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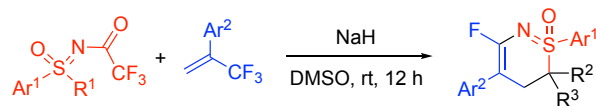
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A One-Pot Domino Reaction Providing Fluorinated 5,6-Dihydro-1,2-thiazine 1-Oxides from Sulfoximines and 1-Trifluoromethyl Styrenes

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• high sequential selectivity • broad substrate scope • up to 96% yield

ABSTRACT: *N*-Trifluoroacetylated (*N*-TFA) sulfoximines react with 1-trifluoromethyl styrenes in a one-pot domino reaction to give fluorinated 5,6-dihydro-1,2-thiazine 1-oxides in good to high yields. The process involves three sequential reaction steps which can be characterized as: First, nucleophilic allylic substitution (S_N2'), second, hydrolysis, and third, intramolecular nucleophilic vinylic substitution (S_NV). The products can further be modified by defluorination. The molecular structure of a resulting product was confirmed by X-ray crystallographic analysis.

Sulfoximines play an important role in medicinal and crop protection chemistry.¹ With the goal to expand their structural diversity, we started a program on incorporating sulfoximidoyl groups into heterocyclic scaffolds resulting in the introduction of a range of new protocols for the preparation of heterocycles such as benzothiazines,² benzo[*c*]isothiazole 2-oxides,³ and several other related compounds.⁴

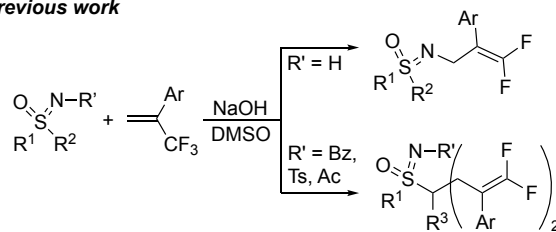
Recently, the construction of fluorine-containing heterocycles by double defluorinations of 1-trifluoroalkenes has become a popular research topic.^{5–8} To achieve such transformations, base-mediated,⁵ transition metal-catalyzed,⁶ and photocatalytic reactions⁷ as well as combinations thereof have been developed.⁸ Very prominent roles play base-mediated heterocycle formations, which typically involve sequential S_N2' - and S_NV -type reactions.

In previous work, we observed site-selective couplings of sulfoximines with 1-trifluoromethyl styrenes to yield either *N*- or *C*-gem-difluoroalkenylated products depending on the *N*-substituent of the starting material.⁹ With simple *NH*-derivatives, *N*-difluoroalkenylations occurred, whereas *N*-protected compounds gave (double) *C*-functionalized products (Scheme 1, top). While screening more substrate combinations, we observed an unusual behavior of sulfoximines with *N*-trifluoroacetyl (*N*-TFA) substituents. Those compounds led to significant amounts of unexpected heterocycles (Scheme 1, bottom), which resulted from a three-step reaction sequence involving an initial nucleophilic allylic substitution (S_N2') at the carbon site, followed by a hydrolytic cleavage of the *N*-trifluoroacetyl group, and a termination by an intramolecular nucleophilic vinylic substitution (S_NV) via the sulfoximine nitrogen.¹⁰ The optimization of the process and the preparative opportunities are described here.

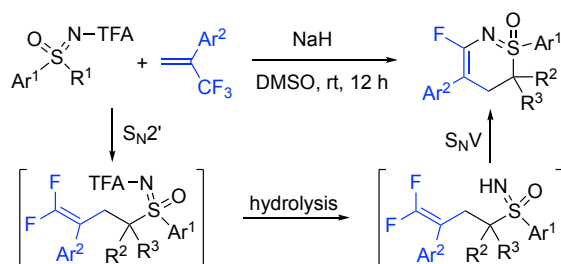
For the initial investigation of the process, *N*-TFA *S*-isopropyl *S*-phenyl sulfoximine (**1a**) was selected a sulfur component. Reacting it with 1-trifluoromethyl styrene (**2a**) under the previously optimized conditions⁹ with NaOH as base in DMSO gave 5,6-dihydro-1,2-thiazine 1-oxide **7aa** in 38% yield (as determined by ¹H NMR spectroscopy with mesitylene as internal standard; Table 1, entry 1). In addition,

