

Cite this: *RSC Adv.*, 2019, 9, 30952Received 26th July 2019
Accepted 24th September 2019

DOI: 10.1039/c9ra07694h

rsc.li/rsc-advances

Copper-catalyzed chemoselective synthesis of 4-trifluoromethyl pyrazoles†

Jiaqing Lu,^a Yuning Man,^a Yabin Zhang,^a Bo Lin,^a Qi Lin^{*b} and Zhiqiang Weng^{†*a}

A series of 4-trifluoromethyl pyrazoles have been prepared *via* the copper-catalyzed cycloaddition of 2-bromo-3,3,3-trifluoropropene with a variety of *N*-arylsydnone derivatives under mild conditions. This new protocol under optimized reaction conditions [Cu(OTf)₂/phen, DBU, CH₃CN, 35 °C] afforded 4-trifluoromethyl pyrazoles in moderate to excellent yields with excellent regioselectivity.

Introduction

Methods for introduction of a fluorine atom or fluorinated group into organic molecules have emerged over the last decade as powerful synthetic tools that allow the construction of organofluorine compounds, which are of immense interest in materials sciences, agrochemical development, and medicinal chemistry.^{1–4} Indeed, derivatization of organic compounds with fluorinated units often alters their chemical, physical, and biological properties, by comparison with the corresponding non-fluorinated derivative and often improves their pharmacological properties.^{5–10}

Among organofluorinated molecules, trifluoromethylated pyrazoles¹¹ are particularly important compounds because many of them exhibit diverse biological activities and have found applications as drugs and agrochemicals (Fig. 1). Key examples include Celecoxib, a nonsteroidal anti-inflammatory drug used to treat pain or inflammation,¹² and Razaxaban, a factor Xa inhibitor potentially for the treatment of thrombosis.¹³ In addition, trifluoromethylated pyrazoles form the core of several agrochemicals currently in development. Specifically, penthiopyrad has shown fungicidal activity against foliar pathogens and soilborne pathogens,¹⁴ compounds A have shown insecticidal activity for control of *Spodoptera littoralis*,¹⁵ and compounds B has potential application as an acaricide for control of *Tetranychus urticae*.¹⁶

While the vast array of procedures to synthesize 3-trifluoromethyl pyrazoles have been established,^{17–19} there were considerably less efforts devoted to the development of

synthetic methods that allow effectively access to 4-trifluoromethyl pyrazoles. Conventionally, 4-trifluoromethyl pyrazoles were synthesized by the cycloaddition/cyclization reaction with CF₃-containing building blocks.^{20–23} For example, the synthesis of 4-(trifluoromethyl)pyrazole derivatives from cycloaddition of hydrazines to β-trifluoromethylated vinamidinium salt or 2-(trifluoromethyl)-1,3-diketones was independently reported by the research groups of Yamanaka and Yamakawa (Scheme 1a).^{20,21} Recently, Tsui and co-workers developed a copper-mediated synthesis of 4-(trifluoromethyl)pyrazoles from reaction of α,β-alkynic tosylhydrazones with trifluoromethyltrimethylsilane through domino cyclization, trifluoromethylation, and deprotection sequence (Scheme 1b).²⁴ Meazza and co-workers reported the preparation of trifluoromethyl-substituted pyrazoles *via* 1,3-dipolar cycloaddition from sydnones and 1-aryl-3,3,3-trifluoropropynes (Scheme 1c).²² The methods described above and some other reported methods are useful,^{25–30} and have found extensive applications in synthesis; however, some of reactions suffered from tedious procedures for the synthesis of trifluoromethylated sources, the requirement of a stoichiometric amount of metal catalyst, and harsh reaction conditions, as well as poor regioselectivities. Therefore, the development of more general and practical approaches

