A Highly Efficient and Recyclable Ionic Liquid Anchored Pyrrolidine Catalyst for Enantioselective Michael Additions

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Abstract: Highly enantioselective Michael addition of cyclohexanone to aryl nitroolefins in the presence of an ionic liquid anchored pyrrolidine (10 mol%) and TFA (5 mol%) generated the corresponding adducts in high yields (up to 95%) with excellent diastereoselectivities (up to >99:1 dr) and enantioselectivities (up to >99% ee). Furthermore, the catalyst could be recycled and reused at least eight times without loss of its catalytic activity.

Key words: chiral ionic liquid, pyrrolidine unit, organocatalyst, asymmetric Michael reaction, aryl nitroolefin, cyclohexanone

The asymmetric Michael addition reaction is widely recognized as one of the most powerful enantioselective carbon–carbon bond-forming reactions in synthetic organic chemistry.[1] Due to the growing need for its transformation to an environment-friendly metal-free catalyzed asymmetric synthesis, the development of efficient small-molecule asymmetric organocatalysts have attracted considerable attention from a large number of organic chemists working in the area of asymmetric synthesis. In 2001, Barbas and co-workers[2] and List et al.[3] independently reported the first organocatalytic addition of ketones to *trans*-β-nitrostyrene with L-proline as the catalyst in good yields, but with very low enantioselectivities (0–23% ee). Since these preliminary studies, very effective catalytic systems, such as pyrrolidine-based catalytic derivatives,[4] thiourea-amine bifunctional catalysts,[5] cinchona alkaloid-based bifunctional organocatalyst,[6] chiral diaime,[7] etc. have been developed for the asymmetric Michael reaction of ketones with nitroalkenes, and the process is generally *syn*-selective. However, these organocatalysts are generally more complex, and therefore have to be prepared by multistep synthesis. Furthermore these organocatalysts could not be recovered and recycled.

In recent years, ionic liquids have become an exciting area of research. Ionic liquids (ILs) are salts and entirely composed of ions, possess attractive properties, for example, negligible volatility, high thermal stability, viscosity, and water immiscibility.[8] Therefore ILs have been extensively investigated as easily recycled and reused reaction media instead of conventional molecular organic solvents in numerous catalytic reactions. In addition, ionic liquids with functional groups [called 'task-specific' ionic liquids (TSILs)][9] have been further applied as soluble and supportable organocatalysts for asymmetric reaction by attachment of catalytically active chiral groups onto the side chains of ionic liquids. Very recently, some recyclable supported organocatalysts for asymmetric reaction have been developed with high enantioselectivities. For example, Luo et al.,[10] Headley and co-workers,[11] Xu et al.,[12] and Liang and co-workers[13] have independently reported excellent ionic liquid supported organocatalysts for the asymmetric Michael reaction to nitrostyrenes. Most recently, Wang and co-workers have reported a mild and efficient procedure for asymmetric Michael additions of cyclohexanone to chalcones catalyzed by an amino acid ionic liquid.[14] These protocols provide unique methodology in asymmetric Michael additions. In this context, a modular and more efficient approach to constructing chiral ionic liquids (CILs) through 'click chemistry', which introduces a chiral pyrrolidine moiety into an imidazolium ionic liquid, was developed (Scheme 1). Major advantages of the ionic liquid-anchored pyrrolidine are that they not only serve as organocatalysts, but also are easily recovered from reaction mixture, making it a recyclable green ionic liquid. Chiral ionic liquids (CILs) **3**, were prepared uneventfully from L-proline as shown in Scheme 1. We were pleased to find that the designed novel organocatalysts **3a**, **3b**, and **3c**, catalyzed the reaction of cyclohexanone with aryl nitroolefins smoothly in high yields with excellent diastereoselectivities and enantioselectivities (Scheme 1).

Initially, various solvents were examined at room temperature using **3a** as a catalyst and *trans*-nitroolefin as a substrate. The Michael addition of cyclohexanone to nitrostyrene was chosen as a model reaction. As shown in Table 1, in polar solvents, such as THF, $CHCl_3$, CH_2Cl_2, MeCN, H_2O, MeOH, and EtOH, the Michael additions proceeded smoothly to give the corresponding product in moderate to excellent conversions with good to high enantioselectivities (Table 1, entries 1–7), whereas in nonpolar solvents, such as hexane, only a trace amount of the desired adduct was observed (Table 1, entry 8). It is probably due to the insolubility of the chiral ionic liquid **3a** in the nonpolar solvent of hexane. Since catalyst **3a** proved to be an efficient catalyst in terms of asymmetric induction of Michael addition, we then screened different anion

