

Comparison of enantioselective reductions using bead and monolith ‘disk’ polymer formulations of CBS catalysts

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Received 15 December 2006; revised 8 February 2007; accepted 9 February 2007

Available online 15 February 2007

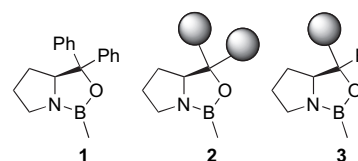
Abstract—Two polymer-supported versions of the Corey, Bakshi, and Shibata (CBS) catalyst were prepared and examined. Polymeric beads, with the auxiliary bound in pendant and crosslinked fashion, were prepared utilizing an improved procedure based upon earlier work. Optimization of a procedure for ketone reduction gives results that match those in solution. Attempted reuse gave mixed results. For comparison purposes, CBS functionalized monoliths were formed and tested but performed poorly.

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1. Introduction

The original homogenous CBS catalyst **1** gives excellent enantiomeric excess and conversion in the course of promoting the borane reduction of prochiral carbonyl compounds.^{1,2} However, as with many homogenous systems, it is not ideally suited for separation and recycling of the catalyst. Other methods of homogenous borane-based asymmetric reduction have been developed and used with success similar to that of the CBS model, but also suffer from the same problem.³ We have developed and optimized a heterogeneous, polymer-supported method based upon the *B*-methylated CBS system. We considered its diphenyl functionality as a promising site for modification so as to allow well-controlled polymerization; this was achieved successfully to form both crosslinked and pendant species **2** and **3** (R=ⁱPr), respectively, in bead form. As with many heterogeneous systems based upon homogenous analogs, a drop was observed in both activity and selectivity.⁴ In contrast to the solution-phase versions of these reactions, we found that the polymer-supported borane reductions suffered to a varying degree from competition by nonstereoselective solution-phase reduction. We demonstrated previously that the polymer-bound crosslinked catalyst **2** could achieve enantiomeric excess (ee) reasonably close to those of solution-phase systems.⁵ The pendant system **3**, however, gave poorer results. Using a method of ‘seeding’ resin **2** with borane we have been able to achieve enantioselectivities virtually

identical to those found in solution phase. However, a number of attempts to recycle and/or regenerate the polymer-bound catalyst have not given satisfactory results. In the course of this work we determined the enantiopurities of the chiral monomers used in the polymerization in order to properly calibrate the polymer-supported reduction results.



2. Results and discussion

2.1. Monomer syntheses

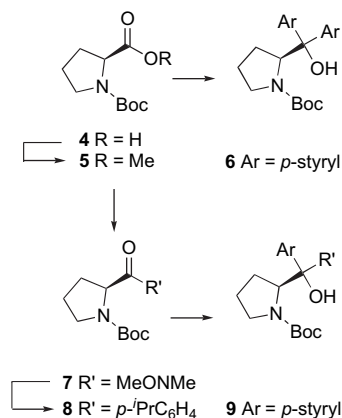
In our initial work the crosslinking monomer was formed by using commercially available *N*-Boc-L-proline **4** and converting it into the corresponding methyl ester **5** using dicyclohexylcarbodiimide (DCC). Grignard addition of *p*-vinylphenylmagnesium bromide provided the polymeric precursor **6** (Scheme 1). Premature polymerization was occasionally observed by the presence of insoluble solid during workup of the Grignard reaction. We minimized this complication by purifying the product immediately after aqueous workup and storing it under argon as a standardized solution in chlorobenzene.

The pendant monomer was formed in a similar fashion using Weinreb amide **7**.⁶ Treatment of **7** with

Keywords: CBS catalyst; Crosslinking monomer; Enantioselective reduction; Polymer beads; Polymer disks.

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p-isopropylphenylmagnesium bromide to form ketone **8**, followed immediately by the addition of *p*-vinylphenylmagnesium bromide gave the pendant polymerization monomer **9** (Scheme 1).

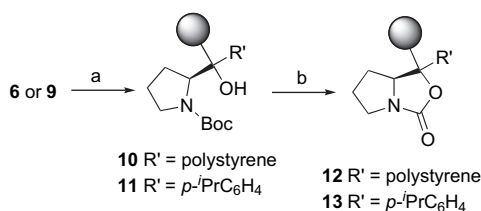


Scheme 1. See Ref. 5.

2.2. Polymer synthesis and deprotection

As we previously reported, suspension co-polymerization of Boc-protected **6** with styrene to form beads of resin **10** proceeded in high yield. Divinylbenzene was added as a crosslinker to monomer **9** form beads of the pendant resin **11**.

