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Chiral Primary Amine Catalyzed Asymmetric Direct Cross-Aldol Reaction of Acetaldehyde

Shenshen Hu,[a] Long Zhang,[a] Jiuyuan Li,[a] Sanzhong Luo,*[a] and Jin-Pei Cheng*[a]

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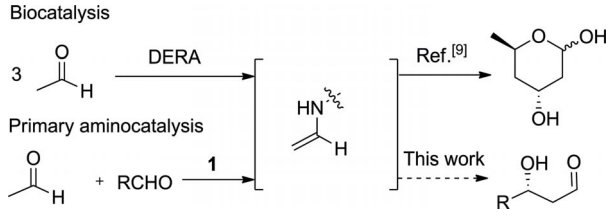
The first primary aminocatalytic direct cross-aldol reaction of acetaldehyde is presented. Among the various vicinal diamines screened, the L-*tert*-leucine derivative **1c** in conjunction with $(H_4SiW_{12}O_{40})_{0.25}$ was identified as the optimal catalyst; good catalytic activity (up to 99 % yield in 4 h), and high enantioselectivities (up to 92 % *ee*) were achieved for a range of donors, including aromatic aldehydes and isatin derivatives. Aqueous acetaldehyde solution and paraldehyde can be conveniently applied in this system.

Introduction

The aldol reaction, first discovered by Wurtz in 1872,[1] is one of the most important methods for carbon–carbon bond formation both in nature and in modern organic synthesis.[2] During the past decade, enamine-based organocatalysts have enabled a range of asymmetric direct aldol reactions.[3] Nevertheless, the direct cross-aldol reactions of acetaldehyde, which is the simplest enolizable carbonyl compound, are being known to be difficult.[4] The fundamental challenge is to suppress undesired side reactions, such as multi/poly-aldolization, dehydration, and polymerization of the products. The direct asymmetric self-aldolization of acetaldehyde was first reported by Barbas and coworkers who used L-proline as the catalyst and obtained (+)-(5*S*)-hydroxy-(2*E*)-hexenal with low conversion and moderate enantioselectivity.[5] In 2008, Hayashi and coworkers reported the first example of an asymmetric direct cross-aldol reaction of acetaldehyde with the aid of a diarylprolinol-based catalyst.[6] Subsequently, the cross-aldol reaction between acetaldehyde (as the nucleophile) and a ketone (as an electrophile) were also achieved by the application of chiral secondary amine organocatalysts.[7]

The acetaldehyde-dependent aldol reaction is also an enzymatic process. In nature, 2-deoxyribose-5-phosphate aldolase (DERA) is the only known aldolase that utilizes an aldehyde (acetaldehyde) as the donor. In the enzymatic pathway, the ε-primary amine of a lysine residue is the catalytic functional group, promoting the reaction through the proved enamine intermediate.[8] In the 1990s, DERA-based aldol reactions have often been applied in the asymmetric synthesis of aza-sugars.[9] However, despite these advances and the prevalence of organocatalysis, to our surprise, there have been no reports on primary amine catalyzed acetaldehyde aldol reactions.[10]

Inspired by the primary amino catalysts found in Nature, we previously developed the vicinal primary–tertiary diamines **1** and **2** as both functional and mechanistic mimics of natural aldolases.[11,12] To further expand their applications in some organocatalytic reactions such as those mentioned above, we explored the use of these chiral primary amines in the acetaldehyde aldol reaction (Scheme 1). Indeed, vicinal diamines such as **1** were found to be effective catalysts for the acetaldehyde aldol reaction, showing much improved activity over typical secondary amines[6,7] and enabling the cross-aldol reactions with aromatic aldehydes and isatin derivatives.



Scheme 1. Direct cross-aldol reaction of acetaldehyde catalyzed by primary amines.

