ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2023, 59, 6885

Received 6th April 2023,
Accepted 11th May 2023

DOI: 10.1039/d3cc01687k

rsc.li/chemcomm

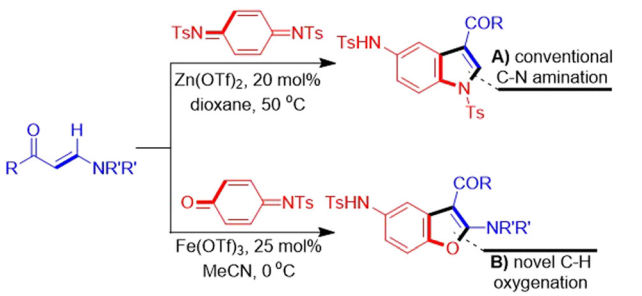
Annulation of enaminones with quinonediimides/quinoneimides for selective synthesis of indoles and 2-aminobenzofurans†

Zukang Zhong,‡[a] Lihua Liao,‡[b] Yunyun Liu,[a] Ming Zhang[a] and Jie-Ping Wan*[a]

The annulation reactions of enaminones with quinonediimides/quinoneimides for the selective synthesis of indoles and 2-aminobenzofurans have been realized. With Zn(II) catalysis, quinonediimides reacted with enaminones to give indoles *via* $HNMe_2$-elimination-based aromatization. With Fe(III) catalysis, the reactions of quinoneimides with enaminones provided 2-aminobenzofurans *via* a key dehydrogenative aromatization.

The direct activation or functionalization of C–H bonds offers powerful tools for the synthesis of numerous functional molecules.[1] One representative application of such bond transformation is the construction of heterocycles by means of either direct intramolecular or cascade ring formation.[2] Accordingly, as fundamental and highly useful heterocyclic motifs, the indoles and benzofurans have been reported to be accessible by different methods based on the conversion of C–H bonds. For example, the direct intramolecular C–H arylation of enamines provides indoles.[3] In addition, the C–H/N–H annulation of anilines or their derivatives with alkynes,[4] the annulation based on aryl C–H activation of oxime esters,[5] the electrochemical C–H/N–H annulation,[6] the C–H/N–O bond functionalization of nitrones,[7] the aryl C–H annulation with diazo compounds,[8] and various other annulation reactions of aryl C–H donors[9] have been developed for indole synthesis. On the other hand, benzofurans have also been accessed by annulation reactions based on C–H functionalization.[10] The C–H/O–H annulation of phenols and their surrogates,[11] the direct intramolecular C–H oxygenation,[12] and other C–H annulations forming C–C bonds with oxygenated substrates,[13] for instance, have been reported successively. Yet, considering the high value of both indoles and benzofurans in the discovery of new functional molecules, developing more synthetic methods,[14] especially methods free of noble metal catalysis, is still a critical task.

In recent years, enaminones have been disclosed as useful building blocks in the construction of both carbo-aryls and heterocyclic aromatic systems.[15] The typical feature of a C–N bond cleavage in enaminones in the fashion of amine elimination has been identified as an individual advantage of enaminone-based aromatization.[16] In addition, the flexible transformation pathways of the enaminones' α-C–H bonds are reliable in the formation of various new chemical bonds.[17] In light of these known transformations, we assumed that employing enaminones in the designation of new synthetic protocols toward indoles and benzofurans would be feasible. Herein, we report our results in the enaminone-based annulation reaction for the selective synthesis of indoles and benzofurans. The reactions using quinonediimide provide indoles *via* amine elimination-induced aromatization with Zn(II) catalysis (Scheme 1A). On the other hand, when quinoneimide is used as a reaction partner, the dehydrogenative aromatization takes place to provide 2-aminobenzofurans selectively under modified conditions of Fe(III) catalysis (Scheme 1B).



Scheme 1 Selective synthesis of indoles and benzofurans by enaminone-involved aryl ring formation.

