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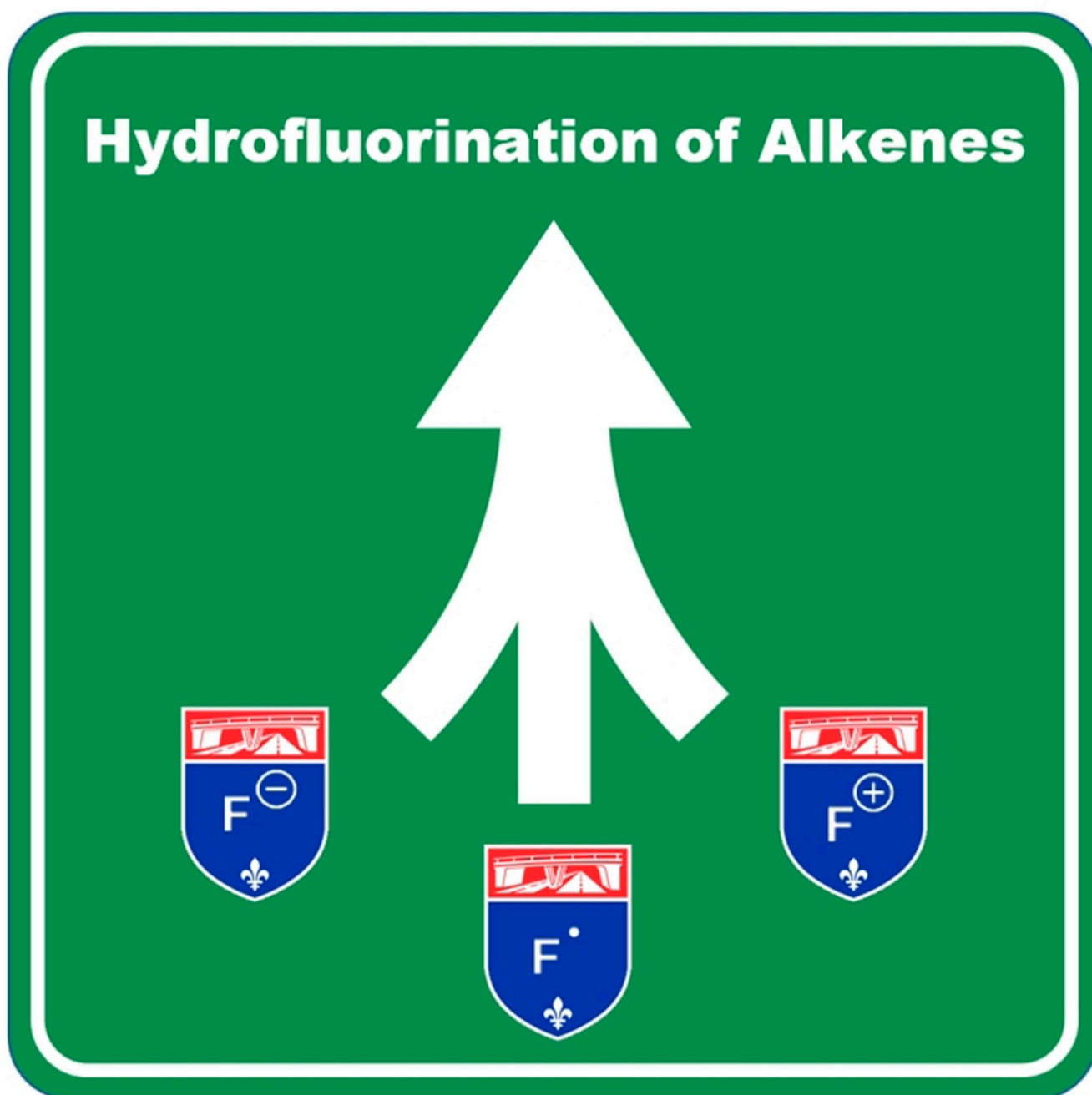
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## Hydrofluorination of Alkenes: A Review

Xavier Bertrand,<sup>[a]</sup> Laurent Chabaud,<sup>[b]</sup> and Jean-François Paquin\*<sup>[a]</sup>



**Abstract:** In this minireview, we explore the different approaches used to perform the hydrofluorination reaction of alkenes. Contrary to other hydrohalogenation reactions, the hydrofluorination requires specific conditions due to the lower reactivity of HF. Over the years, many different approaches have been explored among which the use of HF complexes has particularly proved to be useful as these reagents are easier to handle. The enantioselective hydro-

fluorination has been demonstrated using electrophilic sources of fluorine, while radical fluorination proved compatible with a vast range of functional groups that are generally problematic with strong acids and some fluoride sources. This review will cover the different conditions developed through the years, starting with the first reported addition using gaseous HF, up to the most recent method described in October 2020.

## 1. Introduction

The interest of fluorine in numerous fields of chemistry is largely recognized especially in pharmaceuticals,<sup>[1]</sup> agrochemicals,<sup>[2]</sup> and material sciences.<sup>[3]</sup> This has led to more and more research group focusing on the development of efficient and economical methods of incorporation of fluorine.<sup>[4]</sup>

The hydrofluorination of alkenes represents an efficient and straightforward strategy for the formation of a single C<sub>(sp<sup>3</sup>)</sub>-F bond. This type of fluorine represents about 15% of all fluorinated drugs approved by the FDA.<sup>[5]</sup> This transformation can be separated into three main categories based on the general pathway of the addition (Scheme 1). For the purpose of this review, the different methods were categorized according to the mechanism of fluorination, i.e., nucleophilic hydrofluorination, electrophilic hydrofluorination and radical hydrofluorination that use respectively fluoride, electrophilic fluorine sources and radical fluorine sources. For all these methods, the sources of hydrogen can vary based on the mechanism and were not considered for the classification.

In this review, the different synthetic methods developed throughout the years will be described and discussed. To the best of our knowledge, this represents the first exhaustive report on the subject.

## 2. Nucleophilic hydrofluorination

Theoretically, the most straightforward and atom economical way to perform a hydrofluorination is with hydrogen fluoride. However, this reagent poses many issues. Not only is it an extremely toxic gas, it also has many chemical incompatibilities, mainly in glassware, and requires specific handling precautions. Yet, one example was described by Grosse and Linn back in 1938.<sup>[6]</sup> Anhydrous hydrogen fluoride was condensed in an autoclave with ethylene or propylene to afford the corresponding fluorides (Scheme 2). The impracticability of these con-

ditions on laboratory-scale as well as the rising concern on security urged chemists to develop safer alternatives. One of the main research axes investigated is the complexation of hydrogen fluoride on different molecules to obtain either a liquid or a solid, that significantly reduces the risk.

