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Oxazaborolidines as Functional Monomers: Ketone Reduction Using Polymer-Supported Corey, Bakshi, and Shibata Catalysts

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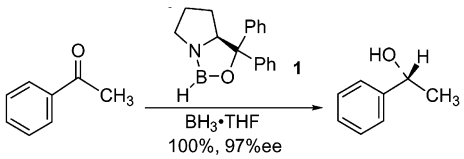
The first two polymer-supported versions of the Corey, Bakshi, and Shibata (CBS) catalyst have been prepared. Functional monomers based structurally upon the original *B*-methylated catalyst have been used to prepare catalytic polymers containing the CBS moiety bound both in a pendant fashion and in the form of a cross-link. Enantioselective reductions of two prochiral ketones have been carried out using the original catalyst in the solution phase as well as the two solid-state systems. While the pendant-bound system shows reduced stereoselectivity, the cross-linked version affords enantioselectivities almost identical to those of the solution-phase model.

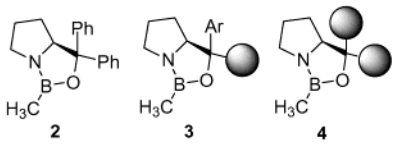
Introduction

The system devised by Corey, Bakshi, and Shibata, known as the CBS catalyst (**1**), represented a major breakthrough in catalytic enantioselective chemistry.[1] Used in conjunction with BH_3·THF, it permits the reduction of prochiral ketones to the corresponding alcohols very rapidly, in high chemical yield, and with excellent enantioselectivity (eq 1).[2,3]



(1)

The *B*-methylated version of this catalyst, **2**, adds the practical advantages of air and moisture insensitivity. As part of our ongoing program to critically compare the reactivity of systems of synthetic significance in a variety of physical environments, we decided to prepare two polymer-supported versions, **3** and **4**, of the CBS catalyst.



Polymer-supported species **3** and **4** also offer the opportunity to compare and contrast pendant vs cross-link bonding as the site of polymer-supported functionality. We noted stereoselectivity differences in a previous study comparing the two environments[4] and were interested to see how this would play out in the enantioselectivity of ketone reduction.

Results and Discussion

Catalyst Synthesis. We built upon both Corey's procedures and the sequence described by Kanth and Periasamy[2] to synthesize **2** and applied parallel methodology as much as possible in the preparation of **3** and **4**. We converted *N*-(*t*-BOC)-L-proline (**5**) into its methyl ester (**6**), followed by addition of excess phenylmagnesium bromide. Conventional procedures for liberation of less hindered carbamate-protected amines gave ring closure to the bicyclic oxazolidinone **9**. We found instead that hydrolysis with KOH in methanolic DMSO gave **8a** in 50% overall yield for the three steps on a large scale. Once this route was established, it was repeated using (*p*-vinylphenyl)magnesium bromide, providing **8b**, the monomer precursor to the cross-link-bound polymeric catalyst **4**, in similar overall yield (Scheme 1). Premature polymerization of **8b** was observed (TLC) during the workup after deprotection. This appeared to be the result of concentration of the product in the presence of adventitious initiators. To circumvent this problem, we devised the simple solution of diluting the reaction mixture while still hot with several volumes of water, which caused precipitation of **8b** upon cooling.

To access the single-site polymer-bound catalyst **3**, we made use of Weinreb amide **10**, obtained from reaction of **5** with *N*,*O*-dimethylhydroxylamine hydrochloride. Subsequent addition of *p*-isopropylphenyl Grignard and hydrolysis furnished ketone **11**, which upon addition of *p*-styryl Grignard yielded alcohol **12** (Scheme 2). Choice of R = *p*-isopropylphenyl as the nonpolymerizable group in this system was based on its steric and electronic similarity to the polystyrene moiety. Monomer **12** and, ultimately, polymer **3** are of course mixtures of diaster-

(1) For reviews see Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012 and Srebnik, M.; Deloux, L. *Chem. Rev.* **1993**, *93*, 763−784. A portion of this work has been the subject of a presentation: Sui, J. K.; Price, M. D.; Kurth, M. J.; Schore, N. E. *Abstr. Pap.*—*Am. Chem. Soc.* **2001**, *221st*, CHED-249.