[a] *National Engineering Research Center for Carbohydrate Synthesis, College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang, 330022, China. E-mail: wanjieping@jxnu.edu.cn, chemwanjp@sina.com*

[b] *School of Food and Chemical Engineering, Shaoyang University, Shaoyang 422000, China*

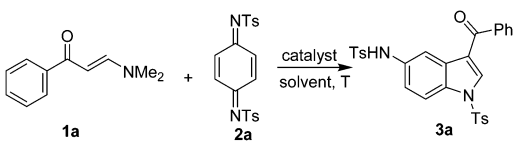
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, and NMR spectra. CCDC 2236958. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d3cc01687k

‡ Z. Zhong and L. Liao contributed equally to this work.

Initially, the reaction of enaminone **1a** and quinonediimide **2a** was conducted in 1,4-dioxane in blank or in the presence of a Brønsted/Lewis acid. The results proved that an acid catalyst was important, and $Zn(OTf)_2$ was amongst the most appropriate catalyst (entries 1–4, Table 1). The subsequent efforts in varying the reaction medium by using DMF, MeCN, water and THF did not give better results (entries 5–8, Table 1). While running the reaction at different temperatures or with different reaction times did not improve the result (entries 9–12, Table 1), increasing the loading of **2a** gave **3a** with an evidently higher yield (entry 13, Table 1).

To verify the scope of the method toward indoles, a broad variety of enaminones **1** were used to react with **2** under the optimal conditions (Scheme 2). According to the results, the aroyl-based enaminones were generally tolerated to the title indole synthesis. While most benzoyl-based enaminones afforded products with excellent yields (**3a–3g**, **3j** and **3n**, Scheme 2), the strong electron-withdrawing effect displayed a negative impact by giving the related products with lower yields (**3h** and **3i** and **3k–3m**, Scheme 2). Moreover, enaminone bearing a fused naphthyl group reacted with **2** to provide product **3o** with a good yield. Heteroaryls, such as thiophenyl- and pyrrolyl-functionalized enaminones were also smoothly utilized to give products **3p** and **3q** with practical results. More noteworthy, the natural product 16-dehydropregenolone acetate could be elaborated to produce product **3r** with a high yield *via* such indole formation. The reaction using substrate 2 with a different sulfonyl structure (phenyl sulfonyl) was used to provide product **3s** with an excellent yield. On the other hand, the alkyl-derived *N*,*N*-dimethyl enaminone as well as *N*,*N*-dimethyl nitroenamine did not react with **2a** to give the expected products. As extended entries, the 1,3-diketone could react with **2a** to give indole **3t**, and 1,4-benzoquinone reacted with **2a** to afford benzofuran **3u** under the standard conditions (Scheme 2).

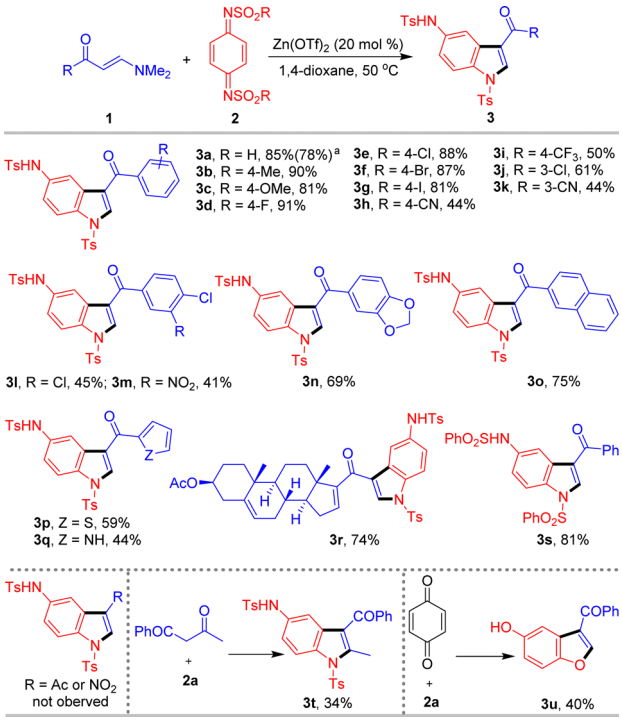
Table 1 Optimization of the reaction conditions[a]



