DOI: 10.1002/ejoc.200700834

Use of (*S*)-5-(2-Methylpyrrolidin-2-yl)-1*H*-tetrazole as a Novel and Enantioselective Organocatalyst for the Aldol Reaction

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Keywords: Aldol / Enantioselectivity / Methylproline / Organocatalysis / Tetrazole

The novel organocatalyst (*S*)-5-(2-methylpyrrolidin-2-yl)-1*H*-tetrazole (**4**) catalyzes the aldol reaction between acetone and various aldehydes with superior enantioselectivity to the existing organocatalysts (*S*)-proline (**1**) and (*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole (**3**).

Introduction

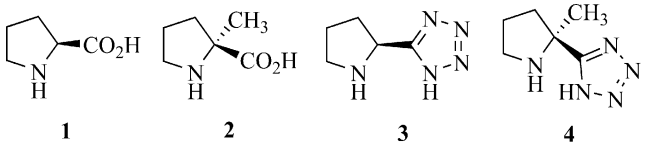
Asymmetric organocatalysis has recently emerged as a "hot field" in synthetic chemistry providing an operationally simple, economic and environmentally friendly strategy to prepare enantioenriched compounds.[1] The aldol reaction can now be carried out enantioselectively using a variety of organocatalysts, many of which are based on a proline scaffold.[2,3] These proline-based catalysts contain the minimum structural requirements required for organocatalytic activity namely a cyclic secondary amine and an acidic proton in the correct spatial geometry as found in (*S*)-proline **1**.[2c,2h,2q]

Significantly, examples of organocatalysts based on an α-alkylproline scaffold are rare. (*S*)-α-Methylproline (**2**) was shown to be ineffective as an organocatalyst for the α-hydroxylation of cyclohexanone,[4] but proved better than proline (**1**) for the α-hydroxylation of aldehydes.[5] In the intermolecular aldol reaction between acetone and *p*-nitrobenzaldehyde, use of **2** resulted in lower yields and enantioselectivity than proline,[2h] whilst the recently reported intramolecular α-alkylation of aldehydes involving catalysis by **2** proceeded in better yield and enantioselectivity than when proline was used.[6]

In general the aldol reactions between acetone and aromatic aldehydes catalysed by proline **1** only proceeded in modest yield and enantiomeric excess (<80% *ee*).[2c,2d,2h] There are, however, recent examples of aldol reactions with other ketones and aromatic aldehydes in which higher *ee* values are obtained.[2r,2s] Given the remarkable improvement in the stereoselectivity of α-alkylation and α-hydroxylation of aldehydes using α-methylproline **2** as the organocatalyst, we decided to re-examine the effect of α-substitution in proline-based catalysts on the efficiency and enantioselectivity of the aldol reactions of acetone.

The pyrrolidine derivative **3** has emerged as a useful organocatalyst for various reactions.[2j,3a–3c,7–11] Substitution of the carboxylic acid group in proline for a tetrazole moiety reduced the aldol reaction times from 1–2 days to less than half a day.[2h,3a,3b] This dramatic improvement in efficiency was attributed to the presence of a more acidic tetrazole proton in DMSO as solvent and the larger size of the tetrazole unit resulting in a more favourable transition state.[3a,12] Whilst proline is known to react with aliphatic aldehydes and ketones to form oxazolidinones,[2c,13–15] and with aromatic aldehydes to give azomethine ylides,[2c,16–17] NMR studies by Hartikka and Arvidsson showed that **3** did not participate in these reactions.[3b] They attributed the major reason for the enhanced efficiency of **3** over proline **1** to be due to the lack of side reactions between **3** and the aldehyde and ketone substrates. Notably, however, **3** did not improve the enantioselectivity of these aldol reactions.[3a]

We therefore envisaged that "α-methylproline tetrazole" **4** might prove to be a better organocatalyst in that it combined the presence of an additional α-methyl substituent to improve the stereoselectivity of the aldol reaction with the incorporation of a tetrazole moiety to increase the reaction rate. We therefore herein report the use of α-methylproline (**2**) and the synthesis and use of the novel derivative **4** as organocatalysts for intermolecular aldol reactions (Figure 1).



1 **2** **3** **4**

Figure 1. Structures of the existing organocatalysts **1**, **2** and **3** and the novel organocatalyst **4**.

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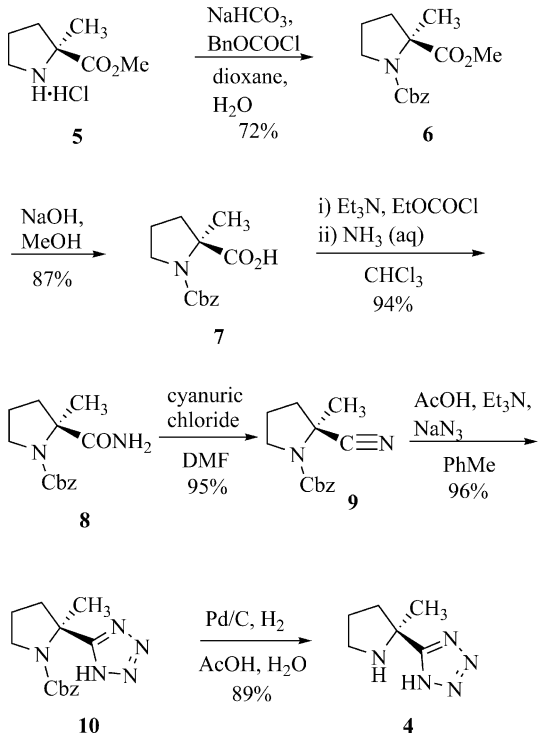
Results and Discussion

α-Methylproline (**2**) was prepared via Wang and Germanas's modification[18] of Seebach's method[19] for the preparation of α-branched amino acids. Tetrazole **4** was prepared by adaptations of previously reported methods for the synthesis of tetrazole **3** or its intermediates,[3b,20–22] starting from the readily available (*S*)-α-methylproline methyl ester (**5**) (Scheme 1).[23]

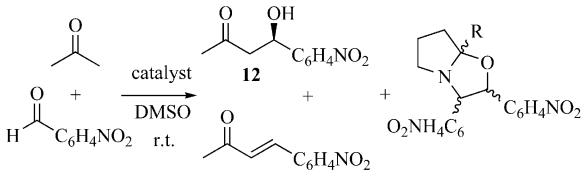


Scheme 1. Synthesis of (*S*)-5-(2-methylpyrrolidin-2-yl)-1*H*-tetrazole (**4**).

