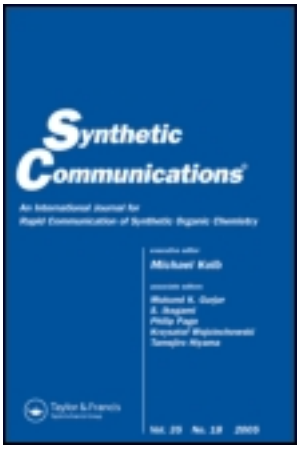

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Synthesis of New Functionalized Chiral Ionic Liquid and Its Organocatalytic Asymmetric Michael Addition

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SYNTHESIS OF NEW FUNCTIONALIZED CHIRAL IONIC LIQUID AND ITS ORGANOCATALYTIC ASYMMETRIC MICHAEL ADDITION

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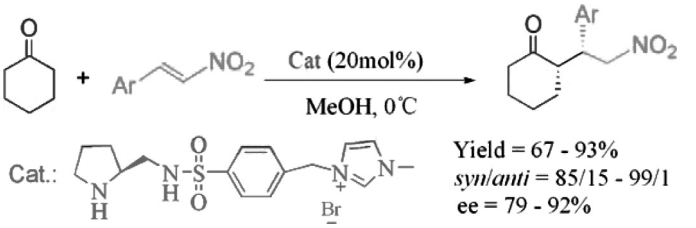
GRAPHICAL ABSTRACT



Abstract *A novel recyclable functionalized chiral ionic liquid has been developed to promote asymmetric Michael additions of cyclohexanone to both aryl and alkyl nitroolefins in the presence of 20 mol% of organocatalyst* ***4*** *in MeOH. The process affords synthetically valuable chiral products in good yields (up to 93%) and high enantioselectivities (up to 92%). The chiral ionic liquid could be easily reused six times without remarkable decrease in yields and enantioselectivities.*

Keywords Asymmetric Michael addition; chiral ionic liquid; recyclable

INTRODUCTION

Ionic liquids that contain tethered specialized groups are called functionalized ionic liquids (FILs), which have been used as supports for reagents and catalysts.[1] They are also recyclable. As FILs, chiral ionic liquids (CILs) have been designed and synthesized in an attempt to influence the outcomes of asymmetric organic reactions.[2] There are only a few CILs that can effectively influence the outcomes of asymmetric reactions, such as Baylis–Hillman reactions,[3] the Michael additions,[4] and aldol reactions.[5] The design and synthesis of CILs opens up a green chemistry approach to asymmetric catalysis. The addition of carbonyl compounds to nitroalkenes, which in many respects may be considered a Michael-type addition, is a key

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reaction in synthetic organic chemistry for the formation of new C-C bonds.[6] It is well known that pyrrolidine–base catalytic systems have been very effective for asymmetric Micheal addition reactions, often yielding high enantioselectivites.[7] Recently, some simple pyrrolidine-derived CILs were reported as efficient catalysts for the addition of cyclic ketones and some aldehydes to nitroolefins.[8]

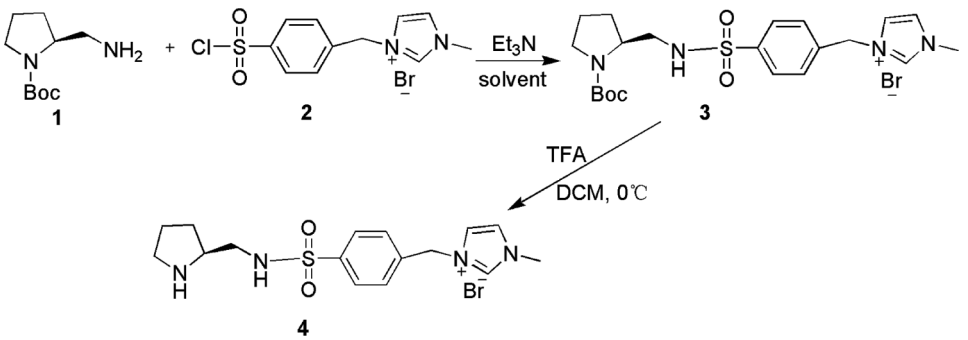
Our research involves the design and synthesis of pyrrolidine-derived CILs that exhibit the ability to influence the outcomes of asymmetric reactions. In this study, we report the design, synthesis, characterization, and application of a new type of task-specific ionic liquid, which is derived from L-proline.