1a 2a 3a

Entry	Catalyst	Solvent	t (°C)	Yield[b] (%)
1	—	1,4-Dioxane	50	9
2	$Zn(OTf)_2$	1,4-Dioxane	50	70
3	$Cu(OTf)_2$	1,4-Dioxane	50	56
4	TFA	1,4-Dioxane	50	46
5	$Zn(OTf)_2$	DMF	50	63
6	$Zn(OTf)_2$	CH_3CN	50	68
7	$Zn(OTf)_2$	H_2O	50	0
8	$Zn(OTf)_2$	THF	50	52
9	$Zn(OTf)_2$	1,4-Dioxane	30	67
10	$Zn(OTf)_2$	1,4-Dioxane	70	62
11[c]	$Zn(OTf)_2$	1,4-Dioxane	50	45
12[d]	$Zn(OTf)_2$	1,4-Dioxane	50	70
13[e]	$Zn(OTf)_2$	1,4-Dioxane	50	85

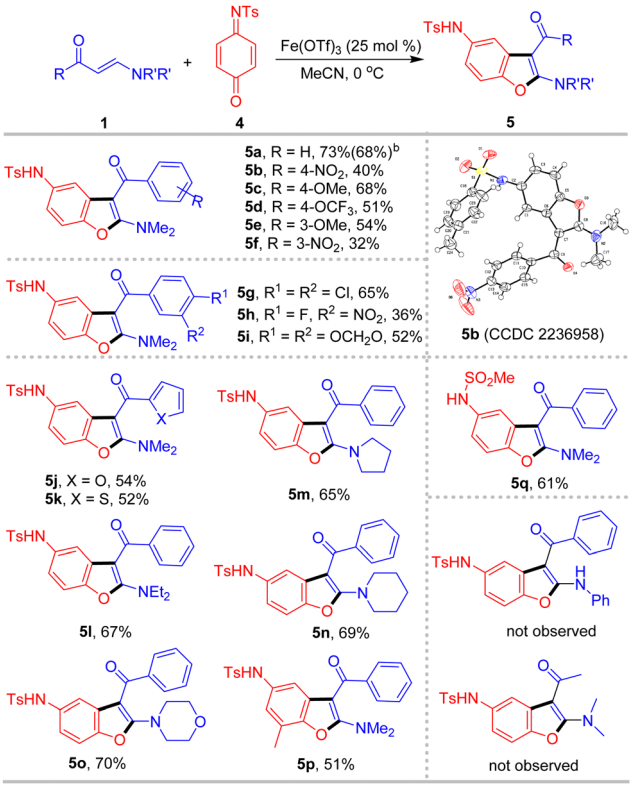
[a] General conditions: **1a** (0.2 mmol), 2 (0.24 mmol), catalyst (20 mol%), and solvent (2 mL), stirred in a sealed tube for 24 h. [b] Yield of isolated product. [c] Stirred for 12 h. [d] Stirred for 26 h. [e] With 0.3 mmol of **2**.



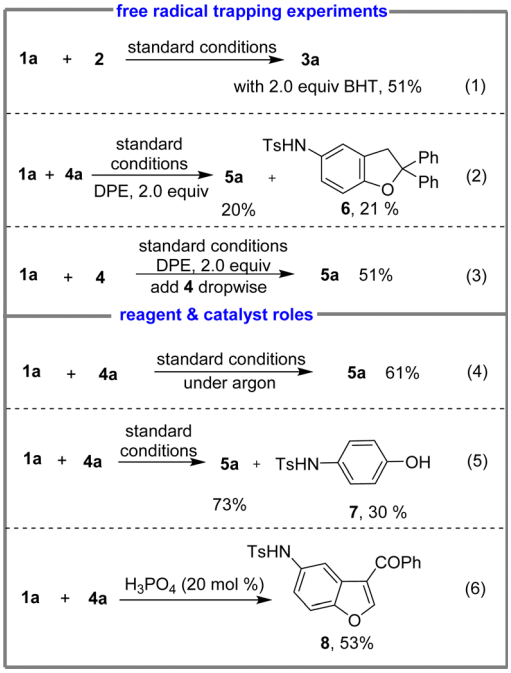
Scheme 2 Scope for the synthesis of indoles ([a]yield from 1 mmol scale reaction).

