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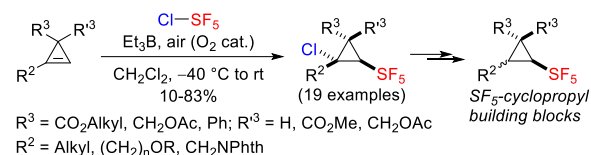
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Radical Addition of SF₅Cl to Cyclopropenes: Synthesis of (Pentafluorosulfanyl)cyclopropanes

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ABSTRACT: With the goal of accessing yet unknown SF₅-cyclopropyl building blocks, the radical addition of SF₅Cl to cyclopropenes was investigated. Addition of the SF₅ radical occurs regioselectively at the less substituted carbon of cyclopropenes and *trans* to the most hindered substituent at C3, while chlorine atom transfer proceeds with moderate to high levels of diastereocontrol. The carbon-chlorine bond in the resulting adducts can undergo subsequent radical reduction or be involved in a radical cyclization.

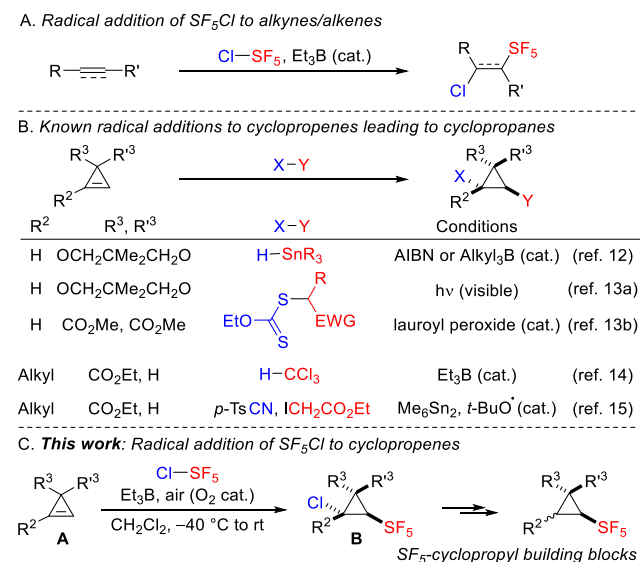
Appearing in the top ten of the most encountered ring systems in drugs,¹ the cyclopropyl fragment is frequently used to improve the potency, the selectivity and the pharmacokinetic properties of a lead compound and hence overcome bottlenecks in drug discovery and development.² Fluorine or fluorinated groups can likewise address many roadblocks during the development phases of a drug candidate and are found in nearly a third of marketed pharmaceuticals and agrochemicals.³ As a logical consequence, the development of synthetic methods toward cyclopropanes bearing fluorinated groups, which combine both these latter structural elements, has elicited significant interest.⁴

The pentafluorosulfanyl group (SF₅) which belongs to the so-called “emerging fluorinated motifs” beyond the trifluoromethyl group (CF₃),⁵ surpasses the latter substituent in terms of electronegativity, lipophilicity, steric demand (with a unique octahedral geometry) and also hydrolytic stability.⁶ Not surprisingly, pentafluorosulfanyl organic compounds have attracted attention in medicinal chemistry, agrochemistry and in material science.⁷ To date, (hetero)aromatic compounds incorporating a SF₅ group are undoubtedly the most represented structures,⁶⁻⁸ hence the development of new SF₅-aliphatic building blocks remains highly desirable.⁹ Despite their potential interest, SF₅-substituted cyclopropanes are still unknown compounds to our knowledge. To date, the most general and practical entry to SF₅-aliphatic compounds remains the radical addition of SF₅Cl to alkynes or alkenes using Et₃B as the initiator (Scheme 1A).^{10,11} Cyclopropenes are known to behave as radical acceptors, as illustrated by the hydrostannylation of cyclopropenone acetals,¹² the addition of carbon-centered electrophilic radicals generated from xanthates to similar substrates or cyclopropene *gem*-dicarboxylates,¹³ the addition of the trichloromethyl radical to cyclopropenates¹⁴ and the more recently disclosed radical carbocyanation reaction¹⁵ (Scheme 1B).¹⁶

Herein, we report our results on the radical addition of SF₅Cl to cyclopropenes **A**, the investigation of the substrate scope and

subsequent manipulation of the carbon-chlorine bond in the resulting adducts **B**, with the goal of accessing new diversely substituted SF₅-cyclopropyl building blocks (Scheme 1C).