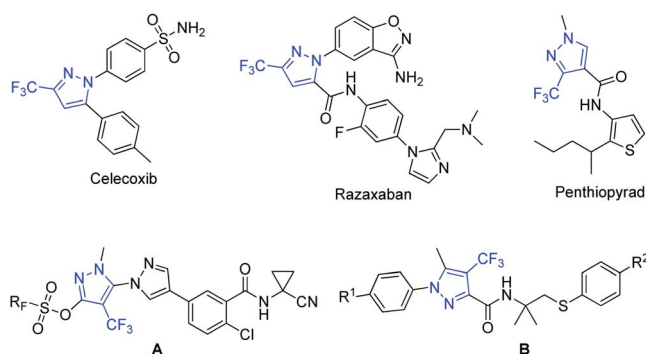


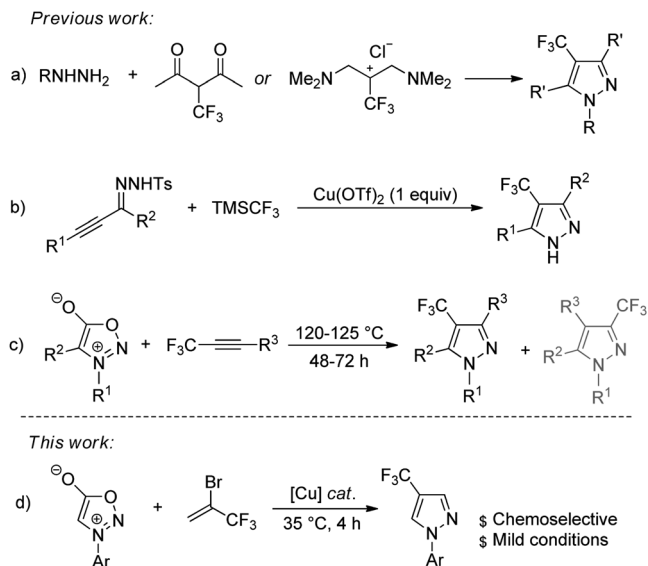
Fig. 1 Some biologically active trifluoromethylated pyrazoles.

^aFujian Provincial Key Laboratory of Electrochemical Energy Storage Materials, College of Chemistry, Fuzhou University, Fuzhou, 350108, China. E-mail: zweng@fzu.edu.cn; Fax: +86 591 22866247; Tel: +86 591 22866247

^bOcean College, Minjiang University, Fuzhou, 350108, China. E-mail: qlin1990@163.com

† Electronic supplementary information (ESI) available. CCDC 1934789. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9ra07694h





Scheme 1 Recent examples for the preparation of 4-trifluoromethyl pyrazoles.

employing easily accessible starting materials under mild conditions is highly desirable.

As part of our ongoing research into the development of copper-catalyzed reactions for the preparation of organofluorine compounds,^{31,32} we aimed to investigate an alternative protocol for the synthesis of these scaffolds using easy-to-operate synthetic tools. Based on the fact that 3,3,3-trifluoropropyne could be generated *in situ* from a dehydrobromination reaction of readily available 2-bromo-3,3,3-trifluoropropene (**1**) under base conditions,³³ and our recent work on 1,3-dipolar cycloaddition reaction,³⁴⁻³⁶ we wondered if 2-bromo-3,3,3-trifluoropropene could be used for the selective synthesis of 4-trifluoromethyl pyrazoles (Scheme 1d). We report here a new method for the synthesis of 4-trifluoromethyl pyrazoles through copper-catalyzed reaction of sydnone with 2-bromo-3,3,3-trifluoropropene (**1**).