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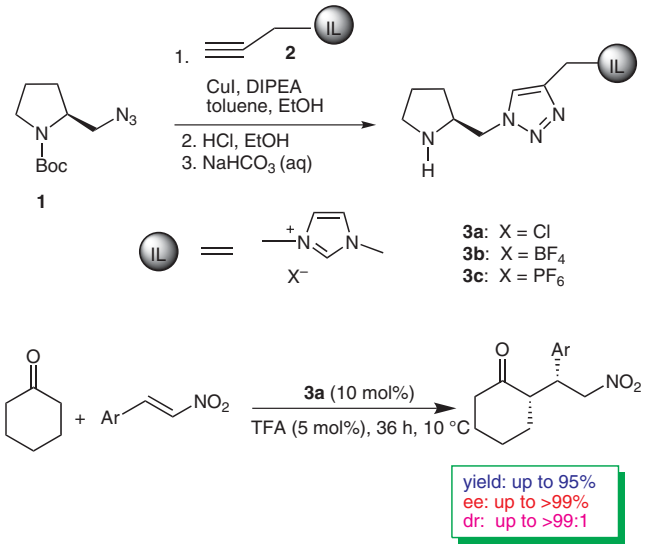
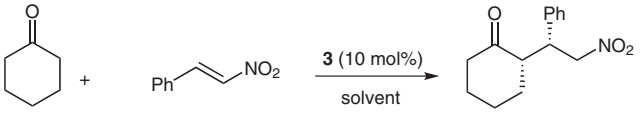


Scheme 1 Synthesis of chiral ionic liquids **3a**, **3b**, and **3c** and their application in the Michael addition

swapped chiral ionic liquid. The exchange of Cl^- to BF_4^-, and Cl^- to PF_6^- afforded comparable catalysts, **3b** and **3c**, respectively, with slightly detrimental effect on both the activities and selectivities (Table 1, entries 9 and 10). In addition, in the absence of TFA, they could not decrease the reaction rate dramatically and formed the product with slight loss of enantiomeric excess (Table 1, entry 11).

Table 1 Effect of Catalyst and Solvent on the Michael Reaction[a]

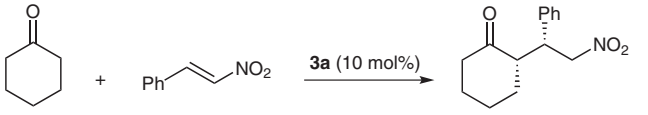


Entry	Catalyst	Solvent	Yield (%)[b]	ee (%)[c]	dr (*syn*/*anti*)[d]
1	**3a**	THF	82	90	94:6
2	**3a**	$CHCl_3$	85	92	97:3
3	**3a**	CH_2Cl_2	87	91	95:5
4	**3a**	MeCN	86	93	96:4
5	**3a**	H_2O	72	95	98:2
6	**3a**	MeOH	90	96	99:1
7	**3a**	EtOH	97	98	99:1
8	**3a**	hexane	10	–	–
9	**3b**	EtOH	94	96	99:1
10	**3c**	EtOH	89	97	98:2
11	**3a**[e]	EtOH	87	93	98:2

[a] Reaction conditions: nitrostyrene (1.0 mmol), cyclohexanone (2.0 mmol), catalyst **3** (containing 0.10 mmol of active loading), and TFA (0.05 mmol) in solvent (2 mL) at r.t. for 36 h.
[b] Isolated yields.
[c] Determined by HPLC using chiral column.
[d] Diastereomeric ratio, determined by ^{1}H NMR spectroscopy.
[e] In the absence of TFA.

The effect of reaction temperature and time on the Michael reaction was also investigated. The results are listed in Table 2. At room temperature (25 °C), the reaction took place smoothly with excellent isolated yield, good enantioselectivity, and high diastereoselectivity (Table 2, entry 1). An excellent enantioselectivity (>99% ee) was obtained along with high yield and diastereoselectivity (>99:1 dr) when the reaction was performed at 10 °C (Table 2, entry 3). Meanwhile, a lower yield was observed when the reaction was performed at 0 °C (Table 2, entry 2). It is interesting to note that isolated yields, both of ee and dr values, were maintained up to 95%, >99%, and >99:1, respectively, when up to 10 mol% of ionic liquid anchored pyrrolidine **3a** was added to the reaction mixture. A lower yield of the Michael addition product was isolated when less than 10 mol% of **3a** loading was used in the reaction. It was found that the reaction needed more than 36 hours to complete at 10 °C.

Table 2 Effect of Temperature and Time on the Michael Reaction[a]



Entry	Temp (°C)	Time (h)	Yield (%)[b]	ee (%)[c]	dr (*syn*/*anti*)[d]
1	25	36	97	98	99:1
2	0	36	80	>99	>99:1
3	10	36	95	>99	>99:1
4	10	24	90	>99	>99:1
5	10	48	96	>99	>99:1
6[e]	10	36	82	>99	>99:1
7[f]	10	36	95	>99	>99:1

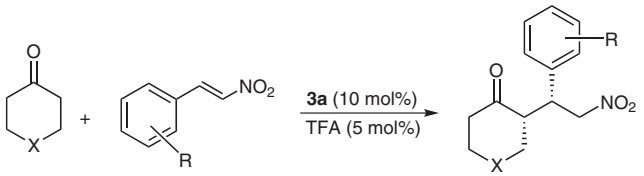
[a] Reaction conditions: nitrostyrene (1.0 mmol), cyclohexanone (2.0 mmol), catalyst **3a** (containing 0.10 mmol of active loading), and TFA (0.05 mmol) in EtOH (2.0 mL) at the reaction temperature and time indicated in Table 2.
[b] Isolated yields.
[c] Determined by HPLC using chiral column.
[d] Diastereomeric ratio, determined by ^{1}H NMR spectroscopy.
[e] In the presence of **3a** (0.05 mmol).
[f] In the presence of **3a** (0.20 mmol).

