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Asymmetric Reduction of Aromatic Ketone in a Continuous Flow System

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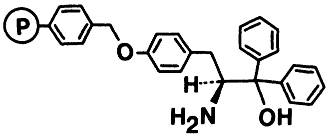
Synopsis. When THF–borane (1/1) and aromatic ketone were supplied continuously to the column containing polymer-supported (*S*)-(−)-2-amino-3-(*p*-hydroxyphenyl)-1,1-diphenyl-1-propanol, the chiral product, secondary benzylic alcohol, could be obtained successfully (>90% ee). Large quantities of highly optically pure alcohol could be produced by the continuous flow system by the use of only a small amount of polymeric auxiliary.

Though many procedures have been known for syntheses of optically active alcohols by the asymmetric induction in solutions,[1)] there are relatively few methods involving the use of the chiral polymer-supported reagent.[2)] We have reported that polymer-supported (*S*)-(−)-2-amino-3-(*p*-hydroxyphenyl)-1,1-diphenyl-1-propanol (**1**) was an excellent chiral auxiliary reagent for asymmetric reduction of ketones with BH_3·THF.[3)] This insoluble cross-linked polystyrene gel supporting chiral amino alcohol, which was prepared from L-tyrosine, could be readily recovered as its hydrochloride by simple filtration after acidic hydrolysis of the reaction mixture. Recovered polymer-supported hydrochloride was neutralized and could be reused. Chiral product secondary alcohol was obtained from the filtrate quantitatively with high enantioselectivity (>90% ee). Indeed the high chemical and enantiomeric yields were reproducible during several recyclings.[3,4)]



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During studies for the asymmetric reduction with polymer-supported chiral amino alcohol **1**–borane complex, an interesting fact was observed. After reduction of ketone with the polymeric reagent, careful filtration of the reaction mixture under a dry nitrogen stream without hydrolytic process gave the THF solution, which was successively hydrolyzed to yield the optically active secondary alcohol quantitatively with high enantioselectivity. Even after the filtration the chiral polymer containing the amino alcohol–borane complex had the ability to induce chirality in the ketone reduction with borane. Thus, if borane and substrate ketone are supplied continuously to the polymer complex, the chiral product may be obtained successively.

In a preliminary experiment, repeated asymmetric reduction in the batch system was attempted. Glassware being made up of two flasks (**A**, **B**) and glass filter was used for this system (Fig. 1). A THF solution of the chiral product yielded in the asymmetric reduction in the flask **A** was filtered into the flask **B**. Table 1 lists the results obtained from the batch system in the asymmetric reduction of valerophenone with **1**-BH_3 complex. In the first run valerophenone was reduced asymmetrically (90% ee) with the reagent prepared from **1** and 2 equiv of BH_3. Reaction was completed within a few minutes in THF at ambient temperature. After separation of the product by filtration under nitrogen 2 equiv of borane and 0.8 equiv of valerophenone were added again (flask **A**). Another optically active 1-phenyl-1-pentanol was obtained in 82% ee from the filtrate (Batch No. 2). In this batch system optical yields were reproducible on five repeated runs. Accumulated yield of isolated optically active alcohol was about 2.4 times the molar quantity of the chiral auxiliary reagent **1** after five repetitions. Although the conversion of ketone to alcohol was 100% by GC analysis, isolated yield was somewhat low owing to handling loss during the purification by distilling a small amount of the product in each fraction. Asymmetric reduction of some other alkyl phenyl ketones was performed. Large amount of optically active purified alcohols were isolated in this system. Results are summarized in Table 2.

The fact that the product was not bonded covalently to the polymeric chiral complex and optically active alcohol was obtained from the filtrate successively by hydrolysis implies this reaction could be conducted

Table 1. Asymmetric Reduction of Valerophenone in Batch System

Batch No.	Optical yield[a)]/% (Config)	[Isolated yield]/[**1**] (Accumulated)
1	90(*R*)	0.42
2	82(*R*)	0.97
3	84(*R*)	1.40
4	92(*R*)	2.00
5	81(*R*)	2.37

a) Values for maximum rotation and confguration taken from Ref. 7).