Results and Discussion

Initial Trial and Screening of the Catalysts

We started the study with our previously developed primary amine catalyst **1a**, in the presence of trifluoromethanesulfonic acid (TfOH), and investigated the cross-aldol reaction between acetaldehyde and *p*-nitrobenzaldehyde as

[a] Beijing National Laboratory for Molecular Sciences (BNLMS), CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, P. R. China
E-mail: luosz@iccas.ac.cn
chengjp@most.cn

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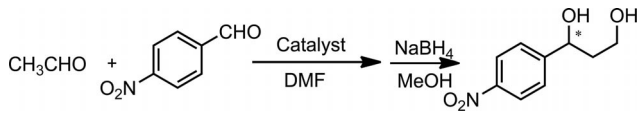
a model reaction. Although **1a**/TfOH was previously shown to be an effective catalyst in the *syn*-selective cross-aldol reaction of aldehydes,[11f] this catalytic system showed low activity in the reaction between acetaldehyde and *p*-nitrobenzaldehyde under the same conditions, giving only trace amounts of the desired product (Table 1, Entry 3). In our continuing studies, it was found that substantial activity and enantioselectivity could be achieved by changing the acidic additives from TfOH to 2-sulfobenzoic acid (2-SBA) (Table 1, Entry 4).

Table 1. Catalyst screening for direct cross-aldol reaction of acetaldehyde.



Entry[a]	Catalyst[b]	Yield [%][c]	*ee* [%][d]
1	L-Ala-OH	trace	n.a.
2	L-Phe-OH	trace	n.a.
3	**1a**/TfOH	trace	n.a.
4	**1a**/2-SBA	81	73 (*R*)
5	**1b**/2-SBA	76	80 (*R*)
6	**1c**/2-SBA	82	86 (*R*)
7	**1d**/2-SBA	60	75 (*S*)
8	**1e**/2-SBA	74	68 (*R*)
9	**1f**/2-SBA	47	71 (*R*)
10	**1g**/2-SBA	62	62 (*R*)
11	**1h**/2-SBA	66	53 (*R*)
12	**2a**/2-SBA	71	71 (*S*)
13	**2b**/2-SBA	62	66 (*S*)
14	**2c**/2-SBA	74	68 (*S*)
15	**2d**/2-SBA	64	72 (*S*)
16	**2e**/2-SBA	41	66 (*S*)
17	**3a**/2-SBA	14	46 (*S*)
18	**3b**/2-SBA	34	85 (*S*)
19	**4**/2-SBA	44	34 (*S*)
20	**5**/2-SBA	8	30 (*S*)
21	**6**/2-SBA	trace	n.a.

[a] Reagents and conditions (unless otherwise stated): *p*-nitrobenzaldehyde (0.4 mmol), acetaldehyde (1.6 mmol), catalyst (0.04 mmol), DMF (0.4 mL), 25 °C, 8 h. [b] 2-SBA: 2-sulfobenzoic acid. [c] Isolated yield. [d] Determined by chiral HPLC.

With 2-SBA as the selected acidic additive, a range of chiral primary amines were then examined (Figure 1). Primary–tertiary vicinal diamines such as **1**, **2**, and **3** were found to be viable catalysts for this type of cross-aldol reaction, with moderate to good activity and good enantioselectivity (Table 1, Entries 4–18). Other types of primary amines, such as natural primary amino acids, primary secondary diamines **4**, aminoquinuclidine **5**, and primary amino amide **6** were much less active, with low stereoselectivity, which highlights the critical role of the primary–tertiary vicinal diamines in this reaction. Among the primary–tertiary vicinal diamines screened, diamine organocatalysts **1** derived from amino acids were apparently superior, both in terms of enantioselectivity and activity, to those of **2** and **3** (Table 1, Entries 4–11 vs. 12–18), and the catalytic efficacy steadily improved when the bulkiness of the R^3 group in diamines **1** was increased (Table 1, Entries 4, 5, and 6). Eventually, chiral primary amine **1c**, derived from L-*tert*-leucine, was identified as the optimal catalyst, which provided 82% yield and 86% *ee* with 2-sulfobenzoic acid (2-SBA) as the acidic additive (Table 1, Entry 6).

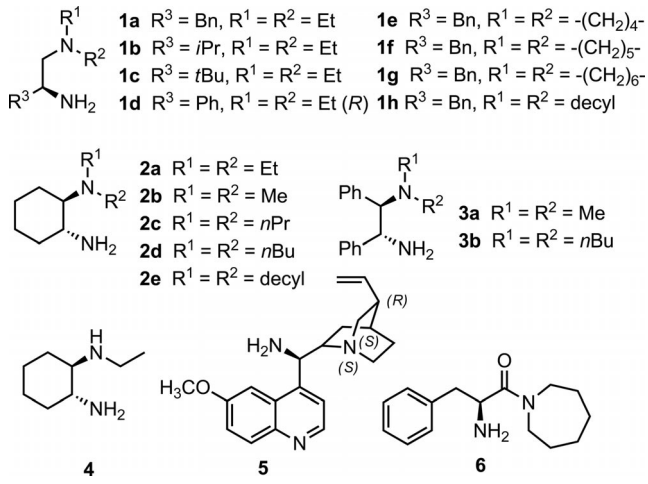


Figure 1. Chiral primary amines used in this study.

