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Heterogeneous catalysis of the asymmetric aldol reaction by solid-supported proline-terminated peptides

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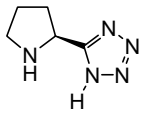
Abstract—Peptides with prolyl N-termini, attached to a PEG–polystyrene (TG) synthesis resin, have been tested as heterogeneous catalysts for the aldol reaction between acetone and *p*-nitrobenzaldehyde. Proline directly attached to TG showed good activity but poor enantioselectivity. However, in combination with serine or threonine, the selectivity improved considerably. At −25 °C, the dipeptide H-Pro-Ser-NH-TG achieved 82% ee. The H-Pro-Ser/Thr dipeptides may be seen as self-contained 'catalytic head-groups' for the development of more sophisticated aldol organocatalysts.

1. Introduction

Organocatalysis via enamine intermediates has proven to be an effective strategy in asymmetric synthesis.[1] The proline-catalysed intramolecular aldol reaction (the Hajos–Parrish–Eder–Sauer–Wiechert reaction) stood for many years as an elegant, classical example of enantioselective catalysis.[2] Recently, the scope was extended through the discovery of an intermolecular version, by List et al.,[3] and since then the field has developed at pace. Proline **1**, and other chiral pyrrolidines, have been used for the enantioselective catalysis of a wide range of aldol reactions[4] as well as Mannich reactions,[5] conjugate additions[6] and a variety of oxidative transformations.[7] The reactions proceeded via enamine intermediates, as in Scheme 1 for the proline-catalysed aldol addition. An important feature in most cases is a hydrogen bond between an acidic proton in the catalyst and an acceptor atom in the substrate. In transition state **2**, the H-bond donor is the proline carboxyl unit, while the acceptor is the carbonyl oxygen. The carboxyl can be replaced by other groups as in pyrrolidines **3**,[4e,8] **4**[9] and **5**.[4b,10] However in simple amides such as **6**[4b] it seems that the CONH is insufficiently acidic, and these molecules are therefore less effective.

This requirement for an acidic proton places two limitations on the development of proline-based catalysts. Firstly, it is useful to immobilise catalysts on insoluble polymers, so that they can be easily recovered.[11] However, if proline is attached to a resin via its carboxyl group, the ester or amide linkage will not promote enantioselective catalysis.[12] Secondly, there is potential for creating more complex catalysts, perhaps with enzyme-like features, by using proline to acylate larger architectures (e.g., peptides). Again, immobilisation is useful as it allows the preparation and screening of large libraries of catalysts, for example, of form **7**.[13] Unfortunately, most such structures will lack acidic protons and should therefore be less active than proline itself.[14]



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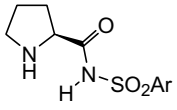

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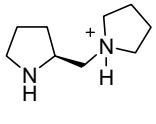

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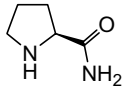

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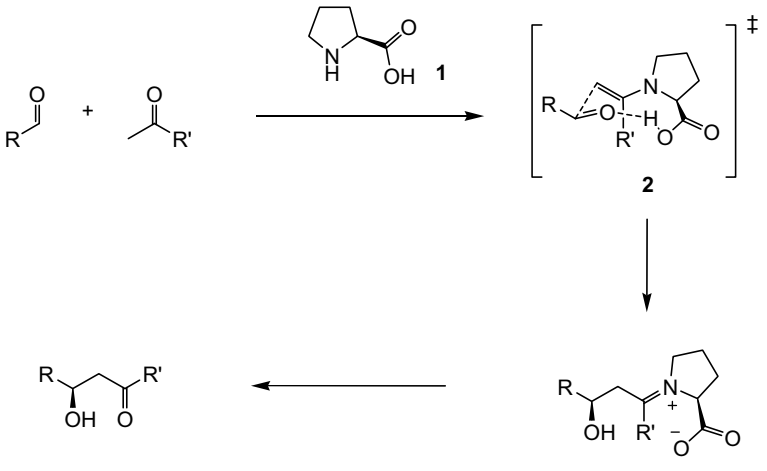
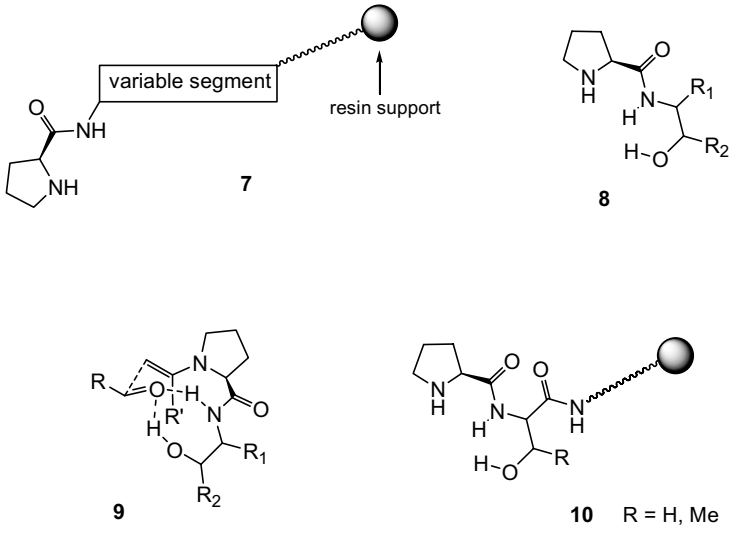


