RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2018, **8**, 31603

Acid-promoted iron-catalysed dehydrogenative [4 + 2] cycloaddition for the synthesis of quinolines under air†

Jinfei Yang,* Xiao Meng, Kai Lu, Zhihao Lu, Minliang Huang, Chengniu Wang and Fei Sun*

Received 15th August 2018
Accepted 5th September 2018

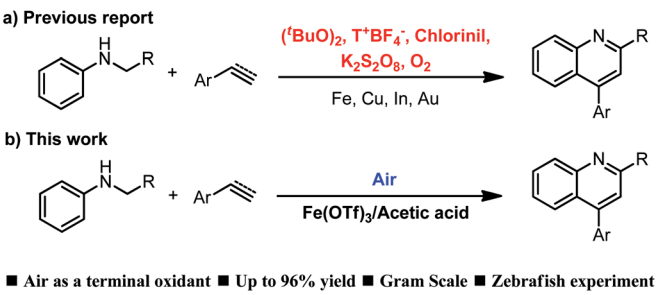
DOI: 10.1039/c8ra06826g

rsc.li/rsc-advances

An acid-promoted iron-catalysed dehydrogenative [4 + 2] cycloaddition reaction was developed for the synthesis of quinolines using air as a terminal oxidant. Acetic acid was the best cocatalyst for the cycloaddition of *N*-alkyl anilines with alkenes or alkynes under air. Various quinoline derivatives were obtained in satisfactory-to-excellent yields, and no other byproducts besides water were produced in the reaction. The zebrafish model has become an important vertebrate model for evaluating drug effects. We tested the activity of **3n** in zebrafish. The test results showed that 1 μg mL^{-1} **3n** treatments resulted in morphological malformation, and 0.01–0.1 μg mL^{-1} **3n** treatments led to potent angiogenic defects in zebrafish embryos. The results of this study will be of great significance for promoting drug research in cardiovascular and cerebrovascular diseases.

The construction of quinoline motifs has received intensive attention owing to their potential application in photovoltaic devices[1] and pharmaceuticals,[2] such as anticancer, antiviral, antifungal, antiplatelet aggregation, antimalarial, antibacterial, antileishmanial and anti-inflammatory medicine.[3] Because of their importance, many methods have been reported for the synthesis of quinolines.[4] Among them, the most attractive strategy for the synthesis of these compounds is the dehydrogenative [4 + 2] cycloaddition through transition-metal catalysis and Lewis/Bronsted acid catalysis. In its most general and classical form, dehydrogenative [4 + 2] cycloaddition catalysed by transition metals such as Fe,[5] Cu,[6] Pd,[7] and others,[8] has been used as a potent tool for the synthesis of quinolone derivatives (Scheme 1a). However, these methods require the presence of excess peroxides, chloranil, potassium persulfate or other oxidants to promote the cycloaddition reaction and to obtain good product yields. Furthermore, in these processes, the formation of stoichiometric amounts of acid or tetrachlorohydroquinone waste as byproducts is a substantial problem that has limited their use. To overcome these drawbacks, several methods that utilise oxygen as a terminal oxidant have been reported.[9] However, in many cases, the industrial use of these methods is problematic owing to operational difficulty. Therefore, the development of more efficient and economical synthetic methods is still necessary. Undoubtedly, the use of air as a terminal oxidant is the best choice. In addition, in the field of transition-metal catalysis, iron is one of the most commonly used base metals and has been widely applied in various coupling reactions.[10] Therefore, it is desirable to develop an iron-catalysed dehydrogenative cycloaddition for the synthesis of quinoline under air.

Herein, we report the first acid-promoted iron-catalysed dehydrogenative [4 + 2] cycloaddition of *N*-alkyl anilines with alkenes or alkynes using air as a terminal oxidant (Scheme 1b). Iron-catalysed cycloaddition reaction for the synthesis of quinolines under air has always been a challenge because of metal deactivation after the end of the catalytic cycle. We commenced our studies by treating *N*-benzylaniline (**1a**) and styrene (**2a**) with 5 mol% iron as a catalyst. Initially, we tried to use a variety of iron catalysts to catalyse the cycloaddition of *N*-alkyl anilines and olefins under air (Table 1, entries 1–6). Trace amounts of the desired product (**3a**) were obtained with $FeCl_2$, $Fe(OTf)_2$, $Fe_2(SO_4)_3$ and Fe_2O_3, as detected by GC analysis, and a 28% or 33% yield was observed when $FeCl_3$ or $Fe(OTf)_3$ was used as a catalyst. To improve the reaction efficiency, different solvents

