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Letter

Chlorotrifluoromethylthiolation of Sulfur Ylides for the Formation of Tetrasubstituted Trifluoromethylthiolated Alkenes

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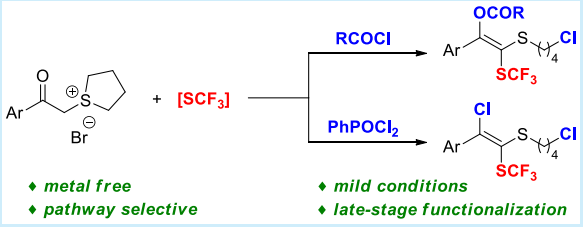
ABSTRACT: Tetrasubstituted trifluoromethylthiolated alkenes can be accomplished directly through the chlorotrifluoromethylthiolation of sulfur ylides utilizing nucleophilic halide reagent and electrophilic SCF_3 reagent. This cascade reaction is mild, highly practical, easy to manipulate, uses catalyst-free conditions, and demonstrates a wide substrate range with excellent functional group tolerance, furnishing *E*-selective products in good to high yields. The synthetic utility of this approach is documented through gram-scale preparation and late-stage modification of pharmaceutically relevant compounds, making it suitable for drug discovery.



Organofluorine compounds are extensively utilized in medicinal chemistry, agrochemistry, and materials science owing to their special chemical, physical, and biological properties.[1,2] Among the various fluorine-containing moieties, the trifluoromethylthio group (SCF_3) is particularly interesting because of its unique features of extremely strong electron-withdrawing character, high lipophilicity (Hansch constant of 1.44), and metabolic stability.[3] This may be beneficial in improving the pharmacokinetics of drug molecules. Various efforts have been devoted to the design of general and efficient protocols for the selective incorporation of an SCF_3 motif into organic molecules over the past decades.[4] However, there are still relatively few efficient approaches to straightforwardly access alkenes bearing a trifluoromethylthio group. Traditional methods for the construction of the trifluoromethylthio alkenes typically involve electrophilic substitution of alkenes,[5] cross-coupling of vinyl boronic acids,[6] vinyl halides,[7] or vinyl carboxylic acids,[8] C−H bond activation of alkenes,[9] nucleophilic substitution of enamines,[10] and ring-opening of methylenecyclopropanes[11] by employing nucleophilic, electrophilic, or radical SCF_3 reagents (Figure 1a). Furthermore, these molecules can also be formed through the difunctionalization based on trifluoromethylthiolation of alkynes (Figure 1b).[12] However, most of these methods required transition-metal catalysts and/or excess bases.

As the safer carbene precursors and readily available building blocks, sulfur ylides[13] have been broadly applied in the field of organic synthetic chemistry. They are more stable and less hazardous than diazo compounds, which are the most commonly used carbene precursors. In addition, a strategy based on multifunctionalization of carbonyl sulfur ylides to establish trifluoromethylthioalkenes has not been reported. Based on our continued interest in the preparation of organofluorine compounds,[14] we herein present the successful development of catalyst-free methodology that affords a general and efficient tandem procedure for gram-scale synthesis of multifunctionalized alkenes. The current transformation provides a new route to access trifluoromethylthiolated alkenes (Figure 1c).

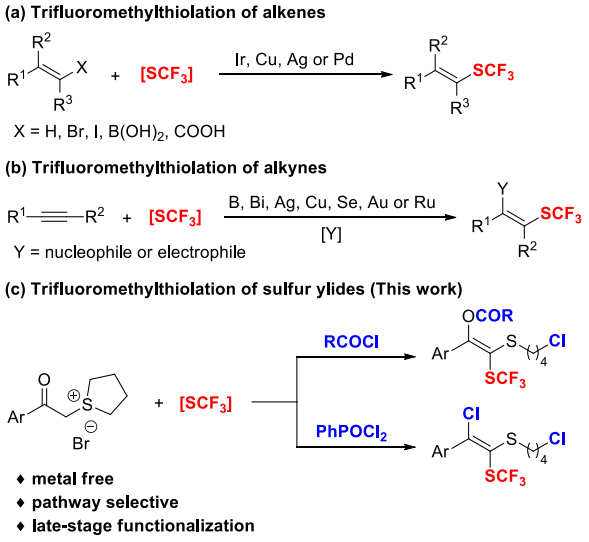


Figure 1. Synthesis of trifluoromethylthioalkenes.

