Organic LETTERS
Letter
Cite This: Org. Lett. XXXX, XXX, XXX−XXX
pubs.acs.org/OrgLett

Bunte Salt CH_2FSSO_3Na: An Efficient and Odorless Reagent for Monofluoromethylthiolation

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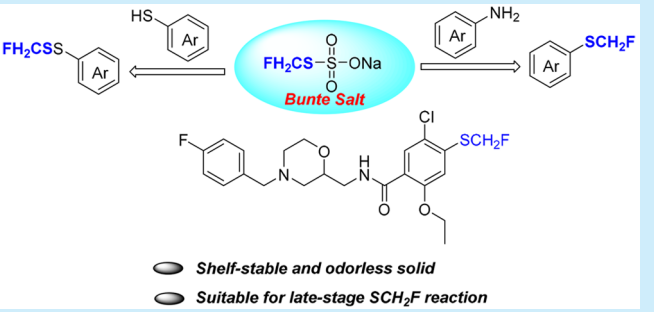
Supporting Information

ABSTRACT: A practical and efficient monofluoromethylthiolation that employs the typical Bunte salt, sodium *S*-(fluoromethyl) sulfurothioate, as the sulfur source is described. This reagent reacts readily with a variety of aryl amines and aryl thiols. The high tolerance of functional groups demonstrates the potential of this reaction. In addition, this method is suitable for the late-stage monofluoromethylthiolation of complex bioactive molecules.



Over the past few decades, the selective introduction of fluorine atom(s) into organic molecules has attracted increased attention in the fields of agrochemicals and pharmaceuticals, since fluorine has been described as a crucial element to modify the chemical and physical properties of the original compounds.[1] Among numerous fluorinated compounds known to date, fluoroalkylthio groups (such as SCF_3, SCF_2H, and SCH_2CF_3) are often encountered in biologically active molecules such as antibiotics, antiulcers, antibacterials, and pesticides.[2] However, there are few studies on the monofluoromethylthio group, mainly due to the lack of monofluoromethylthiolating reagents and instability of some compounds.[3] As one of the strategic fluorine-containing substituents, the monofluoromethylthio group is widely used by the pharmaceutical industry in many drugs and drug candidates. Well-known examples include antiflammatory drug Androstanes[4] and Fluticasone,[5] nonsteroidal antiflammatory agent fluoro-analogues of Sulindac,[6] and cathepsin K inhibitors (Figure 1).[7]

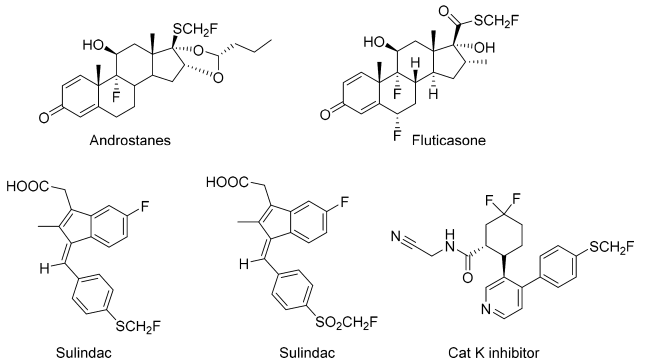
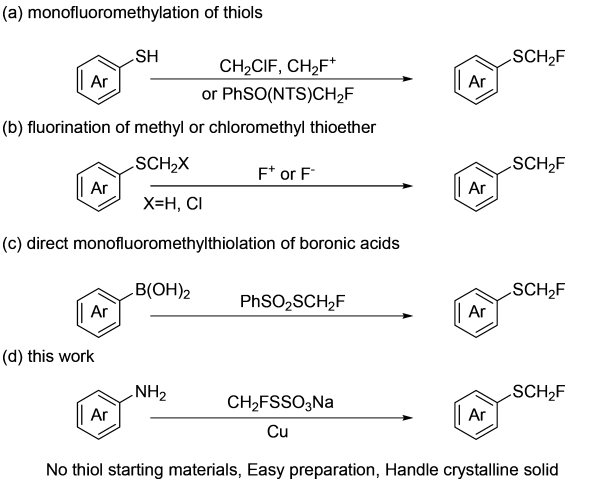


Figure 1. Monofluoromethylthioester based drugs and bioactive molecules.

