

EDGE ARTICLE

View Article Online
View Journal | View IssueCite this: *Chem. Sci.*, 2021, 12, 9556

All publication charges for this article have been paid for by the Royal Society of Chemistry

Catalyst-free arylation of sulfonamides *via* visible light-mediated deamination†

Yong Luo,^a Hao Ding,^b Jing-Song Zhen,^a Xian Du,^a Xiao-Hong Xu,^a Han Yuan,^a Yi-Hui Li,^a Wan-Ying Qi,^a Bing-Zhe Liu,^a Shi-Man Lu,^a Can Xue^c and Qiuping Ding^{*b}

A novel arylation of sulfonamides with boronic acids to afford numerous diaryl sulfones *via* a visible light-mediated N–S bond cleavage other than the typical transition-metal-catalyzed C(O)–N bond activation is described. This methodology, which represents the first catalyst-free protocol for the sulfonylation of boronic acids, is characterized by its simple reaction conditions, good functional group tolerance and high efficiency. Several successful examples for the late-stage functionalization of diverse sulfonamides indicate the high potential utility of this method in pharmaceutical science and organic synthesis.

Received 23rd April 2021
Accepted 4th June 2021

DOI: 10.1039/d1sc02266k
rsc.li/chemical-science

Introduction

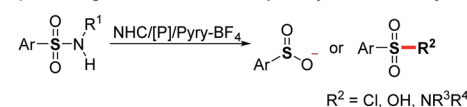
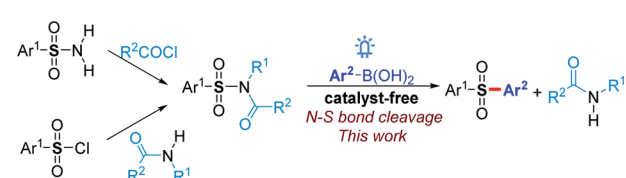
Sulfonamide drugs discovered in the 1930s first systemically used as antibacterials have continuously received renewed interest for the treatment of numerous diseases.¹ Since then, a large number of synthetic routes towards diverse sulfonamides have been developed, which make the sulfonamide moiety prevalent in bioactive molecules and commercial chemicals.² Therefore, the transformation of sulfonamide skeleton to other groups, such as sulfones, is a convenient method to construct a pharmacophore-containing molecule library for drug discovery. Moreover, the activation of sulfonamides could be used for the deprotection of sulfonyl group-protected amines,³ late-stage functionalization of sulfonamide drugs,⁴ and sulfonylation with sulfonamides as stable and good functional group-tolerant reagents. However, sulfonamides are usually considered as the final products of the construction of N–S bonds rather than reactive substrates because efficient strategies for the functionalization of N–S bonds are limited.

Previous exploration on the N–S bond cleavage of sulfonamides mainly focused on desulfonylation to generate corresponding amines.³ The functionalization of the sulfonyl group resulted from the deamination of sulfonamides still meets great challenges. Recently, Fier and Maloney⁴ reported an efficient pathway to convert primary and secondary sulfonamides to sulfinate anions in the presence of an NHC catalyst or

phosphine reagent (Scheme 1a). Further with the addition of electrophiles, a variety of sulfones and modified sulfonamides could be obtained. By utilizing Pyry-BF₄, Cornella⁵ found that primary sulfonamides could react with nucleophiles to generate sulfonyl chlorides, fluorides, and sulfonic acids. Despite these significant progresses, the functionalization of tertiary sulfonamides, which are usually considered as terminal functional groups to synthesize sulfones and related compounds, has not been achieved yet.

On the other hand, despite sulfonyl chlorides,⁶ sodium sulfonates,⁷ and sulfur dioxide⁸ being widely used for sulfonylation towards aryl sulfones in recent years, novel sulfonylation reagents still need to be explored to extend the research in this area. The stability and good tolerance for other functional groups make tertiary sulfonamides to be good sulfonylation reagents. Herein, we report that *N*-acylsulfonamides as novel sulfonyl radical precursors react with aryl boronic acids to generate various diaryl sulfones *via* visible-light-mediated N–S

a) Late-stage functionalization of primary and secondary sulfonamides

b) Arylation of *N*-acylsulfonamides

Scheme 1 Strategies for the functionalization of sulfonamides and the synthesis of sulfones.

