Enantioselective Fluorination Mediated by Cinchona Alkaloid Derivatives/Selectfluor Combinations: Reaction Scope and Structural Information for *N*-Fluorocinchona Alkaloids

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Received March 26, 2001

Abstract: Cinchona-alkaloid/Selectfluor combinations efficiently fluorinate a variety of carbonyl compounds in a highly enantioselective manner to furnish chiral α-fluorocarbonyl compounds. The DHQB/Selectfluor combination is effective for the enantioselective fluorination of indanones and tetralones **1** in up to 91% ee. The first enantioselective syntheses of chiral derivatizing reagents **3** was accomplished with high ee and in high chemical yields by the DHQDA/Selectfluor combination. 3-Fluorooxindoles **7** were prepared with ee up to 83% using the $(DHQ)_2AQN$/Selectfluor or the $(DHQD)_2PYR$/Selectfluor combination. Since the combinations are conveniently prepared in situ from readily available reagents, the present system represents a practical method for enantioselective fluorination. X-ray crystallography and ^1H NMR analyses of the cinchona alkaloids/Selectfluor combination have established that the species that mediate this novel reaction are *N*-fluoroammonium cinchona alkaloid tetrafluoroborates, which adopt open conformations.

Introduction

The synthesis of cyclic and acyclic, chiral fluoro-organic compounds is an important topic in modern pharmaceutical chemistry.[1] The replacement of hydrogen or hydroxy with fluorine is an extensively used strategy for enhancement of biological activity in the design of analogues of biologically important molecules. The several advantages of fluorine substitution include an increase in stability, changes in lipophilicity, introduction of a center of high electronegativity, and altered patterns of reactivity of the C−F vs the C−H bond. Included in recently developed[2] routes to chiral fluoro-organic compounds are procedures for diastereoselective fluorination[3] of chiral organic compounds and enantioselective alkylation[4] of monofluoro-organic compounds. A more elegant method involves asymmetric introduction of a fluorine substituent into a molecule by reagent-controlled enantioselective fluorination. In this process, fluorine is directly transferred enantioselectively to an achiral anion.[5] Chiral sulfonamide-type fluorinating reagents have been developed for this purpose.[6,7] Differding and Lang, who first introduced this idea, reported electrophilic enantioselective fluorination of enolates using *N*-fluorocamphorsultam in 1988.[6a] Several other reagents of this type including Davis's reagents[6b,c] and our CMIT-F,[7a] BNBT-F,[7b] and SCBT-F[7c] reagents. However, these are far from ideal because of low chemical yields and low optical enrichments of the fluorinated products. Furthermore, the reagents themselves are still relatively unavailable because their preparation requires tedious and multistep procedures, including fluorination with toxic molecular fluorine or explosive gaseous perchloryl fluoride.[6,7] Due to these disadvantages, there are no reports of the use of these reagents for asymmetric fluorination except for the original papers.[6,7]

We recently communicated a fundamentally new approach to enantioselective fluorination. This approach, based on cinchona alkaloid derivatives/Selectfluor combinations, represents a far more practical procedure for reagent-controlled

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(1) (a) *Biomedical Aspects of Fluorine Chemistry*; Filler, R., Kobayashi, Y., Eds.; Kodansha/Elsevier Biomedical Press: Tokyo, Amsterdam-New York-Oxford, 1982. (b) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; ACS Symp. Ser. No. 639; American Chemical Society: Washington, DC, 1996. (c) *Fusso & Yakugaku*; Kobayashi, Y., Kumadaki, I., Taguchi, T., Eds.; Hirokawa Publishing Co.: Tokyo, 1992.

(2) (a) *Enantiocontrolled Synthesis of Fluoro-organic Compounds*; Soloshonok, V. A., Eds.; John Wiley & Sons: Chichester, 1999. (b) Bravo, P.; Resnati, G. *Tetrahedron: Asymmetry* **1990**, *1*, 661−692.

(3) (a) Welch, J. T.; Seper, K. W. *J. Org. Chem.* **1988**, *53*, 2991−2999. (b) Ihara, M.; Kai, T.; Taniguchi, N.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2357−2358. (c) Davis, F. A.; Han, W. *Tetrahedron Lett.* **1992**, *33*, 1153−1156. (d) Davis, F. A.; Reddy, R. E. *Tetrahedron: Asymmetry* **1994**, *5*, 955−960. (e) Genet, J.-P.; Durand, J.-O.; Roland, S.; Savignac, M.; Jung, F.; *Tetrahedron Lett.* **1997**, *38*, 69−72. (f) Enders, D.; Potthoff, M.; Raabe, G.; Runsink, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2362−2364. (g) McAtee, J. J.; Schinazi, R. F.; Liotta, D. C. *J. Org. Chem.* **1988**, *53*, 2161−2167. (h) Davis, F. A.; Kasu, P. V. N. *Tetrahedron Lett.* **1998**, *39*, 6135−6138.

(4) (a) Arai, S.; Oku, M.; Ishida, T.; Shioiri, T. *Tetrahedron Lett.* **1999**, *40*, 6785−6789. (b) Myers, A. G.; McKinstry, L.; Gleason, J. L. *Tetrahedron Lett.* **1997**, *38*, 7037−7040.

(5) Davis, F. A.; Qi, H.; Sundarababu, G. In *Enantiocontrolled Synthesis of Fluoro-organic Compounds*; Soloshonok, V. A., Eds.; John Wiley & Sons: Chichester, 1999; pp 1−32.

(6) (a) Differding, E.; Lang, R. W. *Tetrahedron Lett.* **1988**, *29*, 6087−6090. (b) Davis, F. A.; Han, W. *Tetrahedron Lett.* **1991**, *32*, 1631−1634. (c) Davis, F. A.; Zhou, P.; Murphy, C. K.; Sundarababu, G.; Qi, H.; Han, W.; Przeslawski, R. M.; Chen, B.-C.; Carroll, P. J. *J. Org. Chem.* **1998**, *63*, 2273−2280.

(7) (a) Takeuchi, Y.; Suzuki, T.; Satoh, A.; Shiragami, T.; Shibata, N. *J. Org. Chem.* **1999**, *64*, 5708−5711. (b) Shibata, N.; Liu, Z.; Takeuchi, Y. *Chem. Pharm. Bull.* **2000**, *48*, 1954−1958. (c) Liu, Z.; Shibata, N.; Takeuchi, Y. *J. Org. Chem.* **2000**, *65*, 7583−7587.

10.1021/ja010789t CCC: $20.00
Published on Web 06/30/2001

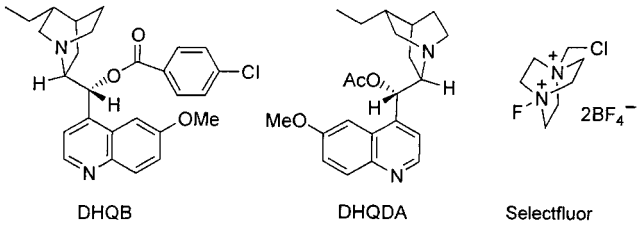
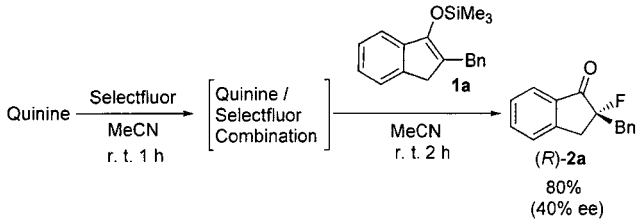


Figure 1.

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



enantioselective fluorination.[8] This method can be carried out with commercially available reagents without any special requirements. Thus, fluorination of carbanions occurs in a highly enantioselective manner (up to 91% ee) when done with Selectfluor[9] in the presence of cinchona alkaloid derivatives, such as dihydroquinine 4-chlorobenzoate (DHQB) or dihydroquinidine acetate (DHQDA) (Figure 1). *N*-Fluorocinchona alkaloids seem to be the actual reactive species for the enantioselective fluorination.[9,10]

As a followup to our communication,[8] we now present full details of our studies, including an investigation of the scope of the reaction and structural information for intermediate *N*-fluorocinchona alkaloids, including the results of X-ray crystallography. The mechanism of this new enantioselective fluorination is also discussed in the last section.

