Available online at www.sciencedirect.com
ScienceDirect
Journal of Molecular Catalysis A: Chemical 263 (2007) 186–194
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
www.elsevier.com/locate/molcata

A new class of efficient poly(ethylene-glycol)-supported catalyst based on proline for the asymmetric Michael addition of ketones to nitrostyrenes

Liuqun Gu, Yongyong Wu, Yazhu Zhang, Gang Zhao *

Laboratory of Modern Synthetic Organic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 FengLin Lu, Shanghai 200032, China

Received 9 March 2006; received in revised form 21 August 2006; accepted 21 August 2006
Available online 26 August 2006

Abstract

A new class of efficient poly(ethylene-glycol)-supported catalysts based on proline was designed to catalyze the asymmetric Michael addition of ketones to nitrostyrenes. Using 5 mol% of the best catalyst, the products of the Michael reactions were obtained in good yields (up to 94%), moderate to good enantioselectives (up to 86%) and high diastereoselectivities (>98/2, *syn*/*anti* ratios). The enantiomeric excesses were higher than those obtained with non-supported proline. Recovery and recycling of the poly(ethylene-glycol)-supported catalyst were also described.

Keywords: Proline; Michael addition; Polymer-supported catalyst; Nitrostyrene

1. Introduction

Nitroalkanes are versatile synthetic intermediates in organic chemistry owing to the various transformations of the nitro group into other useful functional groups. As one useful synthetic method for preparation of nitroalkanes, the Michael addition of ketones or aldehydes to nitroalkenes has received much attention [1]. Since Hanessian and Pham [2], List et al. [3], and Enders and Seki [4] reported L-proline catalyzed asymmetric Michael reactions of ketones and aldehydes as nucleophiles, many efficient organocatalysts such as pyrrolidinyltetrazole [5], aminomethyl pyrrolidine [6], 2,2′-bipyrrolidine [7], pyrrolidine–pyridine [8], pyrrolidine sulfonamide [9a] and diphenylprolinol silyl ethers [9b] were reported for the reaction. Very recently, acyclic amine catalysts by Xu and Cordova [10a] and new thiourea-amine bifunctional organocatalysts by Tsogoeva and Wei [10b] were employed in the Michael addition of ketones to nitroalkenes as efficient catalysts.

Being interested in the development of mild and convenient methodologies of asymmetric reactions using recyclable catalysts, we have focused on the immobilization of chiral ligands on polymeric supports including insoluble polymers [11] and dendrimers [12]. On the other hand, polymer-supported organic catalysts with the aim of facilitating catalyst recovery and recycling have proved to be the powerful synthetic tools readily available to the chemical community in organic synthesis [13]. Recently, Benaglia et al. [14] developed a poly(ethylene-glycol)-supported proline for the enantioselective aldol and iminoaldol reactions in good yields and high enantiomeric excess, however, for Michael reaction of ketones with nitrostyrenes in lower enantiomeric excesses, comparable to those obtained using non-supported proline as the catalyst. So, the development of more effective polymer-supported catalysts in terms of both enantioselectivity and substrate scope is still desirable.

Herein, we developed a new class of poly(ethylene-glycol)-supported catalysts based on proline, which catalyzed the asymmetric Michael addition of ketones to nitrostyrenes at room temperature with higher enantiomeric excesses (up to 86%) compared to those obtained with non-supported proline.

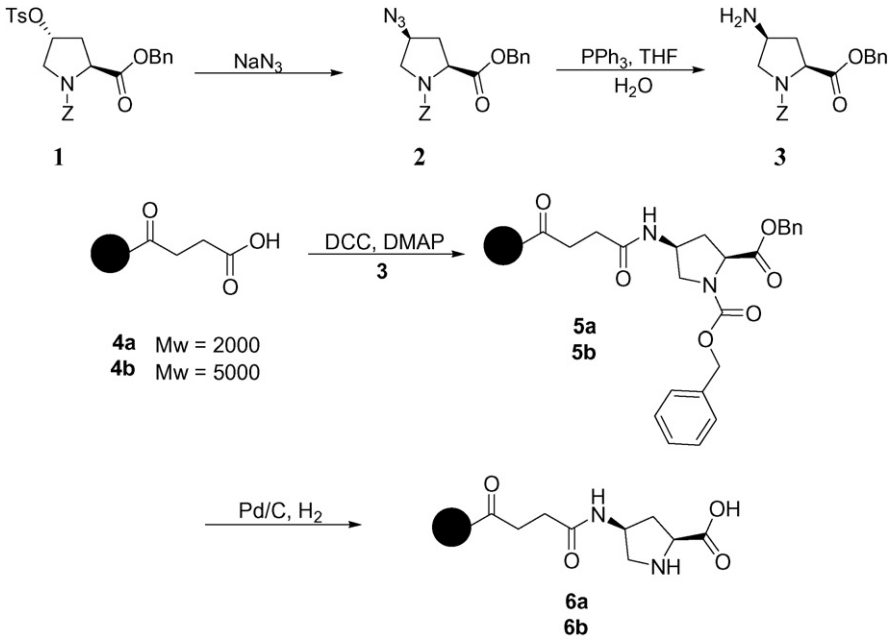
2. Results and discussion

2.1. Synthesis of the poly(ethylene-glycol)-supported catalysts

S_{N2} displacement of the tosylate of the compound **1** with azide resulted in the 4-*cis*-azide (**2**) with an inverted chiral center at the 4-position. Reduction of azide of compound **2**

* Corresponding author. Fax: +86 21 64166128.
E-mail address: zhaog@mail.sioc.ac.cn (G. Zhao).

