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Enantioselective Reduction of Ketones Catalyzed by Polymer-Supported Sulfonamide Using $NaBH_4/Me_3SiCl$ (or $BF_3 \cdot OEt_2$) as Reducing Agent**

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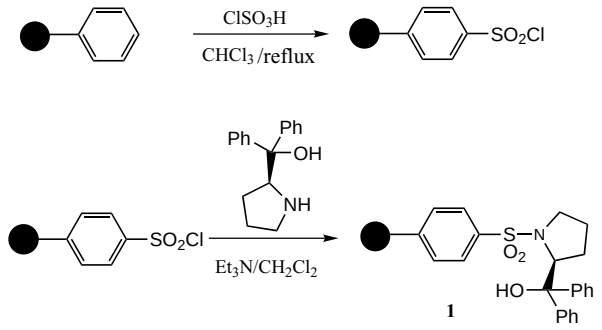
The enantioselective reduction of ketones to form optically active secondary alcohols is a major area of research in organic chemistry, and a large number of reducing agents and chiral catalysts have been developed that facilitate this reaction under a wide range of conditions.[1] One of the most successful reduction reactions involves the use of borane in the presence of homogeneous catalysts derived from chiral amino alcohols.[2] These catalysts often provide higher enantioselectivities than heterogeneous catalysts, but the development of efficient heterogeneous catalysts is still a challenging target, because workup of the reaction and the recovery of heterogeneous catalysts are more convenient than those of homogeneous catalysts. In the past decade, various groups have reported the preparation and application of heterogeneous catalysts for the enantioselective reduction of ketones,[3] and several reducing agents were used: BH_3,[4] $NaBH_4$,[5] and $LiAlH_4$.[6] Of these reducing agents, BH_3 was most widely applied and gave the best results in the presence of polymer-supported chiral amino alcohols. However, only a few of the reducing agents displayed high reactivity and enantioselectivity owing to the diffusion limitations caused by the polymer matrix. Furthermore, the use of BH_3 as a reducing agent requires a lot of precautions because of its toxicity. It is therefore necessary to develop new reducing systems that can easily be employed and that give high enantiomeric excesses.

It has been reported that diborane can be generated by treating $NaBH_4$ with Me_3SiCl[7] or $BF_3 \cdot OEt_2$.[8] Herein, to the best of our knowledge, we report the first asymmetric reduction of ketones by employing $NaBH_4/Me_3SiCl$ (or $BF_3 \cdot OEt_2$) as reducing agents, and polymer-supported chiral sulfonamide **1** as the catalyst (Scheme 1).

The two-step synthetic route to **1** is outlined in Scheme 1. In the first step, the polymer beads of polystyrene resin (2% divinylbenzene, 200 – 400 mesh) were treated with excess



Scheme 1.

chlorosulfonic acid in refluxing chloroform to give the chlorosulfonylated polymer according to a literature procedure.[9] This polymer was synthesized several times; the yield was typically 96%, and the degree of chlorosulfonylation determined by elemental analysis was 4.72 mmol Cl and 4.73 mmol S per gram of polymer. In the second step, (*S*)-diphenylprolinol was grafted onto the chlorosulfonylated polymer in the presence of Et_3N at room temperature over four days. After the reaction was complete, the insoluble chiral polymer **1** was isolated from the reaction mixture by filtration, and then thoroughly washed with water and methanol. Chiral polymer **1** was characterized by IR spectroscopy, which revealed the characteristic absorptions of the SO_2 group at 1154 and 1359 cm^{-1}, and by elemental analysis, which showed that the N content was 2.29 mmol per gram of **1**.

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[**] This work was supported by the Ministry of Sciences and Technology, the State Key Project of Basic Research (Project 973, No. G 2000048007).

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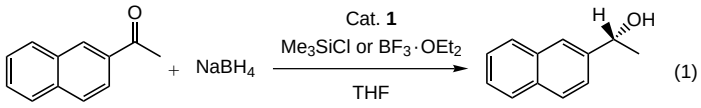
To determine the best reaction conditions, we chose the reduction of β-acetonaphthone as a model reaction [Eq. (1)],



(1)

and the results are shown in Table 1. We used THF as the solvent because the diborane produced can form a borane–THF complex.[7] The reductions proceeded smoothly with both $NaBH_4/Me_3SiCl$ and $NaBH_4/BF_3\cdot OEt_2$ as reducing agents, and excellent yields were obtained under all the reaction conditions studied. The results given in Table 1 show that the level of enantiomeric excess is sensitive to the reaction temperature. As in similar cases, a decrease in the reaction temperature leads to a reduction of the stereoselectivity (Table 1, entries 1 and 2).[4d, 5, 10] The enantioselectivity is significantly affected by temperature probably because of the increased flexibility of the chiral polymer and the better mobility of the substrates in the polymer at higher temperature, hence making the catalytic sites on the polymer beads more accessible to the substrates.

