Angewandte Chemie

Enantioselective Fluorination

Enantioselective Formation of Stereogenic Carbon–Fluorine Centers by a Simple Catalytic Method**

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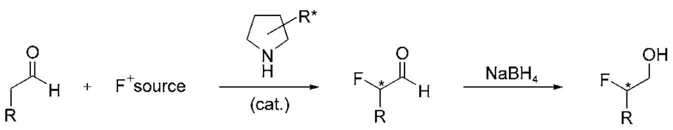
The unique properties of fluorinated molecules have led to the wide interest in these compounds in organic syntheses, medicinal and agricultural chemistry, as well as materials sciences.[1] This interest has been manifested in the enormous number of publications relating to organofluorine compounds.[2] In this context, structures in which the fluorine atom is attached to a chiral center are gaining increasing importance. Despite this great interest, there is still no simple and direct catalytic method to obtain optically active fluorinated compounds.[3] The development of stable electrophilic fluorine sources such as Selectfluor, 1-fluoropyridinium salts, and *N*-fluorodibenzenesulfonimide (NFSI) has marked an important milestone for the realization of these reaction types.[4] As a consequence, the first examples of catalytic enantioselective fluorinations of β-keto esters that apply both metal- and organocatalytic approaches were reported.[5,6] Recently, these methods were also applied toward the synthesis of chiral fluorinated β-keto phosphonates.[7]

To our knowledge, no enantioselective catalytic method for the direct α-fluorination of aldehydes has been described. Recently, asymmetric carbon–heteroatom bond formation reactions that proceed via enamine intermediates were reported in which chiral secondary amines are used as catalysts.[8–11] These procedures also showed promise for application toward fluorination reactions. So far, the only access to α-fluorinated aldehydes uses a chiral auxiliary strategy that involves a multistep process.[12] The authors state that the resulting α-fluorinated products decompose rapidly on silica and as a result, they must be derivatized directly from the crude mixture.

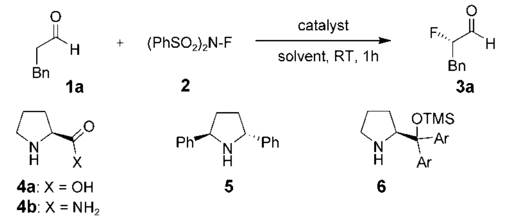
Herein we present a new and easy access to stereogenic carbon–fluorine centers through the direct enantioselective α-fluorination of aldehydes with an organocatalytic approach. The general reaction is shown below, including the functionalization of α-fluorinated aldehydes in situ to optically active α-fluoroalcohols, which are important organic compounds[1] and which have found direct use in liquid crystal compositions.[13]



As fluorine is the most electronegative element, the reaction conditions must be chosen carefully under the following terms: 1) *N*-fluorination of the catalyst is likely; therefore, the α-fluorination reaction must be faster than this process. 2) Undesired racemization and difluorination events must be rigorously avoided. Taking these considerations into account, we started our screening experiments with catalysts that had been previously applied with success in asymmetric C–Cl[10b,c] and C–S[11] bond formation reactions. The results of the screening in which 3-phenylpropanal (**1a**) was used as substrate with the commercially available NFSI (**2**) as the fluorinating reagent are presented in Table 1.

The use of L-proline (**4a**), L-prolinamide (**4b**), and the C_2-symmetric catalyst **5** gave low yields and moderate enantioselectivities (Table 1, entries 1–3). This behavior was not a surprise, as the chemical and physical properties of fluorine amplify some of the problems that are encountered in the related chlorination reaction. Because of the high electronegativity of fluorine, the catalyst easily forms enamine

Table 1: Screening of catalysts and reaction conditions for the α-fluorination of 3-phenylpropanal (**1a**) with NFSI (**2**) as F^+ ion source.[a]



Entry	**1a** [equiv]	**2** [equiv]	Cat. [mol%]	Solvent	Conv. [%][b]	*ee* [%][c]
1	1	1.2	**4a** (20)	CH_2Cl_2	<10	30
2	1	1.2	**4b** (20)	CH_2Cl_2	24	40
3	1	1.2	**5** (20)	CH_2Cl_2	17	48[d]
4	1	1.2	**6** (20)	CH_2Cl_2	40	87
5	1	1.2	**6** (20)	MeCN	61	93
6	1	1.2	**6** (20)	MTBE	53	93
7	1	1.2	**6** (10)	MTBE	62	93
8	1	1.2	**6** (5)	MTBE	74	93
9	1.5	1	**6** (5)	MTBE	88	93
10[e]	1.5	1	**6** (1)	MTBE	>90	93
11[f]	1.5	1	**6** (0.25)	MTBE	90	93

