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Convenient synthesis of spiroindolenines from tryptamine-derived isocyanides and organic azides by cobalt catalysis in pure water†

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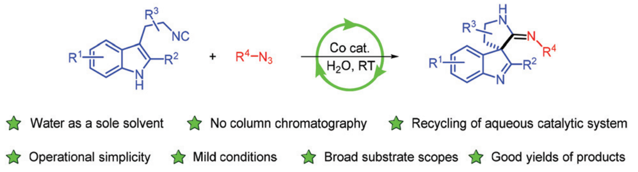
A Co-catalyzed coupling of 3-(2-isocyanoethyl)indoles with organic azides in pure water for accessing spiroindolenine derivatives was developed. This strategy features mild reaction conditions, high atom-economy, excellent yields, wide substrate scopes, and broad functional group tolerance. The products were obtained simply by sequential operation involving extraction, concentration, precipitation, and filtration, without tedious column chromatography. More importantly, the aqueous catalytic system could be recycled at least ten times without reducing the catalytic activity. The strategy provides a green and efficient method for the construction of spiroindolenine derivatives.

Using water as a medium for organic reactions has aroused broad interest due to its low cost, abundant reserves, non-toxicity and strong hydrogen-bonding nature.[1] Existing studies have shown that water as a solvent has a positive impact on reaction rates and selectivity.[2] Recently, Kobayashi and co-workers divided the catalytic reactions performed in water into seven types depending on which phase the catalyst is in.[3] According to the new version of the Twelve Principles of Green Chemistry published by Anastas and Leitner in 2020,[4] the development of organic reactions involving cheap metal catalysts, a green solvent system with low toxicity and recyclability, and a simple separation process is highly desired. As to the known reactions in the aqueous phase,[5] there are still some deficiencies to be overcome in order to meet the demand of green organic synthesis. Thus, we are committed to developing green organic transformations featuring atom-economy, step-economy, and low solvent and metal catalyst consumption.

On the other hand, spiroindolenine derivatives exist in a wide range of natural products and biologically active molecules.[6] Because of the importance of these compounds, many methods have been established for their synthesis.[7] Although significant advances have been achieved, the existing methods often suffer from complicated steps and limited substrate scope. Tryptamine-derived isocyanide, as an organic synthon with multiple reactive sites, has been proven to be a highly efficient building block for the synthesis of spiroindolines.[8] Among those approaches reported, tedious work-up and the use of organic solvents as the reaction medium are often required. Hence, a green reaction mode has become an urgent pursuit to construct such skeletons. We envision whether it is possible to realize efficient synthesis of spiroindolenines in pure water by the cascade reaction of tryptamine-derived isocyanides with a simple purification procedure.

To our delight, a coupling reaction of tryptamine-derived isocyanides with organic azides in pure water for accessing spiroindolenine derivatives was reasonably designed and performed. The products were purified by simple extraction operation without tedious column chromatography, and the aqueous phase catalytic system could be recycled at least ten times without reducing the catalytic activity (Scheme 1). Hence, we report a systematic study on the green synthesis of spiroindolenines by using this method.

Initially, the tandem reaction of tryptamine-derived isocyanide **1a** with tosyl azide **2a** was performed in pure water at 25 °C in the presence of cobalt oxalate (CoC_2O_4), and the



Scheme 1 Coupling of tryptamine-derived isocyanides with organic azides.

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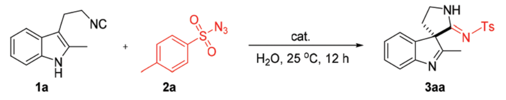
desired product **3aa** could be isolated in 96% yield by column chromatography (Table 1, entry 1). To our delight, when the product was separated by simple extraction instead of column chromatography (for details, see the ESI†), the product **3aa** was also obtained successfully with high purity, and the yield was comparable (Table 1, entry 2). Afterwards, several water-soluble catalysts such as $CoCl_2$ and $Co(OAc)_2·4H_2O$ were screened as well (Table 1, entries 3 and 4), and a similarly high yield of 94% was obtained by using $Co(OAc)_2·4H_2O$ as the catalyst. The product was again purified by extraction with no need for column chromatography (Table 1, entry 4). However, when the catalyst loading was reduced to 2 mol%, only 86% yield of the target product was isolated (Table 1, entry 5).

