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An Acid/Base-Regulated Recyclable Strategy for Homogeneous Cinchona Alkaloid-Derived Primary Amine Organocatalysts in Aldol, Vinylogous Michael and Double-Michael Cascade Reactions

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A practical, recyclable strategy for homogeneous cinchona alkaloid-derived primary amine organocatalysts was developed by controlling the solubilities in an aqueous/organic biphasic system through regulating the pH of the aqueous phase, effecting the protonation and deprotonation of primary amino, tertiary amino and pyridyl groups. By means of model aldol, vinylogous Michael and double-Michael cascade reactions, the reusability of the organocatalysts *epi*-$CDNH_2$, DeMe-$QNNH_2$ and H-$CDNH_2$ over three cycles was investigated in detail. It was found that the organocatalysts were highly effective with respect to catalytic performance, including the yields and stereoselectivities. Furthermore, the recovered organocatalysts in the tenth cycle retained similar excellent enantioselectivities to fresh organocatalysts. However, the formation of inactive intermediates between organocatalyst and reactants resulted in decreased yields.

Introduction

Natural cinchona alkaloid-derived primary amines have proved to be among the most powerful asymmetric organocatalysts capable of efficiently promoting a variety of asymmetric organocatalytic reactions,[1] including iminium catalysis,[2] enamine catalysis,[3] dienamine catalysis[4] and cascade reactions.[5] From the perspective of green chemistry, the potential application of homogeneous organocatalysts in the chemical industry is rather limited due to their high cost and difficult isolation from reaction mixtures. One efficient strategy to overcome this problem is heterogenization by entrapment or grafting of organocatalysts on the surfaces or inside the pores of solid supports, including organic polymers,[6] inorganic materials[7] and magnetic nanoparticles.[8] However, in heterogeneous catalysis, diffusion of molecules is the sum of two contributions: the diffusion of molecules in the solvent and diffusion of molecules inside the pore of the supporting matrix, which generally results in decreased catalytic performance. At this point, homogeneous catalysis theoretically has an advantage over heterogeneous catalysis. To combine the advantages of both homogeneous and heterogeneous catalysis, one-phase catalysis and two-phase separation of supported catalysts provides an ideal strategy to achieve homogeneous-like heterogeneous catalysis, avoiding the mass transfer limitations. Among them, soluble organic polymer-supported organocatalysts were seen as the most valuable alternative, where a reaction can be run under homogeneous conditions while the organocatalyst itself can be precipitated and easily recovered by filtration.[9] Recently, the homogenization of inorganic material-supported catalysts was also realized in asymmetric catalysis.[10] Even though better catalytic properties were obtained for a few examples due to the contribution of the site-isolation and steric confinement effects, most of them suffered from lowered catalytic activity and enantioselectivity due to the restrictions of supporting matrix.

In this paper, based on the concept of one-phase catalysis and two-phase separation, we provide a practical solution to the easy recovery and recycling of free homogeneous cinchona alkaloid-derived primary amine organocatalysts

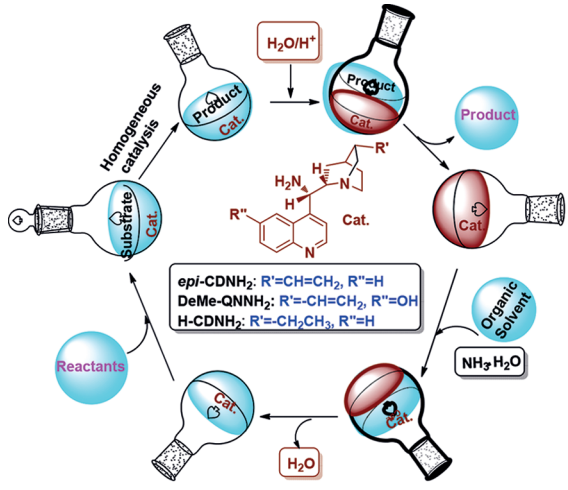

Figure 1. A depiction of one-phase catalysis and two-phase separation and recycling of free primary amine organocatalyst.

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(Figure 1). Due to the protonation of primary and tertiary amines and pyridyl groups in acidic medium, cinchona alkaloid-derived primary amine organocatalysts had a high partition coefficient in an aqueous/organic biphasic system, which could facilitate organocatalyst recovery from reaction mixtures by liquid/liquid separation. This recoverable strategy without structural modification of the organocatalyst efficiently avoided the restrictions of supporting matrix and possessed the merits of both homogeneous and heterogeneous catalysis. Furthermore, the reusability and structural changes of the organocatalysts were evaluated by three model asymmetric reactions including aldol, vinylogous Michael and double-Michael cascade reactions.

Results and Discussion

Acid/Base-Regulated Recyclable Strategy

Due to the protonation of primary amino, tertiary amino and pyridyl groups, cinchona alkaloid-derived organocatalysts *epi*-CDNH$_2$, DeMe-QNNH$_2$ and H-CDNH$_2$ easily afford their corresponding ammonium salts in acidic medium.[11] Generally, it is well known that the protonated ammonium salts possess better water solubilities than the original unprotonated structures. The concentrations of organocatalysts *epi*-CDNH$_2$, DeMe-QNNH$_2$ and H-CDNH$_2$ in aqueous/organic biphasic systems can be expressed by the distribution coefficient (D). Most importantly, the distribution coefficient of homogeneous organocatalysts in aqueous/organic biphasic systems is a crucial parameter in achieving the concept of one-phase homogeneous catalysis and two-phase separation, where the high D values in aqueous and organic phases favor two-phase separation and one-phase catalysis, respectively.

The distribution coefficients of *epi*-CDNH$_2$ in an aqueous/organic biphasic system could be accurately determined by ultraviolet spectroscopy at λ = 320 nm. In the aqueous/cyclohexanone (CYC) system, the effect of pH on the D values of *epi*-CDNH$_2$ is shown in Figure 2 (a). It was found that the distribution coefficients were similar (D = 0.15–0.33) in the pH = 1–4 range. However, there was a sharp increase in D value at pH = 0, due to the full protonation of primary and tertiary amines and pyridyl groups. Theoretically, a value of D = 5.3 at pH = 0 in water/cyclohexanone implied that 99.6% of *epi*-CDNH$_2$ could be recovered after being extracted three times by isometric aqueous solution. In place of cyclohexanone, trichloromethane (TCM), dichloromethane (DCM), ethyl acetate (EA) and toluene, also gave good D values (D = 4.0–4.9) in water at pH = 0, as shown in Figure 2 (b). These high D values in aqueous phase provided a powerful theoretical principle for the recovery of *epi*-CDNH$_2$ from organic medium upon the completion of reaction.

The distribution coefficients of DeMe-QNNH$_2$ in an aqueous/trichloromethane (TCM) system at different pH values and an aqueous/organic system at pH = 0 were also determined quantitatively by ultraviolet spectroscopy at 252 nm. As in Figure 3 (a and b), DeMe-QNNH$_2$ exhibited

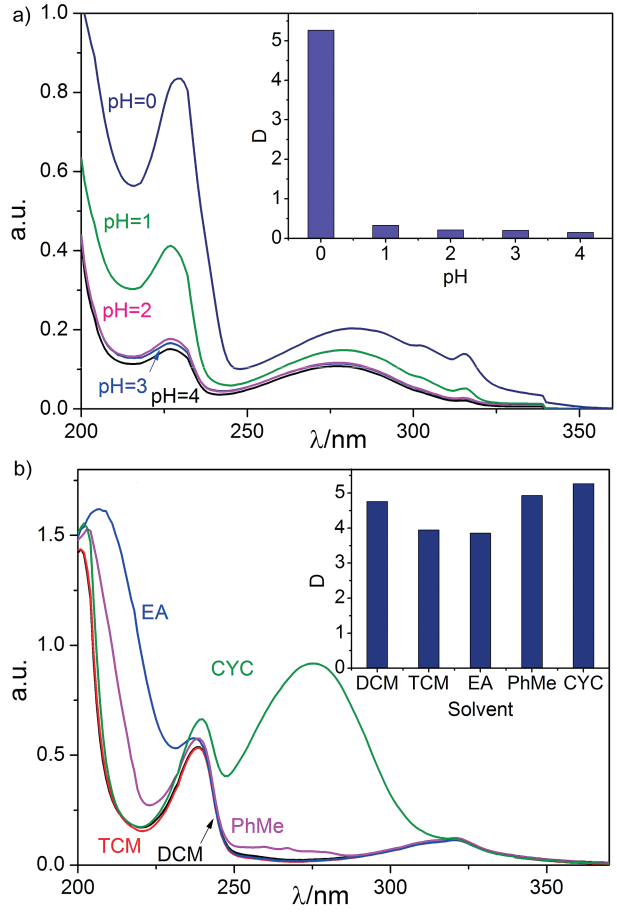


Figure 2. The UV spectra and distribution coefficients of *epi*-CDNH$_2$ in the aqueous phase: a) water/cyclohexanone system at different pH values; b) water/various solvents at pH = 0.

