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Crystallization-Induced Dynamic Resolution of Fox Chiral Auxiliary and Application to the Diastereoselective Electrophilic Fluorination of Amide Enolates

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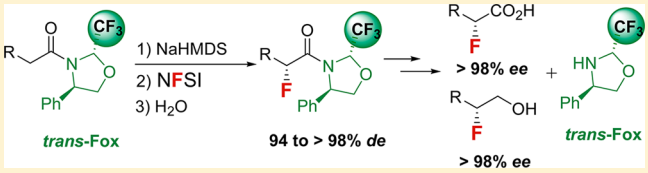
Supporting Information

ABSTRACT: A highly efficient crystallization-induced dynamic resolution (CIDR) of *trans*-**Fox** (fluorinated oxazolidine) chiral auxiliary is reported. This chiral auxiliary was used for highly diastereoselective (>98% *de*) electrophilic fluorination of amide enolates. After removal of the chiral auxiliary, highly valuable enantiopure α-fluorocarboxylic acids and β-fluoroalcohols are obtained.



Chiral fluorinated compounds are playing an increasing role in the design of pharmacologically relevant molecules.[1−3] Several methods are reported in the literature for their stereoselective syntheses involving nucleophilic, electrophilic or radical methodologies.[4−11] For the specific case of the stereoselective synthesis of α-fluorocarbonyl compounds, the electrophilic fluorination of an enolizable carbonyl group is obviously the most direct method. To this end, catalytic and chiral auxiliary-based methodologies have been reported for the electrophilic fluorination of enols or enolates. Davis et al.[12−15] and others[16−18] reported the efficient diastereoselective fluorination of oxazolidinone-based lithium amide enolates using *N*-fluoro-*o*-benzenedisulfonimide (NFOBS) or *N*-fluorobenzenesulfonimide (NFSI) as the fluorinating reagent. Although the diastereoselectivity of the fluorination reaction was good (87−97% *de*), a decreased of enantioselectivity was observed after the removal of the oxazolidinone chiral auxiliary giving enantioenriched α-fluorocarboxylic acids (69−90% *ee*) and β-fluoroalcohols (89 to >95% *ee*). However this epimerization could be controlled when the α-fluorocarboximide was converted into a Weinreb amide precursor of α-fluoroketones.[19] The diastereoselective synthesis of quaternarized α-fluorocarbonyl compounds using oxazolidinone chiral auxiliaries has also been more recently reported.[20,21]

In the course of our investigations on a fluorinated oxazolidine (**Fox**) as chiral auxiliary,[22−27] we decided to consider its performance for the challenging electrophilic fluorination of amide enolates. Moreover, conversely to oxazolidinones, it was anticipated that the nonbasic conditions suitable for the removal of this chiral auxiliary would lead to chiral α-fluorocarboxylic acids and β-fluoroalcohols without decrease of enantioselectivity. In order to enlarge the scope of the use of this attracting chiral auxiliary, we had first to optimize its large scale preparation. Indeed, until now the fluorinated oxazolidines (**Fox**) prepared by condensation of fluoral or its hemiacetal with (*R*)-phenylglycinol[28] were obtained as a 60:40 to 70:30 mixtures of *trans* and *cis* diastereomers, and the separation of both diastereomers was quite difficult. However this was not a redhibitory limitation for amide enolates chemistry because the *trans* and *cis* *N*-acyl oxazolidines were very conveniently separated by silica gel chromatography.[22] However, we established that in fact the only *trans*-**Fox** was an efficient chiral auxiliary because of its C_2 pseudosymmetry.[22,23] As a consequence, the *cis*-*N*-acyl oxazolidines were useless. As a major improvement in the use of the **Fox** chiral auxiliary, we report herein an efficient and scalable procedure for the selective synthesis of the *trans*-**Fox** chiral auxiliary. We also report its use for the highly diastereoselective electrophilic fluorination of amide enolates.

The **Fox** chiral auxiliary was obtained in high yield (91%) by condensation of (*R*)-phenylglycinol and fluoral ethyl hemiacetal as a 62:38 *trans*/*cis* diastereomeric mixture (Scheme 1).[28] The two diastereomers are configurationally stable in neutral medium, but their separation proved to be very difficult. In order to increase the ratio of *trans*-**Fox** we envisioned to shift the equilibrium in favor of the *trans*-**Fox** in acidic medium. A large screening of acids (AcOH, PPTS, PTSA, TFA) and solvent mixtures (cyclohexane, Et_2O, AcOEt, MeOH, EtOH) was considered. In most cases, a diastereomeric mixture of *trans*- and *cis*-**Fox** salts was obtained. However excellent results were obtained when the epimerization was carried out with *p*-toluenesulfonic acid (PTSA) in AcOEt (Scheme 1). In these conditions, the only *trans*-**Fox** diastereomer crystallized to give a pure *p*-toluenesulfonate salt of *trans*-**Fox** in 79% yield after filtration. This diastereomeric enrichment is a nice illustration of the crystallization-induced dynamic resolution (CIDR) concept.[29−35] After neutralization of the *p*-toluenesulfonate salt, the *trans*-**Fox** was obtained in excellent yield (99%) and large scale (27.75 g).

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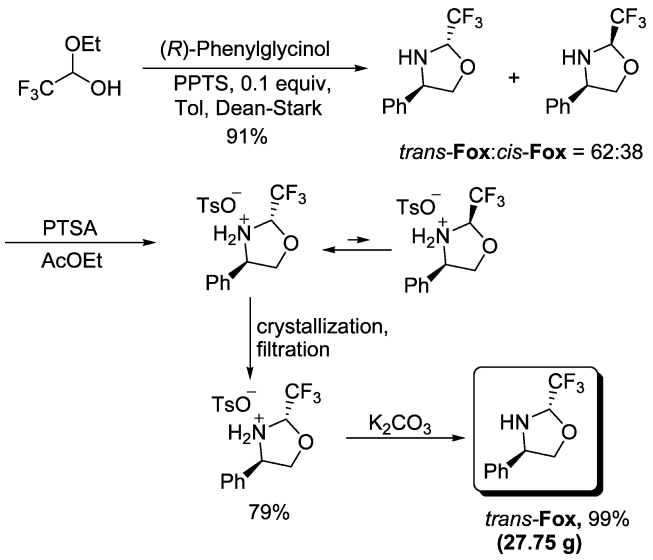
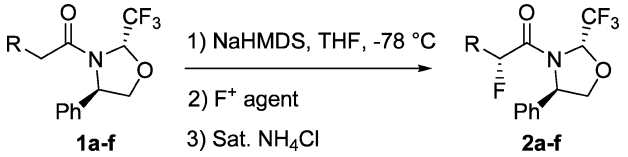
Scheme 1. Crystallization-Induced Dynamic Resolution (CIDR) of the *trans*-Fox Chiral Auxiliary



After *N*-acylation of the *trans*-**Fox** according to our previously reported procedures,[22,23] the electrophilic fluorination reactions of the sodium enolates of *N*-acyloxazolidines **1a–f** were investigated (Table 1). No reaction occurred when

