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Chiral, Bicyclic Proline Derivatives and their Application as Ligands for Copper in the Catalytic Asymmetric Allylic Oxidation of Olefins

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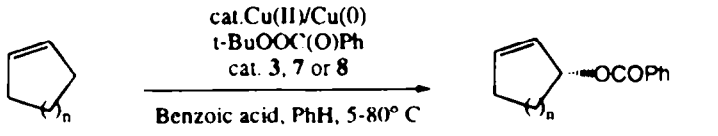
Abstract: The preparation of the unnatural, bicyclic α-amino acids 7 and 8 is described, along with their utility as chiral ligands in the copper-catalyzed enantioselective allylic oxidation of cyclohexene with tert-butyl perbenzoate. These bicyclic amino acids were found to be superior to (L) proline and gave optically active 2-cyclohexenyl benzoate in 48-67% yield and up to 65% e.e.

The development of methodology for asymmetric functionalization of C-H bonds remains a challenge in the strive for rapid access to optically active building-blocks from simple starting materials. The Kharasch-Sosnovsky reaction,[1] in which the allylic carbon of an alkene is acyloxylated, offers an expedient route to chiral allylic alcohols and has indeed been subject to substantial attention lately, with the employment of amino acids as chiral ligands to copper.

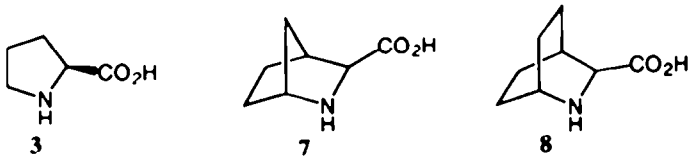
In their studies of α-amino acids as chiral ligands for the asymmetric allylic oxidation of olefins, Muzart[2] and Feringa[3] independently reported (*L*)-proline **3** (Scheme 1) itself to be the most efficient ligand within a group of proline derivatives with various steric and/or electronic substituents. Inspired by these results, we wanted to investigate rigid chiral ligands that might lead to a more ordered transition-state and thereby increase the asymmetric induction in the reaction. The bicyclic amino acids **7** and **8** are more rigid homologues of proline, and would thus represent good candidates for ligands used in such a study.

Scheme 1



1a: n=1
1b: n=2

2a: n=1; 42-54% (up to 60% *e.e.*)
2b: n=2; 30-67% (up to 65% *e.e.*)

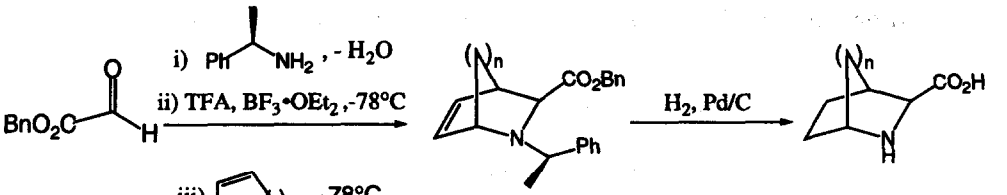


3 **7** **8**

The bicyclic amino acid **7** was prepared *via* a diastereoselective aza-Diels-Alder reaction[4] (scheme 2), with the chirality induced by an auxiliary on the dienophile. The dienophile was prepared in accordance with a

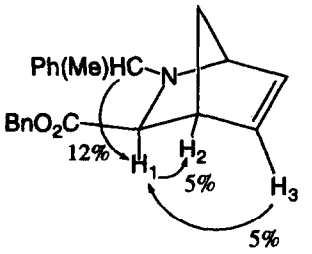
literature procedure,[4] where freshly prepared benzyl glyoxylate **4**[5] was condensed with (+)-1-phenylethyl amine in the presence of molecular sieves. The resulting imine was treated with trifluoroacetic acid and BF_3•OEt_2 to

