Asymmetric Michael Reaction of Aldehydes with β-Nitroalkenes Catalyzed by Pyrrolidine–Camphor Derived Organocatalysts Bearing Hydrogen-Bond Donors

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ABSTRACT Several pyrrolidine–camphor derived organocatalysts were designed and synthesized. These organocatalysts were used for direct Michael reaction of aldehydes with nitroalkenes to give the desired γ-nitrocarbonyl compounds in high yields (up to 99%), high diastereoselectivities (*syn*:*anti* up to 92:8), and good to excellent enantioselectivities (up to 94% *ee*). Possible transition-state model was also proposed for this asymmetric transformation, which may involve hydrogen-bond interactions between the nucleophilic enamine formed in situ and the nitroalkenes. *Chirality 24:271–275, 2012.* © 2012 Wiley Periodicals, Inc.

KEY WORDS: asymmetric catalysis; organocatalysis; camphor; sulfonamide; Michael reaction; nitroalkene; aldehyde; hydrogen bond

INTRODUCTION

Chiral γ-nitrocarbonyl compounds are important precursors for many bioactive compounds such as oseltamivir,[1] nakadomarin A,[2] baclofen,[3] rolipram,[4] and esermethole.[5] Considerable efforts have been paid on the development of efficient synthetic methods for these versatile compounds.[6] Among them, asymmetric Michael reaction of carbonyl compounds to nitroalkenes is perhaps the most straightforward and useful approach.[7] On the other hand, organocatalytic reactions have attracted much attention in recent years.[8] In 2001, Betancort and Barbas[9] reported the first organocatalytic asymmetric Michael reaction of unmodified aldehydes to nitroolefins using chiral secondary amine as catalyst. Afterward, numerous selective and efficient catalysts including chiral proline derivatives and bifunctional primary amine-thioureas were developed in this transformation.[10–12]

Recently, we have developed a series of new perhydroindole derived organocatalysts, which readily facilitated the reaction of a wide range of aldehydes and nitroalkenes, providing Michael adducts in nearly optically pure form (99% *ee*), good yields, and high diastereoselectivities (*syn/anti* up to 99:1).[13] In continuation of our interest in using rigid cyclic compounds, such as perhydroindole,[14] binaphthalene,[15] and camphor,[16] as backbones of catalysts or ligands, we decided to investigate the potential of pyrrolidine–camphor derived organocatalysts **1–3** (Fig. 1), whose bulky rigid camphor ring could exert stereocontrolling influence, while the inherent secondary amine and sulfonamide (or amide) moieties could activate both the nucleophilic and the electrophilic substrates via the enamine formation process and hydrogen-bond activation simultaneously.

It should be noted that during our research, several pyrrolidine–camphor organocatalysts linked with amine, amide, and sulfide functionalities (**4–6**) were developed and applied in asymmetric Michael reactions with high diastereoselectivity and enantioselectivity.[17–19] In contrast, sulfonamide-linked catalysts **1–3** have never been used in similar reactions, although **1–2** have already been used in direct α-amination of aldehyde with dialkylazodicarboxylates and afforded the desired α-aminated products in good chemical yields and stereoselectivities.[20] Herein, we wish to report our results on the camphorsulfonamide-based proline derivatives and their impacts on the organocatalytic Michael reactions of aldehydes with nitroalkenes.

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EXPERIMENTAL

General Methods

Unless otherwise stated, all reagents were used as purchased from commercial suppliers without additional purification. The solvents were distilled from standard drying agents. Air and/or moisture sensitive reactions were performed under the inert atmospheric conditions. Purification of reaction products was carried out by flash column chromatography with silica gel (200–300 mesh) purchased from Qingdao Haiyang Chemical Co. Ltd. ^{1}H NMR spectra were recorded on a Bruker AVANCE 400 spectrometer. Chemical shifts were reported as parts per million (ppm) in the δ scale downfield from tetramethylsilane. Peaks are labeled as singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). ^{13}C NMR spectra were recorded on Bruker spectrometer with complete proton decoupling, and chemical shifts were reported in ppm from TMS with the solvent as the internal reference ($CDCl_3$, δ = 77.0 ppm). High-performance liquid chromatography (HPLC) analyses were conducted on Agilent 1200 instrument using Chiralcel OD-H, Chiralpak AD-H or AS-H columns (0.46 cm diameter × 25 cm length). Optical rotations were recorded on a Perkin Elmer polarimeter (Model 341). MS spectra were recorded on an electrospray ionization (ESI)-ion trap Mass spectrometer (Shimadzu LCMS-IT-TOF). Key intermediate **7** and organocatalysts **1–3** were prepared using similar procedures with literatures.[21–23]