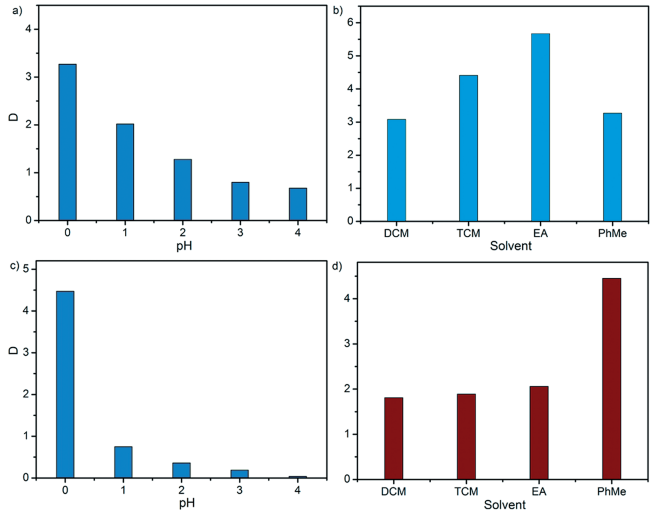


Figure 3. Distribution coefficients in the aqueous phase of: a) DeMe-QNNH$_2$ at different pH, b) DeMe-QNNH$_2$ in various solvents at pH = 0, c) H-CDNH$_2$ at different pH, and d) H-CDNH$_2$ in various solvents at pH = 0.

increased distribution coefficients (D = 0.68→2.02) in aqueous solution with a pH decrease from 4 to 1. At pH = 0, DeMe-QNNH$_2$ had a high distribution coefficient (D =

3.27), which implied that 98.7% of DeMe-QNNH$_2$ could be theoretically recovered by three extractions using isometric aqueous solution with pH = 0. Similar trends in the distribution coefficient of H-CDNH$_2$ in aqueous solution were also observed, and are shown in Figure 3 (c, d).

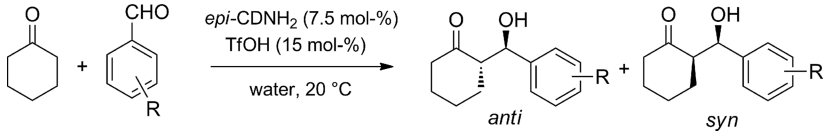
Based on the fact that the distribution coefficients of organocatalysts *epi*-CDNH$_2$, DeMe-QNNH$_2$ and H-CDNH$_2$ in aqueous or organic phase could be controlled by means of regulating the pH of the aqueous phase, one-phase organocatalysis was carried out in the organic phase with pH > 1. After the completion of the reaction, over 98% of protonated *epi*-CDNH$_2$, DeMe-QNNH$_2$ and H-CDNH$_2$ could be transferred into the aqueous phase by three extractions using an isometric aqueous solution with pH = 0. Subsequently, the pH of the combined aqueous solutions was adjusted by adding aqueous ammonia to pH = 9–10, and deprotonation of the catalyst occurred. Therefore, free *epi*-CDNH$_2$, DeMe-QNNH$_2$ and H-CDNH$_2$ could be recovered by extraction using organic solvents such as toluene and reused directly without any treatment in the following catalytic cycle.

Asymmetric Aldol Reaction

The asymmetric aldol reaction provided straightforward access to the optically active β-hydroxycarbonyl structural unit found in natural drugs.[12] From the standpoint of a green economy, a perfect asymmetric aldol reaction requires a reusable organocatalyst, a green solvent and high stereoselectivity under mild conditions. Based on the concept of two-phase separation and one-phase catalysis, the model asymmetric aldol reaction of cyclohexanone with benzaldehyde derivatives in aqueous solution was used to evaluate the reusability of homogeneous *epi*-CDNH$_2$ according to the technology route shown in Figure 1.

The catalytic performances of *epi*-CDNH$_2$ in the first and 3rd uses are listed in Table 1. It was found that the asymmetric aldol reaction of cyclohexanone with various benzaldehyde derivatives catalyzed by *epi*-CDNH$_2$ showed higher yields, diastereoselectivities and enantioselectivities than the reported results,[13] and remained unchanged during the first three runs due to good recovery of *epi*-CDNH$_2$. Based on the distribution coefficients (D = 0.15–0.33) of

Table 1. The asymmetric aldol reaction of cyclohexanone with various benzaldehydes in the first and 3rd uses.[a]



Entry	R	Time [h]	Yield [%][b]	*dr* (*anti*/*syn*)[c]	% *ee anti*[d]
1	2-NO_2	24 (1st)	>99	88:12	98
		24 (3rd)	>98	84:16	98
2	3-NO_2	24 (1st)	>99	90:10	97
		24 (3rd)	97	89:11	96
3	4-NO_2	8 (1st)	>99	90:10	97
		16 (3rd)	98	88:12	97
4	2-CN	24 (1st)	92	86:14	97
		24 (3rd)	90	84:16	96
5	3-CN	24 (1st)	95	82:18	95
		24 (3rd)	93	80:20	95
6	2-Cl	48 (1st)	87	98:2	97
		48 (3rd)	86	96:4	96
7	3-Cl	48 (1st)	86	94:6	96
		48 (3rd)	85	95:5	95
8	4-Cl	48 (1st)	97	94:6	93
		48 (3rd)	95	94:6	93
9	2-CH_3	48 (1st)	84	90:10	89
		48 (3rd)	83	89:1	88
10	3-CH_3	48 (1st)	92	89:11	86
		48 (3rd)	90	89:11	85
11	4-CH_3	48 (1st)	97	94:6	80
		48 (3rd)	96	95:5	80
12	2-OCH_3	48 (1st)	35	96:4	92
		48 (3rd)	32	94:6	90
13	3-OCH_3	48 (1st)	59	84:16	91
		48 (3rd)	58	86:14	91
14	4-OCH_3	48 (1st)	60	88:12	80
		48 (3rd)	57	87:13	80

[a] 20 °C, benzaldehyde (0.4 mmol), cyclohexanone (0.7 g, 7.1 mmol), 7.5 mol-% *epi*-CDNH$_2$, water (1.0 mL), 15 mol-% TfOH (9.0 mg, 0.06 mmol). [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy. [d] Monitored by chiral HPLC with Daicel Chiralpak AD-H/OD-H column.

epi-$CDNH_2$ in water/cyclohexanone in the pH = 1–3 range, it was known that 75.2–87.0% of *epi*-$CDNH_2$ existed in the cyclohexanone phase during the aldol addition. Even so, *epi*-$CDNH_2$ could be recovered in 95–98% yields from the reaction mixture after being extracted three times with water at pH = 0 and subsequently with cyclohexanone at pH = 9–10 due to the high distribution coefficients in aqueous solution or organic phase, respectively, at different pH values. To further investigate the reusability of *epi*-$CDNH_2$, the aldol reaction between cyclohexanone with 4-nitrobenzaldehyde was carried out under the same conditions over repeated cycles. As shown in Figure 4, it was found that the high yields and excellent enantioselectivities of the aldol adduct were almost constant after the sixth cycle. However, the catalytic performance decreased gradually after the seventh cycle, especially the loss in diastereoselectivity from *anti*/*syn* = 9.0 to 2.0.