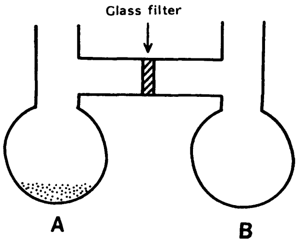

Fig. 1. Glassware for batch system.

Table 2. Asymmetric Reduction of Alkyl Phenyl Ketones in Batch System

Ketone	Number of repetition	[Isolated yield]/[**1**] (Accumulated)	Optical yield/% (Average)	Configuration
CH_3COPh	14	5.8	66[a]	*R*
C_2H_5COPh	16	8.6	72[b]	*R*
C_4H_9COPh	14	6.1	90	*R*

a) Value for maximum rotation taken from U. Nagai, T. Shishido, R. Chiba, and H. Mitsuhashi, *Tetrahedron,* **21**, 1701 (1965). b) Value for maxmum rotation taken from H. Kwart and D. P. Hoster, *J. Org. Chem.,* **32**, 1867 (1967).

Table 3. Asymmetric Reduction of Valerophenone Using Continuous Flow System[a]

Fraction No.	Rate of injection		1-Phenyl-1-pentanol		
	BH_3/THF [ml/min(mmol/min)]	Ketone/THF [ml/min(mmol/min)]	Optical yield/% (Config)	Isolated yield/mg (Accumulated)	[Isolated yield]/[**1**]
1	0.31 (0.14)	0.06 (0.11)	87 (*R*)	455	0.65
2	0.47 (0.21)	0.09 (0.17)	93 (*R*)	741	1.06
3	0.63 (0.27)	0.12 (0.23)	91 (*R*)	899	1.28
4	0.31 (0.14)	0.06 (0.11)	86 (*R*)	1196	1.70
5[b]	—	—	83 (*R*)	1502	2.14
6[c]	—	—	85 (*R*)	1824	2.60

a) 2.49 g (4.27 mmol) of **1** was used. b) Only eluent (THF) was made to flow. c) 1-Phenylpentanol remained in gel.

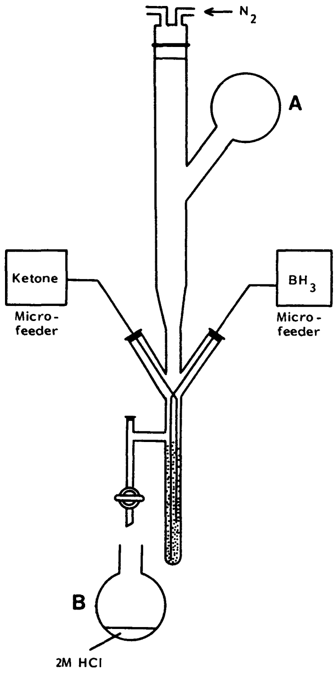

Fig. 2. Apparatus for conducting continuous flow reaction.

by a continuous flow system which avoids the repetition of a batch system process. Thus, large quantities of the highly optically pure product could be yielded through the continuous flow system by the use of only a small amount of polymeric chiral auxiliary **1**.

The procedure found to be most effective involves the two slow injections of 0.8:1.0 molar ratio of valerophenone and borane in THF to the bottom of a THF-presaturated column containing polymeric **1**-BH_3 complex through a syringe needle (Fig. 2). The polymeric **1**-BH_3 complex was prepared in the flask **A** prior to use this system. The flow rate and the ratio of borane and the ketone was controlled by means of microfeeder. The overflowed THF solution was collected in the flask **B** in which alkoxyborane was hydrolyzed with 2M HCl (1 M=1 mol dm^{-3}) to give the optically active alcohol continuously in high enantioselectivity (83—93% ee, Table 3). Optically active alcohol of 2.6 equiv to the chiral auxiliary **1** was obtained from six fractions. Rate of injection seems not to be an important factor for the asymmetric reduction in this system (Fraction No. 1—3).

