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Activation of Aromatic C-F Bonds by a *N*-Heterocyclic Olefin (NHO)

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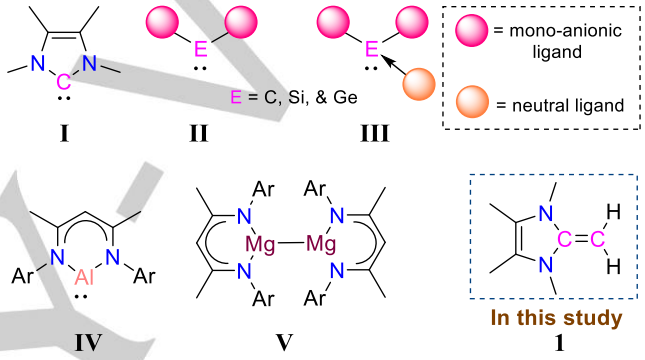
Dedicated to Professor K. V. R. Chary on the occasion of his 65th birthday.

Abstract: A *N*-heterocyclic olefin (NHO), a terminal alkene selectively activates aromatic C-F bonds without the need of any additional catalyst. As a result, a straightforward methodology was developed for the formation of different fluoroaryl substituted alkenes in which the central carbon-carbon double bond is in a twisted geometry.

Compounds containing C-F bond(s) are extremely important in diverse fields ranging from materials chemistry [1] to medicinal chemistry.[2] In comparison to the C-H bond, the most striking differences of the C-F bond are its reverse polarity and higher bond energy.[3] These features contribute to the unique physical and chemical properties of fluorinated compounds. The synthesis of such compounds and the ability to selectively activate C-F compounds in this family is an important area of research. Low-valent low-coordinate transition metal complexes have been known to activate the C-F bond by an oxidative addition.[4] Strong Lewis acids as well as frustrated Lewis pairs (FLPs) are also known for electrophilic activation of the C-F bond.[5] In 1998, Kuhn *et al*. reported a nucleophilic aromatic C-F activation using the *N*-heterocyclic carbene (NHC) **I** (Scheme 1).[6] Since then, nucleophilic activation of aromatic C-F bonds have been achieved employing various two-coordinate divalent Group 14 compounds such as different NHCs, cyclic(alkyl)(amino)carbenes (CAACs), *N*-heterocyclic silylene **II**,[7] and base stabilized three-coordinate divalent Group 14 compounds such as base stabilized silylenes and germylenes **III** (Scheme 1).[8] Also, aromatic C-F activation has been reported using *N*-heterocyclic aluminylene, **IV**[9] and Jones's Mg(I)-Mg(I) bonded compound, **V** (Scheme 1).[10]



Scheme 1. Selected examples of low-valent main group compounds that activate aromatic C-F bond (Ar = 2,6-*i*Pr$_2$C$_6$H$_3$).

However, all the above mentioned C-F activation of fluoroarenes are restricted in their utility for the synthesis of any general family of organofluorine compounds. This and the consideration of the lack of *direct* synthetic methodologies for an important class of compounds viz., fluoroorgano substituted (fluoro, fluoro-alkyl, fluoro-aryl) alkenes[11] prompted us to consider a *N*-heterocyclic olefin (NHO) 1,3,4,5-tetramethyl-2-methyleneimidazoline **1** (Scheme 1).[12] We report that this terminal alkene is an excellent reagent for the nucleophilic activation of aromatic C-F bond under the *direct* formation of different fluoroaryl substituted alkenes without using any additional catalyst. Previous syntheses of fluoroaryl substituted alkenes have been reported using transition-metal complex-catalyzed alkenylation of fluoroarenes.[13] Very recently Berkessel and his group have reported carbene-derived pentafluorophenyl substituted alkenes using corresponding fluoroarylaldehyde as a precursor.[14] Our method, apart from its novelty, has the advantage of being applied to a wide range of aromatic fluoro hydrocarbons, and also reveals an excellent selectivity.

