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[3 + 2]-Cycloaddition Reactions of *gem*-Difluorocyclopropenes with Azomethine Ylides – Access to Novel Fluorinated Scaffolds

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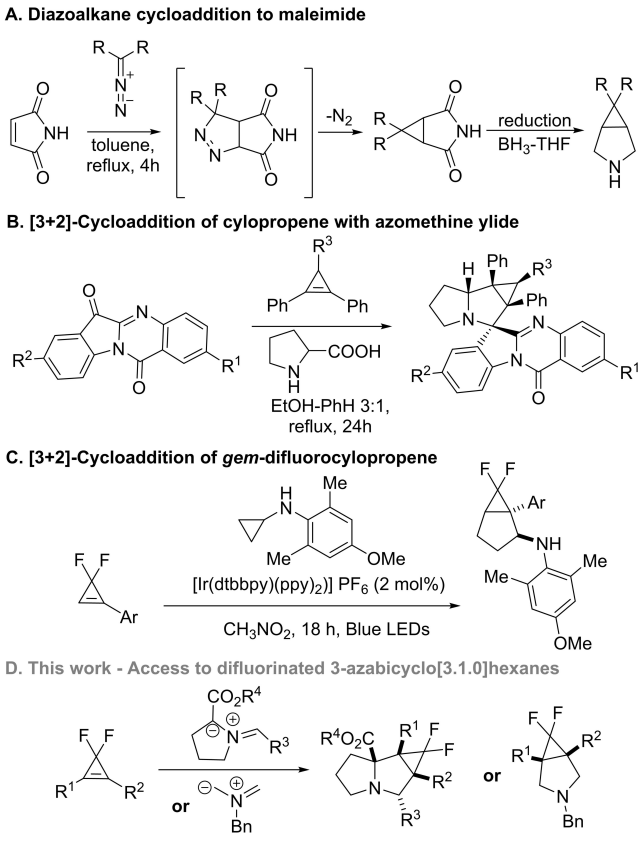
The introduction of fluorinated moieties into drugs as well as the increase of their overall three-dimensionality have become key strategies amongst medicinal chemists to generate sets of compounds with favorable drug-like properties. However, the introduction of fluorinated cyclopropane ring systems which combines both strategies is not widely exploited to date. This paper reports synthetic strategies exploiting the reactivity of *gem*-difluorocyclopropenes in dipolar cycloaddition reactions with azomethine ylides to afford sets of new fluorine-containing 3-azabicyclo[3.1.0]hexanes. In addition, the unexpected formation of complex trifluorinated scaffolds arising from proline esters and *gem*-difluorocyclopropenes is highlighted along with computational studies to elucidate the underlying mechanism. This study presents new avenues towards pharmaceutically relevant fluorinated 3-azabicyclo[3.1.0]hexanes that are accessible via robust and short synthetic sequences.

Introduction

The incorporation of fluorine into molecules is a common tactic used in medicinal chemistry to modify their pharmacological properties.[1] This has proved successful over recent decades as evidenced by the large number of marketed drugs which contain fluorine. More recently, a significant focus has been placed on developing methods for accessing more three-dimensional (sp^3-rich) moieties as another strategy to achieve desired pharmacological properties in drug candidates.[2] One such moiety is the 3-azabicyclo[3.1.0]hexane system which has appeared in a number of drug molecules including nirmatrelvir which has been used in conjunction with ritonavir for the treatment of SARS-CoV-2.

Multiple strategies exist for accessing this moiety including the Corey–Chaykovsky cyclopropanation of 2,5-dihydropyrrole derivatives.[3] The same reactivity has been reported for maleimide derivatives, which following reduction of the resulting imide gives the desired 3-azabicyclo[3.1.0]hexane scaffold (3-ABH).[4] Similarly, various reports exist of [3 + 2]-cycloadditions of a diazo species with maleimide derivatives, which following expulsion of N_2 gas and subsequent reduction afford the corresponding 3-ABH (Scheme 1a).[4–5] Recently, this strategy was employed by Hai, Wu and co-workers to access CF_3 and CF_2H substituted 3-ABHs.[6][7] While useful, these strategies face the challenge of functional group compatibility, particularly with the final reduction step.



Scheme 1. Synthetic strategies towards the synthesis of 3-azabicyclo[3.1.0]hexanes.

