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Radical Addition of SF_5Cl to Cyclopropenes: Synthesis of (Pentafluorosulfanyl)cyclopropanes

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Cite This: *Org. Lett.* 2021, 23, 5491−5495 Read Online

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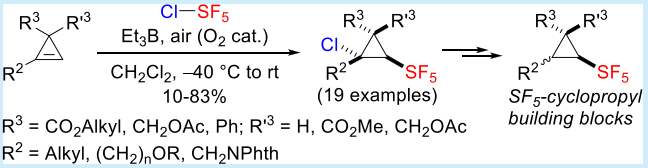
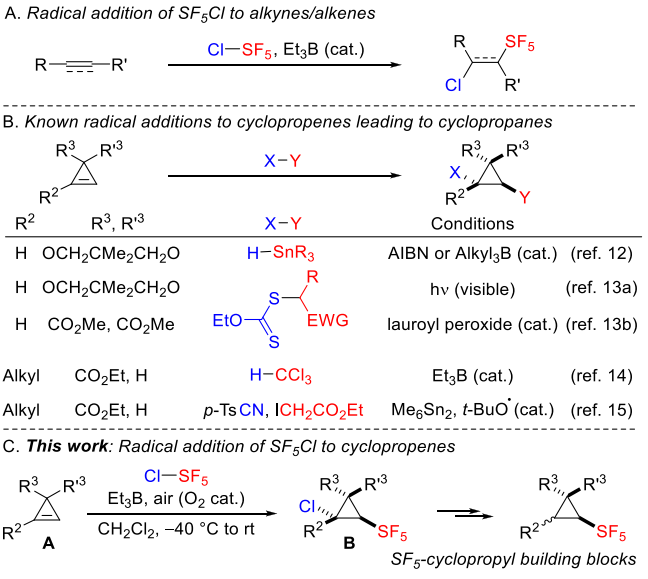
ABSTRACT: With the goal of accessing yet unknown SF_5-cyclopropyl building blocks, the radical addition of SF_5Cl to cyclopropenes was investigated. Addition of the SF_5 radical occurs regioselectively at the less substituted carbon of cyclopropenes and *trans* to the most hindered substituent at C3, 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 10 of the most encountered ring systems in drugs,[1] the cyclopropyl fragment is frequently used to improve the potency, selectivity, and 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 one-third of marketed pharmaceuticals and agrochemicals.[3] As a logical consequence, the development of synthetic methods toward cyclopropanes bearing fluorinated groups, which combine both of these latter structural elements, has elicited significant interest.[4]

The pentafluorosulfanyl group (SF_5), which belongs to the so-called "emerging fluorinated motifs" beyond the trifluoromethyl group (CF_3),[5] surpasses the latter substituent in terms of electronegativity, lipophilicity, steric demand (with a unique octahedral geometry), and hydrolytic stability.[6] Not surprisingly, pentafluorosulfanyl organic compounds have attracted attention in medicinal chemistry, agrochemistry, and material science.[7] To date, (hetero)aromatic compounds incorporating a SF_5 group are undoubtedly the most represented structures;[6−8] hence, the development of new SF_5-aliphatic building blocks remains highly desirable.[9] Despite the potential interest in them, SF_5-substituted cyclopropanes are still unknown compounds to the best of our knowledge. To date, the most general and practical entry to SF_5-aliphatic compounds remains the radical addition of SF_5Cl to alkynes or alkenes using Et_3B 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 cyclopropenoates,[14] and the more recently disclosed radical carbocyanation reaction[15] (Scheme 1B).[16]

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



Herein, we report our results on the radical addition of SF_5Cl to cyclopropenes **A** and 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

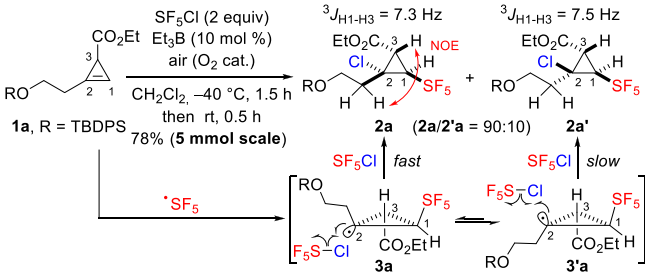
Received: June 2, 2021
Published: June 25, 2021

https://doi.org/10.1021/acs.orglett.1c01840
Org. Lett. 2021, 23, 5491−5495

diversely substituted SF_5-cyclopropyl building blocks (Scheme 1C).