Subsequent deprotection attempts on these polymers using methanolic DMSO under basic (KOH) conditions yielded significant amounts of the cyclic carbamates **12** and **13**. Although we previously found a narrow range of conditions to permit hydrolysis of these compounds to the desired supported amino alcohols, this process was difficult to carry out reproducibly in acceptable yield (Scheme 2). We therefore considered alternative means of protection to circumvent this problem.



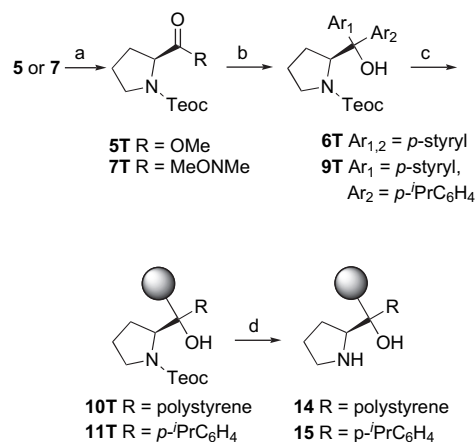
Scheme 2. (a) For **6**→**10**, $\text{C}_6\text{H}_5\text{CH}=\text{CH}_2$, $(\text{C}_6\text{H}_5\text{CO}_2)_2$, $\text{C}_6\text{H}_5\text{Cl}$, H_2O , 85°C , 24 h; for **9**→**11**, $\text{C}_6\text{H}_5\text{CH}=\text{CH}_2$, $p\text{-(CH}_2=\text{CH)}_2\text{C}_6\text{H}_4$, $(\text{C}_6\text{H}_5\text{CO}_2)_2$, $\text{C}_6\text{H}_5\text{Cl}$, H_2O , 85°C , 24 h; (b) KOH, DMSO, MeOH, 65°C , 4 days.

2.3. Teoc-protected monomers: enantiopurity and polymerization

Compounds **5** and **7** were deprotected with TFA and immediately reprotected using 1-[[2-(trimethylsilyl)ethoxy]carbonyloxy]pyrrolidin-2,5-dione (Teoc-OSu) to form the corresponding silyl carbamates. In the NMR both the Teoc-protected ester **5T** and amide **7T** showed distinct rotomers at 25°C , presumably due to restricted rotation about the bond from the ring nitrogen to the carbonyl carbon of

the Teoc group. Both compounds were subjected to Grignard reactions to form the Teoc-protected monomers **6T** and **9T**. Based upon chiral HPLC measurements both of these monomers showed reasonable retention of the integrity of the original proline stereocenter. Monomer **6T** consisted of a 95:5 *S/R* mixture (90% ee) while **9T** exhibited 94:6 *S/R* (88% ee). Separation of the diastereomers arising from the second side-chain stereocenter in **9T** was not observed under our chiral HPLC conditions.

Suspension polymerization of monomers **6T** and **9T** was performed successfully in a manner similar to that used to form the Boc-protected crosslinking and pendant resins to yield beads of polymers **10T** and **11T**, respectively. Teoc deprotection using tetrabutylammonium fluoride (TBAF) and $\text{KF}\cdot 2\text{H}_2\text{O}$ proceeded cleanly to form the CBS precursors **14** and **15** (Scheme 3). In the infrared we observed complete disappearance of the carbamate stretch at 1690 cm^{-1} and no trace of absorption corresponding to polymer-bound cyclic carbamate.



Scheme 3. (a) Teoc-OSu, Et_3N , CH_3CN , $0\text{--}25^\circ\text{C}$, 18 h; (b) For **5T**→**6T**, $p\text{-CH}_2=\text{CHC}_6\text{H}_4\text{MgBr}$, THF, $0\text{--}25^\circ\text{C}$, 4 h; for **7T**→**9T**, $p\text{-}^i\text{PrC}_6\text{H}_4\text{MgBr}$, THF, 45°C , 24 h, then after workup $p\text{-CH}_2=\text{CHC}_6\text{H}_4\text{MgBr}$, THF, $0\text{--}25^\circ\text{C}$, 4 h; (c) For **10T**, same as for **10**; for **11T**, same as for **11**; (d) TBAF, $\text{KF}\cdot 2\text{H}_2\text{O}$, THF, H_2O , 72 h, 65°C .

We also attempted to make resins with higher catalyst loading by combining monomers **6T** and **9T** in polymerizations in which **6T** would be the sole crosslinker. However, numerous attempts to make such resins via suspension polymerization failed. At best we obtained only minute amounts (<20 mg) of solids that would not swell in THF, DCM or benzene.

