Asymmetric Catalysis

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Organocatalyzed Enantioselective Fluorocyclizations[**]

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Asymmetric halogen-promoted cyclizations have been the object of extensive investigations, the ultimate aim being the emulation of nature's remarkable ability to construct architecturally complex enantiopure halogenated compounds from prochiral precursors. Progress has been slow, but significant advances have recently been made in iodo-, bromo-, and chlorocyclizations.[1] A catalytic enantioselective fluorocyclization induced by an electrophilic fluorinating reagent has not been reported to date. This fact represents a significant gap since such a transformation can streamline synthetic access to enantiopure fluorinated heterocycles, a class of compounds that plays an important role in medicinal chemistry.[2] We became interested in this problem because of the information available on organocatalytic enantioselective fluorination[3] and our recent work in cascade fluorination–heterocyclizations.[4] Herein, we disclose the first successful catalytic process that delivers enantioenriched fluorinated heterocyclic products upon fluorocyclization of prochiral precursors.

For this study, we selected the prochiral indoles **1** and **2** with a pendant heteronucleophile tethered at C3 or at the nitrogen atom, respectively, based on the typical position of this heteroaromatic motif in nitrogen-containing natural products (Figure 1).[5] The established reactivity profile of indoles towards achiral electrophilic fluorinating reagents offered a starting point to identify suitable reaction conditions to allow for organocatalyzed enantioselective fluorocyclizations.[6] Two recent discoveries support the use of cinchona alkaloids to induce enantiocontrol. Shibata and co-workers reported that N–F reagents in the presence of catalytic amounts of cinchona alkaloids induce asymmetric fluorination of activated substrates.[7] In addition, we demonstrated that asymmetric fluoroetherification of a silyl-activated homoallylic alcohol can be performed with stoichiometric amounts of chiral N–F reagents prepared in situ from Selectfluor and $(DHQ)_2PHAL$. Although the enantioselectivity of this fluorocyclization was modest, the lead result was encouraging.[4a]

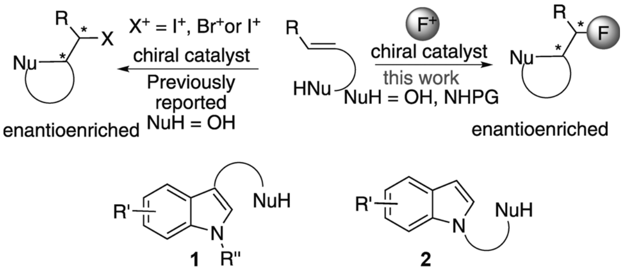

Figure 1. Enantioselective fluorocyclization of prochiral indoles. PG = protecting group.

From the onset, we appreciated the conceptual difficulties in developing such a catalytic asymmetric fluorocyclization. The uncatalyzed reaction must be significantly slower than the catalyzed process, a requirement difficult to meet as any in situ generated transient chiral N–F cinchona species will be of similar reactivity or less reactive with respect to the parent achiral fluorinating agent. In addition, the paucity of information on the factors that control the catalytic asymmetric delivery of halogens onto alkenes in the presence of cinchona alkaloids is limiting.[1,7] Our studies commenced with the fluorocyclization of the prototypical indole **1a**, a substrate that requires the creation of a stereogenic fluorinated quaternary benzylic carbon center upon fluorocyclization (Table 1).