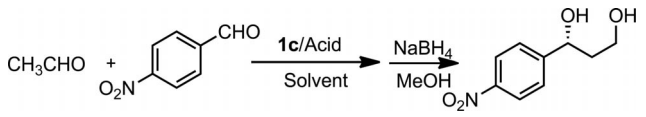
Optimization of Reaction Conditions

During the course of the catalyst screening, minor amounts of a dehydration byproduct and self-condensation products of acetaldehyde were observed in the catalysis of **1c**/2-SBA. Bearing in mind the dramatic effect of acidic additives in the primary–tertiary diamine catalytic system,[11] we then examined a range of acidic additives to further improve the catalytic efficiency and suppress the side reactions.[13] In the present case, we were delighted to find that the use of silicontungstic acid ($H_4SiW_{12}O_{40}$), which was previously used as a catalyst support for chiral amines,[14] led to a much cleaner reaction, with slightly improved activity and enantioselectivity than that of 2-SBA and TfOH (Table 1, Entry 6 vs. 1 and 2). In the presence of **1c**/$(H_4SiW_{12}O_{40})_{0.25}$, the reaction proceeded cleanly to afford 83% yield and 86% *ee* in 5 h. In comparison, the reaction required 24 h for complete conversion with typical secondary amine catalysts such as diarylprolinol.[6]

The use of other solvents in the model reaction with catalyst **1c**/$(H_4SiW_{12}O_{40})_{0.25}$ was examined, and the activity of the reaction was found to be highly solvent-dependent, probably due to the different solubility of **1c**/$(H_4SiW_{12}O_{40})_{0.25}$. The catalyst **1c**/$(H_4SiW_{12}O_{40})_{0.25}$ tends to aggregate in chlorinated solvents and showed poor solubility in less polar solvents, such as toluene, diethyl ether, and tetrahydrofuran (THF), leading to poor catalytic efficiency (Table 2, Entries 8–13). Although the reactions seem to favor polar solvents such as *N*,*N*-dimethylformamide (DMF) and MeCN, probably due to their better solvating ability for **1c**/$(H_4SiW_{12}O_{40})_{0.25}$, the solvent screening did not show any clear improvement on the catalytic results (Table 2, Entries 6 and 7). The employment of neat conditions (with 16 equiv. of acetaldehyde) was found to afford a slightly increased *ee* with a quantitative yield in 2 h

(Table 2, Entry 14). The enantioselectivity could be further improved to 92% *ee* at lower temperatures (10 °C; Table 2, Entry 15). It should be pointed out that the use of a large excess of acetaldehyde is not essential in this case; thus, the loading could be significantly reduced, because the reaction was equally fast with 4 equiv. of acetaldehyde (Table 2, Entry 6). In addition, industrial sources of acetaldehyde, such as aqueous acetaldehyde and paraldehyde, could be equally applied in the catalytic system **1c**/$(H_4SiW_{12}O_{40})_{0.25}$, with acceptable enantioselectivity and activity under the developed conditions, without further optimization (Table 2, Entries 17 and 18). Because analytically pure acetaldehyde is inexpensive and readily available, neat conditions were employed for subsequent studies.

Table 2. Optimization of the reaction conditions.



