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Bond Activation

Single C–F Bond Activation of the CF_3 Group with a Lewis Acid: CF_3-Cyclopropanes as Versatile 4,4-Difluorohomoallylating Agents

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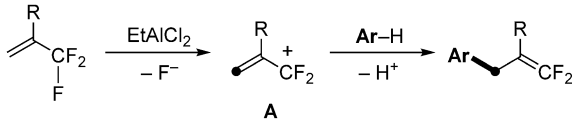
Abstract: The selective activation of one C–F bond (single activation) of the CF_3 group on cyclopropanes was achieved for the first time. When (trifluoromethyl)cyclopropanes were treated with arenes, allylsilanes, silyl enol ethers, or hydrosilanes in the presence of Me_2AlCl, fluoride elimination and the subsequent ring opening proceeded to afford 4,4-difluorohomoallylated products. In the absence of external nucleophiles, an alkyl group of AlR_3 was effectively introduced to provide the corresponding 1,1-difluoroalkenes.

Among the C–F bond activation reactions of CF_3-bearing compounds,[1] the selective activation of one of the C–F bonds constitutes a great challenge, while the other two C–F bonds remain unreacted.[2] This is due to the harsh reaction conditions required to cleave the first sp^3 C–F bond, which is indeed stronger than the second and third C–F bonds. To date, the single activation of the CF_3 group has been mainly performed on $ArCF_3$ platforms,[3] which has facilitated the straightforward synthesis of various fluorine-containing aromatic compounds.[4,5]

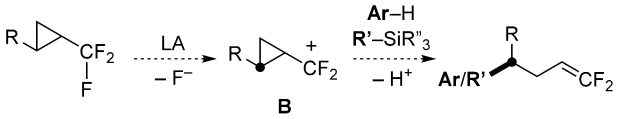
Recently, we developed an ethylaluminum dichloride ($EtAlCl_2$)-promoted single activation of the CF_3 group on alkene moieties (2-trifluoromethyl-1-alkenes, CF_3-alkenes, Scheme 1 a).[6] In this system, the fluorine substituents stabilize the α-carbocations by donating their unshared electron pair to the vacant p orbital of the cationic centers (i.e., α-cation stabilizing effect of fluorine).[7] Thus, upon elimination of F^- from the CF_3-alkenes promoted by $EtAlCl_2$, stabilized allylic CF_2 cations (**A**) are generated, which in turn react with arenes (Ar–H) through a Friedel–Crafts-type mechanism leading to the corresponding 3,3-difluoroallylation products.[8]

Motivated by this success, we next turned our attention on the single activation of the CF_3 group on cyclopropane moieties [(trifluoromethyl)cyclopropanes, CF_3-cyclopropanes, Scheme 1 b]. In this case, the cyclopropane ring, which has electron-donating C–C σ bonds,[9] would promote the elimination of F^- from CF_3-cyclopropanes to generate stabilized cyclopropyl-bearing CF_2 cations (**B**). Their ring opening and subsequent bond formation with nucleophiles (Ar–H or R'–SiR"$_3$) might lead to 4,4-difluorohomoallylated products. It is worth noting that there has been only a few ring-opening reactions[10] and heterocycle formations[11] involving CF_3-cyclopropanes and that there is little precedent for C–C bond-forming reactions of CF_3-cyclopropanes. In this paper, we describe a novel function of CF_3-cyclopropanes in organic synthesis as versatile 4,4-difluorohomoallylating agents.[12]

(a) Single Activation of CF_3-Alkenes (3,3-Difluoroallylation)



(b) Single Activation of CF_3-Cyclopropanes (4,4-Difluorohomoallylation): **this work**



Scheme 1. Single activation of CF_3-alkenes and CF_3-cyclopropanes.

The required CF_3-cyclopropanes were prepared following our improved procedure for (trifluoromethyl)cyclopropanation. Carreira reported on the FeCl(TPP)-catalyzed (trifluoromethyl)-carbene transfer reaction of styrenes with diazo(trifluoro)-ethane generated in situ from trifluoroethylamine hydrochloride (TPP = tetraphenylporphine).[13] We adopted Aggarwal's method, which facilitates the decomposition of sodiohydrazones to diazoalkanes with quaternary ammonium salt (PTC) at mild temperature (40 °C).[14] Thus, we treated styrenes with trifluoroacetaldehyde tosylhydrazone in the presence of tetrabutylammonium chloride, a FeCl(TPP) catalyst, and sodium methoxide (Table 1). The in situ generated trifluoroacetaldehyde sodiohydrazone readily underwent decomposition, followed by the desired Fe^{III}-catalyzed (trifluoromethyl)cyclopropanation. It should be noted that the generation of diazo(trifluoro)ethane was readily achieved, starting from a commercially available trifluoroacetaldehyde hemiacetal.

