Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/d4ob01213e

Received 23rd July 2024,
Accepted 12th August 2024

DOI: 10.1039/d4ob01213e

rsc.li/obc

A portal to highly valuable indole-functionalized vinyl sulfonyl fluorides and allylic sulfonyl fluorides†

Wenzhuo Huang,[a] Eman Fayad,[b] Ola A. Abu Ali[c] and Hua-Li Qin *[a]

A practical and efficient method for the C-3 site selective alkenylation of indoles was developed for constructing novel indole-functionalized vinyl sulfonyl fluorides and indolyl allylic sulfonyl fluorides. The reaction is accomplished with exclusive regio- and stereoselectivity without using transition metal catalysts, providing novel products of great potential value in medicinal chemistry, chemical biology, and drug discovery.

The indole skeleton is one of the most ubiquitous heterocycles in nature, with broad applications in organic synthesis and medicinal chemistry.[1] More than 10 000 biologically active indole derivatives have been discovered to date, and over 200 of these are currently being marketed as pharmaceuticals or undergoing clinical trials, including blockbuster drugs such as osimertinib (Tagrisso), etodolac (Lodine) and vilazodone (Viibryd) (Fig. 1a).[2] Due to the great importance of indole moieties, the development of practical and efficient methods to modify the indole unit continues to be of great significance. It is well known that direct functionalization of indoles is an atom- and step-economical strategy. Numerous elegant methods have been developed, including alkylation,[3] arylation,[4] acylation,[5] trifluoromethylthiolation[6] and sulfonylation[7] of indoles. Despite the considerable number of methods reported, the alkenylation of indoles has been received much less attention. Although transition metal catalysts have been developed for the synthesis of vinylindoles,[8] their high cost and scarcity hinder their widespread applications. Therefore, constructing vinylindoles without transition metal catalysts offers tremendous advantages in the fields of medicinal chemistry, drug discovery, and chemical biology.

On the other hand, sulfur fluoride exchange (SuFEx) chemistry, introduced by K. B. Sharpless and co-workers in 2014, has rapidly gained preference as a valuable tool for the formation of S–O, S–N, and S–C bonds.[9] Aliphatic sulfonyl fluorides are crucial functionalities that have been employed for decades as privileged "warheads" in enzyme inhibitors.[10] And vinyl sulfonyl fluorides, a class of selectively addressable bis-electrophiles, have emerged as important building blocks in medicinal chemistry,[11] polymer synthesis,[12] and organic chemistry.[13]

Given the well-established biological activity of indoles and the growing significance of sulfonyl fluorides in medicinal

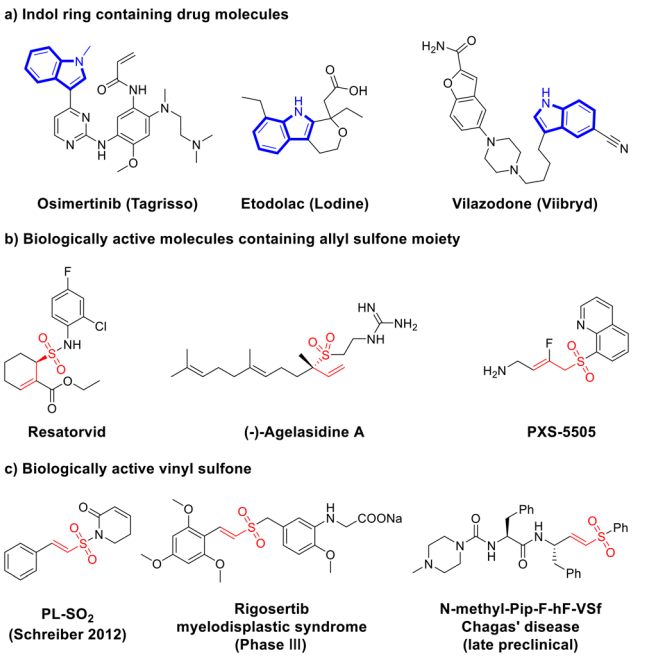


Fig. 1 Representative indole-containing molecules and biologically active sulfone compounds.