Table 1. α-Fluorination of *trans*-Fox Amide Enolates



1a-f **2a-f**

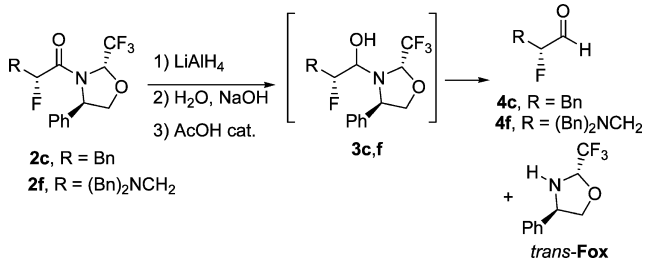
entry	F^+ agent (equiv)	R	yield (%)[a]	*de* (%)[b]	product
1	Selectfluor (2)	Me	0		
2	NFDPT[c] (1.5)	Me	0		
3	NFSI[d] (2)	Me	67	>98	**2a** (*R*)
4[e]	NFSI (2)	Ph	73	>98	**2b** (*R*)
5	NFSI (2)	Bn	73	>98	**2c** (*R*)
6	NFSI (2)	*n*Bu	35	>98	**2d** (*R*)
7	NFSI (2)	*i*Pr	29	>98	**2e** (*R*)
8	NFSI (2)	$(Bn)_2NCH_2$	73	>98	**2f** (*R*)

[a]Yield of pure isolated product. [b]Determined by ^1H and ^{19}F NMR on the crude mixture. [c]*N*-Fluoro-2,6-dichloropyridinium tetrafluoroborate. [d]*N*-Fluorobenzenesulfonimide. [e]The enolate was generated from 1.1 equiv of NaHMDS. The use of 2 equiv of NaHMDS gave **2b** in 13% yield and the corresponding difluorinated compound in 60% yield.

Selectfluor or *N*-fluoro-2,6-dichloropyridinium tetrafluoroborate (NFDPT) were used (Table 1, entries 1 and 2). However *N*-fluorobenzenesulfonimide (NFSI) showed to be a suitable electrophilic fluorine source. The electrophilic fluorination of amides **1a–c** occurred in 67–73% yield with a complete diastereoselectivity (>98% *de*)[36] (Table 1, entries 3–5). The reactions with more sterically hindered amide enolates were also achieved with an excellent diastereoselectivity (>98% *de*) but in lower yields (Table 1, entries 6 and 7). In order to have access to highly valuable α-amino-α-fluoro compounds, the electrophilic fluorination reaction was applied to the α-amino-substrate **1f**. The expected fluorinated compound **2f** was obtained in 73% yield with a total diastereoselectivity (Table 1, entry 8).

The removal of the *trans*-**Fox** chiral auxiliary and its recovery without epimerization of the target α-fluorocarbonyl compounds is a crucial step. The α-fluoro amides **2c** and **2f** were chosen as representative starting material to study this transformation. According to our previously reported procedure[26] the $LiAlH_4$ reduction of **2c** and **2f** followed by a slightly acidic treatment gave the α-fluoro aldehydes **4c** and **4f** together with the *trans*-**Fox** chiral auxiliary (Scheme 2). The synthesis of

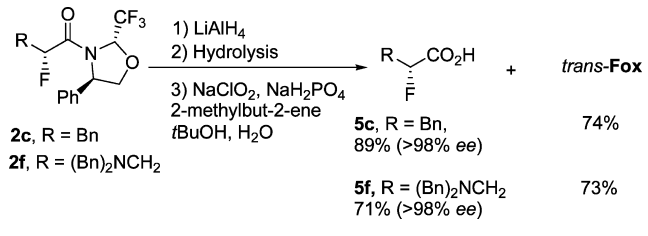
Scheme 2. Removal of the *trans*-Fox Chiral Auxiliary



similar α-fluoroaldehydes in enantioenriched form has already been reported by means of organocatalytic methods.[37–41] The hemiaminals **3c** and **3f** were identified to be the intermediates of the reaction.

As the α-fluoroaldehydes **4c,f** and the *trans*-**Fox** chiral auxiliary could not be easily separated by silica gel chromatography at this stage, we decided to oxidize the aldehydes **4c,f** into the coresponding α-fluorocarboxylic acids without separation of the intermediate aldehyde/oxazolidine mixture. Hence, the amides **2c,f** were submitted to a $LiAlH_4$ reduction/acidic hydrolysis/oxidation sequence to give enantiopure α-fluorocarboxylic acids **5c** and **5f** in 89 and 71% yield, respectively (Scheme 3). The *trans*-**Fox** chiral auxiliary was

Scheme 3. Two-Step Procedure for the Synthesis of Enantiopure Carboxylic Acids 5c,f with an Efficient Recovery of the Chiral Auxiliary *trans*-Fox



recovered in 73–74% yield. The excellent enantiomeric purity of **5c** and **5f** was confirmed by chiral HPLC analysis or NMR analysis of the corresponding (*S*)-phenylethylamide derivative. The (*R*) configurations were assigned by correlation with the corresponding aminoalcohols configurations (vide infra).

According to a similar strategy the α-fluoroamides **2c,f** were submitted to a $LiAlH_4$ reduction/hydrolysis/$NaBH_4$ reduction sequence to provide the β-fluoroalcohols **6c,f** without isolation of the intermediate α-fluoroaldehydes **4c,f** (Scheme 4). The enantiopure β-fluoroalcohols **6c,f** were obtained in 77% yield. The (*R*) configurations of **6c** and **6f** were assigned by comparison of their optical rotation value with literature data.[39,40,42] The enantiopurity of the fluoroalcohols **6c** and **6f**

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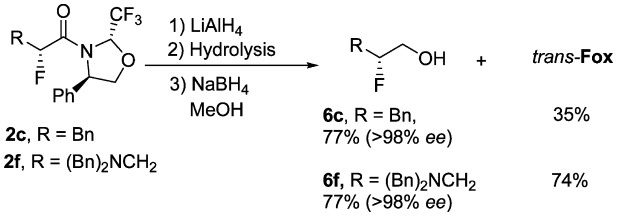
Scheme 4. Two-Step Procedure for the Synthesis of Enantiopure β-Fluoroalcohols 6c,f



was confirmed by formation of their diastereomerically pure (*R*)-Mosher's esters.

The *re* face fluorination of the chiral enolates providing the (*R*) configuration of the newly formed stereocenter is consistent with our previously reported experimental and theoretical studies on the alkylation[22,23] and the hydroxylation[26] of Fox-amide enolates. We propose a chelated transition state presenting both Na···F and Na···O interactions leading to a very highly diastereoselective carbon−fluorine bond formation (Figure 1). The involvement of the Na···O (sulfonamide oxygen) interaction activating the NFSI reagent is crucial. This could explain the reason why no fluorination reactions occurred with Selectfluor or *N*-fluoropyridinium salt.

