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Applications of 2-Chloro-3,3,3-trifluoroprop-1-ene (HCFO-1233xf): A Rapid Entry to Various β-Substituted-trifluoromethyl-ethenes

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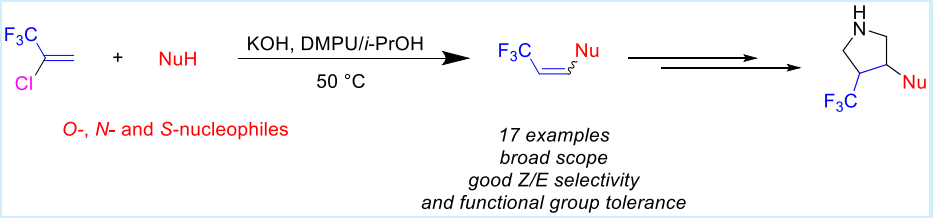

ABSTRACT: An efficient base-promoted reaction of *O*-, *N*-, and *S*-nucleophiles with 2-chloro-3,3,3-trifluoprop-1-ene (HCFO-1233xf) is described providing access to various β-substituted-trifluoromethyl-ethenes under mild reaction conditions. Mechanistic investigations shed some light on the regio-, chemo-, and stereoselectivities observed. The olefins prepared represent attractive intermediates in chemical discovery: some applications include their conversion to pyrrolidines via a [3 + 2] dipolar cycloaddition reaction. These weakly basic amines represent novel synthons that could be readily elaborated through a range of reactions.

The trifluoromethyl group ($-CF_3$) is a privileged substituent in pharmaceutical and agrochemical research.[1] Its introduction into organic molecules can significantly alter their properties such as pK_a,[2] lipophilicity,[3] and conformation,[4] thereby influencing their hydrolytic and metabolic stability.[5] In this context, CF_3-containing reagents that are inexpensive, sustainable, and available in bulk quantities are of high interest in the life sciences.[1] The present approach complements existing trifluoromethylation reaction strategies. However while significant advances have been made in recent years, they remain prohibitive in terms of cost and atom efficiency for large-scale application.[6] In recent years, some low-cost trifluoromethylated alkenes, such as 2,3,3,3-tetra-fluoropropene (HFO-1234yf) or 2-chloro-3,3,3-trifluoroprop-1-ene (**1**, HCFO-1233xf), have emerged as important compounds or intermediates in the refrigerant industry due to their low global warming potential (GWP) and zero or near-zero ozone depletion potential.[7] Despite their large-scale production, only a few publications have reported their conversion into trifluoromethylated fine chemicals, including reports of oxidative Heck couplings,[8] cross-coupling reactions,[9] C−F activation reactions,[10] and reactions with nucleophiles.[11] The latter have been reported as base-promoted reactions that require either a large excess of olefin or high temperatures. In addition, only a few nucleophiles have been reported as suitable to access β-substituted-trifluoromethyl ethenes. While the chemistry of the related 2-bromo-3,3,3-trifluoroprop-1-ene is more advanced (coupling reactions,[12] 1,2-additions,[13] cycloadditions,[14] reaction with nucleophiles[15]) owing to its ease of handling (liquid at room temperature), the scope of its application to generate β-substituted-trifluoromethyl-ethenes remains limited. We were therefore interested to expand the utility of the inexpensive reagent 2-chloro-3,3,3-trifluoroprop-1-ene **1**, as it could prove an attractive building block for applications on a technical scale.

Herein, we report the reaction of *O*-, *S*-, and *N*-nucleophiles on olefin **1** to afford the corresponding β-trifluoromethyl enol ethers and vinyl sulfides as well as nitrogen substituted β-trifluoromethyl-ethenes under mild reaction conditions. Furthermore, [3 + 2] dipolar cycloadditions between these electron-deficient olefins and *N*-benzyl azomethine ylide allow the synthesis of β-trifluoromethyl-substituted pyrrolidines. These advances highlight the potential of this readily available fluorinated feedstock in novel and cost-effective fine-chemicals synthesis.