In response to the growing demand in life and material science, organic chemists have developed several reagents and methods for the introduction of fluoroalkylthio groups into aromatic rings.[8,9] Nevertheless, methods for the introduction of a monofluoromethylthio group are still lacking, with the monofluoromethylthioester being the least understood. Therefore, strategies to synthesize organic molecules containing the monofluoromethylthio group have emerged as an active field in organic chemistry. The typical method for the synthesis of monofluoromethyl sulfides focuses on the monofluoromethylation of thiols (Scheme 1). For example, electrophilic monofluoromethylation of thiols with chlorofluormethane or

Scheme 1. Strategies for the Preparation of Monofluoromethylthioester



Received: August 28, 2018

DOI: 10.1021/acs.orglett.8b02753
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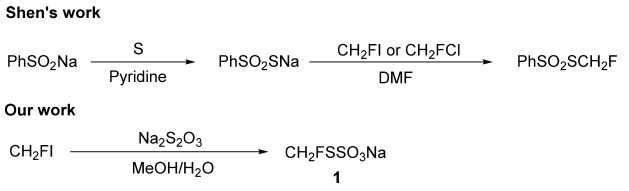
S-(monofluoromethyl)diarylsulfonium tetrafluoroborate has been applied to construct these compounds.[10] Later, Hu's group developed $PhSO(NTS)CH_2F$ as a radical monofluoromethylating reagent to introduce the monofluoromethyl moiety to thiols.[3a] Yet, smelly and unstable thiol derivatives might be a restriction for further application in more complicated molecules. Alternative approaches involved the fluorination of aromatic thioethers with an electrophilic fluorination agent or halogen exchange reaction with chloromethyl phenyl sulfides.[11] However, these strategies suffer from some limitations, such as harsh reaction conditions, use of toxic or hazardous reagents, and narrow functional group tolerance. The first direct electrophilic monofluoromethylthiolating reagent, *S*-(fluoromethyl) benezenesulfonothioate, was developed by Shen and co-workers in 2017.[12] This reagent was smoothly synthesized by treatment of easily available $PhSO_2Na$ with CH_2FI in two steps. The reagent is shelf-stable and has substrate generality, which enables reaction with a variety of aryl boronic acids to form monofluoromethylthioester. Despite this progress, the discovery of new, readily accessible, and solid monofluoromethylthiolating reagents that are effective with a broad range of substrates is still highly desirable. Interestingly, we find that the stable and easy-to-handle Bunte salt has a similar scaffold with this reagent.

Historically, Bunte salts, reported by Hans Bunte in 1874,[13] have been proven to be valuable synthetic intermediates.[14] Due to the masked effect and their high stability and being odorless, they have been widely used in the development of sulfides as sulfur sources.[15] Inspired by these seminal works and our continuous research interests in fluorine-containing sodium salts,[16] we decided to disclose a typical Bunte salt, sodium *S*-(fluoromethyl) sulfurothioate, that could be a potential monofluoromethylthiolating reagent.

According to the previous report, Bunte salt can be conveniently prepared by the reaction of odorless and inexpensive sodium thiosulfate with alkyl halides.[17] Similarly, sodium *S*-(fluoromethyl) sulfurothioate **1** was efficiently synthesized by mixing fluoromethyl iodide[18] with sodium thiosulfate in $MeOH/H_2O$ (Scheme 2). Subsequently, the

Scheme 2. Preparation of Sodium *S*-(Fluoromethyl) Sulfurothioate 1

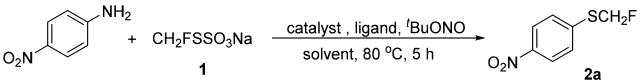


reaction was scaled up to over 5.0 g, and the desired product was isolated as a crystalline white solid in 66% yield and fully characterized by ^1H, ^{13}C, and ^{19}F NMR spectroscopies. The compound **1** decomposes without melting at 170 °C. The reagent is fairly stable without deterioration when stored in a refrigerator for a month. Around 20% of detectable decomposition was observed after storage at room temperature after a week.