A noteworthy feature of the continuous flow method is the absence of destruction of the chiral gel since no stirring was required. The chiral gel column method reported in this note offers several advantages over alternative modes, especially with regard to the extreme tractability of the reaction and the yield of large quantities of optically active alcohol by the use of the small amount of chiral auxiliary. Such a procedure as well as high enantioselectivity would be required for the practical asymmetric synthesis.

Experimental

All reactions were carried out under an atmosphere of nitrogen. Tetrahydrofuran (THF) was heated under reflux over sodium metal and distilled from lithium aluminum hydride in a nitrogen atmosphere. Valerophenone, acetophenone, and propiophenone commercially purchased were dried and distilled over calcium hydride and checked for purity by GLPC and ^{1}H NMR. Borane was prepared by the reaction of sodium borohydride with trifluoroborane–diethyl ether (1/1) according to the procedure of Brown.[5] (S)-Tyrosyne (from Kyowa Hakko Co.) was used without purification. Polymer-supported (*S*)-(−)-2-amino-3-(*p*-hydroxyphenyl)-1,1-diphenyl-1-propanol (**1**) was prepared from chloromethylated polystyrene gel (2% cross linking, 2.92 meq Cl/g) by method described previously.[3,6] GLPC analysis was performed on a Yanaco G180 instrument with a stainless steel analytical column (3 mm×3 m) packed with PEG20M on Diasolid L. ^{1}H NMR spectra were recorded by a JEOL JNM PMX-60 spectrometer. Optical rotations were measured with a microcell. IR spectra were recorded by JASCO A-3 instrument for Nujol mulls. TLC was run on silica gel 60F-254 precoated plates with chloroform as mobile phase.

Repeated Asymmetric Reduction of Valerophenone with Polymer-Supported Chiral Amino Alcohol (1)-Borane Complex in Batch System. In the flask **A** (Fig. 1) the asymmetric reducing agent was prepared from **1** (1.6 meq amino alcohol/g, 3.0 g) and 2 equiv of borane (9.6 mmol) at first by the method described previously.(3) After addition of THF solution of valerophenone (0.6 g, 3.7 mmol) reaction was checked by TLC. When no ketone was detected by TLC the polymer was filtered through glass filter under nitrogen. THF solution collected in the flask **B** was hydrolyzed with 2M HCl and THF was evaporated. The ether extract was washed with saturated NaCl (2×10 ml), dried ($MgSO_4$) and evaporated to give a colourless oil. The conversion was checked by GLPC (100%). The crude product was then distilled by bulb-to-bulb distillation to give 1-phenyl-1-pentanol (0.33 g); α_D^{20} +1.80° (neat, l=1.0 cm), corresponding to an enantiomeric excess of 90% ee.(7) To the polymer kept in the flask **A** THF (10 ml), borane (9.6 mmol), and valerophenone (3.7 mmol) was added again. After ketone was reduced the same work up as above was used to give (*R*)-1-phenyl-1-pentanol of 82% ee.

Asymmetric Reduction of Valerophenone Using Continuous Flow System. The polymer-supported chiral reagent prepared in the flask **A** (Fig. 2) from **1** (1.71 meq of amino alcohol/g, 2.49 g) and 2 equiv of borane (8.5 mmol) by the method described previously, was transfered into the column by turning the apparatus upside down. The column (the inside diameter of 1 cm) was filled with a 14 cm of the column of the chiral gel. Borane (0.14 mmol min^{-1}) and ketone (0.11 mmol min^{-1}) were injected at the bottom of the column through the syringe needle by means of microfeeder. The overflow was collected in the flask **B** containing 2M HCl. After 30 min collected fraction was worked up according to the procedure outlined above to give (*R*)-1-phenyl-1-pentanol of 87% ee. After four fractions were collected only eluent (THF) was made to flow to give the same alcohol of 83% ee (Fraction No. 5). by means of hydrolysis of the chiral gel taken out of the column, the another fraction of the same alcohol was obtained in 85% ee (Fraction No. 6).

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