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ORIGINAL PAPER

The organocatalytic highly enantioselective Knoevenagel condensation: applications in the synthesis of various chiral amide derivatives

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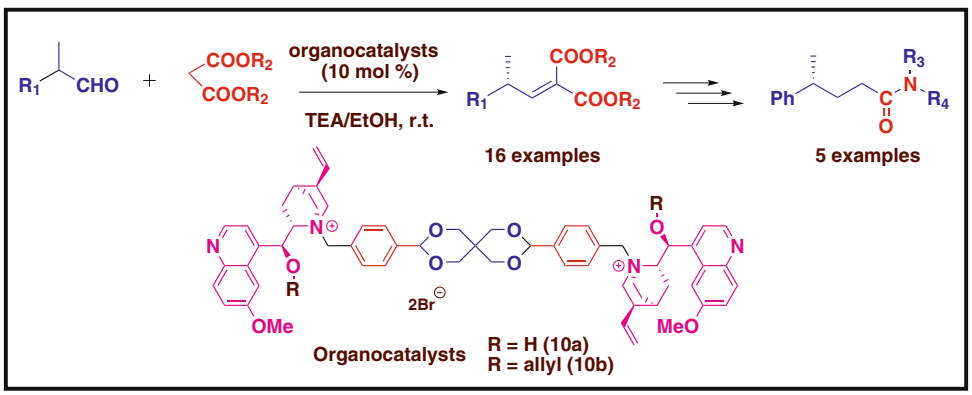
Abstract

In this work, efficient organocatalysts were designed, synthesized and successfully applied to the Knoevenagel condensation. In this reaction, different α-branched aldehydes were treated with various malonate compounds to give the desired products up to 97% yield and excellent e.r up to 99.68:0.32 under the mild reaction conditions. Moreover, the Knoevenagel product was converted into different chiral amide derivatives in higher enantioselectivity.

Graphical abstract

We have designed and synthesized efficient chiral organocatalysts and successfully applied to the Knoevenagel condensation reaction. In this reaction, the different α-branched aldehydes were treated with various malonate derivatives to give enantiomerically enriched Knoevenagel products with higher chemical yield (up to 97%) and excellent e.r up to 99.68 0.32 via dynamic kinetic resolution. Further the Knoevenagel adduct was converted into enantiomerically enriched valuable γ-alkyl-substituted amides without loss in enantiomeric ratio.



Keywords Organocatalysts · Enantioselectivity · Knoevenagel condensation · Dynamic kinetic resolution · Chiral amide

Introduction

The Knoevenagel condensation is a powerful, general, and frequently used reaction for the construction of C–C bonds [1–5], and archetype of modern organocatalysis [6–10]. The reaction has been successfully utilized for the synthesis of different kinds of organic compounds including coumarin derivatives [11], cosmetics [12], perfumes [13] and pharmaceutical chemicals [14]. Various catalysts,

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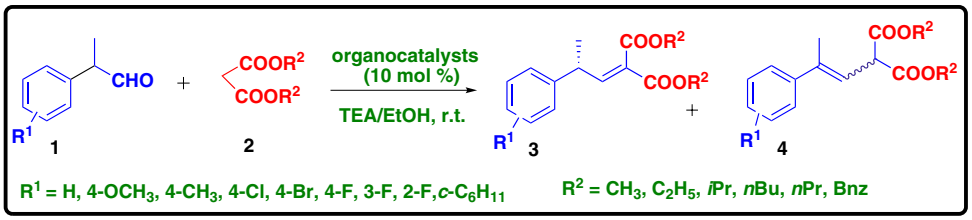
Scheme 1 Asymmetric Knoevenagel condensation reaction via dynamic kinetic resolution



such as Lewis acids [15], zeolites [16], calcite [17], ionic liquids [18, 19], surfactants [20], ammonium salts [21, 22], aminoacids [23–25], dimethylaminopyridine [26], potassium fluoride mixture, synthetic phosphates [27–29], urea-derived catalysts [30, 31] and organocatalyst [32, 33], have been employed to catalyse this kind of reactions in recent decades. First, in 2011, List's group reported an example of asymmetric Knoevenagel condensation of racemic-branched aldehydes to give the corresponding enantiomerically enriched products in dynamic kinetic resolution (DKR) using cinchona catalysts [34–37].

The dynamic kinetic resolution (DKR) is one of the most significant approaches to prepare optically active compounds [38–43]. In spite of their potential utility, some of these methods are limited by low yields, longer reaction times, harsh conditions, and the use of toxic solvents. Thus, there is an increasing interest in the development of new catalysts under mild reaction conditions with cleaner reaction profiles, good yields, less catalyst loading, and simple experimental procedures. The synthesis of chiral amides has received wide attention given its presence as the most common structural motifs in modern pharmaceuticals and biologically active compounds [44–48]. In this connection, here we have explored an asymmetric Knoevenagel condensation reaction that proceeds through dynamic kinetic resolution (DKR) of α-branched aldehydes with malonate compounds, catalysed by cinchona-derived organocatalysts under mild reaction conditions (Scheme 1). Further, the desired γ-substituted chiral amide derivatives can be obtained from the Knoevenagel product, by reacting with different amine compounds in higher chemical yield and excellent enantiomeric ratio. Herein, we present a new method to obtain γ-alkyl-substituted chiral amides in an asymmetric fashion using Knoevenagel products obtained.

Experimental section

Materials and methods

All the chemicals and reagents used in this work were of analytical grade. Mesitylene, allylbromide, (+)-quinine, and benzoyl peroxide were obtained from Alfa Aesar, benzaldehyde, 4-methylbenzaldehyde, 4-fluorobenzaldehyde, 3-fluorobenzaldehyde, 2-fluorobenzaldehyde, diethylmalonate, dimethyl malonate, and diisopropyl malonate, *N*-bromosuccinimide were obtained from Sigma-Aldrich, acetic acid and $ZnCl_2$ were purchased from Merck, and all the solvents were obtained from Laboratory Grade.

The ^1H and ^{13}C NMR spectra were recorded on a Bruker (Avance) 300 and 400 MHz NMR instrument using TMS as an internal standard and $CDCl_3$ as a solvent. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (δ-scale), and the coupling constants are given in Hertz. Silica gel-G plates (Merck) were used for TLC analysis with a mixture of n-hexane and ethyl acetate as an eluent. Column chromatography was carried out in silica gel (60–120 mesh) using n-hexane and ethyl acetate as an eluent. High-resolution mass spectroscopic (HRMS) data were obtained using Bruker Apex IV RTMS. The HPLC was recorded in SHIMADZU LC-6AD with Chiral Column (Chiralcel OD-H), using HPLC grade n-hexane and isopropanol as solvents.

Experimental procedure

Preparation of compound 7

About 1 g (7.3 mmol) of pentaerythritol was dissolved in 1:1 ratio of ethanol and acetic acid at 80 °C under constant stirring. Then, 1.64 mL (14.7 mmol) of *p*-tolualdehyde was added and followed by the addition of anhydrous $ZnCl_2$ in a catalytic amount. Then, the mixture was allowed to reflux for about 12 h. After completion of the reaction, the reaction mixture was extracted with ethyl acetate and the solvent was removed under vacuum. The crude reaction mass was purified by column chromatography using pet. ether and ethyl acetate as an eluent, and isolated yield of **7** is 2 g, 80% yield. ^1H NMR (300 MHz, CDCl3) δ_H 2.19 (s, 6H), 3.74 (s, 8H), 5.99 (s, 2H), 7.11 (d, $J = 6.0$ Hz, 4H), 7.38 (d, $J = 6.1$ Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 21.33, 31.90, 68.67, 109.34, 127.33, 128.86, 134.31, 137.58.

Preparation of compound 8

Compound **7** (1 g, 2.9 mmol), NBS (1.1 g 6.1 mmol) and the catalytic amount of benzoyl peroxide and benzene (15 ml) were taken in a 100-ml RB flask. The reaction mixture was refluxed for about 6 h at 70 °C. The reaction was monitored

by TLC, after completion of reaction, and the reaction mixture was poured into 10% sodium bicarbonate solution, extracted with ethyl acetate, washed with brine and dried over sodium sulphate. The product was concentrated and purified by column chromatography using pet. ether and ethyl acetate as an eluent. The isolated yield of **8** is 1.05 g, 72% yield. ^{1}H NMR (300 MHz, CDCl3) δ_H 3.74 (s, 8H), 4.56 (s, 4H), 5.98 (s, 2H), 7.32 (d, $J = 6.2$ Hz, 4H), 7.46 (d, $J = 6.0$ Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 31.87, 33.33, 68.53, 109.32, 127.71, 128.89, 137.13.

Synthesis of quinine (containing free C_9-OH)-based chiral organocatalyst (10a)

A mixture of compound **8** (0.5 g, 1 mmol) and quinine with free C9-OH **9a** (0.68 g, 2.1 mmol) was dissolved in 15 ml of EtOH/DMF/ACN (30:50:20 ratio), and the whole reaction mixture was refluxed overnight. The off-white solid was filtered off, washed with diethyl ether and dried, to get pure white organocatalyst (**10a**) (2.12 g, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.23 (m, 2H), 1.47 (m, 8H), 2.60 (m, 2H), 3.37–3.46 (m, 8H), 3.73 (s, 8H), 3.81 (s, 6H), 3.86 (m, 2H), 4.50 (s, 4H), 5.03–5.17 (m, 6H), 5.41 (d, $J = 8.2$ Hz, 2H), 5.70 (m, 2H), 5.98 (s, 2H), 7.19 (d, $J = 9.3$ Hz, 4H), 7.37–7.39 (m, 6H), 7.52 (d, $J = 9.2$ Hz, 4H), 7.85 (d, $J = 8.4$ Hz, 2H), 8.65 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 23.81, 26.19, 28.24, 31.97, 38.85, 52.81, 55.82, 59.34, 63.81, 65.23, 79.95, 101.3, 109.34, 117.69, 122.03, 122.62, 126.13, 127.39, 128.60, 128.95, 129.61, 130.67, 134.31, 137.55, 142.81, 147.18, 148.21, 157.36. HRMS (ESI+) *m/z* calculated for $C_{61}H_{70}N_4O_8{}^{2+}$ $2Br^{-}Na(M + Na^{+})$ 1167.3441, found 1167.3445.