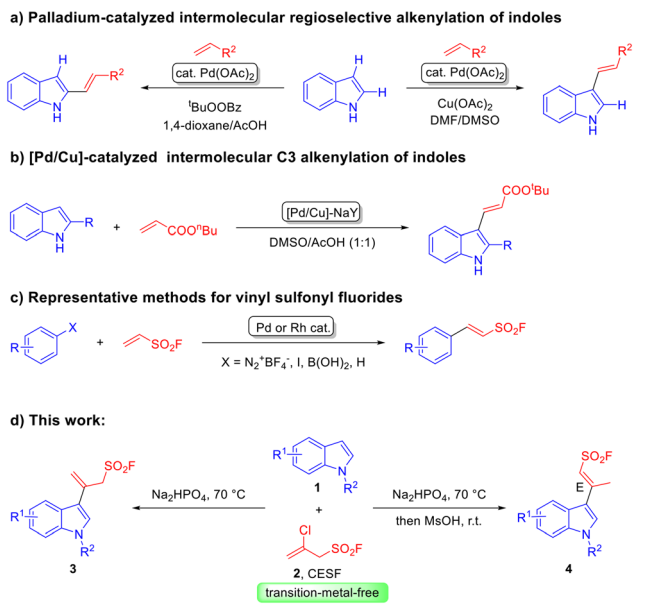
[a]State Key Laboratory of Silicate Materials for Architectures; and School of Chemistry, Chemical Engineering and Life Sciences, Wuhan University of Technology, Wuhan 430070, China. E-mail: qinhuali@whut.edu.cn
[b]Department of Biotechnology, College of Sciences, Taif University, P.O. Box 11099, Taif 21944, Saudi Arabia. E-mail: e.esmail@tu.edu.sa
[c]Department of Chemistry, College of Science, Taif University, Taif 21944, Saudi Arabia. E-mail: o.abuali@tu.edu.sa

†Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d4ob01213e

chemistry and organic synthesis, we envisioned that the construction of a class of indole-functionalized vinyl sulfonyl fluorides and allylic sulfonyl fluorides is worthy of extensive investigation, since it will enhance the likelihood of discovering lead compounds and identifying new drug candidates. In 2005, Gaunt and co-workers[14] realized a palladium-catalyzed alkenylation of indoles *via* a solvent-controlled regioselective C–H functionalization (Scheme 1a). Then Djakovitch and Rouge[15] described an environmentally friendly [Pd/Cu]-catalyzed C-3 alkenylation of NH-free indoles (Scheme 1b). Despite tremendous advancements in this field, practical and efficient methods for chemo- and site-selective functionalization of indoles remain critical to drug development. As for sulfonyl fluoride groups, previous studies in the literature have mainly focused on the synthesis of basic vinyl sulfonyl fluoride units without the installation of vinyl sulfonyl fluorides into pharmaceutical molecules. For example, straightforward one-step methods to access vinyl sulfonyl fluorides were Pd-catalyzed Heck-type coupling reactions[16] and Rh-catalyzed C–H alkenylation reactions of arenes (Scheme 1c).[17] Importantly, performing these transformations without the assistance of transition metals is highly desirable in view of the strict limits on the level of trace transition metals used in pharmaceutical research.[18] Herein, we report a transition-metal-free direct C-3 alkenylation of indoles (**1**) with 2-chloroprop-2-ene-1-sulfonyl fluoride (**2**, CESF) for the selective synthesis of indole-functionalized allylic sulfonyl fluorides (**3**) and vinyl sulfonyl fluorides (**4**) (Scheme 1d).

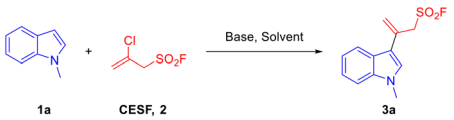
Due to the innate electrophilicity and excellent reactivity of CESF (**2**), we assumed that the reaction of indoles (**1**) with CESF (**2**) under alkaline conditions would be feasible for constructing novel indole-functionalized allylic sulfonyl fluorides (**3**) and vinyl sulfonyl fluorides (**4**). Our investigation commenced with testing the feasibility of the reaction of 1-methylindole (**1a**) and CESF (**2**) in the presence of KF and toluene at 60 °C. The desired product (**3a**) was obtained in 18% yield (Table 1, entry 1). Subsequent optimization was conducted by screening different reaction solvents, and CH_3CN was found to be the most effective solvent (Table 1, entries 1–4). Subsequently, the effects of bases were also assessed, and Na_2HPO_4 appeared to be the most suitable base, affording the desired product (**3a**) in 50% yield (Table 1, entries 4–7). Meanwhile, the influence of temperature was briefly investigated (Table 1, entries 7 and 8). To our delight, the yield reached 64% when the temperature was 70 °C. In addition, the amount of Na_2HPO_4 to be used was also assessed, and 3.2 equivalents of Na_2HPO_4 was found to be appropriate for this reaction (Table 1, entries 8 and 9). Finally, the reaction time was examined, and it was shown that 18 hours were needed to achieve the desired transformation (Table 1, entries 9 and 10). Accordingly, the reaction conditions shown in Table 1, entry 10 were eventually selected as the standard operating conditions for further examination of the substrate scope and functional group tolerance.

