JOC Article

2,4-Dinitrophenol as an Effective Cocatalyst: Greatly Improving the Activities and Enantioselectivities of Primary Amine Organocatalysts for Asymmetric Aldol Reactions

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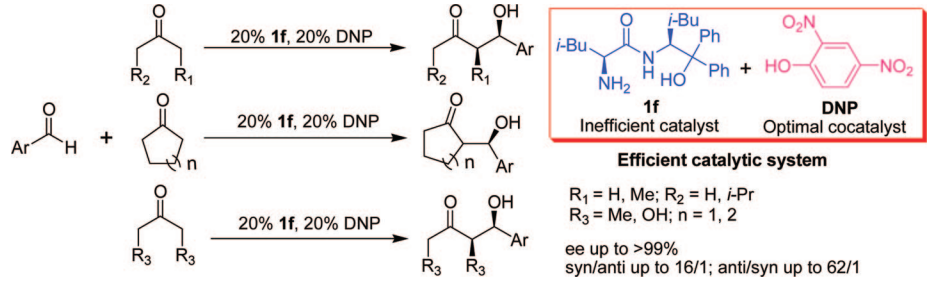

Seven primary amine organocatalysts **1a**−**g** were readily prepared from natural primary amino acids via two steps and then were used to catalyze the direct asymmetric aldol reaction, but they showed very poor enantioselectivities and activities. As an effective cocatalyst, 2,4-dinitrophenol (DNP) dramatically elevated the activities and enantioselectivities of these very inefficient primary amine organocatalysts. This remedial course to the very inefficient organocatalysts by selection and employment of the optimal cocatalyst was particularly cost-effective and environment-beneficial compared with de novo development of catalysts. The highest efficient organocatalytic system that was composed of **1f** and DNP showed high enantioselectivities and good to high diastereoselectivities with a broad spectrum of seven ketones. The linear ketones and cyclopentanone got predominant syn products whereas cyclohexanone mainly gave anti products.

Introduction

Catalytic asymmetric synthesis is now the most popular and important protocol to synthesize optically active compounds.[1] The development of efficient chiral catalysts is crucial to a successful catalytic asymmetric course. However, not all chemists have the good fortune to always obtain satisfying catalysts from design and synthesis. Even one optimal catalyst is probably not obtained on occasion. This occasion will probably result in throwing off those "useless" catalysts, and lead to redesign and synthesis of compounds to search for efficient catalysts again. So the used materials and energy are vainly wasted, and new harmful effects on the environment will probably be produced because of the discarded catalysts.[2] Instead of redesign and synthesis of compounds, we can learn from enzymes, the particularly efficient biological catalysts, to improve the efficiencies of the inefficient catalysts. Many enzymatic proteins exhibit high activities and enantioselectivities only when they are combined with coenzymes, such as coenzymes I and II (nicotinamide adenine dinucleotide (NADH) and the phosphate derivative (NADPH)), and are indispensable for the high efficiencies of hydrogenase and dehydrogenase.[3] We could obtain instructive inspiration from the enzymatic systems, which consist of apoenzymes and effective coenzymes, to achieve high

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activities and enantioselectivities by introduction and selection of proper commercially or readily available additives to the catalysts. Improvement of the activities and enantioselectivities via such a remedial course should be cost-effective and environmentally benign when compared with de novo development of catalysts. Some groups have already documented that proper additives could effectively increase the efficiencies of chiral catalysts.[4] Herein we disclose that the cocatalyst DNP remarkably improved the efficiencies of a series of very inefficient primary amine organocatalysts for the asymmetric aldol reaction.

