Synthetic Applications of Fluorodesilylation

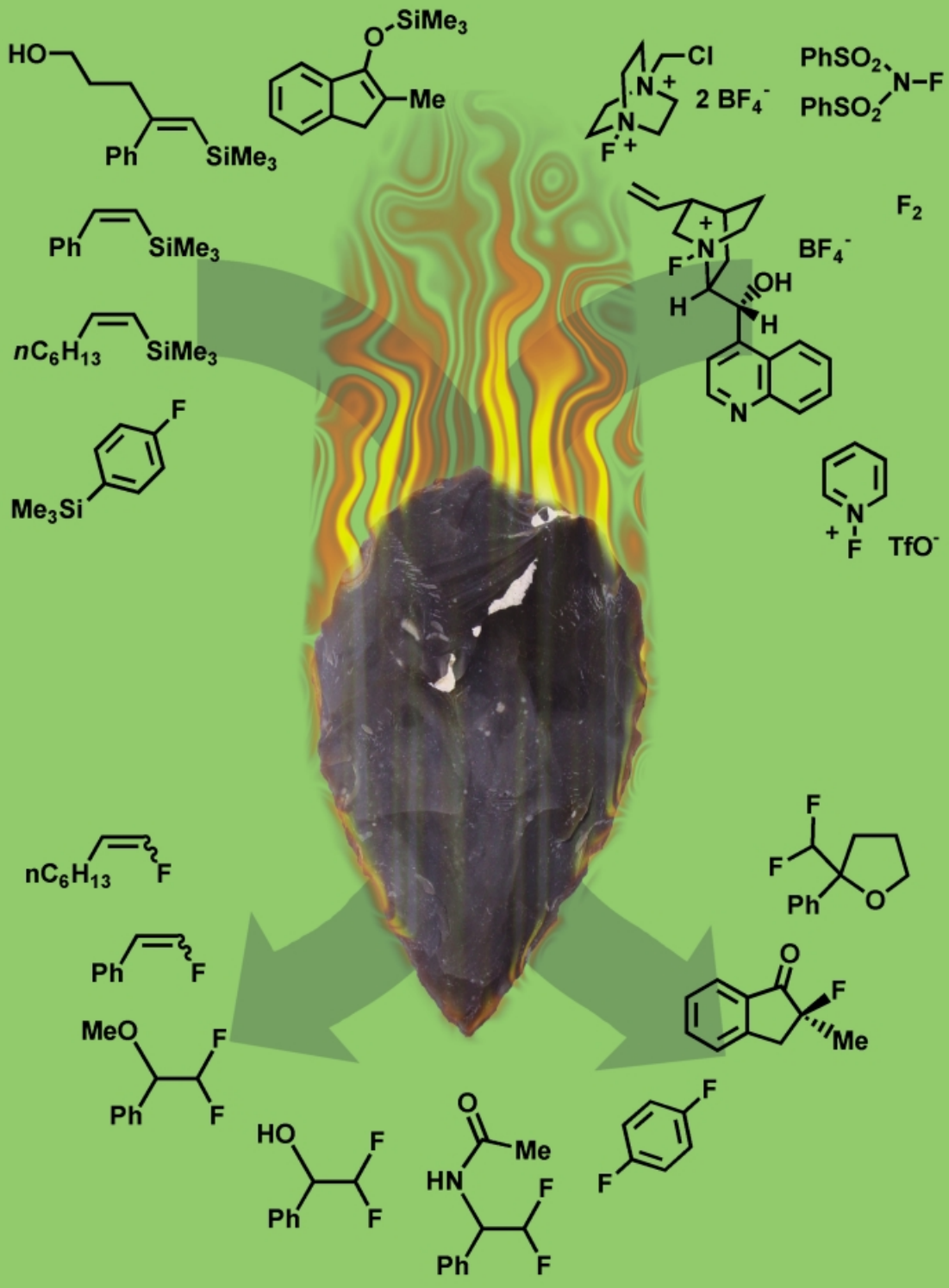

Image inspired from the Latin “silicus” meaning flint and the very reactive fluorine gas. Image created by Dr. Karl Harrison with the Flint axe blade from the PADMAC Unit, Pitt Rivers Museum, University of Oxford.

