ChemComm

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2021, 57, 12603

Received 8th October 2021,
Accepted 27th October 2021

DOI: 10.1039/d1cc05690e

rsc.li/chemcomm

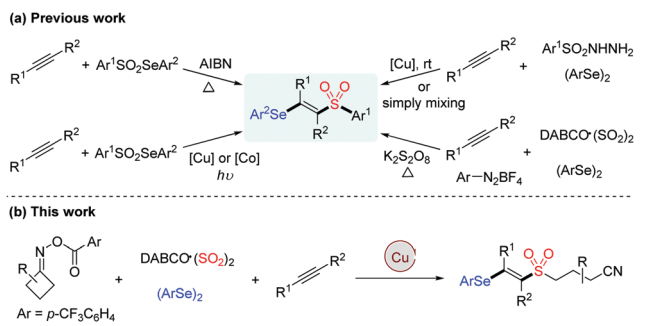
Synthesis of β-cyanoalkylsulfonylated vinyl selenides through a four-component reaction†

Fu-Sheng He,*[a] Yanfang Yao,[ab] Zhimei Tang,[a] Yanjie Qiu,[a] Wenlin Xie[b] and Jie Wu *[acd]

A mild copper-catalyzed four-component selenosulfonylation of alkynes, cycloketone oxime esters, DABCO $(SO_2)_2$ and diselenides has been developed. This method enables the rapid assembly of β-cyanoalkylsulfonylated vinyl selenides in moderate to good yields. Advantages of this protocol include a broad substrate scope, good functional group tolerance and the late-stage functionalization of complex molecules. Moreover, the potential utility of this methodology is demonstrated through simple oxidation of the products to access synthetically important alkynyl sulfones. Mechanistic studies suggest that a cyanoalkylsulfonyl radical intermediate is involved in this process.

Owing to their widespread synthetic applications and important biological properties, sulfone derivatives have attracted considerable attention from both synthetic and medicinal communities.[1] In particular, vinyl sulfones are not only present in many pharmaceuticals serving as neuroprotective agents, nuclear factor erythroid 2-related factor 2 activators and cysteine protease inhibitors, but they are also valuable building blocks in modern organic synthesis.[2] Accordingly, various methodologies for the assembly of vinyl sulfones have been developed, such as the Knoevenagel condensation of aldehydes with sulfonylacetic acids, β-elimination of halosulfones and oxidation of vinyl sulfides, which generally require prefunctionalized reagents, harsh reaction conditions or tedious steps.[3] On the other hand, vinyl selenides are versatile intermediates and important therapeutic entities, which exhibit a variety of biological activities.[4] By combining vinyl sulfone and vinyl selenide units, β-selenovinyl sulfones can be easily transformed into valuable products such as allenes, acetylenes and β-keto sulfones,[5] thus rendering the significance of developing efficient approaches towards these compounds (Scheme 1a).[6]

Vicinal difunctionalization of alkynes represents an attractive and efficient method for the synthesis of highly functionalized olefins, which results in the simultaneous incorporation of two functional moieties across the triple bond.[7] In this context, sulfonyl radical-involved 1,2-difunctionalization of alkynes has emerged as a powerful strategy for accessing structurally diverse vinyl sulfones with high stereoselectivity.[8] In recent years, the generation of sulfonyl radicals through the insertion of sulfur dioxide has been extensively employed in a variety of sulfonylation reactions.[9] Among these, considerable efforts have been devoted to constructing sulfonyl compounds by utilizing DABCO·$((SO_2)_2)$,[10] inorganic metabisulfite[11] or thiourea dioxide[12] as the efficient sulfur dioxide surrogates. Moreover, as an alternative approach for the preparation of β-selenovinyl sulfones, a selenosulfonation of alkynes with aryldiazonium tetrafluoroborates, DABCO $(SO_2)_2$ and diselenides was reported by Sun *et al.*[13] However, this approach had some limitations, such as the safety and stability of using aryldiazonium tetrafluoroborates and the requirement of using



Scheme 1 Synthesis of β-selenovinyl sulfones.