In 1973, Olah and coworkers reported the first hydrofluorination of alkenes without the direct use of HF.<sup>[7]</sup> The reagent used, now known as the Olah's reagent, is a complex of 70%w/w hydrogen fluoride in pyridine (Table 1, entry 1). This reagent allowed the fluorination of simple, unfunctionalized alkenes with moderate to good yields (Scheme 3). In 1983, Yoneda showed that using melamine as the amine instead of pyridine raised the stability of the complex (Table 1, entry 2).<sup>[8]</sup> In 1990, Olah used a solid-supported version of his reagent, poly-4-vinylpyridinium poly(hydrogenfluoride) (PVP-HF), which contains between 35% and 60% of hydrogen fluoride in weight, to perform the hydrofluorination of the same alkenes (Table 1, entry 3).<sup>[9]</sup> One of the main advantages of this reaction was the nature of the reagent, which, as a solid, allowed for a safer handling of hydrogen fluoride and an easier purification. Finally, Olah developed a complex of hydrogen fluoride on dimethyl ether. The complex can be made from one to five equivalents of HF on the ether and allows for a variety of fluorination reactions including the hydrofluorination of alkenes. It was shown that 5 equivalents of HF gave the best yields (Table 1, entry 4).<sup>[10]</sup>

In 1995, Sekiya reported that a mixture of KHF<sub>2</sub> and SiF<sub>4</sub> was able to produce the fluoroalkyl compounds, although the mechanism was not clearly defined (Scheme 4).<sup>[11]</sup>

In 1996, Yoneda and coworkers reported the first conditions that tolerated functionalized alkenes (Scheme 5). Using a complex of 5 or 6 hydrogen fluoride on triethylamine, they were able to hydrofluorinate alkenes in the presence of ketone, alcohol, and ester (Table 1, entry 5).<sup>[12]</sup>

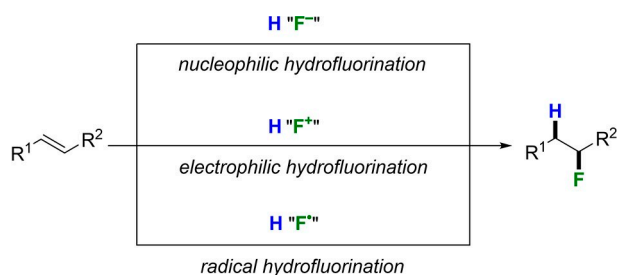
**Table 1.** Composition of the different complexes used by Olah and Yoneda.

Entry	Molecule	HF quantity <sup>[a]</sup>	Molar ratio
1	Pyridine (1)	70%	~9:1
2	Melamine (2)	86%	~3:1
3	Poly-4-vinylpyridine (3)	60%	7:1 <sup>[b]</sup>
4	Dimethyl ether (4)	68%	5:1
5	Triethylamine (5)	50–54%	5:1–6:1

[a] % w/w [b] per unit of 4-vinylpyridine.

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Scheme 1. General pathways of hydrofluorination of alkenes.

**Xavier Bertrand** was born in Québec City, Canada in 1996. He pursued undergraduate studies in chemistry from 2015 to 2018 at Université Laval, during which he studied a semester at Université de Strasbourg. He undertook graduate studies under the supervision of Prof. Jean-François Paquin in 2018. Since 2020, his Ph.D. is under the co-supervision of Prof. Jean-François Paquin and Dr. Laurent Chabaud. His research focuses on the formation of the C–F bond with a particular interest for flow chemistry.



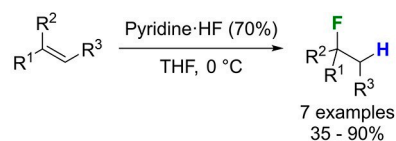
**Laurent Chabaud** received his PhD degree in 2005 at Bordeaux University under the supervision of Prof. Y. Landais and Prof. P. Renaud (Bern, CH). In 2006, he joined the group of Prof. J. Clayden in Manchester for postdoctoral studies, then moved to the ICSN (Gif-sur-Yvette), where he was appointed CNRS researcher in 2008. In 2018 he joined the group of Dr M. Pucheault at the Institute of Molecular Sciences (Bordeaux). His current research interests are dealing with the chemistry of organoboron compounds and their applications, especially in materials science.



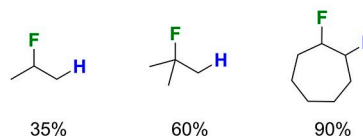
**Jean-François Paquin** received his PhD in 2004 from the University of Toronto under the supervision of Prof. Mark Lautens. After a postdoctoral stay in Prof. Erick M. Carreira's lab at the ETH Zürich, he was appointed assistant professor in 2005 at the Université Laval in Quebec City. He was promoted to associate professor in 2010 to full professor in 2014. His research interests include the development of novel methodologies for the synthesis of organofluorine compounds and their applications for the preparation of bioactive fluorinated compounds or fluorinated biological probes. In 2016, he was awarded the Keith Fagnou Award from the Canadian Society for Chemistry.



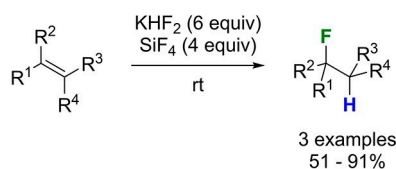
Scheme 2. Anhydrous hydrogen fluoride addition on ethylene reported by Grosse and Linn in 1938.



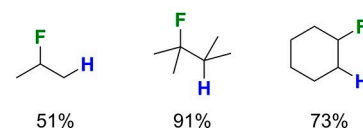
Selected examples



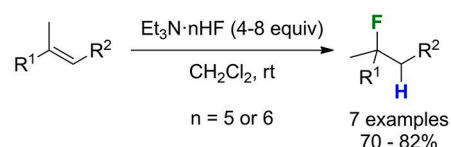
Scheme 3. Hydrofluorination of simple alkenes using pyridine-HF by Olah and coworkers.



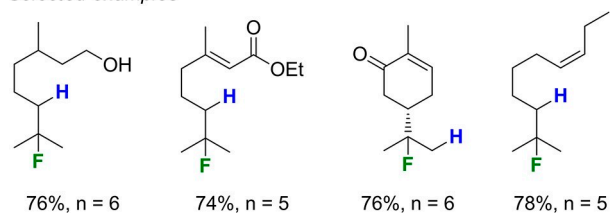
Selected examples



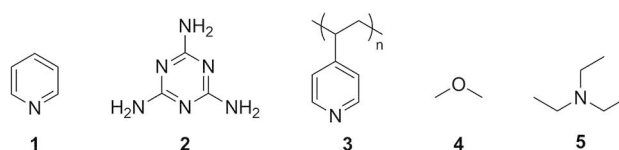
Scheme 4. Sekiya's conditions for the hydrofluorination of simple alkene.



Selected examples

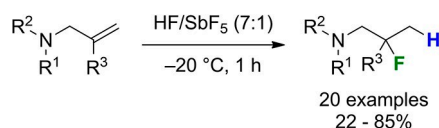


Scheme 5. Hydrofluorination conditions developed by Yoneda and co-workers.

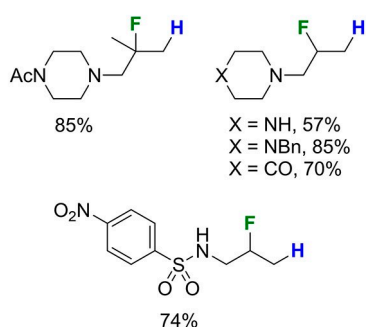


These pioneering conditions were, for a long time, the only efficient ways to perform a hydrofluorination reaction on alkenes. However, these conditions still required a very large excess of reagents. In 2007, the group of Thibaudeau reported that the use of a superacid, HF-SbF<sub>5</sub>, allowed the fluorination of allylic amines (Scheme 6).<sup>[13]</sup> This represents a great method of obtaining β-fluoroamines. The reaction, proceeding through a dicationic mechanism, showed great selectivity when an excess of HF was used. However, as the molar fraction of antimony pentafluoride rose, many undesired products were formed. The best results were obtained using a 7:1 HF:SbF<sub>5</sub> molar ratio.