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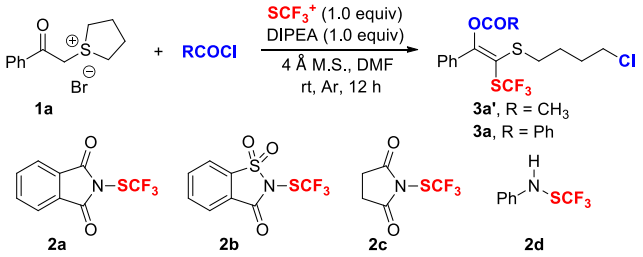
As the precursor of sulfur ylides, sulfonium salts are very stable solids and can readily be synthesized from commercially available and inexpensive haloalkanes and thioethers. It can be easily converted into sulfur ylide under basic conditions. Thus, we initiated our investigation on this sequential trifluoromethylthiolation using the carbonyl-substituted sulfonium salt **1a** as a model substrate to identify the reaction conditions. When **1a** was reacted with Munavalli's[15b] SCF_3 reagent **2a** and AcCl using DIPEA as base in DMF, the expected chlorotrifluoromethylthiolated enolate **3a′** was observed in 33% yield (Table 1, entry 1). To our delight, upon addition of 4 Å MS

Table 1. Optimization of the Reaction Conditions[a]



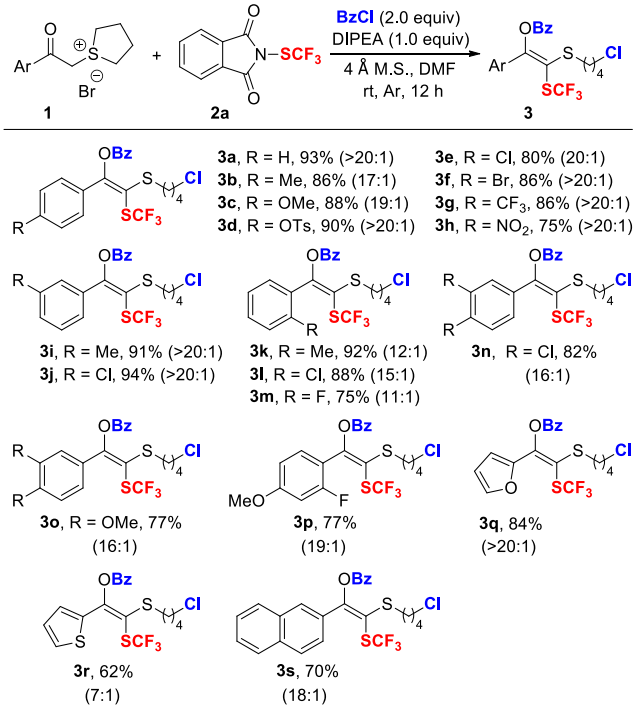
entry	2	R	solvent	yield[b] (%)	E/Z[c]
1[d]	2a	CH_3	DMF	33	8:1
2	2a	CH_3	DMF	60	8:1
3	2b	CH_3	DMF	17	4:1
4	2c	CH_3	DMF	58	7:1
5	2d	CH_3	DMF	ND	ND
6	2a	CH_3	THF	12	6:1
7	2a	CH_3	DCM	20	10:1
8	2a	CH_3	toluene	trace	ND
9	2a	CH_3	MeCN	30	10:1
10	2a	CH_3	DMAC	56	8:1
11	2a	CH_3	DMSO	ND	ND
12	2a	Ph	DMF	93	>20:1

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), AcCl or BzCl (0.2 mmol), DIPEA (0.1 mmol), and 4 Å M.S. (40 mg) in solvent (1.0 mL) at room temperature for 12 h. [b]Yields were determined by ^{19}F NMR analysis using $PhCF_3$ as an internal standard. [c]The *E*/*Z* ratio was determined by ^1H NMR and ^{19}F NMR analysis of a crude reaction mixture. [d]Without 4 Å molecular sieves. ND = not detected.