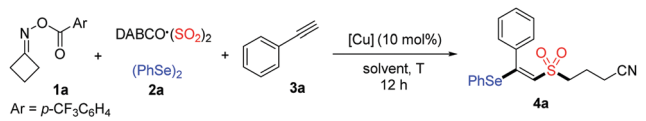
[a] School of Pharmaceutical and Materials Engineering & Institute for Advanced Studies, Taizhou University, 1139 Shifu Avenue, Taizhou 318000, China. E-mail: jie_wu@fudan.edu.cn, hefs@tzc.edu.cn
[b] School of Chemistry and Chemical Engineering, Hunan University of Science and Technology, Xiangtan 411201, China
[c] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China
[d] School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang 453007, China

† Electronic supplementary information (ESI) available: Experimental details and spectral data, copies of ^{1}H and ^{13}C NMR spectra. CCDC 2102437. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1cc05690e

excess $K_2S_2O_8$ as the oxidant. Therefore, the development of efficient methods for the synthesis of β-selenovinyl sulfones from sulfur dioxide is still highly desirable. Driven by the recent advances in iminyl radical-triggered C–C bond cleavage reactions[14] and our continuous interest in the chemistry of sulfur dioxide insertion, herein, we described a facile copper-catalyzed selenosulfonylation of alkynes, cycloketone oxime esters, DABCO $(SO_2)_2$ and diselenides, affording β-cyanoalkylsulfonylated vinyl selenides in moderate to good yields under mild conditions (Scheme 1b). Moreover, the synthetic utility of this methodology is illustrated by the late-stage functionalization of complex molecules and the successful application of products to generate alkynyl sulfones.

Initially, cycloketone oxime ester **1a**, DABCO·$(SO_2)_2$, diphenyl diselenide **2a** and phenylacetylene **3a** were selected as the model substrates to optimize the reaction conditions (Table 1). To our delight, the desired product **4a** was obtained in 53% yield when the reaction occurred in the presence of CuOAc at 80 °C for 12 h in DCE (Table 1, entry 1). A brief screening of other copper salts such as $Cu(OTf)_2$, $Cu(TFA)_2$, $CuBr_2$, $CuCl_2$ and $Cu(OAc)_2$ indicated that $Cu(OAc)_2$ was the best choice, affording to product **4a** in 60% yield (Table 1, entries 2–6). Subsequently, the effect of other solvents, including CH_3CN, THF and DMSO, was examined (Table 1, entries 7–9). However, better results were not obtained. A survey of temperatures revealed that increasing the reaction temperature to 100 °C would lead to a slightly decreased yield, whereas it increased when the reaction was at 60 °C (Table 1, entries 10 and 11). Gratifyingly, the yield of product **4a** could be further improved to 72% when the amounts of cycloketone oxime ester **1a** and phenylacetylene **3a** were changed (Table 1, entry 12).

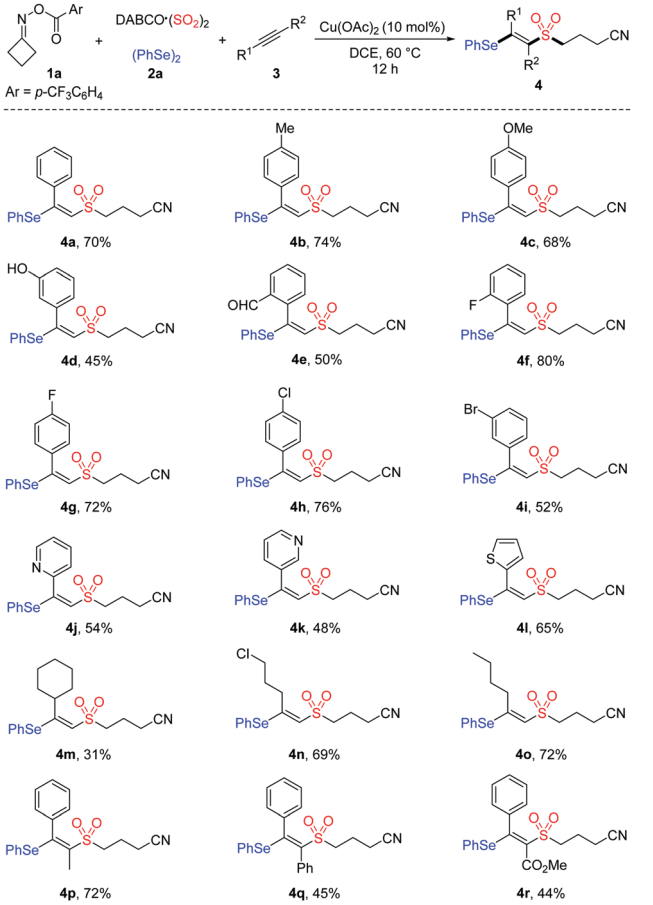
Table 1 Initial studies for the reaction of cycloketone oxime ester **1a**, DABCO·$(SO_2)_2$, diphenyl diselenide **2a** and phenylacetylene **3a**[a]



