A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

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This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202000119
Angew. Chem. 10.1002/ange.202000119

Link to VoR: http://dx.doi.org/10.1002/anie.202000119
http://dx.doi.org/10.1002/ange.202000119

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10.1002/anie.202000119

RESEARCH ARTICLE

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Difluoroacetaldehyde *N*-Triftosylhydrazone (DFHZ-Tfs) as a Bench-Stable Crystalline Diazo Surrogate for Diazoacetaldehyde and Difluorodiazoethane

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Abstract: Despite the growing importance of volatile functionalized diazoalkanes in organic synthesis, their safe generation and utilization remain a formidable challenge due to their difficult handling along with storage and security issues. In this study, we developed a bench-stable difluoroacetaldehyde *N*-triftosylhydrazone (DFHZ-Tfs) as an operationally safe diazo surrogate that can in situ release two low-molecular-weight diazoalkanes, diazoacetaldehyde ($CHOCHN_2$) or difluorodiazoethane (CF_2HCHN_2), in a controlled fashion under specific conditions. DFHZ-Tfs has been successfully employed in the Fe-catalyzed cyclopropanation and Doyle–Kirmse reactions, thus highlighting the synthetic utility of DFHZ-Tfs in the efficient construction of molecule frameworks containing CHO or CF_2H groups. Moreover, the reaction mechanism for the generation of $CHOCHN_2$ from CF_2HCHN_2 was elucidated by density functional theory (DFT) calculations.

Introduction

Diazo compounds are versatile building blocks for numerous chemical transformations.[1] However, the safe generation and utilization of low-molecular-weight diazo compounds remain a formidable challenge owing to their volatility, explosiveness, and carcinogenicity.[2] Diazomethane (CH_2N_2), the simplest and well-known volatile diazo compound, was first discovered by Pechmann in 1894.[3] Since then, it has been exploited as a versatile reagent in organic synthesis. The diazo group has rich and tunable reactivity patterns; therefore, chemists have derivatized the parent diazomethane with one or two functional groups to construct functionalized diazomethanes, and then introduce functional groups into organic molecules by virtue of the highly reactive diazo functionality (Figure 1a).[1a][4] However, the routine utilization of functionalized diazomethanes in organic synthesis is mostly limited to stable diazoesters,[1] diazoketones,[1] or aryl diazomethanes.[4] In sharp contrast, the synthetic applications of volatile low-molecular-weight functionalized diazomethanes are largely underdeveloped.[5] Diazoacetaldehyde ($CHOCHN_2$)[6] and difluorodiazoethane (CF_2HCHN_2)[7] are two valuable low-molecular-weight diazo compounds that have shown to act as formylating (CHO) and difluoromethylating (CF_2H) reagents, respectively. Nevertheless, in stark contrast to the remarkable achievement in the utility of trifluorodiazoethane (CF_3CHN_2) in organic synthesis,[8] the broad applicability of CF_2HCHN_2 and $CHOCHN_2$ remain in infancy, suffering from difficulties associated with practical generation, storage, and reaction operation.

Despite the several attempts since 1971,[7a][7c] the CF_2HCHN_2 was first prepared in situ in 2015 by Mykhailiuk by heating a solution of commercially available difluoroethylamine with *tert*-butyl nitrite under oxidative acidic conditions (Figure 1b, right side).[7b] Subsequently, the research groups of Koenigs[9a] and Jamison[9b] have improved the technology by generating the CF_2HCHN_2 using continuous-flow technology. Later, Han and Chen group described an ex-situ generation of CF_2HCHN_2 using the double champer system.[9c] In 2018, Ma group developed an alternative masked CF_2HCHN_2 reagent, phenylsulfone difluorodiazoethane ($PhSO_2CF_2CHN_2$).[9d] On the other hand, since the first discovery of $CHOCHN_2$ in 1966 by Meloy, there are two protocols are known for their preparation: 1) acylation of diazomethane with either formyl fluoride[6a] or acetic formic anhydride (Figure 1b, left side);[6b] 2) by heating excess *p*-toluenesulfonyl azide with β-*N*-methylanilinoacrolein.[6c] Nevertheless, the generation and utilization of CF_2HCHN_2 and $CHOCHN_2$ remains problematic, for example, the CF_2HCHN_2 generation methods requiring oxidative acidic conditions or flow conditions/two-chamber system, and the practicality of $CHOCHN_2$ generation being restricted by the use of explosive diazomethane, giving a crude mixture, and/or requiring multi-step process. Therefore, the development of new methods for the safe generation and handling of these two species is a key to their practical utilization.

A promising solution for the safe and scalable generation and use of these volatile diazo compounds is the controlled release of the diazo species in situ from a bench-stable diazo surrogate. With this in mind, and our continued interest in low-temperature decomposition of *N*-sulfonylhydrazones for the in situ generation of diazo compounds,[10] we herein report difluoroacetaldehyde *N*-triftosylhydrazone (DFHZ-Tfs) as a new, bench-stable, and operationally safe diazo surrogate for in situ divergent release of $CHOCHN_2$ and CF_2HCHN_2 under specific conditions. Furthermore, these in situ-generated diazo species displayed remarkable carbene reactivity in the Fe(III)-catalyzed cyclopropanation and Doyle–Kirmse reactions, affording a wide variety of formyl- and difluoromethyl-containing organic molecules in a regio- and stereoselective manner (Figure 1c).