The asymmetric aldol reaction is one of the most useful chiral C−C bond-forming reactions because it can produce versatile biologically active intermediates.[5] Three protocols, which are of biological catalysts,[6] chiral metal-involved catalysts especially zinc-involved catalysts,[7] and chiral organocatalysts,[8] have been successfully developed in the direct asymmetric aldol reaction. Among them, the organocatalytic asymmetric direct aldol reaction is currently particularly interesting and important because it has no metal, is environmentally friendly, and small chiral organocatalysts are readily prepared from natural amino acids and other available chiral amines. The explosive excellent results have promoted the organocatalytic asymmetric aldol reaction to rapidly grow to adolescence[9] after the first successful report on the direct aldol condensation catalyzed by L-proline.[10] Most of the successful organocatalysts are secondary amine organocatalysts, which are mainly derived from chiral secondary amines such as L-proline.[11] However, primary amine organocatalysts are quite seldom used in this reaction and so still in their infancies.[12] To date, the reported successful primary amine organocatalysts could mainly catalyze highly enantioselective aldol reactions of cycloketones[13] and protected or unprotected hydroxy and dihydroxy acetones.[14] But for methyl alkyl ketones, good results with high enantioselectivities are quite rare.[15] Only Luo and co-workers reported a highly efficient primary amine catalyst derived from (1*R*,2*R*)-cyclohexanediamine with a broad spectrum of ketones.[15d,16] Compared with the great success of secondary amine organocatalysts with a broad spectrum of substrates, primary amine organocatalysts from natural acyclic amino acids have not been reported in the highly enantioselective aldol reaction of methyl alkyl ketones such as acetone to date although all of the 20 natural amino acids are primary amino acids except for L-proline. It was believed that the stereoselectivity of acyclic amino acids had played a role in the origins of biological homochirality in carbohydrates and the evolution of aldolase enzymes.[17] And it has been clarified that the type I aldolase has a catalytic primary amine group of a strictly conserved L-lysine residue in its active site such as the fructose-1,6-bisphosphate aldolase.[6] Primary amine organocatalysts from primary amino acids should have more important, broad, and successful applications in aldol reactions. So development of highly efficient primary amine organocatalysts especially from abundant primary amino acids with a broad spectrum of ketones is more difficult and desired. We initially focused on this very interesting and challenging topic, and designed a series of primary amine organocatalysts from natural acyclic amino acids.

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SCHEME 1. Synthesis of the Catalysts 1a−g

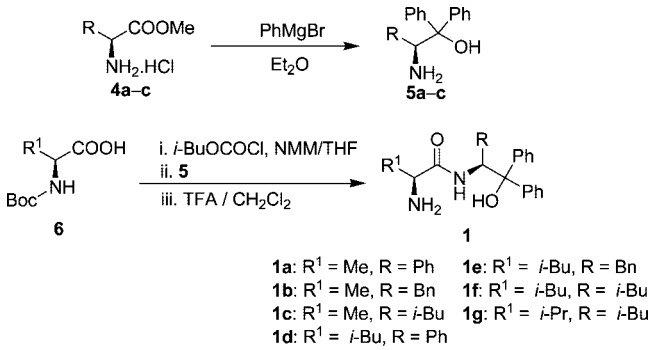

TABLE 1. Organocatalytic Asymmetric Aldol Reaction of Acetone with 4-Nitrobenzaldehyde[a]

entry	catalyst (%)[b]	additive (%)[c]	time (h)	yield (%)[d]	ee (%)[e]
1	**1a** (10)		65	nd	43
2	**1b** (10)		65	nd	49
3	**1c** (10)		65	nd	49
4	**1d** (10)		50	nd	30
5	**1e** (10)		50	nd	46
6	**1f** (10)		50	nd	56
7	**1g** (10)		50	nd	37
8	**1f** (10)	F_3CCOOH (10)	60	nd	82
9	**1f** (10)	CH_3COOH (10)	67	nd	86
10	**1f** (10)	F_3CSO_3H (10)	100	nd	79
11	**1f** (10)	CH_3SO_3H (10)	100	nd	75
12	**1f** (10)	*p*-nitrophenol (10)	100	nd	87
13	**1f** (10)	$ClCH_2COOH$ (10)	18	66	87
14	**1f** (10)	**DNP (10)**	**14**	**78**	**93**
15	**1f** (10)	HCOOH (10)	45	62	87
16	**1f** (10)	PhCOOH (10)	45	nd	77
17	**1f** (10)	salicylic acid (10)	18	64	88
18	**1f** (10)	EtCOOH (10)	50	nd	75
19	**1f** (10)	**Cl_3CCOOH (10)**	**50**	**67**	**92**
20	**1f** (10)	(±)-BINOL (10)	53	nd	61
21	**1f** (10)	(*S*)-BINOL (10)	53	nd	53
22	**1a** (10)	DNP (10)	22	72	79
23	**1b** (10)	DNP (10)	22	83	82
24	**1c** (10)	DNP (10)	22	86	89
25	**1d** (10)	DNP (10)	22	65	89
26	**1e** (10)	DNP (10)	22	62	91
27	**1g** (10)	DNP (10)	46	50	87