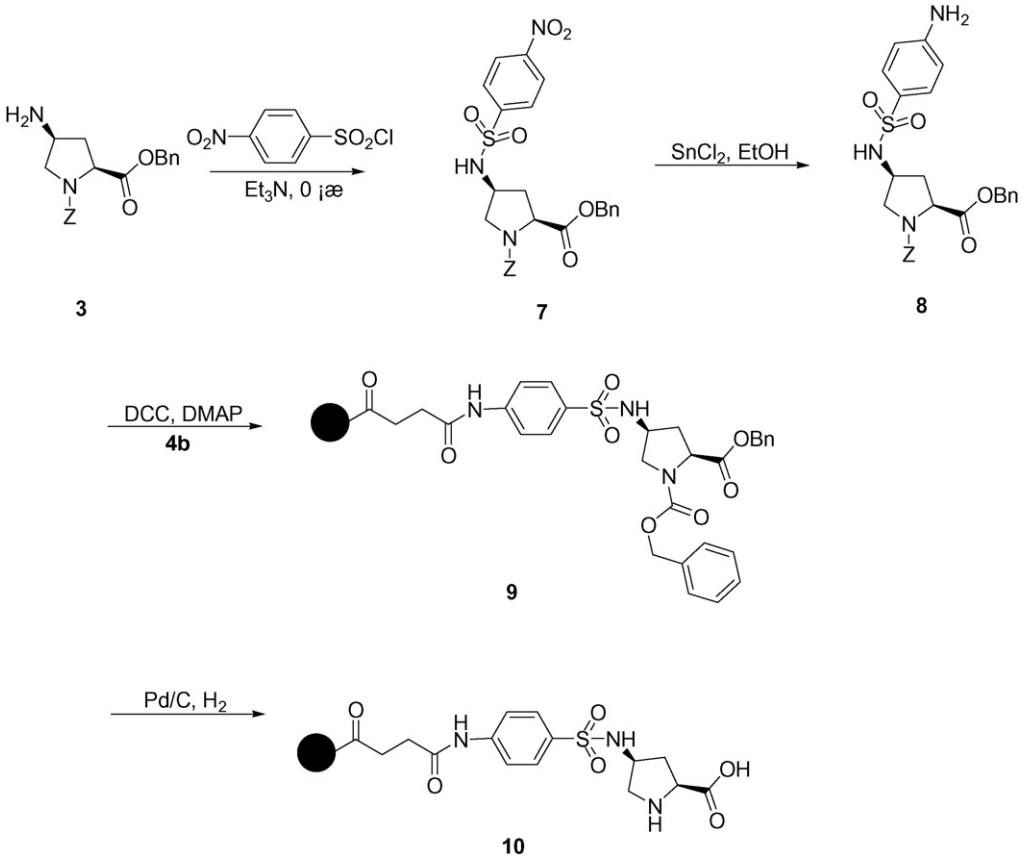
1381-1169/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.molcata.2006.08.068



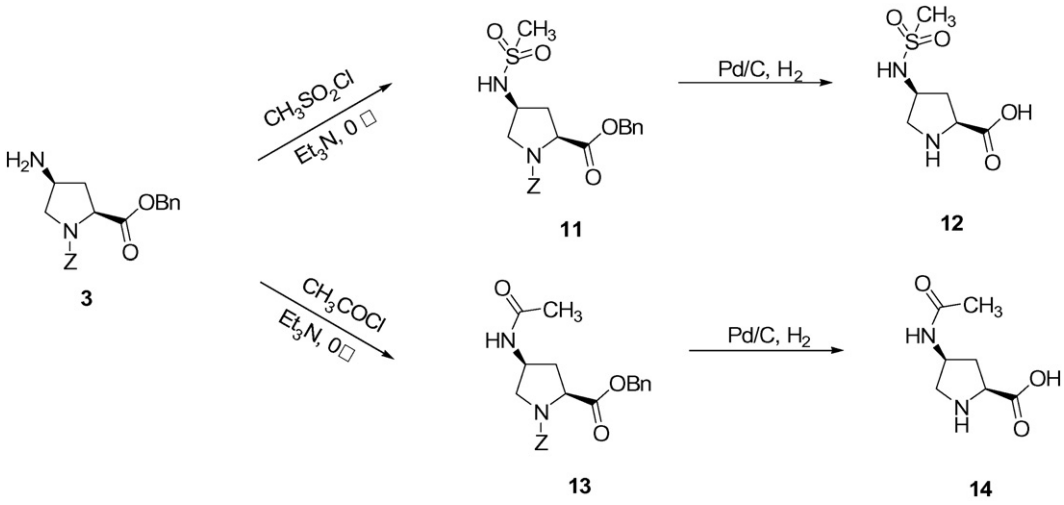
Scheme 1. Synthesis of poly(ethylene-glycol)-supported catalysts **6a** and **6b**.

with PPh_3 in THF and water was accomplished under neutral conditions [15]. Reaction of **3** with MeOPEG monosuccinate (**4**) [16] in the presence of dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine in dichloromethane afforded poly(ethylene-glycol)-supported proline (**5**), which was hydrogenated to remove the protected group giving the desired catalyst **6** (Scheme 1).

Poly(ethylene-glycol)-supported catalyst **10** was synthesized by a similar way (Scheme 2). Reaction of compound **3** with 4-nitrobenzylsulfonyl chloride in the presence of triethylamine



Scheme 2. Synthesis of poly(ethylene-glycol)-supported catalyst **10**.



Scheme 3. Synthesis of small molecular catalysts **12** and **14**.

at 0 °C afforded compound **7**, which was reduced by 10 equiv. $SnCl_2$ in ethyl alcohol at refluxed temperature for only half an hour to give almost pure product **8**. The compound **8** was converted to poly(ethylene-glycol)-supported compound **9** by a path similar to that from compound **3** to compound **5**. Catalytic hydrogenation of compound **9** afforded the desired catalyst **10**.

The structure and the loading of poly(ethylene-glycol)-supported compound were established by ^{1}H NMR or elemental analysis.

2.2. Synthesis of the small molecular catalysts

Comparing with the poly(ethylene-glycol)-supported catalysts, we have also synthesized the two types of small molecular catalysts (Scheme 3). Reaction of compound **3** with methanesulfonyl chloride in the presence of triethylamine at 0 °C afforded compound **11**. Catalytic hydrogenation of compound **11** afforded the desired catalyst **12**. The catalyst **14** was obtained in a similar manner to **12**.

Table 1
The effect of catalyst in the Michael reaction of cyclohexanone and 2-nitrostyrene[a]

Entry	Catalyst	*T* (h)	Yield (%)[b]	d.r. (*syn*/*anti*)[c]	e.e. (%)[d]
1	**6a**	48	44	94/6	30
2	**6b**	48	50	90/10	35
3	**10** (5 mol%)	48	92	>98/2	46
4	L-Proline	48	29	97/3	39
5	**12**	48	59	>98/2	54
6	**14**	48	89	96/4	40

[a] The reaction was carried out in MeOH at room temperature in the presence of 10 mol% catalyst.
[b] Isolated yield.
[c] Determined by ^{1}H NMR spectra.
[d] Reported values refer to the *syn* isomer and were determined by HPLC on a chiral stationary phase.

2.3. Enantioselective addition of ketones to nitrostryene

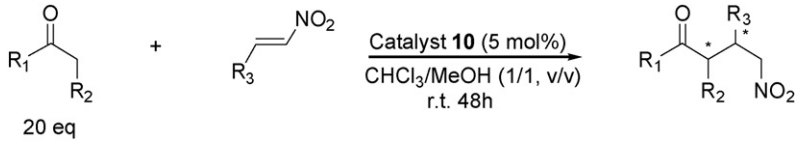
The Michael addition between cyclohexanone (20 equiv.) and 2-nitrostyrene was carried out in methanol at room temperature in the presence of 0.10 or 0.05 equiv. of poly(ethylene-glycol)-supported catalyst **6a**, **6b**, **10** or small molecular catalysts **12** and **14**. Both the catalyst **6a** (MeOPEG M_w = 2000) and the cat-

Table 2
Effect of solvent and temperature on the asymmetric Michael addition of cyclohexanone to *trans*-β-nitrostyrene[a]