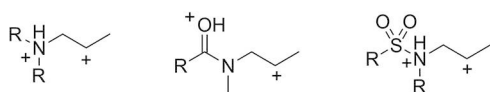
The reaction works well for amines and sulfonamides, but amides produce the hydroxylated product. This is hypothesized to be due to the longer distance between both cations, which reduces its electrophilicity. Amides are indeed protonated at the oxygen instead of the nitrogen on amines or sulfonamides (Figure 1). This is also the case for homoallylic amines that give



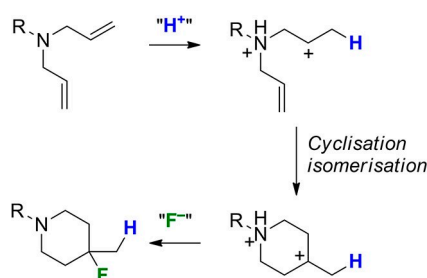
Selected examples



**Scheme 6.** Synthesis of β-fluoroamines reported by Thibaudeau and co-workers.



**Figure 1.** Dicationic intermediates of different functional groups after reacting with HF-SbF<sub>5</sub> complex.



**Scheme 7.** Proposed mechanism for the preparation of fluorinated piperidines from diallylamines.

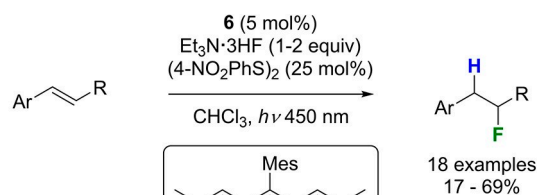
lower yields. When the distance was longer between the cations, no fluorinated product was observed.

In a subsequent paper, they showed that diallyl amines could produce various fluorinated piperidines under similar reaction conditions.<sup>[14]</sup> The reaction proceeds via a protonation, cyclisation, and fluorination sequence (Scheme 7). Interestingly, pyrrolidines could be obtained starting from methyl substituted allyl amines, although the precise mechanism remains unclear.

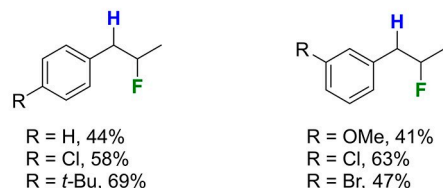
Nicewicz and coworkers reported in 2014 an anti-Markovnikov addition of different mineral acids to styrene.<sup>[15]</sup> Among the different acid tested, they reported a system for the addition of HF to afford homobenzylic fluoride via a photoredox pathway. An acridinium based photocatalyst was used in the presence of triethylamine trihydrofluoride and 4-nitrophenyldisulfide (Scheme 8).

The reaction is initiated via an electronic excitation of the photocatalyst **6** by visible light. A photoinduced electron-transfer (PET) can then take place from the alkene to the activated photocatalyst. The radical cation formed on the substrate can then be fluorinated by triethylamine trihydrofluoride to afford the radical alkyl fluoride. In the meantime, the disulfide can be cleaved homolytically to form a radical thiophenol, that can be reduced to thiophenolate by regenerating the photocatalyst. The thiophenolate is then protonated with the acidic proton of the HF on the triethylamine. This hydrogen is then transferred to the β-fluoro alkyl radical to afford the hydrofluorination product (Figure 2).

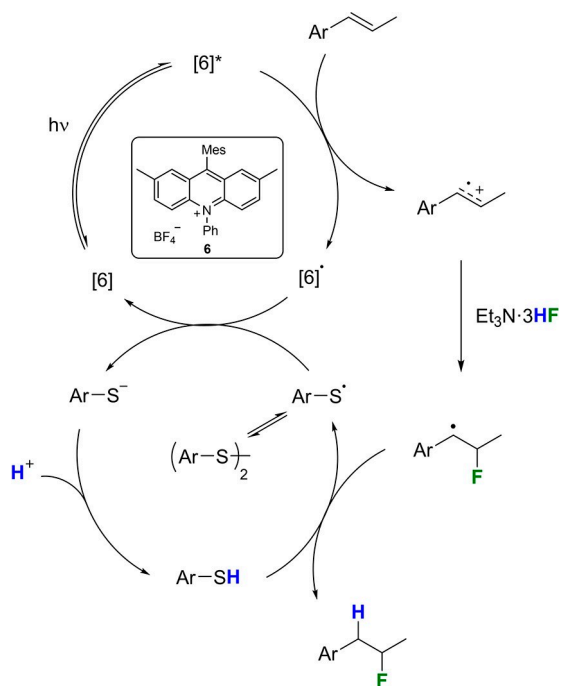
Then, in 2017, an important breakthrough was accomplished in the field of nucleophilic hydrofluorination with the work of Hammond and coworkers.<sup>[16]</sup> By reacting anhydrous hydrogen fluoride with potassium bisulfate, they were able to synthesize a new reagent, KHSO<sub>4</sub>·13HF. This reagent is bench-stable, easy-to-handle, and, now, commercially available. One of its main advantage is that, compared to amine complexes, it remains acidic due to the presence of the proton on the



Selected examples



**Scheme 8.** Anti-Markovnikov hydrofluorination of styrene derivatives reported by Nicewicz and coworkers.

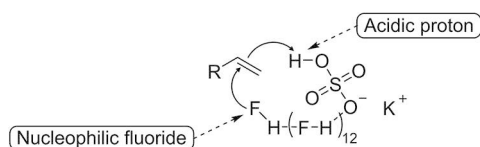


**Figure 2.** Catalytic cycle proposed by Nicewicz and coworkers for the anti-Markovnikov addition of HF to styrene derivatives.

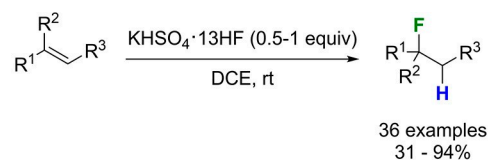
bisulfate. It also possesses a strong H-bond acceptor that can complex many hydrogen fluoride molecules. This allows for a bifunctionalization of the alkene with the same reagent delivering the proton and the fluoride (Figure 3).

This significant contribution was the first nucleophilic method to use near stoichiometric reagent with a wide range of substrates and functional groups. Mono-, di- and trisubstituted alkenes all reacted to afford the corresponding compounds in good yields (Scheme 9). Free alcohols, amines and carboxylic acids were all compatible without any significant drop in yield. The reagent also shows a great chemoselectivity, not reacting with alkynes and only with the more nucleophilic alkene when two are present.