[a] The reaction was performed in acetone at room temperature. [b] Datum in parentheses is the used amount of catalyst. [c] Datum in parentheses is the used amount of additive. [d] Isolated yield; nd = "not determined". [e] Determined by chiral HPLC. The configuration was determined by the HPLC retention time or the sign of the optical rotation with the literature data.[11,15]

Results and Discussion

Seven organocatalysts **1a−g** were readily prepared by use of the routine mixed anhydrous method to condense the Boc-protected amino acids **6** with the diphenyl aminoalcohols **5a−c**, and successive deprotection of the Boc group with TFA (Scheme 1).[11c] Then they were employed to catalyze the typical model aldol reaction of acetone with 4-nitrobenzaldehyde (Table 1). However, the results were very disappointing to us when compared with the mostly used secondary amine organocatalysts (entries 1−7). The enantioselectivities were varied from the lowest 30% for **1d** (entry 4) to the highest 56% for **1f** (entry 6). Furthermore, the reactions promoted by these catalysts were quite sluggish. Design of these catalysts seemingly gave a failing result. Inspired by the great functions of coenzymes in enzymes and the successful reports of additives by research groups,[4] we experimented with a series of additives to improve the activities and enantioselectivities of these inefficient organocatalysts.

TABLE 2. Further Optimization of the Asymmetric Aldol Reaction

entry	catalyst[a]	additive[b]	solvent	temp (°C)	time (h)	yield (%)[c]	ee (%)[d]
1	**1f** (1)	DNP (1)	acetone	rt	200	nd	91
2	**1f** (5)	DNP (5)	acetone	rt	36	nd	93
3	**1f** (12)	DNP (12)	acetone	rt	12	72	93
4	**1f** (15)	DNP (15)	acetone	rt	8	nd	93
5	**1f** (20)	DNP (20)	acetone	rt	7	82	93
6	**1f** (20)	DNP (20)	acetone	0	22	85	95
7	**1f (20)**	**DNP (20)**	acetone	−10	**26**	**82**	**96**
8	**1f** (10)	DNP (10)	H_2O	rt	57	62	82
9	**1f** (10)	DNP (10)	DMF	rt	94	45	83
10	**1f** (10)	DNP (10)	DMSO	rt	90	nd	nd
11	**1f** (10)	DNP (10)	MeOH	rt	90	50	86
12	**1f** (10)	DNP (10)	EtOH	rt	84	63	88
13	**1f** (10)	DNP (10)	MeCN	rt	132	59	86
14	**1f** (10)	DNP (10)	acetone	rt	**14**	**78**	**93**
15	**1f** (10)	DNP (10)	THF	rt	57	46	88
16	**1f** (10)	DNP (10)	Et_2O	rt	68	45	81
17	**1f** (10)	DNP (10)	CH_2Cl_2	rt	132	nd	73
18	**1f** (10)	DNP (10)	xylene	rt	26	73	91
19	**1f** (10)	DNP (10)	toluene	rt	102	47	73
20	**1f** (10)	DNP (10)	hexane	rt	36	56	88
21	**1a** (20)	DNP (20)	acetone	−10	20	83	90
22	**1b** (20)	DNP (20)	acetone	−10	30	84	90
23	**1c** (20)	DNP (20)	acetone	−10	30	74	92
24	**1d** (20)	DNP (20)	acetone	−10	20	79	92
25	**1e** (20)	DNP (20)	acetone	−10	50	80	92
26	**1g** (20)	DNP (20)	acetone	−10	50	75	88

[a] Datum in parentheses is the used amount of catalyst. [b] Datum in parentheses is the used amount of additive. [c] Isolated yield; nd = "not determined". [d] Determined by chiral HPLC.