Cyclopropenyl ester **1a**, possessing a 2-(*tert*-butyldiphenylsilyloxy)ethyl group (TBDPS = Si-*t*-BuPh$_2$),[17] was treated with SF_5Cl (2 equiv), and the reaction was initiated by addition of Et_3B (10 mol %) and air (CH_2Cl_2, −40 °C, 1.5 h; then rt, 0.5 h). Under these conditions, the radical chain addition of SF_5Cl across the double bond of **1a** proceeded smoothly, with perfect control of the regioselectivity, and delivered a diastereomeric mixture of *β*-chloro(pentafluorosulfanyl)cyclopropanes **2a** and **2′a** in a 90:10 ratio (78%, 5 mmol scale experiment). Analysis of the ^{1}H NMR spectrum of **2a** and **2′a** indicated a similar vicinal coupling constant between cyclopropyl protons H1 and H3 in both diastereomers,[18] thereby confirming that addition of the SF_5 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 intermediates[19] **3a** and **3′a** suffer from a steric interaction between the $(CH_2)_2$OTBDPS substituent and the SF_5 group (at C1) or the ester moiety (at C3), respectively. However, the less stable invertomer **3a** should undergo a faster chlorine atom transfer from SF_5Cl (*trans* to the sterically demanding SF_5 substituent at C1) compared to that of **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]

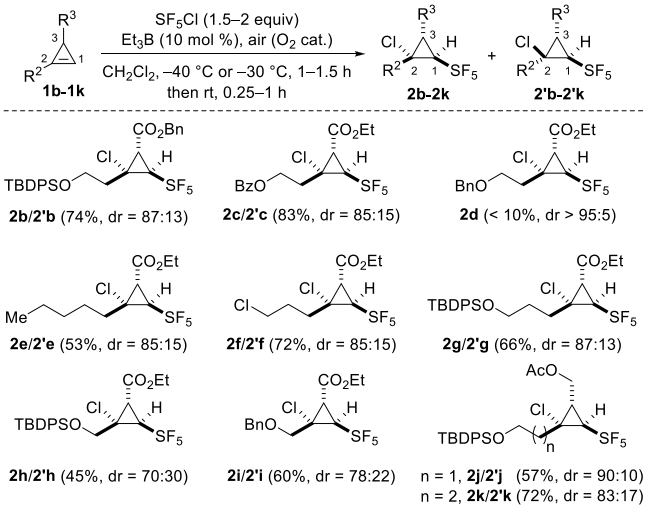
Scheme 2. Addition of SF_5Cl to Cyclopropene 1a



The reactivity of cyclopropane **1a** was also compared to that of the terminal alkyne and alkene possessing the same $(CH_2)_2$OTBDPS substituent. A competition experiment revealed that the radical addition of SF_5Cl 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 those for ethyl ester **1a**, and the radical addition of SF_5Cl afforded cyclopropanes **2b** and **2′b** in 74% yield (dr = 87:13). Cyclopropene **1c**, in which the alcohol was protected as a benzoate, exhibited a reactivity comparable to that of silyl ether **1a** and provided cyclopropanes **2c** and **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 an *n*-pentyl chain at C2 cleanly led to cyclopropanes **2e** and **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 SF_5Cl and was converted to **2f** and **2′f**

Scheme 3. Scope of the Addition of SF_5Cl to Disubstituted Cyclopropenes[a]



[a]The structure of the major diastereomer is shown. Indicated dr values refer to the ratio of the two observed diastereomers (among the four possible). Experiments on a 1−15 mmol scale for **1b**−**1j**.

