Direct Asymmetric Aldol Reaction Catalyzed by C_2-Symmetrical Chiral Primary Amine Organocatalysts

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Abstract: Three novel C_2-symmetrical chiral primary amines were synthesized from chiral BINOL and diamines. Then their catalytic activities in the asymmetric aldol reactions were evaluated, and the result indicated that **1c** was the optimal organocatalyst. The reaction of a variety of aromatic aldehydes with aliphatic ketones, catalyzed by 20 mol % **1c** in the addition of benzoic acid in carbon tetrachloride, afforded the aldol products in high yields (up to 92%) and good enantioselectivities (up to 71%).

Keywords: Aldol reaction, asymmetric organocatalysis, chiral primary amine, C_2-symmetry, benzoic acid.

1. INTRODUCTION

The aldol reaction has long been recognized as one of the most fundamental tools for the construction of new carbon-carbon bonds [1]. Inspired by the exquisite stereocontrol in the enzymatic enamine processes, chemists have long been pursuing a simple chemical mimic for asymmetric enamine catalysis, and this aim has now been partially fulfilled with the renaissance of organocatalysis [2]. However, the most successful enamine organocatalysts mainly utilize secondary amines instead (e.g. chiral pyrrolidine derivatives) at present [3, 4]. In this context, exploration of efficient and stereoselective primary amine catalysts has become a much-attempted research endeavor [5]. Recently, simple primary amino acids and simple peptides having a *N*-primary amino group were found to act as effective catalysts for the direct asymmetric aldol reactions [6-9]. And we [10, 11] and other groups [12] have successfully demonstrated the effectiveness of chiral primary amine catalysts for the highly enantioselective aldol reactions for a broad spectrum of ketones. Although remarkable progress in effective chiral primary amine catalysts has been made in the past few years, new strategies regarding the design of novel primary amine catalysts with high efficiency and high stereoselectivity remains a challenge. Furthermore, primary amine organocatalysts with structural C_2-symmetry have not been disclosed in this transformation to date. This is a more interesting and greatly desired topic. Herein, we first report the preparation of three novel C_2-symmetrical chiral organocatalysts from the chiral BINOL and diamines and their effective application in aldol reaction.

2. RESULTS AND DISCUSSION

C_2-symmetrical primary amines (**1a-c**) were prepared from commercially available starting materials (*R*)-BINOL and corresponding Boc-protected chiral diamines according to the synthetic route shown in Scheme **1**. The hydroxyl groups of **2** were protected as methoxymethyl (MOM) ethers [4]. The resulting **3** was subjected to *ortho*-lithiation [13], followed by carboxylation to give the corresponding 3,3'-dicarboxylic acid (**4**). The diacid chlorides, which was readily prepared by exposure of diacid (**4**) to thionyl chloride, was successively treated with mono-Boc protected diamines (**5**) and then directly with TFA to give the corresponding C_2-symmetrical primary amine organocatalysts **1a-b**. When (*S*)-BINOL was used to be the starting reagent instead of (*R*)-BINOL, **1c** was achieved according to the same synthetic procedure as **1a-b** in the end.

Initially, the asymmetric catalytic activities of **1a-c** were tested in the model reaction of 4-nitrobenzaldehyde with acetone in the presence of 10 mol% catalyst at room temperature. The best catalytic efficiency was observed with **1c** (Table **1**, entry 4). Compounds **1a-b** exhibited lower catalytic activity and enantioselectivity (entries 5 and 6). As can be seen, 20 mol% acidic additive TFA (trifluoroacetic acid) was shown to be essential for effective catalysis. The reaction was very sluggish, affording only trace product if TFA was absent (Table **1**, entries 1-3). Both catalysts **1a** and **1b** could catalyze the reaction jointly with TFA, while **1c** gave the optimal results (Table **1**, entry 4). In comparison of **1a** with **1c**, both of them achieved the (*R*)-aldols. Therefore, it could be concluded that the asymmetric sense was determined by the chiral diamine moiety instead of the BINOL scaffold, and the catalyst **1c** from (*S*)-BINOL and (1*S*,2*S*)-cyclohexanediamine is the superior combination to **1a** from (*R*)-BINOL and the same diamine.