[a] The catalyst and the aldehyde were mixed in the solvent at room temperature for 15 min before addition of NFSI (0.2 mmol); Ar = Ph-3,5-$(CF_3)_2$; Bn = benzyl. [b] Conversion determined by GC after 1 h; entries 1–5: incomplete consumption of NFSI; entries 6–10: full consumption of NFSI (the difference to 100% conversion refers to the difluorinated product). [c] Percent *ee* values were determined by GC on a chiral-phase column (Astec G-TA) and verified by HPLC (Chiralcel OJ column) after reduction of **1a** to the alcohol and acetylation; for details, see Supporting Information. [d] 23% *ee* after 3 h. [e] Conversion and % *ee* were determined by GC after 2 h. [f] 10 mmol NFSI, 8 h.

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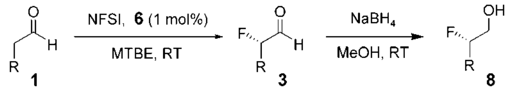
species with both the starting material and the fluorinated product. The enhanced acidity of the α proton in the fluorinated product even favors its enamine formation, as discussed below. Furthermore, in contrast to the chlorination reaction, the small fluorine atom does not contribute to an added steric shielding that would disfavor the enamine equilibrium. This second enamine formation causes either difluorination or racemization.

Use of the silylated prolinol derivative **6** as a catalyst significantly improved the conversion and enantioselectivity of the reaction (Table 1, entry 4). NMR spectroscopy studies revealed that the catalyst is slowly desilylated upon mixing with NFSI. The desilylated **6** shows very low catalytic activity (10 % conversion after 20 h and 61 % *ee*). Therefore, the low conversion was caused by inactivation of the catalyst. We rationalized that the solvent could influence the reaction rate and deprotection of the catalyst. Acetonitrile still did not lead to full conversion, because of catalyst degradation (entry 5). However, an improvement was observed with methyl-*tert*-butyl ether (MTBE); all reactions performed in this solvent showed complete consumption of NFSI, but a significant amount of the difluorinated product was formed as well. Lowering the amount of catalyst to 5 mol % decreased the difluorination problem. Finally, the use of only 1 mol % of catalyst **6** and an excess of the aldehyde **1a** resulted in more than 90 % yield of the monofluorinated product within 2 h (entry 10). Performing the reaction on a larger scale (10 mmol) allowed us to further decrease the catalyst loading to only 0.25 mmol %. Furthermore, 90 % conversion was obtained, maintaining the enantioselectivity of 93 % *ee* after 8 h reaction time (entry 11). Other commercially available F^+ ion sources such as Selectfluor turned out to be unsuitable for the reaction, as the silylated catalyst **6** is immediately deprotected in the presence of the BF_4^- counterion.

With these optimized conditions in hand, the general scope of the reaction was probed by application to a series of aldehydes. As mentioned above, α-fluorinated aldehydes easily decompose on silica gel.[12] Notably, α-fluoroaldehydes are more volatile than the starting compounds. The formation of α-fluorinated aldehydes was confirmed by GC–MS and NMR spectroscopic analysis of the crude reaction mixtures. The α-fluoroaldehydes **3a**, **3d**–**f**, and **3h** were reduced directly to the resulting β-fluoroalcohols without loss of enantiomeric excess, and the isolated yields given in Table 2 confirm the high conversion in the organocatalytic enantioselective fluorination step. For the volatile substrates **1b**, **1c** and **1g**, yields were calculated according to GC analysis of the crude reaction mixtures before reduction to the β-fluoroalcohols. The results are presented in Table 2.

