Synthetic Methods

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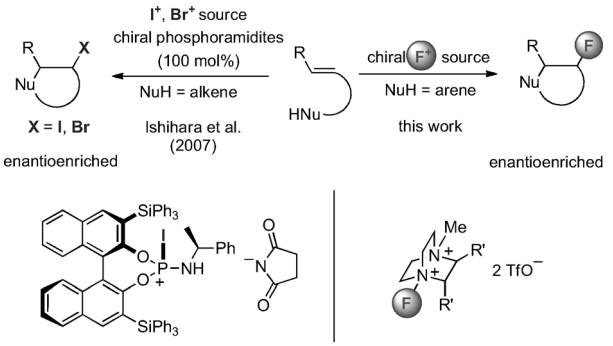
Asymmetric Electrophilic Fluorocyclization with Carbon Nucleophiles**

*Jamie R. Wolstenhulme, Jessica Rosenqvist, Oscar Lozano, John Ilupeju, Nathalie Wurz, Keary M. Engle, George W. Pidgeon, Peter R. Moore, Graham Sandford, and Véronique Gouverneur**

The electrophilic halogenation reaction of olefins coupled with cascade carbocyclization is an iconic biomimetic process for the construction of complex molecules.[1] In 2007, Ishihara and co-workers reported the first example of enantioselective iodocarbocyclization of polyenes with *N*-iodosuccinimide, a reaction promoted by stoichiometric quantities of a chiral phosphoramidite nucleophile.[2] This system was less effective for bromo- and chlorocarbocyclizations. Indeed, the enantiopurity of the products was significantly lower with *N*-bromosuccinimide, and the reaction did not proceed in the presence of *N*-chlorosuccinimide. As a matter of fact, the identification of competent electrophilic halogen sources which allow high-yielding product formation is not trivial, and conceptual advances to control enantioselectivity of these complex processes are in high demand. Since 2007, progress has been slow and in line with the well-recognized challenges associated with halocyclizations involving carbon nucleophiles.[3]

To the best of our knowledge, the synthesis of enantioenriched fluorinated carbocycles from prochiral polyenes is limited to the recent contribution of Gagné and co-workers who reported a unique transformation using a chiral dicationic platinum catalyst.[4] However, this transition-metal-catalyzed process is characterized by a stereoretentive electrophilic fluorination of a cyclized cationic platinum/alkyl intermediate and is therefore distinct from a mechanistic scenario in which a fluorinated cation is formed prior to π cyclization. Herein, we disclose the first metal-free fluorination/carbocyclization process for the synthesis of fluorinated carbocyclic products from prochiral precursors. A new class of chiral N-F reagents based on the dicationic structural core of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]-octane bis(tetrafluoroborate) (Selectfluor) allowed access to enantioenriched fluorocyclized products (Scheme 1).



Scheme 1. Metal-free asymmetric halocyclization with a C nucleophile. Tf = trifluoromethanesulfonyl.

In the first instance, we focused our efforts towards developing a non-enantioselective version of the envisioned transformation, since cation–π cyclizations induced by an electrophilic fluorine source are not known (Table 1).[5] The prototypical structure selected for validation and optimization studies was the indene **1a** bearing a 2-phenylethyl substituent at the C2 position. The pendant phenyl group was chosen as a C nucleophile to encourage chemo- and regioselective electrophilic fluorination at the carbon–carbon double bond. The resulting intermediate would undergo aryl cyclization leading to the tetracyclic fluorinated product **2a**.

When **1a** was reacted with 1.1 equivalents of Selectfluor in acetonitrile in the presence of an excess $NaHCO_3$ (3 equiv), **2a** was formed together with the product **3a**, which arises from competitive capture of the fluorinated carbocationic intermediate by the reaction solvent, acetonitrile (Table 1).[6] Under these reaction conditions, **2a** was isolated in 26% yield (entry 1). Varying the reaction temperature or the nature of the base did not prove beneficial (entries 2–4). *N*-Fluorobenzenesulfonimide (NFSI) was less satisfactory than Selectfluor as this fluorinating agent led predominantly to **4a**, thus resulting from regioselective net NFSI addition across the double bond. The formation of **4a** with NFSI encouraged us to reconsider Selectfluor. The replacement of acetonitrile

