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Organocatalytic Asymmetric Direct Aldol Reactions of Trifluoroacetaldehyde Ethyl Hemiacetal with Aromatic Methyl Ketones

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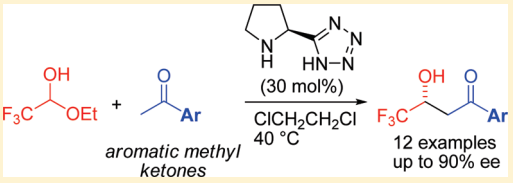
Supporting Information

ABSTRACT: The organocatalytic asymmetric direct aldol reaction of trifluoroacetaldehyde ethyl hemiacetal with aromatic methyl ketones in the presence of a catalytic amount of (*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole in dichloroethane at 40 °C proceeds smoothly to produce (*R*)-4,4,4-trifluoro-1-aryl-3-hydroxy-1-butanones in high yields with up to 90% ee.



In the decade since List and Barbas reported the L-proline-catalyzed asymmetric direct aldol reaction of aliphatic ketones with aldehydes,[1] tremendous attention has been paid to organocatalytic asymmetric reactions.[2] Most notably, there are many successful examples of organocatalytic asymmetric direct aldol reactions of aliphatic ketones and aldehydes as donor carbonyl compounds.[3] However, only a few reports have described the organocatalytic direct aldol reactions of *aromatic methyl ketones* with aldehydes by chiral pyrrolidine derivatives[4] or H_8-BINOL-derived phosphoric acid[5] catalysts.

Catalytic asymmetric syntheses of fluorine-containing molecules have also attracted a great deal of attention in organofluorine chemistry.[6] Among these, trifluoroacetaldehyde (CF_3CHO)[7] and trifluoromethyl ketones[8] are the most attractive acceptor carbonyl compounds in the aldol reaction, like fluorine-free aldehydes and ketones, for the construction of α-trifluoromethylated alcohol moieties, which are commonly found as subunits in chiral drugs or materials.[9] However, in the case of CF_3CHO, it should be generated from its hemiacetal or hydrate using an excess amount of concentrated. sulfuric acid under a high reaction temperature just before the use of CF_3CHO,[10] since CF_3CHO normally exists as a hemiacetal or hydrate due to the strong electron-withdrawing property of the trifluoromethyl group. Moreover, CF_3CHO must be handled carefully because of its troublesome properties such as the fact that it is a gas at room temperature, is very miscible with moisture, and is highly reactive, leading to self-polymerization.

Recently, we[11] and Yamamoto[4a] have developed organocatalytic asymmetric direct aldol reactions of CF_3CHO ethyl hemiacetal with acetone and cyclic ketones, to produce 5,5,5-trifluoro-4-hydroxypentan-2-one and 2-(2,2,2-trifluoro-1-hydroxyethyl)cycloalkanes in good yields with high diastereoselectivities and enantioselectivities. Notably, these reactions do not require a step for the generation of CF_3CHO, in contrast to other methods for the catalytic asymmetric aldol reaction of CF_3CHO.[7] However, these organocatalytic asymmetric direct aldol reactions of CF_3CHO hemiacetal include only limited examples of aliphatic ketones.[4a,11] Although Gong reported a pyrrolidine-catalyzed direct aldol reaction of CF_3CHO ethyl hemiacetal with a few aromatic methyl ketones, the trifluoromethylated aldol products, 4,4,4-trifluoro-1-aryl-3-hydroxy-1-butanones, were obtained only as racemic compounds.[12]

We report here, for the first time, the (*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole catalyzed asymmetric direct aldol reaction of not only various aromatic methyl ketones but also aliphatic methyl ketones with CF_3CHO ethyl hemiacetal, which provides (*R*)-4,4,4-trifluoro-1-aryl- and 1-alkyl-3-hydroxy-1-butanones in high yields with up to 94% ee.

The direct asymmetric aldol reaction of 1-phenylethanone (acetophenone) (**2a**) with 3 equiv of CF_3CHO ethyl hemiacetal **1a** in the presence of 30 mol % of (*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole (**3a**) in dichloroethane ($ClCH_2CH_2Cl$) at 40 °C for 7 d gave (*R*)-4,4,4-trifluoro-3-hydroxy-1-phenyl-1-butanone (**4a**) in 88% yield with 86% ee (Table 1, entry 2). The results of these reactions under various conditions are summarized in Table 1.

The direct aldol reaction at room temperature gave the aldol product **4a** in only 24% yield with the same enantioselectivity (entry 1). A decrease in the amount of catalyst **3a** to 5 mol % resulted in a significant decrease in the yield (45%) with a similar enantioselectivity (entry 3). The reaction of hemiacetal **1a** with acetophenone **2a** at reflux temperature for a shorter reaction time (3 d) gave the aldol product **4a** in 20% yield with very low enantioselectivity (66% ee) (entry 4). Other solvents, such as hexane, toluene, and acetonitonile (MeCN), did not give better results than $ClCH_2CH_2Cl$ (entries 5−7). Dimethyl formamide (DMF) gave a much lower yield with a lower enantioselectivity than the other solvents (entry 8). The reaction by the use of other organocatalysts, such as L-proline (**3b**) and L-prolinamide (**3c**), did not occur at all due to their weaker acidic protons of the carboxyl and amide groups compared to that of the tetrazole group.[13]

Scheme 1 summarizes the organocatalytic direct asymmetric aldol reactions of the hemiacetal of CF_3CHO **1a** with various

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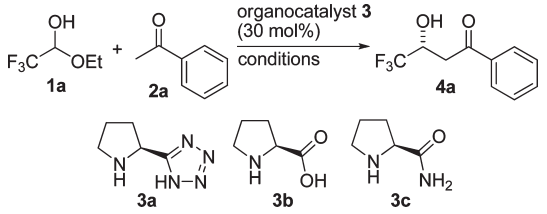
Table 1. Screening of the Reaction Conditions