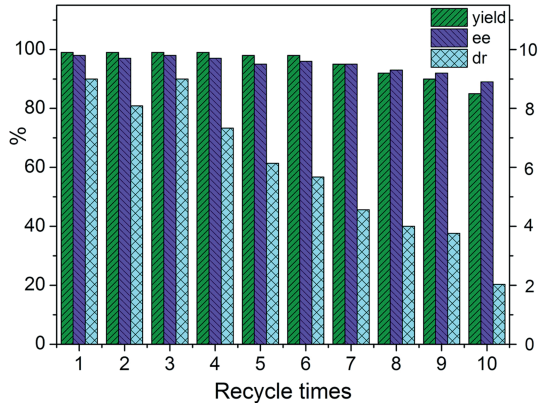


Figure 4. The reusability of homogeneous *epi*-$CDNH_2$ in the asymmetric aldol reaction of cyclohexanone with 4-nitrobenzaldehyde.

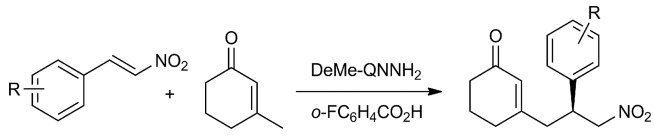
Furthermore, a huge amount of cyclohexanone with respect to aldehyde was crucial for *epi*-$CDNH_2$ to achieve excellent stereoselectivity. It was found that catalytic performance declined with the decreased molar ratio of cyclohexanone to 4-nitrobenzaldehyde. The good to excellent catalytic performances (95–99% yield, 91–97% *ee* and *anti*/*syn* = 4.9–9.0) were achieved in the molar ratio range of 3–24. The optimum molar ratio of cyclohexanone to 4-nitrobenzaldehyde was found to be 20. Unfortunately, unsatisfactory catalytic performances (23% yield, 89% *ee* and *anti*/*syn* = 4.6) were obtained at a 1:1 molar ratio of cyclohexanone to 4-nitrobenzaldehyde. Therefore, excess cyclohexanone played two pivotal roles: as the solvent and also as an accelerating agent.

Vinylogous Michael Reaction

To date, vinylogous addition of a nucleophile is the most effective enantioselective carbon–carbon bond formation γ to a carbonyl group. Within this context, the recycled behavior of versatile DeMe-$QNNH_2$ was investigated by means of a vinylogous Michael reaction of cyclohexenone with β-nitrostyrene as a model reaction.[14]

From Table 2, it was found that DeMe-$QNNH_2$ exhibited good to excellent catalytic performances (68–96% yield and 86–99%*ee*) in the asymmetric vinylogous Michael addition of 3-methylcyclohex-2-enone to β-nitrostyrene derivatives bearing electron-withdrawing and -donating groups at the *o*-, *m*- or *p*-positions. Regardless of the electronic properties and *o*-, *m*- or *p*-positions, all the substituents attached to β-nitrostyrene were well tolerated. It was noteworthy that β-nitrostyrene derivatives bearing strong electron-withdrawing substituents such as nitro groups at the *o*-, *m*- or *p*-positions gave relatively low yields (68–80%). Compared with the reported results of β-nitrostyrene possessing 2-Cl, 4-CH_3 and 4-OCH_3 substituents, better isolated yields with the same enantioselectivities were observed.[14]

Table 2. The asymmetric vinylogous Michael reaction of β-substituted cyclohexenone with β-nitrostyrene derivatives.[a]



Entry	R	Times	Yield [%][b]	% *ee* (R) [c]
1	H	1st	88	98
		3rd	87	98
1	2-NO_2	1st	68	92
		3rd	68	92
2	3-NO_2	1st	78	95
		3rd	76	95
3	4-NO_2	1st	80	>99
		3rd	78	>99
4	2-Cl	1st	87	98
		3rd	85	98
5	3-Cl	1st	90	97
		3rd	90	97
6	4-Cl	1st	93	99
		3rd	92	99
7	2-CH_3	1st	85	>99
		3rd	85	>99
8	3-CH_3	1st	90	86
		3rd	88	86
9	4-CH_3	1st	92	98
		3rd	91	98
10	2-OCH_3	1st	90	99
		3rd	89	99
13	3-OCH_3	1st	93	97
		3rd	92	97
11	4-OCH_3	1st	96	98
		3rd	95	98

[a] 40 °C, 48 h, toluene (1.0 mL), 3-methylcyclohex-2-enone (44.1 mg, 0.4 mmol), β-nitrostyrene (0.2 mmol), 2-F-$PhCO_2H$ (20 mol-%). [b] Isolated yield. [c] Monitored by chiral HPLC with Daicel Chiralpak AD-H column.

After the completion of the vinylogous Michael addition, 97–98% of DeMe-$QNNH_2$ could be recovered in each catalytic run through extraction three times by isometric aqueous solution with pH = 0 and subsequent with toluene at pH = 9–10. In the third cycle, DeMe-$QNNH_2$ satisfactorily retained its high catalytic performance, including the yields and enantioselectivities for various β-nitrostyrene derivatives. Using a model vinylogous Michael addition of 3-

methylcyclohex-2-enone to β-nitrostyrene, the reusability of DeMe-QNNH$_2$ was further investigated, as shown in Figure 5. The excellent enantioselectivities (98% *ee*) remained unchanged during the ten catalytic runs. However, the yields gradually decreased to 70% at the tenth run.

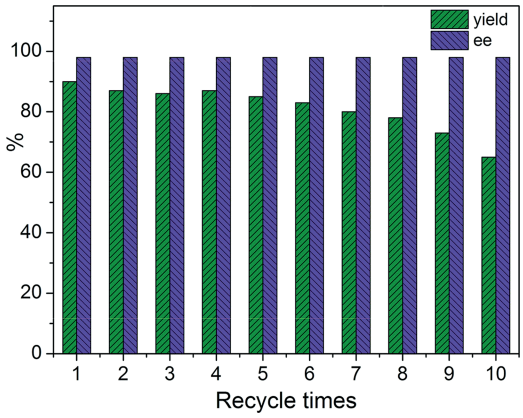


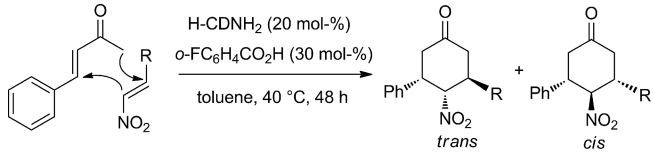
Figure 5. The reusability of DeMe-QNNH$_2$ in the vinylogous Michael addition of 3-methylcyclohex-2-enone to β-nitrostyrene.

