Chiral Allylic Fluorides

Regio- and Enantioselective Synthesis of Allylic Fluorides by Electrophilic Fluorodesilylation of Allyl Silanes**

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Organofluorine compounds are extremely rare in nature and it is only recently that a fluorinase enzyme was discovered that catalyzes carbon–fluorine bond formation.[1] However, the chemistry of bioactive fluoroorganic compounds is a rapidly developing area of research because of their importance in biomedical applications.[2] Methodologies for enantioselective fluorination (C–F bond formation) are still in demand despite recent advances in this field, which include the synthesis of new chiral N–F reagents and the development of the first catalytic enantioselective fluorination of β-ketoesters.[3] Most of these studies have been aimed at creating an efficient and general process for the enantioselective preparation of α-fluorocarbonyl compounds. In contrast, methods for the enantioselective preparation of allylic fluorides are rare, and only one protocol that uses electrophilic N–F reagents is known.[4]

The nucleophilic displacement of allylic alcohols with reagents such as (diethylamino)sulfur trifluoride (DAST) has been used to produce allylic fluorides, but this transformation suffers from problems of low stereo- and regioselectivity as a result of allylic transposition.[5] Important exceptions have been reported in the area of sugar chemistry in which anchimeric assistance minimizes these problems, and in transition-metal chemistry, as exemplified by the work of Gree et al.[6] However, the total absence of a strategy based on the use of an enantioselective electrophilic fluorination process prompted us to embark on a study aimed at the development of such a reaction.

The electrophilic cleavage of activated silanes provides the synthetic organic chemist with many opportunities.[7] These reactions take advantage of the β effect of a silicon center and thus require substrates that have adjacent π systems, such as vinyl, aryl, and allyl silanes. With the appearance of electrophilic sources of fluorine, the concept of electrophilic fluorodesilylation emerged,[8] and our group recently reported the first fluorodesilylation reactions of vinyl

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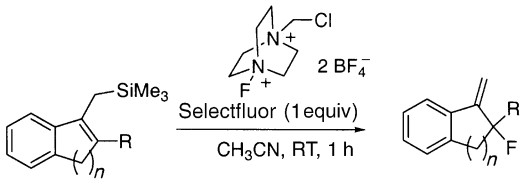
silanes with the electrophilic fluorinating reagent Selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)).[9] As an extension of this methodology, we now report a conceptually new approach to chiral nonracemic allylic fluorides, based on the enantioselective electrophilic fluorodesilylation of allyl silanes. We anticipated that we could take advantage of both the β effect of a silicon center and the availability of new enantiopure N–F reagents to address the problems of regio- and enantioselectivity, respectively.

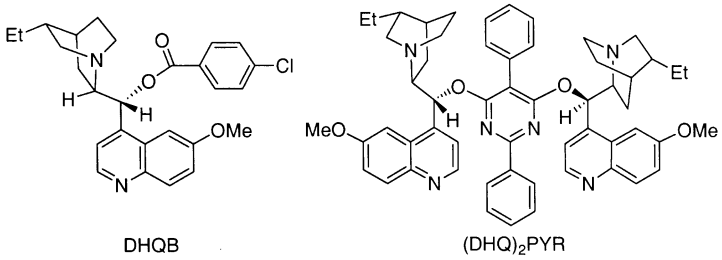
We carried out a preliminary study with the model allyl silanes **1a–f**, all of which were prepared according to literature procedures.[10] A screening of several commercially available N–F compounds revealed Selectfluor to be the best reagent for the electrophilic fluorodesilylation of compound **1a**. All allyl silanes **1a–f** reacted at room temperature in MeCN with 1 equivalent of Selectfluor to afford the corresponding allylic fluorides within just 1 hour. Compounds **2a** and **2c–f** were isolated in yields ranging from 63 to 78%. In the reaction of compound **1b** to give **2b**, 100% conversion was observed. However, the fluorinated product **2b** was unstable to purification and unfortunately no yield can be reported for this compound. These results showed that the electrophilic fluorodesilylation of allyl silanes was feasible, and that it occurred at a vastly accelerated rate relative to the fluorination of vinyl silanes (Scheme 1).[9]



