Use of trifluoroacetaldehyde N-tfsylhydrazone as a trifluorodiazoothane surrogate and its synthetic applications

Xinyu Zhang¹, Zhaohong Liu¹, Xiangyu Yang¹, Yuanqing Dong¹, Matteo Virelli², Giuseppe Zanoni², Edward A. Anderson³ & Xihe Bi¹,⁴

Trifluoroacetaldehyde (CF₃CHN₂), a highly reactive fluoroalkylating reagent, offers a useful means to introduce trifluoromethyl groups into organic molecules. At present, CF₃CHN₂ can only be generated by oxidation of trifluoroethylamine hydrochloride under acidic conditions; due to its toxic and explosive nature, its safe generation and use remains a prominent concern, hampering wider synthetic exploitation. Here we report the development of trifluoroacetaldehyde N-tfsylhydrazone (TFHZ-Tfs) as a CF₃CHN₂ surrogate, which is capable of generating CF₃CHN₂ in situ under basic conditions. The reaction conditions employed in this chemistry enabled a difluoroalkenylation of X–H bonds (X = N, O, S, Se), affording a wide range of heteroatom-substituted gem-difluoroalkenes, along with Doyle-Kirmse rearrangements and trifluoromethylcyclopropanation reactions, with superior outcomes to approaches using pre-formed CF₃CHN₂. Given the importance of generally applicable fluorination methodologies, the use of TFHZ-Tfs thus creates opportunities across organic and medicinal chemistry, by enabling the wider exploration of the reactivity of trifluoroacetaldehyde.
Trifluorodiazocane (CF₃CH₄N₂, also known as trifluoromethyl diazomethane) is a highly reactive trifluoromethylating agent employed in transformations such as cycloadditions, X-H insertions, coupling reactions, and homologations (Fig. 1a). CF₃CH₄N₂ is generated by the oxidation of trifluoroethylamine hydrochloride (CF₃CH₂NH₂·HCl) under acidic conditions, but being a toxic and explosive gas, handling of CF₃CH₄N₂ at room temperature is extremely hazardous if a significant buildup occurs. Although first described in 1943, only in the last decade have improvements to this method been made, involving slow addition of aqueous NaN₃ to trifluoroethylamine to avoid an accumulation of large amounts of CF₃CH₂N₂. More recently, other operational improvements have been developed, such as the small-scale preparation of CF₃CH₂N₂ in solution, the recycling of gaseous CF₃CH₄N₂, and the use of continuous-flow chemistry. Nevertheless, the use of specifically designed equipment and/or operating conditions remains a general limitation, and reagents that are easily handled but capable of slowly generating CF₃CH₂N₂ in situ under mild conditions (ideally complementing current oxidative/acidic methods) are of high appeal.

We targeted the use of trifluorinated N-sulfonylethylaziridines as a trifluorodiazocane surrogate. As a class of stable precursors to diazo compounds, sulfonylethylaziridines are widely used in synthesis, but, however, trifluoroacetalddehyde-derived sulfonylethylaziridines have not been explored as surrogates for CF₃CH₂N₂. Gem-Difluoroalkenes are important motifs in the design of mechanism-based enzyme inhibitors, and as bioisosters of the carbonyl group, and are typically prepared by Wittig or Julia–Kocienski-type reactions, or by cross-coupling. These methods are mostly effective only for the synthesis of C-substituted gem-difluoroalkenes, while the synthesis of their heteroatom-substituted counterparts is comparatively rare and suffers from narrow substrate scope, or requires strong bases or toxic reagents.

We report here the development of trifluoroacetalddehyde N-tfislyhydrazone (TFHZ-Tfs) as a bench-stable CF₃CH₂N₂ precursor, which decomposes in a controlled manner under basic conditions to release CF₃CH₂N₂ into the reaction system (Fig. 1b); this strategy circumvents the need for slow addition or manual handling of CF₃CH₂N₂, thus minimizing exposure and reducing the potential explosion risk. Importantly, this base-mediated approach also led to the discovery of novel reactivity of CF₃CH₂N₂: we describe its use in the difluoroalkenylation of X-H (X = N, O, S, Se) bonds, overcoming limitations in previous routes to these motifs, and also in Doyle–Kirmse and cyclopropanation reactions, which display excellent stereoselectivity and yields, and collectively demonstrate the potential utility of TFHZ-Tfs as a trifluorodiazocane surrogate.

### Results

#### Synthesis of TFHZ-Tfs

TFHZ-Tfs could be easily accessed by condensation of the α-trifluoromethylbenzenesulfonyl hydrazone with trifluoroacetalddehyde monohydrate under acidic conditions. The reaction proved readily scalable, TFHZ-Tfs could be prepared in high yield (91%) on 85 mmol scale as a bench-stable crystalline solid, and in a cost-effective manner, which is attractive for synthetic applications. In addition, TFHZ-Tfs could be stored at ambient temperature for at least 5 months without degradation (as characterized by ¹H NMR spectroscopy).

