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2-Trifluoromethyl-2-methyl-4-phenyloxazolidine: A new chiral auxiliary for highly diastereoselective enolate alkylation☆

Arnaud Tessier, Julien Pytkowicz, Thierry Brigaud *

Université de Cergy-Pontoise, Laboratoire SOSCO, F-95000 Cergy-Pontoise, France

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ABSTRACT

The alkylation reactions of an amide sodium enolate derived from a C-2 disubstituted trifluoromethylated oxazolidine (Fox) chiral auxiliary occurred in good yields with a very high diastereoselectivity (>98% de). Compared to the C-2 monosubstituted trifluoromethyl analogue, this chiral auxiliary is much more stable towards bases at temperature over −35 °C because the dehydrofluorination reaction is avoided. However asymmetric enolates quaternarization was not successfully achieved with this new chiral auxiliary.

1. Introduction

The asymmetric alkylation reaction of enolates is one of the most extensively used reactions for the synthesis of chiral compounds. Several chiral auxiliaries such as oxazolidinones [1] and related heterocyclic structures [2], sultames [3] and amino alcohols [4] are most commonly used for this reaction. We recently reported that the *trans* 2-trifluoromethyloxazolidine (*trans*-Fox) is a useful chiral auxiliary for highly diastereoselective amide enolates alkylation [5,6] and we could rationalize that the trifluoromethyl and the phenyl groups are playing a crucial role in the diastereoselectivity because of the existence of fluorine–metal and π electron–metal interactions [7]. Moreover the trifluoromethyl group stabilizes the oxazolidine ring and prevents the ring opening because of its strong electron withdrawing effect. We also recently reported that the *trans*-Fox proved to be an excellent chiral auxiliary for molecular oxygen oxidation of enolates [8] and could also be used for aldol reactions [9] (Scheme 1).

During our investigations we found that a limitation of the use of Fox chiral auxiliary was the dehydrofluorination reaction occurring over −50 °C. This side reaction led to partial degradation of the Fox-amide starting material. As most of the reactions were performed at −78 °C, this side reaction could be easily circumvented [5–9]. However in order to experiment reactions requiring higher temperatures such as for example α-quaternarization reactions, we became interested in a chiral auxiliary stable towards basic conditions at higher temperatures. We designed that C-2 disubstituted chiral fluorinated oxazolidines would be valuable candidates (Scheme 2).

2. Results and discussion

The oxazolidine (*S*)-**1** was very conveniently obtained by condensation of trifluoromethyl acetone with (*R*)-phenylglycinol under PPTS acidic catalysis [10]. Interestingly, as already reported in the literature [11], the only (*S*)-**1** diastereoisomer was obtained in this reaction (Scheme 3). In order to evaluate the performance of the other diastereomer as a chiral auxiliary, we were also interested in the preparation of the (*R*)-**1** compound. This was achieved by $BF_3{\cdot}OEt_2$ promoted partial isomerization of (*S*)-**1** into (*R*)-**1** (Scheme 3).

☆ The group "organofluorine chemistry and asymmetric synthesis" of the laboratory SOSCO (Synthèse Organique Sélective et Chimie bioOrganique) of the University of Cergy-Pontoise (North Paris) was founded in 2002 and is animated by five permanent researchers: Thierry Brigaud (Professor), Julien Pytkowicz, Grégory Chaume, Nathalie Lensen and Evelyne Chelain (Assistant Professors). The recent major accomplishments of the group are dealing with the synthesis of trifluoromethylated α- and β-amino acids, amino alcohols and diamines in enantiopure form. More recently, we reported the efficient incorporation of these fluorinated amino acids into peptides. We are now involved in the synthesis of biologically relevant fluorinated amino acid containing peptides, the synthesis of enantiopure fluorinated pseudoprolines, their incorporation into peptides and their conformational analysis. In other respect, we recently reported the outstanding performance of fluorinated oxazolidines as chiral auxiliaries for highly diastereoselective amide enolates alkylation, molecular oxygen oxidation. It was rationalized that the trifluoromethyl and the phenyl groups were playing a crucial role in the diastereoselectivity because of the existence of fluorine–metal and π electron–metal interactions.

