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A Highly Efficient Large-Scale Asymmetric Direct Intermolecular Aldol Reaction Employing L-Prolinamide as a Recoverable Catalyst

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Abstract: A new, simple bifunctional, recoverable and reusable L-prolinamide organocatalyst that promotes aldol reactions while achieving a respectable level of enantioselectivity is reported. This organocatalyst is applicable to the reactions of a wide range of aromatic and heteroaromatic aldehydes with cyclic and acyclic ketones, and the *anti*-aldol products could be obtained with up to 99:1 *anti/syn* ratio and 98% *ee*. The catalyst can be easily recovered and reused, and only a slight decrease of enantioselectivity was observed for five cycles. This novel catalyst can be efficiently used in large-scale reactions with the enantioselectivity being maintained at the same level, which offers a great possibility for application in industry.

Keywords: aldol reaction; asymmetric organocatalysis; large-scale reaction; recoverable catalyst

Introduction

Asymmetric synthesis is dedicated to the preparation of chiral compounds with defined three-dimensional molecular structures. Its importance is probably best appreciated in the context of drug-receptor interactions, because most biological targets are chiral entities.[1] During the past few years, the field of asymmetric catalysis, previously dominated by biocatalysis and metal catalysis, has been complemented by organocatalysis using small organic molecules as a third powerful tool. The advent of organocatalysis brought the prospect of a complementary mode of catalysis, with the potential for savings in cost, time and energy, an easier experimental procedure, and reductions in chemical waste.[2] On the other hand, the aldol reaction is one of the most powerful methods for the formation of C–C bonds in organic synthesis.[3] The classical aldol reaction is highly atom-economic but suffers from problems with selectivity, notably, with respect to chemo- and regioselectivity. One of the difficult challenge is the design of sustainable organocatalyzed processes, which are not only more economical but also more benign towards the environment and more practicable in both industry and experiment.[4] Stimulated by this challenge, a great deal of effort is currently being made in the search for elegant and practical solutions for aldol reaction. Impressive achievements in asymmetric aldol methodology have been made which, in general, rely on the use of the organocatalysts. List et al. reported the intermolecular direct aldol addition reaction of acetone to various aldehydes catalyzed by proline in 2000.[5] Since then, a tremendous amount of research has been directed towards identifying new types of chiral enamine catalysts. Barbas,[6] Hayashi,[7] Gong,[8] Xiao[9] et al. reported the intermolecular aldol reactions of the ketone-aldehyde type and aldehyde-aldehyde type catalyzed by L-proline or its derivatives and analogues. However, their shortcomings have also been realized. One of the major limitations using organocatalyst catalyzed reactions is the high catalyst loading (10–30 mol%) generally required to complete the transformations in reasonable timescales. This will raise a cost concern when large amounts of chiral materials are used for a large-scale synthesis in industrial applications. In spite of significant efforts devoted to the development of highly active organocatalysts aimed at lowering catalyst loading, it has proved to be a significant challenging task, and only limited success has been achieved so far. An alternative strategy is to design recyclable and subsequently reusable organo-

catalysts. Meanwhile efforts also have been made on organocatalyst recycling using ionic liquids, solid-phase supports, and fluorous technologies.[10,11] Herein, we wish to report a new, simple bifunctional, recoverable and reusable L-prolinamide organocatalyst that promotes aldol reactions while achieving a respectable level of enantioselectivity, and this catalyst can be used in large-scale reactions with the enantioselectivity being maintained at the same level.

