Highly Diastereoselective Electrophilic Fluorination of Cyclic *syn*-β-Hydroxysilanes

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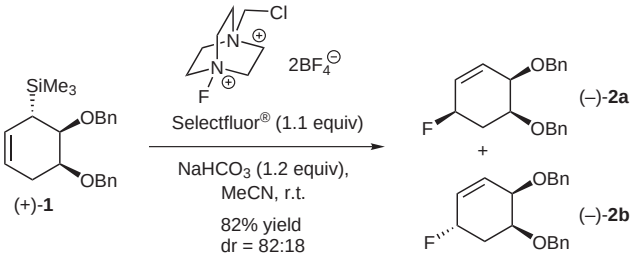
Received 17 November 2006

Abstract: A synthesis of enantioenriched fluorinated carbocycles has been developed combining a sequential enantioselective silyl-allylboration–ring-closing metathesis with a highly diastereoselective electrophilic fluorination.

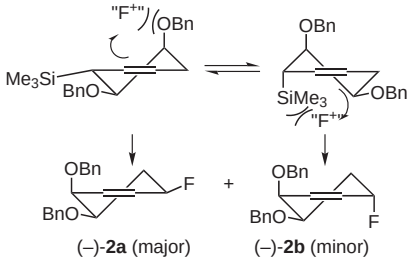
Key words: allylsilane, fluorine, stereoselectivity, silicon

Allylsilanes are versatile intermediates in organic synthesis. They react with numerous electrophiles such as carbonyl or imine compounds in highly stereoselective processes leading to the formation of new C–C bonds.[1] The paramount importance of organofluorine compounds in biological and medicinal chemistry prompted us to examine the reactivity of allylsilanes with electrophilic fluorinating reagents.[2] These studies led to the development of a novel transformation for the preparation of allylic fluorides, the fluorodesilylation of allylsilanes.[3] This electrophilic fluorination process takes advantage of the stabilizing β-effect of silicon and proceeds regioselectively with full transposition of the double bond, an observation consistent with an S_E2' mechanism. Chiral acyclic and cyclic allylsilanes were found to react with the fluorinating reagent Selectfluor®, leading to valuable fluorinated building blocks with the fluorine substituent on a stereogenic center.[4] Using this approach, enantioenriched fluorinated cyclitols were prepared from various readily available *anti*,*syn*-allylsilanes.[5] For these substrates, the preferential stereochemical outcome of the fluorination is the result of an *anti* addition of the fluorinating reagent with respect to the silyl group. Although high-yielding, a notable limitation of this methodology is the modest level of stereocontrol with the best diastereomeric ratio not exceeding 82:18 (Scheme 1).

The formation of two diastereomers upon fluorination originates from the relative stereochemistry of the starting allylsilane. Indeed, for the *anti*,*syn*-allylsilane precursor **1**, the preferential axial approach of the fluorinating reagent is hampered by either the benzyloxy group or the trimethylsilyl group when the cyclohexene adopts one or the other half-chair conformation (Scheme 2).

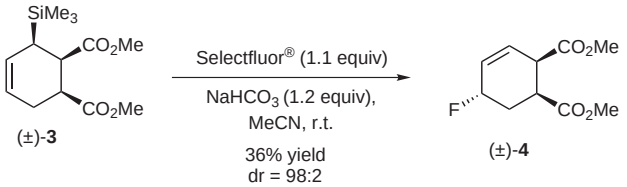


Scheme 1



Scheme 2

These results prompted us to examine the reactivity of all-*syn* cyclic allylsilanes as we anticipated that the *syn* positioning of all the substituents on the ring would prevent unfavorable interactions with the approaching fluorinating reagent, thereby leading to a highly diastereoselective fluorination process. This hypothesis was challenged with the fluorination of the racemic *syn*-allylsilane **3** prepared using a known *endo* Diels–Alder reaction as the key step.[5] Upon fluorination, the corresponding *anti*,*syn*-product was isolated in moderate yield but with excellent diastereocontrol. The only diastereomer seen in the crude reaction mixture resulted from a highly favorable axial attack of Selectfluor® taking place *anti* to the trimethylsilyl group, an approach free from steric interactions with the ring substituents (Scheme 3).