In order to further improve enantioselectivity, a series of acid additives were screened in the same model aldol reaction. These subsequent investigations revealed that benzoic acid served as the best additive, which was able to increase the enantioselectivity to 38% ee within a comparably short reaction time in comparison with TFA and other acidic additives (Table **1**, entry 9). With these results in mind, we next tried to evaluate the catalyst loading and the solvents. A notable improvement on the enantioselectivity was obtained when the catalyst loading changed from 10

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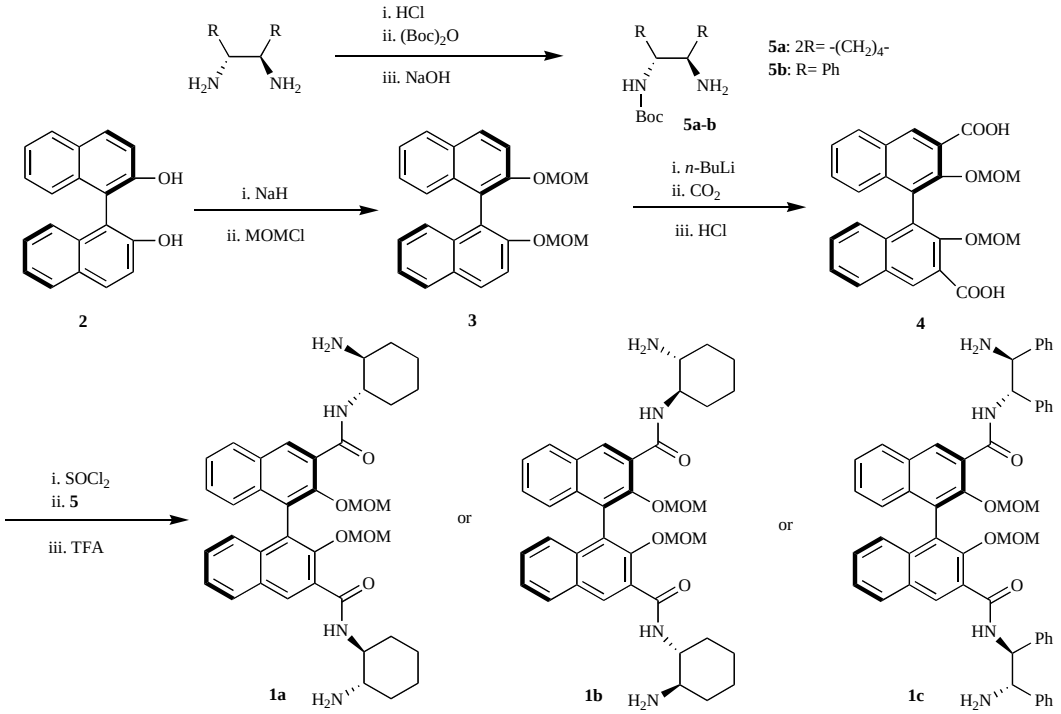
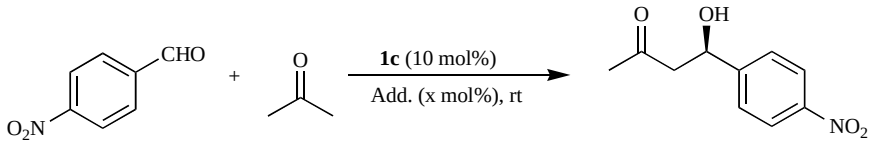


Scheme 1. Synthesis of catalysts **1a-c**.

Table 1. Screening of the Catalysts and Acidic Additives



Entry	Catalyst	Additive[a]	Time (h)	Yield (%)[b]	ee (%)[c]
1	**1a**	none	>144	<5	—
2	**1b**	none	>144	<5	—
3	**1c**	none	>144	<5	—
4	**1c**	TFA (20)	120	51	30
5	**1b**	TFA (20)	120	46	18
6	**1a**	TFA (20)	120	45	25
7	**1c**	DNP (20)	72	33	7
8	**1c**	CH_3COOH (20)	72	64	27
9	**1c**	C_6H_5COOH (20)	60	75	38
10	**1c**	HCOOH (20)	120	trace	—
11	**1c**	CCl_3COOH (20)	120	trace	—
12	**1c**	TsOH (20)	120	35	20
13	**1c**	C_6H_5COOH (5)	96	49	12
14	**1c**	C_6H_5COOH (10)	75	63	27
15	**1c**	C_6H_5COOH (15)	68	76	37
16	**1c**	C_6H_5COOH (30)	60	75	38

[a]Data in the parenthesis is the amount of the additive.
[b]Isolated yields.
[c]The ee values were determined by chiral HPLC on a AS-H column. The configuration was determined by the HPLC retention time or the sign of the optical rotation with the literature data [10a].

mol% to 20 mol%. However, further improvement was not obtained when the catalyst loading increased to 30 mol%; therefore 20 mol% was the preferred loading. CCl_4 was found superior over more polar solvents (Table **2**, entries 9-11). Under the optimized conditions, enantioselectivities of the other two catalysts were rechecked and **1c** was still revealed to exhibit the highest level of enantioselectivity (Table **2**, entries 12-13).