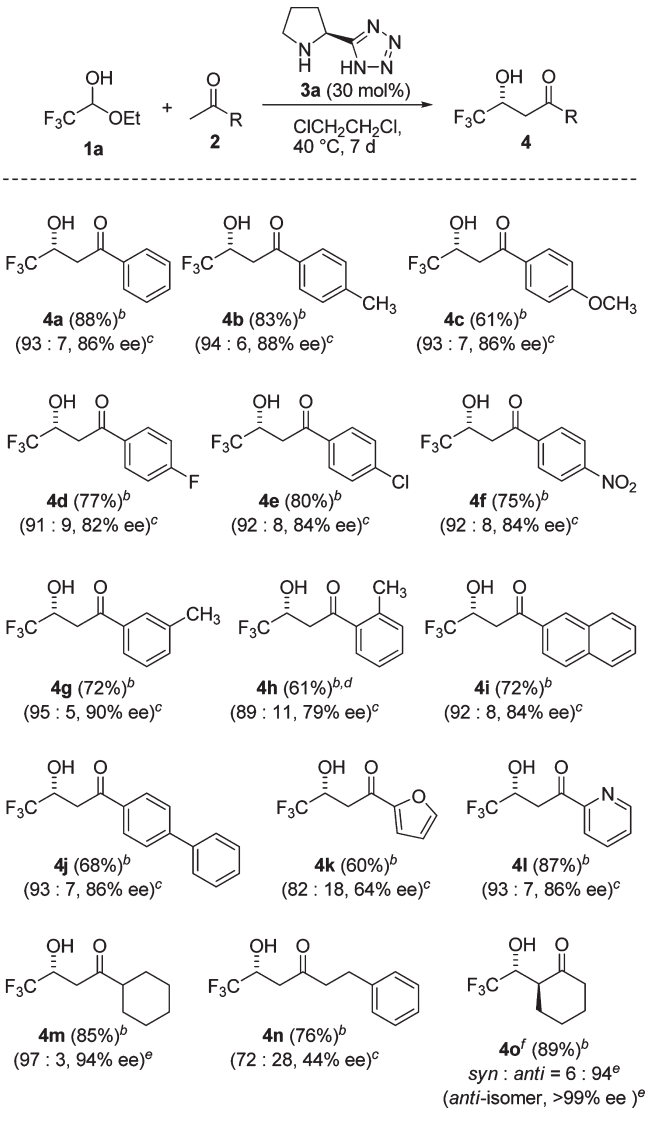
entry[a]	catalyst	solvent	conditions	yield[b](%)	(*R*:*S*, % ee)[c]
1	**3a**	$ClCH_2CH_2Cl$	rt, 7 d	24	(93:7, 86)
2	**3a**	$ClCH_2CH_2Cl$	40 °C, 7 d	88	(93:7, 86)
3	**3a**[d]	$ClCH_2CH_2Cl$	40 °C, 7 d	45	(91:9, 82)
4	**3a**	$ClCH_2CH_2Cl$	reflux, 3 d	20	(83:13, 66)
5	**3a**	hexane	40 °C, 7 d	60	(90:10, 80)
6	**3a**	toluene	40 °C, 7 d	50	(91:9, 82)
7	**3a**	MeCN	40 °C, 7 d	54	(92:8, 84)
8	**3a**	DMF	40 °C, 7 d	44	(82:18, 64)
9	**3b**	$ClCH_2CH_2Cl$	40 °C, 7 d	0	
10	**3c**	$ClCH_2CH_2Cl$	40 °C, 7 d	0	

[a] All of the reactions were carried out with trifluoroacetaldehyde ethyl hemiacetal **la** (1.5 mmol) and acetophenone **2a** (0.5 mmol) in solvent (1 mL). [b] Yields of isolated products. [c] Determined by HPLC. [d] 5 mol % of **3a** was used.

aromatic, heteroaromatic, and aliphatic methyl ketones **2** under the optimized conditions. The reaction of the hemiacetal **1a** with aromatic methyl ketones **2b**−**g**, which have not only various substituents on the phenyl group, such as methyl, methoxy, fluoro, chloro, and nitro groups at the 4- and 3-positions, but also naphthyl and biphenyl groups, afforded (*R*)-4,4,4-trifluoro-1-aryl-3-hydroxy-1-butanones (**4b**−**g**,**i**,**j**) in 61−83% yields with 82−90% ee. Although use of the ketone **2h** with a 2-methylphenyl group provided the aldol product **4h** in only 19% yield with 86% ee under the optimized reaction conditions, probably due to the steric hindrance of the methyl group at 2-position on the phenyl group, the reaction of the ketone **2h** in the presence of 100 mol % of (*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole (**3a**) proceeded smoothly to give **4h** in good yield (61%) but with slightly lower ee (79% ee). A couple of methyl ketones with heteroaromatic groups, such as 2-furyl and 2-pyridyl groups, also participated in the organocatalytic direct asymmetric aldol reactions with the hemiacetal **1a** under the optimized conditions to produce 4,4,4-trifluoro-1-(2-furyl- and 2-pyridyl-)-3-hydroxy-1-butanones (**4k**,**l**) in 60−87% yields with 64−86% ee. The reaction of CF_3CHO ethyl hemiacetal **1a** with 1-cyclohexylethanone (**2m**) and 4-phenylbutan-2-one (**2n**) also proceeded smoothly to give 1-cyclohexyl-4,4,4-trifluoro-3-hydroxybutan-1-one (**4m**) in 85% yield with the highest enantioselectivity (94% ee) due to the bulkiness of the cyclohexyl group and 6,6,6-trifluoro-5-hydroxy-1-phenylhexan-3-one (**4n**) in 76% yield with very low enantioselectivity (44% ee), without formation of the regioisomer 5,5,5-trifluoro-4-hydroxy-3-phenethylpentan-2-one.

Notice that (*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole (**3a**)-catalyzed direct asymmetric aldol reactions of the hemiacetal of CF_3CHO **1a** with cyclohexanone (**2o**) smoothly occurred in much shorter reaction time (3 h) to give the corresponding aldol product **4o** in 89% yield with highly diastereo- (88% de) and enantioselectivity (>99% ee). The reaction with 2-methyl-1-phenylpropan-1-one (**2p**) as an α,α-disubstituted ketone did not occur at all, and the ketone **2p** was recovered in quantitative yield.

Scheme 1. Organocatalytic Direct Asymmetric Aldol Reactions of CF_3CHO Hemiacetal 1a with Various Methyl Ketones 2



[a] All of the reactions were carried out with CF_3CHO enthyl hemiacetal **1a** (1.5 mmol), ketone **2** (0.5 mmol), and organocatalyst **3a** (30 mol%) in dichloroethane (1 ml). [b] Yields of isolated products. [c] Determined by HPLC. [d] Organocatalyst **3a** (100 mol%) was used. [e] Determined by GC. [f] Carried out for 3h.