Synthesis of allylated quinine-based chiral organocatalyst (10b)

A mixture of compound **8** (0.5 g, 1 mmol) and allylated quinine **9b** (0.77 g, 2.1 mmol) was dissolved in 15 ml of EtOH/DMF/ACN (30:50:20 ratio), and the whole reaction mixture was refluxed overnight. The off-white solid was filtered off, washed with diethyl ether and dried, to get pure white organocatalyst (**10b**) (3.0 g, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.23 (m, 2H), 1.47 (m, 8H), 2.60 (m, 2H), 3.37–3.46 (m, 8H), 3.73 (s, 8H), 3.81 (s, 6H), 4.06 (m, 6H), 4.50 (s, 4H), 5.03–5.17 (m, 6H), 5.31–5.43 (m, 4H), 5.70 (m, 2H), 5.98 (s, 2H), 6.07 (m, 2H), 7.19 (d, $J = 9.3$ Hz, 4H), 7.37–7.39 (m, 6H), 7.52 (d, $J = 9.2$ Hz, 4H), 7.85 (d, $J = 8.4$ Hz, 2H), 8.65 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 24.10, 25.23, 28.27, 31.92, 38.94, 52.57, 55.81, 59.30, 65.33, 72.09, 101.38, 109.25, 117.66, 121.22, 122.01, 122.36, 126.14, 127.32, 128.60, 128.85, 129.51, 130.85, 137.55, 142.89, 147.15, 148.27, 157.34. HRMS (ESI+) *m/z* calculated for $C_{69}H_{78}N_4O_8{}^{2+}$ $2Br^{-}Na(M + Na^{+})$ 1247.4067, found 1247.4064.

General procedure for the catalytic enantioselective Knoevenagel condensation reaction

The catalyst **10a/10b** (0.01 mmol) and aldehyde **1** (0.1 mmol) were dissolved in ethanol (2.0 mL). The reaction mixture was stirred for about 10 min, and then malonate **2** (1.0 mmol) and triethylamine (0.2 mmol) were added at room temperature. After vigorous stirring for about 48–72 h, the reaction mixture was poured into water (3 mL) and extracted with ethyl acetate (3×15 mL). The organic fraction was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography to afford **3a–p** as desired products.

Characterization of Knoevenagel products

(*R*)-diethyl 2-(2-phenylpropylidene)malonate (3a)

Colourless oil, Yield: 92%, e.r: 97.58:2.48. ^{1}H NMR (300 MHz, CDCl3) δ_H 1.27 (t, $J = 7.2$ Hz, 3H), 1.34 (t, $J = 7.2$ Hz, 3H), 1.44 (d, $J = 5.8$ Hz, 3H), 3.88 (m, 1H), 4.21 (q, $J = 6.3$, Hz, 2H), 4.34 (q, $J = 6.3$ Hz, 2H), 6.98 (d, $J = 6.4$ Hz, 1H), 7.24–7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δc 14.14, 14.24, 20.15, 39.48, 61.39, 126.94, 127.17, 128.84, 142.49, 151.85, 164.02. HRMS (ESI+) *m/z* calculated for $C_{16}H_{20}O_4Na(M + Na^{+})$ 299.1254, found 299.1256. The enantiomeric excess was determined by HPLC, Chiralcel (OD-H), 254 nm, hexane/IPA 97:3, flow rate: 1 mL min^{-1}, retention time: 14.19 min (major), 19.97 min (minor).

(*R*)-diethyl 2-(2-(4-methoxyphenyl)propylidene)malonate (3b)

Colourless oil, Yield: 95%, e.r: 98.32:1.68. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.27 (t, $J = 7.1$ Hz, 3H), 1.32 (t, $J = 6.9$ Hz, 3H), 1.42 (d, $J = 6.7$ Hz, 3H), 3.51–3.49 (m, 1H), 3.80 (s, 1H), 4.22 (q, $J = 7.0$ Hz, 2H), 4.33 (q, $J = 6.7$ Hz, 2H), 6.86 (d, $J = 8.0$ Hz, 2H), 6.93 (d, $J = 6.4$ Hz, 1H), 7.15 (d, $J = 7.0$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 14.11, 14.21, 20.21, 29.74, 38.73, 55.34, 61.38, 114.14, 126.14, 128.15, 152.07, 165.83. HRMS (ESI+) *m/z* calculated for $C_{17}H_{22}O_5Na(M + Na^{+})$ 329.1359, found 329.1356. The enantiomeric excess was determined by HPLC, Chiralcel (OD-H), 254 nm, hexane/IPA 97:3, flow rate: 1 mL min^{-1}, retention time: 11.24 min (major), 16.57 min (minor).

(*R*)-diethyl 2-(2-(p-tolyl)propylidene)malonate (3c)

Colourless oil, Yield: 96%, e.r: 98.41:1.59. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.26 (t, $J=7.1$ Hz, 3H), 1.39 (t, $J=7.1$ Hz, 3H), 1.45 (d, $J=7.8$ Hz, 3H), 2.32 (s, 3H), 3.83–3.87 (m, 1H), 4.21 (q, $J=6.9$ Hz, 2H), 4.35 (q, $J=6.9$ Hz, 2H), 6.96 (d, $J=6.7$ Hz, 1H), 7.12–7.16 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 14.11, 14.23, 20.24, 21.04, 39.18, 61.37, 61.39, 126.58, 127.02, 129.44, 136.59, 139.41, 152.01, 164.10, 165.57. HRMS (ESI+) *m/z* calculated for $C_{17}H_{22}O_4Na(M+Na^+)$ 313.1410, found 313.1408. The enantiomeric excess was determined by HPLC, Chiralcel (OD-H), 254 nm, hexane/IPA 97:3, flow rate: 1 mL min^{-1}, retention time: 12.71 min (major), 21.94 min (minor).

(*R*)-diethyl 2-(2-(4-bromophenyl)propylidene)malonate (3d)

Colourless oil, Yield: 85%, e.r: 95.54:4.46. ^{1}H NMR (300 MHz, CDCl3) δ 1.30 (t, $J=5.9$ Hz, 3H), 1.36–1.32 (m, 3H), 1.44 (d, $J=6.4$ Hz, 3H), 3.88–3.84 (m, 1H), 4.22 (q, $J=6.8$, Hz, 2H), 4.32 (q, $J=6.8$ Hz, 2H), 6.91 (d, $J=8.9$ Hz, 1H), 7.13 (d, $J=6.6$ Hz, 2H), 7.43 (d, $J=6.6$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δc 14.02, 14.16, 20.06, 38.95, 61.75, 119.94, 127.65, 128.83, 133.31, 141.36, 150.90, 168.08. HRMS (ESI+) *m/z* calculated for $C_{16}H_{19}O_4Br_1Na(M+Na^+)$ 377.0359, found 377.0357. The enantiomeric excess was determined by HPLC, Chiralcel (OD-H), 254 nm, hexane/IPA 97:3, flow rate: 1 mL min^{-1}, retention time: 17.41 min (major), 29.65 min (minor).

(*R*)-diethyl 2-(2-(4-chlorophenyl)propylidene)malonate (3e)

Colourless oil, Yield: 87%, e.r: 97.45:2.55. ^{1}H NMR (300 MHz, CDCl3) δ 1.28 (t, $J=6.6$ Hz, 3H), 1.37–1.32 (m, 3H), 1.42 (d, $J=5.8$ Hz, 3H), 3.88–3.84 (m, 1H), 4.22 (q, $J=6.7$, Hz, 2H), 4.33 (q, $J=6.7$ Hz, 2H), 6.91 (d, $J=7.1$ Hz, 1H), 7.19 (d, $J=8.1$ Hz, 2H), 7.35 (d, $J=6.4$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δc 14.06, 14.16, 20.15, 38.85, 52.15, 61.48, 61.79, 119.52, 127.15, 127.33, 128.37, 128.47, 128.87, 132.74, 140.88, 151.05, 163.92, 165.38, 168.03. HRMS (ESI+) *m/z* calculated for $C_{16}H_{19}O_4Cl_1Na(M+Na^+)$ 333.0864, found 333.0866. The enantiomeric excess was determined by HPLC, Chiralcel (OD-H), 254 nm, hexane/IPA 97:3, flow rate: 1 mL min^{-1}, retention time: 14.51 min (major), 21.74 min (minor).

(*R*)-diethyl 2-(2-(4-fluorophenyl)propylidene)malonate (3f)

Colourless oil, Yield: 92%, e.r: 97.06:2. 94. ^{1}H NMR (300 MHz, CDCl3) δ 1.27 (t, $J=7.1$ Hz, 3H), 1.34 (t, $J=7.1$ Hz, 3H), 1.44 (d, $J=6.0$ Hz, 3H), 3.88–3.91 (m, 1H), 4.23 (q, $J=6.9$, Hz, 2H), 4.33 (q, $J=6.9$ Hz, 2H), 6.90–6.95 (m, 2H), 6.95–6.97 (m, 1H), 7.02 (d, $J=8.4$ Hz, 1H), 7.25–7.30 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δc 14.10, 14.16, 20.11, 39.21, 61.52, 61.84, 113.78, 113.96, 114.04, 114.21, 122.82, 122.86, 127.32, 130.23, 144.96, 145.00, 150.81, 162.05, 163.94, 164.05, 165.38. HRMS (ESI+) *m/z* calculated for $C_{16}H_{19}O_4F_1Na(M+Na^+)$ 317.1160, found 317.1157. The enantiomeric excess was determined by HPLC, Chiralcel (OD-H), 254 nm, hexane/IPA 97:3, flow rate: 1 mL min^{-1}, retention time: 16.17 min (major), 24.15 min (minor).

(*R*)-diethyl 2-(2-(3-fluorophenyl)propylidene)malonate (3g)

Colourless oil, Yield: 90%, e.r: 94.89:5.11. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.27 (t, $J=7.1$ Hz, 3H), 1.34 (t, $J=7.1$ Hz, 3H), 1.46 (d, $J=6.3$ Hz, 3H), 3.88–3.91 (m, 1H), 4.21 (q, $J=6.9$ Hz, 2H), 4.33 (q, $J=6.9$ Hz, 2H), 6.91–6.98 (m, 3H), 7.06 (d, $J=7.9$, 1H), 7.26–7.30 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δc 14.10, 14.17, 20.10, 39.18, 61.51, 113.79, 113.94, 114.05, 114.21, 122.85, 122.88, 127.27, 130.19, 130.27, 144.95, 145.00, 150.83, 163.93, 165.35, 190.26. HRMS (ESI+) *m/z* calculated for $C_{16}H_{19}O_4F_1Na(M+Na^+)$ 317.1160, found 317.1162. The enantiomeric excess was determined by HPLC, Chiralcel (OD-H), 254 nm, hexane/IPA 97:3, flow rate: 1 mL min^{-1}, retention time: 10.98 min (major), 20.20 min (minor).