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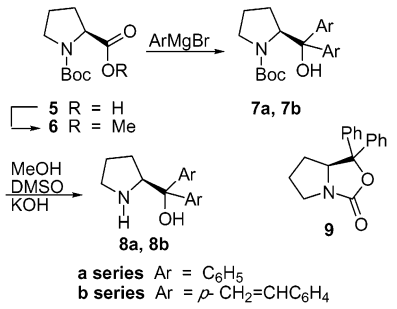
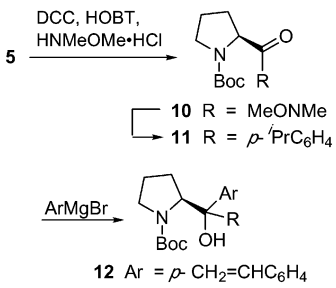
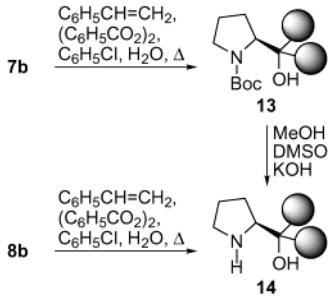
SCHEME 1. Synthesis of Auxiliary Precursors 8a and 8b



SCHEME 2. Synthesis of 12



SCHEME 3. Preparation of Cross-Link-Functionalized Polymer 14



eomers; our hope was to locally minimize any effect of the additional side-chain stereocenter by making the two substituents at this position as indistinguishable from one another as possible.

Polymer Synthesis. Suspension copolymerization of **8b** with styrene yielded resin **14** in rather low (29%) yield. As an alternative we submitted the Boc-protected monomer **7b** to the same procedure, followed by *N*-deprotection (Scheme 3). The latter procedure proved to be superior, affording beads of **14** which contained ca. 0.40 mequiv of diarylprolinol functional units/g of polymer by elemental analysis, corresponding to incorporation of approximately 4.5% of the distyrylprolinol cross-linker. That insoluble beads were formed is de facto evidence that the prolinol-derived moieties were indeed incorporated as cross-linkers.

Because monomer **12** is incapable of cross-linking, its suspension polymerization was carried out in the presence of styrene plus 2% divinylbenzene. Given our experiences with the preparation of polymer **14**, polymerization of only the Boc-protected **12** was attempted; deprotection was carried out postpolymerization to furnish **15**, containing ca. 0.32 mequiv of diarylprolinol functional units/g of polymer by elemental analysis (Scheme 4).

SCHEME 4. Preparation of DVB-Cross-Linked Pendant-Functionalized Polymer 15

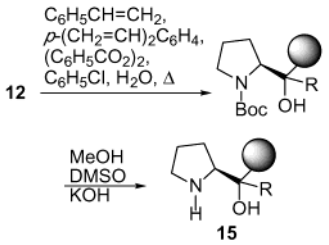


TABLE 1. Reduction of Ketones by Solution-Phase and Polymer-Supported CBS Catalysts

catalyst	substrate	yield[a] (%)	*R*:*S* ratio[b]	ee
2	acetophenone	100	92.9:7.1	85.8
3	acetophenone	100	81.4:18.6	62.8
4	acetophenone	100	92.4:7.6	84.8
2	pinacolone	100	94.4:5.6	88.8
3	pinacolone	100	86.1:13.9	72.2
4	pinacolone	100	94.2:5.8	88.4

[a] No ketone detected by GC. [b] Determined by GC using a chiral capillary column.

Preparation of Oxazaborolidine Catalysts. Following literature procedures,[5] addition of trimethylboroxine to a solution of **8a** in toluene resulted in the formation of **2**. The only purification of **2** we carried out was submission of the crude material to two azeotropic toluene distillations. It is well-established that even slight amounts of moisture or other impurities can have significant deleterious effects on the enantioselectivity of reactions catalyzed by oxazaborolidines. Nevertheless, for the purposes of this study we felt that it was important to preserve comparability between the behavior of **2** and its polymer-supported analogues, for which little else in the way of purification is practical. In the event, the performance of **2** isolated in this way was somewhat poorer than that described in the literature, but more than acceptable for our purposes (vide infra). Indeed, when making comparisons between solution-phase and polymer-supported conditions, it is generally preferable for the former to give *less* than optimal results, so that deviations *in either direction* may be quantified on the polymer.

Treatment of polymeric amino alcohols **14** and **15** with trimethylboroxine under conditions similar to those used for the preparation of **2** resulted in the formation of polymer-supported oxazaborolidines **4** and **3**, respectively.

Catalyzed Reductions. We chose reductions of acetophenone and 3,3-dimethyl-2-butanone (pinacolone) to comparatively evaluate our catalysts. The solution-phase experiments and the solid-phase experiments were allowed to proceed for 30 min and 24 h, respectively. The latter was done to ensure complete consumption of starting materials, which could be compromised by slow diffusion of compounds into the beads. In each case BH_3•THF was initially added to a THF suspension of the catalyst, followed immediately by the ketone. Table 1 gives our results.