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Synthetic Applications of Electrophilic Fluorodesilylation

Véronique Gouverneur* and Benjamin Greedy[a]

Abstract: Recently, with the appearance of electrophilic sources of fluorine including the commercially available N–F reagents, the concept of electrophilic fluorodesilylation has emerged as a new strategy to prepare a variety of fluorine containing compounds. This paper highlights how this concept has been applied to the preparation of a series of fluorinated molecules including fluoroaromatic compounds, fluoroalkenes, difluoroamides, difluoroalcohols, difluoroethers and α-fluorinated carbonyl derivatives.

Keywords: electrophilic addition · fluorine · halogenation · silicon

Introduction

With a typical dissociation energy of 700 kJ mol^{-1}, the strength of the silicon–fluorine bond cannot be overemphasized. It is therefore not surprising that much of organosilicon chemistry is driven by the formation of a silicon–fluorine bond at the expense of other weaker bonds.[1] The fluoride catalyzed cleavage of the Si–C bond followed by in situ C–C bond formation is a well studied and synthetically very useful process.[2] This so-called "nucleophilic fluorodesilylation" strategy involves the use of a source of anionic fluoride such as Bu_4NF, TASF, CsF, KF/18[crown]-6. However, more recently, with the appearance of electrophilic sources of fluorine[3] including N–F fluorinating agents, the concept of electrophilic fluorodesilylation has emerged as a means to synthesise a variety of fluorine containing compounds. A striking feature of these novel transformations is that, in contrast to nucleophilic fluorodesilylation, this strategy allows the generation of a C–F bond instead of the formation of a strong Si–F bond. This paper highlights some of the synthetic applications of electrophilic fluorodesilylation reported to date including its application to arylsilanes, vinylsilanes and silyl enol ethers.

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Electrophilic fluorodesilylation of aryl- and vinylsilanes (cleavage of Si–C bonds): The carbon–silicon bond is generally stable to many common reagents used in organic synthesis. However, the cleavage of activated silanes using an electrophilic source of fluorine has provided the synthetic chemist with new opportunities. Elemental fluorine is potentially a source of cationic fluorine (F^+) but the difficulties associated with its use have stimulated the development of new reagents such as $FClO_3$, CF_3OF, CF_3CF_2OF, CF_3COOF, CH_3COOF, XeF_2 or $CsSO_4F$. Their reactivity towards electron-rich systems suggests that these reagents presumably deliver F^+ although F^+ has only been observed spectroscopically in the gas phase.[4] More recently, the reagents of the NF class, several of which are now commercially available, have allowed the safe and practical introduction of fluorine on electron-rich species. It has been demonstrated that a very wide range of chemical reactivity can be obtained with these N–F reagents by fine-tuning of their structure.[5] As with other electrophile induced desilylation reactions, electrophilic fluorodesilylation takes advantage of the β effect of silicon and could thus be applied to compounds that have adjacent π systems such as aryl-, vinyl-, allyl-, and propargylsilanes.[6]

Due to the presence of fluoroaromatics in many pharmaceutical and agrochemical compounds, it is not surprising that the concept of electrophilic fluorodesilylation of silane derivatives was first applied to arylsilanes. Early reports described the fluorination of arylsilanes for the purpose of introducing ^{18}F into radiopharmaceuticals. The fluorination of 4-substituted phenyltrimethylsilanes with $[^{18}F]_2$ or $CH_3COO[^{18}F]$ afforded products from *ipso*-fluorodesilylation with chemical yields ranging between 20–30%.[7–9] The relative extent of the $[^{18}F]$ substitution processes was found to depend largely upon the presence of other groups on the aromatic ring of the substrate (Table 1).