Double-Michael Cascade Reaction

Recently, chiral primary amine organocatalysts, particularly cinchona alkaloid-derived primary amine organocatalysts, have offered a powerful alternative in the design of novel and synthetically useful organocascade reactions, which have provided highly efficient, operationally simple and atom-economical approaches to one-pot construction of complex chiral molecules useful for modern chemistry and drug discovery.[15]

Herein, the enamine–iminium activation of cinchona alkaloid-derived primary amines for a double-Michael sequence between an acyclic α,β-unsaturated ketone and β-nitrostyrene derivatives to furnish complex cyclohexanones with multiple stereocenters was selected as a model reaction, and is listed in Table 3.[16] We were pleased to find that the double Michael reaction catalyzed by H-CDNH$_2$ (20 mol-%), in combination with 30 mol-% of 2-fluorobenzoic acid as a co-catalyst, showed moderate to high stereocontrol (*trans*/*cis* = 4.2–24.5, 89–94% *ee trans*) with preferential formation of the formal *trans*-products, except that β-nitrostyrene bearing a *m*-Cl substituent gave low diastereoselectivity (*trans*/*cis* = 2.0) owing to its weak steric hindrance. Compared with the reported results of β-nitrostyrene possessing a 4-OCH$_3$ substituent, better yield and diastereoselectivity were achieved.[16] Satisfactorily, in the third cycled run, H-CDNH$_2$ retained its original catalytic performance, including the yield and stereoselectivity. Furthermore, the reusability of H-CDNH$_2$ was investigated in detail by means of a double-Mannich cascade reaction of (*E*)-4-phenylbut-3-en-2-one to β-nitrostyrene as a model example (Figure 6). In the tenth run, H-CDNH$_2$ still retained high stereoselectivity (*trans*/*cis* = 9.4, 91% *ee*, *trans*). However, the isolated yields in each run gradually decreased from 84–60%, although 95–98% of H-CDNH$_2$ could be recovered in each recycle due to the high distribution coefficients in the water/toluene system related to pH (Figure 3).

Table 3. The catalytic asymmetric double-Michael cascade reaction of an α,β-unsaturated ketone with β-nitrostyrene derivatives.[a]



Entry	R	Yield [%] (run)[b]	*dr* (*trans*/*cis*)[c]	% *ee trans*[d]
1	H	84 (1st)	10.0	94
		83 (3rd)	10.5	93
2	2-ClC$_6$H$_4$	76 (1st)	8.9	90
		75 (3rd)	8.8	90
3	3-ClC$_6$H$_4$	81 (1st)	2.0	94
		79 (3rd)	2.1	94
4	2-CH$_3$C$_6$H$_4$	76 (1st)	14.3	90
		76 (3rd)	14.0	91
5	3-CH$_3$C$_6$H$_4$	80 (1st)	4.2	93
		79 (3rd)	4.2	92
6	4-CH$_3$C$_6$H$_4$	81 (1st)	7.7	89
		82 (3rd)	7.8	89
7	2-OCH$_3$C$_6$H$_4$	82 (1st)	24.5	93
		79 (3rd)	24.4	93
8	3-OCH$_3$C$_6$H$_4$	80 (1st)	9.4	93
		80 (3rd)	9.4	92
9	4-OCH$_3$C$_6$H$_4$	86 (1st)	11.1	90
		84 (3rd)	11.0	90

[a] 40 °C, 48 h, 20 mol-% H-CDNH$_2$, 30 mol-% o-FC$_6$H$_4$CO$_2$H, toluene (1.0 mL), nitrostyrene (0.2 mmol), (E)-4-phenylbut-3-en-2-one (58.5 mg, 0.4 mmol). [b] Isolated yield. [c] Isolated yield. [d] Monitored by chiral HPLC with Daicel Chiralpak AD-H column.

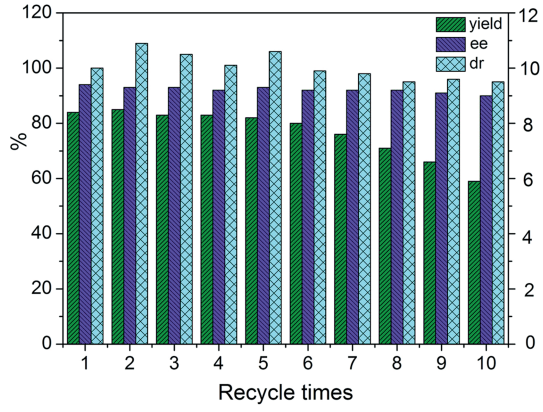


Figure 6. The reusability of H-CDNH$_2$ in the stereoselective Michael/Michael cascade reaction of (*E*)-4-phenylbut-3-en-2-one with β-nitrostyrene.

The Structural Change of Organocatalysts

In order to find out the reasons why the yields gradually decreased, we endeavored to isolate the byproducts by column chromatography after the completion of the tenth cyclic reaction. Several isolated byproducts were monitored by HRMS. From Figure 7, HRMS indicated that several inactive intermediates – adducts of the primary amine to

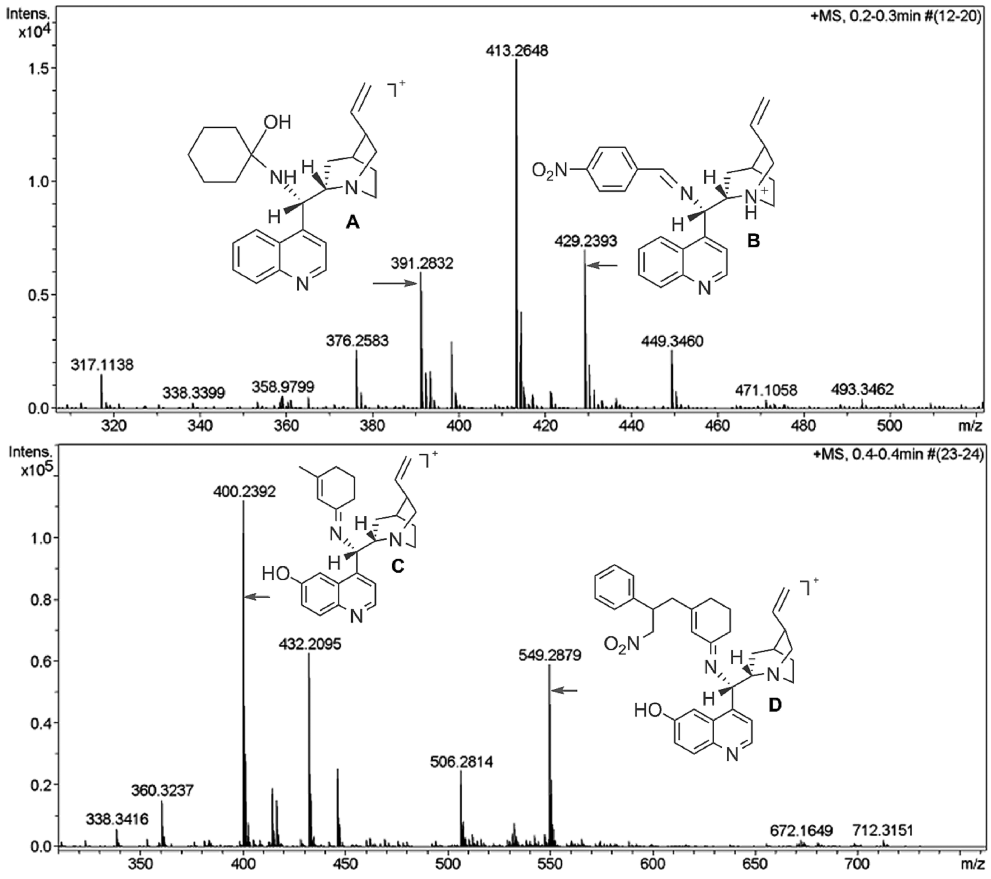


Figure 7. The mass spectrum of the isolated intermediates.

the carbonyl compounds, A and B and thermodynamic extended dienamine, C and D – were found, respectively, in the aldol and vinylogous Michael reactions. Due to the irreversible consumption, the effective content of the organocatalyst isolated from each run contained less organocatalyst than we weighed. It was concluded that the formation of byproducts of organocatalysts *epi*-CDNH$_2$ and DeMe-QNNH$_2$ was responsible for the declined yields of the desired products.

The Practical Study

In order to demonstrate the practicality of this technique, the reusability of organocatalysts *epi*-CDNH$_2$, DeMe-QNNH$_2$ and H-CDNH$_2$ was investigated on a large scale (>10 mmol) in enantioselective aldol, vinylogous Michael and double-Michael organocascade reactions, respectively.

