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[3] Trimethyl aconitate was converted with dienes to Diels – Alder cycloadducts in 50 – 95 % yield (e.g. cyclopentadiene (toluene, 120 °C) 95 %, cyclohexadiene 50 %, *trans,trans*-1,4-diphenylbutadiene 95 %).[2b]
[4] Reaction of trimethyl aconitate with aromatic and aliphatic aldehydes afforded Knoevenagel condensates in 36 – 93 % yield (e.g. benzaldehyde (toluene, piperidinium acetate, reflux) 56 %, *p*-methoxybenzaldehyde 93 %, cyclohexanecarbaldehyde 60 %).[2b]
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[15] To our knowledge no synthesis has been reported to date for the substituted spiro[pyrrolidinone-3,3-dihydropyrrolinone] framework. For an elegant spiro[pyrrolidinone-3,3′-oxindole] synthesis see reference [16a] and references therein. For a spiro[succinimide-3,3′-oxindole] synthesis see reference [16b]. For spiro[pyrrolidinone-3,3′-pyrrolidinone] syntheses starting from dialkyl malonates see reference [16c].
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[18] The crystal structures of the main diastereomers of **6a** and **6b** have the (5*S**, 6*R**) configuration at the two stereogenic centers.
[19] Crystal structures of the compounds **3a**, **4e**, **5a** – **c**, **6a**, **6d**, **7a** – **c** have been obtained. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos CCDC-163546 (**7c**), CCDC-163547 (**5a**), CCDC-169695 (**3a**), CCDC-169696 (**4e**), CCDC-169697 (**5b**), CCDC-169698 (**5c**), CCDC-169699 (**6a**), CCDC-169700 (**6d**), CCDC-169701 (**7a**), and CCDC-169702 (**7b**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Electrophilic Fluorination Mediated by Cinchona Alkaloids: Highly Enantioselective Synthesis of α-Fluoro-α-phenylglycine Derivatives**

Barbara Mohar, Jérôme Baudoux, Jean-Christophe Plaquevent, and Dominique Cahard*

The discovery of efficient methods for asymmetric fluorination is one of the most fascinating aspects of modern organofluorine chemistry.[1] Indeed, molecules bearing a stereogenic fluorinated carbon atom are of great interest in bio- and medicinal chemistry research. For example, fluorinated amino acids are of special interest for the design of new fluorine-containing peptides with unusual folding patterns, due to H···F bonding, which show interesting biological properties.[2] However, there are to date no reports on the enantioselective synthesis of α-fluoro-α-amino acids.[3]

We recently developed a fundamentally new class of enantioselective electrophilic fluorinating reagents (noted hereafter $[N-F]^+$) derived from cinchona alkaloids.[4] Independently, Shibata and co-workers reported a conceptually similar approach,[5] in which the chiral fluorinating agent was not isolated, but generated in situ. While these studies demonstrated the ability of enantioselective F^+ transfer, further work must be undertaken to reach still higher enantioselectivities. Typical substrates used in both studies were ketones and β-ketoesters for the ease of enolate formation. We report herein the first enantioselective α-fluorination of α-amino acid derivatives. We have carried out extensive studies on the relationship between the structure and enantioselectivity of $[N-F]^+$ cinchona alkaloid derivatives and have discovered that a number displayed very high enantioselectivities. Enantioselection as high as 94 % was attained, exceeding all previous records and indicating that electrophilic fluorination mediated by cinchona alkaloids is a powerful method for the construction of fluorinated chiral centers.

Our successful approach to asymmetric electrophilic fluorination was based upon reacting the preformed ester enolate or nitrile anion with modified *N*-fluoro-cinchona alkaloids. In a first set of experiments, we examined the performance of the first generation of $[N-F]^+$ reagents, namely the four naturally occurring cinchona alkaloids, which have an unprotected hydroxy function. We found that these reagents displayed poor to moderate enantioselective fluorination (7 – 48 % *ee*). We then turned our attention to the structure – enantioselectivity relationship operating in various parts of the *N*-fluoro-

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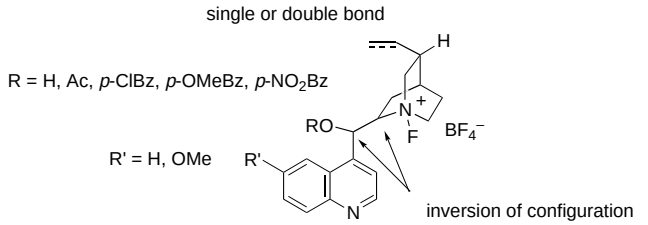
cinchona alkaloids, with a view to improving the enantioselectivity and to pinpointing the factors governing the enantioselection (Scheme 1).