Results and Discussion

Prolinamides have been popularly designed to modulate the catalyst's hydrogen bonding ability to improve the catalytic activity and stereoselectivity. Xiao and co-workers[9] reported a series of bifunctional prolinamide derivative organocatalysts for the direct asymmetric aldol reaction of various aromatic aldehydes and cyclohexanone, and impressive results were obtained. Meanwhile, they found that a subtle change in catalyst structure may effect the catalytic activation. With this knowledge in mind, we investigated some novel (**1b–d**) and known (**1a** and **1e**) bifunctional prolinamide derivative organocatalysts with the aim to develop a practical method for the asymmetric aldol reaction. Catalysts **1b** and **1c** (Figure 1) were prepared in excellent yields by coupling of *N*-Boc-L-Pro[12] and mono-protected-(*R*,*R*)-1,2-cyclohexandiamine[13] followed by deprotection with TFA. Compounds **1a** and **1e** were synthesized following the reported procedure,[14] while **1d** was synthesized by coupling of *N*-Boc-L-Pro and mono-protected-(*R*,*R*)-1,2-cyclohexandiamine followed by deprotection with NH_2NH_2/EtOH.[13]

The organocatalyzed aldol reaction was carried out using cyclohexanone and 4-nitrobenzaldehyde as a model reaction to investigate different parameters, such as the catalysts, the cocatalysts, the stoichiometry of reactants, loading of the catalysts and cocatalysts and temperature. In our initial investigation L-proline and **1a–e** were screened as catalysts. As can be seen from the summarized results in Table 1, all the catalysts can catalyze the asymmetric direct intermolecular aldol reaction of 4-nitrobenzaldehyde and cyclohexanone to give the product in good yields (80–92%) with different *ee* values (63–90% *ee* for *anti*) in CH_3CN at −20 °C (Table 1, entries 1–6). The best enantioselectivity of 90% *ee* was achieved when **1b** was used, while the more sterically hindered **1c** showed a lower enantioselectivity (85% *ee*), which suggested that the steric property is essential to maximize the enantioselectivity. Moreover, other tested catalysts including L-proline only gave moderate enantioselectivities (63–78% *ee*). Therefore, we chose **1b** as a catalyst for the aldol reaction.

A solvent screening was then performed at room temperature to identify the best reaction conditions (Table 1, entries 7–13 and 17). Among the organic solvents tested, THF and CH_3CN were slightly better in terms of both diastereoselectivity and enantioselectivity, and 85% *ee* and 80% *ee* were achieved, respectively (Table 1, entries 13 and 17). When the reaction was performed in DMSO, DCM, $CHCl_3$, toluene or dioxane, the enantioselectivity was slightly inferior to the results obtained in THF and CH_3CN. Moreover, when water was used as a solvent, the very low *ee* value of 34% was obtained (Table 1, entry 10). Thus, we further investigated the reaction in THF and CH_3CN, respectively, at low temperatures. The enantioselectivity increased greatly from 80% *ee* to 95% *ee* in CH_3CN when the reaction temperature was lowered from room temperture to −40 °C (Table 1, entries 17–19). The *ee* value in THF was enhanced evidently from 85% to 92% when the temperature was lowered from room temperture to 0 °C (Table 1, entries 13 and 14). However, no improvement of *ee* was obtained by further lowering the temperature from 0 to −40 °C (Table 1, entries 14–16). Thus, CH_3CN was selected as the solvent for the aldol reaction.

It is well-known that a Brønsted acid additive should be involved in the intricate iminium-enamine equilibrium, and it can also play an important role in the activation of the aldol acceptor by hydrogen bonding. Therefore, a series of Brønsted acids was examined as the cocatalyst in the direct asymmetric aldol reaction (Table 2). An enantioselectivity/cocatalyst profile revealed that optimal enantiocontrol could be achieved when 3-methylbenzoic acid was used as the cocatalyst (Table 2, entry 3). Further examinations documented that the reaction efficiency could be improved if the ratio of 3-methylbenzoic acid to **1b** was changed, but the enantioselectivity was not improved when the variation of this ratio was used in this reac-