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More recently, a significant focus has been placed on [3 + 2]-cycloadditions of substituted cyclopropenes with azomethine ylides to provide access to complex 3-ABH derivatives.[8] In 2018, Deng and co-workers as well as Xu and co-workers separately reported a copper-catalysed stereoselective cycloaddition of substituted cyclopropenes with azomethine ylides to access complex 3-ABH derivatives containing 5-stereogenic centres.[9]

Over the past number of years, Stepakov and co-workers have reported numerous examples of [3 + 2]-cycloadditions between substituted cyclopropenes and complex azomethine ylides providing access to 3-ABH derivatives containing spirocyclic centres (Scheme 1b).[10] While this reactivity has been exploited to efficiently synthesise substituted 3-ABH derivates, no examples have been reported to date which incorporate fluorine into these drug-like molecules despite there being significant interest in developing fluorination methodologies.

Gem-difluorocyclopropenes have been utilised as versatile building blocks for various cycloaddition reactions. In many cases this involved formation of a cyclopropenone intermediate, following loss of fluorine, which then undergoes a cycloaddition reaction with the reaction partner to give the final product.[11] In other examples, one of the fluorine atoms is retained in the final product, however, the cyclopropane moiety is lost upon ring expansion.[12] In 2019, the Waser group reported the synthesis of bicyclo[3.1.0]hexanes by [3 + 2]-annulation of cyclopropenes with amino cyclopropanes under photochemical conditions (Scheme 1c).[13] During this study, it was noted that the reaction scope extended to *gem*-difluorocyclopropenes providing access to fluorinated bicyclo[3.1.0]hexanes. We anticipated that similar results can be harnessed via [3 + 2]-cycloaddition of *gem*-difluorocyclopropenes with azomethine ylides to access a range of difluorinated 3-azabicyclo[3.1.0]hexanes (Scheme 1d).

Results and Discussion

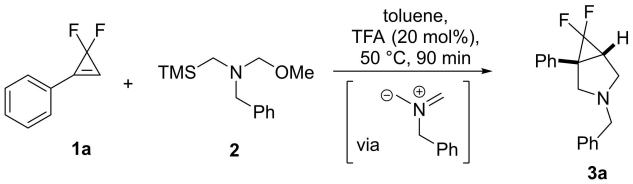
N-(Methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (**2**) is a widely used and commercially available azomethine ylide precursor, which when treated with strong acid or a fluoride source readily decomposes to form the desired ylide. This methodology has previously been exploited to form pyrrolidine containing compounds from activated alkenes,[3,14] however, no reported examples of this reactivity with cyclopropenes exist. We hypothesized that applying this strategy to *gem*-difluorocyclopropenes would provide facile access to fluorinated drug-like building blocks. We thus began investigating the reaction between *gem*-difluorocyclopropenes with azomethine ylide precursor **2**.

Gem-difluorocyclopropenes are typically accessed via difluoro-carbene addition to an alkyne. To achieve practical reaction times (< 6 hr), temperatures in excess of 100 °C are routinely used.[15] As THF (b.p. 66 °C) is the most commonly chosen solvent for this reaction, this can pose significant safety concerns. Thus, we opted to use a continuous flow setup to facilitate rapid synthesis of *gem*-difluorocyclopropenes, while minimising safety concerns (see Supporting Information for experimental details).[16]

(3,3-Difluorocycloprop-1-en-1-yl)benzene (**1a**) was chosen as model substrate. Initial screening found trifluoroacetic acid (TFA) to be the most efficient initiator for the formation of the azomethine ylide (Table 1, entry 1 & 2). A stronger acid, H_2SO_4, yielded similar results, while a decrease in yield was observed using acetic acid (entries 3 & 4). Switching to a fluoride salt, LiF, did promote ylide formation, however, increasing the quantity of fluoride source did not yield any improvements beyond a 50% yield until 2 equivalents of **2** were added which slightly increased the yield to 65% (Table 1, entries 5–7). Variation of the solvent found no improvement over toluene, except for THF, however, toluene was preferred due to its higher boiling point (Table 1, entries 8–10). Increasing the quantity of **2** was found to be beneficial to the reaction yielding the product in 77% yield (entry 11). An increase of TFA from 10 mol% to 20 mol% resulted in a slight increase in yield to 85% (entry 1).

The optimized reaction conditions were then applied to several different *gem*-difluorocyclopropenes (Scheme 2). Using naphthyl substituted cyclopropene **1b** afforded the desired product **3b** in a high yield of 88%, with a minimal decrease to 84% when the reaction was carried out on 1 mmol scale. It is noteworthy that the debenzylation of compound **3b** would provide an easy access to the *gem*-difluorinated equivalent of centanafidine, a drug which is currently in clinical trials for the treatment of adult ADHD. The reaction tolerated both electron-rich and electron-poor substrates (compounds **3c**, **3d**, **3e**), however, it was observed that the reaction of electron-poor cyclopropene **1e** proceeded sluggishly in comparison. The addition of an ester group adjacent to the cyclopropene portion of the substrate did not diminish yield, with compound **3f**