General Procedure for the Michael Addition Reaction

To a solution of nitrostyrene (74.5 mg, 0.5 mmol) and **2** (32 mg, 0.1 mmol) in toluene (0.8 mL), propanal (0.18 mL, 2.5 mmol) was added at room temperature. The reaction mixture was stirred for 24 h. Then, the solvent was removed, and the residue was purified by flash column

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Contract grant sponsor: European Commission funded project; Contract grant number: FP7-201431(CATAFLU.OR).
Contract grant sponsor: Guangdong Recruitment Program of Creative Research Groups.
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Received for publication 28 July 2011; Accepted 5 December 2011
DOI: 10.1002/chir.21991
Published online 25 January 2012 in Wiley Online Library (wileyonlinelibrary.com).

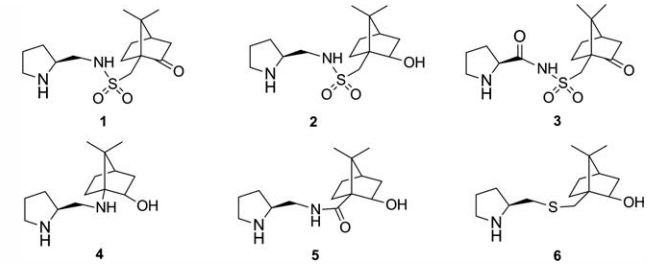


Fig. 1. Various pyrrolidine–camphor organocatalysts.

chromatography on silica gel using ethyl acetate/hexane (1:5) as the eluent to afford the Michael adduct. Assignment of the stereoisomers was performed by comparison with literature data. The value of *syn/anti* ratio was determined by ^{1}H NMR by comparing different integrations of hydrogens of the aldehyde group. The enantiomeric excess was measured by HPLC with Chiralcel OD-H, Chiralpak AD-H or AS-H columns.

Characterization of Micheal Addition Products

(2*R*,3*S*)-2-Methyl-4-nitro-3-phenylbutanal (16a). Colorless oil (91% yield), *ee* = 94%.[13] The enantiomeric excess was determined by HPLC with a Daicel Chiralcel OD-H column (*n*-hexane/*i*-PrOH = 85/15, 0.8 mL/min, λ = 208 nm), t_R = 18.0 min (minor), t_R = 24.0 min (major). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (d, *J* = 7.3 Hz, 3H), 2.64–2.72 (m, 1H), 3.82 (td, *J* = 5.5, 9.2 Hz, 1H), 4.69 (dd, *J* = 9.3, 12.7 Hz, 1H), 4.81 (dd, *J* = 5.5, 12.7 Hz, 1H), 7.16–7.18 (m, 2H), 7.26–7.28 (m, 3H), 9.72 (d, *J* = 1.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, 44.0, 48.4, 78.1, 128.0, 128.1, 129.1, 136.5, 202.2.

(2*R*,3*S*)-2-Methyl-4-nitro-3-(2-methoxyphenyl)-butanal (16b). Colorless oil (87% yield), *ee* = 89%.[13] The enantiomeric excess was determined by HPLC with a Daicel Chiralcel OD-H column (*n*-hexane/*i*-PrOH = 99/1, 1.0 mL/min, λ = 208 nm), t_R = 36.6 min (major), t_R = 40.2 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (d, *J* = 7.5 Hz, 3H), 3.18 (m, 1H), 4.02 (s, 3H), 4.21 (m, 1H), 4.92 (m, 1H), 5.04 (m, 1H), 7.06–7.46 (m, 4H), 9.90 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, 40.5, 47.1, 55.3, 111.1, 120.9, 124.4, 129.3, 130.3, 157.3, 202.8.

(2*R*,3*S*)-2-Methyl-4-nitro-3-(4-methoxyphenyl)-butanal (16c). Colorless oil (77% yield), *ee* = 90%.[13] The enantiomeric excess was determined by HPLC with a Daicel Chiralpak AS-H column (*n*-hexane/*i*-PrOH = 85/15, 1.0 mL/min, λ = 208 nm), t_R = 20.2 min (minor), t_R = 26.9 min (major). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (d, *J* = 7.3 Hz, 3H), 1.21 (d, *J* = 7.2 Hz, 1H), 2.65–2.67 (m, 1H), 3.79 (s, 3H), 4.64 (dd, *J* = 9.4, 12.5 Hz, 1H), 4.62–4.71 (m, 1H), 6.79–6.84 (m, 1H), 7.01–7.06 (m, 3H), 9.71 (d, *J* = 1.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.0, 43.3, 48.6, 55.2, 78.3, 114.4, 128.3, 129.1, 159.3, 202.4.