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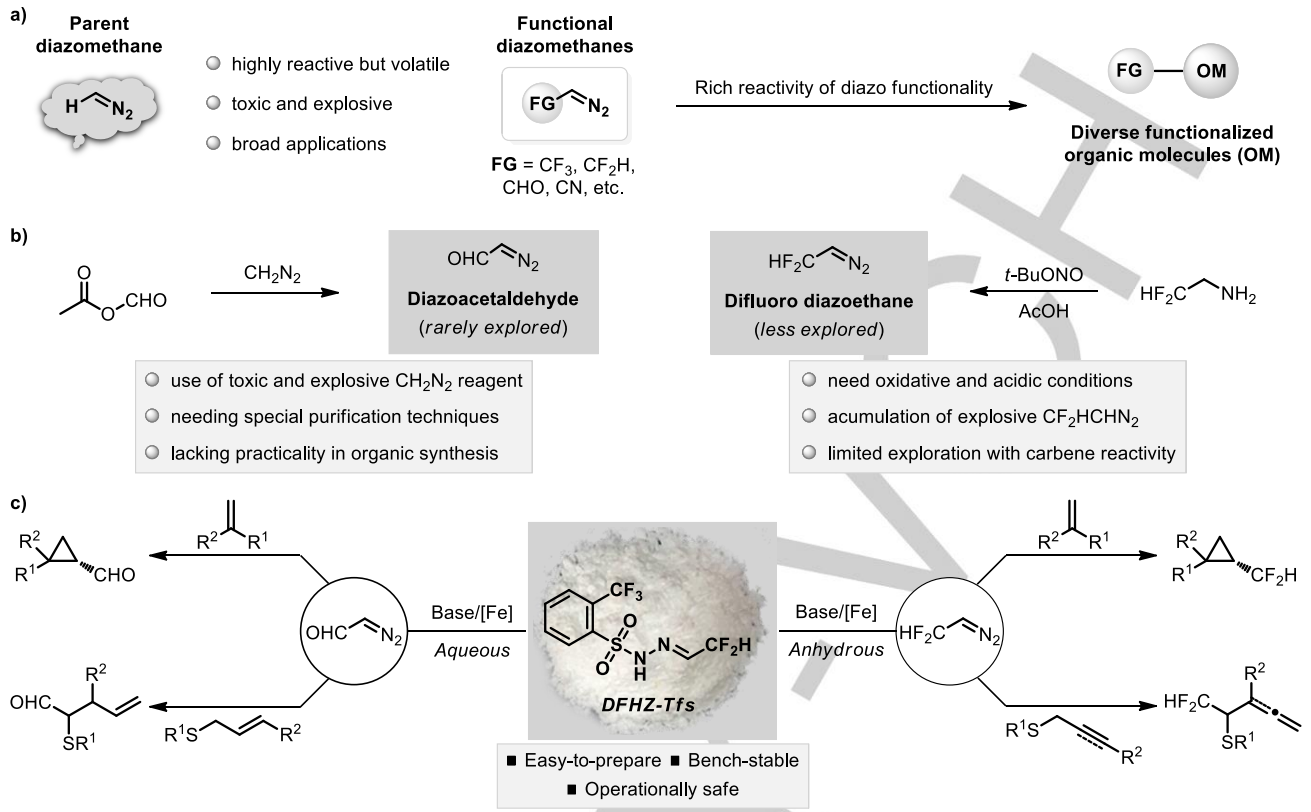
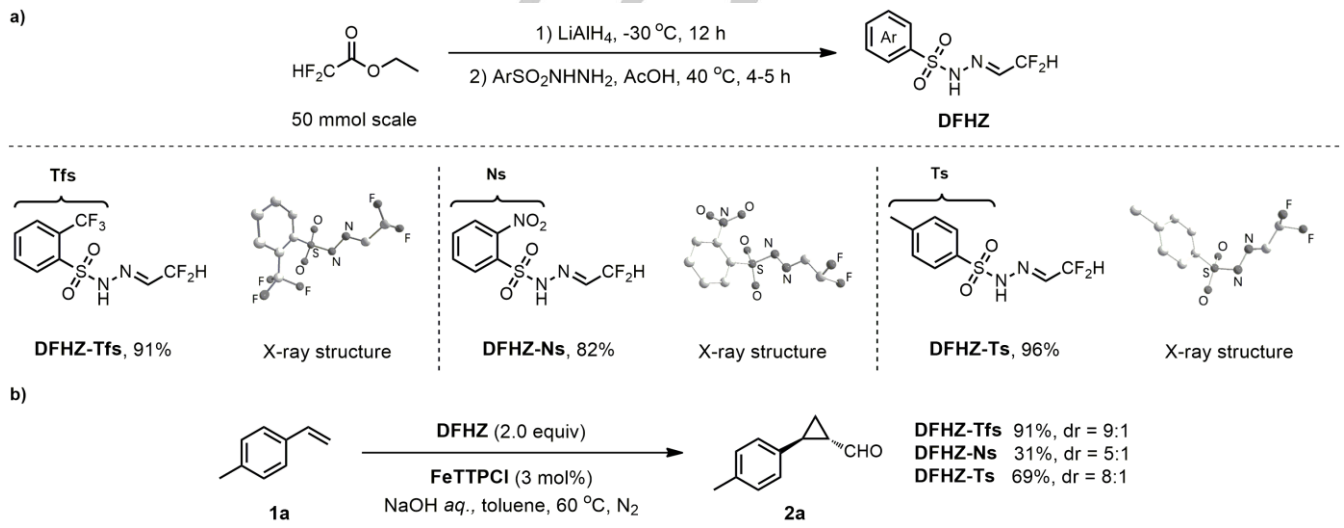


Figure 1. a) The functionalized diazomethane strategy for introducing functional groups into organic molecules by virtue of the reactivity of diazo functionality. b) Previous approaches to the generation of two important volatile functionalized diazomethanes. c) Our strategy for the in situ safe and divergent generation and reactions of diazoacetaldehyde and difluorodiazoethane from DFHZ-Tfs.