The substrate scope and functional-group compatibility of indoles (**1**) were examined, as shown in Table 2. A series of differently substituted indoles (**1**) were reacted with CESF (**2**), and they smoothly afforded the desired products (**3**) in acceptable to excellent isolated yields. Indoles bearing electron donating groups on their aromatic rings furnished the corresponding products in higher yields compared to their counterparts possessing electron withdrawing groups. For example, indoles bearing methyl groups (**1b–1d**) and methoxy groups (**1e**) generally underwent the desired transformation more efficiently compared with electron-deficient indoles (**1v** and **1w**). Subsequently, we optimized the loading of CESF (**2**) and



Scheme 1 Strategies for the alkenylation of indoles.

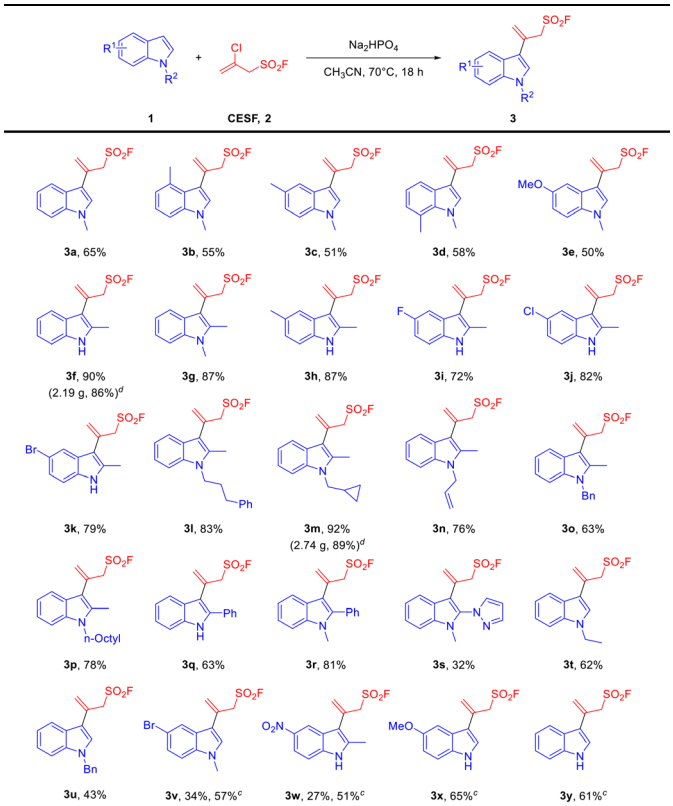
Table 1 Optimization of reaction conditions[a]



Entry	Base (equiv.)	Solvent	Yield[b] (**3a**, %)
1	KF (4.0)	Toluene	18
2	KF (4.0)	THF	14
3	KF (4.0)	EtOAc	26
4	KF (4.0)	CH_3CN	41
5	$KHCO_3$ (4.0)	CH_3CN	10
6	K_3PO_4 (4.0)	CH_3CN	Trace
7	Na_2HPO_4 (4.0)	CH_3CN	50
8[c]	Na_2HPO_4 (4.0)	CH_3CN	64
9[c]	Na_2HPO_4 (3.2)	CH_3CN	64
10[c,d]	**Na_2HPO_4 (3.2)**	**CH_3CN**	**71**

