Recyclable Merrifield Resin-Supported Organocatalysts Containing Pyrrolidine Unit through A^3-Coupling Reaction Linkage for Asymmetric Michael Addition

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ABSTRACT Merrifield resin-supported pyrrolidine-based chiral organocatalysts **A**−**D** through A^3-coupling reaction linkage have been developed and found to be highly effective catalysts for the Michael addition reaction of ketones with nitrostyrenes. The reactions generated the corresponding products in good yields (up to 92%), excellent enantioselectivities (up to 98% ee), and high diastereoselectivities (up to 99:1 dr). In addition, the catalysts can be reused at least five times without a significant loss of catalytic activity and stereoselectivity. *Chirality 22:432–441, 2010.*

KEY WORDS: asymmetric Michael additions; Merrifield resin; supported organocatalysis; A^3-coupling reaction linkage; pyrrolidine unit

INTRODUCTION

As List et al.[1] and Barbas and coworkers[2] reported the enantioselective Michael additions of unmodified ketones using L-proline and (*S*)-1-(2-pyrrolidinylmethyl)-pyrrolidine as organocatalysts, respectively, some new chiral-type amines have been developed for promoting the efficiency of the process.[3–10] Recently, small chiral amines have become attractive and powerful catalysts for C—C bond forming reactions.[11,12] Michael addition reactions of aldehydes or ketones to nitroolefins[13–16] occupy a central position in the playground of organic synthesis and play an important role in C—C bond forming reactions[17] due to the versatility of the nitrofunctionality which can be easily transformed into, for example, amine, nitrile oxide, ketone, carboxylic acid, or hydrogen.[18]

Asymmetric organocatalysis has attracted intense interests in recent years for its environmental friendliness and the generation of multiple stereogenic centers in a single step.[19–30] Various effective organocatalysts for Michael reaction have been developed, such as modified prolines,[31–33] pyrrolidine-based diamines,[34,35] chiral diamines,[36,37] chiral guanidines,[38] cinchona alkaloid-based bifunctional organocatalysts,[39,40] urea(thiourea)-based bifunctional organocatalysts.[41–44] Organocatalytic processes are generally considered as environmentally benign because the use of metals is avoided. However, their catalytic efficiency is usually lower than in metal-catalyzed processes in terms of turnover number. To circumvent this difficulty, the development of immobilized, easily recoverable, and reusable catalysts appears as one of the most promising strategies.[45–47] Recently, there are some reports on the asymmetric reactions using immobilized proline and its derivatives on poly(ethylene glycol) (PEG), mesoporous support, and ionic liquids.[48–62] The development of highly enantioselective and efficient chiral organocatalysts with broad substrate applicability and easy recyclability is essential in this field.[63,64]

We have focused our attention on a general immobilization strategy for organocatalysis for Michael addition of ketones to nitrostyrenes. In this article, we wish to report a class of newly designed, facile, Merrifield resin-supported organocatalysts, **A**−**D** containing pyrrolidine unit through A^3-coupling reaction linkage (three-component coupling of aldehyde, alkyne, and amine), which gave excellent diastereoselectivity (*syn/anti* up to 99:1) and high enantioselectivity (up to 98% ee) for the Michael addition of ketones to nitrostyrenes (Scheme 1).

EXPERIMENTAL

General Remarks

Melting points were recorded on a WRS-2 B melting point apparatus and are uncorrected. All ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were recorded on a 400 MHz Bruker FT-NMR spectrometers. All chemical shifts are given as δ value (ppm) with reference to tetramethylsilane (TMS) as an internal standard. Infrared (IR) spectra were obtained on a Nicolet NEXUS

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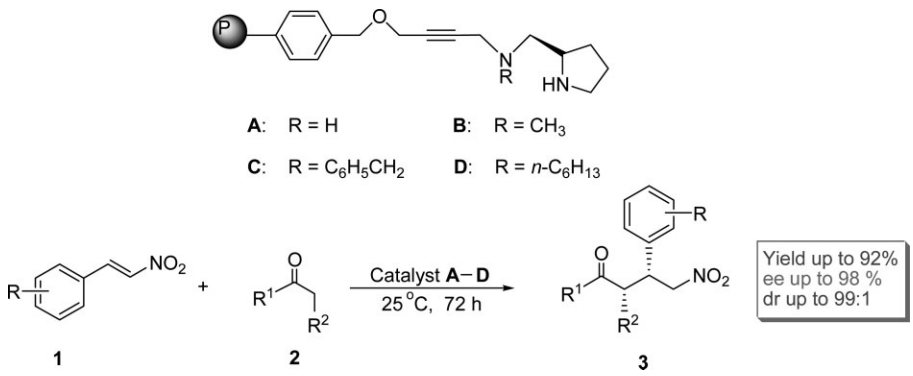


Scheme 1. Merrifield resin-supported organocatalysts and their application in asymmetric Michael addition.

470 spectrophotometer. The CHN analysis was performed on a Vario El III elementary analyzer. Enantiomeric excesses were determined on Agilent 1100 HPLC using Daicel Chiralpak AS-H, OJ-H and AD-H columns with racemic products as standards. Products were purified by flash chromatography on 230–400 mesh silica gel, SiO_2.

The chemicals and solvents were purchased from commercial suppliers (Aldrich, Fluka, Fisher Scientific, and Novabiochem, USA, or Shanghai Chemical Company, China) and were used without purification before use.

Preparation of Merrifield Resin-Supported Organocatalysts A, B, C, and D

Preparation of *N*-Boc-(*S*)-2-(4-toluenesulfonyloxy)-methylpyrrolidine, 5. To an ice-cold solution of *N*-Boc-(*S*)-prolinol, **4** (2.95 g, 14.7 mmol) in pyridine (23 ml) was added 4-toluenesulfonyl chloride (4.94 g, 25.9 mmol). The reaction mixture was stirred for 6 h and then diluted with diethyl ether (200 ml). The organic phase was washed with 10% HCl (3 × 75 ml), $NaHCO_3$ (3 × 75 ml), and NaCl (2 × 75 ml), respectively. The organic phase was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was subjected to flash chromatography on silica gel (eluent:pentane/EtOAc 3/2) to obtain 4.38 g of compound **5** (84% yield).[22] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 9H), 1.84 (br, 4H), 2.44 (s, 3H), 3.28 (br, 2H), 3.93 (br, 2H), 7.33 (br, 2H), 7.76 (d, J = 8.18 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 28.5, 47.1, 55.8, 69.9, 128.1, 130.0.

