Letter

Silver-Catalyzed Anti-Markovnikov Hydroxyfluorination of Styrenes

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Silver-Catalyzed Anti-Markovnikov Hydroxyfluorination of Styrenes

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Supporting Information Placeholder

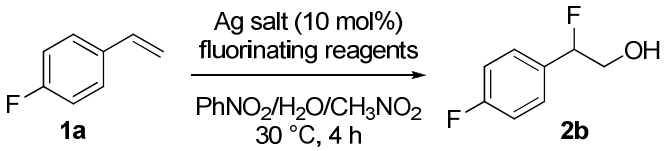
ABSTRACT: A silver-catalyzed radical hydroxyfluorination of styrenes with Selectfluor and H_2O has been explored with exclusive anti-Markovnikov-type regioselectivity, thus affording vicinal fluorohydrins with regioselectivities opposite that of noncatalyzed processes. This reaction is operationally simple, scalable under mild conditions. The mechanism studies and DFT calculations revealed that the reaction go through a radical mechanism.

Fluorinated organic compounds are important in pharmaceuticals, agrochemicals, and materials science.[1] Among them, vicinal fluorohydrins become a subject of particular interest since they act as important precursors in the synthesis of biologically active analogues of natural products,[2] and an array of versatile methods have been developed for the generation of such compounds.[3] But to our best knowledge, no anti-Markovnikov-type hydroxyfluorination of styrenes has been described. Herein, we reported a first example of silver-catalyzed radical hydroxyfluorination of styrenes with Selectfluor and H_2O under mild reaction conditions, with exclusive anti-Markovnikov-type regioselectivity, which affording vicinal fluorohydrins with regioselectivities opposite that of noncatalyzed processes.

Traditional methods for the synthesis of vicinal fluorohydrins includes reduction of α-fluoro carbonyl compounds,[4] and ring opening of epoxides with hydrofluorination reagents,[5] but substrates for these reactions usually require several steps synthesis with the use of some hazardous or toxic chemicals. The straightforward methods to synthesis of vicinal fluorohydrins were hydroxyfluorination of olefins.[6] For example, Appelman and co-workers reported an addition of hypofluorous acid to alkenes to yield vicinal fluorohydrins.[7] However, hypofluorous acid is a volatile compound and thermally unstable. Recently, new electrophilic fluorinating reagents such as Selectfluor, NFSI, and Accufluor were used for selective hydroxyfluorination of alkenes with Markovnikov-type regioselectivity.[8] In addition, Toste and coworkers reported a chiral phosphoric acid catalyzed the asymmetric hydroxyfluorination of enamides.[9] Despite the development of these methods, hydroxyfluorination of styrenes with anti-Markovnikov-type regioselectivity has not been reported so far. The development of a straightforward method to synthesis of vicinal fluorohydrins through the hydroxyfluorination of styrenes with anti-Markovnikov-type regioselectivity is highly desirable.

We began our investigations with employing 4-fluorostyrene (**1a**) as the substrate to optimize the reaction conditions (Table1, see the supporting information for more details). When **1a** was treated with Selectfluor in $PhNO_2/H_2O/CH_3NO_2$ (v/v/v = 2.6/1/0.4) without any catalyst,

