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Electrophilic fluorosulfoxonium cations as hidden Brønsted acid catalysts in (n+2) annulations of strained cycloalkanes

Augustin Manel, ^a Jordan Berreur, ^a Frédéric R. Leroux^a and Armen Panossian*^a

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The highly electrophilic fluorosulfoxonium cation $[Ph_2S(O)F]^+$ $[B(C_6F_5)_4)]^-$ is shown to promote (n+2) annulation on Donor-Acceptor (D-A) strained cycles. This study highlights new reactions catalysed by highly electrophilic sulfoxonium cations and the thin barrier between Lewis acid catalysis and Brønsted acid catalysis.

Among non metal-based Lewis acid catalysts, Electrophilic Phosphonium Cations (EPCs) have attracted interest as efficient promoters for a wide variety of reactions: hydrosilylation of olefins, alkynes, imines and ketones;^{1,2} deoxygenation of ketones,³ amides⁴ and phosphine oxides;⁵ catalytic benzylation/alkylation by hydrodefluorination;⁶ CO₂ capture;⁷ hydrogenation of olefins;⁸ Friedel-Crafts dimerisations;¹ hydroarylation and hydrothiolation of olefins;⁹ cyanosilylation of carbonyls;10,11 pericyclic reactions such as Diels-Alder or Nazarov cyclisations.¹² As a particular type of EPCs, highly electrophilic fluorophosphonium cations seem especially appealing due to their quick access by Umpolung of phosphines (Figure 1).13 They have been extensively investigated by Stephan and coworkers, who prepared and studied a wide variety of new EPCs.¹⁴ Many of these highly electrophilic cations were assessed to be superacids, their Lewis acidity being derived from the $\sigma^*{}_{\text{P-F}}$ orbital lobe oriented opposite to the fluorine ligand and sterically shielded by the surrounding substituents.15

This *Umpolung* strategy for phosphines was extended to sulfoxides to form fluorosulfoxonium cations (Figure 1),¹⁵ which were already known species.^{16–18} However, electrophilic sulfoxonium cation-based catalysis is yet to be fully developed beyond hydroarylation, hydrothiolation and polymerisation of



Figure 1 Umpolung strategy for the obtention of strong Lewis acids from P- and S-based Lewis bases

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THF.¹⁵ Considering their high Lewis acidity and their apparent σ and π activating nature, we reasoned that annulation reactions with polarised cycloalkanes ought to be feasible and an interesting new application of ESC catalysis.

Indeed, small strained ring compounds, such as cyclopropanes or cyclobutanes, have long been of interest in organic synthesis.^{19,20} Their stability and strain have been studied, as well as the preparation of the ring itself, and their application in synthesis. Activated cycloalkanes have been broadly investigated for use in annulations.^{21,22} Electron donating groups activate the cycle, increasing its reactivity toward an electrophile, while the presence of an electron-withdrawing group increases its electrophilicity. These two entities, wisely located on either side of the carbon-carbon bond, result in efficient polarisation through a push-pull mechanism. Various reaction pathways can be imagined, from $S_N 2$ to entirely ionic, which may explain the erosion of the enantiomeric purity.²³

The groups of Wenkert (on donor cyclopropanes)²⁴, Danishefsky (on acceptor cyclopropanes)²⁵ and Reissing (on donor-acceptor cyclopropanes)²⁶ pioneered the study of activated cyclopropanes. While annulations on D-A cyclopropane derivatives (Donor-Acceptor cyclopropanes) catalysed by Lewis acids are amongst the most widespread methodologies to synthetise heterocyclic or carbocyclic substrates, the use of homologous D-A cyclobutane derivatives (Donor-Acceptor cyclobutanes) is less, but continuously, studied.^{19,27–33} Among reactions with activated cyclopropanes or -butanes, annulation with 1,2 dipoles such as carbonyls can lead to the formation of tetrahydrofurans or -pyrans. These are common patterns in natural and pharmaceutical products (e.g. (-)-mucocine, spliceostatine etc.).^{34–37} Lewis and Brønsted acids were previously investigated for the access to these saturated heterocycles.38,39

Herein, we disclose electrophilic fluorosulfoxonium cationpromoted (n+2) annulations of D-A cyclopropane and -butane derivatives with various (hetero)carbonyl sources. Alongside, we will discuss the possible alternative behaviour of the

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Figure 2 Synthesis of a highly electrophilic fluorosulfoxonium

fluorosulfoxonium and compare such results with those of cycloadditions catalysed by TfOH as Brønsted acid.

