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Silica gel supported pyrrolidine-based chiral ionic liquid as recyclable organocatalyst for asymmetric Michael addition to nitrostyrenes

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ABSTRACT

A novel silica gel supported pyrrolidine-based chiral ionic liquid **6a** has been developed and found to be a highly effective catalyst for the Michael addition reaction of ketones with nitrostyrenes. The reactions generated the corresponding products in good yields (up to 94%), excellent enantioselectivities (up to >99% ee), and high diastereoselectivities (up to >99:1 dr). In addition, the catalyst **6a** can be reused at least five times without a significant loss of catalytic activity and stereoselectivity.

1. Introduction

The development of non-metallic asymmetric catalysis has drawn much attention in recent years. Among all the organomolecules catalyzed reactions, asymmetric conjugate addition has received much more attentions because it is one of the most important C–C bond-forming reactions in organic chemistry.[1] The asymmetric Michael addition reactions of nucleophiles to electron deficient nitroalkenes are particularly useful because the products, optically active nitroalkanes, are versatile building blocks for agricultural and pharmaceutical research.[2] In the past decades, various enantioselective processes have been developed for the addition of ketones to nitroalkenes. Chiral metal–ligand complexes[3] and metal-free chiral organocatalysts have been achieved. The organocatalytic asymmetric Michael addition of ketone with nitroolefins was pioneered by List[4] and Barbas,[5] independently. Since then, the interest in the field of asymmetric Michael addition has increased intensively and various effective organocatalysts have been widely developed, such as modified L-proline,[6] pyrrolidine-based diamine,[7] chiral diaime,[8] chiral guanidine,[9] cinchona alkaloids-based bifunctional organocatalyst,[10] urea(thiourea)-based bifunctional organocatalysts,[11] etc. Environmental concerns associated with chemical processes have encouraged the development of more environmentally friendly methodology for organic reactions. In recent years, immobilizing chiral organocatalyst has received considerable interest. A great deal of efforts has gone into the development of asymmetric organic reactions catalyzed by supported organocatalyst.[12] Silica gel, polymer, ionic liquid supported L-proline has been successfully used in aldol reactions.[13] Recently, some recyclable organocatalysts for asymmetric Michael addition of ketone or aldehydes with nitroolefins have also been developed, such as fluorous pyrrolidine sulfonamide,[14] ionic liquid supported pyrrolidine-based catalyst,[15] polymer supported pyrrolidine,[16] polymer supported thiourea catalyst,[17] etc. Herein we wish to report a novel silica gel supported pyrrolidine-based organocatalyst, which was easily prepared from (*S*)-Boc-L-proline as shown in Scheme 1, that catalyzes the reaction of ketones with arylnitroolefins smoothly in excellent yields with high diastereoselectivities and excellent enantioselectivities (up to 94% of yield, up to >99% ee and up to >99:1 dr).

2. Results and discussion

Initially, various solvents and additives were examined at room temperature by using **6a** and **6b** as catalysts, as shown in Table 1. Both silica gel supported catalysts, **6a** and **6b**, were effective to the addition of cyclohexanone with *trans*-β-nitrostyrene, and a slight difference was observed on both activity and selectivity. It was obvious that **6a** is slightly superior to **6b** not only in activity, but