2.4. Oxazaborolidine formation and enantioselective reductions

Treatment of the supported amino alcohols **14** and **15** with trimethylboroxine yielded oxazaborolidines **2** and **3**, respectively.⁵ The newly formed catalysts were readied for use by means of multiple azeotropic distillations with toluene to remove excess boroxine and any moisture that could interfere with borane reduction. The resin was subsequently dried under reduced pressure. Acetophenone was chosen as the prochiral ketone due to the ease of NMR and chiral GC analysis of the reaction mixture and product. Reductions were

Table 1. Reductions of acetophenone to 1-phenylethanol using beads of polymeric CBS catalysts **2** and **3**

| Catalyst | Seeding time | Yield | ee (corr) ^a |
|----------|--------------|-------|------------------------|
| 2 | ~ | 55 | 70 (78) |
| 2 | 15 min | 96 | 86 (96) |
| 2 | 30 min | 96 | 81 (90) |
| 2 | 60 min | 97 | 89 (99) |
| 3 | 60 min | 100 | 55 (63) |

^a Values in parentheses are corrected for the enantiopurity of the polymer precursor.

initially performed by swelling the resin in a minimum amount of THF, followed by cooling and addition of $\text{BH}_3 \cdot \text{THF}$, and followed immediately by the ketone. We found that this method often failed to give complete conversion of the ketone to the alcohol over the course of 24 h. To address the possibilities that either some moisture may have still remained on the resin or that complexation of borane to the polymer-bound catalyst might be slow, we explored a method in which we 'seeded' the polymer with borane prior to addition of the ketone. Borane was added to the swelled resin and cooled to 0 °C for a period of time, after which a second aliquot of borane was added together with the ketone. The reduction was allowed to proceed for 24 h and the reaction worked up. Seeding for short periods gave somewhat erratic results, but the results using a one-hour pre-incubation time were consistently quite good. Not only did this seeding method provide nearly complete conversion of the ketone to the alcohol, but it also gave superior enantioselectivity results (Table 1).

Note that the ee values obtained in several of these reductions using crosslinking monomer **14** (i.e., polymer **2**) approach those of the monomers prior to suspension polymerization. Thus the actual enantioselectivity of reduction corrected for the enantiopurity of the catalysts in several of these cases is quite high.

2.5. Recycling and regeneration experiments

Having found that the 60 min seeding time gave the best results, we attempted reuse and regeneration of this particular resin. The used resin was recovered, dried, seeded with borane, and treated with acetophenone. The reductions were allowed to proceed for 24 h; their results are summarized in Table 2.

Based upon these incomplete conversions and erratic enantioselectivities we considered the possibility that decomposition of the oxazaborolidine may have occurred during the reduction, perhaps including reversion back to the amino alcohol. In addition, although the beads exhibited no visible effects of their prior use, it seemed possible that the internal pore structure may have been compromised, affecting in an

Table 2. Recycling of beads of catalyst **2** (all seeded for 60 min)

| Reuse # | Yield | ee (corr) |
|---------|-------|-----------|
| 1 | 29 | 19 (21) |
| 2 | 98 | 61 (68) |
| 3 | 55 | 40 (44) |

Table 3. Regeneration of beads of previously recycled catalyst **2**

| Reuse # | Yield | ee (corr) |
|---------|-------|-----------|
| 1 | 100 | 46 (51) |
| 2 | 100 | 31 (34) |
| 3 | 100 | 52 (58) |

unpredictable way the ability of the reagents and substrates to access catalytic sites in the interior. Note, however, that examination of the swelling characteristics of the beads before and after use showed no significant changes.

In any event we chose to attempt to completely regenerate the catalyst using the same methods used in its initial formation. The resin recovered from the experiments described in Table 2 was dried, swollen in THF, and trimethylboroxine was added. The regeneration attempt was allowed to proceed for 3 days followed by azeotropic distillation with toluene. The resulting resin was seeded for 60 min and used in three successive reductions, giving the slightly less erratic but still unsatisfactory results shown in Table 3.

The same recycling and regeneration experiments were performed on beads of the pendant resin **3** with little success. All recyclings gave complete conversion, but all products were racemic. In these cases it is clear that non-selective solution phase reduction completely dominates with respect to catalysis by polymer-supported material. A partial explanation may be found in an examination of the CBS-derived material that remains subsequent to solution phase use. We have carried out reductions using the original diphenylprolinol-derived methylboroxazine-based CBS catalyst in sufficient quantity to allow the fate of the catalyst to be at least partially ascertained by NMR. We find that little or no intact CBS material survives the procedure. Instead, a complex mixture is obtained exhibiting NMR signals consistent with dialkoxy and aminoalkoxymethylboranes, as well as derivatives of methylboronic acids.⁷ Thus it appears that the catalyst breaks down to fragments suitable neither for efficient reuse nor regeneration under the conditions that we have employed.