Scheme 1. Defluorination of Trifluoromethyl Styrenes with Sulfoximines

Previous work



This work



N-gem-difluoroalkenylated product **4** was formed suggesting that a hydrolytic cleavage of the TFA group had occurred, and that in a subsequent step the free NH (or its anionic form) had reacted with **2a** following an S_N2' pathway. This *N*-TFA cleavage was confirmed by reacting **1a** in the absence of **2a**, which gave *NH*-sulfoximine **3** in 99% yield (Table 1, entry 2). Using 2 equiv of NaH instead of NaOH the reaction of **1a** and **2a** led to a completely different result. Now, a high crude yield (92%) was obtained, and three products (**5aa**, **6** and **7aa**) were identified in yields of 10%, 62%, and 20% yield, respectively (Table 1, entry 3). Increasing the amount of NaH from 2 equiv to 3 equiv shifted the reaction outcome to an exclusive formation of **7aa**, which was now detected in a yield of 93%. Isolating the product by column chromatography gave **7aa** in 92% yield (Table 1, entry 4). Exchanging DMSO by DMF as solvent gave **7aa** predominantly as well, but the yield was only 73% (Table 1,

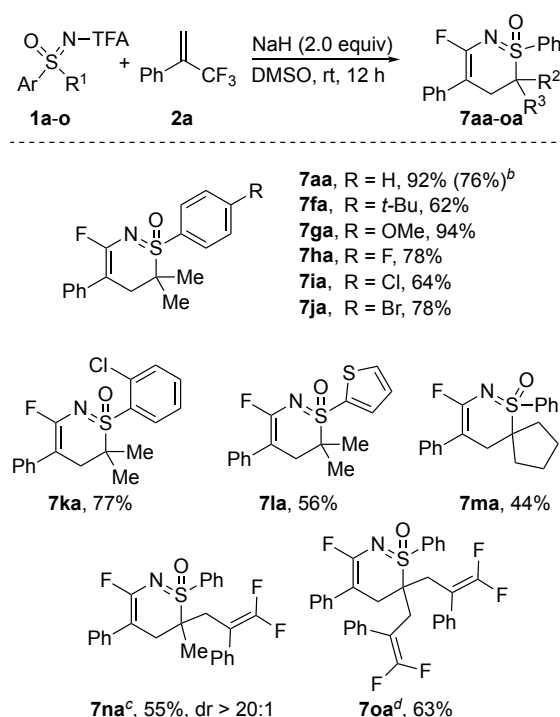
Table 1. Optimization of the Reaction Conditions^a

entry	R	base	solvent	3 (%) ^b	4 (%) ^b	5 (%) ^b	6 (%) ^b	7aa (%) ^b
1	TFA (1a)	NaOH	DMSO	0	33	0	0	38
2 ^c	TFA (1a)	NaH	DMSO	99	0	0	0	0
3	TFA (1a)	NaH	DMSO	0	0	10 (5aa)	62	20
4 ^d	TFA (1a)	NaH	DMSO	0	0	0	0	93 (92)
5	TFA (1a)	NaH	DMF	0	0	4	4	73
6	TFA (1a)	NaH	THF	95	0	0	0	2
7	Acetyl (1b)	NaH	DMSO	0	0	38 (5ba)	0	0
8	Pivaloyl (1c)	NaH	DMSO	0	0	35 (5ca)	0	0
9	Tosyl (1d)	NaH	DMSO	0	0	65 (5da)	0	0
10	Boc (1e)	NaH	DMSO	0	0	41 (5ea)	0	0
11	H (3)	NaH	DMSO	0	57	0	0	0