Scheme 2



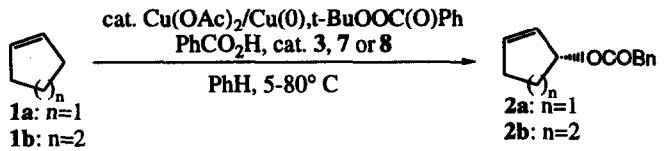
generate the free protonated imine. The iminium ion was then subjected to either cyclopentadiene or cyclohexadiene at -78° C, resulting in a highly *exo*- and diastereoselective cycloaddition. The major adduct was easily isolated by column chromatography, which afforded **5** or **6** as single diastereoisomers.[6-8] The *exo*-configuration of the adduct was confirmed by using NOE difference spectroscopy.[9]

Figure 1



In order to evaluate the chiral ligands, we used the standard conditions described by Muzart,[2] employing *t*-butyl perbenzoate, five equivalents of the alkene, a copper catalyst and benzene as solvent. The catalytic system utilizes a *syn*-proportionation of $Cu(OAc)_2$ and copper bronze as the source of catalytically active Cu(I).in a typical procedure as follows: cupric acetate monohydrate (3.1 mg, 0.016 mmol, 0.05 equiv.), copper bronze (10 mg, 0.16 mmol, 0.5 equiv.), ligand **7**[10-12] (10.9 mg, 0.077 mmol, 0.25 equiv.) and benzoic acid (39.5 mg, 0.29 mmol, 1.0 equiv) were suspended in benzene (0.8 ml). Cyclohexene (127 mg, 1.55 mmol, 5.3 equiv.) and *t*-butyl peroxybenzoate (56 mg, 0.29 mmol, 1.0 equiv.) were added, and the mixture was stirred under argon at room temperature for two days. The reaction mixture was then partitioned between saturated aqueous $NaHCO_3$ (2 mL) and ether (2 mL). The aqueous phase was extracted once with ether (2 mL), and the ether phases were dried ($MgSO_4$). Concentration and purification (silica gel, pentane/ether 95:5) afforded 2-cyclohexenyl benzoate as a colorless oil (38 mg, 40%, 64% *e.e.*). Lowering the temperature gave a much slower reaction (entry 9), with only 25% conversion after three weeks, and without increase in enantioselectivity.

Table 1



entry	substrate	ligand[a]	mol-% $Cu(OAc)_2$	temp (°C)	time	%yield[b]	$[\alpha]_D^{25}$[c]	% *e.e.*[d]
1	**1a**	(+)-**7**	5	reflux	4 hrs	42	+93.3	49
2	**1a**	(+)-**7**	5	20	2 days	54	+114.7	60
3	**1a**	(+)-**8**	5	20	2 days	44	+21.0	11
4	**1b**	(-) -**3**	5	reflux	4 hrs	51	-82.7	44
5	**1b**	(+)-**7**	5	reflux	4 hrs	67	+93.1	50
6	**1b**	(-) -**7**	5	reflux	4 hrs	64	-91.0	49
7	**1b**	(+)-**7**	10	20	2 days	63	+118.8	65
8	**1b**	(+)-**7**	5	20	2 days	40	+117.2	64
9	**1b**	(+)-**7**	10	5	21 days	25	+109.7	60
10	**1b**	(+)-**8**	5	20	2 days	30	+28.2	15

a) In all experiments, a ratio of 5/1 between ligand and $Cu(OAc)_2$ was used. b) Isolated yield. c) In $CHCl_3$ (c=1.5). d) Determined by chiral HPLC (Chiracel OD-H; *i*-PrOH, 0.5% in hexane). Absolute configuration determined by chiroptical comparison. Positive optical rotation of the product corresponds to the (*R*)-isomer.[2]

Conclusion:

We have herein described the preparation of enantiomerically pure bicyclic α-amino acids and investigated their utility as chiral ligands for the copper-catalyzed allylic oxidation of olefins. Ligand **7** was found to be superior to proline, and gave 2-cyclohexenyl benzoate in 63% yield and 65% *e.e.*. This is, to the best of our knowledge, the highest degree of asymmetric induction reported so far for this reaction using amino acids as chiral ligands.[13] Furthermore, the preparation of the bicyclic amino acids **7** and **8** is flexible and offers access to a number of structurally related amino acids in optically pure form. These are currently under investigation as ligands for asymmetric catalysis.

