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Pyroglutamate-derived hydroxyamide ligands: synthesis and application to asymmetric catalysis

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ABSTRACT

The synthesis of a series of chiral hydroxy amide ligands is described. These ligands were used in a ruthenium-catalysed transfer hydrogenation reaction where one ligand gave the product in 72% ee. The ligands were also used in two titanium-catalysed reactions, an alkylation where ee's of up to 74% were achieved and a phenyl acetylene addition where more modest selectivities were observed.

1. Introduction

Chiral β-hydroxyamides are commonly prepared as intermediates in the synthesis of, amongst others, oxazoline or bis-oxazoline ligands.[1–3] They may be synthesised in a relatively facile manner from an amino alcohol and a carboxylic acid derivative. Despite the large number that have been reported and their synthetic availability, their utilisation as ligands in their own right is underexplored.

A relatively small number of individual reports have appeared in the literature indicating that ligands of this type form the basis of selective catalysts in borane reductions,[4,5] transfer hydrogenations,[6] alkylation[7] and alkynylation[8,9] of carbonyl compounds, allylation[10] and Michael addition reactions.[11] The ligands have been used in complexes with titanium,[12,8,9] chromium[10] and ruthenium.[6] They have also been used as organocatalysts in reactions such as the kinetic resolution of alcohols via selective esterification[13,14] and the reduction of imines with silanes.[15]

We have an ongoing interest in the use of amide-based ligands in asymmetric catalysis and the amide functionality is the key to our UNIFIDE and CROSIDE ligands.[16] We have in the past and again herein used the cyclic amide L-pyroglutamic acid as a readily available source of chirality.[17]

2. Results and discussion

2.1. Synthesis of ligands

We have synthesised four new hydroxyamide ligands from the methyl ester of pyroglutamic acid and four different amino alcohols (Scheme 1). The reaction was conducted using 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD)[18] to give the target ligands directly in reasonable yield.

2.2. Ruthenium-catalysed hydrogenation

We initially applied these ligands to the ruthenium-catalysed transfer hydrogenation reduction of a ketone to a secondary alcohol. Enantioselective reductions of this type which employ very mild conditions are widely used from small to large scale synthesis. We thought our ligands may be particularly suited to this reaction because Adolfsson had found that his 'pseudo' dipeptide ligands (Fig. 1) needed to have their N terminus protected by a Boc group for the reaction to be successful.[19,6] In our case the amide of the pyroglutamate would not need to be protected.

The transfer hydrogenation reactions did indeed work, giving the reduced product, albeit, in modest yield (Table 1). The enantioselectivity of the reaction was found to be very dependent on the nature of the substituent on the ligand. The phenyl and benzyl substituted ligands **1** and **3** giving enantioselectivities of 50% and 72%, respectively, which, in the context of this reaction, represents a significant starting point for further ligand development.[20]

2.3. Alkylation of benzaldehyde

We next used the ligands in the titanium-catalysed alkylation of benzaldehyde with diethylzinc. This reaction is a typical catalytic asymmetric benchmark reaction that has been has been carried out in an enantioselective manner using many different ligands.[21] Titanium-based catalyst systems have been found to be both efficient and selective.

The alkylation reaction was again conducted using all four ligands (Table 2). In all cases conversion was high but we only achieved a significant enantioselectivity in the case of ligand **1** where an ee of 74% was achieved. Hydroxyamides have been used as ligands in this reaction in the past. In that case a wide variety of bishydroxyamides were used and the highest enantioselectivity

