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Organocatalytic *anti*-Selective Mannich Reactions with Fluorinated Aldimines: Synthesis of *anti*-γ-Fluoroalkyl-γ-amino Alcohols

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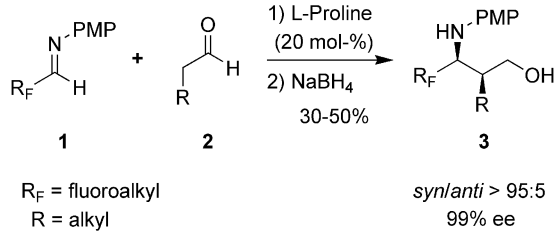
The asymmetric Mannich reaction between fluoroalkyl aldimines and aldehydes catalyzed by α,α-diphenylprolinol trimethylsilyl ether is reported. The corresponding Mannich adducts were reduced in situ to afford *anti*-β-alkyl-γ-fluoroalkyl-γ-amino alcohols in moderate yields and with very high diastereo- and enantioselectivities.

Introduction

The Mannich reaction is a powerful, straightforward tool for synthesizing β-amino carbonyl compounds, including β-amino acids and β-lactams.[1] Of the numerous asymmetric versions of this process that have been developed, organocatalytic methods are some of the most efficient in terms of diastereo- and enantioselectivity; moreover, they do not require the use of expensive and/or toxic metallic catalysts.[2] Seminal work by List,[3] Barbas,[4] and Hayashi[5] used proline as a catalyst for synthesizing *syn*-β-amino aldehydes by means of two- or three-component reactions between a preformed imine and a carbonyl compound, or an amine and two carbonyl compounds, respectively. While many different proline-derived catalysts have been developed since then, *syn* diastereomers are still the usual major reaction products.[6] In contrast, the preparation of the corresponding *anti* isomers has always been a more challenging task, although in the case of nonfluorinated derivatives, new generation catalysts have gone a long way toward solving this problem.[7]

The chemistry of fluorinated analogues of β-amino acid derivatives is an increasingly active field.[8] Our group, for example, previously described the preparation of *syn*-α-alkyl-β-fluoroalkyl-β-amino esters through a stereoselective reduction of γ-fluorinated β-enamino esters.[9] The Mannich reaction of a fluoroalkyl aldimine and the lithium enolate of a chiral acetate also afforded *syn*-β-amino esters, albeit with low selectivity.[9–10] In contrast, the synthesis of the *anti* derivatives has scarcely been described in the literature. Soloshonok, et al. were the first to describe the synthesis of the corresponding *anti* diastereomers by means of a biomimetic reductive amination of racemic fluorinated β-keto esters, achieving a 70:30 *anti*/*syn* ratio in optically pure form after an enzymatic resolution.[11] Very recently, we developed a different method which entails the fully *anti*-selective addition of enantiopure sulfinyl benzyl carbanions to fluoroalkyl aldimines and ketimines.[12]

Despite the versatility of fluorinated imines as synthetic intermediates,[13] they have received little attention as far as organocatalytic processes are concerned. A notable example is the report published by Funabiki and coworkers on the asymmetric Mannich reaction between fluoroalkyl aldimines and ketones catalyzed by L-proline (up to 98% *ee*).[14] More recently, Vovk and co-workers used aryl trifluoromethyl ketimines as Mannich acceptors with acetone in an L-proline-catalyzed reaction (up to 92% *ee*).[15] In the context of our current work on the synthesis of optically active fluorinated molecules with potential biological activity,[16] we recently described the Mannich reaction between fluoroimines **1** and aldehydes **2** catalyzed by L-proline (Scheme 1). The resulting β-amino aldehydes were reduced in situ to give *syn*-β-alkyl-γ-amino alcohols **3** in only moderate yields, but with excellent diastereo- and enantioselectivities.[17–18]



Scheme 1. Synthesis of fluorinated *syn*-γ-amino alcohols **3**.

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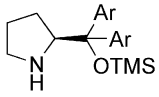
Diarylprolinol ethers **4a**–**b** (Figure 1) were first described by Jørgensen to be effective organocatalysts in many organic processes, including the *anti*-selective Mannich reaction.[7c,19–20] With the purpose of expanding the scope of our method, we envisaged the use of catalysts **4** in the Mannich reaction of fluoroaldimines and aldehydes in order to prepare the corresponding *anti* diastereomers of amino alcohols **3**. It should be noted that the use of catalysts **4** with fluorinated substrates has been very scarce to date.[21]



4a Ar = Ph
4b Ar = 3,5-$(CF_3)_2C_6H_3$

Figure 1. Structures of diarylprolinol ethers **4a** and **4b**.

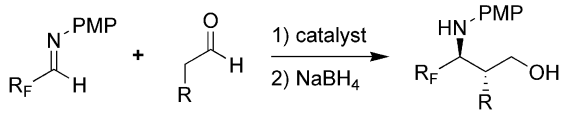
Results and Discussion

We proceeded to carry out the Mannich reaction of aldimines **1** and aldehydes **2**[22] in the presence of catalysts **4a**–**b** through the use of our previously optimized conditions[17] (20 mol-% of catalyst, NMP, –20 to 0 °C, 72 h, then reduction of the crude amino aldehyde with $NaBH_4$), which were based on those reported earlier by Hayashi,[5] although the temperature should be slowly raised for the reaction to occur. Thus, the reaction of aldimine **1a** (R_F = CF_3) with butanal catalyzed by **4a** afforded amino alcohol **5a** in moderate yield and with a remarkable 96:4 *anti*/*syn* ratio, as established through signal integration in the ^{19}F NMR spectrum of the crude mixture (Table 1, entry 1). Furthermore, the *anti* isomer had 98% *ee*, as determined by chiral HPLC analysis. It must be noted that about 30–40% of unreacted reduced imine was recovered as well. While trying to improve the reaction yield, we also tested MeCN, Jørgensen's preferred solvent,[7c] but in this case, the diastereoselectivity dropped to 80:20, while the major isomer exhibited only 49% *ee* (entry 2). Other solvents (THF, CH_2Cl_2, hexane, toluene) or higher reaction temperatures led to a significant decrease in both yield and diastereoselectivity.