Scheme 1. a) Preparation of difluoroacetaldehyde *N*-sulfonylhydrazones (DFHZ). b) Fe-catalyzed cyclopropanation with *p*-methylstyrene.

Results and Discussion

Three difluoroacetaldehyde *N*-sulfonylhydrazones (DFHZ) with different sulfonyl groups were readily prepared from commercially available ethyl difluoroacetate in two-steps, which involving a sequential reduction with $LiAlH_4$ and condensation with sulfonyl hydrazides, affording corresponding DFHZ-Tfs, DFHZ-Ns, and DFHZ-Ts in excellent yields (Scheme 1a). These products are bench-stable crystalline solid that can be stored at ambient conditions for at least three months without significant degradation. With these novel reagents in hand, we first examine their reactivity in the cyclopropanation with alkenes.

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The cyclopropane motif is an important target to organic chemists because it is widespread in natural products and synthetic bioactive agents,[11] and its elaboration with fluorine represents an opportunity for discovering novel compounds with new or increased activity.[12] Particularly, the difluoromethyl group can also act as a bioisostere for carbinol, thiol, hydroxamic acid, and amide groups.[13] Surprisingly, our initial study on the reaction of *p*-methylstyrene **1a** with DFHZ-Tfs by iron catalysis in alkaline aqueous conditions exclusively afforded a cyclopropane carboxaldehyde **2a** in 91% yield with high diastereomeric ratio (9:1), rather than the expected difluoromethylated cyclopropane (Scheme 1b). This result suggests that the exclusive formation of a diazoacetaldehyde species (For conditions optimization, see SI, Table S1). By comparison with DFHZ-Ns and DFHZ-Ts, DFHZ-Tfs afforded the best results regarding the product yield and the diastereomeric ratio.

Attracted by the widespread importance of cyclopropane carboxaldehyde in organic synthesis,[14] we then turned our attention to investigate the reaction scope (Scheme 2a). The protocol demonstrated excellent functional group tolerance, as substrates bearing methoxy, halogen, trifluoromethyl, nitro, cyano, and acyl groups on the benzene ring were converted to desired products **2a**–**2k** in moderate to high yields and high diastereomeric ratios. *p*-Divinylbenzene, a substrate with more than one vinyl group, also smoothly underwent cyclopropanation to give monocyclopropanated product **2l** in 87% yield. Alkenes bearing heterocycles, such as 3-benzothiophene and 3-indole groups were converted into corresponding products **2m** and **2n**, respectively, in good yields and with good diastereoselectivities. The reaction with a conjugated diene or an enyne chemoselectively afforded terminal cyclopropanation products **2o** and **2p** in 95% and 74% yields, respectively, with a decreased diastereomeric ratio for **2p**. 1,1-Disubstituted alkenes were also converted into formyl cyclopropanated products **2q**–**2t**, albeit in relatively lower diastereoselectivities. In stark contrast, 1,1-diphenylethylene was transformed into **2u** in 93% yield with excellent diastereoselectivity. Interestingly, spiro[2.n] compounds **2v** and **2w** were readily obtained from cyclic 1,1-disubstituted alkenes.[15] Further, applying this protocol to alkenes containing ferrocene (**2x**) and Estrone (**Estrone**-**CHO**) moieties demonstrated the synthetic utility of this methodology. To the best of our knowledge, this is the first general and practical catalytic method for accessing cyclopropane carboxaldehydes in a single step from $CHOCHN_2$ and alkenes.[14a][16]

The benefits of CF_2H incorporation have been a major driving force for the booming development of difluoromethylating reagents.[17] To achieve the desired difluoromethylated cyclopropanation reaction, a systematic survey of the reaction parameters were carried out (details see SI, Table S2), and we eventually found the non-aqueous conditions capable of releasing CF_2HCHN_2 and affording difluoromethylated cyclopropanes by iron catalysis (Scheme 2b). Then, the reaction scope was evaluated with a set of alkenes. Various terminal alkenes proved to be suitable for this reaction, affording products **3a**–**3x** in high to excellent yields (up to 98%). Compared to the approach used by Koenigs et al.,[18] and Lin and Xiao et al.[19] to prepare difluoromethylated cyclopropanes (they observed no or poor diastereomeric ratios), our strategy exhibited excellent stereoselectivities (up to > 20:1 dr) in favor of the trans isomer. The electronic properties and position of the substituents on the phenyl ring did not influence the reaction efficiency (**3a**–**3k**) and stereoselectivity observed in the reactions of fused aryl (**3l**) and heteroaryl (**3m**) substrates. The reaction exhibited excellent chemoselectivity with conjugated dienes and enynes, rendering the terminal cyclopropanation products **3n** and **3o** in 79% and 97% yields, respectively. While a decrease in stereoselectivity was observed for methyl-substituted conjugated diene (**3p**) and enyne (**3q**). This result demonstrates that steric hindrance is not a major determinant of the stereoselectivity of this transformation. Likewise, various 1,1-disubstituted alkenes also delivered the corresponding products **3r**–**3t** with moderate diastereoselectivity. Notably, 1,1-diphenylethylene was smoothly converted into the desired product **3u** in 97% yield with high diastereoselectivity. Besides, spiro[2.n] compounds **3v** and **3w** could be easily obtained from cyclic 1,1-disubstituted alkenes. The incorporation of the difluoromethylcyclopropyl motif into a ferrocene (**3x**) is a novel derivatization of this scaffold. Finally, a derivative of Estrone gave the corresponding **Estrone**-$\mathbf{CF_2}$ in 90% yield without a decrease in reactivity.