With the optimal conditions in hand, we then examined a variety of Michael donors and nitroolefins to establish the general utility of this asymmetric transformation, and the results are summarized in Table 3. The reactions worked extremely well with Michael donors and nitroolefins to generate the corresponding adducts in good yields (85–95%), high diastereoselectivities (up to >99:1 dr), and excellent enantioselectivities (up to >99% ee). Both electron-rich and electron-deficient nitrostyrenes were excellent Michael acceptors for cyclohexanone (Table 3, entries 1–12). Generally, substituent groups on the phenyl ring slightly influenced the diastereoselectivities and enantioselectivities; for example, enantioselectivities for

aryl nitroalkenes with substitution at the *para*-position in the phenyl ring were very high (Table 3, entries 2–5). Moving the substituent to the *ortho*-position led to a decrease in the enantioselectivities (Table 3, entries 11 and 12). However, 3,4-disubstituted aryl nitroolefins could also give the desired products with high stereoselectivities (Table 3, entries 7 and 8). The Michael reactions were evaluated with other Michael acceptors and donors as well, and high enantioselectivities and diastereoselectivities were obtained (Table 3, entries 13–15).

The recyclability and reusability of the ionic liquid anchored pyrrolidine catalyst was examined for the reaction of cyclohexanone to aryl nitroolefin with **3a** as the representative catalyst. It was found that **3a** still maintained the biphasic property of ionic liquids and could be easily recycled by precipitation with simple disposal. As revealed in Table 4, the catalyst **3a** was recycled and reused at least eight times without loss of catalytic activity.

Table 3 Ionic Liquid Anchored Pyrrolidine **3a** Catalyzed Michael Addition[a]



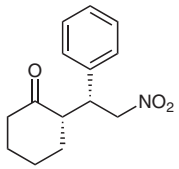
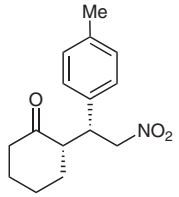
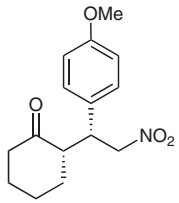
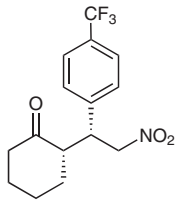
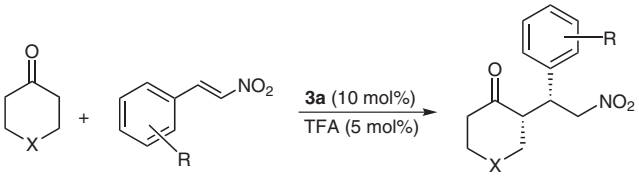
Entry	Product	Yield (%)[b]	ee (%)[c]	dr (*syn*/*anti*)[d]
1		95	>99	>99:1
2		94	>99	>99:1
3		95	>99	>99:1
4		94	>99	>99:1

Table 3 Ionic Liquid Anchored Pyrrolidine **3a** Catalyzed Michael Addition[a] (continued)



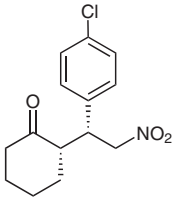
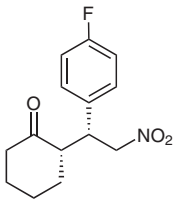
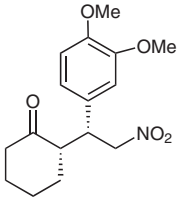
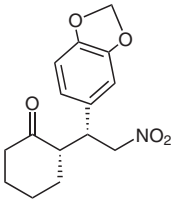
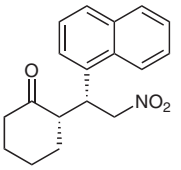
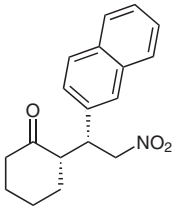
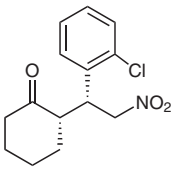
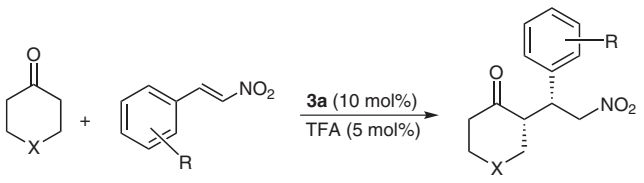
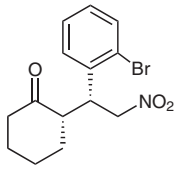
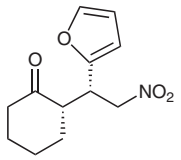
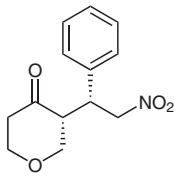
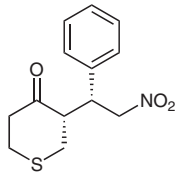
Entry	Product	Yield (%)[b]	ee (%)[c]	dr (*syn*/*anti*)[d]
5		93	>99	>99:1
6		92	97	>99:1
7		88	>99	>99:1
8		85	>99	>99:1
9		93	>99	>99:1
10		95	>99	>99:1
11		93	95	>99:1

