



Communication

Metal-free C(sp²)-H perfluoroalkylsulfonylation and configuration inversion: Stereoselective synthesis of α -perfluoroalkylsulfonyl *E*-enaminones

Qing Yu, Yunyun Liu, Jie-Ping Wan*

College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang 330022, China

ARTICLE INFO

Article history:

Received 2 March 2021

Revised 13 April 2021

Accepted 18 April 2021

Available online 28 April 2021

Keywords:

C-H Functionalization

Enaminone

Perfluoroalkyl sulfonylation

Metal-free

Configuration inversion

ABSTRACT

The perfluoroalkylsulfonylation (CF₃SO₂, C₂F₅SO₂ and CHF₂SO₂) in the enaminone C-H bonds has been developed simply via the promotion of molecular iodine by using stable and cheap sodium perfluoroalkyl sulfonates as coupling partners. The stereoselective synthesis of *E*-configured α -perfluoroalkylsulfonyl enaminones has been realized via unprecedented C-H bond elaboration and C=C double bond configuration inversion by free radical process.

© 2021 Published by Elsevier B.V. on behalf of Chinese Chemical Society and Institute of Materia Medica, Chinese Academy of Medical Sciences.

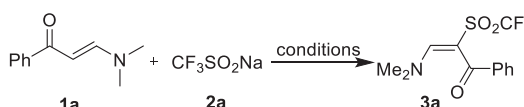
The sodium trifluoromethanesulfonate (CF₃SO₂Na), also known as Anglois reagent, has been used as important source of trifluoromethyl in the synthesis of numerous CF₃-functionalized molecules [1–3]. Generally, this cheap and stable reagent has found application in the trifluoromethylation reaction on a vast variety of chemical bonds, such as aryl C-H bond [4–6], alkenyl/formyl C-H bond [7–10], C-halogen bond [11], single C-C bond [12,13], multiple carbon-carbon bond [14–17], heteroatom-heteroatom bond [18] and heteroatom-H bond [19,20]. Alongside the classical application in trifluoromethylation reactions, discovering new synthetic application in the synthesis of different fluoro-functionalized molecules has emerged as new trend in the chemistry of this reagent. For example, the CF₃SO₂Na has been found to be applicable in the trifluoromethylthiolation reactions by donating “CF₃S” fragment via deoxygenation [21,22]. Several novel synthetic reactions involving CF₃SO₂Na as thiocarbonyl (C=S) or carbonyl source have also been recently reported [23,24]. Notably, the extensive interest in the CF₃SO₂Na participated organic synthesis has also led to the observation that CF₃SO₂Na could act as the trimethylsulfonyl source in the synthesis of molecules functionalized with CF₃SO₂-substructure. For example, Bi and Anderson *et al.* have reported the synthesis of trifluoromethylsulfonyl functionalized β -enaminones via an aryl migration wherein the methylsulfonyl free radical was proposed to trigger the cascade transformations [25]. In addition,

the synthesis of a few other different organic molecules functionalized with trifluoromethylsulfonyl structure have also been reported via the coupling of CF₃SO₂Na to multiple or reactive single carbon-carbon bonds [26,27]. Furthermore, the synthesis of trifluoromethyl sulfonylated aromatics have been accomplished via the coupling of CF₃SO₂Na to the reactive arenediazonium tetrafluoroborates [28] or aryl iodonium salts [29]. Despite these reported works, it can also be found that the trifluoromethylsulfonylation reactions by using CF₃SO₂Na is yet underdeveloped [30]. Especially, the trifluoromethylsulfonylation of stable C-H bond is hardly available, conveying the high urgency for developing practical C-H trifluoromethylsulfonylation protocols with CF₃SO₂Na.

