Enantioselective Conjugate Addition of Ketones to Nitroalkenes Catalyzed by Pyrrolidine-Sulfamides

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ABSTRACT A series of chiral pyrrolidine-sulfamides were prepared and examined as the catalysts for conjugate addition of ketones to nitroalkenes. Benzoic acid was identified as the most efficient additives for the transformation. Excellent enantioselectivities, diastereoselectivities, and yields were achieved for the reaction of cyclohexanone with β-aryl nitroethylenes under solvent free conditions. β-Isopropyl nitroethylene is also applicable and the product could be obtained with excellent enantioselectivity after extended reaction time. A comparison of the catalytic behaviors of pyrrolidine-sulfamide organocatalysts with different side chains demonstrates that the enantioselectivity is mainly controlled by the chiral pyrrolidine unit and the additional chiral center at the side chain exerts neglectable effects. The H-bonding interaction between the sulfamide and the nitro group is proposed to be crucial for the activation of the nitroalkene and the constitution of well-organized transition state. *Chirality 24:232–238, 2012.*

KEY WORDS: asymmetric conjugate addition; chiral pyrrolidine-sulfamide; organocatalysis; nitroalkene; ketone

INTRODUCTION

In recent years, organocatalysis has evolved to be a powerful tool for asymmetric synthesis.[1–5] The activation of carbonyl compounds by chiral primary and secondary amines is the most useful method.[6–8] In these reactions, the combination of concurrent H-bonding interactions (bifunctional catalysis) proved to be important for achieving excellent stereoselectivities and yields.[9–11] Ureas, thioureas, guandiniums, and amidinium ions, which are capable of simultaneously forming two hydrogen bonds, are privileged H-bond donors.[12–15] Recently, we found that readily available sulfamides are also efficient H-bond donors for primary amine-based bifunctional organocatalysts.[16–18] The stronger acidity of N-H bonds in sulfamides is expected to provide more efficient H-bonding interaction than the corresponding thioureas or ureas. Although the primary amine-sulfamide catalysts provided excellent enantioselectivities for conjugate addition of aldehydes to nitroalkenes,[16] they are less efficient for the conjugate addition of ketones to nitroalkenes.[17] A careful investigation of the reported results indicated that pyrrolidine-based organocatalysts are extremely efficient for the transformation.[19,20] Pyrrolidine-based amides,[21–24] thioureas (ureas),[25–29] sulfonamides,[30–34] and the others[35–46] have been developed successfully. Considering the excellent H-bond donation ability of sulfamides, we speculate that pyrrolidine-based sulfamides are also efficient catalysts for the conjugate addition of ketones to nitroalkenes (After we had submitted this article for 5 months, a similar study from Chen et al.'s group was submitted and published).[47] In this article, we report the synthesis and application of novel chiral pyrrolidine-sulfamides in asymmetric conjugate addition of ketones to nitroalkenes.

EXPERIMENTAL SECTION

General Remarks

All solvents were used as commercial anhydrous grade without further purification. All reactions were performed under open air. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AVANCE 400 spectrometer. Peaks are labeled as singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Optical rotations were measured on a Perkin-Elmer 341 digital polarimeter. Melting points were measured on a WRS-2A melting point apparatus and are uncorrected. The high resolution mass spectroscopic data were obtained at Shimadazu LCMS-IT-TOF spectrometer. Infrared (IR) spectra were recorded on a Bruker Tensor 37 spectrophotometer. Enantiomeric excesses were determined by high performance liquid chromatography (HPLC) using a Daicel Chiralcel AS-H, AD-H, or OD-H column and eluting with a hexane/2-propanol solution. Flash chromatography was performed over silica gel (230–400 mesh), purchased from Qingdao Haiyang Chemical Co.

Typical Procedure for the Synthesis of Pyrrolidine-Sulfamides 1a–1d

A 100-ml round bottomed flask was charged with catechol (4.40 g, 40 mmol), pyridine (6.40 g, 80 mmol), and hexane (40 ml). A solution of sulfuryl chloride (5.40 g, 40 mmol) in hexane (10 ml) was then added dropwise over 1 h at −5°C. The reaction mixture was stirred at 0°C overnight and at ambient temperature for another 12 h. The upper layer of the reaction mixture was decanted. The lower layer was diluted with water (100 ml) and extracted with ethyl ether (4 × 60 ml). The combined organic layer was washed with 2% NaOH (3 × 60 ml) and dried over sodium sulfate. After the evaporation of solvent under vacuum, catechol sulfate was obtained as a colorless oil (2.60 g, 38% yield), which was used in the next step without further purification.

To a solution of benzylamine (1.17 g, 10 mmol), triethylamine (1.20 g, 12 mmol), *N,N*-dimethylformamide (DMF) (20 ml), and anhydrous dichloromethane (10 ml) under an ice-bath, a solution of catechol sulfate

Contract grant sponsor: National Natural Science Foundation of China; Contract grant numbers: 20772160, 20972195.
Contract grant sponsor: Ministry of Health of China; Contract grant number: 2009ZX09501-017.
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Received for publication 28 September 2010; Accepted 2 November 2011
DOI: 10.1002/chir.21987
Published online 25 January 2012 in Wiley Online Library (wileyonlinelibrary.com).

(1.72 g, 10.0 mmol) in dichloromethane (20 ml) was added dropwise. The reaction mixture was stirred for 24 h at room temperature and then diluted with dichloromethane (30 ml). The reaction solution was washed with 1 M hydrochloric acid (2 × 20 ml), brine (2 × 20 ml) and dried over anhydrous Na_2SO_4. After the evaporation of solvent under vacuum, the crude product was purified by flash chromatography over silica gel (EtOAc/petroleum ether = 1/1) to give 2-hydroxyphenyl benzylsulfamate as a white solid (2.77 g, 99% yield).

A solution of 2-hydroxyphenyl benzylsulfamate (837 mg, 3 mmol) and (*S*)-*N*-Boc-2-aminomethyl-pyrrolidine (600 mg, 3.0 mmol) in dry dioxane (50 ml) was refluxed for 2.5 h. After dioxane was removed under vacuum, the residue was dissolved in ethyl acetate (100 ml). The solution was washed with water (40 ml), 2% NaOH (3 × 40 ml), brine (40 ml) and dried over anhydrous Na_2SO_4. After the evaporation of the solvent under vacuum, the crude product was purified by flash chromatography over silica gel (MeOH/EtOAc = 1/10) to give *N*-benzyl-*N*′-[(*S*)-(1-Boc-pyrrolidin-2-yl)methyl]-sulfamide as a colorless oil (864 mg, 78% yield).

A solution of *N*-benzyl-*N*′-[(*S*)-(1-Boc-pyrrolidin-2-yl) methyl]-sulfamide (738 mg, 2 mmol), trifluoroacetic acid (2.4 ml) in CH_2Cl_2 (4 ml) was stirred at room temperature for 2 h. The mixture was basified with aqueous NaOH (2 M) and extracted with CH_2Cl_2 (4 × 20 ml). After the evaporation of the solvent under vacuum, the residue was purified through flash column chromatography over silica gel (EtOAc/ methanol/Et_3N = 70:10:1) to give **1b** as a white solid (403 mg, 75% yield).

