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N-Fluorocinchonidinium tetrafluoroborate F-CD-BF_4: purification and structure elucidation of this novel enantioselective electrophilic fluorinating agent

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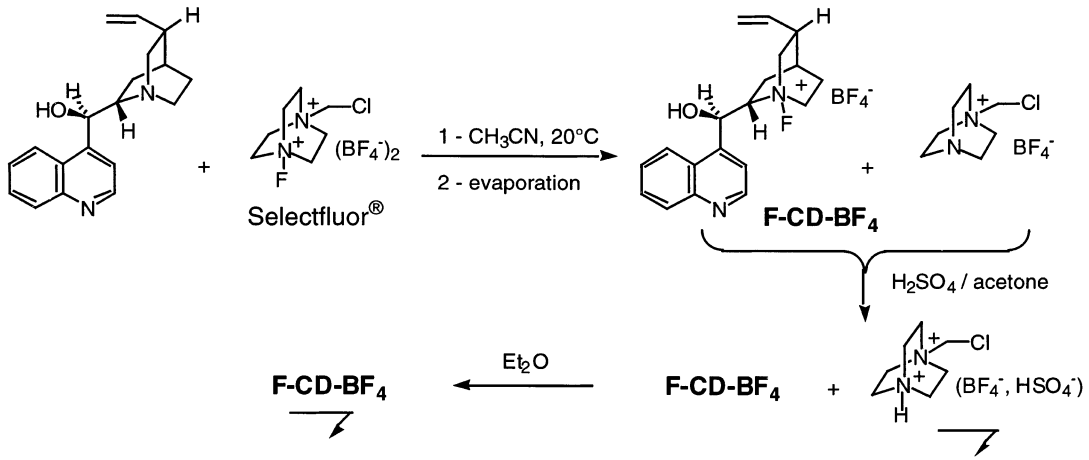
Abstract—The first ever enantiopure *N*-fluoro quaternary ammonium salt of cinchonidine (F-CD-BF_4) was prepared as an enantioselective fluorinating agent. A one-step transfer-fluorination of the quinuclidine moiety with Selectfluor® gave the $[N–F]^+$ reagent. The X-ray structure of F-CD-BF_4 was determined, which shows the N–F distance (1.409(7) Å) close to that found in other N–F compounds.

The fascinating properties of organic molecules containing fluorine, as well as the crucial need to control chirality, have led to huge efforts in the asymmetric synthesis of chiral non-racemic fluoro-organic molecules.[1] Fluorinated chiral building blocks are commonly used for the elaboration of molecules, an alternative method being the late introduction of the fluorine atom.[2]

Recently, we introduced a novel class of enantioselective electrophilic agents,[3] which are the *N*-fluoro ammonium salts of cinchona alkaloids (F-CA-BF_4), as



Scheme 1. Preparation and purification of F-CD-BF_4.

Keywords: alkaloids; enantioselection; fluorine compounds; halogenation; X-ray crystallography.

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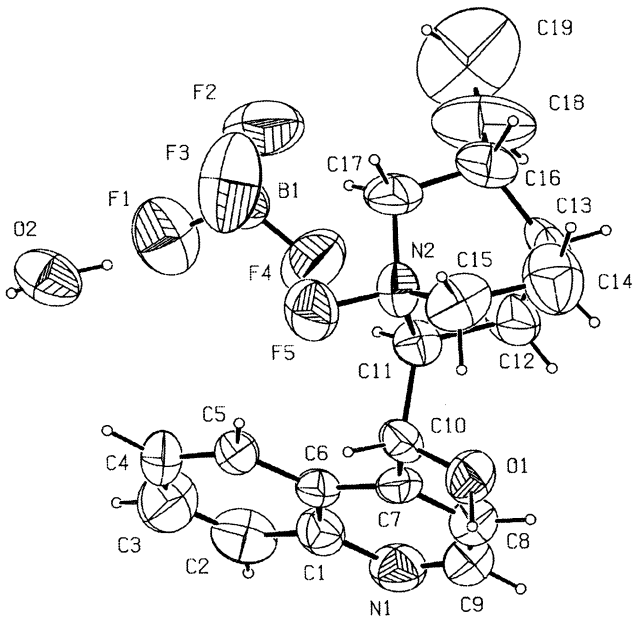