Catalysts **1**, **2**, **3** and **4** were initially examined as organocatalysts for the benchmark aldol reaction between acetone and *p*-nitrobenzaldehyde (**11**). The reactions were carried out in DMSO as the standard solvent.[2c,2d,2h,2k,3a,24] Use of DMSO favours the 1*H*-tautomer of the tetrazole engaged in the favoured transition state.[3a] Catalysis by proline and tetrazole **3** afforded β-hydroxy ketone **12** in 60% yield, and as previously reported, the reaction proceeded much faster using proline tetrazole **3** than (*S*)-proline but with similar enantioselectivity (Table 1). The use of α-methylproline, however, only resulted in formation of racemic **12**. Pleasingly, tetrazole **4** afforded the highest enantioselectivity of the four catalysts examined with the reaction proceeding in comparable yield albeit with a longer reaction time.

An interesting observation was the formation of the oxapyrrolizidine derivative **14** as a by-product in the reactions using proline and α-methylproline (**2**) as catalysts. The pyrrolizidine **14** has previously been reported by Orsini et al.[16] as a mixture of diastereomers from reaction of proline **1** with **11** in DMSO. List and Barbas III carried out their

Table 1. Yields and *ee* values for the aldol reaction between acetone and *p*-nitrobenzaldehyde (**11**) catalysed by **1**–**4**.



Entry	Catalyst	Loading [mol-%]	Time [h]	% Yield **12**	**13**	**SM**[c]	**14**	% *ee*[d]
1[a]	**1**	20	22	54	1	0	8	72
2[a]	**1**	30	18	56	2	0	9	68
3[a]	**2**	20	70	13	0	<1	0	0[e]
4[b]	**2**	20	46	32	0	<1	0	2[e]
5[a]	**2**	30	54	18	0	0	23	0[e]
6[a]	**3**	20	0.7	50	8	0	0	76
7	**3**	20	1.4	61	21	0	0	76
8	**3**	30	0.9	54	6	0	0	76
9	**4**	20	68	60	2	11	0	**88**
10	**4**	30	48	67	6	26	0	**86**
11[a]	**4**	40	50	17	0	24	0	**80**

[a] Performed under anhydrous conditions. [b] The reaction was performed in DMF with 555 mol-% of water. [c] Percentage of recovered aldehyde **11**. [d] *ee* values of **12** as determined by ^{1}H NMR analysis for the Mosher ester derivative. [e] The *ee* value reported by Barbas et al. was not reproduced.[2h]

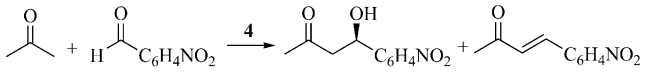
reactions in an excess of acetone in order to circumvent this undesired reaction.[2c] In our case, significant quantities of **14** were observed using proline and α-methylproline as catalysts using their conditions. The fact that **14** was not observed when using the tetrazoles **3** and **4** (Table 1) supports the postulate that tetrazoles offer an additional benefit in the catalytic aldol reactions by eliminating the oxapyrrolizidine side reaction which is observed using the carboxylic acid based catalysts **1** and **2**.

Table 1 illustrates the observation that while catalyst loading had little influence on the reaction outcome, the presence of water had a significant effect. The effect of water on asymmetric aldol reactions using various organocatalysts[3e–3g,25] including proline and tetrazole **3**[2h,2l,2o,3c] has been well documented. In general, water promotes catalytic efficiency but not the stereoselectivity, with use of excessive water leading to reduced stereoselectivity. Indeed in our case, the catalytic efficiency of α-methylproline doubled when water was added, with no effect on the stereoselectivity (Table 1, entry 4). Water possibly serves to hydrolyse any iminium species that forms between substrate **11** and the catalyst, such that they are free to react as intended without participating in side reactions.

We next examined the effect of solvent on the catalysis of the aldol reaction using tetrazole **4** (Table 2). The reaction worked well in DMF (3% water) with minimal effect on the stereoselectivity. Lowering the reaction temperature in DMF has been shown to increase stereoselectivity when using proline,[3a] however, using the tetrazole **4** in DMF at lower temperature only resulted in a low yield of product.

Aldol reactions in dichloromethane and toluene using tetrazole **4** proceeded slowly and less satisfactorily than in DMSO, which proved to be the optimal solvent.

Table 2. The effect of solvent on the catalysis of the aldol reaction between acetone and aldehyde **11** by tetrazole **4**.



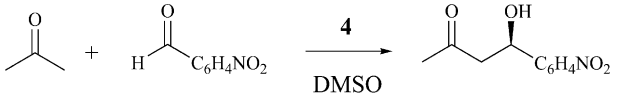
11 **12** **13**

Entry	Solvent	Time [h]	% Yield **12**	**13**	**SM**[b]	% *ee* of **12**
1	DMF, H_2O, room temp.	48	63	3	20	82
2	DMF, –50 °C	72	7	0	71	86
3	DCM	50	31	0	69	68
4	PhMe	69	17	<1	68	74[a]
5	**DMSO**	**68**	**60**	**2**	**11**	**88**

[a] Notably, *ee* of **12** is still higher than those obtained with proline **1** (54% *ee*) and proline tetrazole **3** (61%).[3a] [b] Percentage of recovered aldehyde **11**.

Efforts to improve the catalytic efficiency of α-methylproline tetrazole **4** were next undertaken (Table 3). Several recent reports suggested a positive effect of microwave irradiation or heat on the aldol reaction catalysed by proline **1**, significantly shortening the reaction time whilst maintaining the observed enantioselectivity.[26,27] Running the reaction at 35 °C instead of room temperature shortened the reaction time by one-third, with the same yield and slightly lower selectivity (Table 3, entry 2). Unfortunately, further increases in the temperature diminished the selectivity without improving the yield (Table 3, entry 3). ^{1}H NMR studies in [D_6]DMSO showed that the conversion rate reached a plateau after 2 days (see electronic supporting information) with the optimum yield and *ee* being obtained after 1 day (Table 3, entry 2).