^aReaction conditions: Use of 0.2 mmol of **1**, 0.2 mmol of **2a**, and 0.4 mmol of base. ^bYields as determined by ¹H NMR analysis of the crude mixture using mesitylene as internal standard. The yield of **7aa** isolated by column chromatography was shown in parentheses (entry 3). ^cWithout **2a**. ^dUse of 0.6 mmol of NaH.

entry 5). In THF, 95% of hydrolysis product **3** was detected (Table 1, entry 6). As assumed from our previous results,⁹ sulfoximines with *N*-groups other than TFA behaved very differently, and with the combination of 2 equiv of NaH in DMSO only the corresponding *C-gem*-difluoroalkenylated products **5** were detected (Table 1, entries 7-10). In each case, the *N*-X fragment remained intact, and the yields varied between 38% for **5ba** with an *N*-acetyl group and 65% for *N*-tosylat **5da**. In none of these reactions, was the formation of **7aa** observed. For NH-sulfoximine **3**, the reaction afforded *N*-difluoroalkenylated product **4** in 57% yield. Thus under these conditions, **4** was not deprotonated affording a regioisomer of **7aa** (Table 1, entry 11). Thus, the optimized reaction conditions for the preparation of 5,6-dihydro-1,2-thiazine 1-oxide **7aa** involved stirring of equimolar amounts of **1a** and **2a** with 3 equiv of NaH in DMSO at room temperature for 12 h.

Under the optimized conditions, the substrate scope was evaluated. First, a series of *N*-TFA sulfoximines were reacted with 1-trifluoromethyl styrene (**2a**). The results are shown in Scheme 2. *S*-Aryl-*S*-isopropyl sulfoximines with various substituents on the *S*-aryl reacted smoothly leading to products **7fa-ka** in yields between 62% and 94%. Neither electronic nor steric effects induced by the substituents appeared to significantly impact the reaction outcome. Applying *S*-isopropyl-*S*-2-thienyl sulfoximine (**1l**) in the reaction with **2a** gave **7la** in 56% yield. From *S*-cyclopentyl-*S*-phenyl derivative **1m**, 5,6-dihydro-1,2-thiazine 1-oxide **7ma** was obtained in 44% yield. Until this stage, only *S*-aryl sulfoximines with branched *S*-alkyl groups (i. e. *S*-isopropyl and *S*-cyclopentyl) groups had been tested. Using analogous substrates with linear *S*-alkyl substituents altered the

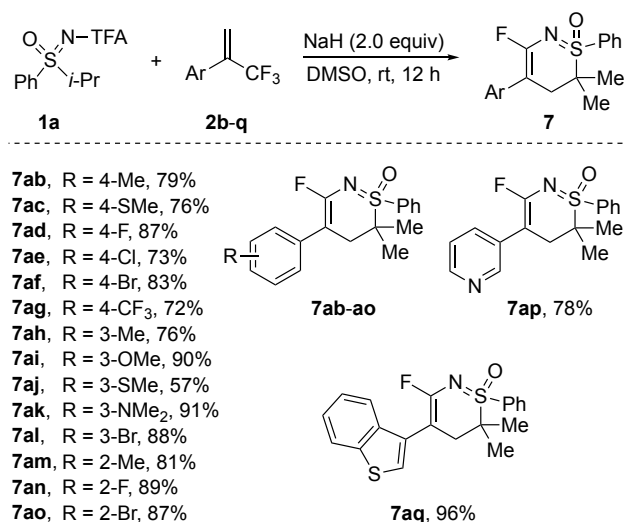
Scheme 2. Substrate Scope: *N*-TFA Sulfoximines^a

^aReaction conditions: **1** (0.2 mmol), **2a** (0.2 mmol), NaH (0.6 mmol). The yields refer to the amounts of products isolated by column chromatography. ^bIn parentheses, the yield of **7aa** for a reaction on a 1 mmol scale. ^cUse of 0.4 mmol of **2a** and 0.8 mmol of NaH. ^dUse of 0.6 mmol of **2a** and 1.0 mmol of NaH.

reaction outcome. Thus, in reactions with *S*-ethyl and *S*-methyl derivatives **1n** and **1o** (in combination with an excess of both **2a** and NaH) double and even triple alkenylations occurred and subsequent cyclizations led to products **7na** and **7oa** in 55% and 63% yield, respectively. Interestingly, the formation of **7na** was highly stereoselective providing the product with > 20:1 dr. Performing the reaction between **1a** and **2a** on a 1 mmol scale, gave **7aa** in 76% yield.

