



Cite this: *RSC Adv.*, 2020, 10, 13815

Received 13th February 2020
Accepted 16th March 2020

DOI: 10.1039/d0ra01408g

rsc.li/rsc-advances

Novel synthesis of divergent aryl imidazoles from ketones involving copper-catalyzed α -amination and oxidative C–C bond cleavage†

Jiangkun Huang,^a Lan Luo,^a Naiguo Xing,^a Linghui Gu,^a Chen Li,^a Qiao Han,^a Shilong Zheng^{id}*^b and Ling He^{id}*^a

A one-pot synthesis, initiated by a copper salt with inorganic (NH₄)₂CO₃ as the nitrogen source, forms divergent aryl imidazole derivatives from ketones via α -amination and oxidative C–C bond cleavage reactions. The approach provides a simple and rapid synthesis of imidazole derivatives and has certain versatility.

The aryl imidazole is a core skeleton for chiral ligands widely used in asymmetric synthesis,¹ as well as many drug molecules and natural products that possess anti-cancer, anti-infection, anti-histamine, anti-ulcer, antihypertensive, and anti-malarial activities (Fig. 1).² Therefore, how to construct an aryl imidazole core is of great significance and has been extensively studied for the development of different synthetic methods.

As early as 1858, imidazoles were first synthesized by Heinrich Debus' research group,³ and many other synthetic methods have been reported since then. These include the Bredereck synthetic method,⁴ the Leusen reaction,⁵ the Debus-Radziszewski reaction,³ the Claisen rearrangement reaction,⁶ the Phillips method,⁷ the isonitrile synthesis,⁸ and the ketones method (Scheme 1a).⁹ These methods mostly involved the traditional amination process which typically employs indirect synthesis from halogenated hydrocarbons, unsaturated bonds, and/or acyl chlorides. This leads to an increase in the number of reaction steps and limits the diversity of the substrates.

In the past decade, metal-catalyzed C–H bond activation and amination and the activation of C–C bond cleavage have been favored.^{10–13} The activation energy of C–H and C–C bonds cleavage can be reduced by directly metal-catalyzed activation of the C–H and C–C bonds, which makes the reaction easier and simplifies the synthetic process. This resulted in the development of synthetic methods for imidazole skeletons involving metal-catalyzed amination.¹⁴ However, a common problem with

these syntheses is that the starting substrates are not readily available so that these solutions are economically unreliable. Recently, a few of the tandem new bond formations after C–C bond cleavage draw our attention. These examples offer the reutilization of the molecule fragments, which can be utilized to synthesize various nitrogen-containing heterocyclic rings with the atomic economy. However, these methods also have some drawbacks and limitations that do not have universal application, such as need of ring tension for C–C bond breaking (Scheme 1b),¹¹ the participation of adjacent groups for C–C bond breaking (Scheme 1c), and C–C bond breaking in α -hydroxyketones and ketones (Scheme 1d and e).¹⁵

Following our interest in tandem metal-catalyzed transformation for the heterocyclic synthesis,¹⁶ especially the α -amination catalyzed by transition metal complexes,¹⁷ which is an attractive reaction for the synthesis of amine derivatives and amino-functionalized heterocycles, we explored the metal-catalyzed α -amination reaction of ketones using ammonia released from ammonium carbonate. In transition metal-catalyzed amination, the simple inorganic ammonium salts as the nitrogen source is a change from the conventional nitrogen sources including iodoimines, chloramines T, organic azides, hydroxylamines, NFSI, aromatic nitroso derivatives, and other organic nitrogen-containing compounds. Furthermore, it is surprising that the catalytic α -amination of the ketone results in the tandem reactions for the synthesis of imidazole while producing a small amount of amide. Herein, we report a novel

^aKey Laboratory of Drug-Targeting and Drug Delivery System of the Education Ministry, Sichuan Engineering Laboratory for Plant-Sourced Drug and Sichuan Research Center for Drug Precision Industrial Technology, Department of Medicinal Chemistry, West China School of Pharmacy, Sichuan University, Chengdu, Sichuan, 610041, P. R. China. E-mail: heling2012@scu.edu.cn

^bDepartment of Chemistry and RCM Cancer Research Center, Xavier University of Louisiana, New Orleans, LA 70125, USA

