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Note

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Abstract: In this work, we thoroughly investigated the effect of structural differentiation of a series of N, N-disubstituted chiral diamine ligands on the catalytic asymmetric aldol reactions between trifluoromethyl ketones and linear aliphatic ketones for the construction of chiral trifluoromethyl tertiary alcohols. A highly efficient primary-tertiary diamine ligand derived from (1R,2R)-1,2-diphenylethylenediamine was developed, which catalyzed the reactions with up to 99% yield and up to 94% enantioselectivity in the presence of *p*-toluenesulfonic acid

(TsOH) using toluene as solvent.

Keywords: organocatalytic asymmetric aldol reaction; primary-tertiary diamine; trifluoromethyl aromatic ketone; linear aliphatic ketone; tertiary alcohol

Ever since List,¹ Barbas,² and MacMillan³ reported their pioneering works on organocatalyzed enantioselective aldol reactions, a lot of effort has been made on the asymmetric organocatalysis and remarkable progress has been achieved.^{4,5} Although many strategies have been developed for the organocatalytic aldol reactions of aldehydes with ketones, it still remains challenging in the organocatalytic ketone-ketone cross-aldol reactions because of the steric hindrance and electronic constrain of ketones.⁶

Owing to the peculiar properties of the fluorine atom, organofluorine compounds are widely used in many fields of the modern society.⁷ More than 20% of medicinal and agrochemical products contain one or more fluorine atoms.⁸ In the big family, α trifluoromethyl tertiary alcohol compounds play an important role due to their bioactivities and stereoelectronic properties.⁹ Therefore, various kinds of transformations have been developed for the syntheses of α -trifluoromethyl tertiary alcohols.¹⁰ There is no doubt that the cross-aldol reactions of ketones with trifluoromethyl ketones could be considered as one of the most useful approaches for

the construction of chiral trifluoromethyl tertiary alcohols. However, until recently, only a few cross-aldol reactions of ketones with trifluoromethyl ketones have been reported. ¹¹⁻¹⁹

In 2005, Zhang and coworkers firstly reported the asymmetric aldol reactions between aliphatic methyl ketones and trifluoromethyl ketones catalyzed by chiral proline, which afforded only low to moderate enantioselectivities (up to 64%).¹¹ Other successful catalytic reaction systems with improved enantioselectivities have also been disclosed by Liu,¹² Yuan,¹³ Nakamura,¹⁴ Berkessel¹⁵ and Kokotos¹⁶ (Figure 1, I-V) with the use of chiral proline derived ligands. Although chiral diamines as organocatalysts have been widely explored in the past decade,^{20,21} examples of diamine-catalyzed asymmetric aldol reactions of ketones with trifluoromethyl ketones are few. In 2014, Liu and He reported the asymmetric aldol reactions of α , β unsaturated ketones with trifluoroacetophenone catalyzed by diamine VI with good to excellent yields and enantioselectivities, but no aliphatic ketone was reported.¹⁸ In the same year, Xu and coworkers used quinine-derived diamine VII in the catalytic asymmetric cross-aldol reactions between aliphatic ketones and trifluoromethyl ketones, obtaining the corresponding tertiary alcohol products with 65-89% ee values.19



Figure 1. Organocatalysts used in the asymmetric aldol reactions of trifluoromethyl ketones with ketones.

Inspired by the pioneers' works, we wondered if it was possible to develop a novel highly efficient diamine-catalyzed reaction system for the asymmetric aldol reactions of trifluoromethyl ketones with aliphatic ketones by structure modification of simple diamines (1R,2R)-1,2-diaminocyclohexane, (1R,2R)-1,2-diphenylethylenediamine and (R)-(+)-1,1'-binaphthyl-2,2'-diamine. To start our investigation, we firstly examined the reaction of 2,2,2-trifluoro-1-phenylethanone with acetone in the presence of 10 mol% of primary-primary diamine (1R,2R)-1,2-diaminocyclohexane **1a**, which proceeded smoothly to give 90% yield of desired tertiary alcohol product **3a** with only 20% *ee* value (Table 1, entry 1). Using N, N-dimethyl substituted primary-tertiray diamine **1b** as the catalyst, *ee* value of **3a** was improved to 44%. Further increasing the sizes of N, N-disubstituents (R¹ and R² groups) enhanced the enantioselectivity gradually in the order of methyl, ethyl and *n*-butyl groups (Table 1, entries 2-5).

However, the enantioselectivity was decreased with much bigger CH_2Bu and/or CH_2Ph groups (Table 1, entries 6-8). In addition, using N-monosubstituted primarysecondary diamine **1i** ($R^1 = CH_2Ph$ and $R^2 = H$) as the catalyst, racemic product was obtained (Table 1, entry 9). These results indicate that N, N-disubstituted groups with medium sizes are helpful for the improvement of enantioselectivity of this catalytic aldol reaction. The best result was obtained with the use of N-(CH_2)₅- disubstituted chiral ligand **1k**, giving the desired tertiary alcohol **3a** in 95% yield and 68% *ee* value (Table 1, entry 11).