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

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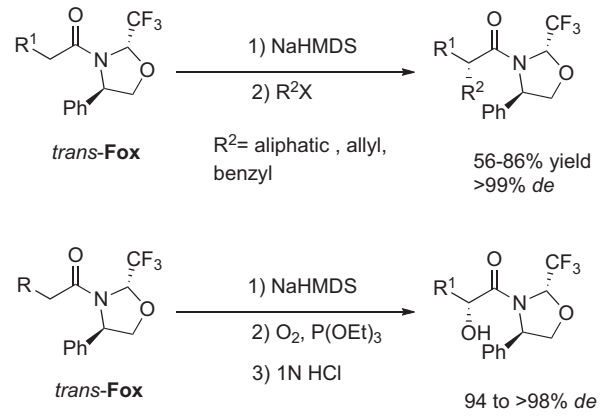
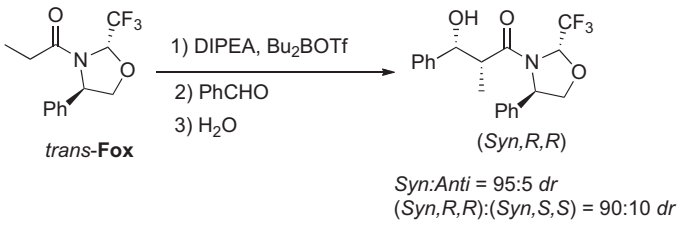
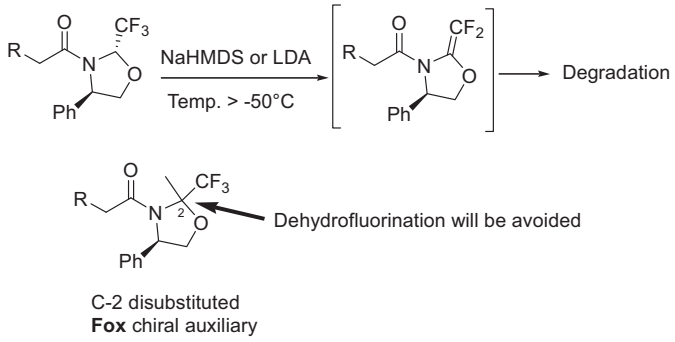
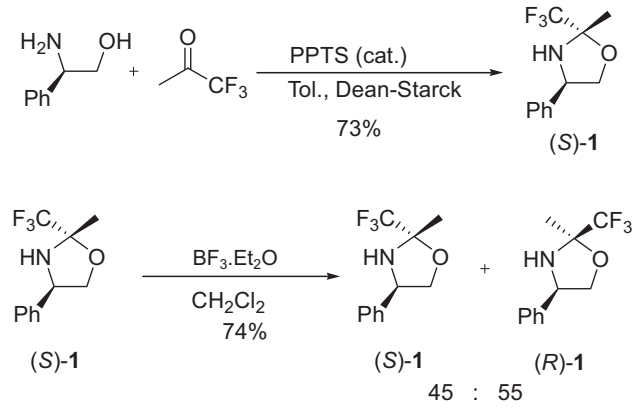




Scheme 1.



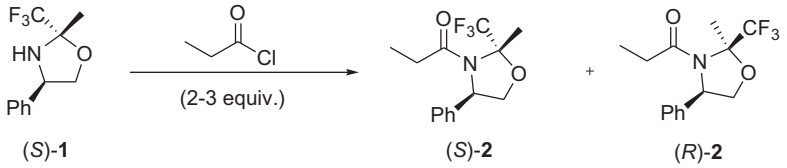
Scheme 2.



Scheme 3.

The *N*-propanoyl Fox-amides (*S*)-**2** and (*R*)-**2** were obtained through the reaction of the Fox chiral auxiliary (*S*)-**1** with propanoyl chloride. As we already reported [5], a highly reactive acyl chloride is required for this reaction because of the deactivation of the nitrogen atom of (*S*)-**1** due to the electron-withdrawing effect of the trifluoromethyl group. In similar conditions, this reaction proved to be less efficient with (*S*)-**1** than with the fluoral-based Fox chiral auxiliary and the *N*-propanoylated Fox (*S*)-**2** and (*R*)-**2** were obtained in only 18–32% yield when the reaction was carried out in the presence of a solvent (Table 1, entries 1–4). This should be explained by the increased steric hindrance caused by the quaternarization of the C-2 carbon of the oxazolidine. The yield of the propanoylation reaction was significantly improved when the reaction was performed without solvent at 60 °C (Table 1, entries 5–7). It should be noticed that in any cases an isomerization of (*S*)-**1** into (*R*)-**1** occurred in these reaction conditions by a reversible ring opening reaction prior to the propanoylation reaction to give a nearly 50:50 diastereomeric mixture of (*S*)-**2** and (*R*)-**2**. We already recently reported such isomerization during the benzoylation reaction of other hindered fluorinated oxazolidines [12]. The *N*-propanoyl oxazolidines are very conveniently separated by silica gel chromatography and do not undergo epimerization after isolation. Because of the epimerization reaction of the starting oxazolidine, it became useless to isolate both (*S*)-**1** and (*R*)-**1** oxazolidines before the acylation reaction. Thus, starting from a 45:55 diastereomeric mixture of (*S*)-**1** and (*R*)-**1**, the *N*-propanoyl oxazolidines (*S*)-**2** and (*R*)-**2** were prepared in high yield (91%) as a 50:50 mixture by

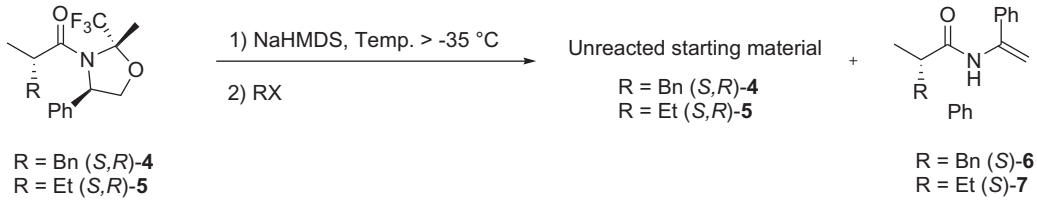
Table 1
Synthesis of *N*-propanoyloxazolidines (*S*)-**2** and (*R*)-**2**.