† Electronic supplementary information (ESI) available. CCDC 1853653, 1882199 and 1882198. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0ra01408g

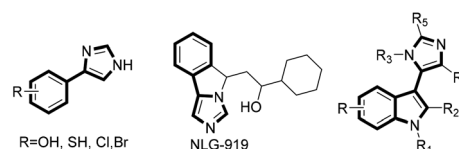
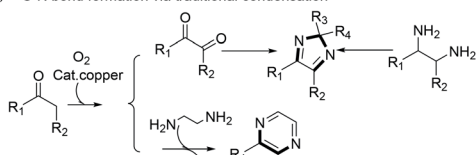


Fig. 1 Bioactive molecules containing aryl imidazole.

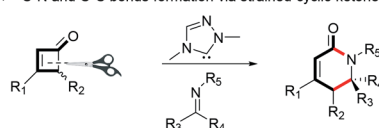


Previous work

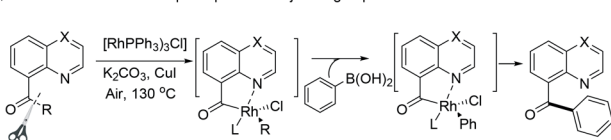
a) C-N bond formation via traditional condensation



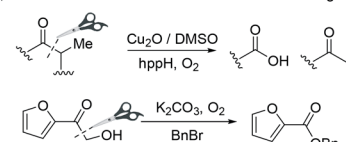
b) C-N and C-C bonds formation via strained cyclic ketone



c) C-C bond formation via participation of adjacent group



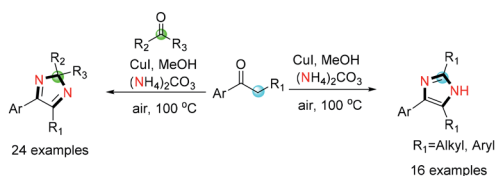
d) C-O bond formation via aerobic oxidative cleavage under oxygen atmosphere



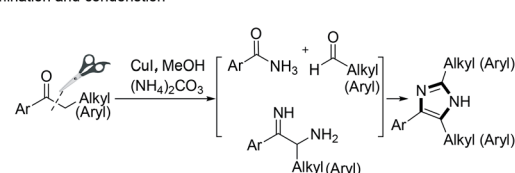
e) C-H and C-N bonds formation via oxidative cleavage under oxygen atmosphere



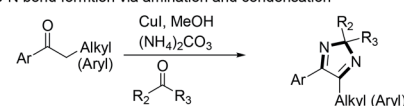
This work



f) C-N bond formation via a cascade of C-C single bond cleavage of tension free ketone, amination and condensation



g) C-N bond formation via amination and condensation



Scheme 1 Formation of imidazole derivatives and C-C single-bond cleavage.

and readily available starting materials makes this protocol economically visible.

Under the optimal reaction conditions, we explored the substrate scope of the reaction (Scheme 2). In this investigation, the corresponding imidazole derivatives (**2a–2p**) were obtained from the reaction of a series of aromatic ketones. The results show that the substrates with electron-withdrawing groups on the aromatic ring have higher reactivity than the substrates with electron-donating substituents on the aromatic ring with the exception of **2k**. The substrates containing electron-withdrawing groups on the aromatic ring afforded moderate to high yield of the imidazole products (**2b–2g**). In addition, the alkyl chain length of the aryl alkyl ketones also affected the yields of the reaction, and the longer the chain length, the lower the reactivity (**2n**, **2o**). The α -aryl substituted aromatic ketones also can afford the corresponding imidazole product (**2p**).

