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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(sp^3)–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 $AlCl_3$. The subsequent synthesis of alkenyl chlorides via F/Cl exchange followed by an elimination can be accomplished using $AlEt_2Cl$ as a fluoride scavenger and halogen source. The defluorinative elimination of acyclic and cyclic *gem*-difluorocarbons to give monofluoroalkenes can be achieved using $AlEt_3$.

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[1–6]. In contrast to the considerable number of reports that focus on the transition-metal-mediated or -catalyzed cleavage of C(sp^2)–F bonds in aromatic and vinylic fluorocarbons[2–4,6], the direct degradation of C(sp^3)–F bonds in unactivated aliphatic fluorides remains challenging[7,8].

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(sp^3)–F bonds[7,9–12]. Although the fluoride moiety in C–F bonds is neither a good leaving group nor a good Lewis base[13,14], 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[7]. In particular, practical and economic protocols that render the scission of the C(sp^3)–F bond feasible include aluminum-based Lewis acids such as aluminum halides, $AlEtCl_2$, $AlEt_2Cl$, $Al(alkyl)_3$, $Al(Oi\text{-}Pr)_3$, or alumina, which are inexpensive, easy to handle, environmentally benign, and commonly used aluminum reagents of low toxicity[15–17]. In 1938, Henne and Newman reported the fluorine/chlorine (F/Cl) exchange between trifluoromethyl benzene and aluminum chloride[18], 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[19]. Not only boron based Lewis acids, antimony, bismuth, arsenic based Lewis acids and silica surface also effectively activate C–F bonds[20–25]. 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[5,7,8] have been studied extensively. However, most of these reports have focused on activated fluoroalkane substrates for further modifications such as benzylic and allylic trifluoroalkanes[26–29], as well as benzylic and tertiary aliphatic monofluoroalkanes[30,31], all of which afford stabilized

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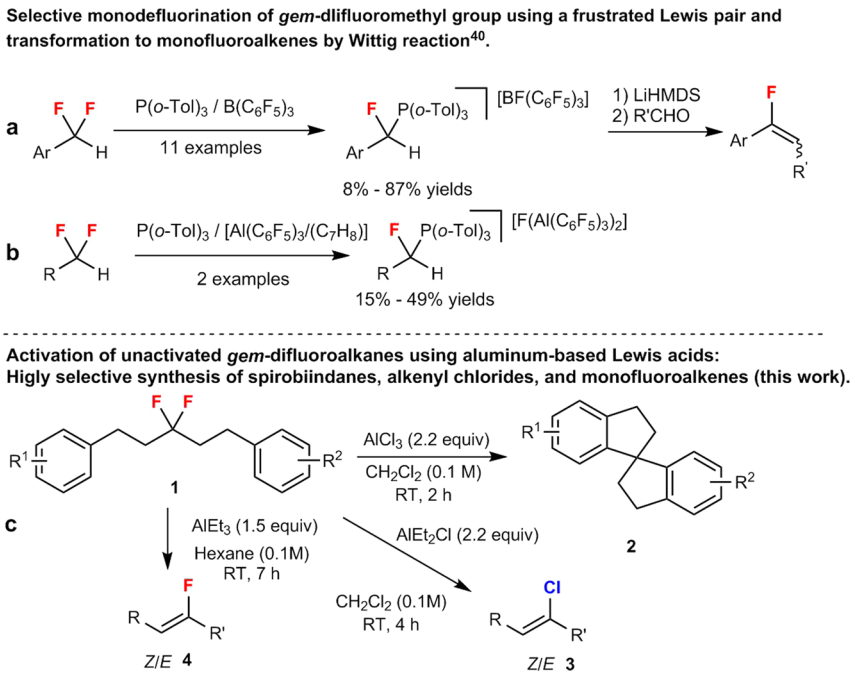