Table 1. Optimization of the Reaction Conditions for the Asymmetric Aldol Reaction of 2,2,2-Trifluoroacetophenone with Acetone.^{*a*}

o o chiral ligand 1 or 2 (X mol%)) HO	$\mathbb{R}^{1}_{\mathbb{N}_{\mathbb{R}^{2}_{0}}}$	r Ph N_{R^2}
temperature, time, Solvent	Ph CF ₃		Ph ^{//} /NH ₂
1.0 mmol 10 equiv	3a	1	2

		n l	D ²	yield ^b	ee ^c			n1	D ²	yield ^b	ee ^c
entry	ligand	R	R ²	(%)	(%)	entry	ligand	R.	R	(%)	(%)
1	1a	Н	Н	90	20	11	1k	-(CH	[₂) ₅ -	95	68
2	1b	Me	Me	93	44	12	2a	Н	Н	85	44
3	1c	Me	<i>i</i> -Pr	85	40	13	2b	Me	Me	94	48
4	1 d	Et	Et	95	61	14	2c	Et	Et	95	66
5	1e	<i>n</i> -Bu	<i>n</i> -Bu	96	62	15	2d	Me	Et	93	65
6	1f	CH ₂ Bu	CH ₂ Bu	87	53	16	2e	<i>n</i> -Pr	<i>n</i> -Pr	92	66
7	1g	$\mathrm{CH}_2\mathrm{Bu}$	CH ₂ Ph	70	46	17	2f	-(CH	[₂) ₄ -	96	62
8	1h	$\mathrm{CH}_{2}\mathrm{Ph}$	$\mathrm{CH}_{2}\mathrm{Ph}$	53	24	18	2g	-(CH	[₂) ₅ -	97	70

9	1i	$\mathrm{CH}_{2}\mathrm{Ph}$	Η	93	1	19 ^{<i>d</i>}	2g	-(CH ₂) ₅ -	98	83
10	1j	-(CH	2)4-	95	58	20 ^{<i>d,e</i>}	2g	-(CH ₂) ₅ -	98	92

^{*a*} Unless otherwise noted, the reaction was carried out on 1 mmol scale, in the presence of 10 mol% chiral ligand and 10 mol% TFA in dry acetone (2 mL), at 0 $^{\circ}$ C ~ r.t., stirred for 10 h. ^{*b*} Isolated yield. ^{*c*} Determined by chiral HPLC. ^{*d*} Toluene (2 mL) was used as solvent. ^{*e*} TsOH (10 mol%) was used as acid, chiral ligand **2g** (5 mol%), stirred for 24 h at 0 $^{\circ}$ C.

Using (1R,2R)-1,2-diphenylethylenediamine **2a** as the chiral ligand, the desired product was obtained with 44% ee value and 85% yield (Table 1, entry 12), which indicates that the backbone of (1R, 2R)-1,2-diphenylethylenediamine is better than that of (1R,2R)-1,2-diaminocyclohexane in this aldol reaction. Then a series of N, Ndisubstituted (1R,2R)-1,2-diphenylethylenediamine ligands **2b-2g** were synthesized and evaluated (Table 1, entries 13-18). Unfortunately, these ligands did not improve the enantioselectivity of the aldol reaction dramatically compared with the ligands derived from (1R,2R)-1,2-diaminocyclohexane 1a. The best result was obtained with chiral ligand 2g, giving the desired product 3a in 97% yield and 70% ee value (Table 1, entry 18). In addition, (R)-(+)-2,2'-diamino-1,1'-binaphthalene could not promote the direct asymmetric aldol reaction of 2,2,2-trifluoro-1-phenylethanone with acetone at all. Therefore, by fine-tuning the structure of diamine ligands, chiral primarytertiary amine 2g was chosen as the optimum catalyst. To maximize the enantioselectivity, various reaction conditions including solvent, acid, the loading of reaction time further catalyst, and temperature were tested (see

Supporting information for details). Finally, the asymmetric catalytic aldol reaction was carried out in toluene with 5 mol% chiral primary-tertiary diamine **2g** and 10 mol% TsOH at 0 °C for 24 h, giving the tertiary alcohol product **3a** with 98% yield and 92% *ee* value as shown in entry 20 of Table 1.

With the optimized reaction conditions in hand, we next evaluated the applicability of the developed organocatalytic system and the results are summarized in Scheme 1. To our delighted, the reactions between acetone and various aryl trifluoromethyl ketones with either electron-rich or electron-deficient substituents gave products **3a**-**3h** in excellent yields (up to 99%) and good to excellent *ee* values (up to 94%). However, once the CF₃ group (**3a**) was replaced by less electon-withdrawing CF₂Cl group (**3i**), lower yield and enantioselectivity were observed (75% yield and 81% *ee* value). Using other aliphatic ketones, 2-butanone and 2-pentanone, the yields and *ee* values of the corresponding tertiary alcohol products (**3j** and **3k**) were also excellent.

