Tetrahedron: *Asymmetry* 22 (2011) 2172–2178

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Enantioselectivity, swelling and stability of 4-hydroxyprolinol containing acrylic polymer beads in the asymmetric reduction of ketones

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ARTICLE INFO

Article history:
Received 23 November 2011
Accepted 6 December 2011
Available online 7 January 2012

ABSTRACT

A new 4-hydroxy-α,α-diphenyl-L-prolinol containing polymethacrylate, prepared without chromatography by a large scale adaptable synthesis, has been evaluated as a catalyst in the asymmetric reduction of 1-arylethanones. Using 1-(4-bromophenyl)ethanone as the model substance, the reduction was tested with various borane sources and solvents. The best swellings of the polymer and reactivity were observed in THF using *N*,*N*-diethylaniline borane complex as the hydride source. The selectivity in the reduction of 1-(4-bromophenyl)ethanone was found to depend on the substrate concentration and catalyst loading. Using the best conditions identified, a series of 1-arylethanones was reduced to their corresponding enantioenriched secondary alcohols. High rates and ee-values were obtained in the reduction of acetophenones containing electron withdrawing groups in the aromatic ring, whereas a moderate selectivity was the result for products containing electron donating aromatic substituents. Upon recovery of the polymer beads, it was found that vacuum drying led to extensive rupturing, while the bead structure was intact if washed with methanol and air dried at atmospheric pressure. Repeated use of the polymer catalyst gave the product alcohol with a lower 90% ee. Elemental analysis showed this to be due to the loss of the chiral prolinol unit.

1. Introduction

The α,α-diphenylprolinol skeleton has been used extensively in asymmetric catalysis,[1–3] with one of the more important transformations being the asymmetric reduction of prochiral ketones to their corresponding enantioenriched secondary alcohols.[4] The homogenous Corey–Bakshi–Shibata reagents derived from diphenylprolinol (**Ia**–**b** and analogues, Fig. 1),[5,6] have previously been used for the reduction of a number of ketones, giving the corresponding alcohols in high enantiomeric excess (ee).[7–11] These catalysts can be pre-made or formed in situ from the diphenylprolinol. The selectivity can be tuned by the choice of solvent, reaction temperature,[12,13] the borane source, catalyst loading and slow addition protocols. The effect on ee of changing these parameters might be related not only to a stabilising effect on the favoured transition state, but also to a disfavouring of the non catalysed borane reduction of the ketone, leading to a racemic product. An alternative strategy to increase the selectivity is to synthesise new catalysts, and the simplest way of introducing diversity is by varying the size and the electronic properties of the R-group in structure **I** (Fig. 1).[13–15] Also, some C2 and C3 symmetric diphenylprolinol based systems have been evaluated in asymmetric borane reductions.[16–21]

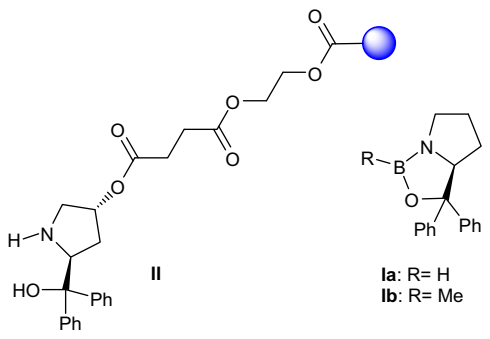

Figure 1. Structure of prolinol based catalyst **Ia**–**b**, and the polymethacrylate supported catalyst **II**.

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doi:10.1016/j.tetasy.2011.12.001

The challenges with low molecular weight catalysts include separation from the product and reuse of the catalyst. These shortcomings have been addressed using fluorous tags,[22–25] magnetically recoverable[26] or ionic liquid based catalysts.[27] Alternatively, the chiral unit can be covalently immobilised on an insoluble carrier matrix.[28] Diarylprolinol catalysts have been made by anchoring to polystyrene via the R-group on the boron atom (Fig. 1),[29] the aryl part,[30–32] via sulfonamides to the nitrogen,[33,34] and to polyethylene.[35] Challenges with such modified or immobilised systems are usually related to the lower activity, and maintaining a high selectivity upon repeated use.

Recently, a new method for preparing polymer linked 4-hydroxy-α,α-diphenyl-L-prolinol catalysts was developed.[36,37] Since this protocol is based on a 'bottom up' approach without any chromatographic purifications, the procedure is well suited for large scale synthesis.[28] In order to investigate the scope of the new and readily obtainable polymethacrylate, **II** (Fig. 1), we herein report its use in the asymmetric borane reduction of ketones.

2. Results and discussion

Polymethacrylate **II** was prepared by a suspension co-polymerisation of *O*-(2-methacryloyloxy-ethylsuccinoyl)-*trans*-4-hydroxy-α,α-diphenyl-L-prolinol, methyl methacrylate and ethyleneglycol dimethacrylate (Scheme 1). 2,2′-Azobis(2-methylbutyronitrile) (AMBN) was used as the initiator, polyvinyl alcohol as a suspension stabiliser, while KI inhibits the polymerisation in the aqueous phase.[36] The acrylic polymer was isolated by filtration, and the appearance of the fresh catalyst is shown in Figure 2.

By having a low degree of cross binder, as for **II**, a microporous polymer bead is formed. These are rather compact in dry form with pores of insufficient size to allow for efficient mass transfer. However, when suspended in a suitable solvent, the polymer can swell, allowing for entry of the reagents. Good swelling of the methacrylate polymer, **II**, was observed in THF (Fig. 3) and dichloromethane (not shown). The swelling was complete within 1.5–2 h depending on the bead size.