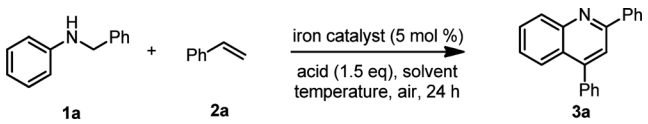


Scheme 1 Different strategies for [4 + 2] cycloaddition of *N*-alkyl anilines and alkenes or alkynes by transition-metal catalysis.

Medical School, Institute of Reproductive Medicine, Nantong University, Nantong 226019, China. E-mail: jfyang@ntu.edu.cn; sunfei@ntu.edu.cn

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c8ra06826g

Table 1 Solvent effect and acid effect. *N*-benzylaniline (0.2 mmol), styrene (0.4 mmol), $Fe(OTf)_3$ (10 μmol), acid (0.3 mmol), toluene (1.0 mL), at 140 °C under air for 24 h



Entry	Catalyst (5 mol%)	Acid (0.3 mmol)	Solvent	*T* (°C)	Yield[a] (%)
1	$Fe(OTf)_2$	No	Toluene	120	Trace
2	$FeCl_2$	No	Toluene	120	Trace
3	$FeCl_3$	No	Toluene	120	28
4	Fe_2O_3	No	Toluene	120	Trace
5	$Fe_2(SO_4)_3$	No	Toluene	120	Trace
6	$Fe(OTf)_3$	No	Toluene	120	33
7	$Fe(OTf)_3$	No	Ethanol	120	0
8	$Fe(OTf)_3$	No	Mysitylene	120	26
9	$Fe(OTf)_3$	No	Dioxane	120	0
10	$Fe(OTf)_3$	No	Nitrobenzene	120	28
11	$Fe(OTf)_3$	No	Acetonitrile	120	23
12	$Fe(OTf)_3$	No	Toluene	150	42
13	$Fe(OTf)_3$	No	Toluene	140	49
14	$Fe(OTf)_3$	No	Toluene	100	16
15	$Fe(OTf)_3$	No	Toluene	80	8
16	$Fe(OTf)_3$	No	Toluene	60	Trace
17	$Fe(OTf)_3$	No	Toluene	40	0
18	$Fe(OTf)_3$	H_2SO_4	Toluene	140	0
19	$Fe(OTf)_3$	TfOH	Toluene	140	0
20	$Fe(OTf)_3$	TFA	Toluene	140	65
21	$Fe(OTf)_3$	PTSA	Toluene	140	61
22[b]	$Fe(OTf)_3$	BNPA	Toluene	140	57
23	$Fe(OTf)_3$	HCOOH	Toluene	140	42
24	$Fe(OTf)_3$	BzOH	Toluene	140	50
25	**$Fe(OTf)_3$**	**AcOH**	**Toluene**	**140**	**82**
26	$Fe(OTf)_3$	$PhB(OH)_2$	Toluene	140	35
27	$Fe(OTf)_3$	$B(OH)_3$	Toluene	140	15
28	$Fe(OTf)_3$	Phenol	Toluene	140	54
29[c]	$Fe(OTf)_3$	AMSA	Toluene	140	51
30	No	AcOH	Toluene	140	Trace

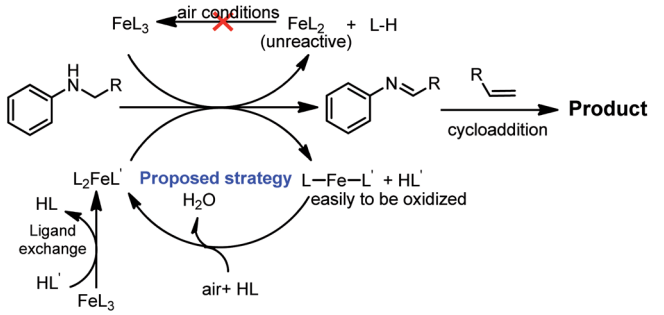
[a] Isolated yields. [b] BNPA = 1,1′-binaphthyl-2,2′-diylhydrogen-phosphate. [c] AMSA = aminomethanesulfonic acid.

such as ethanol, mesitylene, 1,4-dioxane, nitrobenzene, acetonitrile and toluene were tested (Table 1, entries 6–11).