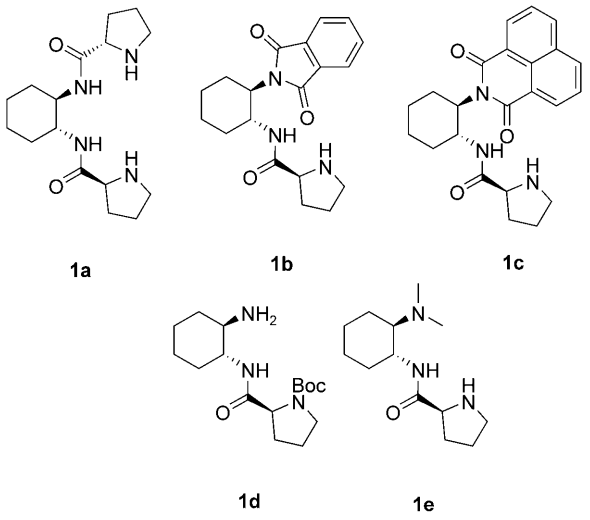
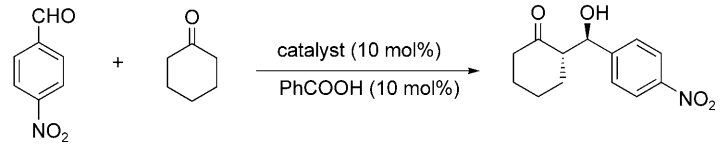


Figure 1. L-Prolinamide organocatalysts.

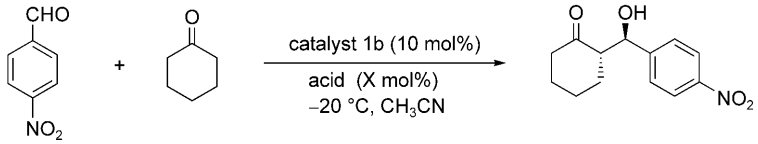
Table 1. Direct aldol reaction of cyclohexanone and 4-nitrobenaldehyde catalyzed by L-prolinamide derivatives.[a]



Entry	Catalyst	Solvent	Temperature [°C]	Time [h]	Yield [%][b]	*dr* (*anti/syn*)[c]	*ee* [%][c]
1	L-proline	CH_3CN	−20	42	80	84:16	71
2	**1a**	CH_3CN	−20	36	85	89:11	78
3	**1b**	CH_3CN	−20	20	90	94:6	90
4	**1c**	CH_3CN	−20	20	87	94:6	85
5	**1d**	CH_3CN	−20	48	82	89:11	63
6	**1e**	CH_3CN	−20	24	92	91:9	78
7	**1b**	DMSO	r.t.	20	89	89:11	78
8	**1b**	DCM	r.t.	20	93	75:25	77
9	**1b**	$CHCl_3$	r.t.	20	82	67:33	75
10	**1b**	water	r.t.	40	65	67:33	34
11	**1b**	toluene	r.t.	16	87	75:25	77
12	**1b**	dioxane	r.t.	16	82	80:20	67
13	**1b**	THF	r.t.	16	92	94:6	85
14	**1b**	THF	0	24	94	95:5	92
15	**1b**	THF	−20	30	94	96:4	92
16	**1b**	THF	−40	48	95	96:4	92
17	**1b**	CH_3CN	r.t.	16	90	90:10	80
18	**1b**	CH_3CN	0	20	95	90:10	85
19	**1b**	CH_3CN	−40	48	95	95:5	95

[a] The reactions were carried out using 4-nitrobenzaldehyde (0.25 mmol) and cyclohexanone (4 equiv.) in the specified solvent (2.0 mL).
[b] Isolated yield after chromatography on silica gel.
[c] Determined by chiral HPLC analysis (AD-H).