The use of other solvents, such as 2-methyltetrahydrofurane, acetonitrile, toluene or diethyl ether gave a low degree of swelling and was therefore not suited as the reaction medium. Poor swelling was also seen in MeOH and water.

Since the selectivity in asymmetric reductions often depends on the electronic properties of the substrate ketone,[12,38,39] and the catalyst loading, the initial investigations were performed with 1-(4-bromophenyl)ethanone **1a** as substrate, using 30 mol % catalyst in THF with borane dimethylsulfide complex as the hydride source (Scheme 2).

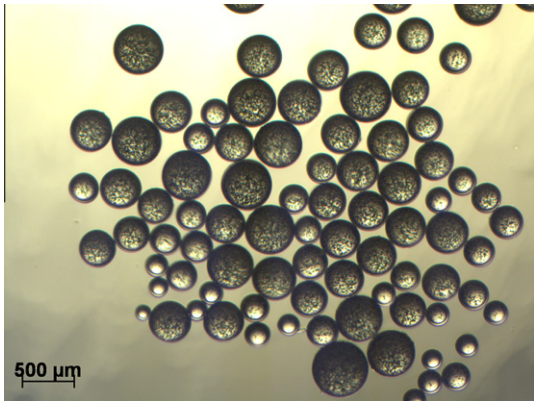
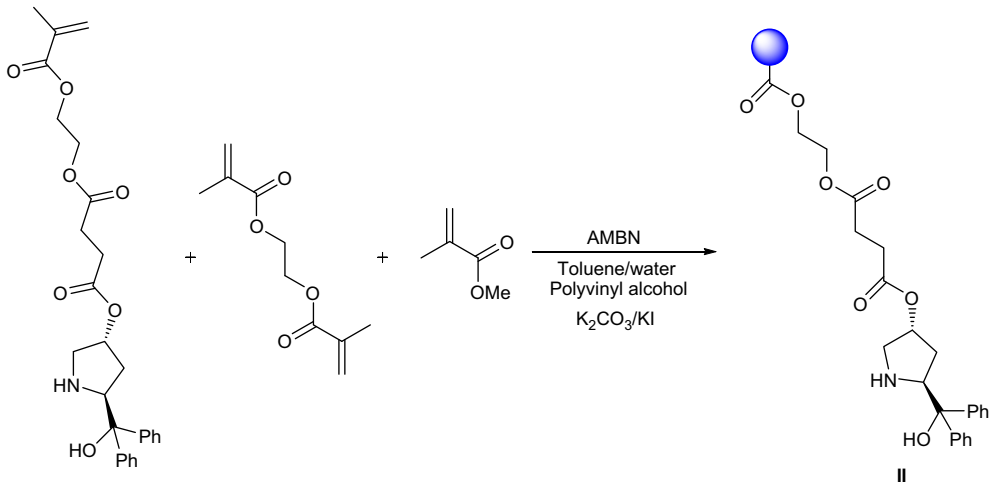


Figure 2. Microscopy image of the methacrylate polymer **II**.

In contrast to homogenous oxazaborolidine catalysts such as **I**, polymer based catalysis is most conveniently performed using an amino alcohol as the pre-catalyst. Polymer **II** was allowed to react with the borane dimethylsulfide complex for 30 min to produce the active catalyst, prior to the addition of substrate ketone. In refluxing THF, this gave a variable 60–90% ee. Lowering the reaction temperature and portion-wise additions of the ketone and the reducing agent did not improve the situation. By allowing catalyst **II** to stir with dimethylsulfide borane complex in THF overnight, analysis of the reaction mixture by ^{1}H NMR spectroscopy indicated decomposition of the polymer as the reason for the variable enantioselectivity. Stability testing of **II** as described above revealed that the use of $NaBH_4$ in combination with BF_3·diethylether also caused decomposition. While the polymer **II** appeared stable to the $NaBH_4$/trimethylsilyl chloride system, it failed to give conversion of **1a** to **5a** in test reactions. On the other hand using the *N*,*N*-diethylaniline borane complex, polymer decomposition was not detected by ^{1}H NMR, and the product **5a** could be obtained with reproducible ee-values. Further testing using **1a** and the *N*,*N*-diethylaniline borane complex, revealed that the reduction could be performed at 30 °C and only required one hour for full conversion.

We then investigated how a change in the catalyst loading and substrate concentration affected the selectivity (Table 1). The experiments in entries 1–6 represent a two-level factorial design with catalyst amount and substrate concentration as variables.



Scheme 1. Synthesis of the methacrylate polymer **II**.

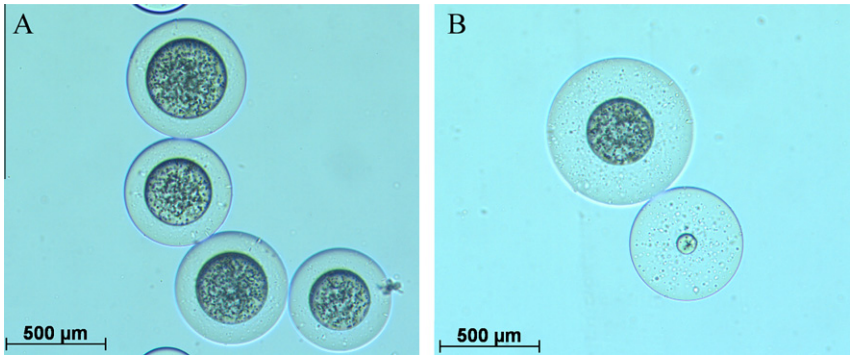
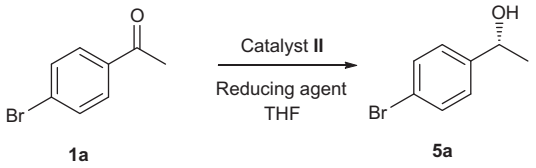


Figure 3. Microscopy image of the methacrylate polymer **II** swelled in THF for 30 min (A) and 60 min (B) at room temperature.