(2*R*,3*S*)-3-(4-Bromophenyl)-2-methyl-4-nitrobutanal (16d). White solid (93% yield), *ee* = 79%.[18] The enantiomeric excess was determined by HPLC with a Daicel Chiralcel OD-H column (*n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, λ = 254 nm), t_R = 27.5 min (major), t_R = 29.6 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (d, *J* = 7.3 Hz, 3H), 2.63–2.92 (m, 1H), 3.51–3.67 (m, 1H), 4.65 (dd, *J* = 9.6, 12.8 Hz, 1H), 4.80 (dd, *J* = 5.2, 12.8 Hz, 1H), 7.13–7.23 (m, 2H), 7.52–7.55 (m, 2H), 9.70 (d, *J* = 1.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.2, 43.5, 48.2, 122.2, 129.7, 129.8, 132.3, 135.6, 201.8.

(2*R*,3*S*)-2-Methyl-3-(1-naphthalenyl)-4-nitrobutanal (16e). Colorless oil (83% yield), *ee* = 75%.[13] The enantiomeric excess was determined by HPLC with a Daicel Chiralcel OD-H column (*n*-hexane/*i*-PrOH = 75/25, 0.8 mL/min, λ = 208 nm), t_R = 26.4 min (major), t_R = 19.5 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 7.3 Hz, 3H), 2.86–2.91 (m, 1H), 4.67–4.85 (m, 3H), 7.25–7.50 (m, 4H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 8.01–8.03 (m, 1H), 9.65 (d, *J* = 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.4, 27.4, 47.8, 76.9, 121.4, 123.0, 124.2, 125.0, 125.8, 127.6, 128.3, 130.0, 132.3, 133.1, 201.5.

(2*R*,3*R*)-2-Methyl-4-nitro-3-(thiophen-2-yl)butanal (16f). Colorless oil (75% yield), *ee* = 87%.[13] The enantiomeric excess was determined by HPLC with a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH = 99/1, 1.0 mL/min, λ = 238 nm), t_R = 29.8 min (major), t_R = 40.8 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (d, *J* = 7.3 Hz, 3H), 2.79 (dd, *J* = 1.2, 6.1 Hz, 1H), 4.25 (dt, *J* = 6.1, 8.2 Hz, 1H), 4.69 (dd, *J* = 8.8, 12.9 Hz, 1H), 4.79 (dd, *J* = 5.8, 12.9 Hz, 1H), 6.88–6.90 (m, 2H), 7.17–7.24 (m, 1H), 9.70 (d, *J* = 1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.5, 39.4, 48.8, 78.4, 125.3, 126.7, 127.1, 138.8, 201.7.

(2*R*,3*R*)-3-Furyl-2-methyl-4-nitrobutanal (16g). Colorless oil (86% yield), *ee* = 80%.[13] The enantiomeric excess was determined by HPLC with a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH = 99/1, 1.0 mL/min, λ = 210 nm), t_R = 24.4 min (major), t_R = 28.0 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (d, *J* = 7.2 Hz, 3H), 2.97–3.11 (m, 1H), 4.31 (m, 1H), 4.88–5.02 (m, 2H), 6.37–6.45 (m, 1H), 6.51–6.56 (m, 1H), 7.58 (d, *J* = 1.7 Hz, 1H), 9.93 (d, *J* = 1.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.0, 37.6, 47.0, 75.8, 108.8, 110.4, 142.7, 149.8, 201.6.

(2*S*,3*R*)-3-Cyclohexyl-2-methyl-4-nitrobutanal (16h). Colorless oil (70% yield), *ee* = 55%.[13] The enantiomeric excess was determined by HPLC with a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH = 99/1, 1.0 mL/min, λ = 210 nm), t_R = 15.2 min (major), t_R = 19.1 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81–0.93 (m, 3H), 0.96–1.00 (m, 2H), 1.13 (d, *J* = 6.8 Hz, 3H), 1.34–1.70 (m, 6H), 2.48–2.67 (m, 2H), 4.29–4.36 (m, 1H), 4.50–4.55 (m, 1H), 9.61 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.7, 25.0, 25.2, 25.3, 28.9, 30.5, 36.9, 42.4, 45.6, 76.4, 202.2.

