Selective synthesis of spirobiindanes, alkenyl chlorides, and monofluoroalkenes from unactivated gem-difluoroalkanes controlled by aluminum-based Lewis acids

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The highly selective synthesis of spirobiindanes, alkenyl chlorides, and monofluoroalkenes via the cleavage of inert C(sp³)–F bonds in unactivated gem-difluoroalkanes using readily available and inexpensive aluminum-based Lewis acids of low toxicity is reported. The selectivity of this reaction can be controlled by modifying the substituents on the central aluminum atom of the promoter. An intramolecular cascade Friedel-Crafts alkylation of unactivated gem-difluorocarbons can be achieved using a stoichiometric amount of AlCl₃. The subsequent synthesis of alkenyl chlorides via F/Cl exchange followed by an elimination can be accomplished using AlEt₂Cl as a fluoride scavenger and halogen source. The defluorinative elimination of acyclic and cyclic gem-difluorocarbons to give monofluoroalkenes can be achieved using AlEt₃.

The widespread use of a variety of readily available organofluorine molecules in the chemical industry and the environmental concerns caused by the longevity of some potentially toxic fluorinated organic compounds has inspired impressive advances of the defluorinative functionalization of carbon-fluorine (C–F) bond. In contrast to the considerable number of reports that focus on the transition-metal-mediated or -catalyzed cleavage of C(sp²)–F bonds in aromatic and vinylic fluorocarbons, the direct degradation of C(sp³)–F bonds in unactivated aliphatic fluorides remains challenging.

Main-group-based Lewis acids that promote fluoride-abstraction processes have dramatically emerged in recent decades as an attractive strategy to selective functionalize inert C(sp³)–F bonds. Although the fluoride moiety in C–F bonds is neither a good leaving group nor a good Lewis base, the formation of more stable covalent bonds (e.g. Si–F, B–F, Al–F, and P–F) provides in many cases the thermodynamic driving force for this heterolytic transformation. In particular, practical and economic protocols that render the scission of the C(sp³)–F bond feasible include aluminum-based Lewis acids such as aluminum halides, AlEtCl₂, AlEt₂Cl, Al(alkyl)₃, Al(Oi-Pr)₃, or alumina, which are inexpensive, easy to handle, environmentally benign, and commonly used aluminum reagents of low toxicity.

In 1938, Henne and Newman reported the fluorine/chlorine (F/Cl) exchange between trifluoromethyl benzene and aluminum chloride, while the pioneering work of C–F bond activation appeared in the report by Olah and co-workers in 1957, the ionization of C–F bond to synthesize long lived carbocations. Not only boron based Lewis acids, antimony, bismuth, arsenic based Lewis acids and silica surface also effectively activate C–F bonds. Inspired by these work, using aluminum-based Lewis acids, a wide range of transformations of saturated fluorocarbons, including hydrodefluorinations, halodefluorinations, Friedel-Crafts alkylations, and the formation of C-heteroatom bonds have been studied extensively. However, most of these reports have focused on activated fluoroalkane substrates for further modifications such as benzylic and allylic trifluoroalkanes, as well as benzylic and tertiary aliphatic monofluoroalkanes, all of which afford stabilized...
carbocation intermediates. Meanwhile, due to their comparatively lower steric congestion, primary mono-fluoroalkanes have been used for Finkelstein-S'N2-type halogen-exchange reactions32,33. However, in spite of recent advances in transition-metal-catalyzed reactions of activated allylic or propargylic gem-difluoroalkanes34,35, there are only a few synthetic methods that use classical aluminum-based Lewis acids on gem-difluorocarbon-type substrates. In early examples, the alkylation and chlorodefluorination of benzylic gem-difluorocarbons has been achieved using an excess of AlCl3, AlMe3, or AlPh328. Subsequently, the SN2′-type alkylation of difluorohomoallyl alcohols can be controlled by trialkylaluminum compounds, which can coordinate to fluorine and adjacent oxygen atoms36,37. Recently, it has been reported that Al(OTf)3 enables the defluorinative cycloaddition/aromatization between benzylic 2,2-difluoroethanol and nitriles to afford oxazoles38. Nevertheless, breaking C(sp3)–F bonds in unactivated gem-difluoroalkanes remains highly challenging39–41. In 2018, Young and co-workers achieved the selective monodefluorination of benzylic and non-benzylic gem-difluoromethyl compounds using a frustrated Lewis pair approach based on B(C6F5)3 and P(o-Tol)3 to generate monofluoro phosphonium salts, which were subsequently convert into monofluoroolefins using Wittig protocols (Fig. 1a). Although the activation of benzylic gem-difluoromethyl groups proceeds in good yields (Fig. 1a), the abstraction of fluoride from unactivated 1,1-difluoroalkanes does not proceed well, and the more fluorophilic Lewis acid [Al(C6F5)3·(C7H8)] (2 equiv.) was required for the transformation, which proceeded in lower yields (Fig. 1b)40.