(molecular sieves) to the reaction system, the yield of product **3a′** was increased to 60% (Table 1, entry 2). The role of 4 Å MS may be to remove traces of water in the reaction. In contrast, other electrophilic SCF_3 sources were also examined. A 17% yield was achieved when Shen's reagent (**2b**)[15c] was investigated (Table 1, entry 3). Haas' (**2c**)[15a] reagent could give the desired product **3a′** in reasonable yield, whereas the use of Billard's reagent (**2d**)[12a] led to no reaction (Table 1, entry 5). Further study of several solvents, such as THF, DCM, toluene, MeCN, and DMAC (*N*,*N*-dimethylacetamide), indicated the yield of **3a′** was not improved (Table 1, entries 6−10). These results demonstrate that an amide solvent such as DMF or DMAC may be able to stabilize acid chloride to give better reactivities.[16] Surprisingly, when DMSO was used as solvent, the expected reaction did not occur (Table 1, entry 11). Importantly, the employment of benzoyl chloride (BzCl) as a substrate could provide the corresponding adduct **3a** in 93% yield with excellent stereoselectivity (*E*/*Z* > 20:1, Table 1, entry 12).

With the above-optimized conditions in hand, the substrate generality and functional group compatibility of the trifluoromethylthiolation were evaluated with respect to different sulfonium salts (Scheme 1). A variety of sulfonium salts were

Scheme 1. Substrate Scope of Trifluoromethylthiolation of Sulfur Ylides with BzCl[a−c]



[a]Reaction conditions: **1** (0.5 mmol), **2a** (0.5 mmol), BzCl (1.0 mmol), DIPEA (0.5 mmol), and 4 Å M.S. (200 mg) in DMF (5.0 mL) at room temperature for 12 h. [b]Reported yields are of isolated products for *E*-configured products. [c]The *E*/*Z* ratio is given in parentheses and was determined by ^1H NMR and ^{19}F NMR analysis of a crude reaction mixture.

converted to the chlorotrifluoromethylthiolated adducts in good to excellent yields. Substrates bearing both electron-donating groups (Me, OMe, OTs) and electron-withdrawing groups (Cl, Br, CF_3, NO_2) on the *para* position of the phenyl ring all proceeded smoothly to give the desired products **3b−h** in 75−90% yield. Excellent results were generally furnished by using *meta*-substituted aryls regardless of the electronic properties of substituents (**3i−j**). The sterically hindered *ortho*-substituted aryls were well tolerated with the reaction conditions, delivering the expected products **3k−m** with 75−92% yields and good stereoselectivity (>10:1, *E*/*Z*). Notably, substrates having two substituents (such as 3,4-dichloro, 3,4-dimethoxy, and 2-fluoro-4-methoxy) on the aromatic ring could be extended to the protocol, and the desired product **3n−p** were detected in excellent yields. Interestingly, the heteroaromatic moieties could also well contained in substrates **1q−r**, as shown by the formation of the resulting 2-furyl and 2-thienyl derivatives **3q−r** in 84% and 62% yields, respectively. Finally, when fused ring substituted substrate **1s** (Ar = 2-naphthyl) was subjected to this process, the corresponding trifluoromethylthiolated alkene was achieved in a satisfactory yield and high stereoselectivity.

To further probe the efficacy of current method, we next turned our attention to building dichlorinated trifluorome-