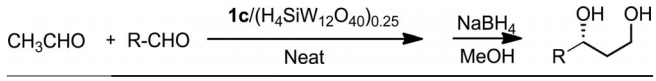
Entry[a]	Acid[b]	Solvent	*t* [h]	Yield [%][c]	*ee* [%][d]
1	2-SBA	DMF	5	73	86
2	TfOH	DMF	5	62	87
3	$(H_3PW_{12}O_{40})_{0.33}$	DMF	5	83	84
4	$(H_3PMo_{12}O_{40})_{0.33}$	DMF	5	56	88
5	$(H_4SiMo_{12}O_{40})_{0.25}$	DMF	5	69	89
6	$(H_4SiW_{12}O_{40})_{0.25}$	DMF	5	89	87
7	$(H_4SiW_{12}O_{40})_{0.25}$	MeCN	5	75	86
8	$(H_4SiW_{12}O_{40})_{0.25}$	toluene	5	45	71
9	$(H_4SiW_{12}O_{40})_{0.25}$	THF	5	27	90
10	$(H_4SiW_{12}O_{40})_{0.25}$	Et_2O	5	24	82
11	$(H_4SiW_{12}O_{40})_{0.25}$	CH_3Cl	5	24	72
12	$(H_4SiW_{12}O_{40})_{0.25}$	$ClCH_2CH_2Cl$	5	51	84
13	$(H_4SiW_{12}O_{40})_{0.25}$	CH_2Cl_2	5	56	82
14[e]	$(H_4SiW_{12}O_{40})_{0.25}$	–	2	99	89
15[e,f]	$(H_4SiW_{12}O_{40})_{0.25}$	–	4	99	92
16[e,g]	$(H_4SiW_{12}O_{40})_{0.25}$	–	24	96	75
17[h]	$(H_4SiW_{12}O_{40})_{0.25}$	–	24	82	87
18[i]	$(H_4SiW_{12}O_{40})_{0.25}$	–	24	79	79

[a] Reagents and conditions (unless otherwise stated): *p*-nitrobenzaldehyde (0.4 mmol), acetaldehyde (1.6 mmol), catalyst **1c**/additive acid (0.04 mmol), solvent (0.4 mL), 25 °C. [b] 2-SBA: 2-sulfobenzoic acid. [c] Isolated yield. [d] Determined by chiral HPLC. [e] Acetaldehyde (0.4 mL) was used. [f] The reaction was carried out at 10 °C. [g] The reaction was carried out at 0 °C. [h] Aqueous acetaldehyde (40%, 0.4 mL) was used at 25 °C. [i] Paraldehyde (0.4 mL) was used at 25 °C.

Substrate Scope

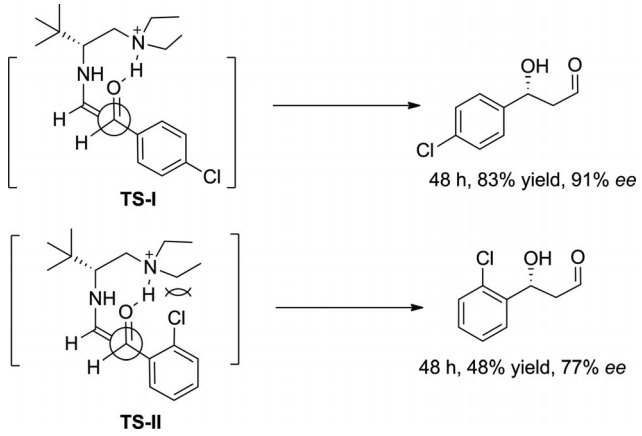
With the optimal conditions in hand, the scope of the direct aldol reaction of acetaldehyde was then examined with respect to both aromatic aldehydes and isatin derivatives in the presence of 10 mol-% **1c**/$(H_4SiW_{12}O_{40})_{0.25}$. The reaction with aromatic aldehydes, including heteroaromatic aldehyde, proceeded quite smoothly to give the desired aldol products with up to 99% yield and 92% *ee* (Table 3). In these cases, the catalytic activity of primary amine **1c** was quite high compared with previous reports on the same substrates.[6] No further aldolization of the cross-aldol products was observed, and only trace amounts of dehydration products were detected in some cases. It was also noted that the activity and selectivity were relatively low with *ortho*-substituted aromatic aldehydes compared with those of *para*-substituted aldehydes (Table 3, Entry 1 vs. 3 and Entry 7 vs. 11), which may be rationalized by considering the steric effect of the *ortho* substituent as illustrated in **TS-II** (Scheme 2). The reaction of electron-rich aldehydes, such as 2-naphthaldehyde, also proceeded smoothly with moderate yield and good *ee* (Table 3, Entry 13) over several batch additions of acetaldehyde. In our studies, aliphatic aldehydes appeared to be poor acceptors due to their low activity and the associated side reactions.

Table 3. Substrate scope of aromatic aldehydes.



