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Facile evolution of asymmetric organocatalysts in water assisted by surfactant Brønsted acids

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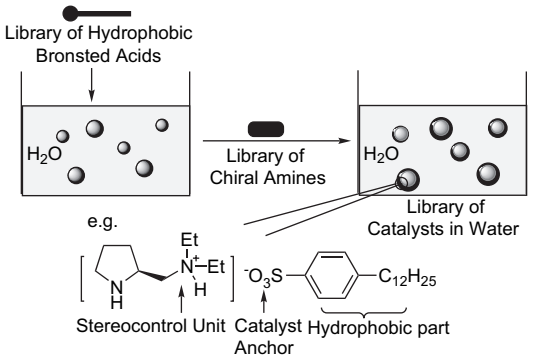
Abstract—Simple mixing of chiral amines and surfactant Brønsted acids such as *p*-dodecyl benzenesulfonic acid (DBSA) leads to highly effective and selective organocatalysts in water. The in situ generated catalysts catalyze highly stereoselective desymmetrization of *prochiral* ketones via direct aldol reactions (up to >16:1 dr, >99% ee) in water using micelle as reaction media. The current strategy was also applied in asymmetric Michael addition leading to a catalytic system with good activity and stereoselectivity.

1. Introduction

The aqueous phase asymmetric catalysis has attracted intensive research interest in the last decade due to the favorable features of water as an inexpensive, safe, and environmentally benign medium.[1] More recently, chiral amines have become another focus in this field because of their divergent nature to form either nucleophilic enamines or electrophilic imminium ions and their structural modifiability to ease diversity-oriented catalysts discovery.[2] Their nontoxic and robust features as well as mild experimental conditions are also beneficial to catalytic reactions in aqueous media.[3] And indeed, quite a few chiral amine-catalyzed reactions in homogeneous aqueous media have been reported recently that showed good stereoselectivity.[4] Water was demonstrated to increase both reactivity and stereoselectivity for some direct aldol reactions.[5]

Despite these remarkable achievements, a modular and efficient methodology that directly transforms the available chiral amines into effective aqueous-phase chiral catalysts without any modification should be highly desirable. Herein, we present a simple strategy for developing asymmetric catalysts that combines chiral amines and surfactant Brønsted acids (SBAs) via non-covalent acid–base interactions in water (Scheme 1). The asymmetric organocatalytic systems obtained here also allowed us to demonstrate the first example of desymmetric direct aldol reactions in water. Using this strategy, highly active and stereoselective catalysts for Michael addition were also developed in water.



Scheme 1. Strategy for the construction of chiral amine catalysts in water.

2. Result and discussion

2.1. The principle of catalyst evolution in water

Though the combination of chiral amine–Brønsted acid is known,[4a,6] the corresponding aqueous catalysis utilizing surfactant Brønsted acids has rarely been attempted.[7] In fact, surfactants are frequently employed in order to perform reactions in water.[8] Recently, Barbas et al.,[9] Hayashi et al.,[10] and this group[11] independently reported tailor-made surfactant-type chiral amine catalysts wherein the connected surfactant moieties were shown to be essential for high activity and

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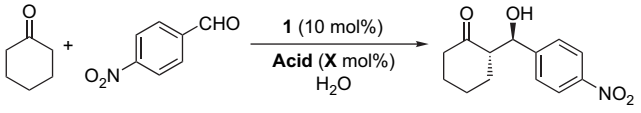
enantioselectivity by forming hydrophobic colloidal dispersions favorable for the reactions.[12] In these cases, the catalysts have to be prepared individually via multiple steps, and are therefore limited for further evolution. In comparison, our approach in the present work takes advantage of a readily available chiral amine library and the quick and quantitative acid–base reaction to in situ generate asymmetric catalysts in water, so that a diverse library of asymmetric catalysts suitable for aqueous catalysis is easily created to fulfill the requirements of the reactions under study. Furthermore, surfactant Brønsted acid in this design would not only act as a surfactant, but also as a non-covalent anchor for chiral amines leading to protonated centers that are critical for stereocontrol (Scheme 1).

Table 1. The acid screening[a]



Entry	Acid[b]	X	Time (h)	Yield[c] (%)	*anti*:*syn*[d]	ee[e] (%)
1	PFDA	10	12	80	66:34	25
2	STEA	10	12	93	63:37	17
3	DDNA	10	12	96	62:38	26
3	DDPA	10	12	45	74:26	52
5	$Zn(DS)_2$	10	12	59	77:23	65
6	PTSA	10	12	24	78:22	53
7	DBSA	10	13	92	83:17	68
8	DBSA	12	13	59	80:20	81
9	DBSA	15	13	45	82:18	84

[a] Aldehyde (0.5 mmol), 1 mmol cyclohexanone, 1 mL media.
[b] DBSA: 4-dodecylbenzenesulfonic acid; PTSA: 4-methylbenzenesulfonic acid; DDNA: dodecanoic acid; PFDA: perfluoroundecanoic acid; STEA: stearic acid; DDPA: didodecyl hydrogen phosphate. DS: dodecyl sulfate.
[c] Isolated yields.
[d] Determined by ^{1}H NMR.
[e] Determined by HPLC on a chiral column.

2.2. Evolution of organocatalysts for direct aldol reaction in water

Asymmetric direct aldol reaction of cyclohexanone was selected for our initial model reaction. A quick scanning of surfactant Brønsted acids (SBAs) with chiral diamine **1** was first conducted (Table 1). The combinations **1** and SBAs could catalyze the reaction with good enantioselectivity (up to 84% ee, Table 1). In contrast, the reaction with a non-surfactant Brønsted acid such as *p*-toluenesulfonic acid gave a low yield and stereoselectivity (Table 1, entry 6), thus validating our hypothesis. Light microscopic studies demonstrated that both the in situ-generated catalyst and the reaction mixture formed good colloidal dispersions in pure water (Fig. 1), suggesting that the reactions occur in the micelles. The acidity of SBAs was found to be a major factor influencing the enantioselectivity and among a series of commercial available surfactant Brønsted acids *p*-dodecyl benzenesulfonic acid (DBSA) gave the best performance, so it was selected for further catalysts' screening. It is noted that increasing the loading of DBSA resulted in improvement on enantioselectivity, but with the sacrifice of activity (Table 1, entries 7–9). This observation suggests the existence of general base catalysis under these conditions.