With the optimized reaction conditions in hand, we investigated the scope of organic azides **2** (Table 2). It was gratifying to find that substituted sulfonyl azides **2a–2m** with electron-donating groups (Me, OMe, *ᵗ*Bu), electron-withdrawing groups (CF_3, CN, NO_2), and halogen atoms (F, Cl, Br, I) exhibited very high reactivity under the optimized reaction conditions (**3aa–3am**). The structure of **3ak** was unambiguously determined by single crystal X-ray crystallography and spectroscopic analysis (CCDC 2034492; see the ESI†). Next, sulfonyl azides **2n–2u** containing naphthalene rings, benzoheterocycles, heterocycles, and alkyl substituents were also tested. Benzoquinoline- and benzotetrahydrofuran-substituted sulfonyl azides could give the desired products **3ap** and **3aq** in excellent yields. Similarly, heterocyclic thiophene- and isoxazole-substituted sulfonyl azides reacted well to afford the corresponding products **3ar** and **3as** in 79% and 88% yields, respectively. In addition to arylsulfonyl azides, alkylsulfonyl azides **2t** and **2u** were also proved to be suitable candidates, producing the target products **3at** and **3au** in 90% and 96% yields.

It should be noted that other azide substrates such as aryl azide and azidotrimethylsilane are not suitable candidates for this reaction, and no spiroindolenines could be obtained.

The substrate scope of tryptamine-derived isocyanides **1** was then examined, and the results are presented in Table 3. Various substituted 3-(2-isocyanoethyl)indoles **1**, possessing 5-Me, 5-MeO, 5-F and 5-Cl on the aromatic ring, were tolerated, and the expected products **3ba–3ea** were isolated in excellent

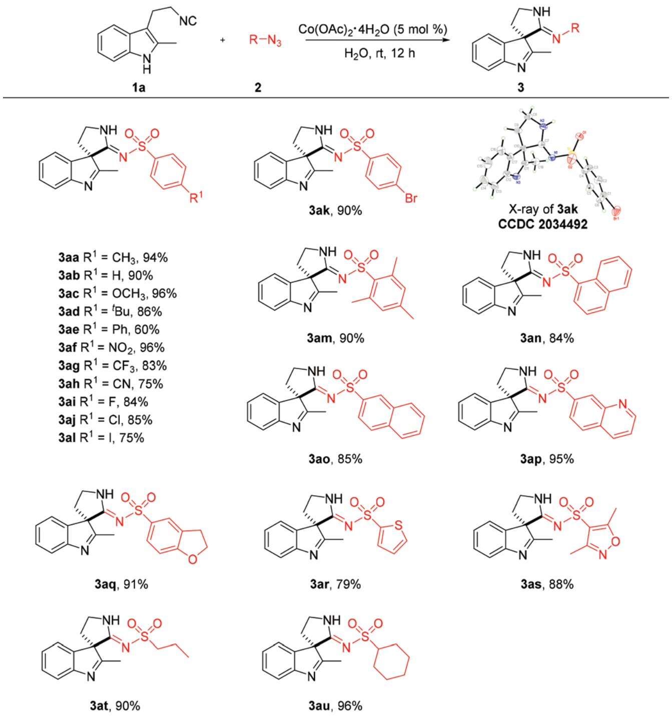
Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst (*x* mol%)	Yield[b] (%)
1	CoC_2O_4 (5)	96[c]
2	CoC_2O_4 (5)	93[d]
3	$CoCl_2$ (5)	90[d]
4	**$Co(OAc)_2·4H_2O$ (5)**	**94**[d]
5	$Co(OAc)_2·4H_2O$ (2)	86[d]

