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Fluorination

Electrophilic Fluorocyclization of Allyl Silanes**

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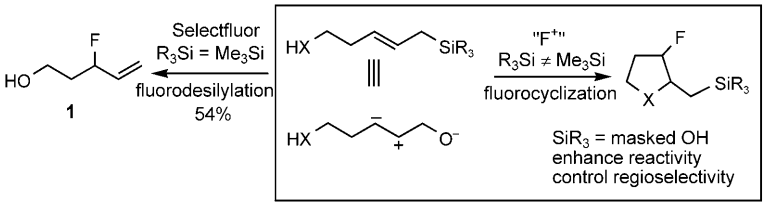
Halocyclization reactions have countless applications throughout organic chemistry.[1] This area of research continues to attract attention, especially in terms of the validation of asymmetric variants for the construction of halogenated natural products.[2] Despite the great utility of fluorinated hetero- and carbocycles as pharmaceuticals and agrochemicals,[3] the development of fluorocyclization reactions has been slow. Such reactions have only been applied to a limited range of alkenes.[4] For the continued advancement of this field, the design and implementation of novel strategies that enable fluorocyclization reactions to become a more general and powerful transformation used by all practitioners of synthetic chemistry is highly desirable. To reach this objective, fundamental problems of reactivity and selectivity must be addressed. The low reactivity of commonly used N–F electrophilic fluorinating reagents towards feedstock olefins (e.g. cyclohexene or acyclic alkenes) is particularly restrictive in the context of fluorocyclization, especially when combined with complications arising from the poor regioselectivity observed with some unsymmetrical substrates. The lack of stereocontrol more often encountered in the nucleophilic and electrophilic fluorocyclization reactions reported to date must also be overcome, ideally with a solution amenable to the development of an asymmetric variant.

Our research group developed the concept of the electrophilic fluorodesilylation of organosilanes. This approach enables the synthesis and manipulation of various fluorinated building blocks and more complex targets.[5] Provoked by the potential of developing a conceptually novel stereoselective fluorocyclization process, we questioned whether the electrophilic fluorination of allyl silanes that contain a pendent nucleophile may be rerouted to deliver fluorinated heterocycles. We reasoned that alkenes temporarily activated by a silyl group other than the trimethylsilyl group would display the reactivity profile necessary for the fluorocyclization to occur and bypass the competing fluorodesilylation process.[6] In this approach, the allyl silane functions as a 1,2-dipole, and the silyl group is amenable to oxidative cleavage after the cyclization event (Scheme 1). We describe herein the first use of allyl silanes in *endo* fluorocyclization reactions, the stereochemical outcome of which is dictated by the alkene geometry.



Scheme 1. Electrophilic fluorocyclization versus fluorodesilylation.

To test the proposed strategy, we carried out initial investigations to identify the optimum F^+ reagent as well as silicon substituents that would promote cyclization versus desilylation. A fluoroetherification was chosen as the model reaction (Table 1).[7]

The silyl groups of the homoallylic alcohols **2a–d** were selected on the basis of the ability of structurally related allyl silanes to participate in various annulations when treated with an aldehyde in the presence of a Lewis acid.[8] Apart from **2a**, all substrates contained silyl groups amenable to oxidative cleavage.[9] Attempts at the fluorocyclization of allyl silanes **2a–c** were successful; the allyl dimethylphenylsilane **2d** was the only substrate to undergo exclusive fluorodesilylation. The benzhydryldimethylsilyl group was not retained for further studies, as side products were formed in significant amounts in reactions of the homoallylic alcohol **2c** (Table 1, entries 5–7). When used in combination with $NaHCO_3$, Selectfluor (**A**) was found to be the reagent of choice for the fluoroetherification of the allyl triisopropylsilane **2a**; with this reagent, the fluorinated tetrahydrofurans **3a** were formed in up to 90% yield (Table 1, entries 1 and 2). The fluorocyclization of the allyl *p*-tolyldiisopropylsilane **2b** was most efficient with *N*-fluorobenzenesulfonimide (NFSI, **B**) in MeCN at reflux (Table 1, entries 3 and 4). This set of preliminary data also indicated that the geometry of the

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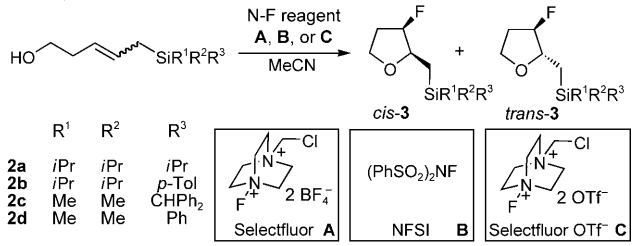
Table 1: Influence of the silyl group and the N–F reagent on the fluorocyclization.