2.6. Synthesis and use of functionalized monolith-derived polymer disks

In addition to resins in bead form, we prepared monoliths from the Teoc-protected monomers **6T** and **9T**, using a method similar to that previously described.⁸ To our knowledge, these are the first monoliths of their kind. In order to maintain good swelling properties we chose a crosslinking level of 2%, about half that of the previously prepared beads, resulting in lower loading of monomer **6T**. After polymerization, the monoliths were cut to form disks roughly 2 mm in height and 5 mm in diameter. These disks were then washed in a Soxhlet apparatus to remove any unreacted monomer and styrene. Upon drying under reduced pressure, the disks were then deprotected using TBAF and treated with trimethylboroxine to presumably form CBS-functionalized disks. In addition to crosslinker and pendant disks, **2D** and **3D**, respectively, a set of 'mixed' disks (**2/3D**) were also formed using a mixture of the crosslinker and pendant monomers in an attempt to increase net loading of catalytic sites.

Each of these three types of disks was placed in a batch-flow type reactor, the entire apparatus was dried under vacuum and flushed with argon to ensure a moisture free environment. The disks were swollen in THF, cooled to 0 °C followed by seeding for 60 min with borane. After this period, the ketone was slowly added via syringe and the reactor agitated for 24 h. The solution was collected, the disks were washed three times with THF, and the filtrates combined. Although this method gave nearly complete conversion in all cases, only disk **2D** gave significant selectivity. The enantioselectivities obtained from the others were very low (Table 4).

Table 4. Reductions using CBS-functionalized disks

| Disk | Yield | ee (corr) |
|-------------|-------|-----------|
| 2D | 100 | 40 (44) |
| 3D | 93 | 3 (3) |
| 2/3D | 95 | 5 (6) |

The low selectivities are clearly attributable to the low loading, perhaps combined with poor diffusion of the reagents into the disks, thus favoring the uncatalyzed solution-phase reduction. Numerous attempts were made to circumvent this problem, e.g., by increasing seeding time; however, all reductions gave similarly poor results. Thus, in contrast to our successful application of the disk methodology to transition-metal catalyzed processes,⁹ it is clear that disks are a poor option in circumstances where competition from a solution-phase process interferes.

3. Conclusions

We have completed optimization studies of several versions of polymer-supported CBS catalysts. The resin derived from crosslinking monomer **6T** is clearly and consistently superior to the pendant resin derived from **9T**, and gives results comparable to solution-phase model reductions. The physical and chemical nature of the polymer significantly affects the outcome of reduction. Attempts to both recycle and regenerate failed, most likely due to a combination of disassembly of the oxazaborolidine and structural breakdown of the polymer itself. Polymer disks derived from monoliths could not be prepared with high loading and showed consistently poor results.

4. Experimental

4.1. General

All reactions were performed in oven-dried glassware unless otherwise stated under an atmosphere of dry argon. ¹H and ¹³C spectra were recorded at 400 MHz in CDCl₃. IR spectra of liquids and solids were recorded neat using a FTIR. Detailed preparations of **5–11** are described elsewhere.⁵ Optical purities of chiral auxiliaries and their precursors were determined using a Daicel Chiralcel OD-RH 0.46 cm by 15 cm (I.D. by length) 5.0 μm column employing a gradient elution of 0–5 min: 100% A, 5–25 min: 0–100% B, 25–30 min: 100–0% B, 30–35 min: 100% A (solvent A: H₂O/0.1% TFA; B: Acetonitrile/0.1% TFA)

monitored from 200–400 nm with a 0.2 mL/min flow rate installed in a system consisting of a Waters 2695 HPLC, a Waters PDA 996, and a Waters Micromass ZQ detector for obtaining low-resolution MS (ESI) data at concentrations of ~1 μg/mL. Reduction products were analyzed using an Astec G-TA β-cyclodextrin trifluoroacetylated 25 m GC chiral column. Elemental analyses were provided by Midwest and Galbraith Laboratories.