Table 3 Ionic Liquid Anchored Pyrrolidine **3a** Catalyzed Michael Addition[a] (continued)



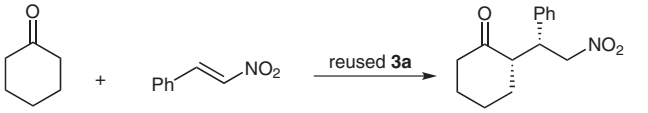
Entry	Product	Yield (%)[b]	ee (%)[c]	dr (*syn*/*anti*)[d]
12		95	98	>99:1
13		89	91	>99:1
14		88	96	>99:1
15		92	94	99:1

[a] Reaction conditions: nitroolefin (1.0 mmol), cyclohexanone (2.0 mmol), catalyst **3a** (containing 0.10 mmol of active loading), and TFA (0.05 mmol) in EtOH (2.0 mL) at 10 °C for 36 h.
[b] Isolated yields.
[c] Determined by HPLC using chiral column.
[d] Diastereomeric ratio, determined by ^{1}H NMR spectroscopy.

In summary, we have developed highly efficient imidazolium anchored pyrrolidine type organocatalysts from L-proline through a click reaction. The catalyst **3a** has been successfully applied to the asymmetric Michael reaction of ketones with aryl nitroolefins. The remarkably better catalytic performance was provided by the reactions in terms of productivities (up to 95%), diastereoselectivities (up to >99:1 dr), and enantioselectivities (up to >99% ee). Moreover, ionic liquid anchored pyrrolidine **3a** could be easily recycled and reused for at least eight times without loss of its catalytic activity. Further investigation on the application of this kind of organocatalysts to the other asymmetric reactions is still in progress in our laboratory.

Melting points were recorded on a WRS-2B melting point apparatus and are uncorrected. All ^{1}H NMR and ^{13}C NMR spectra were recorded on 300 or 400 MHz Bruker FT-NMR spectrometer. Chemical shift are given as δ value with reference to TMS as internal standard. IR spectra were obtained by using a Nicolet NEXUS 470

Table 4 Successive Trials with Recoverable Catalyst **3a**[a]



Trial	Yield (%)[b]	ee (%)[c]	dr (*syn*/*anti*)[d]
1	95	>99	>99:1
2	94	>99	>99:1
3	93	>99	>99:1
4	91	>99	>99:1
5	92	>99	>99:1
6	90	>99	>99:1
7	91	>99	>99:1
8	90	>99	>99:1

[a] Reaction conditions: nitrostyrene (1.0 mmol), cyclohexanone (2.0 mmol), reused catalyst **3a** (containing 0.10 mmol of active loading), and TFA (0.05 mmol) in EtOH (2.0 mL) at 10 °C for 36 h.
[b] Isolated yields.
[c] Determined by HPLC using chiral column.
[d] Diastereomeric ratio, determined by ^{1}H NMR spectroscopy.

1100 using a Chiralpak AD-H or AS-H column purchased from Daicel Chemical Industries, Ltd. The CHN analyses were performed on a Vario El III elementary analyzer. Products were purified by flash chromatography on 230–400 mesh silica gel. The chemicals were purchased from commercial suppliers (Aldrich, USA and Shanghai Chemical Company, China) and were used without purification prior to use. All reactions were carried out directly under air, unless otherwise noted. Nitroolefins were prepared according to literature procedures.[15]

Catalyst 3a

To a solution of **1** (226 mg, 1.0 mmol) in EtOH (5.0 mL) were added **2** (X^- = Cl^-, 121 mg, 1.0 mmol), CuI (10 mg, 0.05 mmol), and DIPEA (170 μL, 2.0 mmol). The mixture was stirred at reflux temperature for 24 h. After removal of the solvent under reduced pressure, the residue was treated with aq HCl (5.0 M)–EtOH mixture (5 mL) to remove the Boc protection group. The obtained solution was subsequently treated with aq sat. $NaHCO_3$ (30 mL) at r.t. After removal of the solvent under reduced pressure, the resulting residue was purified by flash chromatography on silica gel to give **3a** as a pale yellow oil; yield: 180.3 mg (73%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.13 (t, J = 1.2 Hz, 2 H), 9.41 (s, 1 H), 8.58 (s, 1 H), 7.87 (s, 1 H), 7.75 (s, 1 H), 5.58 (s, 2 H), 5.00–4.94 (m, 1 H), 4.88–4.83 (m, 1 H), 3.87 (s, 3 H), 3.25–3.22 (m, 1 H), 3.12 (d, J = 5.6 Hz, 1 H), 2.15–2.12 (m, 1 H), 1.99–1.96 (m, 1 H), 1.89 (t, J = 4.0 Hz, 1 H), 1.74–1.68 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 140.0, 136.7, 125.9, 123.7, 122.5, 58.9, 49.6, 44.6, 43.5, 35.8, 27.9, 22.8.