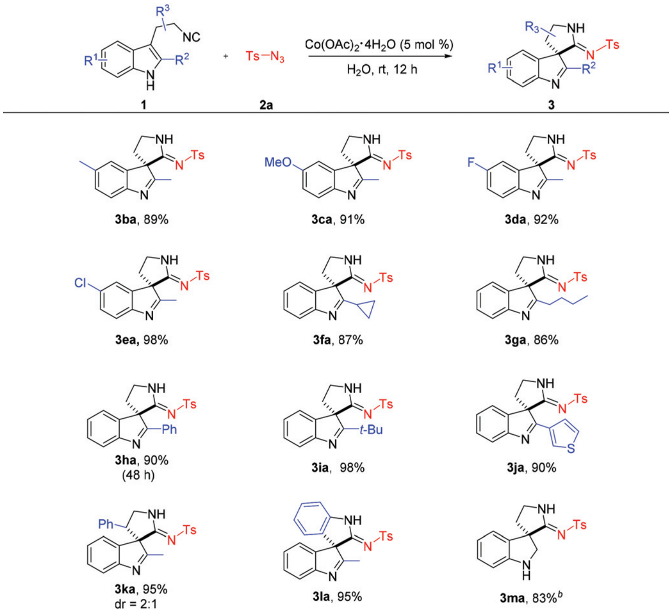
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), catalyst (*x* mol%), water (4 mL) at 25 °C for 12 h. [b] Isolated yield. [c] Purified by column chromatography. [d] Simply purified by extraction.

Table 2 Substrate scope of sulfonyl azides[a]



[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.2 mmol), $Co(OAc)_2·4H_2O$ (5 mol%), H_2O (4 mL) at 25 °C for 12 h.

Table 3 Substrate scope of tryptamine-derived isocyanides[a]



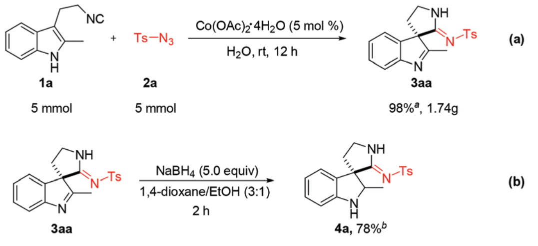
[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.2 mmol), $Co(OAc)_2·4H_2O$ (5 mol%), H_2O (4 mL) at 25 °C for 12 h. [b] Reaction conditions: (1) **1** (0.2 mmol), **2a** (0.2 mmol), $Co(OAc)_2·4H_2O$ (5 mol%), 1,4-dioxane (3 mL) at 25 °C for 12 h. (2) $NH_3·BH_3$ (5.0 equiv.) was added at 25 °C for another 2 h reaction.

yields. Next, some C2-substituted isocyanides were studied and 2-phenyl-substituted 3-(2-isocyanoethyl)indole **1h** could give the corresponding product **3ha** in 90% yield after the reaction time was prolonged to 48 hours. Interestingly, the excellent yield obtained for isocyanide **1i** bearing the 2-*tert*-butyl substituent indicated that steric hindrance had little influence on this transformation. Additionally, α-Ph-substituted isonitrile **1k** could also be converted into the target product **3ka** (dr = 2 : 1) in 95% yield. Unfortunately, C2-unsubstituted isocyanide **1m** could not give the desired cyclization product under the optimized reaction conditions. We speculated that the product may be unstable and decomposed slowly during work-up. Interestingly, product **3ma** could be obtained through an *in situ* reduction strategy in a one-pot process in 83% yield.

To reveal the potential of synthetic applications, a gram-scale reaction under the standard conditions was carried out and the product **3aa** could be obtained in 98% yield (Scheme 2, a). In addition, using 5 equivalents of $NaBH_4$ to reduce **3aa** could furnish the desired product **4a** in 78% yield (Scheme 2, b).

To meet the new principles of green chemistry by Anastas and Leitner, the recyclability of the cobalt catalyst in water was tested under the standard conditions (Fig. 1). After extraction of the product, the aqueous catalytic system could be easily reused for the next reaction. Interestingly, after ten times recycling of the aqueous catalytic system, no visible decrease of catalytic activity was observed.