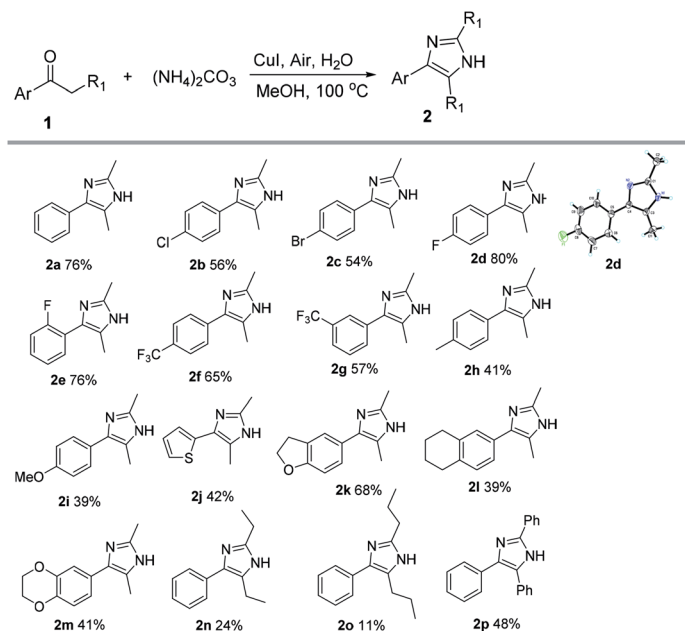
To understand the reaction for novel imidazole synthesis well, we designed a series of experiments to observe the special effects of some conditions on the imidazole synthesis (see ESI†). The effect of the nitrogen source on the reaction was first investigated. No reaction occurred in the absence of $(NH_4)_2CO_3$. This result indicates that $(NH_4)_2CO_3$ is really a nitrogen source for the reaction and it may decompose into ammonia to form a complex with copper and participates in the catalytic cycle. To confirm this point, ammonia-saturated methanol was used as the reaction solvent. The reaction occurred, but the yield of the corresponding product was only 46%. This lower yield may be due to the fact that only a limited amount of ammonia dissolved in methanol. Subsequently, the copper-ammonia complex ($Cu[NH_3]_4SO_4$) was prepared by the reaction of the copper salt with excess ammonia water and was used in the reaction. The result shows that the product was obtained in 72% yield, which confirmed that the copper-ammonia complex was not only the catalyst of the reaction, but also the nitrogen source. In addition, the effects of air and water on the reaction were also investigated. In the absence of water (anhydrous methanol) or air, no target product was obtained, indicating that water and air play an important role in the cleavage of C-C bond of propiophenone. Further, to confirm the α -C-H activation and α -amination in the imidazole formation, α -perdeuterated propiophenone was used as the substrate using deuterated methanol as a solvent in the presence of dry air and D_2O , the product was obtained in only 11% yield. The results show that C-H activation is a prerequisite for the reaction process.

In addition, referring to the C-C bond cleavage reaction,^{11,15} during the formation of imidazoles, we speculated that a portion of propiophenone may undergo cleavage of the C-C bond to produce an aldehyde. In order to confirm this, benzaldehyde was added to the reaction system, and only trace amount of original product **2a** was found. In contrast, the corresponding aldehyde condensation products was obtained in yields of 66%, respectively. If 4 equivalents of benzaldehyde are added, the formation of **2a** can also be completely inhibited. The results indicate that a competitive reaction occurs when an excess of other aldehyde is present, and the root cause is related to more rapidly α -amination than the cleavage of the C-C bond of propiophenone during the reaction. The experimental results

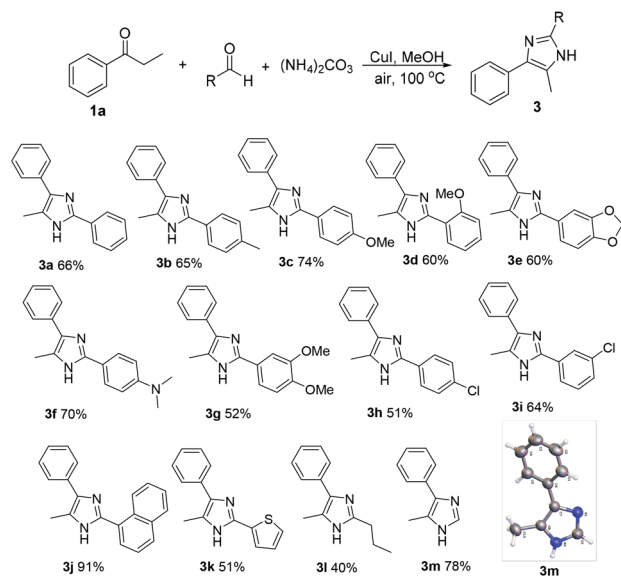
approach of imidazole formation involving α -amination and C-C bond cleavage reaction with an excellent substrate scope.