Figure 1. *N*-Fluorocinchonidinium tetrafluoroborate F-CD-BF_4, H_2O drawn using PLATON-98.[9]

new tools for the direct asymmetric fluorination, a most formidable goal of fluorine chemistry. These new reagents were synthesised, isolated as pure products, and applied in the enantioselective fluorination of enolates and silyl enol ethers of various ketones. Simultaneously and independently Takeuchi and co-workers reported a substantially similar approach consisting of a combination of cinchona alkaloid derivatives and Selectfluor®. They did not isolate the reagent in the solid-state and they presumed, but did not prove, the $[N–F]^+$ structure.[4] Since further investigation was clearly needed for this kind of reagent, we herein report the purification and X-ray structure of the first $[N–F]^+$ chiral fluorinating agent derived from cinchonidine. In gaining structural information of this new reagent $[N–F]^+$, we seek to better understand the nature of the N–F bond, as well as to probe the mechanism of electrophilic fluorinations.

The synthesis of F-CD-BF_4 is straightforward and does not require the handling of elemental fluorine. F-CD-BF_4 was prepared according to Bank's fluorine-transfer procedure[5] by mixing an equimolar amount of cinchonidine and Selectfluor® in acetonitrile at room temperature. The reaction was completed within 20 minutes, as monitored by ^{19}F NMR analysis of the reaction mixture. Acetonitrile was removed under reduced pressure and the resulting white solid was dissolved in acetone. Addition of a solution of 96% H_2SO_4 in acetone caused the precipitation of 1-chloro-4-hydro-1,4-diazoniabicyclo[2.2.2]octane hydrogen sulphate tetrafluoroborate. To the filtrate was added diethyl ether which gave the precipitation of the *N*-fluorocinchonidinium salt (Scheme 1). F-CD-BF_4 was obtained in 84% yield.

The amorphous white solid is non-hygroscopic and melts at 189°C. The stability of F-CD-BF_4 was studied in solution and in the solid-state. CAUTION: an exothermic phenomenon (62 kcal/mol) occurred when the solid was heated at 90–130°C in a glass vessel. ^1H, ^{13}C and ^{19}F NMR spectroscopy and elemental analysis strongly support the structure of the *N*-fluoro ammonium salt. For a thorough structural characterisation, colourless crystals of F-CD-BF_4 were grown by cooling a saturated acetone solution and X-ray structural analysis was performed (Fig. 1).[6] According to the X-ray structure of F-CD-BF_4, the crystals contain 1 molar equivalent of water, and the localisation of the fluorine atom on the nitrogen atom of the quinuclidine moiety is clearly established. The positive charge on the nitrogen is counterbalanced by the non-nucleophilic anion tetrafluoroborate. The N–F bond length of 1.409(7) Å measured in F-CD-BF_4 is similar to that of the *N*-fluoroquinuclidinium triflate (1.407(6) Å)[7] and substantially longer than the N–F bond length in Selectfluor® (1.37(2) Å).[8]

The present results clearly indicate that the asymmetric induction observed in enantioselective fluorination of prochiral substrates, either by isolated reagents[3] or by a combination alkaloid/Selectfluor®,[4] is due to the same *N*-fluoro alkaloid. In addition, the crystal structure herein reported gives crucial information on the conformation of the reagent, which will be a useful tool for rationalising the mechanism of the enantioselective fluorination.

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6. $C_{19}H_{22}ON_2F$, BF_4, H_2O; $M_r=418.21$, orthorhombic, $P2_12_12_1$, $a=9.528(11)$, $b=12.085(3)$, $c=20.805(5)$ Å, $V=1999(2)$ Å^{-3}, $Z=4$. Sample (0.35×0.22×0.11 mm) studied

on an automatic diffractometer CAD4 NONIUS. The data collection gives 2502 reflections from which 2478 were independent with $I>2\sigma(I)$. After Lorenz and polarization the structure was solved with SIR-97 (see Ref. 10) and refined with SHELXL-97 (see Ref. 11) with the resulting $R=0.062$, $R_w=0.11$ and $S_w=0.946$ (residual $\Delta\rho\leq 0.213$ e Å^{-3}). Atomic coordinates, anisotropic displacement parameters, and bond lenghts and torsion angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC).

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