^aSchool of Pharmaceutical Sciences (Shenzhen), Sun Yat-sen University, Guangzhou, 510275, China. E-mail: luoyong5@mail.sysu.edu.cn

^bKey Laboratory of Functional Small Organic Molecules, Ministry of Education, Jiangxi Normal University, Nanchang, 330022, China. E-mail: dingqiuping@jxnu.edu.cn

^cSchool of Chemical Engineering and Technology, Sun Yat-sen University, Zhuhai, 519082, China. E-mail: xuecan@mail.sysu.edu.cn

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d1sc02266k

bond activation without any catalyst (Scheme 1b), while these substrates typically proceed a C(O)–N bond cleavage in the presence of transition metals.⁹ The mechanism investigation showed that a radical cross-coupling is probably involved in our protocol, which provides an alternative strategy for the late-stage functionalization of sulfonamides. Moreover, *N*-acylsulfonamides synthesized from sulfonyl chlorides and amides could act as the surrogates of the sulfonyl chlorides under incompatible reaction conditions to proceed with late-stage sulfonylation.

Results and discussion

In our investigation, sulfonamide **1a** went through arylation with boronic acid **2a** in the presence of K₃PO₄ and CH₃CN under blue LED irradiation, providing diaryl sulfone **3a** with 57% yield (Table 1, entry 1). No ketone product was observed. Further screening showed that DMF, PhCF₃, or DCE was inefficient (entries 2–4). However, ether solvents exhibited superiority in this reaction (entries 5–7), and 70% yield was obtained with 1,4-dioxane. A lower yield was detected when Cs₂CO₃ or K₂CO₃ was employed (entries 8 and 9). CsF (99.99% metal basis) gave the best result in the screening of the bases, affording the desired product **3a** in 75% yield (entry 10). The decomposition of sulfonamide **1a** was observed in these reactions and hampered the elevation of the product yield. Therefore, the ratio of **1a** and **2a** was changed to 2 to 1, resulting in a significant increase of the yield of **3a** (95%, entry 11). The corresponding amide **4** was also collected and identified with a yield of 114% based on **2a** owing to the visible light-mediated desulfonylation of the starting material **1a**. Visible light and base were proved to be necessary since no product was detected when this reaction was performed in dark or without base (entries 12 and 13).

Table 1 Optimization of the reaction conditions^a

Entry	Solvent	Base	Yield (%)
1	CH ₃ CN	K ₃ PO ₄	57
2	DMF	K ₃ PO ₄	Trace
3	PhCF ₃	K ₃ PO ₄	n.r.
4	DCE	K ₃ PO ₄	n.r.
5	THF	K ₃ PO ₄	66
6	DME	K ₃ PO ₄	61
7	1,4-Dioxane	K ₃ PO ₄	70
8	1,4-Dioxane	Cs ₂ CO ₃	53
9	1,4-Dioxane	K ₂ CO ₃	57
10	1,4-Dioxane	CsF	75
11 ^b	1,4-Dioxane	CsF	95 (114 ^c)
12 ^{b,d}	1,4-Dioxane	CsF	n.r.
13 ^b	1,4-Dioxane	—	n.r.

^a Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), base (0.5 mmol), solvent (2 mL), 50 W blue LED, 12 h, 40 °C, isolated yield. ^b **1a** (0.4 mmol), **2a** (0.2 mmol). ^c Yield of **4** in the parenthesis. ^d In dark.