Table 1 Optimization of the reaction conditions^a

Entry	[Cu]	Ligand	Base	Solvent	Temp. (°C)	Time (h)	Yield ^b (%)	3a:3a'
1	CuI	phen	DBU	CH ₃ CN	35	4	47	100 : 0
2	CuBr	phen	DBU	CH ₃ CN	35	4	36	100 : 0
3	CuSCN	phen	DBU	CH ₃ CN	35	4	71	100 : 0
4	CuTc	phen	DBU	CH ₃ CN	35	4	74	100 : 0
5	CuSO ₄	phen	DBU	CH ₃ CN	35	4	9	100 : 0
6	Cu(OTf) ₂	phen	DBU	CH ₃ CN	35	4	99	100 : 0
7	Cu(TFA) ₂	phen	DBU	CH ₃ CN	35	4	85	100 : 0
8	Cu(OTf) ₂	bpy	DBU	CH ₃ CN	35	4	22	97 : 3
9	Cu(OTf) ₂	dmbpy	DBU	CH ₃ CN	35	4	27	99 : 1
10	Cu(OTf) ₂	tmeda	DBU	CH ₃ CN	35	4	23	99 : 1
11	—	—	DBU	CH ₃ CN	35	4	0	—
12	Cu(OTf) ₂	phen	NEt ₃	CH ₃ CN	35	4	0	—
13	Cu(OTf) ₂	phen	NaOt-Bu	CH ₃ CN	35	4	<1	—
14	Cu(OTf) ₂	phen	KOt-Bu	CH ₃ CN	35	4	<1	—
15	Cu(OTf) ₂	phen	NaOH	CH ₃ CN	35	4	<1	—
16	Cu(OTf) ₂	phen	KOH	CH ₃ CN	35	4	<1	—
17	Cu(OTf) ₂	phen	K ₃ PO ₄	CH ₃ CN	35	4	0	—
18	Cu(OTf) ₂	phen	DBU	DMSO	35	4	50	100 : 0
19	Cu(OTf) ₂	phen	DBU	THF	35	4	<1	—
20	Cu(OTf) ₂	phen	DBU	Toluene	35	4	0	—
21	Cu(OTf) ₂	phen	DBU	Dioxane	35	4	<1	—
22	Cu(OTf) ₂	phen	DBU	DMF	35	4	<1	—
23	Cu(OTf) ₂	phen	DBU	CH ₃ CN	25	4	44	100 : 0
24	Cu(OTf) ₂	phen	DBU	CH ₃ CN	35	2	60	100 : 0

^a Reaction conditions: **1** (0.30 mmol, 3.0 equiv.), **2a** (0.10 mmol), solvent (1.0 mL), N₂; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; phen = 1,10-phenanthroline; bpy = 2,2'-bipyridine; dmbpy = 4,4'-dimethyl-2,2'-bipyridine; TMEDA = tetramethylethylenediamine. ^b The yield was determined by ¹⁹F NMR spectroscopy with PhOCF₃ as internal standard.



Results and discussion

We commenced our investigation by using *N*-phenylsydnone (2a) as a model substrate in the reaction with 3.0 equiv. of **1** in the presence of CuI (10 mol%)/phen (10 mol%) as a catalyst and 2.0 equiv. of DBU as a base (Table 1). Gratifyingly, after 4 h at 35 °C in CH₃CN under a nitrogen atmosphere, 4-trifluoromethylated pyrazole **3a** was obtained in 47% yield with excellent regioselectivity (Entry 1). The structure of **3a** was unambiguously determined by NMR spectroscopy and X-ray crystallography (Fig. 2). Encouraged by this initial result, we carried out the reaction under different conditions to optimize the product yield. First, copper catalysts and ligands were screened (Entries 2–10), and the results showed that the use of Cu(OTf)₂/phen presented the highest catalytic activity for this reaction, providing product **3a** in 99% yield (Entry 6). It is worth mentioning that no product formation was observed in the absence of copper salts and ligands (Entry 11), thus implying the importance of the copper catalyst in this transformation. The effects of the base were also examined. When DBU was replaced with NEt₃, NaOt-Bu, KOt-Bu, NaOH, KOH, or K₃PO₄ the reactions only produced trace amounts or no desired product (Entries 12–17). Commonly used organic solvents were also screened. It was found that CH₃CN gave the best yield (Entry 6); solvents such as DMSO gave moderate yields of the product (Entry 18), and THF, toluene, dioxane, and DMF retarded the reaction (Entries 19–22). Reactions performed either at lower temperatures (25 °C) or reducing the reaction time to 2 h resulted in substantially lower product yields (44% and 60% yields, respectively; Entry 23 and 24).