#### Investigation of reaction conditions

An exploration of the reactivity of TFHZ-Tfs began in the difluoroalkenylation of X-H bonds. p-Methylthiophenol was identified as a suitable nucleophile for this study, and to our delight we found that in the presence of aqueous KOH, sodium dodecylbenzenesulfonate (SDBS, 30 mol%), and the iron porphyrin catalyst FeTPPCl₂ (5 mol%) in dichloromethane at 40 °C, TFHZ-Tfs delivered the difluoroalkenylation product 2 in 51% yield, along with 9% of the trifluoroethyl thioether 2′ (Fig. 2, Entry 1). Iron porphyrin complexes have been applied as highly efficient catalysts in carbene-transfer reactions. Screening of other iron porphyrin complexes led to the discovery of the more robust Fe[P2] catalyst, which at just 1 mol% loading afforded 2 in 80% isolated yield, while suppressing the formation of side product 2′ (Entries 2 and 3). Under the same conditions, TFHZ-Ns and TFHZ-Tfs gave 2 in significantly lower yield (Entries 4 and 5). Additional optimization of this S–H gem-difluoroalkenylation led to refinement of the reactions parameters (Entry 3, TFHZ-Tfs (2.0 equiv), 5 mL KOH aq. (20 wt%), and SDBS (30 mol%) in the presence of 1 mol% of Fe[P2] in DCM at 40 °C under air; see Supplementary Table 1 for details).

#### Scope of thiol gem-difluoroalkenylation

Having established the decomposition profile of TFHZ-Tfs, and conditions for thiol difluoroalkenylation, the scope of this insertion was explored. Under the optimized conditions of Fig. 2 Entry 3 (Method A), a broad tolerance of arene substituents was observed (Fig. 3, with thiophenols bearing both electron-donating and electron-withdrawing substituents giving the corresponding difluoroalkenes in good to excellent yields (2–19). Notably, reaction efficiency was not compromised by the positioning of the aryl substituent (ortho, meta, or para), and indeed sterically hindered mono- or bis-ortho-substituted substrates afforded the difluoroalkenes in high yields (20–21). Thienyl, furyl, and 2-naphthalene thiol were also excellent substrates, leading to heteroaryl- and naphthyl sulfides 22–24. We were pleased to find that benzene-selenol performed equally well, affording the selenodifluoroalkene 25 in 66% yield. The difluoroalkenylation structure was unambiguously confirmed by single crystal X-ray diffraction analysis of sultone 9, which was prepared by oxidation of 9 with m-CPBA (see Supplementary Table 7 for X-ray crystallographic data).

#### Scope of amine gem-difluoroalkenylation

We next questioned whether other heteroatoms could also serve as suitable nucleophilic coupling partners, and turned our attention to amine difluoroalkenylation. After extensive screening of reaction parameters, a copper catalyst system was identified that efficiently mediated this transformation, consisting of Cu(OOTf)₂ (20 mol%) and LiOr-Bu (4.0 equiv) in DCE:toluene (3:1) under argon at 40 °C (Fig. 3, Method B, see Supplementary Table 2 for details of reaction optimization). The reaction scope encompassed a variety of aniline derivatives, with ring substituents including halides, nitriles, ketones, esters, and antraquinones, delivering the gem-difluoroanilines in moderate to good yields (26–35). In some cases, incomplete conversions were observed, but the residual amine substrate could be recovered. In addition to primary amines, benzophenone imine proved a viable substrate: product 36 was obtained in 51% yield, suggesting this method could be applied to the N-difluoroalkenylation of other nitrogen-based nucleophiles. Secondary amines did not prove suitable, as shown by the low yield of compound 37.

#### Scope of alcohol gem-difluoroalkenylation

Further expansion of the scope of the methodology was achieved through modification of the copper catalyst to enable the synthesis of difluoroethyl ethers from alcohols (Fig. 3, Method C, for details of optimization see Supplementary Table 3). A wide selection of benzyl-, alkyl-, and heteroaryl-substituted alcohols afforded gem-difluoroethyl ethers in good to excellent yields; for benzyl...
a  Oxidation of trifluoroethylamine hydrochloride under acidic conditions (*the sole method*)

\[
\text{CF}_3\text{CH}_2\text{NH}_2\cdot\text{HCl} \xrightarrow{\text{Oxidants and acidic conditions}} \text{F}_3\text{C}=\text{N}_2
\]