An initial library of chiral diamines was then constructed since this type of catalysts is frequently used in organocatalysis in organic solvent (Fig. 2).[2,6] It was found that successful chiral diamine catalysts in organic solvent could

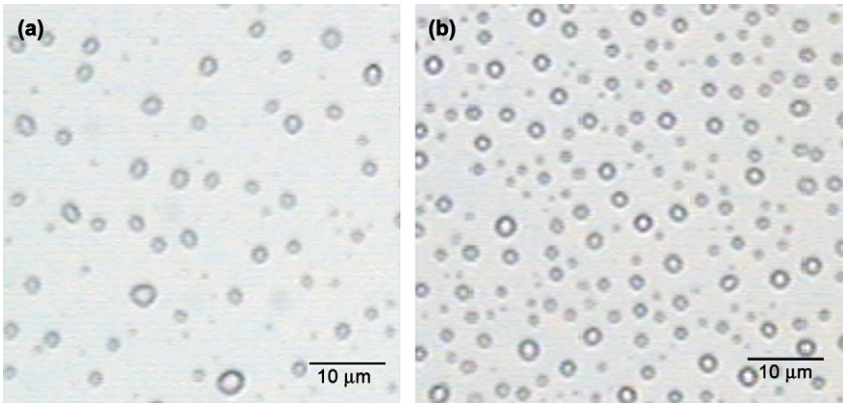


Figure 1. Light microscopy of: (a) mixtures of chiral amine **1** (0.05 M) and DBSA (0.05 M) in water; (b) mixtures of chiral amine **1** (0.05 M), DBSA (0.05 M), cyclohexanone (1 M) and *p*-NO_2PhCHO (0.5 M) in water.

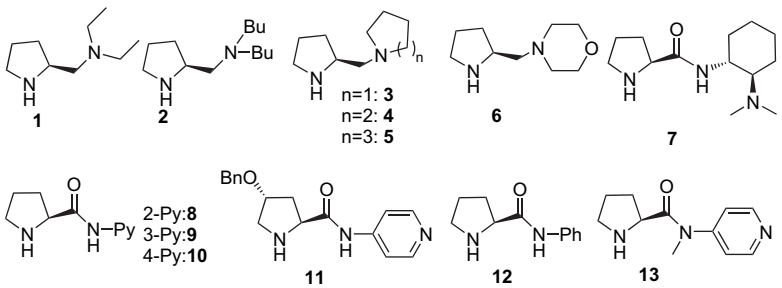
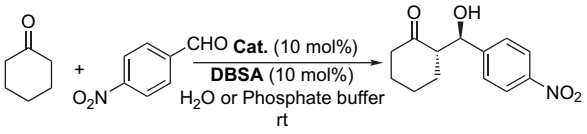


Figure 2. Selected chiral amines.

Table 2. Selected screening results[a]



Entry	Cat.	Media	Time (h)	Yield[b] (%)	*anti*:*syn*[c]	ee[d] (%)
1	**1**	H_2O	13	92	83:17	68
2	**1**	PB	13	88	83:17	81
3	**2**	PB	12	95	76:24	57
4	**3**	PB	12	95	77:23	75
5	**4**	PB	12	95	82:18	79
6	**5**	PB	12	98	80:20	75
7	**6**	PB	12	19	Not determined	
8	**7**	PB	5	85	69:31	32
9	**8**	H_2O	12	No reaction		
10	**9**	H_2O	12	20	96:4	93
11	**9**	PB	12	92	95:5	88
12	**9**	Brine	12	31	95:5	90
13	**9**	H_2O	12	Trace[e]		
14	**10**	H_2O	**12**	**92**	**94:6**	**93**
15	**10**	PB	12	81	92:8	90
16	**10**	H_2O	12	Trace[f]		
17	**10**	Neat	12	81	95:5	90
18	**11**	H_2O	**12**	**90**	**96:4**	**98**
19	**12**	H_2O	24	No reaction		
20	**13**	H_2O	24	No reaction		

[a] Aldehyde (0.5 mmol), 1 mmol cyclohexanone, 1 mL of solvent.
[b] Isolated yields.
[c] Determined by ^{1}H NMR.
[d] Determined by HPLC on a chiral column.
[e] In the absence of DBSA.
[f] Reaction in the presence of *p*-toluenesulfonic acid (10 mol %). PB: phosphate buffer, NaH_2PO_4–Na_2HPO_4, 1 M, pH=7.2.

be transformed into good aqueous catalysts assisted by DBSA (catalysts **1** and **3–5**; Table 2, entries 2 and 4–6). This validates our design strategy and highlights the important role of DBSA (note that the reaction with non-surfactant Brønsted acid gave low yields and poor stereoselectivity in water, see Table 1, entry 6 and Table 2, entry 14). The improved performance in phosphate buffer (1 M, pH=7.2) again suggests general base catalysis should also be working in chiral diamine–DBSA system in pure water (Table 2, entry 2 vs 1).[13]

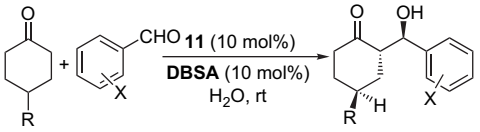
Bearing this in mind, we next explored a series of chiral amide catalysts (catalyst **7–11**) in order to alleviate the background catalysis. Additional basic amine groups were appended in the catalysts to offer proper complex of catalysts with DBSA. To our delight, among this series of catalysts we were able to identify an optimal catalyst **11** with conjugate 4-aminopyridinyl group that promoted the model reaction with 90% yield, 96:4 dr and 98% ee (entry 18) in pure water using the media of colloid dispersion. Interestingly, the reaction with the seemingly similar aminopyridinyl catalysts **8**, **9**, and **10** gave dramatically different results.