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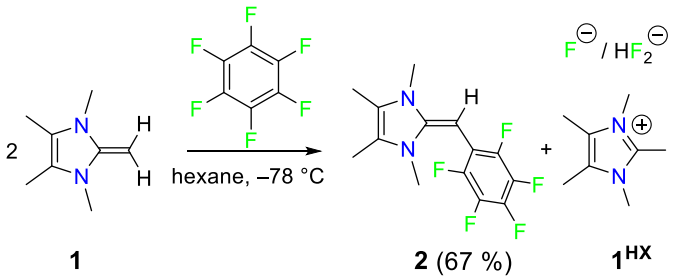


Scheme 2. Reaction of **1** with hexafluorobenzene.

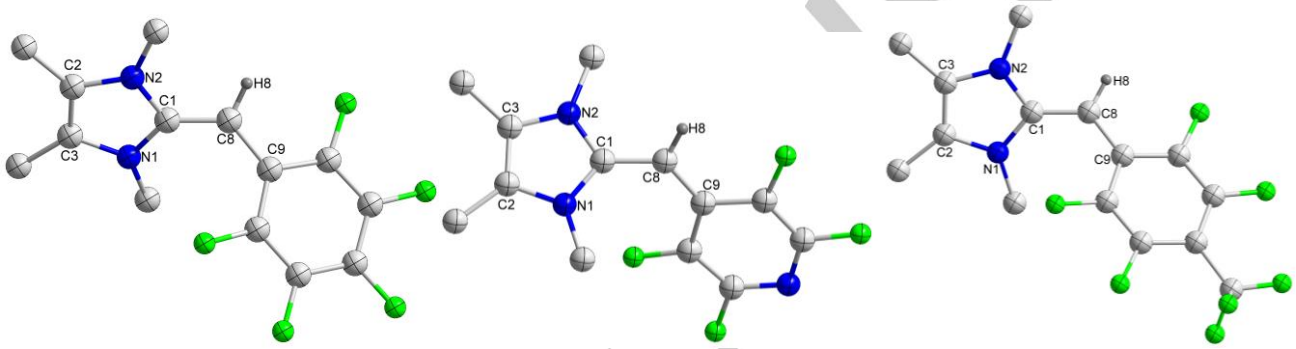
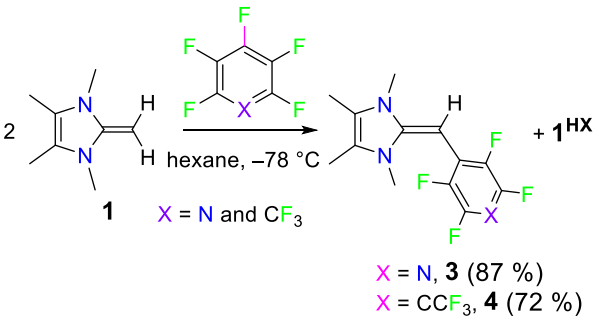


Figure 1. Molecular structures of **2** (left), **3** (middle), and **4** (right) with thermal ellipsoids at 50% probability level. All H atoms except C8–H are omitted for clarity reasons.

The reaction of **1** with hexafluorobenzene in a 2:1 ratio in hexane, resulted in the formation of the fluoroaryl substituted alkene, i.e. a C-F activation product, **2** in 67 % yield along with the imidazolium salt, $\mathbf{1}^{HX}$ (Scheme 2).[15] The formation of compound **2** which is air and moisture sensitive has been confirmed by the presence of three singlet resonances at 1.29, 2.42, and 3.96 ppm in a 6:6:1 ratio, respectively, in the ^{1}H NMR spectrum and three multiplets at −176.68, −167.05, and −149.11 ppm in a 1:2:2 ratio, respectively, in the ^{19}F NMR spectrum. In this reaction **1** also acts as HF scavenger and forms the imidazolium salt, $\mathbf{1}^{HX}$ containing a mixture of fluoride (F^-) and bifluoride (HF_2^-) as counter anions.[15] The solid state molecular structure of **2** revealed that the central C1-C8 bond distance is 1.391(16) Å (Figure 1), which is longer than the corresponding distance in **1** (1.363(3) Å)[12] and imidazole-imidazolium-substituted alkene (1.334(5) Å for *E*-isomer and 1.322(6) Å for *Z*-isomer).[16] The bond elongation is due to the installation of the electron-withdrawing group in place of H-substituent. The notable feature of **2** is a twist angle of 24.79(12)° around the central carbon-carbon double bond.