Next, the behavior of other 1-aryl-substituted 1-trifluoromethylalkenes **2** was studied. *S*-Isopropyl-*S*-phenyl sulfoximine (**1a**) was chosen as the reaction partner, and the results are summarized in Scheme 3. Various substituents including alkyl, halo and heteroatomic groups were tolerated on the 1-aryl substituent of **2**. The yields of the corresponding products **7ab-ao** ranged from 57% (for 3-MeS-containing **7aj**) to 91% (for 3-Me₂N-substituted **7ak**). Positional variations (*para*/*meta*/*ortho*) had no apparent impact as illustrated by the reactions of 1-tolyl-substituted 1-trifluoromethylalkenes leading to **7ab** (*para*-Me), **7ah** (*meta*-Me), and **7am** (*ortho*-Me) in yields of 79%, 76%, and 81%, respectively. Also 1-hetaryl-substituted 1-trifluoromethylalkenes **2p** and **2q** reacted well with **1a** affording the corresponding 3-pyridyl- and 3-benzothienyl-containing products **7ap** and **7aq** in 78% and 96% yield, respectively.

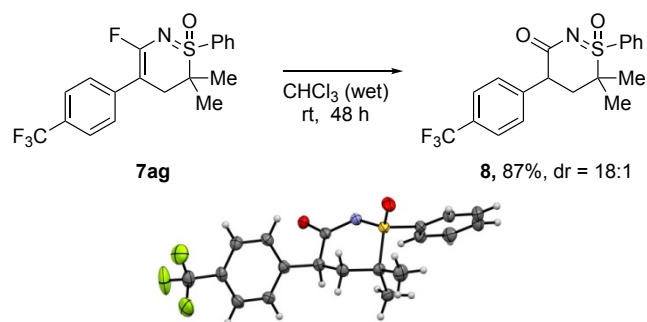
Scheme 3. Substrate Scope: 1-Trifluoromethylalkenes^a



^aReaction conditions: **1a** (0.2 mmol), **2** (0.2 mmol), NaH (0.6 mmol). The yields refer to the amounts of products isolated by column chromatography.

An interesting structural modification was observed when product **7ag** was kept in (wet) chloroform for 48 h (Scheme 4). Under those conditions, hydrolysis occurred leading to 5,6-dihydro-1λ⁶,2-thiazin-3(4*H*)-one 1-oxide **8** (in 87% yield with a dr of 18:1 after isolation by filtration). X-ray diffraction analysis revealed the solid-state structure of **8** and confirmed its assumed three-dimensional arrangement with a clear heterocyclic "flatland" deviation.¹¹

Scheme 4. Hydrolysis of **7ag** and the X-ray Crystal Structure of **8**



In summary, by reacting *N*-TFA-substituted sulfoximines with 1-aryl-substituted 1-trifluoromethylalkenes we obtained mono-fluorinated 5,6-dihydro-1,2-thiazine 1-oxides in good to high yields. The product formations proceeded in one pot by a reaction sequence involving two substitutions and an intermediate hydrolysis (S_N2', hydrolysis, S_NV). The substrate range is broad and the substitution tolerance high. Product hydrolysis led to new defluorinated heterocycle, which was characterized by X-ray crystallographic analysis.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information Statement

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/.....>

Experimental procedures, characterization data, NMR spectra for new compounds, crystal data (PDF)

FAIR data, including the primary NMR FID files, for compounds **1a-o**, **2a-q**, **3**, **4**, **5aa-ea**, **6**, **7aa**, **7fa-oa**, **7ab-aq** and **8**.