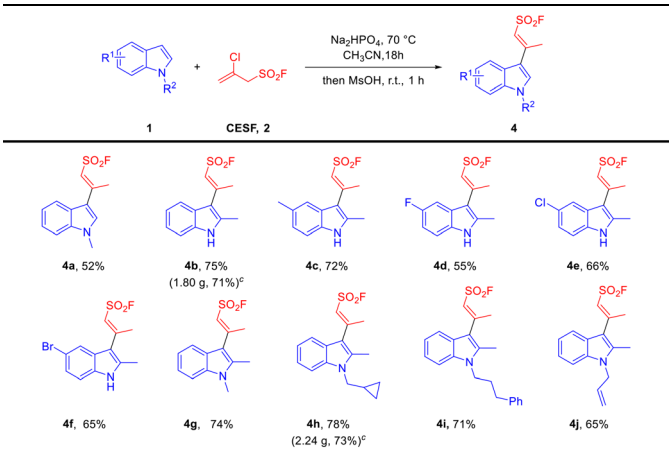
[a] Reaction conditions: 1-methylindole (**1a**, 0.1 mmol, 1.0 equiv.), 2-chloroprop-2-ene-1-sulfonyl fluoride (**2**, 0.2 mmol, 2.0 equiv.), base (*X* mmol), solvent (2.0 mL), 60 °C, 12 h under air. [b] The yield was determined by HPLC using pure **3a** as the external standard ($t_{R,3a}$ = 5.863 min, λ_{max} = 226.4 nm; CH_3CN/H_2O = 60 : 40 (v/v)). [c] Reacted at 70 °C. [d] Reacted for 18 h.

Table 2 Substrate scope using different indoles[a,b]

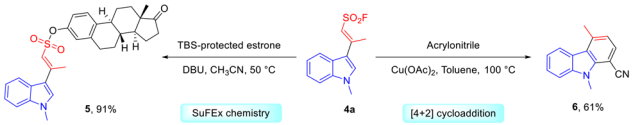


[a] Reaction conditions: **1** (1.0 mmol, 1.0 equiv.), **2** (316 mg, 2.0 mmol, 2.0 equiv.), Na_2HPO_4 (454 mg, 3.2 mmol, 3.2 equiv.) and CH_3CN (10.0 mL), 70 °C, 18 h under air. [b] Isolated yields. [c] **1** (1.0 mmol, 1.0 equiv.), **2** (1110 mg, 7.0 mmol, 7.0 equiv.), Na_2HPO_4 (994 mg, 7.0 mmol, 7.0 equiv.) and CH_3CN, 70 °C, 48 h under air. [d] Gram-scale reaction.

Table 3 Substrate scope using different indoles[a,b]



[a] Reaction conditions: **1** (1.0 mmol, 1.0 equiv.), **2** (316 mg, 2.0 mmol, 2.0 equiv.), Na_2HPO_4 (454 mg, 3.2 mmol, 3.2 equiv.) and CH_3CN (10.0 mL), 70 °C, 18 h under air, then MsOH (577 mg, 6 mmol, 6.0 equiv.), room temperature, 1 h. [b] Isolated yields. [c] Gram-scale reaction.



Scheme 2 Diversification of (*E*)-2-(1-methyl-1*H*-indol-3-yl)prop-1-ene-1-sulfonyl fluoride (**4a**).

reaction time for the indoles (**1v–1y**) with lower yields, and ultimately the corresponding products (**3v–3y**) were obtained in acceptable yields. In order to verify the practicality of this method, reactions using indoles **1f** and **1m** were performed at the 10.0 mmol scale under the optimal conditions, and the corresponding products **3f** and **3m** were formed in yields of 86% and 89%, respectively.

Furthermore, an acid-promoted one-pot transformation was also developed to allow access to a class of novel indole-functionalized vinyl sulfonyl fluorides. After screening the reaction conditions, it was found that the use of 6.0 equivalents of MsOH were necessary to ensure that the indoles were transformed to their vinyl sulfonyl fluorides (**4**). The desired products were generated in moderate to good isolated yields. The configuration of the representative vinyl sulfonyl fluoride **4a** was confirmed by NOE analysis (see the ESI† for details). The substrate scope and functional-group compatibility of indoles (**1**) were examined, as shown in Table 3. In addition, a couple of 10.0 mmol scale reactions were performed under the optimal reaction conditions, with indoles **1f** and **1m** being converted to the corresponding products **4f** and **4m** in yields of 75% and 73%, respectively.