Table 3. Effect of temperature on the catalysis of the aldol reaction between acetone and aldehyde **11** by α-methylproline tetrazole **4**.

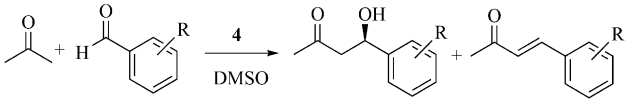


11 **12**

Entry	Temperature	4 h	1 day	2 days	3 days
1	room temp.		44% (90% *ee*)		60% (88% *ee*)
2	35 °C	15%	65% (85% *ee*)	65% (82% *ee*)	67% (81% *ee*)
3	50 °C		67% (78% *ee*)		

With the optimal reaction conditions determined, several aldehydes were screened to determine the generality of tetrazole **4** as an organocatalyst (Table 4). α-Methylproline tetrazole **4** conferred excellent enantioselectivity using a variety of aromatic aldehydes with much better enantiomeric excesses being obtained compared to the use of proline **1** or proline tetrazole **3**. Entry 4 demonstrates the positive impact of water on the catalytic efficiency, where the yield was four times higher than that obtained under anhydrous conditions. Notably, the potential for improvement in efficiency by heating the reaction at 35 °C was also substrate-specific. Whereas **16i** was obtained in 87% yield at 35 °C after 1 day (Table 4, entry 9), heating did not improve the formation of **16e** significantly (Table 4, entry 5). Disappointingly, the increase in temperature appeared to facilitate undesired dehydration, giving more enone **17c** than **16c** (Table 4, entry 3).

Table 4. Yields and *ee* values for the aldol reaction between acetone and various aldehydes **15** catalysed by **4**.



15 **16** **17**

Entry	R	Time [h], temp. [°C]	% Yield **16**, **17**, **SM**[b]	% *ee*[c]	% *ee*[e]	% *ee*[f]
1	4-NO_2, **a**	68, room temp.	60, 2, 11	**88**[d]	72	76
2	2-Cl, **b**	68, room temp.	60, <2, 0	**90**	70	77
3	4-MeO, **c**	143, room temp.	12, 0, 47	**85**		62[3b]
		51, 35 °C	4, 9, 47	–		
4	4-Br, **d**	48, room temp.	33, <5, 13	**87**	65[2h]	66[3b]
		48, room temp.[a]	8, 0, 50	**83**		
5	4-AcNH, **e**	88, room temp.	11, 8, 73	**70**	69[2h]	
		43, 35 °C	16, 9, 51	–		
6	2-naphthyl, **f**	89, room temp.	30, 18, 33	**81**	77[2h]	
7	H, **g**	69, room temp.	22, 0, 0	**80**	60[2h]	65[3b]
8	4-Cl, **h**	72, room temp.	36, 6, 20	**86**		
9	2-NO_2, **i**	67, room temp.	88, 4, 3	**91**		
		24, 35 °C	87, 4, 0	**89**		
10	3-NO_2, **j**	68, room temp.	71, 3, 9	**90**		

[a] Performed under anhydrous conditions. [b] Percentage of recovered aldehyde **15**. [c] *ee* obtained with tetrazole **4** by chiral HPLC. [d] Determined by ^{1}H NMR analysis of the Mosher ester derivative. [e] *ee* obtained with proline. [f] *ee* obtained with tetrazole **3**.

Conclusions

In conclusion, we have examined the effect of α-methyl substitution on proline-based catalysts **1** and **3** by investigating the potential of α-methylproline (**2**) and "α-methylproline tetrazole" **4** as organocatalysts for the aldol reaction. Tetrazole **4** affords remarkable stereoselectivity and this observed enhancement may well be extended to the organocatalysis of other reactions. The detailed mechanistic basis for these observations is currently under investigation.[28] Addition of an α-substituent to other existing proline-based organocatalysts may also improve the observed stereoselectivities. Studies on the use of tetrazole **4** as an organocatalyst for other reactions together with the introduction of α-substituents onto other proline-based organocatalysts are on-going.

Experimental Section

General: Reactions were monitored by TLC, using pre-coated silica gel TLC plates obtained from Merck. Flash chromatography was carried out on silica gel (Riedel-de Haën, particle size 0.032–0.063 mm). Reactions that required anhydrous conditions were run under an atmosphere of nitrogen. Evaporation of solvents was carried out at reduced pressure. Dimethyl sulfoxide was distilled from calcium hydride at reduced pressure and acetone was distilled from anhydrous calcium sulfate. Hexane for flash chromatography was distilled before use. HPLC analysis was performed on a Waters Instrument (2487 dual wavelength absorbance detector with a 600 binary HPLC Pump). The Chiralpak AD-H column was purchased from Daicel Chemical Industries Ltd. Optical rotations were measured on a Perkin–Elmer 341 polarimeter (λ = 589 nm, 0.1 dm cell). Melting point determinations were performed on an Electrothermal® melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance DRX 300 MHz or 400 MHz spectrometers at ambient temperatures. Chemical shifts δ are expressed in ppm and coupling constants J are reported in Hz. TMS served as internal standard (δ = 0 ppm) for ^{1}H NMR, and $CDCl_3$ served as internal standard (δ = 77.0 ppm) for ^{13}C NMR spectroscopy. Where CD_3OD was used as the solvent, chemical shifts δ were reported using residual CHD_2OD (δ = 3.30 ppm for ^{1}H NMR) and CD_3OD (δ = 49.05 ppm for ^{13}C NMR) as internal standards, respectively. Infrared spectra were recorded on a Perkin–Elmer spectrum one FT-IR spectrometer.

