Asymmetric Borane Reduction of Prochiral Ketones by Polymer-Supported Chiral Sulfonamides

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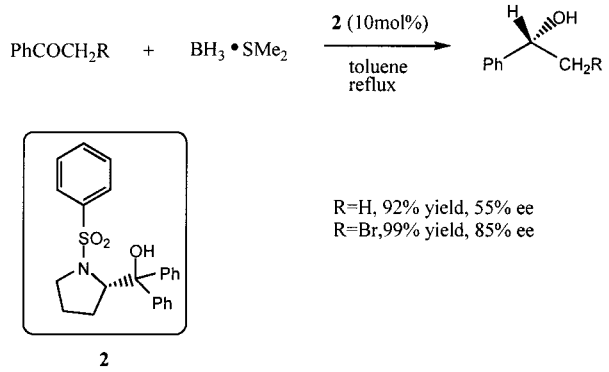
Polymer-supported (PS) sulfonamides have been prepared by treating polymeric sulfonyl chlorides with (*S*)-diphenylprolinol. The PS sulfonamides were investigated as catalysts for the reduction of ketones by borane-dimethyl sulfide complex. When the reductions were conducted in refluxing THF with 15mol % **1f** as catalyst, excellent chemical yields and enantiomeric excess were obtained. In addition to being recyclable, the catalyst provided greater enantioselectivity than the homogeneous catalyst **2**.

The enantioselective reduction of prochiral ketones by chiral catalysts and reagents has received intensive interests in the past 20 years.[1] A variety of homogeneous chiral catalysts and reagents have been developed for the reduction.[2] However, the recovery and purification of these catalysts and reagents are problematic. Immobilization of chiral catalysts or reagents offers a solution to the problem. The intrinsic advantages of polymer-supported catalysts are that they can be used in excess and recovered by filtration at the end of reaction without loss of activity.[3] Several polymer-supported catalysts derived from chiral amino alcohol have been developed for reductions, but only few of them have displayed a high enantioselectivity due to the polymer matrix restricting the mobility of the catalytic site.[4]

Recently, we reported that the reduction of aromatic ketones using a catalytic amount (10 mol %) of homogeneous chiral sulfonamides provided secondary alcohols with 55−91% ee[5] (Scheme 1). We demonstrated that stereoselectivity is temperature dependent, with higher reaction temperatures preferable (refluxing toluene). Under the optimal reaction conditions, homogeneous sulfonamide **2** was applied to the reductions of acetophenone and α-bromoacetophenone to give 55% ee and 85% ee, respectively.

In this paper, we report asymmetric reduction of prochiral ketones in the presence of polymer-supported chiral sulfonamides **1** as catalysts.

Scheme 1. Asymmetric Reduction of Ketones by Homogenous Chiral Sulfonamide 2.



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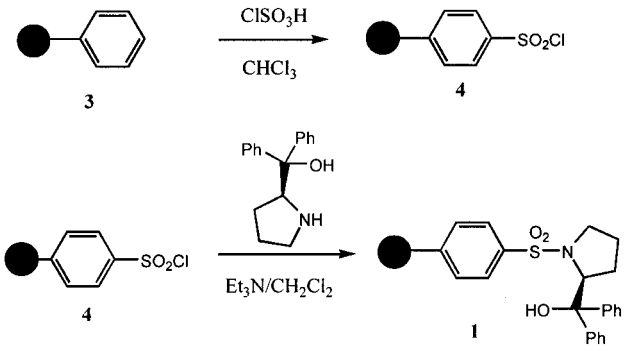
Scheme 2 . Preparation of Polymer-Supported Chiral Sulfonamides



Results and Discussion

Synthesis of Catalysts. The preparation of **1** is a two-step sequence starting from styrene−divinylbenzene cross-linked polymers (1% or 2% divinylbenzene) (Scheme 2). Initially, chlorosulfonylation of the polymer beads was performed as described in the literature.[6] We made an effort to maximize the amount of loading sites in the beads in order to increased the density of reactive sites, but full chlorosulfonylation of **3** was not achieved. Irrespective of the cross-linking in the original resin (1 or 2%), the post-sulfonylated resin has 4.1−4.7 mmol/g of available sulfonyl chloride. The second step, the synthesis of the polymer-supported chiral sulfonamides was accomplished by treating **4** with an excess of (s)-diphenylprolinol in the presence of Et_3N in CH_2Cl_2.