Anal. Calcd for $C_{12}H_{19}ClN_6$: C, 50.97; H, 6.77; N, 29.72. Found: C, 50.81; H, 6.89; N, 29.58.

Catalyst 3b

To a solution of **3a** (247.0 mg, 1.00 mmol) in MeCN and acetone (20 mL, 4:1) was added well-sieved $NaBF_4$ (549.08 mg, 5.00 mmol). The mixture was vigorously stirred at r.t. for 2 d. The mixture was filtered to remove the inorganic salts and the filtrate was triturated with $AgBF_4$ solution (200 mg in MeCN) until no more

precipitate was formed. The filtrate was filtered again and concentrated. The residue was diluted with $CHCl_3$ (50 mL) and the insoluble was removed by filtration. The clear filtrate was concentrated in vacuo and the residue was purified by flash chromatography on silica gel to give **3b** as a pale yellow oil; yield: 317.1 mg (95%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.95 (t, *J* = 1.2 Hz, 2 H), 8.45 (s, 1 H), 8.12 (s, 1 H), 7.59 (s, 1 H), 7.25 (s, 1 H), 5.32 (s, 2 H), 4.98–4.90 (m, 1 H), 4.78–4.69 (m, 1 H), 3.80 (s, 3 H), 3.10–2.91 (m, 1 H), 2.89 (d, *J* = 5.8 Hz, 1 H), 2.10–2.07 (m, 1 H), 1.95–1.91 (m, 1 H), 1.85 (t, *J* = 4.4 Hz, 1 H), 1.70–1.64 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 139.1, 134.9, 125.8, 121.7, 121.5, 58.9, 49.4, 44.7, 43.5, 35.6, 27.7, 22.8.

Anal. Calcd for $C_{12}H_{19}BF_4N_6$: C, 43.14; H, 5.69; N, 25.16. Found: C, 43.29; H, 5.78; N, 25.03.

Catalyst 3c

To a solution of **3a** (247.0 mg, 1.00 mmol) in MeCN and acetone (20 mL, 4:1) was added well-sieved KPF_6 (919.23 mg, 5.00 mmol). The mixture was vigorously stirred at r.t. for 2 d. The mixture was filtered to remove the inorganic salts and the filtrate was triturated with $AgPF_6$ solution (300 mg in MeCN) till no precipitate was formed. The filtrate was filtered again and concentrated. The residue was diluted with $CHCl_3$ (50 mL) and the insoluble was removed by filtration. The clear filtrate was concentrated in vacuo and the residue was purified by flash chromatography on silica gel to give **3c** as a pale yellow oil; yellow: 360.4 mg (92%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.84 (t, *J* = 1.6 Hz, 2 H), 8.25 (s, 1 H), 8.08 (s, 1 H), 7.52 (s, 1 H), 7.21 (s, 1 H), 5.30 (s, 2 H), 4.95–4.89 (m, 1 H), 4.75–4.68 (m, 1 H), 3.82 (s, 3 H), 3.06–2.91 (m, 1 H), 2.88 (d, *J* = 5.6 Hz, 1 H), 2.07–1.97 (m, 1 H), 1.93–1.90 (m, 1 H), 1.84 (t, *J* = 4.6 Hz, 1 H), 1.68–1.63 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 137.8, 132.5, 124.3, 120.1, 119.8, 58.4, 49.0, 44.7, 43.1, 35.6, 27.0, 22.2.

Anal. Calcd for $C_{12}H_{19}PF_6N_6$: C, 36.74; H, 4.85; N, 21.43. Found: C, 36.97; H, 4.68; N, 21.59.

Asymmetric Michael Addition of Cyclohexanone to Nitroolefins; (*S*)-2-[(*R*)-2-Nitro-1-phenylethyl]cyclohexanone;[16] Typical Procedure (Table 3, Entry 1)

An oven-dried round-bottomed flask was charged with ionic liquid anchored pyrrolidine **3a** (18 mg, containing 0.10 mmol of active pyrrolidine unit), nitrostyrene (149 mg, 1.0 mmol), cyclohexanone (196 mg, 2.0 mmol), TFA (57 mg, 0.05 mmol), and EtOH (2.0 mL). The mixture was stirred at 10 °C for 36 h. After completion of the reaction, the mixture was evaporated under reduced pressure and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated, and the residue was purified by flash chromatography on silica gel using EtOAc–hexane as eluent to afford the desired asymmetric Michael adduct as a white solid; yield: 235 mg (95%); $[\alpha]_D^{25}$ –20.9 (*c* 1.2, $CHCl_3$).

