Chinese Chemical Letters 33 (2022) 4293–4297

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Deuterated *N*-difluoromethylthiophthalimide: A stable, scalable reagent for radical and electrophilic deuteriodifluoromethylthiolations

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ARTICLE INFO

Article history:
Received 4 November 2021
Revised 6 January 2022
Accepted 6 January 2022
Available online 13 January 2022

Keywords:
Deuteration
Deuteriodifluoromethylthiolation
Photocatalytic
Electrophilic
Radical

ABSTRACT

A new, stable and scalable reagent for deuteriodifluoromethylthiolation (deuterated *N*-difluoromethylthiophthalimide, PhthSCF$_2$D) has been developed. This reagent can be applied for the photocatalytic radical deuteriodifluoromethylthiolation of various olefins and aldehydes (30 examples). Meanwhile, it can achieve the electrophilic deuteriodifluoromethylthiolation of a series of electrophilic substrates including electron-rich arenes, aryl/vinylboronicacids, alkynes, amines, thiols and β-ketoesters (22 examples). Some complex molecules can also be applied in both radical and electrophilic deuteriodifluoromethylthiolation using PhthSCF$_2$D as the reagent.

Deuteration technology has been widely applied in various fields, such as organic synthesis, drug metabolism, NMR analysis and drug development [1–8]. The C-D bond is more stable than the C–H bond (6–9 times) owing to its larger atomic mass than H, so the deuteration of C–H bonds may greatly alter the metabolism and pharmacokinetic properties of drug candidates [9–14]. Meanwhile, the potency and selectivity of these molecules can be retained since the deuteration of C–H bonds does not change its chemical structure, physical properties, or biological activity [9]. Therefore, the exploration of novel and efficient routes for the incorporation of deuterium to organic molecules is significant and appealing [15–18].

On the other hand, the introduction of difluoromethylthio group (SCF$_2$H) into organic compounds has recently attracted much attention [19–22], because SCF$_2$H is a potential alternate as the lipophilic OH or NH surrogate, and some SCF$_2$H-containing molecules display unique biological and pharmaceutical activity [23–27]. Considering the importance of deuteration and difluoromethylthio group in drug candidates, it is highly desirable to construct SCF$_2$D substituted molecules for drug discovery.

In 2016, Billard and coworkers introduced the first example on the synthesis of SCF$_2$D-containing compounds through the reduction of the PhSO$_2$CF$_2$S group (Scheme 1a) [28]. In 2020, our group described a one-pot deuteriodifluoromethylthiolation of alkyl electrophiles with thiourea and diethyl bromodifluoromethylphosphonate (Scheme 1b) [29]. In 2021, Li's group disclosed the C–H deuteriodifluoromethylation of indole derivatives with CF$_2$DSO$_2$Na (Scheme 1c) [30]. Nevertheless, the substrate scope of all these methods is limited, moreover none of these SCF$_2$D-reagents is commercial reagent owing to their complex synthesis process.

To solve these issues, we envisage to develop a stable and scalable reagent for deuteriodifluoromethylthiolation, which has good reactivity and can be applied to a variety of complex substrates. In 2015, Shen's group disclosed a powerful reagent: *N*-difluoromethylthiophthalimide (PhthSCF$_2$H) that allowed the difluoromethylthiolation of a wide range of nucleophiles [22]. In 2017, the same group has further optimized the preparation process of this reagent (Scheme 1d) [31].

Along this line, we have developed a new SCF$_2$D-reagent deuterated *N*-difluoromethylthiophthalimide (PhthSCF$_2$D) through modifying the synthetic route of PhthSCF$_2$H. This reagent has good stability, and its synthetic route is easy scalable (up to 28.7 g scale) (Scheme 2). Meanwhile, PhthSCF$_2$D is not only an outstanding electrophilic SCF$_2$D-reagent for aryl/vinyl boronic acids, alkynes, amines, thiols, β-ketoesters, and oxindoles and electron-rich arenes, but also an excellent radical SCF$_2$D-reagent for alkenes and aldehydes (Scheme 2).