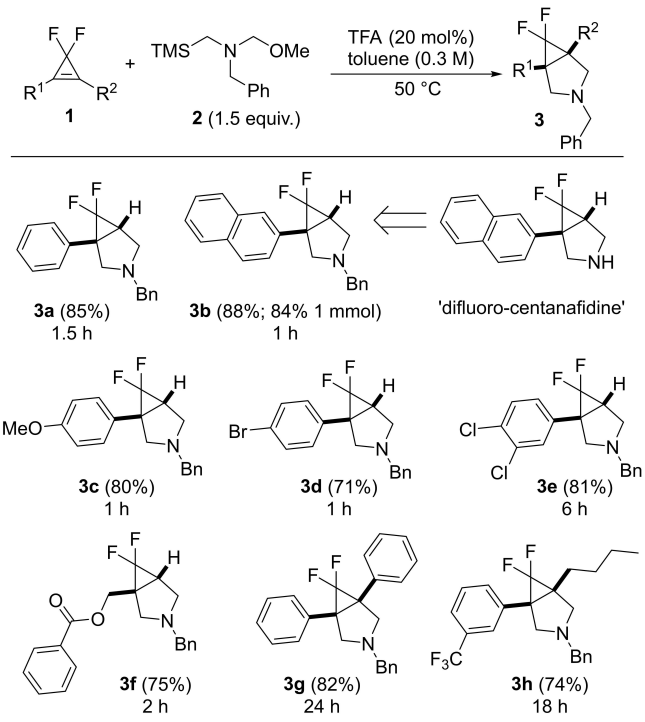
Table 1. Optimization of the [3 + 2]-cycloaddition with azomethine ylide.



1a 2 3a

Entry	Deviation from standard conditions	Equiv. **2**	% Yield[a]
1	None	1.5	85%[b]
2[c]	TFA (10 mol%)	1	62%
3[c]	H_2SO_4 (10 mol%)	1	40%
4[c]	AcOH (10 mol%)	1	29%
5[c]	LiF (1 equiv.), MeCN	1	50%
6[c]	LiF (5 equiv.), MeCN	1	45%
7[c]	LiF (5 equiv.), MeCN	2	65%
8[c]	TFA (10 mol%), MeCN	1	40%
9[c]	TFA (10 mol%), CH_2Cl_2	1	43%
10[c]	TFA (10 mol%), THF	1	65%
11	TFA (10 mol%)	1.5	77%

[a] ^{1}H NMR % yield using ethyl trifluoroacetate as internal standard. [b] Isolated yield. [c] 24-hour reaction time.

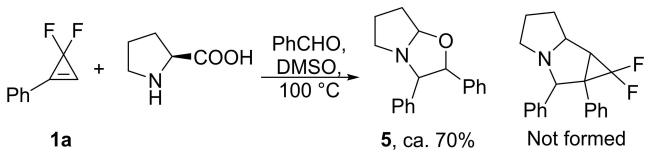


Scheme 2. Substrate scope of [3 + 2]-cycloaddition of gem-difluorocyclopropenes with **2**.

being isolated in 75% yield. While disubstituted cyclopropenes did form the desired product in good yield (compounds **3g** and **3h**), these took significantly longer to react suggesting that sterics have a larger effect than electronics on the rate of the reaction.

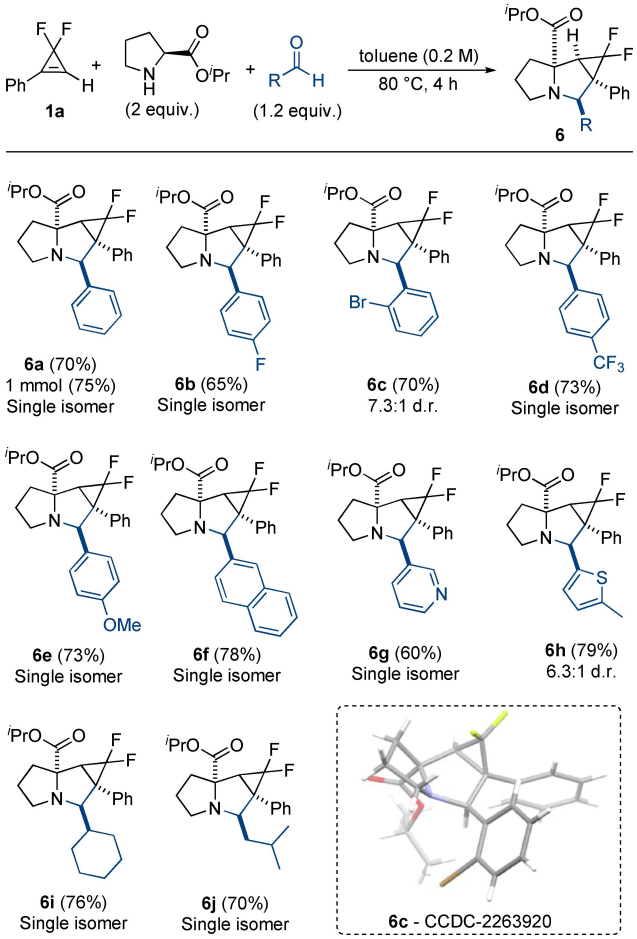
Following successful reaction of *gem*-difluorocyclopropenes with a simple azomethine ylide, we turned our attention to more complex reaction partners. A commonly exploited method for accessing interesting azomethine ylides is through reacting a secondary amine with an aldehyde, which following deprotonation of the α-carbon of the resulting imine forms the desired ylide.[17] In 2019, Stepakov and co-workers reported the three component reaction of proline, tryptanthrin derivatives and diphenylcyclopropenes to access complex molecules containing the azabicyclo[3.1.0]hexane moiety.[10d] Inspired by this report, we expected that a similar strategy, using proline, simple aldehydes and *gem*-difluorocyclopropenes would give access to interesting difluorinated polycyclic systems.