Scheme 1. Enantioselective aldol reactions of fluoroalkylated ketones and linear aliphatic ketones.

$$\begin{array}{c} O \\ Ar \\ 1 \\ mmol \end{array} + \\ \begin{array}{c} O \\ R_{f} \\ 1 \\ mmol \end{array} + \\ \begin{array}{c} O \\ R_{r} \\ R_{r} \\ 10 \\ equiv \end{array} + \\ \begin{array}{c} 2g \\ TsOH (10 \\ mol\%) \\ toluene (2 \\ mL) \\ 0 \\ \circ C, 24 \\ h \end{array} + \\ \begin{array}{c} O \\ HO \\ R_{f} \\ 3a-3k \end{array}$$



In order to explain the excellent enantioselectivity of the direct asymmetric aldol reactions of trifluoromethyl ketones with linear aliphatic ketones, a possible reaction pathway was proposed on the basis of our experimental findings and previously published works in the field of asymmetric aldol reactions. The amine group of chiral ligand **2g** activated acetone by forming an enamine intermediate, while the trifluoromethyl carbonyl group was activated via hydrogen bonding interaction with the quaternary ammonium salt. A transition state, in which the enamine intermediate situated on the *Re*-face of trifluoroacetophenone was favored because the CF₃ group of trifluoroacetophenone preferred to the opposite position of the N-(CH₂)₅- group of

chiral diamine 2g for less steric repulsion to give (S)- product as shown in Figure 2.



Figure 2. Proposed transition states.

In conclusion, by fine-tuning the structure of simple diamines, we have developed a chiral primary-tertiary diamine ligand 2g from (1*R*,2*R*)-1,2-diphenylethylenediamine, which is highly efficient in the catalytic enantioselective cross-aldol reaction between linear aliphatic ketones and trifluromethyl ketones. Under optimized reaction conditions, excellent yields (up to 99%) and enantioselectivities (up to 94%) of the desired trifluoromethyl- β -hydroxy ketones were obtained. A possible transition state was also proposed.

Experimental Section

General Methods

All reactions were carried out under N_2 atmosphere in oven dried glassware with magnetic stirring unless otherwise noted. All solvents were purified prior to use according to the reported method. ²² ¹H NMR (400 MHz), ¹³C NMR (100 MHz) and ¹⁹F NMR (376 MHz) spectra were recorded in CDCl₃ solution using a 400 MHz spectrometer. Chemical shifts were reported in parts per million (ppm, δ) relative to CDCl₃ (δ 7.26 for ¹H NMR), or CDCl₃ (δ 77.0 for ¹³C NMR). Multiplicities are indicated as (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, coupling constants in Hz). All commercially available reagents were used without further purification unless otherwise noted. Optical rotations were measured on a polarimeter and reported as follows: [α]^T_D (c g/100 mL, solvent). HPLC analysis were performed using Chiralcel columns (Chiralcel OD-H, OJ-H, AD-H, and Chiralpak AS-H). High resolution mass spectra (HRMS) were measured on a LTQ FT-ICR mass spectrometer by using Matrix-Assisted Laser Desorption Ionization (MALDI).

Synthesis of chiral ligands 1b-1h, 1j-1k, 2b-2g.

Chiral ligands **1b**, **1d-1e** were synthesized according to the reported method. ^{21b} **1b**: colorless oil; 298 mg, 70% overall yield; $[\alpha]_{D}^{28.7}$ -32.1 (1.0, CHCl₃), ¹H NMR (400 MHz, CDCl₃): δ 0.48-0.79 (m, 4H), 1.12-1.55 (m, 7H), 1.71 (s, 6H), 1.98-2.13 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 19.5, 24.0, 24.6, 34.1, 39.0, 50.4, 68.7.

Chiral ligand 1d: colorless oil; 321 mg, 63% overall yield; [α]_D^{30.1} -140.2 (1.0, CHCl₃), ¹H NMR (400 MHz, CDCl₃): δ 0.90-1.00 (m, 6H), 1.01-1.26 (m, 4H), 1.51-1.77 (m, 3H), 1.77-2.13 (m, 4H), 2.18-2.37 (m, 2H), 2.40-2.63 (m, 3H); ¹³C NMR

(100 MHz, CDCl₃): δ 15.0, 23.1, 25.1, 26.0, 35.1, 43.3, 51.2, 66.4.

Chiral ligand **1e**: colorless oil; 352 mg, 52% overall yield; [α]_D^{29,9} -110.5 (1.0, CHCl₃), ¹H NMR (400 MHz, CDCl₃): δ 0.75-0.98 (m, 6H), 1.00-1.43 (m, 12H), 1.53-1.80 (m, 3H), 1.83-2.07 (m, 4H), 2.15-2.32 (m, 2H), 2.34-2.61 (m, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 14.1, 20.6, 22.8, 25.1, 26.0, 31.7, 35.1, 49.7, 51.3, 66.8.

Chiral ligand **1c** was synthesized according to the reported method.²³ Colorless oil; 178 mg, 35% overall yield; $[\alpha]_{D}^{29.1}$ -45.2 (c 1.00, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ 0.95-1.07 (m, 7H), 1.13-1.27 (m, 3H), 1.57-1.78 (m, 5H), 1.87-2.02 (m, 1H), 2.06-2.21 (m, 4H), 2.44-2.57 (m, 1H), 2.74-2.90 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 20.7, 21.2, 25.2, 25.8, 26.1, 30.9, 35.2, 51.4, 52.3, 66.8.