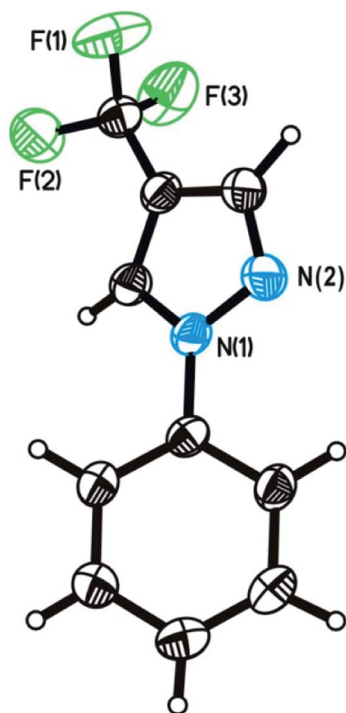


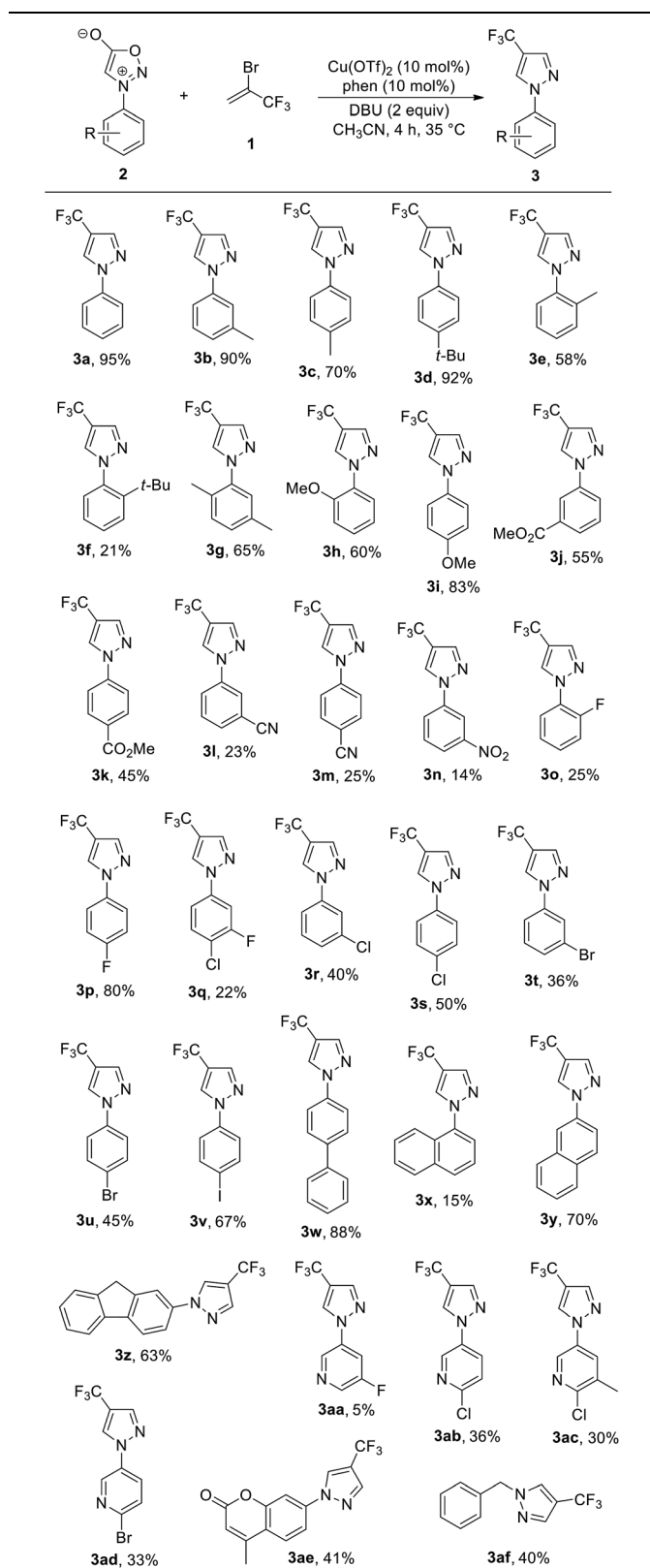
Fig. 2 ORTEP drawing of **3a**. Thermal ellipsoids are drawn at 40% probability.