Scheme 1.



In the context of our work on combinatorial catalysis,[13f–h] we sought to address these problems. Specifically, we required a self-contained catalytic unit, which could transform a polymer-bound amino-derivatised scaffold into a 'synthetic aldolase'. Prolinamide, as in **7**, seemed unpromising as discussed above. However, Gong and Wu et al. had found that hydroxyprolinamides of general form **8** show good activity and enantioselectivity.[15] Presumably the hydroxy group forms a second hydrogen bond to the carbonyl oxygen in the aldol transition state **9**, reinforcing the effect of the NH and restoring activity. The polymer-bound Pro-Ser/Thr dipeptides **10** conform to **8** and we therefore decided to test these units for catalytic activity. We herein report that they are indeed effective enantioselective catalysts for the direct aldol. The results confirm the potential of these combinations as general 'catalytic head-groups', and demonstrate a practical method for performing enantioselective aldol additions with heterogeneous polymer-bound organocatalysts.

2. Results and discussion

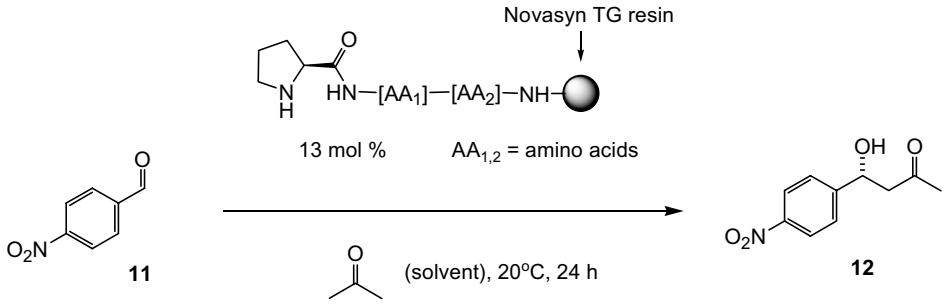
Peptides were synthesised on Novasyn TG amino resin, an amine-terminated PEG–polystyrene graft copolymer chosen for its compatibility with a wide range of solvents.[16] Standard Fmoc-based methodology was employed, using HBTU, HOBt and DIPEA as coupling reagents. Between each coupling step any remaining free amino functions were capped with acetic acid anhydride before Fmoc deprotection of the terminal amino acid. The side-chain protection was removed with 5% TFA in dichloromethane.

The sequences listed in Table 1 were synthesised and tested as catalysts for the addition of acetone (used as solvent) to *p*-nitrobenzaldehyde **11**, to give hydroxyketone **12** (Scheme 2). Reactions were allowed to run for 24 h at room temperature (20 °C) in the presence of 13 mol % of resin-bound catalyst. Control experiments established that no conversion took place in the absence of the catalyst, or in the presence of *N*-acetylated resin.