Entry	Solvent	Reaction conditions	Yields (%)	(*S*)-**2**:(*R*)-**2** *dr*
1	THF	DMAP (cat.) 4 days, 80 °C	31	35:65
2	DMF	DMAP (cat.), TEA, 4 days, 80 °C	28	41:59
3	THF	NaH, KI, 3 days, 80 °C	18	38:62
4[a]	Pyr.	3 days, 60 °C	32	29:71
5	No	16 h, 60 °C	61[b]	54:46
6	No	67 h, 60 °C	79[b]	54:46
7[c]	No	36 h, 50 °C	91[b]	50:50

[a] 5 equiv. of EtCOCl.
[b] Total yield of all separated diastereomers.
[c] Reaction performed from a 45:55(*S*)-**1**:(*R*)-**1** *dr* mixture and 9 equiv. of EtCOCl.

Table 2
Quaternarization reactions attempts.



Entry	Starting material	RX	Reaction conditions	Products
1	(*S*, *R*)-**4**	EtI	Deprotonation: −15 to 0 °C, 2 h Alkylation: −78 to −50 °C, 2 h	(*S*, *R*)-**4**:(*S*)-**6** ratio = 93:7
2	(*S*, *R*)-**5**	BnBr	Deprotonation: −35 °C, 3 h Alkylation: −78 to −35 °C, 3 h	(*S*, *R*)-**5**:(*S*)-**7** ratio = 95:5
3	(*S*, *R*)-**5**	BnBr	Deprotonation: room temp, 2 h Alkylation: −78 to −40 °C, 4 h	(*S*, *R*)-**5**:(*S*)-**7** ratio = 56:44

reaction with propanoyl chloride (9 equiv.) without solvent at 60 °C (Table 1, entry 6). (*S*)-**2** and (*R*)-**2** were isolated by silica gel chromatography.

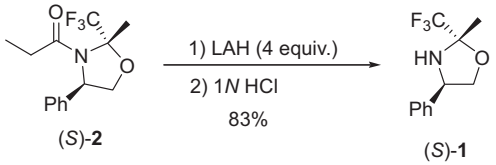
Because of the epimerization of the C-2 center of the oxazolidine ring during the acylation reaction, the configuration of the newly formed *N*-propanoylated oxazolidines had to be confirmed. This was achieved by the removal of the side chain of (*S*)-**2** by a treatment with lithium aluminium hydride [5] giving the (*S*)-**1** diastereomer in 83% yield (Scheme 4).

In order to assess the performance of both (*S*)-**1** and (*R*)-**1** oxazolidines as chiral auxiliaries for the asymmetric alkylation reactions, the sodium enolates of (*S*)-**2** and (*R*)-**2** were submitted to the benzylation reaction with benzyl bromide (Scheme 5). The (*S*)-**1** Fox proved to be a very inefficient chiral auxiliary as the reaction of (*S*)-**2** gave the corresponding (*S*)-**3** benzylated compound as a 59:41 diastereomeric mixture. However, the benzylation reaction of the sodium enolate of (*R*)-**2** proceeded in good yield (80%) to give the amide (*S*, *R*)-**4** with a complete diastereoselectivity. The ethylation reaction was also achieved in a completely diastereoselective manner to give the corresponding (*S*, *R*)-**5** compound in 66% yield. After removal of the chiral auxiliary (vide infra) the absolute configuration of the newly formed asymmetric centre was assigned to be (*S*). Intriguingly, conversely to our previously reported fluoral-based Fox chiral auxiliary [5–8], the C-2 quaternarized chiral auxiliary (*R*)-**1** giving the best diastereoselectivity is bearing the trifluoromethyl group in the relative *cis* position to the phenyl group. According to this observation, we cannot propose similar transition states to explain the high level of diastereoselectivity.

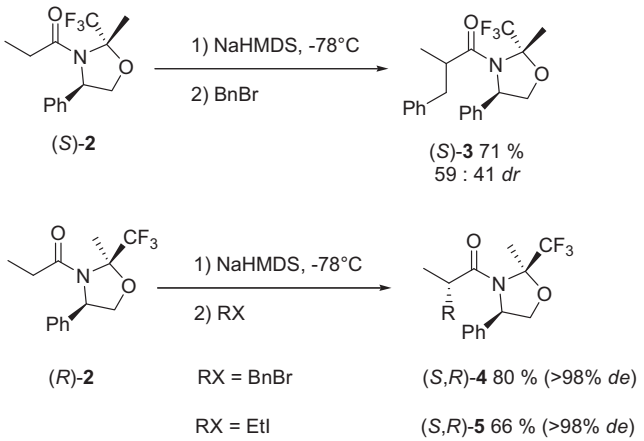
The stereoselective formation of quaternary asymmetric centres is a challenge in organic synthesis. As the main problem for this reaction is the control of the configuration of the enolate, several reported methods of the literature involved cyclic enolate to solve this drawback [13]. In order to investigate the use of the Fox chiral auxiliary (*R*)-**1** for asymmetric quaternarization reactions, the compound (*S*, *R*)-**4** and (*S*, *R*)-**5** were submitted to the sequence NaHMDS deprotonation and reaction with an halogenated compound (Table 2). As the dehydrofluorination reaction at the C-2 centre of the chiral auxiliary was impossible, the deprotonation reaction could be performed over −35 °C. Unfortunately the alkylation reaction of the amide side chain did not occur and the only new products obtained were the amides (*S*)-**6** and (*S*)-**7** resulting from the degradation of the chiral auxiliary. The fact that no epimerization reaction of the amide side chain was detected even at room temperature (Table 2, entry 3) suggests that the deprotonation of the side chain to generate the enolate failed probably because of a great steric hindrance.