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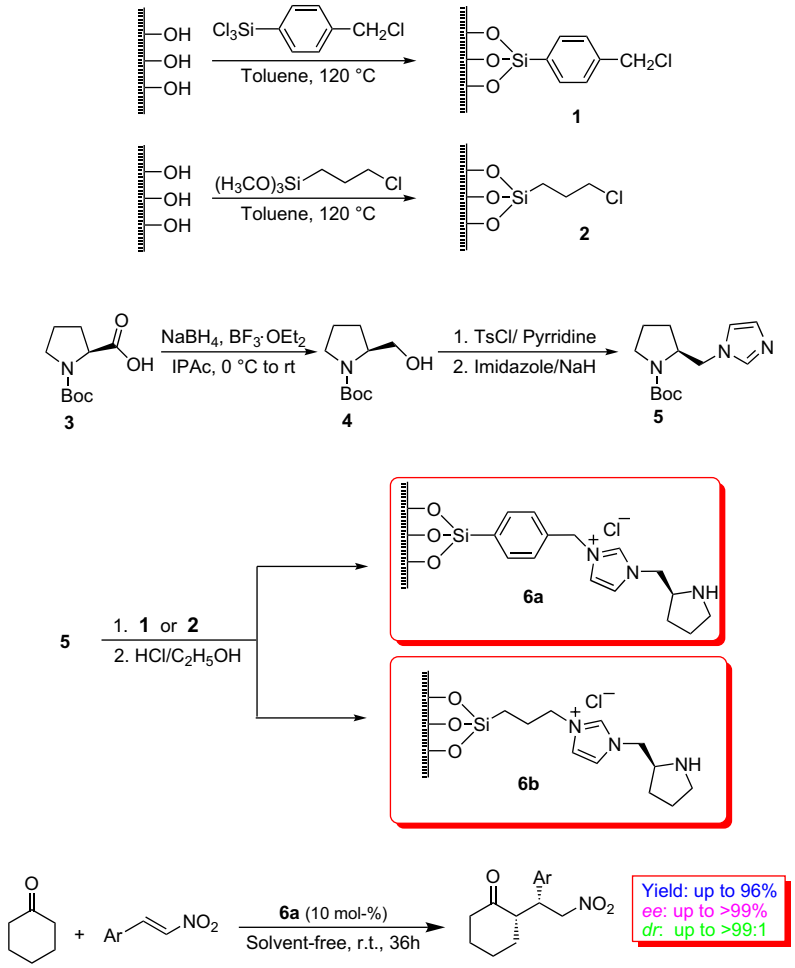


Scheme 1. Synthesis of silica gel supported pyrrolidine-based chiral ionic liquid and its application in asymmetric Michael addition to nitrostyrenes.

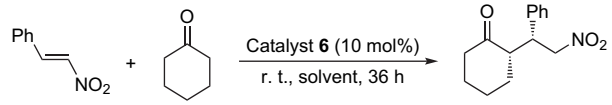
also in selectivity (entry 1 vs 2, entry 3 vs 4, entry 5 vs 6, and entry 12 vs 13, Table 1). As shown in Table 1, the reactions were carried out with 10 mol % of **6a** in a variety of solvents (entries 1, 3, 5, and 7–11, Table 1). In polar solvents, such as EtOH, DMF, CH_2Cl_2, H_2O, the Michael addition reactions proceeded smoothly to give the corresponding products in moderate to good yields with excellent enantioselectivities and diastereoselectivities (entries 1, 3, 5, and 7, Table 1), whereas using Et_2O and THF as solvents resulted in poor yields and similar enantioselectivities and diastereoselectivities (entries 8 and 9, Table 1). In non-polar solvents, such as toluene and hexane, the Michael addition reactions also proceeded smoothly to give the desired products in good yields with excellent enantioselectivities and diastereoselectivities (entries 10 and 11, Table 1). To our delight, under solventless reaction conditions, higher isolated yields and similar enantioselectivities and diastereoselectivities were observed (entries 12 and 13, Table 1). Moreover, slightly higher enantioselectivity and diastereoselectivity were observed when the reaction temperature was down from room temperature (25 °C) to 10 °C without a significant decrease of the reaction rate (entry 17, Table 1). It is noteworthy that the addition of a catalytic amount of organic acids could decrease dramatically the reaction rate without a loss of enantiomeric excess and diastereoselectivity (entry 14, Table 1). To avoid the use of volatile solvents, reduce the environmental pollution, and enhance activity and selectivity, all the Michael reactions were performed under solvent-free reaction conditions.

During the course of our further optimization of the reaction conditions, we observed that the reactions were generally completed in 36 h with 10 mol % of **6a** at room temperature (25 °C) (entries 15 and 16, Table 1). The reaction time, as expected, was inversely proportional to the temperature. Room temperature (25 °C) was found to be optimal. Thus, the optimized reaction conditions for this Michael reaction are **6a** (10 mol %) in neat reaction conditions at room temperature (25 °C) for 36 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). Generally, substituents on aryl groups slightly influenced the 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 >99%) in excellent yields (up 94% of yield). Moreover, the Michael reactions were evaluated with other ketones and found that tetrahydrothiopyran-4-one and tetrahydro-4*H*-pyran-4-one were also suitable substrates as Michael donors (entries 13 and 14, Table 2). However, acetone and cyclopentanone served as efficient Michael donor to produce the desired adducts with excellent yields, but moderate to good enantioselectivities (entries 15 and 16, Table 2).