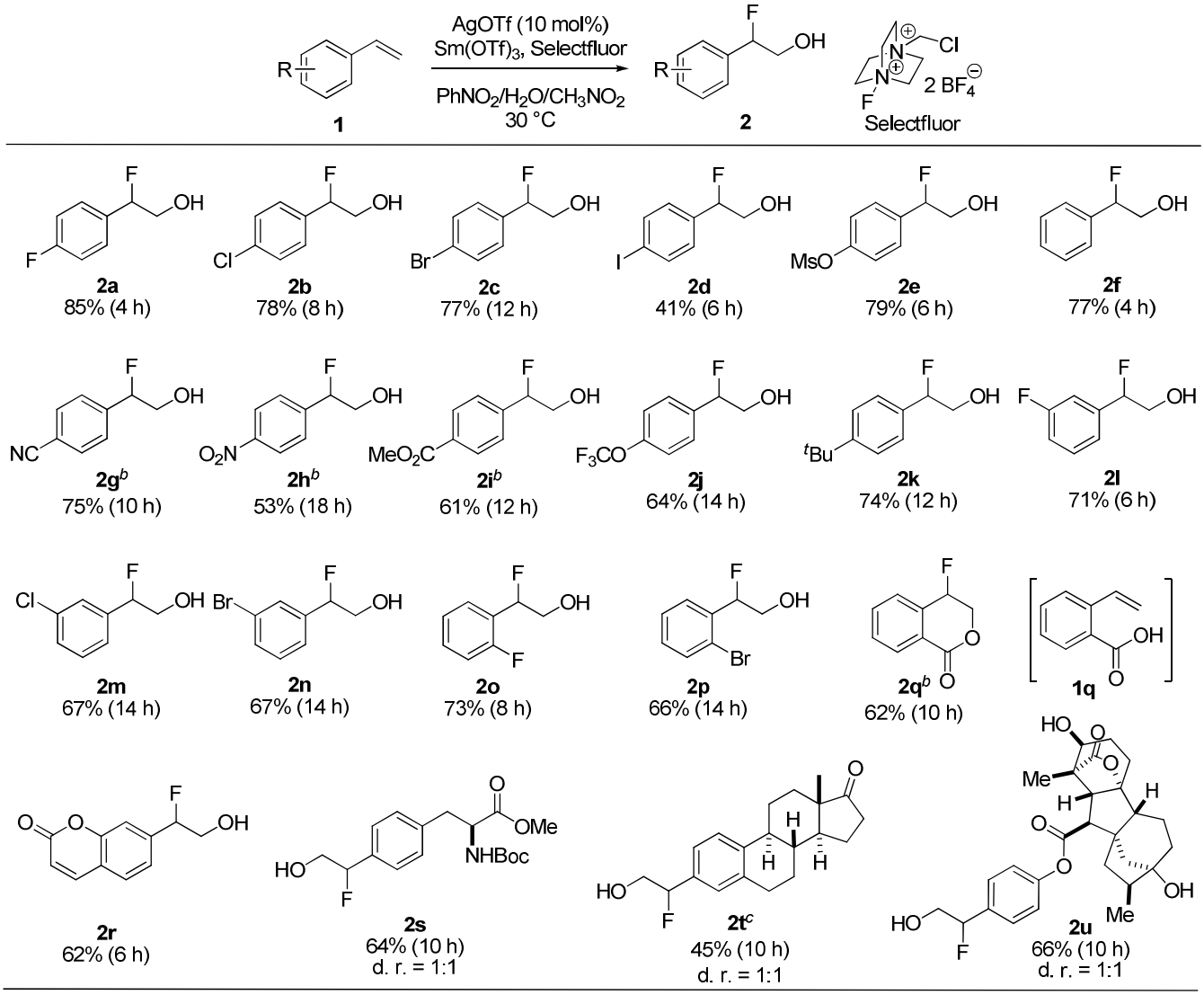
Table 1. Screening of hydroxyfluorination conditions



entry	Ag salt	Fluorinating reagent[a]	Additive[b]	Yield(%)[c]
1	none	Selectfluor	none	0
2	$AgNO_3$	Selectfluor	none	69
3	AgO_2CPh	Selectfluor	none	67
4	Ag_2CO_3	Selectfluor	none	69
5	AgF	Selectfluor	none	72
6	Ag_2SO_4	Selectfluor	none	71
7	$AgSbF_6$	Selectfluor	none	70
8	$AgBF_4$	Selectfluor	none	72
9	Ag_2O	Selectfluor	none	72
10	AgOTf	Selectfluor	none	77
11	AgOTf	Selectfluor	ZnO	60
12	AgOTf	Selectfluor	$Zn(OTf)_2$	75
13	AgOTf	Selectfluor	NaOTf	74
14	AgOTf	Selectfluor	$In(OTf)_3$	80
15	AgOTf	Selectfluor	$Sm(OTf)_3$	85
16	none	Selectfluor	$Sm(OTf)_3$	0
17	AgOTf	NFSI	$Sm(OTf)_3$	0
18	AgOTf	$Me_3NFPYBF_4$	$Sm(OTf)_3$	0

a) 2.0 equiv of fluorinating reagent was used. b) 0.30 equiv of additive was used. c) Yields were determined by ^1H NMR with benzyl chloride as a standard.