Table 1. Catalysis of the direct aldol reaction between **11** and acetone by resin-bound peptides[a]

Entry	Catalyst	Yield (%)[b]	ee (%)[c]
1	H-Pro-NH-TG	93	30
2	H-Pro-Ala-NH-TG	78	22
3	H-Pro-Ser-NH-TG	94	63
4	H-Pro-D-Ser-NH-TG	87	68
5	H-Pro-Thr-NH-TG	Quantitative	60
6	H-Pro-D-Thr-NH-TG	87	61
7	H-Pro-Cys-NH-TG	89	51
8	H-Pro-Ser-Phe-NH-TG	22	77
9	H-Pro-Ser-Trp-NH-TG	13	76
10	H-Pro-Ser-Tyr-NH-TG	29	75

[a] For conditions and general catalyst structure, see Scheme 2.
[b] Determined by HPLC, with internal standard.
[c] Determined by HPLC on Chiralpak-AS-H. The *R* product **12** was preferred in each case.



Scheme 2.

The results of the trials (yields and enantioselectivities) are summarised in Table 1. An initial experiment employing resin-bound L-proline revealed, unexpectedly that activity was quite high (entry 1).[17] However, the enantioselectivity was poor. A number of dipeptides were then tested (entries 2–7). The Pro-Ala combination behaved similarly to that of proline but, as hoped, the dipeptides incorporating serine or threonine were more successful. The enantiomeric excesses, at 60–70%, were in the range achieved by soluble hydroxyprolinamides **8** for the same reaction under similar conditions.[15] Differences between the four combinations were small, but Pro-D-Ser gave slightly higher selectivity. Yields were good throughout. Pro-Cys was appreciably less selective, but still an improvement over Pro-Ala.

As a first move towards more complex catalysts, three tripeptides were also tested (entries 8–10). Modelling suggested that an aromatic side chain in AA_2 (Scheme 2) could make favourable π–π contacts with aromatic aldehyde substrates, so variants incorporating phenylalanine, tryptophan and tyrosine were explored. In the event, selectivities were increased slightly but yields were lowered. The tripeptides may fold in such a way as to reduce activity, perhaps by restricting access to the proline nitrogen. Though disappointing, the results illustrate the potential of Pro-Ser, etc. as catalytic head-groups in wider-ranging studies.

To extract the optimum performance from a catalyst it is necessary to optimise procedures, by varying solvents, temperatures and reaction times. It was therefore of interest to test a TG-bound catalyst under a range of conditions, firstly to maximise selectivity and secondly to explore its compatibility with different media. The addition of acetone to **11**, catalysed by H-Pro-Ser-NH-TG, was investigated in a number of solvents and at several temperatures. The results are summarised in Table 2. Entry 1 is notable, in that it confirms that the catalyst can operate in aqueous conditions.[18] Catalysis seems to be very efficient, although the selectivity is low. Performance in DMSO/acetone was acceptable, but DMF and CH_2Cl_2 were unsuitable as co-solvents. Entries 5 and 6 show that the polymer-bound catalyst may be used at reduced temperatures, and that this improves enantioselectivity. At −25 °C, an enantiomeric excess of 82% was achieved. However, a further decrease in temperature to −45 °C proved unproductive (entry 7).

Finally, to investigate the role of the polymer support, the Pro-Ser dipeptide was synthesised on aminomethyl polystyrene (PS) resin. The product H-Pro-Ser-NH-PS was tested as catalyst for the aldol, following the method shown in Scheme 2 and Table 1. Product **12** was formed in 60% enantiomeric excess, but only in 26% yield. Thus a change from TG to PS had little effect on the enantioselectivity, but did substantially lower the reaction rate. The reason for the reduced activity is unclear at present, but may be connected with the apolar, hydrophobic environment provided by the PS.[19]

Table 2. Catalysis of **11** + acetone → **12** by H-Pro-Ser-NH-TG

Entry	Solvent	Temperature (°C)	Time (h)	Conversion (%)	ee (%)
1	Acetone/water (1:1)	20	16	Quantitative	22
2	DMSO/acetone (4:1)	20	16	70	59
3	DMF/acetone (4:1)	20	16	<10	39
4	CH_2Cl_2/acetone (4:1)	20	16	<4	n.d.[a]
5	Acetone	−15	72	>98	71
6	Acetone	−25	41	>98	82
7	Acetone	−45	48	35	68

Effects of temperature and solvent.
[a] Not determined.

