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Asymmetric aldol reactions using chiral CF_3-Oxazolidines (Fox) as chiral auxiliary

Arnaud Tessier, Julien Pytkowicz, Thierry Brigaud *

Université de Cergy-Pontoise, UMR CNRS 8123, Laboratoire SOSCO, F-95000 Cergy-Pontoise, France

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ABSTRACT

The aldol reactions of amide enolates derived from a trifluoromethylated oxazolidine (Fox) chiral auxiliary occur in good yields with a moderate *anti* diastereoselectivity (Li and Na enolates) to a high *syn* diastereoselectivity (boron enolate). After removal, the Fox chiral auxiliary is very conveniently and efficiently recovered in basic conditions.

1. Introduction

The asymmetric aldol reaction is one of the most extensively used reactions for the synthesis of complex chiral compounds [1]. The asymmetric induction methodologies developed involve chiral auxiliaries [2], chiral metal catalysts [3] and organocatalysis [4]. Because of the unique properties induced by the incorporation of fluorine atoms into molecules, several fluorine containing oxazolidinone-type chiral auxiliaries have been recently used for asymmetric aldol reactions. Hultin and co-workers reported the use of a fluorous oxazolidinone [5] in titanium-mediated aldol reaction [6]. The reaction employing a *syn* oxazolidinone gave comparable results than the classical Evans-type chiral auxiliaries (Scheme 1). The major innovation was that the reaction products were conveniently isolated by solid-phase extraction on fluorous silica.

Recently Fustero and co-workers reported the use of a difluorinated analogue of the well-known 4-benzyloxazolidinone in aldol reactions [7]. Depending on the reaction conditions, these authors could selectively obtain the *syn*-Evans or the *syn*-non-Evans products with a very high diastereoselectivity (Scheme 2).

In other respect we recently reported the use of a 2-trifluoromethyloxazolidine (Fox) as a high performing chiral auxiliary for highly diastereoselective alkylation reactions of amide enolates [8,9] (Scheme 3). One of the properties of the trifluoromethyl group is to stabilize the oxazolidine ring and prevent the ring opening because of its strong electron withdrawing effect. Moreover we could rationalize that it plays a crucial role in the diastereoselectivity because of the existence of fluorine–metal interactions [10]. We report herein our results concerning the use of the Fox chiral auxiliary in aldol reactions.

2. Results and discussion

We decided to study the reactivity of the *N*-propanoylamide **1** enolate with benzaldehyde as a model reaction. The *trans*-Fox-amide **1** was prepared according to our previously reported procedure [8]. Unexpectedly the standard procedure reported by Crimmins [11] failed to give the expected titanium enolate. No reaction occurred with $TiCl_4$ in the presence of DIPEA or TMEDA. No conversion of the starting *trans*-Fox-amide **1** was also achieved in the presence of triethylamine/TMSCl/cat. $MgBr_2$ which are fascinating recent conditions reported by Evans et al. [12,13]. Facing these failures we decided to investigate the reactivity of alkali metal enolates which gave outstanding results in alkylation reactions (Table 1). The reaction of **1** with LDA resulted mainly in the degradation of the Fox chiral auxiliary through dehydrofluorination reaction (Table 1, entry 1). However the *Z* enolates were cleanly obtained using LiHMDS or NaHMDS (Table 1, entries 2 and 3). With these hindered bases the dehydrofluorination reaction was avoided. With LiHMDS the *anti*/*syn* ratio was 70:30. This diastereomeric ratio was raised up to 84:16 by using NaHMDS as the base. The *anti* and *syn* compounds were identified by their ^1H NMR data. The *anti* compounds present higher ^3J coupling constants (4–7 Hz) than the *syn* compounds (2–4 Hz) [14,15]. After cleavage of the chiral auxiliary, the absolute configuration of the unique *syn* diastereomer was determined to be (*R*,*R*). The absolute configuration of each *anti* diastereomer was not assigned.

As there is no doubt about the pure *Z* configuration of the Fox-amide enolates produced with LiHMDS and NaHMDS, we suggest

* Corresponding author. Fax: +33 0 1 34 25 73 81.
E-mail address: thierry.brigaud@u-cergy.fr (T. Brigaud).