The results with CF_3CHO hydrate **1b**, difluoroacetaldehyde (CHF_2CHO) ethyl hemiacetal **1c**, and pentafluoropropionaldehyde (CF_3CF_2CHO) hydrate **1d** are given in Scheme 2.

The use of CF_3CHO hydrate **1b** and CF_3CF_2CHO hydrate **1d** gave yields lower (46−60%) than that of the hemiacetal of CF_3CHO **1a** with almost the same enantioselectivities (84−86% ee). The lower yields are probably due to the presence of a large amount of water. CHF_2CHO ethyl hemiacetal **1c** also reacts with acetophenone **2a** in the presence of the asymmetric organocatalyst **3a** under the optimized reaction conditions to

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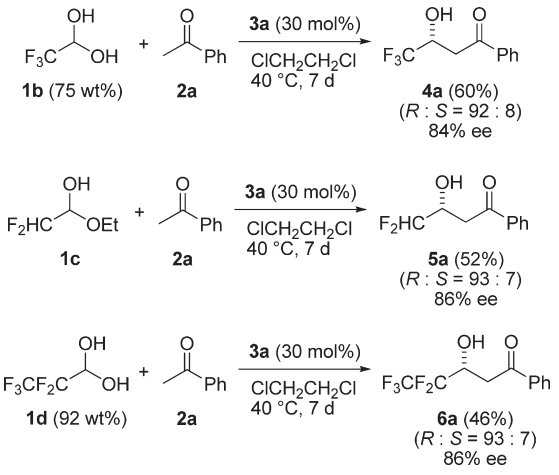
Scheme 2. Organocatalyst 3a-Catalyzed Asymmetric Direct Aldol Reactions of Other Fluoroalkylaldehyde Hemiacetal and Hydrates 1b,c,d with Acetophenone 2a



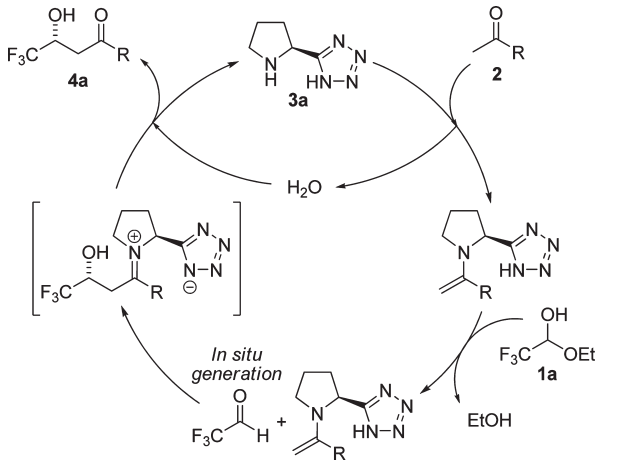


Figure 1. Catalytic cycle of **3a**.

give (*R*)-4,4-difluoro-3-hydroxy-1-phenylbutan-1-one (**5a**) in 52% yield with similar enantioselectivity (86% ee). The low yield seems to be due to the weak electron-withdrawing property of the difluoromethyl group or the higher LUMO level of CHF_2CHO, compared with CF_3CHO. In fact, the (*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole (**3a**)-catalyzed direct aldol reaction of ethyl glyoxalate (EtO_2CCHO), which has a higher LUMO level than CF_3CHO,[14] with the acetophenone **2a** under the same optimized reaction conditions gives only a trace amount of the product with the quantitative recovery of **2a**.

The stereogenic center of 4,4,4-trifluoro-1-phenyl-3-hydroxy-1-butanones (**4a**), which was generated by (*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole (**3a**)-catalyzed direct asymmetric aldol reactions of the hemiacetal of CF_3CHO **1a**, was determined as *R* by the comparison to the reported values such as the optical rotation[15] and the retention time of HPLC using a chiral stationary phase.[16] In the literature,[16] the absolute configuration of 4,4,4-trifluoro-1-phenyl-3-hydroxy-1-butanones (**4a**) was established by single crystal X-ray crystallography. The absolute configuration of 6,6,6-trifluoro-5-hydroxy-1-phenylhexan-3-one (**4n**) was also determined by the optical rotation and comparison to the reported value.[15] On the basis of not only these results but also

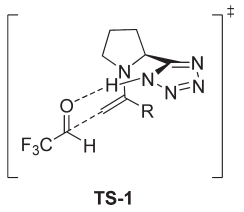
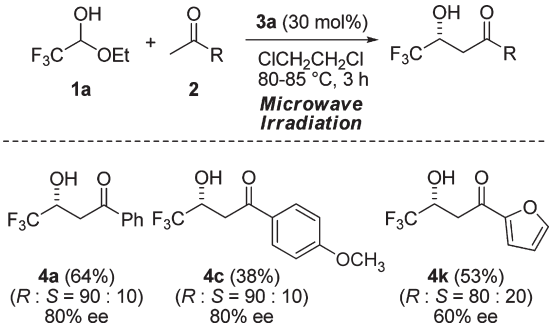


Figure 2. Proposed transition state.

Scheme 3. Microwave-Assisted Organocatalyst 3a-Catalyzed Asymmetric Direct Aldol Reaction of CF_3CHO Hemiacetal 1a with Methyl Ketones 2



comparison to the optical rotation of **4a**, stereochemical assignments of the stereogenic center of other aldol products **4**, **5**, and **6** were made as *R*.

A proposed reaction mechanism is as follows (Figure 1). (*S*)-5-(Pyrrolidin-2-yl)-1*H*-tetrazole (**3a**) reacts with methyl ketones **2** to give chiral enamine. The reaction of the enamine with CF_3CHO hemiacetal gives the ammonium alchoxide, followed by elimination of the ethoxide, which leads to the *in situ* generation of CF_3CHO.[17] CF_3CHO reacts with regenerated enamine **2** through the reaction of iminium ion with the ethoxide via successive asymmetric carbon−carbon bond formation to produce the intermediate. Hydrolysis of the intermediate gives (*R*)-4,4,4-trifluoro-1-aryl- or 1-alkyl-3-hydroxy-1-butanones (**4**) with high enantioselectivities and asymmetric organocatalyst **3a**.

As described in Figure 2, the *in situ* generated CF_3CHO reacts with the chiral enamine through the transition state (**TS-1**). According to the literature, in **TS-1** it is important that (1) there is an *antiperiplanar* relationship between the trifluoromethyl group and the carbon−carbon double bond of enamine, due to the electrostatic interaction of the trifluoromethyl group[14] and (2) there is hydrogen bonding between the oxygen atom of CF_3CHO and the hydrogen atom of the tetrazole group.[18]

Finally, to reduce the reaction time, a microwave-assisted organocatalytic asymmetric direct aldol reaction was examined (Scheme 3).