(*R*)-diethyl 2-(2-(2-fluorophenyl)propylidene)malonate (3h)

Colourless oil, Yield: 87%, e.r: 91.89:8.11. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.25–1.33 (m, 6H), 1.46 (d, $J=6.2$ Hz, 3H), 4.14–4.19 (m, 1H), 4.22 (q, $J=6.9$ Hz, 2H), 4.35 (q, $J=7.0$ Hz, 2H), 7.00–7.05 (m, 2H), 7.07–7.12 (m, 2H), 7.19–7.25 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 14.07, 14.09, 20.12, 33.78, 61.38, 61.43, 115.64, 115.84, 124.41, 124.43, 127.69, 128.23, 128.43, 128.48, 129.47, 129.84, 150.29, 150.63, 159.60, 161.55, 164.04, 165.24. HRMS (ESI+) *m/z* calculated for $C_{16}H_{19}O_4F_1Na(M+Na^+)$ 317.1159, found 317.1157. The enantiomeric excess was determined by HPLC, Chiralcel (OD-H), 254 nm, hexane/IPA 97:3, flow rate: 1 mL min^{-1}, retention time: 18.79 min (major), 25.67 min (minor).

(*R*)-dimethyl 2-(2-phenylpropylidene)malonate (3i)

Colourless oil, Yield: 93%, e.r: 97.00:3.00. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.44 (d, $J=6.4$ Hz, 3H), 3.73 (s, 3H), 3.86 (s, 3H), 3.87–3.89 (m, 1H), 7.03 (d, $J=9.4$ Hz, 1H), 7.21–7.24 (m, 3H), 7.30–7.33 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 20.24, 39.65, 52.34, 126.04, 127.0, 127.12, 128.78, 142.26, 152.76, 164.42, 165.82. HRMS

(ESI+) *m/z* calculated for $C_{14}H_{16}O_4Na(M+Na^+)$ 271.0941, found 271.0942. The enantiomeric excess was determined by HPLC, Chiralcel (OD-H), 254 nm, hexane/IPA 97:3, flow rate: 1 mL min^{-1}, retention time: 9.73 min (major), 17.65 min (minor).

(*R*)-dimethyl 2-(2-(p-tolyl)propylidene)malonate (3j)

Colourless oil, Yield: 95%, e.r: 99.11:0. 89. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.43 (d, $J=6.4$ Hz, 3H), 2.32 (s, 3H), 3.76 (s, 3H), 3.86 (s, 3H), 4.10–4.15 (m, 1H), 7.02 (d, $J=9.4$ Hz, 1H), 7.14 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 20.23, 21.00, 39.26, 52.37, 126.96, 129.46, 136.62, 139.29, 153.09, 164.47, 165.89. HRMS (ESI+) *m/z* calculated for $C_{15}H_{18}O_4Na(M+Na^+)$ 285.1097, found 285.1095. The enantiomeric excess was determined by HPLC, Chiralcel (OD-H), 254 nm, hexane/IPA 97:3, flow rate: 1 mL min^{-1}, retention time: 8.71 min (major), 15.94 min (minor).

(*R*)-diisopropyl 2-(2-phenylpropylidene)malonate (3k)

Colourless oil, Yield: 95%, e.r: 98.58:1.42. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.28–1.24 (m, 6H), 1.33 (dd, $J=6.1$, 4.1 Hz, 6H), 1.45 (d, $J=6.7$ Hz, 3H), 3.86–3.89 (m, 1H), 5.07 (p, $J=6.2$ Hz, 1H), 5.22 (p, $J=6.2$ Hz, 1H), 6.92 (d, $J=9.9$ Hz, 1H), 7.28- 7.23 (m, 3H), 7.38–7.33 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 20.28, 21.71, 39.47, 60.38, 68.95, 126.86, 127.12, 127.57, 128.70, 142.57, 150.81, 163.59, 165.17. HRMS (ESI+) *m/z* calculated for $C_{18}H_{24}O_4Na(M+Na^+)$ 327.1567, found 327.1569. The enantiomeric excess was determined by HPLC, Chiralcel (OD-H), 254 nm, hexane/IPA 97:3, flow rate: 1 mL min^{-1}, retention time: 13.11 min (major), 22.65 min (minor).

(*R*)-diisopropyl 2-(2-(p-tolyl)propylidene)malonate (3l)

Colourless oil, Yield: 96%, e.r: 99.69:0.31. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.26–1.24 (m, 6H), 1.33 (dd, $J=6.1$, 3.0 Hz, 6H), 1.43 (d, $J=6.7$ Hz, 3H), 2.32 (s, 3H), 4.12 (q, $J=7.1$ Hz, 1H), 5.06 (p, $J=6.2$ Hz, 1H), 5.22 (p, $J=6.2$ Hz, 1H), 6.91 (d, $J=9.3$ Hz, 1H), 7.17- 7.12 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 20.22, 20.90, 21.13, 29.12, 39.11, 68.90, 127.05, 127.37, 129.49, 136.47, 139.57, 151.07, 163.62, 165.24. HRMS (ESI+) *m/z* calculated for $C_{19}H_{26}O_4Na(M+Na^+)$ 341.1723, found 341.1721. The enantiomeric excess was determined by HPLC, Chiralcel (OD-H), 254 nm, hexane/IPA 97:3, flow rate: 1 mL min^{-1}, retention time: 12.45 min (major), 27.34 min (minor).

(*R*)-dibutyl 2-(2-phenylpropylidene)malonate (3m)

Colourless oil, Yield: 97%, e.r: 98.94:1.06. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.91 (t, $J=6.1$ Hz, 3H), 0.94 (t, $J=6.2$ Hz, 3H), 1.36–1.44 (m, 4H), 1.45 (d, $J=6.0$ Hz, 3H), 1.56–1.66 (m, 2H), 1.64–1.70 (m, 2H), 3.86–3.89 (m, 1H), 4.16 (t, $J=5.7$ Hz, 2H), 4.26 (t, $J=5.4$ Hz, 2H), 6.98 (d, $J=7.3$ Hz, 1H), 7.22–7.26 (m, 3H), 7.31–7.34 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.67, 19.09, 20.27, 30.59, 39.56, 65.29, 126.92, 126.96, 127.13, 128.75, 142.42, 151.67, 164.15, 165.72. HRMS (ESI+) *m/z* calculated for $C_{20}H_{28}O_4Na(M+Na^+)$ 355.1880, found 355.1882. The enantiomeric excess was determined by HPLC, Chiralcel (OD-H), 254 nm, hexane/IPA 97:3, flow rate: 1 mL min^{-1}, retention time: 11.32 min (major), 19.64 min (minor).

(*R*)-dipropyl 2-(2-phenylpropylidene)malonate (3n)

Colourless oil, Yield: 95%, e.r: 98.42:1.58. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.93 (t, $J=6.1$ Hz, 3H), 0.97 (t, $J=6.0$ Hz, 3H), 1.45 (d, $J=4.3$ Hz, 3H), 1.60–1.70 (m, 2H), 1.71–1.77 (m, 2H), 3.87–3.90 (m, 1H), 4.12 (t, $J=5.3$ Hz, 2H), 4.23 (t, $J=5.2$ Hz, 2H), 6.99 (d, $J=5.9$ Hz, 1H), 7.21–7.26 (m, 3H), 7.31–7.34 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 10.33, 10.43, 20.26, 21.94, 22.00, 39.55, 66.94, 67.01, 126.94, 127.09, 127.15, 128.81, 142.44, 151.73, 164.19, 165.74. HRMS (ESI+) *m/z* calculated for $C_{18}H_{24}O_4Na(M+Na^+)$ 327.1567, found 327.1563. The enantiomeric excess was determined by HPLC, Chiralcel (OD-H), 254 nm, hexane/IPA 97:3, flow rate: 1 mL min^{-1}, retention time: 20.10 min (major), 35.64 min (minor).

(*R*)-dibutyl 2-(2-phenylpropylidene)malonate (3o)

Colourless oil, Yield: 85%, e.r: 93.04:6.96. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.40 (d, $J=5.6$ Hz, 3H), 3.82–3.86 (m, 1H), 5.18 (q, $J=5.4$ Hz, 2H), 5.27 (q, $J=5.2$ Hz, 2H), 7.06 (d, $J=6.0$ Hz, 1H), 7.14–7.30 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 20.31, 39.65, 67.01, 67.28, 126.01, 126.22, 127.00, 127.13, 128.18, 128.29, 128.42, 128.55, 128.66, 128.77, 135.34, 135.47, 142.23, 153.15, 163.90, 165.29. HRMS (ESI+) *m/z* calculated for $C_{26}H_{24}O_4Na(M+Na^+)$ 423.1567, found 423.1561. The enantiomeric excess was determined by HPLC, Chiralcel (OD-H), 254 nm, hexane/IPA 97:3, flow rate: 1 mL min^{-1}, retention time: 25.51 min (major), 39.41 min (minor).

(*R*)-diethyl 2-(2-cyclohexylbutylidene)malonate (3p)

Colourless oil, Yield: 89%, e.r: 95.56:4.44. ^{1}H NMR 300 MHz, CDCl3) δ_H 0.85–0.91 (m, 2H), 0.99 (d, $J=6.7$ Hz, 3H), 1.09–1.21 (m, 4H), 1.24–1.30 (m, 6H), 1.60–1.74 (m, 5H), 2.26–2.28 (m, 1H), 4.19 (dd, $J=7.1$,

7.2 Hz, 2H), 4.25 (dd, $J = 7.1$, 7.2 Hz, 2H), 6.79 (d, $J = 11.3$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 14.1, 14.2, 17.0, 26.3, 26.4, 30.4, 30.9, 40.3, 42.8, 53.5, 61.1, 61.2, 127.6, 153.5, 164.1, 165.9. HRMS (ESI+) *m/z* calculated for $C_{16}H_{26}O_4Na(M + Na^+)$ 305.1723, found 355.1725. The enantiomeric excess was determined by HPLC, Chiralcel (OD-H), 254 nm, hexane/IPA 97:3, flow rate: 1 mL min^{-1}, retention time: 19.21 min (major), 28.16 min (minor).