Entry	**2**	*E*/*Z*	Reagent	Yield of **3** [%][d]	*cis*/*trans*
1	**2a**	2:1	**A**[a]	90	2.5:1
2	**2a**	1:10	**A**[a]	58	1:8
3	**2b**	1:18	**A**[a]	49	1:6
4	**2b**	2:1	**B**[b]	60	3:1
5	**2c**	2:1	**A**[a]	41	3:1
6	**2c**	2:1	**B**[b]	41	2.5:1
7	**2c**	2:1	**C**[c]	37	2.7:1
8	**2d**	4:1	**A**[a]	0[e]	–
9	**2d**	4:1	**B**[b]	0[e]	–

[a] Reaction conditions: **A**, $NaHCO_3$, MeCN, room temperature. [b] Reaction conditions: **B**, $NaHCO_3$, MeCN, reflux. [c] Reaction conditions: **C**, $NaHCO_3$, MeCN, room temperature. [d] Yield of the isolated product. [e] Only fluorodesilylation was observed. Tf = trifluoromethanesulfonyl.

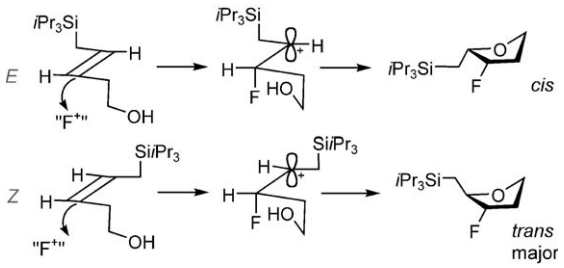
alkene influenced the stereochemical outcome of the fluorocyclization. The cyclization of samples enriched in (*E*)-**2a** and (*Z*)-**2a** led preferentially to the *cis* and *trans* tetrahydrofuran, respectively.

As highlighted in Table 2, a wide range of silyl-activated di- and trisubstituted alkenes are suitable substrates for this reaction. Both *E* and *Z*-allyl silanes underwent fluorocyclization. The desired fluorinated tetrahydrofurans **14**–**22** were isolated in yields ranging from 47 to 83 %.[7,10] In accord with the fluorocyclization of (*E*)- and (*Z*)-**2a**, various *E*- and *Z*-allyl silanes underwent cyclization to give *cis*- and *trans*-substituted fluorinated tetrahydrofurans, respectively. The transfer of stereochemical information was excellent in the fluoroetherification of *E*-allyl silanes (Table 2, entries 1, 2, 5, 7, and 9). In the case of starting materials used as a single *E* isomer (Table 2, entries 2 and 7), only the *cis* product was observed by ^1H or ^{19}F NMR spectroscopy of the crude reaction mixture. No trace of the *trans* isomer was detected. The *trans* products were accessible by the fluorocyclization of *Z*-allyl silanes, albeit with some stereochemical erosion (Table 2, entries 3, 4, 6, and 8). The fluorocyclization of **7b** stands out, as this phenyl-substituted *Z*-allyl silane was converted exclusively into diastereomer **17b** with the fluorine substituent and the silylmethyl group oriented *trans* to one another (Table 2, entry 4).

Fluoroetherification of the homoallylic alcohols **8**–**11** was also successful (Table 2, entries 5–8). The relative configuration at C3 and C2 was still dictated by the alkene geometry, with the best selectivity observed for the *E*-allyl silanes **8a**,**b** and **10a**,**b** (Table 2, entries 5 and 7). Better diastereoselectivity (up to 4:1) was observed for the newly formed fluorinated carbon center (C3) with respect to C4 in cyclization reactions of the *Z*-allyl silanes **9b**, **11a**, and **11b** than for substrates **8a,b** and **10a,b** (Table 2, entries 6–8).

The fluorocyclization was also validated with the more functionalized allyl silane **12a** (Table 2, entry 9). The presence of additional functionality is an important consideration for the synthesis of pharmaceuticals (Table 2, entry 9). The silylated carboxylic acid **13a** was also a suitable substrate for this cyclization procedure (Table 2, entry 10). This interesting result indicates that the reaction conditions are sufficiently mild to prevent β-fluoride elimination after the fluorocyclization event. In this transformation, the *E*/*Z* ratio of **13a** was translated accurately into the *cis*/*trans* ratio of the fluorinated lactone **23a**, which was formed in 80 % yield.

