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Enantioselective electrophilic fluorination: a study of the fluorine-transfer from achiral N–F reagents to cinchona alkaloids

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Abstract

A transfer fluorination on cinchona alkaloids with the aid of achiral N–F fluorine-transfer reagents is described. Ten commercially available reagents were evaluated. Selectfluors™ **9** and **10**, Accufluor™ **11**, *N*-fluorobenzenesulfonimide (NFSi) **13**, and *N*-fluoro-2,6-dichloropyridinium tetrafluoroborate **17** are effective fluorine-transfer reagents. The *N*-fluoroammonium salts of cinchona alkaloids thus prepared were employed in the construction of stereogenic fluorinated carbon centers with enantioselectivity as high as 85%. We also demonstrated that ionic liquids are effective ''green'' solvents for the development of this methodology.

Keywords: *N*-Fluoro compounds; Transfer fluorination; Enantioselective electrophilic fluorination; Ionic liquids

1. Introduction

Commercially available achiral electrophilic fluorinating agents of the N–F class have allowed the development of new methodology for the synthesis of fluorinated molecules [1]. Achiral N–F reagents were used in enantioselective fluorination of β-ketoesters mediated by chiral phase-transfer catalysts [2] or metal catalysts [3,4]. Chiral N–F reagents, described by us and others, have emerged for the asymmetric construction of fluorinated carbon centers [5]. The synthesis of reagents **1–7** requires several steps, the ultimate step being the N–F bond formation, by means of either elemental fluorine F_2 or $FClO_3$ (Fig. 1) [6–11]. In order to overcome the disadvantages of using elemental fluorine, we proceeded by transfer fluorination. Naturally occurring cinchona alkaloids were selected as the source of chirality to prepare in a single step the new class of $[N–F]^+$ reagents **8** (Fig. 1). In this way we demonstrated that *N*-fluoroammonium salts of cinchona alkaloids **8**, prepared by transfer fluorination with Selectfluor™ are efficient enantioselective electrophilic fluorinating agents [12–15].

Chiral $[N–F]^+$ fluorinating agents have thus been highlighted as a class of reagents possessing distinctive stability, reactivity and enantioselectivity, characteristics which compare favourably with the previous class of neutral N–F reagents **1–7**.

In the achiral series, the pioneering work on transfer fluorination not requiring the use of elemental fluorine was reported by Banks and co-workers in the preparation of *N*-fluoroquinuclidinium salts [16]. Taylor and Meier produced *N*-fluoro sulfonamides by transfer fluorination with *N*-fluorobenzenesulfonimide (NFSi) from the corresponding potassium salt of sulfonamides while fluorine-transfer starting from the neutral sulfonamides failed [17]. Singh and Shreeve also reported an application of Selectfluor™ in electrophilic fluorination of primary and secondary amines [18]. In this paper we describe a study of 10 fluorine-transfer reagents for the preparation of chiral *N*-fluoroammonium salts of cinchona alkaloids and their application in enantioselective electrophilic fluorination.

2. Results and discussion

In this investigation, we explored the commercially available fluorine-transfer reagents. Three of these electrophilic fluorinating agents are based on triethylenediamine salts

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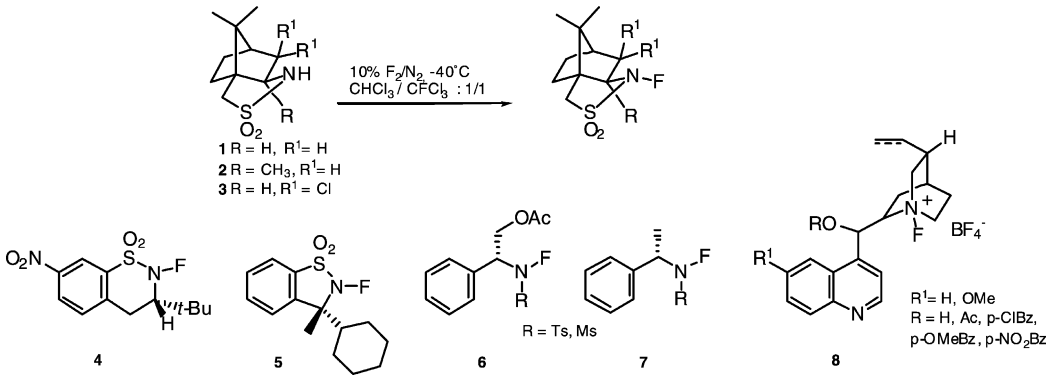


Fig. 1. Chiral electrophilic fluorinating agents.

(F-TEDA **9**–**11**), **12** is derived from quinuclidine, **13** is a sulfonimide, **14** is a sulfonamide and compounds **15**–**18** are a series of agents consisting of a pyridinium ring and its counter anions (Fig. 2).