When other aldehydes such as 3-phenylpropanal, 4-pentenal, propanal and pentanal were used, similar results were obtained (entries 3–7), with the *anti*/*syn* ratio being slightly lower only in the case of propanal. Even so, the reaction was still highly enantioselective (entry 6). In comparison, catalyst **4b** was also employed in the reaction with 3-phenylpropanal. Although the diastereoselectivity remained the same, the yield was considerably lower (entry 4). Finally, other fluorinated aldimines (**1b**, R_F = CF_3CF_2; **1c**, R_F = CF_2Cl) were used to obtain similar stereoselectivities, albeit with lesser yields (entries 8–11).

The relative configuration of compounds **5** was established through comparison with previously reported data for the corresponding *syn* diastereomers **3**. Thus, the NMR spectra of compounds **5a–d**, **g**–**h** diverged substantially from those for compounds **3**, which were prepared by means of an L-proline-catalyzed reaction.[17–18] The absolute configuration, depicted in Table 1, was determined through an X-ray analysis of compound **5i**, which contains a CF_2Cl group[23] (Figure 2).

Table 1. Preparation of fluorinated *anti*-γ-amino alcohols **5**.[a]



1a R = CF_3 **2** **5**
1b R = CF_3CF_2
1c R = CF_2Cl

Entry	Catalyst	5	R_F	R	Yield (%)[b]	*anti*/*syn*[c]	*ee* (%)[d]
1	**4a**	**5a**	CF_3	Et	46	96:4	98
2[e]	**4a**	**5a**	CF_3	Et	57	80:20	49
3	**4a**	**5b**	CF_3	Bn	50	92:8	98
4	**4b**	**5b**	CF_3	Bn	17	92:8	88
5	**4a**	**5c**	CF_3	allyl	60	95:5	97
6	**4a**	**5d**	CF_3	Me	41	86:14	>99[f]
7	**4a**	**5e**	CF_3	*n*Pr	40	97:3	>99
8	**4a**	**5f**	CF_3CF_2	Et	22	93:7	>99
9	**4a**	**5g**	CF_3CF_2	allyl	24	95:5	98
10	**4a**	**5h**	CF_3CF_2	Me	26	98:2	ND
11	**4a**	**5i**	CF_2Cl	allyl	25	86:14	99

[a] Reaction conditions: 1 M solution of **1** in NMP, 3 equiv. of **2**, 20 mol-% of catalyst, –20 °C for 24 h, –10 °C for 24 h, 0 °C for 24 h, then $NaBH_4$, MeOH, 0 °C. [b] Isolated yield. [c] Determined by ^{19}F NMR spectroscopy. [d] Determined by chiral HPLC. [e] Reaction carried out in MeCN at room temp. [f] Determined by chiral GC. ND: Not determined.

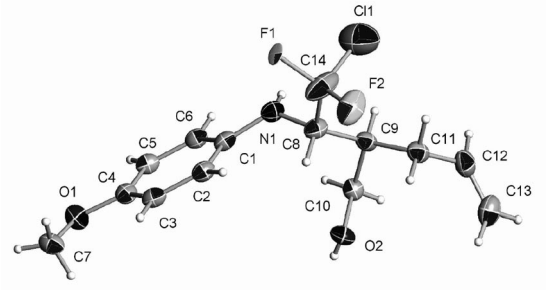


Figure 2. X-ray diffraction analysis of compound **5i**.

The stereoselectivity observed when catalysts **4a**–**b** are used can be rationalized through the proposed transition state in the well-established enamine catalysis mechanism (Figure 3).[7c,7g] Thus, nucleophilic attack on the imine preferentially occurs from the (*Si*,*Si*) *lk* face to afford the corresponding *anti*-β-amino aldehydes as major products. The asymmetric induction caused by the bulky pyrrolidine substituent is the opposite of that induced by hydrogen-bonding when proline is used as catalyst.

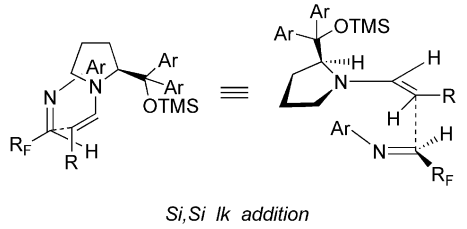
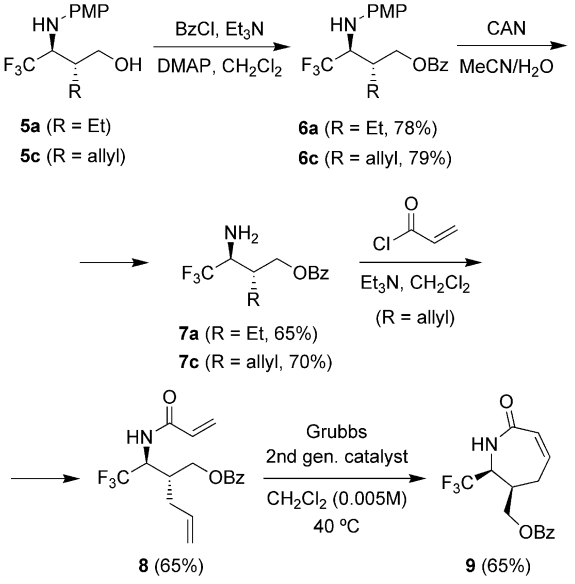


Figure 3. Proposed transition state for the Mannich reaction catalyzed by diarylprolinol ethers **4a** and **4b**.

Finally, we undertook the removal of the PMP protecting group in compounds **5** to render the corresponding free amines. For instance, alcohols **5a** and **5c** were transformed into benzoates **6a** and **6c**, and further reaction with ceric ammonium nitrate (CAN) afforded amines **7a** and **7c**, respectively (Scheme 2). Moreover, compound **7c**, which contains an olefinic chain, was a suitable substrate for preparing more elaborated cyclic structures. Thus, the derived acrylamide **8** was treated with Grubbs' second generation catalsyt under highly dilute conditions (0.005 M) to give seven-membered lactam **9**.



