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Synthesis and evaluation of a new non-cross-linked polystyrene supported hydantoin chiral auxiliary for asymmetric aldol reactions

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ABSTRACT

A new non-cross-linked polystyrene supported chiral hydantoin was prepared and it was shown to be a particularly effective chiral auxiliary for asymmetric aldol reactions, affording high yields and excellent diastereoselectivity. Furthermore, the recovery and recycling of the polymer-supported chiral auxiliary have been successfully achieved without an appreciable reduction in the yield or diastereoselectivity.

1. Introduction

Chiral auxiliary-derived asymmetric reactions have emerged as powerful tools in organic synthesis.[1] Among all the chiral auxiliaries, 2-oxazolidinone[2] and 2-imidazolidinone[3] are the most versatile and widely used, which have been utilized in a wide variety of highly stereoselective reactions. Chiral hydantoin, a new improved chiral auxiliary, developed by Yamaguchi,[4a] provides a superior performance to many other chiral auxiliaries currently in common usage, and has been proven to be particularly efficient in terms of stereoselectivity and yield in asymmetric conjugate addition, aldol, and Mannich reactions.[4]

Crosslinked, insoluble polymer supported chiral auxiliaries, which enable the asymmetric synthesis of libraries of homochiral compounds, have received increasing interest within recent years.[5] Such solid supported chiral auxiliaries offer some advantages including a simple filtration procedure for the isolation of the desired compounds or the recovery of the expensive chiral auxiliaries. However, several shortcomings were shown because of nonlinear kinetic behavior, unequal distribution or access to the chemical reaction, and synthetic difficulties in transferring standard organic reactions to the solid phase. Several groups have explored the use of soluble polymer supports to replace the insoluble polymers.[6] The advantages of solid-phase synthesis are retained, and the synthetic pathway can be carried out under more convenient homogeneous solution conditions, with easier characterization of the covalently bound substrates.

In previous reports, our group has undertaken a research program to develop several chiral auxiliaries by using non-cross-linked polystyrene (NCPS) as a soluble support and to investigate their applications in asymmetric synthesis.[7] Herein we report the preparation of a new soluble NCPS supported hydantoin chiral auxiliary and the preliminary results of our investigations concerning the asymmetric aldol reactions of this compound, and the potential for recycling of the chiral auxiliary.

2. Results and discussion

2.1. Preparation of NCPS supported *N*-propionyl chiral hydantoin 5

As shown in Scheme 1, NCPS supported *N*-propionyl chiral hydantoin was prepared by four steps starting from L-tyrosine methyl ester hydrochloride **1**. According to our previous method,[4b] the compound **1** was reacted with phenyl isocyanate in pyridine, and then after evaporation of pyridine, the residue was refluxed in 2 M HCl to give the homochiral hydantoin **2** in 90% yield by a one-pot reaction. Hydantoin **2** was treated with 4-vinylbenzyl chloride in the presence of K_2CO_3 to afford the compound **3** in 87% yield. Next, **3** was treated with propionyl chloride in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) and Et_3N to give *N*-propionyl compound **4** in 94% yield. Finally, NCPS supported *N*-propionyl chiral hydantoin **5** was obtained by copolymerizing **4** and styrene in a ratio of 1:4 with 92% yield, and the loading capacity (1.2 mmol/g) of chiral auxiliary **5** was analyzed by nitrogen elemental analysis. This chiral auxiliary is soluble in typical organic solvents, such as $CHCl_3$, CH_2Cl_2, EtOAc, THF, or DMF, and insoluble in MeOH, EtOH, or H_2O; this solubility versus recovery relationship of crystalline polymer could lead to a better recovery yield of the chiral auxiliary.