In addition, the recyclability of the supported pyrrolidine **6a** was investigated. After carrying out the reaction, the catalyst was filtered using a sintered-glass funnel and washed with ethyl acetate (3 mL) and dichloromethane (3 mL), respectively. After

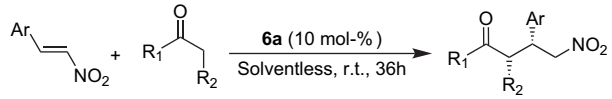
Table 1
Optimization of the reaction conditions[a]



Entry	Catalyst	Solvent	Yield[b] (%)	ee[c] (%)	dr[d]
1	**6a**	EtOH	71	98	99:1
2	**6b**	EtOH	68	97	99:1
3	**6a**	DMF	76	98	98:2
4	**6b**	DMF	72	98	98:2
5	**6a**	CH_2Cl_2	61	98	98:2
6	**6b**	CH_2Cl_2	56	96	98:2
7	**6a**	H_2O	51	98	98:2
8	**6a**	THF	32	98	98:2
9	**6a**	Et_2O	35	98	98:2
10	**6a**	Hexane	72	98	98:2
11	**6a**	Toluene	78	99	98:2
12	**6a**	Neat	91	99	99:1
13	**6b**	Neat	87	98	98:2
14[e]	**6a**	Neat	76	98	98:2
15[f]	**6a**	Neat	69	98	99:1
16[g]	**6a**	Neat	68	98	99:1
17[h]	**6a**	Neat	73	>99	99:1

[a] Nitrostyrene (0.5 mmol), cyclohexanone (1.0 mmol under solvent conditions or 0.4 mL under neat conditions), and catalyst **6** (contains 0.05 mmol of active loading) in solvent (2.0 mL) at room temperature (25 °C) for 36 h.
[b] Isolated yields.
[c] Determined by HPLC using chiralpak AD-H column.
[d] Diasteromeric ratio, dr (*syn*/*anti*), determined by ^{1}H NMR spectroscopy.
[e] TFA (5 mol %) was added at room temperature for 48 h.
[f] The reaction time was 12 h.
[g] Catalyst **6a** (5 mol %) was added.
[h] The reaction temperature was 10 °C.

Table 2
Michael additions of ketones and aldehyde to *trans*-β-nitrostyrenes catalyzed by **6a**[a]



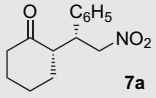
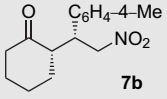
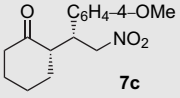
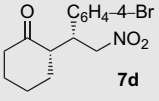
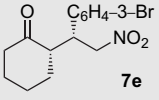
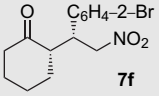
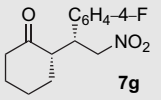
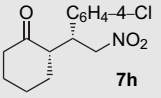
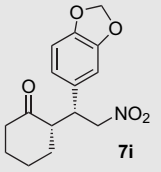
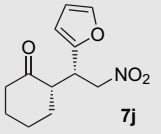
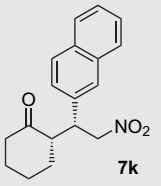
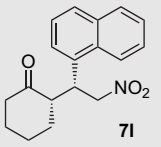
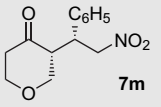
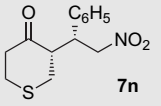
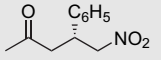
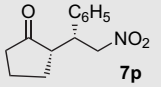
Entry	Product	Yield[b] (%)	ee[c] (%)	dr[d]
1	 **7a**	91	98	99:1
2	 **7b**	93	99	99:1
3	 **7c**	88	99	99:1
4	 **7d**	90	98	99:1
5	 **7e**	89	96	98:2
6	 **7f**	88	98	99:1

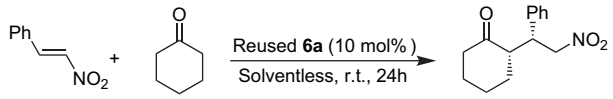
Table 2 (*continued*)

Entry	Product	Yield[b] (%)	ee[c] (%)	dr[d]
7	 **7g**	94	97	98:2
8	 **7h**	92	99	99:1
9	 **7i**	86	98	98:2
10	 **7j**	85	>99	99:1
11	 **7k**	87	>99	>99:1
12	 **7l**	84	98	98:2
13	 **7m**	88	95	95:5
14	 **7n**	85	93	96:4
15	 **7o**	92	52	—
16	 **7p**	87	41	75:25

[a] Nitroolefin (0.5 mmol), ketone (0.4 mL), and **6a** (contains 0.05 mmol of active loading) under solvent-free reaction conditions at room temperature (25 °C) for 36 h.
[b] Isolated yields.
[c] Determined by HPLC using chiralpak AD-H or AS-H column.
[d] Diastereomeric ratio, dr (*syn*/*anti*), determined by ^{1}H NMR spectroscopy.

being dried, **6a** was reused directly without further purification, and it was recovered and reused for six consecutive trials without significant loss of activity and enantioselectivity (entries 1–6, Table 3).