In general, for all these reactions, a large excess of substrate to fluorine (80–100 fold) was used to minimise unwanted fluorination on the phenyl rings of both starting materials and products. A later study carried out by Stuart et al. suggested that similar results could be obtained using a stoichiometric amount of F_2 if the fluorination process is carried out in the presence of boron trifluoride (Table 2).[10]

It is believed that boron trifluoride promotes polarization of the F–F bond. In addition, the heterolytic cleavage of F_2 could also be favoured in polar solvents. In the presence of

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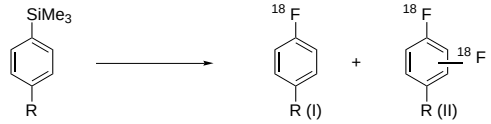
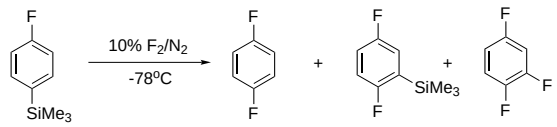
Table 1. Fluorodesilylation of aryltrimethylsilanes with $CH_3CO_2{}^{18}F$ and $[^{18}F]F_2$.



R	Conditions	Radiochemical yield [%] (I)	(II)
H	– 78 °C, $[^{18}F]_2$	24.5	4.0
H	25 °C, $CH_3CO_2[^{18}F]$	10.0	5.9
Me	– 78 °C, $[^{18}F]_2$	27.9	2.5
OMe	– 78 °C, $[^{18}F]_2$	21.3	18.6

Table 2. Elemental fluorination of 4-fluorophenyltrimethylsilane.



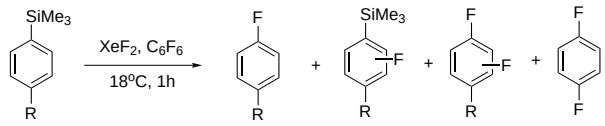
(IV) (I) (II) (III)

Fluorination conditions	(I)	(II)	(III)	(IV)
$CFCl_3$/MeOH (10%)	31	12	2	3
$CFCl_3/CH_2Cl_2$/MeOH (10%), 1 equiv BF_3·MeOH	43	12	5	6
$CFCl_3$/MeOH (10%), BF_3·2 CH_3COOH	50	15	4	5

BF_3·MeOH, the major product in the direct fluorination of 4-fluorophenyltrimethylsilane is 1,4-difluorobenzene produced by the *ipso*-electrophilic substitution of the trimethylsilyl group. Interestingly, 2,5-difluorophenyltrimethylsilane was also formed as the result of a 1,2-migration of the trimethylsilyl group. Similar 1,2-shifts were observed in the fluorinations of 2-fluoro- and 2,4-difluorophenyl-trimethylsilanes. It is believed that the carbocation produced after the 1,2-shift is stabilized both by the β-silicon effect and the mesomeric effect of the α-fluorine. It should be noted that for all these reactions, fluorodeprotonation also occurs but only as a minor process. Finally the same study reveals that the use of trifluoroacetic acid in combination with F_2 also promotes *ipso*-electrophilic fluorosubstitution. However, in the presence of triflic acid, the elemental fluorination of 4-fluorophenyltrimethylsilane proceeds by a protodesilylation process followed by fluorination of fluorobenzene to give the three isomeric difluorinated compounds.

Rapid fluorodesilylation of aryltrimethylsilanes has also been achieved using xenon difluoride (Table 3).[11]

Table 3. The effect of substitutents on fluorodesilylation with XeF_2.



(II) (III) (IV) (V)

R	(II)	(III)	(IV)	(V)
*t*Bu	86.3	7.6	6.1	–
Cl	82.1	11.5	6.4	–
OMe	61.4	38.6	0	–
H	65.2	0	0	34.8

Indeed, when 4-*tert*-butyl- or 4-chlorophenyltrimethylsilane were treated with two equivalents of XeF_2 in C_6F_6 at room temperature, the expected products were isolated in 86% and 82% yield, respectively. Some side products were formed as a result of *ortho*-fluorination processes. As previously described, when other substituents are present on the aromatic ring, competing electrophilic addition pathways are observed. The ultimate outcome of the reaction is dependent on the relative activation provided by the aryl substituents. If a strongly activating group, for example a methoxy group, is present on the aromatic ring, a higher yield of *ortho*-fluorinated product was obtained with XeF_2, but interestingly, the fluorodesilylation process remains the major transformation. It should be noted that the activating effect and *ipso*-directing effect of a trimethylsilyl group is relatively weak for electrophilic aromatic substitution. In terms of mechanism, it has been suggested that in contrast to the use of F_2 or acetyl hypofluorite, an aryl radical is formed as the key intermediate for the fluorination of arylsilanes with XeF_2.