BrCF$_2$P(O)(OEt)$_2$ is most common source of difluorocarbene to synthesize "SCF$_2$H" with different sulfur sources [31–37], so BrCF$_2$P(O)(OEt)$_2$ is selected as the "CF$_2$" source for the synthesis of BnSCF$_2$D. According to Shen's synthetic route for PhthSCF$_2$H

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https://doi.org/10.1016/j.cclet.2022.01.013
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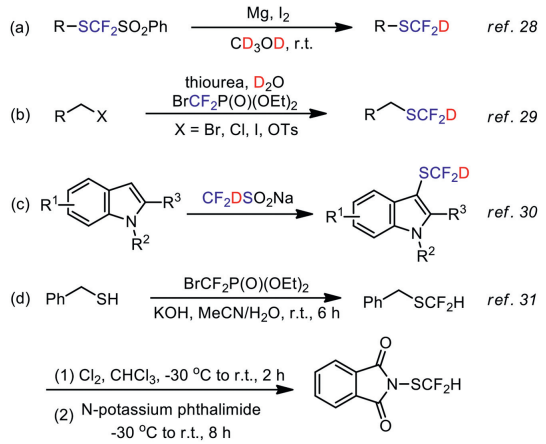


Scheme 1. (a-c) Recent advances in the deuteriodifluoromethylthiolation. (d) The synthesis route of *N*-difluoromethylthiophthalimide.

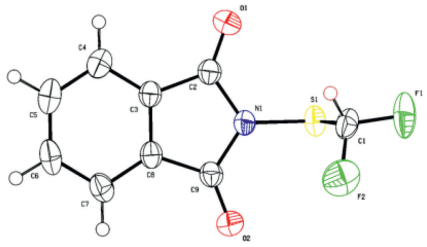


Fig. 1. ORTEP diagrams of PhthSCF$_2$D.

(Scheme 1d) [31], we only replaced H_2O by D_2O initially, but the deuteration rate of the obtained BnSCF$_2$D was poor (34% D). It is likely that there is still a lot of water in solvents and other raw materials. In order to eliminate this issue, anhydrous ether was employed as the solvent, and sodium hydride was applied to remove the trace of water in the system. A high yield of BnSCF$_2$D (95%) with an excellent deuteration rate (97%) could be obtained through the modified approach. Then we further improved Shen's method (Scheme 1d) [31]. Good yield (85%) of PhthSCF$_2$D with a high level of deuterium incorporation (97% D) could be afforded under milder temperature (Scheme 2).

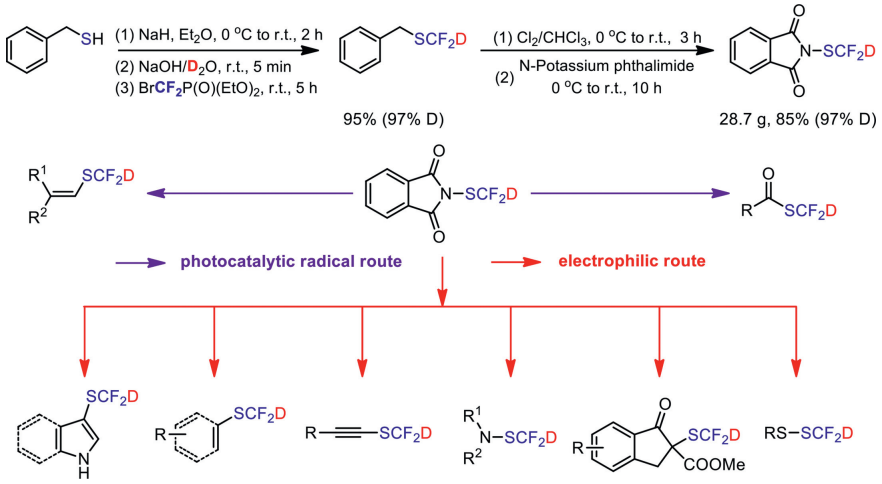
The structural features of reagent **1** are fully confirmed by X-ray analysis of its single crystal (Fig. 1 and Table S1 in Supporting information). PhthSCF$_2$D is a white crystalline solid with a melting point of 116–117 °C. The reagent can be stored for a long time (more than 3 months) in a dry environment. It is stable in weakly polar solvents such as DCE, EA, DCM, toluene, THF, but it has poor stability in strong polar solvents such as DMF, water and alcohol solvents.