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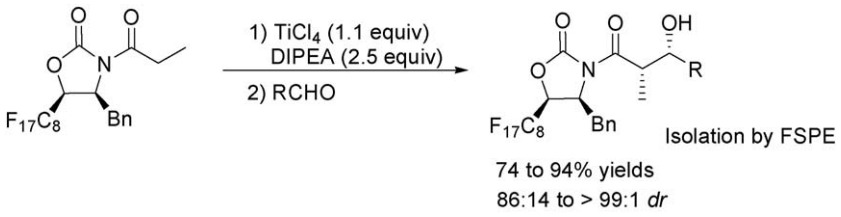
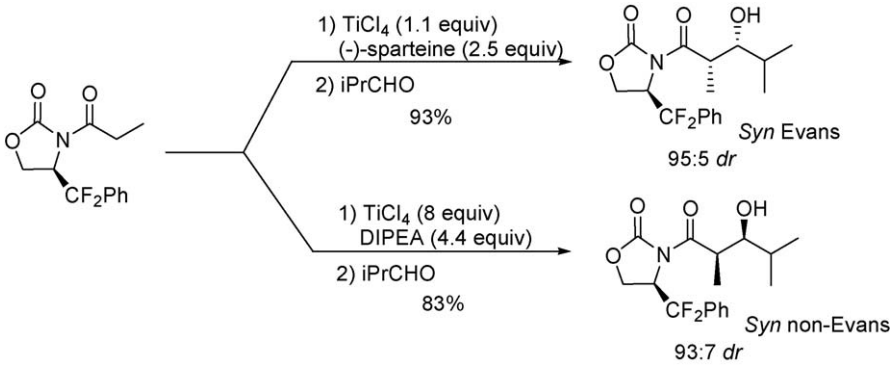
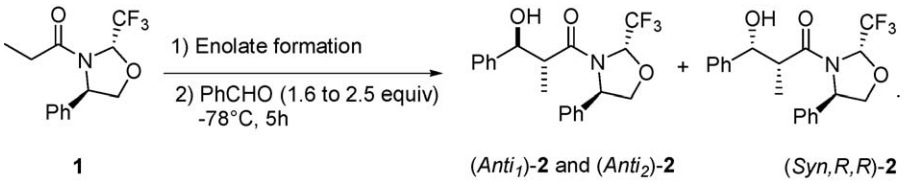


Scheme 1.



Scheme 2.

Table 1
Aldol condensation of alkali metal enolates of **1** with benzaldehyde.



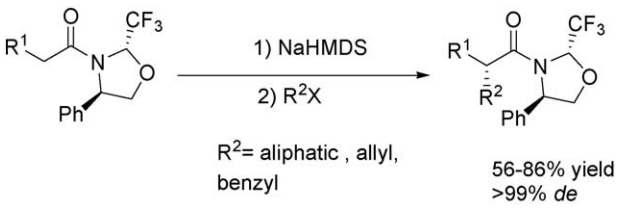
1 (*Anti*$_1$)-**2** and (*Anti*$_2$)-**2** (*Syn*,*R*,*R*)-**2**

Entry	Enolate formation	Yield (%)[a]	*Anti*/*syn* ratio[b]	Yields (%) (*Anti*$_1$)-**2**:(*Anti*$_2$)-**2**:(*Syn*,*R*,*R*)-**2**
1	LDA (1.8 equiv.)			Degradation[c]
2	LiHMDS (1.4 equiv.)	76[d]	70:30	48:4:24
3	NaHMDS (1.3 equiv.)	84[e]	84:16	66:9:9

[a] Total yield of all separated diastereomers.
[b] Ratio determined by ^{19}F NMR of the crude reaction mixture.
[c] Degradation of the chiral auxiliary through dehydrofluorination reaction.
[d] 10% isolated yield of unreacted **1** was recovered after silica gel chromatography.
[e] 9% isolated yield of unreacted **1** was recovered after silica gel chromatography.

that the major *anti* diastereomers are obtained through open transition states (Scheme 4).