Table 2. Organocatalyzed direct aldol reactions in the presence of various acid addictives.[a]

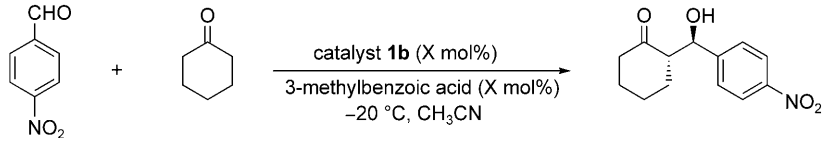


Entry	Cocatalyst	Time [h]	Yield [%][b]	*dr* (*anti/syn*)[c]	*ee* [%][c]
1	None	48	93	90:10	85
2	benzoic acid (10 mol%)	20	90	94:6	91
3	3-methylbenzoic acid (10 mol%)	20	95	98:2	96
4	4-methoxybenzoic acid (10 mol%)	20	90	97:3	95
5	4-nitrobenzoic acid (10 mol%)	30	85	96:4	73
6	4-chlorobenzoic acid (10 mol%)	30	92	94:6	90
7	trifluoroacetic acid (10 mol%)	40	85	90:10	80
8	acetic acid (10 mol%)	40	92	91:9	78
9	3-methylbenzoic acid (5 mol%)	60	78	95:5	96
10	3-methylbenzoic acid (20 mol%)	30	90	93:7	96
11	3-methylbenzoic acid (50 mol%)	30	93	93:7	96

[a] The reaction was carried out using 4-nitrobenzaldehyde (0.25 mmol) and cyclohexanone (4 equiv.) in CH_3CN (2.0 mL) at −20 °C.
[b] Isolated yield after chromatography on silica gel.
[c] Determined by chiral HPLC analysis (AD-H).

tion (Table 2, entries 9–11). Therefore, 3-methylbenzoic acid was chosen as the optimum cocatalyst, and the optimal molar ratio of 3-methylbenzoic acid to **1b** was 1:1.

Table 3. Effects of ketone and catalyst loading on the organocatalyzed direct aldol reaction.[a]



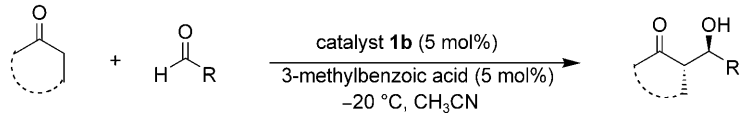
Entry	Ketone [equiv.]	Catalyst [mol%]	Time [h]	Yield [%][b]	*dr* (*anti/syn*)[c]	*ee* [%][c]
1	1	10	48	85	95:5	95
2	4	10	36	95	95:5	95
3	10	10	24	95	95:5	95
4	40	10	12	99	95:5	94
5	4	2	48	76	93:7	96
6	4	5	36	95	96:4	96
7	4	15	30	95	95:5	95
8	4	25	18	94	96:4	94

[a] The reaction was carried out using 4-nitrobenzaldehyde (0.25 mmol) and cyclohexanone in CH_3CN (2.0 mL) at −20 °C.
[b] Isolated yields after chromatography on silica gel.
[c] Determined by chiral HPLC analysis (AD-H).

Then, using CH_3CN as a solvent and 3-methylbenzoic acid as a cocatalyst with the ratio of 3-methylbenzoic acid to **1b** as 1:1, we investigated the effects of ketone and catalyst loading on the reaction of 4-nitrobenzaldehyde and cyclohexanone (Table 3). When 10 mol% of **1b** was used, the reaction could be accelerated by increasing the amount of ketone from 1 to 40 equivalents, but *dr* and *ee* values were not improved (Table 3, entries 1–4). The aldol product could be obtained in high yield with good stereoselectivity even with only 4 equivalents of cyclohexanone. Furthermore, the effect of catalyst loading was also investigated using 4 equivalents of cyclohexanone. When a large amount of catalyst (25 mol%) was used, the reaction was fast but *ee* value was slightly lower than that using lower catalyst loading (Table 3, entries 5–8). Noticeably, using 5 mol% of catalyst after 36 h, we obtained a good yield with excellent stereoselectivity (Table 3, entry 6). Thus, the optimized catalyst loading was chosen as 5 mol% of **1b**.