In order to isolate the enamide (*S*)-**6** and to confirm its base promoted formation, the oxazolidine (*S*, *R*)-**4** was treated with NaHMDS at 5 °C for 2 h. In these conditions (*S*)-**6** was obtained in 25% isolated yield together with 62% of unreacted (*S*, *R*)-**4** starting material (Scheme 6). The postulated mechanism of the formation of (*S*)-**6** involving the deprotonation at the benzylic position of the chiral auxiliary is depicted in Scheme 6. This result confirms that the C-2 disubstituted chiral auxiliary (*R*)-**1** is not suitable, in these conditions, for the asymmetric α-quaternarization of amide enolates. The side reaction resulting from the basic decomposition of the chiral auxiliary could possibly be avoided by replacing the phenyl group of the Fox chiral auxiliary by a more hindered *tert*-butyl group.

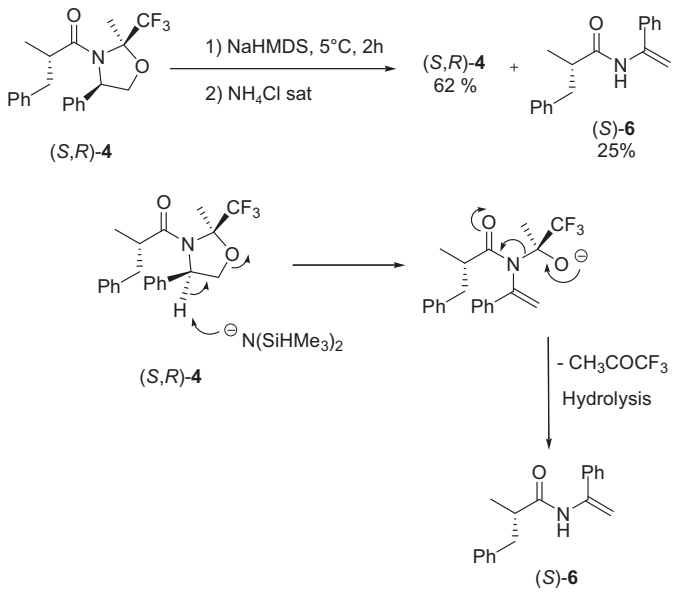
However, as this chiral auxiliary is efficient for highly diastereoselective monoalkylations of enolates, we investigate its removal in order to get an enantiopure hydroxy compound and to assign its absolute configuration. To this end, the amide (*S*, *R*)-**4** was treated by a reductive sequence we already reported involving the formation of an intermediate aldehyde and its reduction into an hydroxy compound [5–8]. According to this procedure, the hydroxy compound (*S*)-**8** was obtained in 72% isolated yield (Scheme 7). The (*S*) configuration of **8** and its enantiomeric purity



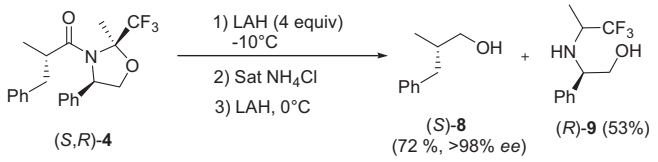
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7.

were assigned by Mosher's ester derivatization experiment [13]. Unfortunately the chiral auxiliary (*R*)-**1** was also reduced into the amino alcohol (*R*)-**9** in these conditions. However, as we already reported [6,8] it is anticipated that the use of sodium borohydride for the reduction of the intermediate aldehyde into (*S*)-**8** would avoid the reduction of the oxazolidines.

3. Conclusion

In summary we demonstrated that a C-2 disubstituted Fox chiral auxiliary is suitable for highly diastereoselective amide enolate alkylation reactions. This chiral auxiliary is stable in basic conditions, even at room temperature, but failed to allow diastereoselective quaternarization reactions.

