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Microgel supported hydantoins as new chiral auxiliaries for asymmetric Mannich reactions

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ABSTRACT

Four distinct microgel supported hydantoin chiral auxiliaries were prepared with four different cross-linkers and evaluated in asymmetric Mannich reactions, which proceeded in good chemical yields and with excellent stereoselectivities. Moreover, the microgel supported hydantoin chiral auxiliaries could be reused for at least four cycles without an appreciable reduction in the yield or stereoselectivity.

1. Introduction

Chiral auxiliary-mediated asymmetric reactions have been studied extensively and are currently one of the most general methods employed in modern organic synthesis.[1] The optically active hydantoin, a new chiral auxiliary, developed by Yamaguchi, has proved to be particularly efficient in terms of stereoselectivity and yield in asymmetric conjugate addition reactions.[2]

As a continuation of Yamaguchi's work, we investigated the asymmetric aldol and Mannich reactions induced by hydantoin chiral auxiliaries.[3] The hydantoin chiral auxiliaries could be recovered by column chromatography for reuse, but this method was not suitable for mass production. Since then, the soluble polymer support—non-cross-linked polystyrene (NCPS), which is a valuable tool to simplify chiral auxiliary recycling, has become a better choice.[4] NCPS has good solubility characteristics, but its solutions become extremely viscous at high concentrations and low temperatures.

Microgel, a new type of soluble support, which is defined as 'intramolecularly cross-linked molecules that form a stable solution in many solvents', exhibits low viscosity even at high concentrations and low temperatures, so it can avoid the above problem.[5] Herein we report the preparation of four microgel supported hydantoin chiral auxiliaries with four different cross-linkers, the application of these chiral auxiliaries in asymmetric Mannich reactions, and the potential for recycling of the chiral auxiliaries.

2. Results and discussion

2.1. Preparation of microgel supported *N*-propionyl chiral hydantoin 3

As shown in Scheme 1, microgel supported *N*-propionyl chiral hydantoin **3** was synthesized from the novel starting material **1**, which was prepared from L-tyrosine methyl ester hydrochloride in three steps as previously described.[4] Compound **1** was copolymerized with styrene and one of four different cross-linkers **2** under polymerization conditions for microgels to prepare four distinct microgel supported *N*-propionyl chiral hydantoin polymers **3a**–**d** respectively in a 78–92% yield.[5] Polymers **3a**–**d** are soluble in typical organic solvents, such as benzene, $CHCl_3$, CH_2Cl_2, CH_3CN, EtOAc, THF, or DMF, and insoluble in MeOH, EtOH, or H_2O; this solubility versus recovery relationship of the crystalline polymer could lead to a better recovery with regard to the yield of the polymer support when precipitated with a poor solvent. Moreover, polymers **3a**–**d** exhibit low viscosity even at high concentrations and low temperatures, and because of their unique properties they seem to be good candidates for use as chiral auxiliaries in asymmetric synthesis and better than NCPS supported chiral hydantoin.

The ^{1}H NMR spectrum of **3c** (taking **3c** as an example) (Fig. 1) shows the aromatic protons of phenyl at 6.5–7.7 ppm (Fig. 1, peak a) and methylene protons of polymer (–Ar–O–C*H*$_2$–Ar–) and the methyne proton (–N–C*H*–) at 4.90–5.25 ppm (Fig. 1, peak b). Methylene protons of the cross-linker (–O–C*H*$_2$–CH$_2$–) were observed at 4.60 ppm (Fig. 1, peak c). Methylene protons of a hydantoin moiety (–N–CH–C*H*$_2$–) and of a propanoyl group (–N–CO–C*H*$_2$–CH$_3$) were observed at 3.35–3.80 ppm (Fig. 1, peak d) and 3.08 ppm (Fig. 1, peak e), respectively. On the basis of the ^{1}H NMR spectroscopic