To further explore the synthetic versatility of DFHZ-Tfs, we studied the Doyle–Kirmse reaction — a unique method for constructing C(sp^3)–S and C–C bonds through [2,3]-sigmatropic rearrangements.[20] A survey of the literature revealed that Doyle–Kirmse reactions involving $CHOCHN_2$ and CF_2HCHN_2 had not been explored. In this context, we first evaluated the Doyle–Kirmse reaction of DFHZ-Tfs with allyl sulfide under the aqueous conditions (3 mol% FeTPPCl as the catalyst in *aq*. NaOH/DCE mixture, details see SI, Table S3) (Scheme 3a, conditions A). A range of aryl allyl sulfides with either electron-donating or electron-withdrawing groups, heteroaryl and alkyl allyl sulfides afforded α-sulfenylated carbonyl compounds **5a**–**5p** in moderate to good yields. Note that the reaction efficiency was not determined by the electronic properties or the positions of the substituents on the aromatic ring. Similarly, cinnamyl and crotyl sulfides were also excellent reaction partners, delivering the desired products **5q** and **5r** in 87% and 85% yields, respectively, albeit with no measurable diastereoselectivity. Notably, the α-sulfenylated carbonyl compounds and structural motifs obtained by this process are found in pharmaceutically active molecules,[21] used as starting materials in biotransformations to produce chiral β-hydroxysulfoxides,[22] and reactive intermediates in a variety of organic transformations.[23] In particular, our synthetic approach offers an attractive alternative to the existing multistep synthetic approaches for α-sulfenylated carbonyl compounds that use toxic reagents and/or expensive transition metal catalysts.[23a][24]

Next, we assessed the synthetic utility of DFHZ-Tfs as a difluoromethyl source in the Doyle–Kirmse reaction. After further optimization of the difluoromethylcyclopropanation reaction conditions (details see SI, Table S4), the conditions of FeTPPCl (3 mol%) as the catalyst and Cs_2CO_3 as the base in THF provides the best reaction (Scheme 3b, conditions B). The α-difluoromethyl sulfide (-SCH_2CF_2H) moiety in the resulting difluoromethylated homoallyl and α-allenyl sulfides is a recurring structural motif in compounds proposed as pest control agents,[25] and treatments of dilated cardiomyopathy.[26] Various aryl, heteroaryl, and alkyl allyl sulfides reacted smoothly with CF_2HCHN_2 to provide the corresponding difluoromethyl homoallyl sulfides **6a**–**6m** in moderate to good yields.

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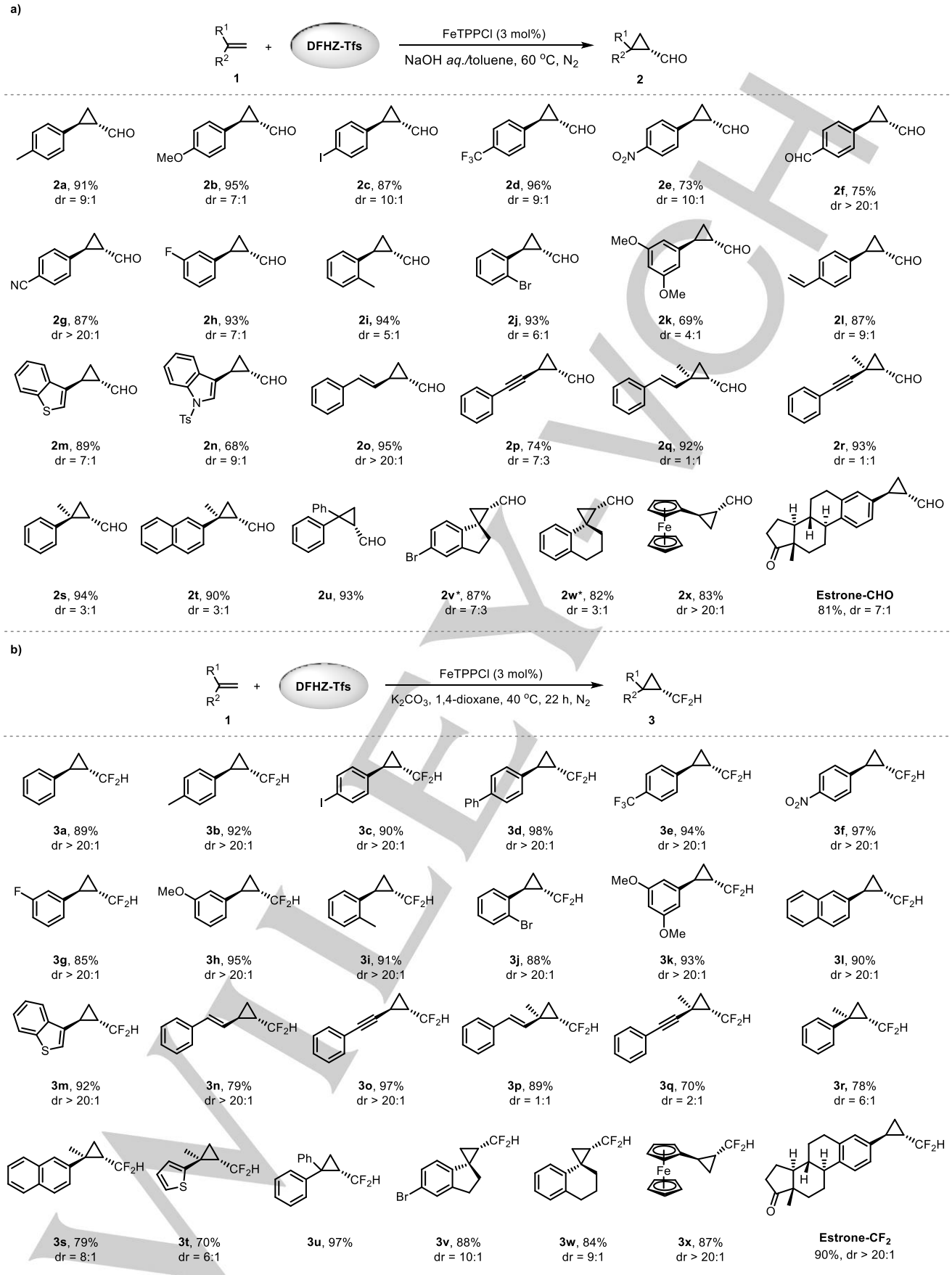