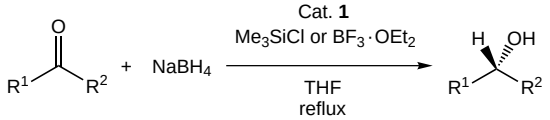
Table 1. Asymmetric reduction of acetonaphthone under different reaction conditions.[a]

Entry	Chiral polymer [mol %]	T [°C]	$NaBH_4/Me_3SiCl$ Yield [%][b]	*ee* [%][c]	$NaBH_4/BF_3\cdot OEt_2$ Yield [%][b]	*ee* [%][c]
1	10	RT	99	9.7	98	0
2	10	reflux	n.d.	n.d.	99	80.3
3	15	reflux	98	89.2	99	95.3
4	20	reflux	99	93.1	98	94.5
5	25	reflux	98(97)[d]	96.3(89.5)[d]	n.d.	n.d.
6	30	reflux	98	95.5	n.d.	n.d.

[a] The solvent for acetonaphthone was added by means of a syringe pump. The absolute configuration was determined to be *R* by comparison with the reported specific rotation (n.d. = not determined). [b] Yields of isolated products. [c] Determined by using chiral HPLC. [d] The solvent for acetonaphthone was added with a dropping funnel.

Apart from the reaction temperature, the ratio of the catalysts has an enormous impact on the reduction. As the amount of catalyst was progressively increased, the enantiomeric excess at first increased and then leveled out. The maximum *ee* levels of 96.3% and 95.3% for $NaBH_4/Me_3SiCl$ or $NaBH_4/BF_3\cdot OEt_2$, respectively, can be obtained with different catalyst ratios (Table 1, 25% mmol and 15% mmol, cf. entries 5 and 3, respectively. Adjidjonou and Caze reported similar effects in reductions using a polymer-supported catalyst.[5]

To extend the scope of the reduction, we studied the reduction of other ketones under the optimum reaction conditions [Eq. (2)], and the results are summarized in Table 2. Our reducing systems were highly efficient in the reduction of ketones. In all cases, the total conversion of the ketones into the corresponding alcohols was obtained in yields of more than 91%. On the other hand, a significant variation in the *ee* values was observed, depending on the nature of the ketones. The two reducing systems were all especially effective in the reduction of aromatic ketones, but much less so in the reduction of the alkyl ketones. The *ee* value obtained in the reduction of aromatic ketones was as high as 96.6%, whereas the maximum *ee* for the alkyl ketones was only 89.5%. Furthermore, the reduction was affected by the electronic effects of the substituents on the phenyl ring. Interestingly, an electron-withdrawing group improved the reactivity and enantioselectivity. *p*-Methoxyacetophenone gave a lower reaction rate than *p*-nitroacetophenone: 3 h and 2 h, respectively, were needed for complete conversion. Furthermore, the *ee* values from the reduction of *p*-methoxyacetophenone were lower than those from *p*-nitroacetophenone (Table 2, 84% and 96%, cf. entries 3 and 4, respectively).



(2)

Table 2. Asymmetric reduction of ketones.[a]

Entry	Ketone	$NaBH_4/Me_3SiCl$ Yield [%][b]	*ee* [%][c]	$NaBH_4/BF_3\cdot OEt_2$ Yield [%][b]	*ee* [%][c]	Config.[e]
1	acetophenone	98	95.7	98	95.1	*R*
2	*p*-bromoacetophenone	97	96.1	98	94.1	*R*
3	*p*-methoxyacetophenone	97	84.1	97	84.2	*R*
4	*p*-nitroacetophenone	99	96.6	98	96.0	*R*
5	α-chloroacetophenone	98	96.1	98	95.8	*S*
6	α-bromoacetophenone	99	96.6	98	94.0	*S*
7	α-tetralone	98	91.0	98	86.1	*R*
8	benzylacetone	97	65.1	98	64.5	*R*
8	1,1,1-triphenylacetone	96	89.5	95	87.0	*R*
9	1-cyclohexyl-1-propanone	95	71.1	96	69.8	*R*
10	2-butanone	91	50.6[d]	92	47.5[d]	*R*

[a] Experiments were performed on a 1 mmol scale. [b] Yields of isolated products after purification by column chromatography or by distillation. [c] Determined by using chiral HPLC. [d] Analytical samples were converted into 3-chlorophenylcarbamates.[11] [e] The absolute configurations were determined by comparison with the reported specific rotations.

After the reduction was complete, the polymer-supported catalyst was easily removed by filtration. The catalyst was regenerated by first washing with refluxing methanol to eliminate the alcohol encapsulated in the polymer matrix, and then washing with hot water to remove the inorganic compounds formed in the reaction. Tests on the reduction of acetophenone (Table 3) show that the chiral polymer-supported catalyst can be recycled at least three times with little or no loss of performance.

Table 3. Recycling of chiral polymer (reduction of acetophenone).[a]

Run	$NaBH_4/Me_3SiCl$ Yield [%][a]	*ee* [%][b]	$NaBH_4/BF_3\cdot OEt_2$ Yield [%][a]	*ee* [%][b]
1	98	95.5	98	95.7
2	97	96.3	98	92.8
3	98	95.4	97	94.6

[a] Yields of isolated products. [b] Determined by using chiral HPLC.