Finally, we found that the fluorodesilylation of trimethylsilylbenzene with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) so-called Selectfluor is a very slow process.[12] At room temperature it was found that no reaction occurred between trimethylsilylbenzene and 1.5 equiv Selectfluor in acetonitrile. However, after 64 hours at reflux, 19% of fluorobenzene was formed along with 21% of *ortho*-fluorotrimethylsilylbenzene. These results suggest that only strong electrophilic fluorinating reagents are suitable for the *ipso* fluorodesilylation of arylsilanes. This could be explained by the fact that during the formation of the intermediate β-silyl cation, the aromaticity of the ring is lost. In addition, the Si–C σ bond and the p orbital to be stabilized are initially orthogonal and consequently, stabilization from the β-effect occurs late in the approach to the transition state.

As with arylsilanes, relatively strong electrophiles are required for the electrophilic fluorination of vinylsilanes.[13] We have shown that the activated trimethylstyrylsilane **1a** reacts with Selectfluor or the corresponding bis(trifluoromethanesulfonate) derivative to give the expected fluoroalkene **2a** as a mixture of *Z* and *E* stereoisomers (Table 4, entry 1).

In contrast, 1-fluoropyridinium pyridine heptafluorodiborate and *N*-fluorobenzenesulfonimide do not react with trimethylstyrylsilane. The less activated vinylsilane **1b** also undergoes fluorodesilylation with Selectfluor. This transformation is more stereoselective yielding a mixture of *Z* and *E* stereoisomers **2b** in a ratio of 80:20 (Table 4, entry 2). The formation of a mixture of geometrical isomers and the faster reaction with more nucleophilic vinylsilanes are consistent with an addition–elimination pathway via a carbocationic intermediate. However, the experimental results could not rule out the possibility of a single electron transfer mechanism. If two equivalents of Selectfluor are used, the vicinal difluoroamides are formed in good yields by a Ritter-type fluoro-functionalisation with acetonitrile. This type of reaction could not be applied to poorly activated vinylsilanes since the primary product of the reaction, the fluoroalkene failed to react further (Table 4, entries 3 and 4). The product outcome is different if these reactions are carried out in the presence of a nucleophilic solvent. In a mixture of MeOH/CH_3CN 1:1, the

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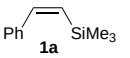
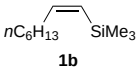
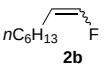
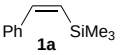
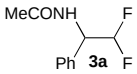
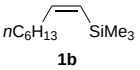
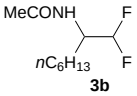
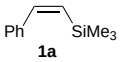
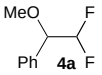
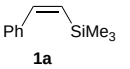
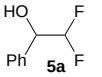
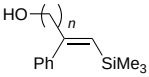
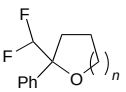
Table 4. Fluorodesilylation of vinylsilanes with Selectfluor.

	Substrate	Product	Method[a]	Yield [%][b] (conversion [%])[c]
1	 **1a**	 **2a**	A	32 (47) *Z*:*E* 65:35
2	 **1b**	 **2b**	A	(45) *Z*:*E* 80:20
3	 **1a**	 **3a**	B	70 (74)
4	 **1b**	 **3b**	B	0
5	 **1a**	 **4a**	C	75 (82)
6	 **1a**	 **5a**	D	45 (46)
7	 *n*=3 or 4		B	**6** (*n* = 1) 62 **7** (*n* = 2) 48

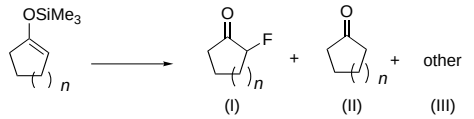
[a] Method A: 1 equiv Selectfluor, CH_3CN, rt; Method B: 2.5 equiv Selectfluor, CH_3CN, rt; Method C: 2.5 equiv Selectfluor, MeOH/CH_3CN, RT; Method D: 2.5 equiv Selectfluor, H_2O/CH_3CN, RT. [b] Chemical yield after column chromatography. [c] Evaluated by GC/MS.

