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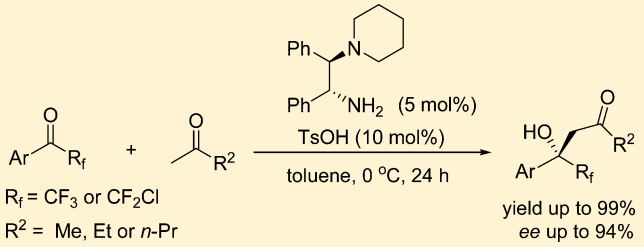
Fine-Tuning the Structures of Chiral Diamine Ligands in the Catalytic Asymmetric Aldol Reactions of Trifluoromethyl Aromatic Ketones with Linear Aliphatic Ketones

Hua Zong, Huayin Huang, Guangling Bian, and Ling Song*

The Key Laboratory of Coal to Ethylene Glycol and Its Related Technology, the State Key Lab of Structural Chemistry, Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences, Fuzhou, Fujian 350002, China

Supporting Information

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 (1*R*,2*R*)-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.



Ever since the List,[1] Barbas,[2] and MacMillan[3] groups 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 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 co-workers first 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 the Liu,[12] Yuan,[13] Nakamura,[14] and Berkessel[15] groups and Kokotos[16] (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, He and co-workers 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 co-workers 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]

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 (1*R*,2*R*)-1,2-diaminocyclohexane, (1*R*,2*R*)-1,2-diphenylethylenediamine, and (*R*)-(+)-1,1′-binaphthyl-2,2′-diamine. To start our investigation, we first examined the reaction of 2,2,2-trifluoro-1-phenylethanone with acetone in the presence of 10 mol % of primary−primary diamine (1*R*,2*R*)-1,2-diaminocyclohexane **1a**, which proceeded smoothly to give 90% yield of the desired tertiary alcohol product **3a** with only 20% *ee* value (Table 1, entry 1). Using *N*,*N*-dimethyl substituted primary−tertiary diamine **1b** as the catalyst, the *ee* value of **3a** was improved to 44%. Further increasing the sizes of N,N-disubstituents (R^1 and R^2 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 primary−secondary dia-

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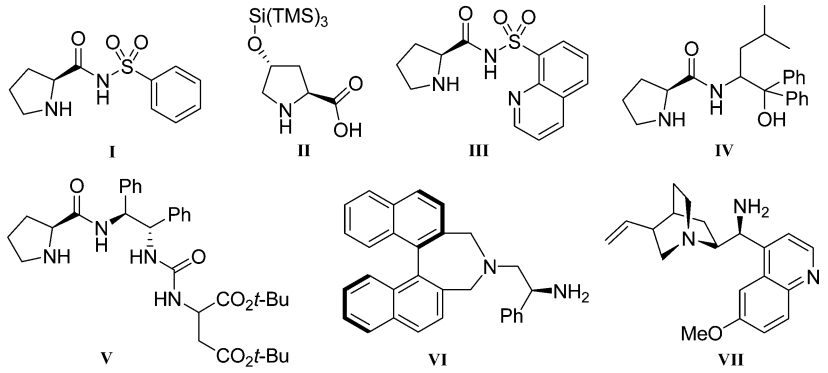
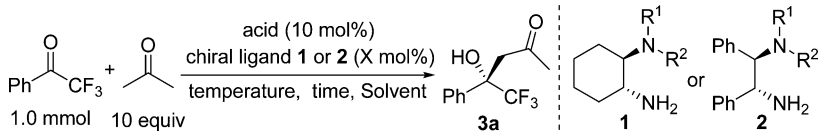


Figure 1. Organocatalysts used in the asymmetric aldol reactions of trifluoromethyl ketones with ketones.