Preparation of *N*-Boc-(*S*)-2-azidomethylpyrrolidine, 6. *N*-Boc-(*S*)-2-(4-toluenesulfonyloxy)methylpyrrolidine, **5** (4.38 g, 12.3 mmol) was dissolved in dry dimethyl sulfoxide (DMSO; 130 ml) and sodium azide (4.81 g, 74.0 mmol) was added. The reaction mixture was heated to 64°C for 19 h, allowed to cool to room temperature, and diluted with diethyl ether (250 ml). The organic phase was washed with H_2O (3 × 200 ml) and NaCl (sat. aq. 100 ml), dried with Na_2SO_4, and the solvent was evaporated. The crude product **6** (2.53 g, 90% yield) was not further purified and was stored in the refrigerator until it was further used.[65] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 9H), 1.86 (m, 4H), 3.37 (m, 4H), 3.80−4.00 (b, 1H); ^{13}C NMR(100 MHz, $CDCl_3$): δ 22.3, 27.6, 28.1, 45.9, 52.7, 55.7.

Preparation of *N*-Boc-(*S*)-2-aminomethylpyrrolidine, 7. *N*-Boc-(S)-2-azidomethylpyrrolidine, **6** (2.53 g, 11.2 mmol) was dissolved in anhydrous tetrahydrofuran (THF) (95 ml), and triphenylphosphine (6.2 g, 22.96 mmol) and H_2O (0.45 ml) were added to it. The reaction mixture was heated to reflux temperature for 24 h until all starting material had been consumed (TLC monitoring). The organic solvent was then removed under reduced pressure and the remaining oil was dissolved in diethyl ether (200 ml). The pH of solution was adjusted to around 2 by using 1.0 mol/L HCl with vigorous stirring, and the aqueous phase was washed with diethyl ether (2 × 40 ml). The pH of the aqueous phase was adjusted to 13 by using 2.0 mol/L NaOH and extracted with CH_2Cl_2 (6 × 30 ml). The organic phase was dried with Na_2SO_4 and concentrated under reduced pressure to afford the crude product **7**, which was not further purified (1.57 g, 78% yield) for the further procedure.[65] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (s, 9H), 1.49 (m, 2H), 1.75 (m, 4H), 2.62 (m, 1H), 2.77 (b, 1H), 3.26 (m, 2H), 3.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1, 22.7, 27.5, 44.2, 45.7, 46.0, 58.7.

General procedure for the preparation of 8. *N*-Boc-(*S*)-2-aminomethylpyrrolidine **7** (1.57 g, 8.77 mmol) was dissolved in anhydrous MeOH (5.0 ml) and was heated to reflux temperature for 0.5 h. Aldehyde (8.77 mmol), such as *para*-formaldehyde, phenylacetaldehyde, and *n*-hexaldehyde, respectively, was added dropwise over a period of 5 min and the mixture was stirred at reflux temperature for 30 min. The solution was allowed to cool to room temperature and sodium borohydride (700 mg, 18.4 mmol) was added in one portion. After the vigorous effervescence had stopped, the mixture was heated to reflux temperature for 15 min. The reaction was then quenched by the addition of water (5 ml) and the aqueous phase extracted with dichloromethane (DCM) (3 × 10 ml). The separated organic phase was dried over potassium carbonate, filtered, and the solvent evaporated to give the corresponding **8a**, **8b,** and **8c**, respectively. **8a:** 1.86 g (99% yield), ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (s, 9H), 1.43 (m, 2H), 2.10 (b, 1H), 2.93 (m, 4H), 3.29 (m, 4H), 3.62 (m, 2H). **8b:** 2.52 g (99% yield), ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (s, 9H), 1.92 (m, 4H), 2.15 (s, 1H), 2.76 (m, 1H), 3.29 (m, 2H), 3.82

(m, 2H), 7.25 (m, 5H). **8c:** 2.35 g (90% yield), ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, 3H), 1.29 (m, 4H), 1.31 (m, 2H), 1.38 (m, 2H), 1.46 (s, 9H), 1.46 (m, 4H), 2.12 (m, 1H), 2.56 (m, 2H), 2.95 (m, 2H), 3.32 (m, 2H), 3.58 (b, 1H).

Preparation of Merrifield resin-supported azide, 9. A Merrifield resin (2.5 mmol/g, 3.0 g) was treated with propargyl alcohol (560 mg) under basic conditions for 24 h at 70°C (NaH 400 mg in THF 50 ml) to provide the Merrifield resin-supported azide, **9** (2.96 g). IR (film, cm^{-1}): 3298, 3058, 3024, 2918, 2848, 1600, 1492, 1451; the loading of Merrifield resin-supported azide **9** was quantified via CHN microanalysis and found to be 2.12 mmol/g.

Preparation of Merrifield resin-supported organocatalysts A, B, C and D. *para*-Formaldehyde (5.0 mmol) and amine **7**, **8a**, **8b**, or **8c** (5.0 mmol) were added to a mixture of the Merrifield resin-supported azide **9** (2.0 g, 2.12 mmol/g) and anhydrous acetonitrile (10 ml) contained in a clean, dry, 25 ml round-bottomed flask under nitrogen atmosphere. The mixture was stirred at 80°C for 24 h in oil bath. After the reaction was completed and cooled to the room temperature, the solid catalyst was flushed by anhydrous acetonitrile (3 × 25 ml) and dichloromethane (3 × 25 ml) in a sintered glass funnel, at last it was dried to ensure removal of the solvent from the surface of catalyst in a vacuum desiccators to afford the *N*-Boc protected Merrifield resin-supported organocatalysts, which was not further purified before deprotection.