During the whole reaction process, the raw materials and products were insoluble in water while the catalyst was soluble, which is in accordance with one of the seven reaction types summarized by Kobayashi.[3] In order to show the reaction process more intuitively, the concentration of cobalt ions in water was determined using an inductively coupled plasma spectrometer (Fig. 2). At first, the reaction proceeded fast due to the high concentration of reactants, resulting in a decrease of the concentration of cobalt ions. With the progress of the reaction, the concentration recovered to 30 ppm after four hours. After that, no obvious alteration of the concentration of cobalt ions was observed. Therefore, we speculate that the reaction occurred on the interface between the substrate and water.



Scheme 2 Gram-scale synthesis and further transformation. [a]Reaction conditions: **1a** (5 mmol), **2a** (5 mmol), $Co(OAc)_2·4H_2O$ (5 mol%), H_2O (60 mL) at 25 °C for 12 h. [b]Reaction conditions: **3aa** (0.2 mmol), $NaBH_4$ (5.0 equiv.), 1,4-dioxane (3 mL), EtOH (1 mL) at 25 °C for 2 h.

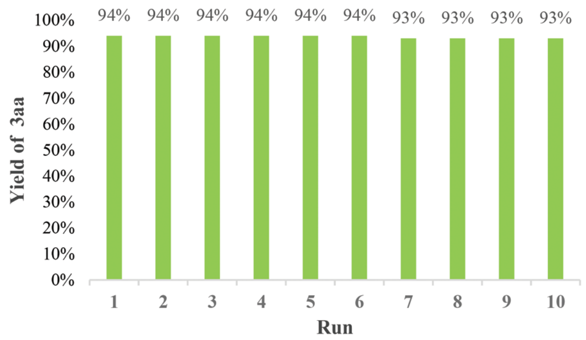


Fig. 1 Catalyst recycling study.

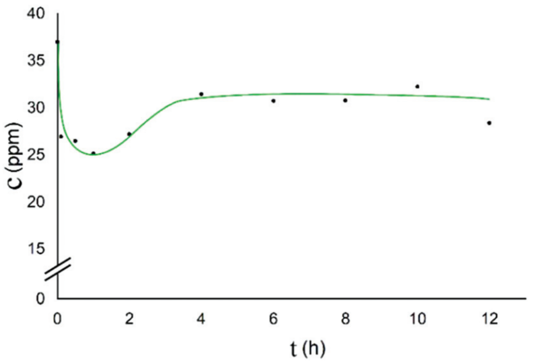
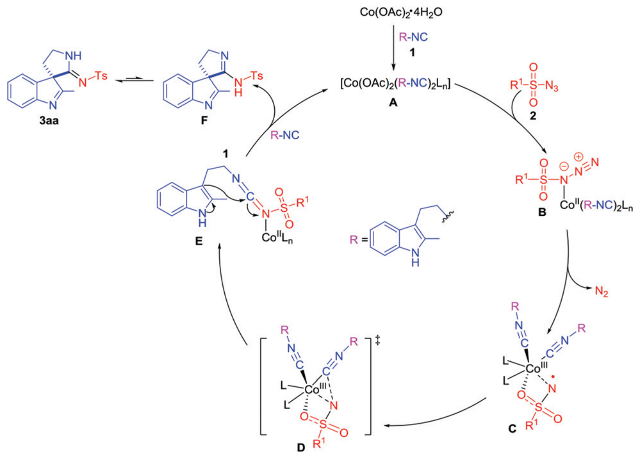


Fig. 2 Variation of the Co^{2+} concentration with the reaction time.

Based on the above observations and previous works,[9] a plausible mechanism was suggested as shown in Scheme 3. First, the fast ligand exchange of tryptamine-derived isocyanides with $Co(OAc)_2·4H_2O$ gives cobalt complex **A** on the interface between the substrate and water. Complex **A** reacts with sulfonyl azides to produce complex **B**, which then generates Co(III)–nitrene intermediate **C** with the release of N_2. Subsequently, carbodiimide intermediate **E** is obtained by the coupling reaction of **C** with the coordinated isocyano group.