Aromatic amines are cheap and readily available substrates, and they can serve as a versatile motif, which can be converted into various functional groups.[19] More recently, Sandmeyer-type trifluoromethylthiolation, difluoromethylthiolation, pentafluoroethylthiolation, and trifluoromethylselenolation of aryl diazonium salts have also been developed.[20] Inspired by the mechanism of the Sandmeyer reaction and the recent advances in this field, we wondered if it was possible to apply the unique property of Bunte salt **1** to develop a similar Sandmeyer-type monofluoromethylthiolation reaction.

Initially, we chose available *p*-nitroaniline and *tert*-butyl nitrite as an aryl diazonium salt precursor and Bunte salt **1** as sulfur sources, 10 mol % $CuSO_4·5H_2O$ as the catalyst, and 10 mol % 2,2-bipyridine as the ligand in $MeOH/H_2O$ (Table 1, entry 1).

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	ligand	solvent	yield (%)[b]
1	$CuSO_4·5H_2O$	Bipy	$MeOH/H_2O$	–
2	CuI	Bipy	$MeOH/H_2O$	–
3	CuCl	Bipy	$MeOH/H_2O$	23
4	CuBr	Bipy	$MeOH/H_2O$	–
5	$CuSO_4$	Bipy	$MeOH/H_2O$	38
6	$CuCl_2$	Bipy	$MeOH/H_2O$	16
7	$Cu(OAc)_2$	Bipy	$MeOH/H_2O$	17
8	$CuSO_4$	Phen	$MeOH/H_2O$	22
9	$CuSO_4$	Et_3N	$MeOH/H_2O$	–
10	$CuSO_4$	–	$MeOH/H_2O$	16
11	$CuSO_4$	Bipy	MeOH	71
12	$CuSO_4$	Bipy	H_2O	trace
13	$CuSO_4$	Bipy	DMF	–
14	$CuSO_4$	Bipy	DMSO	–
15	$CuSO_4$	Bipy	CH_3CN	16
16	$CuSO_4$	Bipy	THF	–
17[c]	$CuSO_4$	Bipy	MeOH	68
18[d]	$CuSO_4$	Bipy	MeOH	56
19[e]	$CuSO_4$	Bipy	MeOH	25

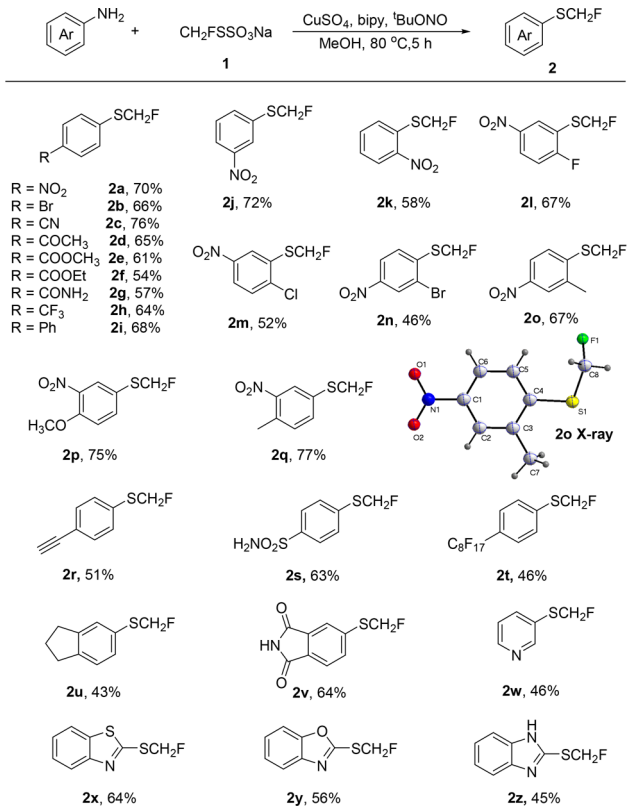
[a]Reaction conditions: *p*-nitroaniline (0.2 mmol), Bunte salt **1** (0.3 mmol), catalyst (10 mol %), ligand (10 mol %), ^{t}BuONO (1.5 equiv) in solvent (1.0 mL) at 80 °C for 5 h. [b]Yield determined by ^{19}F NMR using $PhCF_3$ as an internal standard. [c]20 mol % $CuSO_4$ was used. [d]Ar. [e]2.0 equiv NaCl were used.