Scheme 2. a) Scope of formyl cyclopropanation. Reaction conditions: alkene (0.3 mmol), DFHZ-Tfs (0.6 mmol), FeTPPCl (3 mol%), *aq.* NaOH (5.0 wt%)/toluene, 60 °C, 22 h, N_2 atmosphere. b) Scope of difluoromethylcyclopropanation. Reaction conditions: alkene (0.3 mmol), DFHZ-Tfs (0.6 mmol), FeTPPCl (3 mol%), K_2CO_3 (0.9 mmol), 1,4-dioxane, 40 °C, 22 h, N_2 atmosphere. Yields refer to isolated products. dr = diastereomeric ratio. *At 0 °C.

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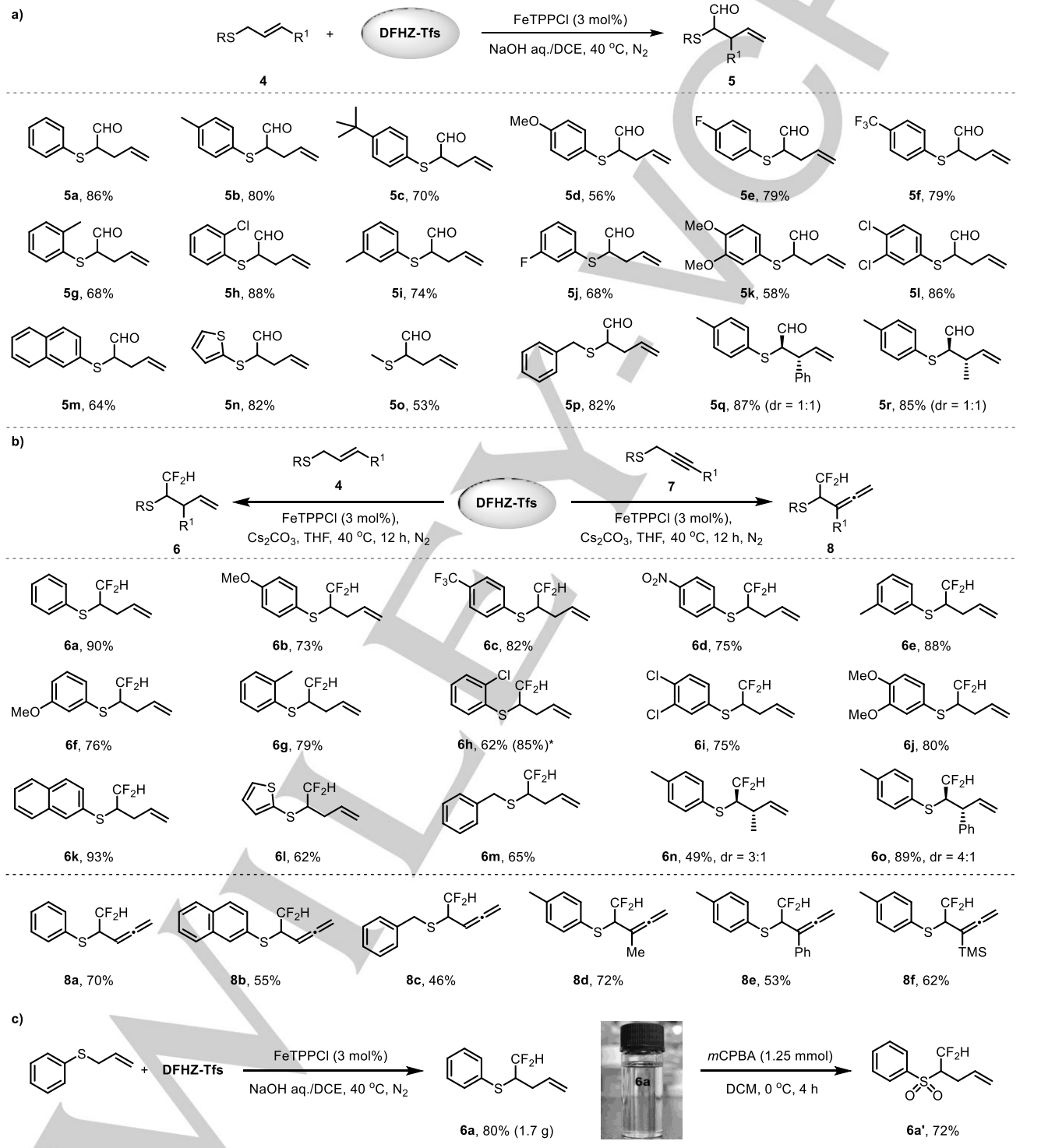
The electronic properties and the position of the substituents on the benzene ring had no significant impact on the reaction outcome. Variations in the substitution pattern of the allyl group did not hamper the reactivity, as demonstrated by cinnamyl and crotyl sulfides, thus resulting in the related products (**6n** and **6o**) with modest diastereomeric ratio.