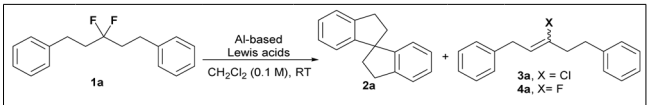
Figure 1. Selective defluorination of unactivated *gem*-difluoroalkanes. (**a,b**) *gem*-Difluoro substrates for C–F bond activation (previous work). (**c**) Selective transformation of *gem*-difluoro substrates controlled by aluminum reagents (this work).

carbocation intermediates. Meanwhile, due to their comparatively lower steric congestion, primary monofluoroalkanes have been used for Finkelstein-S_N2-type halogen-exchange reactions[32,33]. However, in spite of recent advances in transition-metal-catalyzed reactions of activated allylic or propargylic *gem*-difluoroalkanes[34,35], 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 $AlCl_3$, $AlMe_3$, or $AlPh_3$[28]. Subsequently, the S_N2'-type alkylation of difluorohomoallyl alcohols can be controlled by trialkylaluminum compounds, which can coordinate to fluorine and adjacent oxygen atoms[36,37]. Recently, it has been reported that $Al(OTf)_3$ enables the defluorinative cycloaddition/aromatization between benzylic 2,2-difluoroethanol and nitriles to afford oxazoles[38]. Nevertheless, breaking C(sp^3)–F bonds in unactivated *gem*-difluoroalkanes remains highly challenging[39–41]. 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 $B(C_6F_5)_3$ 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 [$Al(C_6F_5)_3{\cdot}(C_7H_8)$] (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 transformations[32,39] 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 $B(C_6F_5)_3$ and hexafluoroisopropanol (HFIP), which exhibits a very high affinity toward fluoride[41]. Although the method is of great importance as a proof-of-concept, the reaction still requires high temperatures and the relatively expensive reagents $B(C_6F_5)_3$ and HFIP, which are critical for this transformation. Our continued interest in the activation and modification of inert C(sp^3)–F bonds[41,42] has led us to examine ubiquitous aluminum-based Lewis acids of low cost for the selective synthesis of spirobiindanes (**2**), alkenyl chlorides (**3**), and monofluoroalkenes (**4**) from unactivated *gem*-difluoroalkanes (**1**) under mild conditions. Specifically, we used stoichiometric amounts of $AlCl_3$, $AlEt_2Cl$, or $AlEt_3$ in this study to induce aluminum-fluorine (Al–F) interactions[29,43,44] for the direct abstraction of fluoride (Fig. 1c).

Results

Optimization study. The results of the screening of Al-based Lewis acids for the cleavage of C(sp^3)–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 $AlCl_3$ 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 $AlCl_3$ were used (entry 3).



Entry	Lewis acids (equiv)	Time (h)	Product[a] (%)		
			2a	3a	4a
1	$AlCl_3$ (2.2)	2	72	ND	ND
2	$AlCl_3$ (1.1)	8	39	24	ND
3	$AlCl_3$ (0.2)	8	6	trace	ND
4	$AlEtCl_2$ (2.2)	8	complex mixture	—	—
5	$AlEt_2Cl$ (2.2)	4	ND	92[b]	ND
6	$AlEt_3$ (2.2)	<0.5	ND	—	51[c]
7	$AlEt_3$ (1.5)	7	ND	—	85[d]