Entry	Catalyst	Solvent	T (°C)	Yield[b] (%)
1	CuOAc	DCE	80	53
2	$Cu(OTf)_2$	DCE	80	52
3	$Cu(TFA)_2$	DCE	80	46
4	$CuBr_2$	DMF	80	52
5	$CuCl_2$	DCE	80	44
6	$Cu(OAc)_2$	DCE	80	60
7	$Cu(OAc)_2$	CH_3CN	60	54
8	$Cu(OAc)_2$	THF	40	39
9	$Cu(OAc)_2$	DMSO	80	50
10	$Cu(OAc)_2$	DCE	100	43
11	$Cu(OAc)_2$	DCE	60	64
12[c]	$Cu(OAc)_2$	DCE	60	72 (70)

[a] Reactions conditions: cycloketone oxime ester **1a** (0.4 mmol), DABCO·$(SO_2)_2$ (0.2 mmol), diphenyl diselenide **2a** (0.2 mmol), phenylacetylene **3a** (0.2 mmol), copper catalyst (10 mol%), solvent (2.0 mL), N_2, 12 h. [b] Yield was determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard (isolated yield in parentheses). [c] Cycloketone oxime ester **1a** (0.2 mmol), phenylacetylene **3a** (0.3 mmol).

Table 2 Reaction of cycloketone oxime ester **1a**, DABCO·$(SO_2)_2$, diphenyl diselenide **2a** and alkynes **3**[ab]



[a] Reaction conditions: cycloketone oxime ester **1a** (0.2 mmol), DABCO·$(SO_2)_2$ (0.2 mmol), diphenyl diselenide **2a** (0.2 mmol), alkynes **3** (0.3 mmol), $Cu(OAc)_2$ (10 mol%), DCE (2.0 mL), 60 °C, N_2, 12 h. [b] Isolated yield based on cycloketone oxime ester **1a**.

With the optimal conditions established, we began to explore the substrate scope of this copper-catalyzed selenosulfonation of alkynes, cycloketone oxime ester **1a**, DABCO $(SO_2)_2$ and diphenyl diselenide **2a**. The results are summarized in Table 2. In general, a variety of terminal and internal alkynes with electron-neutral, electron-rich, or electron-poor substituents were compatible in this reaction, producing the corresponding products in moderate to good yields. Aryl terminal alkynes bearing different functional groups such as Me, OMe, OH, CHO, F, Cl and Br were well tolerated under the reaction conditions, affording the desired β-cyanoalkylsulfonylated vinyl selenides **4b–4i** in 45–80% yields. The structure of product **4i** was unambiguously determined by X-ray diffraction analysis.[15] Moreover, heteroaryl alkynes were also suitable in this transformation to afford the targeted products **4j–4l** in 48–65% yields. The reactions of less reactive aliphatic alkynes, including cyclohexylacetylene, 5-chloro-1-pentyne and 1-hexyne, proceeded smoothly to afford **4m–4o** in 31–72% yields. Notably, this protocol was also applicable to internal alkynes.

For example, unsymmetrical internal alkynes such as 1-phenyl-1-propyne and methyl phenylpropiolate could convert into the corresponding tetrasubstituted vinyl sulfones **4p** and **4r** in 72% and 44% yields, respectively.

Next, the generality of cycloketone oxime esters and diselenides was evaluated. As shown in Table 3, the mono-substituted cycloketone oxime esters with functionalities including ester, phenyl, ether, and alkyl were well tolerated, affording the desired products **5a–5e** with yields from 46% to 72%. In the cases of 3,3-disubstituted cycloketone oxime esters bearing spirocyclic units, the targeted products **5g** and **5h** were obtained in 55% and 65% yields, respectively. This reaction was also suitable with cycloketone oxime ester containing a Cbz protected-amine, delivering product **5i** in 47% yield. Furthermore, diselenides with electron-donating or electron-withdrawing substituents on the aryl ring were all compatible in this transformation (**5j–5m**).