Trifluoroethylamine hydrochloride  Discovery  Method development  Toxic & explosive  

\[
\begin{align*}
\text{R} & \quad \text{X} \\
\text{CF}_3 & \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{CF}_3 & \quad \text{Fe} \\
\end{align*}
\]

b  Decomposition of trifluoroacetaldehyde \(N\)-tfsylhydrazone (TFHZ-Tfs) under basic conditions (*this work*)

\[
\text{F}_3\text{C} \xrightarrow{\text{Basic conditions}} \text{R-XH} \xrightarrow{\text{Fe or Cu cat.}} \text{[Fe]}
\]

Trifluoroacetaldehyde \(N\)-tfsylhydrazone (TFHZ-Tfs)  New surrogate  In situ generation  Operationally simple  Basic reaction conditions  Diffluoroalkenylation  

**Fig. 1** Generation and transformations of trifluorodiazoethane, and synthesis of TFHZ-Tfs. a  Synthesis and applications of trifluoromethyldiazomethane (\(\text{CF}_3\text{CHN}_2\)) in organic synthesis. \(\text{CF}_3\text{CHN}_2\) is a highly reactive trifluoroalkylation reagent, but its simplex synthesis method, inherent toxicity and explosiveness limit its widespread application. Because of its hazardous nature, manifold methods have been developed for the safer use of \(\text{CF}_3\text{CHN}_2\) such as slow addition of oxidants, small-scale preparation of \(\text{CF}_3\text{CHN}_2\) solution, recycling of gaseous \(\text{CF}_3\text{CHN}_2\) and continuous-flow chemistry. b  Method for the generation of \(\text{CF}_3\text{CHN}_2\) from trifluoroacetaldehyde \(N\)-tfsylhydrazone under basic condition and gem-difluoroalkenylation of \(X-H\)

**Fig. 2** Optimization of the iron-catalyzed gem-difluoroalkenylation of \(p\)-methylthiophenol with trifluoromethyl sulfonylehydrazones. Reaction conditions: thiophenol (0.3 mmol), sulfonylehydrazone (0.6 mmol), Fe porphyrin catalyst, SDBS (sodium dodecylbenzenesulfonate) (0.09 mmol), DCM (1.0 mL), and KOH solution (5.0 mL, 20% wt %), 40 °C, 18 h, under air. a  Yields determined by \(^1\text{H} \)NMR spectroscopic analysis with \(\text{CH}_2\text{Br}_2\) as an internal standard. b  Reaction carried out under Ar atmosphere. c  Yield in parentheses is the isolated yield.
Fig. 3 Scope of gem-difluoroalkenylation of X-H (X = N, O, S, Se). Reaction conditions: Method A: thiophenol (0.3 mmol), TFHZ-Tfs (0.6 mmol), Fe[P2] (1 mol%), SDBS (30 mol%), KOH (aq.)/DCM (5:1), air, 40 °C, 18 h. Method B: amine (0.3 mmol), TFHZ-Tfs (0.6 mmol), Cu(OTf)2 (20 mol%), LiOBut (4 equiv), DCE: toluene (3:1), Ar, 40 °C, 24 h. Method C: TFHZ-Tfs (1.0 mmol), NaH (4 equiv) and DCE (8.0 mL) were stirred at rt for 1 h under Ar, then CuBr (30 mol%), alcohol (0.5 mmol), and LiOH (4 equiv) were added and the mixture was stirred at 40 °C under Ar for 24 h. *Reaction performed for 30 h. †Number in parentheses is the yield based on recovered starting material (brsm). ‡The yield was determined by 1H NMR spectroscopic analysis with CH2Br2 as an internal standard.
alcohols, the position of substituents on the arene had little influence on the reaction outcome (38–47), and secondary and tertiary benzyl alcohols also afforded the corresponding products with respectable efficiency (48 and 49). Alkyl alcohols (such as phenethyl and phenylpropyl), and other functionalized alcohols (such as cinnamyl, propargyl, and 2-adamantyl), all proved reactive partners, affording products 50–56 in moderate to high yields. In contrast to aliphatic alcohols, phenols showed poor reactivity; for example, 4-biphenylyl gave the difluoroalkenylation product 57 in just 20% yield, which presumably reflects the poorer nucleophilicity of the phenol compared to the aliphatic substrate.

Scope of gem-difluoroalkenylation with bioactive molecules. To illustrate potential utility, the methodology was applied to the gem-difluoroalkenylation of selected natural products, drugs, and pharmaceutical intermediates. For instance, various terpene and steroid natural products (nerol, pregnenolone, ergosterol, cholesterol, and stigmasterol) were derivatized into the desired difluorovinyl ethers in good yields (58–63). Estradiol benzoate, a highly potent hormone therapy agent used to treat estrogen deficiency, could also be converted to the corresponding gem-difluoroalkenylation product 64 in 72% yield. Further, the synthesis of gem-difluoroalkenylation vitamin D3 65, (the parent being a potent drug for treatment of cutaneous tuberculosis and lupus erythematosus), was achieved in the presence of its potentially sensitive triene functionality, underlining the functional group tolerance of this methodology. It is notable that fluoroalkyl ethers represent the key structure of many insecticides and lubricants; the ready availability of such gem-difluorovinyl ethers may provide new opportunities for the design and construction of such molecules.