The optimization of the base-promoted reaction of nucleophiles with 2-chloro-3,3,3-trifluoroprop-1-ene **1** was investigated using sulfonamide **2a** (Table 1). Employing an excess of base and nucleophile **2a** (2 equiv) in *N*,*N*′-dimethylpropyleneurea (DMPU) gave the bis-substituted product **5a** in 86% yield (entry 1). The use of an excess of **1** (2 equiv) and sodium hydride or potassium *tert*-butoxide as base gave mainly the monosubstituted product **4a**, which was found to be an intermediate for the formation of **5a** (entries 2−3). The addition of *tert*-butyl alcohol as a cosolvent increased the

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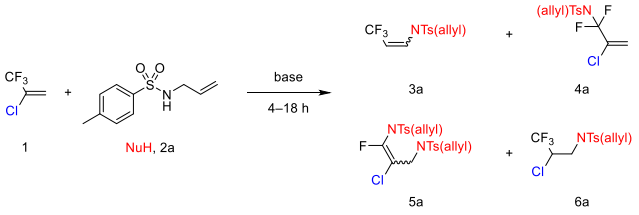
Table 1. Optimization with Sulfonamide 2a and Olefin 1



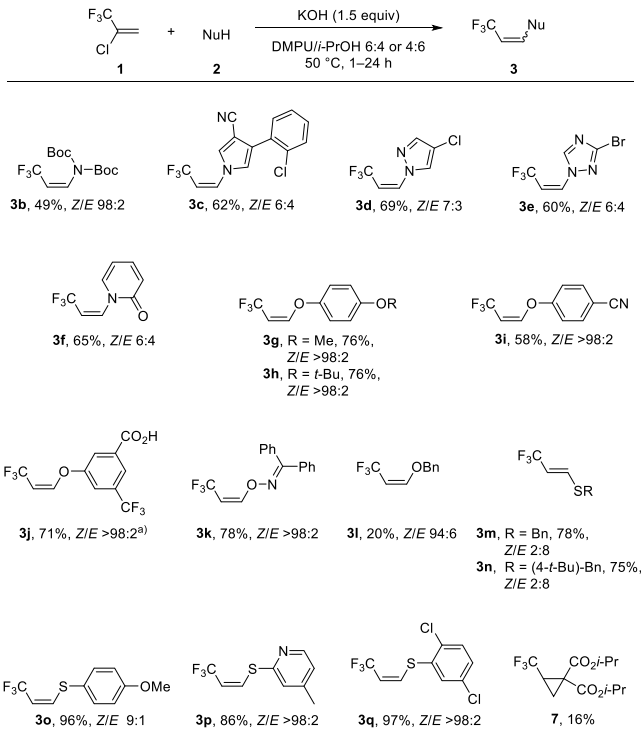
		^{19}F NMR yield (%)[b]			
entry	base (equiv), solvent, temp[a]	3a[c]	4a	5a[d]	6a
1	NaH (2.2), DMPU, rt	13	–	86	–
2	NaH (1.2), DMPU, rt	2	50	23	–
3	*t*-BuOK (1.2), DMPU, rt	6	45	21	2
4	*t*-BuOK (1.2), DMPU/*t*-BuOH 6:4, rt	48	9	5	14
5	KOH (1.2), DMPU/*t*-BuOH 6:4, rt	48	8	4	13
6	KOH (1.2), DMPU/*t*-BuOH 6:4, 50 °C	55	7	3	12
7	KOH (1.2), DMPU/EtOH 6:4, 50 °C	69	2	–	15
8	KOH (1.2), DMPU/*i*-PrOH 6:4, 50 °C	73	–	–	9
9	KOH (1.2), NMP/*i*-PrOH 6:4, 50 °C	60	–	–	16
10	KOH (1.2), DMF/*i*- PrOH 6:4, 50 °C	69	–	–	10
11	KOH (1.2), DMSO/*i*-PrOH 6:4, 50 °C	64	3	–	9
12	KOH (1.2), DMPU/*i*-PrOH 4:6, 50 °C	72	–	–	7
13	KOH (1.5), DMPU/*i*-PrOH 6:4, 50 °C	73[e]	–	–	7
14	KOH (2.0), DMPU/*i*-PrOH 6:4, 50 °C	71	–	–	6

[a]For reactions at room temperature, **1** was added at −30 °C followed by a slow temperature ramp. [b]^{19}F NMR yields were calculated with 1,4-bis(trifluoromethyl)benzene as an internal standard. [c]*Z*/*E* ratio in all reactions ≥97:3. [d]Compounds **5a** were obtained as a mixture of *E* and *Z* isomers. [e]Isolated yield (75% yield by ^{19}F NMR) and *Z*/*E* ratio of 97:3.

formation of **3a**, but also increased the amount of addition product **6a** (entries 4−5). At a higher reaction temperature (50 °C) and using isopropyl alcohol as a cosolvent, the desired product **3a** was obtained in 73% yield (entry 8). Replacing DMPU by other polar aprotic solvents such as *N*-methyl-2-pyrrolidone (NMP), DMF, or DMSO gave **3a** in yields of 60−69% (entries 9−11). Solvents such as THF, dioxane, and acetonitrile, as well as alternative bases, such as NaOH, Cs_2CO_3, K_3PO_4, DBU, and Triton B, did not increase the yield of **3a** (see Supporting Information). Increasing the amount of isopropyl alcohol and potassium hydroxide had only a minor impact on the reaction outcome (entries 12−14).