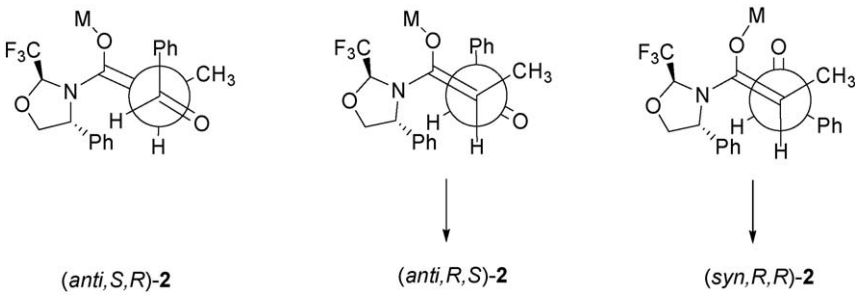
Chiral auxiliary-based aldol reaction with boron enolates have been extensively studied [1]. The formation of the boron enolates is generally performed with dialkylboron triflates in the presence of diisopropylethylamine (DIPEA) and the *syn* products are obtained with a very high diastereoselectivity. The boron enolate-mediated aldol reaction was performed from the Fox-amide **1** according to a standard literature procedure [16] involving Bu_2OTf (2 equiv.) and DIPEA (1.2 equiv.) in diethyl ether (Table 2, entry 1). In these conditions the two *syn* diastereomers were isolated as major compounds. The reaction conditions were significantly improved by using only 1.1 equiv. of Bu_2OTf in dichloromethane [17]. The *syn*/*anti* ratio was raised up to 95:5 and the major (*Syn*,*R*,*R*)-**2** compound was obtained in 74% isolated yield (Table 2, entry 2).



Scheme 3.

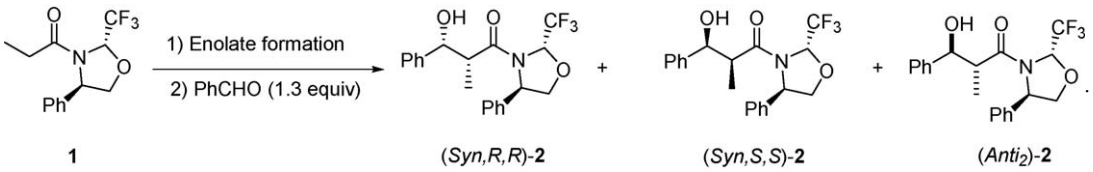
The formation of the major (*Syn*,*R*,*R*)-**2** product can be rationalized by a chelated transition state involving the attack of the *Z* boron enolate on the *Re* face of the aldehyde (Scheme 5).

The clean cleavage of the Fox chiral auxiliary and its efficient recovery is a key step. We already reported that the hydrolysis of the amide bond was unsuccessful in acidic conditions and that basic conditions caused epimerization of the α-carbonyl chiral center [8]. Thus the removal of the chiral auxiliary was carried out with $LiAlH_4$ according to our previously reported procedure. In these conditions the amide bond is selectively reduced into a hemiaminal which is hydrolysed in neutral conditions to give the chiral aldehyde and the Fox chiral auxiliary. In order to avoid its epimerization the chiral



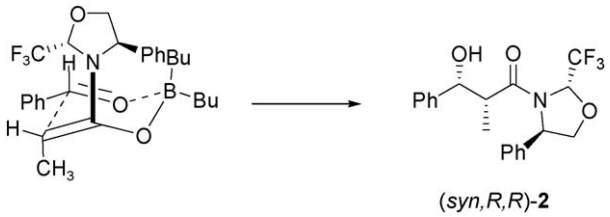
Scheme 4.

Table 2
Aldol condensation of boron enolates of **1** with benzaldehyde.