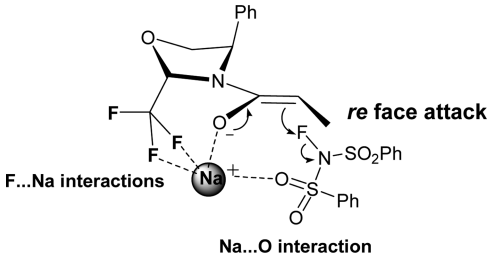


Figure 1. Postulated transition state leading to the *re* face fluorination of the enolate.

In summary, we have reported a highly efficient preparation of *trans*-**Fox** chiral auxiliary based on the crystallization-induced dynamic resolution (CIDR) concept. This chiral auxiliary allowed the electrophilic fluorination of amide enolates with an outstanding diastereoselectivity. Enantiopure α-fluorocarboxylic acids and β-fluoroalcohols were obtained after the removal and the recovery of the chiral auxiliary.

EXPERIMENTAL SECTION

Crystallization-Induced Dynamic Resolution of *trans*-Fox. PTSA·H_2O (46.44 g, 244.1 mmol, 1.5 equiv) was dissolved in ethyl acetate (200 mL). The solvent was partially removed under reduced pressure. Toluene (250 mL) was added, and all the solvents were removed. The dry PTSA was dissolved in ethyl acetate (500 mL) under argon atmosphere. Under vigorous stirring, a 62:38 diastereomeric mixture of oxazolidines *trans*-**Fox** and *cis*-**Fox** (35.35 g, 163.8 mmol, 1.0 equiv) in ethyl acetate (80 mL) was added dropwise. The precipitate was filtrated and washed with a minimum amount of ethyl acetate, and the mother liquors were concentrated to induce a second precipitation. The sequence precipitation/filtration/concentration was repeated at least 3 times to furnish the *p*-toluenesulfonate salt of *trans*-**Fox** (50.25 g, 129.1 mmol, 79%) as a white powder.

The mother liquors were treated with a saturated K_2CO_3 solution and extracted with ethyl acetate. The organic layers were dried over $MgSO_4$, filtrated and concentrated under reduced pressure to afford a remaining mixture of oxazolidines *trans*-**Fox** and *cis*-**Fox** (7.070 g, 32.55 mmol, 20%, 78/22 *dr*) as a yellow oil. This mixture of oxazolidines can be further submitted to another crystallization-induced dynamic resolution sequence.

(2*S*,4*R*)-4-Phenyl-2-trifluoromethyloxazolidine (*trans*-Fox). To a suspension of the *p*-toluenesulfonate salt of *trans*-**Fox** (50.20 g, 128.9 mmol, 1.0 equiv) in ethyl acetate (375 mL) was added a saturated solution of K_2CO_3 (125 mL). After complete solubilization of the precipitate, water (125 mL) was added, and the aqueous layers were carefully extracted with ethyl acetate. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The enantiopure (2*S*,4*R*)-4-phenyl-2-trifluoromethyloxazolidine *trans*-**Fox** (27.75 g, 127.8 mmol, 99%), was obtained as a colorless oil.[28]

Starting *N*-Acylated Oxazolidines (1a−f). The starting *N*-acylated oxazolidines **1a**, **1c**, **1e** and **1f** were prepared according to our previously reported procedures starting from enantiopure *trans*-**Fox** and the corresponding acyl chloride.[22,23]

(2*S*,4*R*)-4-Phenyl-3-phenylacetyl-2-trifluoromethyloxazolidine (1b). Obtained from enantiopure oxazolidine *trans*-**Fox** (1.394 g, 6.42 mmol, 1.0 equiv) and phenylacetyl chloride (1.11 mL, 8.34 mmol, 1.3 equiv). Purification by silica gel chromatography (cyclohexane/ethyl acetate 95/5) yielded the pure amide **1b** (1.719 g, 10.30 mmol, 78%) as a white solid: mp = 94−95 °C; $[\alpha]_D$ −49.9 (*c* = 0.45, $CHCl_3$); IR 3029, 2925, 2168, 1967, 1672, 1492, 1453, 1375, 1280, 1144, 1102, 984, 929, 897, 755, 690 cm^{-1}; ^1H NMR (400 MHz) δ 3.31 (d, 1H, *J* = 15.8 Hz), 3.36 (d, 1H, *J* = 15.8 Hz), 4.01 (d, 1H, *J* = 8.7 Hz), 4.59 (dd, 1H, *J* = 8.70, 6.4 Hz), 4.84 (d, 1H, *J* = 6.4 Hz), 6.16 (q, 1H, J_{H-F} = 5.1 Hz), 6.93−6.95 (m, 2H), 7.19−7.27 (m, 6H), 7.36−7.44 (m, 2H); ^{13}C NMR (100.5 MHz) δ 42.7, 60.3, 76.5, 85.3 (q, *J* = 35.1 Hz), 123.4 (q, *J* = 289.5 Hz), 125.6, 127.1, 128.6, 128.8, 128.9, 129.7, 133.6, 141.4, 171.3; ^{19}F NMR (376.2 MHz) δ −80.3 (d, *J* = 5.1 Hz); HRMS (EI+, direct inlet probe) *m*/*z* [M+] Calcd for $C_{18}H_{16}F_3NO_2$ 335.1133, found 335.1142.

(2*S*,4*R*)-3-Hexanoyl-4-phenyl-2-trifluoromethyloxazolidine (1d). Obtained from enantiopure oxazolidine *trans*-**Fox** (3.000 g, 13.81 mmol, 1.0 equiv) and hexanoyl chloride (3.52 mL, 24.86 mmol, 1.8 equiv). Purification by silica gel chromatography (cyclohexane/ethyl acetate 95/5) yielded the pure amide **1d** (4.094 g, 12.98 mmol, 94%) as a pale yellow solid: mp = 47−48 °C; $[\alpha]_D$ −61.3 (*c* = 1.16, $CHCl_3$); IR 2945, 2867, 1658, 1457, 1400, 1280, 1148, 1099, 984, 921, 838, 747, 689 cm^{-1}; ^1H NMR (400 MHz) δ 0.78 (t, 1H, *J* = 7.1 Hz), 1.02−1.16 (m, 4H), 1.30 (dtdd, 1H, *J* = 14.0, 7.1 Hz, 6.4 Hz, 6.2 Hz), 1.49 (dddt, 1H, *J* = 14.0, 8.7, 8.5, 7.1 Hz), 1.81 (ddd, 1H, *J* = 15.2, 8.7, 6.2 Hz), 2.13 (ddd, 1H, *J* = 15.2, 8.5, 6.4 Hz), 4.07 (d, 1H, *J* = 8.7 Hz), 4.69 (dd, 1H, *J* = 8.7, 6.4 Hz), 4.99 (d, 1H, *J* = 6.4 Hz), 6.14 (q, 1H, J_{H-F} = 5.1 Hz), 7.15−7.40 (m, 5H);.^{13}C NMR (100.5 MHz) δ 14.0, 22.4, 24.3, 31.2, 35.9, 60.8, 76.6, 85.1(q, *J* = 34.5 Hz), 123.5 (q, *J* = 288.5 Hz), 125.7, 128.7, 129.5, 141.6, 170.6; ^{19}F NMR (376.2 MHz) δ −80.69 (d, *J* = 5.1 Hz); HRMS (EI+, direct inlet probe) *m*/*z* [M+] Calcd for $C_{16}H_{20}F_3NO_2$ 315.1446, found 315.1441.