Interestingly, while quinoneimide **4a** was initially found to be inapplicable for the above indole synthesis, the efforts in modifying the reaction conditions enabled us to realize an unprecedented synthetic route to benzofurans **5** (see ESI† for the optimization data). As outlined in Scheme 3, the regioselective synthesis of benzofurans exhibited broad application scope (**5a–5o**). The reactions employing *N*,*N*-dimethyl enaminones (**5a–5k**, Scheme 3), *N*,*N*-diethyl enaminone (**5l**, Scheme 3) and cyclic secondary amino functionalized enaminones (**5m–5o**, Scheme 3) were run smoothly to provide the benzofuran products. Analogously, strong electron-withdrawing groups in the phenyl ring of the enaminones were also negative for the reaction by providing products with lower yields (**5b**, **5f**, **5h**, Scheme 3). When the alkyl-based enaminone of type **1** (R = Me) or NH-based enaminone (*N*-phenyl enaminone) was used to react with **4a**, the corresponding benzofuran formation was not observed (Scheme 3). Later, the attempts by employing quinoneimides with different substructures led to the successful synthesis of products with expanded diversity (**4p** and **4q**, Scheme 3). Using 1,4-benzoquinone to react with **1a** did not provide the 2-aminobenzofuran with Fe(III) catalysis.

For the sake of exploring the reaction mechanism, an array of control experiments were executed. As shown in Scheme 4, the reactions in the presence of free radical scavengers were run first. The reaction providing indole **3a** was not eventually inhibited by BHT (Eqn (1), Scheme 4). Much lower yield of **5a** was afforded in the presence of DPE in the reaction of quinoneimide, but compound **6** resulting from annulation of **4a** and DPE was observed (Eqn (2), Scheme 4), indicating that both reactions were not likely free radical reactions. Complementarily, adding



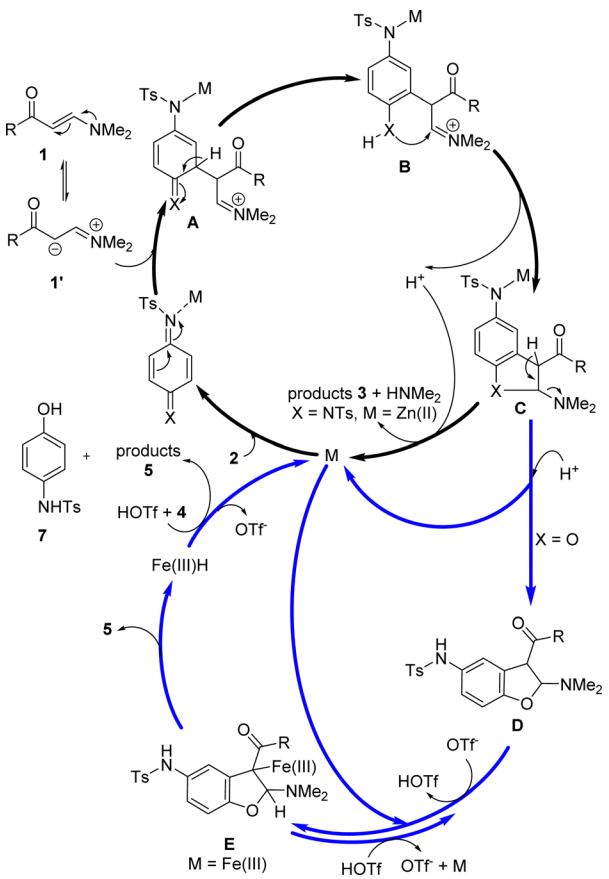
Scheme 3 Scope of the benzofuran synthesis *via* triple fold C–H functionalization (yield from 1 mmol scale reaction).