4.1.1. (2S)-1-([2-Trimethylsilyl]ethoxycarbonyl)-2-(methoxycarbonyl)pyrrolidine (5T). A solution of L-proline methyl ester (2.82 g, 21.8 mmol) in 17 mL of CH₃CN was treated with 8.7 mL of Et₃N and cooled to 0 °C. Commercially available 1-[2-(trimethylsilyl)ethoxycarbonyloxy]pyrrolidin-2,5-dione (Teoc-OSu) (10.1 g, 40.0 mmol) was added at 0 °C and the mixture was allowed to warm to rt, and stirred for 18 h. The solution was then diluted with Et₂O and extracted with water (3×), 3% HCl, water, 10% NaHCO₃, and satd NaCl, and dried (Na₂SO₄). The solvent was removed under reduced pressure to give 5.99 g (99% crude yield) of **5T** as an orange oil. Upon chromatography this compound co-eluted with unreacted Teoc-Su (¹H NMR br s at δ 2.88 ppm) that could not be completely removed without significant loss of material; thus **5T** was used in subsequent transformations without further purification. NMR spectroscopy indicated the presence of two rotomers in approximately of 52:48 ratio. ¹H NMR δ 4.34 and 4.28 (both dd, J=3.4, 8.6 Hz, total 1H), 4.20–4.08 (m, 2H), 3.71 and 3.70 (two s, 3H), 3.60–3.38 (m, 2H), 2.26–2.15 (m, 1H), 2.02–1.84 (m, 3H), 1.00 and 0.92 (dd, J=8.2, 8.6 Hz and dd, J=7.0, 10.2 Hz, total 2H), 0.01 and 0.00 (two s, total 9H) ppm. ¹³C NMR δ 175.0 and 174.9, 156.8 and 156.3, 65.1 and 64.9, 60.5 and 60.3, 53.7 and 53.6, 48.2 and 47.8, 32.5 and 31.4, 25.9 and 25.0, 19.34 and 19.31, 0.1 and 0.0 ppm. LRMS calcd for C₁₂H₂₄NO₄Si (M+1) 274.14; found 274.06. Anal. Calcd for C₁₂H₂₃NO₄Si: C, 52.72; H, 8.48; N, 5.12. Found: C, 54.54, 54.79; H, 8.73, 8.69; N, 4.75, 5.09.

4.1.2. (2S)-2-(N-Methoxy-N-methylcarbamoyl)-1-([2-trimethylsilyl]ethoxycarbonyl)pyrrolidine (7T). To a solution of 5.00 g (19.0 mmol) of **7** in 2.5 mL of CH₂Cl₂ was slowly added 47.5 mL of trifluoroacetic acid (TFA). After 2 h TLC showed the complete absence of starting material. After removal of CH₂Cl₂ and most of the TFA under reduced pressure, the oily residue was taken up in 1:1 ether/hexane, filtered, and solvent was again removed under reduced pressure. The deprotected ester was not characterized, but used immediately for Teoc protection. The crude oil was dissolved in 17 mL of CH₃CN, 8.7 mL of Et₃N was added, and the solution was cooled to 0 °C. Teoc-OSu (10.1 g, 40.0 mmol) was added at 0 °C and allowed to warm to rt and stirred for 18 h. After workup as for **5T**, above, 5.82 g of **7T** was obtained (99% crude yield) as an orange oil. NMR indicated the presence of two rotomers in a ca. 70:30 ratio. As in the case of **5T** this material was used after chromatographic separation from most but not all unreacted Teoc-OSu. ¹H NMR δ 4.73 (major) and 4.67 (minor) (both br dd, J=3.2, 8.4 Hz, total 1H), 4.20–4.07 (m, 2H), 3.78 (major) and 3.73 (minor) (both s, total 3H), 3.59 (m, 1H), 3.44 (m, 1H), 3.19 (s, 3H), 2.17 (m, 1H), 2.04 (m, 1H), 1.87 (m, 2H), 1.02 (major) and 0.92 (minor) (both m, total 2H), 0.02 (major) and 0.01 (minor) (both s, total 9H) ppm.

^{13}C NMR δ 175.0 (minor) and 174.5 (major), 156.9 (major) and 156.3 (minor), 64.9 (major) and 64.8 (minor), 62.79 and 62.75, 58.23 and 58.20, 48.5 (minor) and 48.1 (major), 33.9 (minor) and 33.7 (major), 32.1 (minor) and 31.1 (major), 25.8 (major) and 24.8 (minor), 19.4 (minor) and 19.3 (minor), 0.07 (major) and 0.00 (minor) ppm. LRMS calcd for $\text{C}_{13}\text{H}_{27}\text{N}_2\text{O}_4\text{Si}$ (M+1) 303.17; found 303.06. Anal. Calcd for $\text{C}_{13}\text{H}_{26}\text{N}_2\text{O}_4\text{Si}$: C, 51.63; H, 8.66; N, 9.26. Found: C, 50.65, 50.72; H, 8.33, 8.43; N, 9.33, 9.33.