1-Benzyl 2-Methyl (*S*)-2-Methylpyrrolidine-1,2-dicarboxylate (6): To a solution of methyl (*S*)-2-methylpyrrolidine-2-carboxylate hydrochloride (**5**) (600 mg, 3.10 mmol) in water/dioxane (1:1, 6 mL) was added, at 0 °C, $NaHCO_3$ (0.39 g, 4.65 mmol) in small portions, followed by benzyl chloroformate (3.48 mL, 24.78 mmol) dropwise. The mixture was stirred at 0 °C for 2 hours and then at room temperature for 47 hours. The reaction mixture was concentrated under reduced pressure to remove dioxane and the remaining aqueous phase was extracted with chloroform (3 × 6 mL). The organic extracts were dried ($MgSO_4$) and concentrated to give a crude colourless liquid (4.2 g). The crude was subsequently distilled (20 mbar, 120 °C) to remove benzyl alcohol and the remaining residue was purified by flash chromatography (toluene/EtOAc, 4:1) to furnish the title ester as a pale yellow oil (0.62 g, 72%). $[\alpha]_D^{20}$ = –18 (c = 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.54 and 1.60 (s, 3 H, 2-CH_3, rotamers), 1.82–1.98 (m, 3 H), 2.10–2.24 (m, 1 H), 3.46 and 3.71 (s, 3 H, CO_2CH_3, rotamers), 3.50–3.71 (m, 2 H, 5-H^A and 5-H^B), 4.90–5.22 (m, 2 H, PhCH_2O), 7.25–7.40 ppm (m, 5 H, Ar-H), as a mixture of 1:1 rotamers. ^{1}H NMR spectroscopic data was consistent with literature values.[29]

(*S*)-1-(Benzyloxycarbonyl)-2-methylpyrrolidine-2-carboxylic Acid (7): A solution of ester **6** (578 mg, 2.08 mmol) in 5 N NaOH/MeOH (2:1, 12 mL) was heated at reflux for 2 hours. The mixture was then diluted with water (30 mL) and washed with diethyl ether (20 mL). The aqueous phase was acidified to pH 1 with 2 M HCl and extracted with $CHCl_3$ (3 × 35 mL). The combined $CHCl_3$ extracts were washed with brine (40 mL), dried ($MgSO_4$) and evaporated to give a crude pale yellow oil (492 mg). The crude was recrystallised with dichloromethane/hexane to yield the title acid as a colourless solid (478 mg, 87%); m.p. 89–91 °C (lit.[29] m.p. 121 °C). $[\alpha]_D^{18}$ = –7 (c = 1.0, MeOH) [ref.[30] $[\alpha]_D^{20}$ = –8.8 (c = 1.0, MeOH)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.54 and 1.64 (s, 3 H, 2-CH_3), 1.80–2.00 (m, 3 H), 2.20–2.43 (m, 1 H), 3.49–3.72 (m, 2 H, 5-H^A and 5-H^B), 5.00–5.20 (m, 2 H, PhCH_2CO), 7.20–7.50 (m, 5 H, Ar-H), 9.38–10.60 ppm (br. s, 1 H, OH), as an approximately 1:1 mixture of rotamers. The ^{1}H NMR spectroscopic data are consistent with literature values.[29] MS (EI): m/z (%) = 263 (0.015, M^+), 218 (0.17, M – CO_2H), 174 (0.18), 128 (0.17, M–PhCH_2CO_2), 91 (1.0, PhCH_2). HMRS calculated for $C_{14}H_{17}NO_4$ 263.11576, found 263.11551.

Benzyl (*S*)-2-Carbamoyl-2-methylpyrrolidine-1-carboxylate (8): To a solution of acid **7** (100 mg, 0.38 mmol) in dry chloroform (32 mL) was added, under nitrogen at 0 °C, triethylamine (0.42 mL, 3.04 mmol) and ethyl chloroformate (0.29 mL, 3.04 mmol). The mixture was stirred at 0 °C for 2 hours and aqueous ammonia solution (28%, 4.94 mL) was added, after which the mixture was stirred for another 3 hours. The aqueous phase was separated and extracted with chloroform (2 × 15 mL). The combined organics were washed with cold 5% $NaHCO_3$ solution (30 mL), dried ($MgSO_4$) and evaporated to afford a crude yellow oil, which was purified via flash chromatography (EtOAc/MeOH, 99:1) to furnish the title amide as a sticky yellow gum (94 mg, 94%). $[\alpha]_D^{20}$ = –25 (c = 1.0, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.53 and 1.64 (s, 3 H, 2-CH_3, rotamers), 1.72–2.09 (m, 3 H), 2.09–2.78 (m, 1 H), 3.33–3.78 (m, 2 H, 5-H^A and 5-H^B), 5.12 (s, 2 H, PhCH_2), 6.08–6.56 (m, 1 H, NH), 6.83 (br. s, 1 H, NH), 7.06–7.60 ppm (m, 5 H, Ar-H), as a mixture of rotamers. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.2 (2-CH_3), 22.5 (C-4), 38.9 and 41.2 (C-3, rotamers), 48.2 and 48.4 (C-5, rotamers), 65.9 and 67.0 (C-2, rotamers), 66.7 and 66.8 (PhCH_2, rotamers), 127.5, 127.8, 128.3 (Ar-C), 136.0 and 136.3 (quat. Ar-C), 154.4 and 154.7 (C=O carbamate, rotamers), 177.0 and 177.5 ppm (C=O amide, rotamers). IR (NaCl): $\tilde{\nu}$ = 3401 (amide N–H stretching), 2977 (C–H), 2874, 1691 (carbamate, amide C=O stretching), 1606 (amide, N–H bending), 1497 cm^{-1}. MS (CI+, NH_3): m/z (%) = 263 (0.20, M + H), 218 (0.40, M – $CONH_2$), 174 (0.23), 91 (1.0, PhCH_2). HMRS calculated for $C_{14}H_{19}N_2O_3$ 263.13957, found 263.13897.