After this initial success, we considered more reactive perfluorinated arenes such as pentafluoropyridine and octafluorotoluene for reaction with **1**. The 2:1 reaction of **1** with pentafluoropyridine and octafluorotoluene gave regio-selectively the corresponding fluoroaryl substituted olefins **3** (87 %) and **4** (72 %), respectively as deep yellow colored solids (Scheme 3).

To minimize the employed amount of **1**, we considered Et_3N as a HF scavenger. However, **1** does always compete as proton scavenger with Et_3N even when 10 equivalents of Et_3N were used.[15] Formation of **3** and **4** were confirmed by solution state NMR spectroscopy as well as by single crystal X-ray diffraction analysis (Figure 1). The twist angle of the exocyclic olefin moiety for compound **3** is as high as 45.76(76)° which is higher than that of compound **4** (35.83(12)°) and compound **2** (24.79(12)°).



Scheme 3. Reactions of **1** with pentafluoropyridine and octafluorotoluene.

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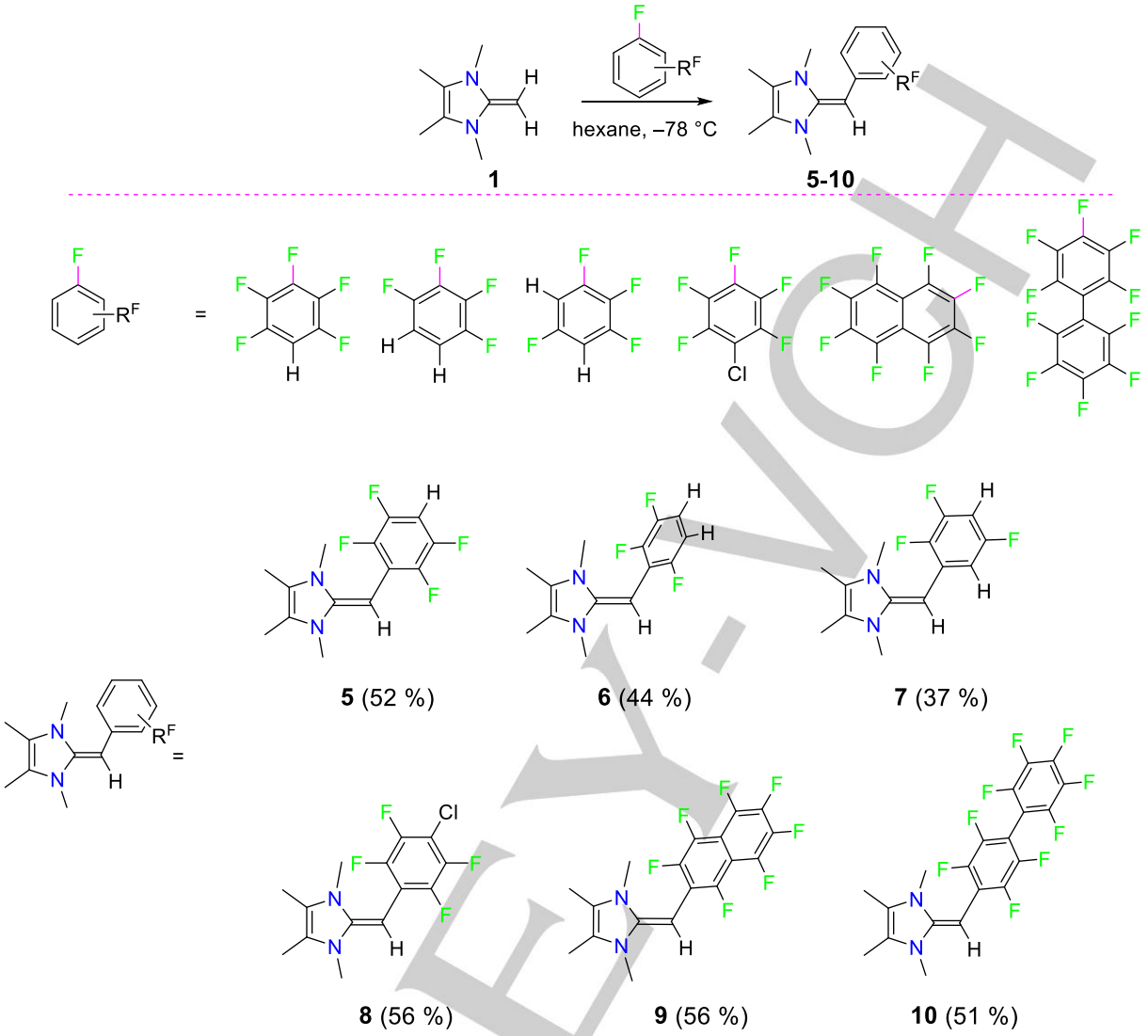