Surprisingly, the organocatalytic asymmetric direct aldol reaction of the CF_3CHO hemiacetal **1a** with the ketone **2a** under microwave heating conditions (multimode, 50 W, preset temp 80 °C, maximum temp 85 °C) in a shorter reaction time (3 h) proceeded smoothly to give the aldol product **4a** in 64% yield with a slightly lower enantioselectivity (80% ee). The use of DMF as a solvent in the microwave-assisted reaction was not effective, giving only trace amount of **4a**. The microwave-assisted direct aldol reaction of **1a** with other ketones, such as **2c**,**k**

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carrying the 4-methoxyphenyl and 2-furyl groups, gave the corresponding products **4c**,**k** in 38% and 53% yields with 80% ee and 60% ee, respectively. The reason for the reduction in time with a slightly lower enantioselectivity by microwave heating is not yet clear at the present time.[19]

In conclusion, we have developed an organocatalytic asymmetric direct aldol reaction of CF_3CHO hemiacetal **1a** with various aromatic and aliphatic methyl ketones **2** to produce (*R*)-4,4,4-trifluoro-1-aryl- and 1-alkyl-3-hydroxy-1-butanones (**4**) in high yields with up to 94% ee. In this method, a single manipulation includes multiple steps, such as (1) the ready formation of enamine from aromatic and aliphatic methyl ketones, (2) the enamine-assisted *in situ* generation of CF_3CHO,[17] (3) successive asymmetric carbon−carbon bond-formation reaction of CF_3CHO, and (4) hydrolysis of the intermediates, to give not only (*R*)-4,4,4-trifluoro-1-aryl- or 1-alkyl-3-hydroxy-1-butanones (**4**) with high enantioselectivities but also reproduction of asymmetric organocatalyst. The present method is the first example of the organocatalytic asymmetric direct aldol reaction of CF_3CHO hemiacetal **1a** with various aromatic methyl ketones and offers several advantages, such as no need for a step to generate CF_3CHO, the use of only a catalytic amount of asymmetric organocatalyts, and no need for complicated manipulations.

EXPERIMENTAL SECTION

Measurement. ^1H NMR spectra were measured at 400 MHz in deuterochloroform ($CDCl_3$) or hexadeuteroacetone (CD_3COCD_3) solutions with tetramethylsilane (Me_4Si) as an internal standard. ^{13}C NMR spectra were obtained at 100 MHz in $CDCl_3$ or CD_3COCD_3 solution with Me_4Si as an internal standard. ^{19}F NMR spectra were recorded at 376 or 372 MHz in $CDCl_3$ or CD_3COCD_3 solutions using trifluoroacetic acid as an external standard.

Materials. Pure products were isolated by column chromatography using Wakogel C-200 (100−200 mesh) or silica gel 60 (spherical, 40−50 μm). Analytical TLC was performed on Merck precoated (0.25 mm) silica gel 60 F_{254} plates. Hexane, 1,2-dichloroethane, toluene, MeCN, and DMF were distilled over calcium hydride under argon or purchased from Kanto Chemical Co. All chemicals were of reagent grade and, if necessary, were purified in the usual manner prior to use.

Typical Procedure. A mixture of (*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole (**3a**) (96 wt %, 0.022 g, 0.15 mmol), acetophenone **2a** (0.060 g, 0.5 mmol), and CF_3CHO ethyl hemiacetal **1a** (96 wt %, 0.225 g, 1.5 mmol) in $ClCH_2CH_2Cl$ (1 mL) was stirred at 40 °C for 7 d. The reaction mixture was quenched with brine (50 mL), extracted with dichloromethane (30 mL × 3), dried over Na_2SO_4, and concentrated under vacuum to give the residue. Purification of the residue by flash chromatography on silica gel (dichloromethane) gave 4,4,4-trifluoro-3-hydroxy-1-phenyl-1-butanone (**4a**) (88%, 0.096 g) in an *R*:*S* ratio of 93:7.

4,4,4-Trifluoro-3-hydroxy-1-phenyl-1-butanone (4a)[15]**.** R_f 0.2 (dichloromethane); mp 43.0−45.0 °C (86% ee (*R*)), 79.4−79.8 °C (racemate, hexane/ethyl acetate); IR (KBr) 1694 (C═O), 3422 (OH) cm^{-1}; $[\alpha]^{17}_{589}$ +26.3° (86% ee (*R*), *c* = 1.0, $CHCl_3$), $[\alpha]^{32}_{589}$ +1.9° (84% ee (*R*), *c* = 1.5, MeOH), (ref $[\alpha]_D$ +2.6° (92% ee (*R*), *c* = 1.7, MeOH));[14] HPLC retention time (DAICEL CHIRALCEL OD-H), t_R = 10.3 min ((*S*)-isomer), t_R = 11.6 min ((*R*)-isomer); ^1H NMR ($CDCl_3$) δ 3.33 (dd, *J* = 17.93, 3.17 Hz, 1H), 3.39 (dd, *J* = 17.93, 8.79 Hz, 1H), 3.74 (s, 1H), 4.69−4.75 (m, 1H), 7.49−7.53 (m, 2H), 7.62−7.66 (m, 1H), 7.97−7.99 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 38.3 (s), 66.8 (q, *J* = 32.0 Hz), 124.8 (q, *J* = 280.7 Hz), 128.2 (s), 128.8 (s), 134.1 (s), 136.0 (s), 197.5 (s); ^{19}F NMR ($CDCl_3$) δ −1.5 (d, *J* = 6.9 Hz, 3F). HRMS (EI) Found: *m*/*z* 218.0553. Calcd for $C_{10}H_9F_3O_2$: M, 218.0555. Anal. Found: C, 54.99; H, 4.21. Calcd: C, 55.05; H, 4.16.