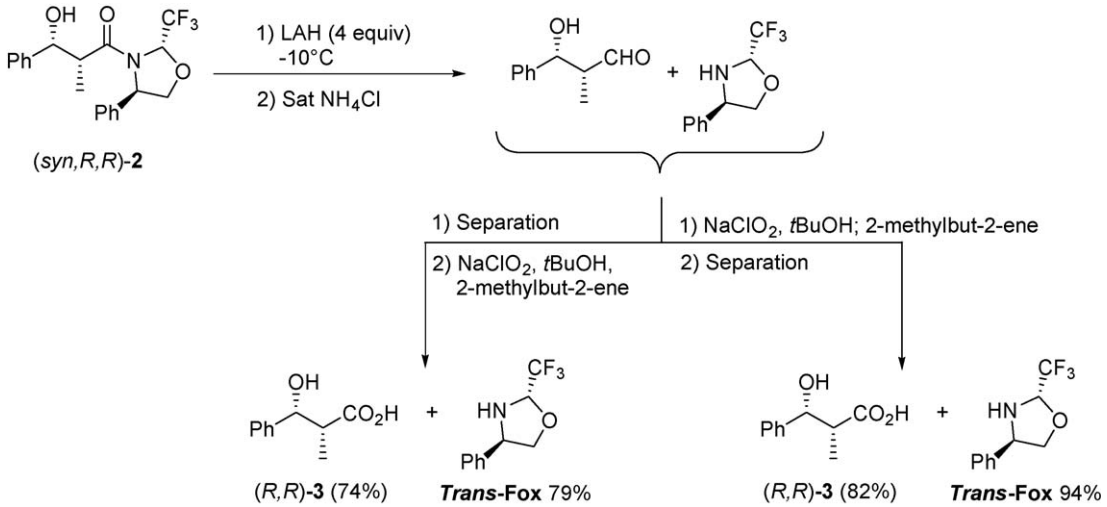
Entry	Enolate formation	Yield (%)[a]	*Syn*/*Anti* ratio[b]	Yields (%) (*Syn*,*R*,*R*)-**2**:(*Syn*,*S*,*S*)-**2**:(*Anti*$_2$)-**2**
1	DIPEA (1.2 equiv.) Bu_2OTf (2 equiv.) Et_2O	52	79:21	16:25:11
2	DIPEA (1.2 equiv.) Bu_2OTf (1.1 equiv.) CH_2Cl_2	87	95:5	74:8:5

[a] Total yield of all separated diastereomers.
[b] Ratio determined by ^{19}F NMR of the crude reaction mixture.



Scheme 5.

aldehyde was oxidized into carboxylic acid (*R*,*R*)-**3** (Scheme 6). In a first experiment, the aldehyde and the Fox were separated by chromatography on silica gel. The Fox chiral auxiliary was recovered in 79% yield. The isolated aldehyde was oxidized into carboxylic acid (*R*,*R*)-**3** in 74% yield [18]. The (*R*,*R*) configuration of **3** was assigned by comparison with literature data [19]. As we anticipated that the Fox chiral auxiliary should be stable in the oxidation conditions, in a second experiment the oxidation step was performed on the Fox and aldehyde mixture. In this case the carboxylic acid (*R*,*R*)-**3** and the Fox chiral auxiliary were very conveniently separated by liquid/liquid extraction. After oxidation the crude mixture was treated with a saturated $NaHCO_3$ solution and the Fox was extracted by a cyclohexane/ethyl acetate mixture (9:1). The chiral auxiliary was recovered in 94% yield. The aqueous solution was treated with a 1 M HCl solution, the carboxylic acid (*R*,*R*)-**3** was extracted with ethyl acetate and obtained in 82% yield. This optimized procedure presents the advantage to avoid chromatographic separation and to provide both carboxylic acid and recovered Fox chiral auxiliary in high yields.



Scheme 6.

3. Conclusion

In summary we demonstrated that the Fox chiral auxiliary is suitable for aldol reactions. Although its performance does not compete with oxazolidinone-type chiral auxiliaries, this chiral auxiliary is efficiently separated from the chiral hydroxy acid product by liquid/liquid extraction in basic medium. Further investigations about synthetic applications of the Fox chiral auxiliary are underway and will be reported in due course.