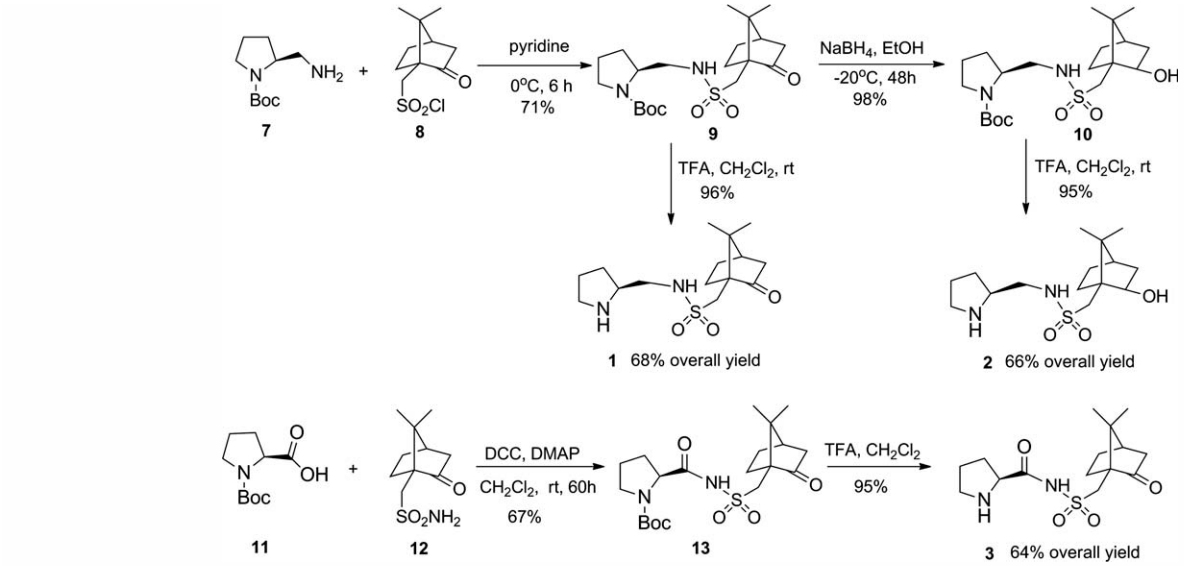
(2*R*,3*R*)-2,5-Dimethyl-3-(nitromethyl)-hexanal (16i). Colorless oil (99% yield), *ee* = 49%.[13] The enantiomeric excess was determined by HPLC with a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH = 99/1, 1.0 mL/min, λ = 210 nm), t_R = 8.2 min (major), t_R = 10.2 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 7.6 Hz, 3H), 0.95 (d, *J* = 7.6 Hz, 3H), 1.14 (d, *J* = 7.1 Hz, 3H), 1.20–1.24 (m, 1H), 1.54–1.62 (m, 2H), 2.50–2.54 (m, 1H), 2.78–2.83 (m, 1H), 4.32–4.34 (m, 1H), 4.42–4.44 (m, 1H), 9.68 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.7, 21.8, 23.0, 25.3, 35.0, 37.4, 47.1, 77.1, 202.6.

(2*R*,3*S*)-2-Ethyl-4-nitro-3-phenylbutanal (16j). Colorless oil (91% yield), *ee* = 72%.[13] The enantiomeric excess was determined by HPLC with a Daicel Chiralcel OD-H column (*n*-hexane/*i*-PrOH = 85/15, 0.8 mL/min, λ = 208 nm), t_R = 18.6 min (major), t_R = 15.3 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.71 (t, *J* = 7.5 Hz, 3H), 1.35–1.44 (m, 2H), 2.56–2.62 (m, 1H), 3.68–3.74 (m, 1H), 4.51–4.69 (m, 2H), 7.09–7.25 (m, 5H), 9.67 (d, *J* = 2.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.5, 20.2, 42.6, 54.9, 78.5, 128.0, 128.2, 129.0, 136.9, 203.3.

(2*R*,3*S*)-2-Propyl-4-nitro-3-phenylbutanal (16k). Colorless oil (83% yield), *ee* = 43%.[13] The enantiomeric excess was determined by HPLC with a Daicel Chiralcel OD-H column (*n*-hexane/*i*-PrOH = 85/15, 0.8 mL/min, λ = 208 nm), t_R = 19.1 min (major), t_R = 14.7 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.69 (t, *J* = 7.1 Hz, 3H), 1.06–1.42 (m, 4H), 2.59–2.66 (m, 1H), 3.67–3.73 (m, 1H), 4.53–4.65 (m, 2H), 7.08–7.27 (m, 5H), 9.60 (d, *J* = 2.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.9, 18.6, 28.3, 42.0, 52.7, 77.4, 127.0, 127.0, 128.0, 135.8, 202.4.