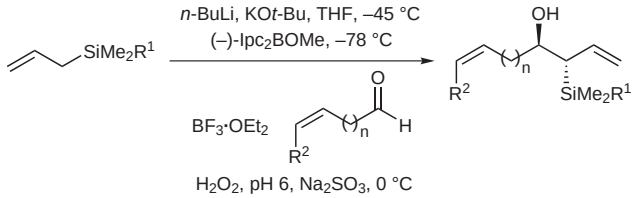


Scheme 3

SYNLETT 2007, No. 7, pp 1166–1168
Advanced online publication: 13.04.2007
DOI: 10.1055/s-2007-977428; Art ID: Y01606ST

This preliminary result encouraged us to further explore the electrophilic fluorodesilylation of nonracemic *syn*-allylsilanes, which we obtained using alternative synthetic routes as preliminary studies suggested that the Diels–Alder reaction of 1-trimethylsilylbutadiene was rather limited in scope. To prepare enantioenriched cyclic *syn*-allylsilanes, we selected a well-precedented synthetic sequence featuring an enantioselective silylallylboration followed by a ring-closing metathesis.[6] This highly convergent strategy developed by Roush et al. was particularly attractive as it allowed access to cyclic *syn*-allylsilanes of different ring size and with good diastereo- and enantioselectivity. A series of enantioselective silylallylborations were performed combining allyldiisopinocampheylboranes derived from trimethylallylsilane or dimethylphenylallylsilane with pentenal or *cis*-3-hexenal, two commercially available aldehydes. *cis*-3-Hexenal was used as a replacement for butenal as we anticipated that the additional ethyl group and the *Z*-geometry of the double bond should not affect the efficiency of the allylboration and of the subsequent ring-closing metathesis.[7] These reactions gave us access to four β-hydroxyallylsilanes **5**–**8** in moderate to good yields, excellent diastereocontrol and with enantiomeric purity circa 85%. The assignment of the *anti* stereochemistry for allylsilanes **5**–**8** was made by comparison with spectroscopic data of known and fully characterized structurally related compounds.[6] In a control experiment, a Peterson elimination carried out on allylsilane (–)-**7**, under basic conditions, gave exclusively a newly formed *Z* double bond, confirming the *anti* stereochemistry of the starting silane (Table 1).

Table 1 Synthesis of β-Hydroxyallylsilanes **5**–**8**

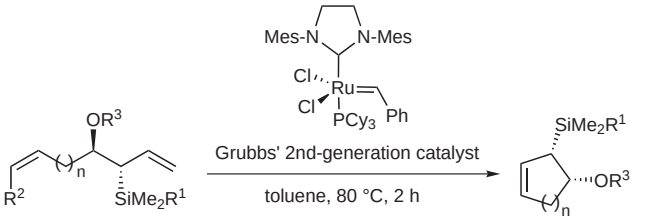


Entry	R^1	R^2	n	Product	Yield (%)	dr	ee (%)
1	Ph	H	2	(–)-**5**	70	>98:2	–[a]
2	Me	H	2	(+)-**6**	47	>98:2	–[a]
3	Ph	Et	1	(–)-**7**	45	>98:2	84
4	Me	Et	1	(+)-**8**	55	>98:2	85

[a] The ee could not be measured.

Acetylation, benzoylation or silylation of **5**–**8** gave the corresponding esters or silyl ethers **9**–**15** in good yields using conventional procedures. The RCM reactions of unprotected or protected allysilanes **7**–**15** were carried out using 5 mol% of the second generation Grubbs' catalyst (Table 2) and were complete within two hours at 80 °C in toluene. These ring closures led to the desired cyclic *syn*-β-hydroxyallylsilanes (+)-**16**–**23** in yields ranging from 42% to 90%. The lowest yield was obtained for the unprotected hydroxyallylsilane (+)-**7**. For the acyclic precursors (+)-**9**–**15**, the nature of the protecting group had little influence on the chemical yield.

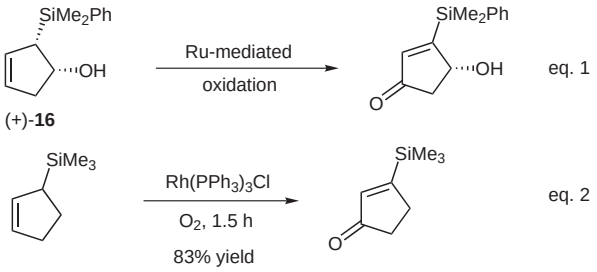
Table 2 Synthesis of Cyclic *syn*-β-Hydroxyallylsilanes (+)-**16**–**23**



Entry	Starting material	R^1	R^2	R^3	n	Product	Yield (%)
1	(–)-**7**	Ph	Et	H	1	(+)-**16**	42
2	(+)-**9**	Me	H	TBS	2	(+)-**17**	80
3	(±)-**10**[a]	Ph	H	Ac	2	(±)-**18**	87
4	(+)-**11**	Me	H	Ac	2	(+)-**19**	81
5	(+)-**12**	Ph	H	Bz	2	(+)-**20**	90
6	(+)-**13**	Me	H	Bz	2	(+)-**21**	85
7	(+)-**14**	Ph	Et	Bz	1	(+)-**22**	62
8	(+)-**15**	Me	Et	Bz	1	(+)-**23**	82

[a] Starting material prepared from allylborane derived from 9-BBN.