Characterization of applications of Knoevenagel product

(*R*)-diethyl-2-(2-phenylpropyl)malonate (11a)

A mixture of compound **3a** (100 mg, 0.362 mmol) and $Pd(OH)_2/C$ (10 mg) in ethyl acetate was stirred for 2 h at room temperature under H_2 (1 atm). The mixture was filtered on Celite, the filtrate was evaporated, and the residue was purified by column chromatography (hexane/ethyl acetate = 8:2). Colourless oil, Yield: 92%, e.r: 98.53:1.47. ^{1}H NMR (300 MHz, CDCl3) δ 1.21 (t, $J = 5.8$ Hz, 3H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.28 (d, $J = 5.8$ Hz, 3H), 2.13–2.25 (m, 2H), 2.70–2.75 (m, 1H), 3.16–3.19 (m, 1H), 4.06–4.12 (m, 2H), 4.13–4.22 (m, 2H), 7.16–7.31(m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δc 14.02, 14.13, 22.43, 36.95, 37.84, 61.31, 61.34, 126.48, 127.15, 128.56, 145.42, 169.49, 169.56. HRMS (ESI+) *m/z* calculated for $C_{16}H_{22}O_4Na(M + Na^+)$ 301.1410, found 301.1405. The enantiomeric excess was determined by HPLC, Chiralcel (OD-H), 254 nm, hexane/IPA 97:3, flow rate: 1 mL min^{-1}, retention time: 8.76 min (major), 21.85 min (minor).

(*R*)-ethyl-4-phenylpentanoate (12a)

A mixture of compound **11a** (60 mg, 0.216 mmol), LiCl (19.4 mg, 0.432 mmol, 2 equiv.) and H_2O (8 µL, 0.432 mmol, 2 equiv.) in dry DMSO was stirred for 20 h at 160 °C. After completion of the reaction the residue was purified by column chromatography (hexane/ethyl acetate = 8:2). Yellow oil, Yield: 90%, e.r: 98.36:1.64. ^{1}H NMR (300 MHz, CDCl3) δ 1.22 (t, $J = 5.8$ Hz, 3H), 1.27 (d, $J = 6.2$ Hz, 3H), 1.87–1.97 (m, 2H), 2.13–2.17 (m, 2H), 2.59–2.68 (m, 1H), 3.98–4.04 (m, 2H), 7.10–7.25 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δc 14.24, 22.18, 32.63, 33.22, 39.47, 60.23, 126.22, 127.07, 128.49, 146.34, 173.74. HRMS (ESI+) *m/z* calculated for $C_{13}H_{18}O_2Na(M + Na^+)$ 229.1199, found 229.1193. The enantiomeric excess was determined by HPLC, Chiralcel (OD-H), 254 nm, hexane/IPA 97:3, flow rate: 1 mL min^{-1}, retention time: 12.75 min (major), 27.84 min (minor).

(*R*)-4-phenylpentanoic acid (13a)

A mixture of compound **12a** (50 mg, 0.242 mmol) and LiOH(11.5 mg, 0.484 mmol, 2 equiv.) was stirred in THF/water (2:1) for 2 h, then we got lithium salt of acid, it was neutralized by dil HCl, and then the residue was purified by column chromatography (hexane/ethyl acetate = 7:3). Colourless oil, Yield: 87%, e.r: 96.38:3.62. ^{1}H NMR (300 MHz, CDCl3) δ 1.28 (t, $J = 4.8$ Hz, 3H), 1.85–2.00 (m, 2H), 2.17–2.30 (m, 2H), 2.68–2.78 (m, 1H), 7.14–7.24 (m, 3H), 7.30 (t, $J = 6.2$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δc 22.18, 32.20, 32.92, 39.32, 126.32, 127.01, 128.58, 146.04, 179.83. HRMS (ESI+) *m/z* calculated for $C_{11}H_{14}O_2Na(M + Na^+)$ 201.0886, found 201.0881. The enantiomeric excess was determined by HPLC, Chiralcel (OD-H), 254 nm, hexane/IPA 97:3, flow rate: 1 mL min^{-1}, retention time: 10.93 min (major), 24.10 min (minor).

General procedure for the synthesis of chiral amide derivatives

A solution of EDCI (0.673 mmol) and HOBt (0.673 mmol) in CH_2Cl_2 (3 mL) was added dropwise to a stirred suspension of acid **13a** (0.561 mmol) and different types of amine (0.616 mmol) in CH_2Cl_2 (3 mL) at 0 °C under argon atmosphere, which were stirred for 12 h. The reaction was monitored by TLC; after the completion of the reaction, the mixture was added with EtOAc (20 ml) and the organic solution was washed with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, PE–EtOAc. 4:1) afforded pure amide derivatives.

(*R*)-*N*,4-diphenylpentanamide (15aa)

White solid, Yield: 92%, e.r: 98.82:1.18. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.16 (d, $J = 6.2$ Hz, 3H), 1.90–1.93 (m, 2H), 1.96 (t, $J = 8.6$ Hz, 2H), 2.48–2.55 (m, 1H), 7.18 (t, $J = 5.8$ Hz, 1H), 7.32 (d, $J = 6.2$ Hz, 2H), 7.38–7.45 (m, 5H), 7.56 (d, $J = 6.4$ Hz, 2H), 7.98 (brS, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 20.44, 32.07, 33.27, 37.85, 109.00, 126.02, 128.19, 128.85, 147.19, 150.22, 155.61, 179.85. HRMS (ESI+) *m/z* calculated for $C_{17}H_{19}NONa(M + Na^+)$ 276.1359, found 276.1355. The enantiomeric excess was determined by HPLC, Chiralcel (OD-H), 254 nm, hexane/IPA 97:3, flow rate: 1 mL min^{-1}, retention time: 11.13 min (major), 28.81 min (minor).

(*R*)-4-phenyl-*N*-(pyridin-4-yl)pentanamide (15ab)

White solid, Yield: 93%, e.r: 98.49:1.51. ^{1}H NMR (300 MHz, DCl_3) δ_H 1.16 (d, $J = 6.2$ Hz, 3H), 1.83–1.90 (m, 2H), 2.04 (t, $J = 7.7$ Hz, 2H), 2.48–2.55 (m, 1H), 7.17–7.29

(m, 5H), 8.41 (d, $J = 6.5$ Hz, 2H), 8.56 (d, $J = 6.5$ Hz, 2H), 8.98 (brS, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 20.42, 32.07, 33.27, 37.85, 109.00, 126.02, 128.19, 128.84, 147.13, 150.22, 155.61, 179.85. HRMS (ESI+) *m/z* calculated for $C_{16}H_{18}N_2ONa(M + Na^+)$ 277.1311, found 277.1307. The enantiomeric excess was determined by HPLC, Chiralcel (OD-H), 254 nm, hexane/IPA 97:3, flow rate: 1 mL min^{-1}, retention time: 9.98 min (major), 23.20 min (minor).

(*R*)-*N*-butyl-4-phenylpentanamide (15ac)

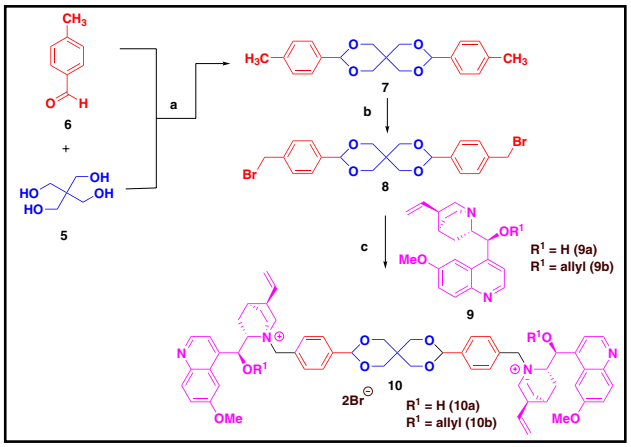
Yellow oil, Yield: 89%, e.r: 96.74:3.26. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.88 (d, $J = 6.0$ Hz, 3H), 1.16 (d, $J = 6.2$ Hz, 3H), 1.29–1.37 (m, 2H), 1.43–1.50 (m, 2H), 1.882–1.89 (m, 2H), 2.04 (t, $J = 6.8$ Hz, 2H), 2.51–2.54 (m, 1H), 3.02 (t, $J = 5.7$ Hz, 2H), 7.16–7.28 (m, 5H), 7.76 (brS, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.82, 19.80, 20.48, 32.42, 33.64, 37.82, 38.96, 126.03, 128.14, 128.82, 147.19, 172.63. HRMS (ESI+) *m/z* calculated for $C_{15}H_{23}NONa(M + Na^+)$ 256.1672, found 256.1668. The enantiomeric excess was determined by HPLC, Chiralcel (OD-H), 254 nm, hexane/IPA 97:3, flow rate: 1 mL min^{-1}, retention time: 7.09 min (major), 19.26 min (minor).

(*R*)-1-morpholino-4-phenylpentan-1-one (15ad)

Colourless oil, Yield: 90%, e.r: 97.66:2.34. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.16 (d, $J = 6.2$ Hz, 3H), 1.79–1.88 (m, 2H), 2.04 (t, $J = 7.4$ Hz, 2H), 2.48–2.59 (m, 1H), 3.40–3.46 (m, 4H), 3.69–3.81 (m, 4H), 7.15–7.28 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 20.47, 31.43, 32.74, 37.83, 48.02, 66.22, 126.01, 128.11, 128.87, 147.13, 172.56. HRMS (ESI+) *m/z* calculated for $C_{15}H_{21}NO_2Na(M + Na^+)$ 270.1464, found 270.1460. The enantiomeric excess was determined by HPLC, Chiralcel (OD-H), 254 nm, hexane/IPA 97:3, flow rate: 1 mL min^{-1}, retention time: 15.78 min (major), 24.87 min (minor).

(*R*)-4-phenyl-1-(pyrrolidin-1-yl)pentan-1-one (15ae)

Colourless oil, Yield: 91%, e.r: 97.87:2.13. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.16 (d, $J = 6.2$ Hz, 3H), 1.80–1.85 (m, 4H), 1.87–1.94 (m, 2H), 2.04 (t, $J = 7.4$ Hz, 2H), 2.52–2.61 (m, 1H), 39.09 (t, $J = 9.6$ Hz, 4H), 7.19–7.29 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 20.44, 25.46, 41.47, 32.75, 37.89, 49.02, 126.04, 128.20, 128.91, 147.13, 176.12. HRMS (ESI+) *m/z* calculated for $C_{15}H_{21}NONa(M + Na^+)$ 254.1515, found 254.1510. The enantiomeric excess was determined by HPLC, Chiralcel (OD-H), 254 nm, hexane/IPA 97:3, flow rate: 1 mL min^{-1}, retention time: 12.07 min (major), 17.18 min (minor).