As expected, the treatment of CF_3-cyclopropane with Lewis acids facilitated the desired single activation of the CF_3 group. A model compound bearing a *p*-phenylphenyl group (**1 a**) re-

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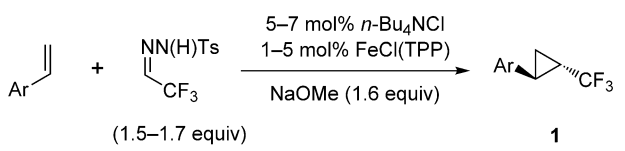
Table 1. Preparation of CF_3-cyclopropanes **1**.



(1.5–1.7 equiv) **1**

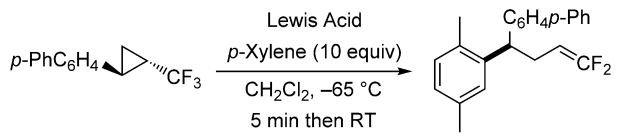
Entry	Ar	Solvent	Conditions	Yield [%][a] (d.r.)[b]
1	C_6H_4*p*-Ph	toluene	40 °C, 21 h	**1a**, 84 (*trans* only)
2	Ph	CH_2Cl_2	reflux, 71 h	**1b**, 35 (96:4)
3	C_6H_4*p*-*i*-Pr	CH_2Cl_2	reflux, 91 h	**1c**, 54 (94:6)
4	C_6H_4*p*-F	CH_2Cl_2	reflux, 132 h	**1d**, 37 (99:1)
5	C_6H_4*p*-Cl	toluene	80 °C, 29 h	**1e**, 56 (*trans* only)
6	C_6H_4*o*-Cl	THF	40 °C, 22 h	**1f**, 59 (99:1)
7	C_6H_4*p*-O*t*Bu	THF	40 °C, 63 h	**1g**, 69 (98:2)
8	1-naphthyl	THF	40 °C, 36 h to 60 °C, 25 h	**1h**, 80 (*trans* only)
9	C_6H_4*o*-Tol[c]	THF	40 °C, 6 h to reflux, 1 h	**1i**, 79 (99:1)
10	Ph, Ph[d]	THF	40 °C, 52 h	**1j**, 40

[a] Isolated yield. [b] *trans*/*cis* ratio determined by ^{19}F NMR spectroscopy. [c] Tol = C_6H_4*p*-Me. [d] 1,1-Diphenylethene.

acted with *p*-xylene in the presence of aluminum, titanium, or zirconium Lewis acids to afford 4,4-difluorohomoallylation product **2a** in 73–88% yields (Table 2, entries 2, 4, and 5). Products that would arise from the attack on the CF_2 carbon of **B** (Scheme 1b) were not observed (see below). $EtAlCl_2$ generated the hydride reduction product **3** in 3% yield (Entry 2), whereas dimethylaluminum chloride (Me_2AlCl) afforded the desired **2a** in an increased yield (92%) without formation of **3** (Entry 3).[4c,d,5j,l,m,6,15,16]

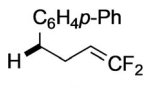
With the optimized conditions in hand, the scope of the reaction regarding the arene substrates was investigated (Figure 1). Using Me_2AlCl, alkylated benzenes and naphthalene, anisole, and thiophene reacted with **1a** to afford the corresponding products **2a**–**f** in 60–95% yields. CF_3-Cyclopropanes

Table 2. Optimization of Lewis acids.