Over the past decades, we and others have identified the functionalization of the vinyl C-H bond in enaminones as a powerful tool in the synthesis of poly-functionalized alkenes and diverse heterocyclic scaffolds via the construction of new C-C or C-heteroatom bonds. Particularly, the intramolecular and intermolecular C-C bond forming reactions [31–34], the intermolecular C-H acyloxylation [35,36], sulfonylation [37,38], amination [39], thiocyanation [40–44], as well as the cascade C-H coupling transformation and annulation providing various chromone derivatives [45–50] *etc.* have brought new perspective to the diversity-oriented synthesis based on enaminones. The coupling of enaminones and CF₃SO₂Na has also been investigated, and

* Corresponding author.

E-mail address: wanjieping@jxnu.edu.cn (J.-P. Wan).

Table 1
Optimization on reaction conditions.^a


Entry	Oxidant	Solvent	T (°C)	Yield (%) ^b
1	I ₂	DMF	80	54
2	I ₂	DMSO	80	67
3	I ₂	MeCN	80	72
4	I ₂	toluene	80	Trace
5 ^c	I ₂	MeCN:DMSO	80	80
6 ^d	I ₂	MeCN:DMSO	80	68
7 ^e	I ₂	MeCN:DMSO	80	74
8 ^c	–	MeCN:DMSO	80	0
9 ^c	K ₂ S ₂ O ₈	MeCN:DMSO	80	12
10 ^c	PhI(OAc) ₂	MeCN:DMSO	80	Trace
11 ^c	KIO ₃	MeCN:DMSO	80	0
12 ^c	TBHP	MeCN:DMSO	80	0
13 ^{c,f}	I ₂	MeCN:DMSO	80	64
14 ^{c,g}	I ₂	MeCN:DMSO	80	79
15 ^c	I ₂	MeCN:DMSO	70	67
16 ^c	I ₂	MeCN:DMSO	90	64

^a General conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), oxidant (0.4 mmol) in solvent (2 mL), stirred for 12 h in sealed tube.

^b Isolated yield based on **1a**.

^c MeCN (1.6 mL) and DMSO (0.4 mL).

^d MeCN (1.8 mL) and DMSO (0.2 mL).

^e MeCN (1.4 mL) and DMSO (0.6 mL).

^f I₂ (0.3 mmol).

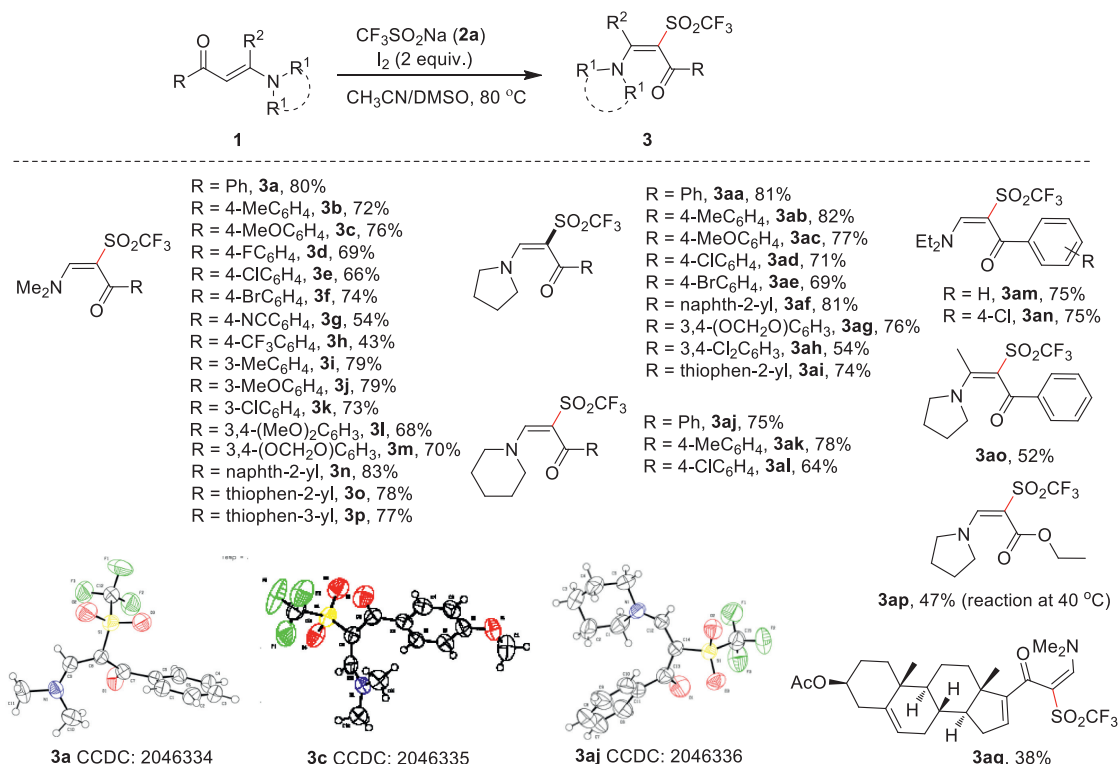
^g I₂ (0.5 mmol).