To our disappointment, only deamination occurred to give the corresponding *p*-nitrobenzene without the formation of the desired monofluoromethylthiolated product. In order to improve its activities, various copper salts, such as CuI, CuCl, CuBr, $CuSO_4$, $CuCl_2$, and $Cu(OAc)_2$, were evaluated (entries 2−7). Fortunately, when using $CuSO_4$ as the catalyst, the monofluoromethylthiolated product, **2a**, was formed in 38% yield. Subsequently, we screened the reaction conditions with different ligands and found that 2,2-bipyridine served as an optimal ligand (entries 8−10). The effect of different solvents was also tested, and the results showed that MeOH was superior to the other solvents such as H_2O, DMF, DMSO, CH_3CN, and THF (entries 11−16). Finally, some control experiments were carried out. For example, increasing the amount of copper salt to 20 mol % or performing the reaction under a Ar atmosphere did not afford the product with higher yields (entries 17−18). It is noteworthy that the lower yield of product was obtained when NaCl were added, which was previously proven to be necessary for the coupling of aryl amines with Bunte salts (entry 19).[15d]

With the optimized conditions in hand, we next explored the scope of the substrates, and the results are summarized in Scheme 3. In general, a variety of aryl-substituted amines were applicable and moderate to excellent isolated yields of the

DOI: 10.1021/acs.orglett.8b02753
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Scope of the Monofluoromethylthiolation of Aryl Amines[a,b]

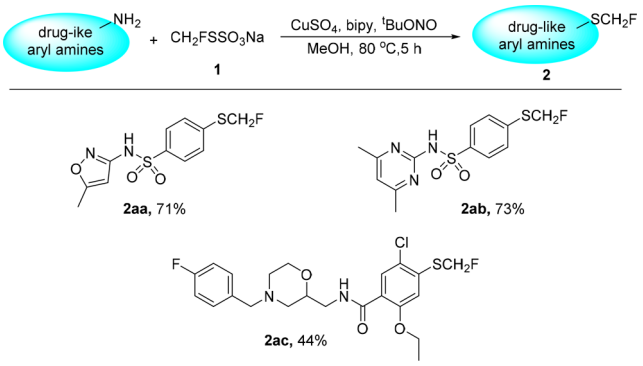


[a]Reaction conditions: aryl amine (0.4 mmol), Bunte salt **1** (0.6 mmol), $CuSO_4$ (10 mol %), 2,2-bipyridine (10 mol %), and ^tBuONO (1.5 equiv) in MeOH (2.0 mL) at 80 °C for 5 h. [b]Yield of isolated product.

products were achieved (**2a**–**z**). Substrates bearing different electron-withdrawing or -donating groups at a different position in the aromatic ring were all compatible with this reaction. A series of common functional groups, such as nitro, halogen, cyano, ketone, ester, amide, trifluoromethyl, and alkyl, were all well-tolerated, thus indicating the generality of the reaction conditions. In particular, the product **2b**, containing a bromine moiety, which was proven to be unstable,[3a] was also applicable to this reaction, giving the corresponding product in moderated isolated yield. In addition, *m*- and *o*-substituted nitroaniline gave the corresponding products in moderate yields, which shows the position of substituents on the phenyl ring has some effect on this reaction (**2j**–**k**). The sterically hindered aryl amines with *o*-substituted groups could also afford the desired products in moderate to good yields (**2k**–**o**). Moreover, disubstituted amines could be converted to the desired product through this reaction (**2l**–**q**). The structure of **2o** was unambiguously confirmed by single-crystal X-ray diffraction analysis. Note that a sensitive coupling precursor, such as a terminal alkyne, was also amenable to this method, generating the monofluoromethylthiolated product **2r** in 51% yields. Remarkably, substrates containing sulfanilamide, 4-perfluorooctyl, Indane, and phthalimide were successfully reacted with Bunte salt **1**, providing the corresponding products in moderate yields (**2s**–**v**). Interestingly, amines with heteroaryl moieties such as pyridine, benzothiazole, benzoxazole, and benzimidazole were also suitable for the current reaction, enabling the synthesis of more useful biologically relevant molecules (**2w**–**z**).