General Procedure for the Synthesis of Fluorinated Amides (2a−f). To a solution of the amide **1a−f** (1.00 mmol, 1.0 equiv) in THF (8 mL) under argon at −78 °C was added a solution of NaHMDS (1.00 mL, 2.0 M in THF, 1.00 mmol, 2.0 equiv). The reaction mixture was stirred at −78 °C for 45 min. Then NFSI (0.632 g, 2.00 mmol, 2.0 equiv) was added. The reaction mixture was stirred at −78 °C for 18 h and quenched with a saturated aqueous NH_4Cl solution (7 mL). The aqueous layer was extracted three times with ethyl acetate. The organic layers were combined and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (cyclohexane/ethyl acetate 95/5) to afford the pure fluorinated product. Because of *cis*/*trans* amide conformers occurrence, NaH epimerization reactions of compounds **2** were performed in order to discriminate *cis*/*trans* conformers and potential diastereomers.

(2*S*,4*R*)-3-[(*R*)-2-Fluoropropanoyl]-4-phenyl-2-trifluoromethyloxazolidine (2a). Obtained from the *N*-acylated oxazolidine **1a** (0.274 g, 1.00 mmol, 1.0 equiv) using the general procedure. After purification by silica gel chromatography (cyclohexane/ethyl acetate 95/5) the pure fluorinated product **2a** (0.195 g, 0.67 mmol, 67%, > 98% *de*) was obtained as a white solid: mp = 47−49 °C; $[\alpha]_D$ −41.0 (*c*

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= 2.0, $CHCl_3$); IR 2984, 2164, 1972, 1670, 1494, 1455, 1413, 1320, 1281, 1142, 1093, 1031, 980, 932, 849, 756, 688 cm^{-1}; ^1H NMR (400 MHz) (Major conformer) δ 1.33 (dd, 3H, J_{H-F} = 25.0 Hz and J = 6.4 Hz), 4.10 (d, 1H, J = 8.5 Hz), 4.25 (dq, 1H, J_{H-F} = 46.7 Hz and J = 6.4 Hz), 4.70 (dd, 1H, J = 8.5, 6.4 Hz), 5.29 (d, 1H, J = 6.4 Hz), 6.18 (q, J_{H-F} = 5.0 Hz), 7.19−7.26 (m, 2H), 5.31−5.40 (m, 3H);.^{13}C NMR (100.5 MHz) (Major conformer) δ 17.1 (d, $^2J_{C-F}$ = 22.0 Hz), 60.3 (d, $^4J_{C-F}$ = 7.7 Hz), 76.8, 85.6 (q, $^2J_{C-F}$ = 34.5 Hz), 87.3 (d, $^1J_{C-F}$ = 179.23 Hz), 123.3 (q, J = 288.5 Hz), 126.1, 128.9, 129.5, 141.0, 170.3 (d, J = 20.1 Hz); ^{19}F NMR (376.2 MHz) (Major conformer) δ −184.4 (dq, 1F, J = 46.7, 25.0 Hz), −81.0 (d, 3F, J = 5.0 Hz); HRMS (EI+, direct inlet probe) m/z [M+] Calcd for $C_{13}H_{13}F_4NO_2$ 291.0882, found 291.0890. Anal. Calcd for $C_{13}H_{13}F_4NO_2$ C, 53.61; H, 4.50; N, 4.81. Found: C, 53.55; H, 4.33; N, 4.80.

(2*S*,4*R*)-3-[(2*R*)-2-Fluoro-2-phenylacetyl]-4-phenyl-2-trifluoromethyloxazolidine (2b). Obtained from the *N*-acylated oxazolidine **1b** (0.336 g, 1.00 mmol, 1.0 equiv) using the general procedure. The enolate was generated with 1.1 equiv of NaHMDS (0.55 mL, 2.0 M in THF, 1.1 mmol, 1.1 equiv). After purification by silica gel chromatography (cyclohexane/ethyl acetate 95/5) the pure fluorinated product **2b** (0.259 g, 0.73 mmol, 73%, >98% *de*) was obtained as a white solid: mp = 82−83 °C; $[\alpha]_D$ −73.7 (c = 1.0, $CHCl_3$); IR 3037, 2165, 2026, 1664, 1495, 1414, 1317, 1269, 1144, 1104, 1035, 976, 925, 843, 761, 687, 632 cm^{-1}; ^1H NMR (400 MHz) (Major conformer) δ 4.14 (bs, 1H), 4.76 (bs, 1H), 5.12 (d, 1H, J_{H-F} = 46.5 Hz), 5.45 (bs, 1H), 6.24 (bs, 1H), 7.04−7.47 (m, 10H); ^{13}C NMR (100.5 MHz) (Major conformer) δ 60.7, 76.8, 85.8 (q, J = 36.4 Hz), 91.0 (d, J = 185.0 Hz), 123.3 (q, J = 289.5 Hz), 126.1, 127.7 (2C), 128.5, 128.9, 129.6, 134.1, 141.3, 169.1 (d, J = 22.0 Hz); ^{19}F NMR (376.2 MHz) (Major conformer) δ −176.2 (d, 1F, J = 46.5 Hz), −80.9 (bs, 3F); HRMS (EI+, direct inlet probe) m/z [M+] Calcd for $C_{18}H_{15}F_4NO_2$ 353.1039, found 353.1034. Anal. Calcd for $C_{18}H_{15}F_4NO_2$ C, 61.19; H, 4.28; N, 3.96. Found: C, 60.99; H, 4.49; N, 4.00.