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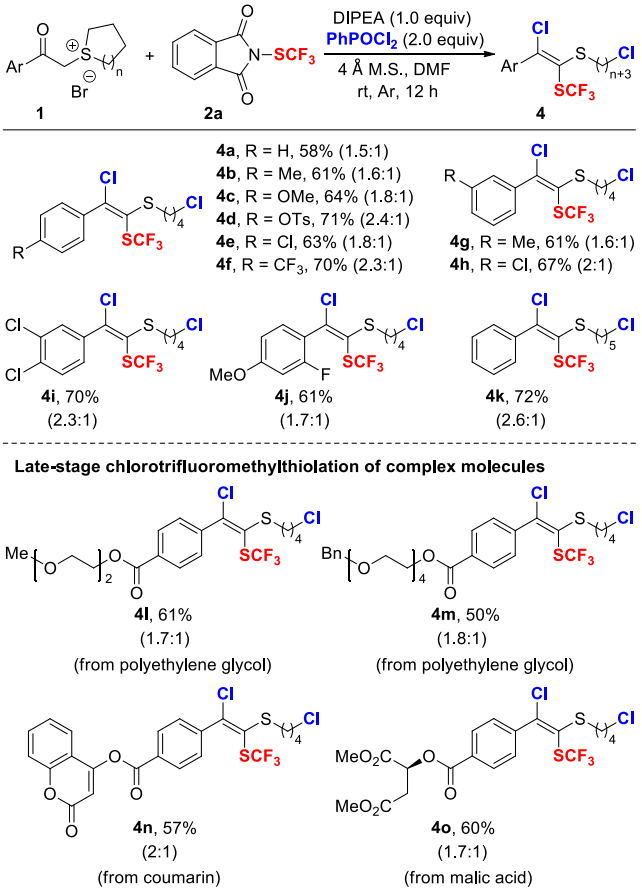
thylthiolated alkenes. As depicted in Scheme 2, when dichloride reagent $PhPOCl_2$ (phenylphosphonic dichloride)

Scheme 2. Substrate Scope of Trifluoromethylthiolation of Sulfur Ylides with $PhPOCl_2$[a–c]



[a]Reaction conditions: **1** (0.5 mmol), **2a** (0.5 mmol), $PhPOCl_2$ (1.0 mmol), DIPEA (0.5 mmol), and 4 Å M.S. (200 mg) in DMF (5.0 mL) at room temperature for 12 h. [b]Reported yields are of isolated products for *E*-configured products. [c]The *E*/*Z* ratio is given in parentheses and it was determined by ^1H NMR and ^{19}F NMR analysis of a crude reaction mixture.

was employed as a chlorine source instead of BzCl, the resulting *E*-configured product **4a** was observed in 58% isolated yield, together with the *Z*-configured product in about 39% yield. Other nucleophilic chlorine reagents, such as TMSCl, $PhSO_2Cl$, PCl_3, and $SOCl_2$, were also examined; no better results were obtained (see the SI for details). Subsequently, the scope of the process was investigated. A variety of carbonyl sulfonium salts proceeded smoothly with Munavalli's SCF_3 reagent **2a** and $PhPOCl_2$ to give the corresponding trifluoromethylthiolated alkenes in good yields. The electronic and steric properties of the substituents on the phenyl ring moderately interfered with the reactivity. For example, the substrates with electron-donating groups (Me, OMe, and OTs) and electron-withdrawing groups (Cl and CF_3) at the *para* position of the phenyl ring were found to be tolerant under the standard conditions, providing the desired products **4b–f** in 61–71% yields. Similarly, good yields were generally furnished in the presence of *meta*-substituted aryls (**4g–h**). Interestingly, sulfonium salts bearing disubstituents on the aryl ring were suitable substrates (**4i–j**). Noticeably, the transformation was also workable when a six-membered episulfide was combined on the sulfonium salt (**4k**).

To highlight the applicability of this protocol further, we evaluated the chlorotrifluoromethylthiolation method with biologically active compounds and natural products. Polyethylene glycols (PEGs), water-soluble, nontoxic, and biocompatible polymers, could be readily chlorotrifluoromethylthiolated from their derived esters with acceptable yields (**4l,m**). Sulfonium salts derived from commercially available nature products, such as coumarin and malic acid, were also suitable substrates, delivering the corresponding tetrasubstituted trifluoromethylthiolated alkenes **4n,o** as the sole adducts in 57% and 60% yields, respectively. These results show that this reaction can be utilized in the late-stage modification of complex compounds. The geometric configuration of trifluoromethylthiolated alkene was established on the basis of single crystal X-ray diffraction analysis of **4d** (Figure 2).