[*] J. R. Wolstenhulme, J. Rosenqvist, Dr. O. Lozano, J. Ilupeju, N. Wurz, K. M. Engle, G. W. Pidgeon, Prof. V. Gouverneur
Chemistry Research Laboratory, University of Oxford
Mansfield Road, Oxford, OX1 3TA (UK)
E-mail: veronique.gouverneur@chem.ox.ac.uk
Dr. P. R. Moore
AstraZeneca Pharmaceutical Development
Macclesfield, Cheshire, SK10 4TG (UK)
Prof. G. Sandford
Department of Chemistry, Durham University
South Road, Durham, DH1 3LE (UK)

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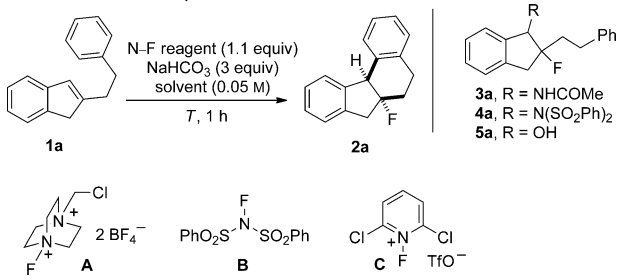
Table 1: Fluorocarbocyclization of indene **1a**.



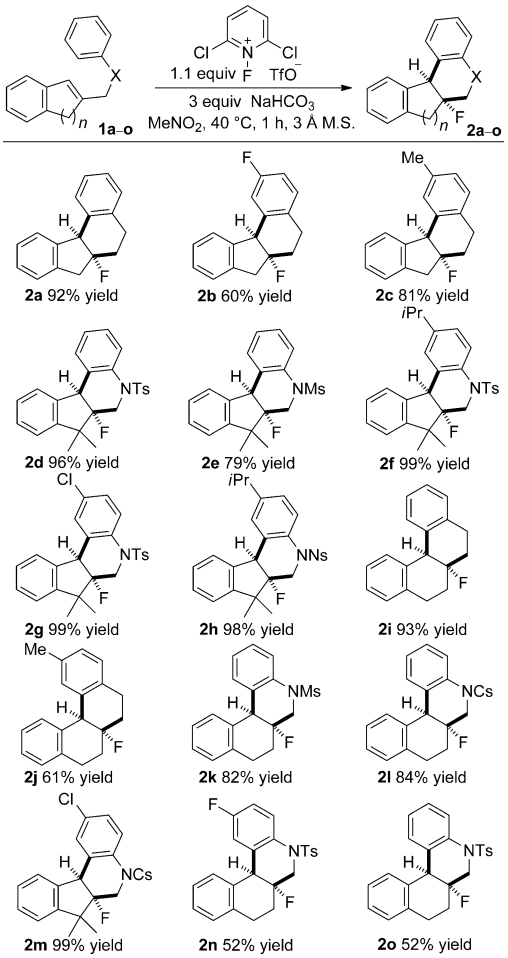
Entry[a]	N-F Source[b]	Solvent	T [°C]	**1a**/**2a**/**3a**/**4a**/**5a**[c]	**2a** Yield [%][d]
1	**A**	MeCN	RT	0:29:63:0:8	26
2	**A**	MeCN	0	0:26:69:0:5	–
3	**A**	MeCN	−40	81:3:14:0:2	–
4[e]	**A**	MeCN	RT	19:22:49:0:10	–
5	**B**	MeCN	RT	56:10:0:33:1	–
6[f]	**A**	$MeNO_2$	RT	0:93:0:0:7	59
7[f]	**C**	$MeNO_2$	RT	0:96:0:0:4	89
8[f]	**C**	$MeNO_2$	0	0:86:0:0:14	72
9[f]	**C**	$MeNO_2$	40	0:98:0:0:2	92

[a] General conditions: **1a** (50 mg), solvent (5 mL), $NaHCO_3$ (3.0 equiv), N-F reagent (1.1 equiv), 1 h. [b] **A** = Selectfluor, **B** = *N*-fluorobenzenesulfonimide (NFSI), **C** = *N*-fluoro-2,6-dichloropyridinium triflate. [c] Determined by integration of the ^{1}H NMR signals using 1-fluoro-3-nitrobenzene as an internal reference. [d] Yield of isolated product. [e] Reaction performed with 3 equivalents of K_2CO_3. [f] Reaction performed in the presence of molecular sieves (3 Å).