To further demonstrate the utility of this reagent in late-stage modification, we applied it to the monofluoromethylthiolation of sulfonamides, an antibacterial drug, which has been used for a few decades (Scheme 4).[21] Satisfyingly, sulfamethoxazole and

Scheme 4. Late-Stage Monofluoromethylthiolation of Drug-like Aryl Amines[a,b]

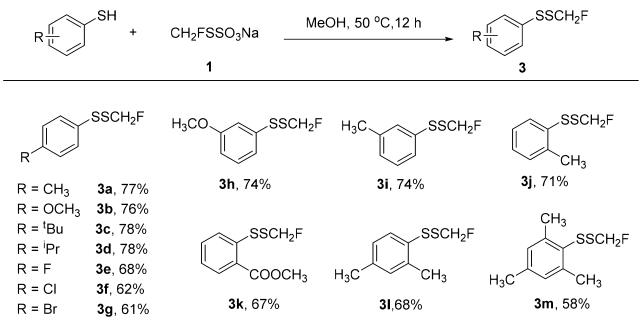


[a]Reaction conditions: aryl amine (0.4 mmol), Bunte salt **1** (0.6 mmol), $CuSO_4$ (10 mol %), 2,2-bipyridine (10 mol %), ^tBuONO (1.5 equiv) in MeOH (2.0 mL) at 80 °C for 5h. [b]Yield of isolated product.

sulfadimidine were also good candidates for this transformation, thus giving the products in moderate yields (**2aa**–**2ab**). These results encourage the application of this method to more complex small molecules. For example, mosapride, which is a gastroprokinetic agent that acts as a selective $5HT_4$ agonist,[22] was selectively converted at the amino group to give the monofluoromethylthiolated product **2ac** in 44% yield.

With the successful development of methods for the preparation of C-monofluoromethylthiolated compounds, we next sought to investigate the reaction of heteroatom monofluoromethylthiolation (Scheme 5). The results for thiols

Scheme 5. Scope of the Monofluoromethylthiolation of Aryl Thiols[a,b]



[a]Reaction conditions: aryl thiol (0.4 mmol) and Bunte salt **1** (0.6 mmol) in methanol (2.0 mL) at 50 °C for 12 h. [b]Yield of isolated product.

show that this reaction is compatible with both electron-donating and -withdrawing aryl thiols (**3a**–**m**). Owing to the mild conditions, aryl thiols possessing many functional groups, including fluoro, chloro, bromo, ether, and ester, were also good coupling partners, providing products in good yields. The monofluoromethylthiolation of ortho- and meta-substituted thiols occurred in moderate to good yields (**3h**–**k**). The connection position had a negligible effect on the yield of the reaction (**3i**–**j**). Di- or multisubstituted monofluoromethyl

DOI: 10.1021/acs.orglett.8b02753
Org. Lett. XXXX, XXX, XXX–XXX

thiolated thiols could also be obtained through this transformation (**3l**–**m**).

In summary, a new monofluoromethylthiolating reagent, sodium *S*-(fluoromethyl) sulfurothioate, has been reported. This reagent can be efficiently synthesized in one step from cheap and available starting materials. Furthermore, it could react with amines and thiols to afford the corresponding monofluoromethylthiolated products in moderate to good yields. Beneficial factors such as ready availability, ease of handing, good functional group compatibility, broad substrate scope, and applicability in late-stage functionalization of drug-like compounds make this reagent a general agent for the synthesis of a variety of monofluoromethylthio-containing compounds. We believe that this reagent may find wider application in the near future.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02753.

