PERKIN 1

Synthesis of *N*-propionylated (*S*)-(−)-2-(pyrrolidin-2-yl)propan-2-ol and its use as a chiral auxiliary and selectivity marker in asymmetric aldol reactions

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The *N*-propionylated pyrrolidine derivative and chiral auxiliary, (*S*)-(−)-2-(pyrrolidin-2-yl)propan-2-ol, was synthesised and used in stereoselective aldol reactions with benzaldehyde. Differences in stereoselectivity were investigated as a function of temperature, solvent, chelating agent and the amount of the chelating agent used by monitoring the ^{1}H NMR spectra of the aldol adducts that were obtained. Among the additives that were investigated, Cp_2ZrCl_2 induced higher *anti*-selectivity, while $SnCl_2$ induced higher *syn*-selectivity respectively. TMSCl was found to induce high selectivity for one *syn*- and one *anti*-diastereomer. Varying the ligand sets on titanium additives was found to induce differences in selectivity, with (i-PrO)$_3$TiCl exhibiting *syn*-selectivity and Cp_2TiCl_2 exhibiting *anti*-selectivity. Differences in reactivity and stereoselectivity were also found to depend upon the amount of Lewis acid that was added. Methods for removal of the auxiliary were also investigated. Acidic hydrolysis was used successfully to obtain the desired 3-hydroxy-2-methyl-3-phenylpropionic acids, but was found to give low yields and resulted in a large amount of epimerisation. Furthermore, the ethyl esters of these hydroxy acids are easy to separate into pure *syn*- and *anti*-diastereomers by LC.

Introduction

Numerous examples can be found in the literature involving the construction of new asymmetric C–C bonds *via* aldol addition reactions.[1] The asymmetric induction may be derived from pre-existing chirality in one of the reaction partners in the construction event (diastereoselective reactions) *e.g.*, when a chiral auxiliary is used in stoichiometric quantities.[2] Several papers have reported the successful application of proline-derived auxiliaries and ligands in diastereoselective aldol reactions.[3] In this paper, however, we report the synthesis and utilisation of an *N*-propionylated chiral auxiliary, (*S*)-(−)-2-(pyrrolidin-2-yl)propan-2-ol[4] **1**, in aldol reactions with benzaldehyde.

Results and discussion

The amino alcohol, (*S*)-(−)-2-(pyrrolidin-2-yl)propan-2-ol was synthesised in optically pure form according to the literature[5] (see Scheme 1). Accordingly, (*S*)-(−)-proline was reacted with gaseous HCl in MeOH to produce a methyl ester hydrochloride in quantitative yield. Then, after treatment with Et_3N the free amine was *N*-benzyl protected in order to give a tertiary alcohol when reacted with 2.4 equivalents of MeMgI. Removal of the benzyl protection with hydrogen, catalysed by Pd/C, gave the aminoalcohol as white crystals in excellent yield. Crystallisation from hexane gave this very hygroscopic aminoalcohol in optically pure form, which after propionylation[6] with propionic anhydride afforded the hydroxyamide **1** in excellent yield.

The general method (see Experimental section) for the aldol reaction involved addition of the hydroxyamide **1** to freshly prepared LDA in order to give the *Z*-lithium amide enolate.[7] Benzaldehyde was then added to the enolate, or alternatively an additive (*cf.* Table 1) was introduced before adding the benzaldehyde. This reaction resulted in the four diastereomers *syn*-2*R*, *syn*-2*S*, *anti*-2*R* and *anti*-2*S* (see Scheme 1).

The crude aldol adduct mixture was analysed by ^{1}H NMR spectroscopy (250 MHz) which made it possible to simultaneously measure both the conversion and the ratio of the diastereomers that were obtained (*syn*-2*R*, *syn*-2*S*, *anti*-2*R* and *anti*-2*S*). The chemical shifts for the methyl groups located next to the tertiary alcohol appeared as singlets and varied significantly between the hydroxyamide and the four aldol adducts; in the hydroxyamide **1** they were found at 1.05 ppm, while in *syn*-2*R*, *syn*-2*S*, *anti*-2*R* and *anti*-2*S* they showed up at 1.03, 0.87, 1.02 and 0.74 ppm, respectively (see Fig. 1). Therefore, this