Scheme 4. Reactions of **1** with different fluoroarenes.

Subsequently, to see the regioselectivity of **1** towards the C-F activation as well as to obtain different fluoroaryl substituted olefins we have considered partially fluorinated compounds such as pentafluorobenzene, 1,2,3,4-tetrafluorobenzene, 1,2,3,5-tetrafluorobenzene, and chloropentafluorobenzene along with octafluoronaphthalene and decafluorobiphenyl (Scheme 4). The reaction of **1** with pentafluorobenzene, 1,2,3,4-tetrafluorobenzene, and 1,2,3,5-tetrafluorobenzene leads to exclusive regio-selective C-F activation products **5**, **6**, and **7**, respectively (Scheme 4). These compounds show unique ^{19}F and ^{1}H splitting patterns due to the presence of an extended ^{19}F-^{19}F/ ^{19}F-^{1}H/^{1}H-^{1}H scalar-coupling network.

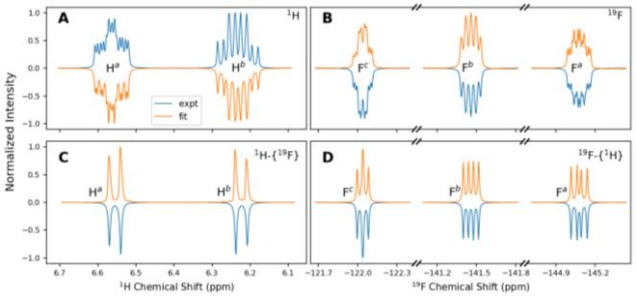


Figure 2. Experimental and simulated ^{1}H (**A**), $^{1}H\{^{19}F\}$ (**C**), ^{19}F (**B**), and $^{19}F\{^{1}H\}$ (**D**) NMR spectra of compound **6**.

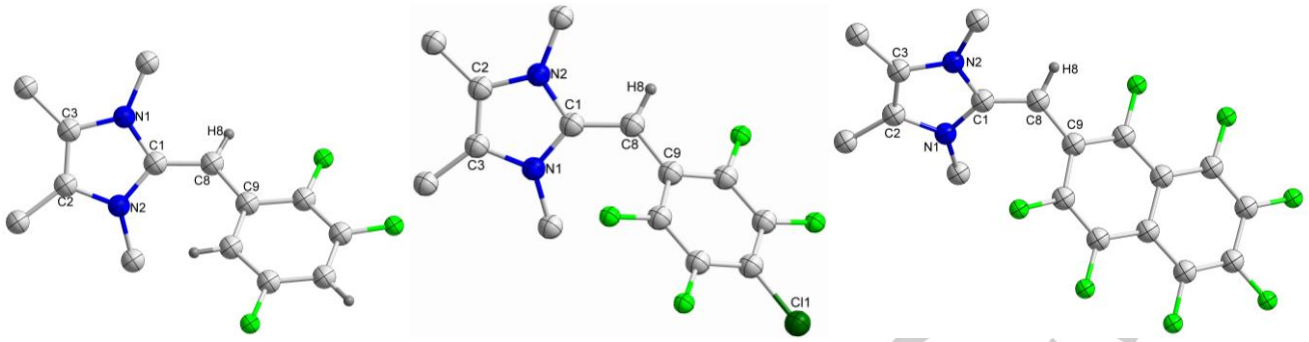
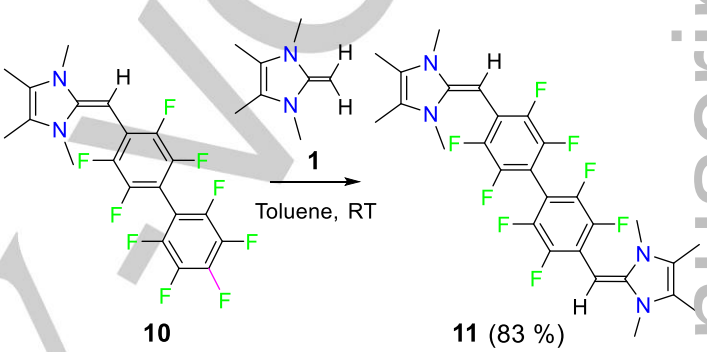