The results showed that all of the acidic additives (Table 1, entries 8−21) improved the efficiency of **1f** except for BINOL (entries 20 and 21). Some of them effectively increased the activity and enantioselectivity of **1f**, such as chloroacetic acid (entry 13), DNP (entry 14),[18] formic acid (entry 15), salicylic acid (entry 17), and trichloroacetic acid (entry 19). Among them, trichloroacetic acid and DNP highly increased the enantioselectivity of **1f** from 56% up to 92% and 93%, respectively. DNP apparently was more active. And the other six catalysts all greatly increased their enantioslectivities and activities when DNP was added (entries 22−27). All of their enantioselectivities were improved to >80% except that **1a** gave 79% ee. The biggest increase in enantioselectivity was that 30% ee was dramatically elevated to 89% ee for the original poorest catalyst **1d**!

Further optimizing experiments (Table 2) showed that even low to 1 mol % amount of **1f** could give 91% ee at the cost of a quite sluggish reaction rate. Increasing the amount of **1f** did not further improve its enantioselectivity but accelerated the reaction. When 20 mol % of **1f** and DNP were used, the highest yield was harvested. A little increase in ee could further be achieved under lower reaction temperatures of 0 and −10 °C (entries 1−7). Solvents had great effects on the activity and enantioselectivity of the organocatalyst. A series of apolar to polar solvents were investigated (entries 8−20). The results

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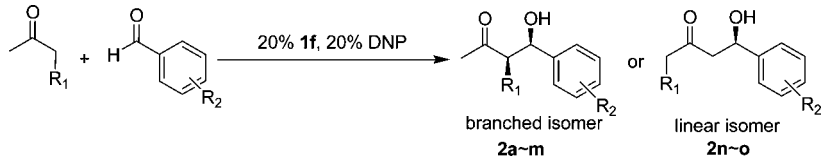
TABLE 3. The Organocatalytic Asymmetric Aldol Reaction of Methyl Alkyl Ketones with Aldehydes[a]



entry	R_1	R_2	time (h)	yield (%)[b]	syn/anti[c]	ee (%)[d]
1	H	4-NO_2	26	82		96
2	H	2-NO_2	23	69		96
3	H	3-NO_2	46	69		97
4	H	2-Cl	20	60		97
5	H	2-Br	18	43		>99
6	H	4-Cl	47	38		92
7	H	4-Br	84	50		95
8	H	2-MeO	60	26		93
9	H	3-MeO	60	31		89
10	H	1-Napth	48	26		91
11	H	2-Napth	48	30		91
12	Me	4-NO_2	18	85	2/1 (3/1)	88
13	Me	2-NO_2	15	89	3/1 (3/1)	92
14	*i*-Pr	4-NO_2	47	65	− (>99%)	91
15	*i*-Pr	3-NO_2	47	70	− (>99%)	95

[a] Entries 1−11, 12−13, and 14−15 were performed in acetone, 2-butone, and methyl isobutyl methyl ketone, respectively. Entries 1−5 and 7−9 were performed under −10 °C and at room temperature, respectively, whereas entries 6 and 10−11 were performed under 0 °C and 20% acetic acid was added. [b] Isolated yield. [c] Determined by ^{1}H NMR. Data in parentheses are the regioselectivity values, and the main product is branched isomer when R_1 = Me, whereas the linear isomer is predominant when R_1 = *i*-Pr. [d] Determined by chiral HPLC. The configuration was determined by the HPLC retention time or the sign of the optical rotation with the literature data.[11,15]

showed that acetone was the optimal reaction medium. It achieved the fastest reaction rate, the highest yield, and the highest enantioselectivity.

Under the optimized reaction conditions, enantioselectivities of the other six catalysts were rechecked (Table 2, entries 21−26). These catalysts had increased their enantioselectivities to ≥90% except that **1g** achieved 88% ee. Because of the introduction of DNP, these original inefficient organocatalysts were dramatically upgraded into highly efficient ones. This result demonstrated that we could learn from the enzymatic systems and select optimal additives to change the inefficient catalysts into highly efficient catalytic systems. And this highly effective remedial protocol to low efficient organocatalysts with an optimal additive or cocatalyst is cost-effective and environment-benign compared with redesign, resynthesis, and reselection of organocatalysts. Apparently, DNP functioned as an effective cocatalyst here. The catalyst **1f** and the cocatalyst DNP composed a highly efficient chiral catalytic system.