(*R*)-4,4,4-Trifluoro-3-hydroxy-1-*p*-tolylbutan-1-one (4b). R_f 0.30 (dichloromethane); mp 66.0−67.7 (87% ee (*R*)), 108.4−108.8 (racemate, hexane/ethyl acetate); IR (KBr) 1682 (C═O), 3464 (OH) cm^{-1}; $[\alpha]^{18}_{589}$ = +21.0° (88% ee (*R*), *c* = 1.4, $CHCl_3$); HPLC retention time (DAICEL CHIRALCEL AS-H), t_R = 11.4 min ((*S*)-isomer), t_R = 17.5 min ((*R*)-isomer) min; ^1H NMR ($CDCl_3$) δ 2.31 (s, 3H), 3.14 (dd, *J* = 17.69, 2.42 Hz, 1H), 3.25 (dd, *J* = 17.69, 9.54 Hz, 1H), 4.01 (br s, 1H), 4.57−4.64 (m, 1H), 7.16 and 7.74 (AB quartet, *J* = 8.09 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 21.6 (s), 38.1 (s), 66.8 (q, *J* = 32.0 Hz), 124.9 (q, *J* = 280.7 Hz), 128.3 (s), 129.5 (s), 133.5 (s), 145.2 (s), 197.1 (s); ^{19}F NMR ($CDCl_3$) δ −1.4 (d, *J* = 6.9 Hz, 3F). HRMS (EI) Found: *m*/*z* 232.0710. Calcd for $C_{11}H_{11}F_3O_2$: M, 232.0711. Anal. Found: C, 56.83; H, 4.72. Calcd: C, 56.90; H, 4.77.

(*R*)-4,4,4-Trifluoro-3-hydroxy-1-(4-methoxyphenyl)butan-1-one (4c). R_f 0.18 (dichloromethane); mp 77.1−79.1 °C (85% ee (*R*)), 104.5−105.1 (racemate, hexane/ethyl acetate); IR (KBr) 1678 (C═O), 3460 (OH) cm^{-1}; $[\alpha]^{17}_{589}$ = +25.5° (85% ee (*R*), *c* = 1.1, $CHCl_3$); HPLC retention time (DAICEL CHIRALCEL OD-H), t_R =24.8 min ((*R*)-isomer), t_R = 33.4 min ((*S*)-isomer); ^1H NMR ($CDCl_3$) δ 3.24 (dd, *J* = 17.45, 2.54 Hz, 1H), 3.34 (dd, *J* = 17.45, 9.42 Hz, 1H), 3.88 (s, 3H), 3.99 (br s, 1H), 4.67−4.70 (m, 1H), 6.95 and 7.93 (AB quartet, *J* = 9.18 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 37.7 (s), 55.5 (s), 67.0 (q, *J* = 32.0 Hz), 114.0 (s), 124.9 (q, *J* = 280.6 Hz), 129.0 (s), 130.6 (s), 164.3 (s), 196.0 (s); ^{19}F NMR ($CDCl_3$) δ −1.4 (d, *J* = 6.9 Hz, 3F). HRMS (EI) Found: *m*/*z* 248.0663. Calcd for $C_{11}H_{11}F_3O_3$: M, 248.0660. Anal. Found: C, 53.11; H, 4.44. Calcd: C, 53.23; H, 4.47.

(*R*)-4,4,4-Trifluoro-1-(4-fluorophenyl)-3-hydroxybutan-1-one (4d). R_f 0.25 (dichloromethane); mp 45.1−46.5 (83% ee (*R*)), 74.0−75.2 (racemate, CH_2Cl_2); IR (KBr) 1686 (C═O), 3472 (OH) cm^{-1}; $[\alpha]^{17}_{589}$ = +26.7° (83% ee (*R*), *c* = 1.3, $CHCl_3$); HPLC retention time (DAICEL CHIRALCEL AS-H), t_R = 12.1 min ((*S*)-isomer), t_R = 17.8 min ((*R*)-isomer); ^1H NMR ($CDCl_3$) δ 3.17 (dd, *J* = 17.57, 2.17 Hz, 1H), 3.31 (dd, *J* = 17.57, 9.54 Hz, 1H), 3.78 (br s, 1H), 4.60−4.67 (m, 1H), 7.08 (dd, *J* = 8.75, 8.69 Hz, 2H), 7.91 (dd, *J* = 8.75, 5.19 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 38.3 (s), 66.7 (q, *J* = 32.2 Hz), 116.0 (d, *J* = 22.1 Hz), 124.8 (q, *J* = 280.7 Hz), 131.0 (d, *J* = 9.8 Hz), 132.5 (d, *J* = 3.3 Hz), 166.3 (d, *J* = 256.4 Hz), 195.8 (s); ^{19}F NMR ($CDCl_3$) δ −1.6 (d, *J* = 6.9 Hz, 3F), −25.36− −25.43 (m, 1F). HRMS (EI) Found: *m*/*z* 236.0458. Calcd for $C_{10}H_8F_4O_2$: M, 236.0460.

(*R*)-1-(4-Chlorophenyl)-4,4,4-trifluoro-3-hydroxybutan-1-one (4e). R_f 0.33 (dichloromethane); mp 60.3−62.0 (84% ee (*R*)), 109.3−110.0 (racemate, hexane/ethyl acetate); IR (KBr) 1690 (C═O), 3464 (OH) cm^{-1}; $[\alpha]^{17}_{589}$ = +14.3° (84% ee (*R*), *c* = 1.2, $CHCl_3$); HPLC retention time (DAICEL CHIRALCEL AS-H), t_R = 12.2 min ((*S*)-isomer), t_R = 15.8 min ((*R*)-isomer); ^1H NMR ($CDCl_3$) δ 3.17 (dd, *J* = 17.69, 2.17 Hz, 1H), 3.30 (dd, *J* = 17.69, 9.30 Hz, 1H), 3.66−3.72 (m, 1H), 4.61−4.69 (m, 1H), 7.18 and 7.86 (AB quartet, *J* = 7.18 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 38.3 (s), 66.7 (q, *J* = 32.2 Hz), 124.8 (q, *J* = 280.5 Hz), 129.2 (s), 129.6 (s), 134.3 (s), 140.7 (s), 196.1 (s); ^{19}F NMR ($CDCl_3$) δ −1.5 (d, *J* = 6.9 Hz, 3F). HRMS Found: *m*/*z* 254.0138. Calcd for $C_{10}H_8{}^{37}ClF_3O_2$: M, 254.0135. Anal. Found: C, 47.54 ; H, 3.30. Calcd: C, 47.55; H, 3.19.