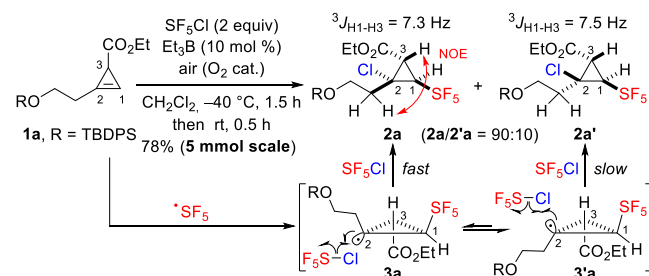
Scheme 1. Chloro(pentafluorosulfanylation) Reactions and Radical Additions to Cyclopropenes



Cyclopropenyl ester **1a**, possessing a 2-(*tert*-butyldiphenylsilyloxy)ethyl group (TBDPS = Sit-BuPh₂)¹⁷ was treated with SF₅Cl (2 equiv) and the reaction was initiated by addition of Et₃B (10 mol %) and air (CH₂Cl₂, -40 °C, 1.5 h; then rt, 0.5 h). Under these conditions, the radical chain addition of SF₅Cl across the double bond of **1a** proceeded smoothly, with perfect control of the regioselectivity, and delivered a diastereomeric mixture of the β-chloro(pentafluorosulfanyl)cyclopropanes **2a** and **2'a** in a 90:10 ratio (78%, 5 mmol scale experiment). Anal-

ysis of the ^1H NMR spectrum of **2a/2'a** indicated a similar vicinal coupling constant between cyclopropyl protons H1 and H3 in both diastereomers,¹⁸ thereby confirming that addition of the SF₅ radical occurred at the less substituted carbon (C1) of cyclopropene **1a** on the face opposite to the ester moiety at C3, as observed in other radical additions to cyclopropenoates.^{14,15} The resulting rapidly interconverting cyclopropyl radical intermediates¹⁹ **3a** and **3'a** suffer from a steric interaction between the (CH₂)₂OTBDPS substituent and the SF₅ group (at C1) or the ester moiety (at C3), respectively. However, the less stable invertermer **3a** should undergo a faster chlorine atom transfer from SF₅Cl (*trans* to the sterically demanding SF₅ substituent at C1) compared to **3'a**. This would account for the formation of **2a** as the major diastereomer, the relative stereochemistry of which was assigned by NMR spectroscopy (NOESY) (Scheme 2).²⁰

Scheme 2. Addition of SF₅Cl to Cyclopropene **1a**

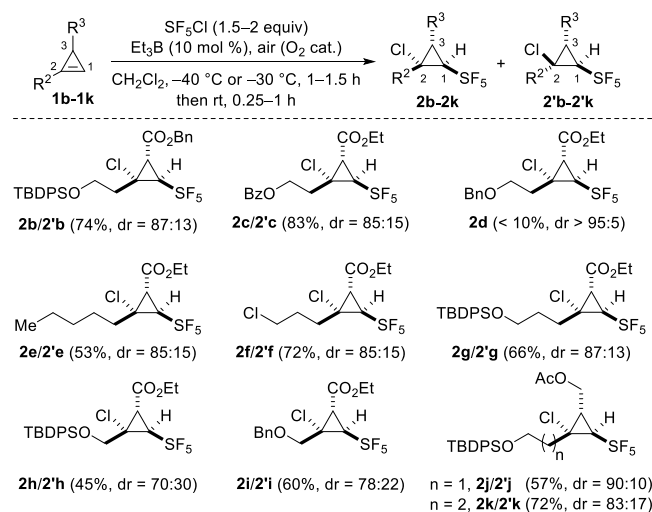


The reactivity of cyclopropene **1a** was also compared to that of the terminal alkyne and alkene possessing the same (CH₂)₂OTBDPS substituent. A competition experiment revealed that the radical addition of SF₅Cl to cyclopropene **1a** and to the terminal alkyne occurred at comparable rates whereas the alkene reacted faster.²⁰