 $[Ph_2S(O)F][B(C_6F_5)_4]$ (**Cat.1**) was selected as catalyst for its high Lewis acidity, assessed computationally by either Fluoride Ion Affinity (FIA) or Global Electrophilicity Index (GEI), and its rather convenient preparation.¹⁵ The first step is the oxidative difluorination with XeF₂ in the presence of catalytic NEt₄Cl.^{17,18} The second step is the monodefluorination with an external fluorophile. Both steps are performed sequentially, without change of the solvent. Stephan et al. described the use of the silylium salt $[Et_3Si \bullet C_7H_8][B(C_6F_5)_4]$ to perform the monodefluorination and installation of the lipophilic noncoordinating counter-ion at the same time. While this elegant strategy is step-economical, the low stability of the silylium salt over time requires its fresh synthesis, which may be inconvenient. Looking for an alternative strategy, we had to consider that the nature of the counter-ion was reported to be primordial for catalytic activities of EPCs, and that such conclusion would most likely apply to highly electrophilic sulfoxonium salts as well. Thus, we developed an alternative preparation, namely the use of BF₃•OEt₂ as fluoride abstractor to form $[R_2S(O)F]^+[BF_4]^-$, followed by an anion metathesis step with potassium salts, which are stable over time at the bench, furnishing the targeted fluorosulfoxonium with the desired counter-ion, namely $[B(C_6F_5)_4]^-$ here (Figure 2). Interestingly, an analogous approach was published very recently on EPCs.⁴⁰ $[B(C_6F_5)_4]^-$ is among the weakest coordinating anions while providing the highest solubility in organic solvents for related EPCs.^{15,41,42} This alternative methodology benefits from the exclusive use of inexpensive, stable and commercially available compounds.

We found that **Cat.1** could efficiently catalyse the (3+2) cyclisation of donor-acceptor cyclopropanes **1** with various aromatic and aliphatic aldehydes (Figure 3). A catalyst loading of 10 mol% and a reaction time of 15 h at room temperature in dichloromethane were sufficient for the full conversion of **1** with most reagents (Table 1). The shortest reaction time observed was 4 h, with *para*-chlorobenzaldehyde as reactant (**2ab**, Table 1, entry 2). This strategy delivered the desired tetrahydrofurans in 18–92 % yields (entries 1–9), depending on the nature of the carbonyl. Aromatic carbonyls, either activated or deactivated, gave the best results (entries 1–5) whereas 2-thiophenecarboxaldehyde afforded complex reaction mixtures from which the tetrahydrofuran **2ai** was nevertheless isolated (entry 9). Heteroaromatic aldehydes were investigated but only the richest ones undergo the (3+2) annulation with low to

moderate yield (**2ah–i**, entries 8–9) while electron deficient heteroaromatics (e.g nicotinaldehydel: 1024)^{39/D6} (100703) pyridinecarboxaldehyde **2ak**) do not undergo conversion under these reaction conditions (entry 10). Diastereoselectivity was dependent on the electron density of the reactant: the more electron-rich the reactant, the higher the diastereoselectivity, in favour of the *cis* diastereomer (entries 1 vs 6). The

in favour of the *cis* diastereomer (entries 1 vs 6). The diastereomeric ratio was measured in the crude reaction mixture, even if, for most products, both diastereomers could easily be separated by chromatography on silica gel.