Entry[a]	R	*t* [h]	Product	Yield [%][b]	*ee* [%][c]
1	4-$O_2NC_6H_4$	4	**7a**	99	92
2	3-$O_2NC_6H_4$	4	**7b**	99	89
3	2-$O_2NC_6H_4$	6	**7c**	92	81
4	4-NCC_6H_4	24	**7d**	97	85
5[d]	4-$F_3CC_6H_4$	12	**7e**	89	90
6[d]	4-BrC_6H_4	48	**7f**	77	90
7[d]	4-ClC_6H_4	48	**7g**	83	91
8	3,4-$Cl_2C_6H_3$	60	**7h**	62	87
9	2,6-$Cl_2C_6H_3$	40	**7i**	34	80
10	2-FC_6H_4	60	**7j**	58	69
11	2-ClC_6H_4	48	**7k**	48	77
12	4-pyridyl	2	**7l**	97	87
13[e]	2-naphthyl	72	**7m**	62	82

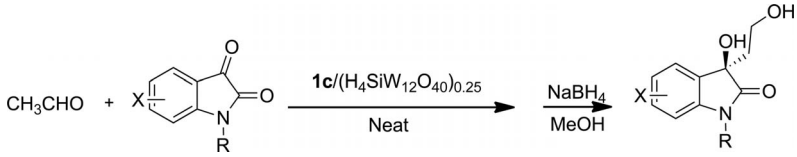
[a] Reagents and conditions (unless otherwise stated): aromatic aldehyde (0.4 mmol), acetaldehyde (0.4 mL), catalyst **1c**/$(H_4SiW_{12}O_{40})_{0.25}$ (0.04 mmol), 10 °C. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Determined by HPLC after conversion of the primary hydroxy group into the monobenzoyl ester.[6] [e] The reaction was carried out at 25 °C; acetaldehyde (0.2 mL) was added three times at 24 h intervals.



Scheme 2. Proposed transition states.

The reactions between isatin derivatives and acetaldehyde were also examined under the optimal conditions. The reactions were completed within 6 h, giving the desired

Table 4. Substrate scope of isatin derivatives.



Entry[a]	R	X	*t* [h]	Product	Yield [%][b]	*ee* [%][c]
1	H	H	2	**8a**	90	69
2[d]	H	4-Br	6	**8b**	92	80 (96)
3[d]	H	5-Br	6	**8c**	92	82 (92)
4	Me	H	6	**8d**	92	80
5	Bn	H	6	**8e**	97	77

[a] Reagents and conditions (unless otherwise stated): isatin derivative (0.4 mmol), acetaldehyde (0.4 mL), catalyst/additive (0.04 mmol), 10 °C. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Value in parentheses is *ee* obtained after a single recrystallization.

products **8a**–**e** with excellent yields and moderate *ee* (Table 4). Although the best enantiomeric excess of this system was approximately 80% *ee*, it could be readily improved to more than 90% *ee* after a single recrystallization (Table 4, Entries 2 and 3). These products are valuable intermediates for the synthesis of convolutamydines E and B.[7c,7d] Compared with the reported catalytic protocols for the same reactions,[7c,7d] **1c**/$(H_4SiW_{12}O_{40})_{0.25}$ demonstrated much better activity, albeit with lower enantioselectivity.

Proposed Transition State

By comparing the optical rotation with the known product, the absolute configuration of **7** and **8** was determined to be (*R*).[17] Enamine transition states **TS-I** and **TS-II** are proposed to account for the observed stereoselectivity (Scheme 2). Consistent with previous reports,[6,11] the protonated amino group plays significant roles in the stereocontrol through hydrogen bonding with the carbonyl group of the aldehyde acceptor. In addition, the large steric bulk of the *tert*-butyl group, together with the substituent on the tertiary amines would also favor the approach of the acceptor to the enamine face. Clearly, in line with this hypothesis, the *ortho*-substituted aromatic aldehyde (e.g., 2-chlorobenzaldehyde) gave a much lower enantioselectivity than its *para*-substituted analogue (e.g., 4-chlorobenzaldehyde), probably as a result of the steric interference between the *ortho* substituent and the tertiary amino group (**TS-II** in Scheme 2).