Next, the reactivity of propargyl sulfides **7** was examined under the same conditions, and resulted in a variety of α-allenyl sulfides **8a**–**8f** in moderate to good yields. Finally, a multi-gram scale synthesis was carried out leading to the product **6a** in a yield comparable to that of a smaller scale; further oxidation of **6a** by *m*CPBA afforded a sulfone derivative (**6a'**) (Scheme 3c). Collectively, a range of novel difluoromethylated homoallylic thioethers and α-allenyl sulfides were obtained by Doyle–Kirmse reaction of DFHZ-Tfs and allyl/propargyl sulfides, which are interesting building blocks for the synthesis of fluorochemicals.[27]



Scheme 3. Scope of Doyle-Kirmse Reaction: a) **4** (0.3 mmol), DFHZ-Tfs (0.6 mmol), FeTPPCl (3 mol%), NaOH *aq.* (5.0 wt%)/DCE, 40 °C, 18 h, N_2 atmosphere; b) **4** or **7** (0.3 mmol), DFHZ-Tfs (0.6 mmol), FeTPPCl (3 mol%), Cs_2CO_3 (0.9 mmol), THF, 40 °C, 12 h, N_2 atmosphere. c) Gram-scale synthesis and further transformation of **6a**: **4a** (10.0 mmol), DFHZ-Tfs (20.0 mmol), FeTPPCl (1 mol%), Cs_2CO_3 (30.0 mmol), THF, 40 °C, 48 h, N_2 atmosphere; **6a** (0.5 mmol), *m*CPBA (1.25 mmol), DCM, 0 °C, 4 h, air atmosphere. Yields refer to isolated products. *Yield based on recovered starting material.

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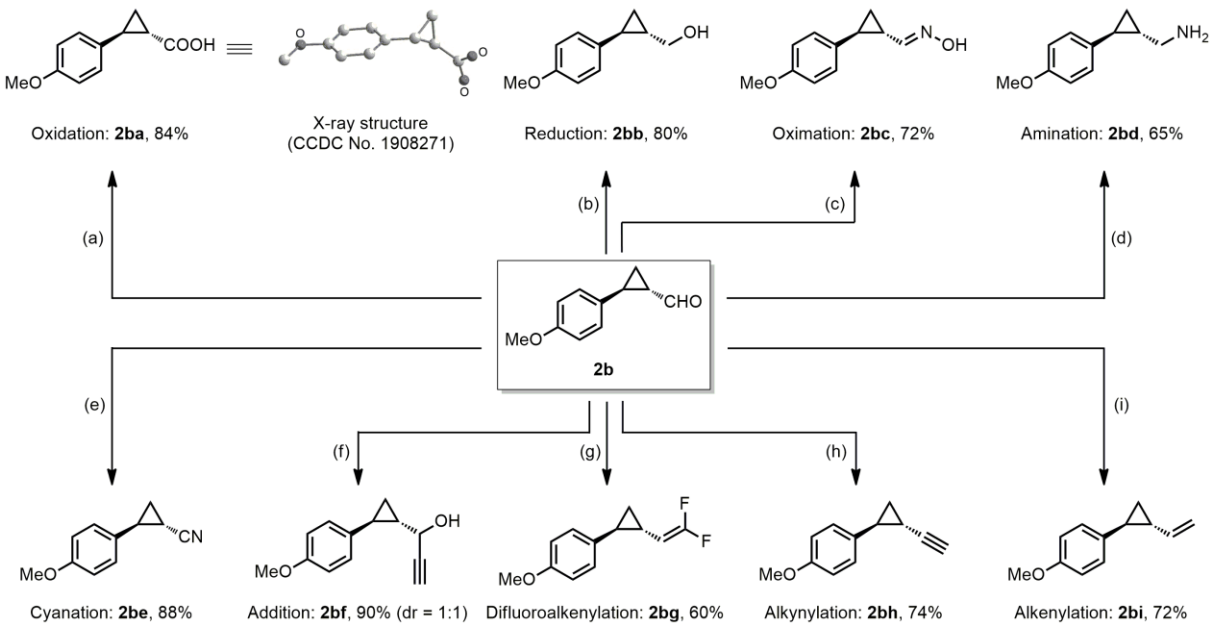
Considering the widespread importance of functionalized cyclopropanes,[28] the functional group interconversions of cyclopropane carboxaldehyde was explored. As summarized in Scheme 4, diverse functionalized cyclopropanes were readily obtained from **2b**, such as acid (**2ba**), alcohol (**2bb**), oxime (**2bc**), amine (**2bd**), nitrile (**2be**), propargyl alcohol (**2bf**), gem-difluoroalkene (**2bg**), alkyne (**2bh**), and alkene (**2bi**). The structure of cyclopropane carboxylic acid **2ba** was unambiguously confirmed by single-crystal X-ray diffraction analysis.