2.2. Diastereocontrolled aldol reactions

In order to test the chemical and stereochemical behavior of NCPS supported chiral auxiliaries for asymmetric synthesis, we

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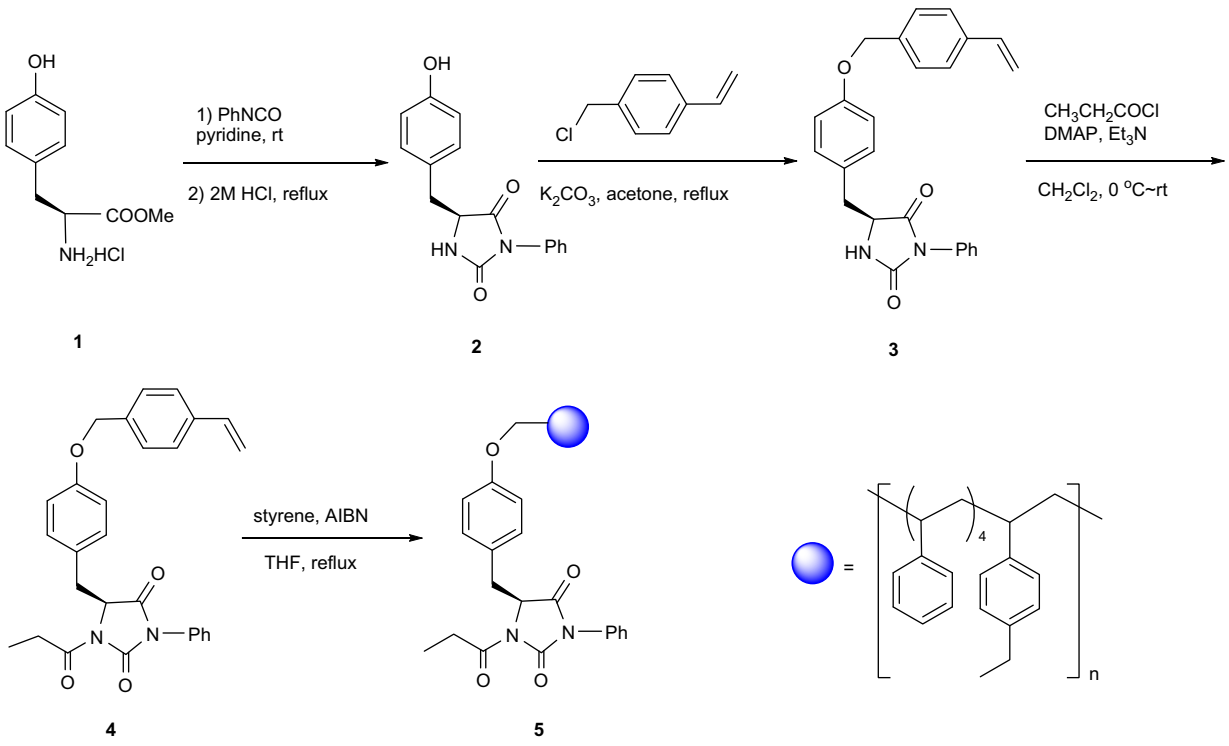


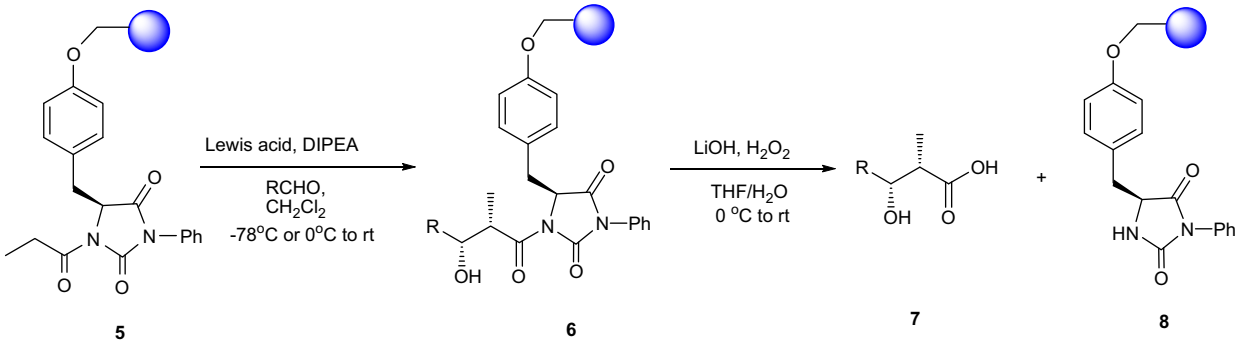
Scheme 1.

evaluated the aldol reactions of *N*-propionylamide **5** with benzaldehydes as a model reaction. The enolate of **5** was generated by reaction with 1.5 equiv of different Lewis acids in CH_2Cl_2 at 0 °C or −78 °C for 30 min followed by the addition of 1.8 equiv of *N*-diisopropylethylamine (DIPEA) at the same temperature and then stirring the resulting brown solution for 1 h. The enolate thus generated was then trapped with benzaldehyde at 0 °C or −78 °C for 4 h and progressively warmed to rt overnight to afford the aldol product **6a**. Aldol product **6a** was then easily hydrolyzed with $LiOH/H_2O_2$ at 0 °C to rt in THF/H_2O to afford the β-hydroxyacid **7a** along with the recovery of the chiral auxiliary **8** (Scheme 2).