trifluoromethylated products resulting from the enaminones' C–H trifluoromethylation are provided in the known reports [51,52]. Interestingly, the C–H trifluoromethylsulfonylation of enaminones has not yet been realized. Herein, based on our longstanding efforts in exploring novel synthetic application of enaminones [53–

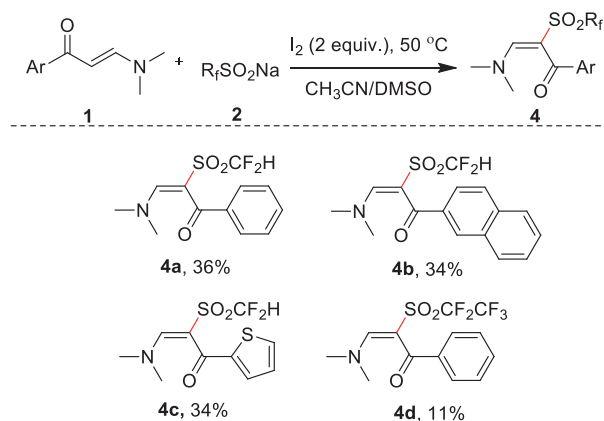
57] and the inherent advantages of stable chemical bond sulfur functionalization in the synthesis of diverse sulfur-containing molecules [58–70], we report the first method on the synthesis of trifluoromethylsulfonyl enaminones *via* the vinyl C–H trifluoromethylsulfonylation reactions of enaminones under transition metal-free conditions by simply using molecular iodine as the oxidant.

Initially, the reaction of enaminone **1a** and CF₃SO₂Na (**2a**) was run in DMF in the presence of molecular iodine. Gratifyingly, the α -trifluoromethylsulfonyl functionalized enaminone **3a** was afforded with fine yield by heating at 80 °C (entry 1). Other solvents such as DMSO, MeCN could also be used as medium for the practical formation of **3a** (entries 2 and 3, Table 1). On the other hand, nonpolar medium such as toluene was found inapplicable (entry 4, Table 1). Delightfully, excellent yield was obtained when the mixed MeCN and DMSO with the volume ratio of 8:2 was employed as reaction medium (entries 5–7, Table 1). The comparison of different oxidant additives and a blank entry proved that molecular iodine was the most proper oxidant for this reaction (entries 8–12, Table 1). Afterwards, the loading of molecular iodine and the reaction temperature was screened, respectively. But no further improved result on the yield of **3a** was provided (entries 13–16, Table 1).