Benzyl (*S*)-2-Cyano-2-methylpyrrolidine-1-carboxylate (9). Method 1: To a solution of amide **8** (1.09 g, 4.17 mmol) in dimethylformamide (14 mL) was added at 0 °C cyanuric chloride (0.58 g, 3.12 mmol) in one shot. The mixture was stirred for 3 hours, by which time it had turned yellow. Water (30 mL) was added to quench the reaction mixture, and the resultant yellow solution was extracted with EtOAc (3 × 30 mL). The combined organics were washed with water (4 × 15 mL), dried ($MgSO_4$) and evaporated to yield the title nitrile as a pale yellow oil (0.97 g, 95%). $[\alpha]_D^{20}$ = –35.58 (c = 2.08, Et_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67 and 1.76 (s, 3 H, 2-CH_3, rotamers), 1.85–2.13 (m, 3 H), 2.41–2.61 (m, 1 H), 3.36–3.55 (m, 1 H, 5-H^A), 3.55–3.75 (m, 1 H, 5-H^B), 5.06–5.32 (m,

2 H, PhCH_2), 7.26–7.54 ppm (m, 5 H, Ar-H), as a 3:2 mixture of rotamers. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.3 and 22.8 (2-CH_3, rotamers), 24.2 and 25.4 (C-4, rotamers), 40.3 and 41.6 (C-3, rotamers), 47.2 and 48.0 (C-5, rotamers), 55.1 and 55.9 (C-2, rotamers), 66.9 and 67.5 (Ph*C*H_2, rotamers), 120.7 (C≡N), 127.8, 127.9, 128.1, 128.3 (Ar-C, rotamers), 135.9 (quat. Ar-C), 153.4 ppm (C=O, carbamate), as a 2:1 mixture of rotamers. IR (NaCl): $\tilde{\nu}$ = 2979 (C–H), 2876, 2237 (C≡N), 1703 (carbamate C=O stretching), 1497 cm^{-1}. MS (EI): *m*/*z* (%) = 263 (0.05, M+), 185 (0.04), 137 (0.05), 128 (0.19, M – $PhCH_2CO_2$), 91 (1.0, $PhCH_2$). HMRS calculated for $C_{14}H_{16}N_2O_2$ 244.12118, found 244.12098.

Method 2: A solution of phosphorus oxychloride (0.18 mL) in dry dichloromethane (0.37 mL) was added at –5 °C under nitrogen to a solution of amide **8** (0.40 g, 1.53 mmol) in pyridine (1.91 mL, 0.024 mol). The mixture was stirred at –5 °C for 5 hours, after which time no starting material was detected by TLC. The mixture was poured onto ice (10 g). The resultant solution was then extracted with diethyl ether (3 × 12 mL). The combined organics were washed with saturated cupric sulfate solution (20 mL), brine (20 mL) and dried ($MgSO_4$) and evaporated to give the title nitrile as a pale yellow oil (0.308 g, 83%). The NMR spectroscopic data were identical to those obtained via method 1.

Benzyl (*S*)-2-Methyl-2-(1*H*-tetrazol-5-yl)pyrrolidine-1-carboxylate (10): To a solution of triethylamine (0.46 mL, 3.27 mmol) in dry toluene (2 mL), under an atmosphere of nitrogen, was added glacial acetic acid (0.19 mL, 3.27 mmol) and the solution was allowed to stir for two minutes. This solution was then transferred to a round-bottomed flask containing nitrile **9** (200 mg, 0.82 mmol) and sodium azide (0.21 g, 3.27 mmol) was added. The mixture was heated at reflux for 24 hours, after which time no nitrile was detected by TLC. Water (4 mL) was added and the aqueous layer was separated. The organic layer was again extracted with water, and the combined aqueous extracts were treated with 2 M HCl (3 mL). The aqueous mixture was then extracted with EtOAc (3 × 10 mL). The combined organics were dried ($MgSO_4$) and evaporated in vacuo to furnish the title tetrazole as a viscous light brown oil (225 mg, 96%). $[\alpha]_D^{18}$ = –72.30 (*c* = 2.96, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.88 and 1.90 (s, 3 H, 2-CH_3, rotamers), 1.90–2.92 (m, 4 H, rotamers), 3.54–3.82 (m, 2 H, 5-H^A and 5-H^B), 4.96 and 5.11 (m, 2 H, PhCH_2, rotamers), 6.85–7.00 and 7.10–7.41 ppm (m, 5 H, Ar-H, rotamers), as a 3:1 mixture of rotamers. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.2 and 22.6 (C-4, rotamers), 24.3 and 24.6 (2-CH_3, rotamers), 40.0 and 43.0 (C-3, rotamers), 48.3 and 48.5 (C-5, rotamers), 59.5 and 59.6 (C-2, rotamers), 67.3 and 67.5 (Ph*C*H_2, rotamers), 127.5, 128.0, 128.3, 128.4 (Ar-C, rotamers), 135.1 and 135.7 (quat. Ar-C, rotamers), 154.5 and 155.2 (C=O, carbamate, rotamers), 160.0 ppm (CN), as a 3:1 mixture of rotamers. IR (NaCl): $\tilde{\nu}$ = 3600–2400, 1702 (carbamate C=O stretching), 1548, 1411, 1354 cm^{-1}. MS (EI): *m*/*z* (%) = 287 (0.14, M+), 217 (0.07), 201 (0.06), 181 (0.06), 111 (0.12), 91 (1.0, $PhCH_2$). HMRS calculated for $C_{14}H_{17}N_5O_2$ 287.13822, found 287.13834.

(*S*)-5-(2-Methylpyrrolidin-2-yl)-1*H*-tetrazole (4): To a solution of tetrazole **10** (652 mg, 2.269 mmol) in HOAc/H_2O (9:1, 25 mL) was added 10% palladium on charcoal (65.2 mg). The mixture was placed under an H_2 atmosphere and stirred for 72 hours. The mixture was then filtered through a pad of celite and the pad washed with methanol. The volatiles were removed in vacuo and the remaining brown solution was azeotroped with acetonitrile to yield a cream solid which was recyrstallised from methanol/diethyl ether to afford the title tetrazole as a colourless solid (308 mg, 89%); m.p. 238–240 °C. $[\alpha]_D^{18}$ = –8 (*c* = 1.0, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 1.82 (s, 3 H, 2-CH_3), 2.05–2.28 (m, 3 H), 2.52–2.65 (m, 1 H), 3.39–3.52 (m, 2 H, 5-H^A and 5-H^B) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 22.6 (C-4), 23.4 (2-CH_3), 37.0 (C-3), 44.5 (C-5), 64.4 (C-2), 162.7 (CN) ppm. IR (NaCl): $\tilde{\nu}$ = 3347 (b), 2112 (b), 1646 (b), 1381 cm^{-1}. MS (EI): *m*/*z* (%) = 153 (0.08, M+), 138 (0.07, M – CH_3), 110 (0.23, M – HN_3), 84 (0.34, M – CN_4H), 43 (1.0, HN_3^+). HMRS calculated for $C_6H_{11}N_5$ 153.10145, found 153.10164.