Analysis of the crude product mixture of **7a** by HPLC is shown in Table 1. With $TiCl_4$, we obtained product **7a** with 56% yield and 90% ee at 0 °C (Table 1, entry 1) and 72% yield and 94% ee at −78 °C (Table 1, entry 2). The diastereoselectivity was improved by the use of the tin enolate generated by the reaction of **5** with the Lewis acid $Sn(OTf)_2$ yielding product **7a** with excellent de values (up to 99% ee), although the chemical yield was only 33% at 0 °C (Table 1, entry 3) and 39% at −78 °C (Table 1, entry 4). A satisfactory result was obtained when the reaction was carried out using the Lewis acid *n*-Bu_2BOTf, the diastereoselectivity was up to 99% ee, while the chemical yield was 73% at 0 °C (Table 1, entry 5) and 81% at −78 °C (Table 1, entry 6). Therefore, we found that the best condition for the aldol reaction was using the Lewis acid *n*-Bu_2BOTf at −78 °C.

The aldol reactions of **5** were then investigated with a variety of aldehydes, including aromatic, heterocyclic, and aliphatic ones, using the optimal conditions as described above. All of the aldol products were then hydrolyzed with $LiOH/H_2O_2$ at 0 °C to rt in THF/H_2O to afford the corresponding β-hydroxyacids **7b–f** along with recovery of the chiral auxiliary **8**. The results are summarized in Table 1 (entries 7–11); the aldol reactions with other aldehydes also exhibited excellent diastereoselectivity and high chemical yields using Lewis acid *n*-Bu_2BOTf at −78 °C. As compared to the same model reactions using monomeric derivative based on phenylalanine system,[4b] the aldol reactions using NCPS supported hydantoin chiral auxiliary exhibited higher diastereoselectivity and almost the same chemical yields.

After silica gel chromatography purification, the *syn* versus *anti* stereochemistry of the products **7a–f** was assigned on the basis of



Scheme 2.

Table 1

Entry	Product	Lewis acid	Temperature	R	ee[a] (%)	Yield[b] (%)
1	**7a**	$TiCl_4$	0 °C to rt	C_6H_5	90	56
2	**7a**	$TiCl_4$	−78 °C to rt	C_6H_5	94	72
3	**7a**	$Sn(OTf)_2$	0 °C to rt	C_6H_5	⩾99	33
4	**7a**	$Sn(OTf)_2$	−78 °C to rt	C_6H_5	⩾99	39
5	**7a**	*n*-Bu_2BOTf	0 °C to rt	C_6H_5	⩾99	73
6	**7a**	*n*-Bu_2BOTf	−78 °C to rt	C_6H_5	⩾99	81
7	**7b**	*n*-Bu_2BOTf	−78 °C to rt	3-$NO_2C_6H_4$	⩾99	86
8	**7c**	*n*-Bu_2BOTf	−78 °C to rt	4-ClC_6H_4	⩾99	82
9	**7d**	*n*-Bu_2BOTf	−78 °C to rt	4-$CH_3OC_6H_4$	⩾99	78
10	**7e**	*n*-Bu_2BOTf	−78 °C to rt	C_4H_3S	⩾99	80
11	**7f**	*n*-Bu_2BOTf	−78 °C to rt	*n*-Pr	⩾99	75

[a] Determined by chiral HPLC.
[b] Overall yield in two steps starting from **5**.