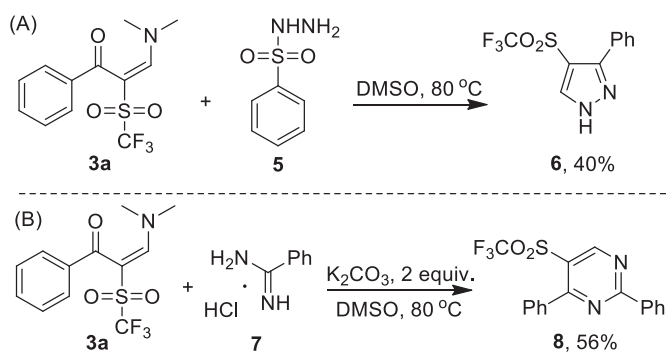
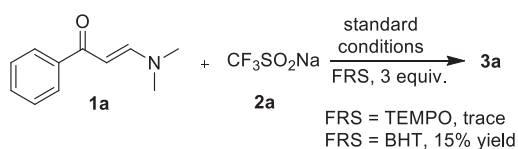
In the section of scope investigation, the reactions employing different enaminones were first conducted. According to the results (Scheme 1), outstanding application scope of the enaminone substrate was identified by fixing CF₃SO₂Na as the reaction partner. When the *N,N*-dimethyl functionalized, phenyl-based enaminones were employed, a broad variety of functional substituents in the phenyl ring, including methyl, methoxyl, halogen, cyano, trifluoromethyl and oxane *etc.*, reacted with CF₃SO₂Na to provide correspondingly diverse products with fair to excellent yields under the optimized conditions (**3b–3p**). Substrates containing strong electron withdrawing group (EWG) in the phenyl ring of enam-



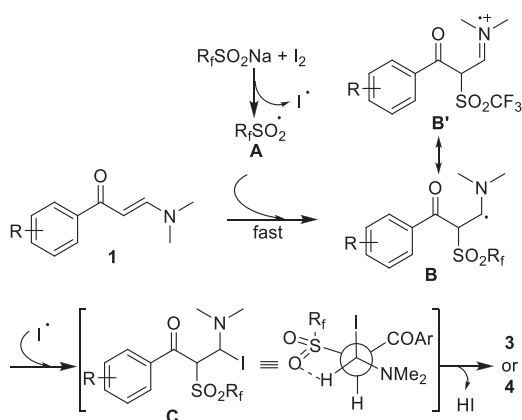
Scheme 1. Scope on the enaminones for the C–H trifluoromethylsulfonylation. General conditions: **1** (0.2 mmol), **2a** (0.4 mmol), I₂ (0.4 mmol) in mixed CH₃CN/DMSO (1.6 mL/0.4 mL). Stirred at 80 °C for 12 h in sealed tube. Isolated yield based on **1**.



Scheme 2. Reactions using different perfluoroalkyl sulfinites.

Scheme 3. Synthetic application of product **3a**.

Scheme 4. Control experiments with free radical scavenger.



Scheme 5. The plausible reaction mechanism.

inones gave products with evidently lower yields (**3d–3h**). What's more, the enaminones featured with various amino structures such as pyrrolidine (**3aa–3ai**), piperidine (**3aj–3al**), diethylamino (**3am–3an**) were also used for the practical synthesis of corresponding products. Besides the phenyl groups, the successful synthesis using enaminones functionalized with other (hetero)aryl structures, such as naphthyl (**3n** and **3af**) and thiophenyl (**3o–3p** and **3ai**) indicated the broad tolerance of this method for enaminone substrates.

More notably, the present C–H trifluoromethylsulfonylation protocol was also expanded to the reactions of β -substituted enaminone (**3ao**), enaminoester (**3ap**) as well as the enaminone derived from the natural product 16-dehydropregesterone (**3aq**), confirming the high application potential of the present synthetic protocol. Interestingly, the configuration of the enaminone C=C double bond in the products was reversed as confirmed by the single crystal structures of **3a** (CCDC: 2046334), **3c** (CCDC: 2046335) and **3aj** (CCDC: 2046336). The target transformation was not observed when an alkyl ketone derived enaminone ($R=R^1=Me$) was employed.

Encouraged by the satisfactory results from the reactions of different enamines, the reactions employing different perfluoroalkyl sulfinites were then executed. Delightfully, the primary efforts proved that HCF_2SO_2Na and $C_2F_5SO_2Na$ could also be used for the C–H functionalization to give difluoromethylsulfonyl (**4a–4c**, Scheme 2) and pentafluoroethylsulfonyl (**4d**, Scheme 2) elaborated enaminones. The yields of these products obtained under the standard reaction conditions were lower than those trifluoromethylsulfonylated products. Further, the $CF_3CH_2SO_2Na$ was also used to react with **1a**, but the C–H sulfonylation did take place, proving the full fluorinated alkyl sulfinites were uniquely suitable for this novel C–H transformation.