Notably, unless these ring-closed compounds were carefully purified to remove all traces of catalyst, we found that they were slowly converted into the corresponding oxidized β-silyl-2-cycloalkenones (Scheme 4, eq. 1). This regioselective oxidation process is not entirely unprecedented as Salomon et al. reported a similar transformation when structurally related cyclic allylsilanes were treated with a catalytic amount of tris(triphenylphosphine)rhodium(I) chloride in the presence of oxygen (Scheme 4, eq. 2).[8]



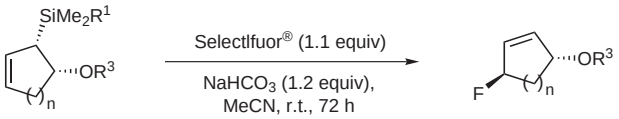
Scheme 4

With the enantioenriched cyclic *syn*-allylsilanes (+)-**16**–**23** in hand, we undertook the key electrophilic fluorodesilylation step. The fluorination of the unprotected substrate (+)-**16** was attempted using 1.1 equivalents of

Selectfluor® in acetonitrile at room temperature. No fluorinated products were formed under these conditions. The starting material was consumed to give a complex reaction mixture. Similarly, the fluorination of the *tert*-butyldimethylsilyl-protected precursor (+)-**17** was not successful and led to unidentified products, a result suggesting that deprotection took place under these conditions to release the corresponding unprotected allylsilane, a class of substrate found unsuitable for subsequent fluorination. In contrast, the protected silanes (±)-**18** and (+)-**19**–**23** were successfully converted into the corresponding allylic fluorides when the reactions were performed in acetonitrile in the presence of Selectfluor® (1.1 equiv) and sodium bicarbonate (1.2 equiv). The reactions were completed within 72 hours (Table 3). All electrophilic fluorodesilylations proceeded with full transposition of the double bond to afford cyclopentene or cyclohexene rings with the endocyclic double bond flanked by a fluorine substituent and the protected alcohol. The yields ranged from 56% to 90% and the level of diastereocontrol was consistently very good to excellent. In most cases, only one diastereomer was detected by ^{1}H NMR and ^{19}F NMR of the crude reaction mixtures. The level of diastereocontrol is not affected by the substituents on the silyl group or the ring size. In contrast, the protecting group of the secondary alcohol is important. Benzoyl-protected hydroxyallylsilanes (+)-**20**–**23** led to complete diastereocontrol (dr >98:2), whereas the corresponding acetyl-protected allylsilanes (±)-**18** and (+)-**19** gave two diastereomeric products in a ratio of 94:6 and 92:8, respectively. As hypothesized, the use of cyclic *syn*-allylsilanes gave predominantly the fluorinated products resulting from an *anti* approach of Selectfluor® with respect to the silyl group. Within experimental error, the enantiomeric excesses of the fluorinated products mirrored those measured for the starting allylsilanes.

In conclusion, we have developed an efficient approach to enantioenriched fluorinated carbocycles featuring an endocyclic allylic fluoride functional group, by electrophilic fluorodesilylation of the corresponding allylsilanes. For the *syn*-allylsilanes under investigation, the chirality transfer upon fluorination was highly efficient and proceeded preferentially *anti* with respect to the silyl group. The use of these novel fluorinated building blocks in the synthesis of biologically important targets is under way in our laboratory and will be reported in due course.

Table 3 Synthesis of Compounds **24**–**29**



Entry	Starting material	R^1	R^3	n	Product	Yield (%)	dr	ee[b]
1	(±)-**18**	Ph	Ac	2	(±)-**24**	69	94:6[a]	–[c]
2	(+)-**19**	Me	Ac	2	(+)-**25**	90	92:8[a]	–[c]
3	(+)-**20**	Ph	Bz	2	(+)-**26**	75	>98:2	77
4	(+)-**21**	Me	Bz	2	(+)-**27**	75	>98:2	83
5	(+)-**22**	Ph	Bz	1	(+)-**28**	56	>98:2	80
6	(+)-**23**	Me	Bz	1	(+)-**29**	79	>98:2	86

[a] Inseparable mixture of diastereomers by column chromatography.
[b] The ee determined by chiral HPLC.
[c] The ee could not be determined by chiral HPLC.

Acknowledgment

We thank the EPSRC and AstraZeneca for generous financial support (S.P.).

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