the reaction of quinoline-8-carbaldehydes and diaryliodoniums was further investigated (Scheme 3). However, almost no conversion was observed under the standard reaction con-



Scheme 3 Rh(III)-catalyzed C–H arylation of *N*-sulfonyl 2-amonibenzaldehyde. [a] Reaction conditions: **4** (0.2 mmol), **2** (0.4 mmol), CsOAc (0.4 mmol), $[Cp^*RhCl_2]_2$ (4 mol%), $AgNTf_2$ (16 mol%), DCM (2.0 mL), under N_2 at 80 °C for 20 h. [b] Reaction conditions: **4** (0.20 mmol), **2** (0.24 mol), $[Cp^*RhCl_2]_2$ (2 mol%), $AgNTf_2$ (16 mol%), cyclohexane (2.0 mL), 4 Å MS (200 mg), under N_2 at 100 °C for 20 h. [c] H_2O (200 mg) was added. [d] CsOAc (0.24 mmol).

ditions. We noticed the crucial role of 4 Å MS in the Ir(III)-catalyzed C–H arylation system reported by Shi's group.[12f] Introduction of 4 Å MS proved to be optimal and necessary (Scheme 3, **6ad**), which likely facilitated the C–H activation processes as well as removed the water. The desired coupling occurred smoothly and gave 8-benzoylquinolines in 85–99% yields. So far only Chang and Wang have reported the arylation of quinoline-8-carbaldehydes, and those systems were restricted to Ru, Pd, or Rh(I) catalysis.[14]

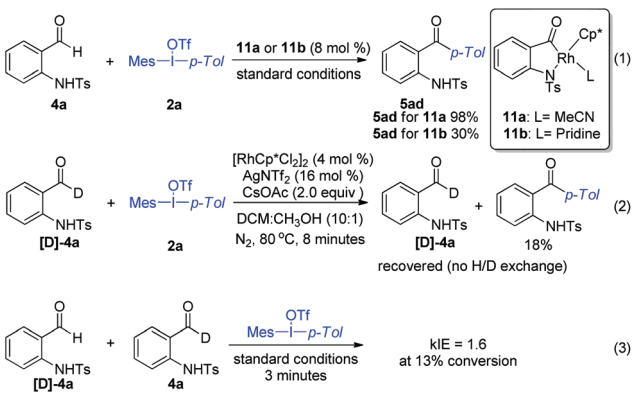
To illustrate the synthetic utility of the C–H arylated products, several transformations of benzophenones are displayed in Scheme 4. For example, the derivative 7 was constructed



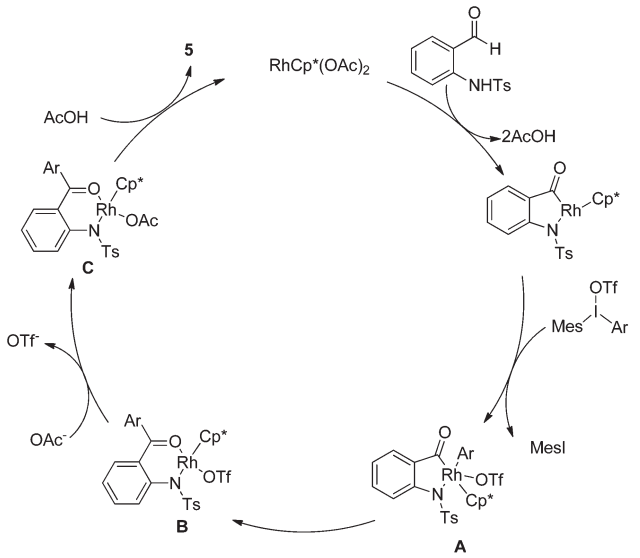
Scheme 4 Divergent transformations of *ortho*-substituted benzophenones.

using substituted 2-hdroxybenzophenones as the starting material.[15] 4-Phenylbenzo[*e*][1,2,3]oxathiazine 2,2-dioxide can be synthesized in high yield by the reaction of 2-hydroxybenzophenones with $ClSO_2NCO$.[16] The biologically active benzofurans could also be easily prepared from 2-hydroxybenzophenones and dimethylacetamide.[1h] The cascade coupling of 1-(2-tosylaminophenyl)-ketones with indoles also provided a useful annulation strategy to obtain 11-phenyl-6*H*-indolo[2,3-*b*]quinoline,[17] which is known to act as a DNA topoisomerase II inhibitor.[18]