Scheme 3 Plausible reaction mechanism.

Then the nucleophilic C3 position of indole triggers spirocyclization to afford the desired product **3aa**.

Conclusions

In conclusion, a new approach for Co-catalyzed coupling of tryptamine-derived isocyanides with sulfonyl azides in water to construct spiroindolenine derivatives has been successfully demonstrated. Instead of column chromatography used for most work-up processes, purification of the products in our case can be realized simply by sequential operation involving extraction, concentration, precipitation, and filtration. This strategy features mild reaction conditions, high atom economy, excellent yields, wide substrate scopes, and broad functional group tolerance. More importantly, the aqueous catalytic system could be recycled at least ten times without a visible decrease of catalytic activity. The strategy is in line with the new green chemistry concept, and it may have a potential application in industrial production. From the *N*-sulfonyl amidine skeleton point of view, the product can also serve as a potential intermediate for diverse organic syntheses.[10]

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 (*a*) M. O. Simon and C.-J. Li, *Chem. Soc. Rev.*, 2012, **41**, 1415; (*b*) C.-J. Li, *Chem. Rev.*, 2005, **105**, 3095; (*c*) C.-J. Li and L. Chen, *Chem. Soc. Rev.*, 2006, **35**, 68; (*d*) R. N. Butler and A. G. Coyne, *Chem. Rev.*, 2010, **110**, 6302; (*e*) H.-X. Song, Q.-Y. Han, C.-L. Zhao and C.-P. Zhang, *Green Chem.*, 2018, **20**, 1662; (*f*) D.-L. Kong, G.-P. Lu, M.-S. Wu, Z.-F. Shi and Q. Lin, *ACS Sustainable Chem. Eng.*, 2017, **5**, 3465; (*g*) W.-B. Liu, L. Lu and C.-J. Li, *Nat. Commun.*, 2015, **6**, 6526.

2 (*a*) L.-Y. Xie, Y.-J. Li, J. Qu, Y. Duan, J. Hu, K.-J. Liu, Z. Cao and W.-M. He, *Green Chem.*, 2017, **19**, 5642; (*b*) X.-P. Fu, L. Liu, D. Wang, Y.-J. Chen and C.-J. Li, *Green Chem.*, 2011, **13**, 549; (*c*) W.-Y. Li, G.-X. Yin, L. Huang, Y. Xiao, Z.-M. Fu, X. Xin, F. Liu, Z.-Z. Li and W.-M. He, *Green Chem.*, 2016, **18**, 4879; (*d*) X. Zhang, W.-B. Cao, X.-P. Xu and S.-J. Ji, *Synthesis*, 2019, 3805; (*e*) V. M. Muzalevskiy, K. V. Belyaeva, B. A. Trofimov and V. G. Nenajdenko, *Green Chem.*, 2019, **21**, 6353; (*f*) S. D. Copley and J. R. Knowles, *J. Am. Chem. Soc.*, 1987, **109**, 5008; (*g*) L.-Y. Xie, Y. Duan, L.-H. Lu, Y.-J. Li, S. Peng, C. Wu, K.-J. Liu, Z. Wang and W.-M. He, *ACS Sustainable Chem. Eng.*, 2017, **5**, 10407.