difluorinated methyl ethers are obtained in good yields while in aqueous acetonitrile (H_2O/CH_3CN 1:1), acceptable yields of the expected difluoromethyl alcohols could be isolated (Table 4, entries 4 and 6). In addition, the same authors have applied the concept of electrophilic fluorodesilylation of vinylsilanes to the preparation of bis-fluorinated tetrahydrofuran **6** and tetrahydropyran **7** derivatives which are difficult to access by other means (Table 4, entries 6 and 7).

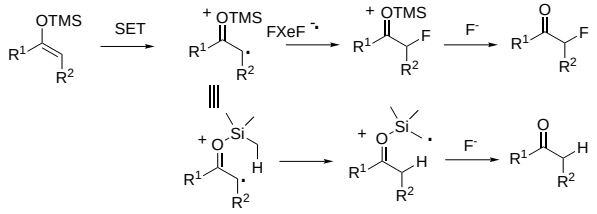
These preliminary studies on the possibility of cleaving a Si–C bond by a fluorodesilylation process are promising. Future work could aim to apply the concept of fluorodesilylation to other silane derivatives and to better understand the mechanism of these transformations.

Electrophilic fluorodesilylation of silyl enol ethers (cleavage of Si–O bonds): The electrophilic fluorodesilylation of silyl enol ethers as an alternative to the use of metal enolates is a common methodology for obtaining α-fluoro carbonyl compounds. By themselves, silyl enol ethers are much weaker nucleophiles than enolates. However, preformed silyl enol ethers react with a wide range of electrophilic fluorinating reagents.[14] Early examples involved the use of hypofluorites and elemental fluorine but only moderate yields of product were obtained. The electrophilic fluorodesilylation of silyl enol ethers using XeF_2 has been investigated in detail by Ramsden et al.[15] These studies have revealed that several products are formed including the desired α-fluoro ketone and the nonfluorinated ketone. The ratio of these two products is dependent on the structures of individual silyl enol ethers and the conditions. The formation of the observed products is consistent with a mechanism involving single electron transfer (SET) giving a radical cation as the key intermediate (Table 5 and Scheme 1).

Table 5. Reaction and mechanism of cyclic TMS enol ethers with XeF_2.



	Solvent	Yield [%] (I)	Yield [%] (II)	Yield [%] (III)
n = 1	CH_3CN	100	0	0
n = 2	CH_3CN	100	0	0
n = 2	$CFCl_3$	55	8	37
n = 2	C_6F_6	56	0	44

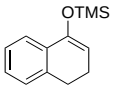
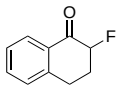
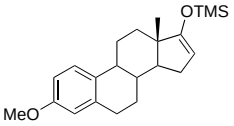
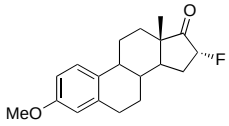


Scheme 1. Reaction and mechanism of acyclic TMS enol ethers with XeF_2. TMS = trimethylsilyl.