^{1}H NMR coupling constants.[8] The measured value for the aldol fragment's vicinal protons was found to be J_{syn} <4 Hz, which was completely in accordance with previously reported values for *syn* aldols. The absolute configurations of products **7a**–**f** were confirmed by comparing their specific rotations with those previously reported. For example, the β-hydroxyacid (*S*,*S*)-**7a** is a known compound in the literature. Comparing the specific rotation of the newly prepared β-hydroxyacid **7a** {$[\alpha]_D^{20} = -28.75$ (*c* 0.4, CH_2Cl_2) versus lit.[9] $[\alpha]_D^{24} = -29.5$ (*c* 1.02, CH_2Cl_2)} allowed us to establish the absolute configuration of **7a** to be (2*S*,3*S*), which could be extended to the β-hydroxyacids **7a**–**f** and the aldols **6a**–**f**.

2.3. Recycling and reuse of the NCPS supported hydrantoin chiral auxiliary

In order to further investigate the ability of recycling NCPS supported chiral auxiliary **8**, recovered **8** was washed and dried, and then subjected to *N*-acylation with propionyl chloride, aldolation with benzaldehyde, and hydrolysis with $LiOH/H_2O_2$ to give once again the corresponding β-hydroxyacid **7a**. We performed four recycling experiments, and the results indicated that the diastereoselectivity of the recovered chiral auxiliary remained almost intact for at least four reaction cycles (ee >99%), while the yield decreased slightly in each cycle (81–79%).

3. Conclusion

In conclusion, we have developed a new NCPS supported hydantoin chiral auxiliary, which has great potential for asymmetric aldol reactions. The aldol products were obtained in high yields with excellent diastereoselectivity. Moreover, the NCPS supported hydantoin chiral auxiliary can readily be recovered by simple precipitation, filtration and dried, and could be reused more than three times without an appreciable reduction in the yield or diastereoselectivity.

4. Experimental

4.1. General

All solvents were obtained from commercial sources and dried or purified by standard procedures before use. Separations by flash chromatography were performed on 30–400 mesh silica gel. Melting points were measured on a WRS-1A digital melting point apparatus and are uncorrected. Optical rotations were measured using a sodium D line on WZZ-2B Automatic Polarimeter. HPLC analyses were carried out on a Dionex chromatograph (Ultimate3000 pump, Chiralcel® OD-H column) equipped with a diode-array UV detector. IR spectra were recorded on a IR-spectrum one (PE) spectrometer. NMR spectra were recorded on Varian Unity Inova 600 spectrometer (^{1}H at 600 MHz and ^{13}C at 150 MHz) or WIPM-400 spectrometer (^{1}H at 400 MHz and ^{13}C at 100 MHz) using TMS as the internal standard. Elemental analyses were done on a VarioEL III (Germany) analyzer. High-resolution mass spectra (HRMS) were recorded on Agilent 1260-6224 LC–MS TOF using ESI (electrospray ionization).

4.2. Preparation of (*S*)-5-(4-hydroxybenzyl)-3-phenylhydantoin 2

L-Tyrosine methyl ester hydrochloride **1** (5.80 g, 25.0 mmol) and phenyl isocyanate (2.75 mL, 25.0 mmol) were vigorously stirred for 2 h at rt in pyridine (50 mL). The resulting mixture was evaporated to dryness under reduced pressure. Aqueous HCl (50 mL, 2 M) was added to the residue and the mixture refluxed for 6 h. A precipitate appeared upon cooling and was recrystallized from hot water to give a white solid **2** (6.36 g, 90%). Mp 181–182 °C, lit.[10] mp 184 °C; $[\alpha]_D^{20} = -86.7$ (*c* 0.3, CH_3COCH_3); IR (KBr): ν = 3314, 1719, 1613, 1515, 1420 cm^{-1}; ^{1}H NMR (600 MHz, CD_3COCD_3): δ 3.09 (dd, J = 4.4, 14.0 Hz, 1H), 3.32 (dd, J = 4.4, 14.0 Hz, 1H), 4.52 (dd, J = 4.4, 8.8 Hz, 1H), 6.80–7.47 (m, 10H), 8.32(s, 1H); ^{13}C NMR (150 MHz, CD_3COCD_3): δ 37.27, 58.74, 115.99, 126.78, 127.29, 128.37, 128.36, 129.32, 131.75, 133.46, 156.50, 157.33, 173.24.