Pyrrolidine-sulfamides **1a**, **1c**, and **1d** were prepared by similar procedures.

N-(2-Phenyl)ethyl-N-[(S)-(pyrrolidin-2-yl)methyl]-sulfamide (1a)

White solid, m.p. 109–110°C, $[\alpha]_D^{20}$ = 29.2 (c 0.25, CH_2Cl_2). ^{1}H NMR (400 MHz, CD_3OD): δ = 7.31–7.19 (m, 5H), 3.21–3.12 (m, 3H), 2.95–2.89 (m, 1H), 2.86–2.80 (m, 5H), 1.92–1.72 (m, 3H), 1.46–1.38 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ = 140.5, 130.0, 129.6, 127.5, 59.3, 47.5, 46.8, 45.5, 37.1, 30.0, 25.9; HRMS (ESI) calcd for $C_{13}H_{20}N_3O_2S$ $(M - H)^-$: 282.1276, found: 282.1281; IR (KBr): 3326, 2952, 2852, 1604, 1496, 1456, 1144, 701 cm^{-1}.

N-Benzyl-N-[(S)-(pyrrolidin-2-yl)methyl]-sulfamide (1b)

White solid, m.p. 96–97°C, $[\alpha]_D^{20}$ = 25.0 (c 0.28, CH_2Cl_2). ^{1}H NMR (400 MHz, CD_3OD): δ = 7.28–7.14 (m, 5H), 4.04 (s, 2H), 3.14–3.08 (m, 1H), 2.87–2.81 (m, 3H), 2.78–2.72 (m, 1H), 1.84–1.75 (m, 1H), 1.72–1.63 (m, 2H), 1.40–1.31 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ = 139.4, 129.6, 129.1, 128.5, 59.5, 47.7, 47.3, 46.8, 29.8, 25.7; HRMS (ESI) calcd for $C_{12}H_{18}N_3O_2S$ $(M - H)^-$: 268.1120, found: 268.1112; IR (KBr): 3285, 2966, 2867, 1496, 1456, 1147, 699 cm^{-1}.

N-[(R)-1-Methyl]benzyl-N-[(S)-(pyrrolidin-2-yl)methyl]-sulfamide (1c)

Colorless oil, $[\alpha]_D^{20}$ = 47.6 (c 0.21, CH_2Cl_2). ^{1}H NMR (400 MHz, CD_3OD): δ = 7.41–7.33 (m, 4H), 7.28–7.24 (m, 1H), 4.45 (q, *J* = 6.8 Hz, 1H), 3.04–2.97 (m, 1H), 2.90–2.75 (m, 3H), 2.70 (dd, *J* = 12.8, 5.6 Hz, 1H), 1.82–1.67 (m, 3H), 1.49 (d, *J* = 6.8 Hz, 3H), 1.35–1.28 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ = 144.1, 128.0, 126.7, 125.9, 57.6, 53.0, 46.0, 45.2, 28.3, 24.3, 22.9; HRMS (ESI) calcd for $C_{13}H_{20}N_3O_2S$ $(M - H)^-$: 282.1276, found: 282.1279; IR (KBr): 3289, 2972, 2874, 1634, 1541, 1493, 1151, 701 cm^{-1}.

N-[(S)-1-Methyl]benzyl-N-[(S)-(pyrrolidin-2-yl)methyl]-sulfamide (1d)

Colorless oil, $[\alpha]_D^{20}$ = 9.6 (c 0.25, CH_2Cl_2). ^{1}H NMR (400 MHz, CD_3OD): δ = 7.40–7.32 (m, 4H), 7.27–7.23 (m, 1H), 4.45 (q, *J* = 7.2 Hz, 1H), 3.14–3.11 (m, 1H), 2.91–2.81 (m, 3H), 2.71 (dd, *J* = 13.6, 7.2 Hz, 1H), 1.85–1.74 (m, 3H), 1.42 (d, *J* = 7.2 Hz, 3H), 1.42–1.37 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ = 145.6, 129.6, 128.3, 127.4, 59.4, 54.5, 47.0, 46.7, 29.7, 25.7, 24.4; HRMS (ESI) calcd for $C_{13}H_{20}N_3O_2S$ $(M - H)^-$: 282.1276, found: 282.1270; IR (KBr): 3282, 2973, 2875, 1681, 1495, 1455, 1151, 701 cm^{-1}.

Typical Procedure for Asymmetric Conjugate Addition of Ketones to Nitroalkenes

A solution of **1b** (11 mg, 0.04 mmol) and $PhCO_2H$ (5 mg, 0.04 mmol) in cyclohexanone (0.5 ml) was stirred for 15 min at 0°C, and then, β-nitrostyrene (30 mg, 0.2 mmol) was added. The reaction mixture was stirred at 0°C until complete consumption of β-nitrostyrene (as monitored by thin layer chromatography (TLC)). The mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography over silica gel (petroleum ether: EtOAc = 8:1) to give **3a** as a white solid (48 mg, 98% yield).

Products **3a–3n**, **4a–4f** are known compounds.[25,31] Their relative and absolute configurations were determined by comparison with the reported ^{1}H NMR spectra, chiral HPLC chromatogram, and optical rotations.

(S)-2-((R)-2-Nitro-1-phenylethyl)cyclohexanone (3a)

$[\alpha]_D^{20}$ = −15.7 (c 0.24, CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.24 (m, 3H), 7.18–7.15 (m, 2H), 4.93 (dd, *J* = 12.4, 4.4 Hz, 1H), 4.64 (dd, *J* = 12.4, 9.6 Hz, 1H), 3.76 (td, *J* = 10.0, 4.8 Hz, 1H), 2.72–2.65 (m, 1H), 2.51–2.34 (m, 2H), 2.12–2.04 (m, 1H), 1.81–1.52 (m, 4H), 1.29–1.19 (m, 1H). The enantiometric excess was determined by HPLC with a Chiralpak AS-H column (hexane:2-propanol = 80:20, λ = 208 nm, 1.0 ml/min); t_R (minor enantiomer) = 8.86 min, t_R (major enantiomer) = 12.16 min, 96% ee.

(S)-2-((R)-2-Nitro-1-p-tolylethyl)cyclohexanone (3b)

$[\alpha]_D^{20}$ = −15.3 (c 0.25, CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 4.91 (dd, *J* = 12.4, 4.8 Hz, 1H), 4.61 (dd, *J* = 12.4, 10.0 Hz, 1H), 3.72 (td, *J* = 10.0, 4.8 Hz, 1H), 2.72–2.63 (m, 1H), 2.50–2.34 (m, 2H), 2.31 (s, 3H), 2.10–2.04 (m, 1H), 1.81–1.55 (m, 4H), 1.27–1.18 (m, 1H). The enantiometric excess was determined by HPLC with a Chiralpak AS-H column (hexane:2-propanol = 80:20, λ = 208 nm, 1.0 ml/min); t_R (minor enantiomer) = 8.35 min, t_R (major enantiomer) = 13.74 min, 90% ee.