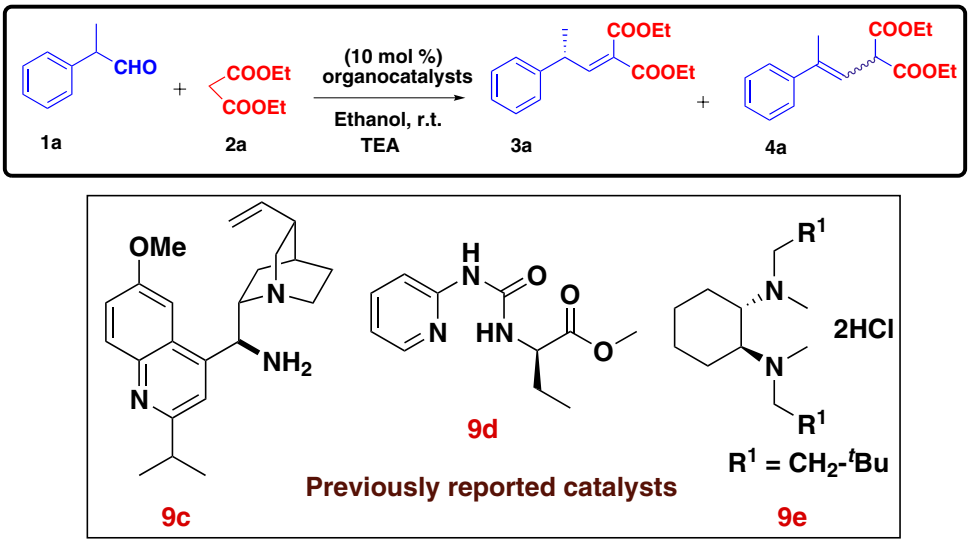
Scheme 2 Synthesis of chiral cinchona-derived organocatalysts (**10a** and **10b**). Reagents and conditions: (a) $ZnCl_2$, CH_3COOH, ethanol. (b) NBS, BPO, benzene, reflux. (c) EtOH/DMF/ACN (30:50:20), overnight reflux

Results and discussion

The compound **7** was obtained from the reaction between *p*-tolualdehyde and pentaerythritol, and then it was brominated with NBS in the presence of benzene to afford the bromo compound **8** in 75% yield. The cinchona-based chiral organocatalysts were synthesized from the reaction of bromo compound **8** with quinine free C_9-OH (**9a**) and *O*-allyl quinine (**9b**) [49–52], respectively, as depicted in scheme 2.

In the initial step of optimization, the catalyst screening was done for enhancing chemical yield and e.r. In 2011, List et al. [32] reported the Knoevenagel condensation of racemic-branched aldehydes using primary amine catalysts derived from cinchona alkaloids (**9c**) to deliver adducts with reasonable yield and e.r. albeit with the addition of 60 mol% of benzene − 1,3,5 tricarboxylic acid as additive and with much higher equivalents of diethyl malonate (50 equvi.) and longer reaction times (up to 168 h) (Table 1, entry 1). Subsequently, Gao and co-workers [33] designed a phenylalanine–urea-catalysed Knoevenagel condensation in a water medium, where they obtained good yields, but poor selectivity using a higher loading (20 mol%) of catalyst (**9d**) (Table 1, entry 2). In 2016, Lu group [35] demonstrated the same methodology using chiral tertiary diamine catalyst (**9e**) offering moderate yields and e.r. for the Knoevenagel adducts under heating conditions (60 °C) and longer reaction times (up to 168 h) (Table 1, entry 3).

Table 1 Catalyst screening for the asymmetric Knoevenagel condensation



Entry	Catalysts	Time (h)	**3a**/**4a**[a] ratio	Yield (%)[b]	E.r[c]Abs.Conf.[d]
1	**9c**	168	60:40	91	95.5:4.5
2	**9d**	72	62:38	82	21.26:78.74
3	**9e**	168	97:3	75	86.5:13.5
4	**10a**	48	90:10	83	92.06:7.93
5	**10b**	48	96:4	92	97.58:2.42

Reaction conditions: **1a** (0.1 mmol), **2a** (1.0 mmol), various catalysts (10 mol%), TEA (0.2 mmol) and ethanol (2 mL) at room temperature condition in 48 h

[a]Determined by GC–MS analysis

[b]Yield of isolated product

[c]Determined by HPLC analysis chiral column (Chiralcel OD-H) with hexane-IPA as an eluent

[d]Absolute configuration was determined by comparison of the HPLC retention time using known literature data [32–37]

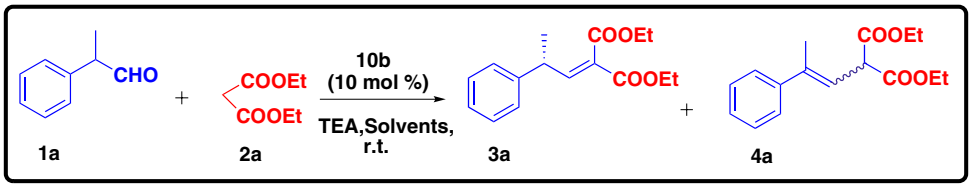
To overcome the issues with prolonged reaction time, higher catalyst loading and heating conditions, we carefully designed multi-active-site-containing organocatalyst derived from cinchona alkaloid using pentaerythritol as a linker. These catalysts yielded the desired adducts with much higher yields and e.r. under mild reaction condition (rt), low catalyst loading (10 mol%) and comparatively lesser reaction time (48 h) (Table 1, entries 4 and 5).

Further, the optimization was focused on the choice of suitable solvents for Knoevenagel condensation reaction. The observed results of Table 2 show that ethanol is the best reaction medium, in which 3a/4 ratio is up to 96:4 along with higher chemical yields and e.r (Table 2, entry 7). The polarity of solvents drastically affected the chemical yield and e.r of Knoevenagel condensation product. The highly polar aprotic solvents gave good 3a/4 ratio and yields, but moderate e.r was obtained (Table 2, entries 1–3). Some other polar aprotic solvents gave lower chemical yields and good e.r (Table 2, entries 4–6). Further, no reaction was observed in the presence of nonpolar solvents (Table 2, entries 8–10). These nonpolar solvents have low dielectric constants (< 5) and are not good solvents for charging species such as anions and cations. Henceforth, we have chosen ethanol as a suitable solvent for further investigations of asymmetric Knoevenagel condensation reaction.

Furthermore, we carried out the optimization of the base for the asymmetric Knoevenagel condensation reaction of hydratropaldehyde (**1a**) with diethylmalonate (**2a**) in the presence of organocatalyst **10b** under identical reaction conditions. From the results, we observed that triethylamine as a more effective base than other inorganic and organic bases, such as K_2CO_3, Cs_2CO_3, K^{t}OBu, NaOH, KOH and DIEA, pyridine, piperidine, morpholine (Table 3, entries 1–10).

The results obtained from Table 4 show that temperature and catalyst loading affect the chemical yields and e.r of

Table 2 Optimization of solvents for asymmetric Knoevenagel condensation



Entry	Solvents	**3a/4a**[a] ratio	Yield (%)[b]	e.r[c] Abs.Conf.[d]
1	DMF	80:20	74	84.96:15.64
2	DMSO	75:25	70	79.48:20.52
3	Acetonitrile	70:30	65	87.18:12.82
4	THF	66:34	62	86.33:13.67
5	DCM	69:31	57	91.02:8.98
6	$CHCl_3$	62:38	52	89.67:10.33
7	Ethanol	96:4	92	97.58:2.42
8	*o*-Xylene	n.r[e]	–	–
9	Toluene	n.r[e]	–	–
10	Cyclohexane	n.r[e]	–	–

Reaction conditions: **1a** (0.1 mmol), **2a** (1.0 mmol), **10b** (10 mol%), TEA (0.2 mmol) and solvents (2 mL) at room temperature in 48 h

[a]Determined by GC–MS analysis

[b]Yield of isolated product

[c]Determined by HPLC analysis chiral column (Chiralcel OD-H) with hexane–IPA as an eluent

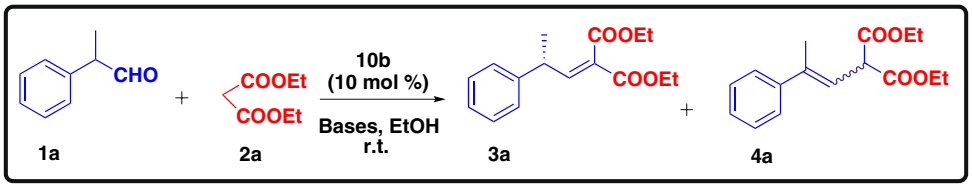
[d]Absolute configuration was determined by comparison of the HPLC retention time using known literature data [32–37]

[e]No reaction

the desired product and that 10 mol% of the catalyst gave a higher chemical yield and excellent e.r when compared to others. This may be due to the catalyst poison taking place in this reaction irrespective of the organocatalysts. Further, the temperature condition of the reaction strongly affected the product yields and e.r. From the observed results of Table 4, a higher chemical yield and e.r were obtained at room temperature, when compared to other temperature conditions, i.e. 60 °C, 0 °C and − 10 °C (Table 4, entries 1–12). Summing up these experimental results, the optimized reaction conditions are: ethanol selected as a solvent triethylamine (TEA) as a base, concentration of catalyst as 10 mol% and the room temperature condition suitable for asymmetric Knoevenagel condensation reaction.