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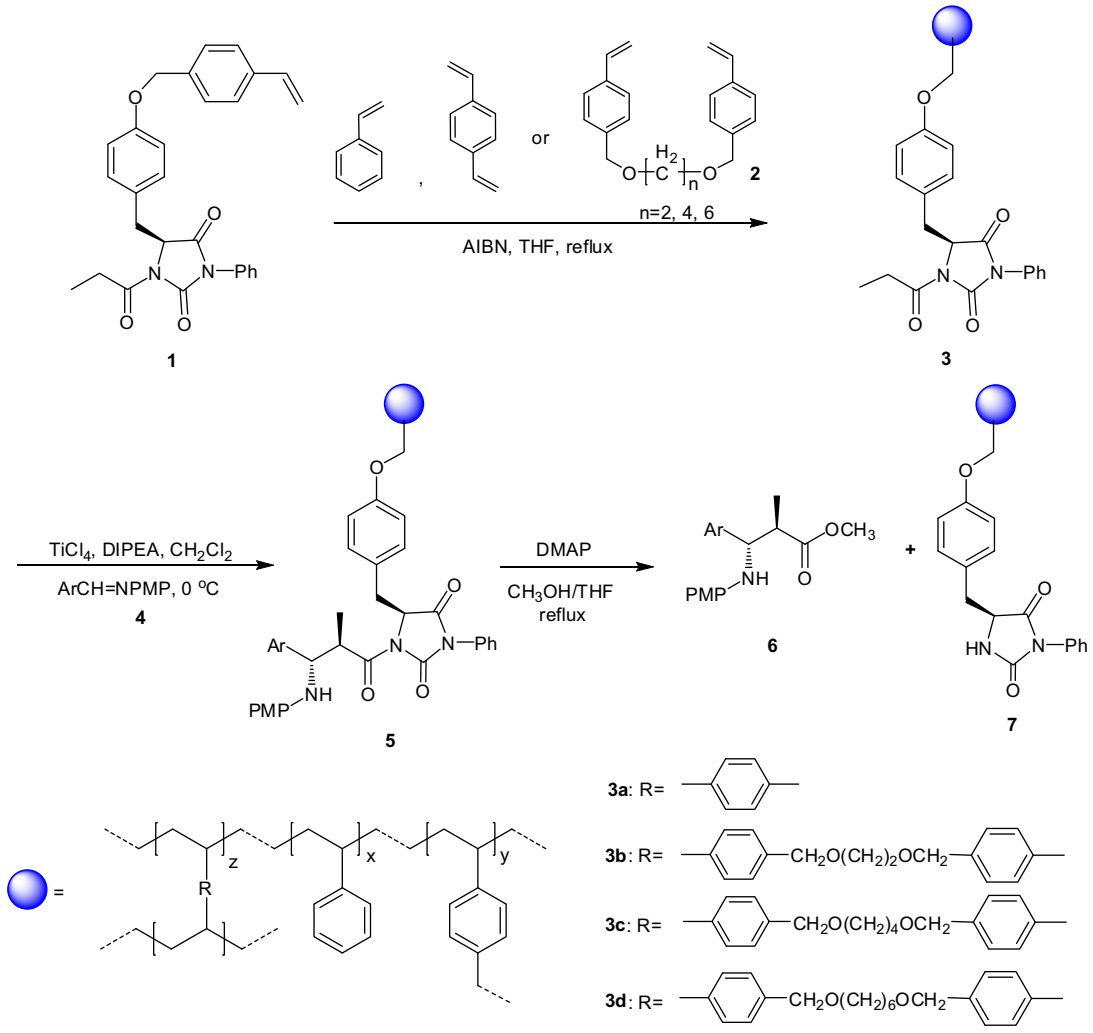

Ar = C_6H_5, 4-ClC_6H_4, 3-$NO_2C_6H_4$, 2,3-$(CH_3O)_2C_6H_3$, 2-furyl, 2-thienyl

Scheme 1.