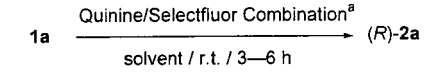
DHQB/Selectfluor Combination: Fluorination of Indanones and Tetralones. The quinine/Selectfluor combination was prepared as follows; a solution of quinine hydrate (1.2 equiv) and Selectfluor (1.2 equiv) was stirred in dry MeCN in the presence of 3 Å molecular sieves (to remove water) at room temperature for 1 h. The resulting quinine/Selectfluor reagent was used without any further treatment. (2-Benzyl-3*H*-inden-1-yloxy)trimethylsilane (**1a**) was the standard substrate used to examine the ability of this and subsequent systems to effect enantioselective fluorinations under different reaction conditions. In our initial experiments, we were encouraged to find that (*R*)-2-benzyl-2-fluoroindanone (**2a**) was formed in 80% yield with 40% ee (Scheme 1). Optimization of the reaction conditions at room temperature by altering the solvent did not improve the yields (Table 1).

After screening several *commercially available* cinchona alkaloids as chiral sources for further optimization, we found that either a DHQB/Selectfluor combination or a $(DHQ)_2PHAL$/Selectfluor combination in MeCN at 0 °C effected the enantioselective fluorination of **1a** to furnish **2a** with more than 80% ee, favoring the *R* stereochemistry (Table 2, entries 4 and 9). Reverse stereoselectivities were observed in the reaction based on both quinidine/Selectfluor and cinchonine/Selectfluor combinations, although lower ee values were obtained (entries 2 and 7). Both procedures using DHQB and $(DHQ)_2PHAL$ gave almost identical results, so that, for reasons of reagent cost, we more frequently used the DHQB/Selectfluor combination.

To examine the generality of the DHQB/Selectfluor combination, we studied the fluorination of silyl enol ethers **1a**−**f.** The fluorination reaction was carried out overnight at −20 °C. As can be seen by the results summarized in Table 3, the corresponding 2-fluoroindanones **2a**−**c** and 2-fluorotetralones **2d**−**f** all were obtained in high yield with moderate to high ee. Performing the reaction at −40 °C afforded the highest ee (91%), although the reaction time was not practical (entry 4).

Having established the validity of our approach, we next investigated further effects of alkaloid structural variations on the fluorination reaction. Using standard esterification methods, a series of DHQ derivatives were prepared in which the 4-chlorobenzoate group was replaced with other benzoates or the acetate group. As shown in Table 4, these DHQ derivatives proved to be as effective as the DHQ chlorobenzoate as the Selectfluor partner. It should be noted that the dihydroquinidine 4-nitrobenzoate/Selectfluor combination fluorinated **1a** to afford (*R*)-**2a** in 91% ee at −20 °C (entry 2).

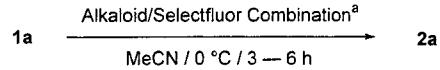
Table 1. Enantioselective Fluorination of **1a** Using the Quinine/Selectfluor Combination: Variation of Solvent



entry	solvent	yield (%)	ee[b,c] (%)
1	MeCN	80	40
2	MeCN/THF = 1/1	76	35
3	MeCN/toluene = 1/1	65	37
4	MeCN/H_2O = 4/1	49	29
5	DMF	53	30
6	DMF/THF = 1/1	61	32

[a] The quinine/Selectfluor combination was prepared from 1.2 equiv of quinine and Selectfluor in solvent in the presence of 3 Å molecular sieves at room temperature for 1 h. [b] Ee values were determined by HPLC analysis using a Chiralcel OB column. [c] The absolute configuration of **2a** was assigned on the basis of the HPLC analysis using Chiralcel compared with the authentic sample prepared according to ref 7a.

Table 2. Enantioselective Fluorination of **1a**: Variation of Cinchona Alkaloid



entry	alkaloid	yield (%)	ee (%)[b]	config.[c]
1	quinine	63	44	*R*
2	quinidine	84	35	*S*
3	DHQ[d]	67	54	*R*
4	DHQB[e]	83	81	*R*
5	DHQ-9-phenantryl ether	61	72	*R*
6	DHQ-4-methyl-2-quinolyl ether	100	70	*R*
7	cinchonine	94	23	*S*
8	cinchonidine	88	42	*R*
9	$(DHQ)_2PHAL$	100	82	*R*
10	$(DHQ)_2PYR$	100	70	*R*
11	$(DHQ)_2AQN$	98	70	*R*

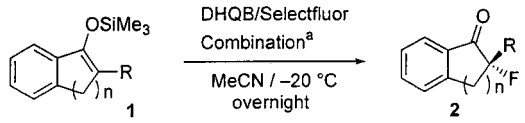
[a] The cinchona alkaloid/Selectfluor combination was prepared from 1.2 equiv of cinchona alkaloid and Selectfluor in MeCN in the presence of 3 Å molecular sieves at room temperature for 1 h. [b] Ee values were determined by HPLC analysis using a Chiralcel OB column. [c] The absolute configuration of **2a** was assigned on the basis of the HPLC analysis using Chiralcel compared with the authentic sample prepared according to ref 7a. [d] DHQ = dihydroquinine. [e] DHQB = dihydroquinine 4-chlorobenzoate.

(8) Shibata, N.; Suzuki, E.; Takeuchi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10728−10729.

(9) Selectfluor, see; (a) Banks, R. E. *J. Fluorine Chem.* **1998**, *87*, 1−17. (b) Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737−1755.

(10) Shortly after we communicated our initial results, an independent report was published describing enantioselective fluorination reactions (36−61% ee) using isolated *N*-fluorocinchona alkaloid dervatives. Cahard, D.; Audouard, C.; Plaquevent, J.-C.; Roques, N. *Org. Lett.* **2000**, *2*, 3699−3701.

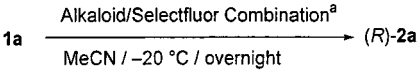
Table 3. Enantioselective Fluorination of Indanones and Tetralones Using the DHQB/Selectfluor Combination



entry	**1**	*n*	R	**2**	yield (%)	ee (%)[b]	config[c]
1	**1a**	1	Bn	**2a**	99	89	*R*
2	**1b**	1	Me	**2b**	93	53	*R*
3	**1c**	1	Et	**2c**	100	73	*R*
4[d]	**1a**	1	Bn	**2a**	86	91	*R*
5	**1d**	2	Me	**2d**	94	40	*R*
6[e]	**1e**	2	Et	**2e**	71	67	*R*
7	**1f**	2	Bn	**2f**	95	71	*S*

[a] The DHQB/Selectfluor combination was prepared from 1.2 equiv of DHQB and Selectfluor in MeCN in the presence of 3 Å molecular sieves at room temperature for 1 h. [b] Ee values were determined by HPLC analysis using a Chiralcel OB or OJ column. [c] The absolute configuration of **2** was assigned on the basis of the HPLC analysis using Chiralcel compared with the authentic samples prepared according to ref 7a. [d] The reaction was carried out at −40 °C for 2 days. [e] The reaction was carried out at −50 °C in MeCN/CH_2Cl_2 (3/4).