3 T. Kitanosono and S. Kobayashi, *Chem. – Eur. J.*, 2020, **26**, 9408.

4 J. B. Zimmerman, P. T. Anastas, H. C. Erythropel and W. Leitner, *Science*, 2020, **367**, 397.

5 (*a*) T. Kitanosono, K. Masuda, P. Y. Xu and S. Kobayashi, *Chem. Rev.*, 2018, **118**, 679; (*b*) B. Li and P. H. Dixneuf, *Chem. Soc. Rev.*, 2013, **42**, 5744; (*c*) T. Murase, Y. Nishijima and M. Fujita, *J. Am. Chem. Soc.*, 2012, **134**, 162; (*d*) C. Fischmeister and H. Doucet, *Green Chem.*, 2011, **13**, 741; (*e*) M. A. Ali, X.-Y. Yao, G.-G. Li and H.-J. Lu, *Org. Lett.*, 2016, **18**, 1386; (*f*) P. Nareddy, F. Jordan and M. Szostak, *Org. Lett.*, 2018, **20**, 341; (*g*) M. A. Ali, X. Yao, H. Sun and H.-J. Lu, *Org. Lett.*, 2015, **17**, 1513; (*h*) P. B. Arockiam, C. Fischmeister, C. Bruneau and P. H. Dixneuf, *Green Chem.*, 2013, **15**, 67; (*i*) P. B. Arockiam, V. Poirier, C. Fischmeister, C. Bruneau and P. H. Dixneuf, *Green Chem.*, 2009, **11**, 1871.

6 (*a*) Y. Sasaki, D. Kato and D. L. Boger, *J. Am. Chem. Soc.*, 2010, **132**, 13533; (*b*) M. Mori, M. Nakanishi, D. Kajishima and Y. Sato, *J. Am. Chem. Soc.*, 2003, **125**, 9801; (*c*) A. B. Dounay, P. G. Humphreys, L. E. Overman and A. D. Wrobleski, *J. Am. Chem. Soc.*, 2008, **130**, 5368; (*d*) W.-G. He, J.-D. Hu, P.-Y. Wang, L. Chen, K. Ji, S.-Y. Yang, Y. Li, Z.-L. Xie and W.-Q. Xie, *Angew. Chem., Int. Ed.*, 2018, **57**, 3806; (*e*) J. Moreno, E. Picazo, L. A. Morrill, J. M. Smith and N. K. Garg, *J. Am. Chem. Soc.*, 2016, **138**, 1162; (*f*) C. Wang, S.-J. Zhang, Y. Wang, S.-H. Huang and R. Hong, *Org. Chem. Front.*, 2018, **5**, 447.

7 (*a*) Z.-R. Xu, Q. Wang and J.-P. Zhu, *Chem. Soc. Rev.*, 2018, **47**, 7882; (*b*) J. M. Saya, E. Ruijter and R. V. A. Orru, *Chem. – Eur. J.*, 2019, **25**, 8916; (*c*) J. Bonjoch and D. Sole, *Chem. Rev.*, 2000, **100**, 3455; (*d*) M. Kizil, B. Patro, O. Callaghan, J. A. Murphy, M. B. Hursthouse and D. Hibbs, *J. Org. Chem.*, 1999, **64**, 7856; (*e*) S.-Z. Zhou, S. Bommezijn and J. A. Murphy, *Org. Lett.*, 2002, **4**, 443; (*f*) M. Mori, M. Nakanishi, D. Kajiishima and Y. Sato, *J. Am. Chem. Soc.*, 2003, **125**, 9801; (*g*) J. Boonsombat, H. Zhang, M. J. Chughtai, J. Hartung and A. Padwa, *J. Org. Chem.*, 2008, **73**, 3539; (*h*) H. Mizoguchi, H. Oikawa and H. Oguri, *Nat. Chem.*, 2014, **6**, 57; (*i*) Y.-S. Wang, J.-S. Lin, X.-Y. Wang, G.-H. Wang, X.-H. Zhang, B. Yao, Y.-D. Zhao, P.-F. Yu, B. Lin, Y.-X. Liu and M.-S. Cheng, *Chem. – Eur. J.*, 2018, **24**, 4026; (*j*) K. Du, H. Yang, P. Guo, L. Feng, G.-Q. Xu, Q.-H. Zhou, L. W. Chung and W.-J. Tang, *Chem. Sci.*, 2017, **8**, 6247; (*k*) L.-W. Feng, H. Ren, H. Xiong, P. Wang, L.-J. Wang and Y. Tang, *Angew. Chem., Int. Ed.*, 2017, **56**, 3055; (*l*) J. Pereira, M. Barlier and C. Guillou, *Org. Lett.*, 2007, **9**, 3101; (*m*) M. E. Kuehne and F. Xu, *J. Org. Chem.*, 1993, **58**, 7490; (*n*) B.-B. Guo, L. Ge, G.-X. Huang, L. Zhao, J. Chen, W.-G. Cao and X.-Y. Wu, *Adv. Synth. Catal.*, 2015, **357**, 4013; (*o*) W. Chen, X.-D. Yang, W.-Y. Tan, X.-Y. Zhang,