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

However, when 1.1 equiv. of $AlCl_3$ 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 alkenyl chlorides represent useful building blocks for the formation of complex organic architectures[45–48], establishing control by preventing such "over reactions" in favor of alkenyl chlorides **3** would most likely be as attractive as it would be challenging. To solve this problem, we aimed at decelerating the heterolysis of $C(sp^3)$–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 alkenyl 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 $AlEtCl_2$ promotes an intermolecular S_N1'-type substitution in 2-trifluoromethyl-1-alkenes[29]. However, when we treated **1a** with 2.2 equiv. of $AlEtCl_2$, we obtained only a tar-like complex mixture (entry 4). Yet, when using the weaker Lewis acid $AlEt_2Cl$, alkenyl 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). $AlEt_2Cl$ 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 $AlEt_3$ under otherwise identical reaction conditions afforded monofluoroalkene **4a** 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 $AlEt_3$, 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 $AlEt_3$-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% ^{19}F 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 $AlEt_3$ (2.0 equiv.) at room temperature[39]. Modifying the substituents on the central aluminum atom ($AlCl_3$, $AlEt_2Cl$, and $AlEt_3$) allowed tuning the reaction selectivity for the heterolysis of the $C(sp^3)$–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 spirobiindanes, whereby C2-substituted substrates (**1a**,**b**) perform slightly better than C4-substituted substrates (**1c**–**e**). Interestingly, when using methoxy-substituted *gem*-difluoride **1 g**, alkenyl chloride 2,2′-(3-chloropent-2-ene-1,5-diyl)bis(methoxybenzene) (**3 g**) was formed in 38% yield, and the desired Friedel-Crafts alkylation product (**2 g**) was not observed. Consistent with our strategy that a modification of the Lewis acidity could potentially control the reaction selectivity, the oxygen atom in **1 g** probably coordinates to the aluminum center of $AlCl_3$ 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 $AlCl_3$, and the corresponding products were generated in acceptable yield (42–64%). Moreover, naphthyl-type **2 m**, mixed product **2n**, and the six-membered spiro-compound **2o** were also obtained in good yield.

Subsequently, we examined the synthesis of tri-substituted alkenyl chlorides (**3**) using $AlEt_2Cl$ 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 alkenyl 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 (**3 s**), and only ~10% of the corresponding terminal alkene was formed. It should also be noted here that cyclic *gem*-difluoroalkanes (**1t**–**v**) are also well tolerated under the $AlEt_2Cl$-mediated conditions, furnishing the targeted cyclic alkenyl chlorides (**3t**–**3v**) in acceptable yield (67–75%).