A number of aldol reactions were carried out under the optimized reaction conditions described above in the presence of 20 mol% **1c** in CCl_4. Examination of the results revealed that aldol processes promoted by **1c** were generally applicable to various aryl aldehyde acceptors (Table **3**, entries 1-11). The 3-nitro and 4-nitrobenzaldehyde afforded very similar yields and enantioselectivities in the reaction with acetone. It was worth noting that the reaction of butanone with 4-nitrobenzaldehyde yielded the aldol product with the highest 71% ee (Table **3**, entry 12). Surprisingly, the reaction of cyclopentanone with aromatic aldehydes displayed high yields but moderate enantioselectivities (Table **3**, entries 13-14). In general, the higher enantioselectivities were obtained with aldehydes carrying strong electron-withdrawing groups. Most of the halo-substituted benzaldehydes furnished the corresponding aldol products in high yields with good enantioselectivities (Table **3**, entries 6-8). When aliphatic aldehydes were used as substrates, no aldols were yielded.

Based on the disclosed speculations on the reactive mechanism of this transformation [8], transition state model analog was proposed in order to clarify the sense of the asymmetric induction of the catalyst **1c**. Both the amides and the hydroxy groups of the phenols would be probably hydrogen-bonded with the aldehyde to activate it. And the enamines, which were formed by the primary amines with acetone, would mainly attack the aldehyde from its *Re* face to predominantly afford the *R*-configuration aldol Fig. (**1**).

In conclusion, starting from commercially available chiral BINOL and diamines, three novel C_2-symmetrical chiral primary amine organocatalysts were readily prepared and then they were employed to catalyze the asymmetric aldol reactions of ketones and aromatic aldehydes. It was found that acidic additive contributed to high activity and enantioselectivity of **1c**; benzoic acid was the most optimized additive. In the addition of 20% benzoic acid, **1c** could successfully catalyze the reaction of several aliphatic ketones with aromatic aldehydes with high yields and moderate to good enantioselectivities.

3. EXPERIMENTAL SECTION

General

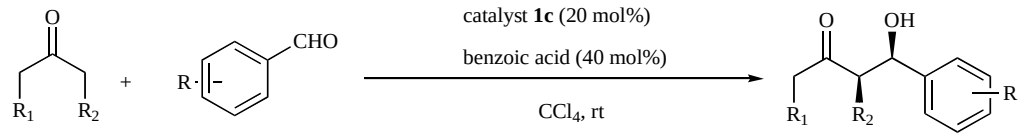
All chemicals were used as received unless otherwise noted. Reagent grade solvents were dried and distilled prior to use. All reported ^{1}H NMR spectra were collected on a Bruker AM-400 NMR and DRX-200 spectrometer with TMS as the internal reference. IR spectra were determined on a Nicolet Magna 550 instrument. High resolution mass spectra (HR-MS) were obtained on a Bruker APEX II instrument using the ESI technique. Chromatography was performed on silica gel (200–300 mesh). Melting points were determined using an X-4 apparatus. Optical rotations were determined on VtrZZ-I polarimeter. Enantiomeric excess was measured by a Waters 600 HPLC equipped with 2996 UV detector with Chiralpak AD-H, Chiralcel OJ-H or Chiralcel AS-H column.

Table 2. Optimization of the Solvents and the Loading of the Catalyst 1c[a]

Entry	Catalyst[b]	Solvent	Time (h)	Yield (%)[c]	ee (%)[d]
1	**1c** (10)	DMF	120	14	5
2	**1c** (10)	EtOH	80	50	51
3	**1c** (10)	MeOH	120	<5	23
4	**1c** (10)	THF	72	45	25
5	**1c** (10)	toluene	80	46	37
6	**1c** (10)	xylene	96	60	47
7	**1c** (10)	CH_2Cl_2	84	71	54
8	**1c** (10)	$CHCl_3$	84	70	50
9	**1c** (10)	CCl_4	40	86	52
10	**1c** (20)	CCl_4	28	91	61
11	**1c** (30)	CCl_4	28	90	58
12	**1a** (20)	CCl_4	30	83	56
13	**1b** (20)	CCl_4	36	82	53

[a]The reactions were performed under room temperature and 20% benzoic acid were added.
[b]Data in the parenthesis is the amount of the catalyst.
[c]Isolated yields.
[d]The ee values were determined by chiral HPLC on a AS-H column. The configuration was determined by the HPLC retention time or the sign of the optical rotation with the literature data [10a].