Firstly, using propiophenone as the substrate, we investigated the effect of different reaction conditions on the reaction. As shown in ESI Table 1.† The use of inexpensive ammonium carbonate as a nitrogen source and copper iodide as a catalyst





Scheme 2 Reactivity of the aryl alkyl ketones^[a]. [a] Reactions conditions: CuI (10 mol%), **1** (0.37 mmol), (NH₄)₂CO₃ (7.4 mmol), air, H₂O (0.37 mmol), MeOH (2 mL), and 100 °C for 6 h in a sealed tube.

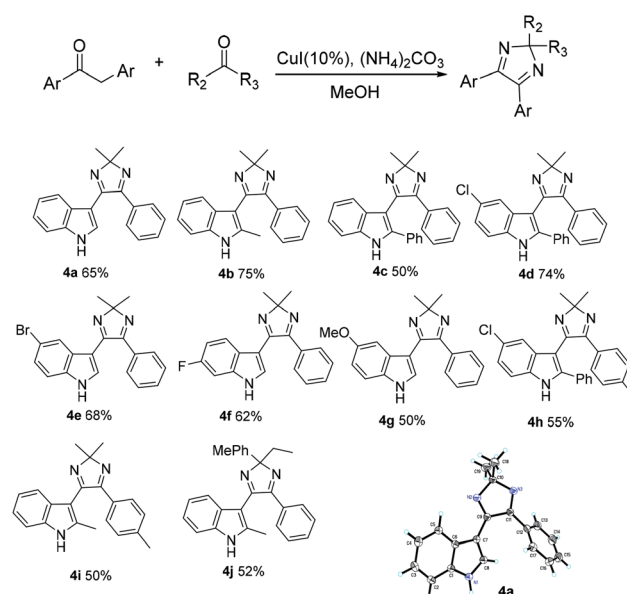


Scheme 3 The formation of divergent imidazoles from propiophenone and aldehydes^[a]. [a] Reactions conditions: CuI (10 mol%), **1a** (0.37 mmol), aldehyde (1.48 mmol), (NH₄)₂CO₃ (7.4 mmol), air, MeOH (2 mL), 24 h, 100 °C, in a sealed tube.

make us to use other aldehydes and ketones in the synthesis of divergent aryl imidazoles. As shown in Scheme 3, divergent imidazoles were obtained in excellent yield by adding four equivalents of the aldehyde to the reaction system. Both aliphatic and aromatic aldehydes yield the ideal results, but ketones failed to afford pure corresponding products, the reaction is messy and complicated. It is interesting that when 1,2-diarylethan-1-one replaces propiophenone **1a**, the addition

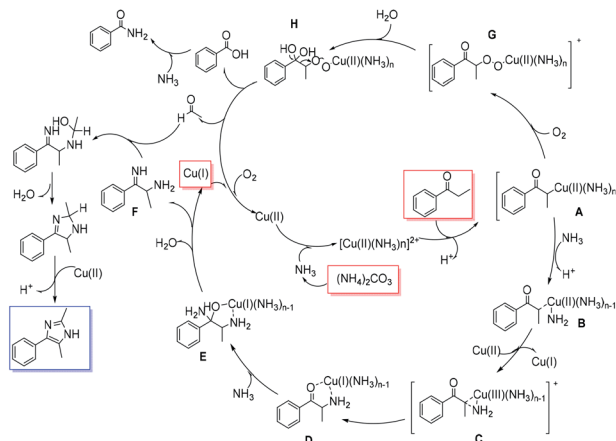
of ketones resulted in the formation of corresponding 2*H*-imidazoles (Scheme 4). Meanwhile, the formation of **4j** further indicates that the reaction rate of α -amination is faster than that of C–C bond cleavage. The structures of **2d** and **3m**, **4a** were further confirmed by the X-ray single crystal analysis (the detailed crystal data are provided in the ESI†).

At the same time, ethylamine was used as a nitrogen source and phenylacetone as a substrate to react under the same reaction conditions. The intermediates α -ethylphenyl-acetone, (*E*)-ethylacetone-1-(ethylimino)-1-phenyl-propan-2-amine and



Scheme 4 The formation of divergent imidazoles from 1, α -biarylethanone.





Scheme 5 A proposed reaction pathway for aryl imidazole synthesis.

N-ethylbenzamide and their products 1,3-diethyl-4-methyl-ene-5-phenyl-2,3-dihydro-1-himidazole were found by LC-MS (see ESI†).

