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Synthesis of Novel Enantiopure Fluorinated Building Blocks from Acyclic Chiral Allylsilanes

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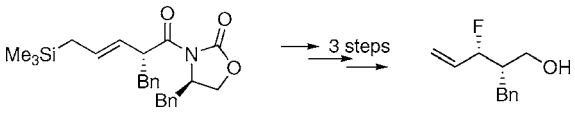
ABSTRACT



Homochiral β-fluorinated γ,δ-unsaturated carboxylic acids with an allylic fluorinated stereogenic center are available from the corresponding enantiopure allylsilanes. The key step for introduction of the fluorine substituent is an electrophilic fluorodesilylation reaction carried out in the presence of Selectfluor. Reduction of the resulting β-fluorinated pentenoic acid into the corresponding fluorinated alcohol was also performed leading to the formation of an enantiopure second-generation fluorinated building block.

The extraordinary range of applications of fluorinated compounds has stimulated the search for inventive and efficient approaches to their synthesis.[1] The incorporation of a fluorine substituent α to a carbonyl group is now well established with several reagent-based enantioselective fluorinations of enolates or silyl enol ethers having been reported in the literature.[2] More recently, it has been found that transition-metal complexes and small organic molecules are efficient catalysts for the formation of enantioenriched α-fluorinated carbonyl derivatives.[3] By way of contrast, only a few synthetic routes have been developed for the preparation of homochiral fluorinated building blocks other than α-fluorinated carbonyl compounds. For example, a general methodology for the preparation of enantiopure β-fluorinated γ,δ-unsaturated carboxylic acids with a stereogenic fluorinated allylic carbon has yet to be developed.[4] As part of a research program aimed at developing innovative methodologies for the preparation of fluorinated compounds, we have reported that nonaromatic organosilanes, such as vinylsilanes, allylsilanes and allenylmethylsilanes, react with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluorobo-

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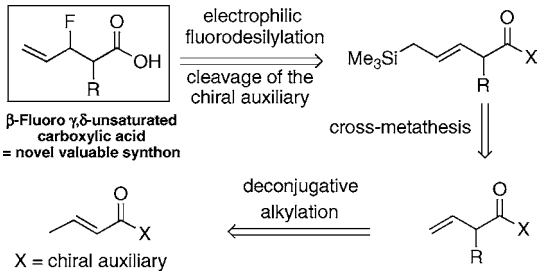
rate) (Selectfluor) to give structurally diverse fluorinated compounds. Indeed, using this methodology for electrophilic fluorination, fluoroalkenes, difluorinated amides, ethers or alcohols, allylic fluorides and fluorodienes were made available.[5] In this paper, we now report the first application of electrophilic fluorodesilylation on acyclic homochiral allylsilanes to prepare enantiopure β-fluorinated α-substituted carboxylic acids with an allylic monofluorinated stereogenic center (Scheme 1).

Scheme 1. Retrosynthetic Approach to Enantiopure β-Fluorinated α-Substituted Carboxylic Acids

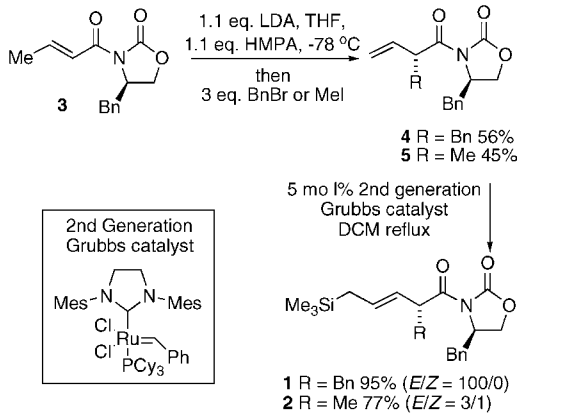


These novel compounds are valuable synthetic intermediates as they provide numerous opportunities for subsequent functional manipulation of the double bond or the carboxylic acid group.[6] In this paper, we also describe how these novel homochiral fluorinated compounds were reduced to give second-generation building blocks with two stereocenters, one of them being fluorinated.

