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Construction of Tertiary Alcohols Bearing Perfluoroalkyl Chains Catalyzed by Prolinamide-Thioureas

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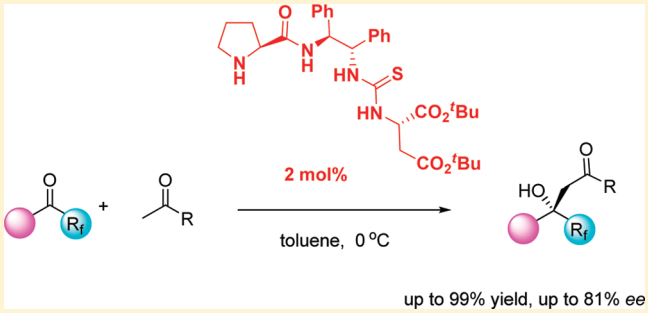
Supporting Information

ABSTRACT: A systematic study to evaluate the ability of various organocatalysts to catalyze the aldol reaction between acetone and 2,2,2-trifluoromethyl-1-phenylethanone was undertaken. Benchmark organocatalysts failed to catalyze this reaction. However, a prolinamide-thiourea consisting of (*S*)-prolinamide, (1*S*,2*S*)-diphenylethylenediamine, and (*S*)-di-*tert* butyl aspartate proved to be an efficient catalyst, providing tertiary alcohols as the products of the reaction between ketones and perfluoroalkyl ketones in high to quantitative yields and high enantioselectivities (up 81% *ee*) at a catalyst loading of 2 mol %.



More than a decade after the rebirth of organocatalysis,[1] its dramatic pace of expansion has constituted it as the third major branch of modern asymmetric catalysis.[2,3] Since then, a plethora of catalysts have been developed, synthesized, and tested for their efficiency in the aldol reaction.[4,5] However, the use of ketones as electrophilic partners, which provides access to chiral tertiary alcohols, remains still a challenge due to their poor reactivity and difficulty in differentiating the two faces of the carbonyl moiety.[5] Zhang and co-workers utilized proline in the reaction between acetone and trifluoromethyl ketones leading to mediocre enantioselectivities.[6] Although the perfluoroalkyl group is one of the most attractive moieties in organic chemistry because of its numerous applications in agricultural, medicinal, and material chemistry,[7,8] there have been only sporadic reports of organocatalytic aldol reactions employing perfluoroalkyl ketones as electrophiles.[6,9] Furthermore, the construction of quaternary stereogenic centers, especially those of tertiary alcohols, remains a great challenge,[10,11] although some elegant contributions, namely by Aggarwal and co-workers,[12] have provided milestone solutions for this long-standing problem. However, for the synthesis of tertiary alcohols bearing perfluoroalkyl groups, little is known, with the use of the Ruppert–Prakash reagent ($TMSCF_3$) being the reagent of choice.[13] It has to be highlighted that a variety of tertiary alcohols bearing trifluoromethyl moieties are of medicinal interest.[14,15] To provide an alternative synthesis of such compounds, the screening of a variety of catalyst templates was undertaken for the reaction between ketones and perfluoroalkyl ketones. While this manuscript was under preparation, Nakamura and co-workers reported the use of a specifically designed proline sulfonamide that was highly efficient for the reaction between aryl trihalomethyl ketones and acetone.[16] In their study, 10 mol % catalyst loading was needed to ensure high yields (>90%), while the enantioselectivities varied (77–92% *ee*). Herein, we present our studies toward the construction of tertiary alcohols bearing perfluoroalkyl chains via organocatalysis.

Since little is known for the reaction between acetone and 2,2,2-trifluoromethyl-1-phenylethanone, a screening of a variety of known organocatalysts was undertaken (Figure 1, Table 1).