The 2-aminopyridinyl **8** was observed to be totally inactive, whereas 3-aminopyridinyl **9** and 4-aminopyridinyl **10** showed contrasting preference to reaction media. Catalyst **9** showed a higher activity in phosphate buffer than in pure water (entry 12 vs 11), whereas catalyst **10** performed better in pure water than in phosphate buffer (entry 14 vs 15). The observation that catalyst **9** performed poorly in brine may rule out the possible salt effect. One may explain the contrasting behavior on the basis of the basicity difference between 3-aminopyridine and 4-aminopyridine (pK_a 5.98 vs 9.17).[14] However, the geometrical difference and molecular orientation of the chiral amines obviously also played a pivotal role because of the fact that the basicity of the inert 2-aminopyridinyl **11** is not too much different from that of the active 3-aminopyridine (pK_a 6.86 vs 5.98), so the difference in their spatial arrangement may be quite substantial in the surfactant micelle.[15]

Other notable results in the catalysts screening included the observation that aniline analogue **12** and *N*-methylated catalyst **13** were inactive for catalysis; this indicates the importance of amino-pyridine structure and the amide linkage (entries 19 and 20). In control reactions, we could also demonstrate that 3(4)-aminopyridinyl catalysts–DBSA complexes were unique for aqueous catalysis as seen from the poor performance either in the absence of DBSA (entry 13), in the presence of non-surfactant *p*-toluenesulfonic acid (entry 16) or under neat conditions (entry 17). It is thus conceived that besides its role as a surfactant and a catalyst anchor, DBSA should also contribute significantly to the enhanced activity and enantioselectivity most likely by protonating the pyridinyl ring that consequently activates the amide hydrogen-bond donor in hydrophobic micellar media.

The substrates' scopes of the identified optimal catalyst **11** were next probed for asymmetric direct aldol reaction in water. Cyclohexanone reacted with a range of aromatic aldehydes to afford the desired products (**14a–14g**) with high yields and stereoselectivity (Table 3, entries 1–6).

Table 3. Substrate scopes[a]



Entry	R	X	Time (h)	Yield[b] (%)	dr[c]	ee[d] (%)
1	H (**14**)	**b**/3-NO_2	24	95	93:7	>99
2		**c**/2-NO_2	24	88	98:2	96
3		**d**/4-CN	24	>99	91:9	98
4		**e**/2-Cl	72	81	95:5	90
5		**f**/H	72	33	94:6	93
6		**g**/3-Br	72	78	93:7	93
7	Me (**15**)	**a**/4-NO_2	12	90	>16:1	99
8		**b**/4-CF_3	48	86	>16:1	98
9		**c**/2-NO_2	16	85	>16:1	98
10		**d**/4-Cl	72	77 (20)[e]	>16:1	91
11		**e**/H	72	41 (56)[e]	>16:1	98
12	Et (**16**)	4-NO_2	31	86 (10)[e]	>16:1	98
13	*t*-Bu (**17**)	H	72	58	>16:1	96
14	N_3 (**18**)	**a**/4-NO_2	40	69 (20)[e]	>10:1	97
15		**b**/4-Cl	72	52	>16:1	94
16	SAc (**19**)	**a**/4-NO_2	36	97	>16:1	99
17		**b**/4-CF_3	60	99	>16:1	>99
18	Br (**20**)	4-NO_2	40	74 (22)[e]	>16:1	96

[a] Aldehyde (0.5 mmol) and 1.0 mmol cyclohexanone in 1 mL water at room temperature with 10 mol % of **11**.
[b] Isolated yields of pure products.
[c] Entries 1–6: dr=*anti:syn*, determined by ^{1}H NMR; entries 7–18: dr=the ratio of the major isomer shown with all the other isomers based on the isolated products.
[d] Determined by HPLC on a chiral column.
[e] Recovered aldehyde.

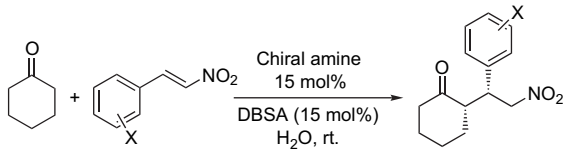
With regard to the aldol donors, a variety of 4-substituted cyclohexanones were applied in the present reactions. Significantly, catalyst **11**–DBSA catalyzed the reactions of 4-substituted cyclohexanones to produce predominantly one single isomer with excellent enantioselectivity (Table 3, entries 7–18, 96 to >99% ee). As known, enantioselective desymmetrizations using asymmetric catalysis are powerful ways to generate chiral products with multiple stereogenic centers.[16] While asymmetric transition metal catalysts[16a] and enzymes[16b] have been widely applied in desymmetrization of *meso* compounds, the examples using asymmetric organocatalysts are rare, especially for intermolecular reactions.[17] Our evolved catalyst **11** provided successful asymmetric desymmetrization of prochiral ketones with excellent stereoselectivity in water under room temperature. For the same reactions in organic solvent, the current well-established organcoatalysts gave either low activity or poor stereoselectivity.[18] The characteristics of our discovery include: (1) selective formation of one isomer out of eight possible stereoisomers (>16:1 dr, up to >99% ee), (2) wide scope of 4-substituted cyclohexanones encompassing 4-alkyl (entries 7–13), and 4-heteroatom functionalized groups (entries 14–18), and (3) highly enantioselective desymmetrizations in pure water conditions. However, the current catalyst also has its limitation such as the reactions with aliphatic aldehydes gave lower yields due to side reactions.

In general, the reactions were started by simple mixing of **11**–DBSA with substrates in bulk water and good colloid dispersions were then formed, indicating that the reactions occur in the micelles. At the end of the reactions the products normally precipitated out or could be easily extracted with organic solvents. The relative and absolute configurations of the optically pure products formed were determined by X-ray analysis.[19] Both of the crystal structures of products **15d** and **20** revealed the absolute configurations to be (1′*R*,2*S*,4*S*) (Scheme 2, left). The observed high stereoselectivity may be explained by the proposed transition state as shown in Scheme 2 (right). This model is in accordance with that of L-proline catalyzed reaction in DMSO.[20] The unique pyridinium-amide moiety may also contribute to effect the orientation of the R group besides providing an activated amide hydrogen-bonding moiety and this hypothesis is under our current investigations.