Initial experiments reacted L-proline, benzaldehyde and **1a** in DMSO at 100 °C. However, rather than forming the desired product, we instead observed the formation of bicycle **5**. This suggested that the desired ylide was indeed formed, however, unusually, the ylide was reacting with remaining benzaldehyde in place of the *gem*-difluorocyclopropene (Scheme 3). While this was surprising, as we had assumed that **1a** would be significantly more reactive than benzaldehyde, similar reactivity had been reported by Orsini and co-workers who found that the reaction of proline and benzaldehyde resulted in the formation of 1-oxapyrrolizidines and 1,3-oxazolidines.[18] This matched our observations, however, we believed that modification of the proline precursor could prevent this undesired reaction.



Scheme 3. Initial 3-component reaction of *gem*-difluorocyclopropene, benzaldehyde and proline.

We found that converting the α-carboxylic acid of proline to an isopropyl ester prevented the formation of these alternative products and instead favoured the reaction with difluorocyclopropene **1a** to give **6a**. Following a brief optimization of reaction conditions, it was found that stirring 2 equivalents of isopropyl prolinate and 1.2 equivalents of benzaldehyde in toluene at 80 °C gave the best yield, with product **6a** being isolated in 70% yield using these conditions. This yield increased slightly to 75% on a 1 mmol scale. These conditions were then applied to a range of substrates to investigate the scope of the reaction (Scheme 4). Variation of the aldehyde in the reaction mixture was well tolerated. Both electron-poor



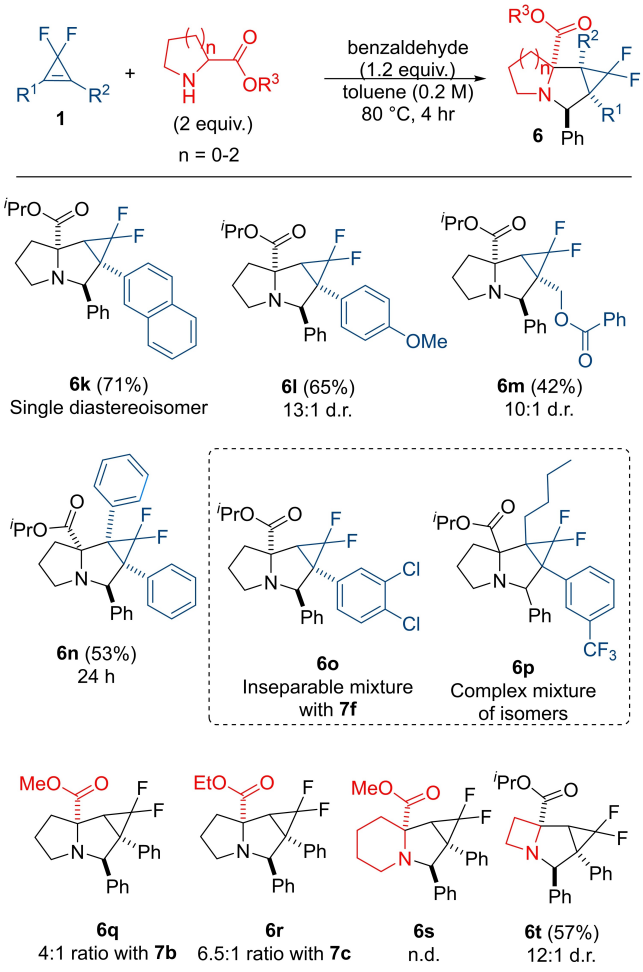
Scheme 4. Variation of aldehyde in 3-component [3 + 2]-cycloaddition reaction.