Table 4. Enantioselective Fluorination of **1a**: Variation of Cinchona Alkaloid



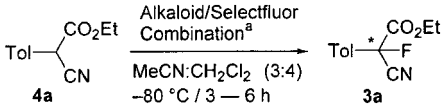
entry	alkaloid	yield (%)	ee (%)[b]
1	DHQ[c]−benzoate	82	90
2	DHQ−4-nitrobenzoate	61	91
3	DHQ−4-methoxybenzoate	80	87
4	DHQ−acetate	67	86
5	DHQ−1-naphthalenecarboxylate	61	87
6	DHQ−anthraquinone-2-carboxylate	100	86
7	DHQ−trifluoroacetate	43	31

[a] The cinchona alkaloid/Selectfluor combination was prepared from 1.2 equiv of cinchona alkaloid and 1.2 equiv of Selectfluor in MeCN in the presence of 3 Å molecular sieves at room temperature for 1 h. [b] Ee values were determined by HPLC analysis using a Chiralcel OB column. [c] DHQ = dihydroquinine.

DHQDA/Selectfluor Combination: Fluorination of Acyclic Esters. 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 derivatizing agents,[11] as chiral building blocks,[2] and as synthetic intermediates for fluorine-containing chiral liquid crystals.[12] However, as a strategy to gain access to such compounds, reagent-controlled enantioselective fluorination of acyclic carbonyl compounds has proven to be quite problematic when compared to results achieved with cyclic ketones.[6,7] Indeed, no general and efficient fluorination system has yet been developed that provides chiral, acyclic fluoro compounds with high enantioselectivities.

We recently have shown that ethyl α-cyano-α-fluoro-tolyl acetate (**3a**),[13] an efficient chiral derivatizing agent, can be used effectively for the determination of absolute configurations of chiral secondary alcohols.[13c] However, **3a** has not achieved general use because of the involved synthetic pathway to the optically active agent. We therefore examined the preparation of chiral **3a** from ethyl α-cyano-tolyl acetate (**4a**) using the alkaloid/Selectfluor combination. Since **4a** has an acidic hydrogen atom on the reactive center, it was not necessary to convert it to the corresponding silyl enol ether before fluorination. The experiments were performed using a slight excess of cinchona alkaloid relative to Selectfluor and **4a** to accelerate the deprotonation of **4a**. Our initial fluorination of **4a** using the DHQB/Selectfluor/MeCN system at −20 °C gave (*R*)-**3a** with 29% ee (Table 5, entry 1). The reaction was complete within 1 h. Lowering the temperature to −80 °C with MeCN/CH_2Cl_2 (3/4) as solvent improved the enantioselectivity (51%, entry 2). However, the quinine derivative variation gave no further improvement (entries 3−9). By again surveying numerous readily available cinchona alkaloids, we found that dihydroquinidine derivatives were optimal chiral sources for fluorination of **4a.** These gave a dramatic improvement in ee along with a

Table 5. Enantioselective Fluorination of Acyclic Ester **4a**: Variation of Cinchona Alkaloid



entry	alkaloid[e]	yield (%)	ee (%)[b]	config.[c]
1[d]	DHQB	58	29	*R*
2	DHQB	100	51	*R*
3	quinine	95	20	*S*
4	DHQ−acetate	89	31	*R*
5	DHQ−pentafluorobenzoate	91	11	*R*
6	DHQ−benzoate	82	40	*R*
7	DHQ−anthraquinone-2-carboxylate	34	33	*R*
8	$(DHQ)_2$PHAL	93	11	*R*
9	$(DHQ)_2$PYR	85	48	*R*
10	quinidine	84	23	*R*
11	DHQD	55	29	*R*
12	DHQD−benzoate	83	79	*S*
13	DHQD−4-nitrobenzoate	78	67	*S*
14	DHQD−4-chlorobenzoate	97	73	*S*
15	DHQD−anthraquinone-2-carboxylate	36	78	*S*
16	DHQD−1-naphthalenecarboxylate	88	64	*S*
17	DHQD−4-methoxybenzoate	27	79	*S*
18	DHQD−pentafluorobenzoate	54	47	*S*
19	DHQDA	80	87	*S*
20	DHQD-propionate	100	72	*S*
21	(DHQD)2PHAL	76	58	*S*
22	cinchonine	83	4	*S*
23	DHC	93	1	*S*
24	DHC−acetate	84	7	*S*
25	DHC−benzoate	86	5	*S*
26	cinchonidine	87	9	*R*
27	DHCD	63	3	*R*
28	DHCD−acetate	90	12	*S*
29	DHCD−benzoate	82	5	*S*

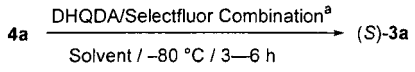
[a] The cinchona alkaloid/Selectfluor combination was prepared from 2.0 equiv of cinchona alkaloid and 1.5 equiv of Selectfluor in MeCN in the presence of 3 Å molecular sieves at room temperature for 1 h. [b] Ee values were determined by HPLC analysis using a Chiralcel OJ column. [c] The absolute configuration of **3a** was assigned on the basis of the HPLC analysis using a Chiralcel column compared with the authentic sample prepared according to ref 13. [d] This reaction was carried out at −20 °C in MeCN. [e] Tol = tolyl, DHQB = dihydroquinine 4-chlorobenzoate, DHQ = dihydroquinine, DHQD = dihydroquinidine, DHQDA = dihydroquinidine acetate, DHC = dihydrocinchonine, DHCD = dihydrocinchonidine.

(11) Takeuchi, Y.; Takahashi, T. In *Enantiocontrolled Synthesis of Fluoro-organic Compounds*; Soloshonok, V. A., Eds.; John Wiley & Sons: Chichester, 1999; pp 497−534.

(12) Kusumoto, T.; Hiyama, T. In *Enantiocontrolled Synthesis of Fluoro-organic Compounds*; Soloshonok, V. A., Eds.; John Wiley & Sons: Chichester, 1999; pp 536−556.

(13) (a) Takeuchi, Y.; Konishi, M.; Hori, H.; Takahashi, T.; Kometani, T.; Kirk, K. L. *Chem. Commun.* **1998**, 365−366. (b) Takeuchi, Y.; Konishi, M.; Hori, H.; Takahashi, T.; Kirk, K. L. *Enantiomer* **1999**, *4*, 339−344. (c) Takahashi T.; Fukushima A.; Tanaka Y.; Takeuchi Y.; Kabuto K.; Kabuto C. *Chem. Commun*. **2000**, 787−788.

Table 6. Enantioselective Fluorination of **4a** Using the DHQDA/Selectfluor Combination: Variation of Solvent



entry	solvent	yield (%)	ee (%)[b]
1	MeCN:CH_2Cl_2 (3:4)	80	87
2[c]	MeCN	88	58
3	MeCN:CH_2Cl_2 (1:4)	90	63
4	MeCN:THF (3:4)	81	62
5	CH_3CH_2CN	63	73
6	DMF	85	50
7	CH_3COCH_3	86	60

[a] The DHQDA/Selectfluor combination was prepared from 2.0 equiv of DHQDA and 1.5 equiv of Selectfluor in solvent in the presence of 3 Å molecular sieves at room temperature for 1 h. [b] Ee values were determined by HPLC analysis using a Chiralcel OJ column. [c] The reaction was carried out at −40 °C.

reversed (*S*)-enantioselection (entries 12−21). Dihydroquinidine benzoate showed good enantioselectivity (entry 12, 79% ee) and other benzoate derivatives produced similar high enantioselectivities (entries 13−17). An exception was dihydroquinidine pentafluorobenzoate (entry 18, 47% ee). Very high enantioselectivity (87% ee) was achieved with the DHQDA/Selectfluor combination (entry 19). By contrast, cinchonine and cinchonidine derivatives, including their benzoates and acetates, showed poor enantioselectivities (entries 22−29). Attempts to optimize the reaction further using the DHQDA/Selectfluor combination by altering the solvent decreased the enantioselectivities (Table 6).

Fluorination of other acyclic esters **4b**−**d** using the optimized conditions, i.e., the DHQDA/Selectfluor combination in MeCN/CH_2Cl_2, provided products with similar high enantiomeric excess (Table 7). Included are the chiral derivatizing agents, **3b**[14] and **3c**.[15] Previously the agents **3a**−**c** had been prepared either by separation of diastereomeric derivatives or by enzymatic resolution,[13−15] and this work represents the first examples of their direct asymmetric syntheses.