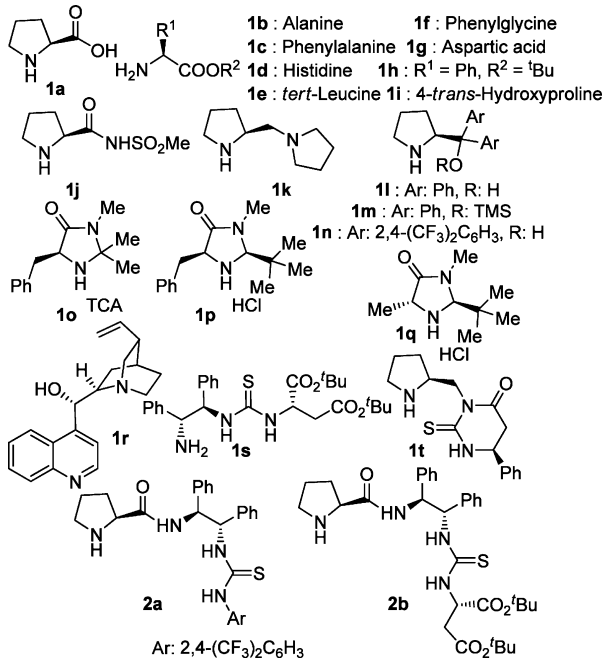


Figure 1. Organocatalysts employed in this study.

Initially, proline (**1a**) was utilized for comparison purposes (entry 1, Table 1). Although an excellent yield was obtained, the *ee* was lower than that reported by Zhang[6] and similar to

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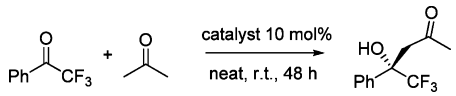
Table 1. Various Organocatalysts Employed in the Asymmetric Aldol Reaction between Acetone and 2,2,2-Trifluoromethyl-1-phenylethanone



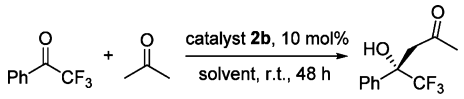
entry	catalyst	yield[a] [%]	ee[b] [%]
1	**1a**	97[c]	30
2	**1b**	98	22
3	**1h**	96	0
4	**1i**	92	15
5	**1j**	100	13
6	**1k**	90	34
7	**1m**	68	−11
8	**1o**	13	15
9	**1r**	traces	
10	**1s**	31	30
11	**1t**	96	19
12	**2a**	93	62
13	**2b**	98	68

[a]Isolated yield after column chromatography. [b]The ee was determined by chiral HPLC. [c]Reaction time: 24 h.

the results of Nakamura.[16] A number of natural acyclic α-amino acids were also utilized (entry 2, Table 1; see also the Supporting Information). The replacement of the secondary amine of the pyrrolidine ring by a primary amine (catalysts **1b**–**h**) led to high yields but decreased selectivities, highlighting the necessity of a five-membered-ring secondary amine. From entry 3 (Table 1), it is obvious that the presence of a free carboxylic group or a moiety able to form hydrogen bonds on the catalyst scaffold is a requirement. 4-Hydroxy proline (**1i**), proline methanesulfonamide (**1j**),[17] and diamine **1k**[18] led to high to quantitative yields, but the enantioselectivity was not significantly improved (entries 4–6, Table 1). The diarylprolinols' family[19] as well as MacMillan's imidazolidinones[20] constitute two classes of organocatalysts that are very frequently employed; however, inferior results were obtained (entries 7–8, Table 1). Cinchonine, a member of the Cinchona alkaloids family, did not furnish the desired product (entry 9, Table 1). Continuing our interest on organocatalysis,[21] we utilized bifunctional organocatalyst **1s**;[21b] however, the reaction did not reach completion, albeit similar enantioselectivity was observed as in the case of proline (entry 10, Table 1). Pyrrolidine-thioxotetrahydropyrimidinone **1t**, which is a highly reactive catalyst for Michael reactions,[21d] led to an almost quantitative yield but poor enantiocontrol (entry 11, Table 1). Recently, the proline scaffold has been successfully combined with functionalities able to act as hydrogen bond donors.[22,23] Our efforts focused on the combination of a prolinamide with a thiourea moiety. Prolinamide-thiourea **2a** has been proven to be an excellent catalyst for the aldol reaction.[21c] Catalyst **2a** afforded enhanced enantioselectivity in the model reaction (entry 12, Table 1). Most recently, we have undertaken a study in order to understand the features required for such a catalyst scaffold, concluding that a tripeptide-like compound such as **2b** is an excellent organocatalyst for the aldol reaction.[24] When catalyst **2b** was employed, the best enantioselectivity was obtained (entry 13, Table 1).