Figure 3. Molecular structures of **7** (left), **8** (middle), and **9** (right) with thermal ellipsoids at 50% probability level. All H atoms except C8–H are omitted for clarity reasons.

In order to characterize and assign these resonances, the splitting patterns of all resonances were fitted using simulations providing values of the scalar couplings and the likely connectivity. In case of compound **6**, for instance, three ^{19}F resonances and two ^{1}H resonances from the fluoroaryl-substituent were unambiguously assigned using their scalar-coupling constants and the experimentally obtained ^{1}H, $^{1}H\{^{19}F\}$, ^{19}F, and $^{19}F\{^{1}H\}$ spectra matches well with the simulated spectra (Figure 2). The formation of compound **7** was further confirmed by its solid state molecular structure determination (Figure 3).

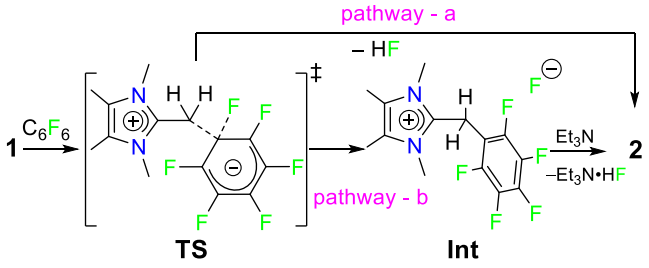
The reaction of **1** with chloropentafluorobenzene leads to selective C-F activation resulting in **8** with 56 % yield (Scheme 4). The molecular X-ray structure of **8** shows a twist angle of the exocyclic olefin moiety of only 18.34(22)° which is more acute than that of **2** (24.79(12)°), **3** (45.76(76)°), **4** (35.83(12)°), and **7** (32.10(11)°). On treatment of **1** with octafluoronaphthalene, compound **9** was obtained in 56 % yield as a bright orange colored solid as a result of selective C2-F activation (Scheme 4). Its structural analysis exhibits a twist angle of the exocyclic olefin moiety of 24.29(16)° (Figure 3).

The reaction of **1** with decafluorobiphenyl leads to compound **10** (Scheme 4). A small amount of the double C-F activation product **11** was also noticed, even when a strict 1:1 stoichiometry was imposed. Subsequently, the bis-alkenyl moiety functionalized octafluorobiphenyl system **11** was synthesized on purpose by reacting **10** with **1** (Scheme 5). The X-ray structural analyses reveal twist angles of the exocyclic olefin moieties of 34.79(11)° in **10** and of 26.74(19)° and 32.34(17)° in **11** (Figure 4).



Scheme 5. Synthesis of **11**.

We propose that the reaction of **1** with fluoarenes proceeds through an aromatic nucleophilic substitution reaction (Scheme 6). A nucleophilic attack of **1** at the electrophilic C-centre of the C-F moiety of fluoroarenes leads to a transition state, **TS**. This **TS** can directly leads to the product **2** by an elimination of HF (pathway – a) or it can evolves into an ionic intermediate (**Int**, **[2H⁺]F⁻**), which has different fates depending on the conditions (pathway - b).



Scheme 6. Proposed mechanism of aromatic C-F bond activation by NHO, **1**.

