

Catalytic HF Shuttling between Fluoroalkanes and Alkynes

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ABSTRACT: In this paper we report a catalytic method to transfer formal equivalents of HF from fluoroalkanes to an alkyne. The method leads to a simple and sustainable approach to generate difluoroalkanes and tolerates numerous sensitive functional groups including halogen, protected amine, ester and thiophene substituents. BF₃-OEt₂ catalyses this new catalytic transformation. Mechanistic studies (DFT, probe experiments) suggest the catalyst is intimately involved in both the defluorination and fluorination steps required for HF transfer, with BF₃ acting as a Lewis acid and OEt₂ a weak Lewis base that mediates proton transfer. Fluoroalkenes are demonstrated as competent intermediates and their conversion to difluoroalkanes was found to be reversible. These results establish the first true HF shuttle process (i.e. bidirectional) and represent a potentially powerful method for recycling fluorocarbons.

Due to their applications in pharmaceuticals, agrochemicals, materials, and next generation refrigerants, there is a growing demand for organofluorine compounds.¹⁻³ This demand has stimulated widespread interest in synthetic methods for fluorination. For example, the addition of HF to unsaturated substrates represents a simple and atom-efficient approach to construct organofluorines.^{4,5} Despite finding widespread use, the approach has its drawbacks; HF is a corrosive and toxic gas and high concentrations can be fatal in contact with skin. Although milder and easier to handle reagents such as pyridinium poly(hydrogen fluoride) or triethylamine trihydrofluoride have been developed, they do not entirely mitigate the risk.⁶

In recent years, we^{7,8} and others have begun developing new catalytic approaches that allow the recycling of the fluorine content of organofluorine compounds. These methods hold promise as a first step toward a circular economy of fluorine, while also obviating the need to handle HF. Our long-term aim is to establish reversible processes such that fluorine content can be moved from one molecule to another without significant energy input. Related approaches have already emerged for shuttling HCl or HBr between substrates. In 2020, Morandi and coworkers reported the iridium chloride catalyzed hydrobromination and hydrochlorination of internal alkynes through HBr or HCl shuttling from bromo- or chloroalkanes (Figure 1).⁹ More recently, the same group documented a rhodium-catalysed transfer hydroiodination of terminal alkynes.¹⁰ Oestreich and coworkers have reported a Lewis-acid catalysed decarboxylative transfer hydrochlorination of alkynes.¹¹ Expansion of these methods to organofluorine compounds is non-trivial. Carbon-fluorine bond strengths are extremely high,¹² oxidative addition of the sp³ C-F bonds to transition metals are essentially unknown,¹³ and in cases that defluorination does occur the resulting metal fluoride can be too thermodynamically stable to engage in catalysis.¹⁴⁻¹⁶

Here we report $\text{BF}_3\text{-OEt}_2$ as an efficient catalyst for the HF shuttling between fluoroalkanes and alkynes to form an alkene and a difluoroalkane. We show that there is an aspect of reversibility to this reaction and that difluoroalkane products can be converted back into fluoroalkene intermediates. Our approach requires $\text{BF}_3\text{-OEt}_2$ to act as a catalyst for both defluorination and fluorination events in a single catalytic sequence. Lewis acidic group 13 compounds have been reported as both reagents and catalysts for the hydrofluorination of internal alkynes^{17–19} and the defluorination of fluoroalkanes,^{20–22} and represented a logical starting point for the development of an HF shuttle catalyst. Very recently, $\text{BF}_3\text{-OEt}_2$ has been reported as a catalyst for the homologation of fluoroalkanes with diazoesters,²³ and the intramolecular fluorocarbonylation of alkynes.²⁴

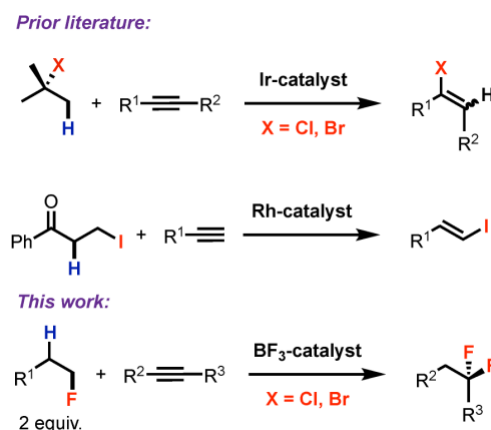


Figure 1. Catalytic methods for HX (X = I, Br, Cl, F) shuttling and transfer between haloalkanes and alkynes