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 or a Brüker Advance 250 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-methyl-2-trifluoromethyl-4-phenyloxazolidines (S)-1

To a solution of (*R*)-phenylglycinol (6 g, 43.7 mmol) in toluene at room temperature (100 mL) was slowly added trifluoroacetone (5.14 g, 45.9 mmol) and PPTS (2.2 g, 8.7 mmol). The flask was equipped with a Dean-Stark apparatus and the solution was warmed to reflux for 20 h. The solution was cooled down to 0 °C and the resulting PPTS precipitate was filtered off. The flask and the precipitate were washed with Et_2O (30 mL) and the combined organic layers were concentrated under reduced pressure. The crude mixture was purified by filtration through a short pad of silica gel (25 g, cyclohexane/ethyl acetate: 90/10) to afford oxazolidines (*S*)-**1** (7.37 g, 73%) as a yellow oil.

(*S*)-**1**, $[\alpha]_D^{23}$ −23.2 (*c* = 1.8, $CHCl_3$); IR (neat): 3356, 3033, 2999, 1458, 1338, 1156 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.63 (s, 3H), 2.29 (d, 1H, ^{3}J = 6.2 Hz), 3.82 (t, 1H, $^{3}J = {}^{2}J$ = 7.9 Hz), 4.40 (dd, 1H, ^{2}J = 7.9, ^{3}J = 7.6 Hz), 4.59 (dd, 1H, ^{3}J = 7.9 Hz, ^{3}J = 7.6 Hz), 7.20–7.50 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 20.6, 62.0, 73.6, 94.2 (q, $^{2}J_{C-F}$ = 30.8 Hz), 124.8 (q, $^{1}J_{C-F}$ = 287.2 Hz), 126.7, 128.2, 128.9, 138.8; ^{19}F NMR (235.35 MHz, $CDCl_3$): δ −82.9 (3 F, s,CF_3); EIMS, *m*/*z* (rel. int.): 232, 200, 162 (100), 132, 120, 77.3; Anal. calcd for $C_{11}H_{12}F_3NO$: C, 57.14; H, 5.23; N, 6.06. Found: C, 56.80; H, 5.05; N, 5.85.

4.2. (2R, 4R)-2-methyl-2-trifluoromethyl-4-phenyloxazolidines (R)-1

To a solution of oxazolidines (*S*)-**1** (1 g, 4.3 mmol) in CH_2Cl_2 (15 mL) was added $BF_3{\cdot}OEt$ (1.1 mL, 8.6 mmol). After 24 h stirring at room temperature, the reaction mixture was poured into a sat $NaHCO_3$ solution. The organic layer was extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. Purification of the crude mixture by flash chromatography (cyclohexane/ethyl acetate: 90/10) afforded 0.74 g (74%) of a 45:55 mixture of (*S*)-**1** and (*R*)-**1**. A pure analytical sample of (*R*)-**1** was obtained.

(*R*)-**1**, $[\alpha]_D^{23}$ −49.2 (*c* = 0.5; $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.36 (s, 3H), 3.71 (dd, 1H, 1H, ^{2}J = 9.2 Hz, ^{3}J = 8.7 Hz), 4.28 (dd, 1H, ^{2}J = 9.2, ^{3}J = 7.6 Hz), 4.59 (ddd, 1H, ^{3}J = 8.7 Hz, ^{3}J = 7.6 Hz, ^{3}J = 6.2 Hz), 7.10–7.40 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.5, 60.8, 75.0, 92.8 (q, $^{2}J_{C-F}$ = 30.8 Hz), 124.5 (q, $^{1}J_{C-F}$ = 287.0 Hz), 126.8, 127.7, 128.6, 138.9; ^{19}F NMR (235.35 MHz, $CDCl_3$): δ −83.3 (3 F, s,CF_3).

4.3. (4R)-2-trifluoromethyl-2-methyl-4-phenyl-3-propanoyloxazolidine (S)-2 and (R)-2

To oxazolidine (*R*)-**1** (7.00 g, 30.3 mmol) was added propanoyl chloride (7.38 mL, 84.6 mmol). After 36 h stirring at 50 °C the mixture was cooled down to room temperature and 1 N HCl solution (50 mL) was added. The aqueous solution was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were successively washed with a 1 N NaOH solution (50 mL), brine (50 mL) and were dried over $MgSO_4$. The resulting crude mixture (9.4 g) was purified by flash column chromatography (cyclohexane/ethyl acetate: 90/10 to 80/20) affording diastereomerically pure (*S*)-**2** (3.13 g, 36%) and pure (*R*)-**2** (3.36 g, 39%).

(2S, 4R)-2-trifluoromethyl-2-methyl-4-phenyl-3-propanoyloxazolidine (S)-**2**, white solid; m.p.: 78 °C; $[\alpha]_D^{23}$ −51.7 (*c* = 1.8, $CHCl_3$); IR (neat): 2986, 2915, 1661, 1396, 1303, 1164, 1078, 1046, 701 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 0.85 (t, 3H, ^3J = 7.3 Hz), 1.85 (dq, 1H, ^2J = 16.7 Hz, ^3J = 7.3 Hz), 2.00 (s, 3H), 2.15 (dq, 1H, ^2J = 16.7 Hz, ^3J = 7.3 Hz), 3.85 (dq, 1H, ^2J = 8.6 Hz, ^5J = 1.75 Hz), 4.45 (ddq, 1H, ^2J = 8.6 Hz, ^3J = 7.0 Hz, ^5J = 1.45 Hz), 4.96 (d, 1H, ^3J = 7.0 Hz), 7.16–7.27 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 8.5, 19.4, 29.5, 61.9, 73.8, 94.4 (q, $^2J_{C-F}$ = 31.2 Hz), 124.6 (q, $^1J_{C-F}$ = 293.5 Hz), 125.7, 128.3, 129.3, 141.6, 172.5; ^{19}F NMR (235.35 MHz, $CDCl_3$): δ −76.7 (s, 3 F, CF_3); EIMS, *m*/*z* (rel. int.): 287 (2), 230 (1), 218 (65), 200 (8), 175 (9), 162 (100), 130 (5), 120 (43), 103 (7); Anal. calcd for $C_{14}H_{16}F_3NO_2$: C, 58.53; H, 5.61; N, 4.88. Found: C, 58.68; H, 5.53; N, 4.82.