To further demonstrate the applicability of this mild protocol, we applied this copper-catalyzed four-component process in the late-stage functionalization of pharmaceutical derivatives and natural products (Table 4), with an anticipation that these compounds would be promising for several biological evaluations in our laboratory. As expected, erlotinib bearing a terminal alkyne and estrone-derived alkyne reacted smoothly with cycloketone oxime ester **1a**, DABCO·$(SO_2)_2$ and diphenyl diselenide **2a**, affording the corresponding products **6** and **7** in 68% and 55% yields, respectively.

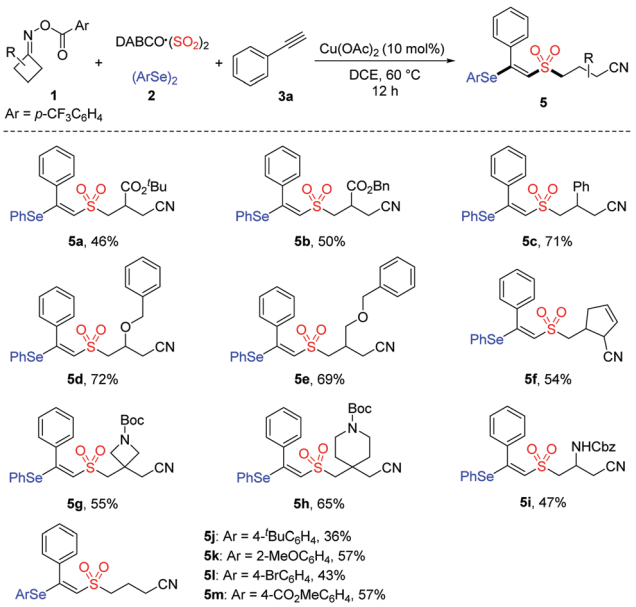
In addition, the synthetic utility of this methodology was investigated through the transformation of the product under oxidation conditions. As illustrated in Scheme 2, the treatment of compound **4a** or **4h** with hydrogen peroxide in THF afforded alkynyl sulfone product **8a** (57%) or **8b** (72%). Given that alkynyl sulfone bearing a cyanoalkyl group could not be accessed by the previous methods, this protocol showed potential application in organic synthesis.

To gain mechanistic insight into the current selenosulfonation reaction, several control experiments were performed (Scheme 3). The formation of product **4a** was completely hindered when 2.0 equivalents of 2,2,6,6-tetramethylpiperidineoxy (TEMPO) were added to the model reaction under standard conditions, indicating that the reaction proceeded *via* a radical pathway (Scheme 3, eqn (1)). Additionally, when 2.0 equivalents of butylated hydroxytoluene (BHT) were introduced into the reaction, the trapping-product **9** was isolated in 18% yield. This result suggested that a cyanoalkylsulfonyl radical intermediate was generated in this transformation (Scheme 3, eqn (2)).

On the basis of the above-mentioned results and literature reports,[6,9,13,14] we proposed a plausible mechanism for this copper-catalyzed selenosulfonation of alkynes, cycloketone oxime esters, DABCO $(SO_2)_2$ and diselenides (Scheme 4). We postulated that initially iminyl radical **A** was generated *via* the Cu(I)-mediated single-electron reduction of cycloketone oxime ester **1**, which would undergo ring-opening by the selective β-C–C bond cleavage to produce a highly reactive cyanoalkyl radical **B**. Then, radical **B** was captured by sulfur dioxide, leading to the generation of cyanoalkylsulfonyl radical **C**. Following that, the regiospecific addition with alkyne **3** would produce vinyl radical **D**, which might react with diphenyl diselenide to afford the targeted product.