Both Selectfluor and NFSI induced fluorocyclization at room temperature to afford tetrahydrofuroindole (±)-**3a** as a single *cis* diastereomer (d.r. > 20:1) with average yields of 70 % (Table 1, entries 1–3). The process was similarly effective at −78 °C with NFSI in acetone (Table 1, entry 4). Premixing various cinchona alkaloids with Selectfluor at room temperature followed by the addition of **1a** at ambient temperature or at −78 °C led to the formation of **3a** with the *ee* value reaching 74 % (Table 1, entries 5–10). The best enantiocontrol was observed when the fluorocyclization was performed with 1.2 equivalents of $(DHQ)_2PHAL$ in acetone at −78 °C (Table 1, entry 9), all other alkaloids that were screened were found to be less efficient.[8] To our great delight, when using a catalytic amount of $(DHQ)_2PHAL$ (20 mol %), **3a** was formed with 66 % *ee* (Table 1, entry 12). This reaction was best performed at −78 °C in acetone with NFSI and an excess of K_2CO_3. Decreasing the catalyst load, changing the base, or using Selectfluor instead of NFSI proved detrimental (Table 1, entries 11–16). The beneficial effect of the use of an inorganic carbonate base for the

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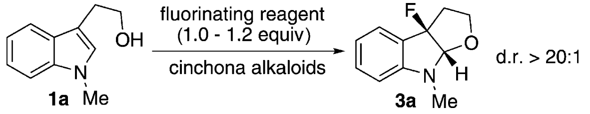
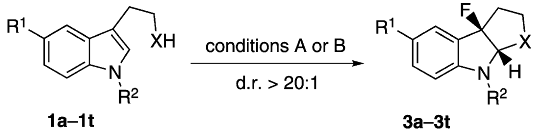
Table 1: Validation and optimization of the fluorocyclization of **1a**.[8]



Entry	F$^+$ source[a]	Alkaloid[b] (mol %)	Base	Solvent	T[e]	Yield [%][f]	ee [%][g]
1	A	–	$NaHCO_3$[c]	MeCN	RT	73	–
2	A	–	$NaHCO_3$[c]	acetone	RT	60	–
3	B	–	$NaHCO_3$[c]	MeCN	RT	76	–
4	B	–	$NaHCO_3$[c]	acetone	−78 °C	73	–
5	A	C (100)	$NaHCO_3$[c]	MeCN	RT	50	20
6	A	D (100)	$NaHCO_3$[c]	MeCN	RT	53	5
7	A	E (100)	$NaHCO_3$[c]	acetone	−78 °C	49	0
8	A	F (100)	$NaHCO_3$[c]	MeCN	RT	72	55
9	A	F (100)	$NaHCO_3$[c]	acetone	−78 °C	56	74
10	A	F (100)	$NaHCO_3$[c]	THF	−78 °C	64	64
11	B	F (10)	K_2CO_3[d]	acetone	−78 °C	50	50
12	B	F (20)	K_2CO_3[d]	acetone	−78 °C	72	66
13	B	F (20)	Cs_2CO_3[d]	acetone	−78 °C	58	66
14	B	F (20)	K_2CO_3[d]	acetone	RT	50	58
15	B	F (20)	–	acetone	−78 °C	36	34
16	A	F (20)	K_2CO_3[d]	acetone	−78 °C	47	32

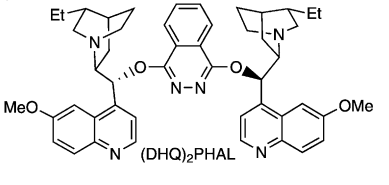
[a] A = 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor), B = *N*-fluorobenzenesulfonimide (NFSI). [b] C = 2,5-diphenyl-4,6-bis(dihydroquininyl)pyrimidine ((DHQ)$_2$PYR), D = hydroquinidine-9-phenanthryl ether, E = 1,4-bis(dihydroquinidinyl)anthraquinone ((DHQD)$_2$AQN), F = 1,4-bis(dihydroquininyl)phthalazine ((DHQ)$_2$PHAL). [c] 1 equiv. [d] 6 equiv. [e] Reaction time up to 5 h at RT and up to 15 h at −78 °C. [f] Yield of isolated product. [g] *ee* value determined by HPLC on a chiral stationary phase.

Table 2: Fluorocyclization of indoles **1a–1t**.