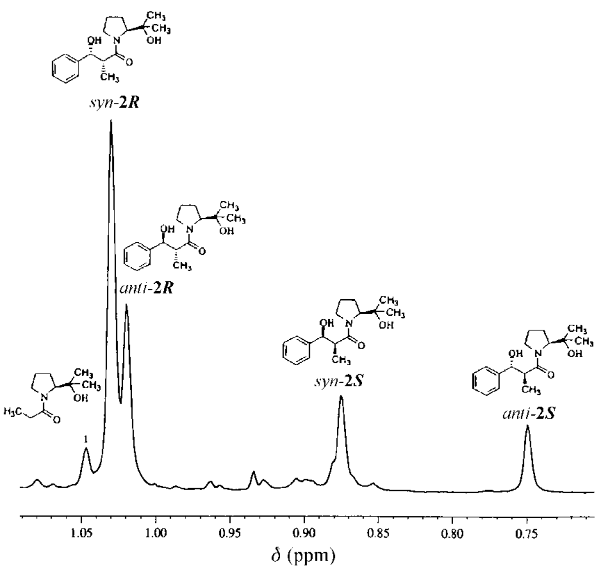
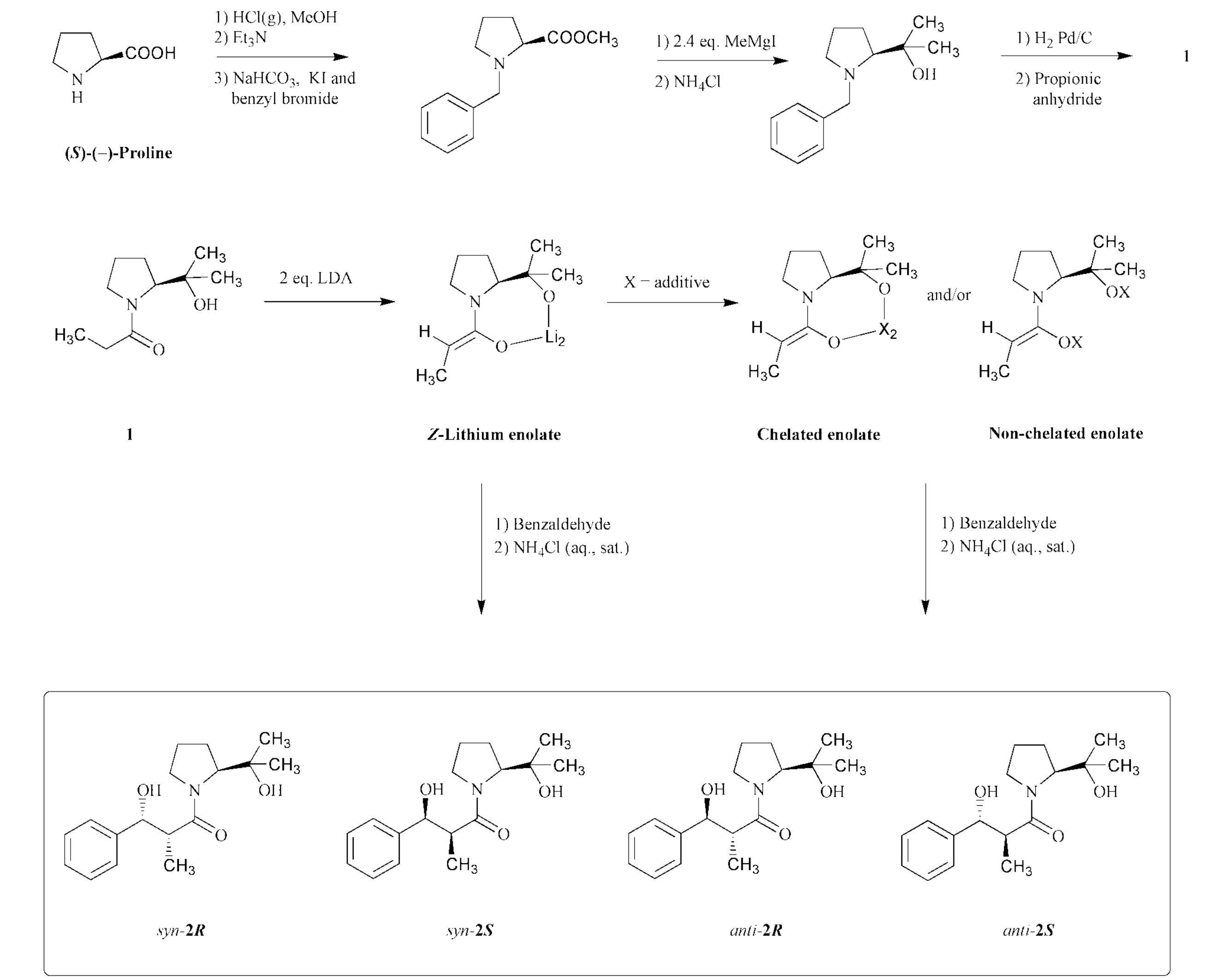


Fig. 1 The methyl region of the 250 MHz ^{1}H NMR spectrum of *N*-propionylated (*S*)-(−)-2-(pyrrolidin-2-yl)propan-2-ol **1** and the four aldol diastereomers that were produced: *syn*-2*S*, *syn*-2*S*, *anti*-2*R* and *anti*-2*S*.



Scheme 1 The synthesis of the *N*-propionylated (*S*)-(−)-2-(pyrrolidin-2-yl)propan-2-ol **1** and the procedure for the aldol reactions which resulted in one or more of the four possible diastereomers: *syn*-2*R*, *syn*-2*S*, *anti*-2*R* and *anti*-2*S*.

proline-derived auxiliary is not only useful as a chiral auxiliary, but also as a selectivity marker when studying aldol reactions.

The results of the stereoselective aldol reactions are summarised in Table 1. Comparing entries 1 and 2 shows that the modest *syn*:*anti* ratio increased from 54:46 to 66:34 when the solvent was changed from THF to Et_2O; the amount of *anti*-2*S* was also somewhat decreased relative to *anti*-2*R*. Lowering the temperature (entry 3) resulted in a lower *syn*:*anti* ratio and almost the same distribution among the four diastereomers with respect to entry 2.