Trifluoroacetic acid (TFA, 5 ml) was added to suspensions of the above *N*-Boc protected Merrifield resin-supported organocatalysts swelled with 5 ml of dichloromethane and the mixture was shaken at 0°C for 2 h, then at room temperature for 2 h. After complete deprotection of *N*-Boc group in catalysts, the catalysts were filtered and washed sequentially with Et_3N solution (3 × 25 ml), CH_2Cl_2 (3 × 25 ml), and EtOEt (3 × 25 ml). The obtained solid was dried under vacuum for 24 h at 40°C to generate the corresponding Merrifield resin-supported organocatalysts **A**, **B**, **C,** and **D** in good yields, respectively. Catalyst **A:** 1.98 g, IR (film, cm^{-1}): 3548, 3059, 2922, 2200, 1389, 699; The loading of catalyst **A** was quantified via CHN microanalysis and found to be 0.55 mmol/g. Catalyst **B:** 2.00 g, IR (film, cm^{-1}): 3547, 3299, 2852, 2109, 1397, 624; the loading of catalyst **B** was quantified via CHN microanalysis and found to be 1.11 mmol/g. Catalyst **C:** 2.01 g, IR (film, cm^{-1}): 3542, 3176, 2870, 2115, 1394, 689; the loading of catalyst **C** was quantified via CHN microanalysis and found to be 1.16 mmol/g. Catalyst **D:** 1.97 g, IR (film, cm^{-1}): 3547, 3299, 2923, 2852, 2116, 1452, 1349, 699; the loading of catalyst **D** was quantified via CHN microanalysis and found to be 0.71 mmol/g.

The Recyclability of the Merrifield Resin-Supported Organocatalysts

After carrying out the reaction, the mixture was vacuum filtered using a sintered glass funnel and washed with CH_2Cl_2 (3 ml), Et_2O (3 ml), C_2H_5OH (3 ml), and hexane (3 ml), respectively. After drying in an oven, the Merrifield resin-supported organocatalysts can be reused directly without further purification.

Representative Experimental Procedure for Michael Addition Reaction in the Presence of Catalyst C in Toluene

Under an atmosphere of nitrogen, an oven-dried round-bottomed flask was charged with *trans*-β-nitrostyrene (0.5 mmol), cyclohexanone (1.0 ml), catalyst **C** (21 mg), and toluene (2.0 ml). The mixture was stirred at room temperature (25°C) for 72 h, then washed with ethyl acetate (3 × 3 ml), the combined ethyl acetate was concentrated. Flash chromatography (hexane:ethyl acetate = 3:1, V/V) furnished the corresponding γ-nitroketone as colorless crystals (112.3 mg, 91% yield).

Representative Experimental Procedure for Michael Addition Reaction in the Presence of Catalyst A Under Neat Reaction Conditions

Under an atmosphere of nitrogen, an oven-dried round-bottomed flask was charged with *trans*-β-nitrostyrene (0.5 mmol), cyclohexanone (1.0 ml), and catalyst **A** (45 mg). The mixture was stirred at room temperature (25°C) for 72 h, then washed with ethyl acetate (3 × 3 ml), the combined ethyl acetate was concentrated. Flash chromatography (hexane:ethyl acetate = 3:1, V/V) furnished the corresponding γ-nitroketone as colorless crystals (86 mg, 70% yield).

(*S*)-2-((*R*)-2-Nitro-1-phenylethyl)cyclohexanone, 3A.[34] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.24 (m, 3H, ArH), 7.16 (d, J = 7.3 Hz, 2H, ArH), 4.93 (dd, J = 4.5, 12.3 Hz, 1H, CH), 4.63 (dd, J = 9.9, 12.0 Hz, 1H, CH), 3.76 (dt, J = 4.5, 9.9 Hz, 1H, CH), 2.70–2.68 (m, 1H, CH), 2.50–2.47 (m, 1H, CH), 2.43–2.38 (m, 1H, CH), 2.14–2.07 (m, 1H, CH), 1.77–1.59 (m, 4H, 2× CH_2), 1.28–1.22 (m, 1H, CH); ^{13}C NMR (100MHz, $CDCl_3$): δ 211.8, 137.7, 128.9, 128.1, 127.7, 78.9, 52.5, 43.9, 42.7, 33.2, 28.5, 25.0. HPLC (Chiralpak AD-H, *i*-propanol/hexane = 10:90, flow rate 1.0 ml/min, λ = 254 nm): t_{minor} = 10.34 min, t_{major} = 12.94 min; ee = 98%.

(*S*)-2-((*R*)-1-(4-Chlorophenyl)-2-nitroethyl)cyclohexanone, 3B.[66] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, J = 8.3 Hz, 2H, ArH), 7.17 (d, J = 8.4 Hz, 2H, ArH), 4.94 (dd, J = 4.6, 12.5 Hz, 1H, CH), 4.63 (dd, J = 10.0, 12.6 Hz, 1H, CH), 3.79–3.73 (m, 1H, CH), 2.71–2.64 (m, 1H, CH), 2.47–2.38 (m, 2H, CH_2), 2.12–2.05 (m, 1H, CH), 1.78–1.55 (m, 4H, 2× CH_2), 1.26–1.22 (m, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.6, 136.3, 133.5, 129.6, 129.1, 122.9, 78.5, 52.4, 43.4, 42.6, 33.2, 29.5, 28.3, 25.1. HPLC (Chiralpak AD-H, *i*-propanol/hexane = 10:90, flow rate 1.0 ml/min, λ = 254 nm): t_{minor} = 17.41 min, t_{major} = 27.86 min; ee = 98%.

