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Enantioselective aldol reactions of α,β-unsaturated ketones with trifluoroacetophenone catalyzed by a chiral primary amine

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ABSTRACT

Chiral primary amine catalyzed direct asymmetric aldol reactions of ketones with trifluoroacetophenone, afforded trifluoromethylated β-hydroxycarbonyl aldol products bearing a quaternary carbon stereogenic center in high yields (up to 93% yield) and with high to excellent enantioselectivities of up to 99% ee.

1. Introduction

The development of highly efficient and enantioselective chiral catalysts for organic transformations that proceed under mild conditions and tolerate a wide scope of substrates is an important subject. Asymmetric aminocatalysis has received much attention and significant advancements have been made over the past few years.[1] Organocatalytic aldol reactions are one of the most powerful methods for rapid access to β-hydroxycarbonyl compounds and the formation of C—C bonds in organic synthesis.[2] Since the pioneering work of List and Barbas III et al., direct aldol reactions have been investigated intensively over the past decade.[3–5] However, direct asymmetric aldol reactions using α,β-unsaturated ketones as the nucleophile have been less explored. Furthermore, using ketones as the electrophile has received less attention due to their low electrophilicity relative to aldehydes.[6]

Trifluoromethylated organic compounds have received increasing attention because the trifluoromethyl motif plays a pivotal role in the enhancement and modification of biological activities.[7,8] Consequently, efficient approaches to valuable CF_3-bearing organic compounds are of considerable synthetic and biological importance.[9] In 2008, we developed a new family of chiral primary amines from enantiomerically pure binaphthol and amino acids. This family was found to be effective in asymmetric aldol reactions of ketone with aldehydes and keto-esters.[10] Very recently, these chiral amines were successfully applied in cross aldol reactions of acetaldehyde with unsaturated keto-esters, yielding enantiomerically enriched tertiary alcohols with excellent enantioselectivity.[11] In our continuous efforts toward exploring primary amine catalyzed aldol reactions with ketones and synthesizing trifluoromethylated organic compounds, we herein report a cross aldol of α,β-unsaturated ketones with trifluoroacetophenone to allow the synthesis of trifluoromethylated β-hydroxycarbonyl compounds bearing a quaternary carbon stereogenic center.

2. Results and discussion

In our initial studies, we undertook an investigation of proline **1a** as the catalyst for the cross aldol reaction of α,β-unsaturated ketone **2a**[12] with trifluoroacetophenone **3a** in the presence of TFA at room temperature. Unfortunately, commonly used proline **1a** was found to be unreactive and no aldol product was isolated even after 96 h (entry 1). We decided to investigate whether primary amine catalyst **1b** would be more amenable to this cross aldol reaction (Fig. 1); the results are summarized in Table 1. The reaction proceeded smoothly to generate trifluoromethylated β-hydroxycarbonyl compound **4a** in high yield but with low enantioselectivity (84% yield and 28% ee, entry 2). A catalyst survey showed that the catalyst has a significant effect on the reactivity and enantioselectivity of the aldol reaction (entries 1–6). For instance, cinchona derived primary amines **1e**–**1g** furnished poor yields and enantioselectivity (entries 5 and 6). Primary amine **1d**, developed by our group[10] turned out to be the most efficient in terms of enantioselectivities (entry 4).

Primary amine **1d** was found to be the best for the reaction in terms of enantioselectivity among all of the organocatalysts tested (Table 1), but it gave only moderate yield and enantioselectivity. In order to further optimize the procedure, we next studied the influence of the acid and solvent on the reaction outcome (Table 2). It was found that no desired product was isolated when TfOH was used or in the absence of an acid (entries 1 and 2); when the reaction was carried out in the presence of TsOH or *N*-Boc-L-phenylglycine,

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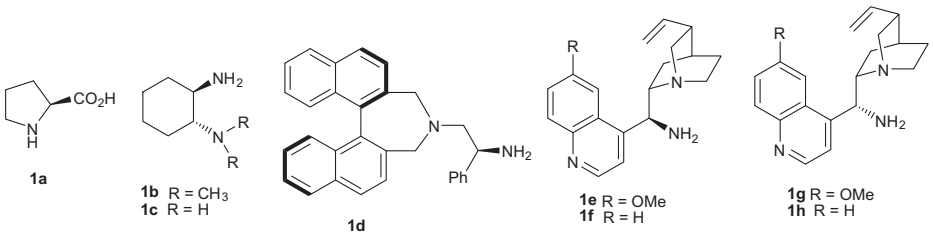
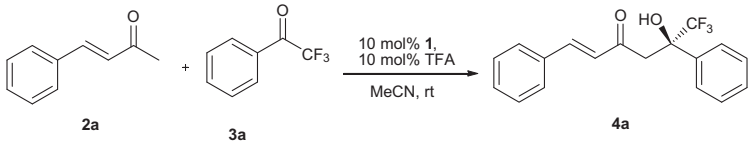


Figure 1. Catalysts evaluated herein.

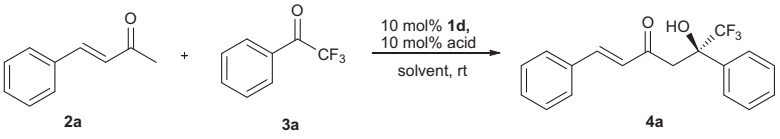
Table 1
Direct asymmetric aldol reaction of α,β-unsaturated ketone **2a** and trifluoroacetophenone **3a**[a]



Entry	Catalyst **1**	Time (h)	Yield[b] (%)	ee[c] (%)
1	**1a**	96	—	—
2	**1b**	64	84	28
3	**1c**	54	36	46
4	**1d**	54	53	56
5	**1e**	48	29	35
6	**1f**	48	24	43
7	**1g**	48	29	39
8	**1h**	48	47	35

[a] The reaction was performed with **2a** (0.1 mmol), **3a** (0.3 mmol), **1** (10 mol %), TFA (10 mol %) in MeCN (0.2 mL) at room temperature.
[b] Isolated yield.
[c] Determined by HPLC analysis.

