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Convenient Asymmetric Borane Reduction of Ketones Catalyzed by Simple Amino Alcohols and Corresponding Amino Acids

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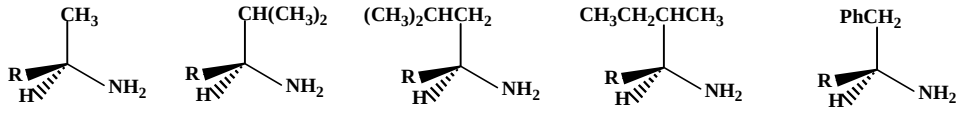
Abstract: An asymmetric borane reduction of prochiral ketones catalyzed by simple amino alcohols and corresponding amino acids was examined to give alcohols with e.e. value up to 92% .

Keyword: Enantioselective borane reduction, amino alcohols, amino acids, ketones.

The catalytic enantioselective borane reduction of ketones is a well-studied theme[1]. Since the pioneering work of Corey[2], a variety of good catalysts have been synthesized through further modification on simple amino alcohols and their corresponding amino acids[3,4] . But when simple amino alcohols were directly used in the reduction their catalytic efficiency was very low. For the first time Buono[5] has reported through carefully chosen reaction condition the catalytic efficiency of a simple amino alcohol and corresponding amino acid, (L)-prolinol and (L)-proline, could be greatly improved. Unfortunately when this method is applied in another simple amino alcohols and amino acids, the e.e. value was low[6]. It prompts us to find a good method in which the catalytic efficiency of simple amino alcohols and amino acids could be greatly improved. Here we report our results by directly using **1**-**5** as chiral auxiliaries in the reduction.

Scheme 1



(s)-**1a** (R=CH_2OH) (s)-**2a** (R=CH_2OH) (s)-**3a** (R=CH_2OH) (s)-**4a** (R=CH_2OH) (s)-**5a** (R=CH_2OH)
(s)-**1b** (R=COOH) (s)-**2b** (R=COOH) (s)-**3b** (R=COOH) (s)-**4b** (R=COOH) (s)-**5b** (R=COOH)

To optimize the reaction condition, some condition experiments were proceeded. Using 10 mol % **5a** as the model catalyst we examined the effect of solvent and temperature on the asymmetric borane reduction of acetophenone. The results were showed in **Table 1**.

The result showed that 110°C is the best suitable reaction temperature. When more catalyst was used, the e.e. did not increase. In a typical procedure **5a** (1 mmol) was suspended in toluene and 3 mL (3 mmol) BH_3/THF was added. The mixture was stirred

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Table 1 Effect of solvent and temperature on asymmetric reductions of PhCOMe with 10mol% **5a**

solvent	temperature (°C)	e.e. (%)	abs.config	solvent	temperature (°C)	e.e (%)	abs.config
THF	30	21	R	Toluene	110	79	R
THF	60	48	R	*p*-xylene	90	76	R
Toluene	30	23	R	*p*-xylene	110	78	R
Toluene	60	50	R	*p*-xylene	125	76	R
Toluene	90	78	R	*p*-xylene	138	74	R
Toluene	100	79	R				

for 15 min at room temperature and then heated to reflux. 10 mL (10 mmol) BH_3/THF and acetophenone (10 mmol) in toluene were added simultaneously *via* syringe over 50 min. After cooling to 25°C, the reaction was quenched by 15 mL HCl (2 mol/L) and the aqueous layer was extracted with diethyl ether (3×15 mL). The combined organic layer was washed by brine, then dried and filtered. The solvent was removed in *vacuo*. The resulting oil was purified by Kugelrohr distillation to afford (*R*)-(+)-1-phenylethanol.

To develop a convenient route, we employed the corresponding amino acid **5b**, a commercial and natural product, instead of **5a** in the reduction. First **5b** was reduced by borane into **5a** that could continue to act as the catalyst without further separation and purification. The result was the same with that of directly using **5a** as catalyst. With **1-4a** and **1-4b** as the catalyst we got the same conclusion. Through this simplification it will be more convenient to process of the reduction. Then the catalysts were used in the reduction of other ketones in the same way, leading to the formation of chiral secondary alcohols in good yield (>75%) with good optical purity (e.e. up to 92%).

Table 2 Results of asymmetric reductions of prochiralketone catalyzed by simple amino acid

prochiral ketones	e.e.(%)[a] [abs. config][b]				
	1b	**2b**	**3b**	**4b**	**5b**
Acetophenone	75[R]	79[R]	81[R]	84[R]	79[R]
p-propylacetophenone	66[R]	83[R]	80[R]	87[R]	81[R]
α-chloroacetophenone	78[S]	92[S]	83[S]	86[S]	83[S]
α-bromoacetophenone	77[S]	86[S]	82[S]	87[S]	81[S]
p-chloroacetophenone	72[R]	82[R]	82[R]	85[R]	82[R]

a. The e.e. value of the products, chiral secondary alcohols, was obtained by HPLC on chiralcel OJ column.
b. Absolute configuration was assigned by comparison of the optical rotation with that reported in the literature.

In summary, we have demonstrated that simple amino alcohols and corresponding amino acids are efficient catalysts in the asymmetric borane reduction of ketones with carefully chosen experiment condition. Thus, the present results are the complement for the precedent report in this area, which is so-called CBS reductions with oxazoborolidine catalysts discovered recently. The ready availability and low cost of these auxiliaries may lead to their application in synthesis. Further investigation is in progress.

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