The reaction was performed either in acetonitrile or in an ionic liquid such as 1-hexyl-3-methylimidazolium hexafluorophosphate [hmim][PF_6]. The transfer fluorination from reagents **9**–**18** to the tertiary nitrogen site in *p*-chlorobenzoylquinine (*p*ClBzQN) was studied and followed by ^{19}F and ^{1}H NMR analysis (Scheme 1). The reaction was found to be complete within 30 min with fluorine-transfer reagents **9**–**11**, **13** and **17** (Table 1). Other reagents tried lacked sufficient fluorinating power to make possible an efficient fluorine-transfer.

In our original study, only Selectfluor^{TM} tetrafluoroborate **9** was explored [12], we now validate the series of F-TEDA salts **10** and **11** as efficient fluorine-transfer reagents. The *N*-fluoroquinuclidinium salt **12** which was described as a less powerful fluorine-transfer reagent [16] did not lead to F-*p*ClBzQN-BF_4. A comparison between *N*-fluorobenzenesulfonimide **13** and sulfonamide **14** revealed that only NFSi was capable of transfer fluorination, demonstrating the necessity of two strong electron withdrawing groups in the sulfonimide. Moreover, NFSi is a cheaper alternative to Selectfluor^{TM}. Within the series of *N*-fluoropyridinium salts, the fluorinating ability is determined by substituents on the pyridine ring. Methyl groups decrease the ability while chlorine atoms have the opposite effect thus making the agents **17** suitable for transfer fluorination. The relationship between variable fluorinating power and ^{19}F NMR chemical shifts of *N*-fluoropyridinium salts was discussed by Umemoto et al. [19].

Particularly interesting among the five effective fluorine-transfer reagents is the *N*-fluoro-2,6-dichloropyridinium tetrafluoroborate **17** which possesses a higher fluorine content (3.94 mmol/g) than other competitive fluorine-transfer

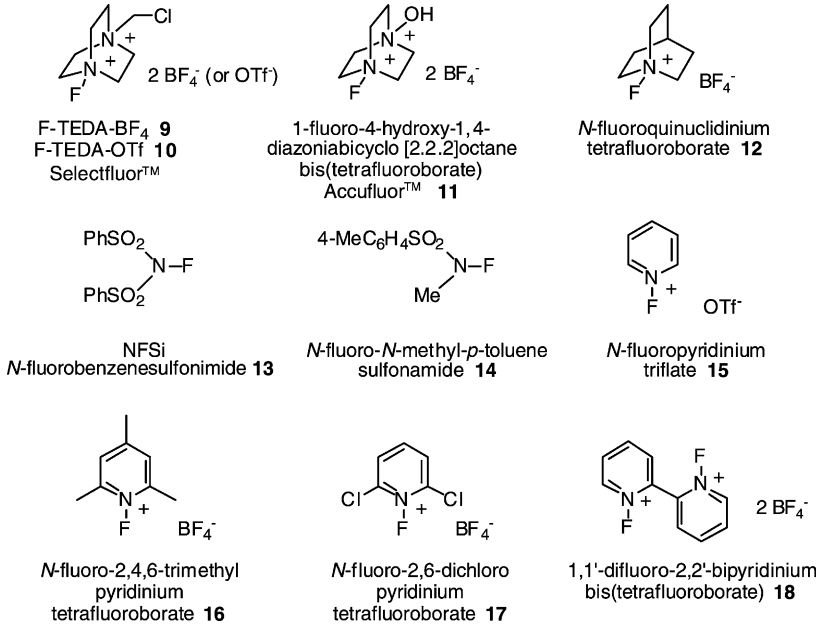
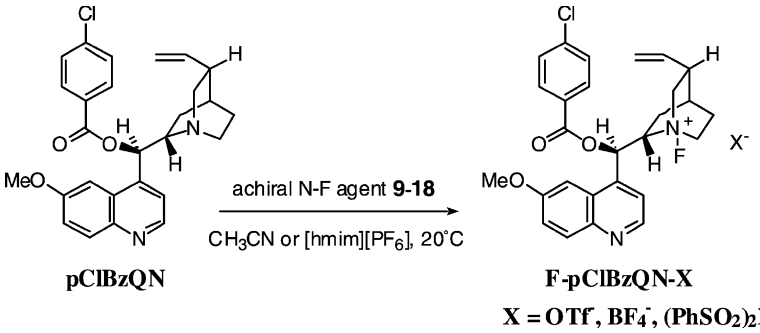


Fig. 2. Achiral electrophilic fluorinating agents.



Scheme 1.