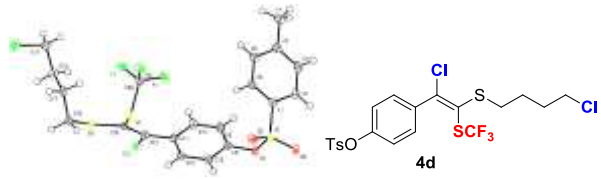


Figure 2. X-ray crystallography of **4d**.

This reaction system is readily scalable as illustrated by the gram-scale preparation, demonstrating a potential opportunity of practical applications. When **1a** was performed on a 3.5 mmol (1.0 g) preparative scale, the resulting trifluoromethylthiolated alkene **3a** could be achieved without loss of reactivity while still maintaining a 84% isolated yield, matching the result observed in the small-scale reaction (Figure 3a).

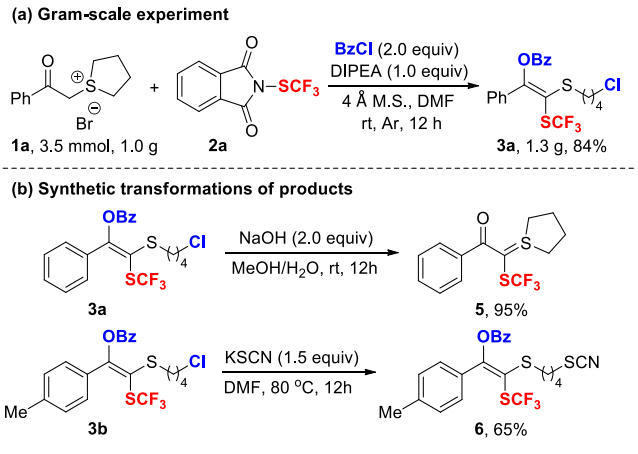


Figure 3. Gram-scale experiment and synthetic applications.

Moreover, the synthetic utility of the current process is illustrated via chemical transformation of trifluoromethylthiolated alkenes. Treatment of adduct **3a** with sodium hydroxide in the mixture solvent of methanol and water (3:1) gave disubstituted ylide **5** with excellent yield (Figure 3b, upper). Notably, the nucleophilic substitution at carbon could be readily achieved by the reaction of trifluoromethylthiolated compound **3b** with potassium thiocyanate to generate thiocyanate **6** in 65% yield (Figure 3b, bottom).

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To probe the mechanism of the current protocol, additional experiments were conducted to examine the possibility of the pathway (Figure 4). First, when sulfonium salt **1a** was treated

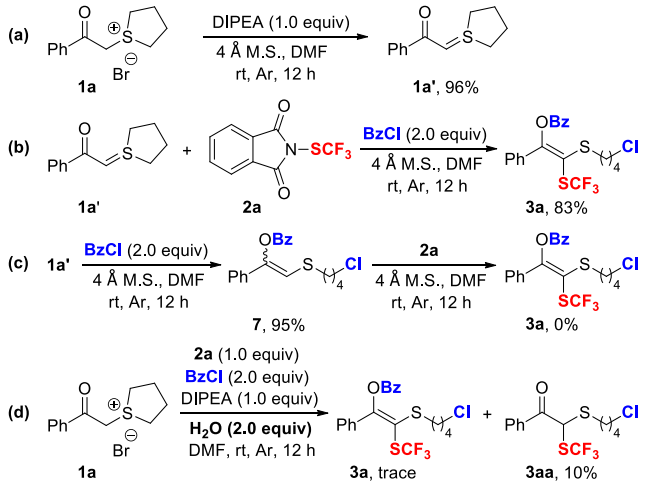

Figure 4. Mechanistic studies.