Table 2: Organocatalytic enantioselective α-fluorination of aldehydes by NFSI, catalyzed by **6** (1 mol %).[a]



Entry	Aldehyde	R	*t* [h]	Yield [%]	*ee* [%][b]
1[c]	**1b**	Pr	6	**3b** >95	96
2[c]	**1c**	Bu	28	**3c** >90	91
3[d,e]	**1d**	Hex	4	**8d** 55	96
4[d]	**1e**	$BnO(CH_2)_3$	2	**8f** 64	91
5[d]	**1a**	Bn	2	**8a** 74	93
6[d]	**1f**	Cy	5	**8g** 69	96
7[c]	**1g**	*t*Bu	2	**3e** >90	97
8[d]	**1h**	1-Ad	2	**8h** 75	96

[a] Compound **2** (0.25 mmol) was added to a mixture of **1** (0.38 mmol) and **6** (0.0025 mmol) in MTBE (0.5 mL) at room temperature for the stated period of time; Ad = adamantyl; Bn = benzyl; Cy = cyclohexyl. [b] Percent *ee* values were determined by GC or HPLC on a chiral phase; see Supporting Information for separation conditions. [c] Yields were based on GC analysis of the crude mixtures before reduction owing to the volatility of the products. [d] Isolated yields of the alcohol after reduction with $NaBH_4$. [e] 1.1 equiv NFSI; 1 equiv aldehyde.

For all examples in which a variety of different R substituents were evaluated, excellent enantioselectivities of more than 91 % *ee* were obtained, and the enantioenriched products were formed in good yields with only 1 mol % of catalyst **6** (Table 2). In the case of substrate **1a** in reaction with 20 mol % of the catalyst, more than 90 % of the catalyst could be recovered after flash chromatography.

The absolute configuration of the β-fluoroalcohols was determined to be *S* by comparison of their optical rotation values with those reported in the literature.[14] The stereochemical outcome of the reaction can be explained by the formation of an *E*-configured enamine, where the sterically demanding substituent of the pyrrolidine ring shields the *Re* face of the enamine.

This hypothesis is confirmed by a model based on DFT calculations of the optimized enamine intermediate at the B3LYP/6-31G(d) level of theory.[15] The lowest-energy structure of the enamine intermediate is presented in Figure 1. The intermediate structure shows that one of the 3,5-di(trifluoromethyl)phenyl groups covers the *Re* face of the enamine. As a consequence, the electrophilic F^+ ion attack occurs from the *Si* face, providing excellent enantioselectivities. This model is in agreement with our experimental observations.

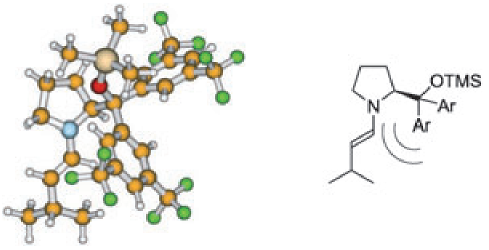


Figure 1. DFT-calculated model of the optimized structure of the enamine formed by isovaleraldehyde and catalyst **6**; Ar = Ph-3,5-$(CF_3)_2$.

The high configurative stability of the α-fluorinated products observed under the reaction conditions is a surprising phenomenon, especially as difluorination is also observed under certain reaction conditions. Figure 2 illustrates our theory to explain such stability of the optically active products. As shown in Figure 1, one of the 3,5-di(trifluoromethyl)phenyl groups points towards the reactive center of the enamine **A**. In the preferably formed (*S*,*S*)-**B** imminium ion, the remaining hydrogen atom is situated in between the