Scheme 2. Asymmetric borane reduction of **1a** using catalyst **II**.

Table 1
Effect of solvent amount and polymer catalyst **II** loading on selectivity in the reduction of **1a**

Entry	Substrate concn (mM)	Cat. loading[a] (mol %)	Conv.[b] (%)	ee[b] (%)
1	50	18	>99	95.0
2	125	6	>99	96.0
3	50	18	>99	95.0
4	31	6	>99	90.0
5	125	30	>99	97.0
6	31	30	>99	96.0
7	125	6	>99	97.0
8	62.5	6	>99	95.0
9	31	6	>99	93.0
10	16	6	>99	90.0

[a] Based on mole of nitrogen/weight unit determined by elemental analysis.
[b] Measured by GC.

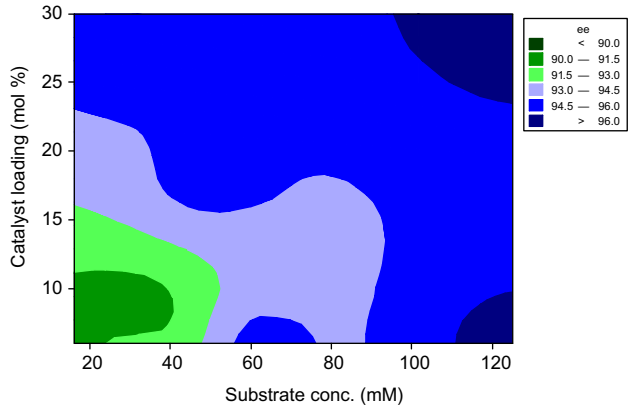


Figure 4. Enantiomeric excess (ee, %) as a function of substrate concentration and mol % of catalyst.

The ee-values increased at higher catalyst loading, but also when applying less solvent (Table 1, entry 2). The effect of substrate concentration was then investigated further (entries 7–10), confirming that less solvent was beneficial in terms of selectivity. A contour plot on how the ee varied with substrate concentration and catalyst loading is shown in Figure 4.

Free borane and diborane are present in equilibrium concentrations depending on both temperature and initial borane amount.[7] A plausible explanation for the effect of substrate concentration on the ee is that at higher solvent volumes more free borane will be available, thus resulting in a higher rate for the non catalysed pathway.

To investigate the substrate scope of the reaction, various ketones were reduced on a 0.25 mmol scale using 6 mol % of catalyst **II** (Scheme 3). The addition of the substrate was carried out in one portion. The reactions were performed in triplicates to reveal the reproducibility and possibly detect shortcomings in the procedure. The mean ee-value and standard deviation are shown in Table 2.

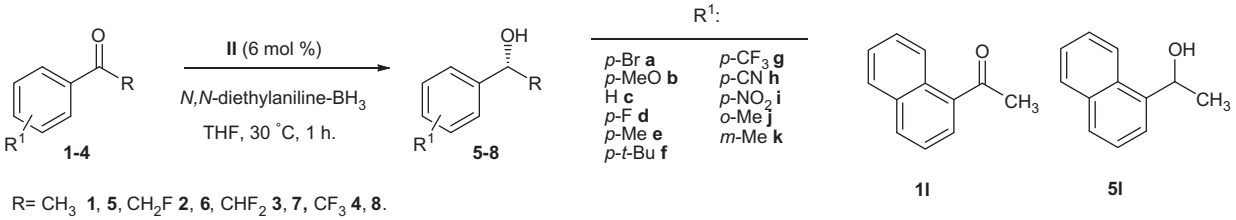
For all substrates, except for **1l** (Table 2, entry 12), full conversion was obtained within 1 h reaction time at 30 °C, indicating a very active catalyst. The highest selectivity was obtained in the reduction of ketones being moderately activated by electron withdrawing groups, thus (*R*)-**5a** and (*R*)-**5g–i** were obtained with ee-values in the range 95–99%. On the other hand, acetophenones containing more electron donating substituents gave mediocre ee-values (77.7–90.7%). In retrospect, this might be due to the lower intrinsic reactivity of these ketones in relation to the stability of the catalyst.

For the ketones containing α-fluorine atoms, the ee-values depended on the number of fluorine atoms. 2-Fluor-1-phenylethanone **2c** (entry 13) was reduced in 94% ee. For the sake of comparison, the use of Me-CBS **Ib** at −20 °C, gave **6c** in 96.5% ee.[9] Reduction of the 2,2,2-trifluoroacetophenones **4a** and **4c** under identical conditions gave the racemic products **8a** and **8c** (entries 15 and 16). Recently, Me-CBS **Ib** has been used in the reduction of **4c** to give **8c** in 1.7% ee.[15] The lack of selectivity in the reduction of **4c** was explained by the low coordinating ability of the carbonyl oxygen to the Lewis acid centre, and the high reactivity for the non-catalysed reduction by borane.[15]

Scale-up of the reductions of **1a** and **1g–i** (2.5 mmol scale) using 6 mol % of catalyst, led to the product alcohols being formed in 92–99% ee. While the ee-values of products **5a** and **5i** were maintained, a slight drop in selectivity was observed for the products **5g–h**. A challenge with reactions using polymer supported catalysts could be that the product of the reaction is trapped within the matrix. In the isolation of **5a**, four washes were required to recover the product from the polymer matrix.