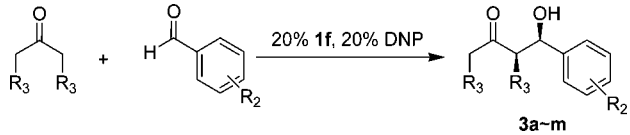
Thus, the catalyst **1f** and DNP were used to catalyze the addition of methyl ketones to aryl aldehydes (Table 3). In the typical series of reactions of acetone with aldehydes, this catalytic system showed high enantioselectivity; all cases achieved >90% enantioselectivities except that 3-methoxybenzaldehyde provided 89% ee.[19] The highest enantioselectivity was >99%. Notably, <90% enantioselectivities were previously afforded by primary amine organocatalysts derived from primary amino acids or directly by those acyclic amino acids themselves.[15] The enantioselective outcomes disclosed here and the results from Luo and co-workers are both the highest values harvested by primary amine organocatalysts in these asymmetric transformations to date. Furthermore, two other methyl ketones were also observed with this catalytic system, both of them affording high enantioselectivities. Previously, 2-butanone has only rarely been used as a substrate for primary amine organocatalysts. Córdova and co-workers reported 75% enantioselectivity with L-alanine.[13b,f] We achieved up to 92% ee using this catalytic system. And herein, 4-methyl-2-pentanone provided the highest enantioselectivity under primary amine organocatalysts so far.

In addition, four symmetrical ketones were investigated to further widen the spectrum of substrates of this catalytic system (Table 4). 3-Pentanone[20] harvested the highest up to 99% ee and 16/1 syn/anti to date. However, it failed to react with the electron-abundant aldehydes such as methoxy-substituted benzaldehyde. Although primary organocatalysts have successfully achieved the highest up to 99% enantioselectivities and high diastereoselectivities with cyclohexanone, they did not obtain >94% enantioselectivities with cyclopentanone. And those from primary amino acids previously achieved <90% enantioselectivities with this smaller cyclic ketone.[13] Herein, cyclopentanone achieved the highest >99% ee with the predominant syn products under primary organocatalysts for the first time. And when cyclohexanone was observed, it also afforded up to 99% enantioselectivity. But its predominant products were anti, and the highest diastereoselectivity was up to 62/1 anti/syn. The aldol reaction of dihydroxy acetone with an aldehyde is an important path to synthesize a carbohydrate. Unprotected dihydroxy acetone was directly used as an electrophile donor to aldehydes. Just as 2-butanone, 3-pentanone, and cyclopentanone did, this ketone also afforded predominant syn products, achieving up to 99% high enantioselectivity and 12/1 high diastereoselectivity.

(19) The alkyl aldehydes butyraldehyde and cyclohexanecarbaldehyde failed to give aldols.

(20) Just when we were performing this research work, Gong and co-workers reported their results about the aldol reaction of 3-pentanone catalyzed by **1f** (ref 14d): reaction of 3-pentanone with 3-NO_2-PhCHO achieved 96% ee and 6/1 syn/anti in brine when 4-NO_2-PhCOOH was used as an additive. It could be clearly found that the catalytic system of **1f** and DNP achieved up to 99% ee and 16/1 syn/anti, enantioselectivity and diastereoselectivity were more satisfying. Herein, 3-pentanone harvested the highest enantioselectivity and diastereoselectivity to date.