Conclusions

We present herein the first biomimetic primary amine catalyzed cross aldol reactions of acetaldehyde. A vicinal primary–tertiary diamine derived from L-*tert*-leucine, in concert with $H_4SiW_{12}O_{40}$, was identified as the optimal catalytic system, facilitating the direct cross-aldol reaction of acetaldehyde with a range of substrates, including aromatic aldehydes and isatin derivatives, with up to 99% yield and 92% *ee*. Although the substrate scope is still limited to aromatic aldehydes, the combined use of readily available and simple catalysts with exceptionally high activity should be of significant practical value.

Experimental Section

General Information: Commercial reagents were used as received, unless otherwise indicated. ^1H and ^{13}C NMR spectra were recorded with a 300 MHz instrument (Bruker DMX 300) as noted, and were internally referenced to the residual protic solvent signals. Chemical shifts are reported in ppm from tetramethylsilane with solvent resonance as the internal standard. The following abbreviations were used to designate the chemical shift multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, br. = broad. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br.). HPLC analysis was performed by using Chiralcel columns. Absolute configurations were determined by correlation to values reported in the literature.[6] Primary amines **1a**,[11d,11f] **2**,[11a–11c,11e] **3**,[15] **4**,[16] **5**, aldol products of aromatic aldehydes[6] **7a**, **7b**, **7c**, **7e**, **7f**, **7i**, **7k**, **7l**, **7n**, and isatin derivatives **9a**–**e**[7] have previously been reported. Primary amines **1b**–**d**, **6**, and aldol products **7d**, **7g**, **7h**, **8j** are new compounds.

Typical Procedure for the Synthesis of Catalyst 1c: The amino acid derivative **1c** was synthesized according to the published procedure.[11d] To a solution of *N*-Boc-L-*tert*-leucine (9.24 g, 40 mmol) in anhydrous CH_2Cl_2 (60 mL) at 0 °C, was slowly added *N*,*N*′-dicyclohexylcarbodiimide (DCC; 8.66 g, 42 mmol) in anhydrous CH_2Cl_2 (40 mL). After stirring for 30 min, diethylamine (2.92 g, 40 mmol) in anhydrous CH_2Cl_2 (20 mL) was added in about 1 h, and the solution was stirred at room temperature for an additional 12 h. The white solid formed was filtered and washed with CH_2Cl_2 (2 × 20 mL). The organic layers were combined and washed with 2% HCl (10 mL), 4% $NaHCO_3$ (20 mL), and brine (20 mL), then dried with anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by flash chromatography and directly used for next step. To the obtained product was added MeOH (80 mL), then CH_3COCl (10 mL) slowly. The solution was heated to reflux for 1 h, and then cooled to room temperature. The solvent was removed, CH_2Cl_2 (120 mL) and H_2O (80 mL) were added, and the pH value was adjusted to 12 by the addition of K_2CO_3. The aqueous phase was extracted with CH_2Cl_2 (40 mL), and the organic layers were combined and dried with anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by flash chromatog-

raphy to afford the intermediate compound (8.58 g, 75% yield). To the above-obtained intermediate (8.58 g) in anhydrous THF (60 mL) at 0 °C was added $LiAlH_4$ (1.14 g, 30 mmol) in portions, then the solution was heated to reflux for 4 h. After cooling to room temperature, saturated aqueous Na_2SO_4 (4 mL) was added. The solid formed was filtered and washed with THF several times. The organic layers were combined and dried with anhydrous Na_2SO_4. The solvent was removed, and pure catalyst **1c** (3.97 g) was obtained as a colorless oil by distillation under reduced pressure (77% yield). $[\alpha]_D^{20}$ = +124.1 (*c* = 0.50, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (s, 9 H, CH_3), 0.97–1.02 (t, *J* = 6.90 Hz, 6 H, CH_3), 1.49 (br., 2 H, NH_2), 2.07–2.15 (m, 1 H, CH), 2.34–2.45 (m, 3 H, CH_2, CH_2), 2.53–2.67 (m, 3 H, CH_2, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.2, 26.4, 33.2, 47.5, 55.6, 57.4 ppm. HRMS: calcd. for $C_{10}H_{25}N_2$ [M + 1] 173.2012; found 173.2013.