(**6b**–**6d**) and electron-rich (**6e**) aldehydes gave the desired products in good yield. Use of the sterically more demanding 3-naphthylcarboxaldehyde afforded **6f** in 78% yield. A slight reduction in yield was noted for the pyridine containing system **6g**, while a high yield in addition to a shorter reaction time of 1.5 h was observed using 2-thiophenecarboxaldehyde as a substrate (**6h**). The use of both cyclic and linear aliphatic aldehydes gave the desired products **6i** and **6j**, respectively, in good yields. Interestingly, all products were formed as a single diastereoisomer except for **6c** (7.3:1 d.r.) and **6h** (6.3:1 d.r.) that formed as a mixture of inseparable diastereomers albeit with good selectivity. A single crystal X-ray structure of **6c** was secured confirming the relative stereochemistry of the product.[19]

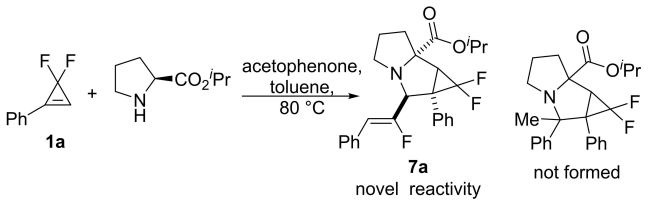
While the reaction tolerated a range of aldehydes, altering the electronics of the *gem*-difluorocyclopropene was more impactful on yield (Scheme 5). Cyclopropene **1b** yielded the desired naphthyl containing product in 71% yield, similar to that of **6a**. Electron-rich cyclopropene **1c** gave **6l** in 65% yield, as a mixture of diastereomers (13:1 d.r.). Product **6m** containing a benzoate ester was successfully isolated in a slightly reduced yield of 42% and as an inseparable mixture of diastereomers (10:1 d.r.). Trisubstituted cyclopropene **1g** afforded the desired product **6n** in 53% yield, however, significantly longer reaction times of 24 h were required. This contrasted with unsymmetrical cyclopropene **1h** which reacted to form an inseparable mixture of multiple isomers. Interestingly, use of electron-poor cyclopropene **1e** favoured the formation of a new and unprecedented product (**7f**, see below). Variation of the ester fragment of the prolinate also had a significant effect on the outcome of the reaction. Switching from isopropyl ester to methyl ester formed **6q** as part of an inseparable mixture with **7b** in a 4:1 ratio. Similar results were observed for ethyl ester **6r**, albeit with improved selectivity (**6r**:**7c** 6.5:1). This suggests that the steric bulk of the ester plays a key role in determining the selectivity of the reaction. Attempts to improve this selectivity included decreasing reaction temperature and increasing the equivalents of benzaldehyde, all of which made no discernible difference.

Increasing the ring size of the α-amino ester resulted in no reaction taking place with **6s** not detected, however, decreasing the ring size provided access to **6t** in 57% yield.

After probing the versatility of the reaction for each of the three reaction partners, we were curious whether ketones could also successfully be utilised. Replacing benzaldehyde with acetophenone, we subjected the reagents to the same conditions used previously. Surprisingly, the desired product did not form, however, analysis of the resulting crude mixture provided some unprecedented insights into the reactivity of *gem*-difluorocyclopropenes (Scheme 6). ^{19}F NMR analysis of the purified reaction mixture indicated three separate fluorine atoms were present in the isolated molecule. Additionally, the ^{1}H NMR spectrum revealed the presence of a peak with the chemical shift characteristic of an alkene. Following further NMR analysis, including HMBC, NOESY and HOESY we determined the structure of the isolated product to be that of **7a** (Figure 1).



Scheme 5. Variation of gem-difluorocyclopropene and prolinate in 3-component [3 + 2]-cycloaddition reaction.



Scheme 6. Attempted replacement of benzaldehyde with acetophenone in [3 + 2]-cycloaddition process.

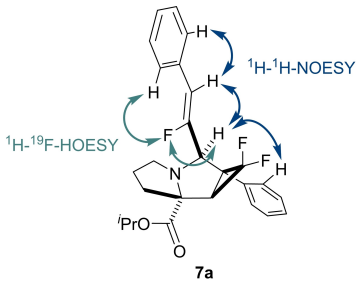


Figure 1. Key NOESY and HOESY NMR correlations for assignment of **7a**.