TABLE 4. Asymmetric Aldol Reaction of Symmetrical Ketones and Aldhydes[a]



3a~m

entry	R_3	R_2	solvent	time (h)	yield (%)[b]	syn/anti[c]	ee (%)[c]
1	Me	4-NO_2	3-pentanone	65	86	14/1[d]	96
2	Me	3-NO_2	3-pentanone	48	87	16/1[d]	99
3	Me	4-F	3-pentanone	144	31	7/1[d]	97[e]
4	Me	2-Cl	3-pentanone	144	51	16/1	99
5	$-(CH_2)_2-$	2-NO_2	cyclopentanone	2	85	2/1	>99
6	$-(CH_2)_2-$	4-NO_2	cyclopentanone	0.5	82	2/1	93
7	$-(CH_2)_3-$	2-NO_2	cyclohexanone	0.5	68	1/62	99
8	$-(CH_2)_3-$	2-Cl	cyclohexanone	120	26	1/11	91
9	OH	2-NO_2	DMF	50	59	3/1	92[e]
10	OH	4-NO_2	DMF	48	48	7/1	95[e]
11	OH	3-NO_2	DMF	28	75	12/1[d]	99
12	OH	4-F_3C	DMF	96	64	12/1	91[e]
13	OH	2-F_3C	THF	120	77	10/1[d]	95

[a] The reaction was performed at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC. The configuration was determined by the HPLC retention time or the sign of the optical rotation with the literature data.[11,13−15] [d] Determined by ^{1}H NMR. [e] Determined with acetate derivative of the aldol product.

As a result, several primary amine organocatalysts from natural primary amino acids showed very low enantioselectivities and activities in the typical aldol reactions of acetone with aldehydes. However, introduction of the optimal cocatalyst DNP dramatically elevated their activities and enantioselectivities. The catalysts and DNP jointly functioned as efficient chiral organocatalytic systems. So this work successfully demonstrated a highly effective remedial course to the quite inefficient organocatalysts instead of redesign, resynthesis, and reselection of organocatalysts. And this remedial course can be characterized by cost-effectiveness and environmental benefit. The highest efficient catalytic system that was composed of **1f** and DNP had a broad spectrum of ketones with high enantioselectivities and good to high diastereoselectivities. Except for butanone and 4-methyl-2-pentanone, the other five ketones harvested the highest up to 99% enantioselectivities. And except for cyclohexanone and dihydroxy acetone among the same seven ketones, the other five ketones exceeded the previously reported highest enantioselectivities with primary amine organocatalysts derived from natural primary amino acids. The linear ketones and cyclopentanone harvested predominant syn aldol products whereas cyclohexanone provided anti products.

Experimental Section

General Procedure for Preparation of Diphenyl Aminoalcohols 5a−c.[21] The freshly prepared Grignard reagent PhMgBr (60 mL, 2.5 N, 150 mmol) in ether was cooled to 0 °C under an argon atmosphere, and 15 mmol of hydrochloride of methyl ester of amino acid **4** was added in ten portions (addition of too much methyl ester hydrochloride in one portion would make the reaction too violent on account of the rapid reaction of HCl with PhMgBr). Then the reaction was naturally warmed to room temperature and allowed to stir overnight. When the reaction was complete (checked by TLC), the mixture was SLOWLY poured into 60 mL of stirring icy water, then 0.25 mmol of concentrated HCl was added. The mixture was stirred for an hour, filtrated, and washed with water three times to afford a yellow solid. The yellow solid was introduced with NaOH (55 mL, 0.25 mmol), stirred for another 30 min, and then extracted with ether three times. The ether layers were combined and concentrated in vacuo, and the resulting solid was recrystallized from ethyl acetate or ethanol to yield the amino alcohols **5a−c**.

(*S*)-Diphenylphenylglycinol (5a):[21a] yield 55%; mp 121−123 °C; $[\alpha]^{20}_D$ −242 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74−7.76 (d, 2H, J = 7.6 Hz), 7.38−7.42 (t, 2H, J = 7.2 Hz, J = 8.4 Hz), 7.26−7.30 (t, 1H, J = 8.0 Hz, J = 6.8 Hz), 7.00−7.25 (m, 10 H), 5.01 (s, 1H), 1.61 (br, 1H).