When the reuse of the methacrylate polymer **II** was tested with **1a** as a substrate, this gave **5a** in 90% ee. Microscopy analysis of the recovered **II** revealed an extensive rupturing of the beads (Fig. 5). No clear indication for loss of the carbonyl function was seen using IR-spectroscopy.

Our investigation revealed that the rupturing of the polymer bead was caused by vacuum drying prior to reuse. This could be



Scheme 3. Substrates investigated in reduction using **II** as catalyst.

Table 2
Asymmetric reduction of **1a–l** and **2c**, **3c**, **4a**, and **4c** in 0.25 mmol scale using catalyst **II** (6 mol %) in THF with *N*,*N*-diethylaniline borane complex (1 mol equiv)

Entry	Compd	R	R^1	Conv. % (1 h)	ee (%)	SD[a]	Configuration
1	**1a**	CH_3	*p*-Br	>99	97.0	0.0	(*R*)
2	**1b**	CH_3	*p*-OMe	>99	77.7	1.2	(*R*)
3	**1c**	CH_3	H	>99	87.3	1.2	(*R*)
4	**1d**	CH_3	*p*-F	>99	89.3	0.6	(*R*)
5	**1e**	CH_3	*p*-Me	>99	81.0	0.0	(*R*)
6	**1f**	CH_3	*p*-*t*-Bu	>99	89.0	1.0	(*R*)
7	**1g**	CH_3	*p*-CF_3	>99	95.3	0.6	(*R*)
8	**1h**	CH_3	*p*-CN	>99	98.3	1.2	(*R*)
9	**1i**	CH_3	*p*-NO_2	>99	99.0	0.0	(*R*)
10	**1j**	CH_3	*o*-Me	>99	86.7	0.6	(*R*)
11	**1k**	CH_3	*m*-Me	>99	90.7	0.6	(*R*)
12	**1l**	CH_3	[b]	~50	78.7	1.5	(*R*)
13	**2c**	CH_2F	H	>99	94.3	1.2	(*S*)
14	**3c**	CHF_2	H	>99	74.0	0.0	(*S*)
15	**4a**	CF_3	*p*-Br	>99	0.0	0.0	*rac*
16	**4c**	CF_3	H	>99	0.0	0.0	*rac*

The reactions were performed at 30 °C for 1 h.
[a] Standard deviation for three parallel runs.
[b] 1-(Naphthalen-1-yl)ethanone see Scheme 3.

avoided if the polymer was dried at atmospheric pressure and especially if it was de-swelled with methanol prior to drying.

A stability test of polymer **II** was performed with *N*,*N*-diethylaniline borane complex in THF for 24 h. When the recovered beads were dried under atmospheric pressure, they appeared intact as judged from IR and microscopy. We were also unable to detect diphenylprolinol fragments by ^{1}H NMR in the concentrated reaction mixture or in the washes. Additional reuse experiments of catalyst **II** with **1a** as the substrate (1 h reaction) did not give the same high selectivity as in the initial run. Also, applying different washing protocols including repeated THF and methanol washes had no apparent effect on the selectivity.

Finally, elemental analysis of the recovered beads revealed a 44% loss of nitrogen content after 24 h. Therefore, it can be concluded that polymer **II** is reductively cleaved by borane liberating the chiral prolinol unit. The stability problem excludes the reuse of this methacrylate polymer in borane reductions, and will direct work towards a further generation of such catalysts. Also, the possible use of **II** as a ligand in the metal catalysed asymmetric transfer hydrogenation with 2-propanol as hydrogen donor will be the subject of continued work.

2.1. Comparison of catalyst II with other prolinol systems

To evaluate the usefulness of 4-hydroxy-α,α-diphenyl-L-prolinol as a structural element in catalysts for borane reduction, a literature review was undertaken. The structures of the most interesting catalysts identified are shown in Figure 6 and the selectivities obtained are compiled in Table 3. In a few cases (**1f**, **1k** and **4a**) diphenylprolinol catalysed borane reductions have previously not been performed.

Catalyst **Ia** has been used with success, but since it is air and moisture sensitive, other derivatives are more attractive.[5] Me-CBS **Ib** reduces acetophenones in high ee.[7,44] However, when using alternative hydride sources, low catalyst loading or ambient temperature the selectivity is not always excellent.[40,42] The use of the phenyl analogue **Ic** seems to have advantages in the reduction of 1-(4-nitrophenyl)ethanone **1i**,[12] while the derivatives **Id–e** are good catalysts for the preparation of the trifluoroalcohol **8c**. Of all the bi- and tridentate catalysts prepared and tested,[16–21] catalyst **IV** appears to be the most efficient. Catalyst **IV**[16] performs especially well in the reduction of 2,2,2-trifluoro-1-phenylethanone **4c** and 1-(3,5-dinitrophenyl)ethanone (95% ee, data not shown). The isolation and reuse of **IV** were carried out by crystallisation with a 70% recovery. The bidentate catalyst **III** used in 10 mol % loading gave a high 97% ee for the reduction of 1-(4-bromophenyl)ethanone **1a** and 1-(4-fluorophenyl)ethanone **1d**.

