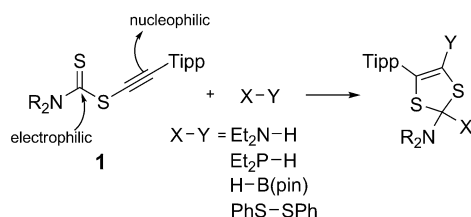


# C–F Bond Activation with an Apparently Benign Ethynyl Dithiocarbamate, and Subsequent Fluoride Transfer Reactions

Gaël Ung<sup>[a, b]</sup> and Guy Bertrand\*<sup>[a, b]</sup>

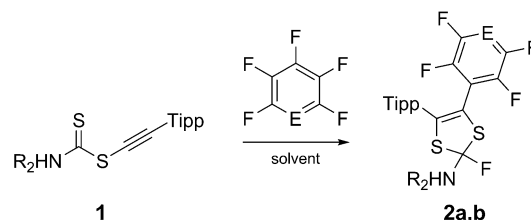
A recent trend in the activation of small molecules and enthalpically strong bonds is the use of non-metal activators.<sup>[1]</sup> In contrast to work on singlet carbenes<sup>[2]</sup> or heavier analogues,<sup>[3]</sup> which are very basic, or on the so-called frustrated Lewis pairs,<sup>[4]</sup> which require strong Lewis acids, our research has recently shown that the simple and mild ethynyl dithiocarbamate **1** was able to activate a variety of enthalpically strong bonds such as N–H, P–H, B–H, and S–S bonds.<sup>[5]</sup> The activation process, which is accompanied by a ring-closure, is due to the cooperative effect of the electrophilic and nucleophilic centers of **1** (Scheme 1). To test the



Scheme 1. Activation of small molecules with ethynyl dithiocarbamate **1**. R<sub>2</sub>N = 1-piperidinyl; Tipp = 2,4,6-triisopropylphenyl; pin = pinacolato.

limits of our activator, we targeted C–F bonds, which are even significantly stronger than C–H bonds, but more polarized; their activation usually requires transition metals<sup>[6,7]</sup> or strong Lewis acids.<sup>[8]</sup> We found that fluorinated adducts, resulting from the activation process with **1**, can be used as non-ionic and anhydrous fluorinating agents.

The addition of **1** to a benzene solution of pentafluoropyridine, a reagent known to react with strong nucleophiles,<sup>[6e,9]</sup> proceeded cleanly (Scheme 2). The multinuclear NMR spec-



Scheme 2. Selective C–F bond activation with ethynyl dithiocarbamate **1**. a: E = N; b: E = CCF<sub>3</sub>.

tra showed three inequivalent isopropyl groups for the 2,4,6-triisopropylphenyl substituent, indicating the presence of a stereogenic center. Additionally, a new doublet in the <sup>13</sup>C NMR spectrum ( $\delta = 136.4$  ppm,  $^1J_{C-F} = 274$  Hz) was observed, consistent with a fluorine directly bound to a carbon atom. In the <sup>19</sup>F NMR spectrum, a new singlet at  $\delta = -37$  ppm was observed, as well as two new multiplets at  $\delta = -91$  and  $-140$  ppm. These data are consistent with the selective activation of the C–F bond at the *para*-position of pentafluoropyridine and the formation of adduct **2a**. Interestingly, in contrast to the results previously reported with strong nucleophiles,<sup>[6e,9]</sup> the substituted fluoride ends up covalently bonded to the activator.

Although the reaction in benzene proceeded cleanly, a long reaction time (18 h) was required. We found that more polar solvents significantly enhanced the rate of the activation process, as shown with experiments performed in THF, 1,4-dioxane, and 1,2-dimethoxyethane (3 to 4 h; Table 1).

Table 1. Solvent optimization for C–F bond activation of pentafluoropyridine.

Entry	Solvent	<i>t</i> [h]	Conv. [%] <sup>[a]</sup>
1	benzene	18	100
2	THF	4	100
3	1,4-dioxane	3	100
4	1,2-dimethoxyethane	3	100

[a] Determined by <sup>19</sup>F NMR spectroscopy using fluorobenzene as an internal standard.

