Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal | View Issue





Cite this: *Org. Biomol. Chem.*, 2020, **18**, 4556

Received 26th April 2020,
Accepted 22nd May 2020

DOI: 10.1039/d0ob00872a

rsc.li/obc

# Novel usage of 2-BTSO$_2$CF$_2$H for metal-free electrophilic difluoroalkanethiolation of indoles†

Jun Wei,[a] Kun Bao,[a,b] Yuan Wang,[a] Rong Sheng *[a] and Jinbo Hu *[c]

**The electrophilic difluoromethylthiolation of indoles with 2-BTSO$_2$CF$_2$H is developed. In the presence of (EtO)$_2$P(O)H and TMSCl, the reaction proceeded under mild conditions to give products in modest to high yields. This is a new application of 2-BTSO$_2$CF$_2$H for electrophilic difluoromethylthiolation.**

In recent years, the introduction of the –SCF$_2$H group into organic molecules has been of growing interest in the pharmaceutical and agrochemical fields.[1] The –SCF$_2$H group possesses moderate lipophilicity ($\pi_R$ = 0.68 for –SCF$_2$H, 0.56 for –CH$_3$ and 1.44 for –SCF$_3$)[2] as well as unique properties. (1) –SCF$_2$H is considered as an enhanced version of CF$_3$ and a lipophilic OH or NH surrogate for bioactive molecules. (2) –SCF$_2$H can serve as a weak hydrogen bond donor with a slightly acidic proton. (3) Incorporation of the –SCF$_2$H group into drugs often significantly improves their metabolic stability.[3] For example, pyriprole, an EP approved novel pesticide for animals; the introduction of the –SCF$_2$H moiety at the pyrozole ring is beneficial for its activity.[4] In addition, the important role of –SCF$_2$H in pharmaceuticals and agrochemicals is evidenced by its frequent presence in other bioactive compounds, *e.g.*, a nifedipine analogue,[5] the herbicide SSH-108,[6] and a thymol analogue[7] (Fig. 1).

The prevalent methods for the construction of the -SCF$_2$H moiety involve the insertion of *in situ* generated CF$_2$ carbene into the RS–H bond using reagents such as ClCF$_2$H,[8] ClCF$_2$CO$_2$Na,[9] TMSCF$_2$Br,[10] PhS(O)(NTs)CF$_2$H[11] and Ph$_3$P$^+$CF$_2$CO$_2^-$.[12] Nevertheless, these indirect methods suffer from the limited availability of thiol substrates, and the incompatibility of harsh thermal and strongly basic reaction conditions to generate reactive thiolates and "CF$_2$" species.

Recently, many efficient direct methods to introduce the –SCF$_2$H group directly into molecules have been disclosed. In 2015, Shen and co-workers demonstrated the copper-promoted Sandmeyer difluoro-methylthiolation of aryl and heteroaryl diazonium salts using the first nucleophilic difluoromethylthiolating reagent, the N-heterocyclic carbene (NHC) ligated difluoromethylthiolated silver complex [(SIPr)Ag(SCF$_2$H)][13] (Fig. 1, **1a**). Complementarily, the same group also developed the *N*-difluoromethylthiophthalimide **1b** as a new electrophilic difluoromethylthiolating reagent.[14] In addition, *S*-(difluoromethyl) benzenesulfonothioate **1c** was also developed as a robust radical difluoromethylthiolating reagent by Shen and Li groups.[15] Recently, a key "*in situ* reduction" concept was made by Shibata *et al.* who delineated the difluoromethanesulfonyl (–SO$_2$ CF$_2$H) hypervalent iodonium ylides **1d** as electrophilic difluoro-methylthiolating reagents for various nucleophiles.[16] Based on this strategy, HCF$_2$SO$_2$Na[17] **1e**, HCF$_2$SO$_2$Cl[18] **1f** and

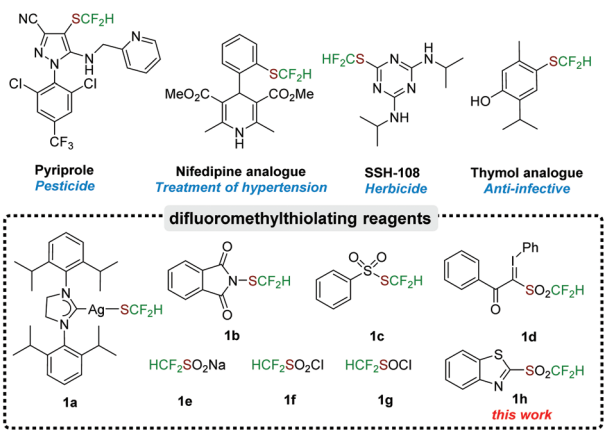



Fig. 1 –SCF$_2$H containing bioactive compounds and direct difluoromethylthiolating reagents.