By anchoring the prolinol unit via a sulfonamide linker to polystyrene, a recyclable catalyst, **Va**, was developed. Using a catalyst loading of 25 mol %, 84–96% ee was obtained under reflux conditions.[33,34] For the sake of comparison, two other sulfonamides, **Vb–c** are included.[27,33] Immobilisation of the chiral prolinol by attachment via the aryl part also seems to be a viable strategy. Catalyst **VI**,[35] containing a polyethylene backbone was tested at 45 °C

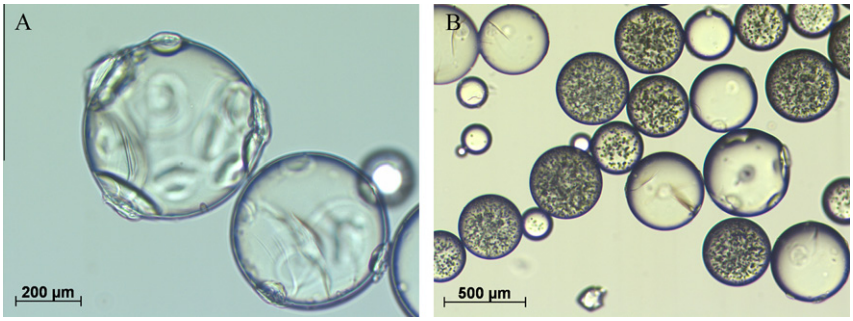


Figure 5. (A) Ruptured recovered polymer after vacuum drying, (B) Ruptured recovered polymer compared with fresh catalyst.

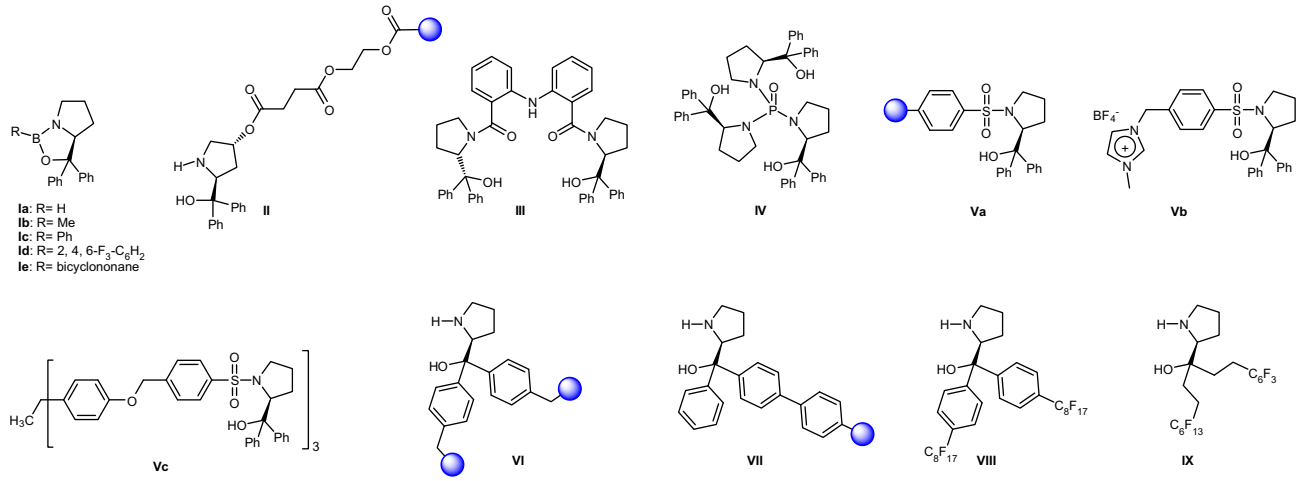


Figure 6. Different prolinol based catalysts.

Table 3
Comparison of selectivities for the use of CBS catalysts **I–IX**

Compd	R	R^1	Selectivity in borane reduction (ee, %)						
			Ib (100 mol %)	**Ib–e**	**II** (6 mol %)	**III–IV**	**Va–c**	**VI–VII**	**VIII–IX**
1a	CH_3	*p*-Br	99.0[a]	97.0 **b**[c] 98.0 **c**[d]	97.0	97.0 **III**[k] 95.0 **IV**[l]	96.0 **a**[m] 92.0 **c**[n]	–	–
1b	CH_3	*p*-OMe	99.5[a]	95.0 **b**[c] 98.0 **c**[d]	78.0	93.0 **III**[k] 93.0 **IV**[l]	84.0 **a**[m] 82.0 **c**[n]	–	91.0 **VIII**[r] 89.0 **IX**[s]
1c	CH_3	H	99.0[a]	95.0 **b**[c] 98.0 **b**[e]	87.5	96.0 **III**[k] 95.0 **IV**[l]	95.5 **a**[m] 88.0 **c**[n]	95.0 **VI**[p] 97.0 **VII**[q]	95.0 **VIII**[t] 93.0 **IX**[s]
1d	CH_3	*p*-F	>99.5[a]	96.0 **c**[d]	89.5	97.0 **III**[k] 95.0 **IV**[l]	75.0 **b**[o] 91.0 **c**[n]		
1e	CH_3	*p*-Me	>99.5[a]	94.0 **b**[e]	81.0	90.0 **III**[k]	–	96.0 **VI**[p]	92.0 **IX**[s]
1g	CH_3	*p*-CF_3	98.5[a]	–	95.5	–	–	–	86.0 **IX**[s]
1h	CH_3	*p*-CN	98.0[a]	94.0 **b**[f]	98.5	–	–	–	–
1i	CH_3	*p*-NO_2	98.5[a]	85.0 **b**[g] 99.0 **c**[d]	99.0	91.0 **III**[k] 95.0 **IV**[l]	96.5 **a**[m] 90.0 **c**[n]	–	–
1j	CH_3	*o*-Me	–	–	86.5	–	91.0 b[o]	–	–
1l	CH_3	Naphthyl	–	96.0 **b**[h] 99.0 **e**[i]	78.5	94.0 **III**[k]	–	61.0 **VII**[q]	–
2c	CH_2F	H	96.5[b]	–	94.5	–	–	–	–
3c	CHF_2	H	–	–	74.0	–	–	–	76.5 **IX**[s]
4c	CF_3	H	–	90.0 **d**[j] 93.0 **e**[i]	0.0	95.0 **IV**[l]	–	–	<1 **IX**[s]