Table 1. Optimization of the Reaction Conditions for the Asymmetric Aldol Reaction of 2,2,2-Trifluoroacetophenone with Acetone[a]



entry	ligand	R^1	R^2	yield[b] (%)	ee[c] (%)	entry	ligand	R^1	R^2	yield[b] (%)	ee[c] (%)
1	**1a**	H	H	90	20	11	**1k**	$-(CH_2)_5-$		95	68
2	**1b**	Me	Me	93	44	12	**2a**	H	H	85	44
3	**1c**	Me	*i*-Pr	85	40	13	**2b**	Me	Me	94	48
4	**1d**	Et	Et	95	61	14	**2c**	Et	Et	95	66
5	**1e**	*n*-Bu	*n*-Bu	96	62	15	**2d**	Me	Et	93	65
6	**1f**	CH_2Bu	CH_2Bu	87	53	16	**2e**	*n*-Pr	*n*-Pr	92	66
7	**1g**	CH_2Bu	CH_2Ph	70	46	17	**2f**	$-(CH_2)_4-$		96	62
8	**1h**	CH_2Ph	CH_2Ph	53	24	18	**2g**	$-(CH_2)_5-$		97	70
9	**1i**	CH_2Ph	H	93	1	19[d]	**2g**	$-(CH_2)_5-$		98	83
10	**1j**	$-(CH_2)_4-$		95	58	20[d,e]	**2g**	$-(CH_2)_5-$		98	92

[a]Unless otherwise noted, the reaction was carried out on a 1 mmol scale, in the presence of 10 mol % chiral ligand and 10 mol % TFA in dry acetone (2 mL), at 0 °C to 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 °C.

mine **1i** (R^1 = CH_2Ph and R^2 = H) as the catalyst, a 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).

Using (1*R*,2*R*)-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 (1*R*,2*R*)-1,2-diphenylethylenediamine is better than that of (1*R*,2*R*)-1,2-diaminocyclohexane in this aldol reaction. Then, a series of N,N-disubstituted (1*R*,2*R*)-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 (1*R*,2*R*)-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 primary−tertiary amine **2g** was chosen as the optimum catalyst. To maximize the enantioselectivity, various reaction conditions, including solvent, acid, the loading of catalyst, reaction time, and temperature, were further tested (see the 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 delight, 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 CF_3 group (**3a**) was replaced by the less electron-withdrawing CF_2Cl group (**3i**), a 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.

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

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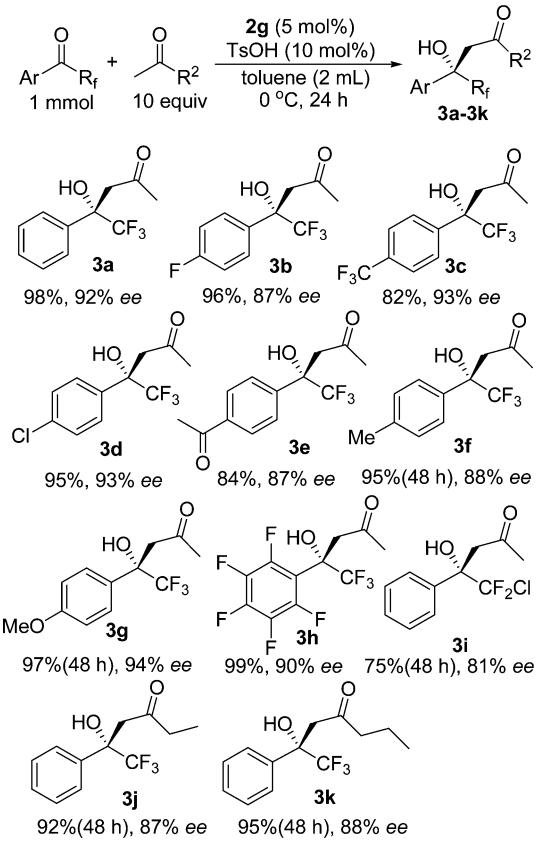
Scheme 1. Enantioselective Aldol Reactions of Fluoroalkylated Ketones and Linear Aliphatic Ketones



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 CF_3 group of trifluoroacetophenone preferred to the opposite position of the *N*-$(CH_2)_5$− group of chiral diamine **2g** for less steric repulsion to give the (*S*)-product as shown in Figure 2.

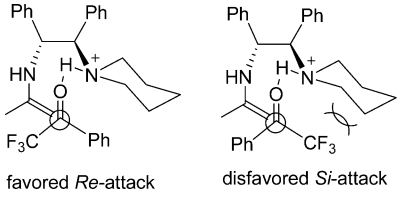


Figure 2. Proposed transition states.