(*R*)-4,4,4-Trifluoro-3-hydroxy-1-(4-nitrophenyl)butan-1-one (4f). R_f 0.20 (dichloromethane); mp 69.7−71.5 °C (86% ee (*R*)), 71.3−71.7 °C (racemate, hexane/ethyl acetate); IR (KBr) 1701 (C═O), 3487 (OH) cm^{-1}; $[\alpha]^{20}_{589}$ = +25.2° (86% ee (*R*), *c* = 1.2, $CHCl_3$); HPLC retention time (DAICEL CHIRALCEL OD-H), t_R = 51.4 min ((*R*)-isomer), t_R = 55.9 min ((*S*)-isomer); ^1H NMR ($CDCl_3$) δ 3.24 (d, *J* = 17.63 Hz, 1H), 3.38−3.45 (m, 2H), 4.68 (br s, 1H), 8.07 and 8.27 (AB quartet, *J* = 8.45 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 39.0 (s), 66.6 (q, *J* = 32.5 Hz), 124.0 (s), 124.6 (q, *J* = 280.7 Hz), 129.3 (s), 140.3 (s), 150.8 (s), 195.6 (s); ^{19}F NMR ($CDCl_3$) δ −1.5 (d, *J* = 6.9 Hz, 3F).

HRMS (EI) Found: m/z 263.0403. Calcd for $C_{10}H_8F_3NO_4$: M, 263.0405. Anal. Found: C, 45.68; H; 3.13; N, 5.41. Calcd for $C_{11}H_{11}F_3O_2$: C, 45.64; H; 3.06; N; 5.32.

(*R*)-4,4,4-Trifluoro-3-hydroxy-1-*m*-tolylbutan-1-one (4g). R_f 0.33 (dichloromethane); mp 44.8−46.3 °C (87% ee (*R*)), 81.1−81.6 °C (racemate, hexane/ethyl acetate); IR (KBr) 1682 (C═O), 3480 (OH) cm^{-1}; $[\alpha]^{18}_{589}$ = +22.9° (87% ee (*R*), *c* = 1.7, $CHCl_3$); HPLC retention time (DAICEL CHIRALCEL OD), t_R = 11.1 min ((*S*)-isomer), t_R = 13.2 min ((*R*)-isomer); ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3H), 3.17 (dd, *J* = 17.87, 2.42 Hz, 1H), 3.30 (dd, *J* = 17.87, 9.42 Hz, 1H), 3.90 (br s, 1H), 4.57−4.66 (m, 1H), 7.26 (t, *J* = 7.49 Hz, 1H), 7.32 (d, *J* = 7.49 Hz, 1H), 7.64−7.66 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.2 (s), 38.3 (s), 66.9 (q, *J* = 32.2 Hz), 124.8 (q, *J* = 280.5 Hz), 125.4 (s), 128.7 (s), 134.86 (s), 134.87 (s) 136.0 (s), 138.7 (s), 197.7 (s); ^{19}F NMR ($CDCl_3$) δ −1.5 (d, *J* = 6.9 Hz, 3F); MS (EI) m/z (rel intensity) 232 (M^+; 11.0). Anal. Found: C, 56.67; H, 5.04. Calcd for $C_{11}H_{11}F_3O_2$: C, 56.90; H, 4.77.

(*R*)-4,4,4-Trifluoro-3-hydroxy-1-*o*-tolylbutan-1-one (4h). R_f 0.40 (dichloromethane); mp 65.4−66.5 °C (79% ee (*R*)), 81.1−81.6 °C (racemate, hexane/ethyl acetate); IR (KBr) 1685 (C═O), 3410 (OH) cm^{-1}; $[\alpha]^{28}_{589}$ +20.4° (79% ee (*R*), *c* = 0.6, $CHCl_3$); HPLC retention time (DAICEL CHIRALCEL OD), t_R = 12.5 min ((*S*)-isomer), t_R = 16.6 min ((*R*)-isomer); ^{1}H NMR ($CDCl_3$) δ 2.47 (s, 3H), 3.19 (dd, *J* = 17.63, 3.02 Hz, 1H), 3.29 (dd, *J* = 17.63, 8.81 Hz, 1H), 3.48 (br s, 1H), 4.60 (m, 1H), 7.21−7.26 (m, 2H), 7.37 (t, *J* = 7.22 Hz, 1H), 7.14 (d, *J* = 7.22 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.5 (s), 40.6 (s), 67.1 (q, *J* = 32.0 Hz), 124.4 (q, *J* = 281.3 Hz), 125.9 (s), 129.1 (s), 132.3 (s), 132.4 (s), 136.2 (s), 139.1 (s), 200.8 (s); ^{19}F NMR ($CDCl_3$) δ −1.4 (d, *J* = 6.9 Hz, 3F). HRMS (EI) Found: m/z 232.0711. Calcd for $C_{11}H_{11}F_3O_2$: M, 232.0711. Anal. Found: C, 56.94; H, 4.77. Calcd: C, 56.90; H, 4.77.

(*R*)-4,4,4-Trifluoro-3-hydroxy-1-(naphthalen-2-yl)butan-1-one (4i). R_f 0.29 (hexane/ethyl acetate =7/3); mp 83.5−85.2 °C (83% ee (*R*), $CHCl_2$), 93.1−94.9 °C (racemate, hexane/ethyl acetate); IR (KBr) 1670 (C═O), 3395 (OH) cm^{-1}; $[\alpha]^{19}_{589}$ = +17.4° (83% ee (*R*), *c* = 1.2, $CHCl_3$); HPLC retention time (DAICEL CHIRALCEL OD-H), t_R = 13.7 min ((*S*)-isomer), t_R = 23.7 min ((*R*)-isomer); ^{1}H NMR ($CDCl_3$) δ 3.42 (dd, *J* = 17.81, 2.54 Hz, 1H), 3.52 (dd, *J* = 17.81, 9.42 Hz, 1H), 3,70 (d, *J* = 4.35 Hz, 1H), 4.71−4.80 (m, 1H), 7.54−7.64 (m, 2H), 7.86−7.90 (m, 2H), 7.95−8.00 (m, 2H), 8.45 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 38.3 (s), 67.0 (q, *J* = 32.2 Hz), 123.3 (s), 124.9 (q, *J* = 280.5 Hz), 127.0 (s), 127.8 (s), 128.7 (s), 129.0 (s), 129.7 (s), 130.3 (s), 132.3 (s), 133.2 (s), 135.9 (s), 197.4 (s); ^{19}F NMR ($CDCl_3$) δ −1.4 (d, *J* = 6.9 Hz, 3F). HRMS (ESI) Found: m/z 291.0602. Calcd for $C_{14}H_{11}F_3NaO_2$: M+Na, 291.0609.

