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Design, Synthesis, and Evaluation of a Novel Class of Enantioselective Electrophilic Fluorinating Agents: *N*-Fluoro Ammonium Salts of *cinchona* Alkaloids (F-CA-BF_4)

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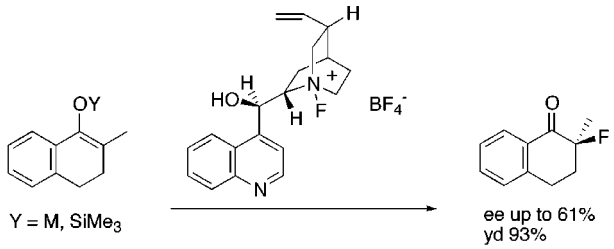
ABSTRACT



The first enantiopure *N*-fluoro quaternary ammonium salts of *cinchona* alkaloids as enantioselective fluorinating agents are reported. A one-step transfer–fluorination on the naturally occurring *cinchona* alkaloids gave the fluorinating agents F-CA-BF_4. This new generation of fluorinating agents exhibited asymmetric induction up to 61% on fluorination of enolates and silyl enol ethers of 2-methyl-1-tetralone.

In the continuing search for improved drugs and agrochemicals, fluorine compounds are known to exert a unique and profound influence on biological activity and selectivity. The importance of chirality in pharmacologically and biologically active molecules associated with the astonishing properties of the fluorine atom has led to huge efforts in the asymmetric synthesis of chiral nonracemic fluoro-organic molecules with a fluorine atom on a stereogenic center.[1] The development of effective methodologies for the preparation of new selectively fluorinated, stereochemically defined compounds is critical to further advances of fluorine chemistry. The auxiliary-controlled asymmetric synthesis of α-fluoro carbonyl compounds has so far been superior to the reagent-controlled processes.[2] Therefore, it is a challenging problem to develop efficient processes for enantioselective fluorination. The pioneering work of Differding and Lang in 1988 led to the development of the *N*-fluorocamphorsultam **1** as the first enantioselective electrophilic fluorinating agent.[3] Davis reported in 1993 and 1998 closely related structures **2**.[4] Recently, Takeuchi designed the saccharin-based agents **3**[5] as well as acyclic *N*-fluoro compounds **4** and **5**[6] (Figure 1).

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(1) *Enantiocontrolled Synthesis of Fluoro-Organic Compounds*; Soloshonok, V. A.; Ed.; John Wiley & Sons. LTD, Chichester, U.K., 1999.

(2) Davis, F. A.; Kasu, P. V. N. *Org. Prep. Proced. Int.* **1999**, *31*(2), 125−143.

(3) Differding, E.; Lang, R. W. *Tetrahedron Lett.* **1988**, *29*, 6087−6090.

(4) (a) Davis, F. A.; Zhou, P.; Murphy, C. K. *Tetrahedron Lett.* **1993**, *34*, 3971−3974. (b) Davis, F. A.; Zhou, P.; Murphy, C. K.; Sundarababu, G.; Qi. H.; Przeslawski, R. M.; Chen, B-C.; Carroll, P. J. *J. Org. Chem.* **1998**, *63*, 2273−2280.

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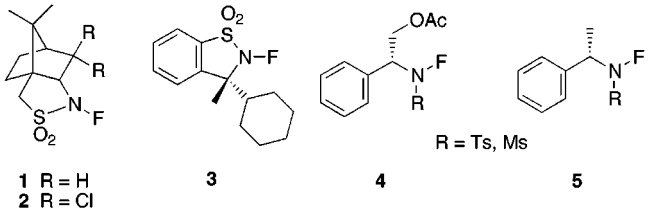
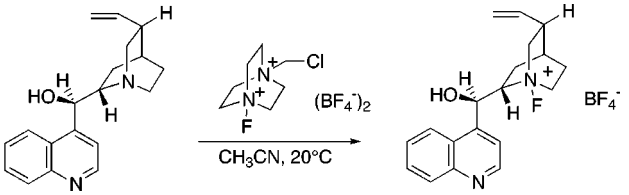


Figure 1. First generation of chiral fluorinating reagents: uncharged N−F reagents.

The synthesis of reagents **1**−**5** requires several steps, the ultimate step being the N−F bond formation, by means of either elemental fluorine F_2 or $FClO_3$. The unwelcome prospect of handling elemental fluorine led us to proceed by transfer fluorination as reported by Banks on quinuclidine with Selectfluor.[7] The 1-azabicyclo[2.2.2]octane cage occurs notably in *cinchona* alkaloids. In this paper we describe the synthesis, characterization, and applications of *N*-fluoro *cinchona* alkaloids, which form a new class of enantioselective fluorinating agents, i.e., charged $[N-F]^+$ reagents.