Scheme 4 Control experiments.

quinoneimide **4a** dropwise after all other reagents and DPE could give **5a** with 51% yield (Eqn (3), Scheme 4), further supporting that the low yield of **5a** in Eqn (2) came from the competition of DPE-quinoneimide annulation, rather than free radical quenching. Actually, analyzing the reaction residue with GC–MS did not show the presence of any plausible free radical adduct species, suggesting also that no free radical pathway was involved. On the other hand, the roles of related reagents and catalysts were also probed. Considering the formal dehydrogenative transformation, we performed the reaction for the synthesis of **5a** under argon, which led to the isolation of **5a** with 61% yield (Eqn (4), Scheme 4), proving that air was not the oxidant in the reactions. Meanwhile, from the standard reaction for **5a** synthesis, the hydroxyl aniline derivative **7** resulting from quinoneimide hydrogenation was obtained with 30% yield (Eqn (5), Scheme 4), implying that quinoneimide acted simultaneously as the oxidant in the reactions. Moreover, altering the Fe(III)-catalyst in the reaction to a proton acid did not yield 2-aminobenzuofuran **5a**. Instead, 2-unsubstituted benzofuran **8** resulting from the elimination of dimethyl amine was formed (Eqn (6), Scheme 4), proving that the Fe-catalyst was crucial for the selective dehydrogenation providing **5a**.

Based on the in hand results, the mechanisms for the title reactions are proposed (Scheme 5). As for the formation of indoles **3**, the reactions may start from the 1,4-nucleophilic addition of enaminones to quinonediimide **2** to afford adduct **A** *via* enaminones' isomeric version **1′** under the assistance of the



Scheme 5 The proposed reaction mechanisms.

metal catalyst (M = Zn) in which the zinc salt acts as a Lewis acid. The successive 1,3-hydrogen transfer gives iminium intermediate **B**. The nucleophilic addition of the nitrogen atom in NTs to the iminium affords **C** and a proton. The *N*-protonation in **C** as well as the elimination of $HNMe_2$ in the heterocyclic moiety leads to the formation of indole products **3,** while the zinc catalyst gets regenerated. On the other hand, in the reactions of quinoneimide, similar transformations take place to the stage of **C**. The cyclization takes place in the C=O (X = O) fragment because the *O*-site in quinoneimide is more nucleophilic. A similar *N*-protonation provides dihydrofuran intermediate **D**. As a typical transition metal catalyst, the Fe(III) is capable of inserting into the α-C–H bond in **D**, which generates intermediate **E** with the assistance of TfO^-. The β-elimination of MH species[18] from **E** provides products **5**. The reaction of the proton and quinoneimide with MH releases the metal ion catalyst for further catalysis and the quinoneimide is thus hydrogenated to *p*-hydroxyl aniline by acting as the oxidant.

In summary, new methods for the synthesis of functionalized indoles and 2-aminobenzofurans have been developed *via* the reactions of enaminones with quinonediimides and quinoneimides, respectively. The catalysis of $Zn(OTf)_2$ in the reactions of quinonediimide and enaminones provides indoles *via* dual C–H bond functionalization and enaminone C–N bond transamination. On the contrary, regioselective synthesis of 2-aminobenzofurans has been realized by $Fe(OTf)_3$-catalyzed annulation of enaminones with quinoneimide *via* the transformation of three C–H bonds in the two substrates. Mechanism analysis demonstrates that the Fe(III) insertion into the C–H bond and the quinoneimide as a hydrogen acceptor are the key factors in inducing the selective synthesis of 2-aminobenzofurans.

J. W. conceived the idea and guided the project. Z. Z. and L. L. conducted most of the experiments. Y. L. and M. Z. participated in the experimental work and the discussion during the research process. J. W. wrote the manuscript with the input of all the authors.

This work is financially supported by the National Natural Science Foundation of China (22161022).

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (*a*) D. Chen, J. Jiang and J.-P. Wan, *Chin. J. Chem.*, 2022, **40**, 2582–2594; (*b*) H. Gu, X. Jin, J. Li, H. Li and J. Liu, *Chin. J. Org. Chem.*, 2022, **42**, 2682–2702; (*c*) D. Mandal, S. Roychowdhury, J. P. Biswas, S. Maiti and D. Maiti, *Chem. Soc. Rev.*, 2022, **51**, 7358–7426.