The enantiopure chiral allylsilanes that we employed were generated by a cross-metathesis coupling of allyltrimethylsilane with the corresponding enantiopure deconjugated carboxylic acid derivative. To prepare these enantiopure α-functionalized building blocks we opted to use Evans-type oxazolidinones as the chiral auxiliaries. This approach raises several points of interest such as whether the existing stereocenters of the homochiral allylsilane will exert some degree of stereocontrol in the fluorination step or whether the key fluorinated intermediate will be subject to elimination or epimerization upon cleavage of the chiral auxiliary. Indeed, there is no precedent in the literature about the way in which the presence of a stereocenter on the allylic carbon not bearing the silyl group might control the diastereoselectivity of electrophilic fluorination with a reagent such as Selectfluor or on the sensitivity of the resulting β-fluorinated product to elimination. However, before addressing such matters, it was necessary to validate the feasibility of the proposed synthetic scheme.

The asymmetric synthesis of two representative homochiral allylsilanes **1** and **2** began with a diastereoselective deconjugative alkylation of the known acylated oxazolidinone[7] **3** with benzyl bromide or methyl iodide using a mixture of THF in the presence of HMPA as the solvent system (Scheme 2).

Scheme 2. Syntheses of Enantiopure Allylsilanes **1** and **2**



With benzyl bromide as the electrophile, this reaction gave product **4** in 56% yield as a single diastereomer after purification. It was assumed that the benzyl group of the chiral auxiliary was shielding the β face of the *Z*-enolate and that the alkylated compound was indeed formulated as **4**. This was proved unambiguously by X-ray analysis.[8] Similarly, the methylation of **3** provided, after purification, compound **5** as a single diastereomer with the configuration of the newly formed stereocenter assigned by analogy with **4**. Upon cross-metathesis with three equivalents of allyltrimethylsilane in the presence of 5 mol % of the second generation Grubbs catalyst at reflux in DCM, the terminal double bond of **4** and **5** was functionalized to give the desired homochiral allylsilanes **1** and **2** in 95% and 77% isolated yield, respectively. Compound **1** was formed as the sole *E*-isomer, but a mixture of *E*- and *Z*-isomers was formed for the methyl-substituted allylsilane **2**. We also prepared the enantiopure allylsilane **6** released from the chiral auxiliary.[8]

We next studied the reactivity of these various allylsilanes toward Selectfluor (Table 1).

The fluorodesilylation of allylsilane **1** with Selectfluor in acetonitrile occurred smoothly at room temperature and afforded the corresponding allylic fluorides *anti*-**7** and *syn*-**7** with an overall chemical yield of 95%. The two diastereomers were formed as a roughly 1/1 mixture (Table 1, entry 1). Changing the reaction solvent or using additives did not improve significantly the level of diastereocontrol (Table 1,

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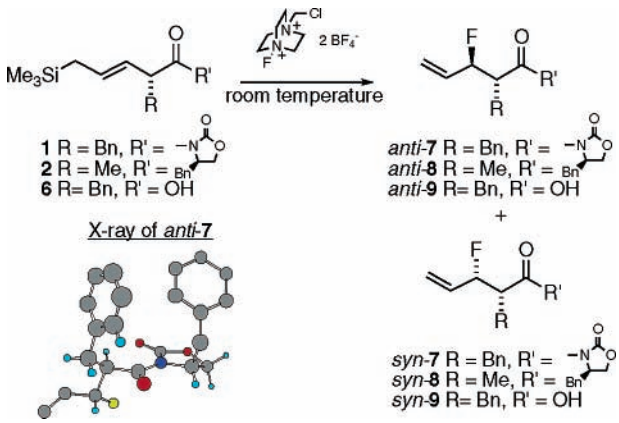
(8) For details, see the Supporting Information.