Entry	Cond.[a]	1	R^1	R^2	XH	3	Yield [%][b]	ee [%][c]
1	A	**1a**	H	Me	OH	**3a**	56	74
2	B	**1a**	H	Me	OH	**3a**	72	66
3	A	**1b**	H	Et	OH	**3b**	51	56
4	B	**1b**	H	Et	OH	**3b**	68	52
5	A	**1c**	H	allyl	OH	**3c**	62	60
6	B	**1c**	H	allyl	OH	**3c**	76	60
7	A	**1d**	H	H	OH	**3d**	33	40
8	A	**1e**	OMe	Me	OH	**3e**	90	86
9	B	**1e**	OMe	Me	OH	**3e**	65	74
10	A	**1f**	OBn	Me	OH	**3f**	69	84
11	B	**1f**	OBn	Me	OH	**3f**	78	74
12	A	**1g**	OEt	Me	OH	**3g**	60	84
13	B	**1g**	OEt	Me	OH	**3g**	78	72
14	A	**1h**	O(allyl)	Me	OH	**3h**	53	86
15	B	**1h**	O(allyl)	Me	OH	**3h**	65	78
16	A	**1i**	Ph	Me	OH	**3i**	55	72
17	B	**1i**	Ph	Me	OH	**3i**	61	62
18	A	**1k**	Mes	Me	OH	**3k**	57	90
19	B	**1k**	Mes	Me	OH	**3k**	55	84
20	A	**1l**	H	Me	NHTs	**3l**	54	76
21	B	**1l**	H	Me	NHTs	**3l**	59	64
22	A	**1m**	OMe	Me	NHTs	**3m**	55	78
23	B	**1m**	OMe	Me	NHTs	**3m**	51	70
24	A	**1n**	Ph	Me	NHTs	**3n**	50	82
25	B	**1n**	Ph	Me	NHTs	**3n**	70	70
26	A	**1o**	Mes	Me	NHTs	**3o**	60	92
27	B	**1o**	Mes	Me	NHTs	**3o**	80	84
28	A	**1p**	H	Me	NHCOMe	**3p**	45[d]	66
29	B	**1p**	H	Me	NHCOMe	**3p**	95	80
30	A	**1q**	Mes	Me	NHCOMe	**3q**	38[d]	92
31	B	**1q**	Mes	Me	NHCOMe	**3q**	65	92
32	A	**1r**	H	Me	$NHCO_2Me$	**3r**	56	78
33	B	**1r**	H	Me	$NHCO_2Me$	**3r**	76	74
34	A	**1s**	H	Me	$NHCO_2Bn$	**3s**	40	78
35	B	**1s**	H	Me	$NHCO_2Bn$	**3s**	47	77
36	A	**1t**	H	Me	NHBoc	**3t**	67	86
37	B	**1t**	H	Me	NHBoc	**3t**	70	78

[a] Conditions A: Selectfluor (1.2 equiv), (DHQ)$_2$PHAL (1.2 equiv), $NaHCO_3$ (1.2 equiv), acetone, −78 °C; conditions B: NFSI (1.2 equiv), (DHQ)$_2$PHAL (0.2 equiv), K_2CO_3 (6 equiv), acetone, −78 °C. [b] Yields of isolated products. [c] *ee* value determined by HPLC on a chiral stationary phase. [d] Conversion determined by ^{1}H NMR spectroscopy of the crude product.



catalytic asymmetric fluorination with cinchona alkaloids is not unprecedented.[7]

The scope and limitation of this organocatalyzed process was investigated with respect to both the substitution pattern of the indolic structural core and the attached nucleophile. To evaluate the efficiency of the catalytic protocol, the yields and enantiomeric excesses of the products of reactions carried out with either an equimolar (conditions A) or a catalytic amount of the cinchona alkaloid (conditions B) were compared (Table 2).[8]