Entry	Solvent	*T* (h)	Yield (%)[b]	d.r. (*syn*/*anti*)[c]	e.e. (%)[d]
1	$CHCl_3$	48	80	>98/2	57
2[e]	$CHCl_3$	48	18	>98/2	49
3	MeOH	48	92	>98/2	46
4[e]	MeOH	48	84	>98/2	50
5	DMSO	48	80	>98/2	30
6	*i*-PrOH	48	88	>98/2	48
7	CH_2Cl_2	48	90	>98/2	48
8	THF	48	88	>98/2	34
9	DMF	48	80	>98/2	26
10	CH_3CN	48	92	97/3	36
11	$CHCl_3$/MeOH (1/1, v/v)	48	94	>98/2	60
12[f]	$CHCl_3$/MeOH (1/1, v/v)	48	57	>98/2	57
13[g]	$CHCl_3$/MeOH (1/1, v/v)	48	89	>98/2	56
14[f,h]	$CHCl_3$/MeOH (1/1, v/v)	48	Trace	n.d.	48

[a] The reaction was carried out at room temperature in the presence of 5 mol% catalyst using 20 equiv. cyclohexanone.
[b] Isolated yield.
[c] Determined by ^{1}H NMR.
[d] Reported values refer to the *syn* isomer and were determined by HPLC on a chiral stationary phase.
[e] The reaction was carried out at −10 °C.
[f] The reaction was carried out at 0 °C.
[g] Using 10 equiv. cyclohexanone.
[h] Using 5 mol% of 4-nitrobenzenesulfonic acid as additive.

Table 3
Michael addition of various ketones to *trans*-β-nitrostyrene catalyzed by **10**[a]



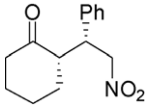
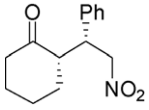
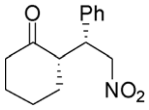
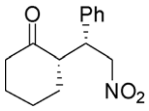
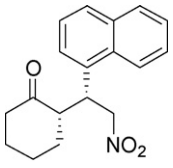
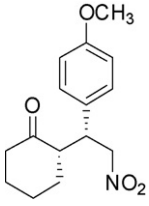
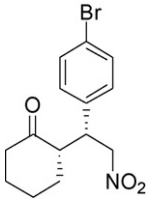
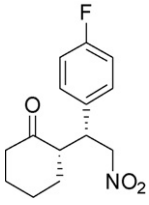
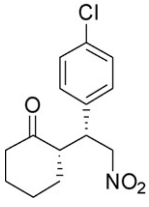
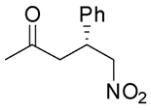
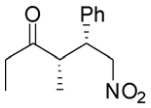
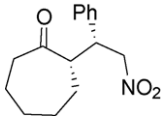
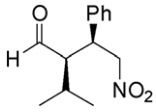
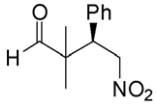
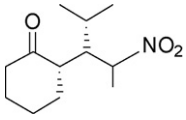
Entry	Product	Yield (%)[b]	d.r. (*syn*/*anti*)[c]	e.e. (%)[d]
1		94	>98/2	60
2[e]		65	>98/2	60
3[f]		27	95/5	45
4[g]		24	91/9	<10
5		88	>98/2	56
6		72	>98/2	57
7		80	>98/2	65
8		83	>98/2	61
9		89	>98/2	64

Table 3 (*Continued*)

Entry	Product	Yield (%)[b]	d.r. (*syn*/*anti*)[c]	e.e. (%)[d]
10		68	–	23
11		61	>98/2	86
12		39	>98/2	43
13		94	>98/2	<5
14		45	–	7
15		60	>98/2	58

[a] The reaction was carried out at room temperature in the presence of 5 mol% catalyst.
[b] Isolated yield.
[c] Determined by ^{1}H NMR.
[d] Reported values refer to the *syn* isomer and were determined by HPLC on a chiral stationary phase.
[e] The reaction was carried out with a catalyst sample recycled after use in entry 1.
[f] The reaction was carried out with a catalyst sample recycled after use in entries 1 and 2.
[g] The reaction was carried out with a catalyst sample recycled after use in entries 1–3.

alyst **6b** (MeOPEG $M_w = 5000$) catalyzed the Michael reaction with good diastereoselectivity and low enantiomeric excesses (Table 1, entries 1 and 2,) compared to the PEG-Pro reported by Benaglia et al. [14a]. However, we observed good yield (up to 92%), high diastereoselectivity (d.r. > 98/2) and moderate enantiomeric excesses (46%) in the Michael addition with the catalyst **10** (Table 1, entry 3). Under the same conditions, the Michael adduct was obtained in only 29% yield, 97/3 (*syn*/*anti*) diastereoselectivity and 39%e.e. using L-proline (10 mol%) as catalyst (Table 1, entry 4). It seemed that the sulfonamide moiety on the 4-position of proline could enhance the diastereoselectivity and the enantioselectivity of adduct. Better disatereoselectivity and enantioselectivity were observed with the small catalyst **12** compared to those with the small catalyst **14** (entries 5 and 6), in agreement with our guess.

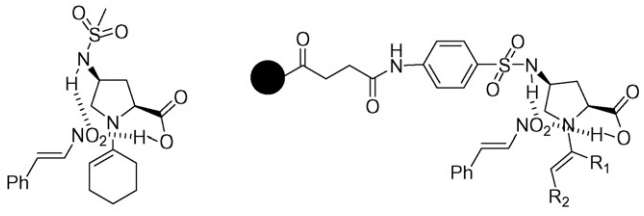
The reaction of cyclohexanone with *trans*-β-nitrostyrene in the presence of the best catalyst **10** (5 mol%) in various solvents at room temperature was investigated. As shown in Table 2, regardless of the solvents used, high yields (80–94%) and excellent diastereoselectivity (d.r. > 98/2) were observed (Table 2). Interestingly, the use of methanol did not lead to high enantiomeric excess value (only 46%e.e.), wherever the use of mixture solvent of methanol and chloroform (1/1, v/v) led to the best result (up to 60%e.e.) (Table 2, entries 3 and 11). The low temperature does not seem beneficial for the enantioselectivity (Table 2, entries 2 and 12). Independently of the solvent, the use of a small excess of cyclohexanone damaged both the yield and the stereoselectivity (Table 2, entry 13). When the reaction was carried out in the presence of 5 mol% equivalent amount of 4-nitrobenzenesulfonic acid, only trace product was obtained with a lower enantioselectivity (down to 48%e.e.) with respect to the adduct obtained without additive (Table 2, entry 14).