Scheme 4. Functional group transformations of cyclopropane carboxaldehydes: Reaction conditions: (a) oxidation: **2b** (0.5 mmol), Ag_2O (0.5 mmol), NaOH *aq.* (10.0 wt%), 60 °C, 30 min; (b) reduction: **2b** (0.5 mmol), $LiAlH_4$ (0.75 mmol), THF, 25 °C, 10 h, N_2 atmosphere; (c) oximation: **2b** (1.0 mmol), NaOH (2.6 mmol), $NH_2OH{\cdot}HCl$ (1.6 mmol), $EtOH/H_2O$, reflux, 18 h; (d) amination: **2bc** (0.5 mmol), $LiAlH_4$ (1.1 mmol), THF, reflux, 2 h, N_2 atmosphere; (e) cyanation: **2b** (0.5 mmol), $NH_2OH{\cdot}HCl$ (0.75 mmol), NMP, 100 °C, 2 h; (f) addition: **2b** (0.5 mmol), BrMgC≡CH (0.5 mmol), THF, 25 °C, 12 h; (g) difluoroalkenylation: **2b** (0.5 mmol), PPh_3 (0.6 mmol), $ClCF_2CO_2Na$ (0.75 mmol), NMP, 100 °C, 2 h; (h) alkynylation: i) **2b** (0.5 mmol), PPh_3 (2.0 mmol), CBr_4 (1.0 mmol), DCM, 0 °C, 3 h; ii) *n*-BuLi (1.4 mmol), THF, −78 °C, 12 h; (i) alkenylation: **2b** (0.5 mmol), Ph_3PCH_3I (0.6 mmol), *n*-BuLi (0.6 mmol), THF, 25 °C, 4 h. Yields refer to isolated products.

To clarify the transformation mechanism of CF_2HCHN_2 into $CHOCHN_2$ under aqueous conditions, we performed DFT calculations starting from the in situ generated CF_2HCHN_2 at the M06-2X/6-31+G(d,p) level of theory (Figure 3).[29] According to the calculations, the cooperative effect of base NaOH and water via hydrogen bonding was found to play a critical role. The transformation could be divided into three steps: the C–F bond activation by NaOH-H_2O, nucleophilic addition of hydroxy group to vinyl carbocation, and the elimination of HF with the assistance of NaOH-H_2O. In the first step, the NaOH only and the NaOH with 1~3 H_2O molecules were considered in the activation of C–F bond (See SI, Figure S1). It was found that the mode catalyzed by NaOH-3H_2O (TS1, 15.9 kcal/mol) is most favored, which is 13.3 kcal/mol lower than that of NaOH only (**TS1'**, 29.2 kcal/mol). In **TS1**, water enhances the nucleophilic activity of base NaOH through the bridged hydrogen bonding, thereby promoting the C–F bond activation by NaOH. In the following step, the nucleophilic addition of dissociative hydroxyl ion to vinyl carbocation leads to 2-diazo-1-fluoroethanol **Int3** with a barrier of only 2.2 kcal/mol (via **TS2**) with respect to **Int2**. Considering the experimentally existing of a strong NaOH base in the system and inspired by the recent report by Zhang and Houk et al. about the hydroxylation and deprotonation of difluorocarbene compound,[30] we first investigated the deprotonation of **Int3** by NaOH to form the sodium alkoxide intermediate **Int4**, and this step is exergonic by 18.5 kcal/mol. The substituent F, which is on the same carbon as the sodium in **Int4**, is a potential leaving group; therefore, in the last step the elimination of NaF with the assistance of 2 molecules of water (**TS3**, 0.5 kcal/mol) occurs to afford the $CHOCHN_2$. The key intermediate **Int3** may also undergo another pathway to produce $CHOCHN_2$, the direct C–F bond activation of **Int3** by NaOH (see SI, Figure S2). Conclusively, the NaOH acts as the base to extract fluorine and the weakly acidic water enhances the electrophilicity of Na ion through the hydrogen bonding to promote the hydration reaction.