3. Conclusion

In conclusion, we have shown that peptides with Pro-Ser/Thr N-termini, bound to a PEG–polystyrene insoluble polymer, can act as heterogeneous enantioselective catalysts for the aldol addition. Catalyst loadings, yields and enantioselectivities are comparable to those for soluble analogues.[15] This research points the way towards the development of more sophisticated aldol catalysts through solid phase parallel synthesis and on-bead screening.

4. Experimental

4.1. General

Synthesis resins were bought from Nova Biochem. UV/vis spectra were recorded on a Thermo Helios γ spectrometer and processed with Vision Pro 1.0 software. Analytical HPLC was performed using an Anachem Gilson Model 156 with Unipoint Version 3.01 software. All conversions were estimated by the comparison of the product peak areas to the sum of all peak areas. (4*R*,4*S*)-Hydroxy-4-(4′-nitrophenyl)butan-2-one *rac*-**12** was prepared according to a literature procedure.[20] Solid phase peptide synthesis was performed in plastic syringes with agitation on a blood tube rotator. The amino acids used were all Fmoc protected. The amino acids Ser, Cys and Thr carried trityl side-chain protection, Tyr was O–*t*-Bu protected.

4.2. Solid phase peptide synthesis general protocol

All peptides were synthesised manually using Nova Syn TG amino resin (HL, 110 μm beads, loading = 0.45 mmol g^{-1} or LL, 130 μm beads, loading = 0.29 mmol g^{-1}) or aminomethyl polystyrene resin HL (loading = 1.3 mmol g^{-1}). Three equivalents of *N*-α-9-fluorenylmethoxycarbonyl amino acids were used in each coupling step. The amino acids were activated in *N*,*N*,-dimethylformamide by the addition of two coupling solutions. Coupling solution **1** was prepared by dissolving *N*-[(1*H*-benzotriazolo-1-yl)(dimethylamino)methylene]-*N*-methylmethanaminium tetrafluoroborate *N*-oxide (HBTU) (3.00 equiv) and 1-hydroxybenzotriazole (HOBT) (3.00 equiv) in *N*,*N*-dimethylformamide (0.5 ml). The second solution consisted of diisopropylethyl amine (3.00 equiv) in *N*,*N*-dimethylformamide (0.5 ml). After an activation time of 3 min, the activated amino acids were added to the pre-swollen resin in *N*,*N*-dimethylformamide (1 ml) and agitated overnight. The resin was then filtered, washed with *N*,*N*-dimethylformamide (3 × 10 ml), methanol (3 × 10 ml) and dichloromethane (3 × 10 ml) and dried under high vacuum. The extent of coupling was monitored visually by the use of the NF31 test.[21] If the test revealed unreacted NH_2 groups (beads stained red), the reaction was repeated. Before the coupling of a new amino acid, the beads were treated with pyridine and acetic acid anhydride in dry dichloromethane to cap the remaining free amino functions. Typically, the resin was suspended in dry DCM (2.8 ml), at which point pyridine (0.17 ml, 2.18 mmol) and acetic anhydride (0.17 ml, 1.80 mmol) were added, and the mixture agitated overnight. After removal of the solution, the beads were washed with DMF (3 × 10 ml), methanol (3 × 10 ml) and DCM (3 × 10 ml). The 9-fluorenylmethoxycarbonyl protecting group was removed after each cycle by shaking with 20% piperidine in *N*,*N*-dimethylformamide. Typically the resin was treated with piperidine in *N*,*N*-dimethylformamide (20%, 2 ml), agitated for 30 min and isolated by filtration. This process was repeated twice, agitating for 30 min in the first case and 2 h in the second. After removal of the solution the beads were washed with DMF (3 × 10 ml), methanol (3 × 10 ml) and DCM (3 × 10 ml). The acid labile protecting groups were deprotected after the addition of the last amino acid by treatment of the beads with 5% trifluoroacetic acid in dichloromethane containing 5% of triisopropylsilane for 1.5 h. Typically the resin was treated with a solution of TFA (5 vol %) and triisopropylsilane (5 vol %) in dry DCM (2 ml), agitated for 30 min and isolated by filtration. This process was repeated twice, agitating for 30 min in the first case and 3 h in the second. After removal of the solution the beads were washed with DMF (3 × 10 ml), methanol (3 × 10 ml) and DCM (3 × 10 ml).