On the basis of experimental results and the previously proposed mechanisms,¹⁸ a reaction pathway for aryl imidazole synthesis was proposed (Scheme 5). First, Cu(I) is oxidized to Cu(II) under an oxygen atmosphere. The Cu(II) species then forms a complex with ammonia (released from ammonium carbonate). Subsequently, the copper–ammonia complex reacts with the substrate to give intermediate A. A is converted into intermediate B after loss of a proton. B then undergoes a disproportionation reaction with NH₂ insertion to afford intermediate C. Intermediate D occurs *via* cleavage of C–Cu bond. Intermediate E forms *via* ammonia 1, 2-addition to species D. The intermediate E is then dehydrated to form compound F. Simultaneously, O₂ insertion into the C–Cu bond of intermediate A results in intermediate G. Addition of water then forms intermediate H. An aldehyde is then formed by electron transfer and cleavage of the C–C bond. Finally, the nucleophilic addition reaction of the aldehyde with intermediate F occurs to obtain the imidazole product by further dehydration and loss of a proton.

In conclusion, under copper catalysis, the aryl alkyl ketones were reacted with an inorganic salt (NH₄)₂CO₃ in one-pot to form the imidazole derivatives by C–H activated amination and C–C oxidative cleavage. We speculate that in the imidazole synthesis, a portion of aryl alkyl ketones underwent the C–C bond cleavage, and the cleavage fragment is further subjected to a multicomponent cascade reaction with other reaction intermediates to form imidazole derivatives. The approach provides a simple and rapid synthesis for imidazole derivatives and has certain versatility. When the applicability of the reaction was further explored, it was found that the addition of other aldehydes in the reaction of the arylalkyl ketone inhibited the formation of the original product, but produced a new imidazole derivative formed by condensation with the aldehydes. In the aryl alkyl ketone reaction, the addition of other aldehydes and ketones can produce more diverse imidazole derivatives.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We gratefully acknowledge the financial support from the National Natural Science Foundation of China (No. 21072131), 111 project (B18035) and Sichuan University – Lu Zhou Strategic Cooperation Projects (No. 2017 CDLZ-S34).

Notes and references

- (a) V. Cesar, S. Bellemin-Lapponnaz and L. H. Gade, *Chem. Soc. Rev.*, 2004, **33**, 619–636; (b) K. Yoshida and R. Yasue, *Chem.–Eur. J.*, 2018, **24**, 18575–18586; (c) Q. Xu, P. Gu, H. C. Jiang, Y. Wei and M. Shi, *Chem. Rec.*, 2016, **16**, 2740–2753; (d) P. Gu, J. Zhang, Q. Xu and M. Shi, *Dalton Trans.*, 2013, **42**, 13599–13606; (e) A. Schumacher, M. Bernasconi and A. Pfaltz, *Angew. Chem., Int. Ed.*, 2013, **52**, 7422–7425; (f) W. Zawartka, A. Gniewek and A. M. Trzeciak, *Inorg. Chim. Acta*, 2017, **455**, 595–599; (g) T. Soeta, Y. Hatanaka, T. Ishizaka and Y. Ukaji, *Tetrahedron*, 2018, **74**, 4601–4605; (h) V. Gauchot, J. Gravel, M. Vidal, M. Charbonneau, V. Kairouz and A. R. Schmitzer, *Synlett*, 2015, **26**, 2763–2779.
- (a) M. Sono and S. G. Cady, *Biochemistry*, 1989, **28**, 5392–5399; (b) Q. Huang, M. F. Zheng, S. S. Yang, C. X. Kuang, C. J. Yu and Q. Yang, *Eur. J. Med. Chem.*, 2011, **46**, 5680–5687; (c) S. Kumar, D. Jaller, B. Patel, J. M. LaLonde, J. B. DuHadaway, W. P. Malachowski, G. C. Prendergast and A. J. Muller, *J. Med. Chem.*, 2008, **51**, 4968–4977; (d) A. Nayak, Z. Hao, R. Sadek, R. Dobbins, L. Marshall, N. Vahanian, J. Ramsey, E. Kennedy, M. Mautino, C. Link, R. Lin, S. Royer-Joo, K. Morrissey, S. Mahrus, B. McCall, A. Pirzkal, D. Munn, J. Janik and S. Khleif, *Eur. J. Cancer*, 2015, **51**, S69; (e) J. Wiesner, R. Ortmann, H. Jomaa and M. Schlitzer, *Angew. Chem., Int. Ed.*, 2003, **42**, 5274–5293; (f) J. Wu, J. L. Mi and C. H. Zhou, *Chin. Pharm. J.*, 2007, **42**, 404–409.
- H. Debus, *Justus Liebigs Ann. Chem.*, 1858, **107**, 199–208.
- (a) T. N. Sorrell and W. E. Allen, *J. Org. Chem.*, 1994, **59**, 1589–1590; (b) W. C. Wong and C. Gluchowski, *Synthesis*, 1995, 139–140; (c) H. Bredereck and G. Theilig, *Chem. Ber.*, 1953, **86**, 88–96; (d) A. Novelli and A. Desantis, *Tetrahedron Lett.*, 1967, 265–269.
- A. M. Vanleusen, J. Wildeman and O. H. Oldenziel, *J. Org. Chem.*, 1977, **42**, 1153–1159.
- (a) N. D. Heindel and M. C. Chun, *Tetrahedron Lett.*, 1971, 1439–1440; (b) I. Lantos, W. Y. Zhang, X. Q. Shui and D. S. Eggleston, *J. Org. Chem.*, 1993, **58**, 7092–7095.
- (a) M. A. Phillips, *J. Chem. Soc.*, 1928, 172–177; (b) M. A. Phillips, *J. Chem. Soc.*, 1928, 2393–2399.
- K. Nunami, M. Yamada, T. Fukui and K. Matsumoto, *J. Org. Chem.*, 1994, **59**, 7635–7642.
- (a) B. S. Schmidt and S. Hauke, *J. Org. Chem.*, 2013, **78**, 5427–5435; (b) J. Jayram and V. Jeena, *Green Chem.*, 2017, **19**, 5841–