Table 3. Asymmetric Aldol Reactions of Ketones with Aromatic Aldehyde Catalyzed by 1c



Entry	R_1	R_2	R	Time (h)	Yield (%)[a]	Anti/syn[b]	ee (%)[c]
1	H	H	4-NO_2	26	92	–	61
2	H	H	3-NO_2	28	82	–	63
3	H	H	2-NO_2	28	82	–	50
4	H	H	2-OCH_3	96	25	–	59
5	H	H	3-OCH_3	96	57	–	51
6	H	H	2-Cl	55	61	–	57
7	H	H	3-Cl	96	91	–	60
8	H	H	2-Br	48	65	–	45
9	H	H	2-CF_3	48	88	–	59
10	H	H	1-Napthyl	65	44	–	49
11	H	H	2-Napthyl	66	83	–	56
12	H	CH_3	4-NO_2	72	87	1/1	71
13	$(-CH_2-)_2$		2-NO_2	24	90	1/1	55
14	$(-CH_2-)_2$		4-NO_2	20	91	1/2	36
15	CH_3	CH_3	4-NO_2	48	80	1/3	66

[a]Isolated yields.
[b]Determined by chiral HPLC.
[c]Determined by chiral HPLC. The configuration was assigned was determined by the HPLC retention time or the sign of the optical rotation with the literature data. And the anti/syn was determined by ^{1}H NMR [10a].

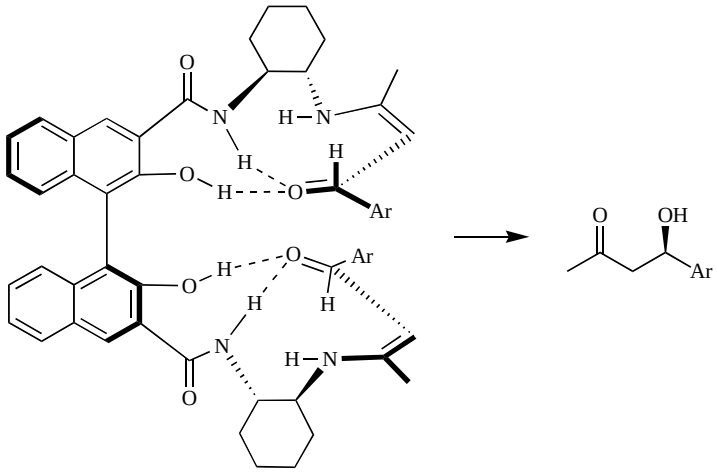


Fig. (1). Proposed transition state model.

General Procedure for the Preparation of mono-Boc Protection Of Diamine (5) [14]

To 150 mL cool MeOH at 0 °C, dry gaseous HCl (1.7 g) was slowly bubbled into with stirring for 15 min. The mixture was stirred for 15 min at room temperature and then carefully added into (1*S*,2*S*)-cyclohexanediamine (4.66 mmol) at 0 °C. The mixture was slowly warmed to room temperature and stirred for another 15 min before adding 5 mL H_2O and stiring further 0.5 h. Then the solution $(Boc)_2O$ (10.1 g, 4.66 mmol) in 20 mL MeOH was added dropwise at room temperature for 15 min, and the resulted solution was

stirred for 1h. The mixture was concentrated to dryness in vacuo and the unreacted diamine was removed by washing with the diethyl ether (30 mL) two times. The residue was treated with 2 N NaOH (50 mL) and extracted with CH_2Cl_2 (30 mL) three times. The combined organic extracts were washed with saturated brine, dried with Na_2SO_4, condensed in vacuo to afford the mono protected diamine, which was recrystallized from methanol-dichloromethane to furnish **5a** as a white crystal.