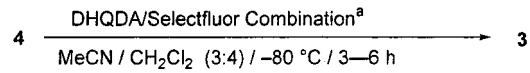
To examine the possibility of re-using the alkaloids, we repeated the fluorination of **4a** using DHQDA recovered from the first reaction mixture by simple acidic/basic extraction. Formation of **3a** having 85% ee (entry 6) demonstrates that recycling of DHQDA causes no erosion in enantioselectivity of the combination (Table 7).

Fluorination of Cyclic *β*-Ketoesters. Cyclic *β*-ketoesters such as **5a** and **5b** can also be efficiently fluorinated with high enantioselection by the DHQDA/Selectfluor combination (78−80% ee) (Table 8, entries 1 and 2). As with the fluorination of **4**, because of the high acidity of the reactive centers, compounds **5** were fluorinated very smoothly without pre-conversion to the silyl enol ethers. However, fluorination of **5c** and **5d** with the DHQDA system afforded the corresponding fluoroesters **6c** and **6d** with only low enantioselectivities (2% ee and 25% ee, entries 3 and 5). These enantioselections were improved to 59% ee and 43% ee when the reaction was mediated by either the dihydroquinidine (DHQD)/Selectfluor or dihydroquinine (DHQ)/Selectfluor combinations (entries 4 and 6, respectively). Although the reason for this observed improvement of enantioselection is not obvious, these results emphasize again the influence on the reaction of steric factors resident in the hydroxyl protecting group.

(14) Takahashi, T.; Fukushima, A.; Tanaka, Y.; Segawa, M.; Hori, H.; Takeuchi, Y.; Burchardt, A.; Haufe, G. *Chirality* **2000**, *12*, 458−463.

(15) (a) Takeuchi, Y.; Itoh, N.; Note, H.; Koizumi, T.; Yamaguchi, K. *J. Am. Chem. Soc.* **1991**, *113*, 6318−6320. (b) Takeuchi, Y.; Itoh, N.; Satoh, T.; Koizumi, T.; Yamaguchi, K. *J. Org. Chem.* **1993**, *58*, 1812−1820.

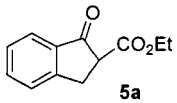
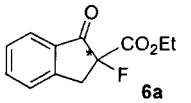
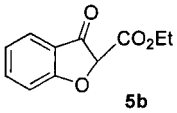
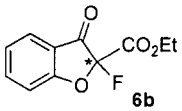
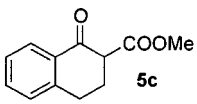
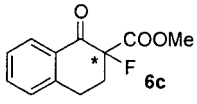
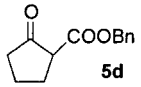
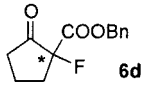
Table 7. Enantioselective Fluorination of Acyclic Esters **4** Using the DHQDA/Selectfluor Combination[a,e]



entry	substrate **4**	product **3**	yield (%)	ee (%)[b,c]
1	Tol-CH(CN)-COOEt **4a**	Tol-C(F)(CN)-COOEt (*S*)-**3a**	80	87
2	Np-CH(CN)-CO_2Me **4b**	Np-C(F)(CN)-CO_2Me **3b**	87	76
3	Ph-CH(CN)-CO_2Et **4c**	Ph-C(F)(CN)-CO_2Et **3c**	81	83
4	*i*Pr-Ph-CH(CN)-CO_2Me **4d**	*i*Pr-Ph-C(F)(CN)-CO_2Me **3d**	82	87
5	Cl-Ph-CH(CN)-CO_2Me **4e**	Cl-Ph-C(F)(CN)-CO_2Me **3e**	56	68
6[d]	**4a**	(*S*)-**3a**	79	85

[a] The DHQDA/Selectfluor combination was prepared from 2.0 equiv of DHQDA and 1.5 equiv of Selectfluor in MeCN in the presence of 3 Å molecular sieves at room temperature for 1 h. [b] Ee values were determined by HPLC analysis using a Chiralcel OJ or Chiralpak AD, AS column. [c] The absolute configuration was not determined except **3a**. [d] The reaction was carried out using recovered DHQDA. [e] Tol = tolyl, Np = 2-naphthyl, *i*Pr-Ph = 4-isopropylphenyl, Cl-Ph = 4-chlorophenyl.

Table 8. Enantioselective Fluorination of Cyclic *β*-Ketoesters[a,d]

entry	substrate **5**	product **6**	alkaloid	yield (%)	ee (%)[b,c]
1	 **5a**	 **6a**	DHQDA	89	78
2	 **5b**	 **6b**	DHQDA	92	80
3	 **5c**	 **6c**	DHQDA	26	2
4	**5c**	**6c**	DHQD	79	59
5	 **5d**	 **6d**	DHQDA	28	25
6	**5d**	**6d**	DHQ	55	43

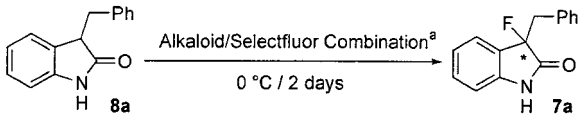
[a] The cinchona alkaloid/Selectfluor combination was prepared from 2.0 equiv of cinchona alkaloid and 1.5 equiv of Selectfluor in MeCN in the presence of 3 Å molecular sieves at room temperature for 1 h. The reaction was carried out in MeCN/CH_2Cl_2 (3/4) at −80 °C for 3−6 h. [b] Ee values were determined by HPLC analysis using a Chiralcel OJ column. [c] Configuration was not determined. [d] DHQDA = dihydroquinidine acetate, DHQD = dihydroquinidine, DHQ = dihydroquinine.

$(DHQ)_2$AQN/Selectfluor, $(DHQD)_2$PYR/Selectfluor Combinations: Fluorination of Oxindoles. Because of the steric relationship between the C−F functionality and both the C−H

and C−OH moieties,[16] 3-fluorooxindoles **7** are potential mimics of both the corresponding oxindoles and 3-hydoroxyoxindoles that are often found as metabolites of indoles.[17] Although several methods are available for the preparation of racemic **7**,[18,19] as yet no enantioselective synthesis of **7** has been reported. Therefore, we examined oxindoles **8** as substrates for enantioselective fluorination using the alkaloid/Selectfluor combinations. Fluorination of **8** using the best combinations described in the previous section (DHQDA and DHQB) gave unsatisfactory enantioselectivities in the formation of 3-benzyl-3-fluorooxindole (**7a**) (37% ee, 7% ee, respectively, Table 9, entries 1 and 2). These fluorination reactions were performed at 0 °C since lower temperatures led to incomplete reaction. In attempts to improve on these results, we found that extensive variation of the cinchona alkaloid derivatives failed to give any improvement in enantioselection over that obtained with DHQDA. However, good levels of enantioselection in the fluorination of **8a** were finally achieved using bis-cinchona alkaloids/Selectfluor combinations (entries 9−15). Thus, the $(DHQ)_2AQN$/Selectfluor combination and $(DHQD)_2PYR$/Selectfluor combination in MeCN afforded excellent yields of **7a** with 78% ee and 72% ee, respectively (entries 9 and 11).