Accession Codes

CCDC-2240873 (for **8**) 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 interests.

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REFERENCES

- (1) For overviews on the use of sulfoximines in medicinal and crop protection chemistry, see: (a) Lücking, U. New Opportunities for the Utilization of the Sulfoximine Group in Medicinal Chemistry from the Drug Designer's Perspective. *Chem. Eur. J.* **2022**, *28*, e202201993. (b) Tilby, M. J.; Willis, M. C. How do we address neglected sulfur pharmacophores in drug discovery? *Expert Opin. Drug Discov.* **2021**, *16*, 1227-1231. (c) Mäder, P.; Kattner, L. Sulfoximines as Rising Stars in Modern Drug Discovery? Current Status and Perspective on an Emerging Functional Group in Medicinal Chemistry. *J. Med. Chem.* **2020**, *63*, 14243-14275. (d) Han, Y.; Xing, K.; Zhang, J.; Tong, T.; Shi, Y.; Cao, H.; Yu, H.; Zhang, Y.; Liu, D.; Zhao, L. Application of Sulfoximines in Medicinal Chemistry from 2013 to 2020. *Eur. J. Med. Chem.* **2020**, *209*, 112885. (e) Zheng, W.; Chen, X.; Chen, F.; He, Z.; Zeng, Q. Syntheses and Transformations of Sulfoximines. *Chem. Rec.* **2021**, *21*, 396-416. (f) Synthesis and Transformations of NH-Sulfoximines. Andresini, M.; Tota, A.; Degennaro, L.; Bull, J. A.; Luisi, R. *Chem. Eur. J.* **2021**, *27*, 17293-17321. (g) Lücking, U. Neglected Sulfur(VI) Pharmacophores in Drug Discovery: Exploration of Novel Chemical Space by the Interplay of Drug Design and Method Development. *Org. Chem. Front.* **2019**, *6*, 1319-1324. (h) Frings, M.; Bolm, C.; Blum, A.; Gnam, C. Sulfoximines from a Medicinal Chemist's Perspective: Physicochemical and in vitro Parameters Relevant for Drug Discovery. *Eur. J. Med. Chem.* **2017**, *126*, 225-245. (i) Bull, J. A.; Degennaro, L.; Luisi, R. Straightforward Strategies for the Preparation of NH-Sulfoximines: A Serendipitous Story. *Synlett*, **2017**, *28*, 2525-2538. (j) Bacci, L.; Convertini, S.; Rossaro, B. A Review of Sulfoxaflor, a Derivative of Biological Acting Substances as a Class of Insecticides with a Broad Range of Action against Many Insect Pests. *J. Entomol. Acarol. Res.* **2018**, *50*, 7836. (k) Arndt, K. E.; Bland, D. C.; Irvine, N. M.; Powers, S. L.; Martin, T. P.; McConnell, J. R.; Podhorez, D. E.; Renga, J. M.; Ross, R.; Roth, G. A.; Scherzer, B. D.; Toyzan, T. W. Development of a Scalable Process for the Crop Protection Agent Isoclast. *Org. Process Res. Dev.* **2015**, *19*, 454-462.
- (2) (a) Dong, W.; Wang, L.; Parthasarathy, K.; Pan, F.; Bolm, C. Rhodium-Catalyzed Oxidative Annulation of Sulfoximines and Alkynes as An Approach to 1,2-Benzothiazines. *Angew. Chem., Int. Ed.* **2013**, *52*, 11573-11576. (b) Cheng, Y.; Bolm, C. Regioselective Syntheses of 1,2-Benzothiazines by Rhodium-Catalyzed Annulation Reactions. *Angew. Chem., Int. Ed.* **2015**, *54*, 12349-12352. (c) Wang, L.; Priebbenow, D. L.; Chen, X. Y.; Pan, F.-F.; Bolm, C. The Synthesis of Chiral Benzothiazine and Thiazinoquinoline Derivatives. *Eur. J. Org. Chem.* **2015**, 3338-3343. (d) Wen, J.; Tiwari, D. P.; Bolm, C. 1,2-Benzothiazines from Sulfoximines and Allyl Methyl Carbonate by Rhodium-Catalyzed Cross-Coupling and Oxidative Cyclization. *Org. Lett.* **2017**, *19*, 1706-1709.
- (3) (a) Lamers, P.; Buglioni, L.; Koschmieder, S.; Chatain, N.; Bolm, C. Benzo[c]isothiazole 2-oxides: Three-Dimensional Heterocycles with Cross-Coupling and Functionalization Potential. *Adv. Synth. Catal.* **2016**, *358*, 3649-3653. (b) Lamers, P.; Bolm, C. Tetrahydrobenzo[c]thieno[2,1-e]isothiazole 4-oxides: Three-Dimensional Heterocycles as Cross-Coupling Building Blocks. *Org. Lett.* **2018**, *20*, 116-118.