(S)-2-((R)-1-(4-Methoxyphenyl)-2-nitroethyl) cyclohexanone (3c)

$[\alpha]_D^{20}$ = − 12.1 (c 0.25, CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 4.91 (dd, *J* = 12.4, 4.8 Hz, 1H), 4.58 (dd, *J* = 12.4, 10.0 Hz, 1H), 3.78 (s, 3H), 3.71 (td, *J* = 10.0, 4.8 Hz, 1H), 2.67–2.61 (m, 1H), 2.49–2.34 (m, 2H), 2.11–2.04 (m, 1H), 1.81–1.52 (m, 4H), 1.28–1.19 (m, 1H). The enantiometric excess was determined by HPLC with a Chiralpak AS-H column (hexane:2-propanol = 80:20, λ = 208 nm, 1.0 ml/min); t_R (minor enantiomer) = 16.26 min, t_R (major enantiomer) = 23.67 min, 97% ee.

(S)-2-((R)-1-(4-Florophenyl)-2-nitroethyl) cyclohexanone (3d)

$[\alpha]_D^{20}$ = − 13.2 (c 0.28, CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16–7.13 (m, 2H), 7.04–7.00 (m, 2H), 4.93 (dd, *J* = 12.4, 4.4 Hz, 1H), 4.60 (dd, *J* = 12.4, 10.0 Hz, 1H), 3.77 (td, *J* = 10.0, 4.8 Hz, 1H), 2.69–2.62 (m, 1H), 2.50–2.32 (m, 2H), 2.12–2.06 (m, 1H), 1.87–1.56 (m, 4H), 1.27–1.18 (m, 1H). The enantiometric excess was determined by HPLC with a Chiralpak AS-H column (hexane:2-propanol = 90:10, λ = 208 nm, 1.0 ml/min); t_R (minor enantiomer) = 16.92 min, t_R (major enantiomer) = 26.25 min, 91% ee.

(S)-2-((R)-1-(4-Chlorophenyl)-2-nitroethyl) cyclohexanone (3e)

$[\alpha]_D^{20}$ = − 15.7 (c 0.24, CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 4.93 (dd, *J* = 12.6, 4.4 Hz, 1H), 4.61 (dd, *J* = 12.6, 10.0 Hz, 1H), 3.76 (td, *J* = 10.0, 4.8 Hz, 1H), 2.69–2.62 (m, 1H), 2.51–2.45 (m, 1H), 2.42–2.34 (m, 1H), 2.13–2.06 (m, 1H), 1.83–1.55 (m, 4H), 1.28–1.18 (m, 1H). The enantiometric excess was determined by HPLC with a Chiralpak AS-H column (hexane:2-propanol = 80:20, λ = 208 nm, 1.0 ml/min); t_R (minor enantiomer) = 10.29 min, t_R (major enantiomer) = 16.83 min, 94% ee.

(S)-2-((R)-1-(4-Bromophenyl)-2-nitroethyl) cyclohexanone (3f)

$[\alpha]_D^{20} = -12.3$ (c 0.24, CH_2Cl_2), ^1H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 4.93 (dd, *J* = 12.4, 4.4 Hz, 1H), 4.60 (dd, *J* = 12.4, 10.0 Hz, 1H), 3.75 (td, *J* = 10.0, 4.4 Hz, 1H), 2.68–2.61 (m, 1H), 2.51–2.49 (m, 1H), 2.38–2.33 (m, 1H), 2.13–2.06 (m, 1H), 1.83–1.52 (m, 4H), 1.28–1.18 (m, 1H). The enantiometric excess was determined by HPLC with a Chiralpak AS-H column (hexane:2-propanol = 90:10, λ = 208 nm, 1.0 ml/min); t_R (minor enantiomer) = 16.34 min, t_R (major enantiomer) = 28.70 min, 93% ee.

(S)-2-((R)-1-(3-Chlorophenyl)-2-nitroethyl) cyclohexanone (3g)

$[\alpha]_D^{20} = -13.1$ (c 0.58, CH_2Cl_2), ^1H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.25 (m, 2H), 7.18–7.17 (m, 1H), 7.09–7.06 (m, 1H), 4.94 (dd, *J* = 12.8, 4.4 Hz, 1H), 4.61 (dd, *J* = 12.8, 10.0 Hz, 1H), 3.76 (td, *J* = 10.0, 4.4 Hz, 1H), 2.69–2.63 (m, 1H), 2.51–2.34 (m, 2H), 2.11–2.07 (m, 1H), 1.83–1.68 (m, 2H), 1.67–1.60 (m, 2H), 1.29–1.19 (m, 1H). The enantiometric excess was determined by HPLC with a Chiralpak AS-H column (hexane:2-propanol = 80:20, λ = 208 nm, 1.0 ml/min); t_R (minor enantiomer) = 10.34 min, t_R (major enantiomer) = 17.49 min, 91% ee.

(S)-2-((R)-1-(2,4-Dichlorophenyl)-2-nitroethyl)cyclohexanone (3h)

$[\alpha]_D^{20} = -41.0$ (c 0.26, CH_2Cl_2), ^1H NMR (400 MHz, $CDCl_3$) δ = 7.41 (d, *J* = 2.1 Hz, 1H), 7.25–7.17 (m, 2H), 4.92–4.87 (m, 2H), 4.27–4.21 (m, 1H), 2.91–2.84 (m, 1H), 2.51–2.45 (m, 1H), 2.42–2.32 (m, 1H), 2.14–2.09 (m, 1H), 1.88–1.81 (m, 1H), 1.77–1.58 (m, 3H), 1.39–1.26 (m, 1H). The enantiometric excess was determined by HPLC with a Chiralpak AD-H column (hexane:2-propanol = 90:10, λ = 208 nm, 1.0 ml/min); t_R (minor enantiomer) = 8.31 min, t_R (major enantiomer) = 10.67 min, 93% ee.

(S)-2-((R)-1-(2-Bromophenyl)-2-nitroethyl) cyclohexanone (3i)

$[\alpha]_D^{20} = -12.1$ (c 0.25, CH_2Cl_2), ^1H NMR (400 MHz, $CDCl_3$): δ =7.58 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.32–7.28 (m, 1H), 7.22 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.13 (td, *J* = 7.6, 1.6 Hz, 1H), 4.96–4.85 (m, 2H), 4.33–4.28 (m, 1H), 2.91 (s, 1H), 2.51–2.32 (m, 3H), 2.14–2.08 (m, 1H), 1.90–1.65 (m, 4H), 1.43–1.26 (m, 1H). The enantiometric excess was determined by HPLC with a Chiralpak AS-H column (hexane:2-propanol = 90:10, λ = 208 nm, 0.8 ml/min); t_R (minor enantiomer) = 17.95 min, t_R (major enantiomer) = 23.55 min, 95% ee.