Table 3
Successive trials by using recoverable organocatalyst **6a**[a]



Run	Yield[b] (%)	ee[c] (%)	dr[d]
1	91	98	98:2
2	89	98	98:2
3	90	97	98:2
4	88	98	98:2
5	81	98	98:2
6	85	98	97:3

[a] Nitrostyrene (0.5 mmol), cyclohexanone (0.4 mL), and reused **6a** (contains 0.05 mmol of active loading) under solvent-free reaction conditions at room temperature (25 °C) for 36 h.
[b] Isolated yields.
[c] Determined by HPLC using chiralpak AD-H column.
[d] Diasteromeric ratio, dr (*syn*/*anti*), determined by ^{1}H NMR spectroscopy.

3. Conclusion

In summary, we have developed a novel silica gel supported pyrrolidine-based chiral ionic liquids, which are capable of catalyzing Michael addition reaction of ketones with nitrostyrenes in good yields, excellent enantioselectivities and high diastereoselectivities. The method is operationally simple, the catalyst can be easily recycled, and reused six times without a significant loss of catalytic activity and stereoselectivity. Further investigation on the application of this supported organocatalyst in asymmetric catalysis is still underway in our laboratory.

4. Experimental

4.1. Physical measurements and materials

All ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 300 MHz FT-NMR spectrometer (300 and 75 MHz, for ^{1}H and ^{13}C NMR, respectively). Chemical shifts were given as δ value with reference to tetramethylsilane (TMS) as the internal standard. HPLC analysis was performed on Agilent 1100 using a Chiralpak AD-H or AS-H column purchased from Daicel Chemical Industries, Ltd. Products were purified by flash column chromatography on 230–400 mesh silica gel, SiO_2.

The chemicals were purchased from commercial suppliers (Aldrich, USA and Shanghai Chemical Company, China) and were used without purification prior to use. All reactions unless otherwise noted were carried out directly under air. Nitroolefins were prepared according to the literature procedures.[18] (*S*)-*N*-(*tert*-Butoxycarbonyl)prolinol (**4**) and (*S*)-*N*-(*tert*-butoxycarbonyl)prolinol *p*-toluenesulfonate were prepared according to the literature.[19]

4.2. Preparation of silica gel supported pyrrolidine-based chiral ionic liquids

*4.2.1. Preparation of benzyl chloride functionalized silica (**1**)*

A 100 mL of round-bottom flask were introduced successively 30 mL of anhydrous toluene, 5.0 g of activated silica, and 2.0 g of trichloro[4-(chloromethyl)phenyl]silane. The solution was refluxed for 24 h at 120 °C under an inert atmosphere. The solution was filtered and the solid was washed subsequently with toluene, dichloromethane, and methanol, and dried under reduced pressure at 80 °C for 10 h. The benzyl chloride functionalized silica was obtained (5.81 g). The loading of the modified silica was readily quantified via CHN microanalysis and found to be 1.12 mmol g^{-1} based on carbon percentage.

The propylchloride functionalized silica (**2**) was prepared according to the above procedure and (3-chloropropyl)trimethoxysilane was used instead of trichloro[4-(chloromethyl)phenyl]silane in the procedure. The loading of the propylchloride functionalized silica was readily quantified via CHN microanalysis and found to be 0.78 mmol g^{-1} based on carbon percentage.

4.2.2. Preparation of silica gel supported pyrrolidine-based chiral ionic liquids

*Preparation of **5**.* Imidazole (680 mg, 10 mmol) and NaH (480 mg, purity 60%, 12 mmol) were added in 30 mL of anhydrous acetonitrile and stirred at room temperature for 0.5 h, then (*S*)-*N*-(*tert*-butoxycarbonyl)prolinol *p*-toluenesulfonate (1.78 g, 5 mmol) was added. The mixture was heated at reflux for 5 h under nitrogen atmosphere and then cooled to room temperature. Solvent was removed under vacuo and the residue was diluted with 10 mL of water. The resulted mixture was extracted with chloroform (20 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatograph on silica gel (eluant, EtOAc/EtOH=5:1, v/v) to give the desired product **5** as colorless crystal (1.08 g, 86% of yield).