The scope and limitations of the optimized procedure was assessed over a broad range of *N*-, *O*-, and *S*-nucleophiles with olefin **1** (Scheme 1). Di-*tert*-butyl-iminodicarboxylate **2b** was successfully converted in high (*Z*)-selectivity to *β*-trifluoromethyl-ethene **3b** in 49% yield. *N*-Vinyl hetereoaromatic nitrogen compounds **3c**−**3f** were obtained in yields of 60−69%, albeit with lower *Z*/*E* ratios. Noteworthy, in the cases of triazole **2e** and pyridinone **2f**, the reaction proceeded with good chemoselectivity and only the regioisomers **3e** and **3f** were obtained. Phenols **2g**−**2j** and oxime **2k** gave enol ethers **3g**−**3k** in good yields (58−78%) with excellent *Z*/*E* selectivities (>98:2). Benzyl enol ether **3l** was isolated in poor yield, which may be a result of incomplete deprotonation of the benzyl alcohol **2l**; replacing the base with potassium *tert*-butoxide did not increase the yield of **3l**. Reactions with benzyl thiols **2m** and **2n** gave (*E*)-vinyl sulfides **3m** and **3n** as main products, in yields of 78% and 75%, whereas reactions with aromatic thiols **2o**, **2p**, and **2q** resulted in the formation of (*Z*)-isomers **3o**, **3p**, and **3q** in yields of 86−97%. Notably, a good *S*- *vs* *N*- chemoselectivity

Scheme 1. Substrate Scope for the Base-Promoted Reaction with a Range of Nucleophiles



[a]2.5 equiv of KOH used.

was obtained with thiopyridine **2p**. The reaction with diisopropyl malonate gave the corresponding cyclopropyl derivative **7** in 16% yield, comparable to a previous result using 2-bromo-3,3,3-trifluoropropene.[16]

To gain a deeper understanding of the origin of selectivity in these transformations, we undertook a series of preliminary mechanistic investigations (Scheme 2). In each reaction shown in Scheme 1, 3,3,3-trifluoroprop-1-yne **8** was detected in small amounts by ^{19}F NMR, implicating it as a possible intermediate in the formation of the olefinic products. Previous experimental studies on nucleophilic additions to trifluoromethylpropyne derivatives exhibited a strong preference for (*Z*)-olefin products (*anti*-addition).[17] This is consistent with *ab initio* molecular orbital studies showing preferential *trans* bending of acetylene in the transition state for nucleophilic attack.[18] This *trans* bending forms the vinylic anion with the lone pair *anti* to the nucleophile. Owing to the high rotation barrier in simple alkyl or aryl substituted vinylic anions, protonation leads to an overall *anti* addition.[19] Indeed, the reaction of various nucleophiles (**2a**, **2g**, **2m**, and **2o**) with alkyne **8** gave the *β*-trifluoromethyl substituted alkenes (**3a**, **3g**, **3m**, and **3o**) with excellent (*Z*)-selectivities (Scheme 2a). These results are consistent with alkyne **8** being a key intermediate leading for many nucleophiles to the formation of (*Z*)-alkenes as the major product (Scheme 1). However, the (*E*)-selectivity observed with benzyl thiols **2m** and **2n** suggests that this particular reaction proceeds either partially or exclusively through another pathway, or that *E*/*Z* isomerization is particularly favored in **3m** and **3n**. A possible *E*/*Z* isomerization pathway leading to (*E*)-**3** could result from a nucleophilic vinylic substitution (S_NV)[20] with a second nucleophile **2** on olefin (*Z*)-**3**. To support such a mechanism, vinyl sulfide **3m** was treated with thiol **2n** under standard conditions (Scheme 2b). However, only a small amount of