- 5845; (c) K. Wu, Z. L. Huang and X. T. Qi, *Sci. Adv.*, 2015, **1**, 1–7.
- 10 (a) R. H. Crabtree, *Chem. Rev.*, 1985, **85**, 245–269; (b) M. Murakami and Y. Ito, *Top. Organomet. Chem.*, 1999, **3**, 97–129; (c) M. Tobisu and N. Chatani, *Chem. Soc. Rev.*, 2008, **37**, 300–307; (d) A. Masarwa and I. Marek, *Chem.–Eur. J.*, 2010, **16**, 9712–9721; (e) M. Murakami and T. Matsuda, *Chem. Commun.*, 2011, **47**, 1100–1105; (f) T. Shen, Y. Q. Zhang, Y. F. Liang and N. Jiao, *J. Am. Chem. Soc.*, 2016, **138**, 13147–13150; (g) P. H. Chen, B. A. Billett, T. Tsukamoto and G. B. Dong, *ACS Catal.*, 2017, **7**, 1340–1360.
- 11 (a) O. G. Kulinkovich, *Chem. Rev.*, 2003, **103**, 2597–2632; (b) M. Rubin, M. Rubina and V. Gevorgyan, *Chem. Rev.*, 2007, **107**, 3117–3179; (c) T. Seiser and N. Cramer, *Org. Biomol. Chem.*, 2009, **7**, 2835–2840; (d) C. A. Carson and M. A. Kerr, *Chem. Soc. Rev.*, 2009, **38**, 3051–3060; (e) T. Seiser, T. Saget, D. N. Tran and N. Cramer, *Angew. Chem., Int. Ed.*, 2011, **50**, 7740–7752; (f) T. Seiser and N. Cramer, *J. Am. Chem. Soc.*, 2010, **132**, 5340–5341; (g) B. S. Li, Y. H. Wang, Z. C. Jin, P. C. Zheng, R. Ganguly and Y. R. Chi, *Nat. Commun.*, 2015, **6**, 6207–6210.
- 12 (a) A. M. Dreis and C. J. Douglas, *J. Am. Chem. Soc.*, 2009, **131**, 412–413; (b) N. Chatani, Y. Ie, F. Kakiuchi and S. Murai, *J. Am. Chem. Soc.*, 1999, **121**, 8645–8646; (c) J. J. Wang, W. Q. Chen, S. J. Zuo, L. Liu, X. R. Zhang and J. H. Wang, *Angew. Chem., Int. Ed.*, 2012, **51**, 12334–12338; (d) F. D. Lewis and J. G. Magyar, *J. Org. Chem.*, 1972, **37**, 2102–2107; (e) N. Zhang and J. Vozzolo, *J. Org. Chem.*, 2002, **67**, 1703–1704; (f) Z. Q. Lei, H. Li, Y. Li, X. S. Zhang, K. Chen, X. Wang, J. Sun and Z. J. Shi, *Angew. Chem., Int. Ed.*, 2012, **51**, 2690–2694; (g) T. Morioka, A. Nishizawa, T. Furukawa, M. Tobisu and N. Chatani, *J. Am. Chem. Soc.*, 2017, **139**, 1416–1419.
- 13 Y. Park, Y. Kim and S. Chang, *Chem. Rev.*, 2017, **117**, 9247–9301.