Guided by the concept of green chemistry [38–43], we choose photocatalysis to realize the application of **1**. Visible-light photocatalytic radical reactions are a powerful tool for the construction of organic compounds [44–47]. Initially, we investigated visible-light-promoted SCF$_2$D of styrenes with PhthSCF$_2$D inspired by Glorius's work [48]. After screen of solvents, bases, phase transfer catalyst and photocatalysts, the combination of MeCN, K_2CO_3 and nBu_4NBr fac-Ir(ppy)$_3$, was the best option (Table S2 in Supporting information). Then, the substrate scope of this protocol was studied (Scheme 3). Styrenes with electron-donating groups in 1-position afforded good to excellent yield of desired products (**3a**-**3g**). Only moderate yields of SCF$_2$D-products were obtained (**3h-3o**), when styrenes with electron-donating groups or weak electron-withdrawing groups in benzene ring were employed.

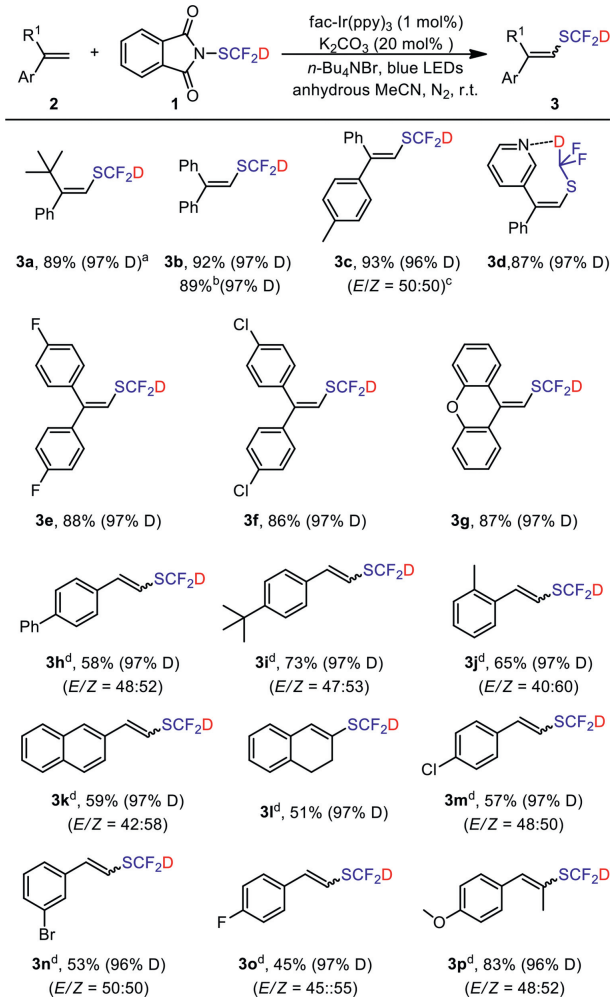
In general, both *E*- and *Z*-isomers were observed, and the stereoselectivity was negligible. *E*- and *Z*-isomers have different chemical shifts and coupling constants (*J*) of alkenyl hydrogen [48], so *E*- or *Z*-isomers of **3** can be identified by ^{1}H NMR, and the ratio of *E*/*Z* is judged by integral ratio of alkenyl hydrogen. In the cases of **3a** and **3d**, only single isomers were obtained, which may be due to steric hindrance (**3a**: Phenyl has greater steric hindrance than *t*–butyl) and hydrogen bonding between N and D (**3d**).