X.-L. Liao and H.-B. Zhang, *Angew. Chem., Int. Ed.*, 2017, **56**, 12327; (*p*) S. B. Jones, B. Simmons, A. Mastracchio and D. W. C. MacMillan, *Nature*, 2011, **475**, 183; (*q*) B. N. Laforteza, M. Pickworth and D. W. C. MacMillan, *Angew. Chem., Int. Ed.*, 2013, **52**, 11269; (*r*) J. Zhu, Y.-J. Cheng, X.-K. Kuang, L.-J. Wang, Z.-B. Zheng and Y. Tang, *Angew. Chem., Int. Ed.*, 2016, **55**, 9224.

8 (*a*) X. Wang, S.-Y. Wang and S.-J. Ji, *Org. Lett.*, 2013, **15**, 1954; (*b*) X.-H. Zhao, X.-H. Liu, Q. Xiong, H.-J. Mei, B.-W. Ma, L.-L. Lin and X.-M. Feng, *Chem. Commun.*, 2015, **51**, 16076; (*c*) X.-H. Zhao, X.-H. Liu, H.-J. Mei, J. Guo, L.-L. Lin and X.-M. Feng, *Angew. Chem., Int. Ed.*, 2015, **54**, 4032; (*d*) J. M. Saya, T. R. Roose, J. J Peek, B. Weijers, T. J. S. de Waal, C. M. L. Vande Velde, R. V. A. Orru and E. Ruijter, *Angew. Chem., Int. Ed.*, 2018, **57**, 15232; (*e*) J. M. Saya, B. Oppelaar, R. C. Cioc, G. van der Heijden, C. M. L. Vande Velde, R. V. A. Orru and E. Ruijter, *Chem. Commun.*, 2016, **52**, 12482; (*f*) L.-H. Li, J.-X. Liu and M. Shi, *Org. Lett.*, 2018, **20**, 7076; (*g*) X.-Q. Li, Q. Xiong, M.-M. Guan, S.-X. Dong, X.-H. Liu and X.-M. Feng, *Org. Lett.*, 2019, **21**, 6096; (*h*) W.-B. Cao, S.-J. Li, M.-M. Xu, H.-Y. Li, X.-P. Xu, Y. Lan and S.-J. Ji, *Angew. Chem., Int. Ed.*, 2020, **59**, 21425; (*i*) G.-S. Chen, S.-J. Chen, J. Luo, X.-Y. Mao, A. S.-C. Chan, R. W.-Y. Sun and Y.-L. Liu, *Angew. Chem., Int. Ed.*, 2020, **59**, 614.

9 (*a*) Z.-Y. Gu, Y. Liu, F. Wang, X.-G. Bao, S.-Y. Wang and S.-J. Ji, *ACS Catal.*, 2017, **7**, 3893; (*b*) T. Jiang, Z.-Y. Gu, L. Yin, S.-Y. Wang and S.-J. Ji, *J. Org. Chem.*, 2017, **82**, 7913.

10 (*a*) X.-X. Zheng, Y.-Y. Liu and J.-P. Wan, *Chin. J. Org. Chem.*, 2020, **40**, 1891; (*b*) D. Mishra, A. J. Borah, P. Phukan, D. Hazarika and P. Phukan, *Chem. Commun.*, 2020, **56**, 8408; (*c*) G.-D. Wang, Y.-H. Guo and J.-P. Wan, *Chin. J. Org. Chem.*, 2020, **40**, 645; (*d*) X.-X. Zheng and J.-P. Wan, *Adv. Synth. Catal.*, 2019, **361**, 5690.