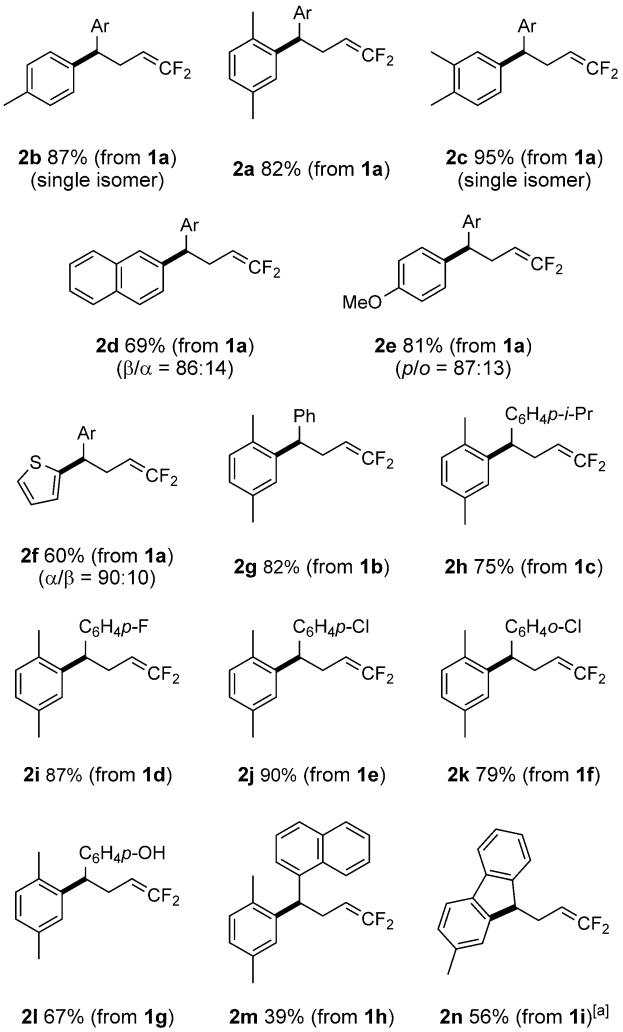
1a **2a**

Entry	Lewis acid (equiv)	*t* [h]	Products [%][a] **2a**	**1a**[b]
1	$BF_3{\cdot}OEt_2$ (3.6)	3.5[c]	0	94
2	$EtAlCl_2$ (1.2)	1	88[d]	0
3	Me_2AlCl (1.2)	1	92	–
4	$TiCl_4$ (3.5)	4	85	0
5	$ZrCl_4$ (1.1)	2	73	trace



3

[a] ^{19}F NMR yield based on $PhCF_3$ as internal standard. [b] Recovery. [c] −65 °C, 5 min then reflux, 3.5 h. [d] Reduction product **3** was obtained in 3% yield.



[a] An external arene was not used.

Figure 1. Difluorohomoallylation of arenes [isolated yield; Ar = C_6H_4*p*-Ph; conditions: CF_3-cyclopropane **1**, arene (3.0 equiv), Me_2AlCl (1.2 equiv), CH_2Cl_2, −65 to 40 °C, 10 min].

1b–**g** also promoted difluorohomoallylation leading to the products **2g**–**l** in 67–90% yields. In the case of **2l**, removal of a *tert*-butyl group was observed. The reaction of **1h** afforded the corresponding **2m** (39% yield). The intramolecular reaction (**1i**) also proved successful, and the corresponding difluoroallylated fluorene **2n** was obtained in 56% yield.

The regioselectivity concerning the nucleophilic arene nuclei was considerably high, presumably due to steric effects: products **2b** (from toluene) and **2c** (from *o*-xylene) were obtained as single products. Meanwhile, naphthalene, which normally undergoes Friedel–Crafts-type reactions on its α carbon, reacted with CF_3-cyclopropane **1a** predominantly at the β carbon (β/α = 86:14).[17] This high and/or abnormal selectivity suggests that the regioselectivity is controlled by the greater steric hindrance of cation **B** (see below).

The following observations could be extracted from a theoretical calculation (structural optimization), which suggests that the cation **B**′ generated from a model CF_3-cyclopropane has a

charge-localized and distorted structure (Figure 2): (i) In the model **B**′, the carbon at the position α to the fluorine substituents has a positive charge value of +0.52. (ii) In the original three-membered ring, the C–C bond distal to the methylene