Initially, a series of group 13 Lewis acid catalysts and bases were screened for the reaction of 1-fluorohexane with diphenylacetylene. $\text{BF}_3\text{-OEt}_2$ in combination with weak Lewis-bases such as 2,6-dichloropyridine or triphenylphosphine proved active for HF transfer in modest yields. Ultimately, it was discovered that the Lewis-base was unnecessary for product formation. The further development of this process was complicated by the generation of the alkyne hydration side product, 1,2-diphenylethan-1-one, in significant yields. While performing reactions in fluorinated ethylene propylene (FEP) tubes reduced the yield of 1,2-diphenylethan-1-one, its formation could not be excluded entirely.

In contrast, side-products from alkyne hydration were not observed with either internal or terminal aliphatic alkynes. Focusing on these substrates, we optimized the reaction temperature, solvent, reaction time, catalyst loading and absolute concentration for formation of the difluoroalkane product. Under the optimized conditions 1-fluoroheptane (2 equiv.) and 1-dodecyne (1 equiv.) react to form a mixture of internal heptene isomers (79%) and 2,2-difluorododecyne (76%) catalyzed by 10 mol% $\text{BF}_3\text{-OEt}_2$ in CHCl_3 at 80 °C (Figure 2). A control reaction that omitted the 1-fluoroheptane gave <2% yield of the HF transfer product.

Using 1-fluoroheptane as the HF donor, a range of cyclic and acyclic alkyl-substituted alkynes could be employed in the HF shuttling reaction to afford respective products with moderate to good yields (**2a-2m**). The reaction scope includes both internal and terminal alkynes substituted by aliphatic groups. Remarkably, substrates with potentially sensitive functional groups were tolerated, including halogens (**2e-2g**), and a phthalimido group (**2h**). The reaction is also selective for a single sp^3 C–F moiety, as the trifluoromethyl group can be carried through unscathed (**2j**) with similar yields to the methylated analogue (**2k**). Coordinating groups including a benzoate ester (**2l**), a thiophene ring system (**2m**) also delivered the gem difluoro products in moderate to good

yields. Catalyst poisoning experiments were conducted by added stoichiometric quantities of methyl benzoate, thiophene, and furan, to the standard catalytic procedure. Yields of **1a** and **2b** ranged from 30-75% and 30-72% respectively in the presence of these additives, and in no case was catalysis completely inhibited. In contrast, addition of pyridine completely shut down the catalytic reactions.

During the formation of **2a**, mixtures of *E/Z*-fluoroalkenes could be observed as reaction intermediates. It was assumed that the formation of the difluoroalkane products occurs by two sequential HF transfer events, the first of which generates a mixture of alkene isomers. Independent synthesis of (*Z*)-6-fluorododec-6-ene and exposure to the catalytic conditions resulted in formation of **2i** in 60% yield alongside (*E*)-6-fluorododec-6-ene in 8% yield, confirming the *Z*-fluoroalkene as a potential reaction intermediate.