[a]College of Pharmaceutical Sciences, Zhejiang University, Hangzhou, 310058, People's Republic of China. E-mail: shengr@zju.edu.cn
[b]Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals, Zhejiang University of Technology, Hangzhou, 310014, P. R. China
[c]Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Ling-Ling Road, Shanghai, 200032, People's Republic of China

†Electronic supplementary information (ESI) available. CCDC 1994911. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0ob00872a

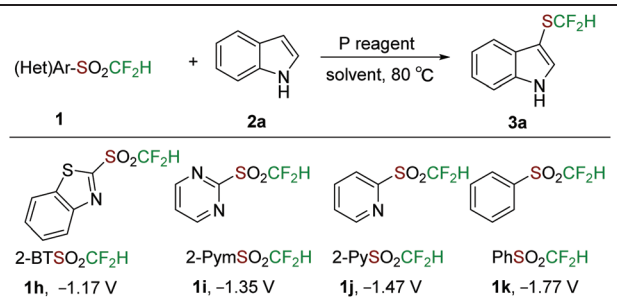
$HCF_2SOCl$[19] **1g** have also been reported as novel electrophilic difluoromethylthiolating reagents under reductive conditions.

Hu and co-workers focused on the research of fluoroalkyl heteroaryl sulfones for many years,[20] and developed a bench-stable, readily available reagent, 2-((difluoromethyl)sulfonyl)-benzo[*d*]thiazole (2-$BTSO_2CF_2H$, **1h**), which can undergo a radical difluoromethylation on various isocyanides under visible light,[21] as well as can serve as a difluoroalkanesulfinate precursor.[22] Recently, we disclosed the trifluoromethylsulfinylation of electron-rich arenes under reductive conditions using 2-$BTSO_2R_f$ ($R_f$ = $CF_3$, $C_4F_9$, $CF_2Br$, $CF_2Cl$, $CF_2CO_2Et$) as $R_fSO$ synthons and $Ph_2P(O)Cl$ as the reducing agent. This is the first example where 2-$BTSO_2R_f$ acts as the $R_fSO$ source in organic synthesis *via* both C(Het)–S and S=O bond cleavage.[23] Inspired by this work, we try to apply a similar strategy and achieve the direct difluoromethylthiolation of indoles with 2-$BTSO_2CF_2H$ (Table 1).

Our initial attempt began by employing indole **2a** as the model substrate with 2-$BTSO_2CF_2H$ (**1h**, 1.1 equiv.) and $(EtO)_2P(O)H$/TMSCl in toluene (1.0 mL) at 80 °C under an inert atmosphere.[17] Gratifyingly, the desired difluoromethylthiolation product **3a** was isolated in 56% yield (entry 1). Subsequent solvent screening revealed that MeCN was more favorable than toluene, DMF and THF (entries 2–4). And no better results were obtained using other difluoromethyl 2-heteroaryl sulfone reagents, including 2-$PymSO_2CF_2H$ **1i**, 2-$PySO_2CF_2H$ **1j**, and $PhSO_2CF_2H$ **1k** (entries 5–7). In particular, the first reduction potential of several difluoromethyl sulfones (**1h**: −1.17 V; **1i**: −1.35 V; **1j**: −1.47 V; **1k**: −1.77 V; *versus* the saturated calomel electrode, SCE) is consistent with their reaction efficiency.[20] Then, the pivotal role played by TMSCl was illustrated by the control experiment as TMSCl free conditions disabled the reaction completely (entries 8–10). Furthermore, the employment of $Ph_2P(O)Cl$ or $Ph_2PCl$ as a reductant cannot improve the yield of the product either (entries 11 and 12). Therefore, the best result was obtained with a combination of indole and **1a** (1.5 equiv.) with $(EtO)_2P(O)H$ (3.0 equiv.) and TMSCl (3.0 equiv.) in MeCN at 80 °C for 4 h to furnish **3a** in 74% yield (entry 2).