(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** and **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** and **2′h** with a decrease in diastereoselectivity (dr = 70:30) and yield (45%) compared to those of **1a**. The steric hindrance of the silyloxy substituent may decrease the efficiency of the chlorine atom transfer from SF_5Cl 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** and **2′i** (60%, dr = 78:22) compared to that of **2h** and **2′h**. The scope is not restricted to cyclopropenoates, as illustrated with the addition of SF_5Cl to cyclopropenes **1j** and **1k** possessing a moderately electron-donating (acetyloxy)methyl group at C3, which delivered the corresponding adducts **2j** and **2′j** (57%, dr = 90:10) and **2k** and **2′k** (72%, dr = 83:17), respectively (Scheme 3). A competition experiment indicated that **1j** undergoes addition of the SF_5 radical 3 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 that of **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 SF_5Cl, and only traces of adducts **2l** and **2m** were detected by analysis of the crude reaction mixture by ^{19}F NMR spectroscopy. The presence of an electron-donating alkyl substituent at C2 [R^2 = $(CH_2)_2$OTBDPS] in cyclopropene **1n** enabled the radical addition of SF_5Cl that provided cyclopropane **2n** (26%) as a single diastereomer (*trans* addition of SF_5Cl). However, partial cleavage of the silyl ether in **2n**, presumably triggered by a fluoride source, also took place and led to crystalline alcohol **4n** (15%), the relative stereo-

https://doi.org/10.1021/acs.orglett.1c01840
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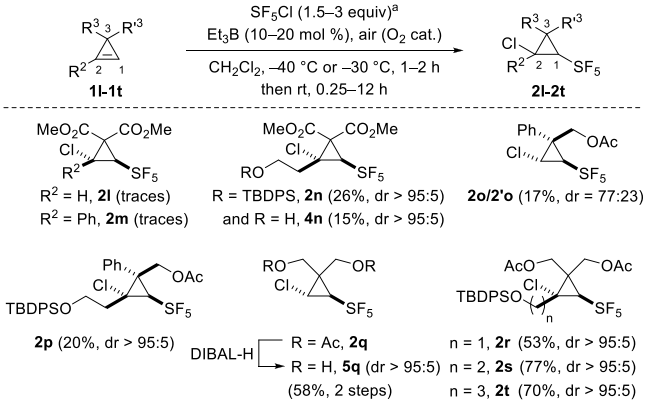
Scheme 4. Scope of the Addition of SF_5Cl to *gem*-Disubstituted or Trisubstituted Cyclopropenes

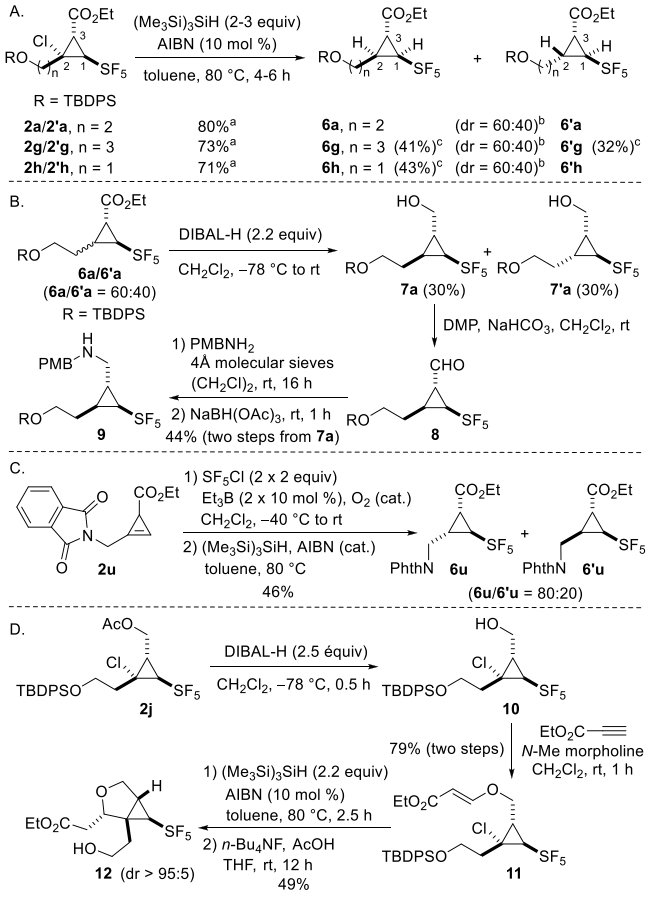


[a]SF_5Cl (2 × 1.5 equiv) and Et_3B (2 × 10 mol %) were used for substrates **1l**–**1o**.