We then examined the reaction of ketones with various nitroalkenes (Table 3). All reactions were performed in $CHCl_3$/MeOH (1/1, v/v) at room temperature in the presence of 5 mol% of poly(ethylene-glycol)-supported catalyst **10**. In each case, reactions smoothly occurred to produce Michael adducts in high diastereoselectivity (d.r. > 98/2) and moderate to good enantioselectivity (up to 86%e.e.). The aromatic substituents on the nitrostyrenes had no noticeable effect on the enantioselectivies (Table 3, entries 1, 6–9), and the nearly same diastereoselectivity and enantioselectivity were obtained in the reaction of

cyclohexanone with *trans*-3-methyl-1-nitrobut-1-ene (Table 3, entry 15). Addition of acetone to nitrostyrene in the presence of the poly(ethylene-glycol)-supported catalyst **10** gave the desired product in moderate yield and lower enantiomeric excesses of 23%, while proline only gave the product of 7%e.e. [3] (Table 3, entry 10). However, when 3-pentanone was used as a Michael donor, the adducts were obtained with much higher diastereoselectivity (d.r. > 98/2) and enantioselectivity (up to 86%e.e.) (Table 3, entry 11) than those observed in the presence of the parent proline (20 mol%, 76%e.e.) [4] or other catalysts such as 2,2′-bipyrrolidine (15 mol%, 67%e.e.) [7]. The reaction time was shortened to 48 h, but 168 and 96 h were needed when 2,2′-bipyrrolidine [7] and the parent proline [4] were used as the catalyst, respectively. Instead of heptanone as the Michael acceptor, decrease in enantioselectivity (down to 43%e.e.) was observed (Table 3, entry 12). Isobutyraldehyde and isovaleraldehyde could also be employed successfully as the Michael donor to afford the corresponding adducts with rather lower enantiomeric excess (Table 3, entries 13 and 14). The absolute configurations of the Michael adducts were determined by comparison with the optical rotation of known compounds.

The recycling of poly(ethylene-glycol)-supported catalyst **10** was performed in the reaction and the results are shown in Table 3 (entries 1–4). Poly(ethylene-glycol)-supported catalyst **10** was readily recovered by precipitation with diethyl ether followed by filtraton (average recovery yields ranged from 80 to 90%), and may be re-used at least two times without loss of chemical efficiency and enantioselectivity. Only a decrease in chemical yield (from 94 to 65%) and no effect on enantioselectivity were observed for the second run (Table 3, entries 1 and 2), and the reaction was performed for the third run with some loss of activity and enantioselectivity (Table 3, entries 3 and 4). The recycling results were similar to those reported by Benaglia et al. [14a].

The *syn* selectivity we observed is in accordance with Seebach's model [17]. It is explained by an acyclic synclinal model, in which there are favorable electrostatic interactions between the nitrogen of the enamine and the nitro group in the transition state. It is presumed that the interaction of phenyl and R_2 favor the *Si* approach of nitrostyrene in **TS1** and **TS2**, and the two hydrogen bonds maybe strengthen the *Si* face. For the stronger acidity of hydrogen in sulfonylamide moiety of 4-position of proline than that in amide moiety, higher enantioselectivity was observed with the catalysts **10** and **12** than those with the catalysts **6a**, **6b** and **14** (Table 1). That may be the reason why the enantioselectivies in the reaction of various nitrostyrenes with ketones are much higher than those obtained with the parent proline and the supported proline reported in Refs. [3,14a] (Scheme 4).



Scheme 4. Proposed transition state in Michael reactions catalyzed by **12** or **10**.

3. Conclusion

In summary, we designed a new class of poly(ethylene-glycol)-supported catalysts based on proline, Using 5 mol% of the catalyst, the products of the Michael reactions were obtained in moderate to good yields (up to 94%) and high diastereoselectivity (up to 98/2, *syn*/*anti*). The enantiomeric excesses (up to 86%) were much higher than those obtained with non-supported proline or supported proline reported in Ref. [14a].

4. Experimental

4.1. General

Unless otherwise indicated, all compounds and reagents were purchased from commercial suppliers and used without further purification. ^{1}H NMR spectra are recorded at 300 or 400 MHz. All chemical shifts (δ) are given in ppm. ^{1}H NMR spectra were recorded on a Varian EM-360A, Varian EM90 or Brucker AMX-300 NMR spectrometer. IR spectra were recorded on a Perkin-Elmer 983G instrument. MS or HR-MS was recorded on a HP-5989A spectrometer. Melting points were determined on a Mettler-Toledo FP62 melting point apparatus without correction. Elemental analysis was performed on a Carlo-ERBA1106 instrument. HPLC analysis was carried out on a NCI901 or WATERS equipment. The compound **3** was prepared from compound **1** as reported in literature [15].

4.1.1. Poly(ethylene-glycol)-supported catalysts *6a* and *6b*

To a stirred solution of MeOPEG monosuccinate (**4**) (1.575 g, M_w = 2000, 0.75 mmol) in dried dichloromethane (30 mL), a solution of compound **3** (0.531 g, 1.50 mmol) in dried dichloromethane (10 mL) was added at room temperature. Then, DMAP (244 mg, 2 mmol) and DCC (309 mg, 1.50 mmol) were added. The solid was filtered off after the mixture stirred overnight. The solution was added to diethyl ether (100 mL) drop by drop. The solid was filtered and dried in vacuo to afford the crude compound **5a**, which was hydrogenated to remove the protected groups giving the desired product **6a** (1.5 g). ^{1}H NMR (300 MHz $CDCl_3$) δ 4.61 (m, 1H), 4.20 (m, 2H), 4.09 (m, 1H), 3.88–3.52 (m, 169H), 3.38 (s, 3H), 2.64 (m, 4H), 2.50 (m, 2H), 2.40 (m, 1H), 1.80 (m, 1H); Analysis: Calcd. for N, 1.26; Found: N, 1.21. Loading: 0.428 mequiv./g. The synthesis of catalyst **6b** is similar to the catalysis **6a**. ^{1}H NMR (300 MHz $CDCl_3$) δ 4.56 (m, 1H), 4.21 (m, 2H), 4.10 (m, 1H), 3.86–3.56 (m, 147H), 3.38 (s, 3H), 2.65 (m, 4H), 2.46 (m, 2H), 2.00 (m, 1H), 1.78 (m, 1H); loading: 0.172 mmol/g.

4.1.2. (2S,4R)-Dibenzyl 4-(4-nitrophenylsulfonamido) pyrrolidine-1,2-dicarboxylate (*7*)

To a stirred solution of (2*S*,4*R*)-dibenzyl 4-aminopyrrolidine-1,2-dicarboxylate (**3**) (3.042 g, 8.6 mmol) and Et_3N (2.24 mL, 16 mmol) in dried dichloromethane (60 mL), a solution of 4-

nitrobenzene-1-sulfonyl chloride (2.530 g, 10.3 mmol) in dried dichloromethane (30 mL) was slowly added under cooling in an ice-water bath. The stirring was continued for 2 h at the same temperature. Saturated $NaHCO_3$ (50 mL) was added to quench the reaction. The reaction mixture was extracted with CH_2Cl_2 (2× 50 mL). The combined organic portions were washed with brine (50 mL) and were dried over $MgSO_4$. The solvent was concentrated to give a residue and silica gel column chromatography (hexane/EtOAc, 2/1) followed to afford compound **7** (2.388 g, 52%). $[\alpha]_D^{23.6}$ −26.6 (c 0.60, $CHCl_3$); mp 135–136 °C; IR (KBr) ν = 3269, 2954, 1741, 1709, 1531, 1351, 1167 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 8.26 (dd, J = 14.7 Hz, 8.4 Hz, 2H), 7.95 (t, J = 9.9 Hz, 2H), 7.33 (m, 10H), 6.28 (dd, J = 18.0 Hz, 10.5 Hz, 1H), 5.29–5.02 (m, 4H), 4.36 (t, J = 13.5 Hz, 1H), 4.09 (brs, 1H), 3.52 (m, 2H), 2.39 (m, 1H), 1.90 (dd, J = 36.0 Hz, 14.7 Hz, 1H); MS (ESI); m/z (%): 538 [M^+ − H] (20%), 475 (100%); Analysis: Calcd. for $C_{26}H_{25}N_3O_8S$: C, 57.88; H, 4.67; N, 7.79; Found: C, 58.01; H, 4.66; N, 7.66.