4. Experimental

General: unless otherwise mentioned, all the reagents were purchased from commercial source. THF was distilled under nitrogen from sodium/benzophenone prior to use. ^{1}H NMR (400.00 MHz), ^{13}C NMR (100.50 MHz) and ^{19}F NMR (376.20 MHz) were measured on a JEOL 400 spectrometer. Chemical shifts of ^{1}H NMR were expressed in parts per million downfield from tetramethylsilane ($\delta = 0$) in $CDCl_3$. Chemical shifts of ^{13}C NMR were expressed in parts per million downfield from $CDCl_3$ as internal standard ($\delta = 77.0$). Chemical shifts of ^{19}F NMR were expressed in parts per million downfield from C_6F_6 as internal standard ($\delta = -164.9$). Coupling constants are reported in hertz. Column chromatography was performed on Merck Kieselgel 60 (0.040–0.063 mm), employing mixture of specified solvent as eluent. Thin-layer chromatography (TLC) was performed on Merck silica gel (Merck 60 PF_{254}) plates. Silica TLC plates were visualized under UV light, by a 10% solution of phosphomolybdic acid in ethanol followed by heating. Mass spectra (MS) were obtained on a GC/MS apparatus HP 5973 MSD with an HP 6890 Series GC. Ionization was obtained by electronic impact (EI 70 eV). Infrared spectra (IR) were obtained by Fourier-transformation on BRÜCKER TENSOR 27, wavenumbers are given in cm^{-1}. Elemental analyses were performed by the CNRS analysis central service. Optical rotations are reported as their specific rotations determined using a JASCO DIP-370 polarimeter. Melting points were obtained on a Büchi apparatus and are uncorrected.

4.1. (2S,4R)-2-trifluoromethyl-3-[anti-3-hydroxy-2-methyl-3-phenylpropanoyl]-4-phenyloxazolidine ((*Anti*$_1$)-**2**, (*Anti*$_2$)-**2**)

Li-enolate, (Table 1, *entry* 2): To a stirred solution of hexamethyldisilazane (HMDS, 0.315 g, 1.95 mmol) in dry tetrahydrofuran (6 mL) was added a *n*-butyllithium solution (2.17 M, 0.76 mL, 1.65 mmol) at 0 °C. The yellow solution was stirred 40 min at 0 °C and cooled down to −78 °C and a solution of the amide **1** (0.325 g, 1.19 mmol) in dry tetrahydrofuran (3 mL) was added. The orange solution was stirred for 1 h at this temperature before the addition of benzaldehyde (0.286 mL, 2.25 mmol). The reaction mixture was stirred for five additional hours at −78 °C, quenched at this temperature with a saturated NH_4Cl solution (15 mL) and extracted with dichloromethane (3× 30 mL). Combined organic layers were dried over magnesium sulfate and concentrated over reduced pressure. Purification of the crude mixture by flash chromatography (cyclohexane/ethyl acetate: 90/10 to 80/20) afforded 215 mg of pure *anti* diastereomer (*Anti*$_1$)-**2** as a white solid (48%), 42 mg of pure *anti* diastereomer (*Anti*$_2$)-**2** (4%) and 145 mg of a mixture of (*Syn*,*R*,*R*)-**2**/amide **1** (70/30).

Na-enolate, (Table 1, *entry* 3): To a stirred solution of the amide **1** (0.32 g, 1.19 mmol) in dry tetrahydrofuran was added a NaHMDS solution (2 M in tetrahydrofuran, 0.79 mL, 1.57 mL) at −78 °C under argon. The reaction was stirred at −78 °C for 1 h and benzaldehyde (0.29 mL, 2.25 mmol) was added dropwise. The reaction mixture was stirred for five additional hours at −78 °C, quenched at this temperature with a saturated NH_4Cl solution (15 mL) and extracted with dichloromethane (3× 30 mL). Combined organic layers were dried over magnesium sulfate and concentrated over reduced pressure. Purification of the crude mixture by flash chromatography (cyclohexane/ethyl acetate: 90/10 to 80/20) afforded 298 mg of pure *anti* diastereomer (*Anti*$_1$)-**2** as a white solid (66%), 42 mg of (*Anti*$_2$)-**2** (9%) and 42 mg of (*Syn*,*R*,*R*)-**2** (9%).

