A Fundamentally New Approach to Enantioselective Fluorination Based on Cinchona Alkaloid Derivatives/Selectfluor Combination

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Several routes to chiral fluoro-organic compounds recently have been developed.[1] These include, for example, procedures for diastereoselective fluorination[2] of chiral organic compounds and enantioselective alkylation[3] of monofluoro-organic compounds. A more elegant method for asymmetric introduction of a fluorine substituent into a molecule involves agent-controlled enantioselective fluorination. In this process, fluorine is directly transferred enantioselectively to an achiral anion.[4] Chiral sulfonamide-type fluorinating agents have been developed for this purpose.[5,6] However, these are far from ideal because of low chemical yield and low optical purity of the fluorinated products. Furthermore, the agents themselves are still relatively unavailable because their preparation requires tedious and multistep procedures including fluorination with toxic molecular fluorine or explosive gaseous perchloryl fluoride.[5] Due to these disadvantages, there is no report of the use of these agents for asymmetric fluorination except the original papers.[5,6] We report herein a far more practical procedure for agent-controlled enantioselective fluorination that is carried out with commercially available agents. Thus, we have discovered that fluorination of carbanions with Selectfluor occurs in a highly enantioselective manner when done in the presence of cinchona alkaloid derivatives, such as dihydroquinine 4-chlorobenzoate (DHQB) or dihydroqunidine acetate (DHQDA) (Figure 1).

We first examined fluorination of (2-benzyl-3*H*-inden-1-yloxy)-trimethyl-silane (**1a**) with quinine/Selectfluor combination[7,8] prepared in situ from quinine and Selectfluor[9] in MeCN at room temperature. We were encouraged to find that (*R*)-2-benzyl-2-fluoroindanone (**2a**) was formed in 80% yield with 40% ee (Scheme 1).

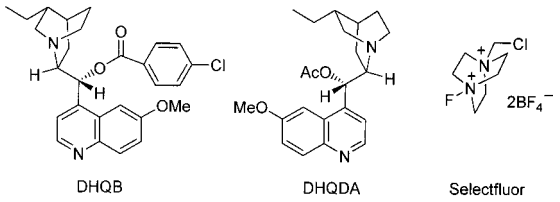


Figure 1.

Scheme 1. Fluorination of **1a** by Quinine/Selectfluor Combination

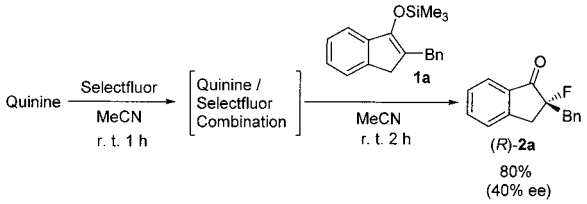
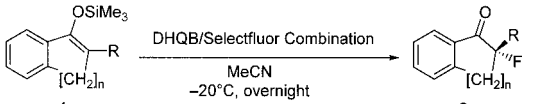


Table 1. Fluorination of Silyl Enol Ether **1** by DHQB/Selectfluor Combination



entry	**1**	*n*	R	**2**	yield (%)	ee (%)[a]	configuration[b]
1	**1a**	1	Bn	**2a**	99	89	*R*
2[c]	**1a**	1	Bn	**2a**	86	91	*R*
3	**1b**	1	Me	**2b**	93	54	*R*
4	**1c**	1	Et	**2c**	99	73	*R*
5	**1d**	2	Me	**2d**	94	42	*R*
6[d]	**1e**	2	Et	**2e**	71	67	*R*
7	**1f**	2	Bn	**2f**	95	71	*S*

[a] Determined by HPLC analysis using a Chiralcel OB or OD. [b] The absolute configuration of **2** was assigned on the basis of the HPLC analysis using a Chiralcel compared with the authentic samples prepared according to ref 6. [c] Fluorination was carried out at −80 °C in MeCN/CH_2Cl_2 (3/4) for 48 h. [d] Fluorination was carried out at −50 °C in MeCN/CH_2Cl_2 (3/4) for 12 h.