Figure 3 (3+2) annulation of D-A cyclopropanes and carbonyl derivatives promoted by ESC Cat.1

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 Table 1 (3+2) annulation of D-A cyclopropanes and carbonyl derivatives promoted by ESC

 Cat.1 (see Figure 3)

Entry	Compound	Yield (%)	d.r.
1	2aa	83	20:1
2	2ab	92	>20:1
3	2ac	71	17:1
4	2ad	72	3:1
5	2ae	43	>20:1
6	2af	77	9:1
7	2ag	73	7:1
8	2ah	51	5:1
9	2ai	18	16:1
10	2aj-2ak	0	-
11	2b-2h	0	-
12	2al	73	-

Variations on the D-A cyclopropane were also investigated. First, the electron-withdrawing substituents were altered: monoester-, dinitrile-, or mixed ester/nitrile-functionalised D-A cyclopropanes (respectively 1f, 1g and 1h) are not suitable for the cyclisation since no conversion was observed under the described conditions (entry 11). Second, the donor part was changed as well, while maintaining the two ester functions of the acceptor moiety. In this case, the phenyl-substituted cyclopropane 1a exhibited the highest reactivity. Indeed, electron-deficient (hetero)aromatic rings (1c-e) as donor were incompatible with the substituents described methodology: no conversion was observed in association with para-chlorobenzaldehyde or para-anisaldehyde (entry 11). Converselv. the more electron-rich *p*-anisyl-derived cyclopropane 1b proved not to be a suitable substrate in association with para-anisaldehyde (2b). The latter association leads to a complex reaction mixture from which no formation of tetrahydrofuran was observed (entry 11).

On the other hand, the analogous synthesis of pyrrolidine derivatives proved unsuccessful. Several imines (*N*-tosyl-4-chlorobenzaldimine, *N*-tosyl-4-nitrobenzaldimine, *N*-benzyl-benzaldimine) or benzaldehyde phenylhydrazone remained unconverted. The NMR follow-up of the reaction with *N*-tosyl benzaldimine under strictly anhydrous conditions exhibits no conversion, although when quenched with commercial grade deuterated solvent, the formation of the corresponding tetrahydrofuran was observed. Additionally and surprisingly, benzonitrile as reactant did not yield any product either, whereas nitriles were previously used successfully for similar reactions by Pagenkopf *et al.* with milder Lewis acids or Brønsted acids.⁴³

For the sake of diversity, the synthesis of tetrahydrothiophene derivatives was attempted with a thionoester as reactant, which is a convenient alternative to thioaldehydes and thioketones. However, after purification, only the opened by-product **2al** was obtained (entry 12). This side product had been observed by Oshima *et al.*, who explained its formation by water substitution followed by a ring-opening reaction.⁴⁴ This result was surprising, especially considering the work of Ruppert *et al.*⁴⁵ (Figure 5, a.) and previous work on moisture-sensitive EPCs and ESCs which urged us, from the beginning, to

work under strictly anhydrous conditions and in a glovebax. Reactions were therefore duplicated with fresh and dry batches of substrate, reagent, catalyst and solvent. It appeared thus that the desired cyclised product could in fact be observed by NMR of the crude when the analysis was carried out using a J. Young valve-equipped NMR tube, but hydrolyzed upon exposure of the reaction medium to air prior to purification leading to **2a**.





Figure 4 (4+2) annulation of D-A cyclobutanes and carbonyl derivatives promoted by ESC Cat.1

 Table 2 (4+2) annulation of D-A cyclobutanes and carbonyl derivatives promoted by ESC

 Cat.1 (see Figure 4)

Entry	Compound	Yield (%)	d.r.
1	4aa	62	14:1
2	4ab	76	19:1
3	4ac	5	-
4	4ad	36	>20:1
5	4ae	48	>20:1
6	4af	1	-
7	4ag	73	7:1
8	4ah	36	6:1
9	4ai-4aj	0	-
10	4b-4d	0	-