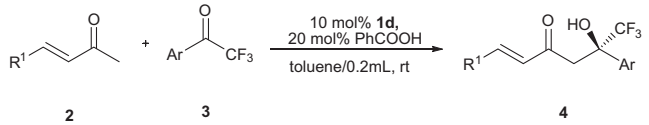
Table 2
Optimization of reaction conditions[a]



Entry	Acid	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	—	CH_3CN	64	—	—
2	TfOH	CH_3CN	64	Trace	—
3	TsOH	CH_3CN	64	83	47
4	TFA	CH_3CN	64	55	56
5	2-$FC_6H_4CO_2H$	CH_3CN	64	79	51
6	4-$NO_2C_6H_4CO_2H$	CH_3CN	64	74	42
7	PhCOOH	CH_3CN	64	69	56
8	CH_3CO_2H	CH_3CN	64	53	53
9	*N*-Boc-L-phenylglycine	CH_3CN	64	80	39
10	*N*-Boc-L-*tert*-leucine	CH_3CN	64	71	37
11	PhCOOH	$CHCl_3$	64	66	83
12	PhCOOH	CH_2Cl_2	64	68	83
13	PhCOOH	Toluene	64	75	84
14	PhCOOH	Xylene	64	78	79
15	PhCOOH	THF	72	34	67
16	PhCOOH	Et_2O	72	47	70
17	PhCOOH	Toluene	64	85	82[d]
18	PhCOOH	Toluene	64	87	82[e]

[a] All reactions were performed with **2a** (0.1 mmol), **3a** (0.3 mmol), **1d** (10 mol %), acid (10 mol %) in solvent (0.2 mL) at room temperature for 64–72 h unless otherwise indicated.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] 20 mol % $PhCO_2H$.
[e] 30 mol % $PhCO_2H$ was used.

Table 3
Scope of the substrates[a]



2 3 4

Entry	R^1	Ar	4	Time (h)	Yield[b] (%)	ee[c] (%)
1	4-FC_6H_4	C_6H_5	**4b**	36	72	87
2	4-ClC_6H_4	C_6H_5	**4c**	36	75	86
3	4-BrC_6H_4	C_6H_5	**4d**	36	85	87
4	4-$CH_3C_6H_4$	C_6H_5	**4e**	36	74	91
5	4-$CH_3OC_6H_4$	C_6H_5	**4f**	36	76	87
6	2-ClC_6H_4	C_6H_5	**4g**	36	74	83
7	2-BrC_6H_4	C_6H_5	**4h**	36	79	83
8	3-ClC_6H_4	C_6H_5	**4i**	36	74	85
9	3-BrC_6H_4	C_6H_5	**4j**	36	72	83
10	3-$CH_3C_6H_4$	C_6H_5	**4k**	36	72	87
11	3-$CH_3OC_6H_4$	C_6H_5	**4l**	36	82	87
12	2-Furyl	C_6H_5	**4m**	64	54	85
13	2-Thiophenyl	C_6H_5	**4n**	64	57	87
14	C_6H_5	4-ClC_6H_4	**4o**	48	77	92
15	4-$CH_3C_6H_4$	4-ClC_6H_4	**4p**	48	93	93
16	C_6H_5	4-BrC_6H_4	**4q**	48	82	99
17	C_6H_5	4-$CH_3C_6H_4$	**4r**	48	68	86
18	C_6H_5	2-Thiophenyl	**4s**	48	65	81
19	*n*-C_3H_7	C_6H_5	**4t**	48	64	93
20	*n*-C_6H_{13}	C_6H_5	**4u**	48	64	92
21	*i*-C_3H_7	C_6H_5	**4v**	36	80	92

[a] All reactions was performed with **2** (0.1 mmol), **3** (0.3 mmol), **1d** (10 mol %), PhCOOH (20 mol %) in toluene (0.2 mL) at room temperature for 36–64 h.
[b] Isolated yield.
[c] Determined by HPLC analysis.

the desired aldol product **4a** was afforded in high yield but with low enantioselectivity (entries 3 and 9). In terms of yield and enantioselectivity, $PhCO_2H$ was the optimal acid giving the desired aldol product **4a** in 69% yield and 56% ee (entry 7). Studies on the solvent effect revealed that the use of CH_2Cl_2 or $CHCl_3$ as the solvent gave moderate yield and high enantioselectivity (entries 11 and 12). Neither THF nor Et_2O was a good solvent for the reaction (entries 15 and 16). Performing the reaction in toluene gave the best results in terms of both yield and enantioselectivity (entry 13). Additional studies on the amount of acid indicated that 20 mol % **1d** was the best choice, affording the desired aldol product **4a** in 85% yield and 82% ee (entry 17). Performing the reaction in the presence of 30 mol % **1d** resulted in the same yield accompanied with no improvement in enantioselectivity (entry 18).