(2*S*,4*R*)-3-[(2*R*)-2-Fluoro-3-phenylpropanoyl]-4-phenyl-2-trifluoromethyloxazolidine (2c). Obtained from the *N*-acylated oxazolidine **1c** (0.350 g, 1.00 mmol, 1.0 equiv) using the general procedure. After purification by silica gel chromatography (cyclohexane/ethyl acetate 95/5) the pure fluorinated product **2c** (0.268 g, 0.73 mmol, 73%, > 98% *de*) was obtained as a white solid: mp = 96−97 °C; $[\alpha]_D$ −52.9 (c = 1.02, $CHCl_3$); IR 3024, 2923, 2168, 1969, 1745, 1659, 1493, 1448, 1396, 1324, 1276, 1149, 1109, 1079, 1024, 977, 927, 840, 751, 691, 636 cm^{-1}; ^1H NMR (400 MHz) δ 3.02 (ddd, 1H, J_{H-F} = 31.7 Hz, J = 14.9, 4.2 Hz), 3.10 (ddd, 1H, J_{H-F} = 23.0 Hz, J = 14.9, 7.8 Hz), 4.09 (d, 1H, J = 8.7 Hz), 4.42 (ddd, 1H, J_{H-F} = 47.3 Hz, J = 7.8, 4.2 Hz), 4.68 (dd, 1H, J = 8.7, 6.6 Hz), 5.30 (d, 1H, J = 6.4 Hz), 6.23 (q, J_{H-F} = 5.1 Hz), 7.02−7.05 (m, 2H), 7.17−7.28 (m, 5H), 7.30−7.39 (m, 3H); ^{13}C NMR (100.5 MHz) δ 37.5 (d, J = 21.1 Hz), 60.4 (d, J = 7.7 Hz), 76.8 (C5), 85.6 (q, J = 36.4 Hz), 90.6 (d, J = 185.0 Hz), 123.2 (q, J = 288.5 Hz), 125.9, 126.9, 128.5, 128.8, 129.5, 135.6, 141.2, 169.5 (d, J = 21.1 Hz); ^{19}F NMR (376.2 MHz) (Major conformer) δ −190.1 (ddd, 1F, J = 47.3, 31.7, 23.0 Hz), −80.9 (d, 3F, J = 5.1 Hz); HRMS (EI+, direct inlet probe) m/z [M+] Calcd for $C_{19}H_{17}F_4NO_2$ 367.1195, found 367.1205. Anal. Calcd for $C_{19}H_{17}F_4NO_2$ C, 62.12; H, 4.66; N, 3.81. Found: C, 62.14; H, 4.42; N, 4.03.

(2*S*,4*R*)-3-[(*R*)-2-Fluorohexanoyl]-4-phenyl-2-trifluoromethyloxazolidine (2d). Obtained from the *N*-acylated oxazolidine **1d** (0.316 g, 1.00 mmol, 1.0 equiv) using the general procedure. After purification by silica gel chromatography (cyclohexane/ethyl acetate 95/5) the pure fluorinated product **2d** (0.115 g, 0.35 mmol, 35%, >98% *de*) was obtained as a white solid: mp = 67−68 °C; $[\alpha]_D$ −33.0 (c = 2.2, $CHCl_3$); IR 2961, 1682, 1390, 1280, 1181, 1149, 848, 702, 685 cm^{-1}; ^1H NMR (400 MHz) δ 0.82 (t, 3H, J = 7.0 Hz), 1.13−1.33 (m, 4H), 1.64−1.87 (m, 2H), 4.11 (d, 1H, J = 8.7 Hz), 4.14 (ddd, J_{H-F} = 47.2 Hz, J = 7.6, 4.1 Hz), 4.70 (dd, 1H, J = 8.7, 6.6 Hz), 5.14 (d, 1H, J = 6.6 Hz), 6.21 (q, J_{H-F} = 5.1 Hz), 7.19−7.40 (m, 5H);.^{13}C NMR (100.5 MHz) δ 13.9, 22.3, 26.3, 31.0 (d, J = 21.1 Hz), 60.4 (d, J = 9.6 Hz), 76.8, 85.6 (q, J = 35.5 Hz), 90.5 (d, $^1J_{C-F}$ = 183.1 Hz), 123.3 (q, $^1J_{C-F}$ = 288.5 Hz), 126.0, 128.8, 129.5, 141.3, 170.3 (d, J = 21.1 Hz); ^{19}F NMR (235.3 MHz) δ −192.0 (ddd, 1F, J = 47.2, 30.6, 23.5 Hz), −81.1 (d, 3F, J = 4.7 Hz); HRMS (EI+, direct inlet probe) m/z [M+] Calcd for $C_{16}H_{19}F_4NO_2$ 333.1352, found 333.1367. Anal. Calcd for $C_{16}H_{19}F_4NO_2$ C, 57.65; H, 5.75; N, 4.20. Found: C, 58.25; H, 5.90; N, 4.11.

(2*S*,4*R*)-3-[(2*R*)-2-Fluoro-3-methylbutanoyl]-4-phenyl-2-trifluoromethyloxazolidine (2e). Obtained from the *N*-acylated oxazolidine **1e** (0.302 g, 1.00 mmol, 1.0 equiv) using general procedure. After purification by silica gel chromatography (cyclohexane/ethyl acetate 95/5) the pure fluorinated product **2e** (0.092 g, 0.29 mmol, 29%, > 98% *de*) was obtained as a white solid: mp = 52−53 °C; $[\alpha]_D$ −37.1 (c = 1.06, $CHCl_3$); IR 2969, 2928, 2164, 2028, 1672, 1458, 1370, 1273, 1183, 1143, 1111, 1041, 993, 937, 844, 751, 693, 645 cm^{-1}; ^1H NMR (400 MHz) (Major conformer) δ 0.84 (d, 3H, J = 6.9 Hz), 0.89 (d, 3H, J = 6.6 Hz), 2.30 (dqqd, 1H, J_{H-F} = 30.5 Hz, J = 6.9, 3.1 Hz), 3.97 (dd, 1H, J_{H-F} = 47.4 Hz, J = 3.1 Hz), 4.08 (d, 1H, J = 8.7 Hz), 4.68 (dd, 1H, J = 8.7, 6.2 Hz), 5.36 (d, 1H, J = 6.2 Hz), 6.25 (q, 1H, J_{H-F} = 5.3 Hz), 7.19−7.39 (m, 5H);.^{13}C NMR (100.5 MHz) (Major conformer) δ 15.3 (d, J = 5.8 Hz), 18.6 (d, J = 2.9 Hz), 30.6 (d, J = 20.1 Hz), 60.7 (d, J = 10.5 Hz), 76.9, 85.5 (q, J = 34.5 Hz), 94.6 (d, J = 188.8 Hz), 123.4 (q, J = 288.5 Hz), 125.9, 128.5, 129.3, 141.7, 172.5 (d, J = 21.1 Hz); ^{19}F NMR (376.2 MHz) (Major conformer) δ −205.0 (dd, 1F, J = 47.4, 30.5 Hz), −81.3 (d, 3F, J = 5.3 Hz); HRMS (EI+, direct inlet probe) m/z [M+] Calcd for $C_{15}H_{17}F_4NO_2$ 319.1195, found 319.1211. Anal. Calcd for $C_{15}H_{17}F_4NO_2$ C, 56.42; H, 5.37; N, 4.39. Found: C, 56.15; H, 5.25; N, 4.38.