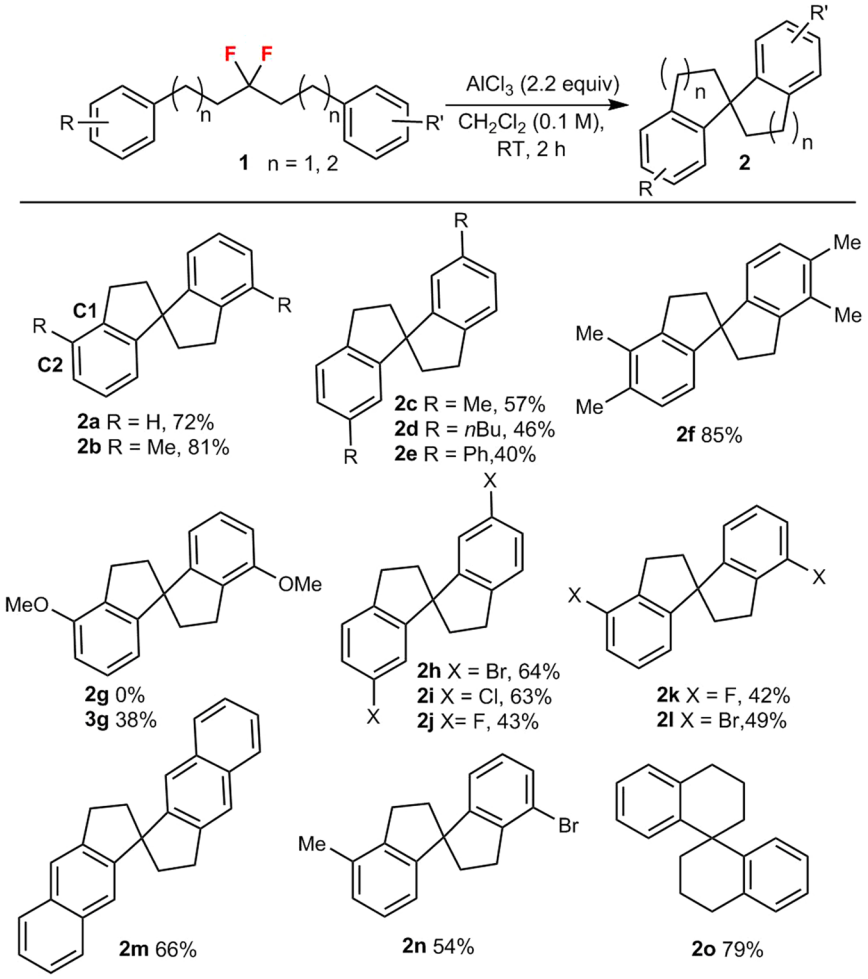
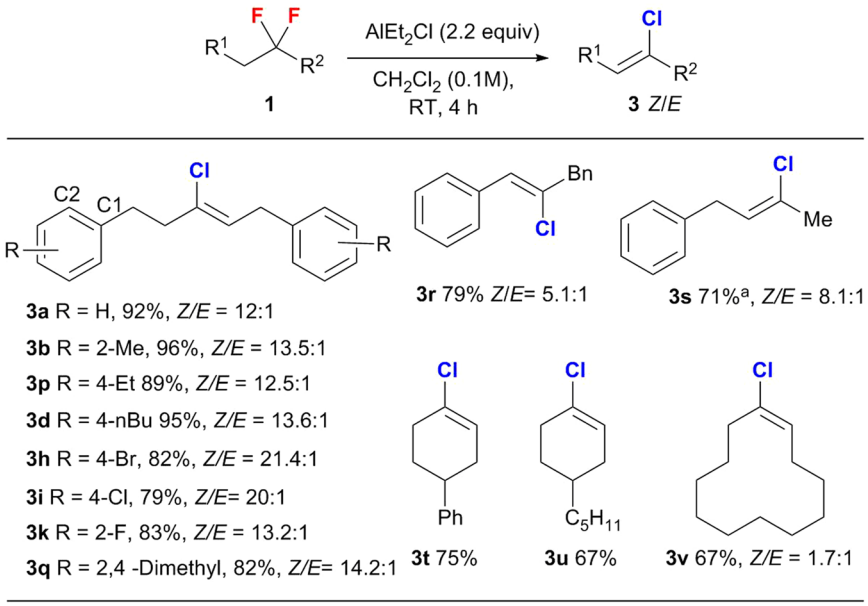


Figure 2. $AlCl_3$-mediated synthesis of spirobiindanes 2.



[a]64% internal alkene and 7% terminal alkene.

Figure 3. $AlEt_2Cl$-mediated synthesis of trisubstituted alkenyl chlorides 3.

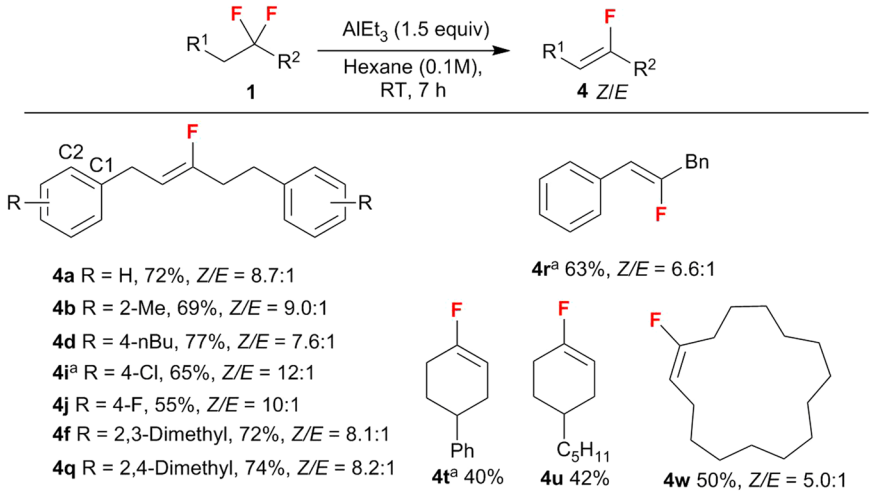


Figure 4. $AlEt_3$-mediated synthesis of monofluoroalkenes 4.