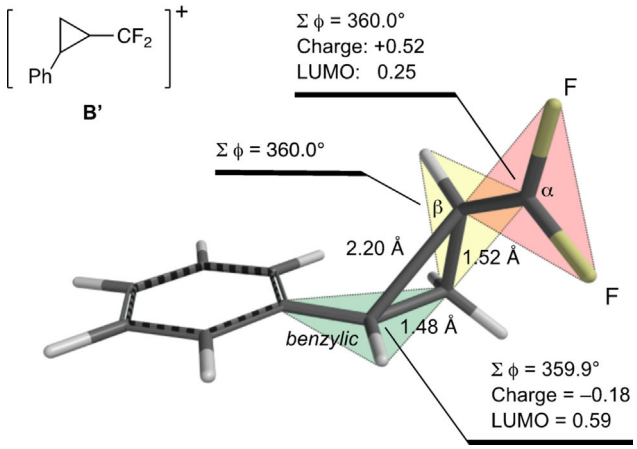
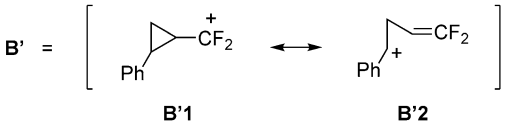


Figure 2. Optimized structure of the cation generated from CF_3-cyclopropane (DFT, B3LYP/6-31G*).

group is lengthened to 2.20 Å, which is much longer than the value of 1.51 Å of the parent cyclopropane. (iii) The carbons at the positions α and β to the fluorine substituents and the benzylic carbon have sp^2-hybridized, planar structures, whose sums of bond angles are almost 360°. Namely, **B**′ has a major contribution from the canonical form **B′2** (Scheme 2). The regioselectivity of the reaction involving the CF_3-cyclopropanes stems most likely from the prevented cyclopropyl(difluoro)methylation due to (a) the relative destabilization of the arenium ion **D** compared to **C** (Figure 3)[8] by the electron-withdrawing inductive effect of the two fluorines and/or (b) the larger LUMO coefficient on the benzylic carbon of **B**′ (0.59 vs. 0.25, Figure 2).



Scheme 2. Resonance structures of cation **B**′.

The single activation of CF_3-cyclopropanes was also applicable to silicon nucleophiles (Scheme 3),[5m,15b,f] allowing the synthesis of functionalized 1,1-difluoroalkenes. Thus, allylsilane **4**

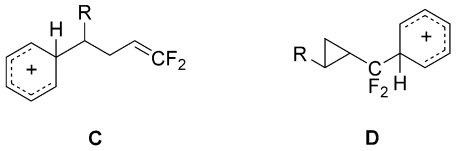
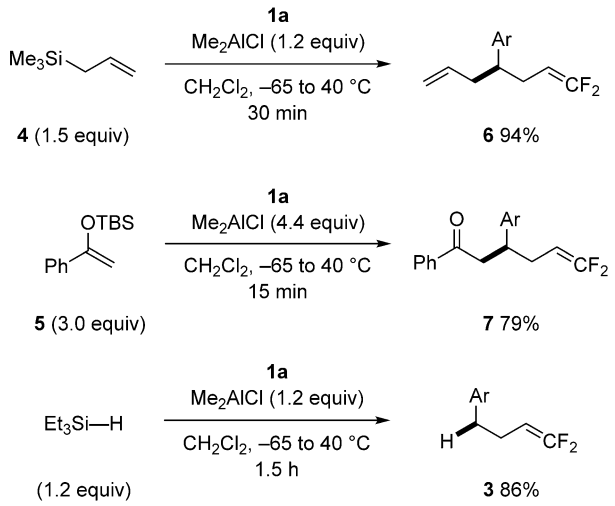


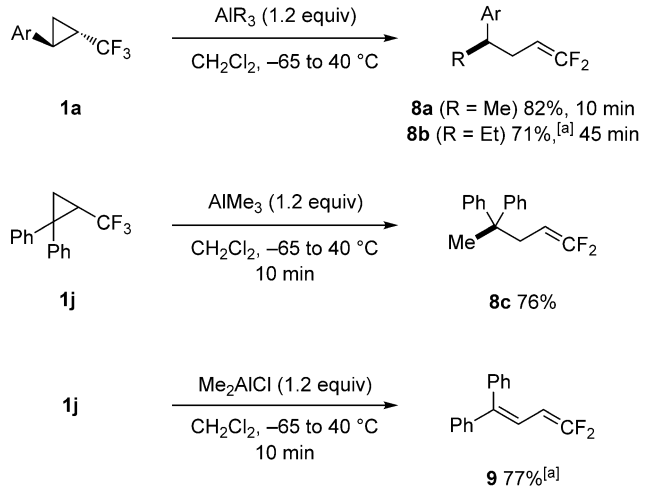
Figure 3. The structures of arenium ions **C** and **D**, leading to **2** and cyclopropyl(difluoro)methylation products (not shown), respectively.