(*S*)-*N*^{1},*N*^{1}-Diethyl-3-methylbutane-1,2-diamine (1b): $[\alpha]_D^{20}$ = +96.2 (*c* = 0.50, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90–0.92 (d, *J* = 6.90 Hz, 6 H, CH_3), 0.97–1.02 (t, *J* = 6.90 Hz, 6 H, CH_3), 1.46–1.57 (m, 3 H, CH, NH_2), 2.10–2.18 (m, 1 H, CH), 2.35–2.47 (m, 3 H, CH_2, CH_2), 2.53–2.65 (m, 3 H, CH_2, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.2, 18.3, 19.6, 32.3, 47.6, 56.3, 58.4 ppm. HRMS: calcd. for $C_9H_{23}N_2$ [M + 1] 159.1861; found 159.1856.

(*R*)-*N*^{1},*N*^{1}-Diethyl-3-phenylethane-1,2-diamine (1d): $[\alpha]_D^{20}$ = –73.5 (*c* = 0.50, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02–1.07 (t, *J* = 6.90 Hz, 6 H, CH_3), 1.92 (br., 2 H, NH_2), 2.41–2.57 (m, 4 H, CH_2), 2.62–2.74 (m, 2 H, CH_2), 4.03–4.08 (m, 1 H, CH), 7.21–7.40 (m, 5 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.1, 47.5, 53.8, 62.5, 126.8, 127.1, 128.5, 144.8 ppm. HRMS: calcd. for $C_{12}H_{21}N_2$ [M + 1] 193.1705; found 193.1699.

(*S*)-2-Amino-1-(azepan-1-yl)-3-phenylpropan-1-one (6): $[\alpha]_D^{20}$ = +68.6 (*c* = 0.50, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47–1.76 (m, 10 H, overlapped with the peak of H_2O, NH_2, CH_2), 2.74–2.81 (m, 1 H, CH_2), 2.99–3.05 (m, 1 H, CH_2), 3.20–3.34 (m, 1 H, CH_2), 3.34–3.42 (m, 2 H, CH_2), 3.43–3.60 (m, 1 H, CH_2), 3.88–3.92 (t, *J* = 7.20 Hz, 1 H, CH), 7.21–7.31 (m, 5 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.1, 47.5, 53.8, 62.5, 126.8, 127.1, 128.5, 144.8 ppm. HRMS: calcd for $C_{15}H_{23}N_2O$ [M + 1] 247.1810; found 247.1804.

Typical Procedure for the Direct Cross-Aldol Reaction of Acetaldehyde: Catalyst **1c** (6.9 mg, 0.04 mmol), $H_4SiW_{12}O_{40}$ (28.8 mg, 0.04 mmol), and 4-nitrobenzaldehyde (60.4 mg, 0.4 mmol) were mixed together in acetaldehyde (0.4 mL, 99% extra pure, Aldrich) at 10 °C. The mixture was stirred for 4 h, then excess acetaldehyde was removed in vacuo. MeOH (2 mL) and $NaBH_4$ (37 mg, 1.0 mmol) were added, and the resulting mixture was stirred at 0 °C for an additional 10 min before quenching by addition of water. The organic materials were extracted with CH_2Cl_2 three times, and the combined organic extracts were dried with anhydrous Na_2SO_4 and concentrated under vacuo. The residue was purified by flash chromatograph on silica gel to afford pure product **7a**.

(1*R*)-1-(4-Nitrophenyl)propane-1,3-diol (7a): Yield: 78 mg (0.039 mmol, 99%);[6] pale-yellow liquid. $[\alpha]_D^{20}$ = +20.2 (*c* = 0.5, MeOH). The enantiomeric excess (92% *ee*) was determined by HPLC (OJ-H column; 254 nm; 2-propanol/*n*-hexane, 1:9; 25 °C; 1.0 mL/min), t_R = 20.75 min (major isomer), t_R = 25.38 min (minor isomer). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.93–1.99 (m, 2 H, CH_2), 2.36 (s, 1 H, OH), 3.62 (s, 1 H, OH), 3.89–3.90 (d, *J* = 2.22 Hz, 2 H, CH_2), 5.07–5.11 (m, 1 H, CH), 7.53–7.56 (d, *J* = 8.76 Hz, 2 H, ArH), 8.18–8.21 (d, *J* = 8.73 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.2, 61.3, 73.3, 123.7, 126.4, 147.2, 151.7.