4.3. Preparation of (*S*)-5-(4-(4-vinylbenzyloxy)benzyl)-3-phenylhydantoin 3

To a solution of compound **2** (5.65 g, 20.0 mmol) in acetone (150 mL) were added 4-vinylbenzyl chloride (3.38 mL, 24.0 mmol), anhydrous K_2CO_3 (8.29 g, 60.0 mmol), and 18-crown-6 (catalytic amount). The resulting mixture was stirred at reflux for 24 h. After cooling to rt, the insoluble salts were filtered off and most of the solvent of the filtrate was evaporated under reduced pressure. Next, the viscous solution was dropped into cold methanol (150 mL), and the precipitated solid was filtered and dried at 45 °C for 4 h under vacuum to afford a white solid **3** (6.94 g, 87%). Mp 170–171 °C; $[\alpha]_D^{20} = -9.3$ (*c* 1.0, CH_2Cl_2); IR (KBr): ν = 3235, 1773, 1707, 1607, 1510, 1456 cm^{-1}; ^{1}H NMR (400 MHz, CD_3COCD_3): δ 2.98 (dd, J = 4.4, 14.0 Hz, 1H), 3.04 (dd, J = 4.4, 14.0 Hz, 1H), 4.50 (dd, J = 4.4, 8.8 Hz, 1H), 5.06 (s, 2H), 5.26 (d, J = 10.8 Hz, 1H), 5.82 (d, J = 17.6 Hz, 1H), 6.70 (dd, J = 11.2, 18.0 Hz, 1H), 6.94–7.49 (m, 13H), 8.51 (s, 1H); ^{13}C NMR (150 MHz, CD_3COCD_3): δ 35.67, 57.02, 68.85, 126.01, 126.32, 127.02, 127.51, 127.67, 128.48, 130.71, 131.89, 136.19, 136.53, 136.70, 155.22, 157.23, 172.35; HRMS calcd for $C_{25}H_{22}N_2O_3$ [M+Na]$^+$: 421.1528, found 421.1518.

4.4. Preparation of (*S*)-5-(4-(4-vinylbenzyloxy)benzyl)-3-phenyl-1-propionylhydantoin 4

To a solution of compound **3** (6.0 g, 15.0 mmol) in CH_2Cl_2 (50 mL) were added DMAP (0.36 g, 3.0 mmol), and Et_3N (2.5 mL, 18.0 mmol), after which propionyl chloride (1.72 mL, 19.5 mmol) in CH_2Cl_2 (10 mL) was added dropwise to the reaction mixture at 0 °C. After stirring at rt for 2 h, the reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (20 mL × 3). The organic layers were combined, washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated. Purification of the crude product by silica gel column chromatography (*n*-hexane/EtOAc, 5:1, v/v) gave a white solid **4** (6.43 g, 94%). Mp 187–188 °C; $[\alpha]_D^{20} = -8.75$ (*c* 0.4, CH_2Cl_2); IR (KBr): ν = 1793, 1735, 1719, 1601, 1509, 1452 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.25 (t, *J* = 6.6 Hz, 3H), 2.94 (m, 2H), 3.29 (dd, *J* = 5.4, 13.8 Hz, 1H), 3.60 (dd, *J* = 6.6, 13.8 Hz, 1H), 4.91 (m, 1H), 5.01 (s, 2H), 5.26 (d, *J* = 10.8 Hz, 1H), 5.76 (d, *J* = 17.4 Hz, 1H), 6.72 (dd, *J* = 9.6, 16.2 Hz, 1H), 6.89-7.42(m, 13 H); ^{13}C NMR(150 MHz, $CDCl_3$): δ 8.57, 30.79, 33.90, 59.70, 69.79, 114.15, 115.27, 125.72, 126.28, 126.62, 127.45, 127.81, 128.74, 129.01, 129.11, 129.38, 130.46, 130.61, 130.95, 136.37, 137.38, 152.48, 158.38, 169.89, 173.27; HRMS calcd. for $C_{28}H_{26}N_2O_4$ $[M+Na]^+$: 477.1790, found 477.1786.