To gain mechanistic insights into the relevancy of C–H activation, cyclometalated Rh(III) complexes **11a** and **11b** stabilized with acetonitrile and pyridine[8d] have been prepared and were designated as a catalyst. Both **11a** and **11b** exhibited catalytic activity, and the product **5ad** was isolated in 98% and 30% yields, respectively (Scheme 5, eqn (1)), indicating that C–H activation was involved. To further probe this C–H activation process, the coupling between [D]-**4a** and **2a** was stopped at about 18% conversion in DCM and CH_3OH (10 : 1, 2 mL). ^1H NMR analysis of the recovered [D]-**4a** revealed no H/D exchange at the formyl position, indicating that this C–H activation process is irreversible (Scheme 5, eqn (2)). The kinetic isotope effect (KIE) has been estimated for the competitive coupling of an equimolar mixture of **4a** and [D]-**4a** with **2a**. ^1H NMR analysis of the level of deuteration of the recovered aldehyde mixture at 13% conversion gave k_H/k_D = 1.6 (see Scheme 5, eqn (3) and ESI†). This moderate value of KIE suggests that cleavage of the C–H bond might be involved in the rate-limiting step. On the basis of our previous studies and the preliminary results,[8d–f,13b] a plausible catalytic cycle has been proposed starting from $RhCp^*(OAc)_2$ as an active catalyst (Scheme 6). Cyclometalation of *N*-tosyl 2-aminobenzaldehyde afforded a rhodacyclic intermediate, to which the diaryliodonium salt oxidatively adds to generate a Rh(V) species. C(aryl)–C(acyl) reductive elimination afforded a Rh(III) intermediate **B**, and subsequent protonolysis of **B** furnished the final product together with regeneration of the active $RhCp^*(OAc)_2$ catalyst.



Scheme 5 Mechanistic studies.



Scheme 6 Proposed catalytic cycle.

Conclusions

In summary, we have realized rhodium- and iridium-catalyzed redox-neutral C–H arylation of benzaldehydes using diaryliodonium triflate as an arylating reagent. A broad scope of formyl-substituted arenes assisted by different directing groups (OH, NTs, OAc, quinoline ring) have been arylated at the formyl position with good functional group compatibility. An iridium(III) catalyst exhibited high activity for salicylaldehyde substrates, while a rhodium(III) catalyst is more efficient for *N*-sulfonyl 2-aminobenzaldehydes. Given the important properties of the arylated products, relatively mild conditions employed, and the tolerance of functional groups, this synthetic method may find applications in the synthesis of related complex molecules, particularly in pharmaceutical research.

Acknowledgements

We thank the Dalian Institute of Chemical Physics, Chinese Academy of Sciences, and the NSFC (no. 21472186 and 21272231) for financial support.

Notes and references

1 (*a*) D. Evans, M. E. Cracknell, J. C. Saunders, C. E. Smith, W. N. Williamson, W. Dawson and W. J. F. Sweatman, *J. Med. Chem.*, 1987, **30**, 1321; (*b*) S. B. Nabuurs, M. Wagener and J. De Vlieg, *J. Med. Chem.*, 2007, **50**, 6507; (*c*) G. Tang, Z. Nikolovska-Coleska, S. Qiu, C. Y. Yang, J. Guo and S. Wang, *J. Med. Chem.*, 2008, **51**, 717; (*d*) S. Zhong, X. Chen, X. Zhu, B. Dziegielewska, K. E. Bachman, T. Ellenberger and A. D. MacKerell Jr., *J. Med. Chem.*, 2008, **51**, 4553; (*e*) G. J. Stokker, *Org. Chem.*, 1983, **48**, 2613; (*f*) J. Y. Yeh, M. S. Coumar, J. T. Horng, H. Y. Shiao, F. M. Kuo, H. L. Lee and C. J. Chen, *J. Med. Chem.*, 2010, **53**, 1519; (*g*) C. Y. Chen, T. Andreani and H. Li, *Org. Lett.*, 2011, **13**, 6300; (*h*) M. J. Moure, R. SanMartin and E. Dominguez, *Angew. Chem., Int. Ed.*, 2012, **51**, 3220.