With the optimised conditions in hand, the substrate scope of the reaction was evaluated using a range of electronically and sterically differentiated *N*-arylsydnone derivatives (Table 2). Overall, it was observed that the reaction could tolerate a variety of functional groups on the phenyl rings of sydnones. For example, *N*-arylsydnones bearing *para*- or *meta*-alkyl-substituted aromatic rings all reacted well with **1** to give the corresponding products **3b–3d** in 70–92% yields. As an exception, *ortho*-alkyl-substituted on phenyl rings of *N*-arylsydnones afforded the products **3e** and **3f** in lower yields (21% and 58%, respectively), probably due to steric hindrance. The dimethyl-substituted *N*-arylsydnone also took part in the reaction to afford the desired product **3g** in 65% yield. *N*-arylsydnone substrates bearing electron-donating substituents, such as methoxy at the *para*-position on the aryl ring was smoothly converted to the corresponding product **3i** in 83% yield, with the exception of substrate bearing a OMe group at the *ortho* position (**3h**, 60% yield). However, reactions of *N*-arylsydnones containing electron-withdrawing substituents, such as ester, cyano, and nitro groups on the aryl ring furnished the desired products **3j–3n** in relatively low yields (14–55%). Likewise, *N*-arylsydnone derivatives bearing electron-withdrawing halogen groups, such as fluoro, chloro, bromo, and iodo on the aryl rings were accommodated and furnished the desired products **3o–3v** in 22–80% yields, thereby providing possibilities for following chemical transformations. Analogously, the reaction with polyaromatic sydnones provided the corresponding trifluoromethylated product **3w**, **3y**, and **3z** in 63–88% yields. In the case of the *N*-1-naphthylsydnone substrate, the desired product **3x** could only be obtained in 15% isolated yield, with the majority of the remaining material attributed to unreacted starting material. This may be due to the steric bulk of the 1-naphthyl group hindering access to the cycloaddition site. The process was applied also to heteroaromatic sydnones, such as *N*-pyridyl- and cumarin sydnone derivatives, the corresponding products **3aa–3ae** were obtained in low to moderate yields (5–41%). Notably, a *N*-benzylsydnone derivative was also proved to be suitable substrate, producing the corresponding trifluoromethylated pyrazole **3af** in promising yield (40%).

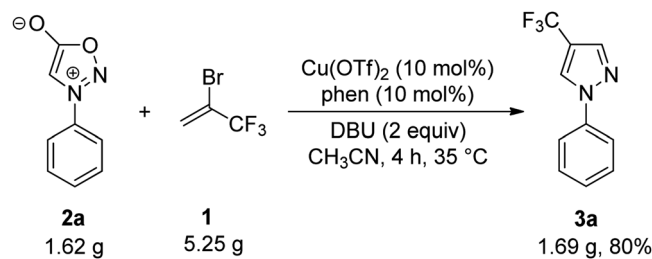
To illustrate the further synthetic utility of this method, a gram-scale reaction of *N*-phenylsydnone (**2a**) with 2-bromo-3,3,3-trifluoropropene (**1**) was performed, and the corresponding 4-trifluoromethyl pyrazole product **3a** was given in 80% isolated yield (Scheme 2). This result demonstrates the scalability of the reaction.

Based on the above results and previous reports by Taran,³⁷ Gomez-Bengoa, and Harrity,³⁸ a plausible reaction mechanism is proposed in Scheme 3. Firstly, the copper species reacted with the *in situ* generated 3,3,3-trifluoropropyne to give Cu(I) acetylide species **I**. In the second step, the cycloaddition of **I** with the sydnone **2** would form the transition state **II**. The tight copper-nitrogen interaction in **II** is probably responsible for its lower the activation barrier compared with other modes of interaction between arylsydnone and Cu(I) acetylide.^{38,39} Subsequently, the Cu–N dissociation and C–N bond formation could generate **III**, which upon CO₂ elimination provided 3-copper(I) pyrazolide **IV**. Finally, protonation of **IV** with new 3,3,3-trifluoropropyne