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Aside from cyclopropanes, this methodology was extended to D-A cyclobutanes, a less strained ring requiring a slightly higher reaction temperature and resulting in a narrower library of reactants (Table 2). Benzaldehyde derivatives proved suitable as reaction partners in most cases, with yields up to 76% (4aaag, entries 1–7). However, no conversion was obtained with aldehydes derived from heteroaromatics, whether electronrich or poor (4ai-aj, Table 2, entry 9). Concerning aliphatic substituents, only the use of pivaldehyde allowed the isolation of the desired tetrahydropyran 4ah (Table 2, entry 8), while other aliphatics yielded complex reactions mixtures that remained hardly refinable. *p*-Anisaldehyde and 2bromobenzaldehyde (leading to 4ac and 4af) also afforded complex reaction mixtures and poor yields (entries 3 and 6).^{46,47} Variation of the donor group (for the obtention of 4b and 4c) on the cyclobutane was then investigated. Even under harsher reaction conditions (higher temperature and/or catalyst loading), neither a proton nor a methyl as donor groups were able to yield cyclised tetrahydropyrans (entry 10). Unlike 3a which succeeded in producing 4aa, the parent monoester 3d was not a suitable substrate under the described reaction conditions, no matter which diastereomer, which highlights the need for a strong electron withdrawing effect.

Considering the known ability of Lewis acids to generate Brønsted acids as competitive catalysts in the presence of trace moisture, $^{\mbox{\tiny 48}}$ we were curious about the exact nature of the catalyst. Indeed, regarding water, highly electrophilic fluorosulfoxonium salts such as Cat.1 should behave like the corresponding difluorosulfurane oxide, which was reported to hydrolyse to the sulfone while concomitantly releasing 2 molecules of HF.49 In the case of Cat.1, one would therefore expect the formation of the sulfone, HF and $[H][B(C_6F_5)_4]$ (Figure 5, a). Test reactions were carried out to assess the stability of the fluorosulfoxonium salt and to distinguish the different catalytically active species. First, the stability of Cat.1 towards moisture was investigated: about 20 equivalents of H₂O were added to a solution of Cat.1 in DCM and monitoring by NMR was performed. Surprisingly, even after 24 hours, the fluorosulfoxonium salt was still in extra majority. Compressed air was then bubbled into a solution of Cat.1 in DCM. The fluorosulfoxonium/sulfone ratio was found unchanged. Then, for the sake of clarity, we decided to carry out (n+2) cyclizations on D-A cycloalkanes in the presence of 2,6-di-tert-butylpyridine as a proton scavenger that would be too congested to quench the Lewis acidity of the fluorosulfoxonium.48 The absence of coordination between the Lewis base and Cat.1 was thus checked beforehand by ${}^{1}H$, ${}^{11}B$, ${}^{13}C$ and ${}^{19}F$ NMR experiments, which showed no observable chemical shift modification of signals of either one of the two species (see ESI). Then, cyclisation reactions were carried out in the presence of 30 mol% of this Brønsted base as added reactant, i.e. an excess of base to trap the expected 10 mol% of HF and 10 mol% of $[H][B(C_6F_5)_4]$ which could be released by the hydrolysis of the 10 mol% of fluorosulfoxonium salt. Interestingly, the cyclisation of both types of D-A cycloalkanes (Figure 5, c) was fully prohibited. The activity of the fluorosulfoxonium salt as a "hidden Brønsted



Figure 5 Control experiments to identify the active catalytic species

acid" is hereby pinpointed.⁴⁸ Out of precaution, the corresponding pyridinium salt was synthesised and used in catalytic amount under identical reaction conditions (Figure 5, d). No conversion of the substrate was observed, as expected. Furthermore, the $B(C_6F_5)_4^-$ analogue of the Brookhart acid as potential "hidden Brønsted acid" catalyst was synthesised, and was shown to promote both cyclisations (Figure 5, b). Yet, the distinct d.r. of the cyclised product when using either the fluorosulfoxonium or $[H \cdot (OEt_2)_2][B(C_6F_5)_4]$ might highlight a difference of active catalytic species, whose exact nature will remain difficult to ascertain.