No reaction took place in the cases of styrenes with electron-withdrawing groups in 1-position or strong electron-withdrawing groups in benzene ring (such as 4-nitrostyrene). (*E*)-Prop-1-en-1-ylbenzene could also react with this reagent to yield final product (**3p**, 83%). All substrates maintained high level of deuteration rate after the reaction (>96% D). In addition, we also carried out a gram-scale reaction to obtain product **3b** in a good yield (1.7 g, 89%). The olefins converted with the drug Fenofibrate are synthesized as a raw material in the protocol, and a moderate yield of **3q** (74%) was obtained (Scheme 4) [49–51].

This photocatalytic system can be also applied to the reaction of aldehydes with **1** with a slight modification (Table S3 in Supporting informaiton). Only a trace amount of **5a** was produced under standard conditions. The yield of **5a** reached 23% in the absence of nBu_4NBr. Finally, when Ir[dF(CF$_3$)(ppy)]$_2$(dtbbpy)PF$_6$ was employed instead of fac-Ir(ppy)$_3$ [52,53], and its amount was increased from 1 mol% to 2.5 mol%, an excellent yield of 93% was afforded.



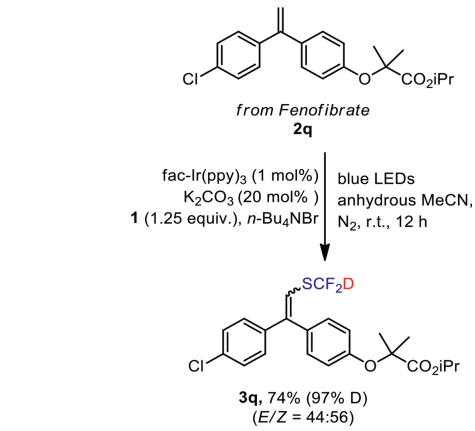
Scheme 2. The synthesis of PhthSCF$_2$D and its applications for radical and electrophilic deuteriodifluoromethylthiolations.



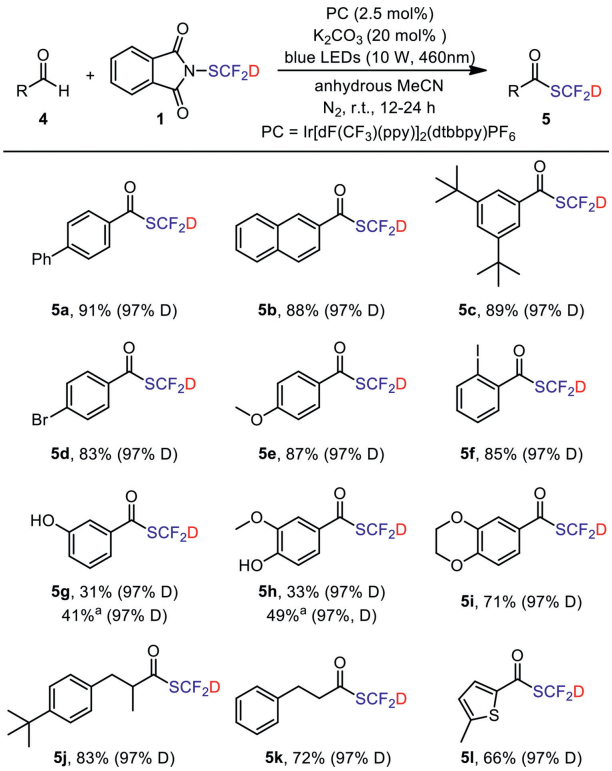
Scheme 3. The photocatalytic deuterated difluoromethylation of various alkenes. Conditions: **2** (0.5 mmol), **1** (1.25 equiv.), nBu$_4$NBr (1 equiv.), fac-Ir(ppy)$_3$ (1 mol%), K_2CO_3 (0.2 equiv.), anhydrous MeCN (4 mL), 10 W blue LEDs, room temperature, 12 h, isolated yields. [a] The deuteration rate was determined by ^{19}F NMR. [b] Yield was obtained at gram scale (1.7 g). [c] The E/Z ratio was determined by ^{1}H NMR. [d] The reaction time was extended to 36 h.