The scope of boronic acids was then explored (Table 2). Substituents with a large π system showed high efficiency. For example, 2- or 1-naphthylboronic acid provided 97% and 87% yields of the desired product, respectively (**3b** and **3c**). Methyl group substitution had nearly no affect on this reaction (**3e**). Methoxy and phenyl group-attached substrates gave lower yields probably owing to the instability of these sulfonamides under blue LED irradiation (**3d** and **3f**). It should be noted that in some cases, product **3** was inseparable from the generated amide **4**. Therefore, **1b**, which showed no obvious reactivity difference compared with **1a**, was employed for the convenience of the isolation of product **3** (**3b**, **3c**, **3e** and **3f**). Heterocycles, such as quinoline and benzofuran, are compatible in this system (**3g–3k**). Aldehyde, ketone, and amide group-attached aryl boronic acids also could afford moderate yields of the desired products (**3l–3o**), although an elevated concentration by the addition of only 1 mL solvent was necessary in several examples. Diverse electron-withdrawing (phenyl, cyano, and silane) and electron-donating group (methoxy, methyl, and

Table 2 Scope of boronic acids^a

3a , 95%	3b , 97% ^b	3c , 87% ^b	
3d , 61%	3e , 85% ^b	3f , 68% ^b	
3g , 64%	3h , 92%	3i , 81%	
3j , 91%	3k , 56% ^c	3l , 53%	
3m , 67% ^c	3n , 77% ^c	3o , 78% ^c	
3p , 81% ^{b,c}	3q , 39% ^c	3r , 75% ^{c,d}	
3s , 60% ^c	3t , 60% ^{c,d}	3u , 60% ^{c,d}	
3v , 71% ^{b,c,d}	3w , 77% ^{b,c,d}	3x , 68% ^{b,c,d}	

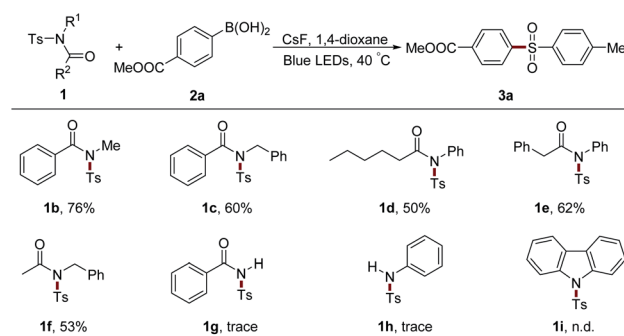
^a Reaction conditions: **1a** (0.4 mmol), **2** (0.2 mmol), CsF (0.5 mmol), 1,4-dioxane (2 mL), 50 W blue LED, 12 h, 40 °C. ^b **1b** was used instead of **1a**. ^c Only 1 mL of 1,4-dioxane was added. ^d K₃PO₄ (0.5 mmol) was used instead of CsF.

amine) substituted diaryl sulfones could be synthesized using corresponding boronic acids (**3p–3v**). The substrate bearing an *ortho* methyl group could afford **3x** in 68% yield. However, aliphatic boronic acids, aryl trifluoroborates, or aryl boronic acid pinacol esters could not result in any product under these reaction conditions or with a photocatalyst.

After that, the scope of sulfonyl groups was investigated (Table 3). With an electron-donating group on either *para*- or *meta*-position, sulfonamide **1** could react smoothly with boronic acid **2a** to generate the desired product in good yield (**3y–3aa**). The arylation of naphthyl and phenyl sulfonamides also proceeded efficiently to afford sulfones **3ab** and **3ac**. Electron-withdrawing groups, such as fluorine, ester, cyano, and sulfone, could all be tolerated in this system very well (**3ad–3ag**). However, the alkyl sulfonyl group-embedded sulfonamide showed no reactivity.

The protecting groups on the nitrogen atom were also examined (Table 4). Alkyl group-attached sulfonamides **1b** and **1c** exhibited an inferior efficiency than **1a**, leading to 76% and 60% yields of **3a**, respectively. Aliphatic acyl group-protected sulfonamides **1d** and **1e** could provide the desired product **3a** with moderate yields. Sulfonamide **1f** bearing acetyl and benzyl units, which were usually used as the protecting groups of nitrogen atom, could also result in **3a** with 53% yield, which largely expands the practical utilization of our protocol in organic synthesis. However, secondary sulfonamides **1g** and **1h** only afforded trace amounts of **3a**. Moreover, the acyl group in **1** was proved to be necessary since the two aryl group-attached substrate **1i** gave no desired product under the standard conditions.