General Procedures for the Enantioselective Direct Aldol Reaction Catalysed by Tetrazole 4

A. Under Anhydrous Conditions: A clean, dry round-bottomed flask was charged with tetrazole **4** (7.66 mg, 0.05 mmol) and the flask flushed with nitrogen and placed under an atmosphere of nitrogen. Anhydrous dimethyl sulfoxide (2 mL) was added via syringe followed by freshly distilled acetone (0.5 mL). The mixture was stirred for 5 minutes. The aldehyde (0.25 mmol) was then added in one shot. The mixture was stirred at room temperature for the reported number of hours. The mixture was quenched with saturated ammonium chloride (1 mL), after which it became warm. The mixture was diluted with water (5 mL) and transferred to a separating funnel where it was extracted with EtOAc or ether until no more product was detected in the aqueous phase by TLC. The combined organics were dried ($MgSO_4$) and evaporated in vacuo to furnish a crude brown liquid, which was purified via flash chromatography (hexane/EtOAc) to provide the aldol adduct.

B. Under Ambient Conditions: To a solution of tetrazole **4** (7.66 mg, 0.05 mmol) in dimethyl sulfoxide (2 mL) acetone (0.5 mL) was added. The mixture was stirred for 5 minutes, after which time the aldehyde (0.25 mmol) was added in one shot. The mixture was stirred at room temperature for the reported number of hours. The mixture was quenched with saturated ammonium chloride (1 mL), after which it became warm. The mixture was diluted with water (5 mL) and transferred to a separating funnel where it was extracted with EtOAc or ether until no more product was detected in the aqueous phase by TLC. The combined organics were dried ($MgSO_4$) and evaporated in vacuo to furnish a crude brown liquid, which was purified via flash chromatography (hexane/EtOAc) to provide the aldol adduct.

4-Hydroxy-4-(4-nitrophenyl)butan-2-one (16a): The ^{1}H NMR spectroscopic data was consistent with literature values.[2h] The product was obtained in 88% *ee*. The optical purity was determined via the synthesis of the corresponding Mosher ester (see below). $[\alpha]_D^{23}$ = +37.5 (*c* = 0.48, $CHCl_3$) [ref.[31] (99% *ee*). $[\alpha]_D^{22}$ = +66.2 (*c* = 0.5, $CHCl_3$)].

4-(2-Chlorophenyl)-4-hydroxybutan-2-one (16b): The ^{1}H NMR spectroscopic data was consistent with literature values.[3k] The product was obtained in 90% *ee*. The optical purity was determined by HPLC with hexane/2-propanol (95:5) as eluent; flow rate 0.5 mL/min; t_R = 24.94 min (*R*), 27.27 min (*S*). $[\alpha]_D^{23}$ 86.7 (*c* = 0.6, $CHCl_3$) [ref.[31] (96% *ee*). $[\alpha]_D^{22}$ = +101.7 (*c* = 0.58, $CHCl_3$)].

4-Hydroxy-4-(4-methoxyphenyl)butan-2-one (16c): The ^{1}H NMR spectroscopic data was consistent with literature values.[31] The product was obtained in 85% *ee*. The optical purity was determined by HPLC with hexane/2-propanol (95:5) as eluent; flow rate 0.5 mL/min; t_R = 52.87 min (*R*), 60.81 min (*S*). $[\alpha]_D^{23}$ = +30.0 (*c* = 0.4, $CHCl_3$) [ref.[32] (67% *ee*). $[\alpha]_D^{16}$ = +25.51 (*c* = 0.24, $CHCl_3$)].

4-(4-Bromophenyl)-4-hydroxybutan-2-one (16d): The ^{1}H NMR spectroscopic data was consistent with literature values.[3k] The product was obtained in 87% *ee*. The optical purity was determined by HPLC with hexane/2-propanol (93:7) as eluent; flow rate 0.5 mL/min; t_R = 38.46 min (*R*), 41.12 min (*S*). $[\alpha]_D^{23}$ = +50.9 (*c* = 0.57, $CHCl_3$) [ref.[3k] (90% *ee*). $[\alpha]_D^{18}$ = +53.3 ($CHCl_3$)].

***N*-[4-(1-Hydroxy-3-oxobutyl)phenyl]acetamide (16e):** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.17 (s, 3 H), 2.20 (s, 3 H), 2.73–2.93 (m, 2 H), 3.29 (br. s, 1 H), 5.00–5.19 (m, 1 H), 7.30 (d, J = 8.5 Hz, 2 H), 7.47 (d, J = 8.5 Hz, 2 H) ppm. The product was obtained in 70% *ee*. The optical purity was determined by HPLC with hexane/2-propanol (90:10) as eluent; flow rate 0.5 mL/min; t_R = 100.40 min (*R*), 108.86 min (*S*). $[a]_D^{23}$ = +15.9 (c = 0.44, $CHCl_3$) [ref.[2h] (69% *ee*). $[a]_D$ +12.5 (c = 1, $CHCl_3$)].

4-Hydroxy-4-(2-naphthyl)butan-2-one (16f): The ^{1}H NMR spectroscopic data was consistent with literature values.[2h] The product was obtained in 81% *ee*. The optical purity was determined by HPLC with hexane/2-propanol (95:5) as eluent; flow rate 0.5 mL/min; t_R = 94.46 min (*R*), 109.57 min (*S*). $[a]_D^{23}$ = +40.0 (c = 0.5, $CHCl_3$) [ref.[27] (74% *ee*). $[a]_D^{20}$ = +34.8 (c = 0.525, $CHCl_3$)].

4-Hydroxy-4-phenylbutan-2-one (16g): The ^{1}H NMR spectroscopic data was consistent with literature values.[3k] The product was obtained in 80% *ee*. The optical purity was determined by HPLC with hexane/2-propanol (93:7) as eluent; flow rate 0.5 mL/min; t_R = 39.13 min (*R*), 42.51 min (*S*). $[a]_D^{23}$ = +31.1 (c = 0.45, $CHCl_3$) [ref.[33] (96% *ee*). $[a]_D^{20}$ = +59.7 (c = 1.7, $CHCl_3$)].