The occurrence of “over reactions” and poor reaction selectivity, which are mainly caused by unexpected transformations32,39 that include hydride shifts, hydrogen fluoride (HF) eliminations, and skeletal rearrangements of unstable fluoro-substituted carbocation intermediates generated from the initial abstraction of fluoride from a gem-difluoromethyl moiety, renders controlled synthetic methods highly desirable. Recently, we have reported the selective synthesis of spirobiindanes and monofluoroalkenes using B(C6F5)3 and hexafluoroisopropanol (HFIP), which exhibit a very high affinity toward fluoride41. Although the method is of great importance as a proof-of-concept, the reaction still requires high temperatures and the relatively expensive reagents B(C6F5)3 and HFIP, which are critical for this transformation. Our continued interest in the activation and modification of inert C(sp3)–F bonds41,42 has led us to examine ubiquitous aluminum-based Lewis acids of low cost for the selective synthesis of gem-difluoroalkanes (1) under mild conditions. Specifically, we used stoichiometric amounts of AlCl3, AlEt2Cl, or AlEt3 in this study to induce aluminum-fluorine (Al–F) interactions29,43,44 for the direct abstraction of fluoride from an unactivated gem-difluoroalkane (Fig. 1c).

**Results**

**Optimization study.** The results of the screening of Al-based Lewis acids for the cleavage of C(sp3)–F bonds are summarized in Table 1. Initially, we selected the simple unactivated aliphatic difluoroalkane 3,3-difluoropentane-1,5-diyl dibenzene (1a) as a substrate. When 2.2 equiv. of AlCl3 was used to initiate an intramolecular Friedel-Crafts cyclizations, the targeted 2,2′,3,3′-tetrahydro-1,1′-spirobi[indene] (2a) was formed in 72% yield (Table 1, entry 1), albeit under heterogeneous conditions. Attempts to render the reaction catalytic were unsuccessful, i.e., the formation of 2a was observed in <10% yield when 0.2 equiv. of AlCl3 were used (entry 3).
tron-rich alkyl substituents to the central aluminum atom (entries 4–7).

3. (0.1 M), and AlEt3) allowed tuning the reaction selectivity for the heterolysis of the C(sp3)–F bonds in unactivated (3a) in 39% yield (entry 2). As alkyl chlorides represent useful building blocks for the formation of complex organic architectures, establishing control by preventing such “over reactions” in favor of alkyl chlorides 3 would most likely be as attractive as it would be challenging. To solve this problem, we aimed at decelerating the heterolysis of C(sp3)–F bonds in gem-difluoroalkanes 1 by tuning the Lewis acidity of the aluminum reagents, which could potentially establish control over the reaction selectivity and exclusively afford alkyl chlorides 3. Therefore, we focused our attention on organoaluminum reagents with reduced Lewis acidity by adding electron-rich alkyl substituents to the central aluminum atom (entries 4–7).

Recently, it has been reported that an equimolar amount of AlEtCl2 promotes an intermolecular S_N1-type substitution in 2-trifluoromethyl-1-alkenes 29. However, when we treated 1 with 2.2 equiv. of AlEtCl2, we obtained only a tar-like complex mixture (entry 4). Yet, when using the weaker Lewis acid AlEt2Cl, alkyl chlorides 3 formed exclusively, i.e., the desired 3a was obtained in 92% yield and the formation of side products was not observed (entry 5; for more details, see also Supplementary Fig. 76 in SI). AlEt2Cl has already been reported to facilitate F/Cl exchange reactions in aliphatic monofluoroalkanes at −78 °C via S_N1- or SN2-type substitution in 2-trifluoromethyl-1-alkenes 29. However, when we treated 1,1-difluorocyclopentane (1.5 M) in a J. Young tube had been treated for 24 h with AlEt3, only ~10% of the corresponding terminal alkene was formed. It should also be noted here that cyclic gem-difluoroalkanes (3a–i) were also obtained in good yield.