Scheme 3. Difluorohomoallylation of silicon nucleophiles (TBS = Si*t*BuMe$_2$, Ar = C_6H_4*p*-Ph).

and silyl enol ether **5** reacted with **1a** in the presence of Me_2AlCl to afford the corresponding difluorohomoallylation products **6** and **7** in 94 and 79% yields, respectively. Introduction of hydride with triethylsilane was facilitated under the identical conditions and the corresponding 1,1-difluoroalkene **3** was obtained in 86% yield.

By conducting the reaction in the absence of external nucleophiles, the alkyl groups on the aluminum Lewis acids were difluorohomoallylated with CF_3-cyclopropanes (Scheme 4).[4c,5l] When CF_3-cyclopropanes **1a** and **1j** were treated with trimethyl- or triethylaluminum, 1,1-difluoroalkenes **8a–c** were obtained in 82, 71, and 76% yields, respectively, whereas dimethylaluminum chloride reacted with **1j** to promote elimination (not methylation), leading to 1,1-difluoro-1,3-diene **9** in 77% yield.



[a] ^{19}F NMR yield based on $PhCF_3$.

Scheme 4. Alkylation and HF elimination of CF_3-cyclopropanes.

In summary, the aluminum Lewis acid-promoted single activation of CF_3-cyclopropanes was achieved for the first time. The reaction was triggered by the elimination of fluoride to generate difluorocarbocations, which were effective for the selective introduction of a 4,4-difluorohomoallyl unit into external and internal nucleophiles such as arenes and organosilicons. A significant regioselectivity was observed in arene nucleophiles.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: aromatic substitution · bond activation · carbocations · cyclopropane · fluorine · trifluoromethyl group

[1] For reviews on activation of sp^3 C–F bonds, including CF_3 groups, see: a) H. Amii, K. Uneyama, *Chem. Rev.* **2009**, *109*, 2119–2183; b) T. Stahl, H. F. T. Klare, M. Oestreich, *ACS Catal.* **2013**, *3*, 1578–1587; c) T. A. Unzner, T. Magauer, *Tetrahedron Lett.* **2015**, *56*, 877–883; d) Q. Shen, Y.-G. Huang, C. Liu, J.-C. Xiao, Q.-Y. Chen, Y. Guo, *J. Fluorine Chem.* **2015**, *179*, 14–22.

[2] For a review on single activation of CF_3 groups, see: a) F. Jaroschik, *Chem. Eur. J.* **2018**, *24*, 14572–14582. b) See also: G. Chelucci, *Chem. Rev.* **2012**, *112*, 1344–1462.

[3] For example, see: a) D. Ferraris, C. Cox, R. Anand, T. Lectka, *J. Am. Chem. Soc.* **1997**, *119*, 4319–4320; b) H. Amii, Y. Hatamoto, M. Seo, K. Uneyama, *J. Org. Chem.* **2001**, *66*, 7216–7218; c) S. Yoshida, K. Shimomori, Y. Kim, T. Hosoya, *Angew. Chem. Int. Ed.* **2016**, *55*, 10406–10409; *Angew. Chem.* **2016**, *128*, 10562–10565; d) K. Chen, N. Berg, R. Gschwind, B. König, *J. Am. Chem. Soc.* **2017**, *139*, 18444–18447; e) H. Wang, N. T. Jui, *J. Am. Chem. Soc.* **2018**, *140*, 163–166.

[4] For complete activation of the three C–F bonds in $ArCF_3$, see for example: a) V. J. Scott, R. Celenligil-Cetin, O. V. Ozerov, *J. Am. Chem. Soc.* **2005**, *127*, 2852–2853; b) C. Douvris, O. V. Ozerov, *Science* **2008**, *321*, 1188–1190; c) J. Terao, M. Nakamura, N. Kambe, *Chem. Commun.* **2009**, 6011–6013; d) T. Yamada, K. Saito, T. Akiyama, *Adv. Synth. Catal.* **2016**, *358*, 62–66.