(*Anti*$_1$)-**2**: White solid, ^{1}H NMR(250 MHz, $CDCl_3$): $\delta = 0.50$ (3H, d, $^3J = 6.6$ Hz), 2.6 (1H, quint., $^3J = 6.6$ Hz), 2.73 (1H, d, $^3J = 1.9$ Hz), 3.97 (1H, d, $^2J = 8.7$ Hz), 4.45 (1H, dd, $^2J = 8.7$ Hz, $^3J = 6.2$ Hz), 4.64 (1H, d, $^3J = 6.2$ Hz), 4.73 (1H, dd, $^3J = 1.9$ Hz, $^3J = 6.6$ Hz), 6.01 (1H, q, $^3J = 5$ Hz), 7.14–7.18 (2H, m), 7.26–7.37 (m, 8H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 11.3$, 48.3, 60.7, 75.9, 76.3, 84.8 (q, $^2J = 35.2$ Hz), 123.0 (q, $^1J_{C-F} = 288.9$ Hz), 125.9, 126.2, 128.5, 128.0, 128.8, 129.6, 141.6, 141.8, 175.6; ^{19}F NMR (235.35 MHz, $CDCl_3$): $\delta = -77.6$ (3 F, $^3J_{H-F} = 5.0$ Hz); EIMS(probe), *m*/*z* (rel. int.): 361(2), 273 (68), 241 (5), 204 (59), 186 (20), 148 (100), 120 (53), 105 (79), 91 (31), 77 (77), 57 (54).

(*Anti*$_2$)-**2**: White solid; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 0.46$ (3H, d, $^3J_{H-F} = 6.8$ Hz), 2.65 (1H, quint., $^3J = 6.6$ Hz), 3.3 (1H, bs), 3.95 (1H, dd, $^2J = 8.5$ Hz), 4.48 (1H, dd, $^2J = 8.5$ Hz, $^3J = 6.92$), 4.65 (1H, d, $^3J = 6.9$ Hz), 4.65 (1H, d, $^3J = 6.6$ Hz), 6.00 (1H, q, $^3J = 5.1$ Hz), 7.15–7.50 (m, 10H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 13.5$, 47.0, 60.3, 76.3, 77.1, 84.7 (q, $^2J_{C-F} = 35.3$ Hz), 122.8 (q, $^1J_{C-F} = 289.3$ Hz), 125.5, 125.6, 127.6, 128.3, 128.5, 129.3, 141.6, 142.3, 175.3; ^{19}F NMR (235.35 MHz, $CDCl_3$): $\delta = -77.11$ (3 F, d, $^3J_{H-F} = 5.1$ Hz); EIMS(probe), *m*/*z* (rel. int.): 361 ($M^{\bullet+}$: 4), 310 (1), 273 (100), 204 (45), 186 (25), 148 (67), 120 (44), 105 (90), 91 (35), 77 (77), 57 (36).

4.2. [2S,4R(2R,3R)]-2-trifluoromethyl-3-[Syn-3-hydroxy-2-methyl-3-phenylpropanoyl]-4-phenyloxazolidine ((*Syn*,*R*,*R*)-**2**)

2.0 equiv. *of Bu$_2$BOTf* (Table 2, *entry* 1): To a stirred solution of the amide **1** (0.190 g, 0.69 mmol) in dry diethylether (1.75 mL) was added a Bu_2BOTf solution (1*M*, 1.39 mL, 1.39 mmol) and the diisopropylethylamine (0.13 mL, 0.764 mmol) at −10 °C under argon. The reaction was stirred from −10 °C to 0 °C for 2 h and cooled to −78 °C before the addition of benzaldehyde (0.092 mL, 0.9 mmol). The reaction mixture was stirred for two additional hours at −78 °C, warmed up to ambient temperature over 2 h and quenched with a buffer solution (15 mL), methanol (10 mL) and an oxygen peroxide solution (30%, 8 mL). After extraction with diethylether (1× 5 mL) and dichloromethane (2× 5 mL), combined organic layers were dried over magnesium sulfate and concentrated over reduced pressure. Purification of the crude mixture by flash chromatography (cyclohexane/ethyl acetate: 90/10 to 80/20) afforded 42 mg of pure *syn* diastereomer (*Syn*,*R*,*R*)-**2** as a white solid (16%) and 95 mg of a mixture of (*Syn*,*S*,*S*)-**2**/(*Anti*$_2$)-**2** (70/30).