(*R*)-1-(Biphenyl-4-yl)-4,4,4-trifluoro-3-hydroxybutan-1-one (4j). R_f 0.1 (hexane/ethyl acetate =9/1); mp 129.8−132.2 °C (86% ee (*R*)), 133.9−136.8 °C (racemate, hexane/ethyl acetate); IR (KBr) 1682 (C═O), 2967 (OH) cm^{-1}; $[\alpha]^{30}_{589}$ +11.5° (86% ee (*R*), *c* = 1.3, $CHCl_3$); HPLC retention time (DAICEL CHIRALCEL OD-H), t_R = 13.6 min ((*R*)-isomer), t_R = 21.3 min ((*S*)-isomer); ^{1}H NMR ($CDCl_3$) δ 3.32 (dd, *J* = 17.75, 2.42 Hz, 1H), 3.43 (dd, *J* = 17.75, 9.42 Hz, 1H), 3.76 (d, *J* = 4.59 Hz, 1H), 4.68−4.78 (m, 1H), 7.41 (t, *J* = 7.12 Hz, 1H), 7.47 (t, *J* = 7.12 Hz, 2H), 7.62 (d, *J* = 7.12, 2H), 7.70 and 8.02 (AB quartet, *J* = 8.09 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 38.3 (s), 67.0 (q, *J* = 32.0 Hz) 124.8 (q, *J* = 280.2 Hz), 127.3 (s), 127.4 (s), 128.5 (s), 128.8 (s), 129.0 (s), 134.6 (s), 139.5 (s), 146.8 (s), 197.1 (s); ^{19}F NMR ($CDCl_3$) δ −1.5 (d, *J* = 6.9 Hz, 3F). HRMS (ESI) Found: m/z 317.0761. Calcd for $C_{16}H_{13}F_3NaO_2$: M+Na, 317.0765.

(*R*)-4,4,4-Trifluoro-1-(furan-2-yl)-3-hydroxybutan-1-one (4k). R_f 0.28 (dichloromethane); oil (64% ee (*R*)), 47.5−48.8 °C (racemate, hexane/ethyl acetate); IR (KBr) 1670 (C═O), 3422 (OH) cm^{-1}; $[\alpha]^{18}_{589}$ = +20.4° (64% ee (*R*), *c* = 1.0, $CHCl_3$); HPLC retention time (DAICEL CHIRALCEL AS-H), t_R = 16.1 min ((*S*)-isomer), t_R = 20.1 min ((*R*)-isomer); ^{1}H NMR ($CDCl_3$) δ 3.08 (d, *J* = 17.27 Hz, 1H), 3.21 (d, *J* = 17.27, 9.42 Hz, 1H), 3.65−3.69 (m, 1H), 4.60 (br s, 1H), 6.52 (br s, 1H), 7.22−7.23 (m, 1H), 7.57 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 38.1 (s), 66.5 (q, *J* = 32.2 Hz), 112.7 (s), 118.7 (s), 124.7 (q, *J* = 281.0 Hz), 147.4 (s), 151.9 (s), 185.8 (s); ^{19}F NMR ($CDCl_3$) δ −4.0 (d, *J* = 6.9 Hz, 3F). HRMS (ESI) Found: m/z 231.0241. Calcd for $C_8H_7F_3NaO_3$: M + Na, 231.0245.

(*R*)-4,4,4-Trifluoro-3-hydroxy-1-(pyridin-2-yl)butan-1-one (4l). R_f 0.10 (dichloromethane); mp 46.0−47.8 °C (86% ee (*R*), $CHCl_2$), 81.7−85.2 °C (racemate); IR (KBr) 1701 (C═O), 3456 (OH) cm^{-1}; $[\alpha]^{19}_{589}$ = +16.2° (86% ee (*R*), *c* = 1.7, $CHCl_3$); HPLC retention time (DAICEL CHIRALCEL AD-H), t_R = 18.9 min ((*R*)-isomer), t_R = 22.8 min ((*S*)-isomer); ^{1}H NMR (CD_3COCD_3) δ 3.24 (dd, *J* = 17.20, 2.42 Hz, 1H), 3.62 (dd, *J* = 17.20, 9.78 Hz, 1H), 4.62−4.69 (m, 1H), 5.41 (br s, 1H), 7.51 (d, *J* = 4.83 Hz, 1H), 7.84−7.90 (m, 2H), 8.59 (d, *J* = 4.10 Hz, 1H); ^{13}C NMR (CD_3COCD_3) δ 39.3 (s), 66.9 (q, *J* = 31.4 Hz), 122.4 (s), 126.8 (q, *J* = 281.0 Hz), 128.6 (s), 138.2 (s), 150.0 (s), 153.7 (s), 197.7 (s); ^{19}F NMR (CD_3COCD_3) δ −1.7 (d, *J* = 6.9 Hz, 3F). HRMS (ESI) Found: m/z 242.0398. Calcd for $C_9H_8F_3NNaO_2$: M + Na, 242.0405.

(*R*)-1-Cyclohexyl-4,4,4-trifluoro-3-hydroxybutan-1-one (4m). R_f 0.28 (dichloromethane); mp oil (95% ee (*R*), CH^2Cl_2), 40.9−41.6 °C (racemate, hexane/ethyl acetate); IR (KBr) 1682 (C═O), 3464 (OH) cm^{-1}; $[\alpha]^{18}_{589}$ = +23.9° (95% ee (*R*), *c* = 1.2, $CHCl_3$); GC retention time (VARIAN CP-CHIRALSIL-D-VAL), t_R = 13.9 min ((*R*)-isomer), t_R = 14.2 min ((*S*)-isomer); ^{1}H NMR ($CDCl_3$) δ 1.16−1.41 (m, 5H), 1.67−1.90 (m, 5H), 2.78 (dd, *J* = 11.89, 2.66 Hz, 1H), 2.87 (dd, *J* = 11.89, 9.42 Hz, 1H), 3.93 (br s, 1H), 4.45−4.53 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 25.31 (s), 25.33 (s), 25.6 (s), 27.9 (s), 28.0 (s), 39.9 (s), 51.3 (s), 66.3 (q, *J* = 32.2 Hz), 124.8 (q, *J* = 280.7 Hz), 211.9 (s); ^{19}F NMR ($CDCl_3$) δ −2.0 (d, *J* = 6.9 Hz, 3F); MS (EI) m/z (rel intensity) 224 (M^+; 3.7). Anal. Found: C, 53.54; H, 6.64. Calcd for $C_{10}H_{15}F_3O_2$: C, 53.57; H, 6.74.