In the large-scale enantioselective aldol reaction, we observed decreased yield (99→92%) and improved stereoselectivity (*anti*/*syn* = 88:12→95:5) compared with the aldol reaction on <1 mmol scale. The recovered *epi*-CDNH$_2$ showed a small decrease in the yield (90%) with the same stereoselectivity in the third cycle. However, consuming a huge amount of cyclohexanone was a limiting factor, although cyclohexanone could be recycled for further cyclic reactions by means of distillation.

In the reaction of β-nitrostyrene bearing an *o*-Cl substituent scaled up to 10 mmol according to the general procedure for cyclic vinylogous Michael and double-Michael reactions, the organocatalysts DeMe-QNNH$_2$ and H-CDNH$_2$ showed good reusability. In the third cyclic vinylogous Michael reaction, the recovered DeMe-QNNH$_2$ gave excellent *ee* (98%) in 86% yield. Similarly, excellent catalytic performance of recovered H-CDNH$_2$, with *trans*/*cis* = 8.7 and 90% *ee* (*trans*) in 73% yield was also achieved in the third cyclic double-Michael cascade reaction. Compared with the fresh organocatalysts, the recovered DeMe-QNNH$_2$ and H-CDNH$_2$ afforded the same stereoselectivity and slightly lower yields in the third cycle. In conclusion, the acid/base-regulated recyclable strategy provided a bright prospect for the homogeneous organocatalysts DeMe-QNNH$_2$, H-CDNH$_2$ and *epi*-CDNH$_2$ to be reused in the large-scale synthesis in industrial application.

Conclusions

Based on the catalytic concept of one-phase catalysis and two-phase separation, we developed a practical acid/base-regulated recyclable strategy for cinchona alkaloid-derived primary amine organocatalysts by means of the protonation and deprotonation of primary amine, tertiary amine and pyridyl groups. In the asymmetric aldol, vinylogous

Michael and double-Michael cascade reactions, the recovered organocatalysts retained excellent stereoselectivity as compared to fresh organocatalysts. This acid/base-regulated recyclable strategy provided a potential avenue for the application of homogeneous cinchona alkaloid-derived primary amine organocatalysts in large-scale synthesis.

Experimental Section

General Remarks: All chemicals were obtained from commercial suppliers and used without further purification. The organocatalysts were prepared according to the literature procedures [17] All reactions were monitored by thin-layer chromatography with Haiyang GF254 silica gel plates. Flash column chromatography was carried out using 230–400 mesh silica gel under increased pressure. The enantiomeric excess was determined with an Agilent LC-1200 HPLC using Daicel Chiralpak OD-H/AD-H 4.6 mm × 25 cm columns. ^{1}H and ^{13}C NMR spectra were recorded with Bruker av-300 and av-600 NMR instruments. Low-resolution mass spectrometry (MS) was performed with a mass spectrometer (Bruker Daltonics, USA, Bruker Co.) with an HCT ultra ion trap. C, H, N elemental analysis was obtained using a FLASHEA1112 automatic elemental analyzer instrument (Italy).

General Procedure for Cyclic Aldol Addition: In a 25-mL vial, the reaction mixture of *epi*-CDNH$_2$ (8.2 mg, 2.8×10^{-2} mmol), cyclohexanone (0.7 g, 7.2 mmol), TfOH (8.4 mg, 5.6×10^{-2} mmol) and water (1 mL) was stirred at 20 °C for 15 min, and then *p*-nitrobenzaldehyde (57.4 mg, 0.38 mmol) was added and allowed to react for 24 h (monitored by TLC). After the completion of the reaction, the organic phase was extracted with hydrochloric acid solution (pH = 0, 2 mL × 3). The organic phase was dried with anhydrous Na_2SO_4, evaporated under reduced pressure and purified by flash column chromatography eluting with petroleum ether/ethyl acetate (*v*/*v* = 8:1) to afford the pure aldol adduct. The combined aqueous phases were adjusted by aqueous ammonia to pH = 9–10, extracted with cyclohexanone (6 mL × 3) and concentrated under reduced pressure to one-fifth of the original volume to afford the recovered *epi*-CDNH$_2$ cyclohexanone solution, which was reused directly for the following cyclic aldol addition.

Large-Scale Cyclic Aldol Reaction: Cyclohexanone (71.0 g), *epi*-CDNH$_2$ (0.825 g), TfOH (0.9 g) and water (45 mL) were stirred at room temperature for 30 min. *o*-Nitrobenzaldehyde (5.6 g, 38 mmol) was added and allowed to stir for another 48 h. The reaction mixture was washed by hydrochloric acid solution (30 mL × 3, pH = 0). The organic phase was dried with anhydrous Na_2SO_4 and evaporated under reduced pressure to afford the crude product, which was purified by flash column chromatography, eluting with petroleum ether/ethyl acetate (v/v = 8:1) to give the pure aldol adduct with 98% *ee* (*anti*) and *antilsyn* = 95:5 in 92% yield.

General Procedure for Cyclic Vinylogous Michael Reaction: To a toluene (3 mL) solution of DeMe-QNNH$_2$ (6.2 mg, 2×10^{-2} mmol), *o*-fluorobenzoic acid (5.6 mg, 4×10^{-2} mmol) was added at room temperature whilst stirring. After 10 min, the reaction was started with the addition of 3-methylcyclohex-2-enone (44.1 mg, 0.4 mmol) immediately followed by and β-nitrostyrene (29.8 mg, 0.2 mmol). The reactants were allowed to reach 40 °C and were stirred for another 48 h. The organic phase was extracted with hydrochloric acid solution (pH = 0, 3 mL × 3), dried with anhydrous Na_2SO_4, evaporated under reduced pressure and purified by flash column chromatography using hexane/ethyl acetate (v/v = 4:1) as eluent to yield the vinylogous adduct. The pH of the combined aqueous phases was adjusted by aqueous ammonia to pH = 9–10, extracted with toluene (5 mL × 3) and concentrated under reduced pressure to one-fifth of its original volume. The recovered DeMe-QNNH$_2$ was used directly for the following cyclic asymmetric vinylogous Michael reaction. The data of new products are shown as follows.

(*R*)-3-[3-Nitro-2-(2-nitrophenyl)propyl]cyclohex-2-enone: 41.4 mg, 68%, 92% *ee*, $[\alpha]_D$ = –17.2 (*c* = 1.06, $CHCl_3$). ^{1}H NMR (600.1 MHz, $CDCl_3$): δ = 7.87 (d, ^3J = 8.4 Hz, 1 H), 7.63 (t, ^3J = 7.8 Hz, 1 H), 7.47 (t, ^3J = 7.8 Hz, 1 H), 7.41 (d, ^3J = 7.8 Hz, 1 H), 5.72 (s, 1 H), 4.74 (dd, *J* = 13.8, 7.8 Hz, 1 H), 4.64 (dd, *J* = 13.8, 6.6 Hz, 1 H), 4.43–4.48 (m, 1 H), 2.77 (dd, *J* = 13.8, 7.8 Hz, 1 H), 2.64 (dd, *J* = 13.8, 7.2 Hz, 1 H), 2.30–2.34 (m, 4 H), 1.93–2.02 (m, 2 H) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 198.9, 159.8, 150.1, 133.4, 132.7, 129.0, 128.9, 128.1, 125.3, 78.5, 41.4, 37.1, 35.9, 29.0, 22.5 ppm. MS: *m*/*z* = 305.1 [M + H]$^+$. $C_{15}H_{16}N_2O_5$ (304.30): calcd. C 59.21, H 5.30, N 9.21; found C 59.18, H 5.34, N 9.12.