Table 1. Fluorodesilylation of Enantiopure Allylsilanes 1, 2, and 6



entry	allylsilane	conditions	product	yield (%)	ratio *anti*/*syn*
1	**1**	MeCN	**7**	95	1.2:1
2	**1**	acetone, $NaHCO_3$	**7**	100[a]	2:1
3	**1**	MeCN, $NaHCO_3$	**7**	100[a]	1.4:1
4	**1**	acetone, $NaHCO_3$, LiCl	**7**	<50[a]	2:1
5	**2**	MeCN	**8**	82	1:1
6	**6**	MeCN	**9**	61	1:1

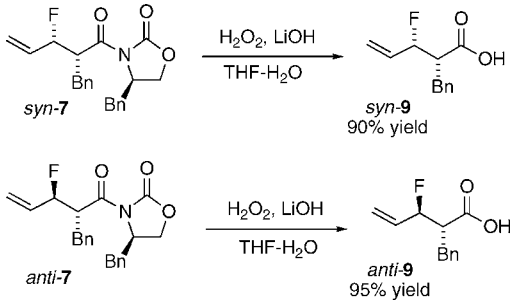
[a] Conversion.

entries 2−4). The two diastereomers *anti*-**7** and *syn*-**7** were separated by careful column chromatography. Their relative stereochemistry was determined unambiguously by X-ray crystallography of the *anti*-**7** isomer.[8] Similarly, a high yield of the desired β-fluorinated α-methylated carboxylic acid derivative was obtained upon treatment of allylsilane **2** with Selectfluor in acetonitrile, the latter process providing the two separable diastereomers *anti*-**8** and *syn*-**8** in equal amounts in an 82% overall yield (Table 1, entry 5). Upon treatment with Selectfluor, allylsilane **6** afforded the two diastereomeric β-fluorinated acids *anti*-**9** and *syn*-**9** as a 1/1 mixture in 61% yield (Table 1, entry 6). These two β-fluorinated acids could not be separated by SiO_2 column chromatography. These data suggested that the poor diastereocontrol observed is not the result of a mismatch of the two stereogenic centers remote from the reacting site in compounds **1** or **2**.

The chiral auxiliary in the *syn* β-fluorinated carboxylic acid derivative **7** could be hydrolytically cleaved with H_2O_2 and LiOH in a THF/H_2O mixture. This transformation proved remarkably efficient, allowing the *syn*-β-fluorinated α-benzylated carboxylic acid **9** to be recovered in 90% yield. No side-product resulting from an elimination process or from partial epimerisation could be detected in the crude reaction mixture or recovered after purification. Similarly, *anti*-**7** was easily converted to the desired carboxylic acid *anti*-**9** in excellent yield (Scheme 3).

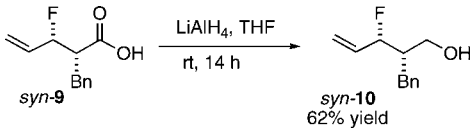
The fluorinated carboxylic acid *syn*-**9** was subjected to further functional group manipulation. The fluorinated alcohol *syn*-**10** was obtained in 62% yield by reduction of the carboxylic acid using $LiAlH_4$ in THF at room temperature

Scheme 3. Synthesis of the β-Fluorinated Carboxylic Acids



(Scheme 4). This alcohol could not be prepared from the fluorinated intermediate *syn*-**7** by direct reductive cleavage of the chiral auxiliary, as a competitive elimination process took place leading to the formation of the nonfluorinated diene.

Scheme 4. Reduction of the β-Fluorinated Carboxylic Acid *syn*-**9** into the Corresponding Alcohol *syn*-**10**



In summary, we have shown that the concept of electrophilic fluorodesilylation can be applied to acyclic chiral allylsilanes for the preparation of enantiopure α-substituted β-fluorinated carboxylic acids featuring an allylic fluoride. These compounds can be reduced to the corresponding fluorinated alcohols. These novel fluorinated building blocks are difficult to obtain by other routes. The main limitation of our strategy is the poor level of diastereocontrol for the fluorodesilylation step. The existence of several reactive conformations for the starting chiral allylsilane is likely to be responsible for this limitation. The presence of an additional stereogenic center on the carbon bearing the silyl group combined with the use of *Z*-allylsilane might allow for better diastereoselectivity in the future. The synthesis of these more elaborated allylsilanes and a study of their reactivity in the presence of Selectfluor is currently ongoing in our laboratory.

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Supporting Information Available: Experimental details and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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