2.3. Asymmetric Michael addition in water

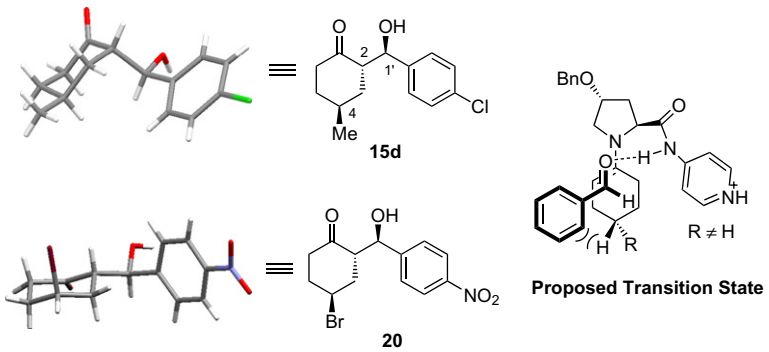
The application of the above strategy in asymmetric Michael addition in water was briefly explored. DBSA was again found to be a proper surfactant Brønsted acid in this reaction. In the presence of DBSA, simple chiral amines such as **1** were able to catalyze the Michael addition of cyclohexanone to nitrostyrene with high activity and stereoselectivity (Table 4). Initial screening revealed that chiral diamines performed better than amide-type catalysts. Amide-type catalysts **7**–**13** were ineffective in the Michael addition reaction, producing either lower yields or lower enantioselectivity (Table 4, entries 7–13). With the assistance of DBSA, chiral diamines such as **1**–**5** could be transformed into effective aqueous phase catalysts affording the desired Michael adducts with good yields and good enantioselectivity (Table 4, entries 1–5, 72–95% yields, 80–87% ee). In contrast, a chiral diamine **3** itself or combined with trifluoroacetic acid produced only low yields of products (<20%) as previously reported.[9b] The applicability of these catalysts was simply demonstrated with chiral diamine **1**–DBSA catalyst in several representative examples, all showing good activity and good stereoselectivity (Table 4, entries 14–18). Although our results did not outperform

Table 4. Asymmetric Michael addition in water[a]



Entry	Chiral amine	X	Time (h)	Yield[b] (%)	*syn*:*anti*[c]	ee[d] (%)
1	**1**	H	24 (36)	85 (95)	95:5	85
2	**2**	H	24	80	94:6	86
3	**3**	H	24	85	92:8	83
3	**4**	H	24	72	90:10	86
5	**5**	H	24	80	93:7	80
6	**6**	H	24	Trace		
7	**7**	H	24	70	87:13	15
8	**8**	H	24	No reaction		
9	**9**	H	24	16	95:5	18
10	**10**	H	24	93	94:6	20
11	**11**	H	24	24	90:10	11
12	**12**	H	24	No reaction		
13	**13**	H	24	No reaction		
14	**1**	4-Cl	48	81	98:2	85
15	**1**	2-Napth	48	99	95:5	87
16	**1**	4-MeO	72	99	96:4	87
17	**1**	3-NO_2	24	67	94:6	81
18	**1**	2-Cl	72	94	95:5	88

[a] Nitrostyrene (0.25 mmol), 1 mmol cyclohexanone in 1 mL H_2O.
[b] Isolated yields.
[c] Determined by ^1H NMR.
[d] Determined by HPLC on a chiral column.



Scheme 2. X-ray crystal structure of **15d** and **20** (left) and the proposed transition state (right).

the previous reports, the current catalytic system represents a much simpler and convenient alternative to many other synthetic catalysts that work in pure water.[4g,9b,11,21] In addition, the chance for better catalyst is still open through screening other types of chiral amines.

3. Conclusion

In summary, our results show a modular and effective approach for the discovery of asymmetric organocatalysts in water by combining chiral amine and surfactant Brønsted acid. Catalyst **11**–DBSA, unique for aqueous catalysis, was evolved by combinatorial screening of libraries of chiral amines that provided the first example of asymmetric desymmetrization reactions in water with excellent diastereoselectivity and enantioselectivity. The current strategy could be equally applied in the asymmetric Michael addition in water.

4. Experimental section

4.1. General information

Commercial reagents were used as received, unless otherwise stated. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard. The following abbreviations were used to designate chemical shift mutiplicities: s=singlet, d=doublet, t=triplet, q=quartet, h=heptet, 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). Mass spectra were obtained using fast-atom bombardment (FAB) spectrometer or electrospray ionization (ESI) mass spectrometer. Optical rotations were measured using a 1 mL cell with a 1 dm path length and are reported as follows: $[\alpha]_D^{rt}$ (*c* in g per 100 mL of solvent).

4.2. General procedure for the synthesis of catalysts

4.2.1. Synthesis of (2*S*,4*R*)-4-(benzyloxy)-*N*-(pyridin-4-yl)pyrrolidine-2-carboxamide (11). To a solution of (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-(benzyloxy)pyrrolidine-2-carboxylic acid (1.61 g, 5 mmol) in 20 mL CH_2Cl_2 was added DCC (1.06 g, 5.1 mmol), HOBt (0.69 g, 5.1 mmol) under 0 °C and stirred for 30 min. Pyridin-4-amine (0.47 g, 5 mmol) was added in one portion. After 12 h, the mixture was filtered through Celite and the resulting solvent was concentrated in vacuo to give crude Boc-protected **11** as yellow oil, which was purified by flash chromatograph on silica gel to afford pure Boc-protected **11** (1.59 g, 80% yield) as white solid. This compound was deprotected in 5 M HCl/EtOH to give the hydrogen chloride salts, which was subsequently dissolved in CH_2Cl_2 (10 mL) and then treated with saturated $NaHCO_3$ solution (50 mL). This mixture was stirred for 1 h. The aqueous layer was extracted with CH_2Cl_2 (30 mL×5), The combined organic phase was dried over anhydrous Na_2SO_4, and concentrated in vacuo after filtration to give essentially pure chiral catalyst **11** (1.1 g, 74% yield overall steps) as white solid. $[\alpha]_D^{20}$ −28.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.94–2.03 (1H, m), 2.49–2.62 (2H, m), 2.76–2.82 (1H, m), 3.21–3.27 (1H, m), 4.03–4.14 (2H, m), 4.43–4.53 (2H, m), 7.28–7.35 (5H, m), 7.50–7.52 (2H, m), 8.46–8.48 (2H, m), 9.88–9.99 (1H, br); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 36.1, 52.6, 60.4, 70.7, 80.3, 113.3, 127.6, 127.8, 128.5, 137.9, 144.5, 150.7, 173.9; HRMS for $C_{17}H_{20}N_3O_2$ $(M+H)^+$, calcd 298.1550, found 298.1547.