4-(4-Chlorophenyl)-4-hydroxybutan-2-one (16h): The ^{1}H NMR spectroscopic data was consistent with literature values.[3k] The product was obtained in 86% *ee*. The optical purity was determined by HPLC with hexane/2-propanol (96:4) as eluent; flow rate 0.5 mL/min; t_R = 42.03 min (*R*), 45.77 min (*S*). $[a]_D^{23}$ = +73.0 (c = 0.49, $CHCl_3$) [ref.[33] (83% *ee*). $[a]_D^{27}$ = +53.5 (c = 1.0, $CHCl_3$)].

4-Hydroxy-4-(2-nitrophenyl)butan-2-one (16i): The ^{1}H NMR spectroscopic data was consistent with literature values.[3f] The product was obtained in 91% *ee*. The optical purity was determined by HPLC with hexane/2-propanol (97:3); flow rate 0.5 mL/min; t_R = 80.84 min (*R*), 84.87 min (*S*). $[a]_D^{23}$ –141.0 (c = 0.546, $CHCl_3$) [ref.[33] (75% *ee*). $[a]_D^{27}$ –108.2 (c = 1.2, $CHCl_3$)].

4-Hydroxy-4-(3-nitrophenyl)butan-2-one (16j): The ^{1}H NMR spectroscopic data was consistent with literature values.[3k] The product was obtained in 90% *ee*. The optical purity was determined by HPLC with hexane/2-propanol (97:3) as eluent; flow rate 0.5 mL/min; t_R = 120.49 min (*R*), 129.38 min (*S*). $[a]_D^{23}$ = +65.9 (c = 0.44, $CHCl_3$) [ref.[3k] (87% *ee*). $[a]_D^{20}$ = +62.1 ($CHCl_3$)].

Procedures for the Synthesis of the Mosher Ester of Adduct 16a: To a solution of (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (15.11 mg, 0.065 mmol) in dry dichloromethane (0.3 mL) was added aldol adduct **16a** (9 mg, 0.043 mmol) and DMAP (1.05 mg, 0.0086 mmol). The mixture was stirred and cooled to 0 °C and dicyclohexylcarbodiimide (22.18 mg, 0.11 mmol) was added. The mixture was stirred overnight, at room temperature, after which time the TLC indicated complete consumption of the starting material. The reaction mixture was filtered, the filtrate was then evaporated in vacuo, the residue dissolved in diethyl ether (4 mL). The solution was washed with 0.5 N HCl (2 × 2 mL), saturated $NaHCO_3$ (2 × 2 mL), dried ($MgSO_4$) and evaporated to yield the Mosher ester as a yellow residue which was directly subjected to ^{1}H NMR analysis: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.09 and 2.17 (s, 3 H, CH_3), 2.80 (dd, J = 3.8, 17.8 Hz, 1 H, CH_2), 3.20 (dd, J = 9.4, 17.8 Hz, 1 H, CH_2), 3.51 (s, 3 H, OMe), 6.41 (dd, J = 4.0, 9.2 Hz, 1 H, CH) and 6.5 (dd, CH), 7.29–7.41 (m, 5 H, Ph-H), 7.70 (d, J = 9.0 Hz, 1 H, $ArNO_2$-H), 8.16 (d, J = 8.6 Hz, 2 H, $ArNO_2$-H), 8.26 ppm (d, J = 9.0 Hz, 1 H, $ArNO_2$-H).

Supporting Information (see also the footnote on the first page of this article): Experimental details, ^{1}H NMR and ^{13}C NMR spectra for all new compounds. ^{1}H NMR spectra and HPLC traces for all aldol adducts.

Acknowledgments

We wish to thank the New Zealand Government for the NZ International Doctoral Research Scholarship (STT) and the University of Auckland for financial assistance.

[1] M. Gaunt, C. Johansson, A. McNally, N. Vo, *Drug Discovery Today* **2007**, *12*, 8–27.

[2] Examples of asymmetric aldol reactions catalysed by proline: a) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496–497; b) Z. Hajos, D. Parrish, *J. Org. Chem.* **1974**, *39*, 1615–1621; c) B. List, R. Lerner, C. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396; d) W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386–7387; e) C. Pidathala, L. Hoang, N. Vignola, B. List, *Angew. Chem. Int. Ed.* **2003**, *42*, 2785–2788; f) B. List, P. Pojarliev, C. Castello, *Org. Lett.* **2001**, *3*, 573–575; g) N. Mase, F. Tanaka, C. Barbas III, *Angew. Chem. Int. Ed.* **2004**, *43*, 2420–2423; h) K. Sakthivel, W. Notz, T. Bui, C. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267; i) J. Suri, D. Ramachary, C. Barbas III, *Org. Lett.* **2005**, *7*, 1383–1385; j) R. Thayumanavan, F. Tanaka, C. Barbas III, *Org. Lett.* **2004**, *6*, 3541–3544; k) A. Cordova, W. Notz, C. Barbas III, *J. Org. Chem.* **2002**, *67*, 301–303; l) A. Cordova, W. Notz, C. Barbas III, *Chem. Commun.* **2002**, 3024–3025; m) A. Northrup, D. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799; n) A. Bogevig, N. Kumaragurubaran, K. A. Jorgensen, *Chem. Commun.* **2002**, 620–621; o) A. Nyberg, A. Usano, P. Pihko, *Synlett* **2004**, *11*, 1891–1896; p) G. Szollosi, G. London, L. Balaspiri, C. Somlai, M. Bartok, *Chirality* **2003**, *15*, S90–S96; q) T. Bui, C. Barbas III, *Tetrahedron Lett.* **2000**, *41*, 6951–6954; r) P. M. Pihko, K. M. Laurikainen, A. Usano, A. I. Nyberg, J. A. Kaavi, *Tetrahedron* **2006**, *62*, 317–328; s) Y. Hayashi, S. Aratake, T. Itoh, T. Okano, T. Sumiya, M. Shoji, *Chem. Commun.* **2007**, 957–959.