[5] For single activation of a C–F bond in CF_3-compounds other than $ArCF_3$, see for example (CF_3-alkenes): a) J.-P. Bégué, D. Bonnet-Delpon, M. H. Rock, *Synlett* **1995**, 659–660; b) J. Ichikawa, H. Fukui, Y. Ishibashi, *J. Org. Chem.* **2003**, *68*, 7800–7805; c) J. Ichikawa, R. Nadano, N. Ito, *Chem. Commun.* **2006**, 4425–4427; d) T. Miura, Y. Ito, M. Murakami, *Chem. Lett.* **2008**, *37*, 1006–1007; e) T. Ichitsuka, T. Fujita, J. Ichikawa, *ACS Catal.* **2015**, *5*, 5947–5950; f) Y. Huang, T. Hayashi, *J. Am. Chem. Soc.* **2016**, *138*, 12340–12343; g) T. Kumar, F. Massicot, D. Harakat, S. Chevreux, A. Martinez, K. Bordolinska, P. Preethalayam, R. Kokkuvayil Vasu, J.-B. Behr, J.-L. Vasse, F. Jaroschik, *Chem. Eur. J.* **2017**, *23*, 16460–16465; h) G. Meißner, K. Kretschmar, T. Braun, E. Kemnitz, *Angew. Chem. Int. Ed.* **2017**, *56*, 16338–16341; *Angew. Chem.* **2017**, *129*, 16556–16559; i) X. Wu, F. Xie, I. D. Gridnev, W. Zhang, *Org. Lett.* **2018**, *20*, 1638–1642. For RCF_2-alkenes, see: j) M. Okada, Y. Nakamura, A. Saito, A. Sato, H. Horikawa, T. Taguchi, *Chem. Lett.* **2002**, *31*, 28–29; k) J.-F. Paquin, *Synlett* **2011**, 289–293; l) H. Yanai, H. Okada, A. Sato, M. Okada, T. Taguchi, *Tetrahedron Lett.* **2011**, *52*, 2997–3000; m) A. Sato, H. Yanai, D. Suzuki, M. Okada, T. Taguchi, *Tetrahedron Lett.* **2015**, *56*, 925–929. For CF_3-ketones and -imines, see: n) H. Amii, T. Kobayashi, Y. Hatamoto, K. Uneyama, *Chem. Commun.* **1999**, 1323–1324; o) K. Uneyama, H. Amii, *J. Fluorine Chem.* **2002**, *114*, 127–131; p) R. Doi, M. Ohashi, S. Ogoshi, *Angew. Chem. Int. Ed.* **2016**, *55*, 341–344; *Angew. Chem.* **2016**, *128*, 349–352.

[6] K. Fuchibe, H. Hatta, K. Oh, R. Oki, J. Ichikawa, *Angew. Chem. Int. Ed.* **2017**, *56*, 5890–5893; *Angew. Chem.* **2017**, *129*, 5984–5987.

[7] a) K. Uneyama, *Organofluorine Chemistry*, Blackwell Publishing, Oxford, **2006**; b) B. E. Smart, *Organofluorine Chemistry, Principles and Commercial Applications*, Plenum Press, New York, **1994**.

[8] For our previous publications on the synthetic use of stabilized CF_2 cations, see: a) J. Ichikawa, M. Kaneko, M. Yokota, M. Itonaga, T. Yokoyama, *Org. Lett.* **2006**, *8*, 3167–3170; b) J. Ichikawa, M. Yokota, T. Kudo, S. Umezaki, *Angew. Chem. Int. Ed.* **2008**, *47*, 4870–4873; *Angew. Chem.* **2008**, *120*, 4948–4951; c) K. Fuchibe, H. Jyono, M. Fujiwara, T. Kudo, M. Yokota, J. Ichikawa, *Chem. Eur. J.* **2011**, *17*, 12175–12185; d) K. Fuchibe, Y. Mayumi, N. Zhao, S. Watanabe, M. Yokota, J. Ichikawa, *Angew. Chem. Int. Ed.* **2013**, *52*, 7825–7828; *Angew. Chem.* **2013**, *125*, 7979–7982. e) See also: M. Yokota, D. Fujita, J. Ichikawa, *Org. Lett.* **2007**, *9*, 4639–4642; f) K. Fuchibe, R. Takayama, T. Yokoyama, J. Ichikawa, *Chem. Eur. J.* **2017**, *23*, 2831–2838.