1.1 equiv. *of Bu$_2$BOTf* (Table 2, *entry* 2): To a stirred solution of the amide **1** (0.32 g, 1.19 mmol) in dry dichloromethane was added a Bu_2BOTf solution (1*M*, 1.31 mL, 1.31 mmol) and the diisopropylethylamine (0.24 mL, 1.43 mmol) at 0 °C under argon. The reaction was stirred from 0 °C to ambient temperature for 2 h and cooled to −78 °C before the addition of benzaldehyde (0.15 mL, 1.43 mmol). The reaction mixture was stirred for one additional hour at −78 °C, warmed up to ambient temperature over 2 h and quenched with a buffer solution (15 mL), methanol (10 mL) and an oxygen peroxide solution (30%, 8 mL). After extraction with dichloromethane (3× 30 mL), combined organic layers were dried over magnesium sulfate and concentrated over reduced pressure. Purification of the crude mixture by flash chromatography (cyclohexane/ethyl acetate: 90/10 to 80/20) afforded 332 mg of pure *syn* diastereomer (*Syn*,*R*,*R*)-**2** as a white solid (74%) and 70 mg of a mixture of (*Syn*,*S*,*S*)-**2**/(*Anti*$_2$)-**2** (62/38).

(*Syn*,*R*,*R*)-**2**: White solid, ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.04$ (3H, d, $^3J = 7.2$ Hz), 2.43 (1H, qd, $^3J = 2.0$ Hz, $^3J = 7.2$ Hz), 4.06 (1H, d, $^2J = 8.8$ Hz), 4.25 (1H, bs), 4.45 (1H, d, $^3J = 2.0$ Hz), 4.66 (1H, dd,

^2J = 8.8 Hz, ^3J = 6.0 Hz), 4.94 (1H, d, ^3J = 6.0 Hz), 6.21 (1H, q, $^3J_{H-F}$ = 5.1 Hz), 6.57 (2H, m), 7.11–7.20 (6H, m), 7.44–7.47 (2H, m); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 10.2, 44.9, 60.5, 71.6, 76.4, 84.9 (q, $^2J_{C-F}$ = 35.2 Hz), 123.2 (q, $^1J_{C-F}$ = 288.9 Hz), 125.5, 125.5, 126.9, 127.6, 129.2, 130.1, 140.8, 141.7, 178.7; ^{19}F NMR (235.35 MHz, $CDCl_3$): δ = −77.84 (3 F, d, $^3J_{H-F}$ = 5.1 Hz); EIMS(probe), *m*/*z* (rel. int.): 364 (9), 273 (60), 241 (60), 204 (65), 186 (25), 148 (100), 120 (55), 105 (89), 91 (33), 77 (89), 57 (56).

(*Syn*,*S*,*S*)-**2**: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.14 (3H, d, ^3J = 7.2 Hz), 2.65 (1H, m), 3.19 (1H, bs), 4.07 (1H, d, ^2J = 8.7 Hz), 4.31 (1H, m), 4.55 (1H, dd, ^2J = 8.7 Hz, ^3J = 6.6 Hz), 4.91 (1H, d, ^3J = 6.6 Hz), 6.14 (1H, q, $^3J_{H-F}$ = 5.0 Hz), 7.15–7.50 (10H, m); ^{19}F NMR (235.35 MHz, $CDCl_3$): δ = −77.27 (3 F, d, $^3J_{H-F}$ = 5.0 Hz). EIMS(probe), *m*/*z* (rel. int.): 361 (20), 346 (2), 292 (1), 204 (1), 186 (1), 145 (100), 117 (45), 91 (17), 77 (4).