(*S*)-2-((*R*)-1-(4-Methylphenyl)-2-nitroethyl)cyclohexanone, 3C.[17] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (d, J = 8.2 Hz, 2H, ArH), 7.04 (d, J = 8.0 Hz, 2H, ArH), 4.92 (dd, J = 4.7, 12.0 Hz, 1H, CH), 4.60 (dd, J = 9.3, 11.9 Hz, 1H, CH), 3.71 (dt, J = 4.6, 10.0 Hz, 1H, CH), 2.66–2.58 (m, 1H, CH), 2.47–2.40 (m, 1H, CH), 2.39–2.34 (m, 1H, CH) 2.31 (s, 3H, CH_3), 1.78–1.76 (m, 1H, CH), 1.76–1.57 (m, 4H, 2× CH_2), 1.24–1.21(m, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.0, 137.4, 134.6, 129.7, 128.0, 79.0,

52.6, 43.6, 42.6, 33.2, 28.5, 25.0, 21.0. HPLC (Chiralpak AD-H, *i*-propanol/hexane = 10:90, flow rate 1.0 ml/min, λ = 254 nm): t_{minor} = 8.99 min, t_{major} = 11.54 min; ee = 80%.

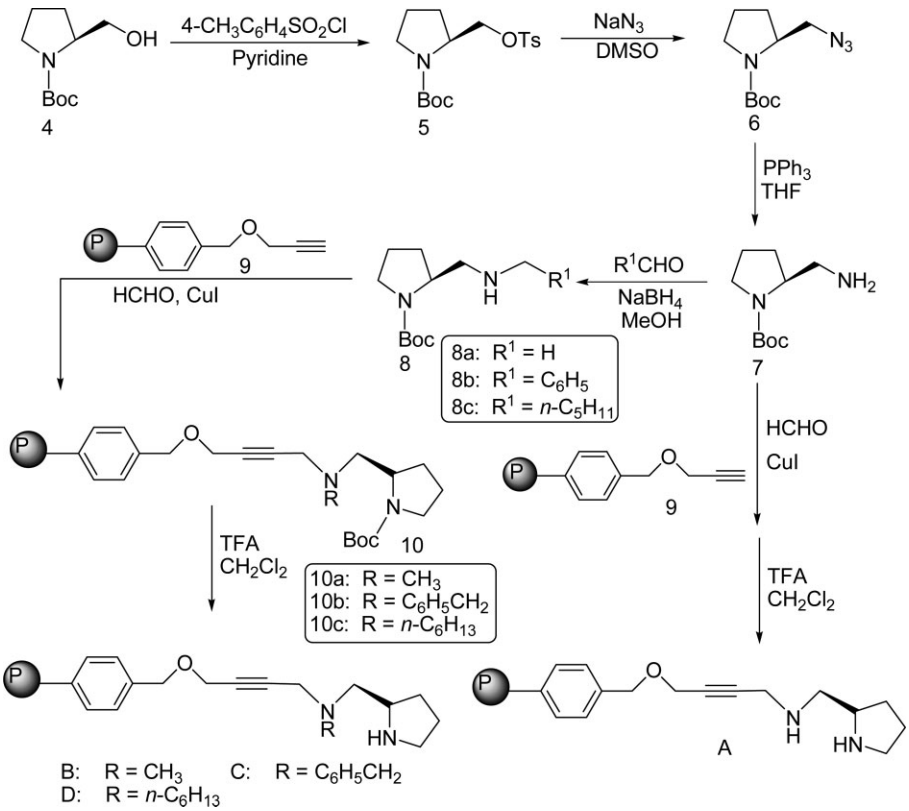
(*S*)-2-((*R*)-1-(2-Chlorophenyl)-2-nitroethyl)cyclohexanone, 3D.[56] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, *J* = 8.0 Hz, 1H, ArH), 7.26–7.20 (m, 3H, ArH), 4.95–4.87 (m, 2H, CH_2), 4.32–4.26 (m, 1H, CH), 2.94–2.90 (m, 1H, CH), 2.47–2.38 (m, 2H, CH_2), 2.13–2.09 (m, 1H, CH), 1.81–1.58 (m, 4H, 2× CH_2), 1.28–1.22 (m, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.6, 135.4, 134.5, 130.3, 129.4, 128.9, 127.3, 77.2, 51.7, 42.8, 41.0, 33.0, 28.5, 25.2. HPLC (Chiralpak AD-H, *i*-propanol/hexane = 10/90, flow rate 1.0 ml/min, λ = 254 nm): t_{minor} = 9.34 min, t_{major} = 15.13 min; ee = 86%.

(*S*)-2-((*R*)-1-(2-Bromophenyl)-2-nitroethyl)cyclohexanone, 3E.[44] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.2 Hz, 1H, ArH), 7.30–7.21 (m, 2H, ArH), 7.15–7.11 (m, 1H, ArH), 4.89 (d, *J* = 8.0 Hz, 2H, CH_2), 4.30 (dd, *J* = 6.3, 6.8 Hz, 1H, CH), 2.91–2.86 (m, 1H, CH), 2.47–2.34 (m, 2H, CH_2), 2.11–2.08 (m, 1H, CH), 1.81–1.58 (m, 4H, 2× CH_2), 1.40–1.21 (m, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.6, 137.2, 133.6, 129.0, 127.9, 77.3, 52.1, 43.0, 42.6, 41.9, 32.9, 28.5, 25.2. HPLC (Chiralpak AD-H, *i*-propanol/hexane = 10:90, flow rate 1.0 ml/min, λ = 254 nm): t_{minor} = 10.32 min, t_{major} = 18.07 min; ee = 98%.

(*S*)-2-((*R*)-1-(4-Fluorophenyl)-2-nitroethyl)cyclohexanone, 3F.[19] ^{1}H NMR (400 Hz, $CDCl_3$): δ 7.15 (d, *J* = 8.2 Hz, 2H, ArH), 7.01 (d, *J* = 8.5 Hz, 2H, ArH), 4.94 (dd, *J* = 4.5, 12.6 Hz, 1H, CH), 4.58 (dd, *J* = 10.0, 12.4 Hz, 1H, CH), 3.80–3.74 (m, 1H, CH), 2.65–2.61 (m, 1H, CH), 2.49–2.37 (m, 2H, CH_2), 2.09–2.07 (m, 1H, CH), 1.79–1.59 (m, 4H, 2× CH_2), 1.25–1.21 (m, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.7, 133.4, 129.7, 129.5, 124.6, 124.4, 116.0, 115.7, 78.8, 52.4, 43.2, 42.7, 33.2, 28.4, 25.0. HPLC (Chiralpak AD-H, *i*-propanol/hexane = 10:90, flow rate 1.0 ml/min, λ = 254 nm): t_{minor} = 11.45 min, t_{major} = 15.57 min; ee = 81%.