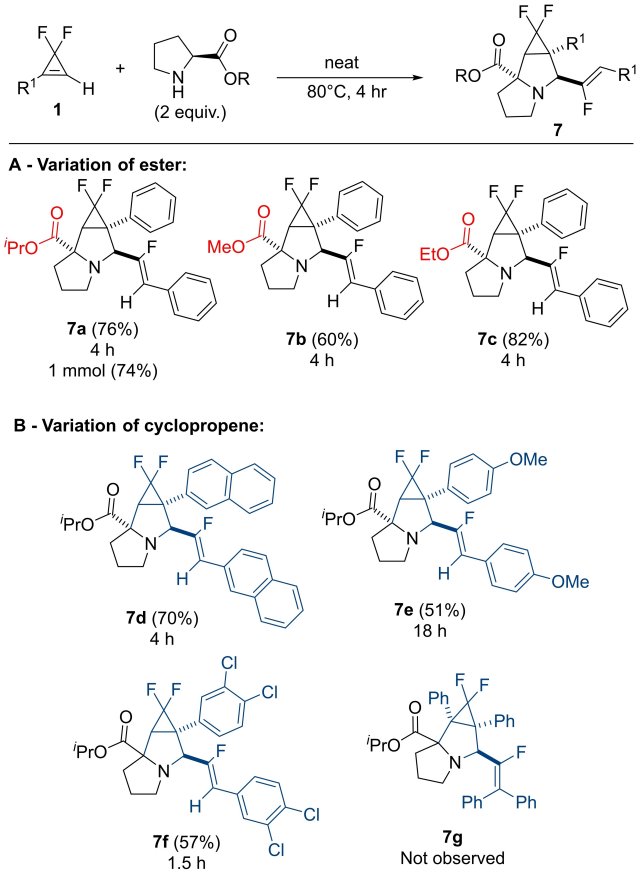
With some optimisation of the reaction conditions, we found that **7a** could be isolated in a yield of 76% by heating a neat mixture of isopropyl prolinate (2 equivalents) and **1a** to 80 °C for 4 h. Following this observation, we began to probe the scope of the reaction (Scheme 7). Use of methyl prolinate gave product **7b** in 60% yield, while a slight increase to 82% yield was observed when ethyl prolinate was used (**7c**). Naphthyl containing cyclopropene **1b** afforded **7d** in 70% yield. Similar to previous reactions, the effect of modifying the electronics of the cyclopropene were pronounced. Electron-rich cyclopropene **1c** gave **7e** in moderate yield (51%), however, the reaction proceeded substantially slower with significant conversion only being reached after 18 h. Conversely, electron-poor cyclopropene **1e** afforded **7f** in only 1.5 h, with a reasonable yield of 57%. Use of a tri-substituted cyclopropene resulted in no reaction with **7g** not being observed in the reaction mixture. Hydrolysis of the ester portion of mono-fluorinated alkene **7a** was also carried out yielding the corresponding acid in high yield (see Supporting Information for details).

While the use of *gem*-difluorocyclopropenes to access mono-fluorinated alkenes has previously been reported, these examples either used transition metal catalysis, or additional steps to yield the final alkene.[19]

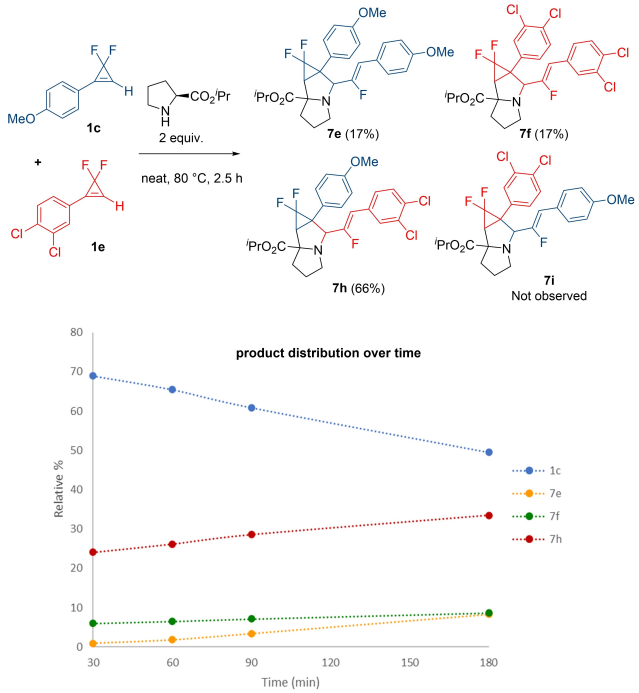
Based on these observations, we decided to carry out experiments to shed some light on this reactivity. We found that the presence of a second alkene reactant (i.e., cyclohexene, methyl acrylate or N–H maleimide) did not result in any changes to reactivity and no products incorporating these alkenes were observed. Next, using the standard conditions, a mixture of cyclopropenes **1c** and **1e** in equimolar amounts were treated with isopropyl prolinate and heated at 80 °C. ^{19}F NMR analysis of the reaction mixture was carried out at 30-minute intervals for 3 h.