The scopes of the catalysts are measured by different substrates under optimized reaction conditions in Table 5. Various substituted α-branched aromatic/aliphatic aldehydes were treated with different malonate compounds. When using both electron-donating and electron-withdrawing substrates, the desired products were obtained in very good yield and e.r (Table 5, entries 1–14). The 2-phenyl propanal was treated with diethyl malonate to give the desired Knoevenagel product with higher yield and e.r (Table 5, entry 1). The yield and e.r obtained were slightly higher, and no by-product was observed in the case of electron-donating substituted aromatic aldehyde used in the reaction (Table 5, entries 2 and 3). The halo-substituted aldehydes also gave the higher yield and e.r (entries 4 and 5). In addition to that, *para*-substituted aromatic aldehydes showed a slightly higher chemical yield and e.r when compared to ortho- and meta-substituted benzaldehydes (Table 5, entries 6–8). When the reaction was carried out in the presence of

Table 3 Optimization of bases for asymmetric Knoevenagel condensation



Entry	Bases	**3a/4a**[a]	Yield (%)[b]	E.r[c] Abs.Conf.[d]
1	K_2CO_3	70:30	75	86.33:13.67
2	Cs_2CO_3	62:38	64	83.72:16.28
3	K'OBu	n.r[e]	–	–
4	NaOH	n.r[e]	–	–
5	KOH	n.r[e]	–	–
6	TEA	96:4	92	97.58:2.48
7	DIEA	92:8	90	95.54:4.46
8	Pyridine	80:20	80	91.02:8.98
9	Piperidine	83:17	78	90.22:9.78
10	Morpholine	85:15	84	87.18:12.82

Reaction conditions: **1a** (0.1 mmol), **2a** (1.0 mmol), **10b** (10 mol%), various bases (0.2 mmol) and ethanol (2 mL) at room temperature in 48 h

[a]Determined by GC–MS analysis

[b]Yield of isolated product

[c]Determined by HPLC analysis chiral column (Chiralcel OD-H) with hexane–IPA as an eluent

[d]Absolute configuration was determined by comparison of the HPLC retention time using known literature data [32–37]

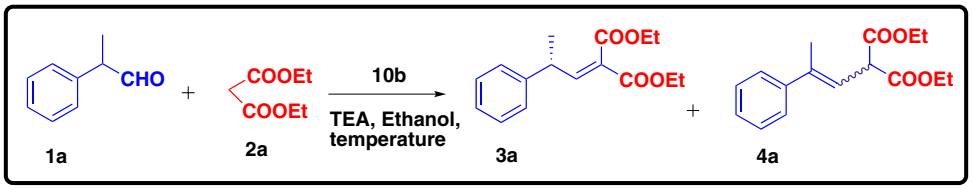
[e]No reaction

dimethyl malonate, we achieved very good yields and e.r (Table 5, entries 9 and 10). Among these malonate compounds, we found that the steric effect of these compounds could create beneficial influence on the enantiomeric excess when using diisopropyl malonate, dibutyl malonate, dipropyl malonate and dibenzyl malonate (Table 5, entries 11–15). Aliphatic aldehydes are found to be suitable substrates for enantioselective Knoevenagel condensation (Table 5, entry 16).

From the observed results, the higher chemical yield and e.r for C_9(*O*)-protected catalyst **10b** (Table 1) are due to the presence of effective ion-pair interaction between the R_4N^+ of the catalyst and the enolate anion of the diethylmalonate and anion of polarized aldehyde. In general, irrespective of free C_9 OH (**10a**) or C_9 (*O*)-protected catalyst (**10b**), there should be three factors which can influence the chemical yield and e.r: (1) an effective ion-pair interaction between R_4N^+ of the catalyst and anion of polarized aldehyde (Fig. 1a), (2) similar interaction happened between the enolate of the diethylmalonate and anion of polarized aldehydes with R_4N^+ of the catalyst (Fig. 1c) and (3) at that same time, the intermolecular hydrogen bonding between the free C_9 –OH of the organocatalyst with anion of polarized aldehyde and carbonyl group of diethylmalonate (Fig. 1b). We strongly believed that the above three possible electrostatic processes are responsible for deciding the chemical yield and e.r. [53–56]. The intermolecular hydrogen bonding prevents the perfect ion-pair interaction between the catalyst and substrates. Therefore, the higher yield and e.r were achieved in the presence of allyl protected catalysts **10b** compared to free C_9 (OH) catalysts **10a** (Fig. 1c).

In addition to observed results, allyl protected catalyst **10b** was more efficient than the free C_9 –OH-containing catalyst **10a** since the allyl protected catalyst has more binding

Table 4 Optimization of temperature and catalyst loading for asymmetric Knoevenagel condensation



Entry	Temperature (°C)	Mol% of catalyst	**3a/4a**[a]	Yield (%)[b]	E.r[c] Abs.Conf.[d]
1	60	5	63:37	67	85.71:14:29
2	60	10	80:20	82	91.88:8.12
3	60	20	57:43	52	76.61:23.39
4	30	5	70:30	75	89.34:10.66
5	30	10	96:4	92	97.58:2.48
6	30	20	60:40	57	79.04:20.96
7	0	5	Trace	–	–
8	0	10	Trace	–	–
9	0	20	Trace	–	–
10	−10	5	n.r[e]	–	–
11	−10	10	n.r[e]	–	–
12	−10	20	n.r[e]	–	–

Reaction conditions: **1a** (0.1 mmol), **2a** (1.0 mmol), 10b (various mol%), TEA (0.2 mmol) and ethanol (2 mL) at different temperature conditions for 36 h

[a]Determined by GC–MS analysis

[b]Yield of isolated product

[c]Determined by HPLC analysis chiral column (Chiralcel OD-H) with hexane-IPA as an eluent

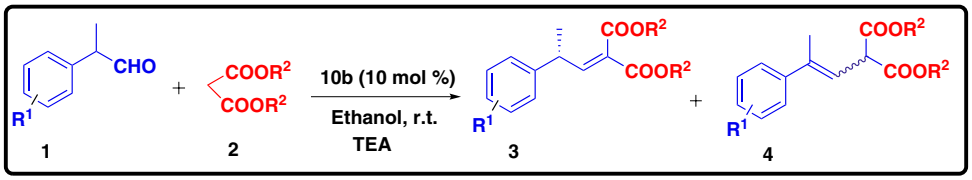
[d]Absolute configuration was determined by comparison of the HPLC retention time using known literature data [32–37]

[e]No reaction

with the substrate. In the case of **10a** as a catalyst, hydrogen bonding between the enolate anion of the diethyl malonate and anion of a polarized aldehyde with the C_9–OH of the catalyst prevented the perfect ion-pair interaction between the catalyst and anion of the substrates; hence, we got a slightly lower yield as well as the e.r (Fig. 2a, b) [57–63].

Based on these results, we proposed plausible transition state for the formation of the catalytic highly enantioselective asymmetric Knoevenagel condensation reaction (Fig. 3). The phenyl group of aldehyde has a π–π stacking interaction with one of the quinoline moiety of the alkaloid moiety of the catalyst. The results also suggested that apart from the ionic interaction between the catalyst and substrates, there is π-π stacking interaction between the quinoline part of the respective C_9(O)-protected catalyst with an aryl group of the aldehyde which can be strongly influenced the binding of the two species as a results we found very good yield as well as enantiomeric excess. In addition to that this in turn shows to facilitate effective ion-pair interaction and thus affected in parallel increasing of yield and e.r than corresponding catalyst containing free C_9 –OH. In addition to that, Cinchona alkaloid catalysts **10a** and **10b** have C_2-symmetric type of catalysts. Hence, the two cinchona units (free C_9 –OH and C_9 (O) protected) should present at the end of the pentaerythritol linker due to steric hindrance of the quinoline moiety of the cinchona alkaloids.[23g] Further, the pentaerythritol-based chiral catalysts (**10a** and **10b**) can strongly bind with the anion of polarized aldehyde and anion of malonate derivatives simultaneously, and hence we found higher yield and e.r at lower concentration of organocatalysts, base and lesser reaction time (Tables 1, 2, 3, 4, 5).

Table 5 Substrate variations in Knoevenagel condensation



Entry	R_1	R_2	Product	3/4[a]	Yield (%)[b]	E.r[c] Abs.Conf.[d]
1	H	Et	**3a**	96:4	92	97.58:2.48
2	4-OMe	Et	**3b**	100:0	95	98.32:1.68
3	4-CH_3	Et	**3c**	100:0	96	98.41:1.59
4	4-Br	Et	**3d**	93:7	85	95.54:4.46
5	4-Cl	Et	**3e**	94:6	87	97.45:2.55
6	4-F	Et	**3f**	97:3	92	97.06:2. 94
7	3-F	Et	**3 g**	95:5	90	94.89:5.11
8	2-F	Et	**3 h**	94:6	87	91.89:8. 11
9	H	Me	**3i**	96:4	93	97.00:3.00
10	4-CH_3	Me	**3j**	98:2	95	99.11:0. 89
11	H	*i*Pr	**3 k**	97:3	95	98.58:1.42
12	4-CH_3	*i*Pr	**3 l**	99:1	96	99.69:0.31
13	H	*n*Bu	**3 m**	96:4	97	98.94:1.06
14	H	*n*Pr	**3n**	98:2	95	98.42:1.58
15	H	Bnz	**3o**	90:10	85	93.04:6.96
16	*c*-C_6H_{11}	Et	**3p**	92:8	89	95.56:4.44

Reaction conditions: **1** (0.1 mmol), 2 (1.0 mmol), catalyst **10b** (10 mol%), TEA (0.2 mmol) and ethanol (2 mL) at room temperature condition in 48–72 h

[a]Determined by GC–MS analysis

[c]Yield of isolated product

[d]Determined by HPLC analysis chiral column (Chiralcel OD-H) with hexane–IPA as an eluent

[e]Absolute configuration was determined by comparison of the HPLC retention time using known literature data [32–37]

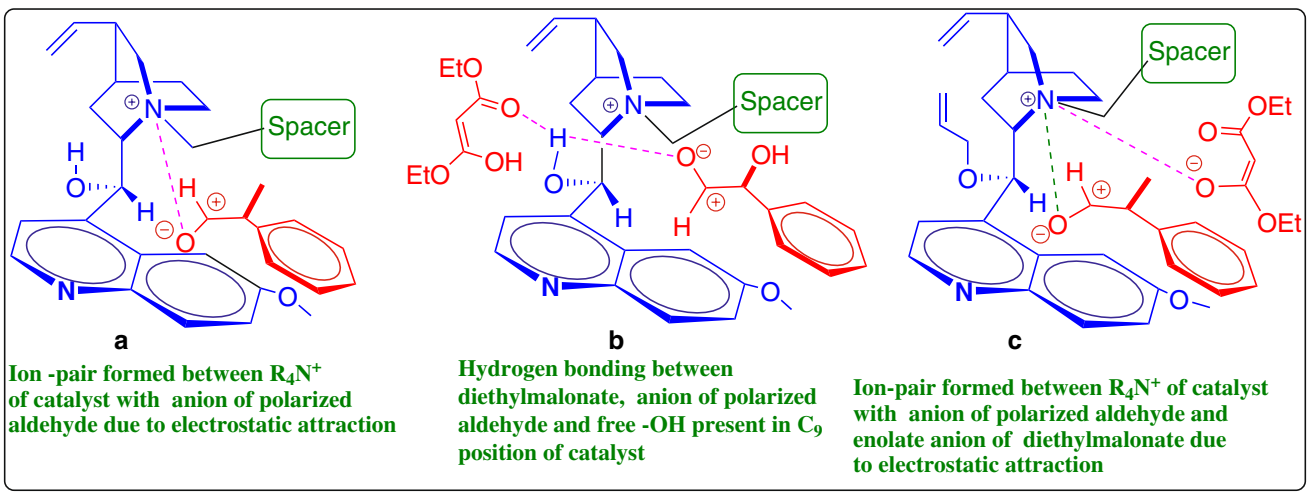


Fig. 1 Formation of various molecular assemblies during Knoevenagel condensation using free C_9 –OH and allyl protected organocatalysts (**10a** and **10b**)