Scheme 2. Synthesis of fluorinated lactam **9**.

Conclusions

A highly diastereo- and enantioselective, one-step reaction between fluoroaldimines and aldehydes catalyzed by Jørgensen's arylprolinols afforded fluorinated *anti*-β-alkyl-γ-amino alcohols, which constitute a valuable class of fluorinated molecules with potential biological activity. Although the yields obtained in this one-step synthesis are, in general, only moderate, they should be compared with the overall yields in previous synthetic approaches employing multi-step strategies.[11–12] This method serves as a complement to our previously described synthesis of the corresponding *syn* diastereomers, and thus expands the applications of organocatalysis in organofluorine chemistry. The amino alcohols with an allyl group can be further cyclized by means of a metathesis reaction to give fluoroalkyl lactams, which may constitute a plausible entry for the synthesis of cyclic fluorinated peptidomimetics.

Experimental Section

General Methods: All reactions were carried out under argon or nitrogen atmosphere. Commercially available anhydrous NMP and MeOH were used without further purification. All reagents were used as received. The reactions were monitored with the aid of thin-layer chromatography (TLC) on 0.25 mm precoated silica gel plates. Visualization was carried out with UV light and aqueous ceric ammonium molybdate solution or potassium permanganate stain. Flash column chromatography was performed with the indicated solvents on silica gel 60 (particle size 0.040–0.063 mm). Melting points are uncorrected. Chemical shifts of NMR spectra are given in ppm (δ), referenced to the residual proton resonances of the solvents or fluorotrichloromethane in ^{19}F NMR experiments. Coupling constants (J) are given in Hertz [Hz]. The letters m, s, d, t, and q stand for multiplet, singlet, doublet, triplet, and quartet, respectively. The letters br. indicate that the signal is broad.

Diastereomeric mixtures were separated by semi-preparative HPLC (Lichrocart column 250–10, R*P*-18, 10 μm) using the appropriate solvent mixture as eluent (2.5 mL/min flow).

Optical purity of the *anti* diastereoisomers was determined by chiral HPLC analysis (ODH column, 0.46 cm I. D. × 25 cm) using the appropriate solvent mixture as eluent (1 mL/min flow). Racemic samples were used as a reference, prepared by using racemic **4a** as catalyst, in order to compare with the optically enriched mixtures.

In the case of compound **5d**, the *anti*/*syn* diastereomers could not be separated. The enantiomeric excess was measured by chiral GC (Beta Dex 120 column; ramp: 130 to 210 °C, 1 °C/min), using as a reference a mixture of the four possible diastereomers, as well as a sample of the pair of *syn* enantiomers, available when using racemic proline as catalyst.[17]

General Procedure for the Mannich Reaction: A mixture of the imine **1** (1.0 equiv.) and catalyst **4a** (20 mol-%) in NMP (1 M) was stirred at room temp. for 15 min. The reaction mixture was cooled to –20 °C, and the corresponding aldehyde **2** (3.0 equiv.) was added. The mixture was kept at –20 °C for 24 h, then at –10 °C for 24 h, and finally allowed to reach 0 °C, and stirred at that temperature for another 24 h. The reaction was quenched with saturated aqueous NH_4Cl solution, extracted with EtOAc, dried with Na_2SO_4 and concentrated in vacuo. The residue was dissolved in methanol (0.5 M), cooled to 0 °C, and $NaBH_4$ (3.0 equiv.) was added in small portions. After 3 h, the reaction was quenched with saturated aqueous NH_4Cl solution at 0 °C, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried with Na_2SO_4 and concentrated in vacuo. The resulting fluorinated γ-amino alcohols were purified by column chromatography on silica (hexane/EtOAc, 4:1) and the diastereomeric mixture separated by reverse-phase HPLC. The corresponding *anti* diastereomers were analyzed by chiral HPLC, or GC in the case of **5d**.

(2*R*,3*S*)-2-Ethyl-4,4,4-trifluoro-3-(4-methoxyphenylamino)butan-1-ol (5a): According to the general procedure, from **1a**[24] (100 mg, 0.49 mmol) and butyraldehyde (106 mg, 1.48 mmol), a mixture of *anti* and *syn* diastereomers (96:4) was obtained (62 mg, 46% yield). The diastereomers were separated by HPLC (MeCN/H_2O, 43:57,

t_R^{anti}: 43.72 min, t_R^{syn}: 37.83 min); *ee* of the *anti* isomer: 98% (hexane/2-propanol 95:5, t_R^{major}: 14.25 min, t_R^{minor}: 9.89 min); m.p. 64–66 °C. $[\alpha]_D^{20}$ = +2.8 (*c* = 0.9, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.5 Hz, 3 H, *Me*–CH_2), 1.59–1.65 (m, 3 H, Me–CH_2), 1.85–1.88 (m, 1 H, C*H*–Et), 3.74 (s, 3 H, Me–O), 3.81 (dd, *J* = 11.3, 3.0 Hz, 1 H, CH_2–O), 3.89–3.91 (m, 1 H, CH–CF_3), 4.07 (dd, *J* = 11.1, 2.6 Hz, 1 H, CH_2–O), 4.61 (br. s, 1 H, NH), 6.64 (d, *J* = 8.9 Hz, 2 H, Ar), 6.77 (d, *J* = 8.9 Hz, 2 H, Ar) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 12.1, 22.1, 41.3, 56.1, 59.7 (q, $^2J_{CF}$ = 28.0 Hz), 62.8, 114.9, 115.2, 127.0 (q, $^1J_{CF}$ = 284.6 Hz), 142.0, 153.0 ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –72.9 (d, J_{FH} = 7.7 Hz, 3 F) ppm. HRMS (EI): calcd. for $C_{13}H_{18}F_3NO_2$ $[M]^+$ 277.1290; found 277.1282.