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 **1 f** and **1q** generated the corresponding monofluoroalkenes (**4 f** 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**, **4 u**, and **4w**) in moderate yield (40–50%)[39,49,50].

Mechanistic investigations. In order to avoid "over reactions" during the modification of inert C(sp^3)-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 defluorinative elimination or F-Cl exchange/elimination stage, while further Friedel-Crafts alkylations did not occur. Indeed, using methoxyl-substituted fluorocarbon **1 g** and $AlCl_3$ (Fig. 2) represents a special case, as it does not generate the desired spiro product **2 g**, but alkenyl chloride **3 g** in 38% yield. Accordingly, the vital importance of the Lewis acidity of the aluminum promotors for the reaction selectivity can feasibly be rationalized under consideration of two points: 1. The abstraction of a fluoride anion from the C(sp^3)–F bonds is facilitated with increasing strength of the Lewis acidity of the main-group promoter, as the fluorine moiety is neither a good Lewis base nor a good leaving group[13]. Indeed, species with a stronger formal positive charge such as $[Ph_3C]^+$, $[R_3Si]^+$, $[R_2Al]^+$, $[(C_6F_5)_3PF]^+$, and even P(III) dications with weakly coordinating anions, have recently been used for the direct cleavage and functionalization of C(sp^3)–F bonds[10,12,51–53]. 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 $AlEt_3$ 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 polymetric framework[54–57], as well as due to the heterogeneous reaction conditions when using aluminum trichloride[58,59], 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(sp^3)–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 $AlEt_3$; 2. Twofold intramolecular Friedel-Crafts alkylation in the presence of $AlCl_3$; 3. F-Cl exchange reaction via S_N1-type substitutions[32] in the presence of $AlCl_3$ or $AlEt_2Cl$. 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 $AlCl_3$ were used, the trisubstituted alkenyl chloride was detected in 24% yield (Table 1, entry 2). Using alkenyl 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 $AlCl_3$, 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-diyl)dibenzene (**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

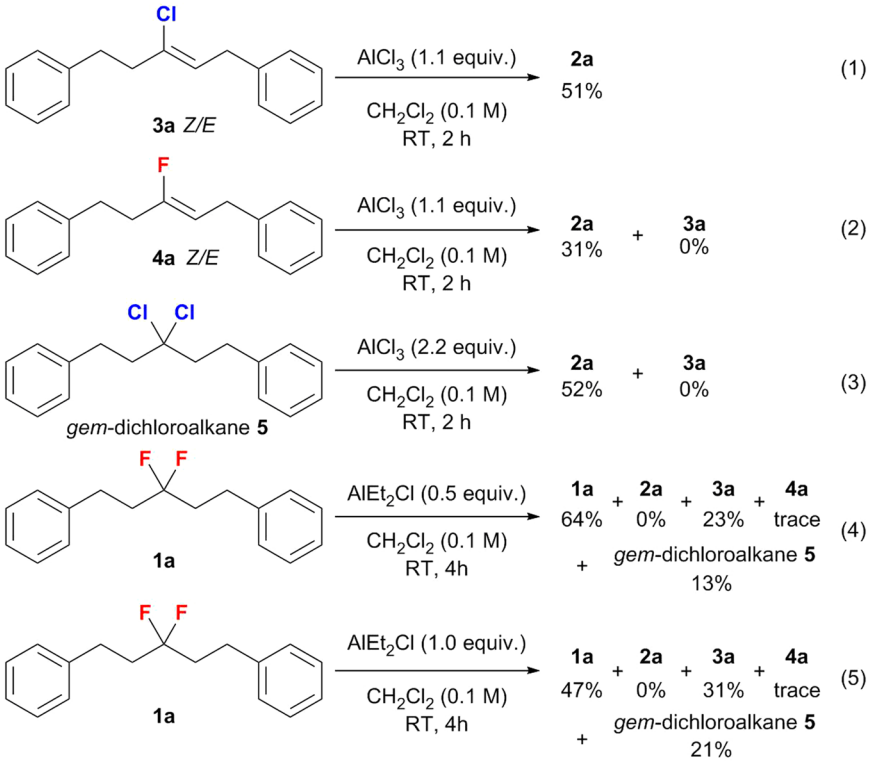


Figure 5. Control experiments to investigate possible reaction intermediates (percentage values refer to the NMR yield).

