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The effect of hydrogen bond donors in asymmetric organocatalytic conjugate additions

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ABSTRACT

A series of primary amine organocatalysts with various hydrogen bond donors were prepared and examined in the conjugate addition of isobutyraldehyde and acetone to *trans*-β-nitrostyrene and (*E*)-methyl 2-oxo-4-phenylbut-3-enoate. The effect of N–H acidity and hydrogen-bonding modes of the catalysts on the catalytic activity and enantioselectivity was studied. The experimental results did not support a general correlation of N–H acidity and hydrogen-bonding modes with catalytic activity and enantioselectivity. The catalysts with double hydrogen-bonding interactions provided better catalytic activities and enantioselectivities than the catalysts with single hydrogen-bonding interactions for the reaction of *trans*-β-nitrostyrene. The catalyst with the most acidic N–H bond showed the best catalytic activity and enantioselectivity for the reaction of (*E*)-methyl 2-oxo-4-phenylbut-3-enoate. These results suggest that the effect of hydrogen bond donors in organocatalytic reactions may be highly dependent on the substrates and the reaction conditions.

1. Introduction

Asymmetric catalysis through explicit hydrogen-bonding interactions has been proved to be a highly successful strategy.[1] Ureas, thioureas, guanidinium and amidinium ions, sulfamides, and sulfonamides are privileged hydrogen bond donors. The hydrogen-bonding interactions with carbonyl groups, imines, and nitro groups of the substrates increase their electrophilic reactivity. Furthermore, the hydrogen-bonding interactions also help to provide pre-organized transition states and to control the stereoselectivity efficiently. As a generally accepted opinion, the more acidic is the involving heteroatom–hydrogen bond the stronger is the resulting hydrogen-bonding interaction. In addition, double hydrogen bond donors or multiple hydrogen bond donors are thought to be more efficient than single hydrogen bond donors. For example, ureas, thioureas, and guandinium ions are expected to provide better catalytic activity than sulfonamides or amides. However, the effect of the different hydrogen bond donors on catalytic activity and stereoselectivity has rarely been studied in detail. Such knowledge should be highly useful for the design of more efficient organocatalysts.

The combination of hydrogen bond donors and amines has led to extremely efficient bifunctional organocatalysts for many asymmetric transformations.[2] These catalysts feature the simultaneous activation of both nucleophiles and electrophiles. Recently we developed a new class of sulfamide-primary amine organocatalysts and found that they are highly efficient for the conjugate addition of aldehydes and ketones to nitroalkenes.[3] In a subsequent study, we also found that the structurally related thioureas are also good catalysts for the reaction.[4] Although we expected that the more acidic N–H bond in the sulfamides could provide better catalytic efficiency than in the corresponding thioureas, a reliable conclusion could not be achieved by the present experiment results. We become interested in the effect of the acidity of the N–H bond and the hydrogen-bonding modes on the catalytic activity and stereoselectivity of bifunctional primary amine organocatalysts. To this end, a series of chiral bifunctional primary amines with various hydrogen bond donors were designed and prepared. These catalysts were examined in the asymmetric conjugate addition of aldehydes and ketones to nitroalkenes and α,β-unsaturated ketoesters. The experimental results are reported herein.

2. Results and discussion

Primary amines **1a**–**1i** with a chiral cyclohexane-1,2-diamine backbone were prepared (Scheme 1). Several kinds of hydrogen bond donors were selected, including urea, thiourea, sulfamide, sulfonamide, and amide. The pK_a values of the selected N–H bonds were calculated with a ACD/Lab 11 program.[5] For the sake of comparison, the phthalimide derivative **1j** was also prepared, which is unable to provide the hydrogen-bonding interaction. Initially the conjugate addition of isobutyraldehyde to *trans*-β-nitrostyrene was explored using **1a**–**1j** as the catalysts.[6] Since the reaction was found to be rather slow in the absence of base additives, DMAP