*Preparation of **6a** and **6b**.* Under nitrogen atmosphere, **5** (0.75 g, 3.0 mmol) and **1** (2.0 g) or **2** (3.0 g) were mixed in toluene (15 mL). The solution was kept at 70 °C and stirred for 24 h. Then the solution was filtered and the solid was washed with chloroform, methanol, and ethyl ether, respectively, and dried under vacuo at 60 °C, the Boc-protected supported chiral ionic liquid was obtained as pale yellow solid. Then the pale yellow solid was deprotected by using 5 M HCl in ethanol solution (20 mL) with vigorously stirring at room temperature for 4 h, and the solution was filtered and subsequently neutralized with NEt_3 (5 mL). The solution was filtered and the solid was washed with ethanol and ethyl ether, respectively, and dried under vacuo at room temperature. Catalyst **6a** was readily quantified via CHN microanalysis and found to be 0.92 mmol g^{-1} of pyrrolidine-based imidazole, and **6b** was readily quantified via CHN microanalysis and found to be 0.61 mmol g^{-1} of pyrrolidine-based imidazole based on nitrogen percentage.

4.3. Typical experimental procedure for Michael addition reaction

The supported catalyst **6a** (54 mg, containing pyrrolidine-based organocatalyst 0.05 mmol), *trans*-β-nitrostyrene (75 mg, 0.5 mmol), and cyclohexanone (0.4 mL) were added to a 5 mL of round-bottom flask, the mixture was stirred at room temperature (25 °C) for 36 h, then washed with ethyl acetate (3 mL×3) and the combined ethyl acetate was concentrated. Flash chromatography (hexane/ethyl acetate=3:1, v/v) furnished the corresponding γ-nitroketone as a colorless crystal (112.3 mg, 91% yield).

*4.3.1. (S)-2-((R)-2-Nitro-1-phenylethyl)cyclohexanone **7a**[7b]*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.23 (m, 3H), 7.19–7.16 (m, 2H), 4.97 (dd, *J*=4.5, 12.0 Hz, 1H), 4.64 (dd, *J*=9.9, 12.3 Hz, 1H), 3.76 (dt, *J*=4.5, 9.9 Hz, 1H), 2.68 (ddd, *J*=7.8, 8.4, 11.7 Hz, 1H), 2.49–2.33 (m, 2H), 2.10–2.04 (m, 1H), 1.80–1.52 (m, 4H), 1.29–1.15 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 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. *syn*/*anti*=99:1; ee=98%; HPLC (Chiralcel AD-H, *i*-propanol/hexane=10:90, flow rate 1.0 mL/min, λ=254 nm): t_{minor}=10.0 min, t_{major}=12.8 min.

*4.3.2. (S)-2-((R)-1-(4-Methylphenyl)-2-nitroethyl)cyclohexanone **7b**[14b]*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10 (d, *J*=8.1 Hz, 2H), 7.01 (d, *J*=8.1 Hz, 2H), 4.89 (dd, *J*=4.8, 12.3 Hz, 1H), 4.57 (dd, *J*=9.6, 12.3 Hz, 1H), 3.69 (dt, *J*=4.8, 9.9 Hz, 1H), 2.66–2.58 (m, 1H), 2.45–2.28 (m, 2H), 2.26 (s, 3H), 2.10–1.99 (m, 1H), 1.78–1.50 (m, 4H), 1.27–1.14 (m, 1H);

^{13}C NMR (75 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. *syn*/*anti*=99:1; ee=99%; $[\alpha]_D^{25}$ −26.3 (*c* 1.2, CH_3Cl); HPLC (Chiralpak AD-H, *i*-propanol/hexane=10:90, flow rate 1.0 mL/min, λ=254 nm): t_{minor}=8.48 min, t_{major}=10.68 min.