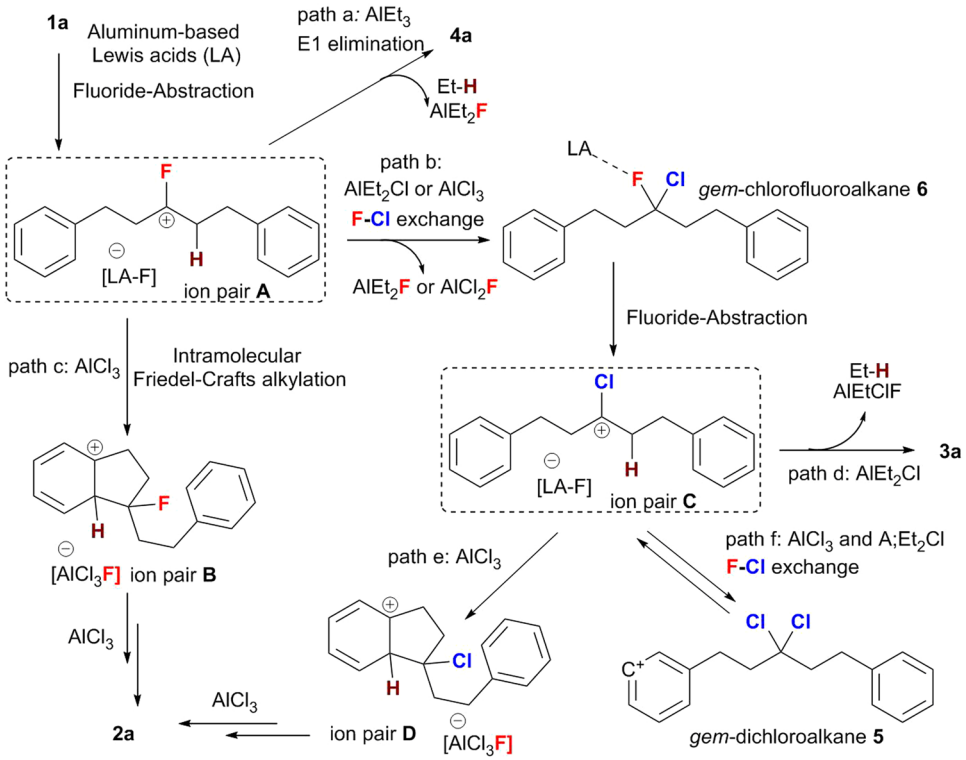


Figure 6. Proposed reaction mechanism.

0.5 equiv. or 1.0 equiv. of $AlEt_2Cl$, 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 monofluoroalkenes **4**, based on the aluminum-induced cleavage of inert $C(sp^3)$–F bonds in unactivated *gem*-difluoroalkanes **1**. The three reaction types can be selectively controlled by using the readily available aluminum-based Lewis acids $AlCl_3$, $AlEt_2Cl$, or $AlEt_3$. 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 $AlCl_3$ (29.3 mg, 0.22 mmol, 2.2 equiv.) in dry CH_2Cl_2 (0.5 mL), *gem*-difluoroalkanes **1** (0.1 mmol) in dry CH_2Cl_2 (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 CH_2Cl_2, dried over Na_2SO_4, 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 spirobitetraline **2o**. In addition, alkenyl chloride **3 g**, 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-*tert*-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 CH_2Cl_2 (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 CH_2Cl_2, dried over Na_2SO_4, 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 ^{1}H 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 CH_2Cl_2, dried over Na_2SO_4, 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 ^{19}F 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.

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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.

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