(2*S*,4*R*)-3-[(2*R*)-3-Dibenzylamino-2-fluoropropanoyl]-4-phenyl-2-trifluoromethyloxazolidine (2f). To a solution of the amide **1f** (1.770 g, 3.78 mmol, 1.0 equiv) in THF (12 mL) under argon at −78 °C was added a solution of NaHMDS (2.27 mL, 2.0 M in THF, 4.54 mmol, 1.2 equiv). The reaction mixture was stirred at −78 °C for 45 min. Then NFSI (1.787 g, 5.67 mmol, 1.5 equiv) was added. The reaction mixture was stirred at −70 °C overnight. The reaction was quenched with a saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was extracted three times with ethyl acetate. The organic layers were combined and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product (2.329 g) was purified by flash chromatography (cyclohexane/ethyl acetate 98/2 to 95/5) to afford the pure fluorinated product **2f** (1.343 g, 2.76 mmol, 73%, > 98% *de*) as a white solid: mp = 88−90 °C; $[\alpha]_D$ −32.5 (c = 1.0, $CHCl_3$); IR 3029, 1679, 1494, 1454, 1379, 1279, 1225, 1179, 1146, 1112, 1077, 1028, 979, 938, 947, 745, 697, 683, 630, 756, 688 cm^{-1}; ^1H NMR (400 MHz) (Major conformer) δ 3.00−3.08 (m, 2H), 3.52 (d, 3H, J = 13.8 Hz), 3.60 (d, 3H, J = 13.8 Hz), 4.13 (d, 1H, J = 8.5 Hz), 4.37 (m, 1H),4.72 (dd, 1H, J = 8.5, 6.2 Hz), 5.33 (d, 1H, J = 6.2 Hz), 6.21 (q, 1H, J_{H-F} = 5.0 Hz), 7.23−7.50 (m, 15H);.^{13}C NMR (100.5 MHz) (Major conformer) δ 53.9 (d, J = 19.2 Hz), 58.4 (2C), 60.3 (d, J = 7.7 Hz), 76.7, 85.4 (q, J = 33.5 Hz), 89.6 (d, J = 188.8 Hz), 123.4 (q, J = 289.5 Hz), 126.0, 128.3, 128.8, 129.4, 138.9, 141.1, 169.1 (d, J = 19.2 Hz); ^{19}F NMR (376.2 MHz) (Major conformer) δ −192.2 (ddd, 1F, J = 49.3, 32.7, 22.6 Hz), −81.0 (bs, 3F, CF_3); HRMS (EI+, direct inlet probe) m/z [M+] Calcd for $C_{27}H_{26}F_4N_2O_2$ 486.1930, found 486.1913. Anal. Calcd for $C_{27}H_{26}F_4N_2O_2$ C, 66.66; H, 5.39; N, 5.76. Found: C, 66.64; H, 5.19; N, 5.88.

(*R*)-2-Fluoro-3-phenylpropanoic acid (5c). To a solution of the amide **2c** (0.500 g, 1.36 mmol, 1.0 equiv) in diethyl ether (14 mL) cooled at −10 °C and under argon atmosphere, was slowly added $LiAlH_4$ (0.207 g, 5.44 mmol, 4.0 equiv). The reaction mixture was stirred at −10 °C for 2 h. Water (195 μL, 10.88 mmol, 8 equiv), aqueous NaOH 15% (56 μL, 0.218 mmol, 0.16 equiv) and water (588 μL, 32.64 mmol, 24 equiv) were sequentially added. The resulting suspension was filtered, and the white powder was abundantly washed with diethyl ether. The filtrate was concentrated under reduced pressure to afford 0.545 g of hemiaminal **3c**. The conversion of the hemiaminal **3c** into aldehyde **4c** and oxazolidine *trans*-**Fox** was completed by stirring the reaction mixture for 2 h in a slightly acidic chloroform solution (0.08 mmol acetic acid in 55 mL chloroform). The reaction mixture was then concentrated under reduced pressure to afford a mixture of aldehyde **4c** and chiral auxiliary *trans*-**Fox** (0.503 g, quant.). The NMR spectral data of (*R*)-2-fluoro-3-phenylpropanal

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4c were determined from the crude mixture: ^{1}H NMR (400 MHz) δ 3.06 (ddd, 1H, J_{H-F} = 23.4 Hz, J = 15.1, 8.2 Hz), 3.17 (ddd, 1H, J_{H-F} = 30.5 Hz, J = 15.1, 4.1 Hz), 4.95 (ddd, 1H, J_{H-F} = 49.0 Hz, J = 8.2, 4.1 Hz), 7.05−7.40 (m, 5H), 9.76 (d, 1H, J_{H-F} = 5.6 Hz); ^{13}C NMR (100.5 MHz) δ 36.9 (d, J = 20.1 Hz), 95.2 (d, J = 182.1 Hz), 127.4, 128.8, 129.6, 134.9, 199.9 (d, J = 35.5 Hz); ^{19}F NMR (376.2 MHz) δ −200.9 (dddd, 1F, J = 49.0, 30.5, 23.5, 5.6 Hz). To a solution of this crude mixture in *t*-butanol (20 mL) at room temperature were added a solution of 2-methylbut-2-ene (7.48 mL, 2 M in THF, 14.97 mmol, 11.0 equiv) and a solution of $NaClO_2$ (1.231 g, 13.61 mmol, 10 equiv) and NaH_2PO_4 (1.699 g, 10.89 mmol, 8.0 equiv) in water (12 mL). The resulting yellow solution was stirred at room temperature overnight. THF and *t*-butanol were removed under reduced pressure. Water (25 mL) was added, and the aqueous layer was extracted with a mixture of cyclohexane and ethyl acetate (90/10) (3 × 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture (0.620 g) was purified by silica gel chromatography (DCM/MeOH 98/2 to 96/4) to give the pure oxazolidine *trans*-**Fox** (0.220 g, 1.13 mmol, 74%) as a colorless oil. The aqueous layer was acidified to pH 2 with an aqueous 1 N HCl solution and was then extracted with ethyl acetate (3 × 25 mL). The acid **5c** (0.205 g, 1.226 mmol, 89%) was obtained as a colorless oil: $[\alpha]_D$ +30.4 (c = 1.36, $CHCl_3$); IR 3434, 3030, 2930, 2546, 1730, 1494, 1443, 1376, 1189, 1076, 933, 857, 795, 742, 695, 647 cm^{-1}; ^{1}H NMR (400 MHz) δ 3.18 (ddd, 1H, J_{H-F} = 22.9 Hz, J = 14.9, 7.9 Hz), 3.28 (ddd, 1H, J_{H-F} = 22.9 Hz, J = 14.9, 3.7 Hz), 5.13 (ddd, 1H, J_{H-F} = 48.8 Hz, J = 7.9, 3.7 Hz), 7.25−7.35 (m, 5H), 8.90 (bs, 1H); ^{13}C NMR (100.5 MHz) δ 38.3 (d, J = 20.1 Hz), 88.7 (d, J = 186.9 Hz), 127.2, 128.5 (2C), 129.3 (2C), 134.9, 173.5 (d, J = 23.9 Hz); ^{19}F NMR (376.2 MHz) δ −201.0 (dddd, 1F, J = 49.5, 27.0, 24.2, 8.5 Hz); HRMS (EI+, direct inlet probe) m/z [M+] Calcd for $C_9H_9FO_2$ 168.0587, found 168.0595.