4.1.3. (2S)-2-[Bis(4-ethenylphenyl)(hydroxy)methyl]-1-[(2-trimethylsilyl)ethoxycarbonyl]pyrrolidine (6T). Into a three-necked round bottom flask equipped with an addition funnel and condenser was placed (3.43 g, 0.141 mol) freshly cut Mg ribbon. The flask was placed under vacuum, flame dried, and flushed with Ar. The Mg pieces were allowed to stir under Ar for 24 h. 4-Bromostyrene (24.29 g, 0.133 mol) was added in THF (243 mL). The solution was allowed to reflux for 30 min and 1,2-dibromoethane (1.52 g, 8.1 mmol) was added followed by an additional 30 min of refluxing. The solution was then cooled to 0 °C and a solution of **5T** (18.00 g, ca. 0.04 mol) in 20 mL of THF was added. The mixture was allowed to warm to rt and stirred for 4 h. It was then cooled to -78 °C and 10 mL of H_2O was slowly added. After warming to rt and stirring for 4 h the mixture was filtered through well-packed Celite, washed with satd NaCl, and dried (K_2CO_3). The solvent was removed under reduced pressure and the crude material was quickly purified via SiO_2 flash chromatography to yield 12.59 g (70% yield) of **6T** as a light yellow solid. ^1H NMR δ 7.35 (m, 8H), 6.71* (dd, $J=11.0$, 17.6 Hz, 2H), 5.75* (dd, $J=3.6$, 17.6 Hz, 2H), 5.24 (br d, $J=11.0$ Hz, 2H), 4.90 (dd, $J=3.8$, 9.0 Hz, 1H), 4.20 (br m, 1H), 4.13 (br m, 1H), 3.41 (br app q, 1H), 2.95 (br s, 1H), 2.09 (m, 1H), 1.92 (m, 1H), 1.50 (m, 1H), 0.97 (br m, 2H), 0.86 (br s, 1H), 0.03 (s, 9H) ppm. The (presumably intramolecularly H-bonded) tertiary alcohol H appears as a very broad absorption around δ 6.5 ppm. The vinyl signals marked by an asterisk show fine (ca. 1 Hz) additional doubling, presumably resulting from diastereotopicity. ^{13}C NMR δ 147.3, 144.7, 137.9, 129.8, 129.2, 127.2, 126.8, 115.4, 115.2, 82.8, 67.4, 65.7, 49.2, 31.1, 24.5, 19.2, 0.0. Enant. comp.: *S* 95% *R* 5%. LRMS calcd for $\text{C}_{27}\text{H}_{36}\text{NO}_3\text{Si}$ (M+1) 450.24; found 450.14. Anal. Calcd for $\text{C}_{27}\text{H}_{35}\text{NO}_3\text{Si}$: C, 72.12; H, 7.85; N, 3.11. Found: C, 71.05, 71.11; H, 8.02, 7.82; N, 3.06, 3.11.

4.1.4. (2S)-2-[(4-Ethenylphenyl)(hydroxy)(4-{1-methyl-ethyl}phenyl)methyl]-1-[(2-trimethylsilyl)ethoxycarbonyl]pyrrolidine (9T). Into a three-necked round bottom flask equipped with an addition funnel and condenser was placed (1.46 g, 60.3 mmol) freshly cut Mg ribbon. The flask was placed under vacuum and flame dried followed by purging with Ar, and the Mg ribbon was allowed to stir for 24 h. 1-Bromo-4-isopropylbenzene (10.0 g, 50.2 mmol) in 90.7 mL of THF was added. The solution was allowed to reflux for 30 min, 1,2-dibromoethane (1.52 g, 8.1 mmol) was added, and the solution was allowed to reflux for additional 30 min followed by cooling to 0 °C. Upon cooling, a solution of **7T** (11.3 g, ca. 37.4 mmol) in 20 mL of THF was added. The mixture was slowly warmed and was allowed to stir at 45 °C for 24 h. The solution was cooled to -78 °C and 10 mL of H_2O was added. After filtration over well-packed Celite, the filtrate was washed with satd NaCl,