(2R, 4R)-2-trifluoromethyl-2-methyl-4-phenyl-3-propanoyloxazolidine (R)-**2**, yellow oil; $[\alpha]_D^{23}$ −79.29 (*c* = 3.15; $CHCl_3$); IR (neat): 2981, 2912, 1680, 1380, 1270, 1168, 1150, 1106, 701 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 0.95 (t, 3H, ^3J = 7.3 Hz), 1.88 (s, 3H), 1.89 (dq, 1H, ^2J = 16.9 Hz, ^3J = 7.3 Hz), 2.12 (dq, 1H, ^2J = 16.9 Hz, ^3J = 7.3 Hz), 3.99 (dd, 1H, ^2J = 8.9 Hz, ^3J = 8.3 Hz), 4.46 (dd, 1H, ^2J = 8.9 Hz, ^3J = 8.3 Hz), 5.06 (t, 1H, ^3J = 8.3 Hz), 7.30–7.40 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 8.6, 20.0, 29.9, 62.5, 73.8, 94.8 (q, $^2J_{C-F}$ = 32.1 Hz), 124.5 (q, $^1J_{C-F}$ = 290.8 Hz), 126.1, 128.5, 129.4, 138.4, 173.7; ^{19}F NMR (235.35 MHz, $CDCl_3$): δ −78.0 (s, 3 F); EIMS, *m*/*z* (rel. int.): 287 (6), 230 (5), 218 (10), 200 (19), 175 (81), 162 (100), 146 (16), 120 (61), 103 (14); Anal. calcd for $C_{14}H_{16}F_3NO_2$: C, 58.53; H, 5.61; N, 4.88. Found: C, 58.40; H, 5.59; N, 4.48.

4.4. (2S, 4R)-2-trifluoromethyl-2-methyl-3-[2-methyl-3-phenylpropanoyl]-4-phenyloxazolidine (S)-3

The oxazolidine (*S*)-**2** (0.33 g, 1.14 mmol) was dissolved in THF (9 mL) under argon atmosphere. The solution was cooled down to −78 °C and NaHMDS was added dropwise (1.07 mL, 2 M in THF, 2.14 mmol). The reaction mixture was stirred for 1.5 h at this temperature and benzyl bromide (0.26 mL, 2.14 mmol) was added slowly. The reaction mixture was stirred for 2 additional hours at −78 °C, quenched with a saturated NH_4Cl solution (15 mL), extracted with diethyl ether (2 × 30 mL) and dichloromethane (30 mL). The combined organic layers were dried over $MgSO_4$, evaporated under reduced pressure and the resulting crude mixture (0.47 g) was purified by flash column chromatography (cyclohexane/ethyl acetate: 98/2 to 95/5) to give a 59:41 diastereomeric mixture of (*S*)-**3** (0.305 g, 71%) as a yellow oil.

(*S*)-**3** major diast, ^1H NMR (250 MHz, $CDCl_3$): δ = 0.74 (d, 3H, ^3J = 6.3 Hz), 2.08 (s, 3H), 2.00–2.20 (m, 1H), 2.55–2.75 (m, 2H), 2.85 (dd, 1H, ^2J = 11.7 Hz, ^3J = 9.1 Hz), 3.80–4.30 (m, 2H), 4.60 (m, 1H), 7.11–7.50 (m, 10H); ^{19}F NMR (235.35 MHz, $CDCl_3$): δ −76.5 (s, 3 F); EIMS, *m*/*z* (rel. int.): 377 (16), 362 (5), 308 (3), 265 (25), 250 (15), 162 (46), 119 (58), 91 (100).

(*S*)-**3** minor diast, ^1H NMR (250 MHz, $CDCl_3$): δ = 1.15 (d, 3H, ^3J = 6.7 Hz), 2.13 (s, 3H), 2.00–2.20 (m, 1H), 2.41 (dd, 1H, ^2J = 13.4 Hz, ^3J = 7.3 Hz), 2.95 (dd, 1H, ^2J = 13.4 Hz, ^3J = 3.5 Hz), 3.80–4.30 (m, 2H), 5.05 (m, 1H), 7.11–7.50 (m, 10H); ^{19}F NMR (235.35 MHz, $CDCl_3$): δ −76.47 (s, 3 F); EIMS, *m*/*z* (rel. int.): 377 (49), 362 (13), 308 (4), 265 (8), 250 (7), 162 (50), 119 (62), 91 (100).