4.5. Preparation of NCPS supported *N*-propionyl chiral hydantoin 5

To a solution of compound **4** (6.0 g, 13.2 mmol) in THF (80 mL) were added styrene (6.06 mL, 52.8 mmol) and AIBN (0.31 g, 1.98 mmol). The mixture was copolymerized at reflux for 96 h under a nitrogen atmosphere. Next, most of the solvent was removed under reduced pressure. The viscous solution was dropped into cold methanol (200 mL), and the precipitated solid was filtered and washed with cold methanol to remove any micromolecules (TLC detecting) and dried at 65 °C for 2 h under vacuum to afford polymer **5** (10.57 g, 92%). IR (KBr): ν = 1736, 1715, 1604, 1493, 1452 cm^{-1}; ^{13}C NMR (150 MHz, $CDCl_3$): δ 8.41, 33.95, 46.20, 59.70, 70.04, 114.96, 125.72, 127.90, 128.13, 129.44, 130.15, 131.22, 133.56, 141.02, 145.16, 152.42, 158.64, 169.80, 173.23. Elementary analysis for polymer **5**: C 80.63, H 6.79, N 3.36; Loading capacity: 1.2 mmol/g.

4.6. General procedure for the aldol reaction

Lewis acid (2.7 mmol) was added dropwise to a solution of NCPS supported *N*-propionyl chiral hydantoin **5** (1.5 g, 1.8 mmol) in anhydrous CH_2Cl_2 (30 mL) at −78 °C under a nitrogen atmosphere, after which solution was allowed to stir for 30 min. Diisopropylethylamine (0.57 mL, 3.24 mmol) was then added dropwise to the mixture and the solution was allowed to stir for 1 h. The appropriate aldehyde (2.7 mmol) was then added directly to the enolate. The reaction was stirred at −78 °C for 4 h and progressively warmed to rt overnight followed by the addition of saturated aqueous NH_4Cl (10 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried over $MgSO_4$ and filtered. Most of the solvent was then removed under reduced pressure, and the viscous solution was dropped into cold methanol (100 mL). The precipitated solid was filtered, washed with methanol to remove any micromolecules (TLC detecting), and dried at 65 °C for 2 h under vacuum to afford polymer **6a**–**f**.

6a Yield: 1.54 g; IR (KBr): ν = 3454, 1771, 1715, 1611, 1510, 1454 cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.25, 34.13, 45.87, 59.01, 60.66, 70.01, 114.21, 115.85, 125.71, 126.96, 128.45, 129.50, 130.18, 133.19, 141.37, 145.86, 152.62, 158.90, 169.73, 176.26.

6b Yield: 1.68 g; IR (KBr): ν = 3388, 1772, 1736, 1720, 1601, 1493, 1452 cm^{-1}; ^{13}C NMR (150 MHz, $CDCl_3$): δ 10.31, 34.05, 46.40, 60.12, 67.38, 72.22, 115.72, 125.80, 127.82, 128.13, 129.44, 130.94, 133.15, 135.16, 141.05, 145.39, 148.61, 155.65, 158.55, 169.66, 171.49.

6c Yield: 1.69 g; IR (KBr): ν = 3525, 1773, 1735, 1711, 1600, 1508, 1451 cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.56, 34.01, 46.27, 59.55, 70.07, 72.11, 115.00, 126.54, 127.59, 128.05, 129.58, 130.88, 131.25, 133.16, 140.96, 145.52, 152.62, 158.43, 166.65, 173.39.

6d Yield: 1.60 g; IR (KBr): ν = 3567, 1773, 1737, 1718, 1260 cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.31, 34.04, 46.70, 55.22, 59.58, 67.43, 70.11, 113.92, 115.10, 126.22, 127.70, 128.06, 130.99, 131.18, 133.56, 140.87, 145.27, 152.67, 158.77, 170.36, 173.47.

6e Yield: 1.57 g; IR (KBr): ν = 3572, 1772, 1735, 1717, 1600, 1503, 1451 cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.20, 34.06, 47.01, 59.74, 70.12, 72.95, 114.75, 125.35, 126.52, 128.08, 129.46, 130.94, 131.22, 133.41, 141.04, 145.30, 152.52, 158.84, 169.99, 173.10.

6f Yield: 1.52 g; IR (KBr): ν = 3567, 1773, 1735, 1717, 1610, 1509, 1454 cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.31, 19.22, 22.73, 31.96, 33.98, 44.29, 59.74, 69.87, 70.82, 114.95, 125.57, 126.51, 129.00, 129.49, 130.95, 140.97, 152.47, 158.53, 170.02, 173.32.