General Procedure for Preparation of Catalysts 1a−g. $ClCOO^iBu$ (0.67 mL, 5.1 mmol) was slowly introduced dropwise into a solution of 5.1 mmol of Boc-protected amino acid **6** (Boc-Ala, Boc-Leu, or Boc-Val) and 0.56 mL of NMM (5.1 mmol) in 25 mL of dry THF under an argon atmosphere at −15 °C. Five minutes later, the amino alcohol **5** was added dropwise into the mixture. After being stirred for 30 min, the reaction was continued at room temperature until it was complete (checked by TLC). Then THF was evaporated in vacuo, and the residue was redissolved with CH_2Cl_2, washed successively with dilute HCl, water, 10% $NaHCO_3$, water, and a little brine, dried with anhydrous Na_2SO_4, and then condensed in vacuo. It was recrystallized from ethyl acetate and petroleum ether to give a crystal or solid. The solid was redissolved with CH_2Cl_2 and cooled to 0 °C, then TFA in CH_2Cl_2 (TFA/CH_2Cl_2 = 1:1) was added dropwise. The mixture was stirred for 1 to 2 h until the reaction was completed (checked by TLC) and then condensed to dryness in vacuo. The residue was redissolved with CH_2Cl_2 and $NH_3\cdot H_2O$ was added to adjust the solution pH to ca. 10.0. The organic layer was separated, and the aqueous layer was re-extracted three times with CH_2Cl_2. Then the combined organic layers were washed with a little brine, dried with anhydrous Na_2SO_4, and condensed to dryness in vacuo. The residue was recrystallized from ethyl acetate and petroleum ether to give the catalyst **1**.

(*S*,*S*)-2-Amino-*N*-(1-hydroxy-4-methyl-1,1-diphenylpentan-2-yl)-4-methylpentanamide (1f):[14d] yield 54%; mp 180−182 °C; $[\alpha]^{20}_D$ −44 (*c* 1.0, DMSO); FT-IR 3389, 3347, 2953, 2297, 2868, 1643, 1518, 1447, 1167, 1135, 1062, 745, 699 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63 (d, 1H, J = 9.6 Hz), 7.50 (d, 4H, J = 7.6 Hz), 7.29 (t, 2H, J = 7.6 Hz), 7.12−7.20 (m, 3H), 7.06−7.09 (t, 1H, J = 7.2 Hz), 5.91 (s, 1H), 4.93−4.98 (m, 1H), 2.86−2.89 (dd, 1H, J = 5.6 Hz, J = 8.8 Hz), 1.49−1.54 (m, 4H), 1.33−1.39 (m, 1H), 0.98−1.04 (m, 2H), 0.89−0.97 (m, 1H), 0.87 (d, 3H, J = 6.8 Hz), 0.76 (d, 3H, J = 6.4 Hz), 0.68 (d, 6H, J = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.4, 146.9, 146.4, 128.0, 127.4, 126.1, 125.9, 125.6, 125.3, 80.1, 53.0, 52.5, 44.1, 39.2, 24.1, 23.8, 23.1, 21.7, 21.6; HRMS calcd for $(C_{24}H_{34}N_2O_2 + H)^+$ 383.2693, found 383.2696. Anal. Calcd for $C_{24}H_{34}N_2O_2$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.49; H, 9.11; N, 7.24.

General Procedure for Asymmetric Aldol Reaction of Methyl Ketone (Acetone, Butanone, and 4-Methyl-2-pentanone) with Aldehydes. A solution of aldehyde (0.2 mmol), **1f** (0.04 mmol), and DNP (0.04 mol) in ketone (acetone, butanone, and 4-methyl-2-pentanone, respectively) (0.4 mL) was stirred at −10 °C until the reaction was completed as judged by TLC. Then 5.0 mL of saturated aqueous NH_4Cl was added to quench the reaction. 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, and purified by preparative TLC or column to achieve the aldol product.

(*R*)-4-Hydroxy-4-(4-nitrophenyl)butan-2-one (2a):[11,15] yield 85%; $[\alpha]^{20}_D$ +48 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.16−8.23 (m, 2H), 7.52−7.58 (m, 2H), 5.24−5.30 (m, 1H), 3.62 (br, 1H), 2.84−2.88 (m, 2H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.5, 149.9, 147.3, 126.4, 123.7, 68.9, 51.5, 30.1; ee 96%, determined by chiral HPLC with AS-H column, eluent:

(21) (a) Dragoli, D. R.; Burdett, M. T.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 10127. (b) Ashby, E. C.; DePriest, R. N.; Goel, A. B.; Wenderoth, B.; Pham, T. N. *J. Org. Chem.* **1984**, *49*, 3545. (c) O'Hagan, D.; Tavasli, M. *Tetrahedron: Asymmetry* **1999**, *10*, 1189.

hexane/^{i}PrOH = 70/30, flow rate:1.0 mL/min, retention time for the major peak 11.1 min (*R* isomer) and the minor peak 15.6 min (*S* isomer).