(S)-2-((R)-2-Nitro-1-(2-nitrophenyl)ethyl) cyclohexanone (3j)

$[\alpha]_D^{20} = -54.2$ (c 0.38, CH_2Cl_2), ^1H NMR (400 MHz, $CDCl_3$): δ = 7.84 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.59 (td, *J* = 7.6, 1.2 Hz, 1H), 7.47–7.42 (m, 2H), 4.98–4.90 (m, 2H), 4.33 (td, *J* = 8.8, 5.2 Hz, 1H), 2.98–2.91 (m, 1H), 2.50–2.35 (m, 2H), 2.15–2.09 (m, 1H), 1.87–1.79 (m, 2H), 1.72–1.43 (m, 3H). The enantiometric excess was determined by HPLC with a Chiralpak AD-H column (hexane:2-propanol = 95:5, λ = 208 nm, 0.9 ml/min); t_R (minor enantiomer) = 34.23 min, t_R (major enantiomer) = 47.31 min, 95% ee.

(S)-2-((R)-1-(Naphthalen-1-yl)-2-nitroethyl) cyclohexanone (3k)

$[\alpha]_D^{20} = -73.8$ (c 0.26, CH_2Cl_2), ^1H NMR (400 MHz, $CDCl_3$): δ = 8.16 (s, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.60–7.36 (m, 4H), 5.07 (dd, *J* = 12.8, 4.4 Hz, 1H), 4.91 (dd, *J* = 12.8, 9.6 Hz, 1H), 4.76 (s, 1H), 2.87 (s, 1H), 2.53–2.38 (m, 2H), 2.11–2.05 (m, 1H), 1.73–1.50 (m, 4H), 1.30–1.20 (m, 1H). The enantiometric excess was determined by HPLC with a Chiralpak AS-H column (hexane:2-propanol = 70:30, λ = 208 nm, 0.7 ml/min); t_R (minor enantiomer) = 14.64 min, t_R (major enantiomer) = 20.58 min, 93% ee.

(S)-2-((S)-1-(Furan-2-yl)-2-nitroethyl)cyclohexanone (3l)

$[\alpha]_D^{20} = -7.5$ (c 0.24, CH_2Cl_2), ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.33 (m, 1H), 6.29–6.28 (m, 1H), 6.18 (d, *J* = 3.2Hz, 1H), 4.79 (dd, *J* = 12.4, 4.8 Hz, 1H), 4.67 (dd, *J* = 12.4, 9.2 Hz, 1H), 3.97 (td, *J* = 9.2, 4.8 Hz, 1H), 2.79–2.72 (m, 1H), 2.48–2.32 (m, 2H), 2.13–2.07 (m, 1H), 1.85–1.83 (m, 1H), 1.79–1.73 (m, 1H), 1.68–1.62 (m, 2H), 1.34–1.23 (m, 1H). The enantiometric excess was determined by HPLC with a Chiralpak AS-H column (hexane:2-propanol = 90:10, λ = 208 nm, 0.7 ml/min); t_R (major enantiomer) = 13.24 min, t_R (minor enantiomer) = 15.81 min, 91% ee.

(S)-2-((S)-2-Nitro-1-(thiophen-2-yl)ethyl)cyclohexanone (3m)

$[\alpha]_D^{20} = -14.5$ (c 0.25, CH_2Cl_2), ^1H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.21 (m, 1H), 6.93 (dd, *J* = 4.8, 3.2 Hz, 1H), 6.88–6.87 (m, 1H), 4.89 (dd, *J* = 12.8, 4.8 Hz, 1H), 4.65 (dd, *J* = 12.8, 9.2 Hz, 1H), 4.13 (td, *J* = 9.2, 4.8 Hz, 1H), 2.72–2.65 (m, 1H), 2.49–2.33 (m, 2H), 2.13–2.08 (m, 1H), 1.93–1.82 (m, 2H), 1.71–1.57 (m, 2H), 1.38–1.28 (m, 1H). The enantiometric excess was determined by HPLC with a Chiralpak AD-H column (hexane:2-propanol = 95:5, λ = 208 nm, 1.0 ml/min); t_R (minor enantiomer) = 15.49 min, t_R (major enantiomer) = 17.80 min, 89% ee.

(S)-2-((S)-3-Methyl-1-nitrobutan-2-yl)cyclohexanone (3n)

$[\alpha]_D^{20} = -6.3$ (c 0.25, CH_2Cl_2), ^1H NMR (400 MHz, $CDCl_3$): δ = 4.64 (dd, *J* = 13.6, 5.6 Hz, 1H), 4.36 (dd, *J* = 13.6, 4.8 Hz, 1H), 2.66–2.61 (m, 1H), 2.42–2.29 (m, 3H), 2.14–2.06 (m, 2H), 1.97–1.89 (m, 2H), 1.74–1.58 (m, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H). The enantiometric excess was determined by HPLC with a Chiralpak AD-H column (hexane:2-propanol = 90:10, λ = 208 nm, 1.0 ml/min); t_R (minor enantiomer) = 5.93 min, t_R (major enantiomer) = 6.90 min, 95% ee.

(R)-Tetrahydro-3-((R)-2-nitro-1-phenylethyl) pyran-4-one (4a)

$[\alpha]_D^{20} = -24.2$ (c = 0.55, CH_2Cl_2), ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.28 (m, 3H), 7.20–7.18 (m, 2H), 4.93 (dd, *J* = 12.8, 4.4 Hz, 1H), 4.65 (dd, *J* = 12.8, 10.0 Hz, 1H), 4.17–4.11 (m, 1H), 3.86–3.74 (m, 2H), 3.70 (ddd, *J* = 11.6, 5.6, 1.2 Hz, 1H), 3.27 (dd, *J* = 11.6, 8.8 Hz, 1H), 2.91–2.85 (m, 1H), 2.70–2.63 (m, 1H), 2.59–2.54 (m, 1H).The enantiometric excess was determined by HPLC with a Chiralpak AD-H column (hexane:2-propanol = 90:10, λ = 208 nm, 1.0 ml/min); t_R (minor enantiomer) = 11.49 min, t_R (major enantiomer) = 19.79 min, 70% ee.