In an effort to improve the stereoselectivity of the reaction, different additives were investigated that had been used in the literature in similar aldol reactions. When $(i\text{-}PrO)_3TiCl$ was added (entry 4), a moderate *syn*-selectivity was still obtained, but the amounts of *syn*-2*S* and *anti*-2*S* increased, indicating a 2*S* selectivity. However, when Cp_2TiCl_2 (*cf.* Procter *et al.*[8]) was used as an additive (entry 9), an *anti*-selectivity resulted (*e.g.* 28:72), mostly because of an increase of *anti*-2*R* and a decrease of *syn*-2*S*, despite the decrease of *anti*-2*S*. Procter *et al.*[8] studied the aldol reaction of the non-chelating *N*-propionylpyrrolidine with benzaldehyde using Cp_2TiCl_2 as an additive and reported a similar increase in *anti*-selectivity (*syn*:*anti* 2:98).

Use of $SnCl_2$ as an additive (entry 5) resulted in the highest *syn*:*anti* ratio obtained in this study (73:27), but the conversion was rather low. The majority of the product consisted of the *syn*-2*R* adduct, corresponding to a hydroxy acid (that would be obtained after removal of the chiral auxiliary) with a theoretical ee value of 84%. Entries 6–8 include varying conditions with $SnCl_2$ as an additive and all of these cases exhibit increased conversion with modest and almost identical *syn*:*anti* ratios (*e.g.* 65:35), though some changes in the selectivity were registered when Et_2O (entry 6) was used instead of THF (entry 5). The solvent change to Et_2O resulted in an increased 2*S* preference, with the ratio of the two *anti*-isomers *anti*-2*R* and *anti*-2*S* becoming inverted and the amount of *syn*-2*S* increasing at the expense of *syn*-2*R*. The opposite preference is obtained when $SnCl_2$ is not added (*cf.* entry 1 and entry 2), indicating that in this case the 2*S* products are disfavoured with Et_2O as the solvent. In THF, the amount of added $SnCl_2$ was found to influence the outcome of the reaction: increasing the amount of $SnCl_2$ from 1.1 eq. (entry 7) to 2.1 eq. (entry 5) lowered the amounts of *syn*-2*S* and *anti*-2*S* that were produced, while increasing the amount of $SnCl_2$ to 5 eq. caused an inversion in the *anti*-2*S*:*anti*-2*R* ratio.

Using Cp_2ZrCl_2 as an additive (entries 10 and 11) resulted in *anti*-selectivity (29:71 and 27:73 respectively), which is opposite to the report by Evans and McGee[9] in which high *syn*-selectivity was obtained using *N*-propionylpyrrolidine as an auxiliary.

Use of TMSCl as an additive (entry 12) resulted in a modest *anti*-selectivity and a very high 2*S* preference, giving high theoretical ee values for the hydroxy acids that would be obtained after removal of the chiral auxiliary (95% for *syn*-2*S* and 98% for *anti*-2*S* respectively, see Table 1). The *syn*-2*S* product probably forms *via* the non-chelated chair transition state,[2a] while the *anti*-2*S* product most likely forms *via* either the non-

Table 1 Aldol reactions of the *Z*-enolate from *N*-propionylated (*S*)-(−)-2-(pyrrolidin-2-yl)propan-2-ol **1** with benzaldehyde

Entry	Solvent	Additive (eq.)	Reaction conditions	Conversion[a] (%)	Yield (%) syn-2*R*[a]	Yield (%) syn-2*S*[a]	Ee_{syn}[b] (%)	Yield (%) anti-2*R*[a]	Yield (%) anti-2*S*[a]	Ee_{anti}[b] (%)	*syn*:*anti*
1	THF	Li (2.2)[c]	−78 °C, 2 h–rt, 2 h	95	35	19	30	5	41	78	54:46
2	Et_2O	Li (2.2)[c]	−78 °C, 2 h–rt, 2 h	94	40	26	21	11	23	35	66:34
3	Et_2O	Li (2.2)[c]	−110 °C, 2 h–rt, 2 h	98	34	28	10	16	22	16	62:38
4	THF	$(i\text{-PrO})_3TiCl$ (2.1)	−78 °C, 1.5 h–0 °C, 1 h	82	14	48	55	6	32	68	62:38
5	THF	$SnCl_2$ (2.1)	−78 °C, 1.5 h–0 °C, 0.5 h	50	67	6	84	22	5	63	73:27
6	Et_2O	$SnCl_2$ (2.1)	−78 °C, 1.5 h–0 °C, 1 h	72	40	27	19	12	21	27	67:33
7	THF	$SnCl_2$ (1.1)	−78 °C, 1.5 h–0 °C, 0.5 h	93	49	15	53	26	10	44	64:36
8	THF	$SnCl_2$ (5.0)	−78 °C, 1.5 h–0 °C, 0.5 h	84	46	18	44	12	24	33	64:36
9	THF	Cp_2TiCl_2 (1.2)	−78 °C, 2 h–rt, 1 h	13	15	13	7	64	8	78	28:72
10	THF	Cp_2ZrCl_2 (2.1)	−78 °C, 2.25 h–rt, 1 h	42	26	3	79	67	4	89	29:71
11	THF	Cp_2ZrCl_2 (1.1)	−78 °C, 2.25 h–rt, 1 h	37	21	6	56	63	10	73	27:73
12	THF	TMSCl (2.2)	−78 °C, 2 h–rt, 2 h	45	<2	>36	>95	<1	>61	>98	38:62