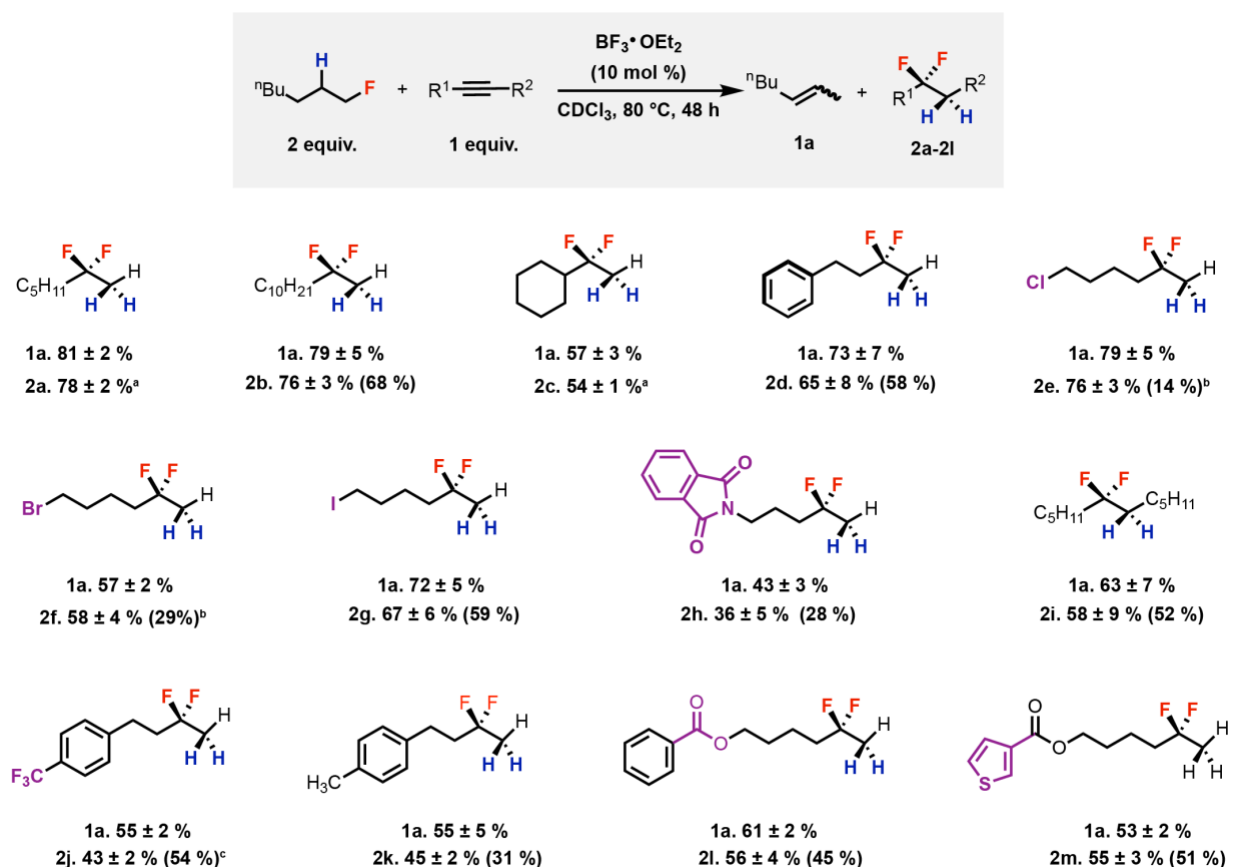


Figure 2. Reaction scope under optimised conditions. Difluoroalkane yield monitored by quantitative ¹⁹F NMR spectroscopy. Alkene yields were monitored by ¹H NMR spectroscopy. Reactions were performed in triplicate and errors based on standard deviation with a 99 % confidence level. Isolated yields provided in parenthesis. ^aproduct could not be isolated. ^blow recovery due to volatility. ^cisolated yield was obtained using 20 mol% BF₃-OEt₂

To gain further insight into the thermodynamics of HF transfer and the mechanism of the reaction, a series of DFT calculations were conducted. To reduce potential issues with the conformational flexibility of medium-length hydrocarbon chains, the reaction of fluoroethane with 1-propyne was considered as a model. The overall reaction of two equiv. of fluoroethane with 1-propyne, is exergonic with $\Delta G^\circ(298\text{K}) = -22.5 \text{ kcal mol}^{-1}$. A series of mechanistic steps for HF transfer were considered. Defluorination can potentially occur by either an E₁ or E₂ mechanism, and fluorination by a stepwise or concerted electrophilic addition mechanism. In all cases the calculations suggest that concerted processes are the most favorable (Figure 3).