[9] a) Y. E. Rhodes, V. G. DiFate, *J. Am. Chem. Soc.* **1972**, *94*, 7582–7583; b) T. Nagasawa, K. Suzuki, *Synlett* **1993**, 29–31; c) W. Rao, P. W. H. Chan, *Chem. Eur. J.* **2008**, *14*, 10486–10495; d) J. I.-C. Wu, P. R. Schleyer, *Pure Appl. Chem.* **2013**, *85*, 921–940.

[10] For the ring opening of perfluoromethylcyclopropane, see: Z.-Y. Yang, P. J. Krusic, B. E. Smart, *J. Am. Chem. Soc.* **1995**, *117*, 5397–5398.

[11] a) D. Gladow, H.-U. Reissig, *Helv. Chim. Acta* **2012**, *95*, 1818–1830; b) O. S. Artamonov, E. Y. Slobodyanyuk, D. M. Volochnyuk, I. V. Komarov, A. A. Tolmachev, P. K. Mykhailiuk, *Eur. J. Org. Chem.* **2014**, 3592–3598.

[12] For the reported syntheses and utility of difluoroalkenes, see: a) J. Ichikawa, *Chim. Oggi* **2007**, *25*, 54–57; b) X. Zhang, S. Cao, *Tetrahedron Lett.* **2017**, *58*, 375–392; c) W. Zhang, Y. Wang, *Tetrahedron Lett.* **2018**, *59*, 1301–1308.

[13] B. Morandi, E. M. Carreira, *Angew. Chem. Int. Ed.* **2010**, *49*, 938–941; *Angew. Chem.* **2010**, *122*, 950–953.

[14] V. K. Aggarwal, E. Alonso, G. Hynd, K. M. Lydon, M. J. Palmer, M. Porcelloni, J. R. Studley, *Angew. Chem. Int. Ed.* **2001**, *40*, 1430–1433; *Angew. Chem.* **2001**, *113*, 1479–1482.

[15] For a review on C–F bond activation by main group Lewis acids, see ref. [1b].

[16] For C–C bond formation with aluminum Lewis acids or reagents, see for example: a) T. Ooi, D. Uraguchi, N. Kagashima, K. Maruoka, *Tetrahedron Lett.* **1997**, *38*, 5679–5682; b) J. Terao, S. A. Begum, Y. Shinohara, M. Tomita, Y. Naitoh, N. Kambe, *Chem. Commun.* **2007**, 855–857; c) M. Ali, L.-P. Liu, G. B. Hammond, B. Xu, *Tetrahedron Lett.* **2009**, *50*, 4078–4080; d) W. Gu, M. R. Haneline, C. Douvris, O. V. Ozerov, *J. Am. Chem. Soc.* **2009**, *131*, 11203–11212; e) A. K. Jaiswal, K. K. K. Goh, S. Sung, R. D. Young, *Org. Lett.* **2017**, *19*, 1934–1937.

[17] It should be noted that toluene, *o*-xylene, and naphthalene afforded "normal" regioisomeric mixtures when subjected to the previous CF_3-alkene/$EtAlCl_2$ system (ref. [6]).

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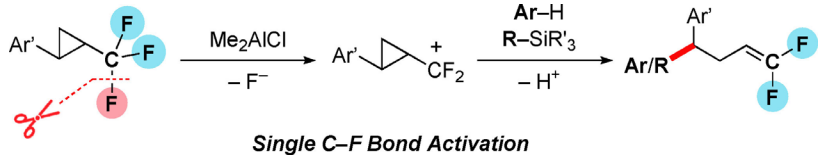
COMMUNICATION



Single C–F Bond Activation

The selective activation of one C–F bond (single activation) of the CF_3 group on cyclopropanes was achieved for the first time. When (trifluoromethyl)cyclopropanes were treated with arenes, allylsilanes, silyl enol ethers, or hydrosilanes in the presence of Me_2AlCl, fluoride elimination and the subsequent ring opening proceeded to afford 4,4-difluorohomoallylated products. In the absence of external nucleophiles, an alkyl group of AlR_3 was effectively introduced to provide the corresponding 1,1-difluoroalkenes.

Bond Activation

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Single C–F Bond Activation of the CF_3 Group with a Lewis Acid: CF_3-Cyclopropanes as Versatile 4,4-Difluorohomoallylating Agents