RESULTS AND DISCUSSION

Our functionalized ionic liquid, shown in Scheme 1, introduces a chiral pyrrolidine into an imidazolium ionic liquid. A major advantage of our current design is that this functionalized CIL cannot only serve as organocatalyst but also is easily recovered from the reaction mixture, making it a recyclable green ionic liquid.

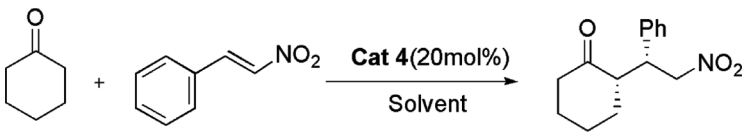
Initially, aminomethylpyrrolidine **1** and sulfonyl chloride **2** were chosen as starting materials, which can be prepared from L-proline[9] and 4-toluene sulfonyl chloride, respectively. It was found that the reaction of **1** with **2** in CH_2Cl_2/CH_3CN ($v/v = 1{:}1$) at room temperature for 8 h, followed by stirring the resulting mixture with trifluoroacetic acid for 2 h, afforded the desired CIL **4** in 72% yield. The FCIL is a viscous liquid at room temperature.

The addition of cyclohexanone to *trans*-β-nitrostyrene was used as the test reaction to explore the feasibility of the enantioselective Michael reaction catalyzed by CIL **4**. The organocatalyst was able to increase the reactivity of *trans*-β-nitrostyrene in the Micheal reaction with cyclohexanone, performed at room temperature in MeOH (Table 1, entries1). Good yield (87%) was achieved after 3 days. To achieve good reactivity and enantioselectivity, various reaction conditions were examined; when the reaction proceeded without solvent, the yield decreased from 87% to 75% and the enantioselectivity slightly decreased from 81% to 77% (Table 1, entries 2). We also studied the influence of acid additive on the reaction. The addition of trifluoroacetic acid (TFA) could decrease dramatically the reaction with worse yield (42%) and enantioselectivity (81%). As with TFA, a lesser amount of the desired



Scheme 1. Synthesis of functionalized chiral ionic liquid **4**.

Table 1. Effects of additives on the reaction of cyclohexanone to *trans*-nitrostyrene[a]



5 **6a** **7a**

Entry	Solvent	Additive	T (°C)	Yield[b] (%)	*Syn*/*anti*[c]	*Ee* [d] (%)
1	MeOH	—	25	87	88:12	81
2	Neat	—	25	75	97:3	77
3	MeOH	—	0	84	99:1	89
4	Neat	—	0	63	95:5	86
5	MeOH	TFA	0	42	94:6	81
6	MeOH	AcOH	0	63	93:7	57
7	MeOH	PhCOOH	0	72	93:7	40
8	MeOH	HCOOH	0	79	94:6	54
9	MeOH	PTSA	0	—	—	—

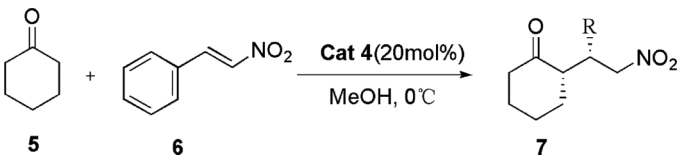
[a]Unless otherwise noted, all reactions were carried out in solvent (100 µl) using **5** (0.0196 g, 2 eq) and **6a** (0.0149 g, 1 eq) in the presence of 20 mol% of **4**.
[b]Isolated yields.
[c]The *trans*/*cis* ratios are determined by ^{1}H NMR.
[d]Determined by HPLC using Chiracel AD-H/AS-H column.

adduct observed when other acids were used (Table 1, entries 6–9). Interestingly, we were pleased to find that cooling the reaction mixture to 0 °C had a positive effect on the enantioselectivity; the product was obtained in 89% *ee* and good levels of yield were maintained.