The reaction tolerates various substituents on the indolic nitrogen atom, including hydrogen, but the highest enantiomeric excess was observed for the fluorocyclized product **3a** derived from N-methyl substituted precursors (Table 2, entries 1–7). The presence of a substituent at position 5 ($R^1 \neq H$) led to a markedly improved control over the enantioselectivity (Table 2, entries 8–19). When an equimolar amount of alkaloid was used (conditions A), enantiomeric excesses ranging from 72 % to 90 % were observed; under catalytic conditions only a slight decrease of enantiomeric excesses (up to 84 % *ee*) was observed with no compromise on yields (conditions B). Indolic precursors with pendant unprotected primary amines did not afford any fluorinated ring-closed products; this behavior is likely due to a competing N-fluorination reaction. Various N-protected amines were found to be efficient nucleophiles (Table 2, entries 20–37). N-Tosylated indoles underwent fluorocyclization to afford the desired tetrahydropyrroloindoles **3l–3o** in good yields and with enantiomeric excesses reaching 84 % under conditions B (Table 2, entry 27). Indoles **1p–1q** with a pendant N-acetamido nucleophile engaged very effectively in organocatalytic asymmetric fluorocyclization (Table 2, entries 28–31). This N-protected nucleophile led to a very efficient control over enantiofacial selectivity (*ee* = 92 %; Table 2, entries 30 and

31). The methyl-, benzyl-, and *tert*-butylcarbamates of *N*-methyl tryptamine (**1r**–**1t**) were also found to be suitable substrates for organocatalysis, and delivered the products in up to 78 % *ee* (Table 2, entries 32–37).

The cyclization products **3a**–**3t** were formed as single *cis* diastereomers, as judged by ^{1}H NMR analysis of the crude products of the reactions.[8] X-ray diffraction studies of the sulfonamide-containing product (3a*R*,8a*S*)-**3o** confirmed its structure (Figure 2).[8,9]

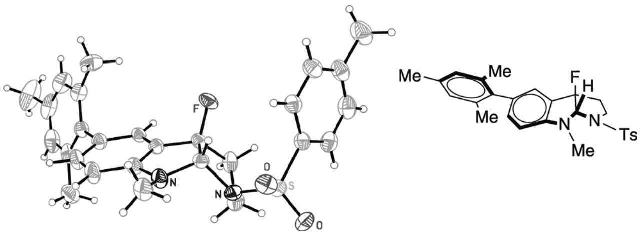


Figure 2. Crystal structure of one molecule of (3a*R*,8a*S*)-**3o** from diffraction data with displacement ellipsoids shown at the 50% probability level.

The fluorocyclization of 6-substituted indoles as well as an indole bearing a phenolic nucleophile were equally successful (Figure 3). The yields and enantiomeric excesses are given for the organocatalytic reactions only. Tetrahydrofuroindoles **3u** and **3v** were formed in moderate yields and with *ee* values in the range of 60 %. The fluorinated tetracyclic dihydrobenzofuro[2,3-*b*]indole **3w** was obtained in 80 % *ee*.

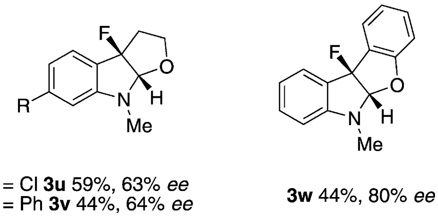
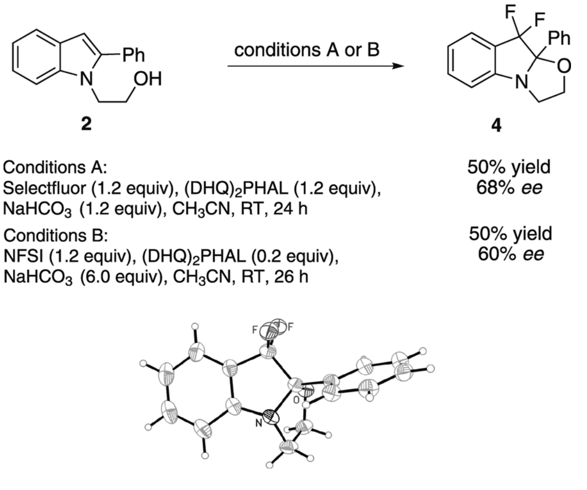


Figure 3. Organocatalytic asymmetric synthesis of **3u**–**3w**.