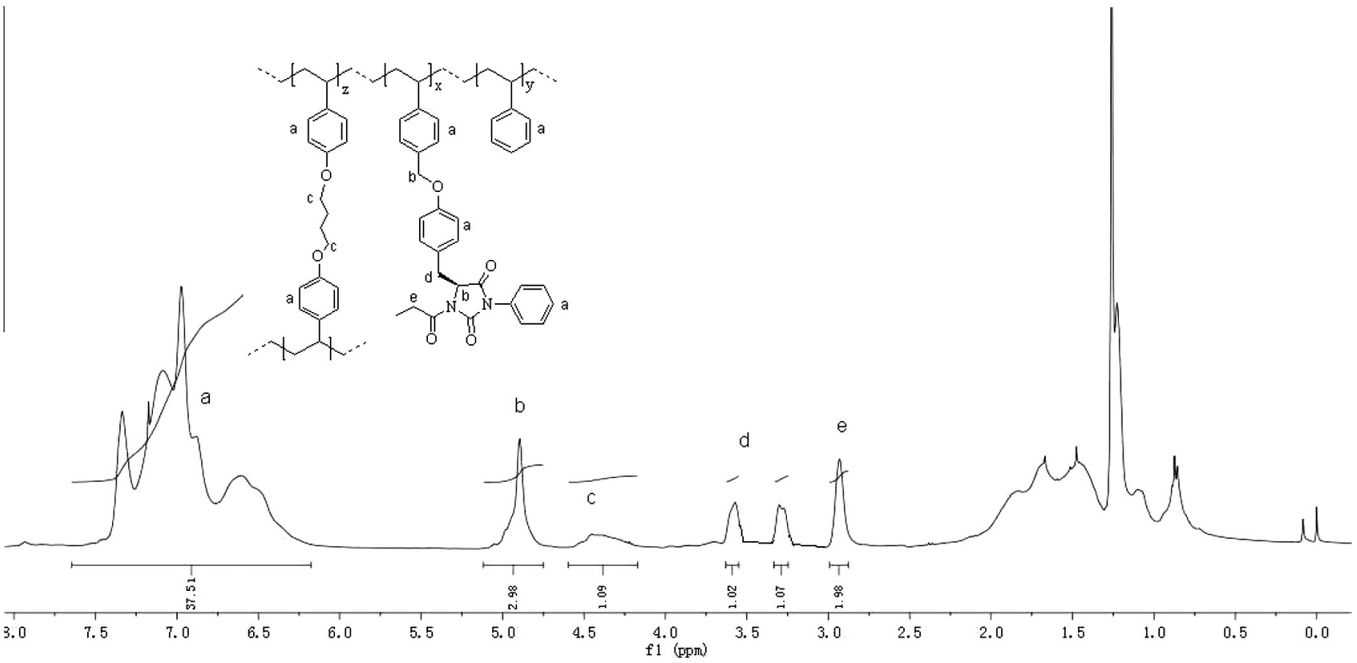

Figure 1. ^1H NMR spectra (400 MHz, $CDCl_3$) of polymer **3c**.

analysis, the calculated ratios (**1**/styrene/**2** = 17.6:77.6:4.8) of the incorporated monomers in **3c** were in agreement with that of the monomer feed (**1**/styrene/**2** = 19:76:5). Thus, the ^{1}H NMR spectrum of **3c** was used to calculate the loading of chiral hydantoin (1.01 mmol/g). The loading capacity of other polymers **3** were calculated by their ^{1}H NMR spectrum respectively as well (Table 1). The results of the molecular weight determination of **3a–d** by gel permeation chromatography (GPC) and molecular weight distribution (*M*w/*M*n) show the expected discrepancy because the GPC was calibrated with linear polystyrene standards (Table 1).

Table 1

Polymer	Yield[a] (%)	Loading[b] (mmol/g)		*Mn*[c]	*Mw*[c]	*Mw*/*Mn*[c]
		Theor	Obsd			
3a	82	1.10	0.91	6700	16,780	2.5
3b	78	1.06	1.00	5560	15,570	2.8
3c	92	1.06	1.01	7320	15,380	2.1
3d	85	1.05	0.90	7030	17,150	2.3

[a] After purification by precipitation in EtOH.
[b] Loading was calculated by the ^{1}H NMR spectrum.
[c] As determined by GPC relative to linear polystyrene standards.

The formation of polymers **3a–d** were further evidenced by TEM (Fig. 2), which provided important information about the morphologies and size distributions of the polymer. The morphology of a typical spherical particle was shown as polymer **3c**, which was prepared with 1,4-bis[4-(vinyl) phenoxy] butane as the cross-linker. Spherical particles (ca. 550–800 nm in diameter) can be observed. It can be seen that the spherical particle and size distributions of the polymer **3c** were more uniform than others. Furthermore, the thermal stability of polymers **3a–d** was investigated by thermogravimetric analysis in order to demonstrate that these polymers are stable at temperatures up to 300 °C (Fig. 3). The good thermal stability of these polymers indicates that they are appropriate for their use in many organic transformations at room temperature or at elevated temperatures.

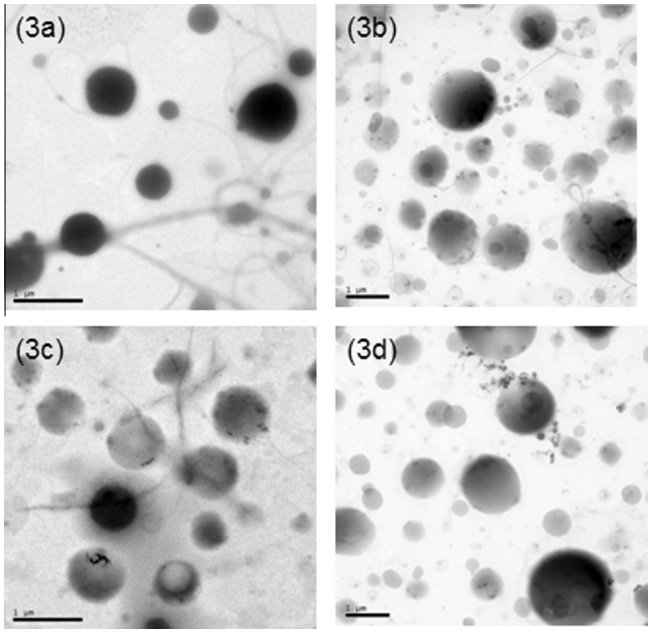

Figure 2. TEM images of **3a–d**. Scale bars = 1 μm.