Substrate scope. As shown in Fig. 2, aliphatic gem-difluoroalkanes substituted with alkyl groups (1a–f) afford moderate to high yields (up to 85%) of the corresponding spirobiphenyls, whereby C2-substituted substrates (1a,b) perform slightly better than C4-substituted substrates (1c–e). Interestingly, when using methoxy-substituted gem-difluoride 1g, alkyl chloride 2,2′-(3-chloropent-2-ene-1,5-diyl)bis(methoxybenzene) (3g) was formed in 38% yield, and the desired Friedel-Crafts alkylation product (2g) was not observed. Consistent with our strategy that a modification of the Lewis acidity could potentially control the reaction selectivity, the oxygen atom in 1g probably coordinates to the aluminum center of AlCl3 and thus reduces its Lewis acidity, which would hamper the fluoride-abstraction process, and thus switch the reaction pathway from the expected Friedel-Crafts alkylation to a chlorination/elimination process. The presence of halogen substituents in the gem-difluoroalkanes (1h–l) was well tolerated when using AlCl3, and the corresponding products were generated in acceptable yield (42–64%). Moreover, naphthyl-type 2m, mixed product 2n, and the six-membered spiro-compound 2o were also obtained in good yield.

Subsequently, we examined the synthesis of tri-substituted alkyl chlorides (3) using AlEt2Cl both as an activator and a chloro source (Fig. 3). High yields and good Z/E stereocontrol were observed in most cases; specifically, long-chain acyclic substrates, independent of their substitution pattern on the benzene ring, afforded the expected Friedel-Crafts alkylation to a chlorination/elimination process. The presence of halogen substituents in the gem-difluoroalkanes (11–ν) are also well tolerated under the AlEt2Cl-mediated conditions, furnishing the targeted cyclic alkyl chlorides (3t–3v) in acceptable yield (67–75%).

Table 1. Optimization of the reaction conditions with respect to Al-based Lewis acids. aIsolated yields for 2a and 3a. b 19F NMR yield for 4a using trifluorotoluene as the internal standard. ND = not detected by 1H or 19F NMR analysis of the crude reaction mixture. c Z/E = 12:1. d Z/E = 7.3:1. e Hexane was used as reaction solvent (0.1 M), Z/E = 8.7:1.

| Entry | Lewis acids (equiv) | Time (h) | Product* (%) |
|-------|---------------------|----------|--------------|
| 1     | AlCl3 (2.2)         | 2        | 72           | ND | ND |
| 2     | AlCl3 (1.1)         | 8        | 39           | 24 | ND |
| 3     | AlCl3 (0.2)         | 8        | 6            | trace | ND |
| 4     | AlEtCl2 (2.2)       | 8        | complex mixture | — |
| 5     | AlEt2Cl (2.2)       | 4        | ND           | 92b | ND |
| 6     | AlEt2 (2.2)         | <0.5     | ND           | 51c |
| 7     | AlEt3 (1.5)         | 7        | ND           | 85c |

However, when 1.1 equiv. of AlCl3 were used for the degradation of fluorinated 1a, the defluorinative chlorination/elimination product (3-chloropent-2-ene-1,5-diyl) dibenzene (3a) was formed in 24% yield, together with 2a in 39% yield (entry 2). As alkyl chlorides represent useful building blocks for the formation of complex organic architectures, establishing control by preventing such “over reactions” in favor of alkyl chlorides 3 would most likely be as attractive as it would be challenging. To solve this problem, we aimed at decelerating the heterolysis of C(sp3)–F bonds in unactivated gem-difluoroalkanes 1 by tuning the Lewis acidity of the aluminum reagents, which could potentially establish control over the reaction selectivity and exclusively afford alkyl chlorides 3. Therefore, we focused our attention on organoaluminum reagents with reduced Lewis acidity by adding electron-rich alkyl substituents to the central aluminum atom (entries 4–7).