Cinchona alkaloids have a venerable history in the field of asymmetric synthesis owing to their established ability to induce asymmetry, and we decided to take advantage of this naturally occurring cheap source of chirality bearing the quinuclidine moiety for the transfer−fluorination approach with Selectfluor. At first Bank's fluorine-transfer procedure was applied to an equimolar mixture of cinchonidine and Selectfluor in acetonitrile. Complete transfer was achieved within 20 min according to ^{19}F NMR analysis of the reaction mixture. A double precipitation procedure yielded the *N*-fluoro cinchonidinium salt, which was recrystallized in acetone to yield pure F-CD-BF_4[8] (Scheme 1). It is a white

Scheme 1. Synthesis of F-CD-BF_4



solid, virtually nonhygroscopic, free flowing, and crystalline, and is high melting (189 °C, dec).

Cinchonine, quinine, and quinidine were also subjected to the analogous fluorine-transfer procedure. Structures are depicted in Figure 2.

To evaluate the ability of these reagents to promote enantioselective fluorination, we targeted α-fluoro carbonyl compounds via their enolates. All previously reported agents for enantioselective fluorination have been tested on the enolate of 2-methyl-1-tetralone as model substrate. The results of our evaluation on the same substrate allowed a direct comparison between the first generation of uncharged

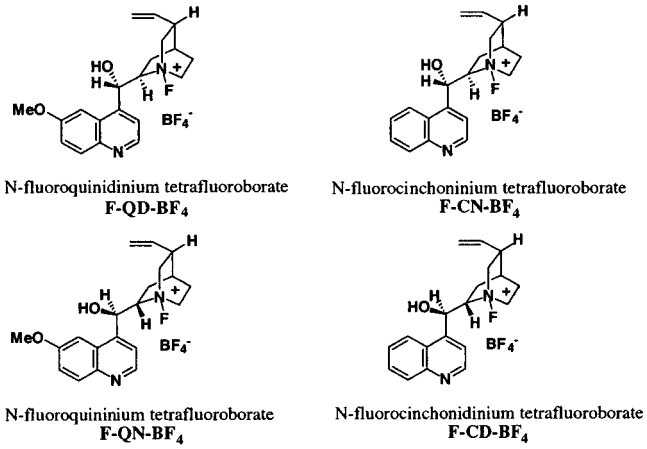
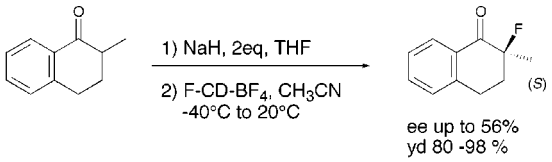


Figure 2. $[N-F]^+$ enantiopure fluorinating reagent.

N−F fluorinating agents and our new class of chiral N-fluoro quaternary ammonium agents $[N-F]^+$. Preliminary experiments demonstrated that sodium hydride in THF was a suitable base for quantitative conversion of 2-methyl-1-tetralone into its sodium enolate; however, the fluorination only yielded a moderate amount (40−50%) of the expected 2-fluoro compound. A protonation of the enolate by the free OH group of the alkaloid could explain the moderate yield of the fluorination. It is interesting to note that protonation occurred enantioselectively since a 20% ee was measured on the recovered 2-methyl-1-tetralone. Indeed we circumvented this problem by using 2 equiv of base, and the fluorination became quantitative (Scheme 2). Alternatively,

Scheme 2. Fluorination of the Enolate of 2-Methyl-1-tetralone



the hydroxyl function could be protected.[9]

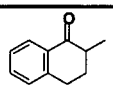
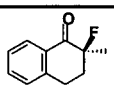
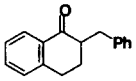
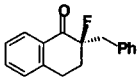
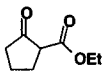
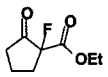
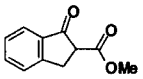
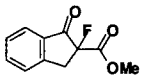
All four *N*-fluoro cinchonium salts were evaluated in the fluorination reaction (Table 1), with F-CD-BF_4 giving the

Table 1. Evaluation of the Four F-CA-BF_4 Agents for the Fluorination of 2-Methyl-1-tetralone Sodium Enolate

entry	$[N-F]^+$ reagent	ee (%)[a]	config[b]	yield (%)
1	F-CD-BF_4	50	*S*	98
2	F-CN-BF_4	40	*R*	70
3	F-QD-BF_4	27	*R*	87
4	F-QN-BF_4	20	*S*	98

[a] The ee values were determined by HPLC analysis using a Chiralcel OB-column (hexane/^{i}PrOH). [b] The absolute configuration was determined by measurement of the optical rotation and comparison with values reported in the literature (ref 4b).