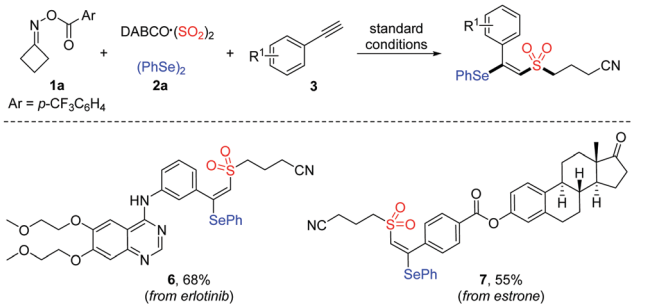
In conclusion, we have disclosed a copper-catalyzed four-component reaction of cycloketone oxime esters, DABCO $(SO_2)_2$, diselenides and alkynes, affording β-cyanoalkylsulfonylated vinyl selenides in moderate to good yields. This vicinal selenosulfonation process proceeded under mild conditions and

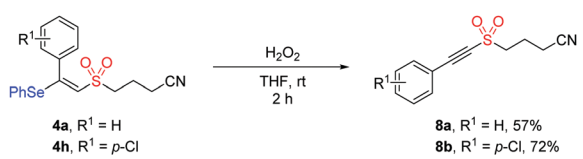
Table 3 Reaction of cycloketone oxime ester **1**, DABCO·$(SO_2)_2$, diphenyl diselenide **2** and phenylacetylene **3a**[ab]



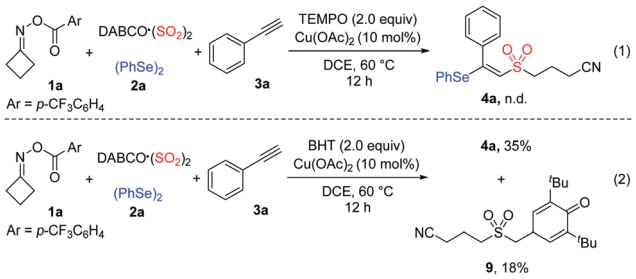
[a] Reaction conditions: cycloketone oxime esters **1** (0.2 mmol), DABCO·$(SO_2)_2$ (0.2 mmol), diselenides **2** (0.2 mmol), phenylacetylene **3a** (0.3 mmol), $Cu(OAc)_2$ (10 mol%), DCE (2.0 mL), 60 °C, N_2, 12 h. [b] Isolated yield based on cycloketone oxime ester **1**.

Table 4 Late-stage functionalization

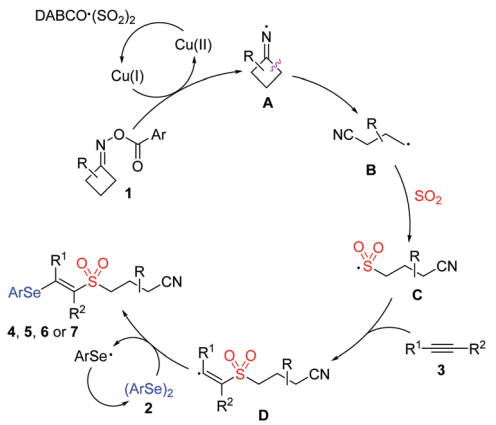




Scheme 2 Synthetic application.



Scheme 3 Control experiments.



Scheme 4 Plausible mechanism.

featured a broad substrate scope and high functional group tolerance. Furthermore, the late-stage functionalization of complex molecules and the successful application of products to generate alkynyl sulfones highlight the potential utility of this methodology. Mechanistic studies indicate that the cyanoalkylsulfonyl radical intermediate has participated.

Financial support from the National Natural Science Foundation of China (No. 21871053, 22101199 and 22171206), the Natural Science Foundation of Zhejiang Province (LQ21B020002), the Leading Innovative and Entrepreneur Team Introduction Program of Zhejiang (2019R01005) and the Open Research Fund of School of Chemistry and Chemical Engineering, Henan Normal University (2020ZD04) is gratefully acknowledged.

Conflicts of interest

There are no conflicts of interest to declare.

Notes and references

1 (*a*) T. Zhou, B. Peters, M. F. Maldonado, T. Govender and P. G. Andersson, *J. Am. Chem. Soc.*, 2012, **134**, 13592; (*b*) J. T. Palmer, D. Rasnick, J. L. Klaus and D. Brömme, *J. Med. Chem.*, 1995, **38**, 3193; (*c*) D. C. Meadows and J. Gervay-Hague, *Med. Res. Rev.*, 2006, **26**, 793.