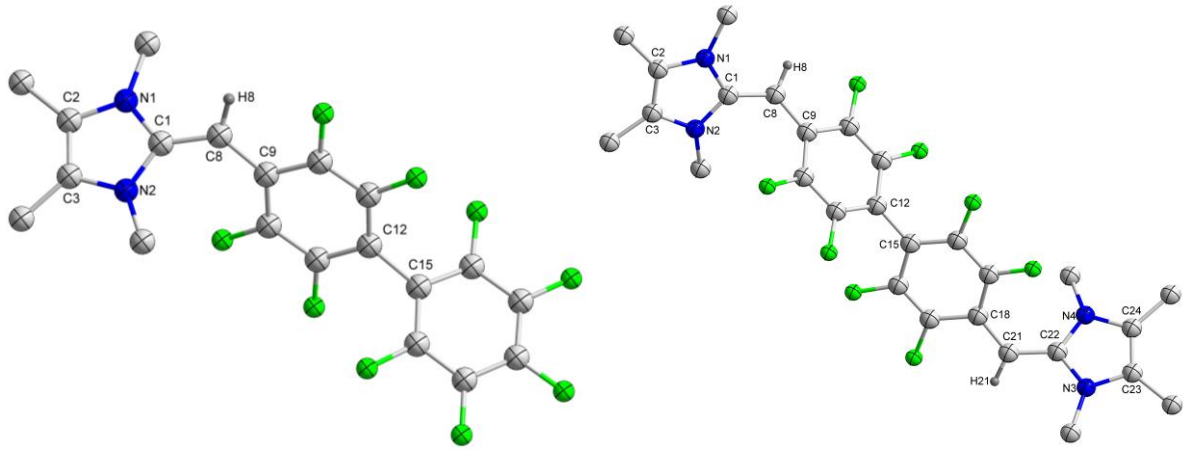


Figure 4. Molecular structures of **10** (left) and **11** (right) with thermal ellipsoids at 50% probability level. All H atoms except C8–H (for **10**) and C8–H and C21–H (for **11**) are omitted for clarity reasons.

One of the observed routs is subsequent elimination of HF leading to **2**. This route was computationally observed when a relaxed surface scan starting with **1** + C_6F_6 was performed in hexane as pseudo solvent, without inclusion of additional molecules. In this case **Int** was not the final structure, but **2** + **HF** (pathway - a). **Int** could be stabilized if a molecule of Et_3N was added, leading to deprotonation of **[2H$^+$]**, through **TS2^{Et_3N}**, and final products **2** + **Et_3N•HF** (pathway – b and see Figure S51 in Supporting Information). This proposed pathway is supported by the theoretical calculation at PBEO/def2-TZVP level of theory.[15] The energy barrier of **TS** in hexane is 22.1 kcalmol^{-1} whereas the formation of **2** is exergonic by ΔG_{300} = –21.7 kcalmol^{-1} (Figure 5).[15] **Int** could also be stabilized if DMF was chosen as pseudo solvent in the calculations (pathway - b), which also resulted in a slight lowering of the activation barrier to 21.3 kcalmol^{-1} (see Figure S50 in Supporting Information).