- 14 (a) J. H. Li and L. Neuville, *Org. Lett.*, 2013, **15**, 1752–1755; (b) H. C. Ma, X. Y. Zhang, L. L. Chen and W. Yu, *J. Org. Chem.*, 2017, **82**, 11841–11847; (c) S. D. Pardeshi, P. A. Sathe, K. S. Vadagaonkar, L. Melone and A. C. Chaskar, *Synthesis*, 2018, **50**, 361–370.
- 15 (a) H. Liu, C. Dong, Z. G. Zhang, P. Y. Wu and X. F. Jiang, *Angew. Chem., Int. Ed.*, 2012, **51**, 12570–12574; (b) L. Zhang, X. H. Bi, X. X. Guan, X. Q. Li, Q. Liu, B. D. Barry and P. Q. Liao, *Angew. Chem., Int. Ed.*, 2013, **52**, 11303–11307; (c) C. H. Tang and N. Jiao, *Angew. Chem., Int. Ed.*, 2014, **53**, 6528–6532; (d) Q. Xing, H. Lv, C. G. Xia and F. W. Li, *Chem. Commun.*, 2016, **52**, 489–492; (e) A. S.-K. . Tsang, A. Kapat and F. Schoenebeck, *J. Am. Chem. Soc.*, 2016, **138**, 518–526.
- 16 (a) C. L. Zhong, B. Y. Tang, P. Yin, Y. Chen and L. He, *J. Org. Chem.*, 2012, **77**, 4271–4277; (b) C. Li, N. Liu, Q. R. Qi, Y. Chen and L. He, *Eur. J. Org. Chem.*, 2015, 2585–2589; (c) L. H. Gu, P. Wang, Q. Zhong, Y. X. Deng, J. P. Xie, F. Liu, F. Xiao, S. L. Zheng, Y. Chen, G. D. Wang and L. He, *RSC Adv.*, 2017, **7**, 9412–9416.
- 17 (a) L. He, J. Yu, J. Zhang and X. Q. Yu, *Org. Lett.*, 2007, **9**, 2277–2280; (b) N. Liu, B. Y. Tang, Y. Chen and L. He, *Eur. J. Org. Chem.*, 2009, 2059–2062; (c) L. H. Gu, D. D. Zhang, Q. R. Qi, P. Yin and L. He, *Tetrahedron*, 2014, **70**, 8155–8160.
- 18 (a) X. D. Tang, J. D. Yang, Z. Z. Zhu, M. F. Zheng, W. Q. Wu and H. F. Jiang, *J. Org. Chem.*, 2016, **81**, 11461–11466; (b) S. Itoh, *Acc. Chem. Res.*, 2015, **48**, 2066–2074; (c) X. D. Tang, H. L. Gao, J. D. Yang, W. Q. Wu and H. F. Jiang, *Org. Chem. Front.*, 2014, **1**, 1295–1298; (d) X. D. Tang, L. B. Huang, Y. L. Xu, J. D. Yang, W. Q. Wu and H. F. Jiang, *Angew. Chem., Int. Ed.*, 2014, **53**, 4205–4208; (e) X. D. Tang, L. B. Huang, J. D. Yang, Y. L. Xu, W. Q. Wu and H. F. Jiang, *Chem. Commun.*, 2014, **50**, 14793–14796.