(*R*)-6,6,6-Trifluoro-5-hydroxy-1-phenylhexan-3-one (4n)[15]. R_f 0.23 (hexane/ethyl acetate =9/1); mp 66.6−68.5 °C (44% ee (*R*)), 72.8−73.4 °C (racemate, hexane/ethyl acetate); IR (KBr) 1717 (C═O), 3460 (OH) cm^{-1}; $[\alpha]^{19}_{589}$ = +10.7° (44% ee (*R*), *c* = 1.5, $CHCl_3$); HPLC retention time (DAICEL CHIRALCEL AS-H), t_R = 9.5 min ((*S*)-isomer), t_R = 10.5 min ((*R*)-isomer); ^{1}H NMR ($CDCl_3$) δ 2.56−2.83 (m, 6H), 3.79 (br s, 1H), 4.38−4.42 (m, 1H), 7.06−7.08 (m, 1H), 7.10−7.12 (m, 1H), 7.17−7.21 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 29.3 (s), 42.1 (s), 45.0 (s), 66.5 (q, *J* = 32.2 Hz), 124.6 (q, *J* = 280.7 Hz), 126.3 (s), 128.2 (s), 128.6 (s), 140.2 (s), 207.6 (s); ^{19}F NMR ($CDCl_3$) δ −1.8 (d, *J* = 6.9 Hz, 3F). HRMS (ESI) Found: m/z 269.0763. Calcd for $C_{12}H_{13}F_3NaO_2$: M + Na, 269.0765.

(*S*)-2-((*R*)-2,2,2-Trifluoro-1-hydroxyethyl)cyclohexanone (4o). R_f 0.28 (dichloromethane); oil (>99% ee), oil (racemate); IR (KBr) 1701 (C═O), 3437 (OH) cm^{-1}; $[\alpha]^{28}_{589}$ = −22.4° (>99% ee (2*S*, 1′*R*), *c* = 1.8, $CHCl_3$); GC retention time (InterCap CHIRAMIX), t_R = 32.6 ((2*S*, 1′*R*)-isomer), t_R = 33.1 ((2*R*, 1′*S*)-isomer) min; ^{1}H NMR ($CDCl_3$) δ 1.67−1.81 (m, 3H), 1.95−1.99 (m, 1H), 2.13−2.16 (m, 2H), 2.37−2.49 (m, 2H), 2.74−2.80 (m, 1H), 4.02−4.11 (m, 1H), 4.47 (d, *J* = 6.52 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 24.8 (s), 28.0 (s), 31.5 (q, *J* = 1.6 Hz), 42.9 (s), 50.3 (s), 71.6 (q, *J* = 30.9 Hz), 124.7 (q, *J* = 282.5 Hz), 129.0 (s); ^{19}F NMR ($CDCl_3$) δ −1.9 (d, *J* = 7.6 Hz, 3F). HRMS (EI) Found: m/z 196.0711. Calcd for $C_8H_{11}F_3O_2$: M, 196.0711.

(*R*)-4,4-Difluoro-3-hydroxy-1-phenylbutan-1-one (5a). R_f 0.20 (dichloromethane); oil (86% ee (*R*)), oil (racemate); IR (KBr) 1686 (C═O), 3460 (OH) cm^{-1}; $[\alpha]^{20}_{589}$ = +38.7° (86% ee (*R*), *c* = 1.3, $CHCl_3$); HPLC retention time (DAICEL CHIRALCEL AS-H), t_R = 17.1 min ((*S*)-isomer), t_R = 22.5 min ((*R*)-isomer); ^{1}H NMR ($CDCl_3$) δ 3.33−3.25 (m, 2H), 3.52 (d, *J* = 4.11 Hz, 1H), 4.40−4.51 (m, 1H), 5.90 (td, *J* = 55.74, 3.46 Hz, 1H),7.47−7.51 (m, 2H), 7.60−7.63 (m, 1H), 7.96−7.98 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 37.7 (t, *J* = 2.9 Hz), 67.7 (dd, *J* = 26.2, 23.8 Hz), 115.5 (t, *J* = 243.7 Hz), 128.2

(s), 128.8 (s), 133.9 (s), 136.2 (s), 198.8 (s); ^{19}F NMR ($CDCl_3$) δ −50.9 (ddd, J = 287.9, 56.0, 9.7 Hz, 1F), −53.8 (ddd, J = 287.0, 56.0, 14.1 Hz, 1F). HRMS (EI) Found: m/z 200.0620. Calcd for $C_{10}H_{10}F_2O_2$: M, 200.0649.

(*R*)-4,4,5,5,5-Pentafluoro-3-hydroxy-1-phenylpentan-1-one (6a). R_f 0.30 (dichloromethane); mp 72.8−74.0 °C (90% ee (*R*)), 98.0−99.0 °C (racemate, hexane/ethyl acetate); IR (KBr) 1682 (C═O), 3406 (OH) cm^{-1}; $[\alpha]^{27}_{589}$ +23.1° (90% ee (*R*), c = 1.3, $CHCl_3$); HPLC retention time (DAICEL CHIRALCEL OD), t_R = 9.8 min ((*S*)-isomer), t_R = 12.3 min ((*R*)-isomer); ^{1}H NMR ($CDCl_3$) δ 3.25 (d, J = 17.75 Hz, 1H), 3.36 (dd, J = 17.75, 9.10 Hz, 1H), 3.88 (s, 1H), 4.71−4.79 (m, 1H), 7.40 (t, J = 7.81 Hz, 2H), 7.54 (td, J = 7.81, 0.97 Hz, 1H), 7.87 (td, J = 7.81, 0.97 Hz, 2H); ^{13}C NMR($CDCl_3$) δ 37.4 (s), 66.4 (dd, J = 23.5, 7.6 Hz), 113.6 (ddt, J = 256.5, 251.8, 36.6 Hz), 119.0 (qt, J = 286.0, 35.4 Hz), 128.2 (s), 128.9 (s), 134.2 (s), 136.0 (s), 198.0 (s) ; ^{19}F NMR ($CDCl_3$) δ −3.8 (s, 3F), −44.4 (dd, J = 276.6, 5.7 Hz, 1F), −53.0 (dd, J = 276.6, 18.7 Hz, 1F); MS (EI) m/z (rel intensity) 268 (M^+; 1.3). Anal. Found: C, 49.28; H, 3.35. Calcd for $C_{11}H_9F_5O_2$: C, 49.26; H, 3.38.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR spectra and enantiomer separation by HPLC or GC for **4**, **5**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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