Reaction of $\text{BF}_3\text{-OEt}_2$ with fluoroethane is calculated to proceed by an initial endergonic formation of **Int-1**, a weakly associated complex, resulting from dissociation of the boron trifluoride etherate complex. Elimination of HF from **Int-1** is calculated to occur in a concerted fashion, via **TS-1**, with an accessible activation barrier under reaction condition of ΔG^\ddagger (298 K) = 33.1 kcal mol⁻¹. to form **Int-2** – a combination of $\text{HBF}_4\text{-OEt}_2$ and ethene. Diethyl ether was modelled explicitly throughout the reaction and is proposed to play the role of a weak base in the E₂ mechanism. The hydrofluorination step from **Int-2** is also calculated to be an exergonic process, where $\text{HBF}_4\text{-OEt}_2$ delivers a proton to the terminal alkyne carbon of 1-propyne and a fluoride to the internal position via **TS-2** with a readily accessible activation barrier of ΔG^\ddagger (298 K) = 24.1 kcal mol⁻¹. While generation of a carbocation intermediate could be suggested, the intrinsic reaction coordinate (IRC) links **TS-2** directly to the product, 2-fluoroprop-1-ene via the adduct **Int-3**. The calculations suggest a barrierless process for the fluorination of the putative vinyl carbocation and reflects the instability of this proposed intermediate. Attempts to optimize a structure of the carbocation intermediate also resulted in 2-fluoroprop-1-ene formation. Despite the concerted nature of **TS-2**, the hydrofluorination step is still expected to generate carbocation character as $\text{HBF}_4\text{-OEt}_2$ reacts with the alkyne. Experimentally, $\text{HBF}_4\text{-OEt}_2$ was observed to form in catalytic runs ($\delta_{1\text{H}} = 10.5$ ppm; $\delta_{19\text{F}} = -152$ ppm). $\text{HBF}_4\text{-OEt}_2$ was also shown to be catalytically competent as the reaction of 1-fluoroheptane, 1-dodecyne, and 10 mol% $\text{HBF}_4\text{-OEt}_2$ formed **2b** in 61% yield alongside a mixture of internal heptene isomers in 71% yield. A mechanistic probe experiment in which pent-4-yn-1-ylbenzene was subjected to the catalytic conditions led to intramolecular Friedel-Crafts alkylation, providing support for formation of a catalytic intermediate with carbocation character (see Supporting Information for details).

Overall the formation of 2-fluoroprop-1-ene from the 1st HF transfer event is exergonic by $\Delta G^\circ(298\text{K}) = -12.2$ kcal mol⁻¹. In presence of a second equivalent of fluoroethene, a 2nd HF transfer event can occur by a similar sequence. The reaction of $\text{HBF}_4\text{-OEt}_2$ with 2-fluoroprop-1-ene is calculated to occur by **TS-3** with ΔG^\ddagger (298 K) = 15.3 kcal mol⁻¹. Again, IRC calculations link **TS-3**, associated with protonation, directly to the product of fluorination, **Int-4**. $\text{BF}_3\text{-OEt}_2$ is subsequently regenerated from the decomplexation to the product, 2,2-difluoropropane.

Comparison of the local energy barriers for the key steps via **TS-1**, **TS-2** and **TS-3** suggests that the hydrodefluorination step should be turnover-limiting for the catalytic sequence. Moreover, the lowest barrier and least exergonic step is associated with **TS-3**. In the reverse direction, this barrier is ΔG^\ddagger (298 K) = 28.5 kcal mol⁻¹, lower than the global activation energy for catalysis. The calculations suggest that the conversion of 1-fluoropropene to 2,2-difluoropropane should be reversible. Such reversibility would offer the opportunity to establish HF shuttling between these substrates. In line with these calculations, the reaction of **2i** with 1-heptyne led to the formation of **2a** along with the fluoroalkene **3**. Similarly, a comproportionation type reaction of **2i** with dodec-6-yne resulted in formation of **3** as an 4:1 mixture of Z:E isomers in 81% yield (Figure 4). BF_3 -mediated isomerization of fluoroalkenes has been observed previously and the Z-isomer is expected to be the thermodynamically more stable product.¹⁹

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

- Synthetic procedures, NMR spectra and computational methods (PDF)
- Cartesian coordinates of optimized structures (XYZ)

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Author Contributions

†These authors contributed equally and are listed joint 1st. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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