and dried (MgSO_4). The solvent was evaporated under reduced pressure. The crude ketone product was immediately added without characterization to a 0 °C solution of 4-vinylphenylmagnesium bromide that had been prepared as described above for **6T** from 4-bromostyrene (13.60 g, 74.3 mmol) and Mg ribbon (2.17 g, 89.1 mmol) in 250 mL of THF. The mixture was allowed to stir for 4 h and cooled to -78 °C. H_2O (10.0 mL) was added slowly and the solution was warmed to rt over a period of 4 h followed by filtration over well-packed Celite, washing with satd NaCl, and drying (K_2CO_3). The solvent was removed under reduced pressure and the residue subjected to flash chromatography to yield 9.04 g of **9T** (52% yield) as a light yellow solid. ^1H NMR δ 7.40–7.12 (m, 8H), 6.71 (dd, $J=11.0$, 17.6 Hz, 1H), 5.74 (d, $J=17.6$ Hz, 1H), 5.23 (d, $J=11.0$ Hz, 1H), 4.89 (dd, $J=3.6$, 8.8 Hz, 1H), 4.19 (br m, 1H), 4.11 (br m, 1H), 3.41 (br app q, 1H), 2.92 (br m, 1H), 2.89 (m, 1H), 2.07 (m, 1H), 1.92 (m, 1H), 1.48 (m, 1H), 1.24 (d, $J=7.2$ Hz, 6H), 0.96 (br m, 2H), 0.79 (br s, 1H), 0.03 (s, 9H). The OH hydrogen was not observed. ^{13}C NMR δ 149.2, 147.6, 142.2, 137.9, 137.7, 129.4, 129.2, 127.1, 127.0, 115.2, 87.8, 67.2, 65.6, 49.2, 35.1, 31.0, 25.5, 24.4, 19.1, 0.0. Enant. comp.: *S* 94% *R* 6%. LRMS calcd for $\text{C}_{28}\text{H}_{40}\text{NO}_3\text{Si}$ (M+1) 466.27; found 466.14. Anal. Calcd for $\text{C}_{28}\text{H}_{39}\text{NO}_3\text{Si}$: C, 72.21; H, 8.44; N, 3.01. Found: C, 72.20, 72.20; H, 8.39, 8.40; N, 2.67, 2.68.

4.1.5. Crosslink-functionalized beads of resin 14 via suspension polymerization of 6T and deprotection. The suspension polymerization of **6T** was performed in the manner previously described⁵ using 185 mL of H_2O , 13.00 g of Gum arabic, 13 mL of chlorobenzene, 0.11 g (0.45 mmol) benzoyl peroxide, 9.44 g (90.6 mmol) of styrene, 0.83 g (1.85 mmol) of **6T**, and 0.18 g (1.75 mmol) of neutral Al_2O_3 . The polymerization yielded 7.39 g (77% yield) of **10T** as white beads. IR: 1690 cm^{-1} . A suspension of 5.00 g of **10T** in 100 mL of THF was treated with 18 mL of 1 M TBAF in THF followed by 2.26 g (24.0 mmol) $\text{KF}\cdot 2\text{H}_2\text{O}$. The mixture was refluxed for 2 days, and 50 mL of water was added followed by an additional 24 h of refluxing. The resin was then isolated by filtration and washed with water, THF, methanol (3 \times), and dichloromethane (3 \times). Drying under high vacuum gave 4.90 g of **14** as white beads. IR: 3310 cm^{-1} (br). Anal. Calcd for 0.50 mequiv **6T**/gram **14**: N 0.70. Found: N 0.69, corresponding to 4.2% crosslinking. Conversion of **14** to **2** has been described elsewhere.⁵

4.1.6. Pendant-functionalized beads of resin 15 via suspension polymerization of 9T and deprotection. The suspension polymerization of **9T** used 180 mL of H_2O , 12.51 g of Gum arabic, 13 mL of chlorobenzene, 0.10 g (0.41 mmol) benzoyl peroxide, 8.77 g (84.2 mmol) of styrene, 0.43 g of 55% divinylbenzene, 0.89 g (1.90 mmol) of **9T**, and 0.18 g (1.75 mmol) of neutral Al_2O_3 . The polymerization yielded 6.86 g (66% yield) of resin **11T**. IR: 1690 cm^{-1} . Deprotection as described for **14** gave 4.75 g of **15** as white beads. IR: 3310 cm^{-1} (br). Anal. Calcd for 0.45 mequiv **9T**/gram **15**: N 0.63. Found: N 0.63. Crosslinking was calcd to be 3.7% based upon the styrene/divinylbenzene ratio. Conversion of **15** to **3** has been described elsewhere.⁵