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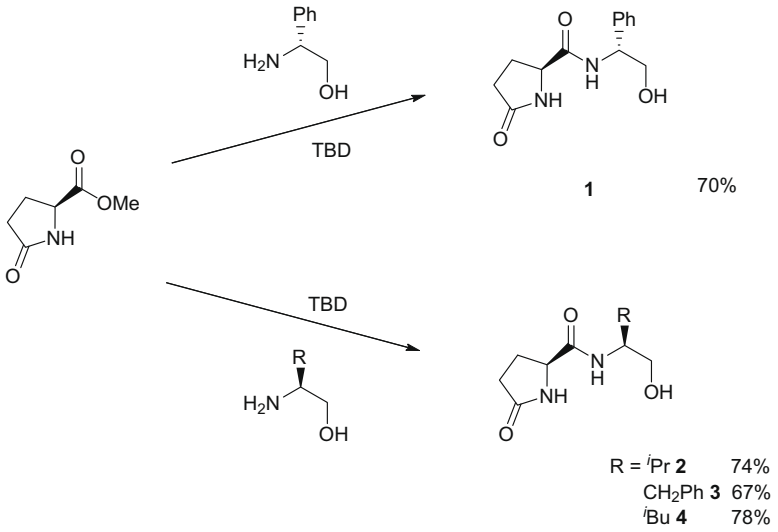


Scheme 1. Synthesis of the ligands **1**–**4** used in this study.

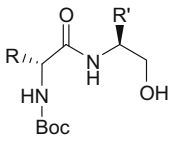


Figure 1. Boc-protected ligands reported by Adolfsson.

achieved was 58%.[7] These bishydroxyamides were found to give better selectivities with other aldehydes particularly aliphatic aldehydes and we are currently exploring our ligands' behaviour with a wide variety of starting materials. It is interesting to note that the most selective catalyst is that derived from the (*R*)-amino alcohol and the (*S*)-pyroglutamic acid. We are continuing to investigate if ligands with this stereochemistry are generally more selective in this reaction.

2.4. Alkynylation of benzaldehyde

The final reaction we report here is the alkynylation reaction of benzaldehyde using phenylacetylene as reported by Hui et al. (Table 3).[8,9]

In this reaction the activity was again quite good with high yields being obtained. The enantioselectivity achieved in this reaction was quite poor regardless of the ligand used. The benzyl-substituted ligand gave the highest selectivity at 34% ee.

3. Conclusions

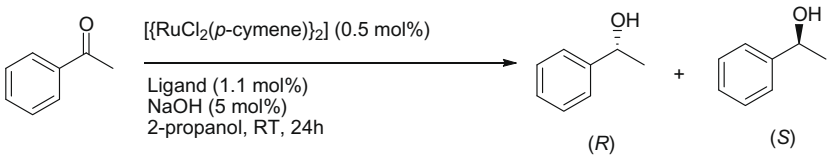
We have succeeded in generating new ligands in a facile manner from the readily available L-pyroglutamic acid and a variety of amino alcohols. These hydroxyamide ligands were successfully used to induce enantioselectivity in three asymmetric transformations. Though the selectivities achieved were good, at 74% ee, there is still quite some scope for improvement. We are currently investigating other applications of these ligands. In addition by establishing the structure–activity relationships in the transformations we have studied to date we hope to deduce the nature of the active species.

4. Experimental

4.1. General information

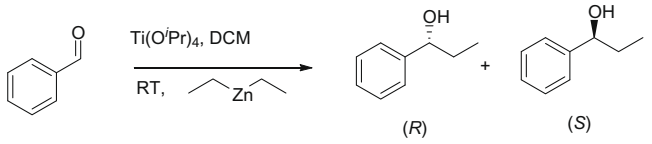
All reactions were conducted under a nitrogen atmosphere. Methyl (2*S*)-5-oxopyrrolidine-2-carboxylate[16] and the amino alcohols[22] were synthesised using literature procedures. All other chemicals were purchased from Aldrich Chemical Company and generally used without further purification. Any necessary reagent purification, along with the drying and distillation of solvents, was carried out according to literature procedures.[23] Melting points were measured on a Stuart Scientific SMP3 apparatus. IR spectra were measured on a Perkin–Elmer Spectrum 1000 FT-IR, or a Perkin–Elmer Spectrum One FT-IR. Optical rotations were measured

Table 1
Ruthenium-catalysed hydrogen transfer using hydroxyamide ligands **1**–**4**