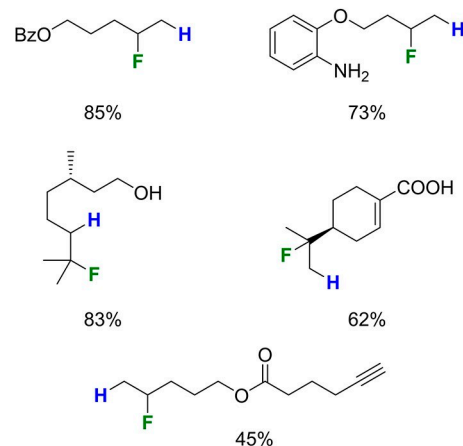
In another paper published in 2019, they developed a solid version of their reagent.<sup>[17]</sup> By adding gaseous hydrogen fluoride on anionic resins, they were able to synthesize a solid equivalent of HF. After testing different commercially available resins, they found out that the Amberlyst A26, bearing a quaternary ammonium was the best candidate. They first reacted the resin with sulfuric acid to replace the hydroxide counterion with a bisulfate, after which they added hydrogen



**Figure 3.** Bifunctionalization of the alkene by the acidic proton and nucleophilic fluoride of the reagent developed by Hammond and coworkers.

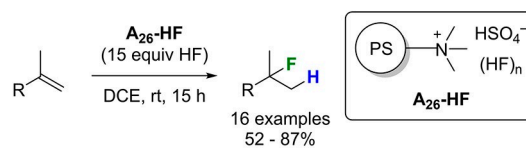


Selected examples

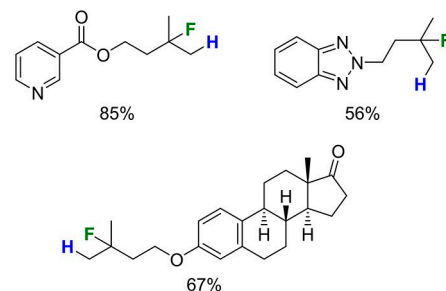


**Scheme 9.** Hydrofluorination conditions developed by Hammond and coworkers.

fluoride to furnish the resin-supported HF at 30% w/w concentration. This resin was used in the reaction of hydrofluorination of various alkenes. It showed better reactivity and a higher quantity of HF per gram of resin than other tested resins e.g., one bearing a free amine and one bearing a sulfonate. The reaction is compatible with di- and trisubstituted alkenes, but monosubstituted alkenes did not react. A wide range of functional groups were tested and shown great yields (Scheme 10). Interestingly, free alcohols and heteroaromatics were tolerated, although the latter needed longer reaction time when a basic moiety was present. By comparing this resin with



Selected examples



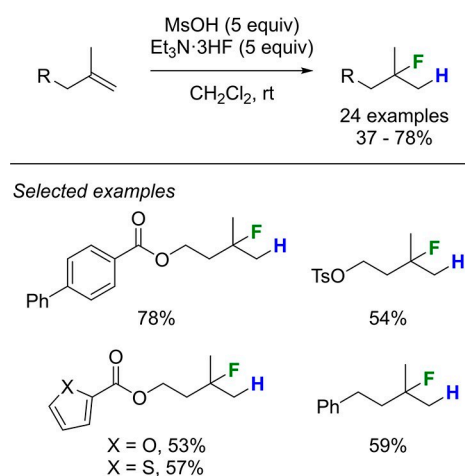
**Scheme 10.** Batch hydrofluorination conditions developed by Hammond and coworkers using a resin-supported HF reagent.



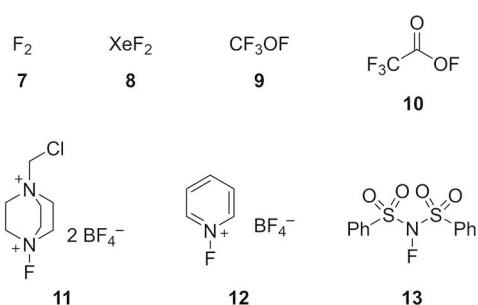
the PVP-HF developed by Olah, they showed that the yields were higher with a lower cost.

With this solid version of HF in hand, they were able to develop a continuous flow system. This was the first example of a hydrofluorination in flow chemistry. To achieve this, they used a packed bed reactor that they filled with their resin. A solution of the alkene is then passed through the column at a 0.5 ml per hour flow rate. The corresponding fluorinated compound is obtained in a 92% yield.

In 2019, Paquin and coworker reported the hydrofluorination of alkenes using a combination of triethylamine trihydrofluoride and methanesulfonic acid.<sup>[18]</sup> Considering the general mechanism of hydrohalogenation of alkenes, they envisioned that "HF" could be added on an alkene in the same way as HCl or HBr. However due to the low acidity of HF, an external acid should be used. After screening different acids and fluorides, they were able to identify a combination that afforded the fluorinated compounds in good yields. This combination of reagent allowed for a two-step mechanism involving the protonation of the alkene to form a carbocation followed by a nucleophilic attack of a fluoride. These conditions are, however, limited to alkenes that form tertiary carbocation, *i.e.*, **1,1-disubstituted alkenes and trisubstituted alkenes** (Scheme 11). The reagents used are all commercially available, cheap, easy-to-handle and safer than the previously reported alternatives. These conditions were used in the development of continuous



**Scheme 11.** Hydrofluorination conditions developed by Paquin and coworker.



**Figure 4.** Electrophilic fluorination reagents.

flow reaction. Preliminary results are reported showing a promising 36% yield for a residence time of 17 minutes.

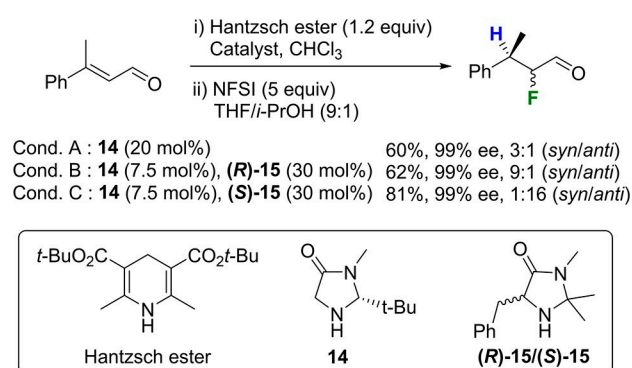
### 3. Electrophilic hydrofluorination

In electrophilic hydrofluorination, the fluorine is used as the electrophile, *i.e.* using a "F<sup>+</sup>" source. Many electrophilic reagents have been developed over the years. The first reagents used were based on the reactivity of O–F, Xe–F and F–F bonds (Figure 4, 7–10).<sup>[19]</sup> They were, however, very reactive, poorly selective or had a poor storage capacity. Nowadays, these have been supplanted by N–F bond-based reagents that show greater selectivity, stability, and safety (Figure 4, 11–13).<sup>[20]</sup>

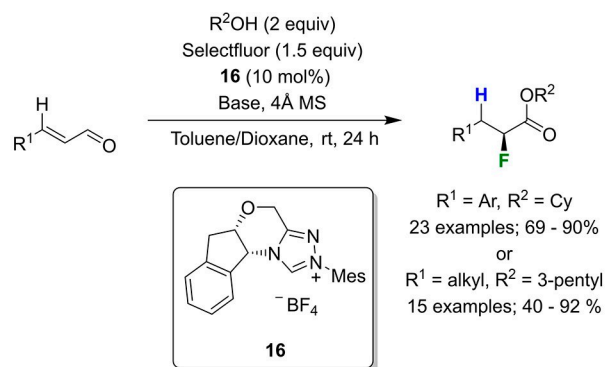
MacMillan's group reported in 2005 an organic-cascade catalysis using a mix of iminium and enamine chemistry.<sup>[21]</sup> This cascade allowed for the incorporation of a nucleophile and an electrophile on the same reaction. This cascade was mainly used to introduce a chlorine and a hydrogen atom onto  $\alpha,\beta$ -unsaturated aldehydes to afford the corresponding  $\alpha$ -chloro aldehyde. They also presented an example with fluorine using NFSI **13** as the electrophilic source of fluorine and Hantzsch ester as the hydrogen source. Although only three different conditions were reported on (*E*)-3-phenylbut-2-enal, the *ee* are all of 99%. Higher yields are obtained when the electrophile is added after complete consumption of the nucleophile.