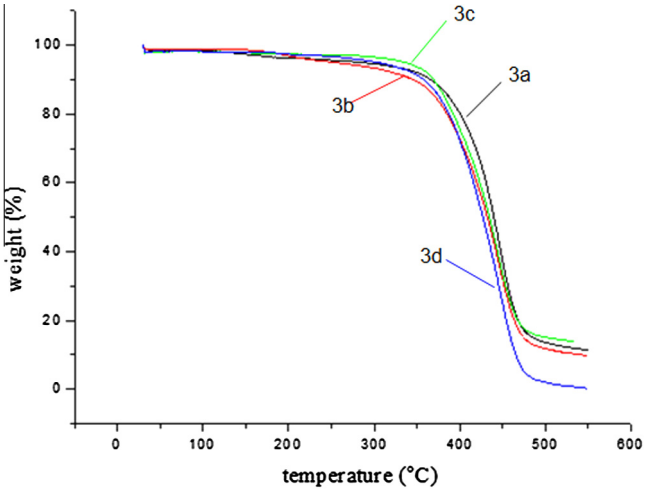

Figure 3. TGA thermograms of **3a–d**.

2.2. Diastereocontrolled Mannich reactions

In order to demonstrate the efficiency of microgel supported chiral hydantoin **3** as a new chiral auxiliary, the asymmetric Mannich reaction of microgel supported chiral hydantoin **3** with *N*-(4-methoxyphenyl)benzaldimine **4a** was chosen as a model reaction. As shown in Scheme 1, microgel supported chiral hydantoin **3a–d** was deprotonated with 1.05 equiv of $TiCl_4$ and 1.5 equiv of DIPEA at 0 °C, to form the *Z*-enolate, which was reacted with *N*-(4-methoxyphenyl)-benzaldimine **4a**, leading to the desired Mannich adduct **5**. The four Mannich adducts **5aa–da** derived from four different microgel supported chiral hydantoin polymers **3a–d** were then alcoholized in a 3:1 mixture of THF/methanol with DMAP as the catalyst to afford the same methyl ester **6a** as well as the quantitative recovery of the chiral auxiliary **7a–d**.

As shown in Table 2, product **6a** was obtained in good chemical yields (50–73%), high diastereoselectivity (dr >99:1) and excellent enantioselectivity (ee >99%) (Table 2, entries 1–4). These data show that the polymer's inner structure had some effect on the

Table 2

Entry	Chiral auxiliary	Ar	Product	Yield[a] (%)	dr[b]	ee[c] (%)
1	**3a**	C_6H_5	**6a**	50	>99:1	>99
2	**3b**	C_6H_5	**6a**	66	>99:1	>99
3	**3c**	C_6H_5	**6a**	73	>99:1	>99
4	**3d**	C_6H_5	**6a**	64	>99:1	>99
5	**3c**	C_6H_5[d]	**6a**	62	>99:1	>99
6	**3c**	C_6H_5[e]	**6a**	55	>99:1	>99
7	NCPS-hydantoin	C_6H_5[f]	**6a**	40	92:8	90
8	NCPS-hydantoin	C_6H_5[g]	**6a**	69	>99:1	>99
9	**3c**	4-ClC_6H_4	**6b**	68	>99:1	>99
10	**3c**	3-$NO_2C_6H_4$	**6c**	82	>99:1	>99
11	**3c**	2,3-$(CH_3O)_2C_6H_3$	**6d**	61	>99:1	>99
12	**3c**	2-Furly	**6e**	63	>99:1	>99
13	**3c**	2-Thienyl	**6f**	67	>99:1	>99

[a] Overall isolated yield in two steps starting from **3**.
[b] Determined by HPLC.
[c] Determined by chiral HPLC.
[d] 2.0 mmol scale in dicholoromethane (20 mL).
[e] 2.0 mmol scale in dicholoromethane (15 mL).
[f] 2.0 mmol scale in dicholoromethane (25 mL).
[g] 2.0 mmol scale in dicholoromethane (40 mL).

reaction conversion but had little impact on stereoselectivity. In agreement with our previous report,[5a] the best result was obtained with microgel supported chiral hydantoin **3c** (Table 2, entry 3), which was prepared with 1,4-bis[4-(vinyl) phenoxy] butane as the cross-linker.