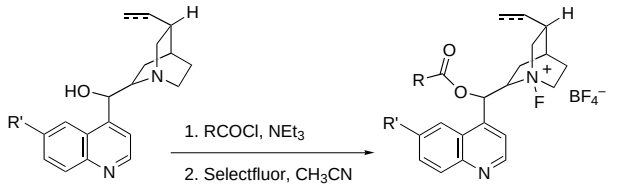


Scheme 1. Structure–enantioselectivity relationship (SER) studies on $[N-F]^+$ cinchona alkaloids.

A new range of $[N-F]^+$ reagents is accessible by capping the hydroxy function of the alkaloid through esterification[6] followed by a transfer-fluorination with Selectfluor (1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane-bis(tetrafluoroborate); Table 1). Unlike the synthesis of chiral uncharged N–F reagents,[7] we have developed an expeditious synthesis which does not require hazardous fluorine sources.

Various imido-protected (phthaloyl, tetrachlorophthaloyl, succinoyl, dimethylmaleoyl) phenylglycine esters (methyl, ethyl, benzyl), phenylglycinonitrile, and phenylglycine *N*,*N*-diethylamide were prepared and subjected to the α-deprotonation/fluorination sequence. Under the general reaction conditions, amino-protected phenylgycine esters and phenylglycinonitrile yielded the corresponding α-fluorinated compounds in good yields, whereas *N*,*N*-diethyl-*N*-phthaloyl-2-phenylglycinoamide did not react with the $[N-F]^+$ reagents. While the ester function on the substrate exerts no significant effect on the asymmetric induction, the phthaloyl amino protecting group induces a higher degree of enantioselection than the succinoyl and dimethylmaleoyl groups. For subsequent studies, we restricted our work to *N*-phthaloyl-α-aminophenylglycine ethyl ester and phenylglycinonitrile (Table 2).

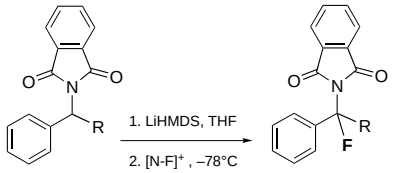
Table 1. Synthesis of $[N-F]^+$ reagents: R′ = H, OMe; R = Me, *p*-ClC_6H_4, *p*-$OMeC_6H_4$, *p*-$NO_2C_6H_4$.



$[N-F]^+$ reagent[a,b]	Yields [%]		$\delta(^{19}F)$[c]	
	esterification	transfer-fluorination	N–F	BF_4
F-AcCD-BF_4	90	95	43.8	−150.4
F-AcCN-BF_4	98	75	37.3	−150.4
F-AcQD-BF_4	96	98	35.7	−149.8
F-AcQN-BF_4	99	96	44.7	−149.8
F-AcDHQD-BF_4	83	83	40.1	−149.6
F-*p*ClBzCD-BF_4	92	90	44.0	−149.7
F-*p*ClBzCN-BF_4	99	87	38.4	−149.7
F-*p*ClBzQD-BF_4	93	89	39.1	−149.7
F-*p*ClBzQN-BF_4	99	97	44.6	−149.7
F-*p*ClBzDHQD-BF_4	80	82	39.5	−149.7
F-*p*ClBzDHQN-BF_4	–[d]	85	45.1	−149.7
F-*p*MeOBzQN-BF_4	95	98	44.4	−149.6
F-*p*NO_2BzQN-BF_4	81	91	44.5	−149.6

[a] The descriptors chosen for $[N-F]^+$ reagent are similar to F-TEDA-BF_4 for Selectfluor. For example, F-*p*ClBzDHQD-BF_4 stands for *O*(9)-*p*-chlorobenzoyl-*N*-fluorodihydroquinidinium tetrafluoroborate. [b] CD = cinchonidine, CN = cinchonine, QD = quinidine, QN = quinine, DHQD = dihydroquinidine, DHQN = dihydroquinine. [c] Measured in $[D_6]$acetone, standard $CFCl_3$. [d] Commercially available.