4.3.3. (S)-2-((R)-1-(4-Methoxyphenyl)-2-nitroethyl)cyclohexanone **7c**[7a]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.08 (d, *J*=8.7 Hz, 2H), 6.84 (d, *J*=8.7 Hz, 2H), 4.93 (dd, *J*=4.5, 12.3 Hz, 1H), 4.58 (dd, *J*=9.9, 12.0 Hz, 1H), 3.78 (s, 3H), 3.72 (dt, *J*=4.5, 9.9 Hz, 1H), 2.68–2.60 (m, 1H), 2.52–2.32 (m, 2H), 2.12–2.03 (m, 1H), 1.82–1.51 (m, 4H), 1.30–1.16 (m, 1H); ^{13}C NMR (75 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. *syn*/*anti*=99:1; ee=99%; $[\alpha]_D^{25}$ −19.2 (*c* 1.2, CH_3Cl); HPLC (Chiralpak AD-H, *i*-propanol/hexane=10:90, flow rate 1.0 mL/min, λ=254 nm): t_{minor}=13.22 min, t_{major}=16.41 min.

4.3.4. (S)-2-((R)-1-(4-Bromophenyl)-2-nitroethyl)cyclohexanone **7d**[15a]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (d, *J*=8.7 Hz, 2H), 7.06 (d, *J*=8.4 Hz, 2H), 4.92 (dd, *J*=4.5, 12.6 Hz, 1H), 4.60 (dd, *J*=9.9, 12.6 Hz, 1H), 3.74 (dt, *J*=4.5, 9.9 Hz, 1H), 2.69–2.59 (m, 1H), 2.52–2.32 (m, 2H), 2.15–2.05 (m, 1H), 1.83–1.54 (m, 4H), 1.30–1.17 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.9, 148.5, 140.1, 134.8, 129.9, 122.9, 78.0, 52.2, 43.6, 42.7, 33.2, 28.3, 25.0. *syn*/*anti*=99:1; ee=98%; HPLC (Chiralpak AD-H, *i*-propanol/hexane=10:90, flow rate 1.0 mL/min, λ=254 nm): t_{minor}=11.92 min, t_{major}=18.65 min.

4.3.5. (S)-2-((R)-1-(3-Bromophenyl)-2-nitroethyl)cyclohexanone **7e**[11g]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 (d, *J*=7.8 Hz, 1H), 7.33 (s, 1H), 7.21 (t, *J*=7.8 Hz, 1H), 7.10 (d, *J*=7.5 Hz, 1H), 4.93 (dd, *J*=4.5, 12.9 Hz, 1H), 4.62 (dd, *J*=9.9, 12.6 Hz, 1H), 3.77–3.68 (m, 1H), 2.65–2.62 (m, 1H), 2.50–2.38 (m, 2H), 2.11–2.05 (m, 1H), 1.79–1.57 (m, 4H), 1.30–1.20 (m, 1H); ^{13}C NMR (75 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. *syn*/*anti*=98:2; ee=96%; HPLC (Chiralpak AD-H, *i*-propanol/hexane=10:90, flow rate 1.0 mL/min, λ=254 nm): t_{minor}=10.86 min, t_{major}=12.21 min.

4.3.6. (S)-2-((R)-1-(2-Bromophenyl)-2-nitroethyl)cyclohexanone **7f**[11f]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57 (d, *J*=8.1 Hz, 1H), 7.32–7.21 (m, 2H), 7.15–7.10 (m, 1H), 4.90 (d, *J*=8.1 Hz, 2H), 4.32 (dd, *J*=6.3, 6.6 Hz, 1H), 2.91–2.88 (m, 1H), 2.45–2.34 (m, 2H), 2.12–2.08 (m, 1H), 1.84–1.53 (m, 4H), 1.40–1.20 (m, 1H); ^{13}C NMR (75 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. *syn*/*anti*=99:1; ee=98%; HPLC (Chiralpak AD-H, *i*-propanol/hexane=10:90, flow rate 1.0 mL/min, λ=254 nm): t_{minor}=10.00 min, t_{major}=15.90 min.

4.3.7. (S)-2-((R)-1-(4-Fluorophenyl)-2-nitroethyl)cyclohexanone **7g**[11g]

^{1}H NMR (300 Hz, $CDCl_3$): δ 7.16 (d, *J*=8.1 Hz, 2H), 7.02 (d, *J*=8.4 Hz, 2H), 4.94 (dd, *J*=4.5, 12.6 Hz, 1H), 4.59 (dd, *J*=10.2, 12.6 Hz, 1H), 3.81–3.73 (m, 1H), 2.69–2.61 (m, 1H), 2.50–2.32 (m, 2H), 2.12–2.05 (m, 1H), 1.88–1.51 (m, 4H), 1.30–1.15 (m, 1H); ^{13}C NMR (75 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. *syn*/*anti*=98:2; ee=97%; HPLC (Chiralpak AD-H, *i*-propanol/hexane=10:90, flow rate 1.0 mL/min, λ=254 nm): t_{minor}=11.69 min, t_{major}=15.79 min.