Under the optimal conditions, a range of α,β-unsaturated ketones with electron withdrawing substituents, as well as electron donating substituents in the phenyl motif were examined for a reaction with trifluoroacetophenone. As recorded in Table 3, the primary amine **1d** exhibited generally high to excellent enantioselectivities ranging from 83% to 93% ee and good yields for most of α,β-unsaturated ketones tested (entries 1–11), with the exception of the case involving heteroaromatic substrates, in which moderate yields were obtained (entries 12 and 13). Extending these reaction conditions to other trifluoroacetophenones was highly successful, giving rise to trifluoromethylated β-hydroxycarbonyl compounds with 86–99% ee (entries 14–17). The heteroaromatic trifluoroacetophenone could also be tolerated with high stereoselectivity and moderate yield, as exemplified by trifluoromethyl 2-thiophenyl ketone (entry 18). Aliphatic substituted α,β-unsaturated ketones could also be used in the aldol reaction, providing the aldol product with good results (entries 19–21). The absolute configuration of the product was unambiguously assigned to be (*R*) by single-crystal X-ray diffraction of **4c** and the other aldol products were assigned by analogy (Fig. 2).[13] Based on the absolute configuration and our early work,[11] a possible activation model via a putative transition state was proposed (Fig. 2). The conjugated amino diene formed from the chiral amine and α,β-unsaturated ketone approaches the trifluoroacetophenone from the *Si*-face, which is activated by the hydrogen bonding shown in Figure 2, thus forming the corresponding (*R*)-isomer.

3. Conclusions

In conclusion, we have discovered a primary amine **1d** catalyzed cross aldol reaction of α,β-unsaturated ketones with trifluoroacetophenone (ketone–ketone) in the presence of benzoic acid, affording trifluoromethylated β-hydroxycarbonyl aldol products bearing a quaternary carbon stereogenic center in high yields (up to 93% yield) and with high to excellent enantioselectivities of up to 99% ee. The discovery of the current protocol is complementary to the aldol reaction with ketones as electrophiles.

4. Experimental

4.1. General

^1H NMR spectra and ^{13}C NMR spectra were recorded in $CDCl_3$ on a spectrometer operating at 400 and 100 MHz, respectively. Chemical shifts are reported in parts per million relative to the appropriate standard: TMS for ^1H and ^{13}C NMR spectra. Coupling constants (*J*) are reported in Hz and refer to apparent peak multiplications. Melting points were recorded using Reichert melting point apparatus and temperatures are uncorrected. Optical

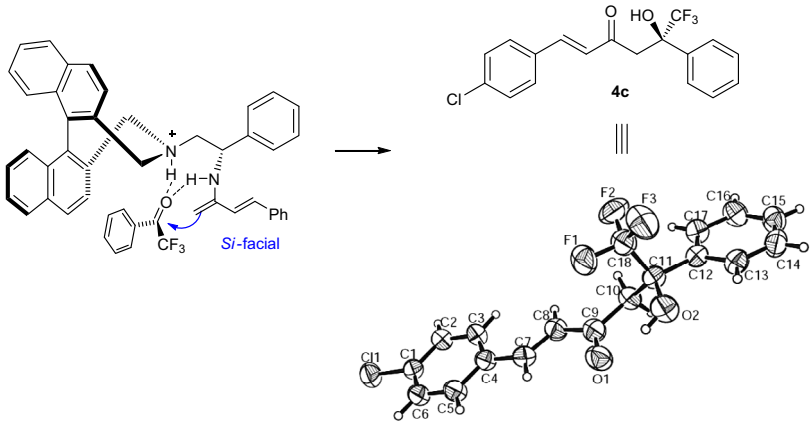


Figure 2. Activation model and absolute configuration of **4c**.

rotations were performed on an OA PLAAR 3005 (589 nm) using a 700-μL cell with a path length of 1 dm. Enantiomeric excesses (ee) were determined by HPLC analysis on a Shimadzu LC-20A, using Daicel Chiralcel AD and OD columns. Flash column chromatography was performed using 200–300 mesh silica gel.

4.2. General procedure for the asymmetric aldol reaction (Table 3)

To a solution of α,β-unsaturated ketones **2** (0.1 mmol) and chiral primary amines **1** (0.01 mmol) in toluene (0.2 mL) were added trifluoroacetophenone **3** (0.3 mmol) and $PhCO_2H$ (0.02 mmol). The reaction mixture was stirred at room temperature until the reaction was complete (monitored by TLC), after which it was quenched with saturated sodium bicarbonate solution and the mixture was extracted with dichloromethane (3×10 mL). The combined organic layers were washed with brine (20 mL) and were dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified through flash column chromatography on silica gel (petroleum ether/dichloromethane = 3:1–2:1) to afford aldol products **4**.

4.3. (*R*,*E*)-6,6,6-Trifluoro-5-hydroxy-1,5-diphenylhex-1-en-3-one 4a

R_f = 0.32 (PE/CH_2Cl_2 = 1:1), yield: 85%, white solid, mp 40–42 °C, $[\alpha]_D^{25}$ = −228.2 (*c* 0.11, CH_2Cl_2). 82% ee determined by HPLC analysis (chiral AD-H column, 5% IPA in hexane, rate: 1.0 mL/min, 254 nm). Retention time: *t*(minor) = 14.8 min, *t*(major) = 16.4 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.65–7.61 (m, 3H), 7.59–7.57 (m, 2H), 7.49–7.34 (m, 6H), 6.74 (d, *J* = 16.1 Hz, 1H), 3.68 (d, *J* = 16.9 Hz, 1H), 3.41 (d, *J* = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 199.2, 145.5, 137.6, 133.6, 131.4, 129.1, 128.7, 128.6, 128.4, 126.3, 125.8, 124.6 (*J* = 282.9 Hz), 76.4 (*J* = 28.8 Hz), 42.3; ESI-HRMS for $C_{18}H_{15}F_3O_2$ $(M+H)^+$: 321.1096, Found: 321.1093.