(4S, 5R)-4-Methyl-6-nitro-5-phenylhexan-3-one (4b)

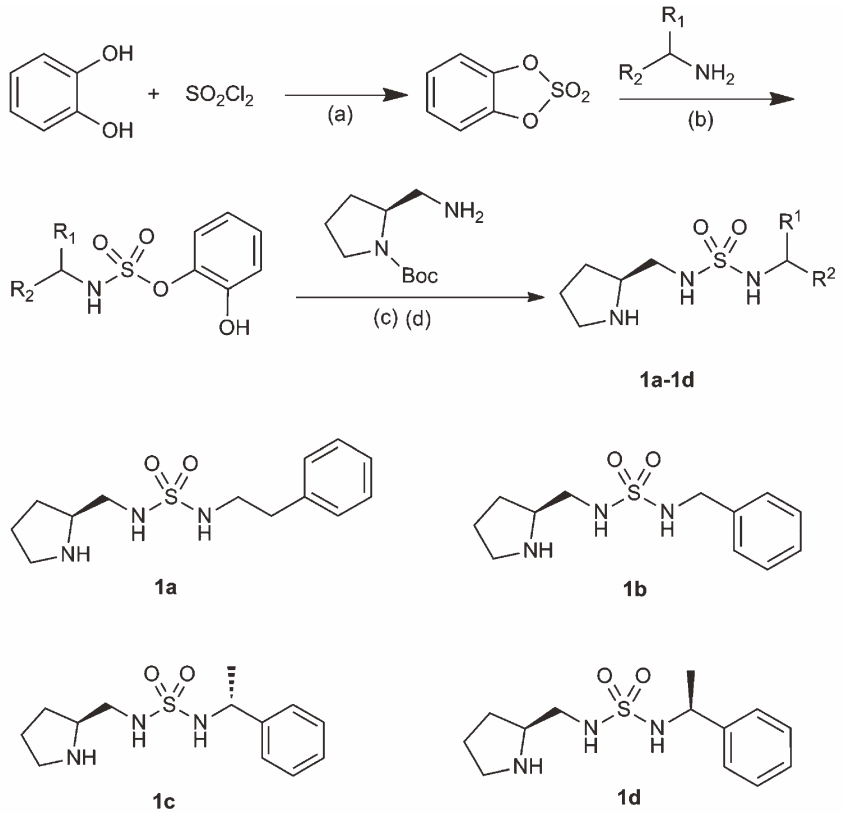
$[\alpha]_D^{20} = 7.5$ (c = 0.12, CH_2Cl_2), ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.28 (m, 3H), 7.17–7.15 (m, 2H), 4.67 (dd, *J* = 12.4, 8.8 Hz, 1H), 4.60 (dd, *J* = 12.4, 4.8 Hz, 1H), 3.70 (td, *J* = 9.2, 4.8 Hz, 1H), 3.02–2.96 (m, 1H), 2.66–2.56 (m, 1H), 2.46–2.36 (m, 1H), 1.07 (t, *J* = 7.2 Hz, 3H), 0.97 (d, *J* = 7.2 Hz, 3H). The enantiometric excess was determined by HPLC with a Chiralpak OD-H column (hexane:2-propanol = 97:3, λ = 210 nm, 0.5 ml/min); t_R (major enantiomer) = 42.05 min, t_R (minor enantiomer) = 53.73 min, 92% ee.

(R)-5-Nitro-4-phenylpentan-2-one (4c)

$[\alpha]_D^{20} = -4.5$ (c 0.24, CH_2Cl_2), ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.02 (m, 5H), 4.69 (dd, *J* = 12.4, 6.8 Hz, 1H), 4.60 (dd, *J* = 12.4, 7.6 Hz, 1H), 4.04–3.97 (m, 1H), 2.92 (d, *J* = 6.8 Hz, 2H), 2.11 (s, 3H). The enantiometric excess was determined by HPLC with a Chiralpak AS-H column (hexane:2-propanol = 80:20, λ = 208 nm, 1.0 ml/min); t_R (minor enantiomer) = 13.28 min, t_R (major enantiomer) = 14.64 min, 48% ee.

(3S, 4R)-3-Hydroxy-5-nitro-4-phenylpentan-2-one (4d)

^1H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.17 (m, 5H + 3H*), 5.03 (dd, *J* = 13.3, 8.0 Hz, 1H), 4.82 (dd, *J* = 13.6, 6.4 Hz, 0.57H*), 4.73 (dd, *J* = 13.6, 7.2 Hz, 1H), 4.65 (dd, *J* = 13.6, 8.0 Hz, 0.57H*), 4.53–4.51 (m, 1H), 4.40–4.38 (m, 0.5H*), 4.03 (td, *J* = 7.6, 2.8 Hz, 1H), 3.85–3.81 (m, 0.57H*), 3.72–3.71 (m, 1H + 0.56H*), 2.18 (s, 3H), 2.07 (s, 1.6H*). The enantiometric excess was determined by HPLC with a Chiralpak AD-H column (hexane:2-propanol = 90:10, λ = 220 nm, 1.0 ml/min); (major



Scheme 1. Synthesis of pyrrolidine-sulfamides **1a–1d**. Reaction conditions: (**a**) pyridine, hexane, ice-bath, 1 day; (**b**) Et_3N, CH_2Cl_2; (**c**) dioxane, reflux, 2.5 h; and (**d**) TFA, CH_2Cl_2.

isomer) t_{minor}= 20.46 min, t_{major} = 43.00 min, 28% ee; (minor isomer) t_{minor} = 21.04 min, t_{major} = 26.63 min, 10% ee.

(R)-2,2-Dimethyl-4-nitro-3-phenylbutanal (4f)

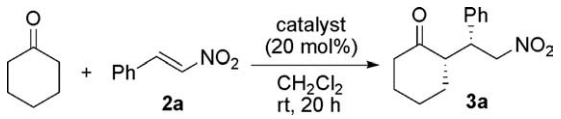
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.29 (m, 3H), 7.21–7.19 (m, 2H), 4.85 (dd, *J* = 12.8, 11.2 Hz, 1H), 4.69 (dd, *J* = 12.8, 4.0 Hz, 1H), 3.78 (dd, *J* = 11.2, 4.4 Hz, 1H), 1.14 (s, 3H), 1.01 (s, 3H). The enantiometric excess was determined by HPLC with a Chiralpak OD-H column (hexane:2-propanol = 80:20, λ = 210 nm, 0.8 ml/min); t_R (major enantiomer) = 18.88 min, t_R (minor enantiomer) = 26.53 min, 72% ee.

RESULTS AND DISCUSSION

Pyrrolidine-sulfamides **1a–1d** were prepared in good yields via stepwise reactions of amines and (*S*)-*N*-Boc-2-aminomethyl-pyrrolidine with catechol sulfate (Scheme 1).[16,48,49] The conjugate addition of cyclohexanone to *trans*-β-nitrostyrene (**2a**) was examined using **1a–1d** as the catalysts, and the results are summarized in Table 1. The catalyst **1a** provided the expected product **3a** in good yield and enantioselectivity (Table 1, entry 1). Slightly better enantioselectivity was achieved with the catalyst **1b** (Table 1, entry 2). The catalysts **1c** and **1d**, which are derived from (*R*)- and (*S*)-1-phenylethylamine, respectively, afforded **3a** in the same absolute configurations, and with similar yields and enantioselectivities (Table 1, entries 3–4). The result suggests that the enantioselectivity of the reaction is mainly controlled by chiral pyrrolidine unit and the additional chiral center at the side chain only exerts neglectable effects.