Quite interestingly, the use of two different amine catalysts can be used to significantly raise the diastereoselectivity of the addition from 3:1 *syn:anti* to 9:1. By changing the enantiomer of one of the catalysts, the product can be obtained in a 1:16 *syn:anti* selectivity (Scheme 12).

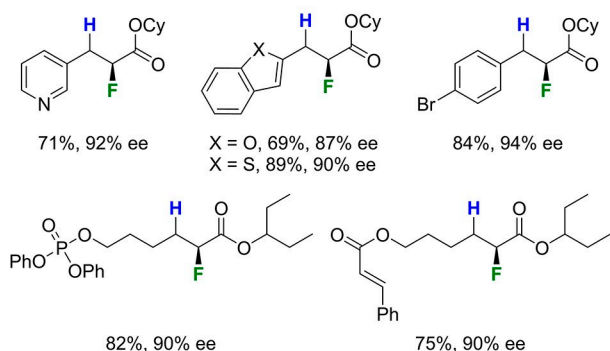
Another hydrofluorination reaction, that was developed by Huang and coworkers uses NHC as a catalyst to perform the reaction.<sup>[22]</sup> This method enables the hydrofluorination and oxidation of  $\alpha,\beta$ -unsaturated aldehydes to  $\alpha$  fluoro ester (Scheme 13). The catalyst allows for a sequential  $\beta$ -protonation followed by an  $\alpha$ -fluorination. The use of a proton instead of a hydride allows for a greater functional group tolerance and hence a wider range of compatible substrates than the MacMillan's method.



**Scheme 12.** Hydrofluorination of (*E*)-3-phenylbut-2-enal by enamine-iminium catalysis.



Selected examples

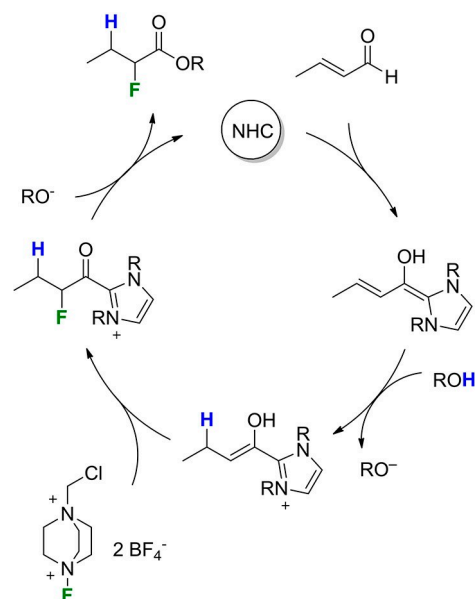


**Scheme 13.** Hydrofluorination of  $\alpha,\beta$ -unsaturated aldehydes catalyzed by NHC to afford  $\alpha$ -fluoro esters.

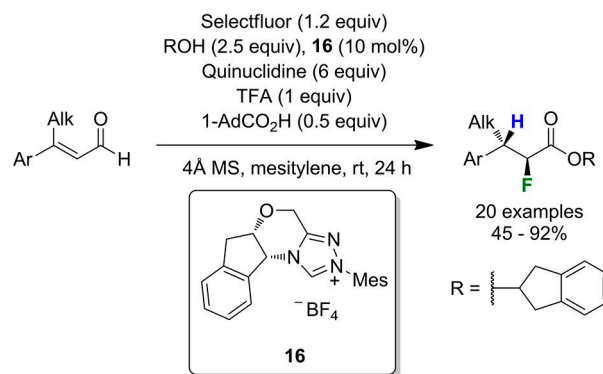
They exploit the umpolung phenomenon of enal in the presence of NHC to produce an homoenolate that can be protonated in the presence of an alcohol. The newly formed enolate can then be fluorinated via an electrophilic fluorine source. The catalytic cycle is completed via the attack of the alkoxide on the carbonyl to liberate the NHC and form the  $\alpha$ -fluoro ester (Figure 5). The choice of the alcohol proved critical as it can cause low conversion if not reactive enough, or premature esterification if too reactive. Cyclohexanol was used for aromatic enals, while 3-pentanol worked best for aliphatic enals. The use of a chiral NHC allowed for the formation of an enantioenriched center at the C–F bond with excellent ee going from 89% to 99%.

When using a  $\beta$ -disubstituted enal, two chiral centres can be created in the same reaction. Once again, a different alcohol must be used, and an acid/base system is employed to ensure the optimal delivery rate of the proton. The enantioselectivity and diastereoselectivity are excellent with ee values generally superior to 99% and d.r. higher than 10:1 (Scheme 14).

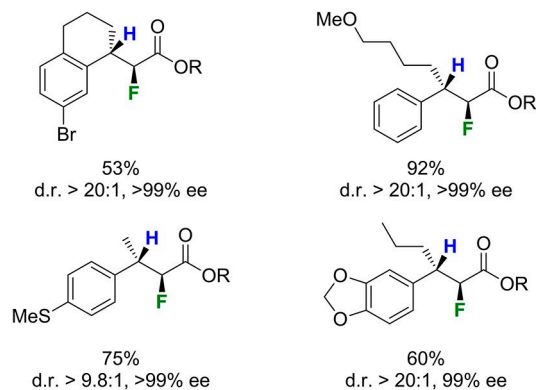
Gouverneur's group was the first to develop an electrophilic hydrofluorination of alkene with a wide scope in 2014.<sup>[23]</sup> Selectfluor and triethylsilane were used as the source of fluorine and hydride. This reaction is performed using a palladium catalyst and appeared to be specific to alkenylarenes. It allowed the formation of a wide range of benzylic fluoride (Scheme 15). The mechanism involves the *syn*-addition of the fluorine and



**Figure 5.** Catalytic cycle proposed by Huang and coworkers for the formation of  $\alpha$ -fluoro esters from  $\alpha,\beta$ -unsaturated aldehydes.



Selected examples



**Scheme 14.** Hydrofluorination of  $\alpha,\beta$ -unsaturated aldehydes catalyzed by NHC to afford  $\alpha$ -fluoro ester.