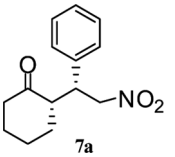
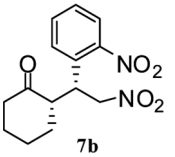
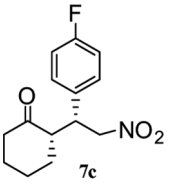
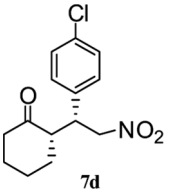
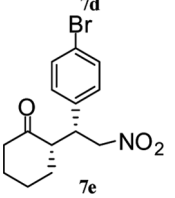
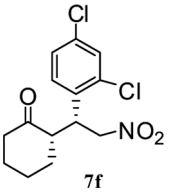
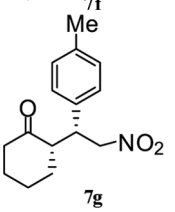
With the optimal conditions in hand, a variety of different substitutions were investigated, and the results are summarized in Table 2. Generally, various nitrostyrenes bearing both electron-withdrawing (Table 2, entries 2) and electron-donating ary group (Table 2, entries 7) gave the desired products with good selectivities (*dr* up to 94:6 and *ee* up to 88) in good yield. Noticeably, when the *para*- position of nitrostyrenes was the methoxyl group, the greatest enantioselectivity (92%) was obtained. This result is better than the result of Headley for the same substitution (*ee* 90%).[8] Compared to Headley's catalyst, there is a benzene ring between sulfonamide group and imidazolium cation in catalyst **4**. It is speculated that the benzene ring has greater steric hindrance and rigidity than aliphatic chain, affecting the value of the reaction enantioselectivity. In addition, alkylnitroolefin also worked in this reaction. For example, (*E*)-1-nitropent-1-ene gave the corresponding product with diastereoselecty (75:25) and enantioselectivity (36%) in moderate yield (45%).

The asymmetric Michael reaction of cyclohexanone with *trans*-β-nitrostyrene under optimal conditions was chosen as the model reaction to examine the recyclability of the functionalized chiral ionic liquid **4**. Because the catalyst **4** was insoluble in ether but soluble in water, it could be easily seperated from product and immobilized in water. After the reaction was completed, the reaction mixture was concentrated, and the remainder was added into water and extracted twice with ether. Concentration and purification by chromatography column led to adduct **7a**. The

Table 2. Micheal addition reaction of cyclohexanone to *trans*-nitroolefins catalyzed by **4**[a]

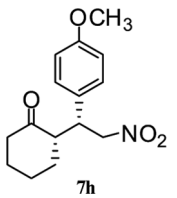
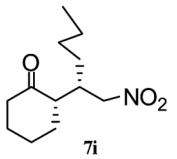


5 **6** **7**

Entry	Product	Yield (%)[b]	*Syn*/*anti*[c]	*Ee* (%)[d]
1	 **7a**	84	99:1	89
2	 **7b**	93	85:15	88
3	 **7c**	76	94:6	89
4	 **7d**	81	93:7	86
5	 **7e**	67	96:4	79
6	 **7f**	72	99:1	91
7	 **7g**	82	94:6	87

(*Continued*)

Table 2. Continued

Entry	Product	Yield (%)[b]	*Syn*/*anti*[c]	*Ee* (%)[d]
8	 **7h**	85	94:6	92
9	 **7i**	45	75:25	36

[a]Unless otherwise noted, all reactions were carried out in solvent (100 μl) using **5** (0.0196 g, 2 eq) and **6** (0.0149 g, 1 eq) in the presence of 20 mol% of **4**.
[b]Isolated yields.
[c]The *trans*/*cis* ratios are determined by ^{1}H NMR.
[d]Determined by HPLC using Chiracel AD-H/AS-H column.

Table 3. Recycling studies of FCIL **4**–catalyzed Micheal reaction of cyclohexanone with *trans*-β-nitrostyrene under standard reaction conditions

Run	Time (d)	Yield[a] (%)	*Ee*[b] (%)
1	3	84	89
2	3	87	89
3	3	82	87
4	3	84	88
5	4	87	89
6	5	81	83

[a]Isolated yields.
[b]Determined by HPLC using Chiracel OD-H column.

functionalized CIL **4** immobilized in water was washed with ether and reused for the next run of the reaction. These recycling processes of the asymmetric reaction could be repeated six times without remarkable decrease in yields and enantioselectivities.