4.7. General procedure for the cleavage using LiOH hydrolysis

The appropriate aldol adduct **6** (1.5 g) was treated at 0 °C with LiOH (0.07 g, 1.8 mmol) and H_2O_2 (0.42 mL, 4.2 mmol) in a 3:1 mixture of THF/H_2O (20 mL). The reaction was stirred for 48 h at rt and then concentrated under reduced pressure. The organic layer was extracted with CH_2Cl_2 (30 mL × 3) and concentrated to recover quantitatively the NCPS supported chiral auxiliary **8**. Acidification of the aqueous layer to pH 1 and extraction with EtOAc furnished the desired acid **7a**–**f**.

7a Yield: 0.25 g, 81 % (overall yield in two steps starting from **5**); IR (KBr): ν = 3439, 1711 cm^{-1}; $[\alpha]_D^{20} = -28.8$ (*c* 0.4, CH_2Cl_2), lit.[9] $[\alpha]_D^{24} = -29.5$ (*c* 1.02, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 1.05 (d, *J* = 7.2 Hz, 3H), 2.75 (dq, *J* = 3.6, 7.2 Hz, 1H), 5.10 (d, *J* = 3.6 Hz, 1H), 7.18-7.28 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 10.54, 46.40, 73.67, 126.14, 127.82, 128.51, 141.31, 180.67.

7b Yield: 0.28 g, 86 % (overall yield in two steps starting from **5**); IR (KBr): ν = 3450, 1715 cm^{-1}; $[\alpha]_D^{20} = -38.0$ (*c* 0.4, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) : δ 1.13 (d, *J* = 7.2 Hz, 3H), 2.88 (dq, *J* = 3.2, 7.2 Hz, 1H), 5.31 (d, *J* = 3.2 Hz, 1H), 7.53-8.25 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 10.23, 46.02, 72.46, 121.29, 122.82, 129.50, 132.19, 143.59, 148.60, 180.04.

7c Yield: 0.29 g, 82 % (overall yield in two steps starting from **5**); IR (KBr): ν = 3455, 1710 cm^{-1}; $[\alpha]_D^{20} = -15.9$ (*c* 0.8, CH_2Cl_2); ^1H NMR (600 MHz, CD_3SOCD_3): δ 1.00 (d, *J* = 7.2 Hz, 3H), 2.59 (dq, *J* = 3.6, 7.2 Hz, 1H), 4.83 (d, *J* = 3.6 Hz, 1H), 7.33-7.37 (m, 4H); ^{13}C NMR (150 MHz, CD_3SOCD_3): δ 11.61, 46.83, 72.54, 127.91, 128.04, 131.25, 143.10, 175.10.

7d Yield: 0.27 g, 78 % (overall yield in two steps starting from **5**). IR (KBr): ν = 3458, 1713 cm^{-1}; $[\alpha]_D^{20} = -19.0$ (*c* 0.4, $CHCl_3$), lit.[11] $[\alpha]_D^{22} = +19.2$ (*c* 1.0, $CHCl_3$) for (2*R*,3*R*)-**7d**; ^1H NMR (600 MHz, CD_3SOCD_3): δ 1.01 (d, *J* = 7.2 Hz, 3H), 2.55 (dq, *J* = 3.6, 7.2 Hz, 1H), 3.72 (s, 3H), 4.74 (d, *J* = 3.6 Hz, 1H), 6.85-7.23 (m, 4H); ^{13}C NMR (150 MHz, CD_3SOCD_3): δ 11.94, 47.05, 54.91, 72.82, 113.13, 127.23, 136.08, 158.08, 175.26.

7e Yield: 0.25 g, 80 % (overall yield in two steps starting from **5**); IR (KBr): ν = 3451, 1706 cm^{-1}; $[\alpha]_D^{20} = +15.5$ (*c* 0.4, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$): δ 1.22 (d, *J* = 7.2 Hz, 3H), 2.88 (dq, *J* = 3.6, 7.2 Hz, 1H), 5.30 (d, *J* = 3.6 Hz, 1H), 6.94–7.23 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 11.22, 46.67, 70.54, 124.18, 124.85, 126.87, 144.82, 180.67.

7f Yield: 0.19 g, 75 % (overall yield in two steps starting from **5**); IR (KBr): ν = 3453, 1714 cm^{-1}; $[\alpha]_D^{20} = +11.2$ (c 0.4, CH_2Cl_2), lit.[8c] $[\alpha]_D^{20} = +12.0$ (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, J = 7.2 Hz, 3H), 1.20 (d, J = 7.2 Hz, 3H), 1.32–1.55 (m, 4H), 2.57 (dq, J = 3.6, 7.2 Hz, 1H), 3.95–3.99 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 9.11, 12.80, 18.24, 34.87, 43.18, 70.57, 179.22.