The ee-values have been rounded to the nearest 0.5-value.
[a] Catalyst **Ib** (100 mol %), CH_2Cl_2, −20 °C.[7]
[b] Catalyst **Ib** (100 mol %), dimethoxyethane, −20 °C.[9]
[c] Catalyst **Ib** (5 mol %), BF_3–OEt_2/LiH.[40]
[d] Catalyst **Ic** (10 mol %), toluene, BH_3–SMe_2, 25 °C.[12]
[e] Catalyst **Ib** (10 mol %), THF, BH_3–SMe_2, 45 °C.[35]
[f] Catalyst **Ib** (5 mol %), THF, BH_3–SMe_2, 25 °C.[41]
[g] Catalyst **Ib** (2 mol %), THF, BH_3–THF, room temp.[42]
[h] Catalyst **Ib** (10 mol %), toluene, *N*,*N*-diethylaniline–BH_3, 23 °C.[43]
[i] Catalyst **Ie** (10 mol %), THF, BH_3–THF, 0 °C.[14]
[j] Catalyst **Id** (10 mol %), THF, BH_3–SMe_2, 40 °C.[15]
[k] Catalyst. **III** (10 mol %), hexane, BH_3–THF, 50 °C.[17]
[l] Catalyst **IV** (5 mol %), THF, BH_3–SMe_2, room temperature.[16]
[m] Catalyst **Va** (25 mol %), THF, $NaBH_4$/Me_3SiCl, reflux.[33,34]
[n] Catalyst **Vc** (5 mol %), THF, BH_3–SMe_2, reflux.[21]
[o] Catalyst **Vb** (15 mol %), toluene, BH_3–SMe_2, reflux.[27]
[p] Catalyst **VI** (10 mol %), THF, BH_3–SMe_2, 45 °C.[35]
[q] Catalyst **VII** (30 mol %), THF, BH_3–SMe_2, 22 °C.[32]
[r] Catalyst **VIII** (10 mol %), THF, BH_3–THF, rt.[23]
[s] Catalyst **IX** (10 mol %), toluene, $B(OMe)_3$, BH_3–THF, rt.[22]
[t] Catalyst **VIII** (10 mol %), THF, $B(OMe)_3$, BH_3–SMe_2, rt.[24]

using 10 mol % of catalyst. It was possible to reuse **VI**, but the selectivity in the second cycle of reduction dropped to 78% ee. Other examples include catalyst **VII**,[32] with a polystyrene backbone. The reductions were performed at room temperature for 18 h using 30 mol % catalyst. The selectivity was maintained over eight cycles with a 3% loss of catalyst per run. Other structurally related polymer catalysts have failed to give enantioselective processes.[31,45]

The fluorous-tag type proline catalyst **VIII** was used at room temperature (10 mol % catalyst) in both THF[23] and hydrofluoroether HFE-7500.[24] In the latter solvent, **VIII** could be recovered by extraction (94% recovery/cycle). A drop in ee from 94% to 88% was observed over eight cycles.[24] The drawback of the method is that the exotic HFE-7500 solvent has to be used. Catalyst **IX**,[22] with a straight chain fluorous tag, was tested in refluxing toluene (10 mol %). The selectivites were slightly lower than in the case of **VIII**. Catalyst **IX** was recovered in 32–84% yield. In the reduction of **1c** the ee-value went from 93% to 37% in the second cycle of use, although the structure and the enantiomeric purity of **IX** were maintained.

The methacrylate based catalyst **II** presented herein, has the benefit of short reaction time compared to the other polymer bonded catalysts. This suggests that the introduction of a linker at the 4-position of the prolinol is a viable strategy. The highest utility of **II** is in the reduction of acetophenones having electron

withdrawing substituents on the aromatic ring, where **II** compares favourably with all other catalysts. In its present form, the use of catalyst **II** in comparison with the low molecular weight catalysts has the benefit of easier product separation.

3. Conclusion

A new polymer supported 4-hydroxy-α,α-diphenyl-L-prolinol catalyst has been prepared by a large scale adaptable suspension co-polymerisation. The microporous polymer beads were investigated in the asymmetric reduction of 1-arylethanones. The catalyst showed good swelling behaviour and high activity in THF at room temperature. Moderate to excellent selectivities were obtained in the reduction of a series of 1-arylethanones using *N*,*N*-diethylaniline borane complex as the reducing agent. The highest ee-values were obtained with ketones having electron withdrawing substituents on the aromatic ring, giving the corresponding secondary alcohols in a 95–99% ee. These selectivities compare favourably with other diphenylprolinol type catalysts. The highly activated trifluoromethyl ketones gave racemic products. Reuse experiments identified a loss in selectivity, due to reductive cleavage liberating the prolinol unit.