Table 2. Scope of the silver-catalyzed hydroxyfluorination of styrenes[a]



a) Reaction conditions: styrene **1** (1.0 equiv), AgOTf (10 mol%), $Sm(OTf)_3$ (0.30 equiv), Selectfluor (2.0 equiv), $PhNO_2/H_2O/CH_3NO_2$ (v/v/v = 2.6/1/0.4), 30 °C, N_2. Yields refer to isolated product. b) Reaction conditions: styrene **1** (1.0 equiv), AgOTf (10 mol%), Selectfluor (2.0 equiv), $(n\text{-}Bu)_4NHSO_4$ (2.5 equiv), H_2SO_4 (1.0 equiv), $PhNO_2/H_2O$ (v/v = 3/1), 50 °C, N_2. c) SDS (20 mol%) was used instead of $Sm(OTf)_3$. SDS = Sodium dodecyl sulfate.

no desired product **2b** was observed (Table 1，entry 1). To our delight, we obtained the fluorohydrin **2b** in 69% yield when $AgNO_3$ was used as the catalyst (Table 1, entry 2). Encouraged by this initial result, we further evaluated the different silver salts and AgOTf was found to be superior (Table 1, entries 3-10). Subsequently, the introduction of additives (0.30 equiv) was investigated and $Sm(OTf)_3$ was found to be the most effective (Table 1, entries 11-15). No product was detected in the presence of $Sm(OTf)_3$ without AgOTf (Table 1, entry 16). Further, Selectfluor emerged as the most suitable fluorinating reagent and no desired product **2b** was observed when *N*-fluorobis(benzenesulfonyl)imide (NFSI) and *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate ($Me_3NFPYBF_4$) were used (Table 1, entries 17-18). The reaction was carried out under a N_2 atmosphere. In contrast, yield was greatly diminished (5% yield) when the reaction was performed under air. In addition, the reaction temperature was important parameter, with hydroxyfluorination best performed at 30 °C. The role of the combined use of $PhNO_2$ and $MeNO_2$ as reaction solvent was not clear. After thoroughly optimizing the reaction conditions, reactions with 10 mol% of AgOTf, 2.0 equiv of Selectfluor and 0.30 equiv of $Sm(OTf)_3$ in the $PhNO_2/H_2O/CH_3NO_2$ (v/v/v = 2.6/1/0.4) under a N_2 atmosphere were found to produce high yields of the desired product.

With the optimal conditions in hand, we explored the scope and limitations of the hydroxyfluorination reaction (Table 2). A variety of styrenes bearing an electron-donating or electron-withdrawing group underwent the hydroxyfluorination to form the corresponding fluorohydrins with isolated yields ranging from 41% to 85%. The mild reaction conditions were compatible with a number of functional groups including ketone, ester, amide, nitrile, nitro, sulfonyl, chloro, bromo, even iodo substituents. The reaction of substrates **1g-1i**, **1q** containing electron-withdrawing groups exhibited slightly lower reactivity and the different reaction conditions were used. With substrate (**1q**), the cyclization product **2q** was obtained in 62% yield. Notably, the reaction was highly regioselective affording anti-Markovnikov-type hydroxyfluorination products. These re-

sults further expanded the substrates scope of the reaction for complex small molecules (**1t**, **1u**) with moderate yields. It is worth mentioning that the reaction time varied with each substrate because fluorohydrins **2** decomposed slightly under reaction conditions. Finally, to showcase the scalability and the practicality of this hydroxyfluorination method, we performed a gram-scale reaction using 4-bromostyrene (**1c**) as the substrate under the standard reaction conditions, and fluorohydrin **2c** was obtained in 72% isolated yield. The limitation of this method was that there's no reactivity for the hydroxyfluorination reaction of more electron-rich styrenes and unactivated olefins, such as 4-methoxylstyrene and 1-tridecene.