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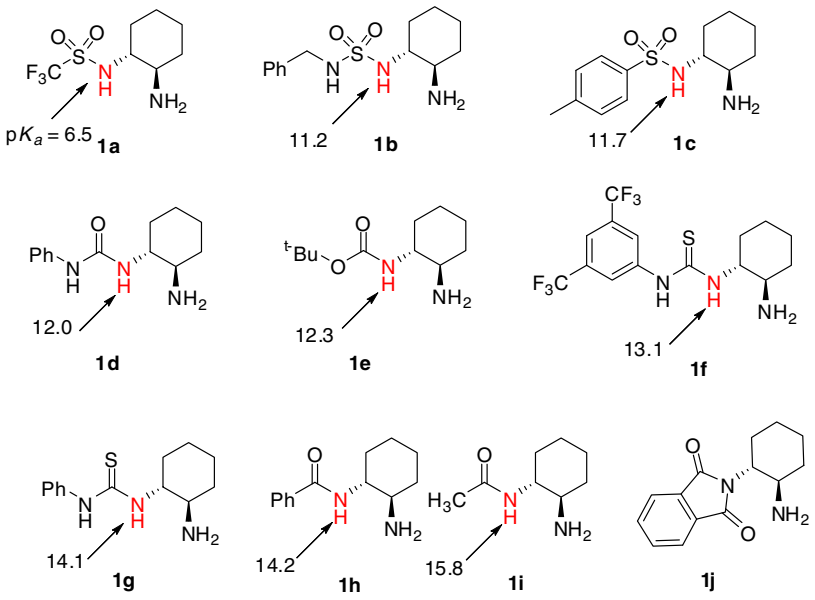
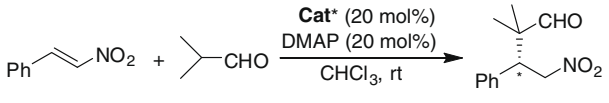


Scheme 1. Chiral primary amine organocatalysts **1a**–**1j**.

was used as the selected additive based on the previous study.[3a] The results are summarized in Table 1.

The reaction did not occur when only a base additive (DMAP) was used (Table 1, entry 1). Catalysts **1a**–**1j** accelerated the reaction and provided good to excellent enantioselectivities. Catalyst **1j**, which is free of the hydrogen bond donor, gave the product in low yield and moderate enantioselectivity. In addition the enantiofacial selectivity was reversed (Table 1, entry 11). The results clearly demonstrate the importance of the hydrogen-bonding interaction for the catalytic behaviors of **1a**–**1j**. However the acidity of the N–H bond in the catalysts is not proportional to the catalytic activity (Table 1, **1a** vs **1b**, **1d**, **1f**, and **1g**). Catalyst **1f** with a more acidic N–H bond did not afford a higher reaction rate than the structurally similar **1g** (Table 1, entry 7 vs entry 8). It is obvious that the double hydrogen-bonding interaction leads to a higher reaction rate and enantioselectivity than the single hydrogen-bonding interaction (**1b**, **1d**, **1f**, and **1g** vs the other catalysts).

Table 1
The reaction of isobutyraldehyde and *trans*-β-nitrostyrene catalyzed by **1a**–**1j**[a]

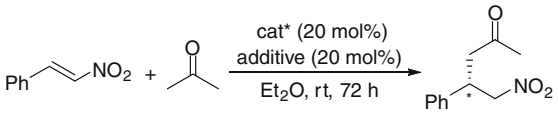


Entry	Cat	pK_a[b]	Time (h)	Yield[c] (%)	ee[d] (%)
1	—	—	24	—	—
2	**1a**	6.5	6	87	92
3	**1b**	11.2	2	83	99
4	**1c**	11.7	24	44	99
5	**1d**	12.0	2	88	98
6	**1e**	12.3	24	52	83
7	**1f**	13.1	2	92	97
8	**1g**	14.1	2	89	98
9	**1h**	14.2	24	49	93
10	**1i**	15.8	6	85	95
11	**1j**	—	24	23	−64

[a] The reactions were carried out with nitrostyrene (0.20 mmol), isobutyraldehyde (0.05 mL), catalyst (0.04 mmol), and DMAP (0.04 mmol) in chloroform (0.3 mL) at room temperature.
[b] The pK_a values were calculated with an ACD/Lab 11 program.
[c] Isolated yield.
[d] Ee values were determined by chiral HPLC analysis.