The preliminary result encouraged us to investigate other systems in an attempt to improve enantioselectivity. After screening several commercially available cinchona alkaloids[10] as our chiral source, we found that the DHQB/Selectfluor combination in MeCN at −20 °C effected the enantioselective fluorination of **1a** to furnish **2a** with 89% ee (Table 1, entry 1). We also investigated the fluorination of other silyl enol ethers **1b**−**f** in this system in order to determine generality of this reaction. As can be seen by the results summarized in Table 1,[11] the corresponding 2-fluoroindanones **2a**−**c** and 2-fluorotetralones **2d**−**f** were obtained in high yields with moderate to high enantiomeric excess (Table 1).

We next investigated the effectiveness of our system for the enantioselective fluorination of acyclic esters, a much more challenging problem. Chiral, nonracemic acyclic monofluoro compounds have many applications, for example as chiral

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(6) (a) Takeuchi, Y.; Suzuki, T.; Satoh, A.; Shiragami, T.; Shibata, N. *J. Org. Chem.* **1999**, *64*, 5708−5711. (b) Takeuchi, Y.; Satoh, A.; Suzuki, T.; Kameda, A.; Dohrin, M.; Satoh, T.; Koizumi, T.; Kirk, K. L. *Chem. Pharm. Bull.* **1997**, *45*, 1085−1088.

(7) A quinine/Selectfluor combination was prepared as follows: A solution of quinine (1.2 equiv) and Selectfluor (1.2 equiv) was stirred in dry MeCN in the presence of molecular sieves 3 Å at room temperature for 1 h. The resultant mixture was used as a quinine/Selectfluor combination without any treatment.

(8) Since quinine is a hydrate, the reaction was carried out in the presence of molecular sieves 3 Å to remove water.

(9) Selectfluor, see; Banks, R. E. *J. Fluorine Chem.* **1998**, *87*, 1−17.

(10) Cinchona alkaloid (ee) (cf. reaction temperature: 0 °C); hydroquinine 4-chlorobenzoate (81%), hydroquinine (54%), hydroquinine 9-phenanthryl ether (72%), hydroquinine 4-methyl-2-quinolyl ether (70%), $(DHQD)_2PHAL$ (46%), $(DHQ)_2PYR$ (70%).

(11) Experimental procedure for the fluorination: see Supporting Information.

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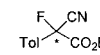
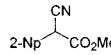
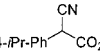
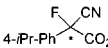
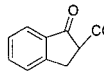
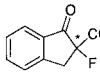
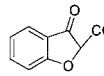
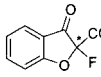
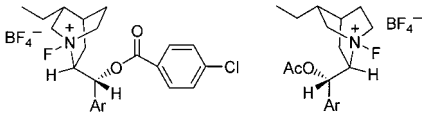
Table 2. Enantioselective Fluorination of **4** with DHQDA/Selectfluor Combination in $MeCN/CH_2Cl_2$ at −80 °C

entry	substrate **4**		product **3**		yield (%)	ee (%)[a]
1[b]		**4a**		**3a**	58	29(*R*[c])
2[d]					99	51(*R*[c])
3					80	87(*S*[c])
4		**4b**		**3b**	87	76
5		**4c**		**3c**	81	83
6		**4d**		**3d**	81	83
7		**4e**		**3e**	89	78
8		**4f**		**3f**	92	80

[a] Determined by HPLC analysis using a Chiralcel OB, OD, AS, or AD. Configuration was not determined unless otherwise indicated. [b] Fluorination was carried out by DHQB/Selectfluor combination in MeCN at −20 °C. [c] The absolute configuration of **4a** was assigned on the basis of the HPLC analysis using a Chiralcel compared with the authentic samples prepared according to ref 14. [d] Fluorination was carried out by DHQB/Selectfluor combination in $MeCN/CH_2Cl_2$(3/4) at −80 °C. Tol = *p*-tolyl, Np = 2-naphthyl, 4-*i*Pr-Ph = 4-isopropylphenyl.