(5) Mathre, D. J.; Jones, T. K.; Xavier, L. C.; Blacklock, T. J.; Reamer, R. A.; Mohan, J. J.; Jones, T. T.; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 751−762.

No attempt was made to optimize reaction enantioselectivities. Several groups have explored polymer-supported ketone reduction using amino alcohol−borane catalysts.[6−9] In general, enantioselectivities using solution-phase catalysts are better than those obtained using (pendant) polymer-supported analogues. In a number of cases, the solid-state results vary considerably from those found in solution, but optimization has brought about comparable results. Slow diffusion of the reagents into the catalyst-bearing beads is typically cited as permitting nonselective uncatalyzed reduction to compete, thus reducing overall enantioselectivity. Our results indicate that cross-linked catalyst **4** is superior to pendant system **3** and quite close to the solution model **2**. Tellingly, the lightly cross-linked beads of catalyst **4** swelled considerably more in THF than did those of divinylbenzene-cross-linked resin **3**. Comparisons between *N*-benzylprolinol and two (pendant) polymer-supported analogues with different spacers showed that increasing the spacer length improved enantioselectivity.[7] These results are consistent with improved accessibility of the auxiliary toward solution-phase species being an important factor for high enantioselectivity in these systems. Whether other issues, such as differences between **3** and **4** in local structural symmetry or in effective kinetic site isolation (that would inhibit catalyst−catalyst interaction), contribute in any significant way must await the results of our continuing, more extensive studies of these systems.

Conclusions

We have prepared and critically examined the performance of what we believe are the first two polymer-supported CBS catalysts. The readily accessible cross-link-based resin **4** is clearly superior to pendant-linked **3** and is comparable to the conventional solution-phase catalyst **2** in its ability to direct stereoselective ketone reduction. While several factors may contribute to these differences, the superior swelling characteristics of **4** relative to **3** are an obvious point in its favor. We plan to expand on this work by preparing systems similar to **3** and **4** with different degrees of cross-linking and, if feasible, defined stereochemistry at the side-chain stereocenter in analogues of **12**. Results of these experiments will be reported in due course.

Experimental Section

General Methods. All reactions were performed in oven-dried glassware under an atmosphere of dry nitrogen or argon. NMR spectra were recorded at 300 MHz in $CDCl_3$. FTIR spectra of liquids were recorded neat and those of solids either as KBr pellets or using ATR. Optical purities were determined by capillary GC using a 25 m Chirasil column (*β*-cyclodextrin on OV-1701). (*S*)-Oxazaborolidine **2** was prepared from **8a** and trimethylboroxine according to the method of Mathre et al.[5] Detailed preparations of **6**,[10] **7a**,[3,5] **7b**, **8a**,[5] and **8b** are described elsewhere.[4]

(5*S*)-1-Aza-3-oxa-4,4-diphenylbicyclo[3.3.0]octan-2-one (9).[11] A solution of 10.0 g of **7a** (0.028 mol) and 15.9 g of KOH (0.283 mol) in 128 mL of MeOH was heated to reflux for 6 h. After addition of 128 mL of water, the product precipitated out within 1 h. It was filtered, washed with cold hexane, and recrystallized from Et_2O and hexane to afford 6.80 g (86%) of **9** as a white solid: mp 148−150 °C. IR 3059, 2972, 1756, 1449 cm^{-1}; ^1H NMR δ 7.6 (m, 10H), 4.5 (dd, J = 10.4, 5.5 Hz, 1H), 3.8−3.6 (m, 1H), 3.4−3.2 (m, 1H), 2.2−1.9 (m, 2H), 1.9−1.8 (m, 1H), 1.2−1.0 (m, 1H); ^{13}C NMR δ 160.7, 143.1, 140.1, 128.5, 128.21, 128.18, 127.6, 125.8, 125.4, 85.8, 69.2, 46.1, 29.1, 25.0; $[\alpha]^{23}_{589}$ = −242.1 (c = 0.025, MeOH). Lit.[11] $[\alpha]_{589}$ −241.6 (c = 0.002, MeOH).