With the optimized reaction conditions in hand, we explored the substrate scope with various indole derivatives, and the results are summarized in Table 2. Substrates with simple functional groups (such as halogen, alkyl, alkoxy) in different sites of indole were the suitable substrates for this transformation and gave the corresponding products **3a–3i** in moderate to excellent yields (50–82%), while the 7-cyano

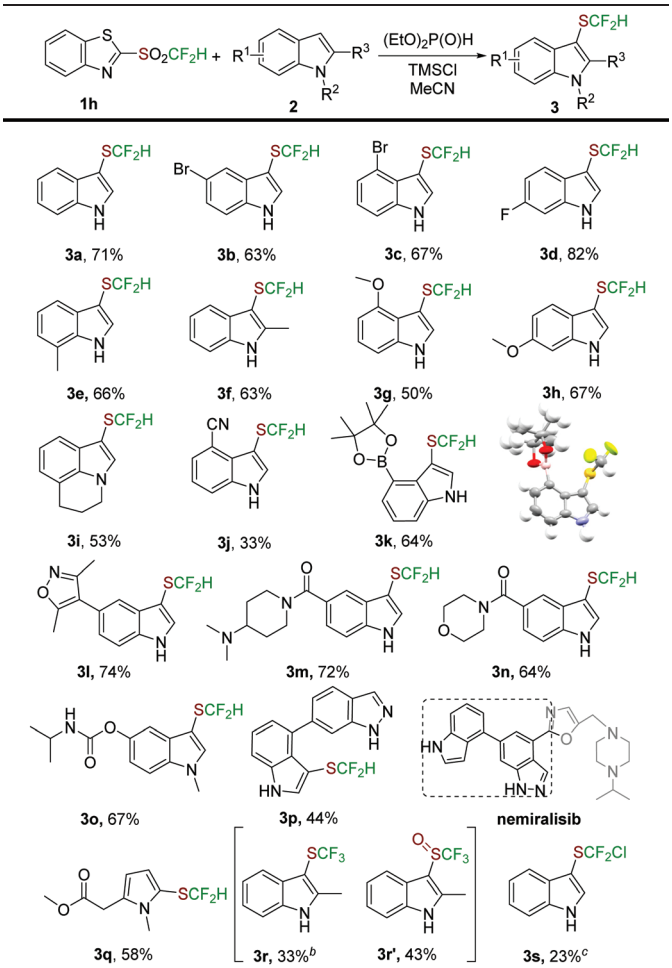
**Table 1** Reaction optimization[a]




| Entry | P reagent | Additive | 1 | Solvent | 3a[b] |
|---|---|---|---|---|---|
| 1 | $(EtO)_2P(O)H$ | TMSCl | **1h** | Toulene | 56 |
| **2** | **$(EtO)_2P(O)H$** | **TMSCl** | **1h** | **MeCN** | **74** |
| 3 | $(EtO)_2P(O)H$ | TMSCl | **1h** | DMF | 49 |
| 4 | $(EtO)_2P(O)H$ | TMSCl | **1h** | THF | 35 |
| 5 | $(EtO)_2P(O)H$ | TMSCl | **1i** | MeCN | 24 |
| 6 | $(EtO)_2P(O)H$ | TMSCl | **1j** | MeCN | 0 |
| 7 | $(EtO)_2P(O)H$ | TMSCl | **1k** | MeCN | 0 |
| 8 | $(EtO)_2P(O)H$ | — | **1h** | MeCN | 0 |
| 9 | $(EtO)_2P(O)H$ | TBAC | **1h** | MeCN | 0 |
| 10 | $(EtO)_2P(O)H$ | HCl | **1h** | MeCN | 0 |
| 11 | $Ph_2P(O)Cl$ | — | **1h** | MeCN | 34 |
| 12 | $Ph_2PCl$ | — | **1h** | MeCN | 32 |

[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.2 mmol), P reagent (0.6 mmol), additive (0.6 mmol), solvent (1 mL), $N_2$, 80 °C, 4 h. [b] Yields were determined by $^{19}F$ NMR using $PhCF_3$ as an internal standard.