General Procedure for Asymmetric Aldol Reaction of Ketone (3-Pentanone, Cyclohexanone, and Cyclopentanone) with Aldehydes. To a solution of 0.04 mmol of **1f** and 0.04 mmol of DNP in 0.8 mL of ketone (3-pentanone, cyclohexanone, and cyclopentanone, respectively) was introduced 0.2 mmol of aldehyde. The mixture was stirred under room temperature until the reaction was complete (checked by TLC). Then 5.0 mL of saturated aqueous NH_4Cl was added to quench the reaction. 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, and purified by preparative TLC or column to achieve the aldol condensation product.

(1*R*,2*R*)-1-Hydroxy-2-methyl-1-(4-nitrophenyl)pentan-3-one (3a):[14d,15d] yield 86%; $[\alpha]^{20}_D$ +26 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, 2H, J = 7.8 Hz), 7.51 (d, 2H, J = 8.7 Hz), 5.23 (s, 1H), 3.60 (d, 1H, J = 2.8 Hz), 2.81−2.89 (dq, 1H, J = 7.2 Hz, J = 3.15 Hz), 2.54−2.68 (m, 1H), 2.39−2.52 (m, 1H), 1.07 (t, 3H, J = 7.2 Hz), 1.04 (d, 3H, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.1, 149.2, 147.2, 126.8, 123.5, 72.0, 51.5, 35.2, 9.9, 7.5; syn/anti 14/1, determined by HPLC; ee 97%, determined by chiral HPLC with OJ-H column, eluent: hexane/^{i}PrOH = 90/10, flow rate 0.8 mL/min, syn isomer retention time for the major peak 24.9 min ((*R*,*R*)-isomer) and the minor peak 34.1 min ((*S*,*S*)-isomer).

General Procedure for Asymmetric Aldol Reaction of Dihydroxy Acetone with Aldehydes. To a solution of 0.4 mmol of dihydroxy acetone (36 mg), 0.04 mmol of **1f** (15.3 mg), and 0.04 mmol of DNP (7.36 mg) in 0.40 mL of dry DMF was introduced 0.2 mmol of aldehyde under room temperature. The mixture was stirred until the reaction was completed (checked by TLC). Then 5.0 mL of saturated aqueous NH_4Cl was added to quench the reaction, and the mixture was extracted with ethyl acetate three times. The organic layers were combined, dried with anhydrous Na_2SO_4, concentrated to dryness under reduced pressure, and purified by preparative TLC or column to achieve the aldol condensation product.

(3*R*,4*S*)-1,3,4-Trihydroxy-4-(2-nitrophenyl)butan-2-one (3i):[14a] yield 59%; $[\alpha]^{20}_D$ −34 (*c* 1.0, MeOH); ^{1}H NMR of **3j** (300 MHz, MeOH-d_4) δ 7.98−8.00 (m, 2H), 7.66−7.75 (m, 1H), 7.47−7.55 (m, 1H), 5.71 (d, 1H, J = 1.8 Hz), 4.62 (s, 2H), 4.49 (d, 1H, J = 2.1 Hz); ^{13}C NMR (75 MHz, MeOH-d_4) δ 212.2, 149.0, 138.4, 134.0, 131.7, 129.4, 125.1, 79.4, 70.6, 67.8; syn/anti 3/1, determined by chiral HPLC; ee 92%, determined by chiral HPLC with AD-H column, eluent: hexane/^{i}PrOH = 90/10, flow rate 0.8 mL/min, syn isomer retention time for the major peak 38.2 min ((*R*,*S*)-isomer) and the minor peak 44.0 min ((*S*,*R*)-isomer).

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Supporting Information Available: Characterization of compounds and spectra (^{1}H NMR, ^{13}C NMR, and HPLC). This material is available free of charge via the Internet at http://pubs.acs.org.

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