(2*R*,3*S*)-2-Isopropyl-4-nitro-3-phenylbutanal (16l). Colorless oil (92% yield), *ee* = 59%.[13] The enantiomeric excess was determined by HPLC with a Daicel Chiralcel OD-H column (*n*-hexane/*i*-PrOH = 85/15, 0.8 mL/min, λ = 208 nm), t_R = 22.1 min (major), t_R = 20.4 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 7.0 Hz, 3H), 1.09 (d, *J* = 7.2 Hz, 3H), 1.66–1.75 (m, 1H), 2.76–2.80 (m, 1H), 4.54–4.69 (m, 2H), 7.18–7.36 (m, 5H), 9.91 (d, *J* = 2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.9, 21.6, 27.9, 41.9, 58.6, 79.0, 127.9, 128.0, 129.1, 137.1, 204.4.

(2*R*,3*S*)-2-Butyl-4-nitro-3-phenylbutanal (16m). Colorless oil (95% yield), *ee* = 51%.[13] The enantiomeric excess was determined by HPLC with a Daicel Chiralcel OD-H column (*n*-hexane/*i*-PrOH = 85/15,



Scheme 1. Preparation of organocatalysts **1–3**.

0.8 mL/min, λ = 208 nm), t_R =16.8 min (major), t_R =13.5 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78 (t, *J* = 6.8 Hz, 3H), 1.12–1.30 (m, 4H), 1.42–1.45 (m, 1H), 1.40–1.44 (m, 1H), 2.62–2.67 (m, 1H), 3.78 (m, 1H), 4.64 (dd, *J* = 9.9, 12.9 Hz, 1H), 4.71 (dd, *J* = 5.1, 12.9 Hz, 1H), 7.08–7.16 (m, 2H), 7.35–7.26 (m, 3H), 9.69 (d, *J* = 2.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 22.5, 27.0, 28.5, 43.1, 53.8, 78.4, 128.0, 128.1, 129.1, 136.7, 203.3.

(2*R*,3*S*)-2-Pentyl-4-nitro-3-phenylbutanal (16n). Colorless oil (95% yield), *ee* = 62%.[13] The enantiomeric excess was determined by HPLC with a Daicel Chiralcel OD-H column (*n*-hexane/*i*-PrOH = 85/15, 0.8 mL/min, λ = 208 nm), t_R = 11.5 min (minor), t_R = 13.8 min (major). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.72 (t, *J* = 6.8 Hz, 3H), 1.01–1.42 (m, 8H), 2.59–2.65 (m, 1H), 3.67–3.73 (m, 1H), 4.53–4.65 (m, 2H), 7.09 (d, *J* = 7.2 Hz, 2H), 7.18–7.27 (m, 3H), 9.61 (d, *J* = 2.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 22.1, 26.0, 27.2, 31.5, 43.1, 53.8, 78.4, 128.0, 128.0, 129.0, 136.9, 203.3.

(*R*)-2,2-Dimethyl-4-nitro-3-phenylbutanal (16o). Colorless oil (67% yield), *ee* = 86%.[13] The enantiomeric excess was determined by HPLC with a Daicel Chiralcel OD-H column (*n*-hexane/*i*-PrOH = 85/15, 0.8 mL/min, λ = 208 nm), t_R = 15.3 min (major), t_R = 20.7 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (s, 3H), 0.99 (s, 3H), 3.67–3.71 (m, 1H), 4.59 (dd, *J* = 4.2, 13.1 Hz, 1H), 4.73–4.79 (m, 1H), 7.09–7.21 (m, 5H), 9.39 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.7, 21.4, 48.2, 48.3, 77.5, 128.0, 128.6, 129.1, 135.5, 204.3.

RESULTS AND DISCUSSION

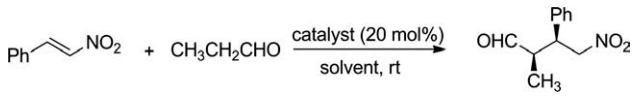
Preparation of Organocatalysts

The chiral pyrrolidine-camphorsulfonamide catalysts were prepared as depicted in Scheme 1. Treatment of Boc-protected (*S*)-2-aminomethylpyrrolidine (**7**) with (1*S*)-camphor-10-sulfonyl chloride (**8**) in pyridine at 0°C gave the corresponding sulfonamide **9** in 71% isolated yield. Then, removal of the *N*-Boc protecting group using trifluoroacetic acid (TFA) provided catalyst **1** in 96% yield. **9** can also be reduced by sodium borohydride at −20°C to afford the corresponding *exo*-alcohol **10** as a single diastereoisomer, which was then treated with TFA to generate organocatalyst **2**. More acidic sulfonamide catalyst **3** was prepared by convenient coupling between *N*-Boc-protected L-proline (**11**) and (1*S*)-10-camphorsulfonamide (**12**) in the presence of *N*,*N*′-dicyclohexylcarbodiimide and 4-(dimethylamino) pyridine, followed by TFA treatment to provide **3**.