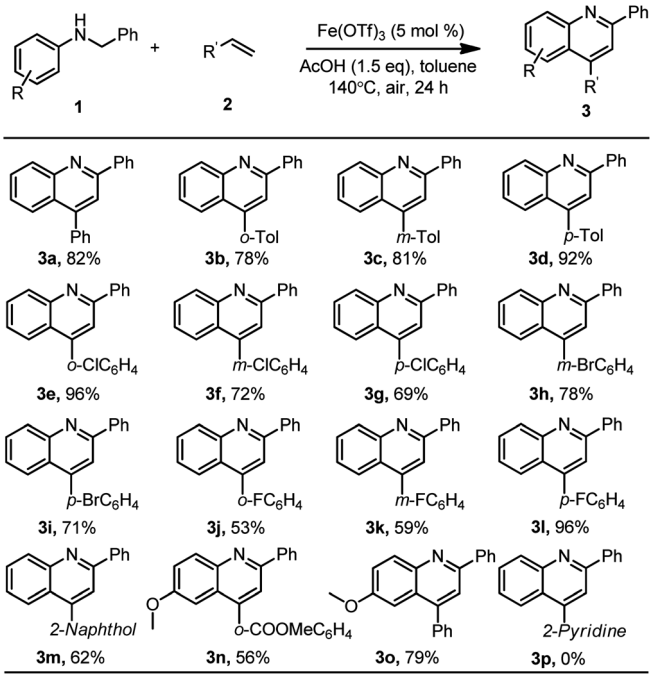
The optimal solvent for the reaction was toluene (Table 1, entry 6). Encouraged by this result, we examined a wide range of reaction temperatures (Table 1, entries 12–17); the best yield was obtained at 140 °C, but it did not meet our expectations.

We reasoned that an unreactive catalytic species, FeL_2 (Scheme 2), could be formed in the reaction from the interaction of the imine intermediate and FeL_3, which could not catalyse the conversion of imines to quinoline. Critically, the FeL_2 species was difficult to oxidize to FeL_3 under air conditions. Inspired by Birk's work,[11] we envisaged that the addition of an acid may promote the oxidation of Fe(II) to Fe(III) under air. Based on this assumption, we proposed that FeL_3 can undergo ligand exchange with HL′ to generate the active catalytic species L_2FeL'. A subsequent oxidation reaction provided LFeL′, which was easier oxidize to L_2FeL' than FeL_2 under air, enabling the next catalytic cycle.

Based on this hypothesis, we investigated some strong acids and moderate acids. Trifluoroacetic acid (TFA) was a cocatalyst that promoted the Fe-catalysed [4 + 2] cycloaddition of *N*-alkyl anilines and alkenes to deliver 2,4-diphenylquinoline in 65% yield (Table 1, entries 18–20). If 1,1′-binaphthyl-2,2′-diylhydrogen phosphate or *p*-toluenesulfonic acid (PTSA) were used instead of TFA, the yield was significantly reduced (Scheme 3, entries 21–22). For further improvement of the reaction, other



Scheme 2 Proposed strategy.



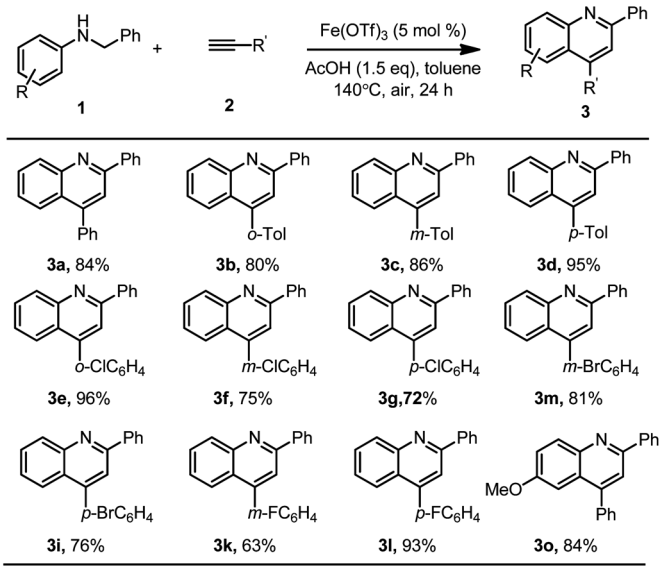
Scheme 3 Reaction conditions: substrate **1** (0.2 mmol), aryl olefin (0.4 mmol), $Fe(OTf)_3$ (10 μmol), AcOH (0.3 mmol), toluene (1.0 mL), at 140 °C under air for 24 h, and isolated yields of the products.