4.1.7. Crosslink-functionalized disks of resin 2D via bulk polymerization of 6T, deprotection, and trimethylboroxine

treatment. Monomer **6T** (0.432 g, 0.96 mmol) was dissolved in a mixture of 8.25 g of 1,2-dichlorobenzene and 5.00 g (48.0 mmol) of styrene in a round bottom flask equipped with a stir bar. The solution was then gently warmed and transferred via pipette to a previously silanized Pyrex test tube containing 0.081 g (2 mol%) benzoyl peroxide. The test tube was then capped with a septum, and argon was bubbled through the solution to ensure a good mixing. The test tube was lowered into an oil bath at 85–90 °C. Argon was bubbled through the solution for 2 h, after which time the Ar line was removed from the solution but not the vessel so as to maintain a continuous Ar purge. The polymerization was judged to be complete when the rod pulled away from the sides of the test tube (2–3 days). The rod was removed from the test tube and cut into disks 1–3 mm thick using a razor. The disks were washed via Soxhlet extraction with hot THF for 2 days. After extraction the disks were dried under vacuum at 50 °C for 24 h. IR: 1670 cm⁻¹. Deprotection of 0.50 g batches of disks followed the procedure described above for resin **14**, followed by Soxhlet extraction with hot THF for 2 days. Anal. Calcd for 0.18 mequiv **6T**/gram: N 0.25. Found: N 0.25, corresponding to 1.5% crosslinking. Conversion to the disk-based CBS catalyst **2D** followed the previously described procedure.⁵ Soxhlet extraction with hot toluene for 2 days followed by drying under vacuum gave the final active disks.

4.1.8. Pendant-functionalized disks of resin 3D via bulk polymerization of 9T, deprotection, and trimethylboroxine treatment. Monomer **9T** (0.447 g, 0.96 mmol), dissolved in a mixture of 8.25 g of 1,2-dichlorobenzene, 5.00 g (48.0 mmol) of styrene, and 0.062 g (0.48 mmol) DVB, was converted to disk **3D** via the sequence of procedures described above for **2D**. Anal. (prior to trimethylboroxine treatment) Calcd for 0.16 mequiv **9T**/gram: N 0.22. Found: N 0.22. Crosslinking was calcd to be 0.9% based upon the styrene/divinylbenzene ratio.

4.1.9. Crosslink/pendant-functionalized disks of resin 2D/3D via bulk polymerization of 6T and 9T, deprotection, and trimethylboroxine treatment. Monomers **6T** (0.173 g, 0.39 mmol) and **9T** (0.268 g, 0.58 mmol), dissolved in a mixture of 6.00 g of 1,2-dichlorobenzene and 3.00 g (28.8 mmol) of styrene, was converted to disks **2D/3D** via the sequence of procedures described above for **2D**. Anal. (prior to trimethylboroxine treatment) Calcd for 0.33 mequiv **6T+9T**/gram: N 0.45. Found: N 0.44. Crosslinking was calcd to be 1.0% based upon the styrene/**6T** ratio.

4.1.10. General procedure for enantioselective reduction using beads. Suspensions of 1.00 g of either **2** (0.25 mmol/g) or **3** (0.225 mmol/g) in 15 mL of THF were cooled to 0 °C and 0.30 mL (0.30 mmol) of 1 M BH₃–THF was added.

The mixture was agitated for 1 h at 0 °C after which time an additional 0.30 mL (0.30 mmol) of BH₃–THF was added followed immediately by 0.06 g (0.50 mmol) of acetophenone. The flask was agitated for 24 h followed by filtration and washing (3× with THF and MeOH). The collected washings were combined and the solvent was removed under reduced pressure, and 5 mL of 0.5 M HCl was added. After 10 min of stirring the mixture was extracted with ethyl acetate (3×20 mL) and the extracts were dried (Na₂SO₄) for 24 h; the results are shown in Table 1.

4.1.11. General procedure for asymmetric reduction using disks. A batch-flow reactor was charged with 0.50 g of either **2D** (0.18 mequiv/g), **3D** (0.16 mequiv/g), or **2/3D** (0.33 mequiv/g). The apparatus was dried under vacuum using a heat gun, followed by purging with Ar. After cooling to rt the disks were swollen by treatment with ca. 5 mL of THF overnight. They were then cooled to 0 °C and treated with 1.2 equiv of 1 M BH₃–THF. The mixture was agitated for 1 h at 0 °C after which time an additional 1.2 equiv of 1 M BH₃–THF was added followed by 2.0 equiv of acetophenone. Workup as described above gave the results shown in Table 4.

Acknowledgements

We gratefully acknowledge support from the National Science Foundation (Grant CHE-0614756).

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