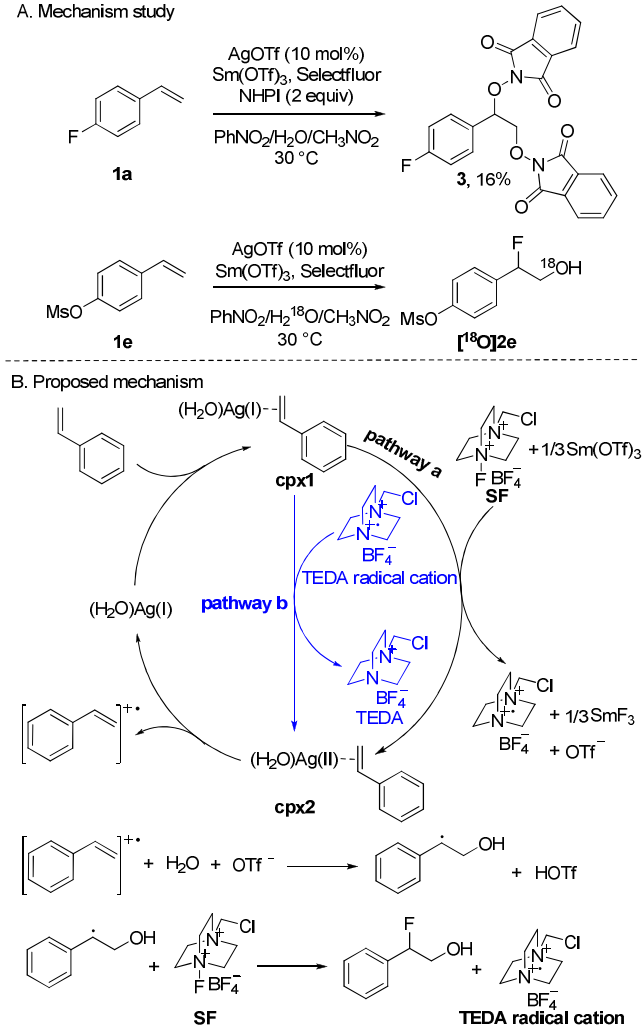


Figure 1. (A) Mechanism study. (B) Proposed Mechanism

Although the mechanistic details of this hydroxyfluorination reaction are not clear, some preliminary mechanistic studies were conducted. No desired fluorinated product was formed when 1.0 equiv of the radical inhibitor butylated hydroxytoluene (BHT) was added. When 2.0 equiv of *N*-hydroxyphthalimide (NHPI) was added, the product **3** was obtained in 16% yield determined by ^{1}H NMR analysis of the crude product (Figure 1A). In addition, much higher yields were observed in the strict absence of O_2 than in its presence.[10] Together, these observations indicated that a radical chain mechanism or single-electron transfer (SET) may be involved in this transformation. In addition, the corresponding product [^{18}O]**2e** was observed in the presence of $H_2{}^{18}O$, with 96% ^{18}O incorporation at the position indicated (Figure 1A), and the corresponding product [^{18}O]**2q** was observed in the presence of $H_2{}^{18}O$, which confirmed that the hydroxyl group in the product came from H_2O.