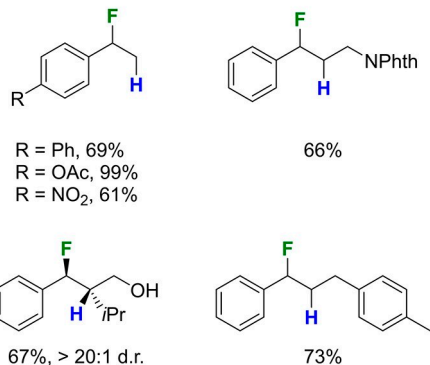
the hydride which was demonstrated via isotopic studies using deuterium.

Mechanistic studies showed that Selectfluor was used both to deliver a "F<sup>+</sup>" and as an oxidant for the catalytic cycle. The





Selected examples



Scheme 15. Palladium-catalyzed hydrofluorination of alkenylarenes.

proposed mechanism starts with the formation of a Pd(II)H species by activation from the silane. That species performs a *syn*-hydropalladation on the alkenylarene to afford a  $\eta^3$ -benzyl complex. Selectfluor can then oxidize the complex to a fluoropalladium (IV) species, which can be reduced via a reductive elimination to afford the final product (Figure 6).

Finally, Yin and coworkers reported the first efficient enantioselective hydrofluorination of alkenylarenes in 2020.<sup>[24]</sup> Inspired by Gouverneur's works, they improved the enantioselectivity of the palladium catalyzed reaction. The chirality is induced via a chiral sulfoxide phosphine ((*R*)-SOP, **18**) that affords the fluorinated compound with an enantiomeric ratio

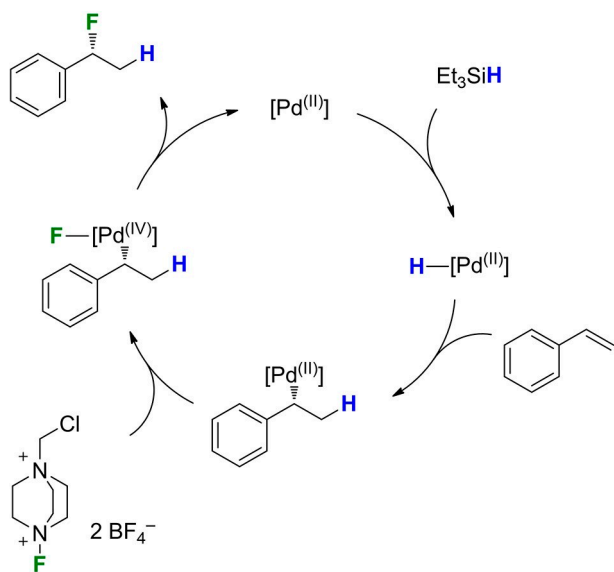


Figure 6. Simplified catalytic cycle proposed by Gouverneur for the *cis*-addition of HF on alkenylarenes. The ligands have been omitted for clarity.

up to 94:6. X-ray crystallography confirmed the formation of a five-member ring between the SOP ligand and the palladium via the coordination of the sulfur and phosphorous atoms. By using a combination of <sup>1</sup>H and <sup>31</sup>P NMR spectroscopy, the authors were able to determine the different intermediate of the catalytic cycle. When the SOP-PdCl<sub>2</sub> complex was mixed with AgNTf<sub>2</sub>, a single phosphorous signal was observed. When PPh<sub>3</sub> was mixed with the silver salts, two doublets were formed arising from the coupling of both silver isotopes with the phosphorous atom of PPh<sub>3</sub>. When combining the complex, the phosphine, the silver salt, and the silane, two new signals were observed, while the previous signals started to disappear. A new signal was also observed on the <sup>1</sup>H NMR corresponding to the hydride bonded to the palladium. This signal was, however, absent when PPh<sub>3</sub> was omitted, showing that a secondary phosphine is needed to stabilize the Pd(II)–H species (Figure 7). The coupling constant of the hydride with both phosphorous suggested a *trans* configuration of both phosphines on the palladium center. The chirality is induced via an insertion of this Pd(II)–H species on the alkene (Figure 8). Finally, the silver salt is also used to generate the cationic palladium complex. After screening the different reagents, they identified the optimal conditions shown in scheme 16.

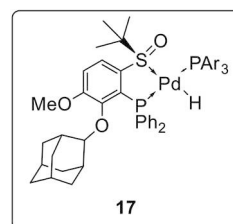


Figure 7. Proposed structure of the Pd(II)–H species involved in the enantioselective hydrofluorination of alkene reported by Yin and coworkers.

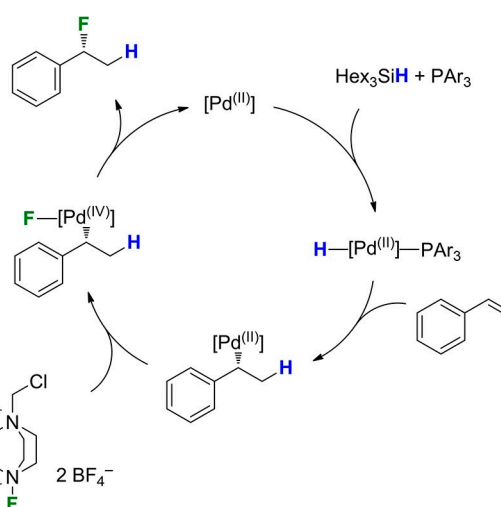
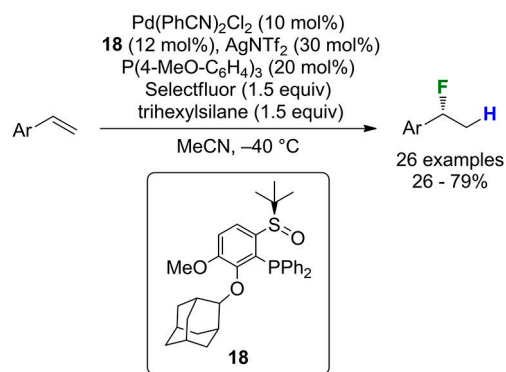
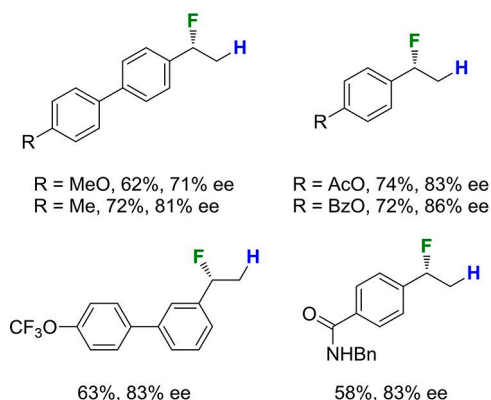


Figure 8. Catalytic cycle proposed by Yin and coworkers for the enantioselective hydrofluorination of styrene derivatives. The ligands have been omitted for clarity.



Selected examples



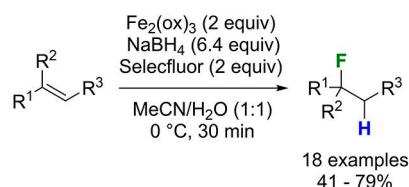
**Scheme 16.** Enantioselective hydrofluorination of styrene derivatives reported by Yin and coworkers.