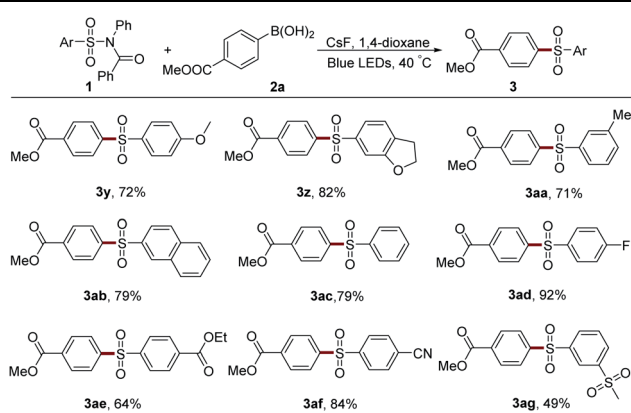
To examine our strategy in the late-stage functionalization of sulfonamides, several commercial drugs were used to proceed acylation and methylation to provide the starting material **1**. After that, diverse aryl groups and heterocycles could be introduced under the standard arylation reaction conditions (Table 5). The 6-quinoline group could be installed into the drugs derived from Celecoxib and Valdecoxib with 67% and

Table 4 Scope of amides^a

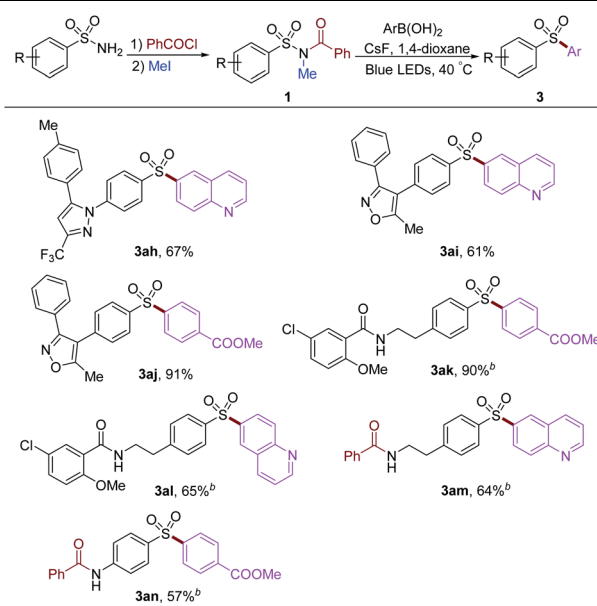
^a Reaction conditions: **1** (0.4 mmol), **2a** (0.2 mmol), CsF (0.5 mmol), 1,4-dioxane (2 mL), 50 W blue LED, 12 h, 40 °C. n.d. = not detected.

61% yields, respectively (**3ah** and **3ai**). 4-Methoxycarbonylphenylboronic acid could give 91% yield of the desired product (**3aj**). The amide group remained intact in this procedure, affording corresponding products **3ak** and **3al** stemmed from glibenclamide precursor in 90% and 65% yields, respectively. Free alkyl and aryl amine groups were protected by acylation under the prefunctionalization conditions, affording the products **3am** and **3an** in moderate yields.

Besides the arylation of the sulfonyl group in sulfonamides, alkylation could also be achieved by altering the reaction conditions. The N-S bond of sulfonamides was cleaved by photocatalysis to deliver the sulfonyl radical. Then, the *in situ* methylation of the sulfinate resulted from the reduction of the sulfonyl radical proceeded to afford methyl sulfones (Table 6).