The substrate scope was then investigated with cyclopropenes **1b-1k** bearing one substituent at C3 and C2 (Scheme 3). Benzyl cyclopropenoate **1b** led to similar results compared to ethyl ester **1a** and the radical addition of SF₅Cl afforded cyclopropanes **2b/2'b** in 74% yield (dr = 87:13). Cyclopropene **1c**, in which the alcohol was protected as a benzoate, exhibited a reactivity comparable to silyl ether **1a** and provided cyclopropanes **2c/2'c** (83%, dr = 85:15). By contrast, benzyl ether **1d** led to a complex mixture of products from which the desired cyclopropane **2d** was isolated in low yield (< 10%).²⁰ Cyclopropene **1e** bearing a *n*-pentyl chain at C2 cleanly led to cyclopropanes **2e/2'e** (53%, dr = 85:15) without formation of a secondary alkyl chloride resulting from a putative 1,5-hydrogen atom transfer triggered by the cyclopropyl radical intermediate.¹⁵ Cyclopropene **1f** possessing a 3-chloropropyl chain underwent an efficient addition of SF₅Cl and was converted to **2f/2'f** (72%, dr = 85:15). Substrate **1g** having the silyl ether located at a more remote position compared to cyclopropene **1a**, led to similar results in terms of yield and diastereoselectivity and afforded adducts **2g/2'g** (66%, dr = 87:13). By contrast, substrate **1h** in which the TBDPS ether is separated from the three-membered ring by a single methylene unit, provided adducts **2h/2'h** with a drop of diastereoselectivity (dr = 70:30) and yield (45%) compared to **1a**. The steric hindrance of the silyloxy substituent may reduce the efficiency of the chlorine atom transfer from SF₅Cl at C2 and hence of the whole radical-chain mechanism.²¹ Replacement of the TBDPS protecting group by the less sterically

hindered benzyl ether in substrate **1i**, improved the yield of the corresponding adducts **2i/2'i** (60%, dr = 78:22) compared to **2h/2'h**. The scope is not restricted to cyclopropenoates, as illustrated with the addition of SF₅Cl to cyclopropenes **1j** and **1k** possessing a moderately electron-donating (acetoxy)methyl group at C3, which delivered the corresponding adducts **2j/2'j** (57%, dr = 90:10) and **2k/2'k** (72%, dr = 83:17), respectively (Scheme 3). A competition experiment indicated that **1j** undergoes addition of the SF₅ radical three times faster than cyclopropenoate **1a**. Indeed, the presence of a carboethoxy group at C3 in substrate **1a**, which is known to withdraw electron density from the HOMO of the cyclopropene C=C bond,²² would slow down the addition of the electrophilic pentafluorosulfanyl radical compared to **1j**.

Scheme 3. Scope of the Addition of SF₅Cl to Disubstituted cyclopropenes^{a,b,c}

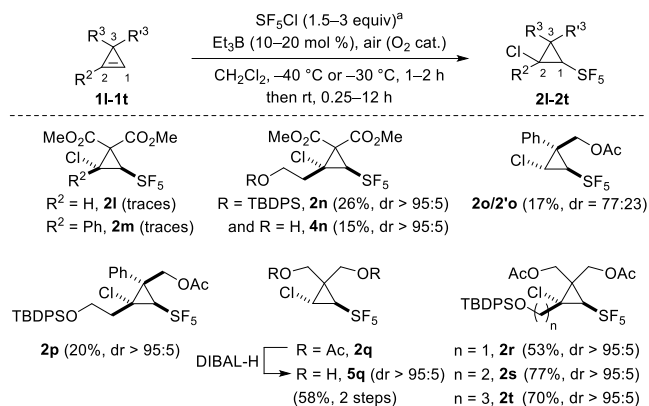


^a The structure of the major diastereomer is shown. ^b Indicated dr values refer to the ratio of the two observed diastereomers (among the four possible). ^c 1-15 mmol scale experiments for **1b-1j**.