We found that within the first 30 min, **1e** had been fully consumed with a mixture of products being formed. The mixed product **7h** and **7f** had been formed in a 4:1 ratio (as determined by ^{19}F NMR), which did not change over time. However, over the remaining 2.5 h, **1c** was slowly consumed to form **7e** (Scheme 8). Interestingly, the alternative mixed product **7i** was not observed in the reaction mixture.

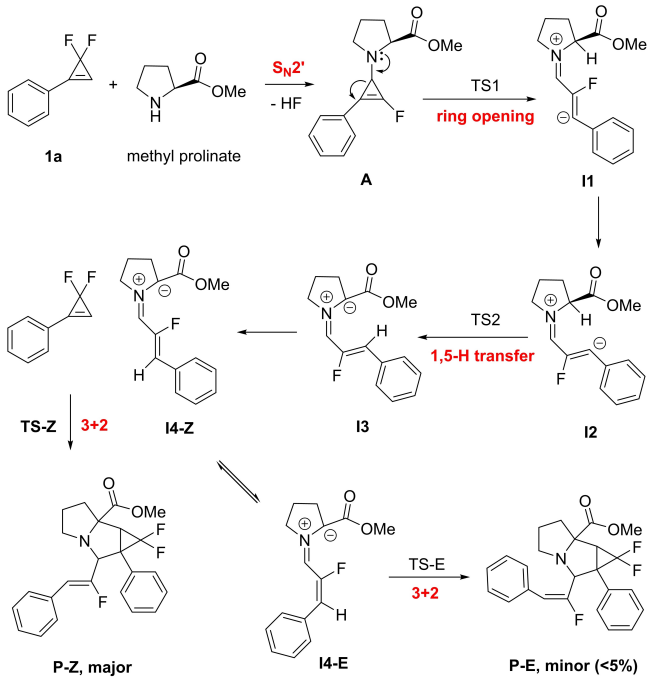
As shown in Scheme 9, the solvent-free cycloaddition reaction between difluorocyclopropene (**1**) and proline esters results in the formation of the Z-isomer of compounds **7** stereoselectively (Z = 95%, E < 5%). To rationalise this experimental observation, we investigated the detailed mechanism for the formation of Z and E isomers of compound **7b** at the M06/def2-TZVP[21–22] level of density functional theory (DFT) using ORCA 5.0.4.[23] Scheme 9 shows the mechanism for the formation of Z and E isomers of compound **7b** through cycloaddition of difluorocyclopropene **1a** and methyl prolinate. Frequency calculations were carried out on the optimized structures to calculate thermal corrections and to characterise various stationary points as minima and transition states, having zero and single imaginary frequencies, respectively. Reaction pathways were traced by performing intrinsic reaction coordinate (IRC) calculations on transition states.[24]



Scheme 7. Scope of vinyl fluoride formation.



Scheme 8. Cross-over experiment with cyclopropenes **1c** and **1e**. Percentage in parenthesis based on ^{19}F NMR ratio of products.



Scheme 9. Mechanism of cycloaddition between difluorocyclopropene **1 a** and methyl prolinate.

All the possible stationary points along the reaction coordinates of cycloaddition of difluorocyclopropene **1 a** and methyl prolinate were optimized and the calculated Gibbs free energy profiles (ΔG) are shown in Figure 2. In the first step, **1 a** and methyl prolinate react with each other in an endergonic reaction leading to the formation of intermediate A (ΔG = 10.5 kcal/mol, Figure 2). The intermediate undergoes opening of the cyclopropropene ring, resulting in the formation of intermediate **I1** via transition state **TS1**. The barrier for this reaction is 23.5 kcal/mol relative to the starting reactants (Figure 2). Intermediate **I1** undergoes 1,5-H transfer via intermediate **I2** and transition state **TS2** leading to the formation of

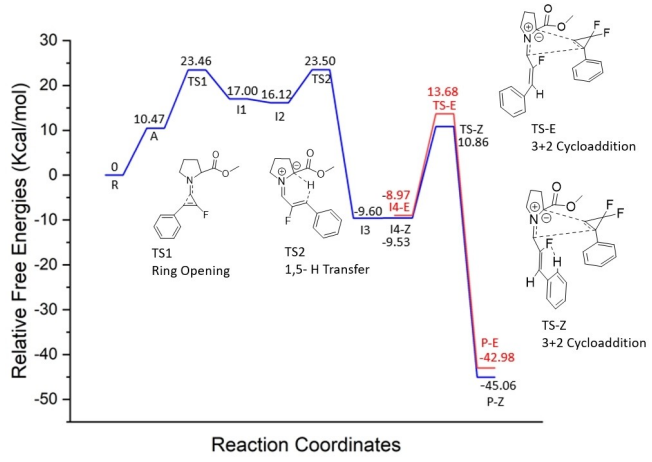


Figure 2. Gibbs free energy profiles of cycloaddition between cyclopropene **1 a** and methyl prolinate.