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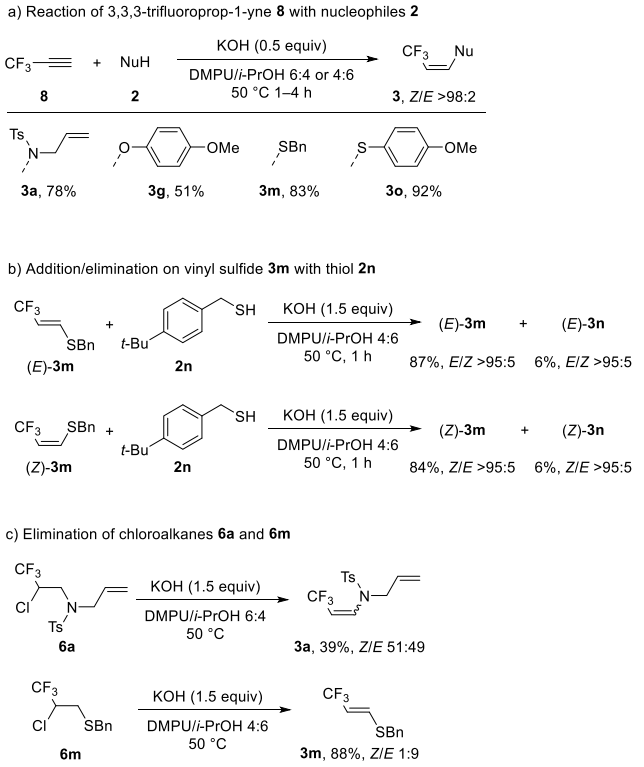
Scheme 2. Mechanistic Studies



nucleophile exchange and no olefin isomerization was observed for (*E*)- and (*Z*)-**3m**, thus disfavoring this pathway for the formation of (*E*)-**3m**. The same result was found with enol ether (*Z*)-**3g** and phenol **2h** (see Supporting Information). A longer reaction time for vinyl sulfide **3m** with thiol **2n** yielded small amounts of the mixed dithioacetal without olefin isomerization. These results reflect fast protonation of the intermediate anion thus hampering the stepwise S_NV mechanism. Jiang et al. described a "Michael-type addition" mechanism for the nucleophilic additions on 2-bromo-3,3,3-trifluoroprop-1-ene to afford a bromo-alkane intermediate that eliminates HBr and gives the observed (*Z*)-trifluoromethyl products.[15c] To assess the viability of such a chloroalkane intermediate in our examples, we conducted the reaction of **1** with thiol nucleophile **2m** using a substoichiometric amount of potassium hydroxide (0.1 equiv) at 0 °C, which yielded the chloroalkane addition product **6m** in 41% yield. Notably, compound **6m** was shown to subsequently convert into **3m** with a reproducible *Z*/*E* ratio of 1:9 under basic conditions, implicating **6** as a potential intermediate in the course of the reaction (Scheme 2c). In contrast, the same reaction with **6a** gave **3a** as a 1:1 *Z*/*E* mixture. The higher (*Z*)-selectivity for **3a** compared to the vinyl sulfide **3m** fragment has been described previously and ascribed to some key orbital interactions.[17d,e] However, the 1:1 *Z*/*E* mixture observed in **3a** derived from **6a** is inconsistent with the high (*Z*)-selectivity observed in the reaction of **1** with **2a**, discrediting **6a** as an intermediate in the formation of **3a** under the reaction conditions shown in Scheme 1.

Based on the above results, we propose the following mechanism depicted in Figure 1. Product **4** could originate from intermediate **A**, itself formed via an S_N2'-type reaction (Path A) favored in polar nonprotic solvents that enhance the nucleophilicity of **2** and disfavor protonation of the intermediate carbanion **E**.[21] Similarly, product **5** could be formed by an S_N2'-

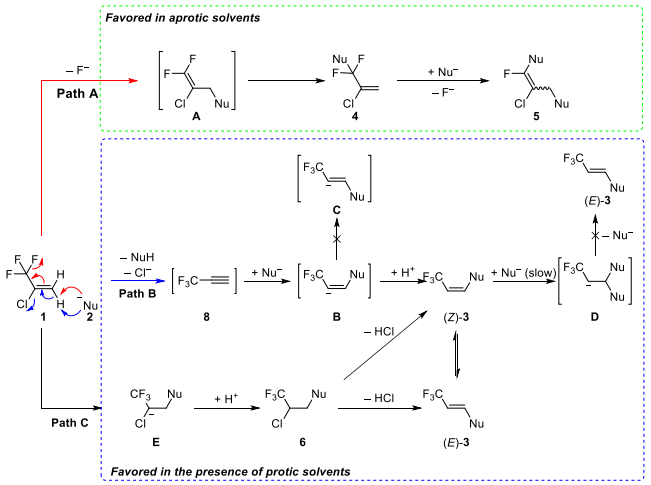


Figure 1. Proposed reaction mechanism.