With the optimized reaction conditions in hand, we then investigated the scope of the transformation with respect to the aldehydes (Scheme 5). In general, benzaldehydes with electron-donating or electron-withdrawing groups were converted smoothly into desired products in good to excellent yields (**5a-5f**, **5i**). Hydroxyl substituted benzaldehydes were less reactive (**5g**, **5h**), so longer reaction time was required. Meanwhile, aliphatic aldehydes can be also applied in the protocol successfully (**5j**, **5k**). In the case of the heterocyclic aldehyde, a moderate yield was obtained (**5l**, 66%). The introduction of SCF_2D into a complex aldehyde (**4m**) were also performed, and the desired product **5m** was synthesized with a moderate yield (49%) (Scheme 6) [54].

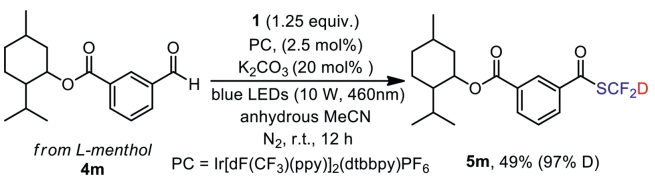
In order to verify its reactivity for nucleophilic substrates, six types of nucleophilic substrates including electron-rich heteroarenes, aryl/vinyl boronic acids, alkynes, amines, thiols, β-ketoesters are implemented (Scheme 7). By comparing the reactivity of PhthSCF$_2$D and PhthSCF$_2$H with different substrates, there is almost no difference in the reactivity of these two reagents for different substrates (Table S4 in Supporting information). For electron-rich heteroarenes, PhthSCF$_2$D exhibited excellent reactivity to gain good to excellent yields of the final products (**7a-7d**). Reactions of aryl or vinyl boronic acids also took place smoothly to give the corresponding SCF$_2$D-prodcuts



Scheme 4. The deuterated difluoromethylation of **2q**.