Acknowledgments

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References

1. (a) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley: New York, 1995; (b) Harada, N. *Synthesis* **2006**, 1899–1930; (c) Farína, V.; Reeves, J. T.; Senenayake, C. H.; Song, J. J. *Chem. Rev.* **2006**, *106*, 2734–2793.
2. Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835–875.
3. (a) Roos, G. H. P. *S. Afr. J. Chem.* **1998**, *51*, 7–24; (b) Lu, C. F.; Hu, L.; Yang, G. C.; Chen, Z. X. *Curr. Org. Chem.* **2012**, *16*, 2802–2817.
4. (a) Yamaguchi, J.; Harada, M.; Narushima, T.; Saitoh, A.; Nozaki, K.; Suyama, T. *Tetrahedron Lett.* **2005**, *46*, 6411–6415; (b) Zhang, J. S.; Lu, C. F.; Chen, Z. X.; Li, Y.; Yang, G. C *Tetrahedron: Asymmetry* **2012**, *23*, 72–75; (c) Li, X. R.; Lu, C. F.; Chen, Z. X.; Li, Y.; Yang, G. C. *Tetrahedron: Asymmetry* **2012**, *23*, 1380–1384.
5. (a) Gaertner, P.; Kundu, A. Chiral Auxiliaries on Solid Support. In *The Power of Functional Resins in Organic Synthesis*; Fernando, A., Tulla-Puche, J., Eds.; Wiley-VCH: Weinheim, 2008; pp 329–363; (b) Chung, C. W. Y.; Toy, P. H *Tetrahedron: Asymmetry* **2004**, *15*, 387–399.
6. (a) Desimoni, G.; Faita, G.; Galbiati, A.; Pasini, D.; Quadrelli, P.; Rancati, F. *Tetrahedron: Asymmetry* **2002**, *13*, 333–337; (b) Enholm, E. J.; Gallagher, M. E.; Jiang, S. J. *Org. Lett.* **2000**, *2*, 3355–3357; (c) Enholm, E. J.; Cottone, J. S. *Org. Lett.* **2001**, *3*, 3959–3962; (d) Kreidler, B.; Baro, A.; Christoffers, J. *Eur. J. Org. Chem.* **2005**, 5339–5348.
7. (a) Hu, F. Q.; Xia, D. X.; Lu, C. F.; Chen, Z. X.; Yang, G. C. *Eur. J. Org. Chem.* **2010**, 5552–5554; (b) Lu, C. F.; Li, D. L.; Wang, Q. Y.; Yang, G. C.; Chen, Z. X. *Eur. J. Org. Chem.* **2009**, 1078–1081; (c) He, X. P.; Li, J.; Lu, C. F.; Chen, Z. X.; Yang, G. C. *Can. J. Chem.* **2011**, *89*, 88–91.
8. For the ^{1}H NMR vicinal coupling constant using the well-established fact that J_{anti} (4–7 Hz)>J_{syn} (2–4 Hz); see: (a) Kim, T. H.; Lee, G. J. *Tetrahedron Lett.* **2000**, *41*, 1505–1508; (b) Oppolzer, W.; Blagg, J.; Rodriguez, I.; Walther, E. *J. Am. Chem. Soc.* **1990**, *112*, 2767–2772; (c) Fécourt, F.; Lopez, G.; Lee, A. V. D.; Martinez, J.; Dewynter, G. *Tetrahedron: Asymmetry* **2010**, *21*, 2361–2366.
9. Casper, D. M.; Burgeson, J. R.; Esken, J. M.; Ferrence, G. M.; Hitchcock, S. R. *Org. Lett.* **2002**, *4*, 3739–3742.
10. Paal, C.; Zitelmann, G. *Chem. Ber.* **1903**, *36*, 3337–3345.
11. Davies, S. G.; Garner, A. C.; Roberts, P. M.; Smith, A. D.; Sweet, M. J.; Thomson, J. E. *Org. Biomol. Chem.* **2006**, *4*, 2753–2768.