Using these optimized conditions, we tested the activation of other aromatic C–F bonds. Octafluorotoluene was successfully cleaved under the same conditions, and the selective activation of the C–F bond in *para* position was also observed (**2b**). Ethynyl dithiocarbamate **1** was however unable to activate hexafluorobenzene, which was ascribed to the lack of polarity of the latter.

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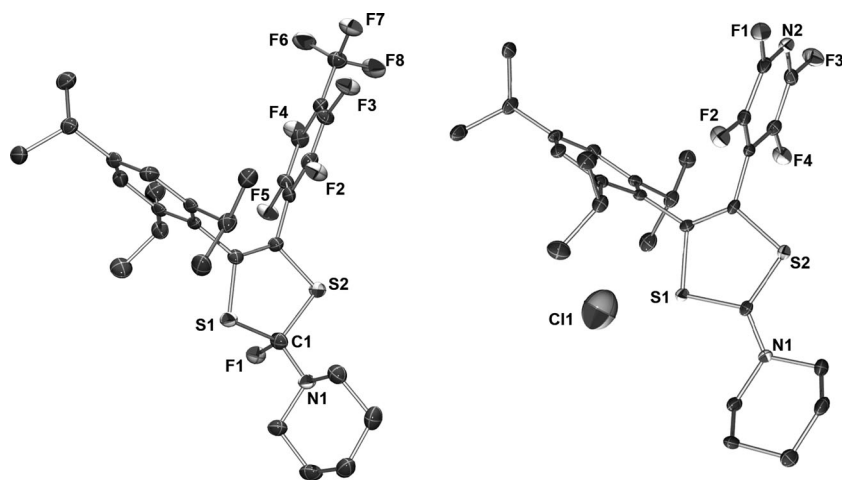


Figure 1. Structure of **2b** (left) and **3** (right) in the solid state (hydrogen atoms have been omitted for clarity; ellipsoids are drawn at 50% probability).<sup>[11]</sup>

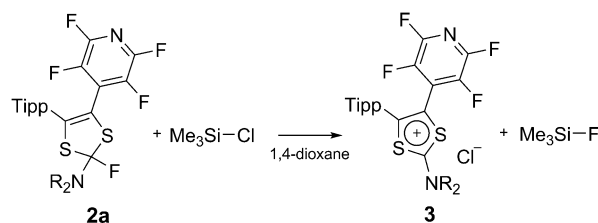
Owing to the four heteroatoms surrounding the carbon atom of the activation adducts **2**, their  $C_{sp^3}-F$  bond is strongly polarized. Indeed, in the solid state, the C1–F1 bond is significantly elongated (1.404(5) Å) compared to other  $C_{sp^3}-F$  bonds (1.32–1.35 Å)<sup>[10]</sup> (Figure 1). This prompted us to investigate the lability of the fluorine atom. Chlorotrimethylsilane was added to a dioxane solution of **2a** and a precipitate appeared immediately. Analysis of the supernatant revealed the presence of fluorotrimethylsilane, and the precipitate was identified as the dithiolium salt **3** (Scheme 3; Figure 1)

Compound **2a** also reacts almost instantaneously with strong electrophiles such as acyl chlorides or *para*-toluenesulfonyl chloride. All fluorinated products were isolated in very good yields (Table 2, entries 2 to 4; 83 to 95%). Nucleophilic aromatic substitutions can as well be achieved in good yields with the electron-poor 1-chloro-2,4-dinitrobenzene (Table 2, entry 4). Additionally, benzyl mesylate, tosylate, and bromide were also successfully converted to their fluorinated counterparts (Table 2, entries 5–7) at a higher temperature. Lastly, the fluoride anion can even be transferred to secondary alkyl triflate, and primary and secondary alkyl iodides (Table 2, entries 8–10), although these transformations require higher temperatures and longer times, which affect their yields.