[a] Determined by ^1H NMR spectroscopy of the crude product. [b] Theoretical ee values for the major *syn*- and *anti*-isomer *i.e.* for the 3-hydroxy-2-methyl-3-phenylpropanoic acids obtained after removal of the auxiliary. [c] From LDA.

chelated boat or the twist-boat transition state[2a] respectively. To fully understand and interpret the outcome of these asymmetric aldol reactions a proline derivative without the possibility of chelating to the additives is now in production in our laboratory. However, the conversion was rather low (entry 12) and did not increase with longer reaction times. Dichlorodimethylsilane was utilised instead of TMSCl in an effort to produce a bicyclic dimethylsiloxane similar to that which was obtained when primary (*S*)-prolinol propionamide was used.[3b] However, no such product was formed in this case. From the various mixtures of diastereomers (see Table 1), each of the four aldol products *syn*-2*R*, *syn*-2*S*, *anti*-2*R* and *anti*-2*S* can be isolated in stereoisomerically pure form by repeated LC (see Experimental section).

In order to obtain either 3-hydroxy-2-methyl-3-phenylpropionic acids or the corresponding diols, four different methods of hydrolysis were tested. Acidic hydrolysis[4] gave somewhat low yields 52–55% of the hydroxy acids and hydrolysis of the stereoisomerically pure aldol product *syn*-2*R* resulted in epimerisation; this was evident from the change in the *syn*:*anti* ratio to 58:42 following hydrolysis. The epimerisation probably occurs at the α-carbon, since Katsuki and Yamaguchi[3c] reported no epimerisation at the β-carbon when hydrolysing an aldol product without an α-methyl substituent under similar conditions. Basic hydrolysis using 2.5 M KOH (10% H_2O in MeOH) resulted in a retro aldol process which gave the starting materials, the hydroxyamide **1** and benzaldehyde instead of the desired acids. The reductive hydrolysis,[10] using a borane–lithium pyrrolidine complex did not undergo appreciable conversion to the desired diols and basic hydrolysis[11] using H_2O_2 (30%) and LiOH in a THF–H_2O mixture also showed no conversion to the acids. The chiral auxiliary (*S*)-(−)-2-(pyrrolidin-2-yl)propan-2-ol was recoverable as the hydroxyamide **1** in optically pure form from the acidic hydrolysis mixture in good yield according to the literature.[4]

The aldol product from entry 12 (*syn*:*anti* ratio 38:62) contained >97% of *syn*-2*S*- and *anti*-2*S*-aldol products which after acidic hydrolysis gave a *syn*:*anti* mixture (42:58) of 3-hydroxy-2-methyl-3-phenylpropionic acids. The acids in the mixture were then converted to their ethyl esters and then separated by LC into pure *syn*- and *anti*-forms.[12] The optical rotation for the ethyl ester obtained from *syn*-2*S* corresponded well to ethyl (2*S*,3*S*)-3-hydroxy-2-methyl-3-phenylpropionate.[12] Based on the sign of optical rotation for the ester obtained from *anti*-2*S*, this ester corresponds to ethyl (2*S*,3*R*)-3-hydroxy-2-methyl-3-phenylpropionate although the difference from the literature value for the enantiomer[12] is significant.

This work represents the first time that this proline-derived chiral auxiliary has been used in asymmetric aldol reactions and it was found to be useful as a selectivity marker when studying such reactions. We are currently investigating the scope and further applications of this chiral auxiliary and its derivatives in asymmetric syntheses.

Experimental

Unless otherwise stated starting materials and solvents were used as received from commercial suppliers. Dry THF (benzophenone and potassium), Et_2O ($LiAlH_4$), diisopropylamine (CaH_2), benzaldehyde and TMSCl (CaH_2) were distilled from the indicated drying agents and either used immediately or stored under argon. $SnCl_2$ was oven dried before use. NMR spectra were recorded on a JEOL JNM-EX 270 FT-NMR (270 MHz ^1H) or a Bruker DMX 250 (250 MHz ^1H and 62.9 MHz ^{13}C) instrument, using $CDCl_3$ as the solvent, $Si(CH_3)_4$ as the internal standard; all shifts are reported in ppm. GC analyses were carried out using a Varian 3300 or a Varian STAR 3400 CX with a 30 m × 0.25 mm id capillary column coated with HP-5, d_f = 0.25 μm, carrier gas: He (12 psi), split ratio: 1:20 or a 30 m × 0.25 mm id capillary column coated with VA-1, d_f =

0.25 µm, carrier gas: He (12 psi), split ratio: 1 : 20 respectively. GC-MS were recorded using a Varian SATURN 2000 GC/MS with a 30 m × 0.25 mm id capillary column coated with DB-5, d_f = 0.25 µm, carrier gas: He (10 psi), split ratio: 1 : 20. Optical rotations were carried out on a Perkin-Elmer 241 Polarimeter and are reported in units of 10^{-1} deg cm^2 g^{-1}. Merck Silica gel 60 (0.040–0.063 mm, 230–400 mesh ASTM) was used in LC separations. TLC (thin layer chromatography) was performed on silica gel plates (Merck 60, pre-coated aluminium foil) eluted with EtOAc (100%), and developed in UV-light and sprayed with vanillin in sulfuric acid or phosphomolybdic acid in aqueous sulfuric acid followed by heating with a heat gun. Boiling points are not corrected and the bulb-to-bulb distillations were performed in a Büchi GKR-51 apparatus. The HRMS measurements were taken on a VG-70E mass spectrometer.