4.3. Preparation of *N*-acetylated TG resin

Nova Syn TG amino resin (HL, 110 μm beads, loading = 0.45 mmol g^{-1}, 100 mg) was suspended in 2.8 ml dry dichloromethane and acetic anhydride (170 μl, 1.80 mmol) and pyridine (170 μl, 2.18 mmol) then added. The mixture was agitated overnight. The resin was then filtered, washed with DMF (3 × 10 ml), methanol (3 × 10 ml) and DCM (3 × 10 ml) and dried under high vacuum.

Table 3. Loadings determined for polymer bound peptide catalysts

Peptide	Loading (mmol g^{-1})
TG-Ser-Pro	0.24
TG-D-Ser-Pro	0.25
TG-Thr-Pro	0.30
TG-D-Thr-Pro	0.28
TG-Ala-Pro	0.20
TG-Cys-Pro	0.25
TG-Pro	0.17
TG-Phe-Ser-Pro	0.35
TG-Phe-D-Ser-Pro	0.34
TG-Trp-Ser-Pro	0.43
TG-Tyr-Ser-Pro	0.36

4.4. Estimation of peptide loading

The loading of the peptides on the resin was determined by UV spectroscopy of the soluble by-product from the final Fmoc deprotection step. 9-Fluorenylmethoxycarbonyl-amino acid resin (~3 mg, weighed accurately) was placed in a 5 ml sample tube and freshly prepared 20% piperidine in *N*,*N*,-dimethylformamide added. The resin was agitated for 20–30 min. Three millilitres of the solution was transferred into a UV cell and the absorbance at 290 nm was read. The loading on the resin in mmol g^{-1} was obtained from the expression $(Abs_{sample} - Abs_{ref})/(1.65 \times mg \text{ of resin})$.[22] Results are given in Table 3.

4.5. General procedure for aldol reactions between 4-nitrobenzaldehyde 11 and acetone (no added solvent)

In a 2 ml vial, 4-nitrobenzaldehyde **11** (7.60 mg, 0.05 mmol) and polymer-supported catalyst (13 mol %) were mixed with 600 μl of acetone (470 mg, 8.2 mmol, 160 equiv). For experiments at room temperature, the mixture was agitated using a blood tube rotator. For reactions at reduced temperature, the vials were suspended in a cold bath and the mixture stirred with a magnetic follower. At the end of the experiment, samples (30 μl) were withdrawn and diluted with 1 ml isopropanol/*n*-hexane (1:9). Conversions and enantiomeric excesses were determined by HPLC [Daicel Chiralpak-AS-H, isopropanol/*n*-hexane (1:9), 1.3 ml/min]. Quantification was performed using naphthalene as the internal standard. Retention times (t_R, min): 4-nitrobenzaldehyde **11**, 22.0; (*R*)-4-hydroxy-4-(4-nitrophenyl)butan-2-one **12**, 25.3; (*S*)-4-hydroxy-4-(4-nitrophenyl) butan-2-one *ent*-**12**, 32.3. In some cases, the by-product (*E*)-4(4′-nitrophenyl)-2-oxo-3-butene was detected at $t_R = 37.5$. Assignment of the absolute configuration was made by comparison with the literature data.[15] Each experiment was repeated, giving self-consistent yields and enantiomeric excesses.

4.6. General procedure for aldol reactions between 4-nitrobenzaldehyde 11 and acetone, catalysed by H-Pro-Ser-NH-TG, in the presence of co-solvents

A stock solution of 4-nitrobenzaldehyde **11** (63 mg, 0.42 mmol) in acetone (1.00 ml) was prepared. In a 2 ml vial, a portion of this solution (120 μl 7.60 mg 4-nitrobenzaldehyde **11**, 0.05 mmol) was mixed with 27 mg (13 mol %) of H-Pro-Ser-NH-TG and an appropriate volume of co-solvent to give the media listed in Table 2 (entries 1–4). The mixture was agitated at room temperature using a blood tube rotator for 24 h. Samples were withdrawn and analysed by HPLC as described above.

Acknowledgements

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