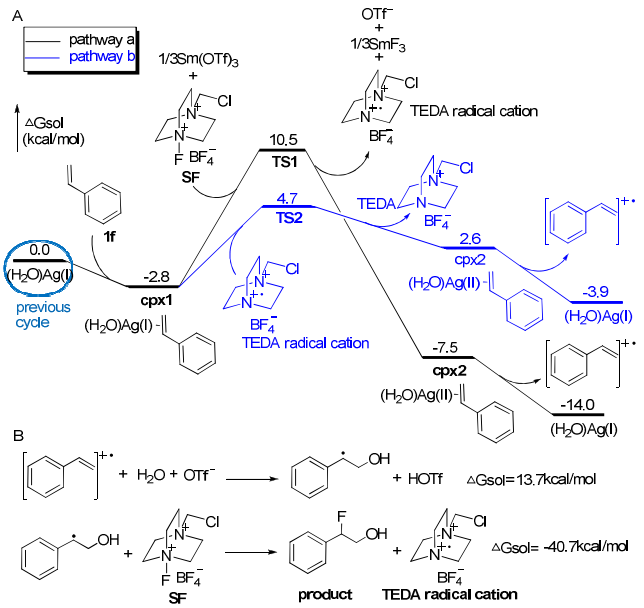


Figure 2. Gibbs free energy profiles for the silver-catalyzed radical hydroxyfluorination of styrene with Selectfluor and H_2O. Energies are calculated using B3LYP/SDD-6-311+G(d,p)/SMD($PhNO_2/H_2O/CH_3NO_2$ (v/v/v = 2.6/1/0.4))

To further understand the details of the mechanism, we performed density functional theory (DFT) calculations for the proposed mechanism (Figure 1B), taking styrene (**1f**) as the model substrate. Our DFT calculation shows that loss of BF_4^- ion from Selectfluor in solution is thermodynamically favorable because for this process the Gibbs free energy decreases by 2.7 kcal/mol. In addition, the electrospray ionization mass spectrum of the Selectfluor solution shows that the cation (*m/z* 267) is the major species due to the loss of BF_4^-.[11] Therefore, we have used the cation (**SF**, as shown in Figure 1B) as an alternative to the Selectfluor in the calculation. Because the coordination of H_2O to the naked Ag(I) ion is thermodynamically favorable by -0.5 kcal/mol, $(H_2O)Ag(I)$ should act as the active catalyst entering the catalytic cycle, as adopted in the DFT study of the mechanism of silver-catalyzed decarboxylative fluorination by Zhang.[12] As shown in Figure 2, firstly, $(H_2O)Ag(I)$ coordinates with styrene and to form the complex **cpx1**. This process is exothermic by 3.3 kcal/mol. Then **cpx1** is oxidized by Selectfluor (**SF**) to produce Ag(II) intermediate **cpx2** and TEDA radical cation (pathway **a** in Figure 2A). Interestingly, in the presence of $Sm(OTf)_3$, this step requires free energy of activation of 13.3 kcal/mol, which is lower than that without $Sm(OTf)_3$ by 17.0 kcal/mol. This is because $Sm(OTf)_3$ can stabilize the F^-, which is formed during this oxidation process, by ligand exchange with OTf^- to form the more stable SmF_3, and thus promotes this oxidation step. Subsequently, the Ag(II) intermediate **cpx2** oxidizes the ligated styrene to afford styrene radical cation, and the $(H_2O)Ag(II)$ is reduced to $(H_2O)Ag(I)$ to complete the catalytic cycle. This redox process is exothermic by 6.5 kcal/mol. Then, coupled with the OTf^-,the styrene radical cation reacts with H_2O to generate the benzylic radical intermediate, which abstracts fluorine from Selecfluor (**SF**) to yield the final product and TEDA radical

cation. The two steps are totally exothermic by 27.0 kcal/mol (Figure 2B).

It is worthwhile to note that once the reaction occurs along pathway **a**, the TEDA radical cation should be obtained. Then TEDA radical cation can also oxidize the Ag(I) complex **cpx1** to continue the catalytic cycle (pathway **b** in Figure 2A). Significantly, the oxidation of **cpx1** by TEDA radical cation requires 5.8 kcal/mol less energy barrier than the oxidation of **cpx1** by Selecfluor (**SF**), which suggests that the catalytic cycle should prefer to continue along pathway **b** after it starts along pathway **a**. We have also considered other possible pathways to afford Ag(II) and Ag(III) species.[13] However, these pathways are ruled out from the favored pathways because reactions along these pathways need to absorb additional energies relative to pathways **a** and **b** (see Scheme S1 in the supporting information).