4.1.3. (2S,4R)-Dibenzyl 4-(4-aminophenylsulfonamido) pyrrolidine-1,2-dicarboxylate (*8*)

To a stirred solution of **7** (0.754 g, 1.54 mmol) in ethanol (35 mL) at ambient temperature was added $SnCl_2$ (3.3 g, 15.4 mmol) in one portion and the reaction mixture was heated at reflux for 1 h. On cooling, the mixture was added with 10% aqueous NaOH for basification. The precipitation was separated and the aqueous phase extracted with ethyl acetate (3× 50 mL). The volatiles were removed in vacuo to afford essentially pure compound as waxy solid **8** (0.688 g, 96.4% yield). $[\alpha]_D^{24.4}$ −16.1 (c 1.05, $CHCl_3$); IR (KBr) ν = 3373, 1703, 1596, 1420, 1152, 1090 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 7.56 (m, 2H), 7.40–7.20 (m, 10H), 6.80 (m, 2H), 5.53 (dd, J = 15.7 Hz, 9.9 Hz, 2H), 5.15 (m, 4H), 4.32 (t, J = 9.9 Hz, 1H), 4.13 (d, J = 13.8 Hz, 2H), 3.94 (m, 1H), 3.50 (m, 1H), 3.40 (t, J = 12.7 Hz, 1H), 2.30 (m, 1H), 1.90 (dd, J = 34.9 Hz, 13.9 Hz, 2H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 173.5, 154.6, 153.9, 150.9, 136.2, 136.1, 135.2, 134.9, 129.1, 128.7, 128.6, 128.5, 128.4, 128.2, 128.0, 127.9, 114.2, 114.1, 67.6, 67.4, 58.0, 57.6, 53.2, 52.9, 52.8, 51.9, 36.7, 35.5; MS(EI); m/z(%): [M^+ + 1] 510; HRMS $C_{26}H_{27}N_3O_6SNa^+$ 532.15128 (MNa^+, Calcd. 532.1513).

4.1.4. Poly(ethylene-glycol)-supported compound *9*

To a stirred solution of MeOPEG monosuccinate (**4**) (4.160 g, M_w = 5000, 0.8 mmol) in dried dichloromethane (30 mL), a solution of compound **8** (1.018 g, 2.0 mmol) in dried dichloromethane (10 mL) was added at room temperature. Then, DMAP (122 mg, 1 mmol) and DCC (309 mg, 1.50 mmol) were added. The solid was filtered off after the mixture stirred overnight. The solution was added to diethyl ether (100 mL) drop by drop. The solid was filtered and dried in vacuo to afford the crude compound **9** (4.081 g, Y: 89.3%). ^1H NMR (400 MHz $CDCl_3$) δ 7.52 (m, 2H), 7.40–7.20 (m, 10H), 6.60 (m, 2H), 5.80 (brs, 1H), 5.10 (m, 4H), 4.30 (t, J = 9.9 Hz, 1H), 4.25 (m, 2H), 4.05 (brs, 1H), 3.98 (m, 1H), 3.90–3.30 (m, 320H), 3.05 (s, 3H), 2.70 (m, 4H), 2.30 (m, 1H), 1.95 (m, 1H).

4.1.5. Poly(ethylene-glycol)-supported catalyst *10*

To a solution of compound **9** (4.050 g, 0.72 mmol) in methanol (30 mL) was added Pd/C (10%, 0.40 g). The mixture was stirred under 1 atm of hydrogen at 40 °C overnight. The catalyst was filtered, and the solvent was removed to obtain a white solid, which was recrystalized in methanol for two times afforded the pure product **10** (3.04 g, Y: 78.6%). ^1H NMR (400 MHz D_2O) δ 7.71 (dd, J = 8.5 Hz, 2.1 Hz, 2H), 6.95 (t, J = 8.5 Hz, 6.5 Hz, 2H), 4.33 (d, J = 2.3 Hz, 4H), 4.10 (m, 1H), 3.90–3.40 (m, 939H), 3.70 (m, 1H), 3.50 (s, 6H), 3.30 (m, 1H), 2.72 (d, J = 4.7 Hz, 2H), 2.67 (d, J = 4.7 Hz, 2H), 2.52 (m, 1H), 2.00 (m, 1H); loading: 0.093 mmol/g.

4.1.6. (2S,4S)-Dibenzyl 4-(methylsulfonamido) pyrrolidine-1,2-dicarboxylate (*11*)

To a stirred solution of (2*S*,4*R*)-dibenzyl 4-aminopyrrolidine-1,2-dicarboxylate (**3**) (1.416 g, 4.0 mmol) and Et_3N (1.12 mL, 8 mmol) in dried dichloromethane (20 mL), a solution of methanesulfonyl chloride (0.687 g, 6.0 mmol) in dried dichloromethane (5 mL) was slowly added under cooling in an ice-water bath. The stirring was continued for 2 h at the same temperature. Saturated $NaHCO_3$ (10 mL) was added to quench the reaction. The reaction mixture was extracted with CH_2Cl_2 (2× 10 mL). The combined organic portions were washed with brine (10 mL) and were dried over $MgSO_4$. The solvent was concentrated to give a residue and silica gel column chromatography (hexane/EtOAc, 1/1) followed to afford compound **11** (1.097 g, 72.0%). White solid, $[\alpha]_D^{29.0}$ −15.3 (c 0.84, $CHCl_3$); mp 149–150 °C; IR (KBr) ν = 3291, 1707, 1750, 1417, 1327, 1154 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 7.36 (m, 10H), 5.55 (d, J = 6.6 Hz, 1H), 5.31–5.00 (m, 4H), 4.47–4.37 (m, 1H), 4.16 (m, 1H), 3.73 (m, 2H), 2.89 (s, 3H), 2.51 (m, 1H), 2.03 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 154.6, 154.0, 136.1, 136.0, 135.1, 134.9, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 67.7, 67.6, 58.0, 57.6, 53.6, 53.4, 52.9, 52.0, 41.8, 37.5, 36.3, 29.7; MS(ESI); m/z(%): [M^+ + 1] 433; HRMS $C_{21}H_{24}N_2O_6SNa^+$ 455.1247 (MNa^+, Calcd. 455.1250).