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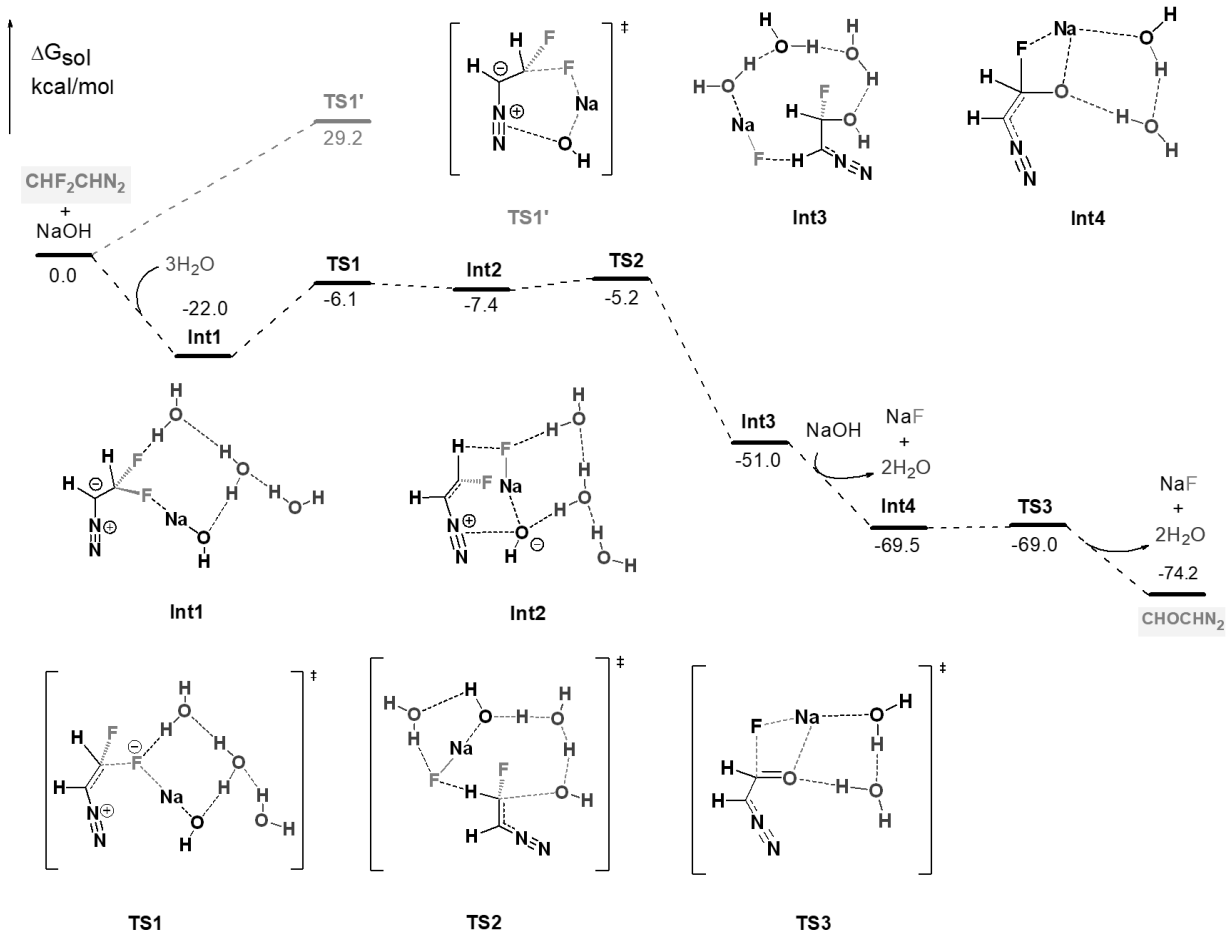

Figure 2. Free energy profiles of the conversion of CF_2HCHN_2 into $CHOCHN_2$.

Conclusion

We have demonstrated DFHZ-Tfs to be an operationally safe and bench-stable diazo surrogate of two important, volatile functionalized diazomethanes, CF_2HCHN_2 and $CHOCHN_2$, which could be independently generated in situ under specific conditions. This strategy circumvents direct human exposure to toxic and explosive diazo reagents and reduces the risk of rapid accumulation of explosive diazo compounds. Furthermore, successful applications of DFHZ-Tfs to cyclopropanation and Doyle–Kirmse reactions demonstrated its great synthetic utilities. The discovery described here represents a significant advance in diazo chemistry, as it has opened up an avenue to the exploration of two classes of important functionalized diazo compounds. In view of the remarkable stability and operational simplicity, as well as the mild and controlled decomposition conditions, DFHZ-Tfs would find wide applications in organic synthesis.

Acknowledgements

Financial support by NSFC (21871043, 21961130376), Department of Science and Technology of Jilin Province (20180101185JC, 20190701012GH), and the Fundamental Research Funds for the Central Universities (2412019ZD001).

Keywords: difluoroacetaldehyde *N*-triftosylhydrazone • diazoacetaldehyde • difluorodiazoethane • cyclopropanation • Doyle–Kirmse reaction

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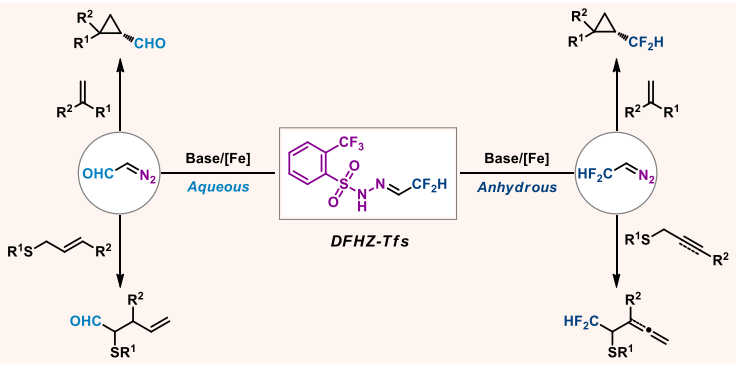

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Page No. – Page No.

Difluoroacetaldehyde *N*-Triftosylhydrazone (DFHZ-Tfs) as a Bench-Stable Crystalline Diazo Surrogate for Diazoacetaldehyde and Difluorodiazoethane

Two from One: An operationally safe and bench-stable crystalline diazo surrogate, difluoroacetaldehyde *N*-triftosylhydrazone (DFHZ-Tfs) was developed for in situ divergent release of two volatile diazo species, $CHOCHN_2$ and CF_2HCHN_2. The synthetic utility of these reagents was successfully demonstrated in the Fe-catalyzed cyclopropanation and Doyle–Kirmse reactions. The reaction mechanism for the formation of $CHOCHN_2$ from CF_2HCHN_2 was elucidated by DFT calculations.

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