The reaction of acetone and *trans*-β-nitrostyrene was also studied using **1a**–**1j** as the catalysts. Since both acid and base additives were found to promote the reaction previously,[3b] the reaction was examined in the presence of benzoic acid and imidazole, respectively. The experimental results are summarized in Table 2.

Table 2
The reaction of acetone and *trans*-β-nitrostyrene catalyzed by **1a**–**1j**[a]

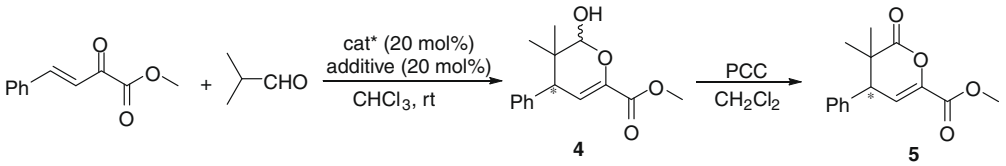


Entry	Cat	PhCOOH		Imidazole	
		Yield[b] (%)	ee[c] (%)	Yield (%)	ee (%)
1	**1a**	51	56	88	39
2	**1b**	74	74	54	70
3	**1c**	62	61	69	55
4	**1d**	87	58	63	50
5	**1e**	56	58	55	45
6	**1f**	95	64	82	67
7	**1g**	93	74	58	65
8	**1h**	55	64	66	49
9	**1i**	60	60	66	46
10	**1j**	19	22	40	−7

[a] The reactions were carried out with nitrostyrene (0.15 mmol), acetone (0.2 mL), catalyst (0.03 mmol), and additive (0.03 mmol) in ether (0.4 mL) at room temperature.
[b] Isolated yield.
[c] Ee values were determined by chiral HPLC analysis.

Generally, catalysts **1b**, **1d**, **1f**, and **1g**, which are able to exert double hydrogen-bonding interactions, provided better enantioselectivities and yields than catalysts **1c**, **1e**, **1h**, and **1i** (Table 2, entries 2, 4, 6, and 7 vs entries 3, 5, 8, and 9). However catalyst **1a**, which exerts a single hydrogen-bonding interaction, provided the best yield amongst the tested catalysts while imidazole was used as the additive (Table 2, entry 1). Its extremely strong acidic N–H bond may account for this result. The different dependence of additives was also observed for these two classes of catalysts. For the former class, benzoic acid gave better enantioselectivities and yields than imidazole (Table 2, entries 2, 4, 6, and 7). For the second

Table 3
The reaction of isobutyraldehyde and (*E*)-methyl 2-oxo-4-phenylbut-3-enoate catalyzed by **1a**–**1j**[a]

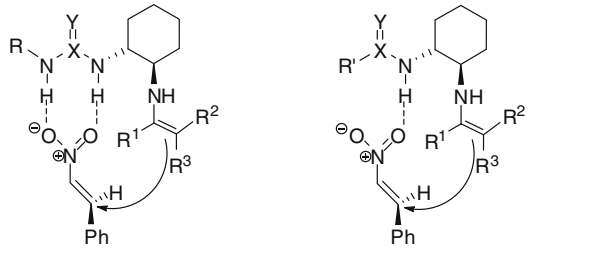


En	Cat	DMAP			PhCOOH		
		Time (h)	Yield[b] (%)	ee[c] (%)	Time (h)	Yield (%)	ee (%)
1	**1a**	24	54	75	30	85	76
2	**1b**	24	66	0	30	60	0
3	**1c**	24	72	0	30	67	5
4	**1d**	24	67	24	24	57	41
5	**1e**	72	54	−29	48	46	−5
6	**1f**	24	58	63	48	82	71
7	**1g**	24	56	51	48	71	58
8	**1h**	30	69	54	48	83	73
9	**1i**	24	59	44	48	69	59
10	**1j**	72	44	60	72	51	51

[a] The reactions were carried out with (*E*)-methyl 2-oxo-4-phenylbut-3-enoate (0.2 mmol), isobutyraldehyde (50 μL), catalyst (0.04 mmol), and additive (0.04 mmol) in chloroform (0.3 mL) at room temperature.
[b] Isolated yield.
[c] Ee values were determined by chiral HPLC analysis.

class, benzoic acid gave better enantioselectivities, but imidazole gave better yields (Table 2, entries 1, 3, 5, 8, and 9). For catalyst **1j**, both benzoic acid and imidazole provided the product in low yields and enantioselectivities (Table 2, entry 10). Again, the acidity of the N–H bond in the catalysts **1a**–**1i** did not show a reliable correlation between the catalytic activity and enantioselectivity.