Screening of Organocatalysts and Optimization of Reaction Conditions

With pyrrolidinylcamphor compounds **1–3** in hand, we explored their catalytic activities in the Michael reaction of aldehydes with nitroalkenes. Initially, propanal and (*E*)-(2-nitrovinyl)-benzene were chosen as model substrates. The reaction was carried out with 20 mol % catalyst at ambient temperature (Table 1). Catalyst **2** bearing a sulfonamide linkage and a hydroxy functionality provided the desired adduct in good yield (91%) and high stereoselectivity (*ee* up to 94%, *syn*:*anti* 88:12). We reasoned that the free hydroxyl group of **2** may play some role in determining the stereochemical outcomes of the reaction through activating nitroalkenes by

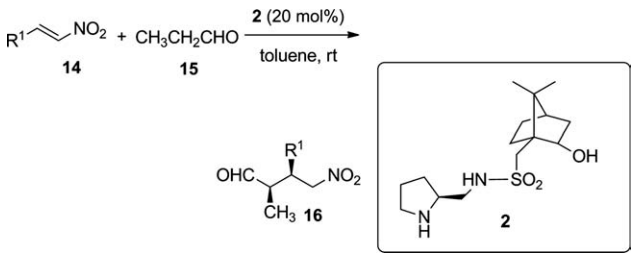
TABLE 1. The effects of organocatalysts and solvents in the Michael reaction of propanal and (*E*)-(2-nitrovinyl)-benzene



Entry	Catalyst	Solvent	Time (h)	Yield (%)[a]	*syn*/*anti*[b]	*ee* (%)[c]
1	**1**	Toluene	25	87	80:20	66
2	**2**	Toluene	23	91	88:12	94
3	**3**	Toluene	18	88	56:44	87
4	**2**	Hexane	23	56	90:10	94
5	**2**	THF	23	86	85:15	77
6	**2**	DCM	23	96	88:12	90
7	**2**	MeCN	23	96	78:22	48
8	**2**	MeOH	23	93	67:33	52
9	**2**	H_2O	23	76	91:9	81
10[d]	**2**	Toluene	36	83	86:14	94

[a]Yield of isolated product.
[b]Determined by ^{1}H NMR spectroscopy (400 MHz).
[c]The *ee* value was determined by HPLC analysis on a chiral phase (Chiralcel OD-H).
[d]The reaction was performed at 0°C.

TABLE 2. Catalytic asymmetric Michael reaction of propanal and nitroalkenes



Entry	Product	Yield (%)[a]	*syn/anti*[b]	*ee* (%)[c]
1		91	88:12	94
2		87	77:23	89
3		77	84:16	90
4		93	73:27	79
5		83	91:9	75
6		75	86:14	87
7		86	84:16	80
8		70	91:9	55
9		99	90:10	49

[a]Yield of isolated product.
[b]Determined by ^{1}H NMR spectroscopy (400 MHz).
[c]The *ee* value was determined by HPLC analysis on a chiral phase (Chiralcel OD-H, Chiralpak AD-H or AS-H).

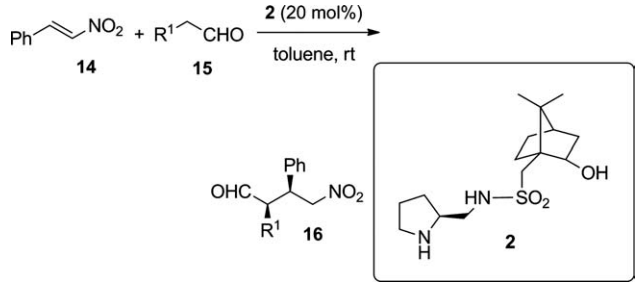
hydrogen bonding (entries 1 vs. 2). Similar phenomenon has also been observed in the literature.[35] The reaction was also sensitive to the structure of catalyst. A slight improvement in the reaction rate was observed when more acidic organocatalyst **3** was used, albeit poor diastereoselectivity was also obtained (entries 2 vs. 3).

Regarding the reactivity and stereoselectivity, **2** was chosen for further optimization (Table 1, entries 1–3). It appeared that toluene was a suitable solvent with respect to reaction time, yield, and diastereoselectivity and enantioselectivity (entry 2). Hexane gave comparable stereoselectivity (*ee* up to 94%, *syn*:*anti* 90:10), but the yield was unsatisfactory (entry 4). Although high yields were also achieved in polar solvents such as MeCN, MeOH, and water, the corresponding diastereoselectivities and enantioselectivities were only moderate (entries 7–9), which can be attributed to the adverse effect of polar solvent for the formation of hydrogen-bond between the catalyst and the substrate. The Michael reaction can also be performed at lower temperature (0°C) without compromising the enantioselectivity and diastereoselectivity, albeit the yield dropped slightly and a longer reaction time as 36 h was needed (entry 10).