It is noteworthy that use of equimolar amounts of Selectfluor and bis-cinchona alkaloids gave the highest yield as well as high stereoselectivity (entry 9; 100% yield, 78% ee). In contrast, use of 2 molar equiv of Selectfluor to bis-cinchona alkaloid (i.e. equivalent amounts of alkaloid base) resulted in an unsatisfactory yield along with a slight decrease in stereoselectivity (entry 10; 50% yield, 64% ee). Qualitatively similar results were obtained for the monomer alkaloid/Selectfluor combinations used in the fluorination (entries 1, 4, 17, and 18). For example, the combination with a molar DHQDA/Selectfluor ratio of 2/1 gave better results (entry 17; 53% yield, 44% ee) than that with a molar DHQDA/Selectfluor ratio of 1/1 (entry 1; 27% yield, 37% ee) with respect to both yield and selectivity. Similarly, while fluorination using a 1/1 molar ratio of DHQDB/Selectfluor gave a 46% yield with 38% ee, this was increased to 77% yield and 55% ee when the fluorination was carried out using a 2/1 molar ratio of DHQDB/Selectfluor (entries 4 and 18). These results suggest that the reaction is facilitated by the additional equivalent of alkaloid (moiety) acting as a base to remove a proton at the reactive center of **8a** to form an anion. Additionally we note that choice of solvent was important for this reaction. For example, when **8a** was treated with the combination in MeOH, the product was obtained in lower enantiopurity and with reversed facial selectivity (compare entries 15 and 16) (Table 9).

Table 9. Enantioselective Fluorination of Oxindole **8a**: Variation of Cinchona Alkaloid and Solvent



entry	alkaloid[h]	solvent	yield (%)	ee (%)[b]	major isomer[c,d]
1	DHQDA	MeCN	27	37	S
2	DHQB[e]	MeCN	60	7	S
3	DHQD	MeCN	17	18	S
4	DHQD−4-chlorobenzoate	MeCN	46	38	S
5	DHC	MeCN	19	0	
6	DHCD	MeCN	26	7	S
7	DHCD−acetate	MeCN	32	18	S
8	DHC−acetate	MeCN	34	9	F
9	$(DHQ)_2AQN$	MeCN	100	78	F
10	$(DHQ)_2AQN$[f]	MeCN	50	64	F
11	$(DHQD)_2PYR$	MeCN	91	72	F
12	$(DHQD)_2AQN$	MeCN	88	10	S
13	$(DHQ)_2PYR$	MeCN	94	42	S
14	$(DHQ)_2PHAL$	MeCN	74	23	F
15	$(DHQD)_2PHAL$	MeCN	99	62	S
16	$(DHQD)_2PHAL$	MeOH	81	17	F
17	DHQDA[g]	MeCN	53	44	S
18	DHQD−4-chlorobenzoate[g]	MeCN	77	55	S

[a] The cinchona alkaloid/Selectfluor combination was prepared from 1.5 equiv of cinchona alkaloid and 1.5 equiv of Selectfluor in MeCN or MeOH at room temperature for 1 h. [b] Ee values were determined by HPLC analysis using a Chiralcel OB column. [c] S: slower isomer. F: faster isomer. [d] The configuration of **7a** was not determined. [e] This reaction was carried out with 3 equiv of cinchona alkaloid and 3 equiv of Selectfluor. [f] This reaction was carried out with 1.5 equiv of cinchona alkaloid and 3.0 equiv of Selectfluor. [g] This reaction was carried out with 3 equiv of cinchona alkaloid and 1.5 equiv of Selectfluor. [h] DHQDA = dihydroquinidine acetate, DHQB = dihydroquinine 4-chlorobenzoate, DHC = dihydrocinchonine, DHCD = dihydrocinchonidine.

On the basis of these results, the alternative Selectfluor combinations derived from bis-cinchona alkaloids [$(DHQ)_2AQN$/Selectfluor and $(DHQD)_2PYR$/Selectfluor] were chosen for the fluorination of a series of 3-substituted oxindoles **8** in MeCN. As summarized in Table 10, both combinations produced optically active 3-substituted 3-fluorooxindoles **7** in modest to good enantioselectivities (up to 82% ee). While there are several reported methods for the preparation of racemic **7**, to our knowledge this is the first example of an enantioselective synthesis of **7** (Table 10).

Structure of the Reactive Intermediate in the Enantioselective Fluorination: *N*-Fluorocinchona Alkaloids. We based our development of alkaloid/Selectfluor combinations as enantioselective fluorinating reagents on the fundamental idea that in situ "transfer fluorination"[20] would generate the *N*-fluorocinchona alkaloid (Scheme 2). Our hope was that such a species would be capable of transferring the fluorine to an enolate with enantioselective bias. The successful realization of enantioselective fluorination is suggestive of this mechanism but, in itself, does not prove that *N*-fluorocinchona alkoloids are intermediates. Therefore, we have examined this question in greater depth. We report here the results of experiments that confirm that this novel enantioselective fluorination reaction, in fact, is mediated

(16) Current evidence indicates that fluorine and oxygen, not fluorine and hydrogen, are nearly isosteric. See: Smart, B. E. In *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum Press: New York, 1994; Chapter 3, pp 57−88.

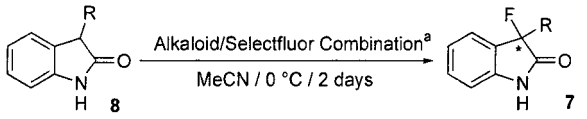
(17) (a) Kato, Y.; Shimokawa, M.; Yokoyama, T.; Mohri, K. *J. Chromatogr. Biomed. Appl.* **1993**, *616*, 67−71. (b) Itakura, K.; Uchida, K.; Kawakishi, S. *Chem. Res. Toxicol.* **1994**, *7*, 185−190. (c) Oestin, A.; Catala, C.; Chamarro, J.; Sandberg, G. *J. Mass Spectrom.* **1995**, *30*, 1007. (d) Thorton, M. J.; Appleton, M. L.; Gonzalez, F. J.; Yost, G. S. *J. Pharmacol. Exp. Ther.* **1996**, *276*, 21−29. (e) Carpenedo, R.; Carla, V.; Moneti, G.; Chiarugi, A.; Moroni, F. *Anal. Biochem.* **1997**, *244*, 74−79. (f) Hu, T.; Dryhurst, G. *J. Electroanal. Chem.* **1997**, *432*, 7−18. (g) Anisimoviene, N. *Biologija* **1997**, 34−39. (h) Yang, Z.; Wrona, M. Z.; Dryhurst, G. *J. Neurochem.* **1997**, *68*, 1929−1941. (i) Mannaioni, G.; Carpenedo, R.; Pugliese, A. M.; Corradetti, R.; Moroni, F. *Br. J. Pharmacol.* **1998**, *125*, 1751−1760. (j) Carpenedo, R.; Mannaioni, G.; Moroni, F. *J. Neurochem.* **1998**, *70*, 1998−2003.

(18) (a) Middleton, W. J.; Bingham, E. M. *J. Org. Chem.* **1980**, *45*, 2883−2887. (b) Torres, J. C.; Garden, S. J.; Pinto, A. C.; da Silva, F. S. Q.; Boechat, N. *Tetrahedron* **1999**, *55*, 1881−1892. (c) Labroo, R. B.; Labroo, V. M.; King, M. M.; Cohen, L. A. *J. Org. Chem.* **1991**, *56*, 3637−3642. (d) Hou, Y.; Higashiya, S.; Fuchigami, T. *J. Org. Chem.* **1997**, *62*, 8773−8776.

(19) Takeuchi, Y.; Tarui, T.; Shibata, N. *Org. Lett.* **2000**, *2*, 639−642.

(20) Transfer fluorination was developed by Banks, see: Abdul-Ghani, M.; Banks, R. E.; Besheesh, M. K.; Sharif, I.; Syvret, R. G. *J. Fluorine Chem.* **1995**, *73*, 255−257.