CONCLUSION

In summary, a new recyclable functionalized CIL has been developed for the Michael reaction of cyclohexanone with *trans*-β-nitrostyrene. The original FCIL promoted asymmetric Micheal additions of cyclohexanone to both aryl and alkyl nitroolefins in the presence of 20 mol% of organocatalyst **4** in MeOH. The process affords synthetically valuable chiral products in good yields (up to 93%) and high enantioselectivities (up to 92%). The FCIL catalyst was easily recycled and reused

up to six times without significant loss of ability to influence the reactivies and enantioselectivities of reactions.

EXPERIMENTAL

^{1}H NMR spectra were determined in $CDCl_3$ on a Brucker ARX-300 (300 MHz) instrument with tetramethylsilane (TMS) as internal standard. High-resolution mass spectral analyses (HRMS) were measured using electrospray ionization (ESI). The enantiomer excess was determined by high-performance liquid chromato (HPLC) analysis on a chiralcel AD-H /AS-H column. *trans*-Nitroalkenes were prepared according to the literature procedures.[10]

General Procedure for Compound 2

4-(Bromomethyl) benzene-1-sulfonyl chloride [11] (2.70 g, 10 mmol) was added to a solution of 1-methylimidazole (0.82 g, 10 mmol) in CH_3CN (10 ml). The mixture was stirred at reflux for 12 h and concentrated. The resulting residue was chromatographed with the eluent (CH_2Cl_2/MeOH: 20/ 1–10/1) to give the yellow oil (1.43 g, 41%) of **2**. ^{1}H NMR (300 MHz, D_2O) δ (ppm): 8.49 (s, 1H), 7.67–7.62 (m, 2H), 7.45–7.42 (m, 2H), 7.35–7.33 (m, 2H), 5.43 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ (ppm): 142.1, 140.2, 139.4, 129.0, 128.5, 125.3, 121.0, 55.1, 45.1; HRMS (ESI) calcd. for $C_{11}H_{12}ClN_2O_2S^+(M^+)$: 271.0303, found; 271.0302.

General Procedure for Compound 4

The corresponding ionic liquid **2** (1.06 g, 3 mmol) was added to a solution of **1** (0.60 g, 3 mmol) in $CHCl_2/CH_3CN$ (10 ml, $v/v = 1{:}1$). The mixture was stirred at room temperature for 8 h (monitored by thin-layer chromatography, TLC) and concentrated. The resulting residue was chromatographed with the eluent (CH_2Cl_2/MeOH: 20/1–10/1) to give the crude yellow oil. The Boc protective group in the obtained pale yellow solid **3** was deprotected by using CF_3COOH/CH_2Cl_2 solution (25 ml, $v/v = 1{:}1$) with shaking at room temperature for 3 h, and the solution was evaporated under reduced pressure. The crude product was chromatographed over silica gel, and elution (MeOH/CH_2Cl_2: 1/7) gave 0.90 g (72%) of **4**. $[\alpha]^D_{25} = -13.3$ (c 1.50, MeOH). ^{1}H NMR (300 MHz, D_2O) δ (ppm): 8.78 (s, 1H), 7.82–7.76 (m, 2H), 7.51–7.38 (m, 4H), 5.40 (s, 2H), 3.81 (s, 3H), 3.44–3.43 (m, 1H), 3.12–3.06 (m, 2H), 2.96–2.93 (m, 2H), 1.88–1.45 (m, 4H); ^{13}C NMR (75 MHz, CD_3OD) δ (ppm):140.2, 139.1, 137.1, 129.0, 127.6, 124.1, 122.5, 119.8, 59.9, 51.8, 45.2, 43.0, 35.4, 34.8, 27.1, 22.8; HRMS (ESI) calcd. for $C_{16}H_{23}N_4O_2S^+(M^+)$: 335.1536; found; 335.1534.

General Procedure for Recycling

Cyclohexanone (196 mg, 2 mmol) and aryl and alkyl nitroolefins (0.1 mmol) were added to the solution of organocatalyst **4** (8.3 mg, 0.02 mmol) in MeOH (100 μl). The reaction mixture was stirred at 0 °C for 3 days and concentrated. The remainder was added into water (10 ml) and extracted with ether (10 ml × 2). The

ether phase was concentrated and purified by chromatography column, which led to adduct **7a**, and the water phase was used for the next cycle.