Chiral ligand **1f** was synthesized according to the reported method.²⁴ Colorless oil; 365 mg, 48% overall yield; [α]^{29.8}_D -80.5 (1.0, CHCl₃), ¹H NMR (400 MHz, CDCl₃): δ 0.73-0.98 (m, 6H), 1.02-1.48 (m, 17H), 1.57-1.87 (m, 3H), 1.93-2.14 (m, 2H), 2.22-2.60 (m, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 14.1, 22.6, 22.9, 25.1, 26.0, 29.2, 29.7, 34.9, 50.1, 51.3, 66.8.

Chiral ligand **1g** was synthesized according to the reported method.²⁵ Colorless oil; 354 mg, 43% overall yield; $[\alpha]_D^{29.8}$ -30.5 (1.0, CHCl₃), ¹H NMR (400 MHz, CDCl₃): δ 0.85 (t, *J* = 7.0 Hz, 3H), 1.11-1.29 (m, 8H), 1.37-1.51 (m, 2H), 1.61-1.70 (m, 1H), 1.74-1.83 (m, 1H), 1.86-1.94 (m, 1H), 1.95-2.08 (m, 1H), 2.21-2.25 (m, 1H),

2.31-2.42 (m, 1H), 2.44-2.54 (m, 1H), 2.60-2.68 (m, 1H), 2.71 (s, 2H), 3.35 (d, J = 13.8 Hz, 1H), 3.79 (d, J = 13.8 Hz, 1H), 7.17-7.35 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 14.1, 22.5, 22.8, 25.0, 25.8, 28.6, 29.6, 34.4, 49.7, 51.3, 54.3, 65.5, 126.7, 128.2, 128.7, 140.8.

Chiral ligand **1h** was synthesized according to the reported method.²⁶ Colorless oil; 590 mg, 67% overall yield; $[\alpha]_D^{29,8}$ -110.5 (1.0, CHCl₃), ¹H NMR (400 MHz, CDCl₃): δ 0.90-1.31 (m, 4H), 1.63-1.87 (m, 4H), 1.92-2.09 (m, 2H), 2.11-2.25 (m, 1H), 2.61-2.79 (m, 1H), 3.43 (d, J = 13.3 Hz, 2H), 3.86 (d, J = 13.3 Hz, 2H), 7.11-7.53 (m, 10H); ¹³C NMR (100 MHz, CDCl₃): δ 22.6, 25.2, 25.8, 35.0, 51.2, 53.8, 64.8, 126.9, 128.3, 128.9, 140.3.

Chiral ligand **1j-1k** was synthesized according to the reported method.²³ **1j**: Colorless oil; 302 mg, 60% overall yield; $[\alpha]_D^{29.8}$ -51.2 (1.0, CHCl₃), ¹H NMR (400 MHz, CDCl₃): 1.05-1.40 (m, 4H), 1.42-1.56 (m, 1H), 1.58-2.00 (m, 6H), 2.10-2.27 (m, 1H), 2.48-2.74 (m, 5H), 2.75-2.91 (m, 1H), 5.16 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 22.0, 23.6, 24.5, 24.8, 32.1, 47.3, 52.8, 62.6.

Chiral ligand **1k**: colorless oil; 355 mg, 65% overall yield; [α]_D^{29.8} -35.6 (1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 1.01-1.22 (m, 4H), 1.32-1.66 (m, 7H), 1.68-1.80 (m, 2H), 1.86-2.03 (m, 4H), 2.16-2.34 (m, 2H), 2.48-2.68 (m, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 22.6, 25.06, 25.11, 25.9, 26.9, 35.1, 49.7, 50.7, 71.2. Chiral ligand **2b** was synthesized according to the reported method.^{21b} Colorless oil; 288 mg, 40% overall yield; $[\alpha]_D^{20.7}$ -91.1 (1.0, CHCl₃), ¹H NMR (400 MHz, CDCl₃): δ 2.07 (s, 2H), 2.24 (s, 6H), 3.66 (d, *J* = 10.5 Hz, 1H), 4.45 (d, *J* = 10.5 Hz, 1H), 6.98-7.31 (m, 10H); ¹³C NMR (100 MHz, CDCl₃): δ 40.9, 55.6, 75.3, 126.8, 127.3, 128.0, 129.8, 134.0, 143.3.

Chiral ligand **2c** was synthesized according to the reported method.²⁷ Colorless oil; 442 mg, 55% overall yield; $[\alpha]_D^{29,7}$ -52.0 (1.0, CHCl₃), ¹H NMR (400 MHz, CDCl₃): δ 1.19 (t, J = 7.1 Hz, 6H), 2.14-2.26 (m, 2H), 2.41 (s, 2H), 2.77-2.98 (m, 2H), 3.89 (d, J = 10.6 Hz, 1H), 4.48 (d, J = 10.6 Hz, 1H), 6.98-7.36 (m, 10H); ¹³C NMR (100 MHz, CDCl₃): δ 14.4, 43.5, 55.8, 70.4, 126.7, 128.8, 127.5, 128.0, 128.1, 129.6, 136.1, 143.5.