(*R*)-3-[3-Nitro-2-(3-nitrophenyl)propyl]cyclohex-2-enone: 47.4 mg, 78%, 95% *ee*, $[\alpha]_D$ = –20.0 (*c* = 1.30, $CHCl_3$). ^{1}H NMR (600.1 MHz, $CDCl_3$): δ = 8.17 (s, 1 H), 8.10 (s, 1 H), 7.55 (d, ^3J = 4.8 Hz, 2 H), 5.77 (s, 1 H), 4.61–4.68 (m, 2 H), 3.89–3.94 (m, 1 H), 2.71 (dd, *J* = 15.0, 6.6 Hz, 1 H), 2.65 (dd, *J* = 14.4, 9.0 Hz, 1 H), 2.23–2.35 (m, 4 H), 1.91–1.99 (m, 2 H) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 198.7, 159.5, 148.8, 140.3, 133.6, 130.3, 128.7, 123.4, 122.2, 79.3, 41.6, 41.2, 37.1, 29.5, 22.5 ppm. MS: *m*/*z* = 305.1 [M + H]$^+$. $C_{15}H_{16}N_2O_5$ (304.30): calcd. C 59.21, H 5.30, N 9.21; found C 59.20, H 5.32, N 9.18.

(*R*)-3-[2-(3-Chlorophenyl)-3-nitropropyl]cyclohex-2-enone: 52.7 mg, 90%, 97% *ee*, $[\alpha]^D$ = –16.1 (*c* = 0.82, $CHCl_3$). ^{1}H NMR (600.1 MHz, $CDCl_3$): δ = 7.28 (d, ^3J = 3.0 Hz, 1 H), 7.27 (d, ^3J = 6.0 Hz, 1 H), 7.18 (s, 1 H), 7.07 (t, ^3J =2.4 Hz, 1 H), 5.78 (s, 1 H), 4.57 (d, ^3J = 7.2 Hz, 2 H), 3.74 (m, 1 H), 2.64 (dd, *J* = 13.8, 6.0 Hz, 1 H), 2.58 (dd, *J* = 14.4, 9.0 Hz, 1 H), 2.29–2.31 (m, 2 H), 2.17–2.26 (m, 2 H), 1.91–1.97 (m, 2 H) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 198.7, 160.0, 140.2, 135.2, 130.5, 128.6, 128.5, 127.5, 125.5, 79.7, 41.8, 41.4, 37.1, 29.6, 22.5 ppm. MS: *m*/*z* = 294.1 [M + H]$^+$. $C_{15}H_{16}ClNO_3$ (293.75): calcd. C 61.33, H 5.49, N 4.77; found C 61.21, H 5.52, N 4.68.

(*R*)-3-[2-(4-Chlorophenyl)-3-nitropropyl]cyclohex-2-enone: 54.5 mg, 93%, 99% *ee*, $[\alpha]_D$ = –25.0 (*c* = 1.32, $CHCl_3$). ^{1}H NMR (600.1 MHz, CD_3COCD_3): δ = 7.42 (dd, *J* = 8.4, 1.8 Hz, 2 H), 7.36 (dd, *J* = 8.4, 1.8 Hz, 2 H), 5.69 (s, 1 H), 4.83–4.92 (m, 2 H), 3.84–3.89 (m, 1 H), 2.76 (dd, *J* = 13.2, 6.0 Hz, 1 H), 2.68 (dd, *J* = 12.6, 9.0 Hz, 1 H), 2.27–2.40 (m, 2 H), 2.15–2.23 (m, 2 H), 1.85–1.92 (m, 2 H) ppm. ^{13}C NMR (150.9 MHz, CD_3COCD_3): δ = 198.2, 161.8, 138.9, 133.3, 130.0, 129.2, 128.2, 80.0, 42.0, 41.5, 37.3, 29.8, 22.9 ppm. MS: *m*/*z* = 294.1 [M + H]$^+$. $C_{15}H_{16}ClNO_3$ (293.75): calcd. C 61.33, H 5.49, N 4.77; found C 61.26, H 5.49, N 4.66.

(*R*)-3-[3-Nitro-2-(*o*-tolyl)propyl]cyclohex-2-enone: 46.4 mg, 85%, >99% *ee*, $[\alpha]_D$ = –16.7 (*c* = 1.20, $CHCl_3$). ^{1}H NMR (600.1 MHz, $CDCl_3$): δ = 7.17–7.20 (m, 2 H), 7.13 (d, ^3J = 7.2 Hz, 1 H), 5.78 (s, 1 H), 4.55 (d, ^3J = 7.8 Hz, 2 H), 4.06–4.11 (m, 1 H), 2.61 (d, ^3J = 7.2 Hz, 2 H), 2.38 (s, 3 H), 2.28 (t, ^3J = 6.6 Hz, 2 H), 2.19 (t, ^3J = 6.0 Hz, 2 H), 1.89–1.93 (m, 2 H) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 198.7, 160.9, 136.4, 136.0, 131.3, 128.3, 127.8, 126.9, 125.6, 79.6, 41.4, 37.2, 37.1, 29.7, 22.6, 19.4 ppm. MS: *m*/*z* = 274.2 [M + H]$^+$. $C_{16}H_{19}NO_3$ (273.33): calcd. C 70.31, H 7.01, N 5.12; found C 70.27, H 7.06, N 5.07.

(*R*)-3-[3-Nitro-2-(*m*-tolyl)propyl]cyclohex-2-enone: 49.1 mg, 90%, 86% *ee*, $[\alpha]_D$ = –15.6 (*c* = 0.92, $CHCl_3$). ^{1}H NMR (600.1 MHz, $CDCl_3$): δ = 7.21 (t, ^3J = 7.8 Hz, 1 H), 7.08 (d, ^3J = 7.2 Hz, 1 H),

6.96–6.97 (m, 2 H), 5.77 (s, 1 H), 4.56 (d, ^3J = 7.2 Hz, 2 H), 3.68–3.73 (m, 1 H), 2.57–2.64 (m, 2 H), 2.33 (s, 3 H), 2.26–2.29 (m, 2 H), 2.14–2.24 (m, 2 H), 1.88–1.93 (m, 2 H) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 199.1, 161.1, 138.9, 137.9, 129.0, 128.9, 128.3, 128.0, 124.3, 80.1, 42.1, 41.5, 37.1, 29.5, 22.5, 21.4 ppm. MS: *m*/*z* = 274.2 $[M + H]^+$. $C_{16}H_{19}NO_3$ (273.33): calcd. C 70.31, H 7.01, N 5.12; found C 70.24, H 7.02, N 5.10.

(*R*)-3-[2-(2-Methoxyphenyl)-3-nitropropyl]cyclohex-2-enone: 52.0 mg, 90%, 99% *ee*, $[\alpha]_D$ = –10.6 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (600.1 MHz, $CDCl_3$): δ = 7.24 (d, ^3J = 7.2 Hz, 1 H), 7.06 (d, ^3J = 7.8 Hz, 1 H), 6.87–6.91 (m, 2 H), 5.74 (s, 1 H), 4.71 (dd, *J* = 12.6, 6.6 Hz, 1 H), 4.63 (dd, *J* = 12.6, 7.8 Hz, 1 H), 4.01–4.06 (m, 1 H), 3.86 (s, 3 H), 2.75 (dd, *J* = 13.8, 9.6 Hz, 1 H), 2.63 (dd, *J* = 13.8, 6.0 Hz, 1 H), 2.17–2.30 (m, 4 H), 1.81–1.92 (m, 2 H) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 199.2, 162.0, 157.2, 129.3, 128.9, 128.0, 125.8, 121.0, 111.3, 78.7, 55.4, 39.9, 38.1, 37.2, 29.5, 22.6 ppm. MS: *m*/*z* = 290.1 $[M + H]^+$. $C_{16}H_{19}NO_4$ (289.33): calcd. C 66.42, H 6.62, N 4.84; found C 66.37, H 6.70, N 4.75.