acid such as formic acid (HCOOH), benzoic acid (BzOH), acetic acid (AcOH), phenylboronic acid, boric acid, phenol and carbamic acid were tested (Table 1, entries 23–29). The results showed that the addition of 1.5 equivalents of acetic acid was the best choice, furnishing the corresponding 2,4-diphenylquinoline in 82% yield (Table 1, entry 25). Under the acidic conditions, a strong acid was completely inefficient (Table 1, entry 18), which suggested that the strength of the acid was critical to the reaction. Other acids did not give better results. Therefore, we performed the subsequent reactions between the *N*-alkyl anilines with alkenes or alkynes in the presence of $Fe(OTf)_3$/AcOH at 140 °C under air conditions for 24 h.

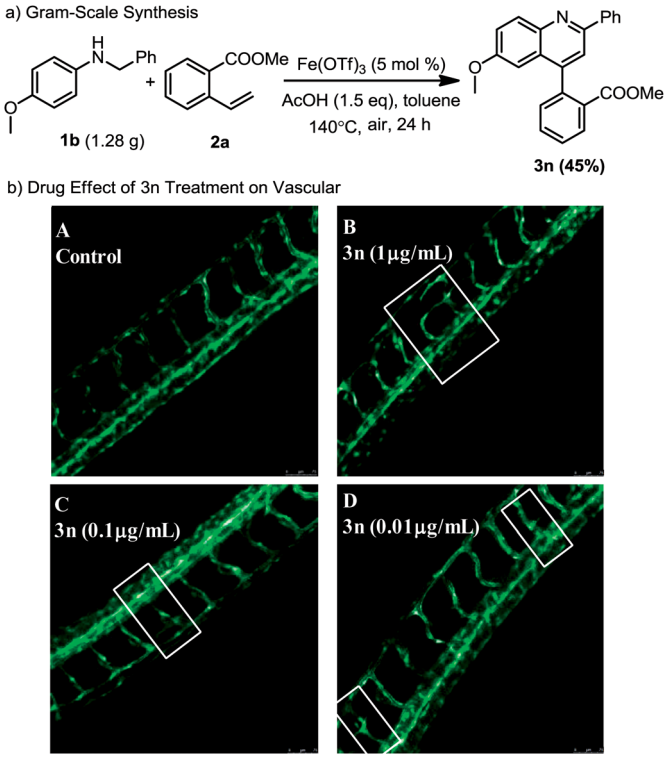
With the optimized reaction conditions in hand, a series of aryl ethylenes were investigated for extending the substrate scope (Scheme 3). This acid-promoted iron-catalysed dehydrogenative [4 + 2] cycloaddition reaction displayed good functional group tolerance. Aryl ethylenes with electron-neutral or electron-donating groups on the aryl rings, such as alkyl, phenyl and naphthyl, all gave the corresponding 2,4-diarylquinoline with high selectivity in good yields. Aryls containing an electron-withdrawing group such as fluoro, chloro, bromo and ester were also tolerated and afforded the corresponding 2,4-diarylquinolines **3e–3n** in moderate to good yields. Moreover, the reaction of *N*-benzylaniline **1b** containing a substituent (MeO) at the *para*-position of the aniline ring also produced the corresponding quinoline products **3o** in 79% yield. These results indicated that different groups, such as methyl, phenyl, fluoro, chloro, bromo and methoxyl on benzene rings, were tolerated under the optimized reaction conditions. Notably, the retention of the F, Cl and Br atoms in the structures of the products should make the products considerably useful in organic transformations. Unfortunately, the current method could not be applied to olefins containing N heteroatoms, which was likely because of the strong coordination of N atoms with iron.