4.4. (*R*,*E*)-6,6,6-Trifluoro-1-(4-fluorophenyl)-5-hydroxy-5-phenylhex-1-en-3-one 4b

R_f = 0.35 (PE/CH_2Cl_2 = 1:1), yield: 72%, white solid, mp 54–56 °C, $[\alpha]_D^{25}$ = −256.3 (*c* 0.16, CH_2Cl_2). 87% ee determined by HPLC analysis (chiral OD-H column, 5% IPA in hexane, rate: 1.0 mL/min, 254 nm). Retention time: *t*(minor) = 22.2 min, *t*(major) = 27.9 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.64–7.55 (m, 5H), 7.43–7.36 (m, 3H), 7.15–7.11 (m, 2H), 6.66 (d, *J* = 16.1 Hz, 1H), 3.65 (d, *J* = 16.9 Hz, 1H), 3.40 (d, *J* = 16.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 198.9, 165.8, 163.3, 144.0, 137.6, 130.7 (*J* = 8.7 Hz), 129.9 (*J* = 3.5 Hz), 128.7, 128.4, 126.3, 125.4 (*J* = 2.2 Hz), 123.2 (*J* = 283.1 Hz), 116.5, 116.3, 76.4 (*J* = 29.0 Hz), 42.6; ESI-HRMS for $C_{18}H_{14}F_4O_2$ $(M+H)^+$: 339.1002, Found: 339.0995.

4.5. (*R*,*E*)-1-(4-Chlorophenyl)-6,6,6-trifluoro-5-hydroxy-5-phenylhex-1-en-3-one 4c

R_f = 0.32 (PE/CH_2Cl_2 = 1:1), yield: 75%, white solid, mp 53–55 °C, $[\alpha]_D^{25}$ = −217.2 (*c* 0.18, CH_2Cl_2). 86% ee determined by HPLC analysis (chiral AD-H column, 5% IPA in hexane, rate: 1.0 mL/min, 254 nm). Retention time: *t*(minor) = 27.3 min, *t*(major) = 30.5 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.71–7.62 (m, 2H), 7.57 (d, *J* = 16.1 Hz, 1H), 7.51–7.49 (m, 2H), 7.45–7.32 (m, 5H), 6.70 (d, *J* = 16.1 Hz, 1H), 3.66 (d, *J* = 16.9 Hz, 1H), 3.41 (d, *J* = 16.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 198.9, 143.8, 137.6, 137.5, 132.1, 129.8, 129.4, 128.8, 128.4, 126.3, 126.1, 124.6 (*J* = 283.2 Hz), 76.4 (*J* = 29.0 Hz), 42.7; ESI-HRMS for $C_{18}H_{14}ClF_3O_2$ $(M+Na)^+$: 377.0526, Found: 377.0520.

4.6. (*R*,*E*)-1-(4-Bromophenyl)-6,6,6-trifluoro-5-hydroxy-5-phenylhex-1-en-3-one 4d

R_f = 0.30 (PE/CH_2Cl_2 = 1:1), yield: 85%, white solid, mp 59–61 °C, $[\alpha]_D^{25}$ = −233.2 (*c* 0.22, CH_2Cl_2). 87% ee determined by HPLC analysis (chiral AD-H column, 5% IPA in hexane, rate: 1.0 mL/min, 254 nm). Retention time: *t*(minor) = 27.9 min, *t*(major) = 30.4 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.63–7.53 (m, 5H), 7.44–7.36 (m, 5H), 6.71 (d, *J* = 16.1 Hz, 1H), 3.65 (d, *J* = 16.9 Hz, 1H), 3.40 (d, *J* = 16.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 198.9, 143.9, 137.6, 132.6, 132.4, 130.0, 128.8, 128.4, 126.3, 126.1, 125.9, 124.6 (*J* = 283.1 Hz), 76.2 (*J* = 28.9 Hz), 42.7; ESI-HRMS for $C_{18}H_{14}BrF_3O_2$ $(M+Na)^+$: 421.0021, Found: 421.0025.

4.7. (*R*,*E*)-6,6,6-trifluoro-5-hydroxy-5-phenyl-1-(*p*-tolyl)hex-1-en-3-one (4e)

R_f = 0.34 (PE/CH_2Cl_2 = 1:1), yield: 74%, white solid, mp 64–66 °C, $[\alpha]_D^{25}$ = −283.0 (*c* 0.10, CH_2Cl_2). 91% ee determined by HPLC analysis (chiral OD-H column, 5% IPA in hexane, rate: 1.0 mL/min, 254 nm). Retention time: *t*(minor) = 16.5 min, *t*(major) = 22.1 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.65–7.59 (m, 3H), 7.48–7.34 (m, 5H), 7.26–7.24 (m, 2H), 6.69 (d, *J* = 16.1 Hz, 1H), 3.66 (d, *J* = 16.8 Hz, 1H), 3.39 (d, *J* = 16.8 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 199.3, 145.6, 142.2, 137.7, 130.9, 129.9, 128.8, 128.7, 128.4, 126.3, 124.8, 123.2 (*J* = 283.2 Hz), 76.4 (*J* = 28.9 Hz), 42.2, 21.6; ESI-HRMS for $C_{19}H_{17}F_3O_2$ $(M+Na)^+$: 357.1075, Found: 357.1071.