2 (*a*) K. D. Parris, D. J. Hoover, D. B. Damon and D. R. Davies, *Biochem.*, 1992, **31**, 8125; (*b*) T. D. Venu, S. Shashikanth, S. A. Khanum, S. Naveen, A. Firdouse, M. A. Sridhar and J. S. Prasad, *Bioorg. Med. Chem.*, 2007, **15**, 3505; (*c*) W. B. Motherwell and S. Vázquez, *Tetrahedron Lett.*, 2000, **41**, 9667.

3 G. Dannhardt, B. L. Fiebich and J. Schweppenhäuser, *Eur. J. Med. Chem.*, 2002, **37**, 147.

4 (*a*) H. Rao and C. J. Li, *Angew. Chem., Int. Ed.*, 2011, **50**, 8936; (*b*) J. Hu, E. A. Adogla, Y. Ju, D. Fan and Q. Wang, *Chem. Commun.*, 2012, **48**, 11256; (*c*) T. Ramani, P. Umadevi, K. L. Prasanth and B. Sreedhar, *Eur. J. Org. Chem.*, 2013, 6021.

5 (*a*) F. Mo, L. J. Trzepkowski and G. Dong, *Angew. Chem., Int. Ed.*, 2012, **51**, 13075; (*b*) G. Shan, X. Yang, L. Ma and Y. Rao, *Angew. Chem., Int. Ed.*, 2012, **51**, 13070; (*c*) V. S. Thirunavukkarasu and L. Ackermann, *Org. Lett.*, 2012, **14**, 6206; (*d*) M. Xia and Z. Chen, *Synth. Commun.*, 2000, **30**, 531; (*e*) F. Weng, C. Wang and B. Xu, *Tetrahedron Lett.*, 2010, **51**, 2593; (*f*) P. Y. Choy and F. Y. Kwong, *Org. Lett.*, 2013, **15**, 270; (*g*) N. Nowrouzi, M. Zarei and F. Roozbin, *RSC Adv.*, 2015, **5**, 102448; (*h*) N. Nowrouzi, S. Motevalli and D. Tarokh, *J. Mol. Catal. A: Chem.*, 2015, **396**, 224; (*i*) T. Satoh, T. Itaya, M. Miura and M. Nomura, *Chem. Lett.*, 1996, 823.

6 (*a*) B. Xiao, T. J. Gong, J. Xu, Z. J. Liu and L. Liu, *J. Am. Chem. Soc.*, 2011, **133**, 1466; (*b*) M. Bhanuchandra, M. R. Yadav, R. K. Rit, M. R. Kuram and A. K. Sahoo, *Chem. Commun.*, 2013, **49**, 5225; (*c*) Q. Z. Zheng, Y. F. Liang, C. Qin and N. Jiao, *Chem. Commun.*, 2013, **49**, 5654; (*d*) K. Raghuvanshi, D. Zell, K. Rauch and L. Ackermann, *ACS Catal.*, 2016, **6**, 3172.

7 For selected reviews see: (*a*) T. Satoh and M. Miura, *Chem. – Eur. J.*, 2010, **16**, 11212; (*b*) G. Song, F. Wang and X. Li, *Chem. Soc. Rev.*, 2012, **41**, 3651; (*c*) N. Kuhl, N. Schroder and F. Glorius, *Adv. Synth. Catal.*, 2014, **356**, 1443; (*d*) G. Song and X. Li, *Acc. Chem. Res.*, 2015, **48**, 1007.

8 (*a*) M. Shimizu, H. Tsurugi, T. Satoh and M. Miura, *Chem. – Asian J.*, 2008, **3**, 881; (*b*) Z. Shi, N. Schröder and F. Glorius, *Angew. Chem., Int. Ed.*, 2012, **51**, 8092; (*c*) E. Jijy, P. Prakash, M. Shimi, P. M. Pihko, N. Joseph and K. V. Radhakrishnan, *Chem. Commun.*, 2013, **49**, 7349; (*d*) T. Zhang, Z. Qi, X. Zhang, L. Wu and X. Li, *Chem. – Eur. J.*, 2014, **20**, 3283; (*e*) X. Zhang, Z. Qi, J. Gao and X. Li, *Org. Biomol. Chem.*, 2014, **12**, 9329; (*f*) H. Wang, F. Xie, Z. Qi and X. Li, *Org. Lett.*, 2015, **17**, 920.