Two bifunctional catalytic mechanisms could be suggested for catalysts **1a**–**1i** (Scheme 2).[3a,7] The catalysts provide the primary amine group to generate the enamine intermediates with isobutyraldehyde or acetone, and at the same time exert hydrogen-bonding interactions with *trans*-β-nitrostyrene. While the hydrogen bond donors are ureas, thioureas and sulfamides, double hydrogen-bonding interactions are proposed. For the other hydrogen bond donors, only single hydrogen-bonding interactions are possible. The hydrogen-bonding interactions affect the reaction in two ways: (1) increasing the electrophilicity of nitrostyrene; and (2) pre-organizing the reaction substrates and controlling the enantioselectivity. It is expected that the double hydrogen-bonding interactions provide a better acceleration effect and enantiocontrol ability.



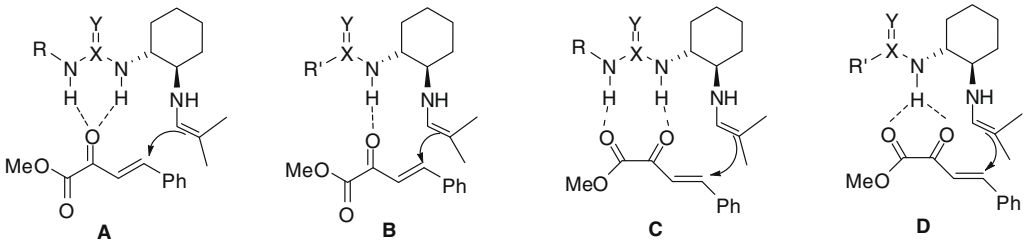
Scheme 2. Proposed catalytic mechanism of **1a**–**1i** for the reaction of *trans*-β-nitrostyrene with isobutyraldehyde and acetone.

The reaction of isobutyraldehyde and (*E*)-methyl 2-oxo-4-phenylbut-3-enoate was further studied using **1a**–**1j** as catalysts.[8] The primary product was a hemiacetal **4**, which was oxidized by PCC to give **5**. The reaction was found to be accelerated by both acid and base additives. Generally the acid additives provided better yields and enantioselectivities. The experimental results are summarized in Table 3.

For this reaction the best catalyst was found to be **1a**, which possesses the most acidic N–H bond among the catalysts **1a**–**1i** (Table 3, entry 1). Sulfamide **1b** and sulfonamide **1c** provided racemic products (Table 3, entries 2 and 3). *t*-Butoxycarbamide **1e** provided the product with reverse enantiofacial selectivity (Table 3, entry 5). Catalysts **1f** and **1h** provided comparable yields and enantioselectivities with **1a** (Table 3, entries 6 and 8 vs entry 1), although **1a** (pK_a = 6.5), **1f** (pK_a = 13.1), and **1h** (pK_a = 14.2) have quite different pK_a values. Catalysts **1a** and **1h** can only provide a single hydrogen-bonding interaction, but **1f** exerts a double hydrogen-bonding interaction. These results are different from those obtained in the reaction of *trans*-β-nitrostyrene. Although a reliable explanation could not be presented, the different hydrogen-bonding modes are speculated for the reaction of (*E*)-methyl 2-oxo-4-phenylbut-3-enoate (Scheme 3). Among the four possible hydrogen-bonding modes, C and D are thought to be unfavorable because two vicinal carbonyl groups take an approximately parallel arrangement. In modes A and B, two carbonyl groups are antiparallel. In the case of *trans*-β-nitrostyrene, the two N–O bonds are at an angle of about 120° (Scheme 2). This structural difference may account partially for the different catalytic behavior of **1a**–**1j**.