(2*R*,3*S*)-2-Benzyl-4,4,4-trifluoro-3-(4-methoxyphenylamino)butan-1-ol (5b): According to the general procedure, from **1a**[24] (100 mg, 0.49 mmol) and 3-phenylpropanal (198 mg, 1.48 mmol), a mixture of *anti* and *syn* diastereomers (92:8) was obtained (84 mg, 50% yield). The diastereomers were separated by HPLC (MeCN/H_2O, 48:52, t_R^{anti}: 42.25 min, t_R^{syn}: 37.5 min); *ee* of the *anti* isomer: 98% (hexane/2-propanol 95:5, t_R^{major}: 19.81 min, t_R^{minor}: 23.53 min); m.p. 122–125 °C. $[\alpha]_D^{20}$ = –21.6 (*c* = 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.25–2.32 (m, 1 H, C*H*–Bn), 2.89 (d, *J* = 7.9 Hz, 2 H, CH_2–Ph), 3.76 (s, 3 H, Me–O), 3.81 (dd, *J* = 11.1, 2.9 Hz, 1 H, CH_2–O), 3.85–3.87 (m, 1 H, CH–CF_3), 4.10 (dd, *J* = 11.2, 2.8 Hz, 1 H, CH_2–O), 6.57 (d, *J* = 9.0 Hz, 2 H, Ar–N), 6.76 (d, *J* = 8.9 Hz, 2 H, Ar–N), 7.06–7.29 (m, 5 H, *Ar*–CH_2) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 35.5, 41.6, 56.1, 58.8 (q, $^2J_{CF}$ = 28.7 Hz), 62.9, 115.0, 115.2, 126.9, 128.9, 129.6, 139.3, 141.6, 153.0 ppm (the CF_3 signal was obscured due to its low intensity). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –72.6 (d, J_{FH} = 8.6 Hz, 3 F) ppm. HRMS (EI): calcd. for $C_{18}H_{20}F_3NO_2$ $[M]^+$ 339.1446; found 339.1446.

(*R*)-2-[(*S*)-2,2,2-Trifluoroethyl-1-(4-methoxyphenylamino)]pent-4-en-1-ol (5c): According to the general procedure, from **1a**[24] (100 mg, 0.49 mmol) and pent-4-enal (124 mg, 1.48 mmol), a mixture of *anti* and *syn* diastereomers (95:5) was obtained (85 mg, 60% yield). The diastereomers were separated by HPLC (MeCN/H_2O, 48:52, t_R^{anti}: 19.98 min, t_R^{syn}: 17.08 min); *ee* of the *anti* isomer: 97% (hexane/2-propanol 95:5, t_R^{major}: 14.40 min, t_R^{minor}: 10.15 min); m.p. 47–50 °C. $[\alpha]_D^{20}$ = +40.0 (*c* = 0.8, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.03–2.09 (m, 1 H, C*H*–allyl), 2.33 (t, *J* = 7.2 Hz, 2 H, CH_2–CH=CH_2), 3.74 (s, 3 H, Me–O), 3.81 (dd, *J* = 11.5, 3.7 Hz, 1 H, CH_2–O), 3.90–3.95 (m, 1 H, CH–CF_3), 4.07 (dd, *J* = 11.1, 3.0 Hz, 1 H, CH_2–O), 4.58 (br. s, 1 H, NH), 4.98 (dd, *J* = 16.9, 1.5 Hz, 1 H, CH=CH_2), 5.07 (dd, *J* = 10.2, 1.2 Hz, 1 H, CH=CH_2), 5.75 (ddt, *J* = 17.0, 10.1, 3.0 Hz, 1 H, C*H*=CH_2), 6.63 (d, *J* = 9.0 Hz, 2 H, Ar), 6.76 (d, *J* = 8.9 Hz, 2 H, Ar) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 33.8, 39.5, 56.1, 59.1 (q, $^2J_{CF}$ = 28.7 Hz), 63.1, 115.1, 115.2, 118.6, 135.8, 141.7, 153.0 ppm (the CF_3 signal was obscured due to its low intensity). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –72.9 (d, J_{FH} = 8.6 Hz, 3 F) ppm. HRMS (EI): calcd. for $C_{14}H_{18}F_3NO_2$ $[M]^+$ 289.1290; found 289.1285.

(2*R*,3*S*)-4,4,4-Trifluoro-3-(4-methoxyphenylamino)-2-methylbutan-1-ol (5d): According to the general procedure, from **1a**[24] (100 mg, 0.49 mmol) and propionaldehyde (86 mg, 1.48 mmol), a 86:14 mixture of *anti* and *syn* diastereomers was obtained (53 mg, 41% yield). The diastereomers could not be separated. *ee* of the *anti* isomer: >99%, as determined by chiral GC (t_R^{major}: 60.14 min). Data of *anti* isomer: ^1H NMR (300 MHz, $CDCl_3$): δ = 1.15 (d, *J* = 7.2 Hz, 3 H, *Me*–CH), 1.58 (br. s, 1 H, OH), 2.11–2.19 (m, 1 H, Me–C*H*), 3.68–3.73 (m, 1 H, CH_2–O), 3.74 (s, 3 H, Me–O), 3.77–3.87 (m, 1 H, CH–CF_3), 3.94 (dd, *J* = 10.9, 3.6 Hz, 1 H, CH_2–O), 4.20 (br. s, 1 H, NH), 6.65 (d, *J* = 8.9 Hz, 2 H, Ar), 6.78 (d, *J* = 9.0 Hz, 2 H, Ar) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 15.1, 35.7, 56.1, 60.8 (q, $^2J_{CF}$ = 25.7 Hz), 65.5, 115.3, 115.4, 141.6, 153.3 ppm (the CF_3 signal was obscured due to its low intensity). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = 72.6 (d, J_{FH} = 7.7 Hz, 3 F) ppm. Data of *syn* isomer: ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –72.7 (d, J_{FH} = 7.7 Hz, 3 F) ppm. HRMS (EI): calcd. for $C_{12}H_{16}F_3NO_2$ $[M]^+$ 263.1133; found 263.1127.