Michael Addition of Various Aldehydes and Nitroalkenes

To explore the substrate generality of this asymmetric reaction, we examined the reaction of propanal with various

TABLE 3. Catalytic asymmetric Michael reaction of (*E*)-(2-nitrovinyl)-benzene with various aldehydes



Entry	Product	Yield (%)[a]	*syn/anti*[b]	*ee* (%)[c]
1		91	88:12	94
2		91	70:30	72
3		83	82:18	43
4		92	92:8	59
5		95	81:19	51
6		95	82:18	62
7		67	–	86

[a]Yield of isolated product.
[b]Determined by ^{1}H NMR spectroscopy (400 MHz).
[c]The *ee* value was determined by HPLC analysis on a chiral phase (Chiralcel OD-H, Chiralpak AD-H or AS-H).

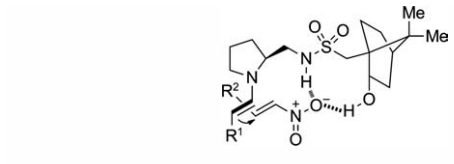


Fig. 2. Proposed transition state model for the Michael reaction.

substituted β-nitroalkenes under optimal condition, and the results were summarized in Table 2. The reaction proceeded smoothly in toluene at room temperature in the presence of **2**. High chemical yields, good diastereoselectivities, and enantioselectivities (75–94% *ee*) were obtained when aromatic nitroalkenes were used. Electron-rich aromatic nitroalkenes performed better over the electron-deficient aromatic nitroalkenes (entries 2–5). Heteroaryl-substituted nitroalkenes, such as **14f** and **14g**, also yielded the corresponding adducts with good selectivities (87% and 80% *ee* respectively; entries 6–7). The reaction with alkyl-substituted nitroalkenes resulted lower enantioselectivities (entries 8–9), and longer reaction time was needed for complete conversion.

A variety of aldehydes were also used in the asymmetric Michael reaction of *trans*-β-nitrostyrene, affording the desired γ-nitro aldehyde products in good yields and diastereoselectivities (Table 3). The enantioselectivities were influenced by the length of the chains of aliphatic aldehydes (entries 1–3 and 5–6) and the steric hindrance around α-carbon of aldehydes (entries 4 and 7). Best results were achieved for propanal in 91% yield, 88:12 diastereoselectivity (*syn*:*anti*), and 94% enantioselectivity. Branched aldehydes, such as isobutylaldehyde and isovaleraldehyde, need longer reaction time to ensure full conversions (entries 4 and 7).

Proposed Transition-State Model

According to the general mechanism of enamine catalysis and the stereochemical outcome in the current Michael reactions, we propose that pyrrolidine-camphorsulfonamide **2** catalyze the reaction of aldehydes with nitroalkenes via the transition state shown in Figure 2. The pyrrolidine reacts with aldehyde to form an enamine intermediate. Meanwhile, the nitroalkene could be activated through the formation of hydrogen bond with NH and OH groups on the camphorsulfonamide moiety. The rigid camphor scaffold could selectively shield the approach of the nitroalkene from the *Re*-face of enamine to generate the major isomer.

CONCLUSIONS

In conclusion, we have used bifunctional pyrrolidine-camphorsulfonamide organocatalysts in the reaction of a wide range of aldehydes and nitroalkenes and obtained Michael adducts in high yields (up to 99%), high diastereoselectivities (*syn*:*anti* up to 92:8), and good to excellent enantioselectivities (up to 94%). Besides the pyrrolidine structural unit and the camphor scaffold, the appropriate linker functionality as well as the free hydroxyl group also contributed significantly toward the diastereoselectivity and enantioselectivity of the reaction. Further studies on the application of these pyrrolidine-camphorsulfonamide catalysts in asymmetric Michael reaction and other stereoselective synthesis are now in progress.