With the optimum catalyst in hand, various reaction conditions were tested to maximize the enantioselectivity. Initially, the reaction medium was studied (entries 1–5, Table 2). Among a range of solvents, toluene provided the best results

Table 2. Optimization of the Reaction Conditions on the Reaction between Acetone and 2,2,2-Trifluoromethyl-1-phenylethanone Using Catalyst 2b



entry	catalyst loading (%)	solvent	yield[a] [%]	ee[b] [%]
1	10	neat	98	68
2	10	THF	93	55
3	10	CH_2Cl_2	95	60
4	10	MeCN	100	55
5	10	toluene	97	74
6	2	toluene	98	74
7	1	toluene	98	72
8[c]	2	toluene	97	80
9[c]	0.1	toluene	67	69

[a]Isolated yield after column chromatography. [b]The ee was determined by chiral HPLC. [c]The reaction was performed at 0 °C.

(entry 5, Table 2; see also the Supporting Information). The use of 2 mol % led to quantitative yield and 74% *ee* (entry 6, Table 2), whereas with only 1 mol %, the enantioselectivity dropped (entry 7, Table 2). The catalyst loading can be successfully reduced to 0.5 mol % without any considerable impact on both yield and enantioselectivity (see the Supporting Information). When the reaction was carried out at 0 °C with 2 mol % catalyst loading, an excellent yield (97%) and good enantioselectivity (80% *ee*) were obtained (entry 8, Table 2). When only 0.1 mol % catalyst was applied, the desired product was isolated in good yield and enantioselectivity (entry 9, Table 2).

The scope and limitations of the current methodology were also investigated (Scheme 1). The use of substituted aromatic trifluoromethyl ketones led to similar results as in the model reaction (**3b**–**d**). Once one of the fluorine atoms was replaced by a chlorine, an excellent yield but lower enantioselectivity were observed (**3e**). When the phenyl ring was replaced by a perfluorophenyl moiety, the enantioselectivity dropped significantly (**3f**). The use of the ethyl ester functionality instead of the phenyl ring was also well tolerated, leading to a high yield and good enantioselectivity (**3g**). Recently, a number of trifluoromethyl and perfluoroalkyl ketones have been identified as enzyme inhibitors exhibiting interesting medicinal properties.[25] Perfluoroalkyl ketones can be efficiently synthesized from the corresponding Weinreb or morpholine amides.[26] Unfortunately, when such a ketone, where the phenyl ring is not adjacent to the carbonyl moiety but rather four carbon atoms away, was used, a high yield was observed; however, the enantioselectivity dropped significantly (**3h**). Interestingly, other methyl ketones can also be utilized in the place of acetone. 2-Butanone led to a single regioisomer in a high yield and good enantioselectivity (**3i**). It has to be highlighted that in the same reaction, proline affords a mixture of regioisomers (data not shown). Acetophenone led to inferior results (21% yield, 42% *ee*, after 7 days, data not shown), while cyclohexanone did not lead to the desired product. Furthermore, when 2-hydroxyacetone was utilized, an inseparable mixture of two diastereomers was obtained in almost equal amounts in good yield and good enantioselectivity (**3j**). In the case of

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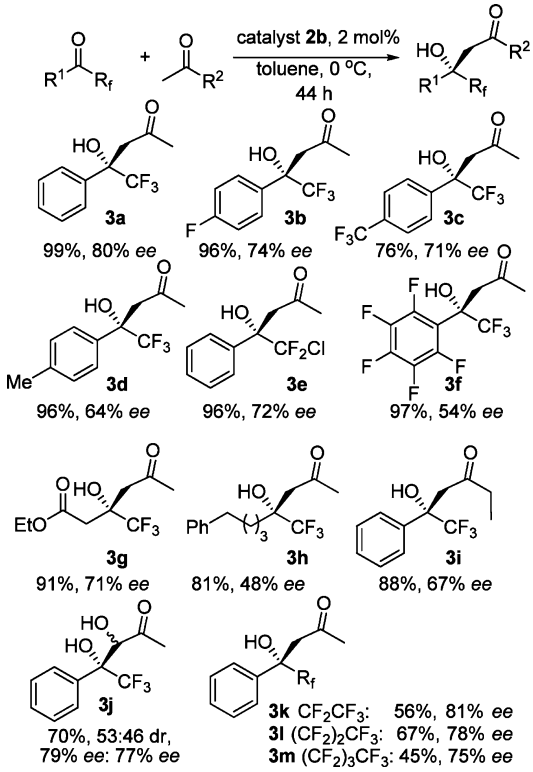
Scheme 1. Direct Asymmetric Aldol Reaction between Ketones and Various Perfluoroalkyl Ketones Using Catalyst 2b



perfluoroalkylphenyl ketones, lower yields but the same levels of enantioselectivity were observed (**3k**–**m**).