Acknowledgements: Financial support from the Swedish Natural Science Research Council is gratefully acknowledged. We are also indebted to Dr. A. Gogoll for helpful discussions concerning NMR experiments.

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1) Kharasch, M. S.; Sosnovsky, G.; Yang, N. C. *J. Am. Chem. Soc.* **1959**, *81*, 5819.

2) Levina, A.; Muzart, J. *Tetrahedron: Asymmetry* **1995**, *6*, 147; *Synth. Commun.* **1995**, *25*, 1789.

3) Rispens, M. T.; Zondervan, C.; Feringa, B. L. *Tetrahedron: Asymmetry*, **1995**, *6*, 661.

4) Stella, L.; Abraham, H. *Tetrahedron Lett.* **1990**, *31*, 2603.

5) Bishop, J. E.; O'Conell, J. F.; Rapoport, H. *J. Org. Chem.* **1991**, *56*, 5079. The product obtained is a mixture of benzyl glyoxylate and its trimer, of which both components are active in the following condensation reaction.

6) **Benzyl (1*S*,3*S*,4*R*)-2-[(1*R*)-1-phenylethyl]-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate (5)** (major *exo*-isomer): Benzyl glyoxylate (0.69 g, 4.7 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (30 mL), containing 3 g of activated 4A MS beads. The solution was cooled to 0° C and (*R*)-(+)-1-phenylethylamine (0.59 g, 4.9 mmol, 1.05 equiv.) was added. After 30 min, the solution was cooled to -78 °C, followed by addition of trifluoroacetic acid (0.43 g, 4.7 mmol, 1.05 equiv.), BF_3•OEt_2 (0.66 g, 4.7 mmol, 1.05 equiv.), and finally the cyclopentadiene (0.40 g, 6.1 mmol, 1.3 equiv.). The reaction was kept at -78 °C for five hours before it was allowed to warm to room temperature. The molecular sieves were separated and the reaction mixture was washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), and dried ($MgSO_4$). Concentration and purification by flash chromatography (silica gel, pentane/EtOAc/Et_3N 97:2:1) afforded (in order of elution) minor *exo*-isomer (35 mg), major *endo*-isomer (not characterized) and major *exo*-isomer (1.23 g, 83%) as colorless oils.

7) Selected spectroscopic data for **5**: $[\alpha]_D^{25}$ +71.6° ($CHCl_3$, c=1.0); ^1H NMR (300 MHz, $CDCl_3$, ref $CHCl_3$; 7.26 ppm): δ 7.4-7.0 (10H, m), 6.5-6.4 (1H, m), 6.28 (1H, dd, J=6.1, 2.0 Hz), 4.81 (1H, d, J=12.4 Hz), 4.75 (1H, d, J=12.4 Hz), 4.33-4.30 (1H, m), 3.05 (1H, q, J=6.7 Hz), 2.94-2.90 (1H, m), 2.28 (1H, s), 2.15 (1H, ddd, J=8.4, 1.9 and 1.6 Hz), 1.42 (1H, dm, J=8.4 Hz), 1.41 (3H, d, J=6.7 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$, ref $CDCl_3$; 77.0 ppm): δ 174.1, 144.9, 136.2, 135.7, 133.1, 128.2, 128.0, 127.98, 127.9, 127.8, 127.0, 66.0, 64.8, 63.8, 62.5, 49.1, 45.1, 22.6; IR(neat): 3061, 3030, 2971, 1745, 1454, 1158, 700 cm^{-1}; MS (EI), *m/z* (relative intensity): 333 (M^+, 3), 198 (48), 106 (18), 105 (100), 103 (11), 79 (17), 77 (20).