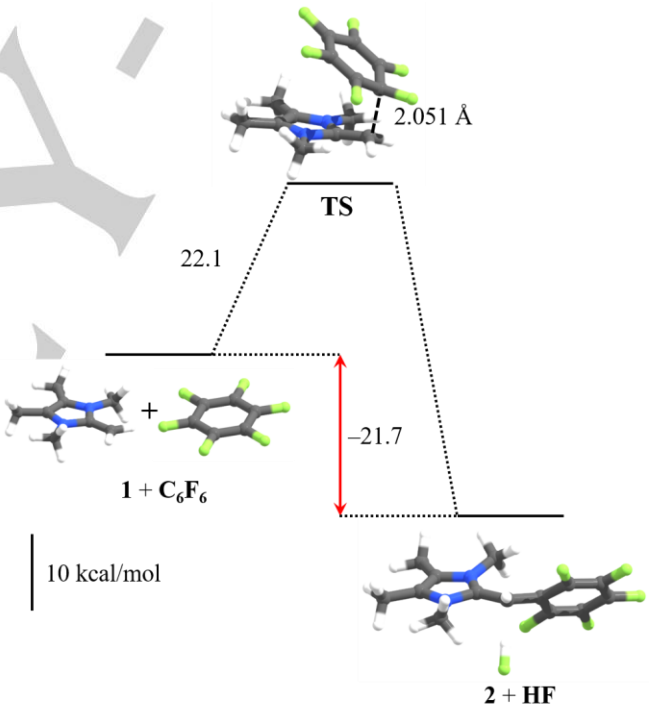


Figure 5. The reaction energy profile diagram for the C–F bond activation of C_6F_6 by **1** (all energy values are in kcalmol^{-1}).

In conclusion, we have demonstrated that the *N*-heterocyclic olefin (NHO), as a terminal alkene selectively activates a large variety of aromatic C-F bonds without any additional catalyst. The aromatic C-F activation by NHO results in a straightforward formation of fluoroaryl substituted alkenes, which have a twisted central carbon-carbon double bond with an angle varying from 18.34° to 45.76°, depending on the fluoroaryl substituent. Considering that a large variety of NHOs are already available,[17] and that new NHO designs can be readily adapted

to our strategy, our reported synthetic methodology is extremely versatile.

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Keywords: alkenes • C-F activation • fluorine • *N*-heterocyclic olefins • nucleophilic substitution

[1] a) M. Pagliaro, R. Ciriminna, *J. Mater. Chem.* **2005**, *15*, 4981–4991; b) Z. L. Chu, S. Seeger, *Chem. Soc. Rev.* **2014**, *43*, 2784–2798; c) C. Martinelli, G. M. Farinola, V. Pinto, A. Cardone, *Materials* **2013**, *6*, 1205–1236.

[2] a) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev*. **2008**, *37,* 320–330; b) S. Preshlock, M. Tredwell, V. Gouverneur, *Chem. Rev*. **2016**, *116*, 719–766; c) Y. Zhou, J. Wang, Z. N. Gu, S. N. Wang, W. Zhu, J. L. Acena, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, *116*, 422–518.

[3] D. O'Hagan *Chem. Soc. Rev.*, **2008**, *37*, 308–319.

[4] a) H. Amii, K. Uneyama, *Chem. Rev*. **2009**, *109*, 2119–2183; b) R. N. Perutz, T. Braun, *Transition-Metal Mediated C-F Bond Activation. In Comprehensive Organometallic Chemistry III*; R. H. Crabtree, D. M. P. Mingos Eds.; Elsevier: Amsterdam, The Netherlands, **2007**; Vol. **1**, pp 725–758.

[5] a) T. Stahl, H. F. T. Klare, M. Oestreich *ACS Catal.* **2013**, *3*, 1578–1587; b) C. B. Caputo, D. W. Stephan *Organometallics* **2012**, *31*, 27–30.

[6] N. Kuhn, J. Fahl, R. Boese, G. Henkel *Z. Naturforsch., B: Chem. Sci.* **1998**, *53*, 881–886.

[7] a) S. Styra, M. Melaimi, C. E. Moore, A. L. Rheingold, T. Augenstein, F. Breher, G. Bertrand, *Chem. Eur. J*. **2015**, *21*, 8441–8446; b) Y. Kim, E. Lee, *Chem. Commun*. **2016**, *52*, 10922–10925; c) Z. R. Turner, *Chem. Eur. J.* **2016**, *22*, 11461–11468; d) J. E-. King, S. A. Hauser, A. B. Chaplin, *Org. Biomol. Chem*. **2017**, *15*, 787–789; e) U. S. D. Paul, U. Radius, *Chem. Eur. J.* **2017**, *23*, 3993–4009; f) M. Pait, G. Kundu, S. Tothadi, S. Karak, S. Jain, K. Vanka, S. S. Sen, *Angew. Chem.* **2019**, *131*, 2830–2834; *Angew. Chem. Int. Ed*. **2019**, *58*, 2804–2808.