Table 2. Selected results of the enantioselective electrophilic fluorination of *N*-phthaloylphenylglycine derivatives using various $[N-F]^+$ cinchona alkaloids.



94% *ee*

$[N-F]^+$	R = CO_2Et		R = CN	
	ee [%][a]	Yield [%][b]	*ee* [%][a]	Yield [%][b]
F-CD-BF_4	8	65	36	48
F-AcCD-BF_4	42	87	52	91
F-AcQN-BF_4	76	79	80	88
F-*p*ClBzQN-BF_4	68	73	91	70
F-*p*ClBzDHQN-BF_4	76	86	92	65
F-*p*MeOBzQN-BF_4	66	64	94	56
F-*p*NO_2BzQN-BF_4	60	60	90	58
F-CN-BF_4	26	62	48	68
F-*p*ClBzCN-BF_4	28	67	66	70
F-AcDHQD-BF_4	50	60	75	72
F-*p*ClBzDHQD-BF_4	38	65	82	64

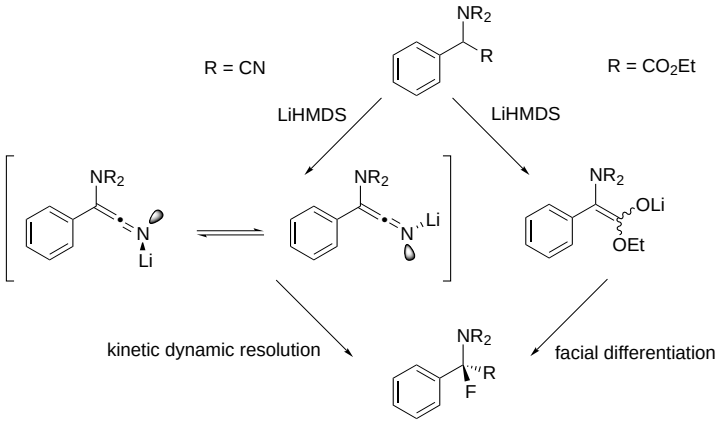
[a] Determined by HPLC analysis using a column Chiralcel OD. [b] Isolated, chromatographically pure material.

Under the usual fluorination conditions, the enantiomeric excesses of *N*-phthaloylphenylglycinonitrile determined by HPLC were consistently higher than those of *N*-phthaloylphenylglycine ethyl ester. Systematically, $[CD-F]^+$ and $[QN-F]^+$ fluorinating agents (for abbreviations see legend to Table 2) gave better enantioselectivities than their corresponding pseudoenantiomers, $[CN-F]^+$ and $[QD-F]^+$, respectively, yielding opposite configurations of the fluorinated compound as confirmed by HPLC analysis. In addition, the enantioselectivity was higher when $[QN-F]^+$ was used rather than $[CD-F]^+$ and when $[QD-F]^+$ was used rather than $[CN-F]^+$, suggesting the participation of the methoxy substituent on the quinoline moiety in the stereoselection.

We have shown that protection of the hydroxy group in the $[N-F]^+$ reagent was crucial to achieve high enantioselectivity. Furthermore, in the ester series, enantioselectivity was higher with acetyl protection than with benzoyl protection. By contrast, in the case of the nitrile derivative, the enantioselectivity was higher with benzoyl protection than with acetyl protection. There was no significant improvement in enantioselectivity by changing the nature of the *para* substituents of the benzoyl protecting group. The best result was obtained with the *O*-(*p*-methoxybenzoyl)-*N*-fluoroquininium tetra-

fluoroborate: an enantiomeric excess of 94% was achieved in the fluorination of *N*-phthaloylphenylglycinonitrile.

The significantly higher enantiomeric excesses observed for the nitrile derivative compared to the ethyl ester derivative could be explained by the different nature of corresponding metalated intermediates. Deprotonation of the ester typically leads to a prochiral sp^2 enolate (mixture of *Z* and *E* isomers), and the asymmetric step consists of a facial enantiodifferentiation. On the other hand, nitrile anions presumably exist as metalated ketenimines bearing axial chirality which undergo racemization rapidly even at low temperature.[8] In this case, enantioselective fluorination results from a kinetic dynamic resolution of the two enantiomers (Scheme 2). We are currently studying this hypothesis, in order to develop models to further rationalize our observations.