**Table 2** Fluoromethylthiolation of indoles[a]



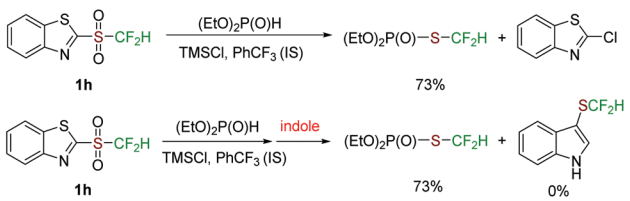

[a] Reaction conditions: **1** (1.5 mmol, 1.5 equiv.), **2** (1.0 mmol, 1.0 equiv.), $(EtO)_2P(O)H$ (3.0 mmol, 3.0 equiv.), TMSCl (3.0 mmol, 3.0 equiv.), MeCN (5 mL), $N_2$, 80 °C for 4 h. Isolated yields. [b] 2-$BTSO_2CF_3$ was used. [c] 2-$BTSO_2CF_2Cl$ was used.

indole **2j** afforded the desired products **3j** in poor yield (33%), probably due to the steric effect. This method tolerates indoles that contain various functional groups, including borate **2k**, isoxazole **2l**, dibasic chain **2m**, morpholino methanone **2n** and carbamate **2o**, and afford the corresponding target compounds in moderate to good yields (**3k–3o**). The reaction of **1h** with 6-(1*H*-indol-4-yl)-1*H*-indazole **2p**, the active skeleton of the selective PI3Kδ inhibitor nemiralisib,[24] only gave the 3-difluoromethylthiolated indole **3p**, indicating the excellent selectivity between indole and carbazole under the standard conditions. A reaction with electron-rich substituted pyrrole also can produce the corresponding difluoromethylthiolated product **3q** in 58% yield. In addition, trifluoromethylthiolation and halodifluoro-methylthiolation of indole can be achieved in moderate yields by using 2-BTSO$_2$CF$_3$ and 2-BTSO$_2$CF$_2$Cl as fluorine sources. Notably, 2-BTSO$_2$CF$_3$ formed the two products **3r** and **3r′** in yields of 33% and 43%, respectively. The structure of **3k** was confirmed by single crystal X-ray analysis (see the ESI†).[25]

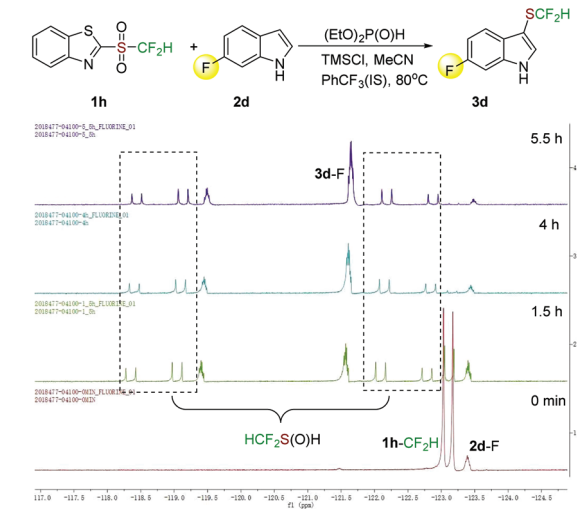
To gain insight into the mechanism of this transformation, a control reaction was conducted and monitored by $^{19}$F NMR. First, 2-BTSO$_2$CF$_2$H **1h** was subjected to the reaction conditions in the absence of indole, and (EtO)$_2$P(O)-SCF$_2$H ($\delta$ = 87.47 ppm) was obtained in 73% yield with a quantitative amount of 2-chlorobenzothiazole. Thereafter, indole **2a** was subjected to the above mixture, and surprisingly, with or without heating, the corresponding targeted molecule **3a** cannot be detected, which indicated that (EtO)$_2$P(O)-SCF$_2$H is not the reactive species for this transformation (Scheme 1).

Then, an *in situ* $^{19}$F NMR analysis of this transformation was conducted using **1h** and **2d** as reactants (Scheme 2, see the ESI† for details). The reagent **1h** (−123.3 ppm) promptly disappeared within 1.5 h at 80 °C, and small friable signals appeared between −118.5 and −123.0 ppm, which is believed to be HCF$_2$S(O)H according to a previous report.[26]