4.2.2. Spectra data for chiral amines catalysts 7–10 and 13.

4.2.2.1. (*S*)-*N*-((*1R*,*2R*)-2-(Dimethylamino)cyclohexyl)pyrrolidine-2-carboxamide (7). The title product was prepared from Boc-protected L-proline and (1*R*,2*R*)-*N*,*N*-dimethylcyclohexanediamine according to the general procedure with 50% yield as white solid. $[\alpha]_D^{20}$ −87.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01–1.32 (4H, m), 1.60–1.71 (3H, m), 1.74–1.80 (2H, m), 1.88–2.13 (3H, m), 2.17 (3H, s), 2.18 (3H, s), 2.24–2.29 (2H, m), 2.81–2.97 (2H, m), 3.46–3.57 (1H, m), 3.67 (1H, dd, *J*=5.3, 5.3, 8.7 Hz), 7.53–7.63 (1H, br); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.1, 24.8, 25.3, 25.9, 30.9, 33.0, 40.1, 47.2, 50.4, 60.9, 66.6, 174.9; HRMS for $C_{13}H_{26}N_3O$ $(M+H)^+$, calcd 240.2070, found 240.2069.

4.2.2.2. (*S*)-*N*-(Pyridin-2-yl)pyrrolidine-2-carboxamide (8). The title product was prepared from Boc-protected L-proline and 2-aminopyridine according to the general procedure with 86% yield as pale yellow oil. $[\alpha]_D^{20}$ −56.0 (*c* 1.0, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.74–1.83 (2H, m), 1.96–2.07 (1H, m), 2.21–2.33 (1H, m), 3.08–3.17 (2H, m), 4.13 (1H, dd, *J*=5.5, 5.3, 9.0 Hz), 4.87–5.44 (1H, br), 6.94–6.98 (1H, m), 7.59–7.65 (1H, m), 8.12 (1H, d, *J*=8.3 Hz), 8.25 (1H, d, *J*=4.1 Hz), 10.3 (1H, br); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.7, 30.7, 47.0, 60.8, 113.7, 119.6, 138.1, 147.9, 151.0, 173.0; HRMS for $C_{10}H_{14}N_3O$ $(M+H)^+$, calcd 192.1131, found 192.1132.

4.2.2.3. (*S*)-*N*-(Pyridin-3-yl)pyrrolidine-2-carboxamide (9). The title product was prepared from Boc-protected L-proline and 3-aminopyridine according to the general procedure with 76% yield as pale yellow oil. $[\alpha]_D^{20}$ −53.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.78–1.86 (2H, m), 1.98–2.09 (1H, m), 2.24–2.35 (1H, m), 3.08–3.19 (2H, m), 4.08–4.13 (1H, m), 4.49–5.28 (1H, br), 7.20–7.25 (1H, m), 8.13–8.18 (1H, m), 8.28–8.32 (1H, m), 8.73–8.76 (1H, m), 9.79–10.76 (1H, br); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.8, 30.6, 47.0, 60.7, 123.5, 126.5, 134.7, 140.9, 144.7, 172.8; HRMS for $C_{10}H_{14}N_3O$ $(M+H)^+$, calcd 192.1131, found 192.1131.

4.2.2.4. (*S*)-*N*-(Pyridin-4-yl)pyrrolidine-2-carboxamide (10). The title product was prepared from Boc-protected L-proline and 4-aminopyridine according to the general procedure with 89% yield as white solid. $[\alpha]_D^{20}$ −69.7 (*c* 1.0, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.67–1.74 (2H, m), 1.90–2.01 (1H, m), 2.10–2.20 (1H, m), 2.56 (1H, br), 2.88–3.07 (2H, m), 3.77–3.83 (1H, m), 7.46–7.49 (2H, m), 8.40–8.43 (2H, m), 9.94 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.3, 30.7, 47.3, 61.0, 113.3, 144.5, 150.6, 174.5; HRMS for $C_{10}H_{14}N_3O$ $(M+H)^+$, calcd 192.1131, found 192.1130.

4.2.2.5. (*S*)-*N*-Methyl-*N*-(pyridin-4-yl)pyrrolidine-2-carboxamide (13). The title product was prepared from

Boc-protected L-proline and 4-methylaminopyridine according to the general procedure with 72% yield as pale yellow oil. $[\alpha]_D^{20}$ −81.6 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.99–2.09 (2H, m), 2.23–2.31 (2H, m), 2.77 (1H, s), 2.79 (3H, s), 6.41–6.43 (2H, m), 8.19–8.23 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.7, 26.1, 31.2, 48.6, 63.1, 107.9, 149.8, 151.9, 172.8; HRMS for $C_{11}H_{16}N_3O$ $(M+H)^+$, calcd 206.1288, found 206.1285.

4.3. General experimental procedure for aldol reaction in water

Catalyst **11** (10 mol %, 0.05 mmol, 14.9 mg) and DBSA (10 mol %, 0.05 mmol, 16.4 mg) were stirred in water (1 mL) for 10 min. The corresponding ketone (1 mmol) and aldehyde (0.5 mmol) was then added and the resulted mixture was stirred for the time given in Tables 1 and 2 at ambient temperature. The aqueous layer was decanted from the precipitated products and extracted with ether (2 mL×3). The organic was combined with the precipitant and loaded onto silica gel. The desired product was obtained by flash chromatography. Products **14a–14g** are known compounds.[4a,4h,9a]