(*S*)-2-((*R*)-1-(4-Methoxyphenyl)-2-nitroethyl)cyclohexanone, 3G.[3] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07 (d, *J* = 8.3 Hz, 2H, ArH), 6.84 (d, *J* = 8.9 Hz, 2H, ArH), 4.92 (dd, *J* = 4.5, 12.2 Hz, 1H, CH), 4.58 (dd, *J* = 10.2, 12.3 Hz, 1H, CH), 3.78 (s, 3H, OCH_3), 3.71 (dt, *J* = 4.8, 10.4 Hz, 1H, CH), 2.65–2.63 (m, 1H, CH), 2.54–2.43 (m, 1H, CH), 2.44–2.38 (m, 1H, CH), 2.11–2.07 (m, 1H, CH), 1.80–1.55 (m, 4H, 2× CH_2), 1.25–1.21 (m, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.1, 137.4, 134.6, 129.6, 128.0, 79.0, 52.6, 43.6, 42.7, 33.2, 28.5, 25.0, 21.0. HPLC (Chiralpak AD-H, *i*-propanol/hexane = 10:90, flow rate 1.0 ml/min, λ = 254 nm): t_{minor} = 11.99 min, t_{major} = 14.86 min; ee = 94%.

(*S*)-2-((*S*)-1-(Furan-2-yl)-2-nitroethyl)cyclohexanone, 3H.[34] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, *J*



Scheme 2. Synthetic route of the Merrifield-supported organocatalysts.

= 1.3 Hz, 1H, ArH), 6.29 (dd, J = 1.8, 3.3 Hz, 1H, ArH), 6.18 (d, J = 3.2 Hz, 1H, ArH), 4.80 (m, 1H, CH), 4.67 (dd, J = 8.9, 12.2 Hz, 1H, CH), 3.96 (dt, J = 9.3 Hz, 1H, CH), 2.75–2.73 (m, 1H, CH), 2.45–2.36 (m, 2H, CH_2), 2.11–2.09 (m, 1H, CH), 1.84–1.61 (m, 4H, 2× CH_2), 1.28–1.26 (m, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.9, 150.8, 142.3, 110.3, 108.9, 76.6, 51.0, 42.5, 37.5, 32.4, 28.2, 25.0. HPLC (Chiralpak AD-H, *i*-propanol/hexane = 10:90, flow rate 1.0 ml/min, λ = 254 nm): t_{major}=10.22 min, t_{minor} = 12.40 min; ee = 78%.

(*S*)-2-((*R*)-1-(3,4-Dimethoxyphenyl)-2-nitroethyl) cyclohexanone, 3I.[22] ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.81 (d, J = 8.2 Hz, 1H, ArH), 6.68 (m, 2H, ArH), 4.91 (dd, J = 4.6, 7.8 Hz, 1H, CH), 4.60 (dd, J = 2.4, 9.9 Hz, 1H, CH), 3.87 (s, 6H, 2× OCH_3), 3.70 (m, 1H, CH), 2.66–2.64 (m, 1H, CH), 2.49–2.45 (m, 1H, CH), 2.41–2.38 (m, 1H, CH), 2.07–2.04 (m, 1H, CH), 1.80–1.60 (m, 4H, 2× CH_2), 1.27–1.23 (m, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.2, 149.2, 148.6, 130.2, 120.5, 111.5, 79.1, 56.0, 52.7, 43.8, 42.6, 33.3, 28.5, 27.5, 25.1. HPLC (Chiralpak As-H, *i*-propanol/hexane = 30:70, flow rate 1.0 ml/min, λ = 254 nm): t_{minor} = 12.31 min, t_{major} = 22.31 min; ee = 83%.

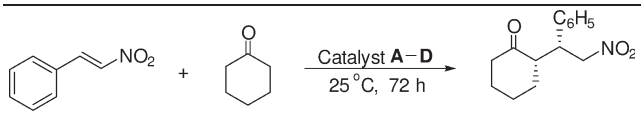
(*S*)-2-((*R*)-1-(4-Trifluoromethyl)phenyl)-2-nitroethyl)-cyclohexanone, 3J.[44] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, J = 8.1 Hz, 2H, ArH), 7.30 (m, 2H, ArH), 4.98 (dd, J = 4.5, 12.6 Hz, 1H, CH), 4.67 (dd, J = 9.8, 12.2 Hz, 1H, CH), 3.86 (m, 1H, CH), 2.72–2.70 (m, 1H, CH), 2.51–2.47 (m, 1H, CH), 2.41–2.38 (m, 1H, CH), 2.11–2.07 (m, 1H, CH), 1.83–1.57 (m, 4H, 2× CH_2), 1.27–1.23 (m, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.8, 149.1, 136.9, 130.0, 121.7, 121.6, 78.9, 52.9, 42.7, 43.1, 33.6, 28.8, 25.5. HPLC (Chiralpak AD-H, *i*-propanol/hexane = 10:90, flow rate 1.0 ml/min, λ = 254 nm): t_{minor} = 9.81; t_{major} = 19.25 min; ee = 88%.

(*S*)-2-((*R*)-1-(Benzo[d][1,3]dioxol-5-yl)-2-nitroethyl) cyclohexanone, 3K.[7] ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.74 (d, J = 7.9 Hz, 1H, ArH), 6.64–6.61 (m, 2H, ArH), 5.96 (s, 2H, OCH_2O), 4.91 (dd, J = 4.5, 12.4 Hz, 1H, CH), 4.54 (dd, J = 4.5, 10.0 Hz, 1H, CH), 3.67 (dt, J = 4.5, 9.9 Hz, 1H, CH), 2.63–2.58 (m, 1H, CH), 2.51–2.37 (m, 2H, CH_2), 2.15–2.07 (m, 1H, CH), 1.79–1.58 (m, 4H, 2× CH_2), 1.35–1.23 (m, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.7, 148.0, 147.1, 131.2, 121.6, 108.5, 108.0, 101.2, 78.9, 52.5, 43.6, 42.6, 33.2, 28.3, 25.1. HPLC (Chiralpak AD-H, *i*-propanol/hexane = 10:90, flow rate 1.0 ml/min, λ = 254 nm): t_{minor} = 16.56 min, t_{major} =18.72 min; ee = 92%.