derivatizing agents,[12] as chiral building blocks,[1] and as synthetic intermediates for fluorine-containing chiral liquid crystals.[13] However, as a strategy to gain access to such compounds, agent-controlled enantioselective fluorination of acyclic esters has proven to be quite problematic when compared to results achieved with cyclic ketones.[5,6]

Ethyl α-cyano-α-fluoro-tolyl acetate (**3a**),[14] an efficient chiral derivatizing agent, was selected as a target molecule. Fluorination of ethyl α-cyano-tolyl acetate (**4a**) by the use of our DHQB/Selectfluor/MeCN system at −20 °C to give (*R*)-**3a** with 29% ee (Table 2, entry 1). When the reaction was carried out in $MeCN/CH_2Cl_2$ (3/4) at −80 °C, the ee was increased to 51% (entry 2). By again surveying a series of cinchona alkaloid derivatives, we found that DHQDA was an excellent chiral auxiliary for fluorination of **4a**, giving a dramatic improvement in ee to 87% with a reversed (*S*)-enantioselection (entry 3). Fluorination of other acyclic esters **4b**−**d** using DHQDA/Selectfluor combination in $MeCN/CH_2Cl_2$ provided products including chiral derivatizing agents, **3b**[15] and **3c**,[16] with similar high enantiomeric excess. Previously, chiral agents **3a**−**c** had been prepared either by separation of diastereomeric derivatives or by enzymatic resolution,[14−16] and this work represents the first examples of their direct asymmetric syntheses. In addition, cyclic, active methylene compounds such as **4e** and **4f** can be efficiently fluorinated with high enantioselection (78−80% ee) (entries 7 and 8).[11]



*N*F-DHQB·BF_4 *N*F-DHQDA·BF_4

Figure 2.

It is very important to note that the cinchona alkaloid derivative and Selectfluor must be mixed first for generating the combination in situ before addition of substrates to achieve enantioselective fluorination. For example, after a mixture of **4a** and DHQDA was stirred in $MeCN/CH_2Cl_2$ at room temperature for 1 h, addition of Selectfluor at −80 °C gave racemic **3a** in 76% yield. This result gives useful information on the reaction mechanism of this new fluorination procedure, since this seems to rule out the involvement of a cinchona alkaloid-enolate complex. As a logical alternative, it seems likely that the cinchona alkaloid must produce an asymmetric environment around the fluorine atom.

Currently, we propose that this novel enantioselective fluorination reaction is mediated by a chiral *N*-fluoro species, *N*F-DHQB·BF_4 and *N*F-DHQDA·BF_4, generated in situ by "fluorine transfer"[17] of the cinchona alkaloid by Selectfluor. This structure of the species produced by the DHQB/Selectfluor combination was presumed by ^{19}F NMR spectroscopy, although further investigation for this structure is necessary (Figure 2).[18]

In conclusion, we have developed a practical enantioselective fluorination reaction applicable to both cyclic and acyclic carbonyl compounds using commercially or readily available cinchona alkaloid derivatives and Selectfluor. A clearer understanding of the mechanism by the alkaloid confers enantioselectivity to the process will require more study. Indeed, we feel this novel approach will provide principals and insights into the developing area of enantioselective fluorination. For example, it should be possible to develop the best chiral auxiliary for each target compound simply by changing the OH protective group of cinchona alkaloids. Our ongoing experiments are focused on expanding applications in this manner, in isolation of the putative *N*F-DHQB·BF_4 and *N*F-DHQDA·BF_4 in the solid-state, and in clarification of the reaction mechanism of enantioselection. A catalytic version of this fluorination reaction is also under investigation.[19]

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Supporting Information Available: Experimental details of enantioselective fluorination of **4** and **1**, details of ^{19}F NMR studies of *N*F-DHQB·BF_4. These material is available free of charge via the Internet at http://pub.acs.org.

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(18) The 254 MHz ^{19}F NMR spectrum of Selectfluor and the combination are available. See Supporting Information.

(19) The DHQB and DHQDA are recoverable by simple acidic/basic extraction of the reaction mixture.