Scheme 2. Postulated intermediates in enantioselective fluorination.

In conclusion, we have developed the first enantioselective electrophilic α-fluorination of α-amino acid derivatives using modified *N*-fluoro-cinchona alkaloid reagents. A study of the relationship between structure and enantioselectivity led to a new range of $[N-F]^+$ reagents that display enantiomeric excesses as high as 94% in the synthesis of α-fluoro-*N*-phthaloylphenylglycinonitrile with *O*-(*p*-methoxybenzoyl)-*N*-fluoroquininium tetrafluoroborate.

Experimental Section

Synthetic procedures and spectroscopic data for the $[N-F]^+$ reagents can be found in the Supporting Information.

General procedure for the enantioselective fluorination: LiHMDS (1.06 M in THF, 1.5 equiv; HMDS = hexamethyldilazanide) was added dropwise to a solution of *N*-phthaloylphenylglycine ethyl ester (0.1 mmol, 30.9 mg) at $-78\,^{\circ}C$. After 15 min, *O*-(*p*-chlorobenzoyl)-*N*-fluorodihydroquininium tetrafluoroborate (0.11 mmol, 62.8 mg, 1.1 equiv) was added under nitrogen in one portion. The mixture was stirred at $-78\,^{\circ}C$ for 3 h and then hydrolyzed with H_2O. The mixture was partitioned between CH_2Cl_2 and H_2O, the organic layer dried over $MgSO_4$, and concentrated. For further analyses the crude product was purified by chromatography on preparative silica gel plates with hexane/EtOAc, which yielded α-fluoro-*N*-phthaloylphenylglycine ethyl ester in 86% yield. ^1H NMR (300 MHz): $\delta = 1.31$ (t, $J = 7.1$ Hz, 3H), 4.34 (m, 2H), 7.10–7.90 (m, 9H); ^{13}C NMR (75 MHz): $\delta =$ 13.78, 63.20, 94.33 (d, $J = 220$ Hz), 124.05, 125.65 (d, $J = 8$ Hz), 128.26, 129.51, 131.33, 133.00 (d, $J = 25$ Hz), 134.96, 165.39 (d, $J = 32$ Hz), 166.02 (d, $J = 2$ Hz); ^{19}F NMR (282 MHz): $\delta = -128.8$; HR-MS (EI, 70 eV) for $C_{18}H_{14}FNO_4$ [M^+]: calcd 327.0907, found 327.0908; HPLC: Chiralcel OD, hexane/*i*PrOH (97/3), 1 mL min^{-1}, $t_1 = 23.2$ min, $t_2 = 36.0$ min (76% *ee*); $[\alpha]_D^{20} = +19.0$, $[\alpha]_{578}^{20} = +20.3$ ($c = 4.0$, $CHCl_3$).

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[3] In previous studies, we explored α-fluorination of *N*-phthaloylphenylglycine ethyl ester under a solid–liquid phase-transfer catalysis with the aid of an achiral fluorinating reagent (*N*-fluorobenzenesulfonimide) and a chiral quaternary ammonium salt (Corey's *O*-allyl-*N*-(9-anthracenylmethyl)ammonium bromide catalysts derived from cinchona alkaloids). The best enantiomeric excess noted was 7% with 60% yield. More details can be found under http://www.mdpi.org/ecsoc-4.htm. α-Fluorinated-α-amino acids derivatives can also be constructed from fluorinated building blocks and resolved through diastereomeric amides (E. Hayashi, H. Fukaya, T. Abe, *J. Fluorine Chem.* **1991**, *52*, 133–147) or esters (Y. Takeuchi, M. Asahina, K. Nagata, T. Koizumi, *J. Chem. Soc. Perkin Trans. 1* **1987**, 2203–2207; Y. Takeuchi, M. Kamezaki, K. Kirihara, G. Haufe, K. W. Laue, N. Shibata, *Chem. Pharm. Bull.* **1998**, *46*, 1062–1064).

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