Methyl (*S*)-(*N*-benzylpyrrolidin-2-yl)methanoate

HCl(g) was bubbled through a solution of (*S*)-(−)-proline (103 g, 0.90 mol) in methanol (700 ml, p.a.) at −5 °C until no more HCl(g) was taken up (3.5 h). The solvent was removed by rotary evaporation, the residue treated with CH_2Cl_2 (300 ml) and the CH_2Cl_2 subsequently removed *in vacuo*. This process was repeated 3 times to remove the water formed. The residue was then dissolved in CH_2Cl_2 (300 ml), dried ($MgSO_4$) and evaporated to give the title compound (149 g, 0.90 mol). The hydrochloride was checked by ^{1}H NMR spectroscopy and used in the next step without further purification.

The (*S*)-proline methyl ester hydrochloride (130 g, 0.785 mol) was dissolved in methanol (180 ml, p.a.) and cooled to 0 °C when dry Et_3N (120 ml, 0.858 mol) was added drop by drop (0.7 h). Et_2O (1650 ml, p.a.) was added and after 0.5 h the triethylammonium chloride formed was filtered off. Removal of the solvent gave the free base (74.7 g, 0.579 mol). This was immediately dissolved in dry toluene (150 ml) and added to a suspension of $NaHCO_3$ (53.4 g, 0.636 mol) and a few crystals of KI in dry toluene (750 ml). Benzyl bromide (69.4 ml, 0.578 mol) was then added. The mixture was heated to reflux until 10 ml of water had been collected (2 h). After cooling, the solvent was evaporated off and the residue distilled (102 °C/0.10 mmHg) to yield the title compound (118 g, 0.538). $[a]_D^{20}$ −73.6 (*c* 1.2, methanol). ^{1}H NMR (250 MHz): δ 1.70–2.21 (4H, m), 2.34–2.44 (1H, m), 3.01–3.09 (1H, m), 3.19–3.27 (1H, m), 3.57 (1H, d, *J* = 12.7 Hz), 3.64 (3H, s), 3.88 (1H, d, *J* = 12.7 Hz), 7.19–7.35 (5H, m) ppm. ^{13}C NMR (62.9 MHz): δ 22.92, 29.33, 51.71, 53.26, 58.75, 65.29, 127.07, 128.14 (2 C), 129.22 (2 C), 138.20, 174.56 ppm. MS (EI) *m*/*z* (relative intensity): 220 (27%, MH^+), 219 (7, M^+), 218 (29, M^+ − H), 160 (100), 142 (3), 91 (3).

(*S*)-2-(*N*-Benzylpyrrolidin-2-yl)propan-2-ol

To the methyl Grignard reagent prepared from magnesium chips (30.2 g, 1.147 mol) the methyl ester from above (104 g, 0.478 mol) in dry Et_2O (450 ml) was added dropwise at 0–7 °C. The mixture was heated to reflux (2 h) and then stirred at ambient temperature overnight before quenching with aqueous saturated NH_4Cl (1000 ml). The organic phase was separated and the aqueous phase extracted with Et_2O (4 × 300 ml). The pooled organic phases were dried ($MgSO_4$) and the solvent evaporated off to give the alcohol after distillation (97–99.5 °C/0.10 mmHg) as a light brown oil (79.7 g, 0.371 mol). $[a]_D^{20}$ −49.3 (*c* 0.9, methanol). ^{1}H NMR (250 MHz): δ 1.17 (3H, s), 1.26 (3H, s), 1.64–1.96 (4H, m), 2.37–2.47 (1H, m), 2.66 (1H, br s, disappeared on shaking with D_2O), 2.73–2.78 (1H, m), 2.85–2.94 (1H, m), 3.59 (1H, d, *J* = 13.9 Hz), 4.14 (1H, d, *J* = 13.9 Hz), 7.20–7.39 (5H, m) ppm. ^{13}C NMR (62.9 MHz): δ 25.16, 25.20, 27.76, 28.66, 55.36, 63.14, 72.69, 72.92, 126.80, 128.05 (2 C), 128.30 (2 C), 140.51. MS (EI) *m*/*z* (relative intensity): 220 (31%, MH^+), 219 (8, M^+), 218 (22, M^+ − H), 202 (20), 160 (100), 142 (1), 91 (3).

(*S*)-(−)-2-(Pyrrolidin-2-yl)propan-2-ol

(*S*)-(−)-2-(*N*-Benzylpyrrolidin-2-yl)propan-2-ol (41.2 g, 0.188 mol) and Pd/C (2.9 g, 10%) were stirred in methanol (200 ml) for three days under 1 atm of hydrogen. The catalyst was filtered off and the solvent removed by rotary evaporation to give a golden oil that crystallised upon standing (23.3 g, 0.180 mol, 96%). The crude product was crystallised twice from hexane and dried over phosphoric pentaoxide in a vacuum desiccator to yield the optically pure aminoalcohol (6.52 g, 0.052 mol). Mp = 37–39 °C, lit.[4] mp = 37–38 °C, $[a]_D^{25}$ −35.8 (*c* 1.1, MeOH), lit.[4] $[a]_D^{20}$ −35.8 (*c* 1.1, MeOH). ^{1}H NMR (270 MHz): δ 1.13 (3H, s), 1.17 (3H, s), 1.53–1.79 (4H, m), 2.69 (2H, two overlapping br s, disappeared on shaking with D_2O), 2.87–3.05 (3H, m) ppm.