3. Conclusion

In conclusion, a series of primary amine organocatalysts with various hydrogen bond donors were prepared and studied for the conjugate addition of butyraldehyde and acetone to *trans*-β-nitrostyrene and (*E*)-methyl 2-oxo-4-phenylbut-3-enoate. For the reaction of *trans*-β-nitrostyrene, the catalysts with double hydrogen-bonding interactions are more efficient than the catalysts with single hydrogen-bonding interactions concerning both the catalytic activity and enantioselectivity. The acidity of N–H bond of the catalysts is not proportional to the catalytic activity. However for the reaction of (*E*)-methyl 2-oxo-4-phenylbut-3-enoate, the catalyst with the most acidic N–H bond showed the best catalytic activity and enantioselectivity. The present experimental results cannot support a general correlation of the acidity of N–H bond and hydrogen-bonding modes with the catalytic activity and enantioselectivity of the catalysts. The catalytic behavior of the catalysts seems to be highly dependent on the reaction sub-



Scheme 3. Possible hydrogen-bonding modes for the reaction of (*E*)-methyl 2-oxo-4-phenylbut-3-enoate.

strates and conditions. These observations should be taken into account during the design of new organocatalysts with hydrogen-bonding interactions.

4. Experimental

4.1. General method

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AVANCE 400 spectrometer. Chemical shifts of protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.26 and CH_3OH: δ 4.84, 3.31). Chemical shifts of carbon are referenced to the carbon resonances of the solvent ($CHCl_3$: δ 77.0 and CH_3OH: δ 46.0). Peaks are labeled as singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Optical rotations were measured on a Perkin Elmer digital polarimeter. Melting points were measured on a WRS-2A melting point apparatus and are uncorrected. The mass spectroscopic data were obtained at the Thermo DSQII and Agilent 6120 mass spectrometer. The high resolution mass spectroscopic data were obtained at the Shimadzu IT-TOF mass spectrometer. Infrared (IR) spectra were recorded on a Bruker Tensor 37 spectrophotometer. The data are represented as follows: frequency of absorption (cm^{-1}) and intensity of absorption (vs = very strong, s = strong, m = medium, and w = weak). Enantiomeric excesses were determined by HPLC using a Daicel Chiralpak AD-H, AS-H column and eluting with a hexane/*i*-PrOH solution.

4.2. Synthesis of catalysts

Catalysts **1b**,[3a] **1c**,[9] **1d**,[10] **1f**, **1g**,[11] **1i**,[12] and **1j**[13] were prepared according to the reported procedures.

4.2.1. *N*-((1*R*,2*R*)-2-Aminocyclohexyl)-1,1,1-trifluoromethanesulfonamide 1a [6h]

To a solution of catalyst **1j** (488 mg, 2.0 mmol) in 15 mL of dried CH_2Cl_2 was added dropwise a solution of Tf_2O (0.4 mL, 2.40 mmol) in 5 mL of dried CH_2Cl_2 at 0 °C under N_2 atmosphere over 1 h. The resulting mixture was stirred overnight. Then CH_2Cl_2 (50 mL) and HCl (l mol/L, 20 mL) were added. After the separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layer was washed with brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo to provide a white solid, which was refluxed with hydrazine hydrate (0.4 mL) in ethanol (15 mL) for 2 h. The reaction solution was diluted with diethyl ether to precipitate phthaloyl hydrazide. The insoluble solid was filtered and the filtrate was evaporated in vacuo. The crude product was purified by column chromatography over silica gel (ethyl acetate/methanol = 15/1) to provide a white solid (160 mg, 31%). $[\alpha]_D^{20} = -7.2$ (*c* 1.06, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD) δ: 3.08–3.02 (m, 1H), 2.68–2.62 (m, 1H,), 2.03–1.97 (m, 2H), 1.78–1.73 (m, 2H), 1.42–1.29 (m, 4H); ^{13}C NMR (100 MHz, CD_3OD) δ: 123.1 (d, $^1J_{CF}$ = 323.8 Hz), 59.4, 57.9, 35.4, 31.1, 25.8, 25.4; IR (thin film) ν/cm^{-1}: 2943(m), 2863(m), 1622(m), 1453(w), 1365(m), 1267(s), 1202(s), 1092(m), 968(m); MS (ESI, M^++1): 247.1.