Recently, it has been reported that an equimolar amount of AlEtCl2 promotes an intermolecular S_N1-type substitution in 2-trifluoromethyl-1-alkenes 29. However, when we treated 1a with 2.2 equiv. of AlEtCl2, we obtained only a tar-like complex mixture (entry 4). Yet, when using the weaker Lewis acid AlEt2Cl, alkyl chlorides 3 formed exclusively, i.e., the desired 3a was obtained in 92% yield and the formation of side products was not observed (entry 5; for more details, see also Supplementary Fig. 76 in SI). AlEt2Cl has already been reported to facilitate F/Cl exchange reactions in aliphatic monofluoroalkanes at −78 °C via S_N1- or S_N2-type mechanisms, albeit that these reactions exhibit a very limited substrate scope 32. Using AlEt3 under otherwise identical reaction conditions afforded monofluoroalkene 3a in 51% yield without producing any Friedel-Crafts alkylation products (2a). Further improvement of the yield of 4a to 85% was observed upon conducting the reaction in n-hexane, using 1.5 equiv. of AlEt3, and prolonging the reaction time (entry 7; for more details, see also Supplementary Table 1 in SI). However, it should be noted here that the AlEt3-mediated defluorinative elimination of 1,1-difluorocyclopentane has already been reported by Ozerov, albeit only in one special case 39. Specifically, the formal HF-abstraction product 1-fluorocyclopent-1-ene was observed in 24% 19F NMR yield after a C_6D_12 solution of 1,1-difluorocyclopentane (1.5 M) in a J. Young tube had been treated for 24 h with AlEt3 (2.0 equiv.) at room temperature 39. Modifying the substituents on the central aluminum atom (AlCl3, AlEt2Cl, and AlEt3) allowed tuning the reaction selectivity for the heterolysis of the C(sp3)–F bonds in unactivated gem-difluoroalkanes 1.

Substrate scope. As shown in Fig. 2, aliphatic gem-difluoroalkanes substituted with alkyl groups (1a–f) afford moderate to high yields (up to 85%) of the corresponding spirobiphenyls, whereby C2-substituted substrates (1a,b) perform slightly better than C4-substituted substrates (1c–e). Interestingly, when using methoxy-substituted gem-difluoride 1g, alkyl chloride 2,2′-(3-chloropent-2-ene-1,5-diyl)bis(methoxybenzene) (3g) was formed in 38% yield, and the desired Friedel-Crafts alkylation product (2g) was not observed. Consistent with our strategy that a modification of the Lewis acidity could potentially control the reaction selectivity, the oxygen atom in 1g probably coordinates to the aluminum center of AlCl3 and thus reduces its Lewis acidity, which would hamper the fluoride-abstraction process, and thus switch the reaction pathway from the expected Friedel-Crafts alkylation to a chlorination/elimination process. The presence of halogen substituents in the gem-difluoroalkanes (1h–l) was well tolerated when using AlCl3, and the corresponding products were generated in acceptable yield (42–64%). Moreover, naphthyl-type 2m, mixed product 2n, and the six-membered spiro-compound 2o were also obtained in good yield.

Subsequently, we examined the synthesis of tri-substituted alkyl chlorides (3) using AlEt2Cl both as an activator and a chloro source (Fig. 3). High yields and good Z/E stereocontrol were observed in most cases; specifically, long-chain acyclic substrates, independent of their substitution pattern on the benzene ring, afforded the desired alkyl chlorides (3a,b,3p,3d,3h–k,3q), including halogen-substituted products, in good to high yield (up to 96%) with good Z/E stereoselectivity (up to 21:4:1). In addition, moderate regioselectivity was observed for the defluorinative chlorination/elimination to provide the inner alkene product (3-chlorobut-2-en-1-yl)benzene (3s), and only ~10% of the corresponding terminal alkene was formed. It should also be noted here that cyclic gem-difluoroalkanes (11–ν) are also well tolerated under the AlEt2Cl-mediated conditions, furnishing the targeted cyclic alkyl chlorides (3t–3v) in acceptable yield (67–75%).
Figure 2. AlCl₃-mediated synthesis of spirobiindanes 2.

Figure 3. AlEt₂Cl-mediated synthesis of trisubstituted alkanyl chlorides 3.

a64% internal alkene and 7% terminal alkene.
Monofluoroalkenes 4 were obtained via a defluorination/elimination process (Fig. 4). As expected, long-chain acyclic substrates, independent of their substitution pattern on the benzene ring, furnished the desired monofluoroalkenes (4a-b, 4d, 4i-j, 4f, and 4q) in moderate to good yield (up to 77%) with good Z/E stereocontrol (up to 12:1). In particular, dialkyl-substituted substrates 1f and 1q generated the corresponding monofluoroalkenes (4f and 4q) in 72% and 74% yield, respectively. Furthermore, the defluorination of cyclic substrates including large-ring-type gem-difluoroalkanes proceeded smoothly to afford the corresponding cyclic monofluoroalkenes (4t, 4u, and 4w) in moderate yield (40–50%)39,49,50.