4.1.7. (2S,4S)-4-(Methylsulfonamido) pyrrolidine-2-carboxylic acid (*12*)

To a solution of compound **11** (1.050 g, 2.43 mmol) in methanol (10 mL) was added Pd/C (10%, 105 mg). The mixture was stirred under 1 atm of hydrogen at room temperature overnight. The catalyst was filtered, and the solvent was removed to obtain a white solid, which was recrystalized in methanol two times to afford the pure product **12** (0.368 g, Y: 72.7%). White solid, $[\alpha]_D^{24.8}$ −42.4 (c 0.68, H_2O); mp 295–296 °C; IR (KBr) ν = 3475, 2874, 1625, 1574, 1310, 1150 cm^{-1}; ^1H NMR (300 MHz D_2O) δ 4.15–4.04 (m, 2H), 3.52–3.46 (dd, J = 12.3 Hz, 7.2 Hz, 1H), 3.32–3.26 (dd, J = 12.3 Hz, 6.0 Hz, 1H), 2.99 (s, 3H) 2.67–2.57 (m, 1H) 2.04–1.94 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ 173.3, 59.7, 51.7, 50.1, 39.6, 34.6; MS(ESI); m/z(%): [M^+ + 1] 209; HRMS $C_6H_{12}N_2O_4SNa^+$ 231.0410 (MNa^+, Calcd. 231.0412).

*4.1.8. (2S,4S)-Dibenzyl 4-acetamidopyrrolidine-1,2-dicarboxylate (**13**)*

Y: 69.0%; colorless oil, $[\alpha]_D^{29.1}$ −21.1 (c 2.20, $CHCl_3$); IR (neat) ν = 1745, 1707, 1419 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 7.36–7.24 (m, 10H), 6.50 (d, J = 8.4 Hz, 1H), 5.29–5.02 (m, 4H), 4.64 (dd, J = 13.2 Hz, 5.4 Hz, 1H), 4.49–4.39 (m, 1H), 3.71–3.52 (m, 2H), 2.46 (m, 1H), 1.94 (dd, J = 18.6 Hz, 12.9 Hz, 1H), 1.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 169.5, 154.7, 154.1, 136.2, 135.2, 134.9, 128.7, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 67.5, 67.4, 58.2, 57.8, 53.5, 53.2, 48.6, 47.7, 36.8, 35.7, 29.7; MS(ESI); m/z(%): [M^+ + 1] 397; HRMS $C_{22}H_{25}N_2O_5S^+$ 397.1758 (M^+, Calcd. 397.1757).

*4.1.9. (2S,4S)-4-Acetamidopyrrolidine-2-carboxylic acid (**14**)*

Y: 60.3%; White solid, $[\alpha]_D^{24.6}$ −13.4 (c 0.29, H_2O); mp 280–281 °C; IR (KBr) ν = 3444, 3329, 1657, 1564, 1387 cm^{-1}; ^1H NMR (300 MHz D_2O) δ 4.37 (t, J = 6.6 Hz, 1H), 4.14 (t, J = 8.1 Hz, 1H), 3.55 (dd, J = 12.3 Hz, 7.2 Hz, 1H), 3.29 (dd, J = 12.3 Hz, 5.7 Hz, 1H), 2.67–2.57 (m, 1H), 2.08–1.99 (m, 1H), 1.90 (s, 3H); ^{13}C NMR (75 MHz, D_2O) δ 174.3, 173.6, 60.1, 49.3, 48.7, 33.8, 21.8; MS(ESI); m/z(%): [M^+ + 1] 173; HRMS $C_7H_{13}N_2O_3^+$ 173.0921 (M^+, Calcd. 173.0922).

4.2. General procedure for Michael reaction between ketones and trans-β-nitrostyrene

A mixture of ketone (0.1 mmol), catalyst 54 mg (0.0005 mmol) in MeOH (2 mL) or in other appropriate solvent (2 mL) was stirred at room temperature for 48 h. Then, the mixture was added into Et_2O (20 mL) drop by drop. The catalyst precipitated and was filtered off. The precipitate was washed with diethyl ether several times and recovered (average 80–95%). The filtrate was concentrated under vacuum. Purification by flash chromatography afforded pure products, which was analyzed by ^1H NMR spectroscopy to assess the diastereoisomeric ratio. The relative and absolute configurations of the Michael adducts were determined by comparison with NMR spectroscopic analysis and optical rotation studies of the known compound. The enantiomeric excess was determined by HPLC with Chiralcel-AS or AD.

4.2.1. (S)-2-((R)-2-Nitro-1-phenylethyl)cyclohexanone [3]

White solid, $[\alpha]_D^{20.3}$ −23.5 (c 0.41, $CHCl_3$); mp 121–122 °C; IR (KBr): ν = 1698, 1552 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 7.33 (m, 1H), 7.15 (m, 2H), 4.95 (m, 1H), 4.63 (m, 1H), 3.76 (m, 1H), 2.73 (m, 1H), 2.46 (m, 2H), 2.08 (m, 1H), 1.80–1.46 (m, 2H), 1.25 (m, 1H); enantiomeric excess: 60%, determined by HPLC (Daicel Chiralpak AD, *i*-PrOH/hexane 10/90), UV 254 nm, flow rate 1.0 mL/min, t_{minor} 14.2 min and t_{major} 16.8 min.

4.2.2. (S)-2-((R)-1-(Naphthalen-1-yl)-2-nitroethyl) cyclohexanone [8]

White solid, $[\alpha]_D^{20.0}$ −73.8 (c 0.41, $CHCl_3$); mp 133–134 °C; IR (KBr) ν = 2939, 1705, 1551 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 8.15 (s, br, 1H), 7.87 (s, 1H), 7.84 (s, 1H), 7.79 (s, 1H), 7.76 (s, 1H), 7.57–7.43 (m, 4H), 5.08 (m, 1H),4.92 (m, 1H), 4.76 (s, br, 1H), 2.86 (s, br, 1H), 2.52–2.35 (m, 2H), 2.10–2.04 (m, 1H), 1.69–1.43 (m, 4H), 1.21 (m, 1H); enantiomeric excess: 56% determined by HPLC (Daicel Chiralpak AS, *i*-PrOH/hexane 50/50), UV 254 nm, flow rate 0.7 mL/min, t_{minor} 11.4 min and t_{major} 14.8 min.