Examination of Reaction Conditions. It is well-known that the stereoselectivity of reduction is effected profoundly by solvent, temperature and the amount of catalyst. To examine these effects, the reduction of acetophenone was investigated at various reaction conditions. Two solvents (THF and toluene) and a wide range of 1% and 2% cross-linked polystyrene resins with different degrees of functionalization were investigated. Typical procedure for the reduction: $BH_3{\cdot}SMe_2$ (0.11 mmol) was added to a suspension of the catalyst in THF (5 mL). The suspension was stirred and refluxed for 1h. Then a THF (5 mL) solution of acetophenone (0.121 g, 0.1 mmol) was added slowly in 30 min. After the reaction

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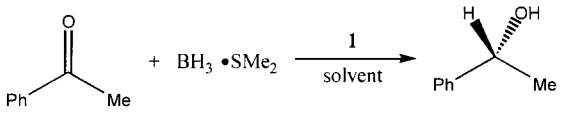
Table 1. Effect of Temperature, Solvent, and Catalyst[a,b]

entry	polymer catalyst	amount of catalyst (%)	solvent	*T* (°C)	yield[c] (%)	ee[d] (%)
1	**1a**	15	THF	reflux	87	63.5
2	**1b**	15	THF	reflux	89	75.0
3	**1c**	15	THF	reflux	93	84.5
4	**1d**	10	THF	reflux	92	65.6
5	**1e**	10	THF	reflux	90	68.2.
6	**1f**	5	toluene	reflux	92	50.5
7	**1f**	10	toluene	reflux	91	63.3
8	**1f**	15	toluene	reflux	91	89.1
9	**1f**	20	toluene	reflux	89	84.8
10	**1f**	15	toluene	rt	86	0
11	**1f**	10	THF	reflux	91	71.8
12	**1f**	15	THF	reflux	95	**92.5**
13	**1f**	20	THF	reflux	89	75.0
14	**1f**	15	THF	rt	86	24.2

[a] Molar ratio, $PhCOCH_3/BH_3{\cdot}SMe_2$ = 1.0:1.1 and the absolute configuration was *R*. [b] Cross-linking in the original resin for **1a**−**c** and **1d**−**f** are 1% and 2%, respectively. Sulfonamide content in resin **1a** (2.23 mmol/g), **1b** (2.26 mmol/g), **1c** (2.29 mmol/g), **1d** (2.12 mmol/g), **1e** (2.28 mmol/g), and **1f** (2.29 mmol/g). [c] Isolated yield after column purification. [d] Determined by HPLC analysis using Diacel chiralcel OJ column (eluent: hexane/2-propanol = 9:1).

was completed, the mixture was treated with water and filtered, washing several times with EtOAc and water. The results are showed in Table 1.



Several conclusions can be drawn: (1) Higher reaction temperatures afforded higher enantiomeric excess (entry 9 vs 11, 13 vs 14). (2) In both solvent systems, the ee increased as the molar percentage of catalyst increased, but only up to 15 mol %. (3) THF is a more effective solvent for the reduction. The best ee was obtained when the reaction was carried out in refluxing THF with 15mol % catalyst **1f**. Accordingly, all subsequent reductions were performed under this condition. (4) Under similar reaction conditions, the polymeric catalyst **1f** was better than the homogeneous catalyst **2** (see entry 7 and Scheme 1). (5) Comparison of entries 1, 2 vs 3 and 4, 5 vs 11 indicated that enantioselectivity was influenced by the degree of functionalization. Better enantiomeric excess can be obtained with higher degree of functionalization. (6) Entries 3 and 12 suggested that the polymer catalyst from 2% DVB was better than that from 1% DVB.

Having established the best reaction conditions, the application of **1f** to the reduction of other prochiral ketones was investigated using a catalytic amount 15mol % **1f** in refluxing THF. Table 2 summarized these results.

All reductions gave excellent yields and good enantiomeric excess. The results demonstrated that electron density of the aromatic ring had a significant impact on the enantioselectivity. Comparison of the results obtained with acetophenone, p-methoxyacetophenone and *p*-nitroacetophenone indicated that an electron-withdrawing group was helpful for high enantioselectivity.