Next, the scope of arylacetylenes was also investigated, and the results are summarized in Scheme 4. Arylacetylenes could be used instead of arylethylenes for the synthesis of 2,4-diarylquinoline under the optimized reaction conditions. Similar good results were obtained, as shown in Scheme 4. Quinoline derivatives **3a–3g**, **3i**, **3k–3m** and **3o** were obtained in satisfactory to good yields (63–96%).

To test the synthetic utility of the current method, a gram scale dehydrogenative [4 + 2] cycloaddition reaction of *N*-benzyl-4-methoxyaniline with methyl-2-vinylbenzoate was conducted under the optimal conditions, providing the target **3n** in 45% yield. To demonstrate the potential of our approach, we conducted molecular docking studies of human phenylethanolamine *N*-methyltransferase (hPNMT) and the quinoline derivatives. The studies were performed to help visualize possible interactions between hPNMT and the quinoline derivatives. The results showed that methyl-2-(6-methoxy-2-phenylquinolin-4-yl)benzoate **3n** may have π–π interactions with ARG 90, and π–cation interactions with TYR 27 in hPNMT. Based on this docking result, **3n** is highly likely to be a potent inhibitor of hPNMT. The results of the docked poses of hPNMT and **3n** are shown in the ESI.† The zebrafish model has become an important vertebrate model for evaluating drug effects. [12] To demonstrate the drug effect of **3n** on the vascular system in the trunk of zebrafish embryos, we tested the activity of **3n** in zebrafish. The test results showed treatment of zebrafish embryos with 1 μg mL^{-1} **3n** resulted in morphological malformation, and treatment with 0.01–0.1 μg mL^{-1} **3n** led to potent angiogenic defects (Scheme 5b). The results of this study will be of great significance for promoting drug research in cardiovascular and cerebrovascular diseases.

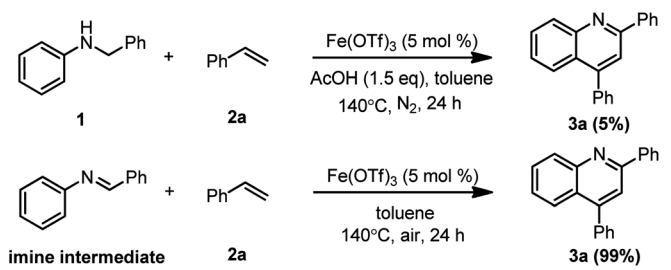


Scheme 4 Reaction conditions: substrate **1** (0.2 mmol), aryl alkyne (0.4 mmol), $Fe(OTf)_3$ (10 μmol), AcOH (0.3 mmol), toluene (1.0 mL), at 140 °C under air for 24 h, and isolated yields of the products.



Scheme 5 Gram-scale synthesis and the drug effect of **3n** treatment on vascular in the trunk of Tg(kdrl:EGFP) zebrafish embryos at 48 hpf. (A–D) control group and 1, 0.1, 0.01 μg mL^{-1} **3n** treated groups. Scale bar, 75 μm.

To gain a better understanding of the role of the acid, air and iron in the current cycloaddition reaction, additional experiments were conducted. First, control experiments showed that the absence of any of the three components, air, AcOH and $Fe(OTf)_3$, significantly reduced the reaction yield, implying that each of the components was essential to this reaction. To clarify that the reaction was undergoing the production of an imine intermediate, we employed *N*-benzylideneaniline as a substrate to test if 2,4-diphenylquinoline could be obtained (Scheme 6). To our great surprise, **3a** was obtained in 99% yield. The results showed that a cycloaddition reaction occurred after *N*-benzylaniline was oxidized to an imine. Based on these results, we proposed the following catalytic cycle: FeL_3 first underwent ligand exchange with AcOH to generate an active catalytic species L_2FeOAc, leading to subsequent oxidative dehydrogenation to provide the imine intermediate and intermediate LFeOAc while releasing HL. The imine intermediate can then undergo a [4 + 2] cycloaddition with an alkyne or alkene, forming the desired 2,4-diarylquinoline or dihydroquinoline. A subsequent dehydrogenation reaction of dihydroquinoline provided the target product. The intermediate LFeOAc underwent an oxidation reaction in the presence of air to regenerate the catalytic species L_2FeOAc.