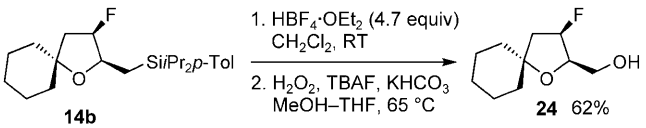
The stereochemical outcome of these kinetically controlled reactions[7,11] is consistent with a predominant overall *syn* addition to the double bond. According to our studies on the fluorodesilylation of allyl silanes and allenyl silanes,[5] the electrophilic addition of the N–F reagent is expected to take place *anti* to the silyl group. In the reactive conformation of the allyl silanes, the C–Si bond is probably aligned parallel to the empty p orbital of the carbocation intermediate to enable σ–p hyperconjugative stabilization. Subsequent cyclization through the addition of the alcohol to the β-silyl cation occurs preferentially *anti* to the bulky silyl group (Scheme 2).



Scheme 2. Predominant *syn* addition in the fluorocyclization.

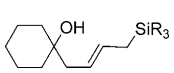
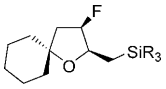
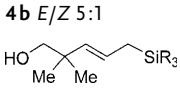
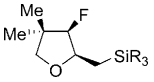
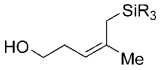
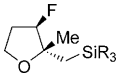
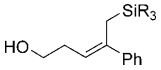
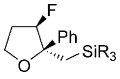
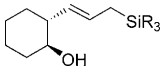
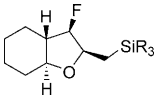
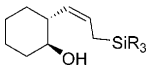
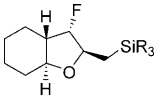
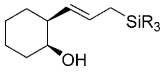
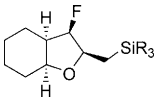
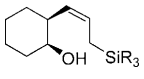
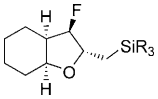
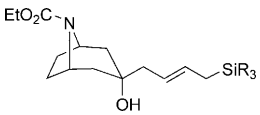
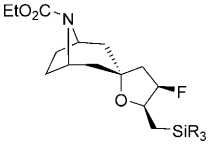
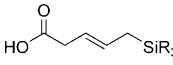
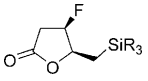
These fluorocyclization reactions follow a stereochemical pathway that contrasts with the well-documented overall *anti* addition observed for the *endo* iodocyclization of nonsilylated alkenes.[12] The stereochemical erosion observed for *Z*-allyl silanes indicates that a competing reaction pathway leads to overall *anti* addition to the double bond.

To demonstrate the applicability of the methodology to the synthesis of fluorinated tetrahydrofurans, the silyl group of **14b** was subjected to oxidative cleavage. Protodesilylation of the tolyl group, followed by oxidation, gave the hydroxylated tetrahydrofuran **24** in 62 % overall yield (Scheme 3).[9]



Scheme 3. Oxidative cleavage of **14b**. TBAF = tetrabutylammonium fluoride.

Table 2: Scope of the electrophilic fluorocyclization.[a]

Entry	Allyl silane **a** $SiR_3 = SiiPr_3$ **b** $SiR_3 = SiiPr_2p$-Tol	Product[b] **a** $SiR_3 = SiiPr_3$ **b** $SiR_3 = SiiPr_2p$-Tol	Yield [%][c]	*cis*/*trans*[d]
1				
	4a *E*/*Z* 6:1	**14a**	73	7:1
	4b *E*/*Z* 5:1	**14b**	52	5:1
2				
	5a *E*/*Z* > 20:1	**15a**	72	> 20:1
	5b *E*/*Z* > 20:1	**15b**	47	> 20:1
3				
	6b *Z*/*E* > 20:1	**16b**	67	1:16
4[e]				
	7b *Z*/*E* > 20:1	**17b**	65	1:20
5				
	8a *E*/*Z* 10:1	**18a**	83	16:1[f,g]
	8b *E*/*Z* 13:1	**18b**	62	16:1[f,g]
6				
	9b *Z*/*E* > 20:1	**19b**	58	1:12[f,h]
7				
	10a *E*/*Z* > 20:1	**20a**	83	> 20:1[f,i]
	10b *E*/*Z* > 20:1	**20b**	55	> 20:1[f,j]
8				
	11a *Z*/*E* 12:1	**21a**	59	1:6[f,k]
	11b *Z*/*E* > 20:1	**21b**	62	1:11[f,l]
9				
	12a *E*/*Z* 6:1	**22a**	54	6:1
10				
	13a *E*/*Z* = 3:1	**23a**	80	3:1