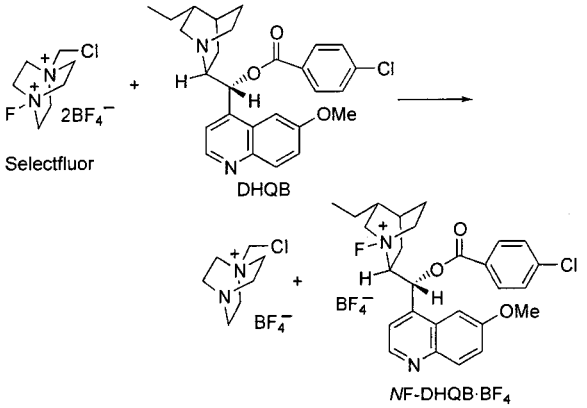
Table 10. Enantioselective Fluorination of Oxindole **8** Using the Bis-cinchona Alkaloids/Selectfluor Combination



entry	8	R	7	alkaloid	yield (%)	ee (%)[b]	major isomer[c,d]
1	**8a**	Bn	**7a**	$(DHQD)_2PYR$	91	72	F
2	**8a**		**7a**	$(DHQ)_2AQN$	100	78	F
3	**8b**	*p*-MeOBn	**7b**	$(DHQD)_2PYR$	79	82	F
4	**8c**	Me	**7c**	$(DHQD)_2PYR$	94	67	S
5	**8c**		**7c**	$(DHQ)_2AQN$	56	52	S
6	**8d**	Et	**7d**	$(DHQD)_2PYR$	79	76	S
7	**8d**		**7d**	$(DHQ)_2AQN$	90	58	S
8	**8e**	^{i}Pr	**7e**	$(DHQ)_2PHAL$	12	40	F
9	**8f**	COOEt	**7f**	$(DHQD)_2PYR$	93	37	S
10	**8f**		**7f**	$(DHQ)_2AQN$	91	23	S

[a] The cinchona alkaloid/Selectfluor combination was prepared from 1.5 equiv of cinchona alkaloid and 1.5 equiv of Selectfluor in MeCN at room temperature for 1 h. [b] Ee values were determined by HPLC analysis using a Chiralcel OB or a Chiralpak AD column. [c] S: slower isomer. F: faster isomer. [d] The configurations of **7** were not determined.

Scheme 2. Transfer-Fluorination of DHQB with Selectfluor



by chiral *N*-fluorocinchona alkaloids (*N*-fluoroammonium cinchona alkaloid tetrafluoroborates), i.e., *N*F-Q·BF_4, *N*F-DHQB·BF_4, *N*F-DHQDA·BF_4, *N*F-$(DHQ)_2AQN$·BF_4, and *N*F-$(DHQD)_2$PYR·BF_4 (Figure 2).

An important piece of evidence is the fact that the cinchona alkaloid derivative and Selectfluor must be mixed prior to 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 (Scheme 3). This result seems to rule out the involvement of a cinchona alkaloid−enolate complex in stereochemical control. As a logical alternative, it seems likely that the cinchona alkaloid must produce an asymmetric environment around the fluorine atom.

We next examined the structure of the species produced by the DHQB/Selectfluor combination with ^{19}F NMR spectroscopy ($CFCl_3$ was used as a reference). The 254 MHz ^{19}F NMR spectrum of Selectfluor in CD_3CN at room temperature showed a peak at 49 ppm (singlet, Selectfluor *N*-F), whereas the spectrum of DHQB/Selectfluor (0.5:1) combination in CD_3CN displayed singlets of equal entensity at 49 ppm and at 44 ppm. As we expected, the signal at 49 ppm disappeared completely with the addition of DHQB (1.0 equiv) while the peak at 44

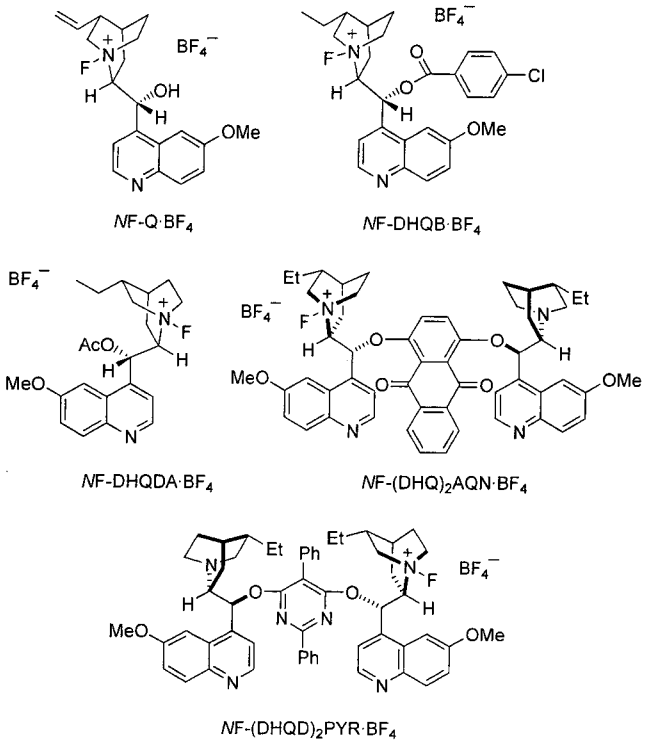


Figure 2. Structures of *N*-fluorocinchona alkaloid tetrafluoroborates.

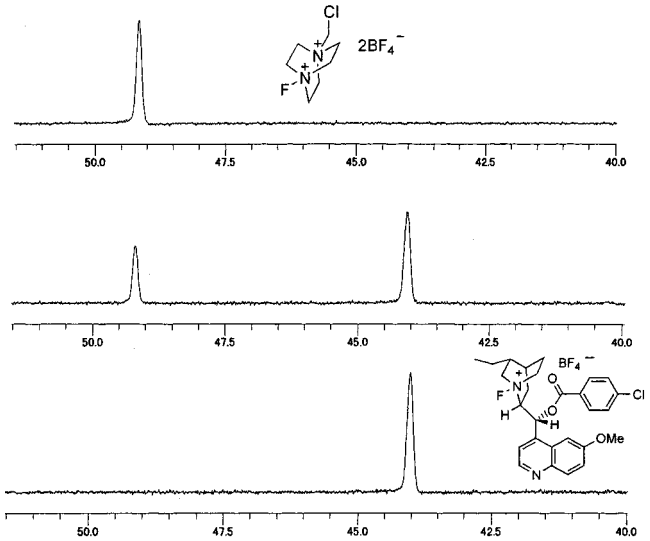
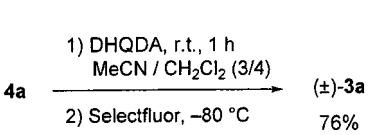


Figure 3. The 254 MHz ^{19}F NMR spectrum of Selectfluor and the combination in CD_3CN. Top: Downfield region of the ^{19}F NMR spectrum of Selectfluor in CD_3CN. Middle: The same region after the addition of 0.5 equiv of DHQB. Bottom: The same region after the addition of 1.0 equiv of DHQB, leading to the quantitative formation of *N*F-DHQB·BF_4.

Scheme 3



ppm remained. These initial NMR spectroscopic studies strongly support the proposed presence and involvement of *N*F-DHQB·BF_4 in the reaction solution (Figure 3). Finally, we examined the possibility of isolation of the putative *N*F-cinchona alkaloids in the solid-state as a means to provide definitive proof of our proposed mechanism. After attempted crystallization of various cinchona alkaloids/Selectfluor combinations, we determined that

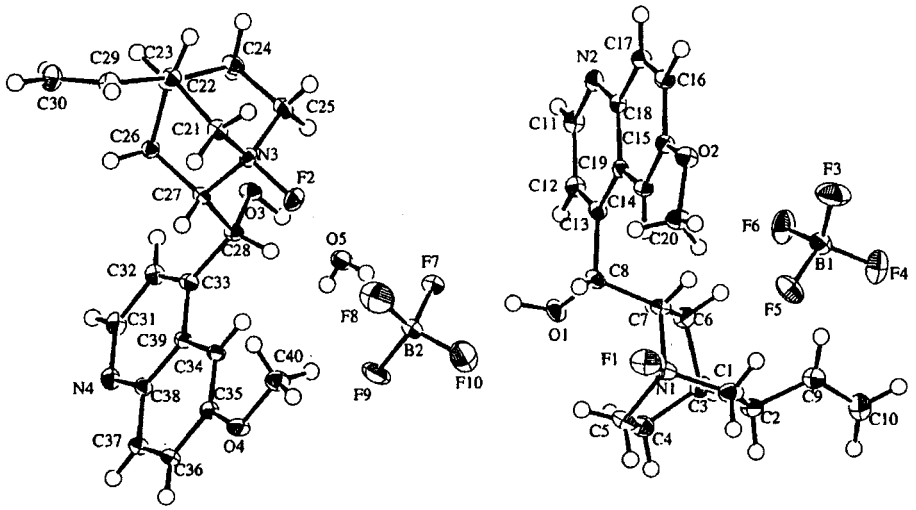


Figure 4. X-ray crystallographic structure of *N*F-Q·BF_4.

the crystalline *N*F-Q·BF_4 isolated from quinine/Selectfluor combination was suitable for X-ray structure determination.