9 T. Yang, T. Zhang, S. Yang, S. Chen and X. Li, *Org. Biomol. Chem.*, 2014, **12**, 4290.

10 D. Wang and S. Cui, *Tetrahedron*, 2015, **71**, 8511.

11 (*a*) K. C. Nicolaou, T. Montagnon, P. S. Baran and Y. L. Zhong, *J. Am. Chem. Soc.*, 2002, **124**, 2245;

(*b*) V. V. Zhdankin and P. J. Stang, *Chem. Rev.*, 2002, **102**, 2523; (*c*) P. J. Stang, *J. Org. Chem.*, 2003, **68**, 2997; (*d*) T. Wirth, *Angew. Chem., Int. Ed.*, 2005, **44**, 3656; (*e*) R. D. Richardson and T. Wirth, *Angew. Chem., Int. Ed.*, 2006, **45**, 4402; (*f*) E. A. Merritt and B. Olofsson, *Angew. Chem., Int. Ed.*, 2009, **48**, 9052.

12 (*a*) D. Kalyani, N. R. Deprez, L. V. Desai and M. S. Sanford, *J. Am. Chem. Soc.*, 2005, **127**, 7330; (*b*) N. R. Deprez and M. S. Sanford, *J. Am. Chem. Soc.*, 2009, **131**, 11234; (*c*) E. Cahard, H. P. J. Male, M. Tissot and M. J. Gaunt, *J. Am. Chem. Soc.*, 2015, **137**, 7986; (*d*) G. Fumagalli, S. Boyd and M. F. Greaney, *Org. Lett.*, 2013, **15**, 4398; (*e*) O. Daugulis and V. G. Zaitsev, *Angew. Chem., Int. Ed.*, 2005, **44**, 4046; (*f*) P. Gao, W. Guo, J. Xue, Y. Zhao, Y. Yuan, Y. Xia and Z. Shi, *J. Am. Chem. Soc.*, 2015, **137**, 12231; (*g*) J. Peng, C. Chen and C. Xi, *Chem. Sci.*, 2016, **7**, 1383.

13 (*a*) F. Xie, Z. Qi and X. Li, *Angew. Chem., Int. Ed.*, 2013, **52**, 11862; (*b*) F. Xie, Z. Qi, S. Yu and X. Li, *J. Am. Chem. Soc.*, 2014, **136**, 4780; (*c*) F. Xie, Z. Zhang, X. Yu, G. Tang and X. Li, *Angew. Chem., Int. Ed.*, 2015, **127**, 7513; (*d*) F. Wang, X. Yu, Z. Qi and X. Li, *Chem. – Eur. J.*, 2016, **22**, 511.

14 (*a*) S. Ko, B. Kang and S. Chang, *Angew. Chem., Int. Ed.*, 2005, **44**, 455; (*b*) J. Wang, W. Chen, S. Zuo, X. Zhang and J. Wang, *Angew. Chem., Int. Ed.*, 2012, **51**, 12334; (*c*) J. Wang, S. Zuo, W. Chen, X. Zhang, K. Tan, Y. Tian and J. Wang, *J. Org. Chem.*, 2013, **78**, 8217.

15 S. Kamino, H. Ichikawa, S. I. Wada, Y. Horio, Y. Usami, T. Yamaguchi and M. Doi, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 4380.

16 Y. Q. Wang, C. B. Yu, D. W. Wang, X. B. Wang and Y. G. Zhou, *Org. Lett.*, 2008, **10**, 2071.

17 S. Ali, Y. X. Li, S. Anwar, F. Yang, Z. S. Chen and Y. M. Liang, *J. Org. Chem.*, 2011, **77**, 424.

18 L. Guittat, P. Alberti, F. Rosu, S. Van Miert, E. Thetiot, L. Pieters and J. L. Mergny, *Biochimie*, 2003, **85**, 535.