(*S*)-(−)-2-(*N*-Propionylpyrrolidin-2-yl)propan-2-ol, 1

To the aminoalcohol (2.72 g, 21.1 mmol, from above), propionic anhydride (3.01 g, 23.2 mmol) was added drop by drop (0.3 h) with stirring under an argon atmosphere. The mixture was heated at 70 °C (0.5 h), then cooled and basified to pH 10 with NaOH (aq. 30%) and stirred for an additional 1.5 h. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (5 × 20 ml). The combined organic phases were washed with 10% aq. HCl (20 ml), brine (40 ml) and finally dried ($MgSO_4$). Evaporation of the solvent and bulb-to-bulb distillation (162–163 °C/0.5 mbar) gave the optically pure hydroxyamide **1** (3.78 g, 20.4 mmol). $[a]_D^{25}$ −96.5 (*c* 5.4, MeOH), lit.[4] $[a]_D^{20}$ −93.2 (*c* 5.4, MeOH). ^{1}H NMR (270 MHz): δ 1.05 (3H, s), 1.17 (3H, t, *J* = 7.4 Hz), 1.19 (3H, s), 1.57–2.15 (4H, m), 2.39 (2H, q, *J* = 7.4 Hz), 3.32–3.43 (1H, m), 3.62–3.70 (1H, m), 4.13 (1H, apparent t, *J* = 7.6 Hz), 5.90 (1H, br s, disappeared on shaking with D_2O). ^{13}C NMR (62.9 MHz): δ 9.14, 23.18, 24.47, 27.80, 28.64, 28.71, 48.81, 68.13, 73.48, 175.75 ppm. MS (EI) *m*/*z* (relative intensity): 186 (25%, MH^+), 168 (5), 127 (67), 98 (31), 70 (100), 57 (9).

Aldol reactions: general procedure

To a cooled solution (0 °C) of diisopropylamine (0.510 g, 5.0 mmol) in either THF or Et_2O (4 ml) under an argon atmosphere in a two-necked flask (50 ml) was added 1.6 M *n*-butyllithium in hexane (2.75 ml, 4.4 mmol). The mixture was stirred at 0 °C (1 h), and to this solution of LDA was added dropwise a solution of hydroxyamide **1** (0.371 g, 2.0 mmol) dissolved in THF or Et_2O (4 ml). After stirring at 0 °C (1 h) the solution was cooled to −78 °C followed by addition of benzaldehyde (0.255 g, 2.4 mmol) in THF or Et_2O (4 ml). The mixture was then stirred at −78 °C (2 h) and slowly warmed to room temperature (2 h).

Alternatively. before the addition of benzaldehyde a Lewis acid was added (1.1–5.0 eq.) neat (Cp_2TiCl_2, (i-PrO)$_3$TiCl and TMSCl) or dissolved in either THF or Et_2O (10–17 ml). The reaction mixture was stirred at low temperature (0.2–0.5 h) followed by warming to 0 °C or to room temperature (0.5–2.0 h). The mixture was again cooled to −78 °C for 0–1 h, followed by addition of benzaldehyde (0.255 g, 2.4 mmol, 1.2 eq.) in THF or Et_2O (4 ml). For exact equivalents of Lewis acid, reaction temperatures and times *etc*., see Table 1. The reaction mixture was quenched by dropwise addition of aqueous saturated NH_4Cl (20–30 ml). Precipitated materials were filtered off and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (5 × 25 ml) and the combined organic phases were dried ($MgSO_4$). (In the case of remaining precipitated material the combined organic phases were washed with brine and water before drying.) Concentration by evaporation afforded the crude aldol products.

For entry 12 (*cf*. Table 1) the silyl ether was formed and had to be removed in order to afford the desired aldol product. The crude product was dissolved in MeOH (30 ml) and TsOH (10 mg) was added. After stirring overnight at room temperature, MeOH was evaporated off and the residue dissolved in CH_2Cl_2 (30 ml) and washed with Na_2CO_3 (aq. 10%, 10 ml). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (20 ml). The combined organic phases were dried ($MgSO_4$) and evaporation afforded the crude aldol product.

The crude product was adsorbed on SiO_2 (approx. 5 times the weight of the crude product) and applied to the top of a column (id 12.5 mm) with SiO_2 (approx. 30 times the weight of the crude product in SiO_2). Eluting with EtOAc in cyclohexane, 0, 1.25, 2.5, 5, 10, 20, 40, 80, 100% and MeOH in EtOAc, 1.25, 2.5, 5, 10, 20%, gave after one repetition of this procedure pure *syn*-2*R* as determined by ^{1}H NMR spectroscopy.