Polymer-Supported Boc-Protected Cross-Linking Amino Alcohol 13. Into a 500 mL two-necked indented flask with a 45/50 joint equipped with a propeller-shaped mechanical stirrer were added 184.9 mL of water and 12.9 g of Gum Arabic, and a stir rate of 475 rpm was maintained. A mixture of 9.44 g (90.59 mmol) of styrene, 0.107 g (0.442 mmol) of benzoyl peroxide, 13.4 mL of chlorobenzene, and 0.75 g (1.85 mmol) of monomer **7b** was prepared and added to the stirred aqueous mixture. The reaction vessel was heated to 85 °C while the 475 rpm stir rate was maintained. After 2 h the stir rate was lowered to 215 rpm, and 0.178 g of Al_2O_3 (1.75 mmol) was added to inhibit droplet coalescence. The temperature and stir rate were maintained at 85 °C and 215 rpm, respectively, for an additional 24 h. The newly formed resin was collected by filtration and washed in turn with water, THF, CH_2Cl_2, MeOH, CH_2Cl_2, MeOH, CH_2Cl_2, and MeOH. The beads were dried under vacuum overnight to yield 7.03 g (69% yield) of resin **13**.

Polymer-Supported Cross-Linking Amino Alcohol 14. A mixture of 5.00 g of resin **13**, 1.07 g of KOH (19.0 mmol), 28 mL of DMSO, and 6.3 mL of MeOH was heated to 65 °C for 4 d. The resin was filtered and washed with water, THF, CH_2Cl_2, MeOH, CH_2Cl_2, MeOH, CH_2Cl_2, and MeOH. The beads were dried under vacuum overnight to yield 4.52 g of resin **14**: IR 3312 cm^{-1} (br), no absorption in the vicinity of 1670 cm^{-1}. Elemental analysis (calcd, N, 0.56; found, N, 0.56) indicated the presence of 0.40 mequiv of auxiliary/g of resin, and a cross-link density of 4.53 mol %.

Polymer-Supported Cross-Linking Amino Alcohol 14 (Direct Preparation from 8b). In the manner described for the polymerization of monomer **7b**, 0.56 g of monomer **8b** was copolymerized with styrene to afford 2.9 g (29% yield) of resin **14**.

2-(Hydroxy[4-vinylphenyl][4-{1-methylethyl}phenyl]-methyl)pyrrolidine-1- carboxylic Acid *tert*-Butyl Ester (12). Freshly cut Mg ribbon (1.46 g, 60.3 mmol) was placed under vacuum, flame dried, and stirred under vacuum for 24 h. A solution of 10.0 g of 4-isopropyl-1-bromobenzene (50.2 mmol) in 90 mL was added, the mixture was refluxed for 30 min, and 1.52 g of 1,2-dibromoethane (8.09 mmol) was added, followed by 30 min of additional refluxing. The Grignard solution was cooled to 0 °C, and a solution of 11.3 g of *N*-(*t*-BOC)-L-proline *N*′-methoxy-*N*′-methylamide (**10**)[12] (43.7 mmol) in 20 mL of THF was added. The solution was slowly warmed to rt and then heated at 45 °C for 24 h. The solution was cooled to −78 °C, and 10 mL of water was slowly added. After the mixture was allowed to warm to rt, the solution was decanted and the precipitated salts were washed with Et_2O. The combined solution was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. The crude ketone product **11** was not characterized but added directly at 0 °C to a solution of 4-vinylphenylmagnesium bromide, which had been

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(12) (a) Sibi, M. P.; Stessman, C. C.; Schultz, J. A.; Christensen, J. W.; Lu, J.; Marvin, M. *Synth. Commun.* **1995**, *25*, 1255−1264. (b) De Luca, L.; Giacomelli, G.; Taddei, M. *J. Org. Chem.* **2001**, *66*, 2534−2537.

prepared as described above from 13.6 g of 4-bromostyrene (74.3 mmol) and 2.17 g of Mg (89.1 mmol) in 250 mL of THF. The solution was allowed to stir for 4 h and then cooled to −78 °C. Workup as above (except for drying over anhydrous K_2CO_3) gave the crude product, which was subjected to flash chromatography (silica, EtOAc−hexane) to yield 8.98 g of **12** (49% overall yield): mp 83−84 °C; IR 3317(br), 1662, 1169 cm^{-1}; ^1H NMR δ 7.4 (m, 4H), 7.3 (d, J = 8.2 Hz, 2H) 7.1 (d, J = 8.2 Hz, 2H), 6.7 (dd, J = 17.7, 10.9 Hz, 1H), 5.7 (dd, J = 17.6, 0.8 Hz, 1H), 5.2 (dd, J = 10.9 Hz, 1.0 Hz, 1H), 4.9 (dd, J = 8.9, 3.7 Hz, 1H), 3.4−3.2 (m, 1H), 3.0−2.8 (m, 2H), 2.2−2.0 (m, 1H), 2.0−1.8 (m, 1H), 1.5−1.3 (m, 10H), 1.2 (d, J = 6.9 Hz, 6H), 0.8 (s, 1H); ^{13}C NMR δ 147.7, 146.3, 140.9, 136.6, 136.3, 128.0, 127.9, 125.7, 125.4, 113.8, 81.5, 80.6, 65.8, 48.1, 33.9, 30.0, 28.6, 24.3, 23.1; $[\alpha]^{23}_{589}$ −130.6 (c = 0.027, MeOH). Anal. Calcd for $C_{27}H_{35}NO_3$: C, 76.92; H, 8.37. Found: C, 76.65; H, 8.35.