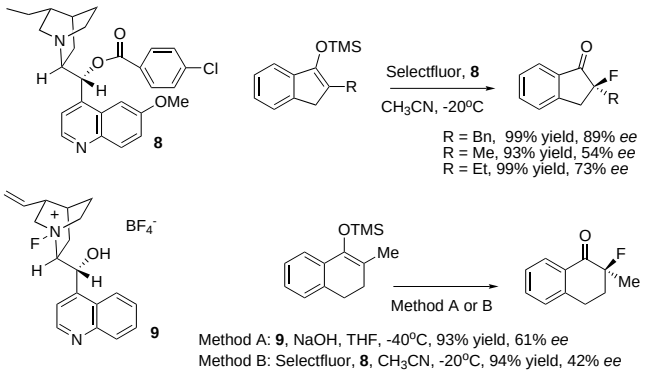
N–F type reagents have also been studied and selected examples are presented in Table 6.[16] These studies have shown that the chemical yields of the expected fluorocarbonyl derivatives are dependent both on the reagent employed and the substrate. As expected, prolonged reaction times at room temperature are required for the fluorination of silyl enol ethers with N–F reagents such as NFSi or NFOBS. In contrast to these neutral reagents, the higher reactivity of the N–F ammonium salts, including Selectfluor and its derivatives or *N*-fluoropyridinium salts, allows these reactions to be carried out at lower temperatures. It is therefore not surprising that recently, new chiral *N*-fluoroammonium salts were synthesised and used successfully for the preparation of enantiomerically enriched fluorinated carbonyl derivatives from silyl enol ethers.[17] Two groups have independently reported new *N*-fluoroammonium salts derived from cinchona alkaloids. Takeuchi and co-workers developed a practical approach to enantioselective fluorination that has been applied to cyclic silyl enol ethers.[18] The active fluorinating species generated in situ from Selectfluor and readily available cinchona alkaloid derivatives, reacts at $-20\,^{\circ}C$ or $-50\,^{\circ}C$ with a series of substituted silyl enol ethers derived from indanone and tetralone. Yields ranging between 71% and 99% and enantiomeric excesses up to 91% are obtained (Scheme 2).

Simultaneously, Cahard and co-workers reported the synthesis of a series of preformed cinchona alkaloid ammonium salts (Scheme 2).[19] In contrast to Takeuchi et al., they have used their reagents mainly for the fluorination of cyclic metal enolates but they also successfully fluorinated the trimethyl silyl enol ether of 2-methyl-1-tetralone at $-40\,^{\circ}C$ with a

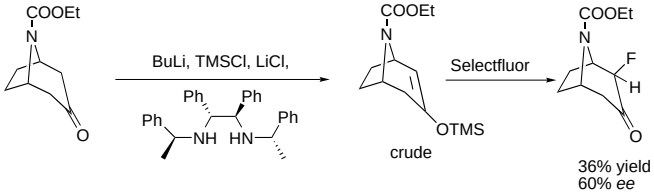
Table 6. Selected examples of fluorinations of silyl enol ethers and ketene monosilyl acetal with N–F reagents.[a]

Substrate	Product	Conditions	Yield [%]
		NFOBS, CH_2Cl_2 2.5 h, RT	62 – 79
		NFOBS, CH_2Cl_2 4 h, RT	67
		NFOBS, $CDCl_3$, 10 h, RT	31 – 40
		 , 3 h, RT	50
		 , 16 h, RT	78

NFOBS = *N*-fluoro-*ortho*-benzenedisulfonimide.



Scheme 2. Enantioselective fluorination of TMS enol ethers with quaternary *N*-fluoroammonium salts.



Scheme 3. Enantioselective desymmetrisation followed by electrophilic fluorodesilylation.

chemical yield of 93% and an enantiomeric excess of 61%. Under similar conditions, the fluorination of the corresponding metal enolate gave the expected product with a higher chemical yield (96%) but a lower enantiomeric excess (42%). The authors conclude that the approach involving silyl enol ethers is more promising and this is confirmed by the work of Takeuchi. Another isolated example for the preparation of an enantiomerically pure fluorinated carbonyl from a silyl enol ether has been reported in 1998 by the group of Armstrong.[20] He has shown that using Selectfluor, the fluorination of the silyl enol ether obtained by desymmetrisation of *N*-ethoxycarbonyltropinone with a chiral lithium amide base gave the expected fluorinated tropinone derivative with an unoptimised yield of 36% and an enantiomeric excess of 60% (Scheme 3). This strategy has not been further developed.

Conclusion

The availability of mild sources of electrophilic fluorine, including NF reagents allows the introduction of a fluorine atom at a late stage in a synthesis. Despite the current mechanistic uncertainties for some of these electrophilic fluorodesilylation processes, it appears that a door has been opened for exciting and promising further development of this new type of transformations including the use of allyl- and propargylsilanes. Particularly, further development in asymmetric electrophilic fluorodesilylation methodology including the development of a catalytic strategy could potentially provide direct access to a very diverse array of compounds difficult to obtain by other means.

Acknowledgements

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