4.2.2. *N*-((1*R*,2*R*)-2-Aminocyclohexyl)benzamide 1h[14]

To a solution of (1*R*,2*R*)-cyclohexane-1,2-diamine (1.14 g, 10 mmol) in CH_2Cl_2 (15 mL) was added dropwise a solution of benzoyl chloride (231 μL, 2 mmol) in 5 mL CH_2Cl_2 at −20 °C over 30 min. The reaction mixture was stirred overnight at room temperature. Then water (20 mL) was added. The organic layer was separated and dried over Na_2SO_4. After the evaporation of the solvent in vacuo, the residue was purified by column chromatography over silica gel (ethyl acetate/methanol = 10/1) to provide **1h** as a white solid (150 mg, 34%). Mp 176.5–179.8 °C; $[\alpha]_D^{20} = -49.0$ (*c* 1.0, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD) δ: 7.86 (d, *J* = 7.6 Hz, 2H), 7.53 (t, *J* = 7.0 Hz, 1H), 7.46 (t, *J* = 7.4 Hz, 2H), 3.75–3.69(m, 1H), 2.68–2.62 (m, 1H), 2.02–1.99 (m, 2H), 1.78–1.77 (m, 2H), 1.38–1.24 (m, 4H); ^{13}C NMR (100 MHz, CD_3OD) δ: 170.6, 136.0, 132.6, 129.5, 128.4, 57.5, 55.2, 35.3, 33.1, 26.3, 26.1; IR (thin film) ν/cm^{-1}: 3342(m), 3047(m), 2926(s), 2858(m), 1649(s), 1602(w), 1532(m), 1445(m), 1328(m), 1141(m), 1086(w); MS (ESI, M^++1): 219.2.

4.3. Typical procedure for the conjugate addition of isobutyraldehyde to *trans*-β-nitrostyrene catalyzed by 1a–1j

A mixture of *trans*-β-nitrostyrene (0.2 mmol), **1g** (0.04 mmol), DMAP (0.04 mmol), isobutyraldehyde (50 μL), and chloroform (0.3 mL) was stirred at room temperature for 2 h. After the evaporation of the solvent in vacuo, the residue was separated by flash chromatography over silica gel (petroleum ether/ethyl acetate = 10/1) to give 2,2-dimethyl-4-nitro-3-phenyl-butanal **2** as a colorless oil (39 mg, 89%). $[\alpha]_D^{20} = +7.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.51 (s, 1H), 7.31–7.24 (m, 5H), 4.85 (dd, *J* = 12.9, 11.1 Hz, 1H), 4.68 (dd, *J* = 12.9, 4.2 Hz, 1H), 3.78 (dd, *J* = 11.1, 4.2 Hz, 1H), 1.14 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 204.0, 135.2, 129.0, 128.6, 128.0, 76.3, 48.5, 48.2, 21.7, 19.0; MS (EI): *m/z* = 221 (M^+), 187, 170, 159, 145, 117, 105, 91, 77, 72; IR (thin film) ν/cm^{-1}: 2925(w), 1726(m), 1638(m), 1556(s), 1456(w), 1380(m), 705(m); The enantiomeric excess was determined by HPLC with Chiralpak AD-H column at 208 nm (hexane/^{i}PrOH = 98/2, 0.5 mL/min; $t_{R(major)}$ = 24.9 min, $t_{R(minor)}$ = 25.9 min).

4.4. Typical procedure for the conjugate addition of acetone to *trans*-β-nitrostyrene catalyzed by 1a–1j

A solution of *trans*-β-nitrostyrene (0.15 mmol), **1g** (0.03 mmol), PhCOOH (0.03 mmol), and acetone (0.2 mL) in ether (0.4 mL) was stirred at room temperature for 72 h. The reaction solution was concentrated in vacuo. The residue was purified by flash column chromatography over silica gel (petroleum ether/ethyl acetate = 6/1) to give 5-nitro-4-phenylpentan-2-one **3** as a white solid (29 mg, 93%). Mp 114 −116 °C; $[\alpha]_D^{20} = +5.3$ (*c* 1.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35–7.20 (m, 5H), 4.70 (dd, *J* = 12.2,