Table 1
Study of the transfer fluorination on *p*-chlorobenzoylquinine (*p*ClBzQN)

Achiral N–F reagent	^{19}F NMR (δ in ppm)	Chiral $[N–F]^+$ reagent	^{19}F NMR (δ in ppm)
9	46.2; −149.5; −149.6	F-*p*ClBzQN-BF_4	43.6; −149.9; −150.0
10	46.1; −78.1	F-*p*ClBzQN-OTf	43.7; −78.1
11	42.2; −149.8; −149.9	F-*p*ClBzQN-BF_4	43.6; −149.9; −150.0
12	57.8; −150.1	No reaction	
13	−38.6	F-*p*ClBzQN-N(SO_2Ph)$_2$	43.7
14	−37.6	No reaction	
15	47.4; −78.1	No reaction	
16	17.2; −149.7; −150.4	No reaction	
17	31.4; −149.2; −150.2	F-*p*ClBzQN-BF_4/2,6-dichloropyridine	43.6; −149.9; −150.0
18	43.7; 35.2; −148.8; −149.0; −150.1	No reaction	

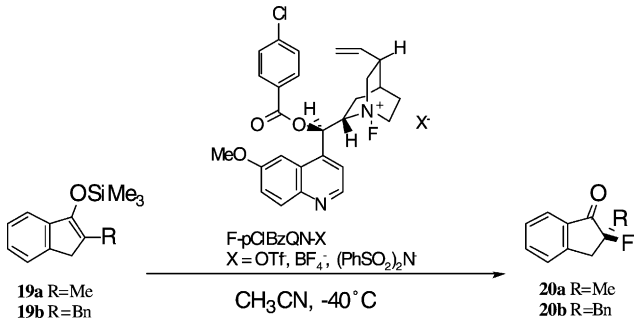
reagents (2.82 mmol/g for **9**, 2.09 mmol/g for **10**, 3.11 mmol/g for **11**, and 3.17 mmol/g for **13**) and is therefore more cost effective.

Some fluorine-transfer reagents used in the preparation of F-*p*ClBzQN salts lead to by-products. For instance, Selectfluors^{TM} **9**, **10** and Accufluor^{TM} **11** produce TEDA monoquaternary ammonium salts. *N*-Fluoro-2,6-dichloropyridinium tetrafluoroborate **17** produces an equimolecular amount of 2,6-dichloropyridine while NFSi **13** leads to nothing else other than the expected salt F-*p*ClBzQN-N(SO_2Ph)$_2$.

Having prepared these F-*p*ClBzQN salts bearing either a BF_4^-, a OTf^- or a $(PhSO_2)_2N^-$ counter anion, we examined their behaviour in enantioselective electrophilic fluorination on trimethylsilyl enol ether of methyl and benzyl indanone **19a** and **19b** (Scheme 2). This step was performed in acetonitrile, however the choice of solvent was broadened to ionic liquids [20]. Results are reported in Table 2.

With fluorine-transfer reagents which are not effective, we attempted the transfer fluorination on a mixture cinchona alkaloid, silyl enol ether and N–F reagent, but the fluorinated product was not obtained.

As summarised in Table 2, the substrates were fluorinated in excellent yields with good enantioselectivities. Ee's are similar whatever the chiral $[N–F]^+$ salt and whatever their synthetic route since the tetrafluoroborate salt prepared from



Scheme 2.

Table 2
Enantioselective electrophilic fluorination of silyl enol ethers

Fluorine-transfer reagent	Chiral $[N–F]^+$ agent	Substrate[a]	Product	Yield (%)	Ee (%)[b]
9	F-*p*ClBzQN-BF_4	**19a**	**20a**	90	64
13	F-*p*ClBzQN-N(SO_2Ph)$_2$	**19a**	**20a**	91	62
17	F-*p*ClBzQN-BF_4	**19a**	**20a**	97	67
9	F-*p*ClBzQN-BF_4	**19b**	**20b**	98	84
10	F-*p*ClBzQN-OTf	**19b**	**20b**	88	81
11	F-*p*ClBzQN-BF_4	**19b**	**20b**	92	82
13	F-*p*ClBzQN-N(SO_2Ph)$_2$	**19b**	**20b**	94	85
17	F-*p*ClBzQN-BF_4	**19b**	**20b**	97	81

[a] The enantioselective fluorination was run at −40 °C in acetonitrile.
[b] Determined by HPLC analysis.

Selectfluor™ **9**, Accufluor™ **11** or *N*-fluoro-2,6-dichloropyridinium tetrafluoroborate **17** gave ee's ranging from 81 to 84%.