To disclose the synthetic application of the synthesized products, compound **3a** was employed to react with different reaction patterners. Delightfully, the synthesis of nitrogen heteroaryls, including trifluoromethylsulfonyl functionalized pyrazole **6** and trifluoromethylsulfonyl functionalized pyrimidine **8** were successfully synthesized by reacting with sulfonyl hydrazine **5** (Scheme 3A) and amidine **7** (Scheme 3B) *via* facile operation, respectively.

For the sake of probing possible reaction mechanism, the model reaction was then conducted in the presence of free radical scavenger (FRS). As shown in Scheme 4, the formation of product **3a** was evidently suppressed in presence of either TEMPO or BHT, suggesting that the titled reactions proceeded *via* free radical process.

On the basis of the results from both the product synthesis and the control experiments, the plausible mechanism for the reactions is proposed. As shown in Scheme 5, the incorporation of R_fSO_2Na and molecular iodine provides perfluoroalkyl sulfonyl free radical **A** *via* thermo-induced iodine homo-cleavage. The free radical **A** adds quickly to the enaminone C=C double bond and give free radical intermediate **B** or its tautomeric species **B'**. The radical-radical coupling of **B** and iodine free radical takes places successively and led to the formation of intermediate **C**. As shown in the Neuman structure of **C**, the stronger hydrogen bond effect between the sulfonyl group and the β -H determines that the antiperiplanar elimination of HI from **C** affords the *E*-configured perfluoroalkyl sulfonyl enaminones *via* formal reversion of the double bond configuration.

In summary, by means of functionalizing the vinyl C–H bond in tertiary enaminones in the presence of perfluoroalkyl sulfonyl sulfinites, we have realized the synthesis of α -*E*-perfluoroalkyl sulfonyl enaminones by a novel C–H perfluoroalkyl sulfonylation and the conversion of the double bond configuration in the presence of only I_2 . This featured new protocol brings new perspective on the synthesis of polyfunctionalized alkenes possessing perfluoroalkyl structure without employing any metal catalyst or additive. In addition, the broad substrate tolerance as well as the relatively mild conditions are also favorable for its further application in organic synthesis.

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

This work is financially supported by National Natural Science Foundation of China (No. 21861019) and Natural Science Foundation of Jiangxi Province (No. 20202ACBL203006).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ccl.2021.04.037.