In order to account for the good enantioselectivity of the reaction, the transition state in Figure 2 is proposed. The

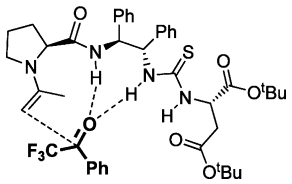


Figure 2. Proposed transition state model for the aldol reaction.

pyrrolidine functionality activates the methyl ketone through the formation of an enamine intermediate, while the trifluoromethyl carbonyl compound may be activated through multiple hydrogen bonding.

In conclusion, in an effort to broaden the applicability of the aldol reaction, a variety of the most common organocatalysts were tested for their activity in the model reaction of acetone with phenyltrifluoromethyl ketone. Our prolinamide-thiourea catalyst combining the (*S*)-prolinamide unit with (1*S*,2*S*)-diphenylethylenediamine and (*S*)-di-*tert* butyl aspartate proved to have the best catalytic activity for the aldol reaction that was studied. A variety of parameters were scrutinized in order to find the optimum reaction conditions for this transformation that provides tertiary alcohols bearing a perfluoroalkyl moiety. A number of substituted aryl trifluoromethyl ketones and perfluoroalkyl ketones are well tolerated leading to good to excellent yields and moderate to high enantioselectivities. Finally, other methyl ketones instead of acetone were successfully used.

EXPERIMENTAL SECTION

General Remarks. Chromatographic purification of products was accomplished using forced-flow chromatography. Thin-layer chromatography (TLC) was performed on aluminum backed silica plates (0.2 mm, 60 F_{254}). Visualization of the developed chromatogram was performed by fluorescence quenching using phosphomolybdic acid, anisaldehyde, or ninhydrin stains. IR spectra are reported in terms of frequency of absorption (cm^{-1}). ^1H and ^{13}C NMR spectra are internally referenced to residual solvent signals ($CDCl_3$). Data for ^1H NMR are reported as follows: chemical shift (δ ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, bs = broad signal, bs m = broad signal multiplet), coupling constant, and assignment. Data for ^{13}C NMR are reported in terms of chemical shift (δ ppm). For mass spectra, only molecular ions and major peaks are being reported with intensities quoted as percentages of the base peak. Chiral high performance liquid chromatography (HPLC) analyses were performed using Chiralpak AD-H, OD-H, and AS-H columns. The configuration of the products has been assigned either by comparison to literature data (compounds **3a**, **3b**, **3d**, and **3m**) or by analogy (all other compounds). Catalysts **1a**–**t** and **2a** were either commercially available or prepared following literature procedures.

General Procedure for the Synthesis of the Catalyst 2b. The catalyst **2b** was first described in reference 24. The same procedure for its synthesis was followed.

(*S*)-Di-*tert*-butyl 2-{3-[(1*S*,2*S*)-1,2-Diphenyl-2-[(*S*)-(pyrrolidine-2-carboxamido]-ethyl]thioureido}succinate (2b). White solid: mp 89–91 °C; $[\alpha]_D$ = +35.3 (*c* = 0.88, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 8.56 (1H, d, *J* = 8.6 Hz), 8.05–7.87 (1H, br m), 7.46–7.01 (10H, m), 6.92–6.66 (1H, br m), 5.98–5.65 (1H, m), 5.33–5.06 (2H, m), 3.97–3.68 (1H, m), 3.09–2.76 (4H, m), 2.19–2.03 (1H, m), 1.87–1.55 (4H, m), 1.43 (9H, s), 1.36 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 182.6, 170.4, 170.1, 169.9, 138.7, 138.6, 128.5, 128.3, 128.0, 127.7, 127.5, 127.4, 82.2, 81.4, 64.2, 60.3, 58.8, 54.0, 47.1, 37.8, 30.5, 28.0, 27.9, 25.8.