A number of reaction solvents were screened using **1b** as the catalyst and the results are listed in Table 2. $CHCl_3$ provided similar result with CH_2Cl_2 (Table 2, entry 2). Hexane afforded for slightly lower yield and enantioselectivity (Table 2, entry 3). Toluene gave better yield, however with moderate enantioselectivity (Table 2, entry 4). The reaction did not occur in isopropanol (Table 2, entry 5). Interestingly better yield and enantioselectivity were obtained in neat cyclohexanone; in addition, the reaction became faster (Table 2, entry 6). Furthermore, the effect of acid additives was studied (Table 2, entries 7–9). $PhCO_2H$ significantly accelerated the reaction and provided **3a** in excellent yield and enantioselectivity (Table 2, entry 7). CH_3CO_2H is less efficient than PhCOOH (Table 2, entry 8). On the other hand, the reaction was inhibited completely while CF_3CO_2H was

TABLE 1. Screening of pyrrolidine-sulfamides 1a–1d[a]



Entry	Catalyst	Yield (%)[b]	*Dr*[c] (*syn*:*trans*)	*Ee* (%)[d,e] *syn*
1	**1a**	82	94:6	89
2	**1b**	79	96:4	92
3	**1c**	76	96:4	91
4	**1d**	73	97:3	89

[a]The reactions were performed with cyclohexanone (1.60 mmol), **2a** (0.20 mmol), and **1a–1d** (0.04 mmol) in CH_2Cl_2 (0.5 ml) at room temperature for 20 h.
[b]Isolated yields.
[c]Determined by ^{1}H NMR analysis.
[d]Determined by chiral HPLC analysis.
[e]The absolute configuration of **3a** was assigned as (1′*R*, 2*S*) by comparing the optical rotation with the reported data.[25]

TABLE 2. Effect of reaction solvents, additives, and temperature[a]

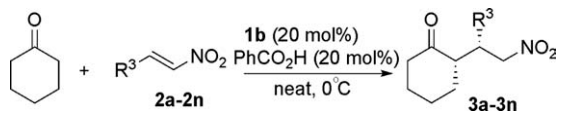
Entry	Solvent	Additive	Time (h)	Yield (%)	*Dr* (*syn*:*trans*)	*Ee* (%) *syn*
1	CH_2Cl_2	–	20	79	96:4	92
2	$CHCl_3$	–	20	78	96:4	93
3	Hexane	–	20	74	95:5	90
4	Toluene	–	20	88	93:7	84
5	^{i}PrOH	–	20	trace	–	–
6[b]	–	–	11	80	95:5	94
7[b]	–	$PhCO_2H$	6	98	96:4	94
8[b]	–	CH_3CO_2H	6	90	94:6	91
9[b]	–	CF_3CO_2H	20	trace	–	–
10[b,c]	–	$PhCO_2H$	12	98	97:3	96
11[b,d]	–	$PhCO_2H$	22	91	96:4	95

[a]The reactions were performed with cyclohexanone (1.60 mmol), **2a** (0.20 mmol), **1b** (0.04 mmol), and the additive (0.04 mmol) in solvent (0.5 ml) at room temperature.
[b]Cyclohexanone (0.5 ml) was used.
[c]The reaction was performed at 0°C.
[d]10 mol % **1b** was used.

used as the additive (Table 2, entry 9). The decrease of reaction temperature resulted in better enantioselectivity and diastereoselectivity (Table 2, entry 10). The loading of **1b** could be reduced to 10 mol % without the erosion of enantioselectivity, however lower yield was obtained (Table 2, entry 11).

The reaction of cyclohexanone with a variety of β-aryl-nitroethylenes was examined, and the results are summarized in Table 3. Excellent yields, enantioselectivities, and diastereoselectivities were generally achieved for *ortho*-, *meta*-, and *para*-substituted β-nitrostyrenes (Table 3, entries 1–10). Both electron-withdrawing groups and electron-donating groups were tolerated very well. In addition, β-naphthyl-nitroethylene and β-heteroaryl nitroethylenes also provided the products in excellent yields and enantioselectivities (Table 3, entries 11–13). β-Isopropyl nitroethylene showed lower reactivity than β-aryl-nitroethylenes. After extended reaction time, the corresponding product could be obtained in excellent enantioselectivity and good yield (Table 3, entry 14).

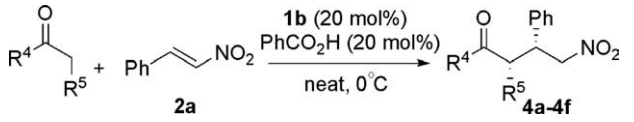
TABLE 3. Reaction of β-aryl-nitroethylenes with cyclohexanone catalyzed by 1b[a]

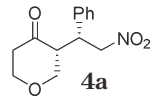
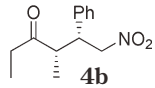
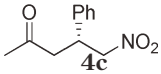
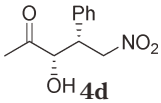
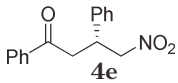
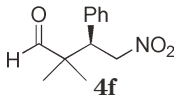


Entry	R^3	Time (h)	Product	Yield (%)[b]	*Dr*[c] (*syn*:*trans*)	*Ee* (%)[d] *syn*
1	Ph	12	**3a**	98	97:3	96
2	4-Me-C_6H_4	12	**3b**	99	96:4	90
3	4-MeO-C_6H_4	14	**3c**	99	98:2	97
4	4-F-C_6H_4	12	**3d**	99	95:5	91
5	4-Cl-C_6H_4	12	**3e**	96	97:3	94
6	4-Br-C_6H_4	11	**3f**	97	95:5	93
7	3-Cl-C_6H_4	12	**3g**	92	93:7	91
8	2,4-diCl-C_6H_4	11	**3h**	98	98:2	93
9	2-Br-C_6H_4	12	**3i**	99	97:3	95
10	2-NO_2-C_6H_4	11	**3j**	99	99:1	95
11	1-Naphthyl	13	**3k**	95	99:1	93
12	2-Furanyl	12	**3l**	96	92:8	91
13	2-Thiophenyl	12	**3m**	98	89:11	89
14	2-Propyl	108	**3n**	78	99:1	95

[a]The reactions were performed with cyclohexanone (0.5 ml), **2a** (0.2 mmol), $PhCO_2H$ (0.04 mmol), and **1b** (0.04 mmol), at 0°C under solvent free condition.
[b]Isolated yields.
[c]Determined by ^{1}H NMR analysis.
[d]Determined by chiral HPLC analysis.