Recycling of Catalyst 1f. As we described above, one of the advantages of polymer-supported catalyst is its easy recovery by filtration. The recycling of **1f** was investigated by the reduction of *p*-nitroacetophenone. The catalyst was recovered and reused five times with no loss of catalytic efficiency (95.8−96.5% ee).

Table 2. Asymmetric Reduction of Prochiral Ketones Using Polymer-Supported Chiral Sulfonamide 1f[a]

entry	ketone	yield (%)	ee (%)	config[g]
1	*p*-bromoacetophenone	98	94.2[b]	*R*
2	α-chloroacetophenone	98	91.2[b]	*S*
3	p-methoxyacetophenone	96	84.0[c]	*R*
4	*β*-acetonaphthone	98	89.7[b]	*R*
5	*p*-nitroacetophenone	99	95.9[d]	*R*
6	α-bromoacetophenone	99	93.8[b]	*S*
7	benzylacetone	99	52.9[e]	*R*
8	1,1,1-triphenylacetone	86	82.7[f]	*R*

[a] Molar ratio: ketone/$BH_3{\cdot}SMe_2$ = 1.0:1.1; isolated yields after column purification. [b] Determined by HPLC analysis using Daicel chiralcel OJ column (eluent: hexane/2-propanol = 9:1). [c] Determined by chiralcel AS column (eluent: hexane/2-propanol = 8:2). [d] Determined by chiralcel OJ column (eluent: hexane/2-propanol = 85:15). [e] Determined by chiralcel OD column (eluent: hexane/2-propanol = 9:1). [f] Determined by chiralcel AD column (eluent: hexane/2-propanol = 9:1). [g] The absolute configuration were determined by optical rotation.

Conclusion

In summary, we have developed a new heterogeneous catalyst of polymer-supported sulfonamides for the enantioselective borane reduction of prochiral ketones. The enantiomeric excess with polymer catalyst **1f** were better than those obtained with homogeneous catalyst **2**. The catalyst can be recycled at least five times with minimal loss of catalytic performance.

Experimental Section

All reactions were carried out under nitrogen. THF was dried over sodium and freshly distilled before use. Toluene was distilled over calcium hydride. Acetophenone and benzylacetone were dried and distilled over calcium hydride. Other ketones were further purified by recrystallization before use. (*S*)-Diphenylprolinol was prepared according to the literature procedures.[7] Borane-dimethyl sulfide was obtained from Aldrich Chemical Co. 1 and 2% cross-linked polystyrene resins (200−400 mesh) were obtained from Merck Company. The purity of all reagents were checked by NMR spectroscopy.

General Procedure for Preparation of Polymeric Catalyst 1. To (*S*)-diphenyprolinol (1.0 g, 4 mmol) in CH_2Cl_2 (30 mL) and Et_3N (0.14 mL, 1 mmol) was added polymeric sulfonyl chloride **4f** (2% divinylbenzene; Cl = 4.73 mmols/g; 0.214 g; 1 mmol of Cl) at room temperature. The mixture was stirred for 3 days. The polymer was then filtered and washed with methanol, water, methanol−water (V/V = 1:1), and methanol, respectively. After drying in vacuo at 50 °C for 5 h, 0.451 g polymer was obtained. The chemical composition is summarized in Table 1.

General Procedure for Asymmetric Reduction of Prochiral Ketones Using Polymer-Supported Catalyst 1 and Borane. $BH_3{\cdot}SMe_2$ (1.1 mmol) was added to a suspension of polymeric catalyst **1f** (2.29 mmol/g; 200−400 mesh; 0.061 g; 0.15 mmol of N) in THF (5 mL). The suspension was stirred and refluxed for 1 h. Then a THF (5 mL) solution of acetophenone (0.121 g, 1 mmol) was added within 30 min. After the addition was completed, the mixture was treated with water and filtered and washed several times with EtOAc and water. The filtrate and washings were combined, extracted with EtOAc (3 × 10 mL), and dried with $MgSO_4$. The solution was evaporated and purified by silica gel chromatography to give pure product in 95% yield: $[\alpha]_D^{20}$ 48.6 (*c* 1.24, $CHCl_3$). The ee was determined to be 92.5% by chiralcel OJ column.

Supporting Information Available: Experimental procedures, chiral HPLC, and ^1H NMR data for the reduction of ketones. The material is available free of charge via the Internet at http://pubs.acs.org.

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