In order to compare the efficiency of microgel supported chiral hydantoin with NCPS supported hydantoin chiral auxiliaries,[4] we performed the same Mannich reaction with both microgel supported hydantoin chiral auxiliaries and NCPS supported hydantoin chiral auxiliaries under different concentration conditions (Table 2, entries 5–8). Using microgel supported hydantoin as chiral auxiliary and under higher concentration conditions, product **6a** was obtained with the same stereoselectivity, but lower chemical yields. This indicates that the above concentration with 2.0 mmol scale in dicholoromethane (25 mL) is the best concentration. When using the same concentration, product **6a** with an NCPS supported hydantoin chiral auxiliary was afforded in 40% chemical yield, 92:8 dr and 90% ee, which is lower than with a microgel supported hydantoin chiral auxiliary. With a lower concentration on a 2.0 mmol scale in dicholoromethane (40 mL), using NCPS supported hydantoin as the chiral auxiliary, product **6a** was obtained with the same stereoselectivity and in a similar chemical yield (69%). Hence the low viscosity of the microgel is important in the asymmetric reaction, both in terms of the chemical yield, and also stereoselectivity.

The Mannich reactions of microgel supported chiral hydantoin **3c** with other aldimines also exhibited excellent stereoselectivity and produced the corresponding methyl esters **6b–f** in good chemical yields as shown in Table 2. Compared to the same reactions using non-supported hydantoin chiral auxiliary,[3b] the Mannich reactions using the chiral auxiliary **3c** exhibited higher chemical yields and the same stereoselectivities.

All products **6a–f** are known compounds and were identified by comparison of their physical and spectroscopic data with those of authentic samples.[3b,6] The *syn* versus *anti* stereochemistry of the Mannich adducts may be assigned on the basis of ^{1}H NMR coupling constants of the products **6a–f**. The measured $J_{3,4}$ coupling constant in the ^{1}H NMR spectrum was found to be 1.8 Hz, which was consistent with the *anti*-stereochemistry reported in the literature.[3b,6] The absolute configurations of products **6a–f** were confirmed by comparing their specific rotations with those previously reported.

2.3. Recycling and reuse of microgel supported hydantoin chiral auxiliary

In order to further investigate the ability of recycling microgel supported chiral auxiliary **7**, recovered chiral auxiliary **7c** (taking **7c** as an example) was washed and dried, and then subjected to *N*-acylation with propionyl chloride, Mannich reaction with *N*-(4-methoxyphenyl)benzaldimine, and alcoholysis to give the corresponding β-amino ester **6a**. After the continuous second to fourth asymmetric Mannich reactions, the desired β-amino ester was obtained with high diastereoselectivity (dr >99:1) and excellent enantioselectivity (ee >99%) (Table 3). Although the product's stereoselectivity remained almost intact, the yield decreased in each cycle. Thus the greatest advantage of microgel supported hydantoin chiral auxiliary over non-supported hydantoin chiral auxiliary is that it can be recovered by simple precipitation and filtration, and can be reused for at least four cycles without an appreciable reduction in the yield or stereoselectivity.

Table 3

Cycle	Ar	Product	Yield[a] (%)	dr[b]	ee[c] (%)
1	C_6H_5	**6a**	73	>99:1	>99
2	C_6H_5	**6a**	69	>99:1	>99
3	C_6H_5	**6a**	68	>99:1	>99
4	C_6H_5	**6a**	65	>99:1	>99

[a] Overall isolated yield in two steps starting from **3**.
[b] Determined by HPLC.
[c] Determined by chiral HPLC.

3. Conclusions

In conclusion, we have efficiently synthesized four distinct microgel supported hydantoin chiral auxiliaries with four different cross-linkers and evaluated them in asymmetric Mannich reactions. Using microgel supported chiral hydantoin **3c** with 1,4-bis[4-(vinyl) phenoxy]butane as the cross-linker provided the best results in the mode reaction, and all of the Mannich adducts using microgel supported chiral hydantoin **3c** were obtained in high yields and with excellent stereoselectivity. Moreover, microgel supported hydantoin chiral auxiliaries can be readily recovered by simple precipitation, filtration and dried, and then be reused more than three times without an appreciable reduction in the yield or stereoselectivity.