In order to test the substrate generality of this organocatalyzed direct aldol reaction, the reactions of various aromatic and heteroaromatic aldehydes with cyclic and acyclic ketones were studied under the optimized conditions. The results are summarized in Table 4. It can be seen that a wide range of aromatic and heteroaromatic aldehydes can effectively participate in the reaction. In general, the reaction between cyclohexanone and aromatic aldehydes bearing electron-withdrawing substituents furnished β-hydroxy carbonyl aldol products in excellent yields (89–97%) within 32 h (Table 4, entries 1–8). In contrast, longer reaction times (40 h) were required for aromatic aldehydes containing an electron-donating group to give comparatively lower yields (80–88%) (Table 4, entries 9–11). This can be explained in that electron-withdrawing groups enhance the electrophilicity of carbonyl carbons in aldehydes which facilitates the reaction, while electron-donating groups lessen the electrophilicity. Moreover, the heteroaromatic aldehydes 2-furaldehyde and 2-thiophenaldehyde both reacted smoothly with cyclohexanone under optimal conditions to give the corresponding aldol products in good yields of 90% after 40 h (Table 4, entries 13 and 14). All the reactions of cyclohexanone with aromatic and heteroaromtic aldehydes provided the corresponding products with good enantioselectivities (89–98% *ee* for *anti*-isomers) and excellent diastereoselectivities (*anti/syn* 90:10–99:1) (Table 4, entries 1–14). Interestingly, the reaction appears quite tolerant with respect to the steric contribution of the substituents in substituted benzaldehydes, and the most sterically hindered 2,6-dicholobenzaldehyde provided the best enantioselectivity (98% *ee*) and diastereoselectivity (99:1) (Table 4, entry 4). In contrast, the least sterically hindered benzaldehyde gave the lowest enantioselectivity (89% *ee*) and diastereoselectivity (90:10) (Table 4, entry 12). It seems like that the steric hindrance of the substituents in substituted benzaldehydes has an effect on the stereoselectivity. Furthermore, when cyclopentanone was used as an aldol donor, a good yield of 90% with excellent *ee* (96%) for the *anti*-isomer was received; however, the diastereomeric ratio obtained was only 77:23 (*anti/syn*) (Table 4, entry 15). In addition, we have examined the feasibility of using acyclic ketones as aldol donors. Although longer reaction times were required in comparison with cyclic ketones, satisfactory results were obtained. Both acetone and diethyl ketone reacted smoothly with 4-nitrobenzaldehyde under optimal conditions to give the corresponding aldol products in good yields of 85% (Table 4, entries 16 and 17). In the case of

Table 4. Scope of the organocatalyzed direct aldol reaction under optimal conditions.[a]



2 **3** **4**

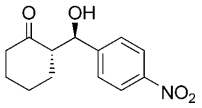
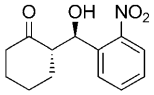
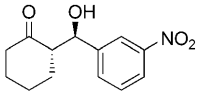
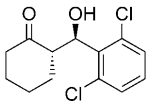
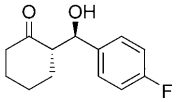
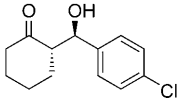
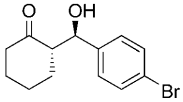
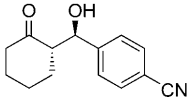
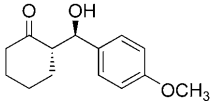
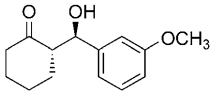
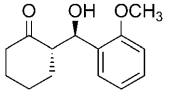
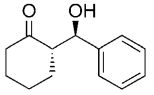
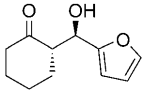
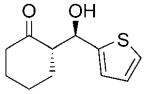
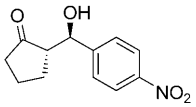
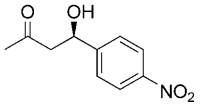
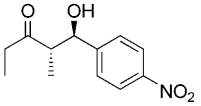
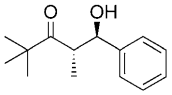
Entry	Product	No.	Time [h]	Yield [%][b]	*dr* (*anti*/*syn*)[c]	*ee* [%][c]
1		**4a**	30	95	93:7	96
2		**4b**	30	97	92:8	93
3		**4c**	30	90	95:5	90
4		**4d**	32	95	99:1	98
5		**4e**	32	90	93:7	90
6		**4f**	32	94	92:8	91
7		**4g**	32	97	95:5	93
8		**4h**	32	89	85:15	92
9		**4i**	40	80	97:3	95
10		**4j**	40	88	95:5	94
11		**4k**	40	85	95:5	93
12		**4l**	32	92	90:10	89
13		**4m**	40	90	95:5	93
14		**4n**	40	90	96:4	92