Table 3 Scope of sulfonyl groups^a

^a Reaction conditions: **1** (0.4 mmol), **2a** (0.2 mmol), CsF (0.5 mmol), 1,4-dioxane (2 mL), 50 W blue LED, 12 h, 40 °C.

Table 5 Late-stage arylation of drugs^a

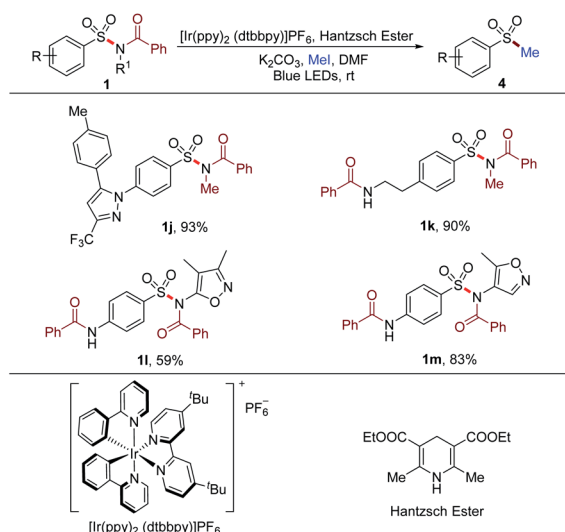
^a Reaction conditions: **1** (0.4 mmol), **2** (0.2 mmol), CsF (0.5 mmol), 1,4-dioxane (2 mL), 50 W blue LED, 12 h, 40 °C. Isolated yields of the arylation step. ^b **1** (0.2 mmol), **2** (0.4 mmol).



Substrates **1j** and **1k** synthesized from primary sulfonamides furnished the methylated products with 93% and 90% yields, respectively. Secondary sulfonamide-based substrates **1l** and **1m** could also be prefunctionalized and methylated with this method. These successful transformations implied the potential for the rapid construction of a molecule library from not only tertiary but also primary and secondary sulfonamides for the screening of new lead compounds.

The mechanism of this reaction was investigated by measuring the UV-Vis absorption spectra of substrates and reaction solutions (Scheme 2). Individual solutions of sulfonamide **1a** and boronic acid **2a** in 1,4-dioxane showed a maximum absorption at approx. 250 nm, and a very low absorption at 460 nm (blue LED). A mixture of **1a** and **2a** displayed a slight red-shift of the absorption peak. When CsF was added, a further red-shift and higher absorption under a blue LED were observed. These details suggested that complex **A**, which was formed with **1a**, **2a**, and base could be directly photoexcited by blue LED without the presence of a photocatalyst (Scheme 2b). The Cs⁺-coordinated six-membered ring in complex **A** might also explain the indispensability of the acyl group (Table 4) in the substrate. This phenomenon of the combination of a substrate and a reagent affording a photo-excitable complex *in situ* has been reported in several

Table 6 Late-stage methylation of drugs^a



^a Reaction conditions: **1** (0.2 mmol), Hantzsch ester (0.4 mmol), [Ir(ppy)₂(dtbbpy)]PF₆ (5 mol%), K₂CO₃ (1.0 mmol), MeI (1.0 mmol), DMF (2 mL), 50 W blue LED, 15 h, 40 °C.

studies.¹⁰ With blue LED irradiation, complex **A** gave a rise to the amide radical **B** and the sulfonyl radical **C**.³ After that, the attack of a nitrogen radical to the boron complex **D** resulted in an aryl radical **E** (ref. 11) with the concomitant generation of amide **4**. The capture of the sulfonyl radical by **E** provided the product sulfone **3**. This reaction was inhibited by the addition of the radical scavenger TEMPO (Scheme 2b), also indicating the involvement of a radical process.