HPLC: Chiralpak AD-H, *i*-PrOH–hexane (10:90), flow rate 1.0 mL/min, λ = 254 nm; t_{minor} = 10.03 min, t_{major} = 12.66 min; dr (*syn*/*anti*) >99:1; ee >99%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.23 (m, 3 H), 7.19–7.16 (m, 2 H), 4.97 (dd, *J* = 4.5, 12.0 Hz, 1 H), 4.64 (dd, *J* = 9.9, 12.3 Hz, 1 H), 3.76 (dt, *J* = 4.5, 9.9 Hz, 1 H), 2.68 (ddd, *J* = 7.8, 8.4, 11.7 Hz, 1 H), 2.49–2.33 (m, 2 H), 2.10–2.04 (m, 1 H), 1.80–1.52 (m, 4 H), 1.29–1.15 (m, 1 H).

^{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.

(*S*)-2-[(*R*)-1-(4-Methylphenyl)-2-nitroethyl]cyclohexanone[17] (Table 3, Entry 2)

$[\alpha]_D^{25}$ –26.3 (*c* 1.2, $CHCl_3$).

HPLC: Chiralpak AD-H, *i*-PrOH–hexane (10:90), flow rate 1.0 mL/min, λ = 254 nm; t_{minor} = 11.97 min, t_{major} = 15.30 min; dr (*syn*/*anti*) >99:1; ee >99%.

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

^{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.

(*S*)-2-[(*R*)-1-(4-Methoxyphenyl)-2-nitroethyl]cyclohexanone[4b] (Table 3, Entry 3)

$[\alpha]_D^{25}$ –19.2 (*c* 1.2, $CHCl_3$).

HPLC: Chiralpak AD-H, *i*-PrOH–hexane (10:90), flow rate 1.0 mL/min, λ = 254 nm); t_{minor} = 13.22 min, t_{major} = 16.51 min; dr (*syn*/*anti*) >99:1; ee >99%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.08 (d, *J* = 8.7 Hz, 2 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 4.93 (dd, *J* = 4.5, 12.3 Hz, 1 H), 4.58 (dd, *J* = 9.9, 12.0 Hz, 1 H), 3.78 (s, 3 H), 3.72 (dt, *J* = 4.5, 9.9 Hz, 1 H), 2.68–2.60 (m, 1 H), 2.52–2.32 (m, 2 H), 2.12–2.03 (m, 1 H), 1.82–1.51 (m, 4 H), 1.30–1.16 (m, 1 H).

^{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.

(*S*)-2-[(*R*)-1-(4-Trifluoromethylphenyl)-2-nitroethyl]cyclohexanone[4d] (Table 3, Entry 4)

$[\alpha]_D^{25}$ –20.1 (*c* 1.25, $CHCl_3$).

HPLC: Chiralpak AD-H, *i*-PrOH–hexane (5:95), flow rate 1.0 mL/min, λ = 254 nm; t_{minor} = 16.66 min, t_{major} = 36.52 min; dr (*syn*/*anti*) >99:1; ee >99%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 8.1 Hz, 2 H), 7.30 (m 2 H), 4.98 (dd, *J* = 12.6, 4.5 Hz, 1 H), 4.67 (dd, *J* = 12.2, 9.8 Hz, 1 H), 3.90–3.82 (m, 1 H), 2.72–2.70 (m, 1 H), 2.51–2.47 (m, 1 H), 2.41–2.38 (m, 1 H), 2.11–2.07 (m, 1 H), 1.83–1.57 (m, 4 H), 1.27–1.23 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.7, 149.5, 136.7, 130.4, 121.9, 121.2, 78.9, 52.9, 43.7, 42.1, 33.6, 27.8, 25.5.

(*S*)-2-[(*R*)-1-(4-Chlorophenyl)-2-nitroethyl]cyclohexanone[18] (Table 3, Entry 5)

$[\alpha]_D^{25}$ –29.8 (*c* 1.0, $CHCl_3$).

HPLC: Chiralpak AD-H, *i*-PrOH–hexane (10:90), flow rate 1.0 mL/min, λ = 254 nm; t_{minor} = 27.54 min, t_{major} = 41.96 min; dr (*syn*/*anti*) >99:1; ee >99%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 8.4 Hz, 2 H), 7.16 (d, *J* = 8.4 Hz, 2 H), 4.93 (dd, *J* = 4.5, 12.6 Hz, 1 H), 4.60 (dd, *J* = 9.9, 12.6 Hz, 1 H), 3.78–3.70 (m, 1 H), 2.68–2.60 (m, 1 H), 2.50–2.32 (m, 2 H), 2.12–2.05 (m, 1 H), 1.83–1.56 (m, 4 H), 1.29–1.15 (m, 1 H).

^{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.

(*S*)-2-[(*R*)-1-(4-Fluorophenyl)-2-nitroethyl]cyclohexanone[18] (Table 3, Entry 6)

HPLC: Chiralpak AD-H, *i*-PrOH–hexane (5:95), flow rate 1.0 mL/min, λ = 254 nm; t_{minor} = 17.08 min, t_{major} = 23.36 min; dr (*syn*/*anti*) >99:1; ee = 97%.