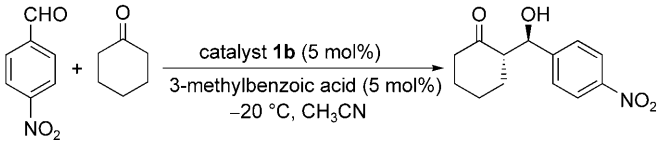
Table 4. (Continued)

Entry	Product	No.	Time [h]	Yield [%][b]	*dr* (*anti*/*syn*)[c]	*ee* [%][c]
15		**4o**	25	90	77:23	96
16		**4p**	60	85	–	79
17		**4q**	72	85	80:20	85
18[d]		**4r**	80	74	94:6	87

[a] Unless otherwise note, the reactions were carried out using aldehyde (0.5 mmol) and ketone (4 equiv.) in CH_3CN (2.0 mL) at −20 °C.
[b] Isolated yield after chromatography on silica gel.
[c] Determined by chiral HPLC analysis (AD-H, OD-H, AS-H or OJ-H).
[d] Performed with 10 equivalents of ketone.

tert-butyl ethyl ketone, a higher ketone loading of 10 equivalents was used to achieve an acceptable yield of 74% with benzaldehyde (Table 4, entry 18). Notably, acetone as the smallest ketone only gave a low *ee* of 79%, while diethyl ketone and *tert*-butyl ethyl ketone gave good *ee* values of 85% and 87% for *anti*-isomers, respectively. Besides, an excellent diastereoselectivity of 94:6 (*anti*/*syn*) was obtained using the more sterically hindered *tert*-butyl ethyl ketone. Meanwhile, the less sterically hindered diethyl ketone only gave a moderate *dr* of 80:20 (*anti*/*syn*). The results suggested that the steric hindrance of the acyclic ketones also has an effect on the stereoselectivity.

Table 5. Recycling and reuse of catalyst **1b**.[a]



Cycle	Time [h]	Yield [%][b]	*dr* (*anti*/*syn*)[c]	*ee* [%][c]
1	20	95	98:2	96
2	20	92	95:5	94
3	20	92	95:5	90
4	28	90	93:7	88
5	48	85	90:10	85

[a] The reactions were carried out using 4-nitrobenzaldehyde (2 mmol) and cyclohexanone (4 equiv.) in CH_3CN (8 mL) at −20 °C.
[b] Isolated yield after chromatography on silica gel.
[c] Determined by chiral HPLC analysis (AD-H).

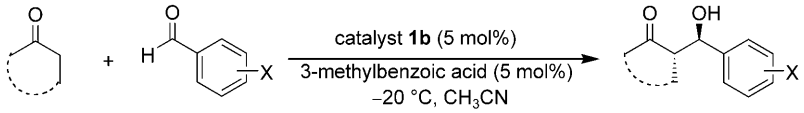
Meanwhile, in order to verify that the catalyst **1b** could be recovered and reused, we performed a recycling study of **1b** using the aldol reaction between cyclohexanone and 4-nitrobenzaldehyde (Table 5). The catalyst **1b** could be easily recovered from the reaction mixture after completion of the reaction by acid treatment, extraction, alkalization of aqueous phase, extraction, concentration, and directly used it in subsequent aldol reaction without adding any new catalyst. In each reuse, the same amounts of substrates were used, and the recovered **1b** without further purification retained essentially its catalytic activity, and only slightly a decrease of enantioselectivity was observed for five cycles (Table 5).