4. Experimental

4.1. Materials

The aldimines were prepared by condensation of the corresponding aldehyde and *p*-methoxyphenylamine under standard conditions in the literature.[7] All other reagents were purchased and dried or purified by standard procedures before use. Reactions were monitored by TLC using precoated plates of silica gel plates (HF254, 0.5 mm, Yantai, China). Column chromatography was performed with a silica gel column (300–400 mesh, Yantai, China).

4.2. Measurements

NMR spectra were recorded on a Varian Unity Inova 600 spectrometer (^{1}H at 600 MHz and ^{13}C at 150 MHz) or a WIPM-400 spectrometer (^{1}H at 400 MHz and ^{13}C at 100 MHz) using TMS as the internal standard. Coupling constants are recorded in Hz. Melting points were determined on a WRS-1A digital melting point apparatus. Optical rotations were measured using a sodium D line on WZZ-2B Automatic Polarimeter. IR spectra were recorded on a Perkin-Elmer IR-spectrum one spectrometer. HPLC analyses were carried out on a Dionex chromatograph (UltiMate 3000 pump, Chiralcel® OD-H column and Chiralcel® AD-H column, Daicel) using hexane/2-propanol mixtures as the eluent. A UV detector (UVD-3000) was used for peak detection. Gel permeation chromatographic analyses (GPC) were carried out on a PL GPC-50 preparative liquid chromatograph with a Cirrus™ integrator and a PL-RI detector using polystyrene standards. Transmission electron microscopy (TEM) was recorded on a TecnaiG20 (Philips, Netherlands) microscopy. TEM samples were prepared by placing a drop of a freshly prepared solution of microgel supported hydantoin chiral auxiliaries onto the carbon-coated copper grids (300 mesh), which were then dried in air overnight. Thermal gravimetric analysis was tested under nitrogen with a heating rate of 20 °C/min using U.S. PERKIN ELMER Company Diamond TG / DTA thermal analysis system.

4.3. General procedure for the preparation of microgel supported *N*-propionyl chiral hydantoin 3

To a solution of compound **1** (0.45 g, 1.0 mmol) in THF (14 mL) was added styrene (0.46 mL, 4.0 mmol), cross-linker **2**

(0.26 mmol), and AIBN (22 mg, 0.15 mmol, 3 mol %). The resulting mixture was stirred at reflux for 4 d under nitrogen. After cooling to room temperature, the reaction mixture was concentrated in vacuo to approximately 3 mL, and then slowly added to cold vigorously stirred methanol (100 mL). The precipitated polymer was filtered, washed with cold methanol, and dried in vacuo to give microgel supported *N*-propionyl chiral hydantoin **3** as a colorless finely divided powder in a 78–92% yield.

3a: IR (KBr) ν: 1773, 1737, 1721 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.88–1.93 (30H), 2.96 (2H), 3.29–3.63 (2H), 4.82–5.09 (3H), 6.87–7.37 (43H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.72, 29.92, 31.03, 34.18, 40.51, 59.94, 70.22, 115.13, 125.83, 126.73, 127.89, 128.19, 129.24, 129.47, 129.70, 130.59, 130.99, 131.14, 145.34, 152.71, 158.80, 170.19, 173.58.

3b: IR (KBr) ν: 1793, 1736, 1707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.87–1.96 (27H), 2.95(2H), 3.29–3.63 (2H), 4.25–4.60 (1H), 4.78–5.10 (3H), 6.57–7.41 (38H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.62, 29.80, 30.91, 34.06, 40.47, 59.80, 69.82, 73.04, 115.08, 126.60, 126.76, 127.07, 127.77, 128.09, 128.61, 129.10, 129.34, 130.50, 130.87, 145.21, 152.61, 158.70, 170.07, 173.44.

3c: IR (KBr) ν: 1794, 1737, 1719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.85–1.87 (29H), 2.93 (2H), 3.30–3.57 (2H), 4.20–4.57 (1H), 4.75–5.10 (3H), 6.60–7.34 (37H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.69, 22.89, 29.89, 31.00, 34.15, 40.48, 59.92, 70.19, 73.02, 115.11, 125.65, 126.63, 126.69, 127.85, 128.17, 128.64, 129.20, 129.43, 130.57, 130.98, 145.34, 152.70, 158.76, 170.14, 173.53.

3d: IR (KBr) ν: 1794, 1737, 1706 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.90–1.85 (30H), 2.93 (2H), 3.34–3.58 (2H), 4.21–4.55 (1H), 4.75–5.00 (3H), 6.46–7.41 (42H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.68, 22.89, 29.55, 29.88, 31.00, 34.11, 40.51, 59.88, 70.13, 72.87, 115.06, 125.68, 125.85, 126.67, 127.85, 128.13, 129.19, 129.42, 129.52, 130.50, 130.94, 145.34, 152.67, 158.73, 170.14, 173.51.