Investigation of the scope was pursued with cyclopropenes *gem*-dicarboxylates **1l-1n** (Scheme 4). Cyclopropenes **1l** and **1m** bearing two electron-withdrawing groups at C3 did not react with SF₅Cl, and only traces of adducts **2l** and **2m** were detected by analysis of the crude reaction mixture by ¹⁹F NMR spectroscopy. The presence of an electron-donating alkyl substituent at C2 (R² = (CH₂)₂OTBDPS) in cyclopropene **1n** enabled the radical addition of SF₅Cl which provided cyclopropane **2n** (26%) as a single diastereomer (*trans* addition of SF₅Cl). However, partial cleavage of the silyl ether in **2n**, presumably triggered by a fluoride source, also took place and led to the crystalline alcohol **4n** (15%), the relative stereochemistry of which was unambiguously assigned by X-ray diffraction analysis.²³ A phenyl group at C3 also altered the efficiency of the addition of SF₅Cl to di- and trisubstituted cyclopropenes **1o** and **1p**, respectively, and led to incomplete conversions despite the presence of the electron-donating CH₂OAc substituent at the same position. Adducts **2o/2'o** were isolated in low yield (17%, dr = 77:23) whereas **2p** was generated as a single detectable diastereomer (20%). In both cases, addition of the SF₅ radical occurred preferentially *trans* to the more hindered phenyl group.²⁰ By contrast, cyclopropenes **1q-1t** with *gem*-di(acetoxymethyl)

substitution, reacted smoothly with SF₅Cl. After reduction of the initial adduct **2q** with DIBAL-H, the tetrasubstituted cyclopropane **5q** was obtained as a single detectable diastereomer in 58% yield (two steps from **1q**). Cyclopropenes **1r-1t** led to the pentasubstituted cyclopropanes **2r-2t** (53–77%), respectively. The radical addition of SF₅Cl was more efficient for cyclopropenes **1s** and **1t** having the TBDPS located at a more remote position on the chain compared to substrate **1r** (Scheme 4).

Scheme 4. Scope of the Addition of SF₅Cl to *gem*-Disubstituted or Trisubstituted Cyclopropenes

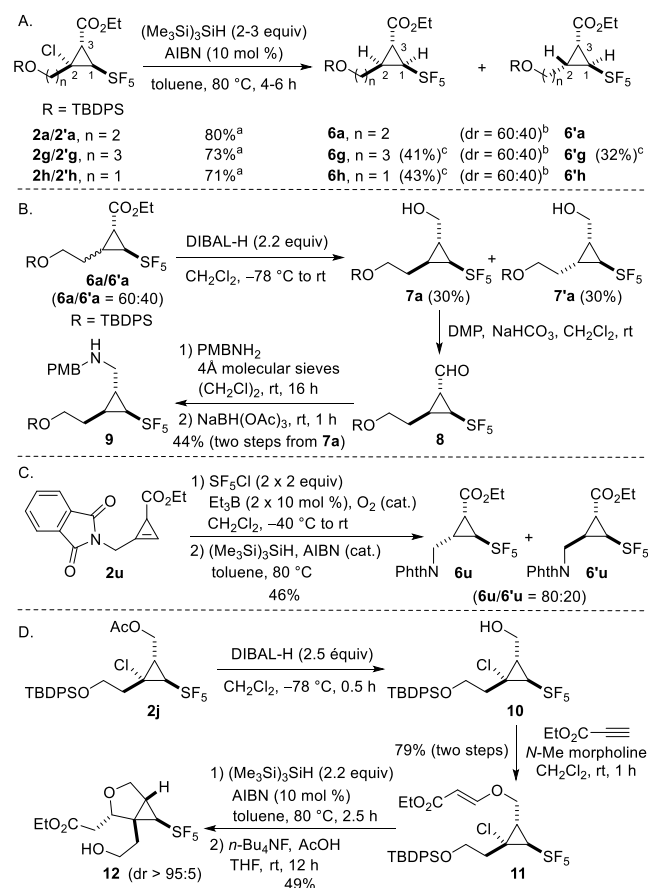


^a SF₅Cl (2 x 1.5 equiv) and Et₃B (2 x 10 mol %) were used for substrates **1l-1o**.