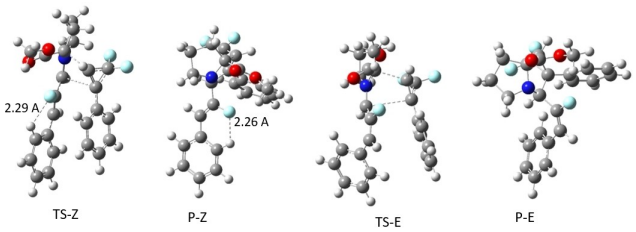


Figure 3. Optimized structures of **TS**–**Z**, **P**–**Z**, **TS**–**E** and **P**–**E**.

intermediate **I3**. The formation of **I3** is thermodynamically favoured, having an energy −9.5 kcal/mol lower than reactants and the barrier to form this stable intermediate is approximately iso-energetic with the initial barrier (ΔG* = 23.5 kcal/mol, Figure 2). As a result of bond rotations intermediate **I3** converts to intermediate **I4**–**Z**. The cycloaddition reaction between intermediate **I4**–**Z** and cyclopropene **1 a** through transition state **TS**–**Z** (imaginary frequency = 325.71i cm^{-1}) results in the formation of the Z-isomer denoted as **P**–**Z** in Scheme 9. The energy profile shows that the energy barrier to form **TS**–**Z** is 20.4 kcal/mol, relative to intermediate **I4**–**Z** with the final formation of **P**–**Z** being strongly exergonic (45.1 kcal/mol, Figure 2).

The formation of the E-isomer, **P**–**E**, is possible due to the rapid equilibrium between **I4**–**Z** and **I4**–**E** (Scheme 9), with the latter being only 0.5 kcal/mol higher in energy. However, the formation of the product from **I4**–**E** has a larger barrier relative to the Z-isomer (ΔG*(**I4**–**E** → **TS**–**E**) = 22.7 kcal/mol, Figure 2). If the barrier is surmounted then the product (**P**–**E**) is formed in a similarly non-reversible exergonic reaction (ΔG = 37.3 kcal/mol). Thus, the stereoselectivity of the Z-isomer is kinetically controlled due to the lower barrier associated with the final cyclization step for this isomer, in agreement with experimental results (Figure 2).

The optimized structures of transition state **TS**–**Z** and Z-isomer **P**–**Z** show that intramolecular H-bonding Ar–H···F with distances 2.29 Å and 2.26 Å, respectively, could be a crucial factor in fixing the stereoselectivity (Figure 3).

The presence of an Ar–H···F hydrogen bond is supported by a blue shift in the C–H stretching frequency of Ar–H···F in comparison to Ar–H without H-bonding. In the vibrational analysis of **P**–**Z**, Ar–H···F protons shows stretching vibrations at 3223 cm^{-1}, while the other four Ar–H protons show stretching vibrations at 3194 cm^{-1}. Similarly in the case of the transition state **TS**–**Z**, Ar–H···F this proton has stretching vibrations at 3216 cm^{-1} and the remaining four Ar–H have stretching vibrations at 3195 cm^{-1}. In contrast, for the transition state and product corresponding to E-isomer, **TS**–**E** and **P**–**E** all five Ar–H have stretching vibrations at 3196 cm^{-1} and 3197 cm^{-1}, respectively.

Conclusions

We report on the synthesis of novel *gem*-difluorocyclopropane containing heterocycles exploiting the cycloaddition reaction

between *gem*-difluorocyclopropenes and azomethine ylides. The resulting products can be generated in high yields and diastereoselectivities thus representing a valuable entry into these medicinally relevant architectures. Additionally, it was discovered that the solvent-free reaction between *gem*-difluorocyclopropene and proline esters (2 equiv.) affords new products that embed two fluorinated moieties in the form of a Z-configured vinyl fluoride and a difluorinated 3-azabicyclo[3.1.0]hexane. Computational data are presented that account for this transformation and its mechanism which pinpoints to the presence of an intramolecular Ar–H···F bond that determines the alkene geometry. Overall, the discussed transformations expand the toolbox of readily accessible fluorinated heterocycles that are rich in three-dimensionality and thus are expected to find applications in medicinal chemistry programs.

Supporting Information

The authors have cited additional references within the Supporting Information.[25–33]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Ar–H···F bonding · difluorocyclopropene · dipolar cycloaddition · fluorinated heterocycle · reaction mechanism

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