#### 4. Radical hydrofluorination

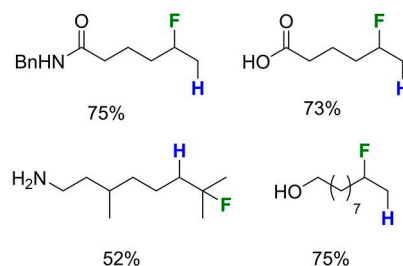
It was demonstrated in 2012 that electrophilic reagent based on the N–F bond could be used in a radical pathway.<sup>[25]</sup> This quickly led to a new field of research on fluorination. Later that year, Boger's group reported the first radical hydrofluorination of alkenes.<sup>[26]</sup> By using iron (III) oxalate, Selectfluor and sodium borohydride, a wide range of alkenes could be converted to their corresponding fluoroalkanes. Terminal, di- and trisubstituted alkenes were effectively used for this transformation with an average yield of 63% (Scheme 17).

The reaction, performed at 0 °C, shows great tolerance to various functional groups, air, and even water, but uses an overstoichiometric amount of iron. The reaction times are short (~30 min.) which is particularly interesting for <sup>18</sup>F labelling, as well as the use of NaBH<sub>4</sub> as the hydride source that can be replaced by readily available NaBD<sub>4</sub> for deuterium incorporation. This helped the authors determine that the addition is not diastereospecific.

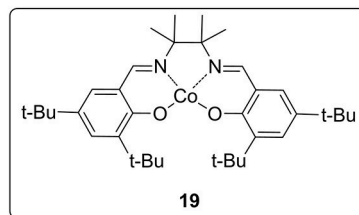
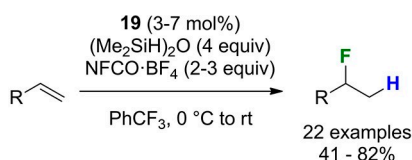
Shigehisa and coworkers reported in 2013 another radical hydrofluorination of olefins that is catalyzed by a cobalt complex.<sup>[27]</sup> Similarly to Boger's method, the functional group tolerance is quite extended with good compatibility to fluoride-sensitive and acid-sensitive groups such as silyl ether, PMB, acetal and Boc (Scheme 18). The radical fluorine is delivered by *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (NFCO·BF<sub>4</sub>),



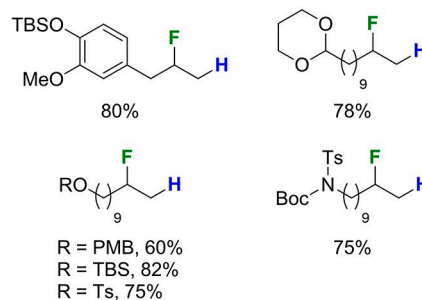
Selected examples



**Scheme 17.** Radical hydrofluorination conditions developed by Boger and coworker.



Selected examples

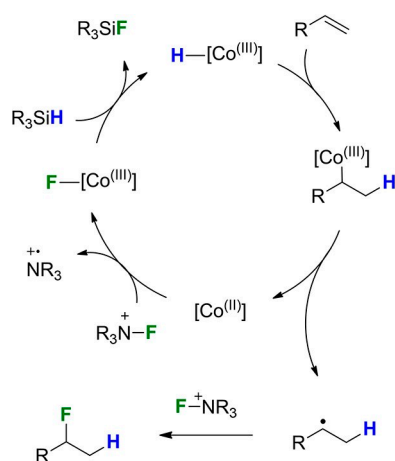


**Scheme 18.** Hydrofluorination conditions developed by Shigehisa and coworkers.

and 1,1,3,3-tetramethyldisiloxane is used as a radical hydrogen source.

The authors propose a mechanism which involves a Co(II)/Co(III) redox couple. The fluoropyridinium serves as the oxidant and as the source of "F" (Figure 9). The reaction can be run on a 1-gram scale without significant decrease of yield.

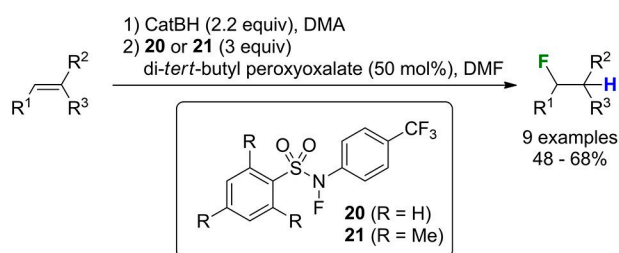
In 2018, Zipse and Renaud reported a new class of reagents suitable for radical fluorination.<sup>[28]</sup> Based on the N–F bond, these reagents show bond dissociation energies that are 30 to 45 kJ/



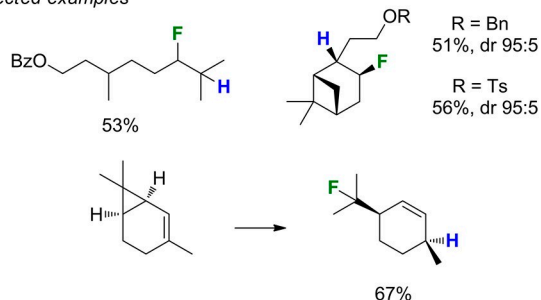
**Figure 9.** Catalytic cycle proposed by Shigehisa and coworkers for the cobalt-catalyzed hydrofluorination of alkenes. The ligands have been omitted for clarity.

mol lower than more common reagent such as NFSI or Selectfluor. To examine the potential of these *N*-fluoro-*N*-arylsulfonamides, they performed a hydrofluorination of alkene via a two-step mechanism. Catecholborane is first added on the alkene to hydroborate the compound, which is then fluorinated with the reagent **20** or **21**. The resulting product is an anti-Markovnikov hydrofluorination. The yields are good, ranging from 48% to 68% (Scheme 19). The authors also showed some interesting rearrangement through radical cyclization or cyclopropane openings.

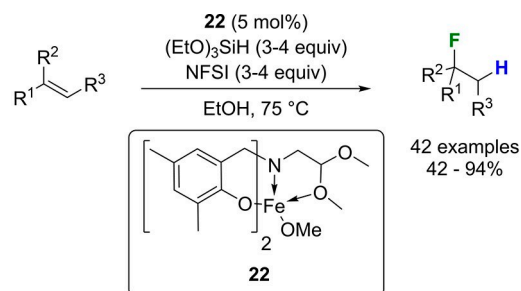
Another iron(III)-catalyzed hydrofluorination was reported in 2019 by Ye and coworkers. Using a specific multidentate ligand, they were able to reduce the quantity of iron to only 5 mol% (Scheme 20).<sup>[29]</sup>