Mechanistic investigations. In order to avoid “over reactions” during the modification of inert C(sp3)-F bonds in saturated gem-difluoroalkanes (1), we reduced the Lewis acidity of the Al-based promoters. We observed that such “controllable reactions” stopped at the defluorinating elimination or F-Cl exchange/elimination stage, while further Friedel-Crafts alkylations did not occur. Indeed, using methoxyl-substituted fluorocarbon 1g and AlCl3 (Fig. 2) represents a special case, as it does not generate the desired spiro product 2g, but alkyl chloride 3g in 38% yield. Accordingly, the vital importance of the Lewis acidity of the aluminum promoters for the reaction selectivity can feasibly be rationalized under consideration of two points: 1. The abstraction of a fluoride anion from the C(sp3)-F bonds is facilitated with increasing strength of the Lewis acidity of the main-group promoter, as the fluoride moiety is neither a good Lewis base nor a good leaving group13. Indeed, species with a stronger formal positive charge such as [Ph3C]+, [R3Si]+, [R,Al]+, [(C6F5)3PF]+, and even P(III) dications with weakly coordinating anions, have recently been used for the direct cleavage and functionalization of C(sp3)-F bonds10,12,51–53. 2. Weaker Lewis acids favor elimination over substitution reactions of carbocation intermediates, which is due to the higher Lewis basicity of the conjugated Lewis bases [LA–F]− (LA = Lewis acid) generated form the heterolytic cleavage of the C–F bonds. Thus, the weaker LA AlEt3 afforded only monofluoroalkenes 4 via a defluorinative elimination, commensurate with the formal loss of one molecule of HF. Although proposing a clear mechanism is difficult due to the potential complexity of the structures of the conjugated Lewis bases [LA–F]−, which may form fluoride-bridged polymeric framework34–37, as well as due to the heterogeneous reaction conditions when using aluminum trichloride38,39, control experiments were conducted (Fig. 5) and a feasible reaction mechanism that would explain the high reaction selectivity is outlined in Fig. 6.

Initially, the strong Al-F interaction could promote the cleavage of one C(sp3)-F bond in gem-difluoroalkanes to give one tight ion pair (A) between a fluorinated carbocation and a conjugated Lewis base [LA–F]− counter ion. Then, the reaction could proceed via three competitive reaction pathways: 1. Direct elimination of the acidic α-proton of the fluorinated carbocation intermediate to give monofluoroalkenes 4, which is favored in the presence of AlEt3. 2. Twofold intramolecular Friedel-Crafts alkylation in the presence of AlCl3 or AlEt2Cl. Subsequently, the second abstraction of a fluoride anion could generate the tight ion pair C, which bears a chlorinated carbocation. In a similar fashion, the direct Friedel-Crafts alkylation, the F-Cl exchange, and the E1-type elimination represent three competitive reaction pathways. As mentioned above, when 1.1 equiv. of AlCl3 were used, the trisubstituted alkyl chloride was detected in 24% yield (Table 1, entry 2). Using alkyl chloride 3a as the chlorinated carbocation precursor furnished the intramolecular Friedel-Crafts type product 2a in 51% yield in the presence of 1.1 equiv. of AlCl3, while 31% yield were observed when using monofluorinated olefin 4a as the precursor for the fluorinated carbocation intermediate under otherwise identical reaction conditions (Fig. 5). Meanwhile, the F-Cl-exchange-type product 3,3-dichloropentane-1,5-diyldibenzene (5) also generated spirobiindane 2a in 52% yield. These results indicate that the cascade intramolecular Friedel-Crafts cyclization is a complex transformation that involves fluorinated carbocations and chlorinated carbocation intermediates, as well as competitive F-Cl exchange reaction pathways. Although we were unable to capture any F-Cl exchange products such as gem-chlorofluoroalkane 6 when using
Figure 5. Control experiments to investigate possible reaction intermediates (percentage values refer to the NMR yield).

Figure 6. Proposed reaction mechanism.
0.5 equiv. or 1.0 equiv. of AlEt₂Cl, the double F-Cl exchange product gem-dichloroalkane 5 was observed in 13% and 21% yield, respectively (Fig. 5; for more details, see the NMR study in Supplementary Figs. 78–85 in SI). Thus, alkenyl chloride 3 is probably generated from the double F-Cl exchange product gem-dichloroalkane 5, which may serve as a reservoir for the chlorinated carbocation intermediate in the tight ion pair C.

**Discussion**

In conclusion, we have developed a highly selective synthetic route to spirobiindanes 2, trisubstituted alkenyl chlorides 3, and monofluoroalkanes 4, based on the aluminum-induced cleavage of inert C(sp³)–F bonds in unactivated gem-difluoroalkanes 1. The three reaction types can be selectively controlled by using the readily available aluminum-based Lewis acids AlCl₃, AlEt₂Cl, or AlEt₃. Since the reaction can be performed using ubiquitous and cheap aluminum-based Lewis acids at room temperature, these methods should be of high practical utility.