8) Selected spectroscopic data for **6**: $[\alpha]_D^{25}$ +84.6° ($CHCl_3$, c=1.5); ^1H NMR (300 MHz, $CDCl_3$, ref $CHCl_3$; 7.26 ppm): δ 7.3-7.0 (10H, m), 6.27 (1H, app. t, J=8.1 Hz), 6.16 (1H, app.t, J=8.1 Hz), 4.83 (2H, br s), 3.53 (1H, q, J=6.9 Hz), 2.90-2.85 (1H, m), 2.68-2.60 (1H, m), 2.00-1.85 (1H, m), 1.54-1.40 (1H, m), 1.25-1.13 (1H, m), 1.19, (3H, d, J=6.9 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$, ref $CDCl_3$; 77.0 ppm): δ 173.7, 144.9, 136.1, 132.9, 128.4, 128.1, 128.0, 127.9, 126.4, 66.0, 65.3, 63.1, 47.6, 33.9, 26.5, 19.2, 18.7; IR(neat): 3034, 2966, 2898, 1746, 1454, 1152, 699 cm^{-1}; MS (EI), *m/z* (relative intensity): 347 (M^+, 5), 213 (15), 212 (100), 184 (43), 105 (83), 91 (44), 80 (71), 79 (24), 77 (17).

9) Given values represent selected observed NOE enhancements. Absolute configuration assignments are based on comparisons with earlier reported ciroptical data (refs. 2,4).

10) **(1*S*,3*S*,4*R*)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid (7)**. The aza-Diels-Alder adduct **5** (1.00 g, 3.0 mmol) was dissolved in absolute ethanol, and Pd (5% on carbon, 50 mg) was added. The mixture was stirred at room temperature under H_2 (5 atm) for 24 hours. Filtration through a pad of celite and concentration yielded **7** as white crystals (423 mg, 100%).

11) Selected spectroscopic data for **7**: mp 205-208° C (dec.); $[\alpha]_D^{25}$ +5.90° (H_2O, c=1.0); ^1H NMR (300 MHz, D_2O, ref. sodium 3-trimethylsilyl-propane sulfonate (STMPS); 0.016 ppm): δ 4.08-4.02 (1H, br s), 3.54 (1H, br s), 2.74 (1H, br s), 1.75-1.40 (6H, m); ^{13}C NMR (75.4 MHz, D_2O, ref. STMPS; 0.4 ppm) δ 176.8, 67.6, 61.7, 43.5, 37.1, 29.5, 28.3; IR(KBr): 3451, 3111, 3010, 2954, 2733, 2547, 1589, 1456, 1375; MS (EI), *m/z* (relative intensity): 141 (M^+, 3), 96 (50), 80(4), 68 (100), 56 (29).

12) Selected spectroscopic data for **8**: mp 140-145° C (dec.); $[\alpha]_D^{25}$ +15.0° (EtOH, c=0.85); ^1H NMR (300 MHz, D_2O, ref. STMPS; 0.016 ppm): δ 3.78 (1H, br s), 3.55 (1H, br s), 2.06 (1H, br s), 2.0-1.5 (8H, m); ^{13}C NMR (75 MHz, D_2O, ref. STMPS, 0.4 ppm): δ 177.3, 61.8, 48.4, 28.7, 25.9, 24.6, 24.2, 22.2; IR(KBr): 3520-2400,1631, 1458, 1398, 1110 cm^{-1}; MS (EI), *m/z* (relative intensity): 155 (M^+, 5), 122 (12), 111 (18), 110 (95), 109 (19), 82 (100), 80 (33).

13) During the course of this study, the use of bis-oxazoline-type ligands has also been reported, see for example a) Andrus, M.B.; Argade, A.B.; Chen, X.; Pamment, M.G. *Tetrahedron Lett.* **1995**, *36*, 2945; b) Gokale, A. S.; Mindis, A. B. E.; Pfaltz, A. *Tetrahedron Lett.* **1995**, *36*, 1831; c) Gupta, A. D.; Singh, V. K. *Tetrahedron Lett.* **1996**, *37*, 2633.

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