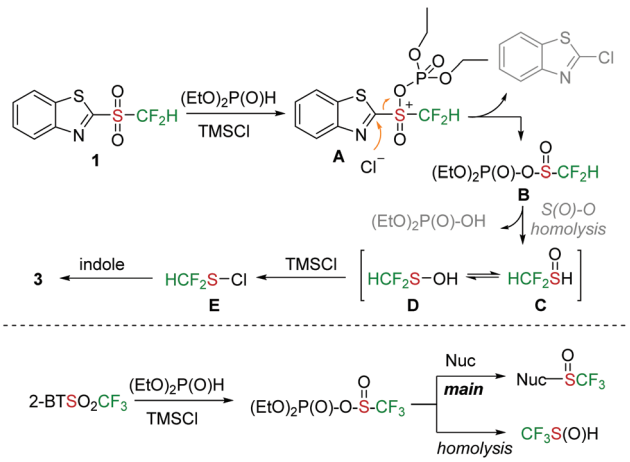
On the basis of the above results and the literature, a plausible mechanism for this reaction was proposed as follows (Scheme 3). First, the oxygen of 2-BTSO$_2$CF$_2$H attacks the phosphorus center of (EtO)$_2$P(O)H to get intermediate **A**, which is converted to (EtO)$_2$P(O)–OS(O)CF$_2$H **B** through eliminating 2-chlorobenzo[*d*]-thiazole. The S(O)–O homolysis of (EtO)$_2$P(O)–OS(O)CF$_2$H gave (EtO)$_2$P(O)–OH (detected by LCMS) and the key Intermediate HCF$_2$S(O)H **C** followed by an intramolecular nucleophilic collapse to form HCF$_2$SOH **D**[25]. Then, HCF$_2$SOH **D** directly converts to HCF$_2$SCl **E** in the presence of TMSCl for direct difluoromethylthiolation. In the case of




**Scheme 1** Preliminary mechanistic study.




**Scheme 2** *In situ* $^{19}$F NMR analysis.




**Scheme 3** Proposed mechanism.

2-BTSO$_2$CF$_3$, compared with the S(O)–O homolysis, (EtO)$_2$P(O)–OS(O)CF$_3$ is more inclined to be attacked by indole, thus obtaining the CF$_3$S(O) decorated product.

## Conclusions

In conclusion, the 2-BTSO$_2$CF$_2$H/(EtO)$_2$P(O)H/TMSCl system has been used for the metal free electrophilic difluoromethylthiolation of various indoles in moderate to good yields. This is the first time to report 2-BTSO$_2$CF$_2$H as a –SCF$_2$H synthon in organic synthesis. The mechanism study shows that HCF$_2$S(O)H probably acts as the reactive intermediate instead of (EtO)$_2$P(O)-SCF$_2$H.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

This work was supported by the National Natural Science Foundation of China (21672187, 21632009, 21421002, 21472221), the Zhejiang Natural Science Foundation (LZ17H300002), the National Basic Research Program of China (2015CB931900), the Key Programs of the Chinese Academy of Sciences (KGZD-EW-T08), and the Key Research Program of Frontier Sciences of CAS (QYZDJ-SSW-SLH049).

## Notes and references

1 (*a*) F. Leroux, P. Jeschke and M. Schlosser, *Chem. Rev.*, 2005, **105**, 827–856; (*b*) C. Ni, M. Hu and J. Hu, *Chem. Rev.*, 2014, **115**, 765–825; (*c*) X.-H. Xu, K. Matsuzaki and N. Shibata, *Chem. Rev.*, 2014, **115**, 731–764.

2 (*a*) T. Fujita, J. Iwasa and C. Hansch, *J. Am. Chem. Soc.*, 1964, **86**, 5175–5180; (*b*) I. Rico and C. Wakselhan, *Tetrahedron Lett.*, 1981, **22**, 323–326.

3 (*a*) B. Bayarmagnai, C. Matheis, K. Jouvin and L. J. Goossen, *Angew. Chem., Int. Ed.*, 2015, **54**, 5753–5756; (*b*) Y. Zafrani, D. Yeffet, G. Sod-Moriah, A. Berliner, D. Amir, D. Marciano, E. Gershonov and S. Saphier, *J. Med. Chem.*, 2017, **60**, 797–804.

4 S. Okui, N. Kyomura, T. Fukuchi, K. Okano, L. He and A. Miyauchi, *US Pat*, 7371768, 2008.

5 L. Yagupolskii, I. Maletina, K. Petko, D. Fedyuk, R. Handrock, S. Shavaran, B. Klebanov and S. Herzig, *J. Fluorine Chem.*, 2001, **109**, 87–94.