under the standard reaction conditions in the absence of SCF_3 reagent **2a**, the reaction proceeded efficiently to afford the stabilized carbonyl sulfur ylide **1a′** in 96% yield (Figure 4a). Subsequently, the corresponding product **3a** was detected with 83% yield when **1a′** was used as a substrate instead of **1a** subjected to the chlorotrifluoromethylthiolation reaction under the same reaction conditions (Figure 4b). In addition, when **1a′** was treated with only BzCl in the absence of electrophilic SCF_3 reagent **2a**, an *O*,*S*-functionalized alkene **7** was observed in 95% yield. It then was employed as a substrate under the above reaction conditions; no desired tetrasubstituted trifluoromethylthiolated alkene **3a** was detected, and the alkene **7** was recovered almost quantitatively (Figure 4c). These results clearly indicate that the intermediate **7** is not involved in the reaction process. Finally, the reaction was carried out in the absence of 4 Å MS; when 2.0 equiv of water was used as an additive, only a trace amount of the expected enolate **3a** was detected and accompanied by the formation of the ketone **3aa** as a side product (Figure 4d). This data might reveal that molecular sieves play an important role in accelerating the enolization of ketone moiety and preventing undesirable hydrolysis of the ester group on the product.

In light of the above experimental results, a plausible reaction pathway for the chlorotrifluoromethylthiolation of sulfur ylides was depicted (Figure 5). The sulfonium salt **1a** would easily suffer deprotonation under basic conditions to generate sulfur ylide species **1a′**. Subsequently, the SCF_3-substituted sulfonium vinyl benzoate **A** or vinyl phosphinate **B** could be formed in the presence of BzCl or $PhPOCl_2$, proceeding through electrophilic trifluoromethylthiolation and alcoholysis processes. The thienyl ring of the species **A** underwent a nucleophilic attack by a chloride anion concerning the ring-opening of cyclic thioether to deliver the SCF_3-substituted chloro benzoate **3a**. Similarly, nucleophilic attack by chloride anions on the thienyl ring and the enol carbon of the species **B** would result in the formation of dichlorinated product **4a**.

In conclusion, we have illustrated an unprecedented example of catalyst-free chlorotrifluoromethylthiolation of sulfur ylides.

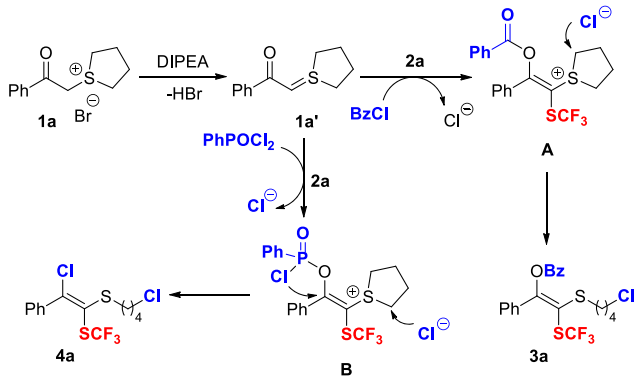

Figure 5. Plausible mechanism.

In contrast to alkenes and alkynes, sulfur ylides displayed unique reactivity toward carbon nucleophilic and electrophilic properties. This protocol provides a general, expeditious, and mild pathway to access tetrasubstituted trifluoromethylthiolated alkenes and shows good functional-group compatibility. The employment of the current transformation as a late-stage derivatization tool has been developed via the successful chlorotrifluoromethylthiolation of biologically relevant compounds. Further efforts are devoted to develop new applications of sulfur ylide derived fluoroalkylation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02747.

Experimental procedures, screening of reaction conditions, characterization data, and copies of ^{1}H, ^{13}C, ^{19}F NMR (PDF)

Accession Codes

CCDC 2021741 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.

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■ REFERENCES

(1) For selected books, see: (a) Hiyama, T. *Organo-fluorine Compounds, Chemistry and Applications*; Springer-Verlag: Berlin, 2000. (b) Kirsch, P. *Modern Fluoroorganic Chemistry, Synthesis Reactivity, Applications*; Wiley-VCH: Weinheim, 2004. (c) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; Wiley-Blackwell: Chichester, 2009.

(2) For select reviews:. Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881−1886. (b) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308−319. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320−330. (d) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470−477. (e) Fujiwara, T.; O'Hagan, D. *J. Fluorine Chem.* **2014**, *167*, 16−29. (f) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016**, *116*, 422−518. (g) Moschner, J.; Stulberg, V.; Fernandes, R.; Huhmann, S.; Leppkes, J.; Koksch, B. *Chem. Rev.* **2019**, *119*, 10718−10801.