General Procedure for the Aldol Reaction. To a stirring solution of catalyst **2b** (4 mg, 0.007 mmol, 2 mol %) in toluene (1.0 mL), perfluoroalkyl ketone (0.34 mmol) followed by acetone or ketone (3.40 mmol) were added at 0 °C. The reaction mixture was left stirring at 0 °C for 44 h. The solvent was evaporated, and the crude product was purified using flash column chromatography eluting with various mixtures of petroleum ether (40–60 °C)/EtOAc to afford the desired product.

(*S*)-5,5,5-Trifluoro-4-hydroxy-4-phenylpentan-2-one (3a).[16] Data: 78 mg, 99% yield; $[\alpha]_D$ = +18.8 (*c* = 0.4, $CHCl_3$); IR (KBr) 3422, 3062, 1707, 1602, 1497, 1246, 1075, 906, 709 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.62–7.52 (2H, m), 7.46–7.34 (3H, m), 5.46 (1H, br s), 3.39 (1H, d, *J* = 17.2 Hz), 3.21 (1H, d, *J* = 17.2 Hz), 2.22 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.1, 137.3, 128.7, 128.4, 126.0, 124.4 (q, *J* = 284.9 Hz), 75.9 (q, *J* = 29.1 Hz), 44.8, 31.8; ^{19}F NMR (188 MHz, $CDCl_3$) δ −13.97 (s); HPLC Diacel Chiralpak AS-H, hexane/^{i}PrOH 95:5, flow rate 0.7 mL/min, retention time = 12.34 (minor) and 17.06 (major).

(*S*)-5,5,5-Trifluoro-4-(4-fluorophenyl)-4-hydroxypentan-2-one (3b).[16] Data: 82 mg, 96% yield; $[\alpha]_D$ = +15.2 (*c* = 1.0, CH_2Cl_2); IR (KBr) 3414, 2925, 1708, 1606, 1512, 1422, 1336, 1238, 1168, 1058, 916, 838, 736 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.58–7.51 (2H, m), 7.08 (2H, t, *J* = 8.7 Hz), 5.49 (1H, br s), 3.33 (1H, d, *J* = 17.2 Hz), 3.20 (1H, d, *J* = 17.2 Hz), 2.21 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 208.9, 162.9 (d, *J* = 248.2 Hz), 133.2 (d, *J* = 3.2 Hz), 128.1 (d, *J* = 8.4 Hz), 124.3 (q, *J* = 283.7 Hz), 115.4 (d, *J* = 21.6 Hz), 75.7 (q, *J* = 29.4 Hz), 44.9, 32.1; ^{19}F NMR (188 MHz, $CDCl_3$) δ −14.15 (s), −46.93 (s); HPLC Diacel Chiralpak AS-H, hexane/^{i}PrOH 95:5, flow rate 0.7 mL/min, retention time = 13.32 (minor) and 19.79 (major).

(*S*)-5,5,5-Trifluoro-4-hydroxy-4-(4-trifluoromethylphenyl)-pentan-2-one (3c). Data: 78 mg, 76% yield; $[\alpha]_D$ = +7.5 (*c* = 1.0, CH_2Cl_2); IR (KBr) 3478, 2929, 1716, 1622, 1416, 1330, 1168, 1100,

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994, 839, 760 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.72 (2H, d, J = 9.1 Hz), 7.66 (2H, d, J = 9.1 Hz), 5.63 (1H, br s), 3.36 (1H, d, J = 17.4 Hz), 3.26 (1H, d, J = 17.4 Hz), 2.24 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 208.6, 141.5, 131.1 (q, J = 32.7 Hz), 126.7, 125.5 (q, J = 3.7 Hz), 124.2 (q, J = 285.2 Hz), 123.8 (q, J = 272.1 Hz), 75.9 (q, J = 29.6 Hz), 44.9, 32.0; ^{19}F NMR (188 MHz, $CDCl_3$) δ 3.58 (s), −13.74 (s); HRMS exact mass calculated for $[M + Na]^+$ ($C_{12}H_{10}F_6O_2Na$) requires m/z 323.0477, found m/z 323.0472; HPLC Diacel Chiralpak AS-H, hexane/^{i}PrOH 97:3, flow rate 0.7 mL/min, retention time = 10.95 (minor) and 16.83 (major).