Chiral ligand **2d** was synthesized according to the reported method.²⁸ Colorless oil; 365 mg, 48% overall yield; $[\alpha]_D^{29.7}$ -62.0 (1.0, CHCl₃), ¹H NMR (400 MHz, CDCl₃): δ 1.16 (t, J = 7.1 Hz, 3H), 2.23 (s, 3H), 2.28-2.37 (m, 3H), 2.45-2.59 (m, 1H), 3.78 (d, J = 10.6 Hz, 1H), 4.48 (d, J = 10.6 Hz, 1H), 7.00-7.32 (m, 10H); ¹³C NMR (100 MHz, CDCl₃): δ 13.7, 36.6, 47.9, 55.5, 74.3, 126.78, 126.85, 127.4, 128.0, 128.1, 129.7, 134.7, 143.3.

Chiral ligand **2e** was synthesized according to the reported method.²⁷ [α]_D^{29.1} -42.3 (c 1.00, CH₂Cl₂); 443 mg, 50% overall yield; ¹H NMR (400 MHz, CDCl₃): δ 1.10 (t,

J = 7.4 Hz, 6H), 1.56-1.71 (m, 4H), 2.12-2.22 (m, 2H), 2.42 (br, 2H), 2.59-2.72 (m, 2H), 3.85 (d, *J* = 10.6 Hz, 1H), 4.49 (d, *J* = 10.7 Hz, 1H), 7.03-7.23 (m, 8H), 7.25-7.33 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 12.1, 21.9, 51.9, 55.9, 70.9, 126.7, 126.8, 127.4, 127.9, 128.2, 129.7, 135.9, 143.6.

Chiral ligand **2f-2g** was synthesized according to the reported method.²⁸ Chiral ligand **2f**: Colorless oil; 535 mg, 67% overall yield; $[\alpha]_D^{29.7}$ -23.0 (1.0, CHCl₃), ¹H NMR (400 MHz, CDCl₃): δ 1.62-1.79 (m, 4H), 2.19 (s, 2H), 2.48-2.66 (m, 4H), 3.88 (d, J = 9.1 Hz, 1H), 4.48 (d, J = 9.1 Hz, 1H), 6.97-7.32 (m, 10H); ¹³C NMR (100 MHz, CDCl₃): δ 22.9, 49.0, 56.8, 72.5, 126.75, 126.84, 127.3, 127.88, 127.91, 129.9, 135.6, 143.4.

Chiral ligand **2g**: white solid, 868 mg, 62% overall yield; Mp 86-87 °C; $[\alpha]_D^{29.7}$ - 61.2 (1.0, CHCl₃), ¹H NMR (400 MHz, CDCl₃): δ 1.30-1.43 (m, 2H), 1.53-1.76 (m, 4H), 2.20 (s, 2H), 2.25-2.43 (m, 2H), 2.44-2.69 (m, 2H), 3.66 (d, J = 10.7 Hz, 1H), 4.51 (d, J = 10.7 Hz, 1H), 7.00-7.30 (m, 10H); ¹³C NMR (100 MHz, CDCl₃): δ 24.7, 26.7, 50.5, 55.0, 76.5, 126.8, 127.3, 128.0, 128.1, 129.6, 134.9, 143.4; Elemental Analysis: Anal. Calcd. for C₁₉H₂₄N₂: C 81.38, H 8.63, N 9.99, found: C 81.43, H 8.57, N 9.90; HRMS (MALDI): (m/z) calcd for C₁₉H₂₅N₂ [M+H]⁺: 281.2014, found: 281.2012.

Synthesis of (1*R*, 2*R*)-1-N-benzylcyclohexane-1,2-diamine 1i.



Compound 4 was prepared according to literature.²⁹

To a solution of 4 (732 mg, 3 mmol) in methanol (30 mL), benzaldehyde (350 mg, 3.3 mmol), molecular sieves (3 g) and three drops of glacial acetic acid were added. After the reaction mixture was stirred for 3 h, NaBH₃CN (473 mg, 7.5 mmol) was added at 0 °C, the reaction was allowed to warm to room temperature and stirred overnight. The molecular sieves were filtered and the solution was concentrated under reduced pressure to give a residue, which was dissolved in CH_2Cl_2 (30 mL) and washed by saturated Na₂CO₃ solution (30 mL). The organic solution was dried over anhydrous MgSO₄ and the solvent was removed under reduced pressure to afford 822 mg white solid, which was used in the next step without further purification. To the solution of the white solid in 10 mL ethanol, hydrazine monohydrate (1.21 mL, 25 mmol) was added and the reaction mixture was stirred at reflux (oil bath 70 °C) for 2 h. After the reaction mixture was cooled to room temperature, diethyl ether (30 mL) and CH₂Cl₂ (30 mL) were added to form precipitates which were removed by filtration. The filtrate was dried over anhydrous MgSO4 and the solvent was removed under reduced pressure to afford a crude product, which was subjected to silica gel column chromatography (MeOH/CH₂Cl₂ = 1/30) affording 373 mg (two steps, 61%) of **1i** as a colorless oil. [α]_D^{29.1} -22.7 (c 1.00, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ 0.95-1.33 (m, 4H), 1.66-1.76 (m, 5H), 1.80-1.94 (m, 1H), 2.04-2.19 (m, 2H), 2.33-2.46 (m, 1H), 3.68 (d, *J* = 13.0 Hz, 1H), 3.94 (d, *J* = 13.1 Hz, 1H), 7.13-7.46 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 25.2, 25.3, 31.4, 35.9, 51.1, 55.4, 63.2, 126.8, 128.1, 128.3, 128.9, 141.1. Elemental Analysis: Anal. Calcd. for C₁₃H₂₀N₂: C 76.42, H 9.87, N 13.71 Found: C 76.38, H 9.89, N 13.73.