Gram-scale synthesis and further transformations. For multigram-scale applications, the Fe[P2] catalyst (which requires a multistep synthesis) could be conveniently replaced with the commercially available FeTPPCl (Fig. 4). Using this alternative catalyst with dichloromethane as solvent, gem-difluorovinyl sulfide 9 was obtained in a yield of 47%, which is comparable to that obtained with Fe[P2] (Method A, 50%). Interestingly, this product could be smoothly mono-defluorinated by treatment with CuCl and B2pin2 to give the (Z)-monofluorovinyl sulfide 66 in 67% yield; to our knowledge, no other routes to selectively access such monofluorinated alkenyl thioethers are known. Alternative functionalization also proved possible, such as substitution of both fluorines in 9 by reaction with excess p-methoxyphenol in the presence of NaH, affording the trisubstituted olefin 67 in 42% yield.

Mechanistic investigations. To gain insight into the reaction mechanism, a CF3CHN2 solution in dichloromethane was prepared according to previous reports (Fig. 5, Eq. 4)5, and then treated with 4-methylbenzenethiol under Method A, which led to 2 and 2′ in 48% and 3% yield respectively as detected by 1H NMR analysis of the crude reaction mixture. However, if neutral water was used instead of aqueous KOH, only 2′ was obtained (61%). These results suggest that base plays a crucial role in the gem-difluoroalkenylation reaction, in that it may either facilitate reaction of the heteroatomic nucleophile by deprotonation, and/or may promote a β-F elimination of a reaction intermediate. To confirm that the trifluoroethyl sulfide 2′ is indeed a side product rather than an intermediate, conversion of 2′ into 2 under Method A was attempted, but without success (Eq. 5). This may imply that the reaction mechanism involves direct fluoride ion elimination from a carbonoid-derived species, rather than elimination of HF from the trifluoroethyl group. The observation that (2,2,2-trifluoroethoxy)methylbenzene 68 was also not converted to 38 under Method C (Eq. 6) supports this hypothesis.

Proposed mechanism. Based on these experimental results, a plausible reaction mechanism is proposed in Fig. 6 in which trifluorodiazoethane is generated in situ from TFHZ-Tfs under the basic reaction conditions, and then reacts with the metal catalyst to form carbonoid intermediate A. The latter is trapped by the substrate (or deprotonated substrate) to form the oxonium ylide 84; Following deprotonation under the basic reaction conditions, the resultant intermediate C undergoes β-fluoride elimination to give the gem-difluoroalkenylation product, regenerating the metal catalyst.

Applications of TFHZ-Tfs in Doyle–Kirmse reaction. The high efficiency observed in the difluoroalkenylation encouraged us to...
test the potential of this reagent in other carbenoid transformations. The Doyle–Kirmse reaction of allyl/propargyl thioethers was first studied, where we were delighted to find that reaction of TFHZ-Tfs with allylic thioethers catalyzed by Fe(TTP)Cl delivered the desired CF₃-substituted homoallyl or alkenyl products in excellent yields (Fig. 7)⁴⁶,⁴⁷. This reaction offers a direct and powerful method for the construction of C(sp³)–S and C–C bonds by [2,3]-sigmatropic rearrangement of diazo-derived ylids⁴⁸,⁴⁹, and again the use of TFHZ-Tfs proved superior for the generation of trifluorodiazoethane compared to the oxidation
of trifluoroethylamine\textsuperscript{50}. The scope of this reaction was found to be quite broad, with aryl thioethers containing electron-donating and electron-withdrawing groups at different positions of aryl ring affording CF\textsubscript{3}-substituted homoallyl products (69–83) in good to excellent yields. Thioethers bearing a disubstituted aryl group also proved suitable, such as a 2,5-dimethyldi- stituent, which gave product 84 in 84% yield. Naphthyl and heteroaryl allyl thioethers also proceeded efficiently to give the corresponding products 85 and 86 (80% and 75%, respectively). Alkyl allyl thioethers, including benzyl, methyl, and bisallyl substituents, were also well-tolerated to produce the desired products (87–89) in good yields.