[3] Examples of asymmetric aldol reactions catalysed by proline-based organocatalysts: a) A. Hartikka, P. Arvidsson, *Tetrahedron: Asymmetry* **2004**, *15*, 1831–1834; b) A. Hartikka, P. Arvidsson, *Eur. J. Org. Chem.* **2005**, 4287–4295; c) H. Torri, M. Nakadai, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem. Int. Ed.* **2004**, *43*, 1983–1986; d) A. Berkessel, B. Koch, J. Lex, *Adv. Synth. Catal.* **2004**, *346*, 1141–1146; e) S. S. Chimni, D. Mahajan, *Tetrahedron: Asymmetry* **2006**, *17*, 2108–2119; f) Y.-Q. Fu, Z.-C. Li, L.-N. Ding, J.-C. Tao, S.-H. Zhang, M.-S. Tang, *Tetrahedron: Asymmetry* **2006**, *17*, 3351–3357; g) S. Guizzetti, M. Benaglia, L. Pignataro, A. Puglisi, *Tetrahedron: Asymmetry* **2006**, *17*, 2754–2760; h) L. He, J. Jiang, Z. Tang, X. Cui, A.-Q. Mi, Y.-Z. Jiang, L.-Z. Gong, *Tetrahedron: Asymmetry* **2007**, *18*, 265–270; i) M. Nakadai, S. Saito, H. Yamamoto, *Tetrahedron* **2002**, *58*, 8167–8177; j) Z. Tang, F. Jiang, X. Cui, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, Y.-D. Wu, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5755–5760; k) Z. Tang, F. Jiang, L.-T. Yu, X. Cui, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, Y.-D. Wu, *J. Am. Chem. Soc.* **2003**, *125*, 5262–5263; l) Z. Tang, Z.-H. Yang, X.-H. Chen, L.-F. Cun, A.-Q. Mi, Y.-Z. Jiang, L.-Z. Gong, *J. Am. Chem. Soc.* **2005**, *127*, 9285–9289; m) M. Vishnumaya, S. Ginotra, V. Singh, *Org. Lett.* **2006**, *8*, 4097–4099; n) X.-Y. Xu, Y.-Z. Wang, L.-F. Cun, L.-Z. Gong, *Tetrahedron: Asymmetry* **2007**, *18*, 237–242.

[4] M. Engqvist, J. Casas, H. Sunden, I. Ibrahem, A. Cordova, *Tetrahedron Lett.* **2005**, *46*, 2053–2057.

[5] A. Cordova, H. Sunden, M. Engqvist, I. Ibrahem, J. Casas, *J. Am. Chem. Soc.* **2004**, *126*, 8914–8915.

[6] N. Vignola, B. List, *J. Am. Chem. Soc.* **2004**, *126*, 450–451.

[7] A. Cobb, D. Shaw, S. Ley, *Synlett* **2004**, *3*, 558–560.

[8] A. J. Cobb, D. M. Shaw, D. Longbottom, J. Gold, S. V. Ley, *Org. Biomol. Chem.* **2005**, *3*, 84–96.

[9] A. J. Cobb, D. Longbottom, D. M. Shaw, S. V. Ley, *Chem. Commun.* **2004**, 1808–1809.

[10] N. Momiyama, H. Torri, S. Saito, H. Yamamoto, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5374–5378.
[11] Y. Yamamoto, N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 5962–5963.
[12] M. Arno, R. J. Zaragoza, L. Domingo, *Tetrahedron: Asymmetry* **2005**, *16*, 2764–2770.
[13] B. List, L. Hoang, H. Martin, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5839.
[14] D. Seebach, M. Boes, R. Naef, W. Schweizer, *J. Am. Chem. Soc.* **1983**, *105*, 5390–5398.
[15] F. Orsinni, F. Pelizzoni, M. Forte, M. Sisti, G. Bombieri, F. Benetollo, *J. Heterocycl. Chem.* **1989**, *26*, 837–841.
[16] F. Orsinni, F. Pelizzoni, M. Forte, R. Destro, P. Gariboldi, *Tetrahedron* **1988**, *44*, 519–541.
[17] G. Rizzi, *J. Org. Chem.* **1970**, *35*, 2069.
[18] H. Wang, J. Germanas, *Synlett* **1999**, 33–36.
[19] A. Beck, S. Job, D. Seebach, T. Sommerfeld, *Org. Synth., Coll. Vol.* **1998**, *9*, 626.
[20] K. Koguro, T. Oga, S. Mitsui, R. Orita, *Synthesis* **1998**, 910–914.
[21] R. G. Almquist, W.-R. Chao, C. Jennings-White, *J. Med. Chem.* **1985**, *28*, 1067–1071.
[22] S. Shatzmiller, B.-Z. Dolithzky, E. Bahar, *Liebigs Ann. Chem.* **1991**, 375–379.
[23] P. Harris, M. Brimble, V. Muir, M. Lai, N. Trotter, D. Callis, *Tetrahedron* **2005**, *61*, 10018–10035.
[24] N. Mase, F. Tanaka, C. Barbas III, *Angew. Chem. Int. Ed.* **2004**, *43*, 2420–2423.
[25] T. Dickerson, K. Janda, *J. Am. Chem. Soc.* **2002**, *124*, 3220–3221.
[26] M. Hosseini, N. Tiasni, V. Barbieri, C. O. Kappe, *J. Org. Chem.* **2007**, *72*, 1417–1424.
[27] S. Mosse, A. Alexakis, *Org. Lett.* **2006**, *8*, 3577–3580.
[28] It is postulated the incorporation of the α-methyl group in **4** alters the conformation of the pyrrolidine ring such that the cyclic secondary amine and the acidic tetrazole proton are optimally positioned to act as an organocatalyst.
[29] C.-O. Chan, C. Cooksey, D. Crich, *J. Chem. Soc. Perkin Trans. 1* **1992**, 777–780.
[30] C. Overberger, Y. Jon, *J. Polym. Sci.: Polymer Chem. Edition* **1977**, *15*, 1413–1421.
[31] S. Chandrasekhar, N. Ramakrishna Reddy, S. Shameem Sultana, Ch. Narsihmulu, K. Venkatram Reddy, *Tetrahedron* **2006**, *62*, 338–345.
[32] Y. Zhou, Z. Shan, *Tetrahedron* **2006**, *62*, 5692–5696.
[33] Y. Zhou, Z. Shan, *Tetrahedron: Asymmetry* **2006**, *17*, 1671–1677.

Received: September 6, 2007
Published Online: November 15, 2007