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 trifluoromethyl 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 a 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] ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), and ^{19}F NMR (376 MHz) spectra were recorded in $CDCl_3$ solution using a 400 MHz spectrometer. Chemical shifts were reported in parts per million (ppm, δ) relative to $CDCl_3$ (δ 7.26 for ^{1}H NMR), or $CDCl_3$ (δ 77.0 for ^{13}C 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: $[\alpha]_D^T$ (*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 an 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 (*c* 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.48−0.79 (m, 4H), 1.12−1.55 (m, 7H), 1.71 (s, 6H), 1.98−2.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 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; $[\alpha]_D^{30.1}$ −140.2 (*c* 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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; $[\alpha]_D^{29.9}$ −110.5 (*c* 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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; $[\alpha]_D^{29.8}$ −80.5 (*c* 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 (*c* 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 (*c* 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6, 25.2, 25.8, 35.0, 51.2, 53.8, 64.8, 126.9, 128.3, 128.9, 140.3.

Chiral ligands **1j−1k** were synthesized according to the reported method.[23] **1j**: Colorless oil; 302 mg, 60% overall yield; $[\alpha]_D^{29.8}$ −51.2 (*c* 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): 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,

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5H), 2.75−2.91 (m, 1H), 5.16 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 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; $[\alpha]_D^{29.8}$ −35.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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; $[\alpha]_D^{29.7}$ −91.1 (*c* 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 (*c* 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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.

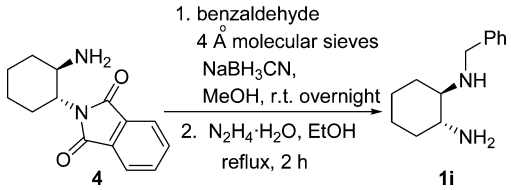
Chiral ligand **2d** was synthesized according to the reported method.[28] Colorless oil; 365 mg, 48% overall yield; $[\alpha]_D^{29.7}$ −62.0 (*c* 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16 (t, *J* = 7.1 Hz, 3H), 2.23 (s, 3H), 2.28−2.37 (m, 3H), 2.45−2.59 (m, 1H), 3.78 (d, *J* = 10.6 Hz, 1H), 4.48 (d, *J* = 10.6 Hz, 1H), 7.00−7.32 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): 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] $[\alpha]_D^{29.1}$ −42.3 (*c* 1.0, CH_2Cl_2); 443 mg, 50% overall yield; ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 ligands **2f**−**2g** were synthesized according to the reported method.[28] Chiral ligand **2f**: Colorless oil; 535 mg, 67% overall yield; $[\alpha]_D^{29.7}$ −23.0 (*c* 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 (*c* 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{19}H_{24}N_2$: 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 $C_{19}H_{25}N_2$ $[M + H]^+$: 281.2014, found: 281.2012.

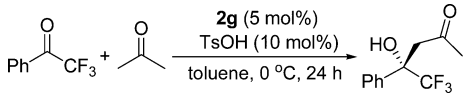
Synthesis of (1*R*, 2*R*)-1-*N*-Benzylcyclohexane-1,2-diamine 1i.



Compound **4** was prepared according to the 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, $NaBH_3CN$ (473 mg, 7.5 mmol) was added at 0 °C, and 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 with saturated Na_2CO_3 solution (30 mL). The organic solution was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to afford 822 mg of a white solid, which was used in the next step without further purification. To the solution of the white solid in 10 mL of 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 CH_2Cl_2 (30 mL) were added to form precipitates, which were removed by filtration. The filtrate was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to afford a crude product, which was subjected to silica gel column chromatography ($MeOH/CH_2Cl_2$ = 1/30) affording 373 mg (two steps, 61%) of **1i** as a colorless oil. $[\alpha]_D^{29.1}$ −22.7 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{13}H_{20}N_2$: 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.