References

- [1] M. Tordeux, B.R. Langlois, C. Wakeselman, *J. Org. Chem.* 54 (1989) 2452–2453.
- [2] C. Zhang, *Adv. Synth. Catal.* 356 (2014) 2895–2906.
- [3] H. Mei, R. Pajkert, L. Wang, et al., *Green Chem.* 22 (2020) 3028–3059.
- [4] P. Ghosh, S. Mondal, A. Hajra, *J. Org. Chem.* 83 (2018) 13618–13623.
- [5] A. Murugan, N.B. Babu, A. Polu, et al., *J. Org. Chem.* 84 (2019) 7796–7803.
- [6] L. Zhou, P. Li, B. Wang, L. Wang, *Chem. Commun.* 55 (2019) 3737–3740.
- [7] X.H. Cao, X. Pan, P.J. Zou, et al., *Chem. Commun.* 50 (2014) 3359–3362.
- [8] L. Wang, Y. Zhang, F. Li, et al., *Adv. Synth. Catal.* 360 (2018) 3969–3977.
- [9] L. Zou, P. Li, B. Wang, L. Wang, *Green Chem.* 21 (2019) 3362–3369.
- [10] Z. Tan, S. Zhang, Y. Zhang, et al., *J. Org. Chem.* 82 (2017) 9384–9399.
- [11] W.G. Shen, Q.Y. Wu, X.Y. Gong, et al., *Green Chem.* 21 (2019) 2983–2987.
- [12] H. Hong, Y. Li, L. Chen, et al., *J. Org. Chem.* 84 (2019) 5980–5986.
- [13] Y. Konik, M. Kudrjashova, S. Kaabel, et al., *Org. Biomol. Chem.* 15 (2017) 4635–4643.
- [14] Z. Li, L. Jiao, Y. Sun, et al., *Angew. Chem. Int. Ed.* 59 (2020) 7266–7270.
- [15] L. Zhao, P. Li, H. Zhang, L. Wang, *Org. Chem. Front.* 6 (2019) 87–93.
- [16] K. Lu, X. Wei, Q. Li, Y. Li, et al., *Org. Chem. Front.* 6 (2019) 3766–3770.
- [17] X.L. Yu, J.R. Chen, D.Z. Chen, W.J. Xiao, *Chem. Commun.* 52 (2016) 8275–8278.
- [18] A. vander Werf, M. Hribersek, N. Selander, *Org. Lett.* 19 (2017) 2374–2377.
- [19] S. Soni, P. Pali, M.A. Ansari, M.S. Singh, *J. Org. Chem.* 85 (2020) 10098–10109.
- [20] S. Liang, J. Wei, L. Jiang, et al., *Chem. Commun.* 55 (2019) 8536–8539.
- [21] L. Jiang, J. Qian, W. Yi, et al., *Angew. Chem. Int. Ed.* 54 (2015) 14965–14969.
- [22] X.L. He, S. Majumder, J. Wu, et al., *Org. Chem. Front.* 6 (2019) 2435–2440.
- [23] Y.Y. Liao, J.C. Deng, Y.P. Ke, et al., *Chem. Commun.* 53 (2017) 6073–6076.
- [24] X.F. Li, L.F. Shi, X.G. Zhang, X.H. Zhang, *Org. Biomol. Chem.* 16 (2018) 6438–6442.
- [25] Y. Ning, A. Mekareeya, K.R. Babu, E. Anderson, X. Bi, *ACS Catal.* 9 (2019) 4203–4210.
- [26] J. Liao, W. Guo, Z. Zhang, et al., *J. Org. Chem.* 81 (2016) 1304–1309.
- [27] Q.L. Wang, Z. Chen, Q. Zhou, *Adv. Synth. Catal.* 361 (2019) 2315–2320.
- [28] K. Zhang, X.H. Xu, F.L. J. *J. Org. Chem.* 80 (2015) 7658–7665.
- [29] S.C. Cullen, S. Shekhar, N.K. Nere, *J. Org. Chem.* 78 (2013) 12194–12201.
- [30] H. Guyon, H. Chachignon, D. Cahard, Beilstein *J. Org. Chem.* 13 (2017) 2764–2799.
- [31] S. Würtz, S. Rakshit, J.J. Neumann, T. Dröge, F. Glorius, *Angew. Chem. Int. Ed.* 47 (2008) 7230–7233.
- [32] R. Bernini, G. Fabrizi, A. Sferrazza, S. Cacchi, *Angew. Chem. Int. Ed.* 48 (2009) 8078–8081.
- [33] X. Mao, T. Tong, S. Fan, et al., *Chem. Commun.* 53 (2017) 4718–4721.
- [34] Y. Zhou, Y. Wang, Z. Song, et al., *Org. Chem. Front.* 7 (2020) 25–29.