4.4. Spectra data for new aldol products

4.4.1. (2*S*,4*S*)-2-((*R*)-Hydroxy(4-nitrophenyl)methyl)-4-methylcyclohexanone (15a). White solid; ee 99%; $[\alpha]_D^{20}$ −39.8 (*c* 0.5, EA); ^1H NMR (300 MHz, $CDCl_3$): δ 1.04 (3H, d, *J*=7.0 Hz), 1.27–1.35 (1H, m), 1.54–1.64 (1H, m), 1.74–1.82 (1H, m), 1.87–1.99 (1H, m), 2.04–2.11 (1H, m), 2.34–2.43 (1H, m), 2.48–2.59 (1H, m), 2.69–2.78 (1H, m), 3.90 (1H, d, *J*=2.8 Hz), 4.92 (1H, dd, *J*=3.2, 3.2, 8.5 Hz), 7.49 (2H, d, *J*=8.7 Hz), 8.20 (2H, d, *J*=8.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.2, 26.6, 32.9, 36.1, 38.2, 52.9, 74.1, 123.6, 127.8, 147.6, 148.4; HRMS for $C_{14}H_{18}NO_4$ $(M+H)^+$, calcd 264.1230, found 264.1230. The enantiomeric excess was determined by HPLC with an AS-H column at 254 nm (2-propanol/hexane=30:70), 25 °C, 0.8 mL/min; t_R=16.05 (major), t_S=22.80 (minor).

4.4.2. (2*S*,4*S*)-2-((*R*)-Hydroxy(4-trifluoromethylphenyl)-methyl)-4-methylcyclohexanone (15b). White solid; ee 98%; $[\alpha]_D^{20}$ −10.0 (*c* 0.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.04 (3H, d, *J*=7.0 Hz), 1.25–1.33 (1H, m), 1.49–1.58 (1H, m), 1.71–1.78 (1H, m), 1.87–1.98 (1H, m), 2.02–2.09 (1H, m), 2.35–2.55 (2H, m), 2.69–2.77 (1H, m), 2.83 (1H, d, *J*=3.0 Hz), 4.87 (1H, dd, *J*=3.0, 2.8, 8.7 Hz), 7.42 (2H, d, *J*=8.1 Hz), 7.60 (2H, d, *J*=8.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.3, 26.6, 33.1, 36.1, 38.1, 53.2, 74.3, 125.3, 125.4, 127.3, 145.1, 215.1; HRMS for $C_{15}H_{18}F_3O_2$ $(M+H)^+$, calcd 287.1253, found 287.1255. The enantiomeric excess was determined by HPLC with an AS-H column at 254 nm (2-propanol/hexane=20:80), 25 °C, 0.5 mL/min; t_R=14.75 (major), t_R=21.53 (minor).

4.4.3. (2*S*,4*S*)-2-((*R*)-Hydroxy(2-nitrophenyl)methyl)-4-methylcyclohexanone (15c). Yellow solid; ee 98%; $[\alpha]_D^{20}$ −11.4 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.04 (3H, d, *J*=7.0 Hz), 1.42–1.50 (1H, m), 1.67–1.98 (3H, m), 2.05–2.10 (1H, m), 2.30–2.51 (2H, m), 2.85–2.92 (1H, m), 3.80–4.13 (1H, br), 5.40 (1H, d, *J*=7.2 Hz), 7.37–7.43 (1H, m), 7.57–7.63 (1H, m), 7.69–7.72 (1H, m), 7.78–7.82 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.3, 26.9, 33.2, 36.7, 38.5, 53.0, 69.8, 124.0, 128.5, 128.9, 133.1, 136.7, 148.8, 214.9; HRMS for $C_{14}H_{18}NO_4$ $(M+H)^+$, calcd 264.1230, found 264.1231. The enantiomeric excess was determined by HPLC with an AD-H column at 254 nm (2-propanol/hexane=20:80), 25 °C, 0.8 mL/min; t_R=10.73 (minor), t_R=11.07 (major).

4.4.4. (2*S*,4*S*)-2-((*R*)-Hydroxy(4-chlorophenyl)methyl)-4-methylcyclohexanone (15d). White solid; ee 91%; $[\alpha]_D^{20}$ −33.1 (*c* 0.5, AE); ^1H NMR (300 MHz, $CDCl_3$): δ 1.03 (3H, d, *J*=6.8 Hz), 1.26–1.35 (1H, m), 1.46–1.55 (1H, m), 1.68–1.77 (1H, m), 1.87–1.99 (1H, m), 2.01–2.08 (1H, m), 2.35–2.56 (2H, m), 2.65–2.74 (1H, m), 3.69 (1H, d, *J*=2.5 Hz), 4.80 (1H, dd, *J*=2.3, 2.5, 8.9 Hz), 7.23–7.26 (2H, m), 7.30–7.33 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.5, 26.7, 33.2, 36.2, 38.2, 53.4, 74.2, 128.3, 128.7, 133.7, 139.7, 215.2; HRMS for $C_{14}H_{17}ClO_2$ (M^+), calcd 252.0917, found 252.0919. The enantiomeric excess was determined by HPLC with an AS-H column at 280 nm (2-propanol/hexane=10:90), 25 °C, 0.8 mL/min; t_R=21.56 (major), t_R=42.44 (minor).

4.4.5. (2*S*,4*S*)-2-((*R*)-Hydroxyphenyl)methyl)-4-methylcyclohexanone (15e). Colorless oil; ee 98%; $[\alpha]_D^{20}$ −17.8 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.01 (3H, d, *J*=6.8 Hz), 1.26–1.35 (1H, m), 1.46–1.55 (1H, m), 1.65–1.73 (1H, m), 1.88–1.99 (1H, m), 2.01–2.09 (1H, m), 2.39–2.54 (2H, m), 2.70–2.79 (1H, m), 3.55–3.59 (1H, br), 4.83 (1H, d, *J*=9.4 Hz), 7.27–7.37 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.8, 26.7, 33.5, 36.3, 38.3, 53.9, 74.9, 126.9, 128.0, 128.5, 141.2, 215.3; HRMS for $C_{14}H19O_2$ $(M+H)^+$, calcd 219.1380, found 219.1381. The enantiomeric excess was determined by HPLC with an AS-H column at 254 nm (2-propanol/hexane=20:80), 25 °C, 0.5 mL/min; t_R=17.40 (major), t_R=27.58(minor).