General Procedure for Compounds 7a–7j [12,13]

Cyclohexanone (196 mg, 2 mmol) and aryl and alkyl nitroolefins (0.1 mmol) were added to the solution of organocatalyst **4** (8.3 mg, 0.02 mmol) in MeOH (100 μl). The reaction mixture was stirred at 0 °C for 3 days and concentrated. The residual was purified by preparative TLC or column chromatography, affording the desired products **7a–7j**.

(S)-2-((R)-2-Nitro-1-phenylethyl)cyclohexanone 7a. The *ee* of the product was determined by chiral HPLC analysis [Chiralpak AS column, hexane/i-PrOH = 90/10, 0.7 ml/min, 238 nm; tr (minor) = 18.20 min, tr (major) = 26.26 min],], 89% *ee*. $[\alpha]^{D}_{25} = -18.3$ (c 0.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.37–7.17 (m, 5H), 4.93 (dd, $J = 12.6$, 4.5 Hz,1H), 4.62 (dd, $J = 12.3$, 9.9 Hz, 1H), 3.74 (m, 1H), 2.76–2.66 (m, 1H), 2.50–2.40 (m, 2H), 2.09–2.07 (m, 1H), 1.78–1.56 (m, 4H), 1.27–1.23 (m, 1H).

(S)-2-((R)-2-Nitro-1-(2-nitrophenyl)ethyl)cyclohexanone 7b. The *ee* of the product was determined by chiral HPLC analysis [Chiralpak AD column, hexane/i-PrOH = 95/5, 1.0 ml/min, 238 nm; tr (minor) = 29.06 min, tr (major) = 42.71 min], 88% *ee*. $[\alpha]^{D}_{25} = -19.8$ (c 0.43, $CHCl_3$);^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.88–7.84 (m, 1H), 7.64–7.58 (m, 1H) 7.49–7.42 (m, 2H), 4.95–4.92 (m, 2H), 4.39–4.33 (m, 1H), 2.98–2.94 (m, 1H), 2.49–2.39 (m, 2H), 2.13–2.11 (m, 1H), 1.87–1.47 (m, 6H), 1.27–1.21 (m, 2H).

(S)-2-((R)-1-(4-Fluorophenyl)-2-nitroethyl)cyclohexanone 7c. The *ee* of the product was determined by chiral HPLC analysis [Chiralpak AS column, hexane/i-PrOH = 90/10, 0.7 ml/min, 238 nm; tr (minor) = 21.28 min, tr (major) = 29.49 min], 89% *ee*. $[\alpha]^{D}_{25} = -25.4$ (c 1.13, $CHCl_3$);^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.18–7.14 (m, 2H), 7.06–7.00 (m, 2H), 4.98 (dd, $J = 12.3$ Hz,4.2 Hz, Hz, 1H), 4.65 (dd, $J = 12.0$ Hz, 9.9 Hz, 1H), 3.76 (m, 1H), 2.72–2.64 (m, 1H), 2.48–2.35 (m, 2H), 2.13–2.09 (m, 1H), 1.78–1.57 (m, 4H), 1.27–1.22 (m, 1H).

(S)-2-((R)-1-(4-Chlorophenyl)-2-nitroethyl)cyclohexanone 7d. The *ee* of the product was determined by chiral HPLC analysis [Chiralpak AS column, hexane/i-PrOH = 90/10, 0.7 ml/min, 238 nm; tr (major) = 18.75 min, tr (minor) = 28.36 min], 86% *ee*. $[\alpha]^{D}_{25} = -30.1$ (c 0.88, $CHCl_3$);^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.33–7.28 (m, 2H), 7.16–7.12 (m, 2H), 4.98 (dd, $J = 12.6$ Hz, 4.5 Hz, 1H), 4.66 (dd, $J = 12.6$ Hz, 10.2 Hz, 1H), 3.79–3.77 (m, 1H), 2.72–2.62 (m, 1H), 2.48–2.35 (m, 2H), 2.16–2.08 (m, 1H), 1.72–1.57(m, 4H), 1.27–1.22 (m, 1H).