In summary, we have developed a novel silver-catalyzed radical hydroxyfluorination reaction of styrenes with Selectfluor and H_2O, providing rapid and efficient access to vicinal fluorohydrins with exclusive anti-Markovnikov-type regioselectivity for the first time. The reaction proceeds under mild conditions with good functional group tolerance, which can be further used for the hydroxyfluorination of complex small molecules. Mechanistic investigations and DFT calculations indicated that a radical mechanism may be involved in this transformation. We anticipate that this mild silver-catalyzed hydroxyfluorination method will find application in the synthesis of fluorinated molecules in the pharmaceuticals, agrochemicals and materials.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization of all new compounds including ^{1}H, ^{13}C and ^{19}F NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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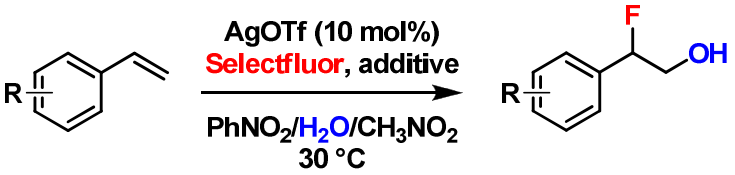

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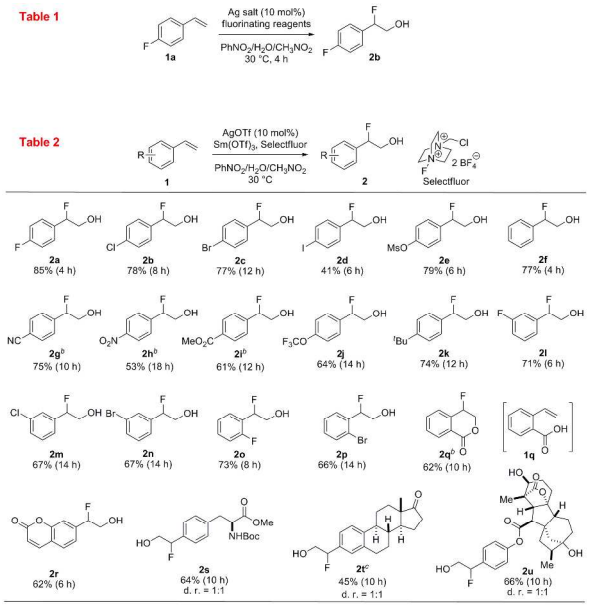

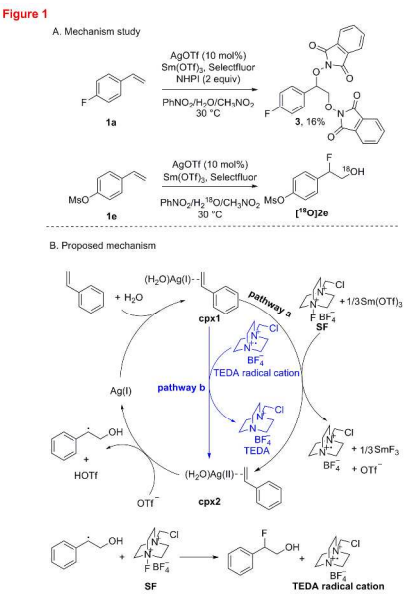

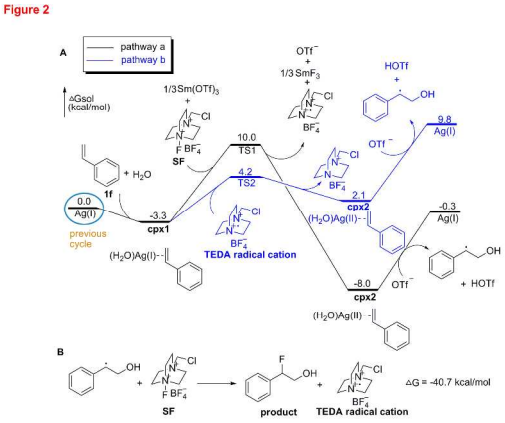

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