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In summary, we have clearly demonstrated that two kinds of reducing systems ($NaBH_4/Me_3SiCl$ or $NaBH_4/BF_3 \cdot OEt_2$) in combination with the new, chiral, polymer-supported *N*-sulfonamide **1** are effective in the reduction of prochiral ketones. The best *ee* values are obtained when the reduction is carried out in refluxing THF. The chiral polymer can be recovered easily and reused. The two reducing systems described should offer advantages over other reducing systems and thus find new applications.

Experimental Section

All reactions were carried out under nitrogen. THF was dried over sodium and freshly distilled before use. (*S*)-Diphenylprolinol was prepared according to a literature procedure.[12] Cross-linked polystyrene resin (2%, 200–400 mesh) was obtained from Merck Company. The purity of all the reagents were checked by NMR spectroscopy.

Preparation of ***1***: Polymeric sulfonyl chloride (0.214 g, 1 mmol) was added to a solution of (*S*)-diphenylprolinol (1.016 g, 4 mmol) in CH_2Cl_2 (30 mL) and Et_3N (0.104 g, 1 mmol) at room temperature. The resulting mixture was stirred for four days. The polymer was then filtered off and washed successively with methanol, water, methanol/water (1:1), and methanol. After drying in vacuo at 50 °C for 5 h, the desired polymer (0.451 g) was obtained in approximately 96% yield.

General procedure for the asymmetric reduction of prochiral ketones using ***1*** *and* $NaBH_4/Me_3SiCl$: Me_3SiCl (0.132 mg, 1.2 mmol) was added to a suspension of $NaBH_4$ (45 mg, 1.2 mmol) in THF (10 mL). The suspension was heated at reflux and stirred for 1 h. Polymer-supported catalyst **1** (98 mg, 0.25 mmol) was added, and the reaction mixture was heated at reflux for a further 0.5 h. A solution of acetophenone (120 mg, 1 mmol) in THF (10 mL) was added at a rate of 3 mL h^{-1} with a syringe pump. After the addition was complete, the mixture was treated with water and filtered. The polymer-supported catalyst was washed several times with EtOAc and water. The resulting aqueous solution was extracted with EtOAc (3 × 10 mL) and dried with $MgSO_4$. The solution was evaporated and purified by silica-gel chromatography to give the pure product (120 mg, 0.98 mmol, 98%). $[\alpha]_D^{20} = +52.6$ ($c = 2.23$, $CHCl_3$). The optical yield was determined to be 95.7% by using chiralcel OJ column chromatography.

General procedure for the asymmetric reduction of prochiral ketones using polymer-supported catalyst ***1*** *and* $NaBH_4/BF_3 \cdot OEt_2$: $BF_3 \cdot OEt_2$ (0.254 mg, 1.8 mmol) was added to a suspension of $NaBH_4$ (46 mg, 1.2 mmol) in THF (10 mL). The suspension was heated at reflux for 0.5 h. Polymer-supported catalyst **1** (59 mg, 0.15 mmol) was added, and the reaction mixture was heated at reflux for a further 0.5 h. A solution of acetophenone (120 mg, 1 mmol) in THF (10 mL) was then added at a rate of 3 mL h^{-1} with a syringe pump. After the addition was complete, the mixture was treated with water and filtered. The polymer-supported catalyst was washed several times with EtOAc and water. The resulting aqueous solution was extracted with EtOAc (3 × 10 mL) and dried with $MgSO_4$. The solution was evaporated and purified by silica-gel chromatography to give the pure product (120 mg, 0.98 mmol, 98%). $[\alpha]_D^{20} = +52.4$ ($c = 1.01$, $CHCl_3$). The optical yield was determined to be 95.1% by using chiralcel OJ column chromatography.

Received: September 6, 2000 [Z15769]

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An Asymmetric Enzyme-Catalyzed Retro-Claisen Reaction for the Desymmetrization of Cyclic β-Diketones**

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The desymmetrization of prochiral compounds is of increasing importance in asymmetric synthesis because, in principle, quantitative yields with absolute optical purity may be obtained.[1] Enzyme-catalyzed approaches to desymmetrization have, for the most part, involved the application of carbon–heteroatom hydrolases such as lipases and esterases.[2] Reactions involving C–C bond cleavage are much rarer, although the group of Taschner was successful in applying an enzyme-catalyzed Baeyer–Villiger reaction to the desymmetrization of a variety of prochiral ketones.[3] The desymmetrization of prochiral β-diketones by a retro-Claisen reaction has been reported using chiral bases, although diastereomeric and enantiomeric excesses were generally

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[**] This work was supported by the BBSRC (grants to N.J.T. and S.L.F.) and the European Commission (grant to J.G.). We also thank Mr. J. Millar and Dr. D. Uhrin for assistance with NMR spectroscopy.