(3) (a) Leo, A.; Hansch, C.; Elkins, D. *Chem. Rev.* **1971**, *71*, 525−616. (b) Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lien, E. J. *J. Med. Chem.* **1973**, *16*, 1207−1216. (c) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195.

(4) For reviews:. Xu, X.-H.; Matsuzaki, K.; Shibata, N. *Chem. Rev.* **2015**, *115*, 731−764. (b) Shao, X.; Xu, C.; Lu, L.; Shen, Q. *Acc. Chem. Res.* **2015**, *48*, 1227−1236. (c) Barata-Vallejo, S.; Bonesi, S.; Postigo, A. *Org. Biomol. Chem.* **2016**, *14*, 7150−7182. (d) Shibata, N. *Bull. Chem. Soc. Jpn.* **2016**, *89*, 1307−1320. (e) Hardy, M. A.; Chachignon, H.; Cahard, D. *Asian J. Org. Chem.* **2019**, *8*, 591−609. (f) Ghiazza, C.; Billard, T.; Tlili, A. *Chem. - Eur. J.* **2019**, *25*, 6482−6495.

(5) (a) Xiang, H.; Yang, C. *Org. Lett.* **2014**, *16*, 5686−5689. (b) Honeker, R.; Garza-Sanchez, R. A.; Hopkinson, M. N.; Glorius, F. *Chem. - Eur. J.* **2016**, *22*, 4395−4399.

(6) (a) Zhang, C.-P.; Vicic, D. A. *Chem. - Asian J.* **2012**, *7*, 1756−1758. (b) Shao, X.; Wang, X.; Yang, T.; Lu, L.; Shen, Q. *Angew. Chem., Int. Ed.* **2013**, *52*, 3457−3460. (c) Pluta, R.; Nikolaienko, P.; Rueping, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 1650−1653. (d) Arimori, S.; Takada, M.; Shibata, N. *Dalton Trans.* **2015**, *44*, 19456−19459. (e) Glenadel, Q.; Alazet, S.; Tlili, A.; Billard, T. *Chem. - Eur. J.* **2015**, *21*, 14694−14698.

(7) (a) Rueping, M.; Tolstoluzhsky, N.; Nikolaienko, P. *Chem. - Eur. J.* **2013**, *19*, 14043−14046. (b) Huang, Y.; Ding, J.; Wu, C.; Zheng, H.; Weng, Z. *J. Org. Chem.* **2015**, *80*, 2912−2917. (c) Zhang, M.; Weng, Z. *Org. Lett.* **2019**, *21*, 5838−5842.

(8) (a) Pan, S.; Huang, Y.; Qing, F.-L. *Chem. - Asian J.* **2016**, *11*, 2854−2858. (b) Li, M.; Petersen, J. L.; Hoover, J. M. *Org. Lett.* **2017**, *19*, 638−641. (c) Cheng, Z.-F.; Tao, T.-T.; Feng, Y.-S.; Tang, W.-K.; Xu, J.; Dai, J.-J.; Xu, H.-J. *J. Org. Chem.* **2018**, *83*, 499−504.

(9) (a) Zhao, Q.; Poisson, T.; Pannecoucke, X.; Bouillon, J.-P.; Besset, T. *Org. Lett.* **2017**, *19*, 5106−5109. (b) Zhao, Q.; Chen, M.-Y.; Poisson, T.; Pannecoucke, X.; Bouillon, J.-P.; Besset, T. *Eur. J. Org. Chem.* **2018**, *2018*, 6167−6175.

(10) (a) Yang, Y.-D.; Azuma, A.; Tokunaga, E.; Yamasaki, M.; Shiro, M.; Shibata, N. *J. Am. Chem. Soc.* **2013**, *135*, 8782−8785. (b) Bu, M.-J.; Lu, G.-P.; Cai, C. *Org. Chem. Front.* **2017**, *4*, 266−270.