The crystal structure of *N*F-Q·BF_4 is shown in Figure 4 and confirms the ^{19}F NMR based assignment of the N−F moiety. The length of N(1)−F(1) is 1.4912(2) Å, longer than that of the N−F bond of Selectfluor (1.37(2) Å).[21] The structure suggests that the C7−C8−C13−C12 dihedral angle is 107° and the H8−C9−C8−H9 dihedral angle is −77°. It is well-known that cinchona alkaloids in principle can adopt four different conformations (two closed-type conformations and two open-type conformations). This X-ray analysis clearly showed that our novel *N*F-Q·BF_4 molecule exists in a so-called open conformation III.[22] The two molecules of *N*F-Q·BF_4 in the asymmetric unit are shown in Figure 4. Both are quite similar in all respects. The only difference in conformation between the two occurs in the rotation of the vinyl side chain. The torsion angles of C1−C2−C9−C10 and C21−C22−C29−C30 are 137.5(2)° and −138.0(2)° for each molecule, respectively. A water molecule hydrogen bonded to one of the *N*F-Q·BF_4 molecules is found in the structural unit.[23]

Discussion

In the investigation of the mechanism of our new enantioselective fluorination reaction, detailed information regarding the structure of the intermediate *N*-fluorocinchona alkaloids is necessary to determine the process by which chirality is transferred to the substrate. To that end, we determined the solid-state structure of *N*F-Q·BF_4 by X-ray analysis (Figure 4). According to molecular mechanics calculations by Kellogg, Wynberg, and Sharpless,[22] four different conformations of cinchona alkaloids can (co)exist in solution (closed conformations I and II; open conformations III and IV). (Dihydro)quinine and (dihydro)quinidine all adopt predominantly the open conformation III in all solvents.[22] It is very interesting that *N*F-Q·BF_4, in the solid state, also adopts the open conformation III in which the quinuclidine nitrogen turns away from the quinoline ring and is oriented in the same direction as the methoxy oxygen. We have also used ^1H NMR in CD_3CN to examine the conformation in solution. The $^3J_{H8,H9}$ coupling constant is 2.9 Hz corresponding to the open conformation (Figure 5).[22] Taking into account our X-ray and ^1H NMR results and the above literature information, the transition state assembly in the fluorination of **1a** with *N*F-Q·BF_4 generated from the quinine/Selectfluor combination is assumed to be as shown in Figure 6. It should be noted that the (*R*)-selectivity of the fluorination product is consistent with this transition state model. The physical relationship between the N−F bond and the quinoline ring makes impossible any contribution of an aromatic $\pi-\pi$ stacking interaction between the indanone and quinoline rings in the transition state. Four possible transition state structures TS−I−TS−IV have been proposed for the fluorination reaction based on experimental findings, as was outlined in Figure 6. Two of them, TS-II and TS-IV, are clearly disfavored orientations based on steric considerations. The proposed TS-I structure becomes less likely due to the fact that the benzyl group positions near the methylene protons of quinuclidinium moiety. Approach by silyl enol ether **1a** to *N*F-Q·BF_4 via TS-III should be favored considering the steric hindrance of the trimethysilyl, benzyl, and methoxy groups, although details of the reaction mechanism remain unknown (Figure 6).

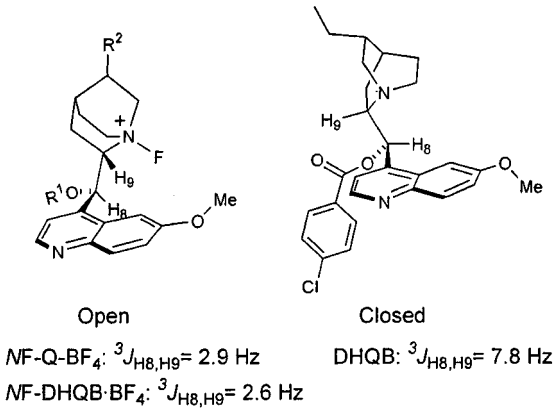


Figure 5. Schematic drawing showing (a) the open and (b) the closed conformation of the quinine derivatives.

The transition state for the (*R*)-selective fluorination of indanones by *N*F-DHQB·BF_4 is presumably via the open conformation similar to that by *N*F-Q·BF_4. DHQB itself has been shown to exist predominantly in the closed conformation II accompanied by small amounts of open conformation III.[22]

(21) Banks, R.; Sharif, I.; Pritchard, R. G. *Acta Crystallogr*. **1993**, *49*, 492−495.

(22) (a) Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H. *J. Org. Chem.* **1990**, *55*, 6121−6131. (b) Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H.; Svendsen, J. S.; Marko, I.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 8069−8076.

(23) Just before submission of this manuscript, a similar paper appeared on the X-ray crystallography of *N*-fluorocinchonidine, although the authors did not discuss the conformational aspect. Cahard, D.; Audouard, C.; Plaquevent, J.-C.; Toupet, L.; Roques, N. *Tetrahedron Lett.* **2001**, *42*, 1867−1869.

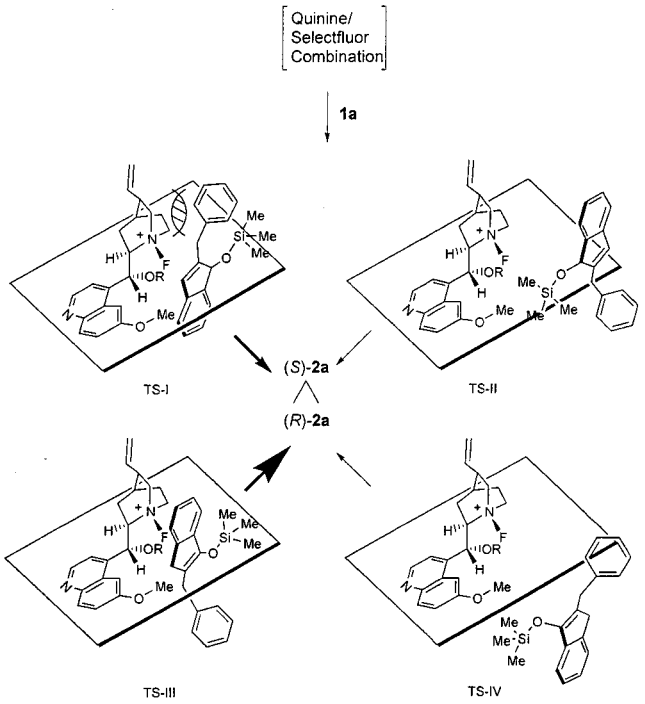


Figure 6. Proposed transition-state assemblies.