Typical procedure for the catalytic asymmetric aldol reaction between 2,2,2-Trifluoroacetophenone with acetone catalyzed by ligand 2g.

Ph
$$CF_3^+$$
 CF_3^+ CF_3^+

To a solution of 2g (14 mg, 0.05 mmol) and TsOH (17 mg, 0.1 mmol) in anhydrous toluene (2 mL), trifluoroacetophenone (174 mg, 1.0 mmol) and acetone (580 mg, 10.0 mmol) were added at 0 °C and the resulting mixture was stirred for 24 h at that temperature. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc = 6: 1) to give 227 mg (98% yield) corresponding product **3a** as a colorless oil. The *ee* value was determined by chiral HPLC analysis.

(S)-5,5,5-trifluoro-4-hydroxy-4-phenylpentan-2-one (**3a**)¹⁶: Colorless oil. 227 mg,

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98% yield; 92% *ee* value was determined by HPLC Chiralcel OD-H column (Hexane/2-propanol = 97: 3, 1.0 mL/min, 210 nm) analysis, minor enantiomer $t_{\rm R}$ = 8.579 min, major enantiomer $t_{\rm R}$ = 12.152 min. [α]_D^{31.1} +25.0 (c 1.0, CHCl₃) [Literature ¹⁶ [α]_D +18.8 (c 0.4, CHCl₃) for 80% *ee* (*S*)]; ¹H NMR (400 MHz, CDCl₃): δ 2.20 (s, 3H), 3.21 (d, *J* = 17.2 Hz, 1H), 3.36 (d, *J* = 17.2 Hz, 1H), 5.44 (s, 1H), 7.32-7.43 (m, 3H), 7.51-7.61 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 32.1, 45.1, 76.0 (q, *J* = 29.1 Hz), 124.5 (q, *J* = 285.4 Hz), 126.1, 128.4, 128.8, 137.5, 208.9; ¹⁹F NMR (376 MHz, CDCl₃): δ -80.3 (s).

(*S*)-5,5,5-trifluoro-4-(4-fluorophenyl)-4-hydroxypentan-2-one (**3b**)¹⁶: Colorless oil. 240 mg, 96% yield; 87% *ee* value was determined by HPLC Chiralcel OJ-H column (Hexane/2-propanol = 90: 10, 1.0 mL/min, 210 nm) analysis, minor enantiomer $t_{\rm R}$ = 7.699 min, major enantiomer $t_{\rm R}$ = 9.960 min. [α]^{30.2} +21.6 (c 1.0, CHCl₃) [Literature¹⁶ [α]_D +15.2 (c 1.0, CH₂Cl₂) for 74% *ee* (*S*)]; ¹H NMR (400 MHz, CDCl₃): δ 2.20 (s, 3H), 3.22 (d, *J* = 17.4 Hz, 1H), 3.33 (d, *J* = 17.4 Hz, 1H), 5.57 (s, 1H), 6.96-7.15 (m, 2H), 7.45-7.62 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 31.8, 45.0, 75.7 (q, *J* = 29.2 Hz), 115.4 (d, *J* = 21.6 Hz), 124.4 (q, *J* = 285.3 Hz), 128.1 (d, *J* = 8.4 Hz), 133.4 (d, *J* = 2.9 Hz), 162.9 (d, *J* = 247.8 Hz), 208.9; ¹⁹F NMR (376 MHz, CDCl₃): δ -80.5 (s), -113.4 (s).

(S)-5,5,5-trifluoro-4-(4-(trifluoromethyl)phenyl)-4-hydroxypentan-2-one (3c)¹⁶:

Colorless oil. 246 mg, 82% yield; 93% *ee* value was determined by HPLC Chiralcel AS-H column (Hexane/2-propanol = 97: 3, 1.0 mL/min, 210 nm) analysis, minor enantiomer $t_{\rm R} = 6.342$ min, major enantiomer $t_{\rm R} = 7.968$ min. [α]_D^{31.1} +25.6 (c 1.0, CHCl₃) [Literature¹⁶[α]_D +7.5 (c 1.0, CH₂Cl₂) for 71% *ee* (*S*)]; ¹H NMR (400 MHz, CDCl₃): δ 2.25 (s, 3H), 3.26 (d, *J* = 17.5 Hz, 1H), 3.33 (d, *J* = 17.5 Hz, 1H), 5.59 (s, 1H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 8.5 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 31.9, 45.0, 75.9 (q, *J* = 29.6 Hz), 123.8 (q, *J* = 272.0 Hz), 124.2 (q, *J* = 285.0 Hz), 125.5 (q, *J* = 3.8 Hz), 126.7, 131.1 (q, *J* = 33.0 Hz), 141.5, 208.6; ¹⁹F NMR (376 MHz, CDCl₃): δ -62.8 (s), -80.1 (s).