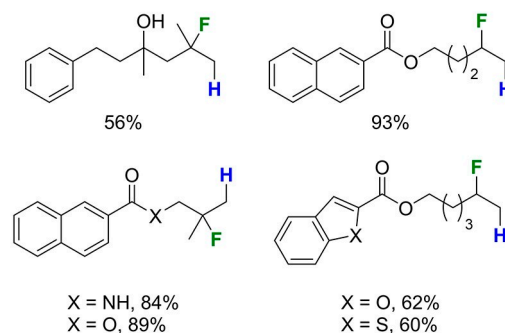
Selected examples



**Scheme 19.** Two-step hydrofluorination reported by Zipse and Renaud in 2018.



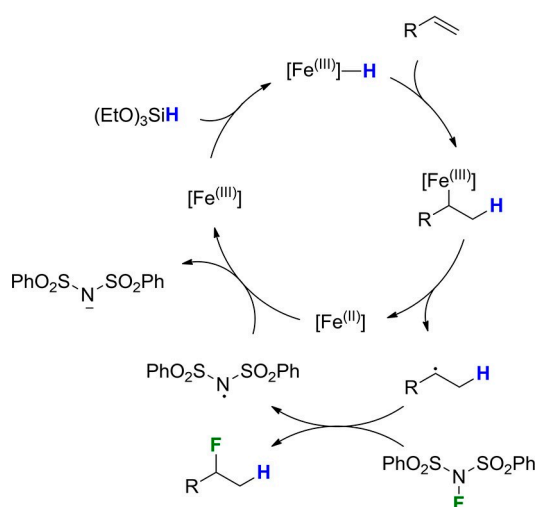
Selected examples



**Scheme 20.** Hydrofluorination conditions developed by Ye and coworkers.

After screening the different sources of fluorine and hydrogen, they found that *N*-fluorobenzenesulfonimide (NFSI) and triethoxysilane were the best options. The multidentate ligand proved essential for the catalytic activity of the iron complex. They found an elegant way to regenerate the catalyst, using the radical formed on the benzenesulfonimide to oxidize the iron(II) to iron(III) (Figure 10).

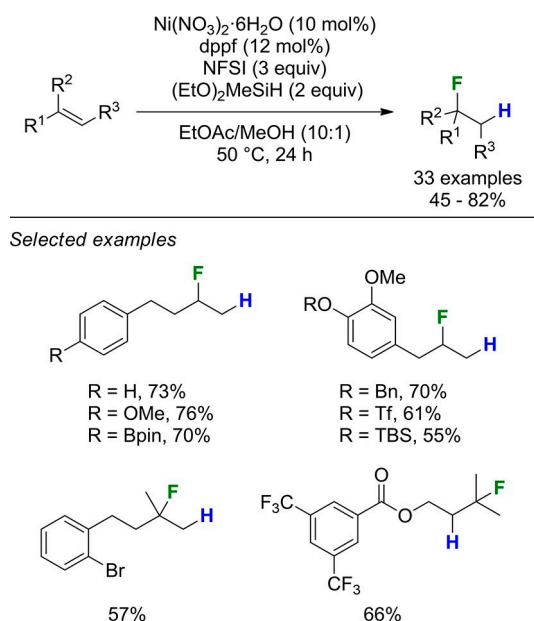
Zhu and coworker reported a nickel-catalyzed hydrofluorination in 2020.<sup>[30]</sup> They showed that nickel(II) nitrate hexahydrate in the presence of diethoxy(methyl)silane and NFSI could



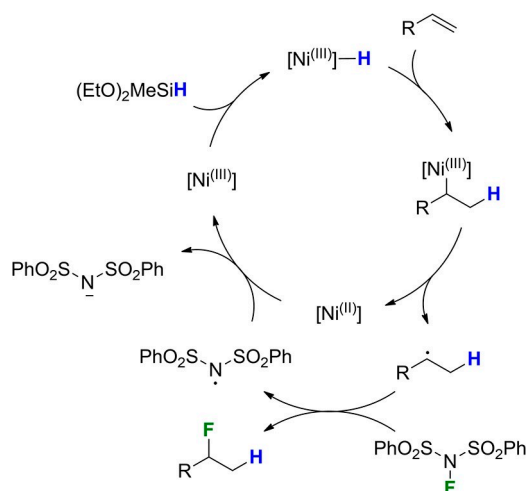
**Figure 10.** Catalytic cycle proposed by Ye and coworkers for the iron-catalyzed hydrofluorination of alkenes. The ligands have been omitted for clarity.

afford the desired fluorinated compound in good yields (Scheme 21). The reaction works well with mono-, di- and trisubstituted alkenes, and has a great chemical compatibility. Notably, easily reduced functional group such as aldehydes are tolerated as well as aryl chlorides, bromides, iodides, triflates and boronic ester which do not take part in any cross-coupling reaction. The reaction also tolerates air and water without significant loss of yields.

The proposed mechanism proceeds through a hydrogen atom transfer from a Ni(III)–H species to the alkene to form the alkyl radical, that can then react with the NFSI to afford the fluorinated product. The Ni(III) can then be regenerated by reduction of the benzenesulfonimide radical (Figure 11).



**Scheme 21.** Hydrofluorination conditions developed by Zhu and coworker.



**Figure 11.** Catalytic cycle proposed by Zhu and coworker for the nickel catalyzed hydrofluorination of alkenes. The ligands have been omitted for clarity.

## 5. Conclusion

Since the first reported hydrofluorination of alkene using anhydrous hydrogen fluoride in 1938, many methods have been described to improve this reaction. Not only has safety been largely improved, but the functional tolerance as well as the yields of the reaction has been enhanced considerably. Three main reaction pathways have been highlighted in the past years, each of them involving a different mechanism as well as various reagents, enabling the fluorination of wide variety of molecules. One of the challenges of hydrofluorination of alkene remains the chiral incorporation of the fluorine atom. Some examples have been reported by Gouverneur, MacMillan, Huang and Lei and Liao. Those reactions are, however, limited to specific types of alkene such as styrene or  $\alpha,\beta$ -unsaturated aldehydes. Therefore, the development of an enantioselective hydrofluorination of a wide range of alkenes would be a considerable breakthrough in the field.

## Acknowledgements

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## Conflict of Interest

The authors declare no conflict of interest.

**Keywords:** hydrofluorination · alkene · hydrogen fluoride · organofluorine compounds · synthetic methodologies

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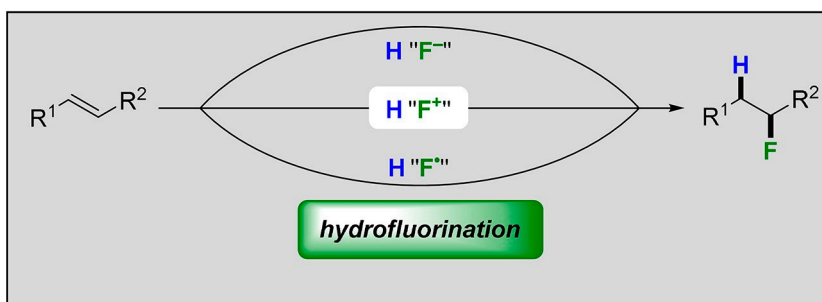
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## MINIREVIEW



*X. Bertrand, Dr. L. Chabaud, Prof. J.-F. Paquin\**

1 – 13

**Hydrofluorination of Alkenes: A Review**

**Hydrofluorination of alkenes has become a powerful tool for the incorporation of a single fluorine atom**, which are useful in a vast array of chemical fields. This review presents the development in this area

from the first reported addition to the most recent examples, separated into the three main possible mechanism: nucleophilic, electrophilic, and radical hydrofluorination.



Hydrofluorination of alkenes has become a powerful tool for the incorporation of a single fluorine – A #Review on it by @jfluorine

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