LITERATURE CITED

1. Ishikawa H, Suzuki T, Hayashi Y. High-yielding synthesis of the anti-influenza neuramidase inhibitor (−)-oseltamivir by three "one-pot" operations. Angew Chem Int Ed 2009;48:1304–1307.
2. Jakubec P, Cockfield DM, Dixon DJ. Total synthesis of (−)-nakadomarin A. J Am Chem Soc 2009;131:16632–16633.
3. Zu LS, Xie HX, Li H, Wang J, Wang W. Highly enantioselective organocatalytic conjugate addition of nitromethane to α,β-unsaturated aldehydes: three-step synthesis of optically active baclofen. Adv Synth Catal 2007; 349:2660–2664.
4. Palomo C, Landa A, Mielgo A, Oiarbide M, Puente A, Vera S. Water-compatible iminium activation: organocatalytic Michael reactions of carbon-centered nucleophiles with enals. Angew Chem Int Ed 2007;46:8431–8435.
5. Bui T, Syed S, Barbas CF III. Thiourea-catalyzed highly enantio- and diastereoselective additions of oxindoles to nitroolefins: application to the formal synthesis of (+)-physostigmine. J Am Chem Soc 2009;131;8758–8759.
6. Roca-Lopez D, Sadaba D, Delso I, Herrera RP, Tejero T, Merino P. Asymmetric organocatalytic synthesis of γ-nitrocarbonyl compounds through Michael and domino reactions. Tetrahedron: Asymmetry 2010;21:2561–2601.
7. Berner OM, Tedeschi L, Enders D. Asymmetric Michael additions to nitroalkenes. Eur J Org Chem 2002;1877–1894.
8. Dalko PI. Enantioselective organocatalysis. Weinheim: Wiley-VCH; 2007.
9. Betancort JM, Barbas CF III. Catalytic direct asymmetric Michael reactions: taming naked aldehyde donors. Org Lett 2001;3:3737–3740.
10. Tsogoeva SB. Recent advances in asymmetric organocatalytic 1,4-conjugate additions. Eur J Org Chem 2007;1701–1716.
11. Almasi D, Alonso DA, Najera C. Organocatalytic asymmetric conjugate additions. Tetrahedron: Asymmetry 2007;18:299–365.
12. Vicario JL, Badia D, Carrillo L. Organocatalytic enantioselective Michael and hetero-Michael reactions. Synthesis 2007;2065–2092.
13. Luo RS, Weng J, Ai HB, Lu G, Chan ASC. Highly efficient asymmetric Michael reaction of aldehydes to nitroalkenes with diphenylperhydroindolinol silyl ethers as organocatalysts. Adv Synth Catal 2009;351:2449–2459.
14. Lin N, Chen MM, Luo RS, Deng YQ, Lu G. Indolinylmethanol catalyzed enantioselective Reformatsky reaction with ketones. Tetrahedron: Asymmetry 2010;21:2816–2824.
15. Lu G, Kwong FY, Ruan JW, Li YM, Chan ASC. Highly enantioselective addition of in situ prepared arylzinc to aldehydes catalyzed by a series of atropisomeric binaphthyl-derived amino alcohols. Chem Eur J 2006; 12:4115–4120.
16. Lu G, Li XS, Jia X, Chan WL, Chan ASC. Enantioselective alkynylation of aromatic ketones catalyzed by chiral camphorsulfonamide ligands. Angew Chem Int Ed 2003;42:5057–5058.
17. Chang C, Li SH, Reddy RJ, Chen KM. Pyrrolidine–camphor derivative as an catalyst for asymmetric Michael additions of α,α-disubstituted aldehydes to β-nitroalkenes: construction of quaternary carbon-bearing aldehydes under solvent-free conditions. Adv Synth Catal 2009;351:1273–1278.
18. Reddy RJ, Kuan HH, Chou TY, Chen KM. Novel Prolinamide-camphor-containing organocatalysts for direct asymmetric Michael addition of unmodified aldehydes to nitroalkenes. Chem Eur J 2009;15:9294–9298.
19. Ting YF, Chang C, Reddy RJ, Magar DR, Chen KM. Pyrrolidinyl-camphor derivatives as a new class of organocatalyst for direct asymmetric Michael addition of aldehydes and ketones to β-nitroalkenes. Chem Eur J 2010;16:7030–7038.
20. Liu PM, Magar DR, Chen, KM. Highly efficient and practical pyrrolidine–camphor-derived organocatalysts for the direct α-amination of aldehydes. Eur J Org Chem 2010;5705–5713.
21. Morris DJ, Partridge AS, Manville CV, Racys DT, Woodward G, Docherty G, Wills M. Asymmetric organocatalysis of the addition of acetone to 2-nitrostyrene using N-diphenylphosphinyl-1,2- diphenylethane-1,2-diamine (PODPEN). Tetrahedron Lett 2009;51:209–212.
22. Liu PM, Chang C, Reddy RJ, Ting YF, Kuan HH, Chen KM. Remarkable reaction rate and excellent enantioselective direct αα-amination of aldehydes with azodicarboxylates catalyzed by pyrrolidinylcamphor-derived organocatalysts. Eur J Org Chem 2010;42–46.
23. Bellis E, Vasilatou K, Kokotos G. 4-Substituted prolyl sulfonamides as enantioselective organocatalysts for aldol reactions. Synthesis 2005;2407–2413.