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) of 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, 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_R = 8.579 min, major enantiomer t_R = 12.152 min. $[\alpha]_D^{31.1}$ +25.0 (*c* 1.0, $CHCl_3$) [Literature[16] $[\alpha]_D$ +18.8 (*c* 0.4, $CHCl_3$) for 80% *ee* (*S*)]; ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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; ^{19}F NMR (376 MHz, $CDCl_3$): 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_R = 7.699 min, major enantiomer t_R = 9.960 min. $[\alpha]_D^{30.2}$ +21.6 (*c* 1.0, $CHCl_3$) [Literature[16] $[\alpha]_D$ +15.2 (*c* 1.0, CH_2Cl_2) for 74% *ee* (*S*)]; ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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; ^{19}F NMR (376 MHz, $CDCl_3$): 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_R = 6.342 min, major enantiomer t_R = 7.968 min. $[\alpha]_D^{31.1}$ +25.6 (*c* 1.0, $CHCl_3$) [Literature[16] $[\alpha]_D$ +7.5 (*c* 1.0, CH_2Cl_2) for 71% *ee* (*S*)]; ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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; ^{19}F NMR (376 MHz, $CDCl_3$): 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

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mL/min, 210 nm) analysis, minor enantiomer t_R = 7.146 min, major enantiomer t_R = 9.126 min. $[\alpha]_D^{30.9}$ +27.7 (*c* 1.0, $CHCl_3$) [Literature[15] $[\alpha]_D^{20}$ +22.8 (*c* 1.0, $CHCl_3$) for 92% *ee* (*S*)]; ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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; ^{19}F NMR (376 MHz, $CDCl_3$): δ −80.4 (s).

(S)-4-(4-Acetylphenyl)-5,5,5-trifluoro-4-hydroxypentan-2-one ***(3e)***. Colorless oil; 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_R = 13.607 min, major enantiomer t_R = 16.745 min. $[\alpha]_D^{30.8}$ +22.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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; ^{19}F NMR (376 MHz, $CDCl_3$): δ −80.0 (s). Elemental Analysis: Anal. Calcd for $C_{13}H_{13}F_3O_3$: 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_R = 6.793 min, major enantiomer t_R = 7.765 min. $[\alpha]_D^{31.1}$ +20.8 (*c* 1.0, $CHCl_3$) [Literature[16] $[\alpha]_D$ +9.6 (*c* 0.5, $CHCl_3$) for 64% *ee* (*S*)]; ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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; ^{19}F NMR (376 MHz, $CDCl_3$): 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_R = 10.574 min, major enantiomer t_R = 10.917 min. $[\alpha]_D^{30.8}$ +24.2 (*c* 1.0, $CHCl_3$) [Literature[15] $[\alpha]_D^{20}$ +23.6 (*c* 1.0, $CHCl_3$) for 95% *ee* (*S*)]; ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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; ^{19}F NMR (376 MHz, $CDCl_3$): 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_R = 4.743 min, major enantiomer t_R = 5.981 min. $[\alpha]_D^{30.6}$ +64.2 (*c* 1.0, $CHCl_3$) [Literature[16] $[\alpha]_D$ +10.8 (*c* 1.0, $CHCl_3$) for 54% *ee* (*S*)]; ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.5, 46.5 (t, *J* = 6.0 Hz), 76.5 (q, *J* = 31.0 Hz), 110.0−148.0 (m), 206.8; ^{19}F NMR (376 MHz, $CDCl_3$): 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 (Hexane/2-propanol = 95:5, 1.0 mL/min, 210 nm) analysis, minor enantiomer t_R = 7.096 min, major enantiomer t_R = 9.869 min. $[\alpha]_D^{31.1}$ +9.5 (*c* 1.0, $CHCl_3$) [Literature[16] $[\alpha]_D$ +6.2 (*c* 1.0, $CHCl_3$) for 72% *ee* (*S*)]; ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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; ^{19}F NMR (376 MHz, $CDCl_3$): 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_R = 6.243 min, major enantiomer t_R = 7.292 min. $[\alpha]_D^{30.4}$ +18.5 (*c* 1.0, $CHCl_3$) [Literature[16] $[\alpha]_D$ +5.7 (*c* 1.0, $CHCl_3$) for 67% *ee* (*S*)]; ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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; ^{19}F NMR (376 MHz, $CDCl_3$): 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_R = 14.227 min. $[\alpha]_D^{31.1}$ +12.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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; ^{19}F NMR (376 MHz, $CDCl_3$): δ −80.2 (s).

■ ASSOCIATED CONTENT

Supporting Information

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

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: songling@fjirsm.ac.cn. Phone: + 86-591-83720913. Fax: +86-591-83722697 (L.S.).

Notes

The authors declare no competing financial interest.

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