Since the (n+2) annulations of cycloalkanes with carbonyl derivatives were apparently catalysed by a "hidden Brønsted acid" derived from the fluorosulfoxonium hydrolysis, we continued our studies with the development of a more practical method using triflic acid as a readily available Brønsted acid. The latter was indeed chosen for its potency as a strong Brønsted acid and as an attempt of continuity with the work of Wang *et al.* and Moran *et al.* on reactions of D-A cyclopropane derivatives mediated by TfOH.^{50,51} Surprisingly, the (3+2) cyclisation of D-A cyclopropanes with carbonyl derivatives under Brønsted acid catalysis was not reported. Accordingly, we assessed TfOH in these reactions and applied the same conditions as for the (3+2) cyclisation mediated by **Cat.1** (Figure 6). Gratifyingly, the method turned out to be effective in the case of electron-rich or -neutral arylaldehydes (Table 3, entries

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1–3). Aliphatic aldehydes proved to be more troublesome. Indeed, only the use of a non-enolisable one, namely pivaldehyde, yielded a viable reaction mixture. Heteroaromatic aldehydes, either electron-rich or -poor, could not be used in this strategy (Table 3, entry 5). Notably, similarly to the case of fluorosulfoxonium Cat.1, the di-cyano functionnalised D-A cyclopropane did not undergo any conversion with TfOH as catalyst either. Surprisingly, in the case of 4-nitrobenzaldehyde and N-tosylbenzaldimine as reaction partners, the tetrahydrofuran was obtained, but was unexpectedly accompanied with diethyl 2-benzylidenemalonate in a nonnegligible 25% and 28% yield respectively (Table 3, entries 7 and 8). The mechanism for the formation of the latter alkene is still unclear. Interestingly, in the successful reactions of Table 3, the d.r. of the product was usually higher (>20:1) than when using Cat.1 as promoter (Table 1, entry 1 and Table 3, entry 1). The variation of the concentration of TfOH over time was investigated, to assess if a high concentration in Brønsted acid



Figure 6 Typical reaction conditions for TfOH-catalysed (3+2) cyclisation of D-A cyclopropanes with carbonyl derivatives

could explain the catalysis of side reactions. However, no improvement of the reaction cleanliness was observed though these tests. Finally, the use of TfOH to catalyse the cycloaddition of D-A cyclobutanes at 50 °C (no conversion was observed at 25 °C) afforded complex reaction mixtures for all investigated reaction partners, with conversions far below the results obtained with **Cat.1**.

able 3 TfOH-ca	talysed (3+2) cyclisa	tion of D-A cyclopro	panes with carbo	onyl derivativ
Entry	Compound	Yield (%)	Alkene	d.r.
1	2aa	68	-	>20:1
2	2ab	99	-	>20:1
3	2ac	63	-	>20:1
4	2af	65	-	>20:1
5	2ah	8	-	-
6	2ag	22	-	1.5:1
7	2ae	5	25	-
8 ^a	2aa	9	28	-
9	2aj	0	-	-

^a N-Tosylbenzaldimine was used instead of the carbonyl derivative

In conclusion, we straightforwardly accessed a highly electrophilic fluorosulfoxonium salt via an anion metathesis strategy employing bench-stable reagents. The fluorosulfoxonium salt was successfully used as a promoter for (n+2) cyclisations of D-A cycloalkanes with carbonyl derivatives, affording tetrahydrofurans and -pyranes. Yet, it appeared that the reaction was not promoted by the fluorosulfoxonium as Lewis acid, but rather by a "hidden Brønsted acid" catalyst arising from reaction of the former with trace moisture. Accordingly, TfOH was also evaluated as catalyst and proved successful in some of the same annulations. Interestingly the use of the fluorosulfoxonium salt nevertheless prevaled over that of TfOH, since a wider library of reactants was tolerated and led to much more selective reactions. Furthermore, TfOH was not potent to catalyse the formation of tetrahydropyrans. The key for the efficiency of such cyclisations of D-A cycloalkanes with carbonyl derivatives might be in the subtle balance between the strength of the elusive Brønsted acid catalyst and its concentration to avoid undesired side-reactions, which are numerous in the chemistry of D-A cyclopropanes.⁵²

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latter then undergoing an acid-mediated Prins reaction with two molecules of 2-bromobenzaldehyde, ideadingoto84be observed dioxane. Such cycloreversion of D-A cyclobutanes upon (Lewis) acid catalysis was very recently described: N. L. Ahlburg, T. Freese, S. Kolb, S. Mummel, A. Schmidt and D. B. Werz, Functionalization of Sydnones with Donor-Acceptor Cyclopropanes, Cyclobutanes, and Michael Acceptors. *Eur. J. Org. Chem.*, 2021, 1603–1606.

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