(*S*)-2-((*R*)-1-(3-Bromophenyl)-2-nitroethyl)cyclo-hexanone, 3L.[44] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, J = 7.7 Hz, 1H, ArH), 7.39 (s, 1H, ArH), 7.21 (t, J = 7.9 Hz, 1H, ArH), 7.10 (d, J = 7.2 Hz, 1H, ArH), 4.94 (dd, J = 4.5, 12.7 Hz, 1H, CH), 4.60 (dd, J = 10.0, 12.7 Hz, 1H, CH), 3.77–3.71 (m, 1H, CH), 2.65–2.59 (m, 1H, CH), 2.48–2.38 (m, 2H, CH_2), 2.09–2.05 (m, 1H, CH), 1.79–1.56 (m, 4H, 2× CH_2), 1.31–1.20 (m, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.2, 140.1, 131.2, 130.9, 130.4, 126.9, 122.8, 78.3, 52.2, 43.6, 42.7, 33.1, 28.4, 25.0. HPLC (Chiralpak AD-H, *i*-propanol/hexane = 10:90, flow rate 1.0 ml/min, λ = 254 nm): t_{minor} = 9.46 min, t_{major} = 10.32 min; ee = 82%.

(*S*)-2-((*R*)-2-Nitro-1-phenylethyl)cyclopentanone, 3M.[10] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.20 (m, 3H, ArH), 7.13–7.08 (m, 2H, ArH), 5.30–5.23 (m, 1H, CH), 4.95 (dd, J = 9.9, 12.6 Hz, 1H, CH), 3.67–3.60 (m, 1H, CH), 2.34–2.25 (m, 2H, CH_2), 2.10–2.06 (m, 1H, CH), 1.87–1.78 (m, 2H, CH_2), 1.72–1.65 (m, 1H, CH), 1.53–1.37 (m, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 218.5, 137.7, 137.4, 128.9, 128.5, 127.9, 78.3, 50.5, 44.2, 38.7, 28.3, 25.0. HPLC (Chiralpak AD-H, *i*-propanol/hexane = 10:90, flow rate 1.0 ml/min, λ = 254 nm): *syn*: t_{major} = 9.96 min, t_{minor} = 11.42 min, *anti*: t_{minor} = 12.90 min, t_{major} = 17.32 min; *syn/anti* = 30:70; ee = 95%.

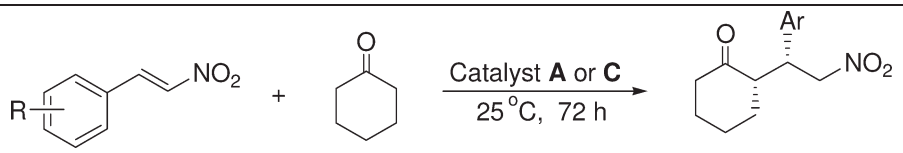
TABLE 1. Catalyst and solvent screening in the direct asymmetric Michael reaction of cyclohexanone with β-nitrostyrene[a]



Entry	Catalyst	Solvent	Yield[b] (%)	ee[c] (%)	dr[d] (*syn/anti*)
1	**A**	Toluene	50	91	91:9
2	**A**	Neat	70	97	96:4
3	**B**	Toluene	57	96	93:7
4	**B**	Neat	66	94	92:8
5	**C**	Toluene	90	98	95:5
6	**C**	Neat	69	93	92:8
7	**D**	Toluene	Trace	–	–
8	**D**	Neat	45	85	84:16
9[e]	**C**	Toluene	62	97	95:5
10[f]	**C**	Toluene	47	98	94:6
11[g]	**C**	Toluene	44	96	97:3
12[h]	**C**	Toluene	58	98	95:5
13[i]	**C**	Toluene	74	98	95:5
14[j]	**C**	Toluene	40	99	97:3
15	**C**	Cyclohexane	Trace	–	–
16	**C**	DMF	Trace	–	–
17	**C**	CH_3OH	12	94	92:8
18	**C**	C_2H_5OH	Trace	–	–
19	**C**	*i*-C_3H_7OH	28	88	85:15
20	**C**	H_2O	13	96	93:7

[a]β-Nitrostyrene (0.50 mmol), cyclohexanone (1.0 mmol), supported catalyst **A** (45 mg, 5 mol % active loading), **B** (23 mg, 5 mol % active loading), **C** (21 mg, 5 mol % active loading), or **D** (35 mg, 5 mol % active loading) at room temperature (25°C) for 72 h with vigorous stirring.
[b]Isolated yields.
[c]Determined by chiral HPLC analysis.
[d]Determined by ^{1}H NMR analysis.
[e]In the presence of TFA (0.10 mmol).
[f]In the presence of citric acid (0.10 mmol).
[g]In the presence of TsOH (0.10 mmol).
[h]In the presence of benzoic acid (0.10 mmol).
[i]In the presence of catalyst **C** (11 mg, 2.5 mol % active loading).
[j]At 0°C.