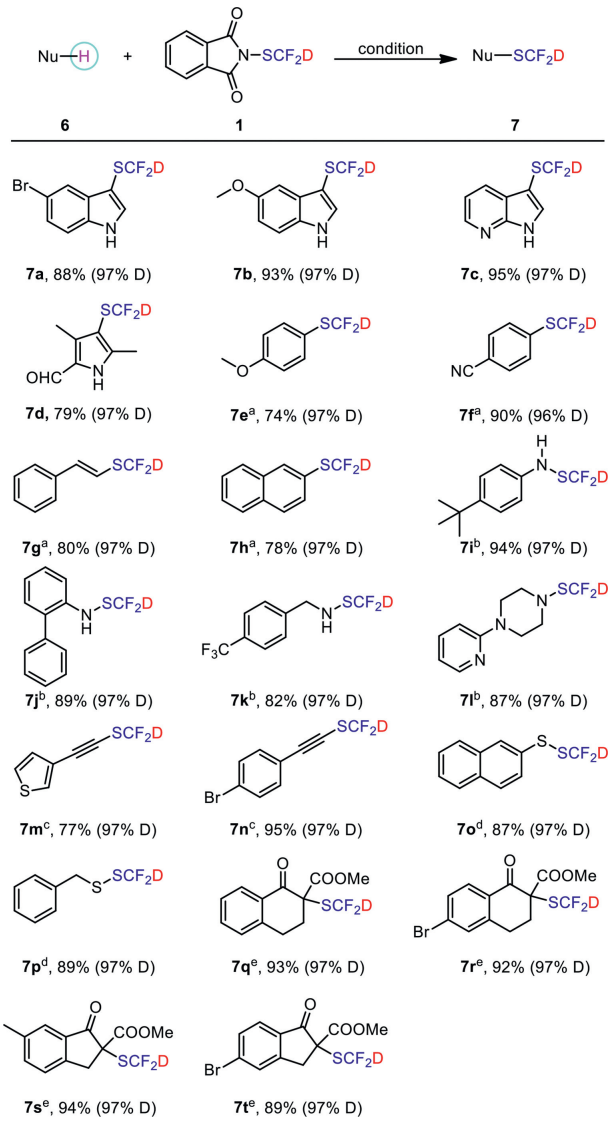


Scheme 5. Substrate scope for the photocatalytic deuterated difluoromethylation of aldehydes. Reaction conditions: **4** (0.5 mmol), **1** (1.25 equiv.), Ir[dF(CF$_3$)(ppy)]$_2$(dtbbpy)PF$_6$ (2.5 mol%), K_2CO_3 (0.2 equiv.), anhydrous MeCN (4 mL), 10 W blue LEDs, r.t., 12 h, isolated yields. [a] The reaction time was 24 h.



Scheme 6. The photocatalytic deuterated difluoromethylation of **4m**.

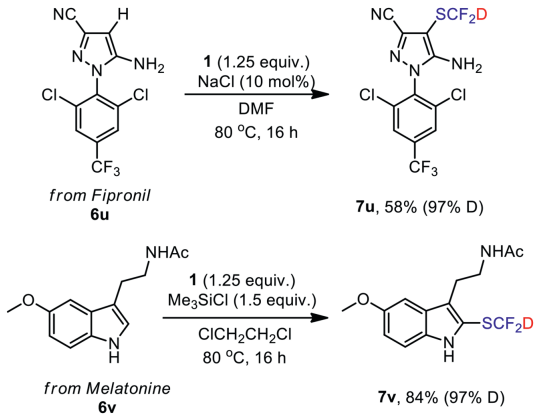
(**7e-7h**). Satisfactory yields could be provided in all the cases of aryl, aliphatic primary and secondary amines (**7i-7l**). Meanwhile, deuter-iodifluoromethylthiolations of alkynes and mercaptans were also implemented, and excellent yields were obtained (**7m-7p**). Adaptive application of β-ketoesters was also successful (**7q-7t**). The deuteration rate of the substrates remains almost un-



Scheme 7. The photocatalytic deuterated difluoromethylation of various nucleophilic substrates. Reaction conditions: heteroarene (0.5 mmol), **1** (1.2 equiv.), Me_3SiCl (1.5 equiv.), DCE (3.0 mL), 80 °C, 16 h, isolated yields. [a] Reaction conditions: boronic acid (0.7 mmol), **1** (1.2 equiv.), Li_2CO_3 (0.35 equiv.), CuI (5 mol%), 2,2′-bipyridine (bpy) (5 mol%), diglyme (5.0 mL), 60 °C, 15 h. [b] Reaction conditions: amines (0.7 mmol), **1** (1.1 mmol), toluene (4.0 mL), 80 °C, 20 h. [c] Reaction conditions: alkyne (0.6 mmol), **1** (1.3 equiv.), Li_2CO_3 (0.5 equiv.), copper(I) thiophene-2-carboxylate (5.0 mol%), 2,2′-bipyridine (bpy) (5.0 mol%), diglyme (4.0 mL), 60 °C, 15 h. [d] Reaction conditions: thiols (0.7 mmol), **1** (1.1 equiv.), DCE (4.0 mL), 80 °C, 20 h. [e] Reaction conditions: β-ketoester (0.7 mmol), **1** (1.2 equiv.), K_2CO_3 (1.1 equiv.), DCM (4.0 mL), r.t., 24 h.

changed, reaching 96% or 97%. To further highlight the potential of PhthSCF$_2$D, this electrophilic method was carried out to introduce SCF$_2$D into two drugs, and high yields of desired prodcut were obtained (**7u**, **7v**) with the deuteration rate of 97% (Scheme 8).