^{1}H NMR (300 Hz, $CDCl_3$): δ = 7.16 (d, *J* = 8.1 Hz, 2 H), 7.02 (d, *J* = 8.4 Hz, 2 H), 4.94 (dd, *J* = 4.5, 12.6 Hz, 1 H), 4.59 (dd, *J* = 10.2, 12.6 Hz, 1 H), 3.81–3.73 (m, 1 H), 2.69–2.61 (m, 1 H), 2.50–2.32 (m, 2 H), 2.12–2.05 (m, 1 H), 1.88–1.51 (m, 4 H), 1.30–1.15 (m, 1 H).

^{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.

(*S*)-2-[(*R*)-1-(3,4-Dimethoxyphenyl)-2-nitroethyl]cyclohexanone[19] (Table 3, Entry 7)

$[\alpha]_D^{25}$ –28.4 (*c* 1.2, $CHCl_3$).

HPLC: Chiralpak AS-H, *i*-PrOH–hexane (30:70), flow rate 1.0 mL/min, λ = 254 nm; t_{minor} = 12.94 min, t_{major} = 24.49 min; dr (*syn*/*anti*) >99:1; ee >99%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.81 (d, *J* = 8.2 Hz, 1 H), 6.70–6.66 (m, 2 H), 4.91 (dd, *J* = 7.8, 4.6 Hz, 1 H), 4.60 (dd, *J* = 9.9, 2.4 Hz, 1 H), 3.87 (s, 6 H), 3.72–3.68 (m, 1 H), 2.66–2.64 (m, 1 H), 2.49–2.45 (m, 1 H), 2.41–2.38 (m, 1 H), 2.07–2.04 (m, 1 H), 1.80–1.60 (m, 4 H), 1.27–1.23 (m, 1 H).

^{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.

(*S*)-2-[(*R*)-1-(Benzo[*d*][1,3]dioxol-5-yl)-2-nitroethyl]cyclohexanone[5f] (Table 3, Entry 8)

$[\alpha]_D^{25}$ –43.8 (*c* 1.5, $CHCl_3$).

HPLC: Chiralpak AD-H, *i*-PrOH–hexane (10:90), flow rate 1.0 mL/min, λ = 254 nm; t_{minor} = 17.43 min, t_{major} = 18.74 min; dr (*syn*/*anti*) >99:1; ee >99%.

^{1}H NMR (300 Hz, $CDCl_3$): δ = 6.75 (d, *J* = 7.8 Hz, 1 H), 6.66 (s, 2 H), 6.64–6.58 (m, 2 H), 5.96 (s, 2 H), 4.92 (dd, *J* = 4.5, 12.3 Hz, 1 H), 4.56 (dd, *J* = 4.5, 9.9 Hz, 1 H), 3.67 (dt, *J* = 4.5, 9.9 Hz, 1 H), 2.68–2.56 (m, 1 H), 2.51–2.33 (m, 2 H), 2.15–2.07 (m, 1 H), 1.83–1.61 (m, 4 H), 1.31–1.25 (m, 1 H).

^{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.

(*S*)-2-[(*R*)-1-(Naphthalen-1-yl)-2-nitroethyl]cyclohexanone[5f] (Table 3, Entry 9)

$[\alpha]_D^{25}$ –99.8 (*c* 1.1, $CHCl_3$).

HPLC: Chiralpak AS-H, *i*-PrOH–hexane (30:70), flow rate 1.0 mL/min, λ = 254 nm; t_{minor} = 10.60 min, t_{major} = 15.43 min; dr (*syn*/*anti* >99:1; ee >99%.

^{1}H NMR (300 Hz, $CDCl_3$): δ = 8.17 (s, 1 H), 7.86 (d, *J* = 7.8 Hz, 1 H), 7.75 (d, *J* = 8.1 Hz, 1 H), 7.60–7.35 (m, 4 H), 5.06 (dd, *J* = 4.5, 12.6 Hz, 1 H), 4.91–4.88 (m, 1 H), 4.76 (s, 1 H), 2.65 (br s, 1 H), 2.45–2.38 (m, 2 H), 2.09–2.04 (m, 1 H), 1.69–1.47 (m, 4 H), 1.29–1.20 (m, 1 H).

^{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.

(*S*)-2-[(*R*)-2-(Naphthalen-1-yl)-2-nitroethyl)cyclohexanone[4d] (Table 3, Entry 10)

$[\alpha]_D^{25}$ –69.2 (*c* 1.1, $CHCl_3$).

HPLC: Chiralpak AD-H, *i*-PrOH–hexane (30:70), flow rate 1.0 mL/min, λ = 254 nm; t_{minor} = 10.06 min, t_{major} = 16.49 min; dr (*syn*/*anti*) >99:1; ee >99%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84–7.79 (m, 3 H), 7.63 (d, *J* = 1.2 Hz, 1 H), 7.49–7.46 (m, 2 H), 7.30–7.26 (m, 1 H), 5.02 (dd, *J* = 4.5, 12.6 Hz, 1 H), 4.73 (dd, *J* = 9.9, 12.3 Hz, 1 H), 3.99–3.92 (m, 1 H), 2.78–2.75 (m, 1 H), 2.50–2.47 (m, 2 H), 2.42–2.39 (m, 1 H), 1.76–1.58 (m, 4 H), 1.29–1.25 (m, 1 H).