TABLE 4. Reaction of ketones and isobutyraldehyde with β-nitrostyrene[a]

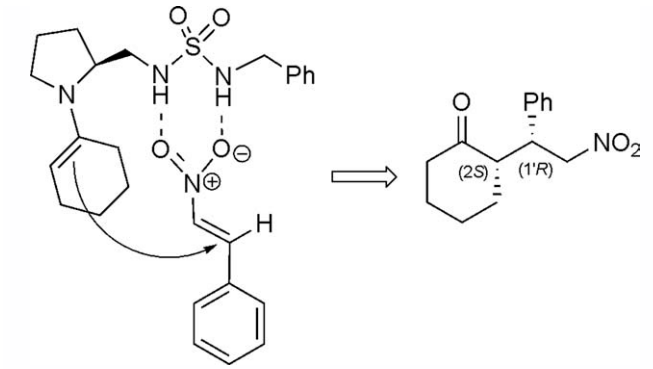


Entry	Product	Time (h)	Yield (%)[b]	*Dr*[c] (*syn*:*trans*)	*Ee* (%)[d] *syn*
1	 **4a**	14	94	99:1	70
2	 **4b**	5d	34	99:1	92
3	 **4c**	15	85	–	48
4	 **4d**	24	94	65:35	28/10
5	 **4e**	120	–	–	–
6[e]	 **4f**	144	40	–	72

[a]The reactions were performed with ketones or isobutyraldehyde (0.5 mL), **2a** (0.2 mmol), $PhCO_2H$ (0.04 mmol), and **1b** (0.04 mmol) at 0°C under solvent free condition.
[b]Isolated yields.
[c]Determined by ^{1}H NMR analysis.
[d]Determined by chiral HPLC analysis.
[e]The reaction was performed at room temperature.

Several other ketones and isobutyraldehyde were also examined in the reaction with β-nitrostyrene, and the results are summarized in Table 4. 4-Oxo-cyclohexanone provided the product in good yield and excellent diastereoselectivity, however with moderate enantioselectivity (Table 4, entry 1). Good yield, diastereoselectivity, and enantioselectivity were achieved for pentan-3-one (Table 4, entry 2). Acetone could also be used in the reaction, but the enantioselectivity is low (Table 4, entry 3). Even lower enantioselectivity was observed for the reaction of 2-hydroxy acetone (Table 4, entry 4). Acetophenone was found to be unreactive under these conditions (Table 4, entry 5). The reaction of isobutyraldehyde provided the product in low yield and with moderate enantioselectivity (Table 4, entry 6).

A reaction transition state is proposed (Scheme 2).[25] The enamine intermediate is generated from the reaction of cyclohexanone and the catalyst **1b**. The H-bonding interac-



Scheme 2. Proposed reaction transition state.

tion between the sulfamide and nitro group increases the electrophilic reactivity of β-nitrostyrene and also provides a preorganized transition state. The consequent attack of enamine intermediate occurs from the *Re*-face of the double bond. (1′*R*, 2*S*)-**3a** is thus obtained with excellent enantioselectivity and diastereoselectivity.

CONCLUSION

In conclusion, we have developed novel chiral pyrrolidine-sulfamides as efficient organocatalysts for the conjugate addition of ketones to nitroalkenes. Excellent enantioselectivities, diastereoselectivities, and yields were achieved for the reaction of cyclohexanone with β-aryl nitroethylenes under solvent free conditions. The substitutions with various electron-withdrawing and electron-donating groups were tolerated very well. β-Alkyl nitroethylene also provided the product with excellent enantioselectivity after extended reaction time. The capability of enantioselective induction of pyrrolidine-sulfamide catalysts is originated from their chiral pyrrolidine units. The chiral center at the side chain does not exert favorable effect on the enantioselectivity. The H-bonding interaction between the sulfamide unit and the nitro group is proposed to be important for the activation of the nitroalkene and the constitution of well organized transition state. Further applications of these novel organocatalysts in other asymmetric transformations are currently under investigation.

LITERATURE CITED

1. Bertelsen S. Jørgensen KA. Organocatalysis-after the gold rush. Chem Soc Rev 2009;36:2178–2189.
2. Guillena G, Nájera C, Ramón DJ. Enantioselective direct aldol reaction: the blossoming of modern organocatalysis. Tetrahedron: Asymmetry 2007;18:2249–2293.
3. Dalko PI. Enantioselective organocatalysis. Weinheim: Wiley-VCH; 2007.
4. Pellissier H. Asymmetric organocatalysis. Tetrahedron 2007;63:9267–9331.
5. Dondoni A, Massi A. Asymmetric organocatalysis: from infancy to adolescence. Angew Chem Int Ed Engl 2008;47:4638–4660.
6. List B. The ying and yang of asymmetric aminocatalysis. Chem Commun 2006:819–824.
7. Barbas CF III. Organocatalysis lost: modern chemistry, ancient chemistry, and an unseen biosynthetic apparatus. Angew Chem Int Ed Engl 2008;47:42–47.
8. Melchiorre P, Marigo M, Carlone A, Bartoli G. Asymmetric aminocatalysis–gold rush in organic chemistry. Angew Chem Int Ed Engl 2008;47:6138–6171.
9. Connon SJ. Organocatalysis mediated by (thio)urea derivatives. Chem Eur J 2006;12:5418–5427.
10. Taylor MS, Jacobsen EN. Asymmetric catalysis by chiral hydrogen-bond donors. Angew Chem Int Ed Engl 2006;45:1520–1543.
11. Ishihara K, Sakakura A, Hatano M. Design of highly functional small-molecule catalysts and related reactions based on acid-base combination chemistry. Synlett 2007;5:686–702.
12. Schreiner PR. Metal-free organocatalysis through explicit hydrogen bonding interactions. Chem Soc Rev 2003;32:289–296.
13. Zhang ZG, Schreiner PR. (Thio)urea organocatalysis—what can be learnt from anion recognition? Chem Soc Rev 2009;38:1187–1198.
14. Yu XH, Wang W. Hydrogen-bond-mediated asymmetric catalysis. Chem Asian J 2008;3:516–532.
15. Doyle AG, Jacobsen EN. Small-molecule H-bond donors in asymmetric catalysis. Chem Rev 2007;107:5713–5743.
16. Zhang XJ, Liu SP, Li XM, Yan M, Chan ASC. Highly enantioselective conjugate addition of aldehydes to nitroolefins catalyzed by chiral bifunctional sulfamides. Chem Commun 2009;7:833–835.
17. Liu SP, Zhang XJ, Lao JH, Yan M. Asymmetric conjugate addition of ketone to nitroalkenes catalyzed by chiral bifunctional sulfamides. ARKIVOC 2009;7:268–280.
18. Lao JH, Zhang XJ, Wang JJ, Li XM, Yan M, Luo HB. The effect of hydrogen bond donors in asymmetric organocatalytic conjugate additions. Tetrahedron: Asymmetry 2009;20:2818–2822.
19. Berner OM, Tedeschi L, Enders D. Asymmetric Michael additions to nitroalkenes. Eur J Org Chem 2002;1877.
20. Sulzer-Mossé S, Alexakis A. Chiral amines as organocatalysts for asymmetric conjugate addition to nitroolefins and vinyl sulfones *via* enamine activation. Chem Commun 2007;3123–3135.
21. Clarke ML, Fuentes JA. Self-assembly of organocatalysts: fine-tuning organocatalytic reactions. Angew Chem Int Ed Engl 2007;46:930–933.
22. Almaşi D, Alonso DA, Gómez-Bengoa E, Nagel Y, Nájera C. Asymmetric conjugate addition of ketones to β-nitrostyrenes by means of 1,2-amino-alcohol-derived prolinamides as bifunctional catalysts. Eur J Org Chem 2007;14:2328–2343.
23. Freund M, Schenker S, Tsogoeva SB. Enantioselective nitro-Michael reactions catalyzed by short peptides on water. Org Biomol Chem 2009;7:4279–4284.
24. Chen JR, Lai YY, Lu HH, Wang XF, Xiao WJ. Highly enantioselective desymmetrization of meso- and prochiral cyclic ketones via organocatalytic Michael reaction. Tetrahedron 2009;65:9238–9243.
25. Cao CL, Ye MC, Sun XL, Tang Y. Pyrrolidine−thiourea as a bifunctional organocatalyst: highly enantioselective Michael addition of cyclohexanone to nitroolefins. Org Lett 2006;8:2901–2904.
26. Shen ZX, Zhang YQ, Jiao CJ, Li B, Ding J, Zhang YW. Enantioselective and diastereoselective Michael addition of ketone/aldehyde to trans-nitroolefins catalyzed by a novel chiral pyrrolidine-thiourea. Chirality 2007;19:307–312.
27. Lu AD, Gao P, Wu Y, Wang YM, Zhou ZH, Tang CC. Highly enantio- and diastereoselective Michael addition of cyclohexanone to nitroolefins catalyzed by a chiral glucose-based bifunctional secondary amine-thiourea catalyst. Org Biomol Chem 2009;7:3141–3147.
28. Chen JR, Gao YJ, Zou YQ, Tan F, Fu L, Zhu XY, Xiao WJ. Novel thiourea-amine bifunctional catalysts for asymmetric conjugate addition of ketones/aldehydes to nitroalkenes: rational structural combination for high catalytic efficiency. Org Biomol Chem 2010;8:1275–1279.
29. Cao YJ, Lai YY, Wang X, Li YJ, Xiao WJ. Michael additions in water of ketones to nitroolefins catalyzed by readily tunable and bifunctional pyrrolidine-thiourea organocatalysts. Tetrahedron Lett 2007;48:21–24.
30. Wang W, Wang J, Li H. Direct, highly enantioselective pyrrolidine sulfonamide catalyzed Michael addition of aldehydes to nitrostyrenes. Angew Chem Int Ed Engl 2005;44:1369–1371.
31. Wang J, Li H, Lou B, Zu LS, Guo H, Wang W. Enantio- and diastereoselective Michael addition reactions of unmodified aldehydes and ketones with nitroolefins catalyzed by a pyrrolidine sulfonamide. Chem Eur J 2006;12:4321–4332.
32. Ni BK, Zhang QY, Headley AD. Functionalized chiral ionic liquid as recyclable organocatalyst for asymmetric Michael addition to nitrostyrenes. Green Chem 2007;9:737–739.
33. Zhang QY, Ni BK, Headley AD. Asymmetric Michael addition reactions of aldehydes with nitrostyrenes catalyzed by functionalized chiral ionic liquids. Tetrahedron 2008;64:5091–5097.
34. Ni BK, Zhang QY, Headley AD. Highly enantioselective Michael addition of ketones to nitroolefins catalyzed by (S)-pyrrolidine arenesulfonamide. Tetrahedron: Asymmetry 2007;18:1443–1447.