- (4) (a) Wang, H.; Frings, M.; Bolm, C. Halocyclizations of Unsaturated Sulfoximines. *Org. Lett.* **2016**, *18*, 2431-2434. (b) Bohmann, R. A.; Unoh, Y.; Miura, M.; Bolm, C. 1,2-Thiazines: One-Pot Syntheses Utilizing Mono and Diaza Analogs of Sulfones. *Chem. Eur. J.* **2016**, *22*, 6783-6786. (c) Cheng, Y.; Dong, W.; Wang, H.; Bolm, C. Rhodium-Catalyzed Ortho-Amidations in the Preparation of Thiadiazine 1-oxides. *Chem. - Eur. J.* **2016**, *22*, 10821-10824. (d) Cheng, Y.; Dong, W.; Parthasarathy, K.; Bolm, C. Rhodium(III)-Catalyzed Ortho Halogenations of N-Acylsulfoximines and Synthetic Applications toward Functionalized Sulfoximine Derivatives. *Org. Lett.* **2017**, *19*, 726-729. (e) Wen, J.; Cheng, H.; Raabe, G.; Bolm, C. Rhodium-Catalyzed [4 + 3] Annulations of Sulfoximines with α,β -Unsaturated Ketones Leading to 1,2-Benzothiazepine 1-oxides. *Org. Lett.* **2017**, *19*, 6020-6023. (f) Zhang, D.; Wang, H.; Cheng, H.; Hernández, J. G.; Bolm, C. An Iodine-Mediated Hofmann-Löffler-Freytag Reaction of Sulfoximines Leading to Dihydroisothiazole Oxides. *Adv. Synth. Catal.* **2017**, *359*, 4274-4277. (g) Yu, H.; Li, Z.; Bolm, C. Three-Dimensional Heterocycles by Iron-Catalyzed Ring-Closing Sulfoxide Imidation. *Angew. Chem., Int. Ed.* **2018**, *57*, 12053-12056. (h) Shi, P.; Tu, Y.; Wang, C.; Kong, D.; Ma, D.; Bolm, C. Synthesis of Benzothiadiazine-1-oxides by Rhodium-Catalyzed C-H Amidation/Cyclization. *Org. Lett.* **2020**, *22*, 8842-8845. (i) Hommelsheim, R.; Núñez-Ponce, H. M.; Truong, K.-N.; Rissanen, K.; Bolm, C. 2-Sulfoximidoyl Acetic Acids from Multicomponent Petasis Reactions and their Use as Building Blocks in Syntheses of Sulfoximine Benzodiazepine Analogues. *Org. Lett.* **2021**, *23*, 3415-3420. (j) Ma, D.; Kong, D.; Wang, C.; Truong, K. N.; Rissanen, K.; Bolm, C. Three-Dimensional Heterocycles by 5-exo-dig Cyclizations of S-Methyl-N-ynonyl-sulfoximines. *Org. Lett.* **2021**, *23*, 8287-8290.
- (5) (a) Fujita, T.; Takazawa, M.; Sugiyama, K.; Suzuki, N.; Ichikawa, J. Domino C-F Bond Activation of the CF₃ Group: Synthesis of Fluorinated Dibenzo [a,c][7] annulenes from 2-(Trifluoromethyl)-1-alkenes and 2,2'-Diceriobiaryls. *Org. Lett.* **2017**, *19*, 588-591. (b) Fuchibe, K.; Takahashi, M.; Ichikawa, J. Substitution of two fluorine atoms in a trifluoromethyl group: regioselective synthesis of 3-fluoropyrazoles. *Angew. Chem. Int. Ed.* **2012**, *51*, 12059-12062. (c) Zeng, H.; Li, H.-Y.; Jiang, H.-F.; Zhu, C.-L. Steric-switched defluorofunctionalization selectivity: controlled synthesis of monofluoroalkene-masked medium-sized heterocyclic lactams and lactones. *Sci. China Chem.* **2022**, *65*, 554-562. (d) Yang, J.; Mao, A.; Yue, Z.; Zhu, W.; Luo, X.; Zhu, C.; Xiao, Y.; Zhang, J. A simple base-mediated synthesis of diverse functionalized ring-fluorinated 4H-pyrans via double direct C-F substitutions. *Chem. Commun.* **2015**, *51*, 8326-8329.
- (6) (a) Ichitsuka, T.; Fujita, T.; Arita, T.; Ichikawa, J. Double C-F Bond Activation through β -Fluorine Elimination: Nickel-Mediated [3+2] Cycloaddition of 2-Trifluoromethyl-1-alkenes with Alkynes. *Angew. Chem. Int. Ed.* **2014**, *53*, 7564-7568.
- (7) (a) Chen, H.; Xiao, T.; Li, L.; Anand, D.; He, Y.; Zhou, L. Synthesis of Fluorinated Benzo[a]quinolizidines via Visible Light-Induced Tandem Substitution of Two Fluorine Atoms in a CF₃ Group. *Adv. Synth. Catal.* **2017**, *359*, 3642-3647. (b) Li, L.; Xiao, T.; Chen, H.; Zhou, L. Visible-Light-Mediated Two-Fold Unsymmetrical C(sp³)-H Functionalization and Double C-F Substitution. *Chem. Eur. J.* **2017**, *23*, 2249-2254.