[a] Reaction conditions: **A**, $NaHCO_3$, MeCN, room temperature when SiR_3 is $SiiPr_3$; **B**, $NaHCO_3$, MeCN, reflux when SiR_3 is $SiiPr_2p$-Tol. [b] The major isomer is shown. [c] Yield of the isolated product. [d] The *cis*/*trans* ratio with respect to the silylmethyl and fluoro substituents at C2 and C3 was determined by ^{19}F NMR spectroscopy of the crude product. [e] Reaction conditions: **A**, $NaHCO_3$, MeCN, room temperature. [f] The *cis*/*trans* ratio with respect to the fluoro substituent at C3 and the hydrogen atom at C4 was determined by ^{19}F NMR spectroscopy of the crude product. [g] *cis*/*trans* (C3,C4): 1.3:1. [h] *trans*/*cis* (C3,C4): 4:1. [i] *trans*/*cis* (C3,C4): 1.7:1. [j] *trans*/*cis* (C3,C4): 1.6:1. [k] *trans*/*cis* (C3,C4): 3:1. [l] *trans*/*cis* (C3,C4): 4:1.

Heartened by these results, we next probed the value of our strategy for the development of a reagent-controlled asymmetric fluorocyclization. This preliminary study was carried out with allyl silane **7b**. An asymmetric fluorocyclization of this prochiral alkene was attempted with a chiral N–F reagent prepared in situ from Selectfluor and a cinchona alkaloid. This type of reagent was previously found to enable access to enantiomerically enriched allylic fluorides.[13] Pleasingly, the allyl silane **7b** reacted with Selectfluor/-$(DHQ)_2$PHAL in the presence of $NaHCO_3$ in MeCN at −20 °C to afford the enantiomerically enriched product (+)-**17b** in 70 % yield with 45 % *ee* (Scheme 4).[14] In accord with the results observed for the racemic substrate **7b**, only one diastereomer was formed, with the fluorine substituent and the silylmethyl group in a *trans* arrangement. This reaction is the first example of an asymmetric fluorocyclization that proceeds through a cascade fluorination–ring-closure process.

In conclusion, we have developed the first fluorocyclization of allyl silanes to give either *cis* or *trans* fluorocyclized products. A preliminary experiment demonstrated that this transformation is amenable to the development of an asymmetric variant. The temporary activation of alkenes with a silyl group is critical to address the reactivity problem encountered with nonsilylated alkenes and serves as a device for the regiocontrol of the fluorocyclization event. The use of easy-to-handle N–F reagents is a particularly attractive feature of the reaction. This study forms a foundation for the development of stereocontrolled syntheses of enantiomerically enriched mono- and polycyclic fluorinated heterocycles. Full details will be disclosed in due course.

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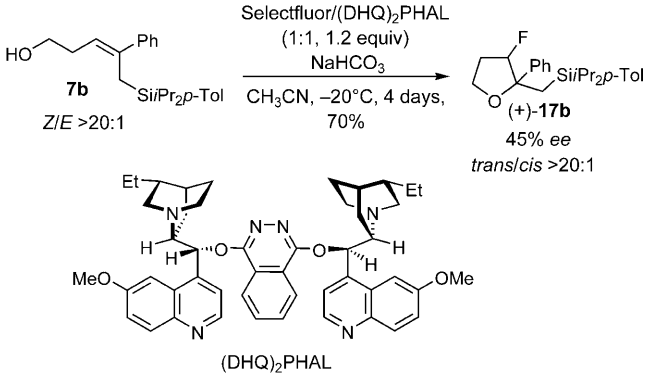

Scheme 4. Asymmetric fluorocyclization of allyl silane **7b**.

Keywords: allyl silanes · asymmetric synthesis · cyclization · fluorination · oxidative cleavage

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[7] Competitive desilylation probably occurs in the case of low-yielding reactions; see the Supporting Information for full details.

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[14] A control experiment was performed on a structurally related nonsilylated diol. The reaction of this substrate with Selectfluor/$(DHQ)_2$PHAL at room temperature was extremely slow. After 12 days, 48% of the starting material was recovered along with an aldehyde resulting from oxidation of the allylic alcohol in 16% yield and the fluorocyclized product (27% *ee*) in 36% yield. See the Supporting Information for details.