(2*R*,3*S*)-4,4,4-Trifluoro-3-(4-methoxyphenylamino)-2-(propyl)butan-1-ol (5e): According to the general procedure, from **1a**[24] (100 mg, 0.49 mmol) and pentanal (127 mg, 1.48 mmol), a mixture of *anti* and *syn* diastereomers (97:3) was obtained (57 mg, 40% yield). The diastereomers were separated by HPLC (MeCN/H_2O, 50:50, t_R^{anti}: 18.30 min, t_R^{syn}: 16.35 min); *ee* of the *anti* isomer: >99% (hexane/2-propanol 96:4, t_R^{major}: 16.34 min, t_R^{minor}: 9.60 min); m.p. 57–59 °C. $[\alpha]_D^{20}$ = +2.9 (*c* = 0.9, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.2 Hz, 3 H, *Me*–CH_2), 1.25–1.45 (m, 2 H, CH_2–CH_2), 1.45–1.65 (m, 2 H, CH_2–CH_2), 1.93–2.05 (m, 1 H, C*H*–Pr), 3.75 (s, 3 H, Me–O), 3.79 (dd, *J* = 11.1, 3.8 Hz, 1 H, CH_2–O), 3.89 (qd, *J* = 8.0, 4.0 Hz, 1 H, CH–CF_3), 4.07 (dd, *J* = 11.1, 2.4 Hz, 1 H, CH_2–O), 4.59 (br. s, 1 H, NH), 6.64 (d, *J* = 9.0 Hz, 2 H, Ar), 6.78 (d, *J* = 9.1 Hz, 2 H, Ar) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.0, 20.2, 30.9, 38.9, 55.7, 59.5 (q, $^2J_{CF}$ = 27.8 Hz), 62.7, 114.6, 114.9, 126.7 (q, $^1J_{CF}$ = 284.8 Hz), 141.6, 152.6 ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –72.9 (d, J_{FH} = 8.1 Hz, 3 F) ppm. HRMS (EI): calcd. for $C_{14}H_{20}F_3NO_2$ $[M]^+$ 291.1446; found 291.1448.

(2*R*,3*S*)-2-Ethyl-4,4,5,5,5-pentafluoro-3-(4-methoxyphenylamino)-pentan-1-ol (5f): According to the general procedure, from **1b**[25] (100 mg, 0.39 mmol) and butyraldehyde (85 mg, 1.18 mmol), a mixture of *anti* and *syn* diastereomers (93:7) was obtained (28 mg, 22% yield). The diastereomers were separated by HPLC (MeCN/H_2O, 46:54, t_R^{anti}: 43.60 min, t_R^{syn}: 43.41 min); *ee* of the *anti* isomer: >99% (hexane/2-propanol 98:2, t_R^{major}: 31.81 min, t_R^{minor}: 15.61 min); m.p. 65–67 °C. $[\alpha]_D^{20}$ = +10.2 (*c* = 0.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.5 Hz, 3 H, *Me*–CH_2), 1.57–1.67 (m, 4 H, C*H*–CH_2–Me, OH), 3.74 (s, 3 H, Me–O), 3.82 (dd, *J* = 11.5, 3.8 Hz, 1 H, CH_2–O), 4.02–4.12 (m, 2 H, CH_2–O, CH–CF_3), 4.55 (br. s, 1 H, NH), 6.60 (d, *J* = 8.9 Hz, 2 H, Ar), 6.76 (d, *J* = 8.9 Hz, 2 H, Ar) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 12.2, 22.6, 41.7, 56.0, 57.2 (dd, $^2J_{CF}$ = 24.7, 20.1 Hz), 62.9, 114.5, 115.3, 141.8, 152.8 ppm (the CF_3CF_2 signals were obscured due to their low intensity). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –82.4 (s, 3 F), –120.0 (dd, J_{FF} = 273.3, J_{FH} = 8.6 Hz, 1 F), –123.3 (dd, J_{FF} = 272.4, J_{FH} = 20.7 Hz, 1 F) ppm. HRMS (EI): calcd. for $C_{14}H_{18}F_5NO_2$ $[M]^+$ 327.1258; found 327.1261.

(*R*)-2-[(*S*)-1-(2,2,3,3,3-Pentafluoropropyl-4-methoxyphenylamino)]-pent-4-en-1-ol (5g): According to the general procedure, from **1b**[25] (100 mg, 0.39 mmol) and pent-4-enal (100 mg, 1.18 mmol), a mixture of *anti* and *syn* diastereomers (95:5) was obtained (32 mg, 24% yield). The diastereomers were separated by HPLC (MeCN/H_2O, 46:54, t_R^{anti}: 35.56 min, t_R^{syn}: 41.24 min); *ee* of the *anti* isomer: 98% (hexane/2-propanol 95:5, t_R^{major}: 11.10 min, t_R^{minor}: 7.96 min); m.p. 58–60 °C. $[\alpha]_D^{20}$ = +24.0 (*c* = 0.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.12–2.17 (m, 1 H, C*H*–allyl), 2.21–2.39 (m, 3 H, CH_2–CH=CH_2, OH), 3.74 (s, 3 H, Me–O), 3.82 (dd, *J* = 11.1, 4.1 Hz, 1 H, CH_2–O), 4.03–4.17 (m, 2 H, CH_2–O, CH–CF_3), 4.96 (dd, *J* = 16.9, 1.5 Hz, 1 H, CH=CH_2), 5.07 (dd, *J* = 10.1, 1.6 Hz, 1 H, CH=CH_2), 5.70 (ddt, *J* = 17.1, 9.9, 3.0 Hz, 1 H, C*H*=CH_2), 6.60 (d, *J* = 9.0 Hz, 2 H, Ar), 6.70 (d, *J* = 8.8 Hz, 2 H, Ar) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 34.1, 39.9, 56.0, 56.6 (dd, $^2J_{CF}$ = 24.1, 19.5 Hz), 63.3, 114.7, 115.2, 118.6, 135.8, 141.5, 152.9 ppm (the CF_3CF_2 signals were obscured due to their low intensity). ^{19}F

NMR (282.4 MHz, $CDCl_3$): δ = –82.4 (s, 3 F), –119.8 (dd, J_{FF} = 273.3, J_{FH} = 8.6 Hz, 1 F), –123.4 (dd, J_{FF} = 273.3, J_{FH} = 21.5 Hz, 1 F) ppm. HRMS (EI): calcd. for $C_{15}H_{18}F_5NO_2$ $[M]^+$ 339.1258; found 339.1245.