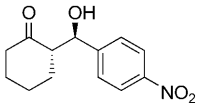
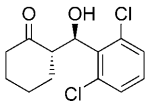
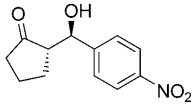
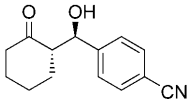
We further performed large-scale asymmetric aldol reactions with 20 mmol of aldehydes and 4 equivalents of ketones. The same catalyst loading of 5 mol% as in the experimental scale was used. The large-scale experiments can be facilely carried out using the same procedure as for the experimental scale reactions. As can be seen from the results summarized in Table 6, delightfully, the enantioselectivity maintained at the same level for the large-scale reactions.

Conclusions

In conclusion, the results from the investigation demonstrate that the L-prolinamide **1b** is a robust and effective catalyst for highly enantioselective aldol reactions. A wide range of aromatic and heteroaromatic aldehydes with cyclic and acyclic ketones can effectively participate in the reaction. The electronic effect

Table 6. Large-scale asymmetric aldol reactions.[a]



Entry	Product	Time [h]	Yield [%][b]	*dr* (*anti/syn*)[c]	*ee* [%][c]
1		30	89	85:15	93
2		36	91	90:10	95
3		30	89	77:23	96
4		36	90	80:20	91

[a] The reactions were carried out using aldehyde (20 mmol) and ketone (4 equiv.) in CH_3CN (100 mL) at −20 °C.
[b] Isolated yield after chromatography on silica gel.
[c] Determined by chiral HPLC analysis (AD-H and AS-H).

and steric effect of the substituents in substituted benzaldehydes as well as the steric effect of acyclic ketones have been discussed. The catalyst can be readily recovered and reused without significant loss of catalytic activity and stereoselectivity. Notably, this organocatalyzed direct asymmetric aldol reaction can be performed on a large-scale with the enantioselectivity being maintained at the same level, which offers a great possibility for applications in industry.

Experimental Section

General Remarks

NMR data were obtained for ^1H at 300 MHz, and for ^{13}C at 75 MHz. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard in $CDCl_3$ solution. High-resolution mass spectra (Varian 7.0T FTICR-MS) were obtained by use of ESI ionization sources. In each case, enantiomer ratios were determined by chiral HPLC analysis on Chiralcel AS-H, AD-H, OD-H or OJ-H in comparison with authentic racemates. Amino acids and diamines obtained from commercial sources were used directly without further purification. *tert*-Butyl ethyl ketone was prepared following the reported procedure.[15] All reactions were monitored by thin-layer chromatography (TLC) with Haiyang GF254 silica gel plates. Flash column chromatography was carried out using 100–200 mesh silica gel at increased pressure.

Preparation of Prolinamide 1b[14b]

To a solution of *N*-Boc-L-proline[12] (4.7 g, 22 mmol) and TEA (2.3 g, 22 mmol) in dry CH_2Cl_2 (80 mL) under argon at 0 °C was added ethyl chloroformate (2.6 g, 24 mmol) dropwise over 15 min. The resulting solution was stirred at 0 °C for 30 min. Then a solution of 2-[(1*R*,2*R*)-2-aminocyclohexyl)isoindoline-1,3-dione[13] (4.9 g, 20 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise over 15 min. The mixture was allowed to warm to room temperature and further stirred for 4 h. The mixture was washed with 1 M $KHSO_4$, saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography using EtOAc/petroleum ether (1:3, v/v) as eluent to afford (*S*)-*tert*-butyl 2-[(1*R*,2*R*)-2-(1,3-dioxoisoindolin-2-yl)cyclohexylcarbamoyl]pyrrolidine 1-carboxylate as white solid; yield: 8.6 g (98%).