6 K. Morita, K. Ide, Y. Hayase, T. Takahashi and Y. Hayashi, *Agric. Biol. Chem.*, 1987, **51**, 1339–1343.

7 Z. Huang, O. Matsubara, S. Jia, E. Tokunaga and N. Shibata, *Org. Lett.*, 2017, **19**, 934–937.

8 J. Hine and J. J. Porter, *J. Am. Chem. Soc.*, 1957, **79**, 5493–5496.

9 V. P. Mehta and M. F. Greaney, *Org. Lett.*, 2013, **15**, 5036–5039.

10 L. Li, F. Wang, C. Ni and J. Hu, *Angew. Chem.*, 2013, **125**, 12616–12620, (*Angew. Chem., Int. Ed.*, 2013, **52**, 12390–12394).

11 W. Zhang, F. Wang and J. Hu, *Org. Lett.*, 2009, **11**, 2109–2112.

12 X. Deng, J. Lin, J. Zheng and J. Xiao, *Chem. Commun.*, 2015, **51**, 8805–8808.

13 (*a*) J. Wu, Y. Gu, X. Leng and Q. Shen, *Angew. Chem., Int. Ed.*, 2015, **54**, 7648–7652; (*b*) J. Wu, Y. Liu, C. Lu and Q. Shen, *Chem. Sci.*, 2016, **7**, 3757–3762.

14 (*a*) D. Zhu, Y. Gu, L. Lu and Q. Shen, *J. Am. Chem. Soc.*, 2015, **137**, 10547–10553; (*b*) D. Zhu, X. Hong, D. Li, L. Lu and Q. Shen, *Org. Process Res. Dev.*, 2017, **21**, 1383–1387.

15 (*a*) D. Zhu, X. Shao, X. Hong, L. Lu and Q. Shen, *Angew. Chem., Int. Ed.*, 2016, **55**, 15807–15811; (*b*) J. Li, D. Zhu, L. Lv and C.-J. Li, *Chem. Sci.*, 2018, **9**, 5781–5786.

16 S. Arimori, O. Matsubara, M. Takada, N. Shibata and M. Shiro, *R. Soc. Open Sci.*, 2016, **3**, 160102–160110.

17 (*a*) Z. Huang, O. Matsubara, S. Jia, E. Tokunaga and N. Shibata, *Org. Lett.*, 2017, **19**, 934–937; (*b*) Q. Yan, L. Jiang, W. Yi, Q. Liu and W. Zhang, *Adv. Synth. Catal.*, 2017, **359**, 2471–2480.

18 L. Jiang, T. Ding, W.-b. Yi, X. Zeng and W. Zhang, *Org. Lett.*, 2018, **20**, 2236–2240.

19 L. Jiang, Q. Yan, R. Wang, T. Ding, W. Yi and W. Zhang, *Chem. – Eur. J.*, 2018, **24**, 18749–18756.

20 X. Tao, R. Sheng, K. Bao, Y. Wang and Y. Jin, *Chin. J. Org. Chem.*, 2019, **39**, 2726–2734.

21 (*a*) J. Rong, L. Deng, P. Tan, C. Ni, Y. Gu and J. Hu, *Angew. Chem., Int. Ed.*, 2016, **55**, 2743–2747, (*Angew. Chem.*, 2016, **128**, 2793–2797); (*b*) J. Wei, D. Gu, S. Wang, J. Hu, X. Dong and R. Sheng, *Org. Chem. Front.*, 2018, **5**, 2568–2572; (*c*) J. Rong, C. Ni, Y. Wang, C. Kuang, Y. Gu and J. Hu, *Acta Chim. Sin.*, 2017, **75**, 105–109.

22 Z. He, P. Tan, C. Ni and J. Hu, *Org. Lett.*, 2015, **17**, 1838–1841.

23 J. Wei, K. Bao, C. Qi, Y. Liu, C. Ni, R. Sheng and J. Hu, *Adv. Synth. Catal.*, 2019, **361**, 5528–5533.

24 K. Down, A. Amour, I. R. Baldwin, A. W. J. Cooper, A. M. Deakin, L. M. Felton, S. B. Guntrip, C. Hardy, Z. A. Harrison, K. L. Jones, P. Jones, S. E. Keeling, J. Le, S. Livia, F. Lucas, C. J. Lunniss, N. J. Parr, E. Robinson, P. Rowland, S. Smith, D. A. Thomas, G. Vitulli, Y. Washio and J. N. Hamblin, *J. Med. Chem.*, 2015, **58**, 7381–7399.

25 CCDC 1994911 contains the supplementary crystallographic data for this paper.†

26 Z. Huang, Y.-D. Yang, E. Tokunaga and N. Shibata, *Org. Lett.*, 2015, **17**, 1094–1097.