type reaction on compound **4**. However, the presence of a protic solvent has two major impacts on the reaction: it lowers the nucleophilicity of **2** and provides a proton. In a first pathway (Path B), the deprotonated form of **2** or potassium hydroxide triggers the elimination of HCl to form alkyne **8**. Nucleophilic addition of the anionic form of **2** forms the intermediate vinylic anion **B**. Since the olefin rotation barrier of this anion is expected to be high, protonation should lead to a stereospecific *anti* addition. Indeed, no (*E*)-isomers were detected from the reaction of trifluoroalkyne **8** with various nucleophiles (Scheme 2a). A second nucleophilic addition of the anion of **2** to form intermediate **D** was found to be slow and no isomerization was observed (Scheme 2b). The second pathway starts with a Michael-type addition of the anion of **2** on olefin **1**, which provides chloroalkane **6** after protonation of **E** (Path C). A base-promoted subsequent elimination of hydrochloric acid yields trifluoromethyl-substituted alkene **3**. The stereoselectivity of this HCl elimination was shown to be substrate dependent (Scheme 2c). The predominance of each pathway is observed to be highly dependent on the nucleophile, as shown by the *E*/*Z* ratios in Scheme 1. For reactive and weakly basic nucleophiles such as **2m** and **2n**, the chloroalkane **6** formation pathway is preferred, yielding an increased amount of (*E*)-**3**. For the less reactive and/or more basic nucleophiles like **2a**, the alkyne **8** formation pathway is preferred, forming higher amounts of (*Z*)-**3**.

The pyrrolidine moiety can be found in many bioactive compounds.[22] A well-known strategy to access *β*-substituted pyrrolidines is a [3 + 2] cycloaddition between electron-deficient alkenes and azomethine ylides.[23] Reaction of olefins of type **I** with the nonstabilized azomethine ylide precursor **9** gave access to *N*-benzylated pyrrolidines **10** in yields of 64−98% (Scheme 3).[2b,24] In agrochemical research, the basicity of amines is an important parameter to optimize bioactive compounds.[25] With pK_A(H) values for the amino groups of pyrrolidines **10** ranging from 3.4 to 6.2, significantly lower than those for 1-benzylpyrrolidine (9.3) and 1-benzyl-3-(trifluoromethyl)pyrrolidine (7.2),[2b] a broad scope of physicochemical properties are accessible from these simple synthons.

Pyrrolidinium salts **11** were obtained from pyrrolidines **10** in gram-scale in very good yield (84−98%) applying two different debenzylation methods: hydrogenation with palladium on charcoal or reaction with 1-chloroethyl chloroformate followed by treatment with methanol (Scheme 4).[26] The oxime derivative

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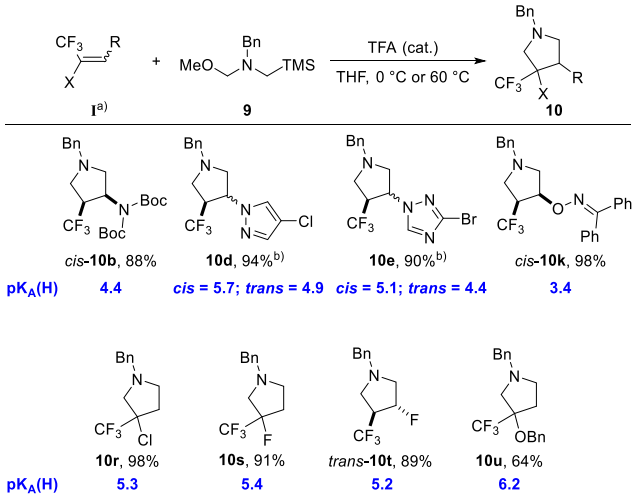
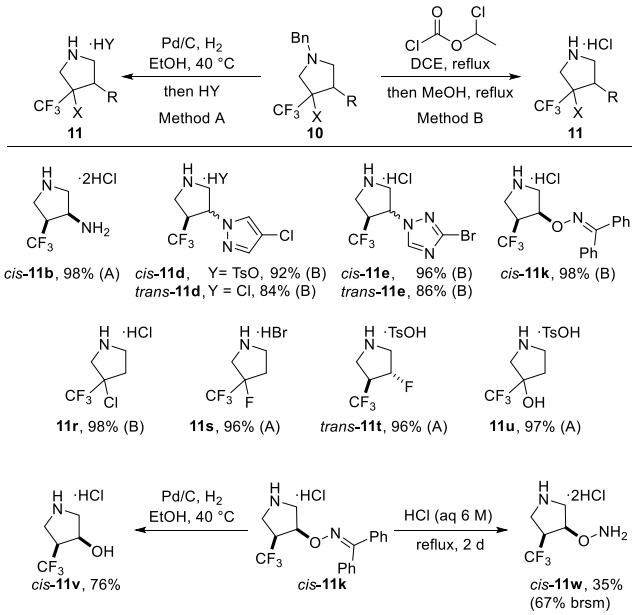
Scheme 3. Synthesis of 1-Benzylpyrrolidines