4. Experimental

4.1. Chemicals

O-(2-Methacryloyloxyethylsuccinoyl)-*trans*-4-hydroxy-α,α-diphenyl-L-prolinol hydrochloride was prepared as described previously.[36] The acetophenones **1a**–**k**, 1-acetonaphthone **1l**, 2,2,2-trifluoro-1-phenylethanone **4c**, borane diethylaniline complex, borane dimethylsulfide complex, (*R*)-1-(naphthalen-1-yl)ethanol **5l**, methyl methacrylate, ethyleneglycol dimethacrylate, 2,2′-azobis(2-methylbutyronitrile), polyvinyl alcohol and potassium iodide were purchased from Aldrich. 1-(4-Bromophenyl)-2,2,2-trifluoroethanone **4a** was from Apollo, 2,2-difluoro-1-phenylethanone **3c** from Alfa Aesar, whereas 2-fluoro-1-phenylethanone **2c** was synthesised as described previously.[46,47]

4.2. Analyses

NMR spectra were recorded with Bruker Avance DPX 400 MHz. ^{1}H chemical shifts are in ppm rel. to TMS. Coupling constants are in Hertz. HPLC was performed using an Agilent 1100 series system with a DAD detector. GC was performed using a Varian 3380. IR was performed with Thermo Nicolet Nexus FT-IR spectrophotometer. Microscopy was performed with a Carl Zeiss Axio Imager.A1 with an AxioCam MRc5 camera. Total carbon, hydrogen and nitrogen were determined by a Carlo Erba EA1110 elemental analyser.

The enantiomeric excess of **5a**–**l**, **6c** and **8c** were determined using GC and a CP-Chirasil-Dex CB column, column pressure: 10 psi, split flow: 30 mL/min, isothermal programs, **5a** (145 °C): (*R*)-**5a**: 10.7 min, (*S*)-**5a**: 12.0 min, **5b** (90 °C): (*R*)-**5b**: 22.8 min, (*S*)-**5b**: 25.2.0 min, **5c** (100 °C): (*R*)-**5c**: 18.3 min, (*S*)-**5c**: 21.2 min, **5d** (125 °C): (*R*)-**5d**: 6.3 min, (*S*)-**5d**: 7.1 min, **5e** (120 °C): (*R*)-**5e**: 9.3 min, (*S*)-**5e**: 10.7 min, **5f** (135 °C): (*R*)-**5f**: 14.8 min, (*S*)-**5f**: 15.5 min, **5g** (115 °C): (*R*)-**5g**: 13.1 min, (*S*)-**5g**: 16.5 min, **5h** (160 °C): (*R*)-**5h**: 10.7 min, (*S*)-**5h**: 12.3 min, **5i** (160 °C): (*R*)-**5i**: 18.7 min, (*S*)-**5i**: 21.4 min, **5j** (140 °C): (*R*)-**5j**: 5.3 min, (*S*)-**5j**: 6.1 min, **5k** (130 °C): (*R*)-**5k**: 6.6 min, (*S*)-**5k**: 7.1 min, **5l** (160 °C): (*R*)-**5l**: 12.1 min, (*S*)-**5l**: 13.0 min, **5l** (160 °C): (*R*)-**5l**: 12.1 min, (*S*)-**5l**: 13.0 min, **6c** (115 °C): (*S*)-**6c**: 14.5 min, (*R*)-**6c**: 16.4 min, **8c** (115 °C): (*S*)-**8c**: 17.0 min, (*R*)-**8c**: 18.3 min. 2,2-Difluoro-1-phenylethanol **7c** and 1-(4-bromophenyl)-2,2,2-trifluoroethanol **8a** were analysed using HPLC and a Chiracel OD column (0.46 cm × 25 cm), mobile phase: hexane/2-propanol (95:5), flow rate 1.0 mL/min, (*S*)-**7c**: 11.7 min, (*R*)-**7c**: 14.0 min, (*R*)-**8a**: 8.3 min, (*S*)-**8a**: 10.6 min.

The absolute configurations were determined as follows: (*S*)-1-aryl-2-ethanols **5a**–**d** and **5g**–**i** were prepared by enzyme catalysed resolution using lipase B from *Candida antarctica* and vinyl acetate as the acyl donor. ^{1}H NMR and the specific rotation corresponded with those reported previously. The absolute configuration of **5e**–**f** and **5j**–**k** were based on the known eluting order of the compounds in the given column.[48,49] The stereochemistry of (*R*)-1-(naphthalen-1-yl)ethanol **5l** was determined using a reference standard from Aldrich, the stereochemistries of **6c**, **7c** and **8c** were determined using reference material from asymmetric transfer hydrogenation, while the stereochemistry of **8a** was determined by the reduction of **4a** using *Geotrichum candidum* acetone powder as described by Nakamura et al.[50]

4.3. Methacrylate polymer II

O-(2-Methacryloyloxyethylsuccinoyl)-*trans*-4-hydroxy-α,α-diphenyl-L-prolinol hydrochloride[36] (5.89 g, 11.4 mmol) was suspended in CH_2Cl_2 (40 mL) and aqueous K_2CO_3 (10%, 40 mL) was added. The mixture was stirred vigorously for 5 min and separated. The aqueous phase was extracted with CH_2Cl_2 (40 mL) and the combined organic phases were dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo to give a nearly colourless oil of *O*-(2-methacryloyloxyethylsuccinoyl)-*trans*-4-hydroxy-α,α-diphenyl-L-prolinol in quantitative yield.