with nitromethane was found to be effective, thus delivering **2a** in 59% yield. The reaction was further optimized using *N*-fluoro-2,6-dichloropyridinium triflate in nitromethane at 40°C. Under these optimal reaction conditions, **2a** was obtained in 92% yield. The use of freshly activated 3 Å molecular sieves (M.S.) was found to be critical to suppress the formation of undesired fluorohydrin **5a**.[7]

A series of variously C2-substituted indenes and 1,2-dihydronaphthalenes effectively participated in the fluorocarbon-cyclization (Scheme 2).[8] The reaction tolerates substitution of the aryl C nucleophile at the *para*-position with fluoro, chloro, and alkyl groups. Substrates with N-sulfonylanilines acting as C nucleophiles also underwent successful fluorocyclization to afford a range of novel fluorinated tetrahydro-5*H*-indeno[2,1-*c*]quinolines and hexahydrobenzo[*k*]phenanthridines which were isolated in yields ranging from 52% to 99%. All products were formed exclusively as the corresponding *syn* diastereomers. The stereochemical assignment was based on the vicinal scalar coupling constant between the fluorine and the hydrogen located at the ring junction. These coupling constants were of the order of 15 Hz for **2d–o** and 21 Hz for **2a–c**.[8] Single-crystal X-ray crystallographic analysis of **2i** [$^3J(F^{6a},H^{12b}) = 14.7$ Hz] revealed its nonplanar helical structure and confirmed that the fluorine substituent is disposed *syn* to the hydrogen atom at C12b (Figure 1).[8]

Our next goal was the development of an asymmetric variant of this reaction. Preliminary experiments revealed the limitations of currently available strategies for (catalytic) asymmetric electrophilic fluorination, many of which were



Scheme 2. Fluorocarbocyclization of indenes and 1,2-dihydronaphtalenes. Cs = 4-chlorobenzenesulfonyl, Ms = methanesulfonyl, Ns = 4-nitrobenzenesulfonyl.

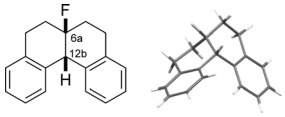


Figure 1. Structure of 6a-fluoro-5,6,6a,7,8,12b-hexahydrobenzo[*c*]phenanthrene (**2i**) from single-crystal X-ray diffraction data.

developed in the context of fluorocyclization with heteroatom nucleophiles. The reaction of **1a** with chiral N-F reagents derived from cinchona alkaloids (type A[9]; Figure 2) failed to proceed.[8] This result contrasts with the ability of these reagents to promote asymmetric fluoroheterocyclization of more nucleophilic substrates, including allylsilanes[10] and indoles.[11] The recovery of **1a** upon treatment with type A N-F reagents highlights the difference of reactivity between N-F reagents derived from quinuclidine and 1,4-diazabicyclo[2.2.2]octane (DABCO). We next considered chiral anion phase-transfer catalysis.[12] This catalytic manifold was applied by Toste and co-workers to Selectfluor, a cationic reagent insoluble in nonpolar media.[13] In the presence of bulky chiral phosphate (10 mol%), anion exchange with tetrafluoroborate

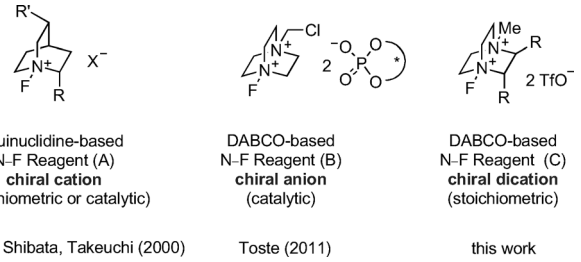
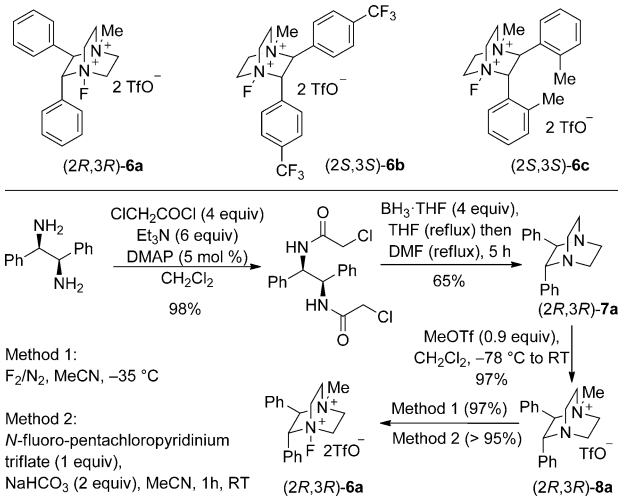