4.4. General procedure for the asymmetric Mannich reactions

At first, $TiCl_4$ (0.23 mL, 2.1 mmol) was added dropwise to a solution of microgel supported *N*-propionyl chiral hydantoin **3** (2.0 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0 °C under nitrogen, after which the solution was allowed to stir at 0 °C for 15 min. Diisopropylethylamine (DIPEA) (0.52 mL, 3.0 mmol) was then added dropwise to the solution and the mixture was allowed to stir at 0 °C for another 30 min, after which a solution of the corresponding aldimine **4** (3.0 mmol) in anhydrous CH_2Cl_2 (5 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 4–8 h, and then quenched with saturated aqueous NH_4Cl (10 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was then concentrated in vacuo to approximately 3 mL, and then slowly added to cold vigorously stirred methanol (100 mL). The precipitated polymer was filtered, washed with cold methanol, and dried in vacuo to give Mannich adduct **5**.

5aa: IR (KBr) ν: 3379, 1773, 1735, 1719 cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.36, 29.89, 32.12, 34.14, 40.57, 46.51, 59.87, 63.57, 70.11, 115.09, 115.77, 125.86, 125.95, 126.69, 127.51, 127.84, 128.19, 129.23, 129.45, 129.74, 145.25, 152.70, 155.69, 158.73, 170.18, 173.57.

5ba: IR (KBr) ν: 3385, 1793, 1736, 1707 cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.36, 29.90, 31.02, 34.13, 40.54, 46.56, 59.91, 62.10, 73.25, 70.13, 115.08, 125.96, 126.69, 127.51, 127.81, 128.15, 129.23, 129.45, 129.74, 130.51, 130.97, 145.31, 152.70, 155.65, 158.80, 170.18, 173.55.

5ca: IR (KBr) ν: 3386, 1793, 1737, 1708 cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.37, 22.91, 29.91, 31.02, 34.14, 40.47, 46.54, 59.93, 63.31, 69.64, 73.18, 113.98, 115.10, 115.79, 125.89, 125.97, 126.42, 126.71, 127.52, 127.88, 128.16, 129.24, 129.46, 130.00, 145.36, 152.71, 155.80, 158.81, 170.19, 173.57.

5da: IR (KBr) ν: 3317, 1794, 1737, 1708 cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.37, 22.92, 29.91, 31.04, 32.14, 34.15, 40.74, 46.52, 59.93, 63.09, 70.20, 73.04, 115.11, 125.97, 126.71, 127.52, 127.43, 127.95, 128.16, 129.47, 145.38, 152.72, 155.65, 158.82, 170.20, 173.57.

5cb: IR (KBr) ν: 3361, 1774, 1737, 1721 cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.36, 22.90, 29.89, 31.01, 34.12, 40.52, 46.48, 59.90, 62.86, 70.14, 73.04, 115.07, 124.99, 125.87, 126.37, 126.68, 127.87, 128.16, 129.22, 129.44, 130.50, 130.94, 145.24, 152.68, 156.12, 158.81, 170.17, 173.54.

5cc: IR (KBr) ν: 3391, 1773, 1736, 1720 cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.36, 22.90, 29.90, 31.02, 34.14, 40.49, 46.50, 59.92, 62.86, 70.24, 73.07, 115.10, 125.91, 126.37, 126.70, 127.83, 128.16, 129.23, 129.45, 129.56, 130.53, 130.96, 145.38, 148.82, 152.70, 155.60, 158.79, 170.19, 173.55.

5cd: IR (KBr) ν: 3368, 1772, 1736, 1719 cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.35, 22.89, 29.88, 31.00, 34.11, 40.43, 46.54, 55.06, 58.28, 59.91, 62.84, 70.18, 73.06, 115.06, 125.64, 125.78, 126.68, 127.79, 128.14, 128.41, 129.22, 129.44, 130.51, 130.98, 145.25, 150.13, 152.70, 156.09, 158.81, 170.17, 173.54.

5ce: IR (KBr) ν: 3401, 1773, 1737, 1719 cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.37, 22.91, 29.90, 31.03, 34.13, 40.48, 46.50, 55.70, 59.92, 70.17, 72.86, 115.08, 125.67, 125.81, 126.38, 126.70, 127.88, 128.17, 129.24, 129.46, 130.51, 130.97, 145.36, 152.71, 155.81, 158.77, 170.18, 173.56.