(*R*)-3-Dibenzylamino-2-fluoropropanoic acid (5f). The same procedure as used for **4c** was followed starting from a solution of the amide **2f** (0.500 g, 1.03 mmol, 1.0 equiv) affording a mixture of aldehyde **4f** and chiral auxiliary *trans*-**Fox** (0.502 g, quant.). The NMR spectral data of (*R*)-3-dibenzylamino-2-fluoropropanal **4f** were determined from the crude mixture: ^{1}H NMR (400 MHz) δ 2.97 (ddd, 1H, J_{H-F} = 24.2 Hz, J = 14.8, 3.3 Hz) 3.04 (ddd, 1H, J_{H-F} = 27.0 Hz, J = 14.8, 6.0 Hz), 3.52 (d, 2H, J = 13.5 Hz), 3.81 (d, 2H, J = 13.5 Hz), 4.90 (ddd, 1H, J_{H-F} = 46.5 Hz, J = 6.0, 3.3 Hz), 7.12−7.41 (m, 10H), 9.54 (d, 1H, J_{H-F} = 8.5 Hz); ^{13}C NMR (100.5 MHz) δ 52.8 (d, J = 20.1 Hz), 59.1, 95.5 (d, J = 184.0 Hz), 127.4, 128.6, 128.9, 129.0, 129.1, 130.1, 135.9, 138.6, 198.6 (d, J = 29.7 Hz); ^{19}F NMR (376.2 MHz) δ −201.0 (dddd, 1F, J = 49.5, 27.0, 24.2, 8.5 Hz). To this crude material was applied the same oxidation protocol as **4c**. Purification of the organic layer by silica gel chromatography (DCM/MeOH 98/2 to 96/4) afforded *trans*-**Fox** (0.163 g, 0.75 mmol, 73%) as a colorless oil. The aqueous layer was acidified to pH 2 with an aqueous 1 N HCl solution and was then extracted with ethyl acetate (3 × 25 mL). The acid **5f** (0.208 g, 0.74 mmol, 71%) was obtained as a colorless oil: $[\alpha]_D$ −1.4 (c = 1.6, $CHCl_3$); IR 3028, 2800, 2361, 1737, 1602, 1494, 1453, 1371, 1211, 1135, 1077, 1027, 974, 908, 729, 696, 646, 619 cm^{-1}; ^{1}H NMR (400 MHz) δ 3.15 (ddd, 1H, J_{H-F} = 21.1 Hz, J = 14.3, 3.9 Hz), 3.24 (ddd, 1H, J_{H-F} = 22.7 Hz, J = 14.3, 6.4 Hz), 3.89 (d, 1H, J = 13.5 Hz), 3.99 (d, 1H, J = 13.5 Hz), 5.01 (ddd, 1H, J_{H-F} = 49.5, J = 6.4, 3.9 Hz), 7.21−7.38 (m, 10H), 10.26 (bs, 1H); ^{13}C NMR (100.5 MHz) δ 53.6 (d, J = 22.0 Hz), 58.1, 86.7 (d, J = 185.9 Hz), 128.6, 128.9, 130.0, 134.2, 171.5 (d, J = 21.1 Hz); ^{19}F NMR (376.2 MHz) δ −190.2 (ddd, 1F, J = 49.5, 22.7, 21.1 Hz); HRMS (EI+, direct inlet probe) m/z [M+] Calcd for $C_{17}H_{18}FNO_2$ 287.1322, found 287.1322.

(*R*)-2-Fluoro-3-phenylpropan-1-ol (6c). The $LiAlH_4$ reduction of **2c** (1.115 g, 3.04 mmol), followed by a slightly acidic medium hydrolysis, gave a mixture of aldehyde **4c** and oxazolidine *trans*-**Fox** (1.104 g, 3.04 mmol, 1.0 equiv). To a solution of this crude mixture in methanol (10.0 mL) was slowly added $NaBH_4$ (0.113 g, 3.04 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature overnight. The reaction was quenched with water (10 mL). The aqueous layer was extracted with dichloromethane (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (DCM/MeOH 100/0 to 95/5) afforded the expected alcohol **6c** (0.216 g, 0.79 mmol, 77%) as a colorless oil, and the oxazolidine *trans*-**Fox** (0.162 g, 1.05 mmol, 35%) as a colorless oil: $[\alpha]_D$ +10.1 (c = 1.8, $CHCl_3$); IR 3348, 3029, 2929, 1604, 1496, 1454, 1355, 1048, 903, 834, 744, 698 cm^{-1}; ^{1}H NMR (400 MHz) δ 2.18 (bs, 1H), 2.92 (ddd, 1H, J_{H-F} = 25.1 Hz, J = 14.2, 6.0 Hz), 3.01 (ddd, 1H, J_{H-F} = 17.2 Hz, J = 14.2, 7.3 Hz), 3.66 (ddd, 1H, J_{H-F} = 25.1 Hz, J = 12.6, 6.0 Hz), 3.75 (ddd, 1H, J_{H-F} = 25.1 Hz, J = 12.6, 2.8 Hz), 4.76 (ddtd, 1H, J_{H-F} = 48.6 Hz, J = 7.3, 6.0, 2.8 Hz), 7.19−7.33 (m, 5H); ^{13}C NMR (100.5 MHz) δ 37.5 (d, J = 22.0 Hz), 64.2 (d, J = 21.1 Hz), 94.8 (d, J = 171.6 Hz), 126.9, 128.7, 129.4, 136.5; ^{19}F NMR (376.2 MHz) δ −190.7 (dqd, 1F, J = 48.6, 25.1, 17.1 Hz); HRMS (EI+, direct inlet probe) m/z [M+] Calcd for $C_9H_{11}FO$ 154.0794, found 154.0789.

(*R*)-3-Dibenzylamino-2-fluoropropan-1-ol (6f). The $LiAlH_4$ reduction of **2f** (0.500 g, 1.03 mmol), followed by a slightly acidic medium hydrolysis gave an equimolar mixture of aldehyde **4f** and oxazolidine *trans*-**Fox** (0.502 g, 1.03 mmol, 1.0 equiv). To this crude material was applied the same reduction protocol as **4c**. Purification by flash chromatography (DCM/MeOH 100/0 to 95/5) afforded the expected alcohol **6f** (0.216 g, 0.79 mmol, 77%) as a colorless oil, and the oxazolidine *trans*-**Fox** (0.165 g, 0.76 mmol, 74%) as a colorless oil: $[\alpha]_D$ +1.0 (c = 0.8, $CHCl_3$); IR 3368, 3027, 2928, 2805, 1595, 1491, 1448, 1367, 1040, 971, 911, 838, 739, 694 cm^{-1}; ^{1}H NMR (400 MHz) δ 2.76 (ddd, 1H, J_{H-F} = 19.0 Hz, J = 14.0, 4.8 Hz), 2.79 (ddd, 1H, J_{H-F} = 16.0 Hz, J = 14.0, 4.8 Hz), 2.99 (bs, 1H), 3.60 (d, 2H, J = 13.4 Hz), 3.66 (ddd, 1H, J_{H-F} = 23.6 Hz, J = 12.4, 4.8 Hz), 3.72 (ddd, 1H, J_{H-F} = 19.9 Hz, J = 12.4, 4.8 Hz), 3.72 (d, 2H, J = 13.4 Hz), 4.63 (dp, 1H, J_{H-F} = 47.8 Hz, J = 4.8 Hz), 7.24−7.37 (m, 10H); ^{13}C NMR (100.5 MHz) δ 54.3 (d, J = 23.0 Hz), 59.72, 64.32 (d, J = 21.1 Hz), 92.0 (d, J = 171.6 Hz), 127.2, 127.5, 128.4, 128.6, 129.2, 138.6, 140.2; ^{19}F NMR (376.2 MHz) δ −194.38 (m, 1F); HRMS (EI+, direct inlet probe) m/z [M+] Calcd for $C_{17}H_{20}FNO$ 273.1529, found 273.1519.