35. Ni BK, Zhang QY, Dhungana K, Headley AD. Ionic liquid-supported (ILS) (S)-pyrrolidine sulfonamide, a recyclable organocatalyst for the highly enantioselective Michael addition to nitroolefins. Org Lett 2009;11:1037–1040.
36. Wang C, Yu C, Liu CL, Peng YG. 4-Trifluoromethanesulfonamidyl prolinol tert-butyldiphenylsilyl ether as a highly efficient bifunctional organocatalyst for Michael addition of ketones and aldehydes to nitroolefins. Tetrahedron Lett 2009;50:2363–2366.
37. Mandal T, Zhao CG. Synthesis of prolinal dithioacetals as catalysts for the highly stereoselective Michael addition of ketones and aldehydes to β-nitrostyrenes. Tetrahedron Lett 2007;48:5803–5806.
38. Xu DQ, Wang LP, Luo SP, Wang YF, Zhang S, Xu ZY. 2-[(Imidazolylthio)-methyl]pyrrolidine as a trifunctional organocatalyst for the highly asymmetric Michael addition of ketones to nitroolefins. Eur J Org Chem 2008;6:1049–1053.
39. Li PH, Wang L, Wang M, Zhang YC. Polymer-immobilized pyrrolidine-based chiral ionic liquids as recyclable organocatalysts for asymmetric Michael additions to nitrostyrenes under solvent-free reaction conditions. Eur J Org Chem 2008;7:1157–1160.
40. Ishii T, Fujioka S, Sekiguchi Y, Kotsuki H. A new class of chiral pyrrolidine−pyridine conjugate base catalysts for use in asymmetric Michael addition reaction. J Am Chem Soc 2004;126:9558–9559.
41. Tan B, Zeng XF, Lu YP, Chua PJ, Zhong GF. Rational design of organocatalyst: highly stereoselective Michael addition of cyclic ketones to nitroolefins. Org Lett 2009;11:1927–1930.
42. Vishnumaya , Singh VK. Highly enantioselective water-compatible organocatalyst for Michael reaction of ketones to nitroolefins. Org Lett 2007;9:1117–1119.
43. Chen HB, Wang Y, Wei SY, Sun J. L-Proline derived triamine as a highly stereoselective organocatalyst for asymmetric Michael addition of cyclohexanone to nitroolefins. Tetrahedron: Asymmetry 2007;18:1308–1312.
44. Luo SZ, Mi XL, Zhang L, Liu S, Xu H, Cheng JP. Functionalized chiral ionic liquids as highly efficient asymmetric organocatalysts for Michael addition to nitroolefins. Angew Chem Int Ed Engl 2006;45:3093–3097.
45. Mase N, Watanabe K, Yoda H, Takabe K, Tanaka F, Barbas CF III. Organocatalytic direct Michael reaction of ketones and aldehydes with β-nitrostyrene in brine. J Am Chem Soc 2006;128:4966–4967.
46. Pansare SV, Pandya K. Simple diamine- and triamine-protonic acid catalysts for the enantioselective Michael addition of cyclic ketones to nitroalkenes. J Am Chem Soc 2006;128:9624–9625.
47. Chen JR, Fu L, Zou YQ, Chang NJ, Rong J, Xiao WJ. Pyrrolidinyl-sulfamide derivatives as a new class of bifunctional organocatalysts for direct asymmetric Michael addition of cyclohexanone to nitroalkenes. Org Biomol Chem 2011;9:5280–5287.
48. Dubois GE, Stephenson RA. Sulfonylamine-mediated sulfamation of amines. A mild, high yield synthesis of sulfamic acid salts. J Org Chem 1980;45:5371–5373.
49. DuBois GE. Amination of aryl sulfamate esters. A convenient general synthesis of aliphatic sulfamides. J Org Chem 1980;45:5373–5375.