4.3.8. (S)-2-((R)-1-(4-Chlorophenyl)-2-nitroethyl)cyclohexanone **7h**[11g]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (d, *J*=8.4 Hz, 2H), 7.16 (d, *J*=8.4 Hz, 2H), 4.93 (dd, *J*=4.5, 12.6 Hz, 1H), 4.60 (dd, *J*=9.9, 12.6 Hz, 1H), 3.78–3.70 (m, 1H), 2.68–2.60 (m, 1H), 2.50–2.32 (m, 2H), 2.12–2.05 (m, 1H), 1.83–1.56 (m, 4H), 1.29–1.15 (m, 1H); ^{13}C NMR (75 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. *syn*/*anti*=99:1; ee=99%; $[\alpha]_D^{25}$ −29.8 (*c* 1.0, CH_3Cl); HPLC (Chiralpak AD-H, *i*-propanol/hexane=10:90, flow rate 1.0 mL/min, λ=254 nm): t_{minor}=15.29 min, t_{major}=18.60 min.

4.3.9. (S)-2-((R)-1-(Benzo[d][1,3]dioxol-5-yl)-2-nitroethyl)-cyclohexanone **7i**[11f]

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.75 (d, *J*=7.8 Hz, 1H), 6.66 (s, 2H), 6.64–6.58 (m, 2H), 5.96 (s, 2H), 4.92 (dd, *J*=4.5, 12.3 Hz, 1H), 4.56 (dd, *J*=4.5, 9.9 Hz, 1H), 3.67 (dt, *J*=4.5, 9.9 Hz, 1H), 2.68–2.56 (m, 1H), 2.51–2.33 (m, 2H), 2.15–2.07 (m, 1H), 1.83–1.61 (m, 4H), 1.31–1.25 (m, 1H); ^{13}C NMR (75 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. *syn*/*anti*=98:2; ee=98%; HPLC (Chiralpak AD-H, *i*-propanol/hexane=10:90, flow rate 1.0 mL/min, λ=254 nm): t_{minor}=17.49 min, t_{major}=18.70 min.

4.3.10. (S)-2-((S)-1-(Furan-2-yl)-2-nitroethyl)cyclohexanone **7j**[7b]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (d, *J*=1.2 Hz, 1H), 6.29 (dd, *J*=1.8, 3.3 Hz, 1H), 6.16 (d, *J*=3.3 Hz, 1H), 4.81–4.62 (m, 2H), 3.99 (dt, *J*=4.8, 9.3 Hz, 1H), 2.79–2.71 (m, 1H), 2.51–2.32 (m, 2H), 2.16–2.07 (m, 1H), 1.92–1.56 (m, 4H), 1.35–1.23 (m, 1H); ^{13}C NMR (75 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. *syn*/*anti*=99:1; ee>99%; $[\alpha]_D^{25}$ −15.2 (*c* 1.5, CH_3Cl); HPLC (Chiralpak AD-H, *i*-propanol/hexane=10:90, flow rate 1.0 mL/min, λ=254 nm): t_{major}=10.53 min, t_{minor}=12.86 min.

4.3.11. (S)-2-((R)-2-(Naphthalen-1-yl)-2-nitroethyl)cyclohexanone **7k**[7d]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84–7.79 (m, 3H), 7.63 (d, *J*=1.2 Hz, 1H), 7.49–7.46 (m, 2H), 7.30–7.26 (m, 1H), 5.02 (dd, *J*=4.5, 12.6 Hz, 1H), 4.73 (dd, *J*=9.9, 12.3 Hz, 1H), 3.99–3.92 (m, 1H), 2.78–2.75 (m, 1H), 2.50–2.47 (m, 2H), 2.42–2.39 (m, 1H), 1.76–1.58 (m, 4H), 1.29–1.25 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.8, 135.1, 133.4, 132.8, 128.9, 127.9, 127.7, 126.5, 126.2, 125.2, 78.8, 76.6, 52.5, 44.1, 42.8, 33.3, 28.5, 25.0. *syn*/*anti*>99:1; ee>99%; $[\alpha]_D^{25}$ −69.2 (*c* 1.1, CH_3Cl); HPLC (Chiralpak AD-H, *i*-propanol/hexane=30:70, flow rate 1.0 mL/min, λ=254 nm): t_{minor}=8.83 min, t_{major}=14.45 min.