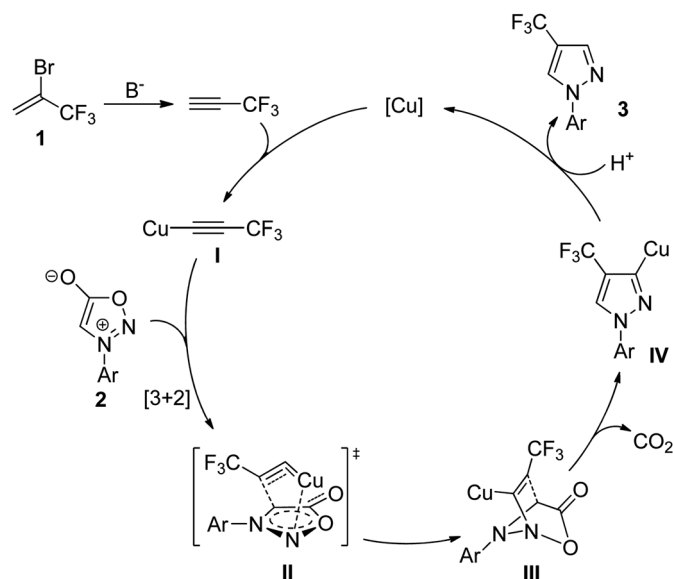


Table 2 Scope of the reaction^a

^a Reaction conditions: **1** (1.5 mmol, 3.0 equiv.), **2** (0.50 mmol, 1.0 equiv.), Cu(OTf)₂ (0.050 mmol, 10 mol%), phen (0.050 mmol, 10 mol%), DBU (1.0 mmol, 2.0 equiv.), CH₃CN (5.0 mL), 35 °C, 4 h, N₂; isolated yields.



Scheme 2 Gram scale experiment.



Scheme 3 Plausible reaction mechanism.

produced the desired 4-trifluoromethyl pyrazole regimer **3** along with regeneration of the starting copper species to complete the catalytic cycle.

Conclusions

In summary, we have developed a simple and efficient method for the synthesis of 4-trifluoromethyl pyrazole derivatives from the copper-catalyzed cycloaddition of 2-bromo-3,3,3-trifluoropropene with a variety of *N*-arylsydones under mild conditions. This approach allowed the rapid assembly of a small library of potentially medicinally relevant 4-trifluoromethylated pyrazoles in moderate to excellent yields with excellent regioselectivity. Investigations directed towards the extension of the scope of the reaction are underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.



Acknowledgements

This work was supported by the National Natural Science Foundation of China (21772022) and Fuzhou University.