4.2.3. (S)-2-((R)-1-(4-Methoxyphenyl)-2-nitroethyl) cyclohexanone [8]

White solid, $[\alpha]_D^{20.1}$ −10.78 (c 0.27, $CHCl_3$); mp 148–149 °C; IR (KBr) ν = 1702, 1553 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 7.08 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 4.93–4.88 (dd, J = 12.3 Hz, 4.8 Hz, 1H), 4.61–4.54 (dd, J = 12.3 Hz, 9.9 Hz, 1H), 3.80 (s, 3H), 3.78–3.67 (m, 1H) 3.53–3.44 (m, 1H), 2.68 (m, 1H), 2.49–2.36 (m, 2H), 2.06 (m, 1H), 1.81–1.48 (m, 3H), 1.21 (m, 1H); enantiomeric excess: 60%, determined by HPLC (Daicel Chiralpak AD, *i*-PrOH/hexane 20/80), UV 254 nm, flow rate 0.5 mL/min, t_{minor} 12.1 min and t_{major} 14.4 min.

4.2.4. (S)-2-((R)-1-(4-Bromophenyl)-2-nitroethyl) cyclohexanone

White solid, $[\alpha]_D^{20.1}$ −15.2 (c 0.92, $CHCl_3$); mp 117–118 °C; IR (KBr) ν = 2939, 1707, 1552 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 7.45 (d, J = 8.1 Hz, 2H), 7.05 (d, J = 8.1 Hz, 2H), 4.95 (m, 1H), 4.60 (t, J = 9.6 Hz, 1H), 3.75 (m, 1H), 2.64 (m, 1H), 2.45 (m, 2H), 2.08 (s, 1H), 1.83–1.70 (m, 4H), 1.20 (m, 1H); MS(EI); m/z(%): [$M^+ - NO_2$ + 1] 280 (56%), 249 (100); Analysis: Calcd. for $C_{14}H_{16}BrNO_3$: C, 51.55; H, 4.94; N, 4.29; Found: C, 51.67; H, 5.06, N, 4.04; enantiomeric excess: 65%, determined by HPLC (Daicel Chiralpak AD, *i*-PrOH/hexane 10/90), UV 254 nm, flow rate 1.0 mL/min, t_{minor} 12.1 min and t_{major} 17.2 min.

4.2.5. (S)-2-((R)-1-(4-Fluorophenyl)-2-nitroethyl) cyclohexanone

White solid, $[\alpha]_D^{20.1}$ −21.4 (c 0.53, $CHCl_3$); mp 88–89 °C; IR (KBr) ν = 2941, 1708, 1552, 1151 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 7.17 (m, 2H), 7.02 (m, 2H), 4.95 (dd, J = 12.3 Hz, 5.4 Hz, 1H), 4.59 (dd, J = 12.3 Hz, 9.6 Hz, 1H), 3.76 (m, 1H), 2.68 (m, 1H), 2.45 (m, 2H), 2.08 (m, 1H), 1.82–1.50 (m, 4H), 1.22 (m, 1H); MS(EI); m/z(%): 218 [$M^+ - NO_2 - 1$] (19%), 44 (100); Analysis: Calcd. for $C_{14}H_{16}FNO_3$: C, 63.39; H, 6.08; N, 5.28; Found: C, 63.20; H, 6.27, N, 5.17; enantiomeric excess: 61%, determined by HPLC (Daicel Chiralpak AD, *i*-PrOH/hexane 5/95), UV 254 nm, flow rate 1.0 mL/min, t_{minor} 30.1 min and t_{major} 39.9 min.

4.2.6. (S)-2-((R)-1-(4-Chlorophenyl)-2-nitroethyl) cyclohexanone

White solid, $[\alpha]_D^{20.1}$ −18.8 (c 0.97, $CHCl_3$); mp 97–98 °C; IR (KBr) ν = 2941, 1707, 1552 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 7.30 (m, 2H), 7.13 (m, 2H), 4.95 (dd, J = 12.6 Hz, 4.5 Hz, 1H), 4.60 (dd, J = 12.6 Hz, 9.6 Hz, 1H), 3.76 (ddd, J = 14.8 Hz, 9.6 Hz, 4.5 Hz, 1H), 2.65 (m, 1H), 2.50 (m, 2H), 2.10 (m, 1H), 1.83–1.50 (m, 4H), 1.26 (m, 1H); MS(EI); m/z(%): [$M^+ - NO_2 - 1$] 234 (52%), 205 (100); Analysis: Calcd. for

$C_{14}H_{16}ClNO_3$: C, 59.68; H, 5.72; N, 4.97; Found: C, 59.58; H, 5.67, N, 4.76; enantiomeric excess: 64%, determined by HPLC (Daicel Chiralpak AD, *i*-PrOH/hexane 10/90), UV 254 nm, flow rate 1.0 mL/min, t_{minor} 21.2 min and t_{major} 30.5 min.

4.2.7. (R)-5-Nitro-4-phenylpentan-2-one [3]

White solid, $[\alpha]_D^{21}$ −2.56 (c 0.45, $CHCl_3$); mp 100–101 °C; IR (KBr) ν = 1712, 1545 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 7.36–7.20 (m, 5H), 4.73–4.57 (m, 2H), 4.00 (m, 1H), 2.92 (d, J = 6.9 Hz, 1H), 2.12 (s, 3H); enantiomeric excess: 23%, determined by HPLC (Daicel Chiralpak AD, *i*-PrOH/hexane 10/90), UV 254 nm, flow rate 0.75 mL/min, t_{minor} 20.4 min and t_{major} 21.7 min.

4.2.8. (4S,5R)-4-Methyl-6-nitro-5-phenylhexan-3-one [4]

Colorless oil, $[\alpha]_D^{17}$ −4.52 (c 0.20, $CHCl_3$); IR (neat) ν = 2924, 1711, 1153 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 7.33 (m, 3H), 7.16 (m, 2H), 4.63 (m, 2H), 3.73 (m, 1H), 3.00 (m, 1H), 2.66 (m, 1H), 2.45 (m, 1H), 1.07 (s, 3H), 0.97 (s, 3H); enantiomeric excess: 86%, determined by HPLC (Daicel Chiralpak AD, *i*-PrOH/hexane 1/50), UV 254 nm, flow rate 1.00 mL/min, t_{minor} 17.3 min and t_{major} 22.2 min.

4.2.9. (S)-2-((R)-2-Nitro-1-phenylethyl)cycloheptanone [6c]

Colorless oil, $[\alpha]_D^{17}$ −9.46 (c 0.25, $CHCl_3$); IR (neat) ν = 2925, 1698, 1552 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 7.36 (m, 3H), 7.18 (m, 2H), 4.67 (m, 2H), 3.69 (m, 1H), 3.02 (m, 1H), 2.55 (m, 2H), 1.95 (m, 2H), 1.89–1.57 (m, 4H), 1.20 (m, 2H); enantiomeric excess: 42%, determined by HPLC (Daicel Chiralpak AD, *i*-PrOH/hexane 1/50), UV 254 nm, flow rate 1.0 mL/min, t_{minor} 25.8 min and t_{major} 35.7 min.