2 (*a*) S. Y. Woo, J. H. Kim, M. K. Moon, S. H. Han, S. K. Yeon, J. W. Choi, B. K. Jang, H. J. Song, Y. G. Kang, J. W. Kim, J. Lee, D. J. Kim, O. Hwang and K. D. Park, *J. Med. Chem.*, 2014, **57**, 1473; (*b*) J. W. Choi, S. Kim, J. H. Park, H. J. Kim, S. J. Shin, J. W. Kim, S. Y. Woo, C. Lee, S. M. Han, J. Lee, A. N. Pae, G. Han and K. D. Park, *J. Med. Chem.*, 2019, **62**, 811; (*c*) M. Uttamchandani, K. Liu, R. C. Panicker and S. Q. Yao, *Chem. Commun.*, 2007, 1518.

3 (*a*) S. Chodroff and W. F. Whitmore, *J. Am. Chem. Soc.*, 1950, **72**, 1073; (*b*) P. B. Hopkins and P. L. Fuchs, *J. Org. Chem.*, 1978, **43**, 1208; (*c*) L. Wang, H. Yue, D. Yang, H. Cui, M. Zhu, J. Wang, W. Wei and H. Wang, *J. Org. Chem.*, 2017, **82**, 6857.

4 For selected reviews, see: (*a*) G. Perin, E. J. Lenardão, R. G. Jacob and R. B. Panatieri, *Chem. Rev.*, 2009, **109**, 1277; (*b*) G. Mugesh, W.-W. du Mont and H. Sies, *Chem. Rev.*, 2001, **101**, 2125.

5 (*a*) T. G. Back and S. Collins, *Tetrahedron Lett.*, 1981, **22**, 5111; (*b*) T. G. Back, M. V. Krishna and K. R. Muralidharan, *J. Org. Chem.*, 1989, **54**, 4146; (*c*) J. V. Comasseto, L. W. Ling, N. Petragnani and H. A. Stefani, *Synthesis*, 1997, 373.

6 For selected examples, see: (*a*) T. G. Back, S. Collins and R. G. Kerr, *J. Org. Chem.*, 1983, **48**, 3077; (*b*) Y. Liu, G. Zheng, Q. Zhang, Y. Li and Q. Zhang, *J. Org. Chem.*, 2017, **82**, 2269; (*c*) K. Sun, X. Wang, F. Fu, C. Zhang, Y. Chen and L. Liu, *Green Chem.*, 2017, **19**, 1490; (*d*) R. Zhang, P. Xu, S.-Y. Wang and S.-J. Ji, *J. Org. Chem.*, 2019, **84**, 12324.

7 M.-H. Huang, W.-J. Hao, G.-G. Li, S.-J. Tu and B. Jiang, *Chem. Commun.*, 2018, **54**, 10791.

8 For selected examples, see: (*a*) A. García-Domínguez, S. Müller and C. Nevado, *Angew. Chem., Int. Ed.*, 2017, **56**, 9949; (*b*) Y. Ning, Q. Ji, P. Liao, E. A. Anderson and X. Bi, *Angew. Chem., Int. Ed.*, 2017, **56**, 13805.

9 For selected reviews, see: (*a*) D. Zheng and J. Wu, *Sulfur Dioxide Insertion Reactions for Organic Synthesis*, Nature Springer, Berlin, 2017; (*b*) G. Qiu, K. Zhou, L. Gao and J. Wu, *Org. Chem. Front.* 2018, **5**, 691; (*c*) K. Hofman, N. Liu and G. Manolikakes, *Chem. – Eur. J.*, 2018, **24**, 11852; (*d*) G. Qiu, L. Lai, J. Cheng and J. Wu, *Chem. Commun.*, 2018, **54**, 10405; (*e*) G. Qiu, K. Zhou and J. Wu, *Chem. Commun.*, 2018, **54**, 12561; (*f*) S. Ye, G. Qiu and J. Wu, *Chem. Commun.*, 2019, **55**, 1013; (*g*) S. Ye, M. Yang and J. Wu, *Chem. Commun.*, 2020, **56**, 4145; (*h*) D. Zeng, M. Wang, W.-P. Deng and X. Jiang, *Org. Chem. Front.*, 2020, **7**, 3956.