(2*R*,3*S*)-4,4,5,5,5-Pentafluoro-3-(4-methoxyphenylamino)-2-methylpentan-1-ol (5h): According to the general procedure, from **1b**[25] (100 mg, 0.39 mmol) and propionaldehyde (69 mg, 1.18 mmol), a mixture of *anti* and *syn* diastereomers (98:2) was obtained (32 mg, 26% yield), but the *ee* was not determined. Data of *anti* isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15 (d, J = 7.2 Hz, 3 H, *Me*–CH), 2.17–2.27 (m, 1 H, Me–C*H*), 3.66–3.75 (m, 1 H, CH_2–O), 3.74 (s, 3 H, Me–O), 3.78–3.82 (m, 1 H, CH–CF_3), 3.94 (dd, J = 10.8, 3.9 Hz, 1 H, CH_2–O), 6.61 (d, J = 9.0 Hz, 2 H, Ar), 6.76 (d, J = 9.1 Hz, 2 H, Ar) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 15.6, 35.9, 56.0, 64.6, 114.7, 115.3, 141.4, 153.0 ppm (the CF_3CF_2CH signals were obscured due to their low intensity). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –82.3 (s, 3 F), –118.5 (dd, J_{FF} = 273.9, J_{FH} = 5.9 Hz, 1 F), –124.6 (dd, J_{FF} = 273.9, J_{FH} = 22.3 Hz, 1 F) ppm. HRMS (EI): calcd. for $C_{13}H_{16}F_5NO_2$ $[M]^+$ 313.1101; found 313.1105.

(*R*)-2-[(*S*)-2-Chloro-2,2-difluoro-1-(4-methoxyphenylamino)ethyl]-pent-4-en-1-ol (5i): According to the general procedure, from **1c**[26] (100 mg, 0.46 mmol) and pent-4-enal, (115 mg 1.37 mmol), a mixture of *anti* and *syn* diastereomers (86:14) was obtained (35 mg, 25% yield). The diastereomers were separated by HPLC (MeCN/H_2O, 46:54, t_R^{anti}: 42.09 min, t_R^{syn}: 33:95 min); *ee* of the *anti* isomer: 99% (hexane/2-propanol 95:5, t_R^{major}: 28.86 min, t_R^{minor}: 16.74 min); m.p. 50–52 °C. $[\alpha]_D^{20}$ = +11.0 (c = 0.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.16–2.24 (m, 1 H, C*H*–allyl), 2.34 (t, J = 6.9 Hz, 2 H, CH_2–CH=CH_2), 3.74 (s, 3 H, Me–O), 3.81 (dd, J = 11.0, 3.6 Hz, 1 H, CH_2–O), 4.01 (br., 1 H, CH–CF_3), 4.08 (dd, J = 11.0, 3.0 Hz, 1 H, CH_2–O), 4.60 (br. s, 1 H, NH), 4.99 (dd, J = 16.9, 1.5 Hz, 1 H, CH=CH_2), 5.07 (dd, J = 9.9, 0.9 Hz, 1 H, CH=CH_2), 5.70 (ddt, J = 17.0, 10.0, 3.0 Hz, 1 H, C*H*=CH_2), 6.64 (d, J = 9.0 Hz, 2 H, Ar), 6.76 (d, J = 9.0 Hz, 2 H, Ar) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 34.3, 40.4, 56.1, 62.9, 64.6 (t, $^2J_{CF}$ = 23.6 Hz), 115.0, 115.1, 118.5, 131.6 (t, $^1J_{CF}$ = 300.1 Hz), 135.8, 141.7, 153.0 ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –56.9 (dd, J_{FF} = 162.9, J_{FH} = 9.5 Hz, 1 F), –58.6 (dd, J_{FF} = 162.9, J_{FH} = 11.2 Hz, 1 F) ppm. HRMS (EI): calcd. for $C_{14}H_{18}ClF_2NO_2$ $[M]^+$ 305.0994; found 305.0994.

X-ray Data of 5i: Monoclinic crystal system, space group $P2(1)$. Unit cell dimensions a = 8.4459(2) Å, α = 90°, b = 5.24480(10) Å, β = 98.2880(10)°, c = 16.8485(3) Å, γ = 90°, V = 738.54(3) Å^3, Z = 2, $d_{calcd.}$ = 1.375 mg/m^3. Absorption coefficient = 2.515 mm^{-1}. $F(000)$ = 320. Crystal size 0.20 × 0.15 × 0.10 mm^3. Reflections collected 5504, independent reflections 2553 (R_{int} = 0.0216), full-matrix least-squares on F^2 refinement method, goodness-of-fit on F^2 = 1.065.

CCDC-726705 contains supplementary crystallographic data for **5i**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(2*R*,3*S*)-1-(Benzoyloxy)-2-ethyl-4,4,4-trifluoro-3-(4-methoxyphenylamino)butane (6a): To a solution of **5a** (70 mg, 0.25 mmol) in CH_2Cl_2 (3.8 mL) at 0 °C, Et_3N (0.11 mL, 0.76 mmol), BzCl (0.09 mL, 0.76 mmol) and DMAP (15 mg, 0.13 mmol) were sequentially added. After stirring at room temp. for 6 h, the reaction was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The organic layer was washed with brine, dried with Na_2SO_4 and concentrated in vacuo. The product was purified by column chromatography on silica (hexane/EtOAc, 10:1) to afford the title compound as a colorless oil (75 mg, 78% yield). $[\alpha]_D^{20}$ = +15.7 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (t, J = 7.4 Hz, 3 H, *Me*–CH_2), 1.62 (quint, J = 7.3 Hz, 2 H, Me–CH_2), 2.15–2.24 (m, 1 H, C*H*–Et), 3.68 (s, 3 H, Me–O), 3.87 (d, J = 9.9 Hz, 1 H, NH), 3.93–4.06 (m, 1 H, CH–CF_3), 4.43 (dd, J = 11.7, 4.3 Hz, 1 H, CH_2–O), 4.51 (dd, J = 11.8, 5.0 Hz, 1 H, CH_2–O), 6.57 (d, J = 9.0 Hz, 2 H, Ar–N), 6.71 (d, J = 9.1 Hz, 2 H, Ar–N), 7.43 (t, J = 7.5 Hz, 2 H, Ar–CO), 7.55 (t, J = 7.4 Hz, 1 H, Ar–CO), 7.99 (d, J = 7.0 Hz, 2 H, Ar–CO) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 11.7, 22.0, 39.9, 55.7, 58.0 (q, $^2J_{CF}$ = 28.0 Hz), 64.0, 114.8, 115.0, 126.3 (q, $^1J_{CF}$ = 284.8 Hz), 128.6, 129.5, 129.9, 133.3, 140.8, 152.9, 166.2 ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –72.0 (d, J_{FH} = 7.9 Hz, 3 F) ppm. HRMS (EI): calcd. for $C_{20}H_{22}F_3NO_3$ $[M]^+$ 381.1552; found 381.1552.