**Scope of Doyle–Kirmse reaction with allyl thioether.** The effect of substituents (R\textsubscript{1}, R\textsubscript{2}, and R\textsubscript{3}) on the allyl thioether unit was similarly evaluated, which revealed that the substituent at the 2'-position substituent on the allyl thioether unit (R\textsuperscript{1}) could be varied (methyl, phenyl, or halogen), giving products 90–93 with high efficiency. Equally, a range of 1,2-disubstituted allylic thioethers (R\textsuperscript{2} = Me/Ph, R\textsuperscript{3} = H/Me) were compatible, affording products (94–98) with high stereoselectivity (up to 10:1 dr, absolute configuration of major isomers was unambiguously confirmed by single crystal X-ray diffraction analysis of its derivatives, details see Supplementary Table 8). Most noteworthy among these variations is the rearrangement to generate a quaternary carbon center in homoollylic sulfide 96. Moreover, a cyclic olefin-substituted thioether afforded the S-to-C transposition product 99 in 77% yield, with high stereoselectivity (7:1 dr).

**Scope of Doyle–Kirmse reaction with propargyl thioether.** We next investigated the scope of the Doyle–Kirmse reaction using propargyl thioethers. Pleasingly, aryl, alkyl, fused aryl, and heteroaryl-functionalized propargyl thioethers all reacted smoothly with THFZ-Tfs to give the expected allene products in good to excellent yields (100–103). Internal alkyln thioethers exhibited outstanding reactivity, as demonstrated by reactions of methyl-, phenyl- and TMS-substituted propargyl thioethers, which gave products 104–106 in 72–75% yield.

**Applications of THFZ-Tfs in cyclopropanation.** Finally, the application of THFZ-Tfs as a diazo precursor in cyclopropanation was examined, with the aim of providing an alternative approach to medicinally-relevant trifluoromethylcyclopropanes\textsuperscript{2,31–33}. To our delight, various terminal olefins underwent smooth reaction with THFZ-Tfs under basic conditions in the presence of Fe(TPP)Cl, giving the desired CF\textsubscript{3}-substituted cyclopropanes in high yields (Fig. 8). Good functional group tolerance and excellent stereoselectivity (>20:1) were observed: electron-neutral, -rich, and -poor styrenes all underwent efficient cyclopropanations, affording the corresponding trifluoromethylcyclopropane products 107–113 in 81–95% yields. Again, naphthyl and heteroaryl groups were accommodated, providing products 114 and 115 in 87% and 81% yields respectively. Other conjugated dienes and enynes were examined, and also generated the corresponding cyclopropanes (116–118) in excellent yields. Finally, the use of 1,1-disubstituted olefins was equally well-tolerated in spite of increased steric hindrance, delivering trisubstituted products 119 and 120 without diminishing the reaction efficiency or stereoselectivity.

**Discussion**

In summary, we report the development of trifluoroacetalddehyde N-tsfyldihydrazone (THFZ-Tfs)—a bench-stable crystalline reagent that represents a versatile trifluorodiazoethane surrogate, which can generate CF\textsubscript{3}CHN\textsubscript{2} under basic conditions in a controlled manner that avoids excessive buildup of the hazardous diazo compound. A number of applications of THFZ-Tfs are described, including the discovery of gem-difluoroalkenylation of X–H bonds (X = S, N, O, Se), Doyle–Kirmse rearrangements, and trifluoromethylcyclopropanation reactions, with superior performance over other sources of CF\textsubscript{3}CHN\textsubscript{2}. Considering the procedural advantages of this trifluorodiazoethane surrogate, and the importance of generally applicable fluorination methodologies, these findings create many opportunities for the wider exploration of the chemistry of trifluorodiazoethane.

**Methods**

**General procedure for the synthesis of gem-difluoro vinyl thioether.** A screw capped reaction vial was charged with THFZ-Tfs (0.6 mmol), toluenethiol (0.3 mmol), FeP(2) (0.003 mmol) and SDBS (sodium dodecylbenzenesulfonate) (0.09 mmol) under air, following by addition of DCM (1.0 mL) and KOH aq. (5.0 mL, 20 wt%) (Fig. 5, Method A). The resulting mixture was stirred at 40 °C for 18 h. Then 10 mL water was added to the mixture, which was extracted with DCM (3 × 10 mL). The organic layer was combined and dried with anhydrous MgSO\textsubscript{4}, then filtered through a short silica gel eluting with DCM. The filtrate was evaporated under reduced pressure to leave a crude mixture, which was separated by flash column chromatography to afford the pure product.

**General procedure for the synthesis of gem-difluoro vinyl amine.** A screw capped reaction vial was charged with THFZ-Tfs (0.6 mmol), amine (0.3 mmol), Cu(OTf)\textsubscript{2} (0.06 mmol) and LiO\textsubscript{2}Bu (1.2 mmol), then evacuated and filled with argon for three times, followed by addition of DCE (3.0 mL) and toluene (1.0 mL) via syringe (Fig. 5, Method B). The resulting mixture was stirred at 40 °C for 24 h. The reaction crude was filtered through a short silica gel eluting with DCM. The filtrate was evaporated under reduced pressure to leave a crude mixture, which was separated by flash column chromatography to afford the pure product.