(*R*)-3-[2-(3-Methoxyphenyl)-3-nitropropyl]cyclohex-2-enone: 53.7 mg, 93%, 97% *ee*, $[\alpha]_D$ = –8.7 (*c* = 1.10, $CHCl_3$). ^{1}H NMR (600.1 MHz, $CDCl_3$): δ = 7.25 (t, ^3J = 7.8 Hz, 1 H), 7.06 (d, ^3J = 7.8 Hz, 1 H), 6.81 (dd, *J* = 8.4, 2.4 Hz, 1 H), 6.76 (d, ^3J = 7.2 Hz, 1 H), 6.70 (s, 1 H), 5.78 (s, 1 H), 4.57 (d, ^3J = 7.2 Hz, 2 H), 3.79 (s, 3 H), 2.57–2.64 (m, 2 H), 2.26–2.30 (m, 2 H), 2.15–2.25 (m, 2 H), 1.89–1.94 (m, 2 H) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 198.9, 160.8, 160.2, 139.6, 130.3, 128.4, 119.5, 113.8, 113.1, 80.1, 55.3, 42.2, 41.5, 37.2, 29.6, 22.6 ppm. MS: *m*/*z* = 290.1 $[M + H]^+$. $C_{16}H_{19}NO_4$ (289.33): calcd. C 66.42, H 6.62, N 4.84; found C 66.40, H 6.69, N 4.78.

General Procedure for Cyclic Double-Michael Organocascade Reaction: To toluene (1 mL) solution of H-CDNH$_2$ (11.8 mg, 4×10^{-2} mmol), *o*-fluorobenzoic acid (8.4 mg, 6×10^{-2} mmol) was added at room temperature whilst stirring. After 10 min, (*E*)-4-phenylbut-3-en-2-one (58.4 mg, 0.4 mmol) was added, immediately followed by β-nitrostyrene (29.8 mg, 0.2 mmol). The reaction mixture was stirred at 40 °C for 48 h. To the organic phase was added toluene (4 mL), and the mixture was extracted with hydrochloric acid solution (pH = 0, 5 mL × 3), dried with anhydrous Na_2SO_4, evaporated under reduced pressure and purified by flash column chromatography using petroleum ether/ethyl acetate (v/v = 8:1) as eluent to afford the pure adduct. The pH of the combined aqueous phases was adjusted by aqueous ammonia to pH = 9–10, extracted with toluene (5 mL × 3) and concentrated under reduced pressure to one-fifth of its original volume. The recovered **H-CDNH$_2$** was used directly for following Michael/Michael cascade reactions. The data of the new products are shown as follows.

(3*S*,4*R*,5*S*)-3-(2-Chlorophenyl)-4-nitro-5-phenylcyclohexanone: 50.0 mg, 76%, *dr* (*trans*/*cis*) = 8.9:1, 90% *ee* (*trans*), $[\alpha]_D$ = –80.3 (*c* = 0.96, $CHCl_3$). ^{1}H NMR (600.1 MHz, $CDCl_3$): δ = 7.44 (dd, *J* = 7.8, 1.8 Hz, 1 H), 7.27–7.35 (m, 6 H), 7.06 (d, ^3J = 6.0 Hz, 2 H), 5.36 (t, ^3J = 4.8 Hz,1 H), 4.42 (dd, *J* = 12.6, 6.6 Hz, 1 H), 3.71–3.74 (m, 1 H), 3.38 (dd, *J* = 16.2, 10.8 Hz, 1 H), 3.19 (dd, *J* = 16.2, 6.6 Hz, 1 H), 2.83 (*trans*, dd, *J* = 16.2, 6.0 Hz, 2 H), 2.78 (*cis*, dd, *J* = 17.4, 3.0 Hz, 0.22 H) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 207.6, 139.2, 134.2, 133.7, 129.9, 129.4, 129.3, 128.2, 128.1, 127.5, 127.5, 89.5, 43.7, 41.2, 39.9, 36.9 ppm. MS: *m*/*z* = 330.1 $[M + H]^+$. $C_{18}H_{16}ClNO_3$ (329.78): calcd. C 65.56, H 4.89, N 4.25; found C 65.51, H 4.93, N 4.18.

(3*S*,4*R*,5*S*)-3-(3-Chlorophenyl)-4-nitro-5-phenylcyclohexanone: 53.3 mg, 81%, *dr* (*trans*/*cis*) = 2.0:1, 94% *ee trans*, $[\alpha]_D$ = –98.6 (*c* = 1.19, $CHCl_3$). ^{1}H NMR (600.1 MHz, $CDCl_3$): δ = 7.31–7.33 (m, 3 H), 7.27–7.29 (m, 4 H), 7.05–7.07 (m, 2 H), 5.30 (dd, *J* = 7.8, 5.4 Hz, 1 H), 3.85–3.90 (m, 2 H), 3.33 (*cis*, dd, *J* = 16.2, 10.2 Hz, 0.5 H), 3.26 (dd, *J* = 16.2, 8.4 Hz, 1 H), 3.08 (*cis*, dd, *J* = 15.6, 6.0 Hz, 0.56 H), 3.01 (*trans*, dd, *J* = 16.2, 5.4 Hz, 1.13 H), 2.75–2.91 (m, *cis*, 1 H, *trans*, 2 H) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = (*trans*) 206.6, 141.3, 136.5, 135.2, 130.6, 129.0, 128.5, 128.4, 127.6, 127.2, 125.4, 91.0, 43.6, 42.6, 42.0, 41.9; (*cis*) 206.9, 139.2, 138.9, 134.9, 130.2, 129.4, 128.6, 128.2, 127.8, 127.5, 125.6, 91.3, 42.9, 42.5, 41.3, 41.2 ppm. MS: *m*/*z* = 330.1 $[M + H]^+$. $C_{18}H_{16}ClNO_3$ (329.78): calcd. C 65.56, H 4.89, N 4.25; found C 65.49, H 4.91, N 4.21.

(3*S*,4*R*,5*S*)-4-Nitro-3-phenyl-5-(*o*-tolyl)cyclohexanone: 47.0 mg, 76%, *dr* (*trans*/*cis*) = 14.3:1, 90% *ee* (*trans*), $[\alpha]_D$ = –71.7 (*c* = 1.35, $CHCl_3$). ^{1}H NMR (600.1 MHz, $CDCl_3$): δ = 7.31–7.34 (m, 3 H), 7.19–7.23 (m, 4 H), 7.07 (d, ^3J = 6.0 Hz, 2 H), 5.25 (dd, *J* = 6.6, 4.8 Hz, 1 H), 4.17 (*trans*, q, ^3J = 7.2 Hz, 1 H), 4.09 (*cis*, q, ^3J = 5.4 Hz, 0.07 H), 3.83–3.86 (m, 1 H), 3.33 (dd, *J* = 15.6, 9.0 Hz, 1 H), 3.03 (dd, *J* = 16.2, 6.0 Hz, 1 H), 2.88 (dd, *J* = 16.2, 6.0 Hz, 1 H), 2.73 (dd, *J* = 16.2, 7.8 Hz, 1 H), 2.33 (*trans*, s, 3 H), 1.90 (*cis*, s, 0.20 H) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 207.7, 137.9, 137.0, 136.0, 131.4, 129.0, 128.3, 127.8, 127.5, 127.0, 125.5, 90.2, 43.4, 42.3, 41.9, 38.3, 19.2 ppm. MS: *m*/*z* = 310.2 $[M + H]^+$. $C_{19}H_{19}NO_3$ (309.36): calcd. C 73.77, H 6.19, N 4.53; found C 73.70, H 6.14, N 4.46.