4.4.6. (2*S*,4*S*)-4-Ethyl-2-((*R*)-hydroxy(4-nitrophenyl)methyl)cyclohexanone (16). White solid; ee 98%; $[\alpha]_D^{20}$ −22.1 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.79 (3H, t, *J*=7.4 Hz), 1.29–1.57 (4H, m), 1.66–1.75 (1H, m), 1.82–1.92 (2H, m), 2.33–2.50 (2H, m), 2.61–2.70 (1H, m), 3.92–3.95 (1H, br), 4.90 (1H, dd, *J*=3.0, 3.0, 8.7 Hz), 7.47–7.50 (2H, m), 8.17–8.21 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.9, 24.9, 30.6, 33.5, 33.7, 38.4, 53.1, 74.1, 123.6, 127.8, 147.6, 148.5, 214.9; HRMS for $C_{15}H_{19}NO_4$ (M^+), calcd 277.1314, found 277.1316. The enantiomeric excess was determined by HPLC with an AD-H column at 254 nm (2-propanol/hexane=20:80), 25 °C, 0.8 mL/min; t_R=14.45 (minor), t_R=15.08 (major).

4.4.7. (2*S*,4*S*)-4-*tert*-Butyl-2-((*R*)-hydroxy(4-nitrophenyl)methyl)cyclohexanone (17). White solid; ee 96%; $[\alpha]_D^{20}$ −75.2 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.77 (9H, s), 1.37–1.46 (2H, m), 1.53–1.57 (2H, m), 1.97–2.03 (1H, m), 2.47–2.52 (2H, m), 2.62–2.69 (1H, m), 3.07–3.09 (1H, m), 4.90 (1H, dd, *J*=3.2, 3.2, 9.8 Hz), 7.33–7.37 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.6, 27.1, 27.9, 32.7, 39.2, 42.1, 55.7, 74.8, 126.9, 128.3, 128.6, 141.4, 215.7; HRMS for $C_{17}H_{24}O_2$ (M^+), calcd 260.1776, found 260.1779. The enantiomeric excess was determined by HPLC with an AS-H column at 254 nm (2-propanol/hexane=20:80), 25 °C, 0.8 mL/min; t_R=17.63 (major), t_R=23.16 (minor).

4.4.8. (2*S*,4*S*)-4-Azido-2-((*R*)-hydroxy(4-nitrophenyl)methyl)cyclohexanone (18a). Pale yellow solid; ee 97%; $[\alpha]_D^{20}$ +12.1 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.69–1.73 (2H, m), 1.89–2.00 (1H, m), 2.22–2.29 (1H, m), 2.36–2.43 (1H, m), 2.66–2.77 (1H, m), 2.96–3.05 (1H, m), 3.94 (1H, d, *J*=3.8 Hz), 3.99–4.04 (1H, m), 4.90 (1H, dd, *J*=3.8, 3.8, 7.9 Hz), 7.49–7.53 (2H, m), 8.19–8.23 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 30.9, 34.2, 37.4, 51.5, 55.9, 73.6, 123.7, 127.8, 147.7, 147.8, 212.4; HRMS for $C_{13}H_{15}N_4O_4$ $(M+H)^+$, calcd 291.1088, found 291.1092. The enantiomeric excess was determined by HPLC with an AD-H column at 280 nm (2-propanol/hexane=20:80), 25 °C, 0.8 mL/min; t_R=17.54 (minor), t_R=20.24 (major).

4.4.9. (2*S*,4*S*)-4-Azido-2-((*R*)-hydroxy(4-chlorophenyl)-methyl)cyclohexanone (18b). White solid; ee 94%; $[\alpha]_D^{20}$ +18.6 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.55 (1H, td, *J*=13.2, 2.8 Hz), 1.66–1.73 (1H, m), 1.86–1.98 (1H, m), 2.18–2.26 (1H, m), 2.34–2.41 (1H, m), 2.69 (1H, td, *J*=13.8, 6.0 Hz), 2.91–3.01 (1H, m), 3.88 (1H, d, *J*=3.2 Hz), 3.95–3.99 (1H, m), 4.77 (1H, dd, *J*=3.0, 3.0, 8.3 Hz), 7.23–7.27 (2H, m), 7.31–7.34 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 30.9, 34.1, 37.4, 51.6, 55.9, 73.7, 76.6, 77.1, 77.5, 128.3, 128.8, 133.9, 138.9, 213.0; HRMS for $C_{13}H_{14}ClN_3O_2$ (M^+), calcd 279.0775, found 279.0777. The enantiomeric excess was determined by HPLC with an AD-H column at 280 nm (2-propanol/hexane=20:80), 25 °C, 0.8 mL/min; t_R=12.24 (minor), t_R=15.74 (major).

4.4.10. *S*-(1*S*,3*S*)-3-((*R*)-Hydroxy(4-nitrophenyl)methyl)-4-oxocyclohexyl ethanethioate (19a). Colorless oil; ee 99%; $[\alpha]_D^{20}$ −66.3 (*c* 2.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.62–1.67 (1H, m), 1.83–1.93 (1H, m), 2.12–2.16 (2H, m), 2.29 (3H, s), 2.41–2.56 (2H, m), 2.75–2.83 (1H, m), 3.85–3.97 (1H, br), 4.00–4.03 (1H, m), 4.91 (1H, d, *J*=7.9 Hz), 7.45–7.48 (2H, m), 8.15–8.18 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 30.9, 32.4, 35.5, 39.1, 39.2, 53.9, 73.4, 123.7, 127.8, 147.6, 147.9, 194.0, 212.3; HRMS for $C_{15}H_{18}NO_5S$ $(M+H)^+$, calcd 324.0900, found 324.0900. The enantiomeric excess was determined by HPLC with an AD-H column at 280 nm (2-propanol/hexane=10:90), 25 °C, 0.8 mL/min; t_R=50.31 (minor), t_R=59.36 (major).