(*R*)-1-(Benzoyloxy)-2-[(*S*)-2,2,2-trifluoroethyl-1-(4-methoxyphenylamino)]pent-4-ene (6c): To a solution of **5c** (41 mg, 0.14 mmol) in CH_2Cl_2 (2.1 mL) at 0 °C, Et_3N (0.06 mL, 0.42 mmol), BzCl (0.05 mL, 0.42 mmol) and DMAP (9 mg, 0.07 mmol) were sequentially added. After stirring at room temp. for 6 h, the reaction was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The organic layer was washed with brine, dried with Na_2SO_4 and concentrated in vacuo. The product was purified by column chromatography on silica (hexane/EtOAc, 10:1) to afford the title compound as a colorless oil (44 mg, 79% yield). $[\alpha]_D^{20}$ = +24.9 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.31–2.44 (m, 3 H, C*H*–CH_2–CH=CH_2), 3.68 (s, 3 H, Me–O), 3.83 (d, J = 10.5 Hz, 1 H, NH), 3.97–4.10 (m, 1 H, CH–CF_3), 4.40 (dd, J = 11.6, 4.2 Hz, 1 H, CH_2–O), 4.50 (dd, J = 11.7, 4.4 Hz, 1 H, CH_2–O), 5.01 (dq, J = 17.0, 1.5 Hz, 1 H, CH=CH_2), 5.09 (ddt, J = 10.2, 1.7, 1.0 Hz, 1 H, CH=CH_2), 5.74 (ddt, J = 17.2, 10.2, 7.0 Hz, 1 H, C*H*=CH_2), 6.57 (d, J = 9.0 Hz, 2 H, Ar–N), 6.70 (d, J = 9.1 Hz, 2 H, Ar–N), 7.43 (t, J = 7.6 Hz, 2 H, Ar–CO), 7.55 (t, J = 7.4 Hz, 1 H, Ar–CO), 7.99 (d, J = 7.1 Hz, 2 H, Ar–CO) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 33.4, 37.9, 55.7, 57.4 (q, $^2J_{CF}$ = 28.2 Hz), 64.1, 114.9, 115.0, 118.8, 126.3 (q, $^1J_{CF}$ = 284.9 Hz), 128.6, 129.5, 129.8, 133.3, 134.8, 140.5, 153.0, 166.2 ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –72.0 (d, J_{FH} = 8.0 Hz, 3 F) ppm. HRMS (EI): calcd. for $C_{21}H_{22}F_3NO_3$ $[M]^+$ 393.1552; found 393.1549.

(2*R*,3*S*)-3-Amino-1-(benzoyloxy)-2-ethyl-4,4,4-trifluorobutane (7a): To a solution of **6a** (75 mg, 0.20 mmol) in MeCN/H_2O (2:1, 5.9 mL) at 0 °C, CAN (323 mg, 0.59 mmol) was added. After stirring at room temp. for 6 h, the reaction was quenched with 5% aqueous $NaHCO_3$ and 20% aqueous $Na_2S_2O_3$, and extracted with EtOAc. The organic layer was washed with brine, dried with Na_2SO_4 and concentrated in vacuo. The product was purified by column chromatography on silica (hexane/EtOAc, 2:1) to afford the title compound as a colorless oil (35 mg, 65% yield). $[\alpha]_D^{20}$ = –11.5 (c = 1.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (t, J = 7.4 Hz, 3 H, *Me*–CH_2), 1.42 (br., 2 H, NH_2), 1.61 (quint, J = 7.3 Hz, 2 H, Me–CH_2), 1.98–2.07 (m, 1 H, C*H*-Et), 3.29 (qd, J = 8.4, 4.4 Hz, 1 H, CH–CF_3), 4.37 (ddd, J = 11.5, 5.0, 0.5 Hz, 1 H, CH_2–O), 4.44 (ddd, J = 11.5, 5.3, 0.7 Hz, 1 H, CH_2–O), 7.39 (t, J = 7.5 Hz, 2 H, Ar), 7.51 (t, J = 7.4 Hz, 1 H, Ar), 7.96 (d, J = 7.0 Hz, 2 H, Ar) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 11.6, 21.9, 39.5, 54.6 (q, $^2J_{CF}$ = 28.2 Hz), 63.7, 126.8 (q, $^1J_{CF}$ = 282.6 Hz), 128.4, 129.5, 130.0, 133.1, 166.4 ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –74.9 (d, J_{FH} = 8.4 Hz, 3 F) ppm. HRMS (EI): calcd. for $C_{13}H_{16}F_3NO_2$ $[M]^+$ 275.1133; found 275.1140.