Spectroscopic data for *syn*-2*R*. ^{1}H NMR (250 MHz): δ 1.03 (3H, s), 1.17 (3H, d, J = 7.0 Hz), 1.19 (3H, s), 1.50–1.69 (2H, m), 1.80–2.13 (2H, m), 2.86 (1H, dq, J = 7.0, 3.6 Hz), 3.22–3.35 (1H, m), 3.55–3.65 (1H, m), 4.14 (1H, apparent t, J = 7.3 Hz), 4.24 (2H, two overlapping br s), 5.09 (1H, d, J = 3.6 Hz), 7.21–7.40 (5H, m) ppm. ^{13}C NMR (62.9 MHz): δ 10.79, 23.30, 24.40, 27.76, 28.56, 44.94, 49.07, 68.15, 73.16, 73.54, 125.97, 127.31, 128.18, 141.63, 178.44 ppm. MS (EI) *m*/*z* (relative intensity): 292 (68%, MH^+), 274 (23), 256 (3), 233 (8), 218 (5), 185 (4), 167 (3), 126 (100), 107 (8), 70 (36). HRMS (EI, 28 eV): (MH^+) 292.1904 and ($MH^+ - C_3H_7O$) 233.1400. $C_{17}H_{26}NO_3$ and $C_{14}H_{19}NO_2$ require 292.1913 and 233.1416 respectively.

Spectroscopic data for *syn*-2*S*. ^{1}H NMR (250 MHz): δ 0.87 (3H, s), 1.13 (3H, d, J = 7.0 Hz), 1.16 (3H, s), 1.54–1.78 (2H, m), 1.84–2.15 (2H, m), 2.84 (1H, dq, J = 7.0, 4.1 Hz), 3.25–3.37 (1H, m), 3.62–3.71 (1H, m), 4.09 (1H, apparent t, J = 7.6 Hz), 4.71 (2H, two overlapping br s), 5.04 (1H, d, J = 4.1 Hz), 7.21–7.40 (5H, m) ppm. ^{13}C NMR (62.9 MHz): δ 10.34, 23.02, 24.40, 27.77, 28.67, 44.91, 48.94, 68.15, 73.32, 73.99, 126.25, 127.40, 128.23, 141.64, 178.09 ppm. MS (EI) *m*/*z* (relative intensity): 292 (16%, MH^+), 274 (5), 233 (31), 218 (27), 185 (14), 167 (3), 126 (100), 107 (13), 70 (75). HRMS (EI, 28 eV): ($MH^+ - C_3H_7O$) 233.1576 and ($MH^+ - C_{10}H_{14}O_2$) 126.0961. $C_{14}H_{19}NO_2$ and $C_7H_{12}NO$ require 233.1416 and 126.0919 respectively.

Spectroscopic data for *anti*-2*R*. ^{1}H NMR (250 MHz): δ 1.02 (3H, s), 1.18 (3H, s), 1.20 (3H, d, J = 7.0 Hz), 1.35–1.64 (2H, m), 1.72–2.08 (2H, m), 3.01 (1H, dq, J = 7.0, 6.4 Hz), 3.17–3.28 (1H, m), 3.49–3.58 (1H, m), 4.10 (1H, apparent t, J = 7.7 Hz), 4.29 (2H, two overlapping br s), 4.79 (1H, d, J = 6.4 Hz), 7.22–7.43 (5H, m) ppm. ^{13}C NMR (62.9 MHz): δ 15.52, 23.22, 24.21, 27.71, 28.55, 45.45, 49.07, 67.96, 73.44, 76.43, 126.15, 127.72, 128.39, 142.55, 177.55 ppm. MS (EI) *m*/*z* (relative intensity): 292 (76%, MH^+), 274 (24), 256 (5), 233 (11), 218 (4), 185 (4), 167 (4), 126 (100), 107 (11), 70 (57). HRMS (EI, 28 eV): ($MH^+ - C_3H_7O$) 233.1594 and ($MH^+ - C_{10}H_{14}O_2$) 126.0953. $C_{14}H_{19}NO_2$ and $C_7H_{12}NO$ require 233.1416 and 126.0919 respectively.

Spectroscopic data for *anti*-2*S*. ^{1}H NMR (250 MHz): δ 0.74 (3H, s), 1.12 (3H, s), 1.20 (3H, d, J = 7.0 Hz), 1.53–1.77 (2H, m), 1.85–2.10 (2H, m), 2.99 (1H, dq, J = 7.0, 5.9 Hz), 3.22–3.40 (1H, m), 3.62–3.71 (1H, m), 4.07 (1H, apparent t, J = 7.5 Hz), 4.71 (2H, two overlapping br s), 4.80 (1H, d, J = 5.9 Hz), 7.22–7.43 (5H, m) ppm. ^{13}C NMR (62.9 MHz): δ 14.61, 22.86, 24.29, 27.71, 28.67, 45.35, 49.05, 68.28, 73.52, 76.56, 126.01, 127.17, 127.47, 128.36, 142.70, 177.28 ppm. MS (EI) *m*/*z* (relative intensity): 292 (45%, MH^+), 274 (12), 233 (18), 218 (5), 185 (5), 167 (4), 126 (100), 107 (14), 70 (61). HRMS (EI, 28 eV): ($MH^+ - C_3H_7O$) 233.1526 and ($MH^+ - C_{10}H_{14}O_2$) 126.0954. $C_{14}H_{19}NO_2$ and $C_7H_{12}NO$ require 233.1416 and 126.0919 respectively.