Figure 2. Chiral N-F reagents of types A, B, and C.

brings the N-F reagent into solution, thus allowing catalytic asymmetric fluoroheterocyclization of various substrates inclusive of 1,2-dihydronaphthalenes. Conceptually, this catalytic system relies on in situ formation of chiral Selectfluor of type B (Figure 2), in which the stereogenic elements are located on the anionic component. In the present reaction, we found that no reaction occurred when **1a** was reacted with 1.5 equivalents of Selectfluor, 1.25 equivalents of $NaHCO_3$, and 10 mol% of the chiral phosphonic acid (*R*)-TRIP (3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diylhydrogenphosphate) in hexanes. The use of nitromethane instead of hexanes induced fluorocarbocyclization, but as expected, this polar solvent afforded **2a** as a racemate. Similarly, the indene **1d** did not react upon treatment at room temperature for 24 hours with Selectfluor (1.5 equiv), $NaHCO_3$ (1.5 equiv), and 10 mol% of (*R*)-TRIP using hexanes, hexanes/fluorobenzene (1:1), or fluorobenzene as solvent.[8]

At this point, we considered a new approach to access enantioenriched fluorocarbocycles resulting from cation–π cyclization induced by an electrophilic fluorine source. Our studies in the racemic series informed us that the critical components necessary to convert **1a** into **2a** are the combined used of nitromethane as the solvent and either Selectfluor or *N*-fluoro-2,6-dichloropyridinium triflate as the fluorine source. These considerations led us to design a new class of chiral N-F reagents (type C; Figure 2) which are based on the structural core of Selectfluor with the stereogenic elements on the dicationic DABCO core. These chiral Selectfluor derivatives are predicted to be more reactive than the type A N-F reagents and offer a platform to investigate how solubility, reactivity, and enantiocontrol can be tuned by varying the R substituents of the DABCO core.

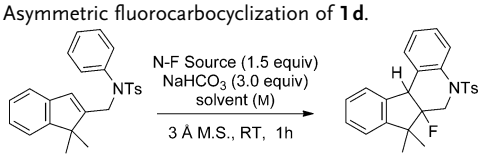
To this end, the chiral N-F reagents (2*R*,3*R*)-**6a**, (2*S*,3*S*)-**6b**, and (2*S*,3*S*)-**6c**, substituted with phenyl, *p*-(trifluoromethyl)phenyl, and *o*-toluoyl groups, respectively, were prepared (Scheme 3). The chiral DABCO (2*R*,3*R*)-**7a** was a necessary precursor to access (2*R*,3*R*)-**6a**. This compound was assembled from the corresponding enantiopure vicinal diamine using a protocol disclosed by Oi and Sharpless.[14] N-Quaternization of (2*R*,3*R*)-**7a** performed with methyl triflate afforded (2*R*,3*R*)-**8a** in 97% yield. The subsequent fluorination was achieved using fluorine gas (10% *v/v* in N_2) in acetonitrile (Method 1). Extensive optimization varying the amount of F_2, the reaction temperature, and the concentration was essential to identify reaction conditions which suppressed indiscriminate fluorination of the aryl groups. The best reaction conditions offered (2*R*,3*R*)-**6a** in 97% yield. Pleasingly, (2*R*,3*R*)-**6a** could also be prepared at room temperature in acetonitrile using commercially available *N*-fluoropentachloropyridinium triflate[15] in the presence of sodium bicarbonate (Method 2). This latter protocol is advantageous as it allows in situ formation of chiral Selectfluor reagents of type C[8] as an alternative to the use of isolated reagents. The chiral N-F reagents (2*S*,3*S*)-**6b** and (2*S*,3*S*)-**6c** were prepared in comparable yields by applying the same reaction sequence.[8]



Scheme 3. Chiral reagents (2*R*,3*R*)-**6a**, (2*S*,3*S*)-**6b**, and (2*S*,3*S*)-**6c**. DMAP = 4-(dimethylamino)pyridine, DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran.