3. Conclusion

The fluorine-transfer long associated with hazardous elemental fluorine can now be achieved with a range of safer N–F reagents. We have demonstrated that transfer fluorination can be performed not only with Selectfluors™ **9** and **10** but also by means of various N–F fluorine-transfer reagents (Accufluor™ **11**, NFSi **13** and *N*-fluoro-2,6-dichloropyridinium tetrafluoroborate **17**). Other reagents possessing lower fluorinating power (**12**, **14**–**16** and **18**) failed to transfer the fluorine atom to the cinchona alkaloids. The chiral *N*-fluoroammonium salts of cinchona alkaloids, thus prepared, are efficient enantioselective electrophilic fluorinating agents.

4. Experimental

All commercially available reagents were used without further purification. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker Avance 300 spectrometer. Chemical shifts are reported in ppm using $CFCl_3$ as internal standard in CD_3CN solvent.

4.1. Transfer fluorination: preparation of N-fluoro-p-chlorobenzoylquininium benzenesulfonimidate F-pClBzQN-N(SO_2Ph)$_2$

N-Fluorobenzenesulfonimide (1.58 g, 5 mmol) in acetonitrile (10 ml) was added slowly to an equimolar amount of *p*-chlorobenzoylquinine (2.31 g, 5 mmol) in acetonitrile (10 ml). The reaction was completed within 30 min. Acetonitrile was removed under reduced pressure and the resulting white solid was dried in vacuo to afford F-*p*ClBzQN-N(SO_2Ph)$_2$ (100% yield). ^{1}H NMR (300 MHz) δ 9.09 (d, $J = 5.6$ Hz, 1H), 8.40–8.00 (m, 8H), 7.84 (dd, $J = 9.1$, 2.3 Hz, 1H), 7.70–7.30 (m, 10H), 5.90 (m, 1H), 5.25 (m, 1H), 5.22 (d, $J = 16.9$ Hz, 1H), 5.10 (d, $J = 10.5$ Hz, 1H), 4.87 (m, 2H), 4.62 (m, 1H), 4.49 (m, 1H), 4.10 (s, 3H), 3.58 (m, 1H), 3.31 (m, 1H), 2.87 (m, 1H), 2.67 (m, 2H), 2.44 (m, 1H); ^{13}C NMR (75 MHz) δ 164.9, 162.1, 149.6, 144.1, 141.6, 138.4, 137.2, 136.9, 133.8, 133.2, 130.6, 129.1, 128.7, 128.4, 128.3, 126.4, 126.1, 121.1, 119.3, 102.8, 73.5 (d, $J = 8.7$ Hz), 69.4 (d, $J = 8.7$ Hz), 68.1 (d, $J = 5.1$ Hz), 59.7 (d, $J = 8.7$ Hz), 57.2, 44.2, 28.4, 28.3, 26.0; ^{19}F NMR (282 MHz) δ 43.7 (1F) ppm; MS (FAB$^+$): 481 (cation).

The procedure was similar when Selectfluor™ **9**, Accufluor™ **11** or *N*-fluoro-2,6-dichloropyridinium tetrafluoroborate **17** were used for the transfer fluorination leading to F-*p*ClBzQN-BF_4, and when Selectfluor™ **10** was used to prepare F-*p*ClBzQN-OTf.

Reactions performed in 1-hexyl-3-methylimidazolium hexafluorophosphate [hmim][PF_6] were stirred for 2 h at 20 °C and the mixture product and solvent directly used in the enantioselective fluorination of silyl enol ethers **19a** and **19b**.

4.2. Enantioselective fluorination: preparation of (R)-2-benzyl-2-fluoro-indan-1-one

N-Fluorobenzenesulfonimide (0.2 mmol, 63.1 mg) and *p*-chlorobenzoylquinine (0.2 mmol, 92.6 mg) were placed in a 10 ml round-bottomed flask containing dry acetonitrile (2 ml) and the mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The reaction mixture was then cooled to −40 °C and (2-benzyl-3*H*-inden-1-yloxy)-trimethyl-silane (0.185 mmol, 54.5 mg) in dry acetonitrile (3 ml) was added dropwise. The reaction was stirred for a further 12 h at −40 °C, which was followed by quenching with water (5 ml). The fluorinated product was extracted with ethylacetate (3× 10 ml). The organic layers were combined and washed with 5% aqueous HCl (20 ml), saturated aqueous $NaHCO_3$ (2× 20 ml), and brine (2× 20 ml). The organic phase was dried over $MgSO_4$, and filtered. Concentration in vacuo and purification by chromatography (silica gel, heptane/diethyl ether 20%) afforded (*R*)-2-benzyl-2-fluoro-indan-1-one (94% yield, 85% ee determined by HPLC analysis using a Chiralcel OB-column (10% *i*PrOH-heptane, 1 ml/min, $\lambda = 254$ nm, retention time: *R* (major) 9.5 min, *S* (minor) 13.4 min). Spectral data are in agreement with literature values [20].

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