From a mechanistic point of view, catalytic enantioselective fluorocyclizations benefit from the fluorination being the stereochemistry-determining step. This fact contrasts advantageously with the complications intrinsic to iodo- and bromocyclizations, which arise from the propensity of iodonium and bromonium to undergo degenerate halogen exchange.[10] Products **3a**–**3w** are therefore likely to result from an irreversible fluoroquaternization at C3 followed by the intramolecular capture of the transient iminium intermediate by the pendant nucleophile. A series of observations led us to speculate on the origin of enantiocontrol. Our data indicate that similar enantiomeric excesses are observed whether the cinchona alkaloid is used in equimolar or catalytic amounts, although the catalyzed reactions were overall slightly less enantioselective. The same enantiomer is formed preferentially under both conditions (A and B), thus suggesting that the same N-fluoroammonium salt of the cinchona alkaloid is responsible for the enantiocontrol.[7] ^{19}F NMR studies confirmed that NFSI (^{19}F NMR: $\delta = -38$ ppm) is able to fully transfer fluorine to $(DHQ)_2$PHAL (F$(DHQ)_2$PHAL$^+$ ^{19}F NMR: $\delta = +45$ ppm) at room temperature within 30 min.[11] Under conditions A (stoichiometric amount of alkaloid), fluorination is therefore likely induced by an N-fluoroammonium salt of the cinchona alkaloid as both NFSI and the alkaloid are premixed prior to the addition of the substrate. Fluorine transfer from NFSI to $(DHQ)_2$PHAL was however found to be ineffective at low temperature (−78 °C), with only a trace amount of F-$(DHQ)_2$PHAL$^+$ (less than 2 %) being detected by ^{19}F NMR spectroscopy in the presence or absence of K_2CO_3. Experimentally, we observed that when all components of the organocatalytic reaction are mixed at −78 °C, the reaction proceeds as expected with the fluorocyclized product **3a** obtained in 50 % *ee*. When the alkaloid (20 mol %) is mixed with NFSI at room temperature prior to reducing the temperature to −78 °C and addition of the prochiral indole **1a** (conditions B), **3a** is isolated with a slightly improved *ee* value of 66 %. Taken together, these experimental observations suggest that a reaction pathway that does not involve F$(DHQ)_2$PHAL$^+$ may operate, and thus account for the observed enantioselectivity. Associative complexation of the alkaloid with the substrate, for example through hydrogen bonding with the pendant nucleophile, cannot be ruled out.[12] This hypothesis would be consistent with the level of selectivity found to be dependent on the nature of the nucleophile. Indeed, while **3a** and **3l** (X = O, NTs) were generated with 66 % and 64 % *ee*, respectively, the selectivity was markedly increased for **3p** (X = NCOMe, 80 % *ee*), **3r** (X = NCO_2Me, 74 % *ee*), **3s** (X = NCO_2Bn, 77 % *ee*) and **3t** (X = NBoc, 78 % *ee*).

Prochiral indole **2**, which bears an O nucleophile at the nitrogen atom, was also subjected to fluorocyclization (Scheme 1). Extensive screening of various alkaloids showed that asymmetric fluorocyclization of **2** using equimolar amounts of Selectfluor and $(DHQ)_2$PHAL delivered the difluorinated tricyclic tetrahydrooxazolo[3,2-*a*]indole **4** in



Scheme 1. Asymmetric difluorocyclization of **2**, and crystal structure of **4**. Displacement ellipsoids shown at the 50% probability level.