4.3.12. (S)-2-((R)-1-(Naphthalen-1-yl)-2-nitroethyl)cyclohexanone **7l**[11f]

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (s, 1H), 7.86 (d, *J*=7.8 Hz, 1H), 7.75 (d, *J*=8.1 Hz, 1H), 7.60–7.35 (m, 4H), 5.06 (dd, *J*=4.5, 12.6 Hz, 1H), 4.91–4.88 (m, 1H), 4.76 (s, 1H), 2.65 (br s, 1H), 2.45–2.38 (m, 2H), 2.09–2.04 (m, 1H), 1.69–1.47 (m, 4H), 1.29–1.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.1, 134.5, 128.9, 128.1, 126.3, 125.7, 125.1, 123.5, 122.4, 78.6, 53.5, 42.7, 36.5, 33.1, 28.5, 25.1. *syn*/*anti*=98:2; ee=98%; HPLC (Chiralpak AS-H, *i*-propanol/hexane=30:70, flow rate 1.0 mL/min, λ=254 nm): t_{minor}=10.60 min, t_{major}=15.61 min.

4.3.13. (R)-Tetrahydro-3-((R)-2-nitro-1-phenylethyl)pyran-4-one **7m**[14b]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39–7.27 (m, 3H), 7.24–7.17 (m, 2H), 4.78–4.62 (m, 2H), 4.11–4.02 (m, 1H), 3.87–3.75 (m, 2H), 3.70 (dd, *J*=4.8, 11.7 Hz, 1H), 3.29 (dd, *J*=9.6, 11.4 Hz, 1H), 2.93–2.85 (m, 1H), 2.73–2.62 (m, 1H), 2.58–2.49 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.3, 136.3, 129.2, 128.3, 128.0, 78.6, 54.7, 44.6, 43.5, 35.2, 31.7. *syn*/*anti*=95:5; ee=95%; HPLC (Chiralpak AS-H, *i*-propanol/hexane=30:70, flow rate 1.0 mL/min, λ=254 nm): t_{minor}=11.63 min, t_{major}=16.93 min.

4.3.14. (R)-Tetrahydro-3-((R)-2-nitro-1-phenylethyl)thiopyran-4-one **7n**[14b]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.28 (m, 3H), 7.23–7.17 (m, 2H), 4.75 (dd, *J*=4.8, 12.6 Hz, 1H), 4.65 (dd, *J*=9.6, 12.3 Hz, 1H), 4.01

(dt, J=4.5, 10.2 Hz, 1H), 3.10–2.77 (m, 5H), 2.62 (ddd, J=1.5, 4.2, 13.8 Hz, 1H), 2.46 (dd, J=9.6, 13.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.6, 136.7, 129.4, 128.6, 127.9, 78.8, 71.9, 69.3, 53.5, 43.0, 41.5. *syn*/*anti*=96:4; ee=93%; HPLC (Chiralpak AS-H, *i*-propanol/hexane=30:70, flow rate 1.0 mL/min, λ=254 nm): t_{minor}=11.85 min, t_{major}=17.63 min.

4.3.15. (R)-5-Nitro-4-phenylpentan-2-one **7o**[15a]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.22 (m, 5H), 4.75–4.51 (m, 2H), 4.05–4.00 (m, 1H), 2.94 (d, J=6.6 Hz, 2H), 2.14 (s, 3H); ^{13}C NMR (75 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. ee=52%; HPLC (Chiralpak AD-H, *i*-propanol/hexane=10:90, flow rate 1.0 mL/min, λ=254 nm): t_{minor}=11.74 min, t_{major}=12.79 min.

4.3.16. (S)-2-((R)-2-Nitro-1-phenylethyl)cyclopentanone **7p**[7d]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28–7.20 (m, 3H), 7.13–7.08 (m, 2H), 5.30–5.23 (m, 1H), 4.95 (dd, J=9.9, 12.6 Hz, 1H), 3.67–3.60 (m, 1H), 2.34–2.25 (m, 2H), 2.10–2.06 (m, 1H), 1.87–1.78 (m, 2H), 1.72–1.65 (m, 1H), 1.53–1.37 (m, 1H); ^{13}C NMR (75 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. *syn*/*anti*=75:25; ee=41%; HPLC (Chiralpak AD-H, *i*-propanol/hexane=10:90, flow rate 1.0 mL/min, λ=254 nm): t_{minor}=8.83 min, t_{major}=14.45 min.

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