**Methods**

**General procedure for the intramolecular Friedel-Craft reaction of gem-difluoroalkanes.** In a flame-dried test tube (10 mL), to the heterogeneous solution of AlCl₃ (29.3 mg, 0.22 mmol, 2.2 equiv.) in dry CH₂Cl₂ (0.5 mL), gem-difluoroalkanes 1 (0.1 mmol) in dry CH₂Cl₂ (0.5 mL) was added dropwise by syringe, and the reaction mixture was stirred at room temperature for 2 hours under a positive pressure of argon with a balloon. Then, the resulting mixture was washed with water, extracted with CH₂Cl₂, dried over Na₂SO₄, filtered, and then concentrated in vacuo. The residue was purified by column chromatography on silica gel using n-hexane as the eluent to afford the desired spirobiindanes 2a-n and spirobiteratranle 2o. In addition, alkenyl chloride 3g, 2,2′-(3-chloropent-2-ene-1,5-diyl)bis(methoxybenzene), was also prepared as one special example. In addition, the gem-difluoroalkanes 1 were prepared based on previous reports via fluorination of corresponding ketones by (diethylamino)sulfur trifluoride or 4-butyl-2,6-dimethylphenylsulfur trifluoride (Fluolead).

**General procedure for the synthesis of alkenyl chlorides 3 from gem-difluoroalkanes 1.** In a flame-dried test tube (10 mL), diethylaluminum chloride (255 μL, ca. 0.22 mmol, 2.2 equiv., ca. 15% in hexane, ca. 0.87 mol/L) was added slowly to the solution of gem-difluoroalkanes 1 (0.1 mmol) in dry CH₂Cl₂ (0.1 M, 1.0 mL), and the reaction mixture was stirred at room temperature for 4 hours under a positive pressure of argon with a balloon. Then, the resulting mixture was washed with water, extracted with CH₂Cl₂, dried over Na₂SO₄, filtered, and then concentrated in vacuo. The residue was purified by column chromatography on silica gel using n-hexane as the eluent to afford the desired alkenyl chloride 3. The ratio for Z/E isomers was determined by ¹H NMR based on previous literature.

**General procedure for the synthesis of monofluoroalkene 4 from gem-difluoroalkanes 1.** In a flame-dried test tube (10 mL), triethylaluminum (150 μL, ca. 0.15 mmol, 1.5 equiv., 15% in hexane, ca. 1.0 mol/L) was added slowly to the solution of gem-difluoroalkanes 1 (0.1 mmol) in n-hexane (0.1 M, 1.0 mL), and the reaction mixture was stirred at room temperature for 7 hours under a positive pressure of nitrogen with a balloon. Then, the resulting mixture was washed with water, extracted with CH₂Cl₂, dried over Na₂SO₄, filtered, and then concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford the desired monofluoroalkene 4. The ratio for Z/E isomers was determined by ¹⁹F NMR.

**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, and also are available from the corresponding author upon reasonable request.

Received: 27 October 2019; Accepted: 25 November 2019;
Published online: 13 December 2019