To a solution of (*S*)-*tert*-butyl 2-[(1*R*,2*R*)-2-(1,3-dioxoisoindolin-2-yl)cyclohexylcarbamoyl]pyrrolidine 1-carboxylate (4.4 g, 10 mmol) in CH_2Cl_2(15 mL) was added TFA (7.5 mL). After stirring at 0 °C for 2.5 hour, the solution was concentrated under vacuum to leave a glutinous phase. The pH of the mixture was brought into the range of ~12 by the addition of 2 M NaOH. The aqueous phase was extracted with ethyl acetate. The ethyl acetate extracts were pooled, washed with brine, dried over anhydrous Na_2SO_4, filtered off and the solvent was evaporated at low pressure to give a crude residue that was purified by recrystallization, affording catalyst **1b** as a white solid; yield: 3.1 g (91%).

Preparation of Prolinamide 1d[13]

A sample of (*S*)-*tert*-butyl 2-[(1*R*,2*R*)-2-(1,3-dioxoisoindolin-2-yl)cyclohexylcarbamoyl]pyrrolidine 1-carboxylate (440 mg, 1 mmol) was refluxed with hydrazine hydrate (0.12 mL) in ethanol (5 mL) for 2 h. After cooling to room temperature the solution was diluted with diethyl ether to precipitate phthaloyl hydrazide. The mixture was filtered and the filtrate evaporated to dryness. The products were purified by extraction into the dilute HCl, followed by neutralization with saturated $NaHCO_3$ solution and back-extraction with dichloromethane. Yield: 85%.

General Procedure for Aldol Reaction of Ketones with Aldehydes

A mixture of the catalyst **1b** (9 mg, 0.025 mmol), 3-methylbenzoic acid (3.5 mg, 0.025 mmol) and ketone (2 mmol) in CH_3CN (2 mL) was stirred for 30 min at −20 °C. Then, aldehyde (0.5 mmol) was added and the reaction mixture was stirred at −20 °C. The reaction was monitored by TLC. It was then quenched with 5 mL saturated NH_4Cl solution, extracted with CH_2Cl_2 (3×10 mL), and dried over Na_2SO_4. Purification by flash chromatography afforded the corresponding pure products.

Procedure for Catalyst Recovery

A mixture of the catalyst **1b** (34 mg, 0.1 mmol), 3-methylbenzoic acid (14 mg, 0.1 mmol) and cyclohexanone (0.8 mL, 8 mmol) in MeCN (8 mL) was stirred for 30 min at −20 °C. Then, 4-nitrobenzaldehyde (302 mg, 2 mmol) was added and the reaction mixture was stirred at −20 °C. The reaction was monitored by TLC. Then, the reaction mixture was diluted with EtOAc (30 mL), and 6 M HCl (3 mL) was added. The mixture was stirred for 10 min at −20 °C. The resulting emulsion was treated with saturated NaCl solution (3× 15 mL). The organic phase was concentrated to furnish the product. The aqueous layer was basified with saturated NaOH until pH 10 and extracted with EtOAc (3×30 mL). The organic phase was dried with Na_2SO_4 and filtered, and the solvent was evaporated under vacuum. The resulting residue was used in the next reaction cycle.

General Procedure for Large-Scale Aldol Reactions

A solution of **1b** (340 mg, 1 mmol), 3-methylbenzoic acid (140 mg, 1 mmol) and ketone (80 mmol) in CH_3CN (50 mL) at −20 °C was stirred for 30 min. Then, a solution of aldehyde (20 mmol) in CH_3CN (50 mL) was added dropwise over 1 hour. The reaction was monitored by TLC. It was then quenched with 50 mL saturated NH_4Cl solution, extracted with CH_2Cl_2 (3×50 mL), and dried over Na_2SO_4. Purification by flash chromatography afforded the corresponding pure products.

Supporting Information

Spectral data for new compounds and HPLC data are available in the Supporting Information

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