4.8. (*R*,*E*)-6,6,6-Trifluoro-5-hydroxy-1-(4-methoxyphenyl)-5-phenylhex-1-en-3-one 4f

R_f = 0.34 (PE/CH_2Cl_2 = 1:1), yield: 76%, white solid, mp 64–66 °C, $[\alpha]_D^{25}$ = −251.9 (*c* 0.16, CH_2Cl_2). 87% ee determined by HPLC analysis (chiral AD-H column, 10% IPA in hexane, rate: 1.0 mL/min, 254 nm). Retention time: *t*(minor) = 24.6 min, *t*(major) = 29.1 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.65–7.52 (m, 5H), 7.43–7.36 (m, 3H), 7.02–6.93 (m, 2H), 6.62 (d, *J* = 16.0 Hz, 1H), 3.88 (s, 3H), 3.64 (d, *J* = 16.8 Hz, 1H), 3.38 (d, *J* = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 199.1, 162.4, 145.4, 137.8, 130.7, 128.7, 128.4, 126.4, 126.3, 124.6 (*J* = 283.1 Hz), 123.5, 114.6, 76.4 (*J* = 29.0 Hz), 55.5, 42.0; ESI-HRMS for $C_{19}H_{17}F_3O_3$ $(M+Na)^+$: 373.1022, Found: 373.1028.

4.9. (*R*,*E*)-1-(2-Chlorophenyl)-6,6,6-trifluoro-5-hydroxy-5-phenylhex-1-en-3-one 4g

R_f = 0.35 (PE/CH_2Cl_2 = 1:1), yield: 74%, colorless oil, $[\alpha]_D^{25}$ = −131.6 (*c* 0.19, CH_2Cl_2). 83% ee determined by HPLC analysis (chiral OD-H column, 3% IPA in hexane, rate: 1.0 mL/min, 254 nm). Retention time: *t*(minor) = 22.2 min, *t*(major) = 34.3 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.06 (d, *J* = 16.2 Hz, 1H), 7.72–7.59 (m, 3H), 7.49–7.46 (m, 1H), 7.44–7.31 (m, 5H), 6.69 (d, *J* = 16.2 Hz, 1H), 3.73 (d, *J* = 16.8 Hz, 1H), 3.43 (d, *J* = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 199.2, 141.1, 137.5, 135.8, 132.1, 131.9, 130.4, 128.8, 128.5, 128.2, 127.8, 127.3, 126.3, 123.1 (*J* = 282.9 Hz), 76.3 (*J* = 29.1 Hz), 42.2; ESI-HRMS for $C_{18}H_{14}ClF_3O_2$ $(M+Na)^+$: 377.0526, Found: 377.0525.

4.10. (*R*,*E*)-1-(2-Bromophenyl)-6,6,6-trifluoro-5-hydroxy-5-phenylhex-1-en-3-one 4h

R_f = 0.30 (PE/CH_2Cl_2 = 1:1), yield: 79%, colorless oil, $[\alpha]_D^{25}$ = −142.3 (*c* 0.26, CH_2Cl_2). 83% ee determined by HPLC analysis (chiral AD-H column, 1% IPA in hexane, rate: 1.0 mL/min, 254 nm). Retention time: *t*(minor) = 19.6 min, *t*(major) = 25.2 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.03 (d, J = 16.2 Hz, 1H), 7.68–7.61 (m, 4H), 7.44–7.30 (m, 5H), 6.64 (d, J = 16.2 Hz, 1H), 3.73 (d, J = 16.8 Hz, 1H), 3.42 (d, J = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 199.1, 143.8, 142.9, 137.5, 133.7, 132.2, 128.8, 128.5, 128.4, 127.9, 127.8, 126.3, 126.2, 123.1 (J = 283.2 Hz), 76.4 (J = 29.0 Hz), 42.1; ESI-HRMS for $C_{18}H_{14}BrF_3O_2$ $(M+H)^+$: 399.0210, Found: 399.0206.

4.11. (*R*,*E*)-1-(3-Chlorophenyl)-6,6,6-trifluoro-5-hydroxy-5-phenylhex-1-en-3-one 4i

R_f = 0.36 (PE/CH_2Cl_2 = 1:1), yield: 74%, colorless oil, $[\alpha]_D^{25}$ = −162.6 (c 0.19, CH_2Cl_2). 85% ee determined by HPLC analysis (chiral OD-H column, 3% IPA in hexane, rate: 1.0 mL/min, 254 nm). Retention time: t(minor) = 32.8 min, t(major) = 40.7 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.72–7.62 (m, 2H), 7.57–7.53 (m, 2H), 7.44–7.35 (m, 6H), 6.72 (d, J = 16.1 Hz, 1H), 3.66 (d, J = 16.9 Hz, 1H), 3.41 (d, J = 16.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 198.9, 143.6, 137.5, 135.5, 135.2, 131.2, 130.3, 128.8, 128.5, 128.3, 126.9, 126.8, 126.3, 124.6 (J = 282.9 Hz), 76.2 (J = 29.0 Hz), 42.8; ESI-HRMS for $C_{18}H_{14}ClF_3O_2$ $(M+Na)^+$: 377.0526, Found: 377.0531.

4.12. (*R*,*E*)-1-(3-Bromophenyl)-6,6,6-trifluoro-5-hydroxy-5-phenylhex-1-en-3-one 4j

R_f = 0.32 (PE/CH_2Cl_2 = 1:1), yield: 72%, colorless oil, $[\alpha]_D^{25}$ = −170.0 (c 0.30, CH_2Cl_2). 83% ee determined by HPLC analysis (chiral AD-H column, 4% IPA in hexane, rate: 1.0 mL/min, 254 nm). Retention time: t(minor) = 16.9 min, t(major) = 18.1 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.81–7.71 (m, 1H), 7.63–7.47 (m, 5H), 7.43–7.29 (m, 4H), 6.71 (d, J = 16.1 Hz, 1H), 3.66 (d, J = 16.9 Hz, 1H), 3.41 (d, J = 16.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 198.8, 143.5, 137.5, 135.7, 134.1, 131.2, 130.6, 128.8, 128.4, 127.3, 126.8, 126.3, 123.2, 123.1 (J = 283.1 Hz), 76.4 (J = 29.0 Hz), 42.8; ESI-HRMS for $C_{18}H_{14}BrF_3O_2$ $(M+Na)^+$: 421.0022, Found: 421.0023.