Conclusions

In summary, we have developed an efficient and practical strategy for the late-stage arylation of sulfonamides *via* a visible light-mediated N–S bond cleavage other than typical transition-metal-catalyzed C(O)–N bond activation. It also represented the first catalyst-free sulfonylation of boronic acids to synthesize aryl sulfones. The employment of diverse boronic acids and sulfonamides exhibited good functional group tolerance and high efficiency. The mechanism investigation revealed that the photo-excitable complex formed from sulfonamide, boronic acid, and base was crucial to afford sulfonyl radicals and furnish the desired products. This achievement inspired us to explore other strategies for the late-stage functionalization of sulfonamides.

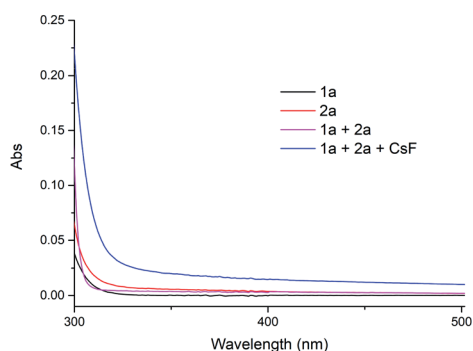
Data availability

The electronic supplementary information include experimental detail, NMR data and HRMS data.

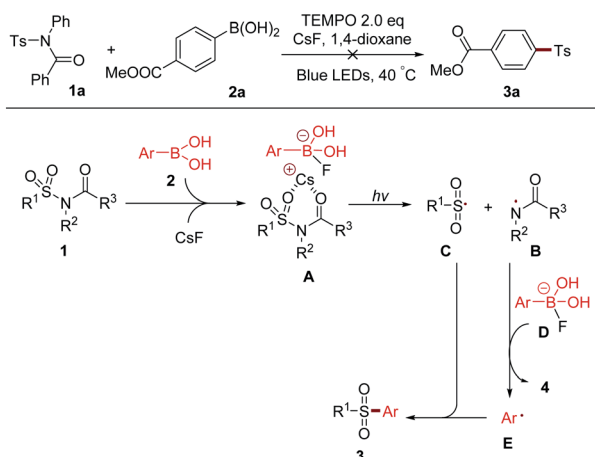
Author contributions

Y. Luo conceived and designed the experiments. H. Ding conducted most of the experiments. J.-S. Zhen and X. Du performed

a. UV-Vis absorption spectra



b. Proposed mechanism



Scheme 2 Mechanism investigation. (a) UV-Vis absorption spectra. (b) Proposed mechanism.



the arylation of sulfonamide drugs. X.-H. Xu, H. Yuan, Y.-H. Li, W.-Y. Qi, B.-Z. Liu and S.-M. Lu synthesized the starting materials. C. Xue contributed to the mechanism research. Q. Ding analyzed the data and prepared the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful for financial support from the National Natural Science Foundation of China (21901260, 21908256, 21662017).