![Fig. 8 Scope of trifluoromethylcyclopropanation. Reaction conditions: olefin (0.3 mmol), THFZ-Tfs (0.6 mmol), FeTPPCl (3 mol%), NaOH (aq.)/DCM (5:1.5), 40 °C, 22 h](attachment:image.png)
General procedures for the synthesis of gem-difluorovinyl ether. A screw capped reaction vial was charged with THF–H2O (1.0 mmol), and NaH (60 wt%, 2 mmol) and was evacuated and filled with argon for three times, followed by addition of dry DCE (8.0 mL) via syringe. The resulting mixture was stirred at room temperature for 1 h (Fig. 5, Method C). Then, alcohol (0.5 mmol) and CuBr (0.15 mmol) were added and the system was stirred at 40 °C for 24 h. The reaction crude was filtered through a short silica gel eluting with DCM. The filtrate was evaporated under reduced pressure to leave a crude mixture, which was purified by column chromatography on silica gel.

General procedures for Doyle–Kirmse reaction. A screw capped reaction vial was charged with THF–H2O (0.6 mmol), FeTPPCl (0.009 mmol), then evacuated and filled with argon for two times, then DCM (1 mL) which dissolved with allyl or propargyl sulfide (0.3 mmol) and NaOH aq. (5 mL, 20 wt%) was successively added by syringe (Fig. 7). The reaction was stirred at 40 °C for 18 h. Then 10 mL water was added to the mixture and layers partitioned. The aqueous layer was extracted with DCM (3 × 10 mL) and the organic layer was combined and dried with anhydrous MgSO4, then evaporated under reduced pressure to leave a crude mixture, which was purified through silica gel flash column chromatography eluting with n-hexane to give the final product.

General procedures for cyclopropanation reaction. A screw capped reaction vial was charged with THF–H2O (0.6 mmol), FeTPPCCI (0.009 mmol), then evacuated and filled with argon for three times, then DCM (1.5 mL) which dissolved with styrene (0.3 mmol) and NaOH aq. (5 mL, 20 w t%) was successively added by syringe (Fig. 8). The reaction was stirred at 40 °C for 22 h. Then 10 mL water was added to the mixture and layers partitioned. The aqueous layer was extracted with DCM (3 × 10 mL) and the organic layer was combined and dried with anhydrous MgSO4, then filtered through a short silica gel eluting with DCM. The filtrate was evaporated under reduced pressure to leave a crude mixture, which was purified through silica gel flash column chromatography eluting with n-hexane to give the final cyclopropane product.

Data availability

The authors declare that all the data supporting the findings of this study are available within the paper and its supplementary information files, or from the corresponding author upon request. The X-ray crystallographic coordinates for structures reported in this article have been deposited at the Cambridge Crystallographic Data Center (Triamterenehydrochloride: CCDC 1814685, Trifluoroacetalddehyde N-trifluoromethyl: CCDC 1814683, Trifluoroacetaldehyde N-trifluoromethyl: CCDC 1827227, 9′: CCDC 1814506, 9: CCDC 1881268). These data could be obtained free of charge from The Cambridge Crystallographic Data Center via https://www.ccdc.cam.ac.uk/structures/.