(*S*)-5,5,5-Trifluoro-4-hydroxy-4-*p*-tolylpentan-2-one (3d).[16] Data: 80 mg, 96% yield; $[\alpha]_D$ = +9.6 (c = 0.5, $CHCl_3$); IR (KBr) 3468, 3038, 2926, 1714, 1516, 1412, 1160, 990, 808, 733 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.45 (2H, d, J = 8.0 Hz), 7.21 (2H, d, J = 8.0 Hz), 5.30 (1H, br s), 3.37 (1H, d, J = 17.0 Hz), 3.19 (1H, d, J = 17.0 Hz), 2.36 (3H, s), 2.21 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.3, 138.9, 134.4, 129.4, 126.4, 124.4 (q, J = 283.4 Hz), 76.1 (q, J = 29.5 Hz), 45.3, 32.3, 21.1; ^{19}F NMR (188 MHz, $CDCl_3$) δ −14.13 (s); HPLC Diacel Chiralpak AS-H, hexane/^{i}PrOH 95:5, flow rate 0.7 mL/min, retention time = 6.50 (minor) and 9.11 (major).

(*S*)-5-Chloro-5,5-difluoro-4-hydroxy-4-phenylpentan-2-one (3e). Data: 81 mg, 96% yield; $[\alpha]_D$ = +6.2 (c = 1.0, $CHCl_3$); IR (KBr) 3464, 3065, 1712, 1448, 1368, 1332, 1169, 1118, 1065, 1014, 955, 890, 757, 719 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.64−7.52 (2H, m), 7.44−7.30 (3H, m), 5.19 (1H, br s), 3.46 (1H, d, J = 17.0 Hz), 3.25 (1H, d, J = 17.0 Hz), 2.18 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.1, 138.0, 130.1 (t, J = 298.9 Hz), 128.8, 128.2, 126.6, 79.4 (t, J = 25.4 Hz), 45.5, 32.2; ^{19}F NMR (188 MHz, $CDCl_3$) δ 2.26 (d, J = 166.3 Hz), 1.10 (d, J = 166.3 Hz); HRMS exact mass calculated for $[M + Na]^+$ ($C_{11}H_{11}F_2O_2ClNa$) requires m/z 271.0308, found m/z 271.0313; HPLC Diacel Chiralpak AS-H, hexane/^{i}PrOH 95:5, flow rate 0.7 mL/min, retention time = 11.74 (minor) and 16.15 (major).

(*S*)-2,2,2-Trifluoro-1-(perfluorophenyl)ethanone (3f). Data: 87 mg, 97% yield; $[\alpha]_D$ = +10.8 (c = 1.0, $CHCl_3$); IR (KBr) 3465, 2940, 1713, 1654, 1530, 1495, 1419, 1358, 1245, 1170, 1135, 1002, 949, 842, 779, 743 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 4.80 (1H, br s), 3.81 (1H, dt, J = 18.3 and 2.7 Hz), 3.14 (1H, dt, J = 18.3 and 3.7 Hz), 2.29 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 206.9, 150.0−110.0 (m), 123.6 (q, J = 285.0 Hz), 78.0−75.0 (m), 46.5 (t, J = 6.0 Hz), 30.5; ^{19}F NMR (188 MHz, $CDCl_3$) δ −15.25 (t, J = 8.3 Hz), −71.65 (m), −85.21 (tt, J = 21.4 and 4.2 Hz), −94.36 (m); HRMS exact mass calculated for $[M + Na]^+$ ($C_{11}H_6F_8O_2Na$) requires m/z 345.0132, found m/z 345.0127; HPLC Diacel Chiralpak AS-H, hexane/^{i}PrOH 97:3, flow rate 0.7 mL/min, retention time = 7.47 (minor) and 11.07 (major).