(*S*)-4-(4-chlorophenyl)-5,5,5-trifluoro-4-hydroxypentan-2-one (**3d**)¹⁵: Colorless oil. 253 mg, 95% yield; 93% *ee* value was determined by HPLC Chiralcel OJ-H column (Hexane/2-propanol = 90: 10, 1.0 mL/min, 210 nm) analysis, minor enantiomer $t_{\rm R}$ = 7.146 min, major enantiomer $t_{\rm R}$ = 9.126 min. [α]^{30.9} +27.7 (c 1.0, CHCl₃) [Literature¹⁵[α]²⁰_D +22.8 (c 1.0, CHCl₃) for 92% *ee* (*S*)]; ¹H NMR (400 MHz, CDCl₃): δ 2.24 (s, 3H), 3.23 (d, *J* = 17.3 Hz, 1H), 3.32 (d, *J* = 17.3 Hz, 1H), 5.51 (s, 1H), 7.39 (d, *J* = 8.7 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 32.0, 45.0, 75.8 (q, *J* = 29.5 Hz), 124.3 (q, *J* = 285.9 Hz), 127.7, 128.7, 135.0, 136.1, 208.7; ¹⁹F NMR (376 MHz, CDCl₃): δ -80.4 (s).

(S)-4-(4-acetylphenyl)-5,5,5-trifluoro-4-hydroxypentan-2-one (3e): Colorless oil.

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230 mg, 84% yield; 87% *ee* value was determined by HPLC Chiralcel AS-H column (Hexane/2-propanol = 90: 10, 1.0 mL/min, 210 nm) analysis, minor enantiomer $t_{\rm R}$ = 13.607 min, major enantiomer $t_{\rm R}$ = 16.745 min. [α]^{30.8} +22.4 (c 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 2.20 (s, 3H), 2.58 (s, 3H), 3.24 (d, *J* = 17.3 Hz, 1H), 3.36 (d, *J* = 17.3 Hz, 1H), 5.53 (s, 1H), 7.66 (d, *J* = 7.9 Hz, 2H), 7.95 (d, *J* = 7.9 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 26.6, 31.9, 45.1, 76.0 (q, *J* = 29.3 Hz), 122.8, 125.7, 126.6, 128.4, 137.3, 142.5, 197.6, 208.6; ¹⁹F NMR (376 MHz, CDCl₃): δ -80.0 (s). Elemental Analysis: Anal. Calcd. for C₁₃H₁₃F₃O₃: C 56.94, H 4.78 Found: C 56.96, H 4.81.

(*S*)-5,5,5-trifluoro-4-hydroxy-4-*p*-tolylpentan-2-one (**3f**)¹⁶: White solid; Mp = 60-62 °C; 234 mg, 95% yield; 88% *ee* value was determined by HPLC Chiralcel OD-H column (Hexane/2-propanol = 97: 3, 1.0 mL/min, 210 nm) analysis, minor enantiomer $t_{\rm R} = 6.793$ min, major enantiomer $t_{\rm R} = 7.765$ min. [α]_D^{31.1} +20.8 (c 1.0, CHCl₃) [Literature¹⁶[α]_D +9.6 (c 0.5, CHCl₃) for 64% *ee* (*S*)]; ¹H NMR (400 MHz, CDCl₃): δ 2.21 (s, 3H), 2.37 (s, 3H), 3.18 (d, *J* = 17.1 Hz, 1H), 3.38 (d, *J* = 17.1 Hz, 1H), 5.41 (s, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 21.0, 32.1, 45.1, 76.0 (q, *J* = 29.2 Hz), 124.5 (q, *J* = 286.9 Hz), 126.1, 129.2, 134.5, 138.7, 209.0; ¹⁹F NMR (376 MHz, CDCl₃): δ -80.5 (s).

(S)-5,5,5-trifluoro-4-hydroxy-4-(4-methoxyphenyl)pentan-2-one $(3g)^{15}$: Colorless

oil. 254 mg, 97% yield; 94% *ee* value was determined by HPLC Chiralcel OD-H column (Hexane/2-propanol = 97: 3, 1.0 mL/min, 210 nm) analysis, minor enantiomer $t_{\rm R} = 10.574$ min, major enantiomer $t_{\rm R} = 10.917$ min. [α]^{30.8} +24.2 (c 1.0, CHCl₃) [Literature¹⁵ [α]²⁰_D +23.6 (c 1.0, CHCl₃) for 95% *ee* (*S*)]; ¹H NMR (400 MHz, CDCl₃): δ 2.18 (s, 3H), 3.16 (d, *J* = 17.0 Hz, 1H), 3.33 (d, *J* = 17.0 Hz, 1H), 3.80 (s, 3H), 5.39 (s, 1H), 6.75-6.95 (m, 2H), 7.39-7.52 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 32.1, 45.1, 55.2, 75.4, 75.8 (q, *J* = 29.3 Hz), 113.8, 124.6 (q, *J* = 284.3 Hz), 127.5, 129.4, 159.9, 209.0; ¹⁹F NMR (376 MHz, CDCl₃): δ -80.7 (s). (*S*)-5,5,5-trifluoro-4-hydroxy-4-(perfluorophenyl)pentan-2-one (**3h**)¹⁶: Colorless oil. 319 mg, 99% yield; 90% *ee* value was determined by HPLC Chiralcel AS-H