(1S,2S)-2-Aminocyclohexylcarbamic acid* tert-*butyl ester (5a)

White crystal: yield 78%; mp 114-115 ^oC; ^1H NMR (200 MHz, $CDCl_3$) δ 4.50 (m, 1H), 3.12 (m, 1H), 1.90 (m, 2H), 1.68 (m, 2H), 1.45 (s, 9H), 1.26 (m, 4H).

(1R, 2R)-2-Amino-1,2-diphenylcarbamic acid* tert-*butyl ester (5b)

Yellow power: yield 80%; mp 102-103 ^oC; ^1H NMR (200 MHz, $CDCl_3$) δ 7.22-7.38 (m, 10H), 5.78 (d, 1H), 4.34 (d, 1H), 1.28 (s, 9H).

General Procedure for the Preparation of (*R*)-2,2′-Bis(methoxymethoxy)-1,1′-binapthyl (3) [4]

To a solution of NaH (60% dispersion in mineral oil, 1.84 g, 46 mmol) in a solution of dry 80 mL THF and 40 mL DMF was added dropwise a solution of 5.90 g (*R*)-BINOL **2** (20.6 mmol) in 24 mL dry THF at 0 ^oC. After stirring for 1 h at room temperature, 6.0 mL chloromethyl methyl ether (MOMCl, 65 mmol) was introduced to the resultant mixture. A white precipitate immediately appeared and the reaction was further stirred for 4 h at room temperature. Then the reaction was quenched with cold water. Extracted the mixture with ethyl acetate three times, combined the organic layers, washed with little saturated brine, dried with Na_2SO_4, condensed in vacuo. The resultant residue was recrystallized with methanol to give the aimed product as a white crystal. 7.2 g, yield 94%; mp 103–104 ^oC; $[\alpha]_D^{20}$ +98 (*c* 0.9, THF); ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 9.2 Hz, 2H), 7.87 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.34 (t, *J* = 8.0 Hz, 2H), 7.25–7.20 (m, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 5.09 (d, *J* = 6.8 Hz, 2H), 4.97 (d, *J* = 6.8 Hz, 2H), 3.14 (s, 6H).

General Procedure for the Preparation of (R)-2,2′-dihydroxy-1,1′-binapthyl-3,3′- dicarboxylic acid (4)

To a solution of **3** (3 g, 8.01 mmol) in dry THF (40 mL) was added *n*-BuLi (15.3 mL, 24.0 mmol) at 0 ^oC, dry CO_2 was carefully bubbled until completion of the reaction monitored by TLC. The aqueous layer was washed by ether and then acidified to pH 2.0 with 5% aqueous HCl. The acidic aqueous layer was extracted with ethyl acetate. The combined organic phase was washed with water, saturated brine, dried over $MgSO_4$ and concentrated under reduced pressure. To the crude residue in THF (10 mL) was added saturated HCl in *i*-PrOH (20 mL) and this mixture was kept for 4 h at room temperature. After removal of solvent, the residue was partitioned into ethyl acetate and water. The organic layers was washed with water, dried over $MgSO_4$ and concentrated. The residue was triturated with $CHCl_3$ to give a yellow powder collected by filtration (1.96 g, yield 66%). This material was used for the next step without further purification. Mp > 290 ^oC; $[\alpha]_D^{18}$ -187 (*c* 1.1, pyridine); ^1H NMR (400 MHz, acetone-d_6) δ: 10.99 (s, 2H), 8.81 (s, 2H), 8.08 (m, 2H), 7.38 (m, 6H), 7.13 (s, 2H).

General Procedure for the Preparation of *C*$_2$-symmetrical primary diamine organocatalysts (1)

A solution of the dicarboxylic acid **3** (0.822 g, 2.2 mmol) in thionyl chloride (10 mL) was refluxed for 4 h. After removal of thionyl chloride by distillation under reduced pressure, the resulted acid chloride was dissolved in CH_2Cl_2 (5 mL). The mixture was added to a stirred solution of **5** (4.0 mmol) and triethylamine (1.6 mL, 12 mmol) in dichloromethane (40 mL) at 0 ^oC. After stirred for 4 h at room temperature, the mixture was acidified to pH 2 with 5% aqueous HCl and extracted with dichloromethane two times. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Then the residue was purified on silica gel (petroleum ether /ethyl acetate = 4:1, v/v) to give a yellow solid product. Deprotection of the Boc group was performed by using TFA for 2 h at room temperature. After evaporation of TFA, the residue was basified to pH 8 with 5% aqueous $NaHCO_3$ and extracted with dichloromethane three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give the catalyst **1** as a yellow solid.