4.13. (*R*,*E*)-6,6,6-Trifluoro-5-hydroxy-5-phenyl-1-(m-tolyl)hex-1-en-3-one 4k

R_f = 0.30 (PE/CH_2Cl_2 = 1:1), yield: 72%, white solid, mp 43–45 °C, $[\alpha]_D^{25}$ = −250.0 (c 0.16, CH_2Cl_2). 87% ee determined by HPLC analysis (chiral OD-H column, 5% IPA in hexane, rate: 1.0 mL/min, 254 nm). Retention time: t(minor) = 20.0 min, t(major) = 27.7 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.65–7.59 (m, 3H), 7.43–7.35 (m, 5H), 7.33–7.28 (m, 2H), 6.72 (d, J = 16.1 Hz, 1H), 3.67 (d, J = 16.8 Hz, 1H), 3.40 (d, J = 16.8 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 199.3, 145.8, 138.9, 137.7, 133.6, 132.3, 129.4, 129.0, 128.7, 128.4, 126.3, 126.0, 125.6, 124.6 (J = 283.0 Hz), 76.4 (J = 28.9 Hz), 42.2, 21.3; ESI-HRMS for $C_{19}H_{17}F_3O_2$ $(M+H)^+$: 335.1253, Found: 335.1253.

4.14. (*R*,*E*)-6,6,6-Trifluoro-5-hydroxy-1-(3-methoxyphenyl)-5-phenylhex-1-en-3-one 4l

R_f = 0.32 (PE/CH_2Cl_2 = 1:1), yield: 82%, colorless oil, $[\alpha]_D^{25}$ = −146.0 (c 0.10, CH_2Cl_2). 87% ee determined by HPLC analysis (chiral OD-H column, 5% IPA in hexane, rate: 1.0 mL/min, 254 nm). Retention time: t(minor) = 38.3 min, t(major) = 57.0 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.64–7.57 (m, 3H), 7.43–7.33 (m, 4H), 7.18–7.00 (m, 3H), 6.71 (d, J = 16.1 Hz, 1H), 3.86 (s, 3H), 3.68 (d, J = 16.9 Hz, 1H), 3.41 (d, J = 16.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 199.2, 160.0, 145.4, 137.6, 135.0, 130.1, 128.7, 128.4, 126.3, 126.0, 123.2 (J = 283.2 Hz), 121.5, 117.4, 113.4, 76.3 (J = 29.0 Hz), 55.4, 42.3; ESI-HRMS for $C_{19}H_{17}F_3O_3$ $(M+Na)^+$: 373.1022, Found:373.1029.

4.15. (*R*,*E*)-6,6,6-Trifluoro-1-(furan-2-yl)-5-hydroxy-5-phenylhex-1-en-3-one 4m

R_f = 0.30 (PE/CH_2Cl_2 = 1:1), yield: 54%, pale yellow oil, $[\alpha]_D^{25}$ = −138.0 (c 0.05, CH_2Cl_2). 85% ee determined by HPLC analysis (chiral OD-H column, 5% IPA in hexane, rate: 1.0 mL/min, 254 nm). Retention time: t(minor) = 15.4 min, t(major) = 23.6 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.62 (d, J = 7.5 Hz, 2H), 7.56 (d, J = 1.4 Hz, 1H), 7.42–7.34 (m, 4H), 6.78 (d, J = 3.4 Hz, 1H), 6.64 (d, J = 15.9 Hz, 1H), 6.54 (dd, J = 1.8, 3.4 Hz, 1H), 3.58 (d, J = 16.8 Hz, 1H), 3.36 (d, J = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 198.8, 150.5, 146.0, 137.7, 131.0, 128.7, 128.4, 126.3, 123.2 (J = 283.0 Hz), 122.7, 118.0, 113.0, 76.3 (J = 29.0 Hz), 42.7; ESI-HRMS for $C_{16}H_{13}F_3O_3$ $(M+H)^+$: 311.0889, Found: 311.0890.

4.16. (*R*,*E*)-6,6,6-Trifluoro-5-hydroxy-5-phenyl-1-(thiophen-2-yl)hex-1-en-3-one 4n

R_f = 0.32 (PE/CH_2Cl_2 = 1:1), yield: 57%, pale yellow oil, $[\alpha]_D^{25}$ = −153.8 (c 0.03, CH_2Cl_2). 87% ee determined by HPLC analysis (chiral OD-H column, 5% IPA in hexane, rate: 1.0 mL/min, 254 nm). Retention time: t(minor) = 18.6 min, t(major) = 24.1 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.75 (d, J = 15.7 Hz, 1H), 7.63 (d, J = 7.5 Hz, 2H), 7.50 (d, J = 5.0 Hz, 1H), 7.43–7.35 (m, 4H), 7.12 (dd, J = 4.0, 4.8 Hz, 1H), 6.53 (d, J = 15.7 Hz, 1H), 3.60 (d, J = 16.8 Hz, 1H), 3.36 (d, J = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 198.6, 139.1, 137.7, 137.6, 133.3, 130.4, 128.7, 128.6, 128.4, 126.3, 124.2, 123.2 (J = 283.3 Hz), 76.4 (J = 28.8 Hz), 42.5; ESI-HRMS for $C_{16}H_{13}F_3O_2S$ $(M+Na)^+$: 349.0490, Found: 349.0490.