column (Hexane/2-propanol = 97: 3, 1.0 mL/min, 210 nm) analysis, minor enantiomer $t_{\rm R} = 4.743$ min, major enantiomer $t_{\rm R} = 5.981$ min. [α]^{30.6}_D +64.2 (c 1.0, CHCl₃) [Literature¹⁶[α]_D +10.8 (c 1.0, CHCl₃) for 54% *ee* (*S*)]; ¹H NMR (400 MHz, CDCl₃): δ 2.27 (s, 3H), 3.12 (dt, *J* = 3.6 Hz, *J* = 18.3 Hz, 1H), 3.79 (dt, *J* = 2.6 Hz, *J* = 18.3 Hz, 1H), 4.82 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 30.5, 46.5 (t, *J* = 6.0 Hz), 76.5 (q, *J* = 31.0 Hz), 110.0-148.0 (m), 206.8; ¹⁹F NMR (376 MHz, CDCl₃): δ -161.1 (m), -152.0 (tt, *J* = 4.1 Hz, 21.5 Hz), -138.3 (m), -81.8 (t, *J* = 8.2 Hz).

(S)-5-chloro-5,5-difluoro-4-hydroxy-4-phenylpentan-2-one (**3i**)¹⁶: Colorless oil. 186 mg, 75% yield; 81% *ee* value was determined by HPLC Chiralcel OD-H column

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(Hexane/2-propanol = 95: 5, 1.0 mL/min, 210 nm) analysis, minor enantiomer $t_{\rm R}$ = 7.096 min, major enantiomer $t_{\rm R}$ = 9.869 min. [α]_D^{31.1} +9.5 (c 1.0, CHCl₃) [Literature¹⁶ [α]_D +6.2 (c 1.0, CHCl₃) for 72% *ee* (*S*)]; ¹H NMR (400 MHz, CDCl₃): δ 2.18 (s, 3H), 3.25 (d, *J* = 17.0 Hz, 1H), 3.45 (d, *J* = 17.0 Hz, 1H), 5.55 (s, 1H), 7.32-7.47 (m, 3H), 7.54-7.65 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 32.1, 45.6, 79.5 (t, *J* = 25.5 Hz), 126.6, 128.3, 128.8, 130.2 (t, *J* = 299.1 Hz), 138.0, 209.1; ¹⁹F NMR (376 MHz, CDCl₃): δ -65.1 (d, *J* = 166.3 Hz), -64.3 (d, *J* = 166.3 Hz).

(*S*)-6,6,6-trifluoro-5-hydroxy-5-phenylhexan-3-one (**3j**)¹⁶: Colorless oil. 226 mg, 92% yield; 87% *ee* value was determined by HPLC Chiralcel OD-H column (Hexane/2-propanol = 97: 3, 1.0 mL/min, 210 nm) analysis, minor enantiomer $t_{\rm R}$ = 6.243 min, major enantiomer $t_{\rm R}$ = 7.292 min. [α]_D^{30.4} +18.5 (c 1.0, CHCl₃) [Literature¹⁶[α]_D +5.7 (c 1.0, CHCl₃) for 67% *ee* (*S*)]; ¹H NMR (400 MHz, CDCl₃): δ 1.00 (t, *J* = 7.3 Hz, 3H), 2.33-2.48 (m, 1H), 2.49-2.65 (m, 1H), 3.18 (d, *J* = 16.9 Hz, 1H), 3.30 (d, *J* = 16.9 Hz, 1H), 5.59 (s, 1H), 7.31-7.46 (m, 3H), 7.50-7.65 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 7.1, 38.2, 44.1, 75.9 (q, *J* = 29.0 Hz), 124.5 (q, *J* = 284.9 Hz), 126.1, 128.4, 128.8, 137.5, 211.8; ¹⁹F NMR (376 MHz, CDCl₃): δ -80.2 (s).

(S)-1,1,1-trifluoro-2-hydroxy-2-phenylheptan-4-one $(3k)^{30}$: Colorless oil. 247 mg, 95% yield; 88% *ee* value was determined by HPLC Chiralcel OD-H column (Hexane/2-propanol = 99.5: 0.5, 1.0 mL/min, 210 nm) analysis, minor enantiomer t_R = 10.735 min, major enantiomer $t_{\rm R}$ = 14.227 min. [α]^{31.1}_D +12.3 (c 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 0.83 (t, *J* = 7.4 Hz, 3H), 1.47-1.60 (m, 2H), 2.30-2.42 (m, 1H), 2.43-2.55 (m, 1H), 3.17 (d, *J* = 17.0 Hz, 1H), 3.31 (d, *J* = 17.0 Hz, 1H), 5.65 (s, 1H), 7.31-7.43 (m, 3H), 7.51-7.63 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 13.3, 16.5, 44.3, 46.7, 76.1 (q, *J* = 29.1 Hz), 124.6 (q, *J* = 285.5 Hz), 126.1, 128.4, 128.8, 137.6, 211.5; ¹⁹F NMR (376 MHz, CDCl₃): δ -80.2 (s).

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Supporting Information

The detailed conditions for optimization of the catalytic asymmetric aldol reaction; copies of NMR spectra (¹H, ¹³C and ¹⁹F) of chiral ligands and asymmetric aldol reaction products; copies of HPLC data of chiral aldol reaction products. This material is available free of charge via the Internet at <u>http://pubs.acs.org</u>.

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