(*S*)-Ethyl 3-Hydroxy-5-oxo-3-(trifluoromethyl)hexanoate (3g). Data: 75 mg, 91% yield; $[\alpha]_D$ = +10.7 (c = 1.0, CH_2Cl_2); IR (KBr) 3399, 3020, 2923, 2853, 1733, 1708, 1464, 1216, 1176, 1113, 761, 699 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.78 (1H, br s), 4.18 (2H, q, J = 7.2 Hz), 3.03 (1H, d, J = 16.2 Hz), 2.95 (1H, d, J = 16.2 Hz), 2.85 (1H, d, J = 15.5 Hz), 2.75 (1H, d, J = 15.5 Hz), 2.29 (3H, s), 1.28 (3H, t, J = 7.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 208.2, 170.4, 124.9 (q, J = 286.0 Hz), 73.8 (q, J = 29.0 Hz), 61.4, 43.1, 37.3 (q, J = 1.1 Hz), 32.3, 13.9; ^{19}F NMR (188 MHz, $CDCl_3$) δ −15.88 (s); HRMS exact mass calculated for $[M + Na]^+$ ($C_9H_{13}F_3O_4Na$) requires m/z 265.0658, found m/z 265.0664; HPLC Diacel Chiralpak OD-H, hexane/^{i}PrOH 99:1, flow rate 0.7 mL/min, retention time = 13.06 (minor) and 15.36 (major).

(*R*)-4-Hydroxy-8-phenyl-4-(trifluoromethyl)octan-2-one (3h). Data: 79 mg, 81% yield; $[\alpha]_D$ = +2.6 (c = 1.0, $CHCl_3$); IR (KBr) 3397, 3022, 2923, 2855, 1707, 1455, 1217, 1172, 1075, 761, 705 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.35−7.08 (5H, m), 5.38 (1H, br s), 2.85 (1H, d, J = 16.9 Hz), 2.69−2.48 (3H, m), 2.24 (3H, s), 1.82−1.34 (6H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 210.4, 142.1, 128.4, 128.3, 125.9 (q, J = 286.8 Hz), 125.8, 75.2 (q, J = 27.6 Hz), 42.3, 35.7, 34.6, 32.1, 31.5, 22.3; ^{19}F NMR (188 MHz, $CDCl_3$) δ −13.97 (s); HRMS exact mass calculated for $[M + Na]^+$ ($C_{15}H_{19}F_3O_2Na$) requires m/z 311.1229, found m/z 311.1226; HPLC Diacel Chiralpak AS-H, hexane/^{i}PrOH 98:2, flow rate 0.5 mL/min, retention time = 19.90 (major) and 32.33 (minor).

(*S*)-6,6,6-Trifluoro-5-hydroxy-5-phenylhexan-3-one (3i). Data: 74 mg, 88% yield; $[\alpha]_D$ = +5.7 (c = 1.0, $CHCl_3$); IR (KBr) 3426, 3023, 2921, 1705, 1455, 1217, 1169, 1076, 1011, 762, 705 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.62−7.50 (2H, m), 7.46−7.32 (3H, m), 5.61 (1H, br s), 3.33 (1H, d, J = 17.0 Hz), 3.18 (1H, d, J = 17.0 Hz), 2.69−2.31 (2H, m), 1.01 (3H, t, J = 7.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 211.8, 137.5, 128.8, 128.4, 126.1, 124.5 (q, J = 284.9 Hz), 75.9 (q, J = 29.0 Hz), 44.1, 38.2, 7.1; ^{19}F NMR (188 MHz, $CDCl_3$) δ −13.85 (s); HRMS exact mass calculated for $[M + Na]^+$ ($C_{12}H_{13}F_3O_2Na$) requires m/z 269.0760, found m/z 269.0766; HPLC Diacel Chiralpak AS-H, hexane/^{i}PrOH 99:1, flow rate 0.5 mL/min, retention time = 20.07 (minor) and 23.64 (major).