10 For selected examples, see: (*a*) D. Zheng, Y. An, Z. Li and J. Wu, *Angew. Chem., Int. Ed.*, 2014, **53**, 2451; (*b*) F. Liu, J.-Y. Wang, P. Zhou, G. Li, W.-J. Hao, S.-J. Tu and B. Jiang, *Angew. Chem., Int. Ed.*, 2017, **56**, 15570; (*c*) J. Zhang, M. Yang, J.-B. Liu, F.-S. He and J. Wu, *Chem. Commun.*, 2020, **56**, 3225; (*d*) X. Wang, Y. Lin, J.-B. Liu, F.-S. He, Y. Kuang and J. Wu, *Chin. J. Chem.*, 2020, **38**, 1098; (*e*) Y. Yao, Z. Yin, F.-S. He, X. Qin, W. Xie and J. Wu, *Chem. Commun.*, 2021, **57**, 2883; (*f*) S. Cao, W. Hong, Z. Ye and L. Gong, *Nat. Commun.*, 2021, **12**, 2377; (*g*) F.-S. He, P. Bao, F. Yu, L.-H. Zeng, W.-P. Deng and J. Wu, *Org. Lett.*, 2021, **23**, 7472; (*h*) F.-S. He, Y. Yao, Z. Tang, W. Xie and J. Wu, *Org. Chem. Front.*, 2021, **8**, 6119.

11 For selected examples, see: (*a*) F.-S. He, X. Gong, P. Rojsitthisak and J. Wu, *J. Org. Chem.*, 2019, **84**, 13159; (*b*) X. Gong, M. Yang, J.-B. Liu, F.-S. He, X. Fan and J. Wu, *Green Chem.*, 2020, **22**, 1906; (*c*) X. Gong, M. Yang, J.-B. Liu, F.-S. He and J. Wu, *Org. Chem. Front.*, 2020, **7**, 938; (*d*) Y. Liu, Q.-L. Wang, Z. Chen, H. Li, B.-Q. Xiong, P.-L. Zhang and K.-W. Tang, *Chem. Commun.*, 2020, **56**, 3011; (*e*) F.-S. He, Y. Yao, W. Xie and J. Wu, *Chem. Commun.*, 2020, **56**, 9469.

12 (*a*) F.-S. He, M. Yang, S. Ye and J. Wu, *Chin. Chem. Lett.*, 2021, **32**, 461; (*b*) Y. Li, J.-B. Liu, F.-S. He and J. Wu, *Chin. J. Chem.*, 2020, **38**, 361; (*c*) H. Zhang, M. Wang and X. Jiang, *Green Chem.*, 2020, **22**, 8238; (*d*) J. Chen, N. Liu, Q. Hu, J. Liu, J. Wu, Q. Cai and J. Wu, *Org. Chem. Front.*, 2021, **8**, 5316.

13 K. Sun, Z. Shi, Z. Liu, B. Luan, J. Zhu and Y. Xue, *Org. Lett.*, 2018, **20**, 6687.

14 For selected reviews and examples, see: (*a*) T. Xiao, H. Huang, D. Anand and L. Zhou, *Synthesis*, 2020, 1585; (*b*) W. Xiao and J. Wu, *Chin. Chem. Lett.*, 2020, **31**, 3083; (*c*) F.-S. He, S. Ye and J. Wu, *ACS Catal.*, 2019, **9**, 8943; (*d*) C. Song, X. Shen, F. Yu, Y. He and S. Yu, *Chin. J. Org. Chem.*, 2020, **40**, 3748; (*e*) F.-S. He, M. Zhang, M. Zhang, X. Luo and J. Wu, *Org. Chem. Front.*, 2021, **8**, 3746; (*f*) X.-Y. Yu, J.-R. Chen and W.-J. Xiao, *Chem. Rev.*, 2021, **121**, 506; (*g*) X.-Y. Yu, Q.-Q. Zhao, J. Chen, W.-J. Xiao and J.-R. Chen, *Acc. Chem. Res.*, 2020, **53**, 1066; (*h*) F. Xiao, Y. Guo and Y.-F. Zeng, *Adv. Synth. Catal.*, 2021, **363**, 120.

15 CCDC 2102437 contains the supplementary crystallographic data for this paper.