2 (*a*) A. Baccalini, G. Faita, G. Zanoni and D. Maiti, *Chem. – Eur. J.*, 2020, **26**, 9749–9783; (*b*) S. Liu, G.-J. Deng and H. Huang, *Synlett*, 2021, 142–158; (*c*) M. Zhang, *Adv. Synth. Catal.*, 2009, **351**, 2243–2270; (*d*) X.-X. Guo, D.-W. Gu, Z. Wu and W. Zhang, *Chem. Rev.*, 2015, **115**, 1622–1651.

3 (*a*) S. Würtz, S. Rakshit, J. J. Neumann, T. Dröge and F. Glorius, *Angew. Chem., Int. Ed.*, 2008, **47**, 7230–7233; (*b*) R. Bernini, G. Fabrizi, A. Sferrazza and S. Cacchi, *Angew. Chem., Int. Ed.*, 2009, **48**, 8078–8081.

4 (*a*) D. R. Stuart, M. Bertrand-Laperle, K. M. N. Burgess and K. Fagnou, *J. Am. Chem. Soc.*, 2008, **130**, 16474–16475; (*b*) D. Zhao, Z. Shi and F. Glorius, *Angew. Chem., Int. Ed.*, 2013, **52**, 12426–12429; (*c*) Z. Shi, C. Zhang, S. Li, D. Pan, S. Ding, X. Cui and N. Jiao, *Angew. Chem., Int. Ed.*, 2009, **48**, 4572–4576; (*d*) C. Wang, H. Sun, Y. Fang and Y. Huang, *Angew. Chem., Int. Ed.*, 2013, **52**, 5795–5798.

5 Y. Tan and J. F. Hartwig, *J. Am. Chem. Soc.*, 2010, **132**, 3676–3677.

6 Z.-W. Hou, Z.-Y. Mao, H.-B. Zhao, Y. Y. Melcamu, X. Lu, J. Song and H.-C. Xu, *Angew. Chem., Int. Ed.*, 2016, **55**, 9168–9172.

7 (*a*) H. Yan, H. Wang, X. Li, X. Xin, C. Wang and B. Wan, *Angew. Chem., Int. Ed.*, 2015, **54**, 10613–10617; (*b*) H. Wang, M. Moselage, M. J. González and L. Ackermann, *ACS Catal.*, 2016, **6**, 2705–2709.

8 (*a*) Y. Li, Z. Qi., H. Wang, X. Yang and X. Li, *Angew. Chem., Int. Ed.*, 2016, **55**, 11877–11881; (*b*) J. Wang, M. Wang, K. Chen, S. Zha, C. Song and J. Zhu, *Org. Lett.*, 2016, **18**, 1178–1181.

9 (*a*) S. Jana, M. D. Clements, B. K. Sharp and N. Zheng, *Org. Lett.*, 2010, **12**, 3736–3739; (*b*) J. Bonnamour and C. Bolm, *Org. Lett.*, 2011, **13**, 2012–2014; (*c*) M. Kumar, A. Rastogi, Raziullah, A. Ahmad, M. K. Gangwar and D. Koley, *Org. Lett.*, 2022, **24**, 8729–8734; (*d*) Y. Luo and L. Dong, *J. Org. Chem.*, 2022, **87**, 5577–5591.

10 S. Agasti, A. Dey and D. Maiti, *Chem. Commun.*, 2017, **53**, 6544–6556.

11 (*a*) L. Hu, M. C. Dietl, C. Han, M. Rudolph, F. Rominger and A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2021, **60**, 10637–10642; (*b*) Z. Zhou, G. Liu, Y. Shen and X. Lu, *Org. Chem. Front.*, 2014, **1**, 1161–1165; (*c*) D.-H. Lee, K.-H. Kwon and C. S. Yi, *J. Am. Chem. Soc.*, 2012, **134**, 7325–7328; (*d*) Y.-L. Mei, W. Zhou, T. Huo, F.-S. Zhou, J. Xue, G.-Y. Zhang, B.-T. Ren, C. Zhong and Q.-H. Deng, *Org. Lett.*, 2019, **21**, 9598–9602.