6.8 Hz, 1H), 4.60 (dd, J = 12.2, 7.8 Hz, 1H), 4.01 (m, 1H), 2.92 (d, J = 7.0 Hz, 2H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 205.4, 138.8, 129.1, 127.9, 127.4), 79.5, 46.1, 39.0, 30.4; MS (EI): m/z = 207 (M^+), 191, 167, 133, 91, 84; IR (thin film) ν/cm^{-1}: 3040(w), 2950(w), 1715(s), 1546(vs), 1384(s), 1362(m), 758(w), 696(w); The enantiomeric excess was determined by HPLC with an AS-H column at 208 nm (hexane/^{i}-PrOH = 75/25, 1.0 mL/min; $t_{R(major)}$ = 10.1 min, $t_{R(minor)}$ = 13.1 min).

4.5. Typical procedure for the conjugate addition of isobutyraldehyde to (*E*)-methyl 2-oxo-4-phenylbut-3-enoate catalyzed by catalysts 1a–1j

A mixture of (*E*)-methyl 2-oxo-4-phenylbut-3-enoate (0.2 mmol), **1a** (0.04 mmol), PhCOOH (0.04 mmol), and isobutyraldehyde (50 μL) in chloroform (0.3 mL) was stirred at room temperature for 30 h. After the evaporation of the solvent in vacuo, the residue was separated by flash chromatography over silica gel (petroleum ether/ethyl acetate = 8/1) to give the cyclic semi-acetal **4** as a white solid (45 mg, 85%). Oxidation of the cyclic hemiacetal was performed in CH_2Cl_2 by adding 5 equiv of PCC at room temperature. After stirring for 24 h, the reaction mixture was partitioned between ethyl acetate and saturated $NaHCO_3$. The EtOAc layer was concentrated in vacuo and the residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate = 8/1) to afford methyl 3,3-dimethyl-2-oxo-4-phenyl-3,4-dihydro-2H-pyran-6-carboxylate **5** as a white solid. Mp 77.5–79.2 °C; $[\alpha]_D^{20} = -19.2$ (c 1.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35–7.29 (m, 3H,), 7.11–7.09 (m, 2H), 6.62 (d, J = 5.4 Hz, 1H), 3.87 (s, 3H), 3.49 (d, J = 5.4 Hz), 1.41 (s, 3H), 1.01 (s, 3H,); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.8, 160.9, 141.1, 136.9, 128.8, 128.5, 128.1, 117.6, 52.65, 50.1, 40.9, 25.9, 21.5; IR (thin film) ν/cm^{-1}: 2924(s), 2853(m), 1742(s), 1696(s), 1496(w), 1469(w), 1456(m), 1387(w), 1312(m), 1254(s), 1112(m), 1068(s), 950(m), 806(m), 760(m), 702(m); MS (ESI, M$^+$+1): 261.1; HRMS (ESI) calcd for $C_{15}H_{15}O_4$ $(M-H)^-$: 259.0970, found: 259.0966. The enantiomeric excess was determined by HPLC with Chiralpak AD-H column at 208 nm (hexane/^{i}-PrOH = 95/5, 1.0 mL/min; $t_{R(minor)}$ = 9.2 min, $t_{R(major)}$ = 10.2 min).