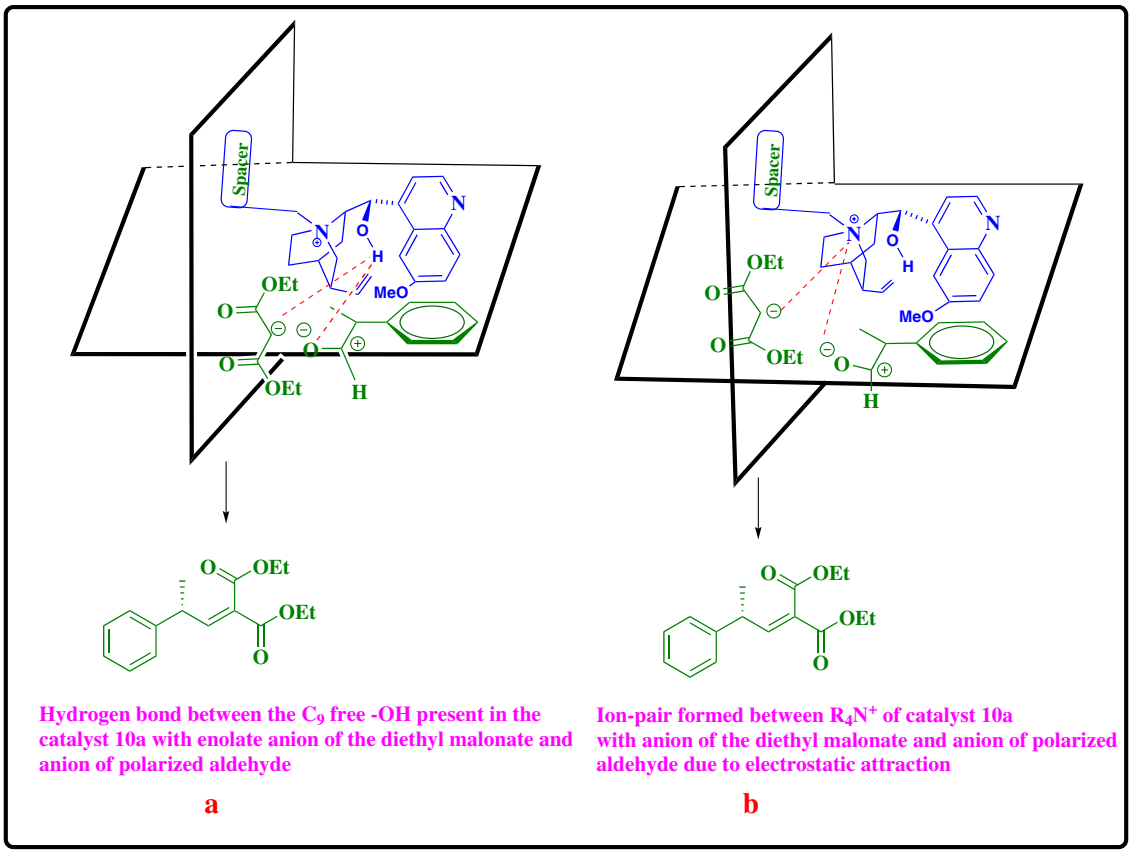


Fig. 2 Plausible transition state for the formation of various intermediates/molecular assemblies during the enantioselective Knoevenagel condensation reaction using free C_9 –OH catalyst (**10a**)

To expose the usefulness of Knoevenagel products, compound **3a** was converted into different γ-alkyl-substituted chiral amides using various amines such as aniline, 4-aminopyridine, n-butylamine, morpholine and pyrrolidine. Interestingly, the optical purity of the amides obtained was very high consistent with the Knoevenagel adduct used.

Applications of Knoevenagel product

See Scheme 3.

Conclusions

We have designed two different types of novel chiral organocatalysts from cinchona alkaloids for enantioselective Knoevenagel condensation reaction. The racemic α-branched aldehydes can be converted into the corresponding enantiomerically enriched products with higher chemical yield (up to 97%) and an excellent enantiomeric ratio (up to 99.68:0.32) via dynamic kinetic resolution. Further the Knoevenagel adduct **3a** was converted into enantiomerically

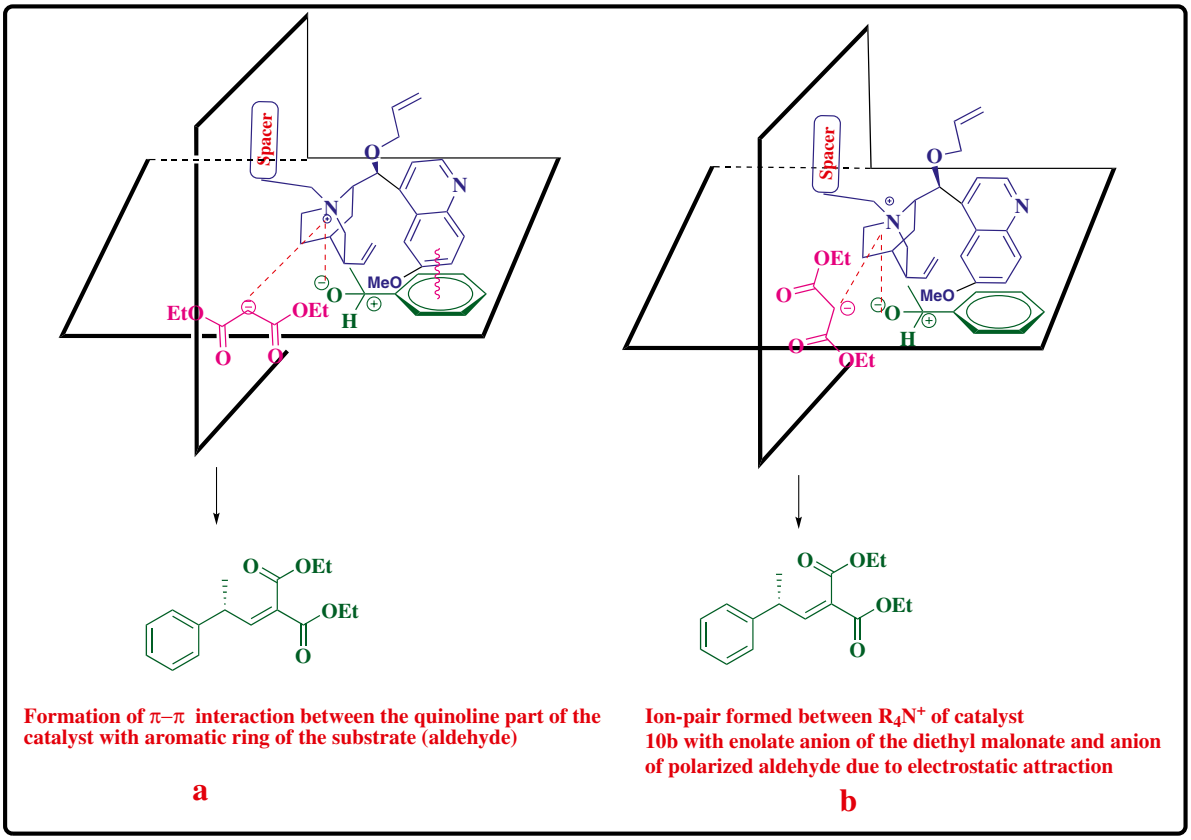
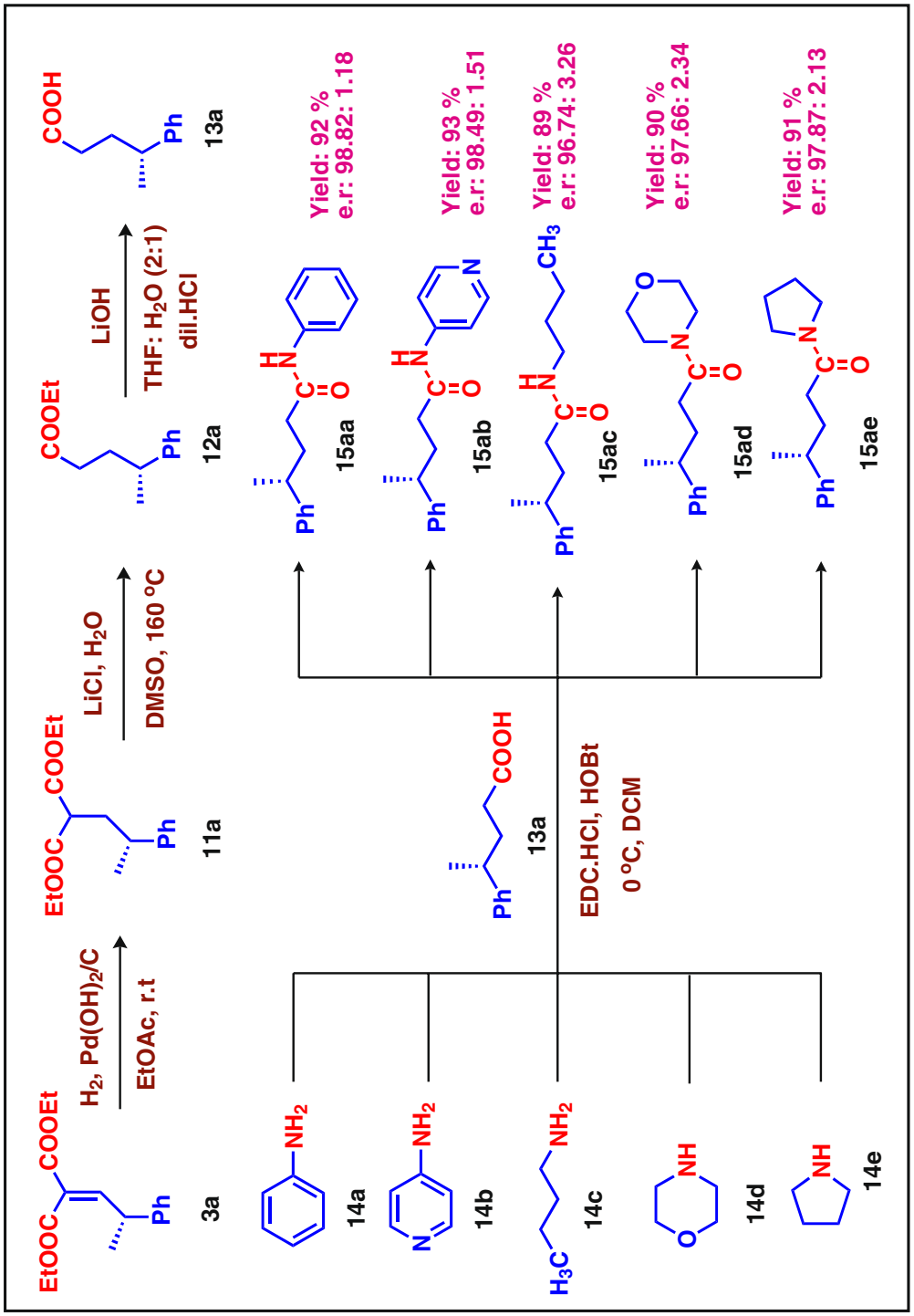