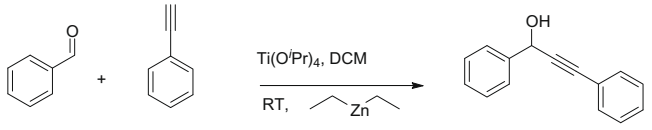
Entry	Ligand	% Conversion	% ee (*R*)
1	**1** R = Ph	30	50
2	**2** R = ^{i}Pr	28	27
3	**3** R = Bn	35	72
4	**4** R = ^{i}Bu	27	18

Table 2
Titanium-catalysed alkylation using hydroxyamide ligands **1**–**4**



Entry	Ligand	% Conversion	% ee (*R*)
1	**1** R = Ph	90	74
2	**2** R = ^{i}Pr	88	5
3	**3** R = Bn	82	24
4	**4** R = ^{i}Bu	79	6

Table 3
Titanium-catalysed alkynylation using hydroxyamide ligands **1**–**4**



Entry	Ligand	% Conversion	% ee (*R*)
1	**1** R = Ph	88	11
2	**2** R = ^{i}Pr	79	20
3	**3** R = Bn	89	34
4	**4** R = ^{i}Bu	78	16

on a Schmidt + Haensch L1000 polarimeter at 589 nm (Na) in a 10 cm cell. Thin layer chromatography (TLC) was carried out on precoated silica gel plates (Merck 60 F254); column chromatography was conducted using Merck Silica Gel 60 or Apollo Scientific Silica Gel 40–63 μ. Elemental analysis was performed on a Perkin–Elmer 2400 analyser. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a JEOL ECX-400 NMR spectrometer. All spectra were recorded at probe temperatures (~20 °C) using tetramethylsilane as internal standard. All chiral liquid–liquid chromatography (HPLC) was carried out on a Varian instrument, with an UV–vis detector at the specified wavelength, with a Daicel CHIRALCEL OD 0.46 cm × 25 cm column, using isopropanol/hexane as the solvent, under conditions described for each experiment.

4.1.1. (2*S*)-*N*-[(1*S*)-2-Hydroxy-1-phenyl-ethyl]-5-oxo-pyrrolidine-2-carboxamide 1

To a stirred mixture of methyl (2*S*)-5-oxopyrrolidine-2-carboxylate (2.14 g, 15 mmol) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) (0.60 g, 4.5 mmol) at 50 °C was added *R*-phenylglycinol (2.27 g, 16.5 mmol). The reaction mixture was warmed to 75 °C and stirred for 12 h, allowed to cool to ambient temperature and concentrated in vacuo. The residue obtained was chromatographed on silica gel using 8% methanol/ethyl acetate as eluent to afford **1** as a solid which was then triturated with cold acetonitrile to give the pure product (2.60 g, 70%) as a white solid; mp 189.8–191.1 °C; $[\alpha]_D^{20} = -81.6$ (*c* 1, MeOH); ^{1}H NMR (DMSO-d_6) 1.72–1.81 (m, 1H), 1.99–2.11 (m, 2H), 2.18–2.28 (m, 1H), 3.53 (t, *J* 5.9, 2H), 4.06 (dd, *J* 8.7, 4.5, 1H), 4.77–4.84 (m, 1H), 4.88 (t, *J* 5.8, 1H,), 7.17–7.23 (m, 1H), 7.24–7.32 (m, 4H), 7.85 (br s, 1H,), 8.29 (br d, *J* 8.2, 1H); ^{13}C NMR (DMSO-d_6) 25.8, 29.8, 55.1, 56.2, 65.1, 127.3, 128.6, 139.5, 172.5, 177.9; IR (solid) 3372, 3287, 1655, 1638; *m*/*z* (ESI) 247 ([M]$^-$, 100%), HRMS (ES$^-$): found [M−H]$^-$ 247.1082, $C_{13}H_{15}N_2O_3$ requires 247.1083.