Table 2. Enantioselective Fluorination of Sodium Enolate with F-CD-BF_4

substrate	T(°C)	product	ee (%)[a]	yield (%)	Literature ee (%) (yield (%)) Chiral reagent[b]				
					1	**2**	**3**	**4**	**5**
	-40 -60		50 56	98 80	25 (28)	76 (53)	74 (67)	8 (8)	32 (16)
	-40		42	96			88 (79)	9 (6)	
	-40		40	98	70 (63)	34 (59)		6 (23)	30 (6)
	-40		36	95					

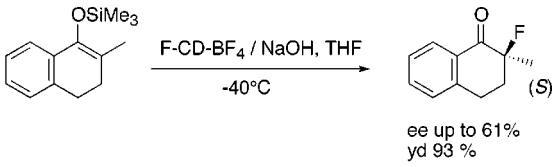
[a] The ee values were determined by HPLC or GC analysis (for more details see Supporting Information). [b] See Figure 1.

highest enantioselectivity with the fluorinated stereocenter having the (*S*)-configuration. The (*R*)-enantiomer was obtained when using the pseudoenantiomeric F-CN-BF_4.

Owing to the solubility characteristics of the $[N-F]^+$ reagents, the reactions were carried out either in a THF/acetonitrile mixture or under heterogeneous conditions with a suspension of F-CA-BF_4 in THF with only minor effect on the enantiomeric excesses. As shown in Table 2, fluorination of 2-benzyl-1-tetralone, ethyl cyclopentanone-2-carboxylate, and methyl indanone-2-carboxylate proceeded in an enantioselective fashion with F-CD-BF_4. Comparison data for these substrates using the reagents **1**−**5** reported in the literature are provided in Table 2. Although moderate enantiomeric excesses were recorded, F-CA-BF_4 appeared less substrate-dependent than reagents **1**−**5**. Moreover, chemical yields are significantly higher with the $[N-F]^+$ reagents. We are currently optimizing both the fluorinating agents and the reaction conditions for a better enantioselectivity in the fluorination of enolates.

We also designed this new class of chiral reagents for their stronger fluorinating power ($[N-F]^+$ vs N−F). Thus fluorination of enol derivatives such as silyl enol ethers can now be considered, where chiral uncharged N−F fluorinating agents were discarded as a result of their low reactivity toward such poor nucleophiles. We herein report the first enantioselective electrophilic fluorination on the trimethylsilyl enol ether of 2-methyl-1-tetralone (Scheme 3). The degree of asymmetric induction exhibited by the $[N-F]^+$ reagents is strongly dependent on the reactions conditions but slightly higher than for the fluorination of enolates. We found that the addition of sodium hydroxide to the fluorinating agent considerably improved both the reactivity and the stereoselectivity. Here again F-CD-BF_4 was the best reagent in terms of enantioselectivity with enantiomeric excesses up to 61% and (*S*)-configuration at the newly created quaternary fluoro stereocenter.

Scheme 3. Fluorination of the Trimethyl Silyl Enol Ether of 2-Methyl-1-tetralone



This approach involving silyl enol ethers is more promising on account of the higher asymmetric induction noted. The optimization and the study of the mechanism of stereoselection are the subject of current investigations.

In summary, a one-step synthesis of a novel class of fluorinating agents has been developed by transfer−fluorination, i.e., $[N-F]^+$ derivatives of *cinchona* alkaloids. Enantioselective fluorination of enolates and silyl enol ethers afforded quaternary α-fluoro carbonyl compounds in excellent yield and promising enantiomeric excess.

Acknowledgment. The authors thank RHODIA Organique Fine for helpful discussions and support.

Supporting Information Available: Representative experimental procedures and characterization data for F-CD-BF_4 and the fluorinated products shown in Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) (a) Takeuchi, Y.; Koizumi, T.; Suzuki. T.; Satoh. A.; Konno. K. Japanese patent JP 09,249,653. *Chem. Abstr.* **1997**, *127*, 262674j. (b) Takeuchi, Y.; Suzuki, T.; Satoh, A.; Shiragami, T.; Shibata, N. *J. Org. Chem.* **1999**, *64*, 5708−5711.

(6) 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) Abdul-Ghani, M.; Banks, R. E.; Besheesh, M. K.; Sharif, I.; Syvret, R. G. *J. Fluorine Chem.* **1995**, *73*, 255−257.

(8) This descriptor was chosen by analogy with F-TEDA-BF_4 for Selectfluor. F-CA-BF_4 stands for fluoro *cinchona* alkaloids tetrafluoroborate, with CD, CN, QD, and QN being the four alkaloids of the series.

(9) *O*-Acetyl, benzoyl, and methyl derivatives of F-CD-BF_4 were also investigated.