(11) (a) Chen, M.-T.; Tang, X.-Y.; Shi, M. *Org. Chem. Front.* **2017**, *4*, 86−90. (b) Chen, M.; Wei, Y.; Shi, M. *Org. Chem. Front.* **2018**, *5*, 2030−2034.

(12) (a) Ferry, A.; Billard, T.; Langlois, B. R.; Bacqué, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 8551−8555. (b) Xiao, Q.; Sheng, J.; Chen, Z.; Wu, J. *Chem. Commun.* **2013**, *49*, 8647−8649. (c) Qiu, Y.-F.; Zhu, X.-Y.; Li, Y.-X.; He, Y.-T.; Yang, F.; Wang, J.; Hua, H.-L.; Zheng, L.; Wang, L.-C.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2015**, *17*, 3694−3697. (d) Tlili, A.; Alazet, S.; Glenadel, Q.; Billard, T. *Chem. - Eur. J.* **2016**, *22*, 10230−10234. (e) Wu, J.-J.; Xu, J.; Zhao, X. *Chem. - Eur. J.* **2016**, *22*, 15265−15269. (f) Wu, W.; Dai, W.; Ji, X.; Cao, S. *Org. Lett.* **2016**, *18*, 2918−2921. (g) Wei, F.; Zhou, T.; Ma, Y.; Tung, C.-H.; Xu, Z. *Org. Lett.* **2017**, *19*, 2098−2101. (h) Li, H.; Liu, S.; Huang, Y.; Xu, X.-H.; Qing, F.-L. *Chem. Commun.* **2017**, *53*, 10136−10139. (i) Jiang, L.; Ding, T.; Yi, W.-B.; Zeng, X.; Zhang, W. *Org. Lett.* **2018**, *20*, 2236−2240. (j) Li, H.; Cheng, Z.; Tung, C.-H.; Xu, Z. *ACS Catal.* **2018**, *8*, 8237−8243. (k) Qiu, Y.-F.; Niu, Y.-J.; Wei, X.; Cao, B.-Q.; Wang, X.-C.; Quan, Z.-J. *J. Org. Chem.* **2019**, *84*, 4165−4178.

(13) (a) McGarrigle, E. M.; Myers, E. L.; Illa, O.; Shaw, M. A.; Riches, S. L.; Aggarwal, V. K. *Chem. Rev.* **2007**, *107*, 5841−5883. (b) Sun, X.-L.; Tang, Y. *Acc. Chem. Res.* **2008**, *41*, 937−948. (c) Lu, L.-Q.; Chen, J.-R.; Xiao, W.-J. *Acc. Chem. Res.* **2012**, *45*, 1278−1293. (d) Burtoloso, A. C. B.; Dias, R. M. P.; Leonarczyk, I. A. *Eur. J. Org. Chem.* **2013**, *2013*, 5005−5016. (e) Lu, L.-Q.; Li, T.-R.; Wang, Q.; Xiao, W.-J. *Chem. Soc. Rev.* **2017**, *46*, 4135−4149. (f) Wu, X.; Sun, S.; Yu, J.-T.; Cheng, J. *Synlett* **2019**, *30*, 21−29.

(14) (a) Fu, M.; Chen, L.; Jiang, Y.; Jiang, Z.-X.; Yang, Z. *Org. Lett.* **2016**, *18*, 348−351. (b) Jia, Y.; Qin, H.; Wang, N.; Jiang, Z.-X.; Yang, Z. *J. Org. Chem.* **2018**, *83*, 2808−2817.

(15) (a) Haas, A.; Möller, G. *Chem. Ber.* **1996**, *129*, 1383−1388. (b) Munavalli, S.; Rohrbaugh, D. K.; Rossman, D. I.; Berg, F. J.; Wagner, G. W.; Durst, H. D. *Synth. Commun.* **2000**, *30*, 2847−2854. (c) Xu, C.; Ma, B.; Shen, Q. *Angew. Chem., Int. Ed.* **2014**, *53*, 9316−9320.

(16) Vilsmeier, A.; Haack, A. *Ber. Dtsch. Chem. Ges. B* **1927**, *60*, 119−122.