12 (*a*) J. Ghorai, A. C. S. Reddy and P. Anbarasan, *Chem. – Eur. J.*, 2016, **22**, 16042–16046; (*b*) L. Guo, F. Zhang, W. Hu, L. Li and Y. Jia, *Chem. Commun.*, 2014, **50**, 3299–3302; (*c*) Y. Moon, Y. Kim and S. Hong, *Chem. Commun.*, 2013, **49**, 8323–8325.

13 (*a*) T. Torigoe, T. Ohmura and M. Suginome, *Chem. – Eur. J.*, 2016, **22**, 10415–10419; (*b*) S. Yu, N. Lv, Z. Liu and Y. Zhang, *Adv. Synth. Catal.*, 2020, **362**, 118–125; (*c*) S. S. Bera, S. Debbarma, S. Jana and M. S. Maji, *Adv. Synth. Catal.*, 2018, **360**, 2204–2210.

14 (*a*) A. J. Kochanowska-Karamyan and M. T. Hamann, *Chem. Rev.*, 2010, **110**, 4489–4497; (*b*) F. E. de Sa Alves, E. J. Barreiro and C. A. M. Fraga, *Mini-Rev. Med. Chem.*, 2009, **9**, 782–793; (*c*) E. Stempel and T. Gaich, *Acc. Chem. Res.*, 2016, **49**, 2390–2402; (*d*) R. J. Nevagi, S. N. Dighe and S. N. Dighe, *Eur. J. Med. Chem.*, 2015, **97**, 561–581.

15 (*a*) Z. Wang, B. Zhao, Y. Liu and J. Wan, *Adv. Synth. Catal.*, 2022, **364**, 1508–2521; (*b*) X.-F. Xia and Y.-N. Niu, *Org. Biomol. Chem.*, 2022, **20**, 282–295; (*c*) J. Huang and F. Yu, *Synthesis*, 2021, 587–610.

16 (*a*) J. Huo, X. Geng, W. Li, P. Zhang and L. Wang, *Org. Lett.*, 2023, **25**, 512–516; (*b*) H. Guo, Y. Liu, C. Wen and J.-P. Wan, *Green Chem.*, 2022, **24**, 5059–5063; (*c*) Y. Guo, Y. Liu and J.-P. Wan, *Chin. Chem. Lett.*, 2022, **33**, 855–858; (*d*) Y. Zhou, L.-S. Wang, S.-G. Lei, Y.-X. Gao, J.-T. Ma, Z.-C. Yu, Y.-D. Wu and A.-X. Wu, *Org. Chem. Front.*, 2022, **9**, 4416–4420; (*e*) B. Qi, S. Guo, W. Zhang, X. Yu, C. Song and J. Zhu, *Org. Lett.*, 2018, **20**, 3996–3999.

17 (*a*) J. Zeng, J.-P. Wan and Y. Liu, *J. Org. Chem.*, 2022, **87**, 13195–13203; (*b*) Z.-W. Wang, Y. Zheng, Y.-E. Qian, J.-P. Guan, W.-D. Lu, C.-P. Yuan, J.-A. Xiao, K. Chen, H.-Y. Xiang and H. Yang, *J. Org. Chem.*, 2022, **87**, 1477–1484; (*c*) X. Duan, H. Li, W. Li, J. Wang and X. Duan, *ChemistrySelect*, 2021, **6**, 6478–6482; (*d*) L. Fu, W. Xu, M. Pu, Y.-D. Wu, Y. Liu and J.-P. Wan, *Org. Lett.*, 2022, **24**, 3003–3008.

18 (*a*) L. Deng, P. Margl and T. Ziegler, *J. Am. Chem. Soc.*, 1999, **121**, 6479–6487; (*b*) Y. Zhang, M. Wang, P. Li and L. Wang, *Org. Lett.*, 2012, **4**, 2206–2209.