Experimental details and copies of ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra of all products (PDF)

Accession Codes

CCDC 1843537 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the National Natural Science Foundation of China (21776138, 21476116), Fundamental Research Funds for the Central Universities (30916011102, 30918011314), Natural Science Foundation of Jiangsu (BK20180476), Qing Lan and Six Talent Peaks in Jiangsu Province, and Priority Academic Program Development of Jiangsu Higher Education Institutions.

■ REFERENCES

(1) (a) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (b) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 8315. (c) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359.

(2) (a) Ni, C.; Hu, M.; Hu, J. *Chem. Rev.* **2015**, *115*, 765. (b) Xu, X.-H.; Matsuzaki, K.; Shibata, N. *Chem. Rev.* **2015**, *115*, 731. (c) Boiko, V. N. *Beilstein J. Org. Chem.* **2010**, *6*, 880.

(3) (a) Shen, X.; Zhou, M.; Ni, C.; Zhang, W.; Hu, J. *Chem. Sci.* **2014**, *5*, 117. (b) Guo, S.-H.; Wang, M.-Y.; Pan, G.-F.; Zhu, X.-Q.; Gao, Y.-R.; Wang, Y.-Q. *Adv. Synth. Catal.* **2018**, *360*, 1861. (c) Wang, L.; Wei, J.; Wu, R.; Cheng, G.; Li, X.; Hu, J.; Hu, Y.; Sheng, R. *Org. Chem. Front.* **2017**, *4*, 214.

(4) Ashton, M. J.; Lawrence, C.; Karlsson, J.-A.; Stuttle, K. A. J.; Newton, C. G.; Vacher, B. Y. J.; Webber, S.; Withnall, M. J. *J. Med. Chem.* **1996**, *39*, 4888.

(5) (a) Howland W, C. *Clin. Exp. Allergy* **1996**, *26*, 18. (b) Zhou, J.; Jin, C.; Su, W. *Org. Process Res. Dev.* **2014**, *18*, 928.

(6) Jung, M.; Wahl, A. F.; Neupert, W.; Geisslinger, G.; Senter, P. D. *Pharm. Pharmacol. Commun.* **2000**, *6*, 217.

(7) Robichaud, J.; Bayly, C. I.; Black, W. C.; Desmarais, S.; Léger, S.; Massé, F.; McKay, D. J.; Oballa, R. M.; Pâquet, J.; Percival, M. D.; Truchon, J.-F.; Wesolowski, G.; Crane, S. N. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3146.

(8) (a) Chen, C.; Xie, Y.; Chu, L.; Wang, R.-W.; Zhang, X.; Qing, F.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 2492. (b) Xu, C.; Ma, B.; Shen, Q. *Angew. Chem., Int. Ed.* **2014**, *53*, 9316. (c) Teverovskiy, G.; Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 7312.

(9) (a) Han, J.-B.; Qin, H.-L.; Ye, S.-H.; Zhu, L.; Zhang, C.-P. *J. Org. Chem.* **2016**, *81*, 2506. (b) Ismalaj, E.; LeBars, D.; Billard, T. *Angew. Chem., Int. Ed.* **2016**, *55*, 4790. (c) Li, L.; Wang, F.; Ni, C.; Hu, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 12390.

(10) (a) Prakash, G. K. S.; Ledneczki, I.; Chacko, S.; Olah, G. A. *Org. Lett.* **2008**, *10*, 557. (b) Zhang, W.; Zhu, L.; Hu, J. *Tetrahedron* **2007**, *63*, 10569.

(11) Umemoto, T.; Tomizawa, G. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3625. (b) Matthews, D. P.; Persichetti, R. A.; McCarthy, J. R. *Org. Prep. Proced. Int.* **1994**, *26*, 605. (c) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. *J. Org. Chem.* **1999**, *64*, 7048.

(12) Zhao, Q.; Lu, L.; Shen, Q. *Angew. Chem., Int. Ed.* **2017**, *56*, 11575.

(13) Bunte, H. *Ber. Dtsch. Chem. Ges.* **1874**, *7* (1), 646.

(14) (a) Stoner, G. G.; Dougherty, G. *J. Am. Chem. Soc.* **1941**, *63*, 987. (b) Distler, H. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 544.