4.17. (*R*,*E*)-5-(4-Chlorophenyl)-6,6,6-trifluoro-5-hydroxy-1-phenylhex-1-en-3-one 4o

R_f = 0.31 (PE/CH_2Cl_2 = 1:1), yield: 77%, white solid, mp 61–63 °C, $[\alpha]_D^{25}$ = −290.0 (c 0.13, CH_2Cl_2). 92% ee determined by HPLC analysis (chiral OD-H column, 4% IPA in hexane, rate: 1.0 mL/min, 254 nm). Retention time: t(minor) = 29.6 min, t(major) = 41.8 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.64 (d, J = 16.1 Hz, 1H), 7.59–7.56 (m, 4H), 7.50–7.37 (m, 5H), 6.74 (d, J = 16.1 Hz, 1H), 3.63 (d, J = 17.0 Hz, 1H), 3.40 (d, J = 17.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 199.0, 145.8, 136.3, 135.0, 133.5, 131.6, 129.2, 128.8, 128.7, 127.9, 125.6, 124.3 (J = 283.2 Hz), 76.0 (J = 29.1 Hz), 42.1; ESI-HRMS for $C_{18}H_{14}ClF_3O_2$ $(M+Na)^+$: 377.0526, Found: 377.0529.

4.18. (*R*,*E*)-5-(4-Chlorophenyl)-6,6,6-trifluoro-5-hydroxy-1-(*p*-tolyl)hex-1-en-3-one 4p

R_f = 0.35 (PE/CH_2Cl_2 = 1:1), yield: 93%, white solid, mp 52–54 °C, $[\alpha]_D^{25}$ = −227.2 (c 0.18, CH_2Cl_2). 93% ee determined by HPLC analysis (chiral AD-H column, 5% IPA in hexane, rate: 1.0 mL/min, 254 nm). Retention time: t(minor) = 20.1 min, t(major) = 36.8 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.62–7.54 (m, 3H), 7.50–7.45 (m, 2H), 7.40–7.35 (m, 2H), 7.25–7.13 (m, 2H), 6.68 (d, J = 16.1 Hz, 1H), 3.60 (d, J = 16.9 Hz, 1H), 3.36 (d, J = 16.9 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 199.1, 146.0, 142.4, 136.3, 134.9, 130.8, 129.9, 128.9, 128.7, 127.9, 124.6, 124.3 (J = 283.1 Hz), 76.0 (J = 29.0 Hz), 41.9, 21.6; ESI-HRMS for $C_{19}H_{16}ClF_3O_2$ $(M+H)^+$: 369.0863, Found: 369.0856.

4.19. (*R*,*E*)-5-(4-Bromophenyl)-6,6,6-trifluoro-5-hydroxy-1-phenylhex-1-en-3-one 4q

R_f = 0.32 (PE/CH_2Cl_2 = 1:1), yield: 82%, white solid, mp 117–119 °C, $[\alpha]_D^{25}$ = −263.6 (*c* 0.20, CH_2Cl_2). 99% ee determined by HPLC analysis (chiral OD-H column, 2% IPA in hexane, rate: 1.0 mL/min, 254 nm). Retention time: *t*(minor) = 45.8 min, *t*(major) = 58.2 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.64 (d, *J* = 16.1 Hz, 1H), 7.59–7.57 (m, 2H), 7.55–7.43 (m, 7H), 6.74 (d, *J* = 16.1 Hz, 1H), 3.63 (d, *J* = 17.0 Hz, 1H), 3.39 (d, *J* = 17.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 199.0, 145.8, 136.8, 133.5, 131.6, 131.6, 129.2, 128.8, 128.2, 125.6, 124.3 (*J* = 283.2 Hz), 123.2, 76.2 (*J* = 29.1 Hz), 42.1; ESI-HRMS for $C_{18}H_{14}BrF_3O_2$ $(M+Na)^+$: 421.0021, Found: 421.0028.

4.20. (*R*,*E*)-6,6,6-Trifluoro-5-hydroxy-1-phenyl-5-(*p*-tolyl)hex-1-en-3-one 4r

R_f = 0.30 (PE/CH_2Cl_2 = 1:1), yield: 68%, white solid, mp 57–59 °C, $[\alpha]_D^{25}$ = −170.0 (*c* 0.21, CH_2Cl_2). 86% ee determined by HPLC analysis (chiral OD-H column, 5% IPA in hexane, rate: 1.0 mL/min, 254 nm). Retention time: *t*(minor) = 15.2 min, *t*(major) = 12.6 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.63 (d, *J* = 16.2 Hz, 1H), 7.59–7.57 (m, 2H), 7.52–7.38 (m, 5H), 7.22–7.14 (m, 2H), 6.74 (d, *J* = 16.1 Hz, 1H), 3.69 (d, *J* = 16.9 Hz, 1H), 3.38 (d, *J* = 16.8 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 199.4, 145.4, 138.6, 134.6, 133.6, 131.4, 129.2, 129.1, 128.8, 126.2, 125.8, 123.2 (*J* = 283.1 Hz), 76.2 (*J* = 29.0 Hz), 42.3, 21.1; ESI-HRMS for $C_{19}H_{17}F_3O_2$ $(M+H)^+$: 335.1253, Found: 335.1261.