(*R*)-2-[(*S*)-1-Amino-2,2,2-trifluoroethyl]-1-(benzoyloxy)pent-4-ene (7c): To a solution of **6c** (39 mg, 0.10 mmol) in MeCN/H_2O (2:1, 3.0 mL) at 0 °C, CAN (163 mg, 0.30 mmol) was added. After stirring at room temp. for 6 h, the reaction was quenched with 5%

aqueous $NaHCO_3$ and 20% aqueous $Na_2S_2O_3$, and extracted with EtOAc. The organic layer was washed with brine, dried with Na_2SO_4 and concentrated in vacuo. The product was purified by column chromatography on silica (hexane/EtOAc, 2:1) to afford the title compound as a colorless oil (20 mg, 70% yield). $[\alpha]_D^{20}$ = –17.7 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (br., 2 H, NH_2), 2.18–2.28 (m, 1 H, C*H*–allyl), 2.35 (t, J = 7.1 Hz, 2 H, CH_2–CH=CH_2), 3.31 (qd, J = 8.5, 3.9 Hz, 1 H, CH–CF_3), 4.34 (ddd, J = 11.5, 5.4, 0.4 Hz, 1 H, CH_2–O), 4.44 (ddd, J = 11.5, 5.3, 0.7 Hz, 1 H, CH_2–O), 5.05–5.13 (m, 2 H, CH=CH_2), 5.75 (ddt, J = 16.9, 10.2, 7.0 Hz, 1 H, C*H*=CH_2), 7.39 (t, J = 7.6 Hz, 2 H, Ar), 7.51 (t, J = 7.4 Hz, 1 H, Ar), 7.97 (d, J = 7.1 Hz, 2 H, Ar) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 33.5, 37.5, 54.2 (q, $^2J_{CF}$ = 28.4 Hz), 63.6 (q, $^4J_{CF}$ = 1.4 Hz), 118.2, 126.8 (q, $^1J_{CF}$ = 282.5 Hz), 128.5, 129.5, 130.0, 133.1, 135.1, 166.3 ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –74.9 (d, J_{FH} = 8.4 Hz, 3 F) ppm. HRMS (EI): calcd. for $C_{14}H_{16}F_3NO_2$ $[M]^+$ 287.1133; found 287.1124.

(*R*)-2-[(*S*)-1-Acrylamido-2,2,2-trifluoroethyl]-1-(benzoyloxy)pent-4-ene (8): To a solution of **7c** (18 mg, 0.06 mmol) in CH_2Cl_2 (0.65 mL) at 0 °C, Et_3N (0.02 mL, 0.12 mmol) and acryloyl chloride (0.01 mL, 0.10 mmol) were sequentially added. After stirring at room temp. for 6 h, the reaction was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was washed with brine, dried with Na_2SO_4 and concentrated in vacuo. The product was purified by column chromatography on silica (hexane/EtOAc, 2:1) to afford the title compound as a colorless oil (14 mg, 65% yield). $[\alpha]_D^{20}$ = +57.8 (c = 0.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.22–2.30 (m, 2 H, CH_2–CH=CH_2), 2.35–2.44 (m, 1 H, C*H*–allyl), 4.37 (dd, J = 11.9, 3.9 Hz, 1 H, CH_2–O), 4.46 (dd, J = 11.7, 5.0 Hz, 1 H, CH_2–O), 4.96 (dqd, J = 10.3, 8.7, 3.5 Hz, 1 H, CH–CF_3), 5.08–5.15 (m, 2 H, CH_2–CH=CH_2), 5.68 (dd, J = 10.3, 1.2 Hz, 1 H, CO–CH=CH_2), 5.72–5.83 (m, 1 H, CH_2–C*H*=CH_2), 6.05 (dd, J = 17.0, 10.3 Hz, 1 H, CO–C*H*=CH_2), 6.28 (dd, J = 17.0, 1.3 Hz, 1 H, CO–CH=CH_2), 6.28 (br. s, 1 H, NH), 7.42 (t, J = 7.6 Hz, 2 H, Ar), 7.55 (t, J = 7.4 Hz, 1 H, Ar), 7.95 (d, J = 7.1 Hz, 2 H, Ar) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 33.5, 37.1, 51.1 (q, $^2J_{CF}$ = 30.0 Hz), 63.7, 119.1, 125.1 (q, $^1J_{CF}$ = 282.4 Hz), 128.4, 128.7, 129.5, 129.6, 129.7, 133.5, 133.9, 165.3, 166.4 ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –72.5 (d, J_{FH} = 8.6 Hz, 3 F) ppm. HRMS (EI): calcd. for $C_{17}H_{18}F_3NO_3$ $[M]^+$ 341.1239; found 341.1229.

(6*R*,7*S*)-6-(Benzoyloxymethyl)-7-(trifluoromethyl)-6,7-dihydro-1*H*-azepin-2(5*H*)-one (9): To a solution of **8** (10 mg, 0.03 mmol) in CH_2Cl_2 (6 mL), Grubbs second generation catalyst (2.5 mg, 0.003 mmol) was added. The reaction was stirred at reflux for 3 h and then concentrated in vacuo. The product was purified by column chromatography on silica (hexane/EtOAc, 5:1 to 1:2) to afford the title compound as a colorless oil (6 mg, 65% yield). $[\alpha]_D^{20}$ = –16.1 (c = 0.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.47–2.68 (m, 2 H, CH_2–CH=CH_2), 2.78–2.87 (m, 1 H, C*H*–CH_2–O), 4.02–4.14 (m, 1 H, CH–CF_3), 4.35 (ddd, J = 11.6, 7.1, 0.8 Hz, 1 H, CH_2–O), 4.40 (dd, J = 11.6, 7.3 Hz, 1 H, CH_2–O), 5.97 (dq, J = 12.5, 1.8 Hz, 1 H, CH=C*H*–CO), 6.25 (br. s, 1 H, NH), 6.29 (ddd, J = 12.5, 5.5, 4.0 Hz, 1 H, C*H*=CH–CO), 7.40 (t, J = 7.6 Hz, 2 H, Ar), 7.53 (t, J = 7.4 Hz, 1 H, Ar), 7.96 (d, J = 7.1 Hz, 2 H, Ar) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 31.4, 38.3, 54.8 (q, $^2J_{CF}$ = 30.4 Hz), 64.0, 124.7 (q, $^1J_{CF}$ = 282.8 Hz), 125.8, 128.6, 129.4, 129.6, 133.4, 139.1, 166.1, 168.6 ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –71.2 (d, J_{FH} = 8.5 Hz, 3 F) ppm. HRMS (EI): calcd. for $C_{15}H_{14}F_3NO_3$ $[M]^+$ 313.0926; found 313.0930.

Supporting Information (see also the footnote on the first page of this article): NMR spectra and chromatograms of new compounds.

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