1a $n=1$ R = H — (±)-**2a** $n=1$ R = H 65%
1b $n=1$ R = Me — (±)-**2b** $n=1$ R = Me 100% (conversion)
1c $n=1$ R = Bn — (±)-**2c** $n=1$ R = Bn 74%
1d $n=2$ R = H — (±)-**2d** $n=2$ R = H 71%
1e $n=2$ R = Me — (±)-**2e** $n=2$ R = Me 63%
1f $n=2$ R = Bn — (±)-**2f** $n=2$ R = Bn 78%

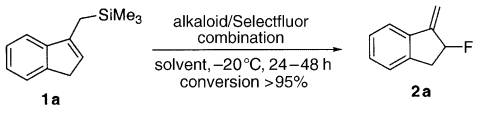
Scheme 1. Electrophilic fluorodesilylation of allyl silanes **1a–f** with Selectfluor.

These preliminary results encouraged us to investigate the use of enantiopure *N*-fluorocinchona alkaloids in an enantioselective version of this new reaction. In recent work by Shibata et al.[11] and Cahard and co-workers[12] on the fluorination of silyl enol ethers with *N*-fluorocinchona alkaloids, α-fluorocarbonyl compounds were prepared with *ee* values of up to 91%. *N*-Fluorocinchona alkaloids have proved to be efficient reagents and are readily prepared from commercially available compounds. We therefore explored the efficiency of this class of reagent for the enantioselective synthesis of allylic fluorides from the corresponding allyl silanes (Scheme 2, Table 1). After a systematic screening of several commercially available cinchona alkaloids used in combination with Selectfluor, we found that the $(DHQ)_2PYR$/Selectfluor combination in MeCN at −20°C effected the enantioselective fluorination of **1a** to furnish



Scheme 2. Representative cinchona alkaloids.

Table 1: Variation of the cinchona alkaloid in the enantioselective fluorination of **1a**.



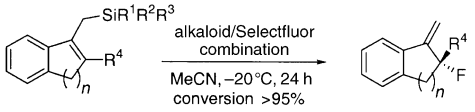
Entry	Alkaloid[a]	Solvent	*ee* [%]
1	DHQB	CH_3CN	28
2	DHQMQE	CH_3CN	32
3	DHQPE	CH_3CN	48
4	$(DHQ)_2PYR$	CH_3CN	60
5	$(DHQ)_2PYR$	CH_2Cl_2	53

[a] DHQMQE = dihydroquinine 4-methyl-2-quinoyl ether; DHQPE = dihydroquinine 9-phenanthyl ether.

compound **2a** in 24 hours, with excellent conversion (> 95%) and 60% *ee* (Table 1, entry 4). Other systems were less efficient, such as DHQB and DHQPE, which yielded **2a** with *ee* values of 28 and 48%, respectively (Table 1, entries 1 and 3). No beneficial effect was observed upon lowering the temperature of the reaction, which led to longer reaction times with no improvement in the enantioselectivity. The use of CH_2Cl_2 instead of MeCN resulted in a decreased enantiomeric excess (Table 1, entries 4 and 5). Furthermore, we found the use of the fluorinated cinchona alkaloids as isolated reagents to be problematic, as the chemical yields observed were less satisfactory.[12,13] In subsequent studies we therefore used the protocol developed by Shibata et al. for the preparation of these reagents in situ.[11]

We next investigated the effectiveness of our system for the enantioselective fluorination of allyl silanes **1c–h**.[14] As can be seen from the results summarized in Table 2, the corresponding allylic fluorides could be formed with very high conversion (in all cases greater than 95%) and with moderate to excellent *ee* values. Of the substrates tested, the benzyl-substituted allyl silane **1c** gave the best results, as reflected by the very high enantiomeric excess observed (96% *ee*) for the allylic fluoride **2c**. As was also observed in the reactions of **1a**, the best reagent for this transformation was $(DHQ)_2PYR$/Selectfluor, which gave **2c** with 96% *ee*. DHQMQE was also very effective and promoted the formation of **2c** with 93% *ee* (Table 2, entries 2 and 4). For allyl silanes **1d–f**, the *ee* values of the products were usually lower, and $(DHQ)_2PYR$ and DHQPE were the alkaloids of choice (Table 2, entries 5–13). As a general trend, we found that better *ee* values were observed when the substrates had a larger R^4 substituent. Indeed, substrate **1f**, with a benzyl group as the R^4 substitu-

Table 2: Enantioselective fluorodesilylation of allyl silanes **1c–h**.