4.5. (2R, 4R)-2-trifluoromethyl-2-methyl-3-[(S)-2-methyl-3-phenylpropanoyl]-4-phenyloxazolidine (S, R)-4

To a solution of oxazolidine (*R*)-**2** (0.8 g, 2.78 mmol) in THF (20 mL) under argon atmosphere at −78 °C was added a solution of NaHMDS (2.65 mL, 2 M in THF, 5.3 mmol). The reaction mixture was stirred for 2 h at this temperature and benzyl bromide (0.63 mL, 5.29 mmol) was added. The reaction mixture was stirred for 4 additional hours at −78 °C, quenched with a saturated NH_4Cl solution (30 mL), extracted with diethyl ether (2 × 50 mL) and dichloromethane (50 mL). The combined organic layers were dried over $MgSO_4$, evaporated under reduced pressure and the resulting crude mixture (1.29 g) was purified by flash column chromatography (cyclohexane/ethyl acetate: 95/5) to give (*S*, *R*)-**4** (0.84 g, 80%) as a single diastereomer.

(*S*, *R*)-**4**, white solid; m.p.: 61 °C; $[\alpha]_D^{23}$ −89.4 (*c* = 2.5, $CHCl_3$); IR (neat): 2982, 2913, 1663, 1373, 1168, 1146, 1103, 701 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 0.77 (d, 3H, ^3J = 6.2 Hz), 1.62 (s, 3H), 2.55 (dd, 1H, ^2J = 11.7 Hz, ^3J = 4.5 Hz), 2.67 (m, 1H), 2.85 (dd, 1H, ^2J = 11.7 Hz, ^3J = 9.1 Hz), 3.77 (tq, 1H, *J* = 8.5 Hz, ^5J = 1.3 Hz), 4.06 (dd, 1H, ^2J = 8.5 Hz, ^3J = 5.8 Hz), 4.35 (m, 1H), 7.15–7.33 (m, 10H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 17.65, 19.2, 41.6, 42.0, 61.9, 73.1, 94.7 (q, $^2J_{C-F}$ = 32.1 Hz), 124.2 (q, $^1J_{C-F}$ = 291 Hz), 126.0, 126.8, 128.4, 128.6, 129.1, 129.3, 138.8, 139.7, 176.3; ^{19}F NMR (235.35 MHz, $CDCl_3$): δ −77.3 (s, 3 F, CF_3); EIMS, *m*/*z* (rel. int.): 377 (9), 362 (2), 308 (3), 265 (37), 250 (15), 162 (34), 146 (11), 119 (60), 91 (100), 77 (9); Anal. calcd for $C_{21}H_{22}F_3NO_2$: C, 66.82; H, 5.88; N, 3.71. Found: C, 66.56; H, 5.99; N, 3.63.

4.6. (2R, 4R)-2-trifluoromethyl-2-methyl-3-[(S)-2-methylbutanoyl]-4-phenyloxazolidine (S, R)-5

To a solution of oxazolidine (*R*)-**2** (0.58 g, 2 mmol) in THF (10 mL) under argon atmosphere at −78 °C was added a solution of NaHMDS (1.9 mL, 2 M in THF, 3.8 mmol). The reaction mixture was stirred for 2 h at this temperature and ethyl iodide (0.3 mL, 3.81 mmol) was added. The reaction mixture was stirred for 3.5 additional hours at −78 °C, quenched with a saturated NH_4Cl solution (30 mL), extracted with diethyl ether (2 × 40 mL) and dichloromethane (40 mL). The combined organic layers were dried over $MgSO_4$, evaporated under reduced pressure and the resulting crude mixture (0.61 g) was purified by flash column chromatography (cyclohexane/ethyl acetate: 90/10) to give (*S*, *R*)-**5** (0.44 g, 66%) as a single diastereomer.

(*S*, *R*)-**5**, yellow oil; $[\alpha]_D^{23}$ −74.9 (*c* = 2.6, $CHCl_3$); IR (neat): 2970, 2936, 2877, 1674, 1168, 1143, 1104 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 0.70 (d, 3H, ^3J = 6.2 Hz), 0.89 (t, 3H, ^3J = 7.4 Hz), 1.33 (m, 1H), 1.61 (m, 1H), 1.87 (s, 3H), 2.27 (m, 1H), 4.00 (dd, 1H, ^2J = 10.3 Hz, ^3J = 8.2 Hz), 4.47 (dd, 1H, ^2J = 10.3 Hz, ^3J = 8.2 Hz), 5.14 (t, 1H, ^3J = 8.2 Hz), 7.26–7.40 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 11.7, 16.3, 19.7, 28.0, 40.6, 62.3, 73.3, 94.5 (q, $^2J_{C-F}$ = 31.8 Hz), 124.3 (q, $^1J_{C-F}$ = 291 Hz), 126.0, 128.2, 129.1, 138.5, 177.0; ^{19}F NMR (235.35 MHz, $CDCl_3$): δ −77.4 (s, 3 F, CF_3); EIMS, *m*/*z* (rel. int.): 315 (4), 287 (3), 246 (6), 203 (56), 188 (40), 175 (7), 162 (65), 146 (12), 120 (29), 103 (13), 85 (48), 57 (100); Anal. calcd for $C_{16}H_{20}F_3NO_2$: C, 60.94; H, 6.39; N, 4.44. Found: C, 61.17; H, 6.52; N, 4.33.