TABLE 2. Catalyst A and C catalyzed asymmetric Michael reaction[a]



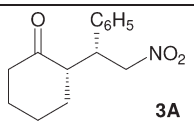
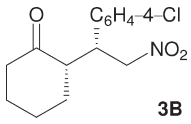
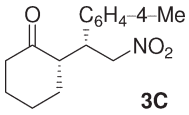
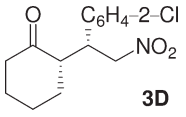
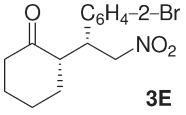
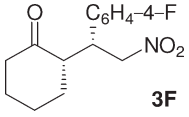
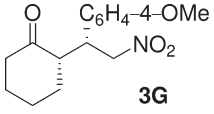
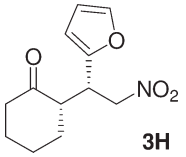
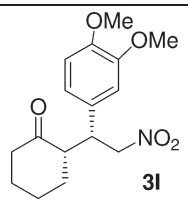
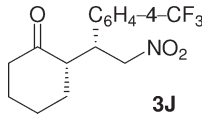
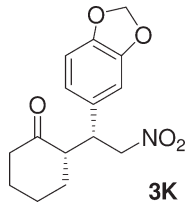
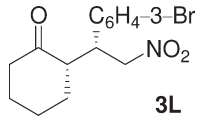
Entry	R	Catalyst	Solvent	Product	Yield[b] (%)	ee[c] (%)	dr[d] syn/anti
1a	H	**A**	Neat	 **3A**	70	97	96:4
1b		**C**	Toluene		91	98	95:5
2a	4-Cl	**A**	Neat	 **3B**	59	96	96:4
2b		**C**	Toluene		86	98	97:3
3a	4-CH_3	**A**	Neat	 **3C**	62	86	98:2
3b		**C**	Toluene		90	80	95:5
4a	2-Cl	**A**	Neat	 **3D**	57	90	99:1
4b		**C**	Toluene		87	86	97:3
5a	2-Br	**A**	Neat	 **3E**	60	88	98:2
5b		**C**	Toluene		89	98	99:1
6a	4-F	**A**	Neat	 **3F**	73	94	98:2
6b		**C**	Toluene		84	81	96:4
7a	4-CH_3O	**A**	Neat	 **3G**	38	87	96:4
7b		**C**	Toluene		86	94	99:1
8a	2-Furyl	**A**	Neat	 **3H**	39	81	98:2
8b		**C**	Toluene		92	78	96:4

TABLE 2. (Continued)

Entry	R	Catalyst	Solvent	Product	Yield[b] (%)	ee[c] (%)	dr[d] syn/anti
9	3,4-$(CH_3O)_2$	**C**	Toluene	 **3I**	80	83	92:8
10	4-CF_3	**C**	Toluene	 **3J**	85	88	93:7
11	3,4-OCH_2O-	**C**	Toluene	 **3K**	75	92	98:2
12	3-Br	**C**	Toluene	 **3L**	73	82	97:3

[a]β-Nitrostyrene (0.5 mmol), cyclohexanone (1.0 mmol), catalyst **A** (45 mg) or **C** (21 mg), toluene (2.5 mL), or in the absence of solvent at room temperature for 72 h with vigorous stirring.
[b]Isolated yields.
[c]Determined by chiral HPLC analysis.
[d]Determined by ^{1}H NMR analysis.

(*R*)-5-Nitro-4-phenylpentan-2-one, 3N.[26] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.21 (m, 5H, ArH), 4.72–4.58 (m, 2H, CH_2), 4.03–4.00 (m, 1H, CH), 2.92 (d, J = 6.8 Hz, 2H, CH_2), 2.12 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.5, 138.8, 129.1, 127.9, 127.4, 79.5, 64.4, 46.1, 39.0, 30.4, 25.3. HPLC (Chiralpak AD-H, *i*-propanol/hexane = 10:90, flow rate 0.6 ml/min, λ = 254 nm): t_{minor} = 11.74 min, t_{major} = 12.79 min; ee = 78%.

RESULTS AND DISCUSSION

The synthesis of the catalysts **A, B, C,** and **D** is illustrated in Scheme 2. They were readily prepared through a multistep procedure.

N-Boc-(*S*)-prolinol **4** in anhydrous pyridine was reacted with 4-toluenesulfonyl chloride at 50°C for 6 h to give *N*-Boc-(*S*)-2-(4-toluenesulfonyloxy)methylpyrrolidine **5** in 84% yield. The obtained **5** in dry DMSO subsequently reacted with sodium azide at 64°C for 19 h to generate *N*-Boc-(*S*)-2-azidomethylpyrrolidine **6** in 90% yield. The formed compound **6** was then reduced to the corresponding amine, *N*-Boc-(*S*)-2-aminomethylpyrrolidine **7** by using PPh_3/THF in 78% isolated yield. The yielded compound **7** was then reacted with aldehydes, such as *para*-formaldehyde, phenylacetaldehyde, and *n*-hexaldehyde respectively to afford the corresponding imines, and followed by reduction with $NaBH_4/CH_3OH$ to give the corresponding amine compounds **8a**, **8b,** and **8c** in good yields. The generated **7**, **8a**, **8b,** and **8c** were then reacted with Merrifield resin-supported azide **9** and *para*-formaldehyde in the presence of catalytic amount CuI via a three-component coupling of aldehyde, alkyne and amine (Mannich A^3-coupling reaction) to generate the corresponding Merrifield resin-supported compounds, and followed by deprotection of *N*-Boc protective group through treatment with TFA in CH_2Cl_2, respectively, to afford the desired Merrifield resin-supported organocatalysts **A, B, C,** and **D** in good yields.