50% yield and with 68% *ee*. The identity of **4** was unambiguously confirmed by single crystal X-ray diffraction studies.[8] The stereochemical stability of **4** was assessed by measuring the enantiomeric excess at various times. No variation or decrease was observed, thus testifying to the remarkable stereochemical integrity of these compounds under the reaction conditions. This result is likely due to the presence of the proximal gem-difluoro motif, which prevents postreaction racemization. A plausible reaction pathway accounting for these difluorocyclizations involves the formation of 3-fluoroindole, which subsequently undergoes enantioselective fluorocyclization. Our attempt to prepare **4** under organocatalytic conditions B was equally successful (60% *ee*). This reaction represents a unique example of organocatalytic asymmetric dihalocyclization.

In conclusion, we have developed an organocatalytic route to enantioenriched fluorinated heterocycles. These are the first examples of organocatalyzed asymmetric fluorocyclizations. The process installs the fluorine substituent on a quaternary benzylic stereogenic carbon center and leads to new fluorinated analogues of natural products featuring the hexahydropyrrolo[2,3-*b*]indole or the tetrahydro-2*H*-furo-[2,3-*b*]indole skeleton. We have also demonstrated that asymmetric dihalocyclization is a feasible process by taking advantage of the newly formed gem-difluoro motif to prevent postreaction racemization. A catalytic asymmetric variant is also presented. Detailed kinetic studies are under way to elucidate the mechanism and origin of enantioinduction in these processes.

Experimental Section

General procedure: (DHQ)$_2$PHAL (20 mol%) and NFSI (1.2 equiv) in acetone (1.5 mL) were stirred under argon at RT for 30 min. K_2CO_3 (6.0 equiv) was then added to the solution, and the reaction mixture was stirred for 30 min at −78°C. A precooled solution (−78°C) of the indole (1 equiv) in acetone (0.5 mL per 20 mg of indole) was added dropwise to the catalyst solution and the reaction was stirred at the same temperature overnight. The reaction mixture was evaporated and the residue was purified on neutral alumina (hexane/EtOAc = 6:4) to give the fluorocyclized product.

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[8] For full details, see the Supporting Information. Compounds **3** are unstable under acidic conditions or when kept neat over an extended period of time, as they slowly convert into defluorinated oxindoles. These compounds are stable in solution (benzene, acetonitrile, acetone).

[9] Low-temperature single-crystal diffraction data were collected by using an Oxford Diffraction (Agilent) SuperNova with $Cu_{K\alpha}$ radiation (**3o**) or a Nonius KCCD diffractometer with $Mo_{K\alpha}$ radiation (**4** & **5**). Data were reduced by using CrysAlisPro or DENZO/SCALEPACK,[13] solved by using SIR92[14] and refined within the CRYSTALS suite.[15] Data were also collected for **3l**, but indicated the structure was modulated at 150 K and room temperature, and thus it could not be solved. Compound **3o** was found to be a non-merohedral twin, thus the Rogers, Flack, and Hooft parameters conventionally used as measures of correct-

ness of the absolute structure,[16] were inappropriate in this context and the crystal was treated as a four-component twin as described in the Supporting Information (CIF). The four twin scale factors refined to c. 0.6 0.4 0 0 (for the identity; rotation about [−1 1 0]; reflection about (−1 1 0) and inversion, respectively). Recrystallization was performed with enantioenriched **3o** (e.r. 93:7), it was therefore concluded that the crystal was twinned purely by rotation (i.e., each component is a single enantiomer) and the absolute configuration was tentatively assigned on the basis that a crystal of the major enantiomer was selected. Full refinement details are given in the Supporting Information. CCDC 827531 (**3o**), 827532 (**4**), 827533 (oxindole of **3m**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.; The absolute configuration for **3o** corroborates with the sense of enantiocontrol observed upon catalytic asymmetric electrophilic fluorination of structurally related oxindoles with $(DHQ)_2PHAL$.[7]

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