■ ASSOCIATED CONTENT

Supporting Information

General information, NMR spectra of all new compounds and *trans*-**Fox**, (*S*)-phenetylamide of **5f**, (*R*)-Mosher's esters of **6c** and **6f** and chiral HPLC chromatogram of the benzylamide of **5c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) *Bioorganic and Medicinal Chemistry of Fluorine*; Begue, J.-P., Bonnet-Delpon, D., Eds.; Wiley: Hoboken, NJ, 2008.

(2) *Fluorine In Medicinal Chemistry And Chemical Biology*; Ojima, I., Ed.; Wiley-Blackwell: Hoboken, NJ, 2009.

(3) *Fluorine in Pharmaceutical and Medicinal Chemistry: From Biophysical Aspects to Clinical Applications*; Gouverneur, V., Muller, K., Eds; Imperial College Press: London, 2012.

(4) *Fluorine-Containing Synthons*; Soloshonok, V. A., Ed.; American Chemical Society: Washington, D.C., 2005.

(5) *Current Fluoroorganic Chemistry*; Soloshonok, V. A, Mikami, K., Yamazaki, T., Welch, J. T., Honek, J. F., Eds; ACS Symposium Series; American Chemical Society: Washington, D.C., 2007.

(6) *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Kirsch, P., Ed.; Wiley-VCH: Weinheim, 2004.
(7) *Organofluorine Chemistry*; Uneyama, K., Ed.; Blackwell Publishing: Oxford, 2006.
(8) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119−6146.
(9) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1−PR43.
(10) Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-A. *Chem. Rev.* **2011**, *111*, 455−529.
(11) Cahard, D.; Xu, X.; Couve-Bonnaire, S.; Pannecoucke, X. *Chem. Soc. Rev.* **2010**, *39*, 558−568.
(12) Davis, F.; Han, W. *Tetrahedron Lett.* **1992**, *33*, 1153−1156.
(13) Davis, F. A.; Qi, H. *Tetrahedron Lett.* **1996**, *37*, 4345−4348.
(14) Davis, F. A.; Qi, H.; Sundarababu, G. *Tetrahedron* **2000**, *56*, 5303−5310.
(15) Davis, F. A.; Kasu, P. V. N.; Sundarababu, G.; Qi, H. *J. Org. Chem.* **1997**, *62*, 7546−7547.
(16) Siddiqui, M.; Marquez, V.; Driscoll, J.; Barchi, J. *Tetrahedron Lett.* **1994**, *35*, 3263−3266.
(17) Less, S. L.; Handa, S.; Millburn, K.; Leadlay, P. F.; Dutton, C. J.; Staunton, J. *Tetrahedron Lett.* **1996**, *37*, 3515−3518.
(18) Brunet, V. A.; O'Hagan, D.; Slawin, A. M. Z. *J. Fluorine Chem.* **2007**, *128*, 1271−1279.
(19) Davis, F. A.; Kasu, P. V. N. *Tetrahedron Lett.* **1998**, *39*, 6135−6138.
(20) Edmonds, M. K.; Graichen, F. H. M.; Gardiner, J.; Abell, A. D. *Org. Lett.* **2008**, *10*, 885−887.
(21) Peddie, V.; Pietsch, M.; Bromfield, K. M.; Pike, R. N.; Duggan, P. J.; Abell, A. D. *Synthesis* **2010**, 1845−1859.
(22) Tessier, A.; Pytkowicz, J.; Brigaud, T. *Angew. Chem., Int. Ed. Engl.* **2006**, *45*, 3677−3681.
(23) Sini, G.; Tessier, A.; Pytkowicz, J.; Brigaud, T. *Chem.—Eur. J.* **2008**, *14*, 3363−3370.
(24) Tessier, A.; Lahmar, N.; Pytkowicz, J.; Brigaud, T. *J. Org. Chem.* **2008**, *73*, 3970−3973.
(25) Tessier, A.; Pytkowicz, J.; Brigaud, T. *J. Fluorine Chem.* **2009**, *130*, 1140−1144.
(26) Lubin, H.; Tessier, A.; Chaume, G.; Pytkowicz, J.; Brigaud, T. *Org. Lett.* **2010**, *12*, 1496−1499.
(27) Tessier, A.; Pytkowicz, J.; Brigaud, T. *J. Fluorine Chem.* **2012**, *134*, 122−127.
(28) Ishii, A.; Higashiyama, K.; Mikami, K. *Synlett* **1997**, 1381−1382.
(29) Stock, H. T.; Turner, N. J. *Tetrahedron Lett.* **1996**, *37*, 6575−6578.
(30) Caddick, S.; Jenkins, K. *Tetrahedron Lett.* **1996**, *37*, 1301−1304.
(31) Kolarovic, A.; Berkes, D.; Baran, P.; Povazanec, F. *Tetrahedron Lett.* **2001**, *42*, 2579−2582.
(32) Kosmrlj, J.; Weigel, L. O.; Evans, D. A.; Downey, C. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 3208−3209.
(33) Xu, H.; Wang, Q.; Zhu, J.; Deng, J.; Cun, L.; Cui, X.; Wu, J.; Xu, X.; Wu, Y. *Org. Biomol. Chem.* **2005**, *3*, 4227−4232.
(34) Anderson, N. G. *Org. Process Res. Dev.* **2005**, *9*, 800−813.
(35) Pellissier, H. *Tetrahedron* **2008**, *64*, 1563−1601.
(36) No trace of minor diastereomer could be detected by ^{19}F and ^{1}H NMR in the crude reaction mixture. Because of *cis*/*trans* amide conformers occurrence, basic epimerization reactions of compounds **2** were performed in order to discriminate conformers and potential diastereomers.
(37) Steiner, D. D.; Mase, N.; Barbas, C. F., III *Angew. Chem., Int. Ed.* **2005**, *44*, 3706−3710.
(38) Franzen, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296−18304.
(39) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjoersgaard, A.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703−3706.
(40) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826−8828.
(41) Enders, D.; Hüttl, M. R. M. *Synlett* **2005**, 991−993.
(42) Engman, M.; Diesen, J. S.; Paptchikhine, A.; Andersson, P. G. *J. Am. Chem. Soc.* **2007**, *129*, 4536−4537.

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