Compound **2a** is therefore able to release a fluoride anion even though the fluorine atom is always covalently bound to the heterocycle, regardless of the polarity of the solvent ( $^1J_{C-F}(C_6D_6) = ^1J_{C-F}([D_8]THF) = 274$  Hz). Note that salt **3** precipitates from the solution, allowing an easy separation of the fluorinated product by simple filtration. Moreover, **2a** is soluble in ethereal solvents and aromatic hydrocarbons, and is remarkably stable in solution at room temperature. Finally, the comparison of our results with those obtained with Olah's

reagent,<sup>[12]</sup> a widely used fluorinating compound, shows that **2a** has a similar reactivity with strong electrophiles but is much more efficient for the other substrates.<sup>[13]</sup>

This work demonstrates that the simple linear ethynyl dithiocarbamate **1** can activate aromatic carbon–fluorine bonds by the cooperative effect of the electrophilic and nucleophilic centers. The selective *para* C–F activation of the electrophilic pentafluoropyridine yields a cyclic adduct capable of transferring nucleophilic fluoride to various substrates. Note that,



Scheme 3. Fluorine transfer to chlorotrimethylsilane.

Table 2. Scope of the fluorine transfer reaction.<sup>[a]</sup>

Entry	Reagent	Product	<i>t</i>	<i>T</i> [°C]	Conv. [%] <sup>[b]</sup>	Yield [%] <sup>[c]</sup>
1	Me <sub>3</sub> Si–Cl	Me <sub>3</sub> Si–F	5 min	RT	100	95 <sup>[d]</sup>
2			5 min	RT	100	87 <sup>[e]</sup>
3			5 min	RT	100	83 <sup>[e]</sup>
4			5 min	RT	100	95
5			2 h	RT	100	92
6			10 h	45	100	86 <sup>[e]</sup>
7			10 h	45	100	85 <sup>[e]</sup>
8			14 h	45	85 <sup>[f]</sup>	73 <sup>[e]</sup>
9			14 h	45	74 <sup>[f]</sup>	74 <sup>[d]</sup>
10			14 h	45	70 <sup>[f]</sup>	54 <sup>[e]</sup>
11			14 h	45	64 <sup>[f]</sup>	64 <sup>[d]</sup>

[a] Reaction conducted using **2a** (0.26 mmol), reagent (0.26 mmol) in 1,4-dioxane (4 mL). [b] Determined by <sup>19</sup>F NMR spectroscopy using fluorobenzene as internal standard. [c] Yield of isolated product. [d] Product is a gas. [e] Product obtained by distillation. [f] Longer reaction times lead to decomposition of the starting material without yielding more product.

although electrophilic fluorination reactions have been extensively developed,<sup>[14]</sup> nucleophilic substitution using fluoride remains limited.<sup>[15]</sup>

## Experimental Section

**Synthesis of 2:** Ethynyl dithiocarbamate **1** was dissolved in 1,4-dioxane (1 mL) in an NMR tube fitted with a J. Young-type Teflon valve. Pentafluoropyridine or octafluorotoluene were added. After 36 h, the product was precipitated with pentane at  $-30^{\circ}\text{C}$  and the supernatant was removed by filtration. A yellow powder was obtained.

**General procedure for fluorine transfer reactions:** In a Schlenk tube, the corresponding reagent was added to a solution of **2a** (0.26 mmol) in 1,4-dioxane (4 mL) containing 5 mol% of fluorobenzene (internal standard). The reaction progress was monitored by  $^{19}\text{F}$  NMR spectroscopy. The reaction was stopped when the signal at  $\delta = -37$  ppm disappeared completely. The reaction mixture was allowed to decant, and the supernatant was filtered. The product was separated from the solvent. Yields are given as an average of three independent runs.

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**Keywords:** bond activation • fluorine transfer • frustrated Lewis pair • synthetic methods

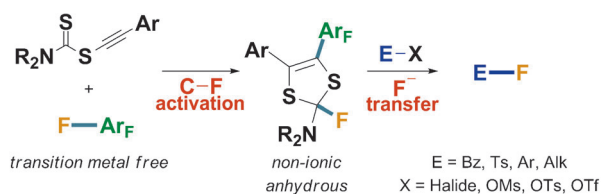
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**Bond Activation**

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**C-F Bond Activation with an Apparently Benign Ethynyl Dithiocarbamate, and Subsequent Fluoride Transfer Reactions**



**F-act finding mission:** Selective activation of the *para* C-F bonds of perfluorinated aromatic derivatives was achieved with a simple ethynyl dithio-

carbamate. The resulting adducts can be used as non-ionic, anhydrous fluoride transfer reagents towards various electrophiles (see scheme).