For the evaluation of the catalytic properties of Merrifield resin-supported organocatalysts, **A**–**D** containing pyrrolidine unit and optimization of the Michael addition conditions, the reaction between *trans*-β-nitrostyrene and cyclohexanone served as a model reaction. The results are summarized in Table 1. As seen from Table 1, the Michael reactions proceeded smoothly at room temperature in the

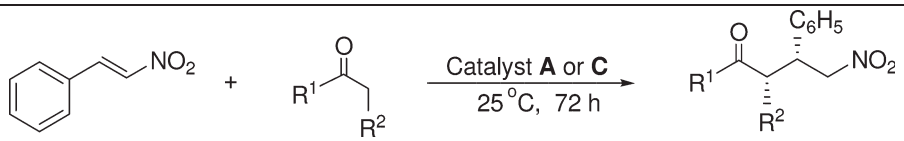
presence of Merrifield resin-supported organocatalysts (5 mol % of active loading) in toluene or under neat reaction conditions to generate the corresponding products in moderate to good yields and fair to good enantiomeric excesses. Among **A–D** tested, the catalytic properties of **A** under neat reaction conditions and **C** in toluene are superior to that of **A**, **B,** and **D** in toluene, and **B**, **C,** and **D** under neat reaction conditions (Entries 1–8, Table 1). Fortunately, **C** was found to be the most efficient for the asymmetric Michael reaction in toluene (Entry 5, Table 1, 90% yield, 98% ee, and 95:5 dr). However, the isolated yields, enantioselectivities, and diastereoselectivities of the reaction were not improved when TFA, citric acid, TsOH, or benzoic acid (10 mol %) were added to the reactions (Entries 9–12, Table 1). As shown in Table 1, the reactions were carried out with 10 mol% of **C** in a variety of solvents (Entries 5, 15−20, Table 1) to examine the solvent effect. However, when the reactions were carried out in cyclohexane, DMF, CH_3OH, C_2H_5OH, i-C_3H_7OH, or H_2O, the Michael addition reactions did not proceed very well and only trace to 28% yield of the corresponding products were isolated, although good enantioselectivities and diastereoselectivities were achieved (Entries 15–20, Table 1). To our delight, when the reactions were carried out in toluene, the Michael addition reactions proceeded smoothly and excellent results were obtained (Entry 5, Table 1). Moreover, slightly higher enantioselectivity and diastereoselectivity were observed when the reaction temperature was reduced from room temperature (25°C) to 0°C with a significant decrease in the reaction rate (Entry 14, Table 1). During the course of our further optimization of the reaction conditions, we observed that the reactions were generally completed in 72 h with 5 mol% of **C** at room temperature (25°C, Entry 5 vs. 13, Table 1). Thus, the optimized reaction conditions for this Michael reaction are catalyst **C** (5 mol %) in toluene at room temperature (25°C) for 72 h.

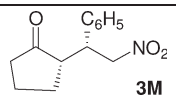
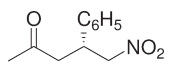
Under the optimized reaction conditions, a variety of nitroolefins with different substituents were investigated, and the results are summarized in Table 2. Various styrene-type nitroolefins reacted smoothly with cyclohexanone in good yields, high diastereoselectivities, and excellent enantioselectivities (Entries 1−12, Table 2). As can be seen in Table 2, the results of Michael reactions carried out in the presence of catalyst **C** in toluene are superior to that of the results in the presence of catalyst **A** under neat reaction conditions. Generally, substituents on aryl groups slightly influenced both diastereoselectivities and enantioselectivities as well as the yields. For example, nitroolefins with aryl rings bearing both electron-withdrawing and electron-donating groups gave the desired products with high selectivity (dr up to 99:1 and ee up to 98%) in excellent yields (up 90%).

Moreover, the Michael reactions were evaluated with other ketones and it was found that cyclopentanone and acetone were also the suitable substrates as Michael donors (Entries 13 and 14, Table 3). However, acetone and cyclopentanone served as Michael donors to produce the desired adducts with moderate yields, and moderate to good enantioselectivities and diastereoselectivities in the presence of catalyst **A** under neat reaction conditions (Entries 13 and 14, Table 3).

In addition, the recyclability of the Merrifield resin-supported organocatalyst containing pyrrolidine unit **C** was investigated. After carrying out the reaction, the catalyst was filtered using a sintered-glass funnel and washed with ethyl acetate (3.0 ml) and dichloromethane (3.0 ml), respectively. After drying, **C** was reused directly without further purification, and it was recovered, and reused for five repetitive cycles without loss of its activity, enantioselectivity, and diastereoselectivity (Entries 1–5, Table 4).

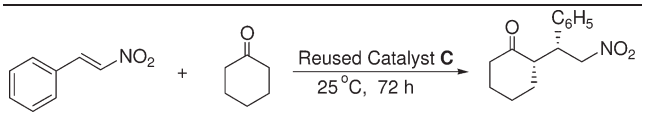
TABLE 3. Catalyst A and C catalyzed Michael reaction of various ketones with β-nitrostyrene[a]



Entry	R^1	R^2	Catalyst	Solvent	T (°C)	Product	Yield[b] (%)	ee[c] (%)	dr[d]
13	$-(CH_2)_3-$		**A**	Neat	0	 **3M**	46	95	70:30
14a	CH_3	H	**A**	Neat	0	 **3N**	43	78	–
14b	CH_3	H	**C**	Neat	25		57	28	–

[a]β-Nitrostyrene (0.5 mmol), ketone (1.0 ml), and catalyst **A** (45 mg) or **C** (21 mg) was stirred at room temperature for 72 h with vigorous stirring.
[b]Isolated yields.
[c]Determined by chiral HPLC analysis.
[d]Determined by ^{1}H NMR analysis (dr: *syn/anti*).

TABLE 4. Recyclability of catalyst C[a]



Cycle	Yield[b] (%)	ee[c] (%)	dr[d] *syn/anti*
1	91	98	96:4
2	90	98	96:4
3	89	97	96:4
4	89	97	95:5
5	87	98	95:5

[a]β-Nitrostyrene (0.50 mmol), cyclohexanone (1.0 mmol), catalyst **C** (21 mg), toluene (2.5 ml) at room temperature for 72 h with vigorous stirring.
[b]Isolated yields.
[c]Determined by chiral HPLC analysis.
[d]Determined by ^{1}H NMR analysis.

CONCLUSIONS

In conclusion, we have developed a novel Merrifield resin-supported pyrrolidine-based chiral organocatalysts through A^3-coupling reaction linkage, which are capable of catalyzing Michael addition reaction of ketones with nitrostyrenes in good yields, excellent enantioselectivies, and high diastereoselectivities. The method is operationally simple, the catalyst can be easily recycled, and reused five times without loss of catalytic activity and stereoselectivity. Further investigations of the application of this supported organocatalyst in asymmetric catalysis are underway in our laboratory.

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