(2*S*,3*S*) and (2*S*,3*R*)-3-Hydroxy-2-methyl-3-phenylpropionic acids. Hydrolysis general method

A diastereomeric mixture of aldol products (0.538 g, 1.85 mmol, *syn*:*anti* = 65:35, determined by ^{1}H NMR spectroscopy) was dissolved in 1,4-dioxane (14 ml) and 3 M aq. HCl (14 ml). The solution was stirred at 90–95 °C (43 h). After cooling to room temperature, the hydrolysis mixture was extracted with CH_2Cl_2 (4 × 25 ml). The combined organic phases were treated with aqueous saturated Na_2CO_3 (50 ml). Acidification of the aqueous phase with 6 M HCl to pH 1–2, extraction with CH_2Cl_2 (5 × 25 ml) and drying ($MgSO_4$) gave after evaporation of the solvent a mixture of acids (0.252 g, 1.40 mmol). Purification by bulb-to-bulb distillation (205 °C/0.3 mbar) gave 0.195 g (1.08 mmol) of the acids with >94.7% purity by GC. The *syn*:*anti* ratio for the mixture was determined by ^{1}H NMR spectroscopy to be 48:52. $[\alpha]_D^{25}$ +4.4 (c 0.90, CH_2Cl_2), lit.[13] for (2*S*,3*S*)-3-hydroxy-2-methyl-3-phenylpropionic acid $[\alpha]_D$ −29.3 (c 0.80, $CHCl_3$) and lit.[13] for (2*S*,3*R*)-3-hydroxy-2-methyl-3-phenylpropionic acid $[\alpha]_D$ +17.8 (c 2.0, $CHCl_3$). ^{1}H NMR (250 MHz): δ 1.04 (3H, d, J = 7.3 Hz, *anti* isomers), 1.16 (3H, d, J = 7.3 Hz, *syn* isomers), 2.81–2.92 (1H, m), 4.77 (1H, d, J = 8.9 Hz, *anti* isomers), 5.18 (1H, d, J = 4.0 Hz, *syn* isomers), 7.26–7.42 (5H, m). MS (EI) *m*/*z* (relative intensity): 180 (3%, M^+), 162 (5), 133 (7), 117 (38), 107 (73), 91 (25), 77 (100), 51 (34), 45 (15).

Hydrolysis of the pure aldol product *syn*-2*R* (0.155 g, 0.53 mmol, 100% purity by ^{1}H NMR spectroscopy) yielded a *syn*:*anti* mixture (58:42) of acids (0.050 g, 0.28 mmol) as determined by ^{1}H NMR spectroscopy. $[\alpha]_D^{25}$ −2.6 (c 0.90, CH_2Cl_2), lit.[13] for (2*R*,3*R*)-2-methyl-3-hydroxy-3-phenylpropionic acid $[\alpha]_D$ +28.5 (c 1.12, $CHCl_3$), and lit.[13] for (2*R*,3*S*)-2-methyl-3-hydroxy-3-phenylpropionic acid $[\alpha]_D$ −17.5 (c 2.3, $CHCl_3$).

Ethyl (2*S*,3*S*)- and (2*S*,3*R*)-3-hydroxy-2-methyl-3-phenylpropionate

Hydrolysis of a mixture of aldol products (76 mg, 0.26 mmol, *syn*-2*S*:*anti*-2*S* = 32:68, 100% pure by ^{1}H NMR spectroscopy) by the same procedure as above yielded a yellow oil (46 mg). The crude product of the acids was dissolved in EtOH (99.5%, 10 ml), and H_2SO_4 (conc., 2 drops) was added. After refluxing (21 h) the reaction mixture was poured into H_2O (20 ml) and extracted with pentane (5 × 20 ml). The combined organic phases were washed with aqueous saturated Na_2CO_3 (2 × 20 ml), brine (20 ml) and finally dried ($MgSO_4$). Evaporation of the solvent gave a yellow oil (30 mg, 0.14 mmol). Separation by LC (using the same procedure as for the separation of aldols, see above) gave 6 mg of (2*S*,3*S*)-3-hydroxy-2-methyl-3-phenylpropionate and 14 mg of ethyl (2*S*,3*R*)-3-hydroxy-2-methyl-3-phenylpropionate both with 100% purity by GC.

Spectroscopic data for ethyl (2*S*,3*S*)-3-hydroxy-2-methyl-3-phenylpropionate obtained from aldol product *syn*-2*S*: $[\alpha]_D^{25}$ −23.4 (c 0.36, $CHCl_3$), lit.[12] $[\alpha]_D^{17}$ −22.0 (c 0.87, $CHCl_3$). MS (EI) *m*/*z* (relative intensity): 208 (7%, M^+), 191 (5), 163 (3), 135 (5), 117 (7), 107 (47), 102 (100), 77 (74), 74 (81), 57 (23).

Spectroscopic data for ethyl (2*S*,3*R*)-3-hydroxy-2-methyl-3-phenylpropionate obtained from aldol product *anti*-2*S*: $[\alpha]_D^{25}$ +47.1 (c 1.12, $CHCl_3$), lit. for ethyl (2*R*,3*S*)-3-hydroxy-2-methyl-3-phenylpropionate[12] $[\alpha]_D^{17}$ −15.3 (c 1.11, $CHCl_3$). MS (EI) *m*/*z* (relative intensity): 208 (3%, M^+), 191 (37), 163 (3), 135 (37), 117 (7), 107 (46), 102 (100), 77 (38), 74 (42), 57 (20).

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