Notes and references

- 1 T. Yamazaki, T. Taguchi and I. Ojima, *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley-Blackwell, Chichester, 2009.
- 2 J. T. Welch and S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry*, John Wiley & Sons, New York, 1991.
- 3 K. Uneyama, *Organofluorine Chemistry*, Blackwell Publishing Ltd., 2006.
- 4 J. Hu and T. Umemoto, *Synthetic Organofluorine Chemistry*, Springer, 2018.
- 5 J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432–2506.
- 6 W. Zhu, J. Wang, S. Wang, Z. Gu, J. L. Aceña, K. Izawa, H. Liu and V. A. Soloshonok, *J. Fluorine Chem.*, 2014, **167**, 37–54.
- 7 L. Chu and F.-L. Qing, *Acc. Chem. Res.*, 2014, **47**, 1513–1522.
- 8 C. Ni, M. Hu and J. Hu, *Chem. Rev.*, 2015, **115**, 765–825.
- 9 S. Barata-Vallejo, B. Lantaño and A. Postigo, *Chem.–Eur. J.*, 2014, **20**, 16806–16829.
- 10 C. Alonso, E. Martínez de Marigorta, G. Rubiales and F. Palacios, *Chem. Rev.*, 2015, **115**, 1847–1935.
- 11 K. Kaur, V. Kumar and G. K. Gupta, *J. Fluorine Chem.*, 2015, **178**, 306–326.
- 12 P. L. McCormack, *Drugs*, 2011, **71**, 2457–2489.
- 13 D. Zhang, N. Raghavan, S.-Y. Chen, H. Zhang, M. Quan, L. Lecureux, L. M. Patrone, P. Y. S. Lam, S. J. Bonacorsi, R. M. Knabb, G. L. Skiles and K. He, *Drug Metab. Dispos.*, 2008, **36**, 303.
- 14 A. K. Culbreath, T. B. Breneman, R. C. Kemerait Jr and G. G. Hammes, *Pest Manage. Sci.*, 2009, **65**, 66–73.
- 15 A. Jeanguenat, M. El Qacemi, A. Stoller, A. Bigot and D. Gribkov, WO2018234240, 2018.
- 16 K. Koyama, I. Okada, T. Fukuchi and Y. Kinoshita, JP2013216634, 2013.
- 17 S. Fustero, M. Sánchez-Roselló, P. Barrio and A. Simón-Fuentes, *Chem. Rev.*, 2011, **111**, 6984–7034.
- 18 J. C. Sloop, C. L. Bumgardner and W. D. Loehle, *J. Fluorine Chem.*, 2002, **118**, 135–147.
- 19 J. C. Sloop, C. Holder and M. Henary, *Eur. J. Org. Chem.*, 2015, **2015**, 3405–3422.
- 20 H. Yamanaka, T.-i. Takekawa, K. Morita, T. Ishihara and J. T. Gupton, *Tetrahedron Lett.*, 1996, **37**, 1829–1832.
- 21 Y. Ohtsuka, D. Uraguchi, K. Yamamoto, K. Tokuhisa and T. Yamakawa, *Tetrahedron*, 2012, **68**, 2636–2649.
- 22 G. Meazza, G. Zanardi and P. Piccardi, *J. Heterocycl. Chem.*, 1993, **30**, 365–371.
- 23 T. Hanamoto, M. Egashira, K. Ishizuka, H. Furuno and J. Inanaga, *Tetrahedron*, 2006, **62**, 6332–6338.
- 24 Q. Wang, L. He, K. K. Li and G. C. Tsui, *Org. Lett.*, 2017, **19**, 658–661.
- 25 I. I. Gerus, R. X. Mironetz, I. S. Kondratov, A. V. Bezdudny, Y. V. Dmytriv, O. V. Shishkin, V. S. Starova, O. A. Zaporozhets, A. A. Tolmachev and P. K. Mykhailiuk, *J. Org. Chem.*, 2012, **77**, 47–56.
- 26 Y.-P. Xiong, M.-Y. Wu, X.-Y. Zhang, C.-L. Ma, L. Huang, L.-J. Zhao, B. Tan and X.-Y. Liu, *Org. Lett.*, 2014, **16**, 1000–1003.
- 27 C.-P. Zhang, Z.-L. Wang, Q.-Y. Chen, C.-T. Zhang, Y.-C. Gu and J.-C. Xiao, *Angew. Chem., Int. Ed.*, 2011, **50**, 1896–1900.
- 28 M. Chen and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2013, **52**, 11628–11631.
- 29 M. Pisset, D. Oehlich, F. Rombouts and G. A. Molander, *J. Org. Chem.*, 2013, **78**, 12837–12843.
- 30 Z. Gonda, S. Kovács, C. Wéber, T. Gáti, A. Mészáros, A. Kotschy and Z. Novák, *Org. Lett.*, 2014, **16**, 4268–4271.
- 31 H. Zheng, Y. Huang and Z. Weng, *Tetrahedron Lett.*, 2016, **57**, 1397–1409.
- 32 W. Wu and Z. Weng, *Synthesis*, 2018, **50**, 1958–1964.
- 33 T. Yamazaki, K. Mizutani and T. Kitazume, *J. Org. Chem.*, 1995, **60**, 6046–6056.
- 34 W. Wu, J. Wang, Y. Wang, Y. Huang, Y. Tan and Z. Weng, *Angew. Chem., Int. Ed.*, 2017, **56**, 10476–10480.
- 35 B. Lin, W. Wu and Z. Weng, *Tetrahedron*, 2019, **75**, 2843–2847.
- 36 Z. Wang, X. Ding, S. Li and Z. Weng, *Tetrahedron*, 2018, **74**, 6631–6634.
- 37 S. Kolodych, E. Rasolofonjatovo, M. Chaumontet, M.-C. Nevers, C. Créminon and F. Taran, *Angew. Chem., Int. Ed.*, 2013, **52**, 12056–12060.
- 38 J. Comas-Barceló, R. S. Foster, B. Fiser, E. Gomez-Bengoa and J. P. A. Harrity, *Chem.–Eur. J.*, 2015, **21**, 3257–3263.
- 39 V. Hladikova, J. Vana and J. Hanusek, *Beilstein J. Org. Chem.*, 2018, **14**, 1317–1348.