4.3. (2R,3R)-3-hydroxy-2-methyl-3-phenylpropanoic acid ((R,R)-3)

Stepwise procedure: To a solution of amide (*Syn*,*R*,*R*)-**2** (155 mg, 0.41 mmol) in anhydrous diethyl ether (5 mL) was slowly added LAH (62 mg, 1.63 mmol) at −10 °C. The mixture was stirred for 1.5 h at this temperature and gently hydrolysed at −10 °C by dropwise addition of a saturated NH_4Cl solution (10 mL). The resulting emulsion was stirred vigorously for 2 h at room temperature, extracted with diethyl ether (2× 20 mL) and dichloromethane (20 mL). Organic layers were washed with a saturated NH_4Cl solution (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the crude mixture (171 mg) by flash chromatography (cyclohexane/ethyl acetate: 98/2 to 70/30) afforded 71 mg of recovered chiral auxiliary (79%) and 50 mg of the intermediate aldehyde (72%). This one was engaged in the oxidation step. To a solution of the intermediate aldehyde in *tert*-butanol (7 mL) was added 2-methyl-2-butene (2 M in THF, 2.2 mL, 4.4 mmol), sodium chlorite (394 mg, 3.48 mmol) and dihydrogenophosphate monohydrate (0.43 g, 2.77 mmol) in water (3 mL). The biphasic mixture was stirred for 1.2 h at room temperature. The crude was concentrated under reduced pressure to evaporate 2-methyl-2-butene and *tert*-butanol. The residue was taken up with water (15 mL) and a saturated $NaHCO_3$ solution (3 mL) and extracted with a cyclohexane/ethyl acetate mixture (9/1, 2× 20 mL). The aqueous layers were acidified (HCl 1 M), extracted with ethyl acetate (3× 30 mL), dried over Na_2SO_4, evaporated under reduced pressure to afford acid (*R*,*R*)-**3** (40 mg, 74%).

Optimized procedure: To a solution of amide (*Syn*,*R*,*R*)-**2** (130 mg, 0.34 mmol) in anhydrous diethyl ether (5 mL) was slowly added LAH (52 mg, 1.37 mmol) at −10 °C. The mixture was stirred for 1.5 h at this temperature and gently hydrolysed at −10 °C by dropwise addition of a saturated NH_4Cl solution (10 mL). The resulting emulsion was stirred vigorously for 2 h at room temperature, extracted with diethyl ether (2× 20 mL) and dichloromethane (20 mL). Organic layers were washed with a saturated NH_4Cl solution (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product (141 mg) was engaged without purification in the oxidation step. To a solution of crude product in *tert*-butanol (7 mL) was added 2-methyl-2-butene (2 M in THF, 2.2 mL, 4.4 mmol), sodium chlorite (394 mg, 3.48 mmol) and dihydrogenophosphate monohydrate (0.43 g, 2.77 mmol) in water (3 mL). The biphasic mixture was stirred for 1.2 h at room temperature. The crude was concentrated under reduced pressure to evaporate 2-methyl-2-butene and *tert*-butanol. The residue was taken up with water (15 mL) and a saturated $NaHCO_3$ solution (3 mL) and extracted with a cyclohexane/ethyl acetate mixture (9/1, 2× 20 mL). The organic layers were dried over $MgSO_4$, concentrated under reduced pressure to afford the *trans*-Fox chiral auxiliary (70 mg, 94%). The aqueous layers were acidified (HCl 1 M), extracted with ethyl acetate (3× 30 mL), dried over Na_2SO_4, evaporated under reduced pressure to afford acid (*R*,*R*)-**3** (51 mg, 82%).

(*R*,*R*)-**3**, colourless oil, $[\alpha]_D^{23}$ = +15.5 (*c* = 1.04; CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.9 (1H, dq, ^3J = 7.2 Hz, ^3J = 3.9 Hz), 5.20 (1H, d, ^3J = 3.9 Hz), 6.84 (m, 2H), 7.17 (3H, d, ^3J = 7.2 Hz), 7.35–7.39 (5H, m); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 10.4, 46.3, 73.5, 126.1, 127.8, 128.3, 141.2, 180.6.

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