(1*R*)-1-(4-Cyanophenyl)propane-1,3-diol (7d): $[\alpha]_D^{20}$ = +16.4 (*c* = 0.54, MeOH). The enantiomeric excess (85% *ee*) was determined by HPLC (AS-H column; 210 nm; 2-propanol/*n*-hexane, 1:9; 25 °C; 1.0 mL/min), t_R = 32.92 min (major isomer), t_R = 38.75 min (minor isomer). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.91–1.96 (m, 2 H, CH_2), 2.38 (br. s, 1 H, OH), 3.56 (br. s, 1 H, OH), 3.87–3.90 (t, *J* = 5.40 Hz, 2 H, CH_2), 5.01–5.15 (t, *J* = 6.00 Hz, 1 H, CH), 7.47–7.49 (d, *J* = 8.10 Hz, 2 H, ArH), 7.64–7.62 (d, *J* = 8.10 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.1, 61.3, 73.5, 110.0, 118.8, 126.3, 132.2. 149.7 ppm. HRMS: clacd. for $C_{10}H_{11}NO_2$ [M] 177.0790; found 177.0792.

(1*R*)-1-(4-Chlorophenyl)propane-1,3-diol (7g): $[\alpha]_D^{20}$ = +18.2 (*c* = 0.50, MeOH). The enantiomeric excess (91% *ee*) was determined by HPLC after conversion of the primary hydroxy group into the monobenzoyl ester (AS-H column; 210 nm; 2-propanol/*n*-hexane, 3:97; 25 °C; 1.0 mL/min), t_R = 40.48 min (major isomer), t_R = 44.70 min (minor isomer). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.86–2.02 (m, 2 H, CH_2), 2.23 (br. s, 1 H, OH), 3.00 (br. s, 1 H, OH), 3.85–3.89 (m, 2 H, CH_2), 4.94–4.98 (m, 1 H, CH), 7.29–7.35 (m, 4 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.4, 61.3, 73.6, 127.0, 128.6, 133.2, 142.8 ppm. HRMS: calcd. for $C_9H_{11}ClO_2$ [M] 186.0448; found 186.0451.

(1*R*)-1-(3,4-Dichlorophenyl)propane-1,3-diol (7h): $[\alpha]_D^{20}$ = +50.2 (*c* = 0.68, MeOH). The enantiomeric excess (87% *ee*) was determined by HPLC (AS-H column; 210 nm; 2-propanol/*n*-hexane, 1:9; 25 °C; 0.5 mL/min), t_R = 18.69 min (major isomer), t_R = 19.98 min (minor isomer). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.84–1.94 (m, 2 H, CH_2), 2.60 (br. s, 1 H, OH), 3.59 (br. s, 1 H, OH), 3.84 (m, 2 H, CH_2), 4.88–4.92 (m, 1 H, CH), 7.15–7.18 (m, 1 H, ArH), 7.39–7.46 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.3, 61.4, 73.1, 125.0, 127.7, 130.4, 131.3, 132.6, 144.6 ppm. HRMS: calcd. for $C_9H_{11}Cl_2O_2$ [M] 220.0058; found 220.0061.

(1*R*)-1-(2-Fluorophenyl)propane-1,3-diol (7j): The enantiomeric excess (69% *ee*) was determined by HPLC (AS-H column; 210 nm; 2-propanol/*n*-hexane, 1:9; 25 °C; 1.0 mL/min), t_R = 10.02 min (minor isomer), t_R = 11.18 min (major isomer). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.99–2.04 (m, 2 H, CH_2), 2.34 (br. s, 1 H, OH), 3.09 (br. s, 1 H, OH), 3.84–3.91 (m, 2 H, CH_2), 5.27–5.31–4.92 (t, *J* = 6.00 Hz, 1 H, CH), 6.99–7.05 (m, 1 H, ArH), 7.14–7.29 (m, 2 H, ArH), 7.52–7.57 (m, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.0, 61.6, 68.5, 115.1, 115.4, 124.3, 124.4, 127.1, 127.2, 128.8, 128.9 ppm. HRMS: calcd. for $C_9H_{11}FO_2$ [M] 170.0743; found 170.0745.

Supporting Information (see footnote on the first page of this article): Detailed results of acid screening, determination of the absolute configuration of **7a** and **8b**, NMR spectra of the chiral primary amines and cross-aldol products, and HPLC traces of the cross-aldol products.

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