Having evaluated the scope of the radical addition of SF₅Cl to cyclopropenes, the subsequent transformation of the carbon-chlorine bond in the resulting adducts was investigated.²⁴ The implementation of a hydrodechlorination process was considered and this operation was achieved under radical conditions by treating **2a/2'a** (dr = 90:10) with (Me₃Si)₃SiH in the presence of AIBN as initiator (10 mol %) (toluene, 80 °C, 6 h). Although reduction of the C–Cl bond occurred efficiently, hydrogen atom transfer from (Me₃Si)₃SiH to the cyclopropyl radical intermediate, generated at C2, proceeded with little stereocontrol and led to the epimeric SF₅-cyclopropanes **6a** and **6'a** in a 60:40 ratio (80%). Reduction of the chlorocyclopropanes **2g/2'g** and **2h/2'h** was likewise accomplished to afford the corresponding SF₅-cyclopropanes **6g/6'g** (73%) and **6h/6'h** (71%), although partial separation of **6g** (41%), **6'g** (32%) and **6h** (43%) could be achieved. The structure of the crystalline **6h** was unambiguously confirmed by X-ray diffraction analysis (Scheme 5A). Reduction of the previously obtained mixture of **6a/6'a** with DIBAL-H afforded the corresponding cyclopropylcarbinols **7a** (30%, dr = 95:5) and **7'a** (30%) after purification by flash chromatography on silica gel. After oxidation of **7a** with Dess-Martin periodinane (DMP), the resulting aldehyde **8** was involved in a reductive amination with *p*-methoxybenzylamine to afford cyclopropylmethyl amine **9** (44%, two steps from **7a**) (Scheme 5B). Another complementary route to SF₅-cyclopropylmethyl amine derivatives²⁵ was devised from cyclopropene **1u** which was involved in a radical addition of SF₅Cl. After dechlorination under radical conditions, a mixture of the epimeric *N*-(phthaloyl)cyclopropylmethyl amines **6u/6'u** was obtained (46%, dr = 80:20) (Scheme 5C). The presence of a carbon-chlorine bond in β-chloro SF₅-cyclopropanes could also be exploited to construct a new ring by a radical cyclization and this

strategy was illustrated in the case of substrate **2j**. After reductive cleavage of the acetyl group, the resulting alcohol **10** was involved in a conjugate addition to ethyl propiolate to afford the corresponding β-alkoxy acrylate **11** (79%, two steps from **2j**). The 5-*exo*-trig radical cyclization was triggered by treatment of **11** with (Me₃Si)₃SiH. Subsequent treatment with *n*-Bu₄NF under buffered conditions (AcOH, THF, rt) induced the cleavage of the silyl ether and facilitated product isolation. The oxabicyclic compound **12** bearing a controlled quaternary stereocenter was formed as a single diastereomer and isolated in 49% yield (two steps from **11**). The relative stereochemistry of **12** was assigned by NMR (NOESY) (Scheme 5D).²⁰

Scheme 5. Access to SF₅-Cyclopropyl Building Blocks



^a Isolated yield of dechlorinated products. ^b Diastereomeric ratio (crude product). ^c Isolated yield of separated diastereomer.

In summary, we have demonstrated that cyclopropenes constitute an interesting class of substrates in radical chloro(pentafluorosulfanylation) reactions. Addition of the electrophilic SF₅ radical occurs regioselectively and with high diastereoselectivity (*trans* to the more sterically hindered substituent at C3) but moderate to high levels of diastereocontrol are observed in the subsequent chlorine atom transfer from SF₅Cl. The carbon-chlorine bond in the resulting adducts can be subsequently involved in a radical dechlorination or in a radical cyclization to access a wide variety of SF₅-cyclopropyl building blocks, which constitute a new family of cyclopropanes possessing fluorinated groups.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, ^1H , ^{13}C and ^{19}F NMR spectra, and characterization data of new compounds (PDF)

Crystallographic data for compounds **4n** and **6h** (cif)

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

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