**References**

1. Amii, H. & Uneyama, K. C–F Bond Activation in Organic Synthesis. *Chem. Rev.* **109**, 2119–2183 (2009).
2. Ahrens, T., Kohlmann, A., Ahrens, M. & Braun, T. Functionalization of Fluorinated Molecules by Transition-Metal-Mediated C–F Bond Activation To Access Fluorinated Building Blocks. *Chem. Rev.* **115**, 931–972 (2015).
3. Eisenstein, O., Milani, J. & Perutz, R. N. Selectivity of C–H Activation and Competition between C–H and C–F Bond Activation in α-Reactions. *Angew. Chem. Int. Ed.* **53**, 3615–3633 (2017).
4. Hanel, I.-D. & Paquin, J.-F. Activation of C–F bonds α to C–C multiple bonds. *Chem. Commun.* **54**, 10224–10239 (2018).
5. Kuehnel, M. F., Lentz, D. & Braun, T. Synthesis of Fluorinated Building Blocks by Transition-Metal-Mediated H2Fluorination Reactions. *Angew. Chem. Int. Ed.* **52**, 3328–3348 (2013).
6. Stahl, T., Klar, H. F. T. & Oestreicher, M. Main-Group Lewis Acids for C–F Bond Activation. *ACS Catal.* **3**, 1578–1587 (2013).
7. Shen, Q. et al. Review of recent advances in C–F bond activation of aliphatic fluorides. *J. Fluorine Chem.* **179**, 14–22 (2015).
8. Caputo, C. & Ozerov, O. V. Hydrodefluorination of Perfluoroalkyl Groups Using Silbury-Carborene Catalysts. *Science* **321**, 1188–1190 (2008).
9. O’Hagan, D. Understanding organofluorine chemistry. *An Introduction to the C–F Bond*. *Chem. Soc. Rev.* **37**, 308–319 (2008).
10. Nolte, C., Ammer, J. & Mayr, H. Nucleofugality and Nucleophilicity of Fluoride in Protic Solvents. *J. Org. Chem.* **77**, 3325–3335 (2012).
53. Forster, F., Metsaenen, T. T., Irran, E., Hrobarik, P. & Oestreich, M. Cooperative Al-H Bond Activation in DIBAL-H: Catalytic
52. Zhu, J., Pérez, M., Caputo, C. B. & Stephan, D. W. Use of Trifluoromethyl Groups for Catalytic Benzylation and Alkylation with
25. Culver, D. B. & Conley, M. P. Activation of C
26. Riera, J., Castañer, J., Carilla, J. & Robert, A. New synthesis of polychloro(trifluoromethyl)benzenes and highly strained
27. Ramchandani, R. K., Wakharkar, R. D. & Sudalai, A. AlCl 3-Catalyzed regiospecific alkylation of aromatics with
24. Christe, K. O., Wilson, W. W., Schack, C. J. & Wilson, R. D. Lewis acid induced intramolecular redox reactions of difluoroamino
34. Drouin, M., Hamel, J.-D. & Paquin, J.-F. Exploiting 3,3-Difluoropropenes for the Synthesis of Monofluoroalkenes.
32. Terao, J. C.-Fluorocarbocations. Inorg. Chem., 932–935 (1964).
37. Hsieh, M.-T., Lee, K.-H., Kuo, S.-C. & Lin, H.-C. Lewis acid-mediated defluorinative [3
30. Ooi, T., Uraguchi, D., Kagashima, N. & Maruoka, K. Organoaluminum-catalyzed new alkylation of tert-alkyl fluorides: Synthetic
28. Terao, J., Nakamura M. & Kambe, N. Non-catalytic conversion of C–F bonds of benzotrifluorides to C–C bonds using
19. Olah, G. A., Kuhn S. & Olah, J. Aromatic substitution. Part III. Alkylation of aromatic compounds by the boron trifluoride-
18. Henne, A. L. & Newman, M. S. The Action of Aluminum Chloride on Fluorinated Compounds.
16. Aromatic substitution. Part II. Conversion of Aromatic to Aliphatic Compounds. J. Am. Chem. Soc., 1980–1982 (1955).
15. Maruoka, K. & Yamamoto, H. Selective Reactions Using Organoaluminum Reagents [New Synthetic Methods (54)]. Angew. Chem.
14. Terao, J., Terao, S., Nakamura M. & Kikuchi, K. Selective introduction of C–F bonds of difluoroethanol systems with nitriles. Angew.
13. Ichikawa, J., Jyono, H., Fujiwara, M. & Yonemitsu, T. Friedel-Crafts Cyclization of 1,1-Difluoroalk-1-enes: Synthesis of Benzene-Fused Cyclic Ketones via α-Fluorocarboxylations. Synthesis, 39–46 (2005).
12. Ichikawa, J., Kudo, T., Fujiwara, M. & Yonemitsu, T. Friedel-Crafts Cyclization of 1,1-Difluoroalk-1-enes: Synthesis of Benzene-Fused Cyclic Ketones via α-Fluorocarboxylations. Synthesis, 39–46 (2005).
11. Ichikawa, J., Jyono, H., Kudo, T., Fujiwara, M. & Yonemitsu, T. Friedel-Crafts Cyclization of 1,1-Difluoroalk-1-enes: Synthesis of Benzene-Fused Cyclic Ketones via α-Fluorocarboxylations. Synthesis, 39–46 (2005).
10. Ichikawa, J., Jyono, H., Kudo, T., Fujiwara, M. & Yonemitsu, T. Friedel-Crafts Cyclization of 1,1-Difluoroalk-1-enes: Synthesis of Benzene-Fused Cyclic Ketones via α-Fluorocarboxylations. Synthesis, 39–46 (2005).
9. Ichikawa, J., Kudo, T., Fujiwara, M. & Yonemitsu, T. Friedel-Crafts Cyclization of 1,1-Difluoroalk-1-enes: Synthesis of Benzene-Fused Cyclic Ketones via α-Fluorocarboxylations. Synthesis, 39–46 (2005).
8. Ichikawa, J., Jyono, H., Kudo, T., Fujiwara, M. & Yonemitsu, T. Friedel-Crafts Cyclization of 1,1-Difluoroalk-1-enes: Synthesis of Benzene-Fused Cyclic Ketones via α-Fluorocarboxylations. Synthesis, 39–46 (2005).
7. Ichikawa, J., Jyono, H., Kudo, T., Fujiwara, M. & Yonemitsu, T. Friedel-Crafts Cyclization of 1,1-Difluoroalk-1-enes: Synthesis of Benzene-Fused Cyclic Ketones via α-Fluorocarboxylations. Synthesis, 39–46 (2005).
6. Ichikawa, J., Jyono, H., Kudo, T., Fujiwara, M. & Yonemitsu, T. Friedel-Crafts Cyclization of 1,1-Difluoroalk-1-enes: Synthesis of Benzene-Fused Cyclic Ketones via α-Fluorocarboxylations. Synthesis, 39–46 (2005).
5. Ichikawa, J., Jyono, H., Kudo, T., Fujiwara, M. & Yonemitsu, T. Friedel-Crafts Cyclization of 1,1-Difluoroalk-1-enes: Synthesis of Benzene-Fused Cyclic Ketones via α-Fluorocarboxylations. Synthesis, 39–46 (2005).
4. Ichikawa, J., Jyono, H., Kudo, T., Fujiwara, M. & Yonemitsu, T. Friedel-Crafts Cyclization of 1,1-Difluoroalk-1-enes: Synthesis of Benzene-Fused Cyclic Ketones via α-Fluorocarboxylations. Synthesis, 39–46 (2005).
3. Ichikawa, J., Jyono, H., Kudo, T., Fujiwara, M. & Yonemitsu, T. Friedel-Crafts Cyclization of 1,1-Difluoroalk-1-enes: Synthesis of Benzene-Fused Cyclic Ketones via α-Fluorocarboxylations. Synthesis, 39–46 (2005).
2. Ichikawa, J., Jyono, H., Kudo, T., Fujiwara, M. & Yonemitsu, T. Friedel-Crafts Cyclization of 1,1-Difluoroalk-1-enes: Synthesis of Benzene-Fused Cyclic Ketones via α-Fluorocarboxylations. Synthesis, 39–46 (2005).
1. Ichikawa, J., Jyono, H., Kudo, T., Fujiwara, M. & Yonemitsu, T. Friedel-Crafts Cyclization of 1,1-Difluoroalk-1-enes: Synthesis of Benzene-Fused Cyclic Ketones via α-Fluorocarboxylations. Synthesis, 39–46 (2005).
56. Laubengayer, A. W. & Lengnick, G. F. The Structure and Properties of Diethylfluoroalane, \( \text{C}_2\text{H}_5\text{AlF} \). *Inorg. Chem.* **5**, 503–507 (1966).