- (8) Sun, Z.; Zhou, L. Synthesis of 5-Fluoro-dihydroindolizines from Pyrrole-2-acetic Acids and Trifluoromethyl Alkenes via Dual C-F Bond Cleavage in a CF₃ Group. *J. Org. Chem.* **2022**, *87*, 4801-4812. (b) Chen, H.; He, Y.; Zhou, L. A photocatalytic decarboxylative/defluorinative [4+3] annulation of *o*-hydroxyphenylacetic acids and trifluoromethyl alkenes: synthesis of fluorinated dihydrobenzoxepines. *Org. Chem. Front.* **2018**, *5*, 3240-3244.
- (9) Wang, X.; Wang, C.; Bolm, C. Superbase-Mediated gem-Difluoroalkenylations of Sulfoximines. *Org. Lett.* **2022**, *24*, 7461-7464.
- (10) For important work related to those substitution reactions, see: (a) Hansen, T.M Vermeeren, P.; de Jong, L.; Bickelhaupt, F. M.; Hamlin, T. A. S_N2 versus S_N2' Competition. *J. Org. Chem.* **2022**, *87*, 8892-8901. (b) Bernasconi, C. F.; Rappoport, Z. Recent Advances in Our Mechanistic Understanding of S_NV Reactions. *Acc. Chem. Res.* **2009**, *42*, 993-1003. (c) Fernández, I.; Bickelhaupt, F. M.; Uggerund, E. Reactivity in Nucleophilic Vinylic Substitution S_NVπ versus S_NVσ Mechanistic Dichotomy, *J. Org. Chem.* **2013**, *78*, 8574-8584.
- (11) (a) Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* **2009**, *52*, 6752-6756. (b) Lovering, F. Escape from Flatland 2: complexity and promiscuity. *Med-ChemComm* **2013**, *4*, 515-519.