4.4.11. *S*-(1*S*,3*S*)-3-((*R*)-Hydroxy(4-trifluoromethylphenyl)methyl)-4-oxocyclohexyl ethanethioate (19b). Colorless oil; ee >99%; $[\alpha]_D^{20}$ −31.8 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.62–1.70 (1H, m), 1.83–1.93 (1H, m), 2.14–2.20 (2H, m), 2.32 (3H, s), 2.43–2.51 (1H, m), 2.56–2.64 (1H, m), 2.78–2.86 (1H, m), 3.83 (1H, d, *J*=3.0 Hz), 4.02–4.07 (1H, m), 4.88 (1H, dd, *J*=3.4, 3.4, 8.1 Hz), 7.44 (2H, d, *J*=8.1 Hz), 7.61 (2H, d, *J*=8.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 30.9, 32.6, 35.5, 39.2, 54.0, 73.8, 124.5 (q, –**C**F_3), 125.4, 125.5, 127.3, 144.5, 194.0, 212.7; HRMS for $C_{16}H_{18}F_3O_3S$ $(M+H)^+$, calcd 347.0923, found 347.0922. The enantiomeric excess was determined by HPLC with an AD-H column at 254 nm (2-propanol/hexane=20:80), 25 °C, 0.8 mL/min; t_R=9.51 (minor), t_R=11.09 (major).

4.4.12. (2*S*,4*S*)-4-Bromo-2-((*R*)-hydroxy(4-chlorophenyl)methyl)cyclohexanone (20). Colorless oil; ee 96%; $[\alpha]_D^{20}$ +38.4 (*c* 0.25, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.92–1.97 (2H, m), 2.15–2.26 (1H, m), 2.38–2.46 (2H, m), 2.99 (1H, td, *J*=6.0, 13.8 Hz), 3.27–3.36 (1H, m), 3.80–4.11 (1H, br), 4.65–4.69 (1H, m), 4.97 (1H, d, *J*=7.7 Hz), 7.52 (2H, d, *J*=8.3 Hz), 8.21 (2H, d, *J*=8.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 35.9, 38.0, 38.9, 49.1, 52.2, 73.3, 123.7, 127.8, 147.6, 147.7, 212.1; HRMS for $C_{13}H_{14}BrNO_4$ (M^+), calcd 327.0101, found 327.0100. The enantiomeric excess was determined by HPLC with an AD-H column at 254 nm (2-propanol/hexane=20:80), 25 °C, 0.8 mL/min; t_R=20.21 (major), t_R=23.09 (minor).

4.5. General experimental procedure for Michael reaction in water

Catalyst **1** (15 mol %, 0.0375 mmol, 5.9 mg) and DBSA (15 mol %, 0.0375 mmol, 12.3 mg) were stirred in water (1 mL) for 10 min. The corresponding nitroolefin (0.25 mmol) and cyclohexanone (1.0 mmol) was then added and the resulted mixture was stirred for the time given in Table 3 at ambient temperature. The aqueous layer was decanted from the precipitated products and extracted with ether (2 mL×3). The organic was combined with the precipitant and loaded onto silica gel. The desired product was obtained by flash chromatography. All the Michael adducts are known compounds.[11]

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Supplementary data

It consists of spectra for all new compounds. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.08.096.

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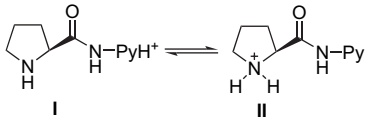
14. For pK_a of aminopyridines, see: Palmer, M. M. *The Structure and Reaction of Heterocycle Compounds*; Edward Arnold: London, 1982; 2-Aminopyridine: pK_a=6.86; 3-aminopyridine: pK_a=5.98; 4-aminopyridine: pK_a=9.17. The variation of activity in different media may be rationalized by the following equilibrium, where only species **I** is catalytically active. (The protonation of pyrrolidinyl nitrogen in a L-prolinamide with strong acids such as *p*-toluenesulfonic acid leads to an inert catalyst, see: Gryko, D.; Zimnicka, M.; Lipiński, R. *J. Org. Chem.* **2007**, *72*, 964–970). In pure water, the protonation of catalyst **9** by DBSA leads predominantly to **II** species due to the lower pK_a of 3-aminopyridine, whereas the use of PB buffer (pH=7.2) helps to shift the equilibrium to **I**, thus higher activity was achieved in this media.



15. It is known that 2-aminopyridine is a good molecular recognition unit for acids. It is therefore likely the complex of DBSA and catalyst **8** will geometrically facilitate protonation of pyrrolidinyl ring, resulting in exclusively formation of species **II** (Ref. 14), as a result totally depleting the catalytic activity of catalyst **8**. For pyrrolidinyl pyridines as organocatalysts in the absence of acidic additives, see: Tang, Z.; Cun, L.-F.; Cui, X.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Org. Lett.* **2006**, *8*, 1263–1266.
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19. CCDC 637019 and CCDC 637018 contain the supplementary crystallographic data for compounds **15d** and **20**, respectively. These data can be obtained free of charge from The Cambridge Crystallo-graphic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Crystal data for **15d**: $C_{14}H_{13}ClO_2$, colorless block, Mr=248.69, crystal size 0.10×0.10×0.10 mm^3, orthorhombic, space group $P2(1)/c$, a=6.71893(4) Å, b=10.43752(8) Å, c=19.1216(4) Å, α=90.00°, β=90.00°, γ=90.00°, V=1340.98(3) Å^3, Z=4, ρ_{calcd}=1.232 g cm^{-3}, T=296(2) K. A total of 3074 reflections and 2282 parameters were used for the full matrix, least-squares refinement on $F2$. R_1=0.0368 [$I>2\sigma(I)$], R_1=0.0488 (all data), wR_2=0.0933 [$I>2\sigma(I)$], wR_2=0.1002 (all data). Crystal data for **20**: $C_{13}H_{14}BrNO_4$, colorless prism, Mr=328.16, crystal size 0.62×0.24×0.20 mm^3, orthorhombic, space group $P2(1)/c$, a=7.2324(14) Å, b=9.6314(19) Å, c=19.391(4) Å, α=90.00°, β=90.00°, γ=90.00°, V=1350.7(5) Å^3, Z=4, ρ_{calcd}=1.614 g cm^{-3}, T=293(2) K. A total of 3095 reflections and 1651 parameters were used for the full matrix, least-squares refinement on $F2$. R_1=0.0310 [$I>2\sigma(I)$], R_1=0.0678 (all data), wR_2=0.0716 [$I>2\sigma(I)$], wR_2=0.0824 (all data).
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