Received: 15 October 2018 Accepted: 19 December 2018

References

1. Liu, C. B. et al. A facile parallel synthesis of trifluoroethyl-substituted alkylones. Angew. Chem. Int. Ed. 54, 6227–6230 (2015).
2. Archipov, A. V., Artyukhov, V. I., Kovtunenko, V. O. & Mykhailik, P. K. Unexpected reactivity of trifluoroethyl dioxazomethane (CF3-CHN2): electrophilicity of the terminal N-atom. Org. Lett. 18, 3406–3409 (2016).
3. Argintaru, O. A., Ryu, D., Aron, I. & Molander, G. A. Synthesis and applications of alpha-trifluoromethylated alkylicarbon compounds. Angew. Chem. Int. Ed. 52, 13656–13660 (2013).
4. Molander, G. A. & Ryu, D. Diastereoselective synthesis of vicinally bis(trifluoromethylated) alkylicarbon compounds through successive insertions of 2,2,2-trifluorodiazooxetane. Angew. Chem. Int. Ed. 53, 14181–14185 (2014).
5. National Research Council. Prudent Practices in the Laboratory: Handling and Management of Chemical Hazards, Updated Version. (The National Academies Press, Washington, DC, 2011).
6. Gilman, H. & Jones, R. G. 2,2,2-Trifluoroethylamine and 2,2,2-trifluorodiazooxetane. J. Am. Chem. Soc. 65, 1458–1460 (1943).
7. Britton, J. & Jamison, T. F. A unified continuous flow assembly-line synthesis of highly substituted pyrazoles and pyrazolines. Angew. Chem. Int. Ed. 56, 8823–8827 (2017).
8. Pieber, B. & Karpe, C. O. Generation and synthetic application of trifluoroethyl dioxazomethane utilizing continuous flow technologies. Org. Lett. 18, 1076–1079 (2016).
9. Mertens, L., Hock, K. J. & Koerings, R. M. Fluoronalkyl-substituted diazomethanes and their application in a general synthesis of pyrazoles and pyrazolines. Chem. Eur. J. 17, 9542–9545 (2011).
10. Barthenga, J. & Valdes, C. Tosylhydrazones: new uses for classic reagents in palladium-catalyzed cross-coupling and metal-free reactions. Angew. Chem. Int. Ed. 50, 7486–7500 (2011).
11. Xia, Y. & Wang, J. N-tosylhydrazones: versatile synths in the construction of cyclic compounds. Chem. Rev. 123, 2306–2362 (2017).
12. Zhang, Z. et al. Catalytic thermodynamic trifluoroilylthiation via triazoliumselective [2,3]-sigmatropic rearrangement of sulfonium ylides. Nat. Chem. 9, 970–976 (2017).
13. Battilochio, C. et al. Iterative reactions of transient boronic acids enable sequential C–C bond formation. Nat. Chem. 8, 360–367 (2016).
14. Barluenga, J., Tomás-Gamasa, M., Aznar, F. & Valdés, C. Metal-free carbon–carbon bond-forming reductive coupling between boronic acids and tosylhydrazones. Nat. Chem. 1, 494–499 (2009).
15. Lin, G.-q., Lei, X., Liu, P., Xu, Q.-Q. & Dong, C. A complementary approach to 3,3-substituted pyrazoles with tosylhydrazones and terminal alkynes mediated by Ti(OH)3. Synlett 23, 2087–2092 (2012).
16. Hu, M., Gaspín, L., Biscarrella, L., Morack, T., Blakemore, D. C. & Ley, S. V. One-pot acid-catalyzed ring-opening/cyclization/oxidation of aziridines with N-tosylhydrazones: access to 1,2,4-triazines. Org. Lett. 19, 1084–1087 (2017).
17. Moore, W. R., Schatzman, G. L., Jarvi, E. T., Gross, R. S. & McCarthy, J. R. Terminal difluoro olefin analogs of squalene are time–dependent inhibitors of squalene epoxidase. J. Am. Chem. Soc. 114, 360–361 (1992).
18. Motherwell, W. B., Tozer, M. J. & Ross, B. A convenient method for replacement of the anameric hydroxy group in carbohydrates by difluoromethyl functionality. J. Chem. Soc. Chem. Commun. 1437–1439 (1989).
19. Gouverneur, V. Fluorine in Pharmaceutical and Medicinal Chemistry: From Biophysical Aspects to Clinical Applications (World Scientific, Singapore, 2012).
20. Burton, D. J., Yang, Z. Y., Qi, W., Ollis, W. J., Battersby, G. & Koenigs, R. M. Fluoromethyl-substituted ylides and related compounds. Chem. Rev. 96, 1641–1716 (1996).
21. Zhao, Y., Huang, W., Zhu, L. & Hu, J. Difluoroethyl 2-pyridyl sulfone: a new gem-difluorodefinitation reagent for aldehydes and ketones. Org. Lett. 12, 1444–1447 (2010).
22. Zheng, J., Cai, J., Lin, J.-H., Guo, Y. & Xiao, J.-C. Synthesis and decarbonylative Wittig reaction of difluoroethylen phosphobetaine. Chem. Commun. 49, 7513–7515 (2013).
23. Ohashi, M. et al. Palladium-Catalyzed coupling reactions of tetrafluoroethylene with arylzinc compounds. J. Am. Chem. Soc. 133, 3256–3259 (2011).
24. Hu, M. et al. Copper-Catalyzed gem-difluorodefinitation of diazo compounds with TMSCF3 via C-F bond cleavage. J. Am. Chem. Soc. 135, 17302–17305 (2013).
25. Hu, M., Ni, C., Li, L., Han, Y. & Hu, J. Gem-Difluorodefinitation of diazo compounds with TMSCF3 or TMSCF3Br: transition-metal-free cross-coupling of two carbene precursors. J. Am. Chem. Soc. 137, 14496–14501 (2015).
26. Wu, G. et al. Switchable 2,2-trifluoroethylthiation and gem-difluoroilylation of organoboron compounds with 2,2,2-trifluorodiazooxetane. Eur. J. Org. Chem. 2014, 4477–4481 (2014).
27. Piettre, S., De Cock, C., Merenyi, R. & Viehe, H. G. Synthesis of fluorinated vinyl sulfides and selenides. Tetrahedron 43, 4309–4319 (1987).
28. Andrews, K. G., Faizova, R. & Denton, R. M. A practical and catalyst-free trifluoroethylation reaction of amines using trifluoroacetic acid. Nat. Commun. 8, 15913 (2017).