4.1.2. (2*S*)-*N*-[(1*S*)-1-(Hydroxymethyl)-2-methyl-propyl]-5-oxo-pyrrolidine-2-carboxamide 2

The reaction was conducted as for the synthesis of 1 mentioned above using methyl (2*S*)-5-oxopyrrolidine-2-carboxylate (2.00 g, 14 mmol), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) (0.49 g, 3.5 mmol) and (*S*)-valinol (1.52 g, 14.7 mmol). The product **2** (2.22 g, 74 %) was isolated as a white solid; mp 144.1–145.9 °C; $[\alpha]_D^{20} = -14.1$ (*c* 0.8, H_2O) ^{1}H NMR (DMSO-d_6) 0.81 (d, *J* 6.8, 3H,), 0.85 (d, *J* 6.8, 3H), 1.75–1.94 (m, 2H), 2.01–2.21 (m, 3H), 3.29–3.41 (m, 2H) 3.51–3.60 (m, 1H,), 4.04 (dd, *J* 8.2, 3.9, 1H), 4.60 (br s, 1H), 7.59 (br d, *J* 8.9, 1H), 7.82 (br s, 1H); ^{13}C NMR (DMSO-d_6) 18.8, 20.2, 26.0, 28.7, 29.8, 56.3, 61.7, 62.9, 172.8, 178.0; IR (solid) 3396, 3323, 3215, 1680, 1640; *m*/*z* (ESI) 213 ([M]$^-$, 100%), HRMS (ES$^-$): found [M−H]$^-$ 213.1238, $C_{10}H_{17}N_2O_3$ requires 213.1239.

4.1.3. (2*S*)-*N*-[(1*S*)-1-Benzyl-2-hydroxy-ethyl]-5-oxo-pyrrolidine-2-carboxamide 3

The reaction was conducted as for the synthesis of **1** mentioned above using methyl (2*S*)-5-oxopyrrolidine-2-carboxylate (1.43 g, 10 mmol), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) (0.28 g, 2.1 mmol) and (*S*)-phenylalaninol (1.51 g, 10 mmol). The product **3** (1.76 g, 67%) was isolated as a white solid; mp 170.6–171.2 °C; $[\alpha]_D^{20} = -32.9$ (*c* 1, MeOH); ^{1}H NMR (DMSO-d_6) 1.63–1.72 (m, 1H), 1.94–2.07 (m, 2H), 2.07–2.19 (m, 1H), 2.61 (dd, *J* 13.5, 8.3, 1H), 2.80 (dd, *J* 13.5, 5.7, 1H,), 3.27–3.39 (m, 2H), 3.83–3.92 (m, 2H), 4.77 (t, *J* 5.5, 1H), 7.13–7.27 (m, 5H), 7.72 (br s, 1H), 7.76 (br s, 1H); ^{13}C NMR (DMSO-d_6) 25.5, 29.1, 36.4, 52.4, 55.7, 62.4, 125.9, 128.1, 129.1, 139.1, 172., 177.4; IR (solid) 3299, 3228, 1686, 1645; *m*/*z* (ESI) 261 ([M]$^-$, 100%), HRMS (ES$^-$): found [M−H]$^-$ 261.1240, $C_{14}H_{17}N_2O_3$ requires 261.1239.

4.1.4. (2*S*)-*N*-[(1*S*)-1-(Hydroxymethyl)-3-methyl-butyl]-5-oxo-pyrrolidine-2-carboxamide 4

The reaction was conducted as for the synthesis of 1 mentioned above using methyl (2*S*)-5-oxopyrrolidine-2-carboxylate (1.66 g, 11.6 mmol), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (0.49 g, 3.5 mmol) and (*S*)-leucinol (1.36 g, 11.6 mmol). The product **4** (2.07 g, 78 %) was isolated as a white solid; mp 122.4–123.9 °C; $[\alpha]_D^{20} = -21.9$ (*c* 1, H_2O); ^{1}H NMR (DMSO-d_6) 0.79 (d, *J* 6.7, 3H), 0.83 (d, *J* 6.6, 3H), 1.21–1.29 (m, 2H), 1.49–1.59 (m, 1H), 1.77–1.86 (m, 1H), 1.98–2.24 (m, 3H), 3.17–3.30 (m, 2H), 3.70–3.80 (m, 1H), 3.93 (dd, *J* 8.0, 3.7, 1H), 4.61 (t, *J* 5.7, 1H), 7.57 (d, *J* 8.7, 1H), 7.74 (br s, 1H); ^{13}C NMR (DMSO-d_6) 22.4, 23.9, 24.7, 26.1, 29.8, 39.9, 49.2, 56.3, 64.2, 172.6, 177.9; IR (solid) 3224, 3093, 1686, 1654; *m*/*z* (ESI) 227 ([M]$^-$, 100%), HRMS (ES$^-$): found [M-H]$^-$ 227.1394, $C_{11}H_{19}N_2O_3$ requires 247.1396.