Acknowledgments

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References

1. For the reviews on catalysis through explicit hydrogen-bonding interactions, see: (a) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289; (b) Zhang, Z. G.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187; (c) Yu, X. H.; Wang, W. *Chem. Asian J.* **2008**, *3*, 516.
2. For reviews of bifunctional organocatalysts, see: (a) Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5418; (b) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520.
3. (a) Zhang, X. J.; Liu, S. P.; Li, X. M.; Yan, M.; Chan, A. S. C. *Chem. Commun.* **2009**, 833; (b) Liu, S. P.; Zhang, X. J.; Lao, J. H.; Yan, M. *Arkivoc* **2009**, *7*, 268.
4. Zhang, X. J.; Liu, S. P.; Lao, J. H.; Du, G. J.; Yan, M.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2009**, *20*, 1451.
5. pK_a Values of the selected N–H bonds were calculated with the program ACD/pK_a DB (version 11, Advanced Chemistry Development, Inc., Toronto, Canada, 2008). The other calculation methods were also used to obtain the pK_a values of organocatalysts, see: (a) Chen, J. R.; Lu, H. H.; Li, X. Y.; Cheng, L.; Wan, J.; Xiao, W. J. *Org. Lett.* **2005**, *7*, 4543; (b) Pansare, S. V.; Kirby, R. L. *Tetrahedron* **2009**, *65*, 4557.
6. For selected publications on the conjugate addition of aldehydes and ketones to nitroalkenes catalyzed by chiral primary amines, see: (a) Xu, L. W.; Luo, J.; Lu, Y. X. *Chem. Commun.* **2009**, 1807; (b) Rasappan, R.; Reiser, O. *Eur. J. Org. Chem.* **2009**, 1305; (c) Liu, J.; Yang, Z. G.; Liu, X. H.; Wang, Z.; Liu, Y. L.; Bai, S.; Lin, L. L.; Feng, X. M. *Org. Biomol. Chem.* **2009**, *7*, 4120; (d) Kokotos, C. G.; Kokotos, G. *Adv. Synth. Catal.* **2009**, *351*, 1355; (e) Gu, Q.; Guo, X. T.; Wu, X. Y. *Tetrahedron* **2009**, *65*, 5265; (f) Gruttadauria, M.; Giacalone, F.; Noto, R. *Adv. Synth. Catal.* **2009**, *351*, 33; (g) Yang, Z. G.; Liu, J.; Liu, X. H.; Wang, Z.; Feng, X. M.; Su, Z. S.; Hu, C. W. *Adv. Synth. Catal.* **2008**, *350*, 2001; (h) Xue, F.; Zhang, S. L.; Duan, W. H.; Wang, W. *Adv. Synth. Catal.* **2008**, *350*, 2194; (i) Peng, F. Z.; Shao, Z. H. *J. Mol. Catal. A: Chem.* **2008**, *285*, 1; (j) Xiong, Y.; Wen, Y. H.; Wang, F.; Gao, B.; Liu, X. H.; Huang, X.; Feng, X. M. *Adv. Synth. Catal.* **2007**, *349*, 2156; (k) Wei, S. W.; Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, S. *Catal. Today* **2007**, *121*, 151; (l) McCooey, S. H.; Connon, S. J. *Org. Lett.* **2007**, *9*, 599; (m) Liu, K.; Cui, H. F.; Nie, J.; Dong, K. Y.; Li, X. J.; Ma, J. A. *Org. Lett.* **2007**, *9*, 923; (n) Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, S. *Adv. Synth. Catal.* **2006**, *348*, 826; (o) Xu, Y. M.; Cordova, A. *Chem. Commun.* **2006**, 460; (p) Xu, Y.; Zou, W.; Sundé, H.; Ibrahem, I.; Códova, A. *Adv. Synth. Catal.* **2006**, *348*, 418; (q) Tsogoeva, S. B.; Wei, S. W. *Chem. Commun.* **2006**, 1451.
7. (a) Huang, H. B.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170; (b) Lalonde, M. P.; Chen, Y. G.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6366.
8. For asymmetric conjugate addition of aldehydes to α,β-unsaturated ketoesters, see: (a) Wang, J.; Yu, F.; Zhang, X. J.; Ma, D. W. *Org. Lett.* **2008**, *10*, 2561; (b) Juhl, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1498.
9. Balsells, J.; Mejorado, L.; Phillips, M.; Ortega, F.; Aguirre, G.; Somanathan, R.; Walsh, P. J. *Tetrahedron: Asymmetry* **1998**, *9*, 4135.
10. Bied, C.; Moreau, J. J. E.; Man, M. W. C. *Tetrahedron: Asymmetry* **2001**, *12*, 329.
11. Kim, Y. K.; Lee, S. J.; Ahn, K. H. *J. Org. Chem.* **2000**, *65*, 7807.
12. Isobe, T.; Fukuda, K.; Tokunaga, T.; Seki, H.; Yamaguchi, K.; Ishikawa, T. *J. Org. Chem.* **2000**, *65*, 7774.
13. Mitchell, J. M.; Finney, N. S. *Tetrahedron Lett.* **2000**, *41*, 8431.
14. Kaik, M.; Gawronski, J. *Tetrahedron: Asymmetry* **2003**, *14*, 1559.