In summary, we have disclosed a new approach for the synthesis of deuterated *N*-difluoromethylthiophthalimide (PhthSCF$_2$D) that is a novel, stable and scalable SCF$_2$D-reagent. This reagent exhibits excellent reactivity in the deuteriodifluoromethylthiolation (SCF$_2$D) of a wide range of substrates including alkenes, aldehydes, electron-rich arenes, aryl/vinyl boronic acids, alkynes, amines, thiols and β-ketoesters (52 examples). All the SCF$_2$D-products have high level deuteration rates (>96% D). This SCF$_2$D-reagent can be also applied in some complex molecules by photocatalytic radical or electrophilic routes.



Scheme 8. The electrophilic deuterated difluoromethylation of **6u** and **6v**.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors gratefully acknowledge the National Natural Science Foundation of China (Nos. 21776138, 22078161), the Fundamental Research Funds for the Central Universities (Nos. 30920021124, 30918011314), the Natural Science Foundation of Jiangsu Province (No. BK20180476), the Postdoctoral Science Foundation Funded Project (No. 2019M661848), the Priority Academic Program Development of Jiangsu Higher Education Institutions, and the Center for Advanced Materials and Technology in Nanjing University of Science and Technology for their financial support.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2022.01.013.

References

[1] M. Miyashita, M. Sasaki, I. Hattori, et al., Science 305 (2004) 495–499.
[2] K.W. Quasdorf, A.D. Huters, M.W. Lodewyk, et al., J. Am. Chem. Soc. 134 (2012) 1396–1399.
[3] K.B. Wiberg, Chem. Rev. 55 (1955) 713–743.
[4] E.M. Simmons, J.F. Hartwig, Angew. Chem. Int. Ed. 51 (2012) 3066–3072.
[5] J. Helfenbein, C. Lartigue, E. Noirault, et al., J. Med. Chem. 45 (2002) 5806–5808.
[6] S.E. Scheppele, Chem. Rev. 72 (1972) 511–532.
[7] B. Belleau, J. Burba, M. Pindell, et al., Science 133 (1961) 102–104.
[8] G.S. Timmins, Expert Opin. Ther. Pat. 24 (2014) 1067–1075.
[9] J. Atzrodt, V. Derdau, W.J. Kerr, et al., Angew. Chem. Int. Ed. 57 (2018) 1758–1784.
[10] Y. Zhu, J. Zhou, B. Jiao, ACS Med. Chem. Lett. 4 (2013) 349–352.
[11] A. Katsnelson, Nat. Med. 19 (2013) 656.
[12] C. Ling, G. Chen, G. Chen, et al., Int. J. Cancer 131 (2012) 2411–2419.
[13] F. Robert, D. Gautier, B. Dubrulle, Space Sci. Rev. 92 (2000) 201–204.
[14] D. Zhou, C. Wang, M. Li, et al., Chin. Chem. Lett. 29 (2018) 191–193.
[15] T.G. Gant, J. Med. Chem. 57 (2014) 3595–3611.
[16] E. Khaskin, D. Milstein, ACS Catal. 3 (2013) 448–452.
[17] J. Zhang, S. Zhang, T. Gogula, et al., ACS Catal. 10 (2020) 7486–7494.
[18] S. Garhwal, A. Kaushansky, N. Fridman, et al., J. Am. Chem. Soc. 142 (2020) 17131–17139.
[19] J. Dong, F. Yue, X. Wang, et al., Org. Lett. 22 (2020) 8272–8277.
[20] Q. Yan, L.Q. Jiang, W.B. Yi, Chin. J. Org. Chem. 40 (2020) 1–14.
[21] J. Li, D. Zhu, L. Lv, et al., Chem. Sci. 9 (2018) 5781–5786.
[22] D. Zhu, Y. Gu, L. Lu, et al., J. Am. Chem. Soc. 137 (2015) 10547–10553.
[23] D. Zhu, X. Shao, X. Hong, et al., Angew. Chem. Int. Ed. 55 (2016) 15807–15811.
[24] B. Bayarmagnai, C. Matheis, K. Jouvin, et al., Angew. Chem. Int. Ed. 54 (2015) 5753–5756.
[25] K. Shimizu, Jpn. J. Antibiot. 12 (1988) 1809.