Entry	**1**	*n*	R^1	R^2	R^3	R^4	Alkaloid	Product[a]	*ee* [%]
1	**c**	1	Me	Me	Me	CH_2Ph	DHQB	(*R*)-**2c**	85
2	**c**	1	Me	Me	Me	CH_2Ph	$(DHQ)_2PYR$	(*R*)-**2c**	96
3	**c**	1	Me	Me	Me	CH_2Ph	DHQPE	(*R*)-**2c**	84
4	**c**	1	Me	Me	Me	CH_2Ph	DHQMQE	(*R*)-**2c**	93
5	**d**	2	Me	Me	Me	H	DHQB	**2d**	9
6	**d**	2	Me	Me	Me	H	$(DHQ)_2PYR$	**2d**	22
7	**d**	2	Me	Me	Me	H	DHQPE	**2d**	30
8	**e**	2	Me	Me	Me	Me	DHQB	(*R*)-**2e**	8
9	**e**	2	Me	Me	Me	Me	$(DHQ)_2PYR$	(*R*)-**2e**	45
10	**e**	2	Me	Me	Me	Me	DHQPE	(*R*)-**2e**	21
11	**f**	2	Me	Me	Me	CH_2Ph	DHQB	(*S*)-**2f**	53
12	**f**	2	Me	Me	Me	CH_2Ph	$(DHQ)_2PYR$	(*S*)-**2f**	83
13	**f**	2	Me	Me	Me	CH_2Ph	DHQPE	(*S*)-**2f**	64
14	**g**	1	Me	Me	Ph	H	DHQB	**2a**	35
15	**g**	1	Me	Me	Ph	H	DHQMQE	**2a**	35
16	**g**	1	Me	Me	Ph	H	$(DHQ)_2PYR$	**2a**	73
17	**h**	1	Ph	Ph	Ph	H	$(DHQ)_2PYR$	**2a**	87

[a] Absolute configuration not determined for **2a** or **2d**.

ent, was fluorinated in the presence of $(DHQ)_2PYR$ to give **2f** with 83% *ee* (Table 2, entry 12). We then investigated the influence of the silyl substituent on the enantiomeric excess of the product (Table 2, entries 14–17). In the reaction of **1g**, which has a dimethylphenylsilyl substituent instead of the trimethylsilyl group, a slight improvement of the *ee* values of **2a** was observed for most alkaloids with no significant decrease of reactivity, relative to **1a**. The best result was obtained in the presence of $(DHQ)_2PYR$, which allowed the formation of the corresponding allylic fluoride **2a** with 73% *ee* (Table 2, entry 16). By further increasing the steric bulk of the substrate with a triphenylsilyl group, **2a** could be prepared (from **1h**) with 87% *ee* (Table 2, entry 17). It is therefore apparent that the steric bulk of the silyl group itself is important with regard to enantioselectivity. The levels of enantioselectivity observed in the reactions to form the allylic fluorides **2a** and **2c–g** compare favorably with the best *ee* values observed by Shibata et al., and Cahard and coworkers, for fluorinated ketones.[11,12]

To assign the absolute configurations of the products, compounds **2c**, **2e**, and **2f** were prepared by an alternative asymmetric method.[14] We assume that the reactive conformation of the *N*-fluorocinchona alkaloids is similar to the one suggested by Shibata et al., as the reactions described herein were performed under similar conditions to those for the fluorination of analogous silyl enol ethers.[11] However, there might be significant differences in the reactive conformations of the allyl silanes relative to analogous silyl enol ethers, as well as in their approach toward the chiral N–F reagent. The observation that fluorinated products are formed with different *ee* values from allyl silanes than from analogous silyl enol ethers in the presence of the same alkaloid supports this hypothesis. We are currently exploring these mechanistic aspects to better understand this novel enantioselective transformation.

In conclusion, we have described herein the first regio- and enantioselective route to allylic fluorides from the corresponding allyl silanes. The concept of electrophilic fluorodesilylation combined with the use of enantiopure *N*-fluorocinchona alkaloids provided a highly efficient method for the preparation of allylic fluorides with *ee* values of up to 96%. A clearer understanding of the mechanism by which this reagent-controlled enantioselectivity originates will require a more detailed study. Furthermore, the extension of this expeditious route to other allyl silanes is the object of current work in our laboratory.

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[14] For details, see Supporting Information.