Notes and references

- 1 J. E. Lesch, *The First Miracle Drugs: How the Sulfa Drugs Transformed Medicine*, Oxford University Press, 2006.
- 2 K. A. Scott and J. T. Njardarson, Analysis of US FDA-Approved Drugs Containing Sulfur Atoms, *Top. Curr. Chem.*, 2018, **376**, 5.
- 3 (a) R. R. Milburn and V. Snieckus, *Angew. Chem., Int. Ed.*, 2004, **43**, 892–894; (b) S. Yoshida, K. Igawa and K. Tomooka, *J. Am. Chem. Soc.*, 2012, **134**, 19358–19361; (c) J. Xuan, B.-J. Li, Z.-J. Feng, G.-D. Sun, H.-H. Ma, Z.-W. Yuan, J.-R. Chen, L.-Q. Lu and W.-J. Xiao, *Chem.-Asian J.*, 2013, **8**, 1090–1094; (d) E. Hasegawa, N. Izumiya, T. Miura, T. Ikoma, H. Iwamoto, S. Takizawa and S. Murata, *J. Org. Chem.*, 2018, **83**, 3921–3927; (e) E. Hasegawa, Y. Nagakura, N. Izumiya, K. Matsumoto, T. Tanaka, T. Miura, T. Ikoma, H. Iwamoto and K. Wakamatsu, *J. Org. Chem.*, 2018, **83**, 10813–10825.
- 4 (a) P. S. Fier and K. M. Maloney, *J. Am. Chem. Soc.*, 2019, **141**, 1441–1445; (b) P. S. Fier, S. Kim and K. M. Maloney, *J. Am. Chem. Soc.*, 2019, **141**, 18416–18420.
- 5 (a) A. Gómez-Palomino and J. Cornella, *Angew. Chem., Int. Ed.*, 2019, **58**, 18235–18239; (b) M. Pérez-Palau and J. Cornella, *Eur. J. Org. Chem.*, 2020, 2497–2500.
- 6 Selected examples: (a) B. P. Bandgar, S. V. Bettigeri and J. Phopase, *Org. Lett.*, 2004, **6**, 2105–2108; (b) Y. Fu, W. Zhu, X. Zhao, H. Hugel, Z. Wu, Y. Su, Z. Du, D. Huang and Y. Hu, *Org. Biomol. Chem.*, 2014, **12**, 4295–4299.
- 7 Selected examples: (a) N. Umierski and G. Manolikakes, *Org. Lett.*, 2013, **15**, 188–191; (b) X. Tang, L. Huang, Y. Xu, J. Yang, W. Wu and H. Jiang, *Angew. Chem., Int. Ed.*, 2014, **53**, 4205–4208; (c) W. Wu, S. Yi, W. Huang, D. Luo and H. Jiang, *Org. Lett.*, 2017, **19**, 2825–2828.
- 8 Selected examples: (a) E. J. Emmett, B. R. Hayter and M. C. Willis, *Angew. Chem., Int. Ed.*, 2013, **52**, 12679–12683; (b) E. J. Emmett, B. R. Hayter and M. C. Willis, *Angew. Chem., Int. Ed.*, 2014, **53**, 10204–10208; (c) Y. Meng, M. Wang and X. Jiang, *Angew. Chem., Int. Ed.*, 2020, **59**, 1346–1353; (d) S. Ye, K. Zhou, P. Rojsitthisak and J. Wu, *Org. Chem. Front.*, 2020, **7**, 14–18; (e) S. Ye, D. Zheng, J. Wu and G. Qiu, *Chem. Commun.*, 2019, **55**, 2214–2217; (f) S. Ye, G. Qiu and J. Wu, *Chem. Commun.*, 2019, **55**, 1013–1019; (g) J. Zhang, M. Yang, J.-B. Liu, F.-S. He and J. Wu, *Chem. Commun.*, 2020, **56**, 3225–3228; (h) S. Ye, M. Yang and J. Wu, *Chem. Commun.*, 2020, **56**, 4145–4155; (i) X. Gong, M. Yang, J.-B. Liu, F.-S. He and J. Wu, *Org. Chem. Front.*, 2020, **7**, 938–943; (j) F.-S. He, M. Yang, S. Ye and J. Wu, *Chin. Chem. Lett.*, 2021, **32**, 461–464.
- 9 (a) X. Li and G. Zou, *Chem. Commun.*, 2015, **51**, 5089–5092; (b) B. J. Simmons, N. A. Weires, J. E. Dander and N. K. Garg, *ACS Catal.*, 2016, **6**, 3176–3179; (c) S. Shi, R. Lalancette, R. Szostak and M. Szostak, *Org. Lett.*, 2019, **21**, 1253–1257.
- 10 (a) M.-C. Fu, R. Shang, B. Zhao, B. Wang and Y. Fu, *Science*, 2019, **363**, 1429–1434; (b) S. Xie, D. Li, H. Huang, F. Zhang and Y. Chen, *J. Am. Chem. Soc.*, 2019, **141**, 16237–16242.
- 11 F. Lima, U. K. Sharma, L. Grunenberg, D. Saha, S. Johannsen, J. Sedelmeier, E. V. V. der Eycken and S. V. Ley, *Angew. Chem., Int. Ed.*, 2017, **56**, 15136–15140.