In addition, further derivatization of the model substrate (**4a**) was accomplished using SuFEx click chemistry (Scheme 2). The treatment of **4a** with TBS-protected estrone using DBU as the catalyst resulted in the novel estrone sulfonate derivative **5** in 91% yield. For further diversification, the vinyl sulfonyl fluoride product **4a** was utilized as a diene to perform a [4 + 2] cycloaddition reaction with acrylonitrile to generate the carbazole derivative **6** in 61% yield.

Conclusions

In conclusion, we have developed a practical and efficient method for the intermolecular C-3 site-selective alkenylation of indoles, achieving a series of novel indole-functionalized vinyl sulfonyl fluorides and indolyl allylic sulfonyl fluorides. The method features exclusive stereoselectivity, a broad substrate scope and mild reaction conditions, providing two classes of novel, highly functionalized and greatly valuable sulfonyl fluorides for medical chemistry and drug discovery. Further studies on these indole-functionalized vinyl sulfonyl fluorides and indolyl allylic sulfonyl fluorides are underway in our laboratory, focussing on their applications in chemical biology, medicinal chemistry and materials science.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful to the National Natural Science Foundation of China (grant No. 22071190), the Wuhan University of Technology, and the Natural Science Foundation of Hubei Province (No. 2023AFA014) for financial support. The authors also extend their appreciation to Taif University, Saudi Arabia, for supporting this work through project number TU-DSPP-2024-85.