(15) (a) Qiao, Z.; Ge, N.; Jiang, X. *Chem. Commun.* **2015**, *51*, 10295. (b) Qi, H.; Zhang, T.; Wan, K.; Luo, M. *J. Org. Chem.* **2016**, *81*, 4262. (c) Liu, F.; Yi, W. *Org. Chem. Front.* **2018**, *5*, 428. (d) Li, Y.; Pu, J.; Jiang, X. *Org. Lett.* **2014**, *16*, 2692. (e) Liu, H.; Jiang, X. *Chem. - Asian J.* **2013**, *8*, 2546. (f) Qiao, Z.; Jiang, X. *Org. Biomol. Chem.* **2017**, *15*, 1942.

(16) (a) Jiang, L.; Qian, J.; Yi, W.; Lu, G.; Cai, C.; Zhang, W. *Angew. Chem., Int. Ed.* **2015**, *54*, 14965. (b) Yan, Q.; Jiang, L.; Yi, W.; Liu, Q.; Zhang, W. *Adv. Synth. Catal.* **2017**, *359*, 2471. (c) Wang, R.; Jiang, L.; Yi, W. *J. Org. Chem.* **2018**, *83*, 7789.

(17) (a) Reeves, J. T.; Camara, K.; Han, Z. S.; Xu, Y.; Lee, H.; Busacca, C. A.; Senanayake, C. H. *Org. Lett.* **2014**, *16*, 1196. (b) Ogura, F.; Yamaguchi, H.; Otsubo, T.; Nakano, T.; Saito, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1257.

(18) Hu, J.; Gao, B.; Li, L.; Ni, C.; Hu, J. *Org. Lett.* **2015**, *17*, 3086.

(19) (a) Xing, B.; Ni, C.; Hu, J. *Angew. Chem., Int. Ed.* **2018**, *57*, 9896. (b) Danoun, G.; Bayarmagnai, B.; Grünberg, M. F.; Gooßen, L. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 7972. (c) Bayle, A.; Cocaud, C.; Nicolas, C.; Martin, O. R.; Poisson, T.; Pannecoucke, X. *Eur. J. Org. Chem.* **2015**, *2015*, 3787. (d) Lishchynskyi, A.; Berthon, G.; Grushin, V. V. *Chem. Commun.* **2014**, *50*, 10237. (e) Bayarmagnai, B.; Matheis, C.; Risto, E.; Goossen, L. J. *Adv. Synth. Catal.* **2014**, *356*, 2343. (f) Danoun, G.; Bayarmagnai, B.; Grünberg, M. F.; Matheis, C.; Risto, E.; Gooßen, L. *Synthesis* **2014**, *46*, 2283.

(20) (a) Danoun, G.; Bayarmagnai, B.; Gruenberg, M. F.; Goossen, L. J. *Chem. Sci.* **2014**, *5*, 1312. (b) Bayarmagnai, B.; Matheis, C.; Jouvin, K.; Goossen, L. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 5753. (c) Wu, J.; Gu, Y.; Leng, X.; Shen, Q. *Angew. Chem., Int. Ed.* **2015**, *54*, 7648. (d) Matheis, C.; Bayarmagnai, B.; Jouvin, K.; Goossen, L. *Org. Chem. Front.* **2016**, *3*, 949. (e) Bertoli, G.; Exner, B.; Evers, M. V.; Tschulik, K.; Gooßen, L. J. *J. Fluorine Chem.* **2018**, *210*, 132.

(21) (a) Calvo, R.; Sarabia, S.; Carlos, R.; Souich, P. D. *Biopharm. Drug Dispos.* **1987**, *8*, 115. (b) Supuran, C. T.; Casini, A.; Scozzafava, A. *Med. Res. Rev.* **2003**, *23*, 535.

(22) (a) Curran, M. P.; Robinson, D. M. *Drugs* **2008**, *68*, 981. (b) Kato, S.; Morie, T.; Yoshida, N. *Chem. Pharm. Bull.* **1995**, *43*, 699.

DOI: 10.1021/acs.orglett.8b02753
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