chemistry of which was unambiguously assigned by X-ray diffraction analysis.[23] A phenyl group at C3 also altered the efficiency of the addition of SF_5Cl to di- and trisubstituted cyclopropenes **1o** and **1p**, respectively, and led to incomplete conversions despite the presence of the electron-donating CH_2OAc substituent at the same position. Adducts **2o** and **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 SF_5 radical occurred preferentially *trans* to the more hindered phenyl group.[20] By contrast, cyclopropenes **1q**–**1t** with *gem*-di(acetoxymethyl) substitution reacted smoothly with SF_5Cl. After reduction of initial adduct **2q** with DIBAL-H, tetrasubstitued cyclopropane **5q** was obtained as a single detectable diastereomer in 58% yield (two steps from **1q**). Cyclopropenes **1r**–**1t** led to pentasubstituted cyclopropanes **2r**–**2t** (53–77%), respectively. The radical addition of SF_5Cl 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).

Having evaluated the scope of the radical addition of SF_5Cl 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** and **2′a** (dr = 90:10) with $(Me_3Si)_3SiH$ in the presence of AIBN as an initiator (10 mol %) (toluene, 80 °C, 6 h). Although reduction of the C–Cl bond occurred efficiently, hydrogen atom transfer from $(Me_3Si)_3SiH$ to the cyclopropyl radical intermediate, generated at C2, proceeded with little stereocontrol and led to epimeric SF_5-cyclopropanes **6a** and **6′a** in a 60:40 ratio (80%). Reduction of chlorocyclopropanes **2g** and **2′g**, and **2h** and **2′h**, was likewise accomplished to afford the corresponding SF_5-cyclopropanes **6g** and **6′g** (73%) and **6h** and **6′h** (71%), respectively, although partial separation of **6g** (41%), **6′g** (32%), and **6h** (43%) could be achieved. The structure of crystalline **6h** was unambiguously confirmed by X-ray diffraction analysis (Scheme 5A). Reduction of the previously obtained mixture of **6a** and **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

Scheme 5. Access to SF_5-Cyclopropyl Building Blocks



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

amination with *p*-methoxybenzylamine to afford cyclopropylmethyl amine **9** (44%, two steps from **7a**) (Scheme 5B). Another complementary route to SF_5-cyclopropylmethyl amine derivatives[25] was devised from cyclopropene **1u**, which was involved in a radical addition of SF_5Cl. After dechlorination under radical conditions, a mixture of the epimeric *N*-(phthaloyl)cyclopropylmethyl amines **6u** and **6′u** was obtained (46%, dr = 80:20) (Scheme 5C). The presence of a carbon–chlorine bond in *β*-chloro SF_5-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 $(Me_3Si)_3SiH$. Subsequent treatment with *n*-Bu_4NF under buffered conditions (AcOH, THF, rt) induced the cleavage of the silyl ether and facilitated product isolation. 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]

In summary, we have demonstrated that cyclopropenes constitute an interesting class of substrates in radical chloro(pentafluorosulfanylation) reactions. Addition of the electrophilic SF_5 radical occurs regioselectively and with high

https://doi.org/10.1021/acs.orglett.1c01840
Org. Lett. 2021, 23, 5491–5495

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 SF_5Cl. 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 SF_5-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 at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01840.

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

Accession Codes

CCDC 2081921−2081922 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the ANR (DEFIS project, ANR-17-CE07-0008) is gratefully acknowledged.

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https://doi.org/10.1021/acs.orglett.1c01840
Org. Lett. 2021, 23, 5491−5495