Asymmetric fluorocyclization of **1d** was carried out in the presence of the chiral N-F reagents (2*R*,3*R*)-**6a**, (2*S*,3*S*)-**6b**, and (2*S*,3*S*)-**6c** (Table 2).[8] For this study, the reaction solvent was reconsidered since we suspected that the solubility profile of the chiral reagents **6a–c** might differ from that of Selectfluor. All reagents mediated the conversion of **1d** into the enantioenriched **2d** when the reaction was performed in nitromethane, with each giving drastically different reactivity and enantioselectivity (entries 1–3). The reagent (2*S*,3*S*)-**6b** with the *para*-electron-withdrawing CF_3 substituents on the aryl rings was the most reactive, as **1d** was entirely converted into **2d** (entry 2). Collectively, these experiments demonstrate that one can tailor the reactivity of this new class of chiral reagents by varying the steric and electronic properties of the substituents located at C2 and C3. Pleasingly, (2*S*,3*S*)-**6b** was also the most effective for enantiocontrol as **2d** was formed in 60% *ee*. The reagents (2*R*,3*R*)-**6a** and (2*S*,3*S*)-**6c** gave *ee* values of 32% and 55%, respectively. Based on this lead result, all subsequent reactions were performed with (2*S*,3*S*)-**6b**. The reaction solvent had an influence on yield and *ee* value (entry 4–10). The compound **2d** was obtained with 81% *ee* in THF but with a significant decrease in yield (entry 6). 1,4-Dioxane afforded **2d** in 88% yield and 74% *ee* (entry 7). The nature of the inorganic base had no effect on the *ee* value but substituting $NaHCO_3$ with K_2CO_3 or Cs_2CO_3 was detrimental to the yield (entries 12 and 13). Notably, the *ee* value was found to be 74% when the reaction was performed at either 50 °C or 10 °C (entries 14 and 15). Thus, under the optimized reaction conditions, treating **1d** with

Table 2: Asymmetric fluorocarbocyclization of **1d**.



1d *syn*-**2d**

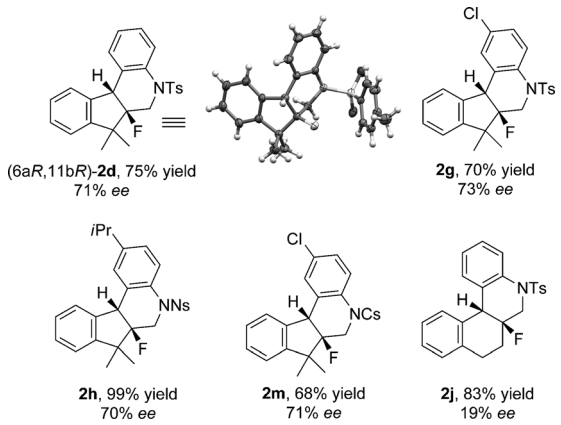
Entry	Solvent	N-F Source	**1d** Recovery [%][a]	Yield [%][a]	*ee* [%][b]
1	$MeNO_2$	(2*R*,2*R*)-**6a**	18	63	−32
2	$MeNO_2$	(2*S*,2*S*)-**6b**	< 5	> 95	60
3[c]	$MeNO_2$	(2*S*,2*S*)-**6c**	38	44	55
4	CH_2Cl2	(2*S*,2*S*)-**6b**	65	14	77
5	DCE	(2*S*,2*S*)-**6b**	30	59	74
6	THF	(2*S*,2*S*)-**6b**	6	22	81
7	1,4-dioxane	(2*S*,2*S*)-**6b**	< 5	88	74
8	DMF	(2*S*,2*S*)-**6b**	92	0	–
9	acetone	(2*S*,2*S*)-**6b**	50	14	72
10	MeCN	(2*S*,2*S*)-**6b**	26	37	52
11[d]	1,4-dioxane	(2*S*,2*S*)-**6b**	38	62	76
12[e]	1,4-dioxane	(2*S*,2*S*)-**6b**	47	39	76
13[f]	1,4-dioxane	(2*S*,2*S*)-**6b**	67	23	79
14[g]	1,4-dioxane	(2*S*,2*S*)-**6b**	39	46	74
15[h]	1,4-dioxane	(2*S*,2*S*)-**6b**	34	47	74
16[i]	1,4-dioxane	(2*S*,2*S*)-**6b**	84	13	80
17[j]	1,4-dioxane	(2*S*,2*S*)-**6b**	32	48	80