3,4-Dihydroxy-8-phenyl-4-(trifluoromethyl)octan-2-one (3j). Data: 1:1 mixture of diastereomers, 72 mg, 70% yield; IR (KBr) 3439, 3021, 2924, 1714, 1453, 1362, 1246, 1169, 1076, 1027, 763, 714 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.72−7.62 (4H, m), 7.52−7.36 (6H, m), 4.84 (1H, br s), 4.65 (1H, br s), 3.72 (2H, br s), 2.17 (3H, s), 1.56 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 207.5, 206.0, 134.0, 133.2, 129.5, 129.4, 128.5, 128.0, 126.4, 125.9, 124.6 (q, J = 287.8 Hz), 124.6 (q, J = 288.2 Hz), 78.7, 78.7, 78.4 (q, J = 25.6 Hz), 77.9 (q, J = 27.4 Hz), 29.7, 28.1; ^{19}F NMR (188 MHz, $CDCl_3$) δ −7.61 (s), −8.65 (s); HRMS exact mass calculated for $[M + Na]^+$ ($C_{11}H_{11}F_3O_3Na$) requires m/z 271.0552, found m/z 271.0549; HPLC Diacel Chiralpak AS-H, hexane/^{i}PrOH 97:3, flow rate 0.5 mL/min, retention time = major diastereomer 49.33 (minor) and 55.65 (major), minor diastereomer 67.27 (minor) and 75.53 (major).

(*S*)-5,5,6,6,6-Pentafluoro-4-hydroxy-4-phenyl-hexan-2-one (3k). Data: 54 mg, 56% yield; $[\alpha]_D$ = +7.8 (c = 1.0, CH_2Cl_2); IR (KBr) 3406, 3066, 1707, 1419, 1341, 1222, 1124, 1000, 842, 709 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.61−7.51 (2H, m), 7.44−7.34 (3H, m), 5.60 (1H, br s), 3.39 (1H, d, J = 16.9 Hz), 3.24 (1H, d, J = 16.9 Hz), 2.17 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.6, 137.5, 134.8−104.2 (m), 128.9, 128.7, 126.1, 76.9 (q, J = 29.4 Hz), 45.1, 32.3; ^{19}F NMR (188 MHz, $CDCl_3$) δ −11.43 (s), −55.1 (m); HRMS exact mass calculated for $[M + Na]^+$ ($C_{12}H_{11}F_5O_2Na$) requires m/z 305.0571, found m/z 305.0576; HPLC Diacel Chiralpak AS-H, hexane/^{i}PrOH 97:3, flow rate 0.5 mL/min, retention time = 14.18 (minor) and 22.33 (major).

(*S*)-5,5,6,6,7,7,7-Heptafluoro-4-hydroxy-4-phenyl-heptan-2-one (3l). Data: 76 mg, 67% yield; $[\alpha]_D$ = +7.5 (c = 1.0, CH_2Cl_2); IR (KBr) 3407, 3068, 1706, 1419, 1340, 1224, 1121, 1000, 844, 709 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.62−7.54 (2H, m), 7.44−7.32 (3H, m), 5.69 (1H, br s), 3.36 (1H, d, J = 16.8 Hz), 3.25 (1H, d, J = 16.8 Hz), 2.16 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.5, 137.6, 136.1−106.9 (m), 128.7, 128.3, 126.2, 77.3 (q, J = 29.2 Hz), 45.5, 32.3; ^{19}F NMR (188 MHz, $CDCl_3$) δ −14.49 (t, J = 11.0 Hz), −51.32 (m), −56.54 (m); HRMS exact mass calculated for $[M + Na]^+$ ($C_{13}H_{11}F_7O_2Na$) requires m/z 355.0539, found m/z 355.0545; HPLC Diacel Chiralpak AS-H, hexane/^{i}PrOH 97:3, flow rate 0.5 mL/min, retention time = 12.25 (minor) and 15.25 (major).

(*S*)-5,5,6,6,7,7,8,8,8-Nonafluoro-4-hydroxy-4-phenyl-octan-2-one (3m).[16] Data: 58 mg, 45% yield; $[\alpha]_D$ = −3.7 (c = 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.63−7.53 (2H, m), 7.44−7.32 (3H, m), 5.67 (1H, br s), 3.35 (1H, d, J = 16.8 Hz), 3.26 (1H, d, J = 16.8 Hz), 2.16 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.5, 137.7, 136.1−106.9 (m), 128.8, 128.5, 126.2, 77.4 (q, J = 29.2 Hz), 45.7, 32.5; HPLC Diacel Chiralpak AD-H, hexane/^{i}PrOH 99:1, flow rate 1.0 mL/min, retention time = 5.42 (minor) and 5.73 (major).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full optimization details, ^1H and ^{13}C NMR spectra, and HPLC data are available. This material is available free of charge via Internet at http://pubs.acs.org.

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