4.1.5. Asymmetric addition of diethylzinc to benzaldehyde

To a solution of ligand (0.1 mmol) in dichloromethane (1 mL) was added titanium tetraisopropoxide (72 μL, 0.20 mmol) and the resulting solution was stirred for 1 h and it was then cooled to 0 °C. Diethylzinc (2 mL, 2 mmol, 1.0 M in hexane) was added and the mixture was stirred for 0.5 h. The aldehyde (1 mmol) in dichloromethane (1 mL) was added and the mixture was stirred for an additional 18 h, allowing the reaction mixture to slowly reach ambient temperature. The reaction was quenched with saturated ammonium chloride solution (2 mL), the reaction mixture was extracted with dichloromethane (3 × 5 mL) and the combined extracts dried over anhydrous magnesium sulfate. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (pet./EtOAc, gradient elution) to afford the pure chiral 1-phenyl-1-propanol as a colourless oil. The enantioselectivity was determined by HPLC analysis [Daicel Chiralcel OD column, hexane/2-propanol 98.0:2.0, 0.5 mL/min, 254 nm (t_R 24.4 min, t_S 31.8 min)].

4.1.6. Asymmetric addition of phenylacetylene to benzaldehyde

The ligand (0.20 mmol) and titanium tetraisopropoxide (0.4 mmol) were mixed in dry DCM (3.0 mL) at room temperature. Diethylzinc (2.0 mL, 1.0 M solution in hexane) was added. After the mixture was stirred at room temperature for 2 h, phenylacetylene (3.3 mL, 3 mmol) was added and the mixture was stirred for 1 h. Then the solution was treated with benzaldehyde (102 μL, 1.0 mmol). After the reaction was completed (TLC, 18 h), the reaction solution was cooled to 0 °C and the reaction was quenched by 5% aqueous HCl. The mixture was extracted with diethyl ether (3 × 10 mL). The extract was washed with brine (3 × 15 mL), dried over anhydrous $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash column chromatography (silica gel, 12.5% EtOAc in petroleum ether) to give 1,3-diphenyl-prop-2-yn-1-ol as a colourless oil. The enantioselectivity was determined by HPLC analysis [Daicel Chiralcel OD column, hexane/2-propanol 90.0: 10.0, 1.0 mL/min, 254 nm (t_R 10.0 min, t_S 17.8 min)].

4.1.7. Hydrogen-transfer to acetophenone

Ligand (0.022 mmol) and $[RuCl_2(\text{-cymene})]_2$ (6.1 mg, 0.01 mmol) were dried under vacuum in a dry Schlenck tube for 15 min. 2-Propanol (degassed, 10 mL) and NaOH (4 mg, 0.1 mmol) were added under a nitrogen atmosphere. The solution was stirred for 30 min and acetophenone (2 mmol) was added. The reaction mixture was stirred at room temperature for 24 h. The reaction was quenched by addition of aqueous NH_4Cl, the reaction mixture extracted with EtOAc and the organic phase was subsequently passed through a short pad of silica (washed through with a little EtOAc) and evaporated under vacuum. The product was purified using SiO_2 column chromatography and was isolated as a colourless oil. The enantioselectivity was determined by HPLC analysis [Daicel Chiralcel OD column, hexane/isopropanol 95:5, 1 ml/min; 254 nm (t_R 11.3 min, t_S 13.6 min)]. The configuration was assigned by comparison with the sign of specific rotation of the known compounds.

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