[8] a) A. Jana, P. P. Samuel, G. Tavčar, H. W. Roesky, C. Schulzke, *J. Am. Chem. Soc.* **2010**, *132*, 10164–10170; b) R. Azhakar, H. W. Roesky, H. Wolf, D. Stalke, *Chem. Commun.* **2013**, *49*, 1841–1843; c) P. P. Samuel, A. P. Singh, S. P. Sarish, J. Matussek, I. Objartel, H. W. Roesky, D. Stalke, *Inorg. Chem*. **2013**, *52*, 1544–1549.

[9] a) M. R. Crimmin, M. J. Butler, A. J. P. White, *Chem. Commun.* **2015**, *51*, 15994–15996; b) T. Chu, Y. Boyko, I. Korobkov, G. I. Nikonov, *Organometallics* **2015**, *34*, 5363−5365.

[10] C. Bakewell, A. J. P. White, M. R. Crimmin, *J. Am. Chem. Soc.* **2016**, *138*, 12763–12766.

[11] a) M. Shimizu, T. Hiyama, *Angew. Chem.* **2004**, *117*, 218–234; *Angew. Chem. Int. Ed.* **2004**, *44*, 214–231; b) J. P. Phelan, R. J. Wiles, S. B. Lang, C. B. Kelly, G. A. Molander, *Chem. Sci.* **2018**, *9*, 3215–3220; c) C. Bakewell, A. J. P. White, M. R. Crimmin, *Angew. Chem.* **2018**, *130*, 6748–6752; *Angew. Chem. Int. Ed.* **2018**, *57*, 6638–6642; d) G. Coates, H. Y. Tan, C. Kalff, A. J. P. White, M. R. Crimmin, *Angew. Chem.* **2019**, *131*, 12644–12648; *Angew. Chem. Int. Ed.* **2019**, *58*, 12514–12518; e) H. Sakaguchi, M. Ohashi, S. Ogoshi, *Angew. Chem.* **2018**, *130*, 334–338; *Angew. Chem. Int. Ed.* **2018**, *57*, 328–332; f) H. Sakaguchi, Y. Uetake, M. Ohashi, T. Niwa, S. Ogoshi, T. Hosoya, *J. Am. Chem. Soc.* **2017**, *139*, 12855–12862; g) J. Hu, Y. Zhao, Z. Shi, *Nat. Catal.* **2018**, *1*, 860–869.

[12] N. Kuhn, H. Bohnen, J. Kreutzberg, D. Bläser, R. Boese, *J. Chem. Soc., Chem. Commun.* **1993**, 1136−1137.

[13] a) H.-Q. Do, O. Daugulis, *J. Am. Chem. Soc.* **2008**, *130*, 1128–1129; b) Y. Nakao, N. Kashihara, K. S. Kanyiva, T. Hiyama, *J. Am. Chem. Soc.* **2008**, *130*, 16170–16171.

[14] a) M. Paul, P. Sudkaow, A. Wessels, N. E. Schlörer, J.-M. Neudörfl, A. Berkessel, *Angew. Chem.* **2018**, *130*, 8443–8448; *Angew. Chem. Int. Ed.* **2018**, *57*, 8310–8315; b) M. Paul, J.-M. Neudörfl, A. Berkessel, *Angew. Chem.* **2019**, *131*, 10706–10710; *Angew. Chem. Int. Ed.* **2019**, *58*, 10596–10600.

[15] See the Supporting Information for the details.

[16] D. C. Georgiou, M. A. Haghighatbin, C. F. Hogan, M. S. Scholz, J. N. Bull, E. J. Bieske, D. J. D. Wilson, J. L. Dutton, *Angew. Chem.* **2017**, *129*, 8593–8600; *Angew. Chem. Int. Ed.* **2017**, *56*, 8473–8480.

[17] M. M. D. Roy, E. Rivard, *Acc. Chem. Res*. **2017**, *50*, 2017–2025

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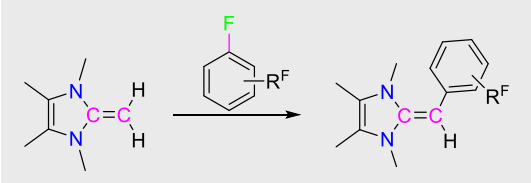

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Page No. – Page No.

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