N,N′-Bis[(1S,2S)-(2-amino)]cyclohexyl-(R)-2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamide (1a)

Yellow powder, 498 mg, yield 88%; mp > 300 ^oC; $[\alpha]_D^{20}$ = –117 (*c* 1.0, DMSO), IR (KBr, cm^{-1}): 3349, 3321, 1643, 1619; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.41 (s, 2H), 7.95 (d, 2H), 7.25-7.50 (m, 28H), 5.49 (d, 2H), 4.91 (d, 2H), 1.90-2.08 (m, 2H); ^{13}C NMR (200 MHz, $CDCl_3$) δ: 167.4, 158.2, 135.5, 130.1, 129.2, 126.5, 125.6, 125.0, 122.0, 121.6, 119.1, 53.7, 52.1, 40.6, 40.2, 39.8, 39.4, 39.0, 38.5, 38.1, 31.5, 31.2, 24.3, 23.6; HR- MS: cacld for $C_{34}H_{38}N_4O_4$ $(M + H)^+$ 567.2966, found 567.2976.

N,N′-Bis[(1R,2R)-(2-amino)]diphenyl-(R)-2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamide (1b)

Yellow powder, 543 mg, yield 89%; mp > 300 ^oC; $[\alpha]_D^{20}$ = + 26 (*c* 2.0, $CHCl_3$), IR (KBr, cm^{-1}): 3379, 1647, 1619; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.49 (s, 2H), 7.83-7.86 (d, 2H), 6.83-7.11 (m, 4H), 6.76-6.78 (d, 2H), 5.15-5.27 (br, 2H), 2.69-2.71 (m, 2H) 1.90-2.08 (m, 2H), 1.19-1.45 (m, 16H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 169.2, 154.3, 141.5, 140.2, 141.5, 140.2, 136.2, 24.7, 123.7, 117.4, 117.0, 77.3, 77.0, 76.67, 59.6, 58.6; HR- MS: cacld for $C_{50}H_{42}N_4O_4$ $(M + H)^+$ 763.3279, found 763.3270.

N,N′-Bis[(1S,2S)-(2-amino)]cyclohexyl-(S)-2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarbox -amide (1c)

Yellow powder, 498mg, yield 88%; mp > 300 ^oC; $[\alpha]_D^{20}$ = + 266 (*c* 2.0, DMSO), IR (KBr, cm^{-1}): 3349, 3321, 1643, 1619; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.59 (s, 2H), 7.86 (d, 2H), 7.08 (m, 4H), 6.79 (d, 2H), 3.72-4.23 (m, 2H), 2.85 (m, 2H) 1.95 (m, 2H), 1.01-1.65 (m, 16H); ^{13}C NMR (200 MHz, $CDCl_3$) δ: 167.4, 158.2, 135.5, 130.1, 129.2, 126.5, 125.6, 125.0, 122.0, 121.6, 119.1, 53.7, 52.153, 40.6, 40.2, 39.8, 39.4, 39.0, 38.5, 38.1, 31.5, 31.2, 24.3, 23.6; HR- MS: cacld for $C_{34}H_{38}N_4O_4$ $(M + H)^+$ 567.2966, found 567.2976.

General Procedure for Asymmetric Aldol Reaction of Ketone (Acetone, Butanone, 3-pentanone and Cyclopentanone) with Aldehydes

In a mixture of **1c** (0.02 mmol), benzoic acid (0.04 mmol) and ketone (acetone, butanone, 3-pentanone and cyclopentanone, respectively) (1 mmol) in CCl_4 (1 mL), aldehyde (0.1 mmol) was added and then stirred at room temperature until the reaction was completed as judged by TLC. Then 5.0 mL saturated aqueous NH_4Cl was added and the mixture was extracted with ethyl acetate three times. Then the organic layers were combined, dried with anhydrous Na_2SO_4, concentrated to dryness under reduced pressure, purified by preparative TLC or column to achieve the aldol product.

4-Hydroxyl-4-(4-nitrophenyl)-butan-2-one [10a]

^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.20 (m, 2H), 7.55 (m, 2H), 5.26 (s, 1H), 3.58 (bs, 1H), 2.85 (m, 2H), 2.22 (s, 3H); HPLC: Chiralcel AS-H, hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, retention time: major peak 17.4 min ((*R*)-isomer), minor peak 23.4 min ((*S*)-isomer).

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