Polymer-Supported Pendant Amino Alcohol 15. In the manner described for the polymerization of monomer **7b**, 8.77 g (84.2 mmol) of styrene, 0.43 g of 55% *p*-divinylbenzene, and 0.80 g (1.90 mmol) of monomer **12** were copolymerized in the presence of 180 mL of water, 12.5 g of Gum Arabic, 0.103 g (0.426 mmol) of benzoyl peroxide, and 13 mL of chlorobenzene. Similar workup gave 7.32 g (73.2% yield) of resin, 5.00 g of which was deprotected directly as follows. A mixture of the resin, 1.07 g of KOH (19.0 mmol), 28 mL of DMSO, and 6.3 mL of MeOH was heated to 65 °C for 4 d. Workup as described above and drying gave 4.59 g of resin **15**: IR 3313 cm^{-1} (br), no absorption in the vicinity of 1670 cm^{-1}. Elemental analysis (calcd, N, 0.45; found, N, 0.39, 0.52) indicated the presence of ca. 0.32 (±0.04) mequiv of auxiliary/g of resin.

Polymer-Supported Oxazaborolidine Catalyst 3. A solution of 0.074 g of trimethylboroxine (0.59 mmol) in 25 mL of THF was added to 2.74 g of **15** (ca. 0.32 mequiv/g). The mixture was gently agitated on an orbital shaker for 48 h, followed by addition of 56 mL of toluene and slow short-path distillation to remove most of the toluene. The toluene "flushing" was repeated twice to ensure removal of water and methylboronic acid, and finally the beads of **3** were dried under vacuum.

Polymer-Supported Cross-Link-Bound Oxazaborolidine Catalyst 4. A solution of 0.10 g of trimethylboroxine (0.80 mmol) in 25 mL of THF was added to 3.00 g of **14** (0.40 mequiv/g). Treatment as described for **3** above afforded beads of **4**.

Representative Procedure for Reductions Using Solution-Phase Catalyst 2. 1-Phenylethanol from Acetophenone Using Catalyst 2. To 20 mL of a 0.074 M solution of **2** in THF at 0 °C was added 1.77 mL of 1 M BH_3·THF. This was followed quickly by the addition of 0.35 g of acetophenone (2.94 mmol) in 0.5 mL of THF. The solution was stirred for 30 min at rt, treated with 5 mL of 0.5 M HCl, and stirred for an additional 10 min. The solution was extracted twice with Et_2O. The extracts were washed with brine, dried (Na_2SO_4), and concentrated. A GC of the crude product was compared to those of acetophenone and a racemic sample of 1-phenylethanol. These data indicated an ee of 85.8% and a yield of 100%.

Representative Procedure for Reductions Using Solid-State Catalysts 3 and 4. 1-Phenylethanol from Acetophenone Using Catalyst 4. To a suspension of 1.84 g of catalyst **4** (0.40 meq/gram) in 15 mL of THF at 0 °C was added 0.88 mL of 1M BH_3·THF, followed quickly by 0.18 g of acetophenone (1.46 mmol). The flask was shaken for 24 h, the mixture filtered, and the resin washed with THF, MeOH, THF, MeOH, and THF. The combined filtrates were evaporated under reduced pressure, treated with 5.0 mL of 0.5 M HCl, and partitioned with Et_2O. The organic extracts were dried (Na_2SO_4) and concentrated. GC analysis indicated an ee of 84.8% and a 100% yield.

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Note added in proof: In a paper that appeared subsequent to the acceptance of this manuscript, Hodge, et. al., report a comparison of solution-phase, pendant, and cross-link polymer-bound diarylprolinol derivatives in the enantioselective addition of dialkylzinc reagents to aldehydes: Kell, R. J.; Hodge, P.: Nisar, M.; Watson, D. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1803−1807.

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