- [35] Y. Guo, Y. Xiang, L. Wei, J.P. Wan, *Org. Lett.* 20 (2018) 3971–3974.
- [36] F. Wang, W. Sun, Y. Wang, et al., *Org. Lett.* 20 (2018) 1256–1260.
- [37] J.P. Wan, S. Zhong, L. Xie, et al., *Org. Lett.* 18 (2016) 584–587.
- [38] Z. Shang, Q. Chen, L. Xing, et al., *Adv. Synth. Catal.* 361 (2019) 4926–4932.
- [39] Y. Yuan, W. Hou, D. Zhang-Negrerie, et al., *Org. Lett.* 16 (2014) 5410–5413.
- [40] Y. Gao, Y. Liu, J.P. Wan, *J. Org. Chem.* 84 (2019) 2243–2251.
- [41] R. Chandran, A. Pise, S.K. Shah, et al., *Org. Lett.* 22 (2020) 6557–6561.
- [42] X. Duan, X. Liu, X. Cuan, et al., *J. Org. Chem.* 84 (2019) 12366–12376.
- [43] G. Li, Q. Yan, X. Gong, et al., *ACS Sustain. Chem. Eng.* 7 (2019) 14009–14015.
- [44] D. Ali, A.K. Panday, L.H. Choudhury, *J. Org. Chem.* 85 (2020) 13610–13620.
- [45] For a review, see: L. Fu, J.P. Wan, *Asian J. Org. Chem.* 8 (2019) 767–776.
- [46] J.P. Wan, Z. Tu, Y. Wang, *Chem. Eur. J.* 25 (2019) 6907–6910.
- [47] S. Mkrtchyan, V.O. Iaroshenko, *Chem. Commun.* 56 (2020) 2606–2609.
- [48] T. Luo, J.P. Wan, Y. Liu, *Org. Chem. Front.* 7 (2020) 1107–1112.
- [49] H. Xiang, Q. Zhao, Z. Tang, et al., *Org. Lett.* 19 (2017) 146–149.
- [50] L. Fu, Z. Xu, J.P. Wan, *Org. Lett.* 22 (2020) 9518–9523.
- [51] H. Jiang, W. Huang, Y. Yu, et al., *Chem. Commun.* 53 (2017) 7473–7476.
- [52] Q. Yu, Y. Liu, J.P. Wan, *Org. Chem. Front.* 7 (2020) 2770–2775.
- [53] L. Gan, Q. Yu, Y. Liu, J.P. Wan, *J. Org. Chem.* 86 (2021) 1231–1237.
- [54] D. Hu, L. Yang, J.P. Wan, *Green Chem.* 22 (2020) 6773–6777.
- [55] G. Wang, Y. Guo, J.P. Wan, *Chin. J. Org. Chem.* 40 (2020) 645–650.
- [56] Y. Liu, J. Xiong, J.P. Wan, *Adv. Synth. Catal.* 362 (2020) 877–883.
- [57] L. Fu, X. Cao, J.P. Wan, *Chin. J. Chem.* 38 (2020) 254–258.
- [58] X.M. Xu, D.M. Chen, Z.L. Wang, *Chin. Chem. Lett.* 31 (2020) 49–57.
- [59] H. Zhang, H. Wang, Y. Jiang, *Fet al.*, *Chem. Eur. J.* 26 (2020) 17289–17317.
- [60] S. Tian, T. Luo, Y. Zhu, J.P. Wan, *Chin. Chem. Lett.* 31 (2020) 3073–3082.
- [61] X. Xu, H. Yang, W. Li, *Chin. J. Org. Chem.* 40 (2020) 1912–1925.
- [62] S. Chen, Y. Li, M. Wang, X. Jiang, *Green Chem.* 22 (2020) 322–326.
- [63] P.F. Zhong, H.M. Lin, L.W. Wang, et al., *Green Chem.* 22 (2020) 6334–6339.
- [64] W.B. He, L.Q. Gao, X.J. Chen, et al., *Chin. Chem. Lett.* 31 (2020) 1895–1898.
- [65] K. Sun, X.L. Chen, Y.L. Zhang, et al., *Chem. Commun.* 55 (2019) 12615–12618.
- [66] L.Y. Xie, T.G. Fang, J.X. Tan, et al., *Green Chem.* 21 (2019) 3858–3863.
- [67] D. Zeng, M. Wang, W.-P. Deng, X. Jiang, *Org. Chem. Front.* 7 (2020) 3956–3966.
- [68] Y. Meng, M. Wang, X. Jiang, *CCS Chem.* 3 (2021) 17–24.
- [69] Y. Li, S. Chen, M. Wang, X. Jiang, *Angew. Chem. Int. Ed.* 59 (2020) 8907–8911.
- [70] M. Wang, X. Jiang, *Chem. Rec.* (2021) doi:10.1002/tcr.202000162.