A three-necked 250 mL round bottomed flask was charged with an egg-shaped magnetic stirring bar (1½ × $^5/_8$ in), potassium iodide (57 mg, 0.34 mmol), K_2CO_3 (193 mg, 1.40 mmol) and 0.5 wt % aqueous polyvinyl alcohol (M_w ~205,000 and 88% hydrolysis, 150 mL). A mixture of all the *O*-(2-methacryloyloxy-ethylsuccinoyl)-*trans*-4-hydroxy-α,α-diphenyl-L-prolinol together with methyl methacrylate (16.05 g, 160 mmol), ethyleneglycol dimethacrylate (0.69 g, 3.50 mmol), toluene (20 mL) and 2,2′-azobis(2-methylbutyronitrile) (218 mg, 1.13 mmol) was prepared and added carefully to the aqueous solution under stirring, and the system was flushed with N_2 for 5 min. The suspension was polymerized under N_2 in a heating mantle at 80 °C for 19 h at a constant stirring rate of 700 rpm. The suspension was allowed to cool and then poured into a beaker containing MeOH (300 mL). The beads were allowed to settle by gravity, and the supernatant was decanted off. The process was repeated once more after the addition of MeOH (300 mL). The beads were then vacuum-filtered and washed with water (2000 mL), MeOH (100 mL), THF (300 mL) and finally MeOH (300 mL). Drying at room temperature for 23 h gave colourless polymer beads (20.21 g). CHN-Analysis: N, 0.88; C, 60.53; H, 7.66. (prolinol loading: 0.62 mmol/g of N). IR (neat, cm^{-1}): 3801, 3734, 3648, 2952, 1718, 1240, 1143.

4.4. Asymmetric reduction

4.4.1. Small scale reactions

Catalyst **II** (25 mg, 0.0155 mmol of N) was weighed out in a 4 mL tube with a screw cap and septum, and the atmosphere was exchanged with argon. Dry THF (1 mL) and the reduction agent (0.25 mmol) were added using a syringe, and the mixture was shaken at 30 °C for 30 min. Then, the ketone (0.25 mmol) dissolved in dry THF (1 mL) was added to the reaction flask using a syringe and the mixture was shaken for another 60 min at 30 °C. For analysis, a sample (0.5 mL) was withdrawn, diluted with CH_2Cl_2, washed with aqueous H_2SO_4 (0.5 M, 3 × 0.5 mL) and water (0.5 mL) and dried. The conversion and ee were analysed by GC or HPLC.

4.5. Preparative scale

4.5.1. (*R*)-1-(4-Bromophenyl)ethanol (*R*)-5a[51]

Catalyst **II** (245 mg, 0.0155 mmol of N) was weighed out in a 30 mL tube with a screw cap and septum, and the atmosphere was exchanged with argon. Dry THF (10 mL) and *N*,*N*-diethylaniline–BH_3 complex (2.5 mmol, 450 μL) were added using a syringe, and the mixture was shaken at 30 °C for 30 min. 1-(4-Bromophenyl)ethanone **1a** (2.5 mmol, 498 mg) dissolved in dry THF (10 mL) was added to the reaction flask in one portion. The reaction was agitated for another 60 min at 30 °C. The solution was filtered, and the filter residue containing the catalyst was washed with THF (5 × 3 mL). The filtrate was concentrated, diluted with CH_2Cl_2 (30 mL), washed with aqueous H_2SO_4 (0.5 M, 3 × 20 mL) and then water (20 mL). After drying over Na_2SO_4, filtration and solvent evaporation at reduced pressure, the crude product was purified by silica-gel column chromatography (pentane/EtOAc, 7:3), yielding a clear oil (442 mg, 2.12 mmol, 88%), ee: 97%, $[\alpha]_D^{22} = +34.8$ (*c* 1.03, $CHCl_3$). lit.[51] 98% ee, $[\alpha]_D^{22} = +39.8$ (*c* 0.375, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.48 (d, *J* = 6.4, 3H), 1.76 (br s, OH), 4.87 (q, *J* = 6.4, 1H), 7.25 (m, 2H), 7.47 (m, 2H).

4.5.2. (*R*)-1-(4-(Trifluoromethyl)phenyl)ethanol (*R*)-5g[52]

The reaction was performed as described in Section 4.5.1 starting with **1g**. This gave 396 mg (2.08 mmol, 83%) of a clear oil, ee: 92% $[\alpha]_D^{20} = +31.6$ (*c* 1.04, $CHCl_3$). lit.[52] ee: 94% $[\alpha]_D^{20} = +34.9$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.51 (d, *J* = 6.5, 3H), 1.85 (br s, OH), 4.98 (q, *J* = 6.5, 1H), 7.49 (m, 2H), 7.61 (m, 2H).

4.5.3. (*R*)-4-(1-Hydroxyethyl)benzonitrile (*R*)-5h[53,54]

The reaction was performed as described in Section 4.5.1 starting with **1h**. This gave 349 mg (2.35 mmol, 95%) of a clear oil, ee: 96.0 $[\alpha]_D^{25} = +43.1$ (*c* 1.02, $CHCl_3$), lit.[55] (*S*)-**5h** ee: 72%, $[\alpha]_D^{25} = -63.6$ (*c* 2.41, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.50 (d, *J* = 6.4, 3H), 1.88 (br s, OH), 4.97 (q, *J* = 6.4, 1H), 7.49 (m, 2H), 7.65 (m, 2H).

4.5.4. (*R*)-1-(4-Nitrophenyl)ethanol (*R*)-5i[56,57]

The reaction was performed as described in Section 4.5.1 starting with **1i**. This gave 390 mg (2.33 mmol, 93%) of a clear oil, ee: 99, $[\alpha]_D^{23} = +32.3$ (*c* 1.03, $CHCl_3$), lit.[56] ee: 88.4, $[\alpha]_D^{23} = +35.1$ (*c* 1.46, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.53 (d, *J* = 6.6, 3H), 1.91 (br s, OH), 5.03 (q, *J* = 6.6, 1H), 7.55 (m, 2H), 8.21 (m, 2H).

Acknowledgements

Anders Jahres Foundation and INNER ERA NET are acknowledged for financial support. Roger Aarvik is thanked for technical assistance and Dr. David Barriet for helpful discussions. Sør-Trøndelag University College is acknowledged for financing a PhD scholarship.

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