^{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.

(*S*)-2-[(*R*)-1-(2-Chlorophenyl)-2-nitroethyl]cyclohexanone[18] (Table 3, Entry 11)

HPLC: Chiralpak AD-H, *i*-PrOH–hexane (10:90), flow rate 0.5 mL/min, λ = 254 nm; t_{minor} = 23.31 min, t_{major} = 39.70 min; dr (*syn*/*anti*) >99:1; ee = 95%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.36 (m, 1 H), 7.24–7.18 (m, 3 H), 4.90 (d, *J* = 1.2 Hz, 1 H), 4.88 (s, 1 H), 4.33–4.25 (dt, *J* = 6.6, 7.2, 9.9 Hz, 1 H), 2.96–2.87 (m, 1 H), 2.50–2.35 (m, 2 H), 2.14–2.06 (m, 1 H), 1.84–1.53 (m, 4 H), 1.39–1.26 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 211.6, 135.5, 134.5, 130.4, 129.5, 128.9, 127.4, 77.2, 51.7, 42.8, 41.0, 33.0, 28.5, 25.3.

(*S*)-2-[(*R*)-1-(2-Bromophenyl)-2-nitroethyl]cyclohexanone[5f] (Table 3, Entry 12)

HPLC: Chiralpak AD-H, *i*-PrOH–hexane (10:90), flow rate 1.0 mL/min, λ = 254 nm; t_{minor} = 10.81 min, t_{major} = 16.32 min; dr (*syn*/*anti*) >99:1; ee = 98%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 8.1 Hz, 1 H), 7.32–7.21 (m, 2 H), 7.15–7.10 (m, 1 H), 4.90 (d, *J* = 8.1 Hz, 2 H), 4.32 (dd, *J* = 6.3, 6.6Hz, 1 H), 2.91–2.88 (m, 1 H), 2.45–2.34 (m, 2 H), 2.12–2.08 (m, 1 H), 1.84–1.53 (m, 4 H), 1.40–1.20 (m, 1 H).

^{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.

(*S*)-2-[(*S*)-1-(Furan-2-yl)-2-nitroethyl]cyclohexanone[16] (Table 3, Entry 13)

HPLC: Chiralpak AD-H, *i*-PrOH–hexane (10:90), flow rate 1.0 mL/min, λ = 254 nm; t_{major} = 10.47 min, t_{minor} = 13.27 min; dr (*syn*/*anti*) >99:1; ee = 91%.

^{1}H NMR (300 Hz, $CDCl_3$): δ = 7.36 (d, *J* = 1.2 Hz, 1 H), 6.29 (dd, *J* = 1.8, 3.3 Hz, 1 H), 6.16 (d, *J* = 3.3 Hz, 1 H), 4.81–4.62 (m, 2 H), 3.99 (dt, *J* = 4.8, 9.3 Hz, 1 H), 2.79–2.71 (m, 1 H), 2.51–2.32 (m, 2 H), 2.16–2.07 (m, 1 H), 1.92–1.56 (m, 4 H), 1.35–1.23 (m, 1 H).

^{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.

(*R*)-Tetrahydro-3-[(*R*)-2-nitro-1-phenylethyl]pyran-4-one[17] (Table 3, Entry 14)

HPLC: Chiralpak AS-H, *i*-PrOH–hexane (30:70), flow rate 1.0 mL/min, λ = 254 nm; t_{minor} = 14.10 min, t_{major} = 17.69 min; dr (*syn*/*anti*) >99:1; ee = 96%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.27 (m, 3 H), 7.24–7.17 (m, 2 H), 4.78–4.62 (m, 2 H), 4.11–4.02 (m, 1 H), 3.87–3.75 (m, 2 H), 3.70 (dd, *J* = 4.8, 11.7 Hz, 1 H), 3.29 (dd, *J* = 9.6, 11.4 Hz, 1 H), 2.93–2.85 (m, 1 H), 2.73–2.62 (m, 1 H), 2.58–2.49 (m, 1 H).

^{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.

(*R*)-Tetrahydro-3-[(*R*)-2-nitro-1-phenylethyl]thiopyran-4-one[17] (Table 3, Entry 15)

HPLC: Chiralpak AS-H, *i*-PrOH–hexane (30:70), flow rate 1.0 mL/min, λ = 254 nm; t_{minor} = 9.81 min, t_{major} = 11.98 min; dr (*syn*/*anti*) = 99:1; ee = 94%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 3 H), 7.23–7.17 (m, 2 H), 4.75 (dd, *J* = 4.8, 12.6 Hz, 1 H), 4.65 (dd, *J* = 9.6, 12.3 Hz, 1 H), 4.01 (dt, *J* = 4.5, 10.2 Hz, 1 H), 3.10–2.77 (m, 5 H), 2.62 (ddd, *J* = 1.5, 4.2, 13.8 Hz, 1 H), 2.46 (dd, *J* = 9.6, 13.8 Hz, 1 H).

^{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.

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