Fig. 3 The plausible transition state for highly enantioselective Knoevenagel condensation reaction catalysed by cinchona-derived C_9 –allyl protected catalyst (**10b**)

enriched valuable γ-alkyl-substituted amides without loss in enantioselectivity. We believed that this study greatly expands the potential of this approach, through the addition of α-branched aldehydes to various malonate derivatives, towards the preparation of synthetic and pharmaceutically valuable Knoevenagel products and therein chiral γ-alkyl-substituted amides.



Scheme 3 Synthesis of chiral amide derivatives from Knoevenagel product obtained

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

References

1. E. Knoevenagel, Chem. Dtsch. Ber. Ges. **27**, 2345 (1894)
2. L.F. Tietze, U. Beifuss, B.M. Trost, *Comprehensive Organic Synthesis*, vol. 2 (Pergamon, Oxford, 1991), p. 341
3. G. Jones, *Organic Reactions*, vol. 5 (Wiley, New York, 1967), p. 204
4. F. Freeman, Chem. Rev. **80**, 329 (1980)
5. L.F. Tietze, Chem. Rev. **96**, 115 (1996)
6. T. Kanzian, S. Lakhdar, H. Mayr, Angew. Chem. Int. Ed. **49**, 9526 (2010)
7. B. List, Angew. Chem. Int. Ed. **49**, 1730 (2010)
8. B. List, J.W. Yang, Science **313**, 1584 (2006)
9. D.W.C. MacMillan, Nature **455**, 304 (2008)
10. B. List, Chem. Commun. **8**, 819 (2006)
11. R.S. Pottorf, N.K. Chadha, M. Katkevics, Tetrahedron Lett. **44**, 175 (2003)
12. N. Yu, J.M. Aramini, M.W. Germann, Z. Huang, Tetrahedron Lett. **41**, 6993 (2000)
13. S. Balalaie, A.M. Sheikh, M. Bararjanian, Catal. Commun. **8**, 1724 (2007)
14. F. Bigi, L. Chesini, R. Maggi, G. Sartori, J. Org. Chem. **64**, 1033 (1999)
15. D. Prajapati, K.C. Lekhok, J.S. Sandhu, A.C. Ghosh, J. Chem. Soc. Perkin Trans. **1**, 959 (1996)
16. T.I. Reddy, R.S. Varma, Tetrahedron Lett. **38**, 1721 (1997)
17. S. Wada, H. Suzuki, Tetrahedron Lett. **44**, 399 (2003)
18. J.S. Yadav, B.V.S. Reddy, A.K. Basak, A.V. Narsaiah, Tetrahedron Lett. **44**, 1047 (2003)
19. B.C. Ranu, R. Jana, Eur. J. Org. Chem. **2006**, 3767 (2006)
20. Z.J. Ren, W.G. Cao, W.Q. Tong, X.P. Jing, Synth. Commun. **32**, 1947 (2002)
21. S. Wang, Z. Ren, W. Cao, W. Tong, Synth. Commun. **31**, 673 (2001)
22. S. Balalaie, M. Bararjanian, Synth. Commun. **36**, 2549 (2006)
23. L.F. Tietze, U. Beifuss, The Knoevenagel reaction, in *Comprehensive organic synthesis*, vol. 2, ed. by B.M. Trost, I. Fleming (Pergamon Press, Oxford, 1991), p. 341
24. K. Sakthivel, W. Notz, T. Bui, C.F. Barbas III, J. Am. Chem. Soc. **123**, 5260 (2001)
25. H. Groger, J. Wilken, Angew. Chem. Int. Ed. **40**, 529 (2001)
26. A.V. Narsaiah, A.K. Basak, B. Visali, K. Nagaiah, Synth. Commun. **34**, 2893 (2004)
27. S. Sebti, A. Smahi, A. Solhy, Tetrahedron Lett. **43**, 1813 (2002)
28. S. Sebti, R. Nazih, R. Tahir, A. Saber, Synth. Commun. **31**, 993 (2001)
29. D. Fildes, V. Caignaert, D. Villemin, P.A. Jaffres, Green Chem. **3**, 52 (2001)
30. M.S. Sigman, P. Vachal, E.N. Jacobsen, Angew. Chem. Int. Ed. **39**, 1279 (2000)
31. C.J. Wang, X.Q. Dong, Z.H. Zhang, Z.Y. Xue, H.L. Teng, J. Am. Chem. Soc. **130**, 8606 (2008)
32. A. Lee, A. Michrowska, S.S. Mosse, B. List, Angew. Chem. Int. Ed. **50**, 1707 (2011)
33. W.J. Le, H.F. Lu, J.T. Zhou, H.L. Cheng, Y.H. Gao, Tetrahedron Lett. **54**, 5370 (2013)
34. S. Sakshi, S. Baldev, Bioorg. Med. Chem. Lett. **22**, 5388 (2012)
35. X. Gu, Y. Tang, X. Zhang, Z. Luob, H. Lu, New J. Chem. **40**, 6580 (2016)
36. T. Murase, Y. Nishijima, M. Fujita, J. Am. Chem. Soc. **134**, 162 (2012)
37. J.J. Han, Y.F. Xu, Y.P. Su, X.G. She, X.F. Pan, Catal. Commun. **9**, 2077 (2008)
38. H. Pellissier, Adv. Synth. Catal. **353**, 659 (2011)
39. K. Horiguchi, E. Yamamoto, K. Saito, M. Yamanaka, T. Akiyama, Chem. Eur. J. **22**, 8078 (2016)
40. H.Z. You, E. Rideau, M. Sidera, S.P. Fletcher, Nature **517**, 351 (2015)
41. S.K. Nimmagadda, S.C. Mallojjala, L. Woztas, S.E. Wheeler, J.C. Antilla, Angew. Chem. Int. Ed. **56**, 2454 (2017)
42. L. Rasu, J.M. John, E. Stephenson, R. Endean, S. Kalapugama, R. Clement, S.H. Bergens, J. Am. Chem. Soc. **139**, 3065 (2017)
43. A.E. Cotman, D. Cahard, B. Mohar, Angew. Chem. Int. Ed. **128**, 5380 (2016)
44. B.L. Bray, Nat. Rev. Drug Discov. **2**, 587 (2003)
45. V.R. Pattabiraman, J.W. Bode, Nature **480**, 471 (2011)
46. E. Valeur, M. Bradley, Chem. Soc. Rev. **38**, 606 (2009)
47. C. Gunanathan, Y.B. David, D. Milstein, Science **317**, 790 (2007)
48. A.K. Schoonen, M.A. Fernandez-Ibanez, M. Fananas-Mastral, J.F. Teicherta, B.L. Feringa, Org. Biomol. Chem. **12**, 36 (2014)
49. M.R. Fernandez, X. Yan, J.F. Collados, P.B. White, S.R. Harutyunyan, J. Am. Chem. Soc. **139**, 14224 (2017)
50. C.E. Song, *Cinchona Alkaloids in Synthesis and Catalysis, Ligands, Immobilization and Organocatalysis*, vol. 359 (Wiley-VCH, Weinheim, 2009)
51. A. Jesin Beneto, J. Sivamani, V. Ashokkumar, R. Balasaravanan, K. Duraimurugan, A. Siva, New J. Chem. **39**, 3098 (2015)
52. J. Sivamani, V. Ashokkumar, V. Sadhasivam, K. Duraimurugan, A. Siva, RSC Adv. **4**, 60293 (2014)
53. V. Ashokkumar, R. Balasaravanan, V. Sadhasivam, S. Mehtob Jenofar, A. Siva, J. Mol. Catal. A. Chem. **409**, 127 (2015)
54. E.J. Corey, F. Xu, M.C. Noe, J. Am. Chem. Soc. **119**, 12414 (1997)
55. E.J. Corey, M.C. Noe, F. Xu, Tetrahedron Lett. **39**, 5347 (1998)
56. E.J. Corey, Y. Bo, J.B. Peterson, J. Am. Chem. Soc. **120**, 13000 (1998)
57. V. Ashokkumar, A. Siva, Org. Biomol. Chem. **13**, 10216 (2015)
58. H.G. Park, B.S. Jeong, M.S. Yoo, M.K. Park, H. Huh, S.S. Jew, Tetrahedron Lett. **42**, 4645 (2001)
59. N. Mase, T. Ohno, N. Hoshikawa, K. Ohishi, H. Morimoto, H. Yoda, K. Takabe, Tetrahedron Lett. **44**, 4073 (2003)
60. K. Maruoka, T. Ooi, Chem. Rev. **103**, 3013 (2003)
61. A. Siva, E. Murugan, J. Mol. Catal. A Chem. **241**, 101 (2005)
62. E. Murugan, A. Siva, Synthesis **12**, 2022 (2005)
63. J. Sivamani, K. Duraimurugan, A. Jesin Benito, P. Subha, R. Balasaravanan, A. Siva, Synlett. **25**, 1685 (2014)

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