4.21. (*S*,*E*)-6,6,6-Trifluoro-5-hydroxy-1-phenyl-5-(thiophen-2-yl)-hex-1-en-3-one 4s

R_f = 0.35 (PE/CH_2Cl_2 = 1:1), yield: 65%, pale yellow oil, $[\alpha]_D^{25}$ = −156.2 (*c* 0.20, CH_2Cl_2). 81% ee determined by HPLC analysis (chiral OD-H column, 3% IPA in hexane, rate: 1.0 mL/min, 254 nm). Retention time: *t*(minor) = 49.1 min, *t*(major) = 40.8 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.65 (d, *J* = 16.2 Hz, 1H), 7.60–7.58 (m, 2H), 7.48–7.42 (m, 3H), 7.34 (d, *J* = 5.1 Hz, 1H), 7.15 (d, *J* = 3.5 Hz, 1H), 7.02 (dd, *J* = 3.7, 5.0 Hz, 1H), 6.75 (d, *J* = 16.2 Hz, 1H), 3.62 (d, *J* = 16.7 Hz, 1H), 3.35 (d, *J* = 16.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 199.1, 145.8, 141.9, 133.6, 131.5, 129.1, 128.8, 127.1, 126.5, 125.8, 125.7, 123.9 (*J* = 283.1 Hz), 75.9 (*J* = 30.7 Hz), 42.9; ESI-HRMS for $C_{16}H_{13}F_3O_2S$ $(M+Na)^+$: 349.0490, Found: 349.0495.

4.22. (*R*,*E*)-1,1,1-Trifluoro-2-hydroxy-2-phenylnon-5-en-4-one 4t

R_f = 0.32 (PE/CH_2Cl_2 = 3:1), yield: 64%, colorless oil, $[\alpha]_D^{25}$ = −71.8 (*c* 0.28, CH_2Cl_2). 93% ee determined by HPLC analysis (chiral AD-H column, 1% IPA in hexane, rate: 1.0 mL/min, 254 nm). Retention time: *t*(minor) = 11.9 min, *t*(major) = 10.3 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.61–7.59 (m, 2H), 7.43–7.36 (m, 3H), 7.01–6.93 (m, 1H), 6.11 (d, *J* = 15.9 Hz, 1H), 3.54 (d, *J* = 16.8 Hz, 1H), 3.28 (d, *J* = 16.8 Hz, 1H), 2.28–2.22 (m, 2H), 1.58–1.49 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 199.5, 151.1, 137.7, 130.6, 128.7, 128.3, 126.3, 123.2 (*J* = 283.4 Hz), 76.2 (*J* = 28.8 Hz), 41.4, 34.6, 21.1, 13.6; ESI-HRMS for $C_{15}H_{17}F_3O_2$ $(M+H)^+$: 287.1181, Found: 287.1188.

4.23. (*R*,*E*)-1,1,1-Trifluoro-2-hydroxy-2-phenyldodec-5-en-4-one 4u

R_f = 0.30 (PE/CH_2Cl_2 = 3:1), yield: 64%, colorless oil, $[\alpha]_D^{25}$ = −90.8 (*c* 0.21, CH_2Cl_2). 92% ee determined by HPLC analysis (chiral OD-H column, 1% IPA in hexane, rate: 1.0 mL/min, 254 nm). Retention time: *t*(minor) = 10.9 min, *t*(major) = 9.4 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.61–7.59 (m, 2H), 7.43–7.36 (m, 3H), 7.01–6.94 (m, 1H), 6.11 (d, *J* = 15.9 Hz, 1H), 3.54 (d, *J* = 16.8 Hz, 1H), 3.27 (d, *J* = 16.8 Hz, 1H), 2.30–2.24 (m, 2H), 1.38–1.29 (m, 8H), 0.95–0.90 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 199.5, 151.4, 137.7, 130.4, 128.7, 128.3, 126.3, 123.2 (*J* = 282.9 Hz), 76.2 (*J* = 28.7 Hz), 41.4, 32.6, 31.5, 28.8, 27.8, 22.5, 14.0; ESI-HRMS for $C_{18}H_{23}F_3O_2$ $(M+Na)^+$: 351.1650, Found: 351.1656.

4.24. (*R*,*E*)-1,1,1-Trifluoro-2-hydroxy-7-methyl-2-phenyloct-5-en-4-one 4v

R_f = 0.30 (PE/CH_2Cl_2 = 3:1), yield: 80%, colorless oil, $[\alpha]_D^{25}$ = −103.0 (*c* 0.16, CH_2Cl_2). 92% ee determined by HPLC analysis (chiral AD-H column, 1% IPA in hexane, rate: 1.0 mL/min, 254 nm). Retention time: *t*(minor) = 10.3 min, *t*(major) = 8.6 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.61–7.59 (m, 2H), 7.43–7.38 (m, 3H), 6.93 (dd, *J* = 6.6, 16.0 Hz, 1H), 6.06 (d, *J* = 16.0 Hz, 1H), 4.18–4.14 (m, 1H), 3.55 (d, *J* = 16.8 Hz, 1H), 3.29 (d, *J* = 16.8 Hz, 1H), 2.00–1.91 (m, 1H), 1.11 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 199.9, 157.1, 137.7, 128.7, 128.3, 127.7, 126.3, 124.6 (*J* = 283.3 Hz), 76.2 (*J* = 28.8 Hz), 41.5, 31.3, 21.0; ESI-HRMS for $C_{15}H_{17}F_3O_2$ $(M+Na)^+$: 309.1181, Found: 309.1175.

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13. CCDC 981450 contains the Supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.can.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Center, 12 Union Road, Cambridge CB21EZ, UK. Fax: (+44) 1223 336033; or deposit@ccdc.cam.ac.uk.