5cf: IR (KBr) ν: 3338, 1774, 1736, 1720 cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.36, 22.89, 29.88, 31.01, 34.11, 40.40, 44.62, 55.68, 59.90, 70.15, 73.02, 115.07, 125.67, 125.79, 126.36, 126.68, 127.58, 128.14, 129.21, 129.44, 130.50, 130.95, 145.38, 152.68, 156.02, 158.73, 170.16, 173.53.

4.5. General procedure for the alcoholysis of Mannich adduct 5

To a solution of Mannich adduct **5** (1.0 mmol) in a 3:1 mixture of THF/methanol (50 mL) was added DMAP (0.244 g, 2.0 mmol), and the reaction mixture was refluxed for 48 h. The reaction mixture was then concentrated in vacuo to approximately 3 mL, and then slowly added to cold vigorously stirred methanol (100 mL). The precipitated polymer was filtered, washed with cold methanol, and dried in vacuo to recover quantitatively microgel supported chiral auxiliary **7**. The filtrate was purified by silica gel column chromatography (*n*-hexane/EtOAc, 6:1, v/v) to furnish β-amino ester **6**. All of the β-amino esters herein are known compounds that exhibited spectroscopic data identical to those reported in the literature.[3b,6]

6a: Yield: 73% (overall yield in two steps starting from **3c**); $[\alpha]_D^{20} = -48.7$ (*c* 0.96, CH_2Cl_2), lit.[3b] $[\alpha]_D^{20} = -50.8$ (*c* 1.02, CH_2Cl_2); the enantiomeric excess of **6a** was determined by chiral HPLC: column, Chiralcel AD-H; eluent, 7:93 2-propanol–hexane; temperature, 30 °C; flow rate, 1.0 mL/min; t_R (*RS*) = 9.25 min, t_R (*SR*) = 8.85 min.

6b: Yield: 68% (overall yield in two steps starting from **3c**); $[\alpha]_D^{20} = -44.6$ (*c* 0.85, CH_2Cl_2), lit.[3b] $[\alpha]_D^{20} = -43.1$ (*c* 0.57, CH_2Cl_2); the enantiomeric excess of **6b** was determined by chiral HPLC: column, Chiralcel AD-H; eluent, 7:93 2-propanol–hexane; temperature, 30 °C; flow rate, 1.0 mL/min; t_R (*RS*) = 10.11 min, t_R (*SR*) = 11.57 min.

6c: Yield: 81% (overall yield in two steps starting from **3c**); $[\alpha]_D^{20} = -47.9$ (*c* 1.12, CH_2Cl_2), lit.[3b] $[\alpha]_D^{20} = -48.2$ (*c* 1.16, CH_2Cl_2); the enantiomeric excess of **6c** was determined by chiral HPLC: column, Chiralcel OD-H; eluent, 10:90 2-propanol–hexane; temperature, 30 °C; flow rate, 1.0 mL/min; t_R (*RS*) = 19.25 min, t_R (*SR*) = 13.25 min.

6d: Yield: 59% (overall yield in two steps starting from **3c**); $[\alpha]_D^{20} = -50.7$ (*c* 1.08, CH_2Cl_2), lit.[3b] $[\alpha]_D^{20} = -53.7$ (*c* 2.20, CH_2Cl_2); the enantiomeric excess of **6d** was determined by chiral HPLC: column, Chiralcel OD-H; eluent, 1:99 2-propanol–hexane; temperature, 30 °C; flow rate, 0.2 mL/min; t_R (*RS*) = 75.12 min, t_R (*SR*) = 72.89 min.

6e: Yield: 63% (overall yield in two steps starting from **3c**); $[\alpha]_D^{20} = -47.8$ (*c* 1.10, CH_2Cl_2), lit.[3b] $[\alpha]_D^{20} = -47.6$ (*c* 1.05, CH_2Cl_2); the enantiomeric excess of **6e** was determined by chiral HPLC: column, Chiralcel AD-H; eluent, 7:93 2-propanol–hexane; temperature, 30 °C; flow rate, 1.0 mL/min; t_R (*RS*) = 9.25 min, t_R (*SR*) = 10.85 min.

6f: Yield: 67% (overall yield in two steps starting from **3c**); $[\alpha]_D^{20} = -45.1$ (*c* 1.24, CH_2Cl_2), lit.[3b] $[\alpha]_D^{20} = -45.8$ (*c* 1.10, CH_2Cl_2); the enantiomeric excess of **6f** was determined by chiral HPLC: column, Chiralcel AD-H; eluent, 7:93 2-propanol–hexane; temperature, 30 °C; flow rate, 1.0 mL/min; t_R (*RS*) = 9.61 min, t_R (*SR*) = 10.30 min.

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