[a]I include olefins **1**, **3**, HFO-1234yf, HFO-1234ze, and 1-(trifluoromethyl)vinyloxymethylbenzene. [b]*cis*- and *trans*-isomers were separated by column chromatography.

Scheme 4. Synthesis of Pyrrolidinium Salts[a]

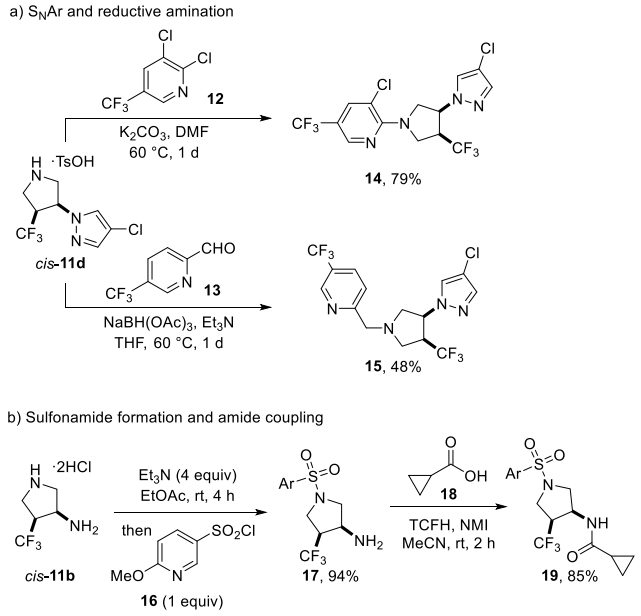


[a]HY are HCl, HBr, or TsOH

cis-**11k** gave access to alcohol *cis*-**11v** by hydrogenation or hydroxylamine *cis*-**11w** by hydrolysis in 76% and 35% yield (67% based on recovered starting material), respectively.

Finally, some preliminary experiments were performed to study the reactivity of pyrrolidine derivatives **11** (Scheme 5). Nucleophilic aromatic substitution (S_NAr) and reductive amination of pyrrolidine *cis*-**11d** with the pyridine derivatives **12** and **13** gave the corresponding tertiary amines **14** and **15** in 79% and 48% yield, respectively. Reaction of sulfonyl chloride **16** with a small excess of pyrrolidine *cis*-**11b** gave exclusively sulfonamide **17** in excellent yield. The amide coupling with cyclopropanecarboxylic acid **18** could successfully be achieved using a combination of *N*,*N*,*N*′,*N*′-tetramethylchloroformamidinium hexafluorophosphate (TCFH) and *N*-methylimidazole (NMI).[27]

Scheme 5. Derivatization Examples of Some Pyrrolidines



We have developed a base promoted addition of various *O*-, *S*-, and *N*-nucleophiles on 2-chloro-3,3,3-trifluoroprop-1-ene **1**. The resulting *β*-trifluoromethyl enol ethers and vinyl sulfides as well as nitrogen substituted *β*-trifluoromethyl-ethenes were obtained under mild reaction conditions in good yields and generally high chemo-, regio-, and stereoselectivities. The *β*-substituted-trifluoromethyl ethenes were further transformed into a variety of pyrrolidines which are of high interest in chemical discovery. Together, these results highlight the potential of the low cost and readily available trifluoromethylethene **1** as a building block in the fine-chemical industry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00931.

Optimization reactions for the reaction of sulfonamide **2a** and olefin **1**, experiments for the mechanistic studies, synthetic procedures, characterization data, and NMR spectra of all compounds (PDF)

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Notes

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