Scheme 6 Mechanistic experiments.

Conclusions

In summary, we successfully developed a highly efficient acid-promoted iron-catalysed dehydrogenative [4 + 2] cycloaddition for the synthesis of quinoline under air conditions. The new method is compatible with alkenes and alkynes, and we performed molecular docking experiments with **3n**, which indicated that this compound might be an inhibitor of hPNMT. Moreover, we used the zebrafish model as an important way to demonstrate the drug effect of **3n** treatment on the vascular system in the trunk of zebrafish embryos. The test results showed that **3n** had a significant effect on angiogenesis. The results of this study will be of great significance for promoting drug research in cardiovascular and cerebrovascular diseases. Further investigation of cell experiments, animal experiments and other reaction types are under way in our laboratory.

Ethics statement

All animal procedures were performed in accordance with the Guidelines for Care and Use of Laboratory Animals of Nantong University and Experiments were approved by the Animal Ethics Committee of SYXK(SU) 2007–0021.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the National Natural Science Foundation of China (81430027 and 81671510), the National Basic Research Program (973 Program) (2014CB943100) for financial support. This work was also supported by the Fundamental Research Funds of Nantong University (03081105 and 03083002).

Notes and references

1 For selected reviews, see: (*a*) A. Danel, E. Gondek and I. Kityk, *Opt. Mater.*, 2009, **32**, 267; (*b*) H. Xu, R. Chen, Q. Sun, W. Lai, Q. Su, W. Huang and X. Liu, *Chem. Soc. Rev.*, 2014, **43**, 3259.
2 For selected reviews, see: (*a*) M. Orhan Puskullu, B. Tekiner and S. Suzen, *Mini-Rev. Med. Chem.*, 2013, **13**, 365; (*b*) K. Gopaul, S. A. Shintre and N. A. Koorbanally, *Anti-Cancer Agents Med. Chem.*, 2015, **15**, 631; (*c*) O. Afzal, S. Kumar, M. R. Haider, M. R. Ali, R. Kumar, M. Jaggi and S. Bawa, *Eur. J. Med. Chem.*, 2015, **97**, 871.
3 For selected reviews, see: (*a*) M. A. ElSohly and W. Gul, *Recent Pat. Anti-Infect. Drug Discovery*, 2007, **2**, 222; (*b*) Y. Zhang, T. Han, Q. Ming, L. Wu, K. Rahman and L. Qin, *Nat. Prod.*

Commun., 2012, **7**, 963; (*c*) P.-Y. Chung, Z.-X. Bian, H.-Y. Pun, D. Chan, A. S.-C. Chan, C.-H. Chui, J. C.-O. Tang and K.-H. Lam, *Future Med. Chem.*, 2015, **7**, 947.

4 For related reviews, see: (*a*) J. Marco-Contelles, E. Pérez-Mayoral, A. Samadi, M. d. C. Carreiras and E. Soriano, *Chem. Rev.*, 2009, **109**, 2652; (*b*) A. Majumder, R. Gupta and A. Jain, *Green Chem. Lett. Rev.*, 2013, **6**, 151; (*c*) S. M. Prajapati, K. D. Patel, R. H. Vekariya, S. N. Panchal and H. D. Patel, *RSC Adv.*, 2014, **4**, 24463; (*d*) R. I. Khusnutdinov, A. R. Bayguzina and U. M. Dzhemilev, *J. Organomet. Chem.*, 2014, **768**, 75; (*e*) B. Eftekhari-Sis and M. Zirak, *Chem. Rev.*, 2015, **115**, 151; (*f*) G. A. Ramann and B. J. Cowen, *Molecules*, 2016, **21**, 986; (*g*) V. F. Batista, D. C. G. A. Pinto and A. M. S. Silva, *ACS Sustainable Chem. Eng.*, 2016, **4**, 4064; (*h*) G. Chelucci and A. Porcheddu, *Chem. Rec.*, 2017, **17**, 200.