ARTICLE NATURE COMMUNICATIONS | https://doi.org/10.1038/s41467-018-08253-z | www.nature.com/naturecommunications
Decostanzi, M., Campagne, J. M. & Leclerc, E. Fluorinated enol ethers: their synthesis and reactivity. Org. Biomol. Chem. 13, 7351–7380 (2015).

Zhang, D., Liu, H., Zhu, P., Meng, W. & Huang, Y. One-pot syntheses of N-(a-fluorovinyl)azole derivatives from N-(diphenylmethylene)-2,2,2-trifluorothanamine. RSC Adv. 6, 73683–73691 (2016).

McCune, C. D. et al. Synthesis and deployment of an elusive fluorovinyl cation equivalent: access to quaternary α-(1-fluorovinyl)amino acids as potential PTP enzyme inhibitors. J. Am. Chem. Soc. 139, 14077–14089 (2017).

Lu, H. & Zhang, X. P. Catalytic C–H activation of fluoroalkyl copper complexes by the oxy cyanupration of tetrafluoroethylene. Angew. Chem. Int. Ed. 56, 11911–11915 (2017).

Kojima, R., Kubota, K. & Ito, H. Stereodivergent hydrodefluorination of gem-difluoroalkanes: selective synthesis of (Z)- and (E)-monofluoroalkanes. Chem. Commun. 53, 10688–10691 (2017).

Moody, J. D., VanDerveer, D., Smith, D. W. Jr & Iacono, S. T. Synthesis of internal fluorinated alkenes via metalloporphyrin-catalyzed preparation of trifluorovinyl ethers. Org. Biomol. Chem. 9, 4842–4849 (2011).

Guo, X. & Hu, W. Novel multicomponent reactions via trapping of protic anion ylides with electrophiles. Acc. Chem. Res. 46, 2427–2440 (2013).

Prakash, G. K. et al. Long-lived trifluoroethanide anion: a key intermediate in nucleophilic trifluoromethylations. Angew. Chem. Int. Ed. 53, 11575–11578 (2014).

Lee, K. et al. Catalytic enantioselective addition of organoboron reagents to fluoroarenes controlled by electrostatic interactions. Nat. Chem. 8, 768–777 (2016).

Wang, F. et al. Divergent synthesis of CF3-substituted allenylnitriles by ligand-controlled radical 1,2- and 1,4-addition to 1,3-enynes. Angew. Chem. Int. Ed. 57, 7140–7145 (2018).

Reggelin, M. in Sulfur-Mediated Rearrangements II (ed. Ernst Schaumann) 1–65 (Springer, Berlin, Heidelberg, 2007).

West, T. H., Spoehrle, S. S. M., Kasten, K., Taylor, J. E. & Smith, A. D. Catalytic stereoselective [2,3]-rearrangement reactions. ACS Catal. 5, 7446–7479 (2015).

Hock, K. J., Mertens, L., Hommelshelm, R., Spitzner, R. & Koenigs, R. M. Enabling iron catalyzed Doyle–Kirmse rearrangement reactions with in situ generated diazo compounds. Chem. Commun. 53, 6577–6580 (2017).

Morandi, B., Mariampillai, B. & Carreira, E. M. Enantioselective cobalt-catalyzed preparation of trifluoromethyl-substituted cyclopropanes. Angew. Chem. Int. Ed. 50, 1101–1104 (2011).

Tinoco, A., Steck, V., Tyagi, V. & Fasan, R. Highly diastereo- and enantioselective synthesis of trifluoromethyl-substituted cyclopropanes via myoglobin-catalyzed transfer of trifluoromethylcarbene. J. Am. Chem. Soc. 139, 5293–5296 (2017).

Kotozaki, M., Chanthatham, S., Fujii, T., Shibatomi, K. & Iwasa, S. Highly enantioselective synthesis of trifluoromethyl cyclopropanes by using Ru (ii)–Pheox catalysts. Chem. Commun. 54, 5110–5113 (2018).

Grygorenko, O. A., Artamonov, O. S., Komarov, I. V. & Mykhailish, P. K. Trifluoromethyl-substituted cyclopropanes. Tetrahedron 67, 803–823 (2011).

Bos, M., Poisson, T., Pannecoucke, X., Charette, A. B. & Jubault, P. Recent progress toward the synthesis of trifluoromethyl- and difluoromethyl-substituted cyclopropanes. Chem. Eur. J. 23, 4950–4961 (2017).