(3*S*,4*R*,5*S*)-4-Nitro-3-phenyl-5-(*m*-tolyl)cyclohexanone: 49.5 mg, 80%, *dr* (*trans*/*cis*) = 4.2:1, 93% *ee* (*trans*), $[\alpha]_D$ = –95.7 (*c* = 1.18, $CHCl_3$). ^{1}H NMR (600.1 MHz, $CDCl_3$): δ = 7.30–7.34 (m, 3 H), 7.24–7.27 (m, 1 H), 7.11 (d, ^3J = 7.2 Hz, 1 H), 7.04–7.08 (m, 4 H), 5.29 (dd, *J* = 7.2, 4.8 Hz, 1 H), 3.95 (*cis*, dd, *J* = 13.8, 6.6 Hz, 0.24 H), 3.90 (*trans*, dd, *J* = 13.8, 6.6 Hz, 1 H), 3.78–3.81 (m, 1 H), 3.32 (dd, *J* = 15.6, 9.0 Hz, 1 H), 3.35 (dd, *J* = 16.2, 6.0 Hz, 1 H), 2.81–2.86 (m, 2 H), 2.35 (*trans*, s, 3 H), 2.31 (*cis*, s, 0.71 H) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 207.5, 139.4, 139.1, 136.9, 129.2, 128.9, 128.8, 128.3, 128.0, 127.5, 124.1, 91.6, 43.2, 42.5, 42.1, 41.7, 21.4 ppm. MS: *m*/*z* = 310.2 $[M + H]^+$. $C_{19}H_{19}NO_3$ (309.36): calcd. C 73.77, H 6.19, N 4.53; found C 73.67, H 6.21, N 4.49.

(3*S*,4*R*,5*S*)-4-Nitro-3-phenyl-5-(*p*-tolyl)cyclohexanone: 50.1 mg, 81%, *dr* (*trans*/*cis*) = 7.7:1, 89% *ee* (*trans*), $[\alpha]_D$ = –108.6 (*c* = 1.27, $CHCl_3$). ^{1}H NMR (600.1 MHz, $CDCl_3$): δ = 7.30–7.36 (m, 3 H), 7.12–7.18 (m, 4 H), 7.06 (d, ^3J = 6.6 Hz, 2 H), 5.26 (dd, *J* = 6.6, 4.8 Hz, 1 H), 3.91 (dd, *J* = 13.8, 7.2 Hz, 1 H), 3.75–3.79 (m, 1 H), 3.33 (dd, *J* = 15.6, 9.0 Hz, 1 H), 3.13 (*cis*, dd, *J* = 6.6, 4.8 Hz, 1 H), 3.05 (*trans*, dd, *J* = 16.2, 6.0 Hz, 1 H), 2.80–2.85 (m, 2 H), 2.34 (*trans*, s, 2.6 H), 2.32 (*cis*, s, 0.35 H) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 207.6, 137.8, 136.9, 136.4, 129.9, 129.6, 129.3, 128.9, 128.3, 127.5, 127.1, 91.7, 43.1, 42.3, 41.9, 41.7, 21.0 ppm. MS: *m*/*z* = 310.2 $[M + H]^+$. $C_{19}H_{19}NO_3$ (309.36): calcd. C 73.77, H 6.19, N 4.53; found C 73.69, H 6.22, N 4.51.

(3*S*,4*R*,5*S*)-3-(2-Methoxyphenyl)-4-nitro-5-phenylcyclohexanone: 53.3 mg, 82%, *dr* (*trans*/*cis*) = 24.5:1, 93%*ee* (*trans*), $[\alpha]_D$ = –105.2 (*c* = 1.36, $CHCl_3$). ^{1}H NMR (600.1 MHz, $CDCl_3$): δ = 7.27–7.32 (m, 4 H), 7.14 (d, ^3J = 7.2 Hz, 1 H), 7.07 (d, *J* = 7.2 Hz, 2 H), 6.93–6.96 (m, 2 H), 5.39 (t, *J* = 4.8 Hz, 1 H), 4.17 (t, ^3J = 6.6 Hz, 1 H), 3.88 (s, 3 H), 3.72–3.75 (m, 1 H), 3.35 (dd, *J* = 16.2, 11.4 Hz, 1 H), 3.07 (dd, *J* = 16.2, 6.6 Hz, 1 H), 2.97 (dd, *J* = 16.8, 7.2 Hz, 1 H), 2.77 (*trans*, dd, *J* = 16.2, 4.8 Hz, 1 H), 2.66 (*cis*, dd, *J* = 16.8, 3.6 Hz, 0.04 H) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 208.5, 156.7, 137.2, 129.3, 128.9, 128.8, 128.1, 127.6, 127.4, 121.2, 111.2, 89.6, 55.4, 41.9, 41.4, 41.0, 39.1 ppm. MS: *m*/*z* = 326.1 $[M + H]^+$. $C_{19}H_{19}NO_4$ (325.36): calcd. C 70.14, H 5.89, N 4.31; found C 70.08, H 5.92, N 4.29.

(3*S*,4*R*,5*S*)-3-(3-Methoxyphenyl)-4-nitro-5-phenylcyclohexanone: 52.0 mg, 80%, *dr* (*trans*/*cis*) = 9.4:1, 93% *ee* (*trans*), $[\alpha]_D$ = –118.9

(c = 1.32, $CHCl_3$). ^1H NMR (600.1 MHz, $CDCl_3$): δ = 7.25–7.31 (m, 4 H), 7.05 (d, J = 6.0 Hz, 2 H), 6.82 (d, ^3J = 6.6 Hz, 2 H), 6.77 (s, 1 H), 5.29 (t, ^3J = 4.8 Hz, 1 H), 3.89 (q, ^3J = 6.6 Hz, 1 H), 3.77 (s, 3 H), 3.73–3.75 (m, 1 H), 3.29 (*trans*, dd, J = 16.2, 9.6 Hz, 1 H), 3.14 (*cis*, dd, J = 17.4, 6.0 Hz, 0.11 H), 3.03 (dd, J = 16.2, 5.4 Hz, 1 H), 2.79–2.85 (m, 2 H) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 207.5, 160.2, 141.0, 136.8, 130.3, 128.9, 128.3, 127.5, 119.2, 113.4, 113.1, 91.4, 55.2, 43.1, 42.5, 42.1, 41.7 ppm. MS: m/z = 326.1 [M + H]$^+$. $C_{19}H_{19}NO_4$ (325.36): calcd. C 70.14, H 5.89, N 4.31; found C 70.11, H 5.90, N 4.27.

(3*S*,4*R*,5*S*)-3-(4-Methoxyphenyl)-4-nitro-5-phenylcyclohexanone: 55.9 mg, 86%, *dr* (*trans*/*cis*) = 11.1:1, 90% *ee* (*trans*), $[\alpha]_D$ = –71.1 (c = 0.92, $CHCl_3$). ^1H NMR (600.1 MHz, $CDCl_3$): δ = 7.30–7.31 (m, 3 H), 7.16 (d, ^3J = 8.4 Hz, 2 H), 7.06 (d, ^3J = 6.6 Hz, 2 H), 6.88 (d, ^3J = 7.8 Hz, 2 H), 5.28 (*cis*, t, ^3J = 5.4 Hz, 0.09 H), 5.23 (*trans*, t, ^3J = 5.4 Hz, 1 H), 3.89 (q, ^3J = 6.6 Hz, 1 H), 3.79 (s, 3 H), 3.74–3.77 (m, 1 H), 3.31 (dd, J = 16.2, 9.6 Hz, 1 H), 3.04 (dd, J = 16.2, 5.4 Hz, 1 H), 2.79–2.84 (m, 2 H) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 207.7, 159.2, 136.9, 131.3, 128.9, 128.3, 128.2, 127.5, 114.6, 91.8, 55.3, 43.1, 41.9, 41.8, 41.7 ppm. MS: m/z = 326.1 [M + H]$^+$. $C_{19}H_{19}NO_4$ (325.36): calcd. C 70.14, H 5.89, N 4.31; found C 70.12, H 5.90, N 4.29.

Supporting Information (see also the footnote on the first page of this article): ^1H and ^{13}C NMR spectra of organocatalysts and products; HPLC spectra of racemic and optically active products.

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