(S)-2-((R)-1-(4-Bromophenyl)-2-nitroethyl)cyclohexanone 7e. The *ee* of the product was determined by chiral HPLC analysis [Chiralpak AS column, hexane/i-PrOH = 90/10, 0.7 ml/min, 238 nm; tr (minor) = 19.99 min, tr (major) = 31.37 min], 79% *ee*. $[\alpha]^{D}_{25} = -22.3$ (c 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.48–7.44 (m, 2H), 7.09–7.06 (m, 2H), 4.97 (dd, J = 12.6 Hz,

4.5 Hz, 1H), 4.65 (dd, $J = 12.6$ Hz, 9.9 Hz, 1H), 3.77 (m, 1H), 2.69–2.58 (m, 1H), 2.46–2.37 (m, 2H), 2.09 (m, 1H), 1.78–1.56 (m, 4H), 1.26–1.21 (m, 1H).

(S)-2-((R)-1-(2,4-Dichlorophenyl)-2-nitroethyl)cyclohexanone 7f. The *ee* of the product was determined by chiral HPLC analysis [Chiralpak AS column, hexane/i-PrOH = 90/10, 0.7 ml/min, 238 nm; tr (minor) = 14.64 min, tr (major) = 24.31 min], 91% *ee*. $[\alpha]^{D}_{25} = -33.9$ (c 0.55, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.43 (d, $J = 2.1$ Hz, 1H), 7.24 (m, 2H), 4.91–4.89 (m, 2H), 4.27 (m, 1H), 2.93–2.84 (m, 1H), 2.48–2.38 (m, 2H), 2.16–2.11 (m, 1H), 1.87–1.60 (m, 4H), 1.41–1.22 (m, 1H).

(S)-2-((R)-2-Nitro-1-p-tolylethyl)cyclohexanone 7g. The *ee* of the product was determined by chiral HPLC analysis [Chiralpak AS column, hexane/i-PrOH = 90/10, 0.7 ml/min, 238 nm; tr (minor) = 13.08 min, tr (major) = 19.93 min],], 87% *ee*. $[\alpha]^{D}_{25} = -11.1$ (c 1.21, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.16–7.13 (m, 2H), 7.08–7.05 (m, 2H), 4.96 (dd, $J = 12.0$ Hz, 4.5 Hz, 1H), 4.66 (dd, $J = 12.3$ Hz, 9.9 Hz, 1H), 3.78 (m, 1H), 2.69 (m, 1H), 2.49–2.39 (m, 2H), 2.33 (s, 3H), 2.08 (m, 1H), 1.79–1.57 (m, 4H), 1.27–1.23 (m, 1H).

(S)-2-((R)-1-(4-Methoxyphenyl)-2-nitroethyl)cyclohexanone 7h. The *ee* of the product was determined by chiral HPLC analysis [Chiralpak AD column, hexane/i-PrOH = 75/25, 0.7 ml/min, 238 nm; tr (minor) = 9.95 min, tr (major) = 11.32 min], 92% *ee*. $[\alpha]^{D}_{25} = -15.4$ (c 0.43, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.28 (m, 2H), 6.88 (m, 2H), 4.95 (dd, $J = 12.6$ Hz, 4.5 Hz, 1H), 4.64 (dd, $J = 12.6$ Hz, 4.5 Hz, 1H), 3.80 (s, 3H), 3.79–3.72 (m, 1H), 2.70–2.62 (m, 1H), 2.47–2.40 (m, 2H), 2.12–2.06 (m, 1H), 1.81–1.57 (m, 4H), 1.27–1.23 (m, 1H).

(S)-2-((S)-1-Nitrohexan-2-yl)cyclohexanone 7i. The *ee* of the product was determined by chiral HPLC analysis [Chiralpak AS column, hexane/i-PrOH = 90/10, 0.5 ml/min, 210 nm; tr (minor) = 12.38 min, tr (major) = 13.82 min], 36% *ee*. $[\alpha]^{D}_{25} = -20.7$ (c 0.25, $CHCl_3$);^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.61–4.55 (m, 1H), 4.45–4.39 (m, 1H), 2.62–2.40 (m, 4H), 2.13–2.11 (m, 2H), 1.93 (m, 1H), 1.48–1.27 (m, 9H), 0.96–0.92 (m, 3H).

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