However, when the quinuclidine nitrogen is protonated, the conformation is changed to the open conformation III. To see if this conformational change also occurs upon fluorination of nitrogen in the DHQB quinuclidine ring, ^{1}H NMR spectra of both DHQB and *N*F-DHQB·BF_4 were examined in CD_3CN (room temperature). Isolation of *N*F-DHQB·BF_4 was achieved as follows; Selectfluor (1.3 equiv) was added to a suspension of DHQB (1.0 equiv). After 10 min of stirring, the clear solution was concentrated under reduced pressure to give a white solid. The solid was suspended in AcOEt and the suspension was filtered. Concentration of the filtrates yielded *N*F-DHQB·BF_4 as a colorless oil accompanied by small amounts of DHQB and Selectfluor, as shown by ^{1}H NMR analysis. The $^3J_{H8,H9}$ coupling constant of DHQB was 7.8 Hz, which corresponds to a closed conformation, whereas the $^3J_{H8,H9}$ of *N*F-DHQB·BF_4 was decreased to 2.6 Hz. This is in good agreement with the open conformation found for the protonated DHQB[22] and for *N*F-Q·BF_4. We feel these data support a predominant open conformation for *N*F-DHQB·BF_4 in solution (Figure 5). However, further investigation using X-ray analysis of *N*F-DHQB·BF_4, ^{1}H NMR NOE studies, and MO analysis will be carried out to clarify this issue further. The details of the mechanism of enantioselective fluorination with other *N*-fluorocinchona alkaloids such as *N*F-DHQDA·BF_4, *N*F-$(DHQ)_2$AQN·BF_4, and *N*F-$(DHQD)_2$PYR·BF_4 cannot be discussed at this time since no structural information is presently available. Isolation and conformational studies of these series of *N*F-cinchona alkaloids are in progress and will be reported in due course.

Fluorination of the silyl enol ethers **1** and the active methylene compounds **4**, **5**, and oxindoles **8** involve different modes of anion generation. As can be seen in the Experimental Section, equimolar amounts of Selectfluor and alkaloids were used for the fluorination of silyl enol ethers **1**, while a slight excess (or 2 equiv) of alkaloids relative to Selectfluor was needed for the fluorination of compounds **4**, **5**, and **8**. In the fluorination of **1**, we assume that desilylation of the enol ethers is preceded by the attack of BF_4^- to produce anions and Me_3SiF (or Me_3Si^+/BF_4^-) as a byproduct, although we do not have any direct evidence for this. In contrast, fluorination of **4**, **5**, and **8** could be catalyzed by alkaloid to produce anions. Especially in the fluorination of **8**, an additional molar equivalent of alkaloid (moiety) plays an essential role in the deprotonation step.

Conclusion

We have developed a mild and practical enantioselective fluorination reaction using commercially or readily available cinchona alkaloid derivatives in combination with Selectfluor. A number of cyclic and acyclic carbonyl compounds were fluorinated enantioselectively to give the corresponding α-fluoro compounds in good to excellent yields. Since a variety of cinchona alkaloid derivatives are readily available, this provides useful flexibility for in situ generation of the *N*-fluoro reagents. Shortly after the publication of our preliminary report,[8] a similar approach for enantioselective fluorination using **isolated** *N*-fluoro cinchona alkaloids appeared independently (up to 61% ee).[10] A clearer understanding of the mechanism by which the alkaloid confers enantioselectivity to the process will require more study, especially concerning the conformation of *N*-fluorocinchona alkaloids. Indeed, we feel this novel approach will provide principles and insights that will advance the developing area of enantioselective fluorination. A catalytic version of this fluorination reaction is under investigation.[24]

Experimental Section

A Typical Experimental Procedure for the Fluorination of 1: 2-Benzyl-2-fluoro-1-indanone (2a). A solution of **1a** (40.0 mg, 0.136 mmol) in MeCN (3 mL) was added to the DHQB/Selectfluor combination [prepared in situ from DHQB (98%, 78.0 mg, 0.163 mmol) and Selectfluor (95%, 60.0 mg, 0.163 mmol) in MeCN (3 mL) stirred in the presence of 3 Å MS at room temperature for 1 h] at −20 °C. After the mixture was stirred overnight, water was added to the reaction mixture and it was extracted with AcOEt. The organic phase was washed with 5% HCl, saturated $NaHCO_3$, and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a crude oil, which was purified by preparative TLC on silica gel (benzene) to give **2a** (32.2 mg, 99%) as a colorless oil. Ee was determined to be 89% by HPLC analysis using a Chiralcel OB column (10% 2-propanol in hexane). $[\alpha^{30}]_D$ +110.2° (*c* 1.53, $CHCl_3$); spectral data for **2a** (^{1}H NMR, ^{19}F NMR, IR, mass, HRMS) corresponded to literature values.[7a]

A Typical Experimental Procedure for the Fluorination of 4: Ethyl α-cyano-α-fluoro-α-tolyl acetate (3a). A solution of **4a** (50.0 mg, 0.246 mmol) in CH_2Cl_2 (4 mL) was added to the DHQDA/Selectfluor combination [prepared in situ from DHQDA (181 mg, 0.493 mmol) and Selectfluor (95%, 138 mg, 0.370 mmol) in MeCN (3 mL) in the presence of 3 Å MS at room temperature for 1 h] at −80 °C. After the mixture was stirred for 2 h, water was added, and the reaction mixture was extracted with AcOEt. Workup similar to that used in the fluorination of **1a** gave **3a** (43.5 mg, 80%) as a colorless oil. Ee = 87% (HPLC, Chiralcel OJ, 1% 2-propanol in hexane); $[\alpha]^{25}_D$ −20.7° (*c* 2.69, $CHCl_3$); spectral data for **3a** (^{1}H NMR, ^{19}F NMR, IR, mass, HRMS, optical rotation) corresponded to literature values.[13b]

A Typical Experimental Procedure for the Fluorination of 8: 3-Benzyl-3-fluorooxindole (7a). A solution of **8a** (20 mg, 0.0896 mmol) in MeCN (4 mL) was added to the $(DHQ)_2$AQN/Selectfluor combination [prepared in situ from $(DHQ)_2$AQN (115 mg, 0.134 mmol) and Selectfluor (97%, 49 mg, 0.134 mmol) in MeCN (3 mL) at room temperature for 1 h] at 0 °C. (The reaction was performed in the absence of 3 Å MS since all the commercially available bis-cinchona alkaloids are anhydrates.) After the mixture was stirred at 0 °C for 1−2 days, water was added, and the reaction mixture was extracted with AcOEt. Workup similar to that used in the fluorination of **1a** gave **7a** (19.7 mg, 91%) as white solid. Ee = 78% (HPLC, Chiralcel OB, 3%

(24) (a) Catalytic bromination and chlorination using a very similar approach has been reported. Wack, H.; Taggi, A. E.; Hafez, A. M.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2001**, *123*, 1531−1532. (b) Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 4359−4362.

2-propanol in hexane); mp 122−124 °C (hexane/CH_2Cl_2); $[\alpha]^{25}_D$ −18.8° (*c* 1.17, MeOH); ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.24 (brs, 1H, NH), 7.19−7.28 (m, 4H, ArH), 7.08−7.09 (m, 2H, ArH), 6.98−7.00 (m, 2H, ArH), 6.79 (d, J = 7.6 Hz, 1H, ArH), 3.57 (dd, 1H, J = 13.2, 10.6 Hz, CH*H*), 3.23 (dd, 1H, J = 22.4, 13.5 Hz, C*H*H); ^{19}F NMR (254 MHz, $CDCl_3$) δ −155.77 (dd, J = 22.2, 10.2 Hz); IR (KBr) ν_{max} 3162, 1718 cm^{-1}; MS *m*/*z* 241 (M^+); HRMS calcd for $C_{15}H_{12}NFO$ 241.0903, found 241.0904.

Acknowledgment. We thank Prof. Yoshio Takeuchi for generously sharing his facilities, for kind encouragement, and for giving us the opportunity to study in the field of fluorine chemistry. We are also much indebted to Dr. Kenneth L. Kirk (National Institutes of Health) for his constant advice. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan. N.S. wishes to thank the Takeda Chemical Industries, Ltd. Award in Synthetic Organic Chemistry, Japan for support.

Supporting Information Available: Complete experimental procedures and spectral data for all new compounds, and ORTEP diagrams of *N*F-Q·BF_4 and detailed crystallographic information (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA010789T