57. Dimitrov, A., Heidemann, D. & Kemnitz, E. F/Cl-Exchange on \( \text{AlCl}_3 \)-Pyridine Adducts: Synthesis and Characterization of trans-Difluoro-tetrakis-pyridine-aluminum-chloride, \( \text{[AlF}_2\text{Py}_4\text{]}\text{Cl} \). *Inorg. Chem.* **45**, 10807–10814 (2006).

58. Petrov, V. A., Krespan, C. G. & Smart, B. E. Isomerization of halopolyfluoroalkanes by the action of aluminum chlorofluoride. *J. Fluorine Chem.* **89**, 125–130 (1998).

59. Krahl, T. et al. Structural Insights into Aluminum Chlorofluoride (ACF). *Inorg. Chem.* **42**, 6474–6483 (2003).

**Acknowledgements**

This work was supported by JSPS KAKENHI grants JP 18H02553 (KIBAN B) and J.P. 18H034401 (Molecular Strategy).

**Author contributions**

N.S. conceived the concept. J.W. conducted the experiments and analyzed the obtained results. J.W. and Y.O. synthesized compounds. Y.O. prepared the starting materials. N.S. designed and directed the project, and N.S. and J.W. wrote the manuscript. All authors contributed to the discussion of the results.

**Competing interests**

The authors declare no competing interests.

**Additional information**

Supplementary information is available for this paper at [https://doi.org/10.1038/s41598-019-55206-7](https://doi.org/10.1038/s41598-019-55206-7).

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