4.7. (S)-2-methyl-N-(1-phenylvinyl)-3-phenylpropanamide (S)-6

To a solution of oxazolidine (*S*, *R*)-**4** (0.14 g, 0.37 mmol) in THF (6 mL) under argon atmosphere at 0 °C was added a solution of NaHMDS (0.32 mL, 2 M in THF, 0.65 mmol). The reaction mixture was stirred for 2 h at 5 °C. The reaction mixture was quenched with a saturated NH_4Cl solution (15 mL) extracted with diethyl ether (2 × 25 mL) and dichloromethane (25 mL). The combined organic layers were dried over $MgSO_4$, evaporated under reduced pressure and the resulting crude mixture (0.14 g) was purified by flash column chromatography (cyclohexane/ethyl acetate: 95/5) to give unreacted (*S*, *R*)-**4** (0.9 g, 62%) and (*S*)-**6** (0.036 g, 25%). ^1H NMR (250 MHz, $CDCl_3$): δ = 1.27 (d, 3H, ^3J = 6.7 Hz), 2.58 (m, 1H), 2.75 (dd, 1H, ^2J = 13.4 Hz, ^3J = 5.8 Hz), 2.99 (dd, 1H, ^2J = 13.4 Hz, ^3J = 9.1 Hz), 5.04 (s, 1H), 5.80 (s, 1H,), 6.55 (sl, 1H), 7.03 (m, 2H), 7.22–7.27 (m, 8H).

4.8. (S)-2-methyl-N-(1-phenylvinyl)-butanamide (S)-7

To a solution of oxazolidine (*S*, *R*)-**5** (0.13 g, 0.42 mmol) in THF (6 mL) under argon atmosphere at −78 °C was added a solution of NaHMDS (0.40 mL, 2 M in THF, 0.79 mmol). The reaction mixture was stirred for 2 h at 0 °C and benzyl bromide (0.095 mL, 0.79 mmol) was added at −78°. The reaction mixture was stirred for 4 additional hours at −78 to −40 °C, quenched with a saturated NH_4Cl solution (15 mL) extracted with diethyl ether (2 × 25 mL) and dichloromethane (25 mL). The combined organic layers were dried over $MgSO_4$, evaporated under reduced pressure and the resulting crude mixture (0.61 g) was purified by flash column chromatography (cyclohexane/ethyl acetate: 90/10) to give 0.12 g of a 56/44 mixture of (*S*, *R*)-**5** and (*S*)-**7**.

(*S*)-**7**, ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.97 (t, 3H, ^3J = 7.4 Hz), 1.22 (d, 3H, ^3J = 7.0 Hz), 1.45 (m, 1H), 1.75 (m, 1H), 2.20 (m, 1H), 5.09 (sl, 1H), 5.91 (s, 1H), 6.85 (s, 1H), 7.28–7.36 (m, 5H).

4.9. Removal of the chiral auxiliary

To a solution of (*S*, *R*)-**4** (297 mg, 0.79 mmol) in anhydrous diethyl ether (7 mL) under argon at −10 °C was added LAH (120 mg, 3.15 mmol). The mixture was stirred for 2 h at −10 °C and was quenched by a dropwise addition of a NaCl saturated solution (10 mL). The mixture was then vigorously stirred for 2.5 h at room temperature. The aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. To this resulting crude material (310 mg) in solution in anhydrous diethyl ether was added LAH (55 mg, 1.46 mmol). The mixture was stirred for 1.5 h at 0 °C and was quenched by a dropwise addition of a 1 N HCl solution (5 mL). The mixture was stirred at room temperature. The aqueous layer was extracted with diethyl ether (2 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture (220 mg) was purified by silica gel chromatography (cyclohexane:ethylacetate 98/2 to 95/5) to afford (*S*)-**8** as a colorless oil (85 mg, 72%) and (*R*)-**9** (97 mg, 52%).

The characterization data of (*S*)-**8** were in accordance with the literature data [5,14].

4.10. (R)-2-(2,2,2-trifluoro-1-methylethylamino)-2-phenylethanol (R)-9

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.20 (d, 3H, ^3J = 6.9 Hz), 3.09 (hept, 1H, ^3J = 6.9 Hz), 3.51 (dd, 1H, ^2J = 10.8, ^3J = 9.3 Hz), 3.73 (dd, 1H, ^2J = 10.8, ^3J = 4.2 Hz), 4.07 (dd, 1H, ^3J = 9.3, ^3J = 4.2 Hz), 7.21–7.34 (m, 5H); ^{19}F NMR (235.35 MHz, $CDCl_3$): δ −76.8 (d, 3F, ^3J = 6.9 Hz).

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