5 (*a*) H. Richter and O. G. Mancheño, *Org. Lett.*, 2011, **13**, 6066; (*b*) P. Liu, Z. Wang, J. Lin and X. Hu, *Eur. J. Org. Chem.*, 2012, 1583; (*c*) P. Liu, Y. Li, H. Wang, Z. Wang and X. Hu, *Tetrahedron Lett.*, 2012, **53**, 6654; (*d*) R. Rohlmann, T. Stopka, H. Richter and O. G. Mancheño, *J. Org. Chem.*, 2013, **78**, 6050.

6 (*a*) H. Huang, H. Jiang, K. Chen and H. Liu, *J. Org. Chem.*, 2009, **74**, 5476; (*b*) C. Huo, Y. Yuan, F. Chen and Y. Wang, *Adv. Synth. Catal.*, 2015, **357**, 3648; (*c*) X. Q. Yu, J. Wang, Z. W. Xu, Y. Yamamoto and M. Bao, *Org. Lett.*, 2016, **18**, 2491; (*d*) G. L. Liu, J. R. Qian, J. Hua, F. Cai, X. Li and L. Liu, *Org. Biomol. Chem.*, 2016, **14**, 1147.

7 (*a*) G. C. Senadi, W.-P. Hu, A. M. Gar-khedkar, S. S. K. Boominathan and J.-J. Wang, *Chem. Commun.*, 2015, **51**, 13795; (*b*) N. Thirupathi, S. Puri, T. J. Reddy, B. Sridhar and M. S. Reddy, *Adv. Synth. Catal.*, 2016, **358**, 303.

8 (*a*) X. Yang, L. Li, Y. Li and Y. Zhang, *J. Org. Chem.*, 2016, **81**, 12433; (*b*) S. Parua, R. Sikari, S. Sinha, S. Das, G. Chakraborty and N. D. Paul, *Org. Biomol. Chem.*, 2018, **16**, 274; (*c*) S. Das, D. Maiti and S. D. Sarkar, *J. Org. Chem.*, 2018, **83**, 2309.

9 (*a*) X.-D. Jia, F.-F. Peng, C. Qing, C.-D. Huo and X.-C. Wang, *Org. Lett.*, 2012, **14**, 4030; (*b*) J. Liu, F. Liu, Y.-Z. Zhu, X.-G. Ma and X.-D. Jia, *Org. Lett.*, 2015, **17**, 1409; (*c*) X. Ma, Y. Zhu, S. Lü, L. Zhang, L. Luo and X. Jia, *Tetrahedron Lett.*, 2016, **57**, 1528; (*d*) M. Ni, Y. Zhang, T. Gong and B. Feng, *Adv. Synth. Catal.*, 2017, **359**, 824; (*e*) W. Ahmed, S. Zhang, X.-Q. Yu, Y. Yamamotoa and M. Bao, *Green Chem.*, 2018, **20**, 261.

10 (*a*) J. Kaschel, T. F. Schneider and D. B. Werz, *Angew. Chem., Int. Ed.*, 2012, **51**, 7085; (*b*) P. Dupau, M. L. Tran Do, S. Gaillard and J. L. Renaud, *Angew. Chem., Int. Ed.*, 2014, **53**, 13004; (*c*) F. Jia and Z. Li, *Org. Chem. Front.*, 2014, **1**, 194; (*d*) W. McNeill and T. Ritter, *Acc. Chem. Res.*, 2015, **48**, 2330; (*e*) R. B. Bedford, *Acc. Chem. Res.*, 2015, **48**, 1485; (*f*) C. Cassani, G. Bergonzini and C.-J. Wallentin, *ACS Catal.*, 2016, **6**, 1640; (*g*) R. Shang, L. Ilies and E. Nakamura, *Chem. Rev.*, 2017, **117**, 9086.

11 R. Birk, H. Berke, G. Huttner and L. Zsolnaib, *Chem. Ber.*, 1988, **121**, 1557.

12 Y.-W. Shi, W. Yuan, X. Wang, J. Gong, S.-X. Zhu, L.-L. Chai, J.-L. Qi, Y.-Y. Qin, Y. Gao, Y.-L. Zhou, X.-L. Fan, C.-Y. Ji, J.-Y. Wu, Z.-W. Wang and D. Liu, *Sci. Rep.*, 2016, **6**, 30189.