[26] M. Ito, T. Ishigami, Infection 19 (1991) S253–S257.
[27] L.M. Yagupolskii, I.I. Maletina, K.I. Petko, et al., J. Fluorine Chem. 109 (2001) 87–94.
[28] E. Ismalaj, D.L. Bars, T. Billard, Angew. Chem. Int. Ed. 55 (2016) 4790–4793.
[29] T. Ding, L. Jiang, W. Yi, Chem. Commun. 56 (2020) 3995–3998.
[30] J. Liang, G. Wang, L. Dong, et al., Org. Lett. 23 (2021) 5545–5548.
[31] D. Zhu, X. Hong, D. Li, et al., Org. Process Res. Dev. 21 (2017) 1383–1387.
[32] X.P. Fu, X.S. Xue, X.Y. Zhang, et al., Nat. Chem. 11 (2019) 948–956.
[33] Y. Zafrani, G. Sod-Moriah, Y. Segall, Tetrahedron 65 (2009) 5278–5283.
[34] T. Ding, L. Jiang, W. Yi, Org. Lett. 20 (2018) 170–173.
[35] Y. Zafrani, D. Yeffet, G. Sod-Moriah, et al., J. Med. Chem. 60 (2017) 797–804.
[36] H. Zhang, F. Yu, C. Li, et al., Org. Lett. 23 (2021) 4721–4725.
[37] H. Zhang, X. Wan, Q. Shen, Chin. J. Chem. 37 (2019) 1041–1050.
[38] L.H. Lu, Z. Wang, W. Xia, et al., Chin. Chem. Lett. 30 (2019) 1237–1240.
[39] L.Y. Xie, T.G. Fang, J.X. Tan, et al., Green Chem. 21 (2019) 3858–3863.
[40] W.H. Bao, Z. Wang, X. Tang, et al., Chin. Chem. Lett. 30 (2019) 2259–2262.
[41] K.J. Liu, T.Y. Zeng, J.L. Zeng, et al., Chin. Chem. Lett. 30 (2019) 2304–2308.
[42] K.J. Liu, J.H. Deng, T.Y. Zeng, et al., Chin. Chem. Lett. 31 (2020) 1868–1872.
[43] J.Y. Chen, C.T. Zhong, Q.W. Gui, et al., Chin. Chem. Lett. 32 (2021) 475–479.
[44] X. Zhang, J. Fang, C. Cai, et al., Chin. Chem. Lett. 32 (2021) 1280–1292.
[45] W. Xu, W. Wang, T. Liu, et al., Nat. Commun. 10 (2019) 4867.
[46] S. Liang, J. Wei, L. Jiang, et al., CCS Chem. 3 (2021) 265–273.
[47] Q.W. Gui, F. Teng, Z.C. Li, et al., Chin. Chem. Lett. 32 (2021) 1907–1910.
[48] R. Honeker, R. Aladgarza-Sanchez, M. Hopkins, et al., Chem. Eur. J. 22 (2016) 4395–4399.
[49] C. Wan, R.J. Song, J.H. Li, Org. Lett. 21 (2019) 2800–2803.
[50] J. Huang, G. Hu, S. An, et al., J. Org. Chem. 84 (2019) 9758–9769.
[51] X. Zhu, C. Liu, Y. Liu, et al., Chem. Commun. 56 (2020) 12443–12446.
[52] Y. Ouyang, X.H. Xu, Q.F. Qing, Angew. Chem. Int. Ed. 58 (2019) 18508–18512.
[53] S. Mukherjee, T. Patra, F. Glorius, ACS Catal. 8 (2018) 5842–5846.
[54] M. Zhang, X.A. Yuan, C. Zhu, et al., Angew. Chem. Int. Ed. 58 (2019) 312–316.