4.2.10. (2R,3S)-2-Isopropyl-4-nitro-3-phenylbutanal [8]

Colorless oil; IR (neat) ν = 2936, 1719, 1552, 1379 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 9.93 (s, 1H), 7.33 (m, 3H), 7.22 (m, 2H), 4.66 (m, 2H), 3.98 (m, 1H), 2.92 (m, 1H), 2.12 (m, 1H), 1.10 (s, 3H), 0.98 (s, 3H); enantiomeric excess: <10%, determined by HPLC (Daicel Chiralpak AD, *i*-PrOH/hexane 1/50), UV 254 nm, flow rate 1.0 mL/min, t_{minor} 19.7 min and t_{major} 24.9 min.

4.2.11. (R)-2,2-Dimethyl-4-nitro-3-phenylbutanal [9]

Colorless oil, $[\alpha]_D^{21}$ −2.98 (c 0.25, $CHCl_3$); IR (neat) ν = 1724, 1553 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 9.47 (s, 1H), 7.25 (d, J = 6.9 Hz, 2H), 7.12 (d, J = 6.9 Hz, 2H), 4.70 (t, J = 12.9 Hz, 1H), 4.60 (dd, J = 12.9 Hz, 3.9 Hz, 1H), 3.70 (dd, J = 11.7 Hz, 4.5 Hz, 1H), 1.07 (s, 3H), 0.94 (s, 3H); enantiomeric excess: 7%, determined by HPLC (Daicel Chiralpak AS, *i*-PrOH/hexane 10/90), UV 254 nm, flow rate 1.0 mL/min, t_{minor} 22.6 min and t_{major} 26.9 min.

4.2.12. (S)-2-((R)-3-Methyl-1-nitrobutan-2-yl) cyclohexanone [17]

Colorless oil, $[\alpha]_D^{26}$ −15.4 (c 0.60, $CHCl_3$); IR (neat) ν = 2934, 1708, 1551, 1383 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 4.65 (dd, J = 13.8 Hz, 5.7 Hz, 1H), 7.12 (dd, J = 13.8 Hz, 5.4 Hz, 1H), 2.65 (m, 1H), 2.42–2.27 (m, 3H), 2.14 (m, 2H), 1.99 (m, 2H), 1.74 (m, 3H), 0.93 (d, J = 6.6 Hz, 1H), 0.89 (d, J = 6.6 Hz, 1H); enantiomeric excess: 58% determined by HPLC (Daicel Chiralpak AD, *i*-PrOH/hexane 10/90), UV 210 nm, flow rate 1.0 mL/min, t_{minor} 13.0 min and t_{major} 10.9 min.

References

[1] For recent reviews of asymmetric Michael addition reactions, see;
(a) K. Tomioka, Y. Nagaoka, M. Yamaguchi, in: E.N. Jacobsen, A. Pfaltz, H. Yamamoto (Eds.), Comprehensive Asymmetric Catalysis, vol. III, Springer, New York, 1999, pp. 1105–1139 (Chapters 31.1 and 31.2);
(b) N. Krause, A. Hoffmann-Röder, Synthesis (2001) 171;
(c) O.M. Berner, L. Tedeschi, D. Enders, Eur. J. Org. Chem. (2002) 1877;
(d) J. Christoffers, A. Baro, Angew. Chem. 115 (2003) 1726;
(e) J. Christoffers, Angew. Chem. Int. Ed. 42 (2003) 1688.

[2] S. Hanessian, V. Pham, Org. Lett. 2 (2000) 2975.

[3] B. List, P. Pojarliev, H.J. Martin, Org. Lett. 3 (2001) 2423.

[4] D. Enders, A. Seki, Synlett (2002) 26.

[5] (a) A.J.A. Cobb, D.A. Longbottom, D.M. Shaw, S.V. Ley, Chem. Commun. (2004) 1808;
(b) A.J.A. Cobb, D.M. Shaw, D.A. Longbottom, J.B. Gold, S.V. Ley, Org. Biomol. Chem. 3 (2005) 84.

[6] (a) J.M. Betancort, C.F. Barbas III, Org. Lett. 3 (2001) 3737;
(b) N. Mase, R. Thayumanavan, F. Tanaka, C.F. Barbas III, Org. Lett. 6 (2004) 2527;
(c) J.M. Betancort, K. Sakthivel, R. Thayumanavan, F. Tanaka, C.F. Barbas III, Synthesis (2004) 1509;
(d) For a review, see;
W. Notz, F. Tanaka, C.F. Barbas III, Acc. Chem. Res. 37 (2004) 580.

[7] (a) A. Alexakis, O. Andrey, Org. Lett. 4 (2002) 3611;
(b) O. Andrey, A. Alexakis, G. Bernardinelli, Org. Lett. 5 (2003) 2559;
(c) O. Andrey, A. Alexakis, A. Tomassini, G. Bernardinelli, Adv. Synth. Catal. 346 (2004) 1147.

[8] T. Ishii, S. Fujioka, Y. Sekiguchi, H. Kotsuki, J. Am. Chem. Soc. 126 (2004) 9558.

[9] (a) W. Wang, J. Wang, H. Li, Angew. Chem. Int. Ed. 117 (2005) 1393;
(b) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, Angew. Chem. Int. Ed. 44 (2005) 4212.

[10] (a) Y. Xu, A. Cordova, Chem. Commun. (2006) 460;
(b) S.B. Tsogoeva, S.W. Wei, Chem. Commun. (2006) 1451.

[11] (a) J.B. Hu, G. Zhao, G.S. Yang, Z.D. Ding, J. Org. Chem. 66 (66) (2001) 303;
(b) J.B. Hu, G. Zhao, Z.D. Ding, Angew. Chem. Int. Ed. Engl. 40 (2001) 1109;
(c) G.Y. Wang, J.B. Hu, G. Zhao, Tetrahydron Asymm. 15 (2004) 807.

[12] X.Y. Liu, X.Y. Wu, Z. Chai, Y.Y. Wu, G. Zhao, S.Z. Zhu, J. Org. Chem. 70 (2005) 7432.

[13] M. Benaglia, A. Puglisi, F. Cozzi, Chem. Rev. 103 (2003) 3401.

[14] (a) M. Benaglia, M. Cinquini, F. Cozzi, A. Puglisi, G Celentano, J. Mol. Catal. A: Chem. 204/205 (2003) 157;
(b) M. Benaglia, G. Celentano, F. Cozzi, Adv. Synth. Catal. 343 (2001) 171;
(c) M. Benaglia, M. Cinquini, F. Cozzi, A. Puglisi, G. Celentano, Adv. Synth. Catal. 344 (2002) 533.

[15] M. Tamaki, G. Han, V.J. Hruby, J. Org. Chem. 66 (2001) 1038.

[16] C. Bolm, A. Gerlach, Angew. Chem. Int. Ed. 36 (1997) 741.

[17] (a) S.J. Blarer, D. Seebach, Chem. Ber. 116 (1983) 3086;
(b) R. Häner, T. Laube, D. Seebach, Chimia 38 (1984) 255;
(c) D. Seebach, A.K. Beck, J. Golinski, J.N. Hay, T. Laube, Helv. Chim. Acta 68 (1985) 162;
(d) D. Seebach, J. Golinski, Helv. Chim. Acta 64 (1981) 1413.