[a] Determined by ^{1}H NMR spectroscopy using 1-fluoro-3-nitrobenzene as internal reference. [b] Determined by HPLC on a chiral stationary phase. [c] N-F Reagent prepared in situ. [d] $NaHCO_3$ replaced with Na_2CO_3 (3 equiv). [e] $NaHCO_3$ replaced with K_2CO_3 (3 equiv). [f] $NaHCO_3$ replaced with Cs_2CO_3 (3 equiv). [g] Reaction at 50 °C. [h] Reaction at 10 °C. [i] Concentration: 0.0025 M. [j] Concentration: 0.025 M. DCE = 1,2-dichloroethane.

3 equivalents of $NaHCO_3$ and 1.5 equivalents of (2*S*,3*S*)-**6b** in 1,4-dioxane at room temperature for 1 hour afforded (+)-**2d** in 62 % yield and 76 % *ee*.

A series of enantioenriched fluorotetrahydro-5*H*-indeno-[2,1-*c*]quinolines was obtained by applying this protocol, with yields reaching 99 % and *ee* values averaging 71 %. Hexahydrobenzo[*k*]phenanthridine (**2j**) was formed in 83 % yield with a diminished *ee* value of 19 %, thus indicating that structural variation of the substrate can have a dramatic influence on the *ee* value (Scheme 4). The absolute configuration of **2d** was assigned as (6a*R*,11b*R*) by single-crystal X-ray crystallographic analysis,[8,16] which also confirmed the *syn* stereochemistry at the ring junction [$^3J(F^{6a},H^{11b}) = 15.7$ Hz]. This fluorocarbocyclization process is a unique example of asymmetric synthesis leading to enantioenriched fluorine-containing helical molecular motifs.

The fluorocarbocyclization presented herein generates various tetracyclic molecules possessing a carbon–fluorine quaternary stereocenter. These compounds would be difficult to access using alternative approaches. The design and preparation of a new class of chiral Selectfluor N-F reagents led to the successful development of an asymmetric variant of this fluorocarbocyclization reaction. These reagents, which are soluble in 1,4-dioxane or THF, are readily synthesized from chiral DABCO derivatives and commercially available *N*-fluoro-pentachloropyridinium triflate. Their preparation is



Scheme 4. Synthesis of enantioenriched fluorotetrahydro-5*H*-indeno-[2,1-*c*]quinolones. Structure of (6a*R*,11b*R*)-**2d** from single-crystal X-ray diffraction data.[17]

operationally simple using shelf-stable *N*-fluoropyridinium salts, which require no special handling procedures. These novel N-F reagents, with their dicationic chiral DABCO core, may find applications for the asymmetric fluorination of other substrates which are problematic using currently available strategies. Since the solubility profile of this new class of chiral N-F reagents can be tuned through variation of the substituents located on the DABCO core, it should be possible to adapt these chiral dicationic salts for use in phase-transfer catalysis.[18] Probing these principles with an eye towards the development of catalytic asymmetric fluorocarbocyclization and other challenging transformations is the subject of a current study in our laboratory.

Experimental Section

General procedure for asymmetric fluorocarbocyclization with (2*S*,3*S*)-**6b** prepared in situ: *N*-fluoro-pentachloropyridinium triflate (1.5 equiv) was added to a solution of pro-reagent (2*S*,3*S*)-**8b** (1.5 equiv) and $NaHCO_3$ (3.0 equiv) in 1,4-dioxane (2.5 mL) over 3 Å molecular sieves at room temperature and the reaction was stirred overnight. The prochiral indene was added and the reaction was stirred for 1–3 h before being concentrated in vacuo. Purification by silica gel column chromatography (EtOAc/petroleum ether) afforded the enantioenriched fluorocarbocyclized products.

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[16] The structures of **2d**, **2g**, and **2i** were determined by single-crystal X-ray diffraction. CCDC 950529 (**2d**), CCDC 950530 (**2g**), and CCDC 950531 (**2i**) 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.
[17] Absolute configuration of assigned by analogy with (6a*R*,11b*R*)-**2d**.
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