References

1 G. R. Humphrey and J. T. Kuethe, *Chem. Rev.*, 2006, **106**, 2875–2911.
2 S. M. Bronner, K. B. Bahnck and N. K. Garg, *Org. Lett.*, 2009, **11**, 1007–1010.
3 (*a*) T. Wang, G. W. Zhang, Y. Teng, J. Nie, Y. Zheng and J. A. Ma, *Adv. Synth. Catal.*, 2010, **352**, 2773–2777; (*b*) T. Hanakawa, K. Isa, S.-I. Isobe, Y. Hoshino, B. Zhou and M. Kawatsura, *J. Org. Chem.*, 2017, **82**, 2281–2287.
4 J. Chen and J. Wu, *Angew. Chem., Int. Ed.*, 2017, **56**, 3951–3955.
5 (*a*) T. J. Williams and M. F. Greaney, *Org. Lett.*, 2014, **16**, 4024–4027; (*b*) Z.-W. Zhang, H. Xue, H. Li, H. Kang, J. Feng, A. Lin and S. Liu, *Org. Lett.*, 2016, **18**, 3918–3921; (*c*) S.-J. Yao, Z.-H. Ren, Y.-Y. Wang and Z.-H. Guan, *J. Org. Chem.*, 2016, **81**, 4226–4234.
6 M.-J. Bu, G.-P. Lu and C. Cai, *Org. Chem. Front.*, 2017, **4**, 266–270.
7 X.-H. Xu, G.-K. Liu, A. Azuma, E. Tokunaga and N. Shibata, *Org. Lett.*, 2011, **13**, 4854–4857.
8 (*a*) P. Kannaboina, K. A. Kumar and P. Das, *Org. Lett.*, 2016, **18**, 900–903; (*b*) H. P. Gemoets, V. Hessel and T. Noel, *Org. Lett.*, 2014, **16**, 5800–5803; (*c*) S. R. Kandukuri, J. A. Schiffner and M. Oestreich, *Angew. Chem., Int. Ed.*, 2012, **51**, 1265–1269.
9 J. Dong, L. Krasnova, M. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2014, **53**, 9430–9448.
10 (*a*) C. Dubiella, H. Cui, M. Gersch, A. J. Brouwer, S. A. Sieber, A. Krüger, R. M. Liskamp and M. Groll, *Angew. Chem., Int. Ed.*, 2014, **53**, 11969–11973; (*b*) R. Artschwager, D. J. Ward, S. Gannon, A. J. Brouwer, H. van de Langemheen, H. Kowalski and R. M. Liskamp, *J. Med. Chem.*, 2018, **61**, 5395–5411.
11 (*a*) M. Gehringer and S. A. Laufer, *J. Med. Chem.*, 2018, **62**, 5673–5724; (*b*) G.-F. Zha, S.-M. Wang, K. Rakesh, S. N. A. Bukhari, H. Manukumar, H. Vivek, N. Mallesha and H.-L. Qin, *Eur. J. Med. Chem.*, 2019, **162**, 364–377; (*c*) X. Chen, G.-F. Zha, J. Q. Wang and X.-H. Liu, *J. Enzyme Inhib. Med. Chem.*, 2018, **33**, 1266–1270; (*d*) Z. Liu, J. Li, S. Li, G. Li, K. B. Sharpless and P. Wu, *J. Am. Chem. Soc.*, 2018, **140**, 2919–2925; (*e*) E. C. Hett, H. Xu, K. F. Geoghegan, A. Gopalsamy, R. E. Kyne Jr, C. A. Menard, A. Narayanan, M. D. Parikh, S. Liu, L. Roberts, R. P. Robinson, M. A. Tones and L. H. Jones, *ACS Chem. Biol.*, 2015, **10**, 1094–1098.
12 (*a*) J. Dong, K. B. Sharpless, L. Kwisnek, J. S. Oakdale and V. V. Fokin, *Angew. Chem., Int. Ed.*, 2014, **53**, 9466–9470; (*b*) J. Yatvin, K. Brooks and J. Locklin, *Angew. Chem., Int. Ed.*, 2015, **54**, 13370–13373; (*c*) B. Gao, L. Zhang, Q. Zheng, F. Zhou, L. M. Klivansky, J. Lu, Y. Liu, J. Dong, P. Wu and K. B. Sharpless, *Nat. Chem.*, 2017, **9**, 1083–1088; (*d*) H. Wang, F. Zhou, G. Ren, Q. Zheng, H. Chen, B. Gao, L. Klivansky, Y. Liu, B. Wu, Q. Xu, J. Lu, K. B. Sharpless and P. Wu, *Angew. Chem., Int. Ed.*, 2017, **56**, 11203–11208.
13 (*a*) C. J. Smedley, Q. Zheng, B. Gao, S. Li, A. Molino, H. M. Duivenvoorden, B. S. Parker, D. J. Wilson, K. B. Sharpless and J. E. Moses, *Angew. Chem., Int. Ed.*, 2019, **58**, 4552–4556; (*b*) A. J. Brouwer, N. H. Álvarez, A. Ciaffoni, H. van de Langemheen and R. M. Liskamp, *Bioorg. Med. Chem.*, 2016, **24**, 3429–3435; (*c*) C. J. O'Connor, H. S. Beckmann and D. R. Spring, *Chem. Soc. Rev.*, 2012, **41**, 4444–4456; (*d*) S. Mahapatra, C. P. Woroch, T. W. Butler, S. N. Carneiro, S. C. Kwan, S. R. Khasnavis, J. Gu, J. K. Dutra, B. C. Vetelino, J. Bellenger, C. W. am Ende and N. D. Ball, *Org. Lett.*, 2020, **22**, 4389–4394.
14 N. P. Grimster, C. Gauntlett, C. R. Godfrey and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2005, **44**, 3125–3129.
15 L. Djakovitch and P. Rouge, *Catal. Today*, 2009, **140**, 90–99.
16 (*a*) H. L. Qin, Q. Zheng, G. A. Bare, P. Wu and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2016, **55**, 14155–14158; (*b*) G. F. Zha, Q. Zheng, J. Leng, P. Wu, H. L. Qin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2017, **56**, 4849–4852; (*c*) P. K. Chinthakindi, K. B. Govender, A. S. Kumar, H. G. Kruger, T. Govender, T. Naicker and P. I. Arvidsson, *Org. Lett.*, 2017, **19**, 480–483; (*d*) G. F. Zha, G. A. Bare, J. Leng, Z. P. Shang, Z. Luo and H. L. Qin, *Adv. Synth. Catal.*, 2017, **359**, 3237–3242.
17 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.
18 M. Chatzopoulou, K. S. Madden, L. J. Bromhead, C. Greaves, T. J. Cogswell, S. Da Silva Pinto, S. R. Galan, I. Georgiou, M. S. Kennedy, A. Kennett, G. Apps, A. J. Russell and G. M. Wynne, *ACS Med. Chem. Lett.*, 2022, **13**, 262–270.