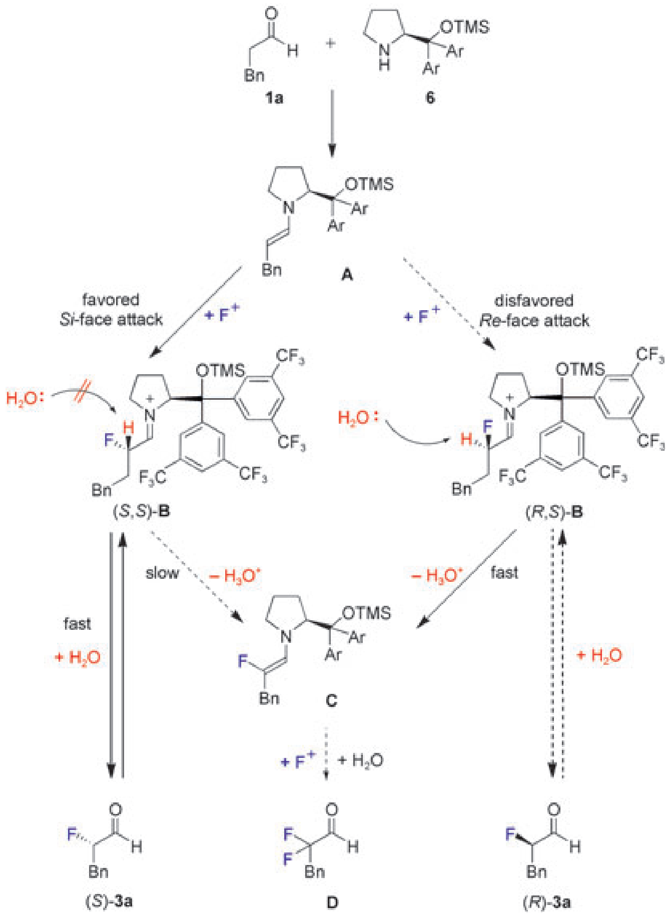
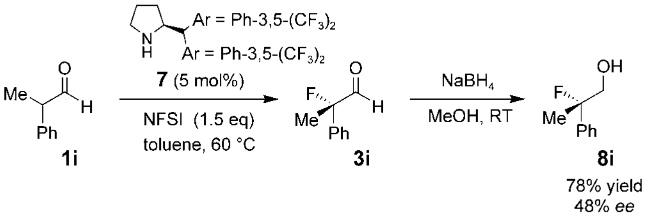


Figure 2. Explanation of the observed configurative stability of the α-fluorinated aldehydes under the reaction conditions in accordance with kinetic resolution experiments; Ar = Ph-3,5-$(CF_3)_2$.

fluorine atom and the shielding substituent of the catalyst. This hydrogen atom is thus placed in a sort of hydrophobic pocket, which prevents its abstraction as a proton from nucleophilic attack by a water molecule. On the other hand, in the disfavored (*R*,*S*)-**B** intermediate, the hydrogen atom is placed on the open *Si* face and can be easily abstracted to form enamine intermediate **C**. We envisaged that a kinetic resolution experiment could support this hypothesis: a racemic mixture of α-fluoroaldehyde **3a** was slowly converted (20 % in 4 h) to the difluorinated product **D** in the presence of 0.5 equiv NFSI (**2**) and 1 mol % of the catalyst **6**. This experiment clearly revealed that (*R*)-**3a** was consumed faster than (*S*)-**3a** and was supported by an enantiomeric excess of the latter of 20 % *ee*. This observation supports our proposal of an embedded proton in the favored (*S*,*S*)-**B** intermediate in the enantiomeric reaction.

We have extended the scope of the reaction to the formation of quaternary stereocenters. A modified protocol was developed for the branched aldehyde **1i**. The sterically encumbered substrate required a sterically less-demanding catalyst and higher temperatures to keep the reaction rate high. With 5 mol % of catalyst **7** in a reaction performed at 60 °C, the β-fluoroalcohol product **8i** was generated in 78 % yield with 48 % *ee*.



Besides the in-situ reduction to alcohols, other direct transformations that proceed without epimerization, for example, the HWE olefination, are described in the literature.[8]

In summary, a simple method for the formation of stereogenic carbon–fluorine bonds through a direct, catalytic α-fluorination of aldehydes has been developed. A range of aldehydes can be directly fluorinated in the α position in good yields and with excellent enantioselectivities. The use of NFSI as a stable, easily handled, and commercially available electrophilic fluorine source in combination with the advantages of organocatalysis affords this simple protocol. Moreover, 1 mol % of a sterically encumbered chiral pyrrolidine derivative that is easily accessible in four steps from L-proline was sufficient for obtaining good to high yields and high enantioselectivities. It should be pointed out that optically active α-fluorinated aldehydes are unstable on silica gel and are more volatile than the starting compounds. Thus, the optically active α-fluorinated aldehydes were directly reduced to the corresponding α-fluorinated alcohols, without loss of enantioselectivity. We believe that this procedure represents an important new organocatalytic reaction and a significant improvement of existing methods, and that it will find intensive use in the synthesis and application of optically active fluorine compounds. [16]

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[16] Note added in proof (April 26, 2005): After the submission of this paper, Enders and Hüttl published the fluorination of carbonyl compounds catalyzed by chiral amines with Selectfluor as the fluorine source. The highest enantioselectivity was obtained for cyclohexanone (36% *ee*): D. Enders, M. R. M. Hüttl, *Synlett* **2005**, 991.