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Enantioselective Reduction of Achiral Ketones with $NaBH_4/I_2$ Catalyzed by (*S*)-Ferrocenyl Amino Alcohols

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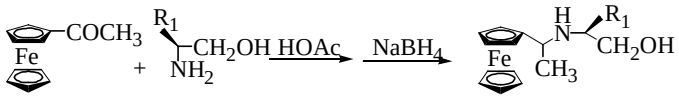
Abstract: The reduction reagents prepared from sodium borohydride, I_2 and a catalytic amount of chiral ferrocenyl amino alcohols **2a-e** have been successfully applied to the enantioselective reduction of ketones. The optically active secondary alcohols were obtained in moderate enantiomeric excess and high chemical yield.

Keywords: (*S*)-Ferrocenyl amino alcohol, asymmetric reduction, enantioselective catalysis, $NaBH_4/I_2$ combination.

In recent years much attention has been devoted to the enantioselective synthesis of optically active alcohols which are important starting materials for many biologically active compounds[1]. Since Corey and co-workers found the chiral oxazaborolidine catalyzed reduction (CBS reduction) of prochiral ketones, the method for the generation of chiral secondary alcohols has become one of the most attractive research fields[2, 3]. But borane and its complexes such as borane-THF or borane-dimethyl sulfide are toxic, expensive and unstable. A new alternative source of hydride would be the combined reagent of $NaBH_4/I_2$ and a catalytic (*S*)-ferrocenyl amino alcohols **2a-e**[4]. (*S*)-Ferrocenyl amino alcohols **2a-e** can be produced from acetylferrocene and (*S*)-amino alcohols **1a-e** which can be easily obtained from natural amino acids[5].



1a-e **2a-e**

R_1: a, $PhCH_2$-; b, $(CH_3)_2CH$-; c, $(CH_3)_2CHCH_2$-; d, $CH_3CH_2CH(CH_3)$-; e, CH_3-.

In this paper, we report the results of the catalytic asymmetric reduction of ketones with the combined reagent of $NaBH_4/I_2$ in the presence of chiral catalysts **2a-e**. A mixture of $NaBH_4$ (12 mmol) and I_2 (12 mmol) in THF was allowed to react at 0°C for one hour, then (*S*)-ferrocenyl amino alcohol **2a-e** (1 mmol) was added to give a reducing

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mixture. To the mixture a ketone (10 mmol) was slowly added for reduction at 25°C for about one hour to yield the corresponding chiral alcohols with main configuration of *R*. The chemical yield is high. The e.e. values and absolute configuration were determined by comparison of their optical rotation with literature[6]. The results are shown in **Table1**.

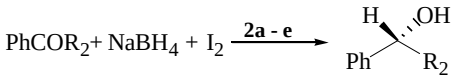

Table 1 Asymmetric reduction of ketone with catalysts **2a-e** and $NaBH_4/I_2$ in THF at 25°C

Ketone	Yield (%)					e.e. (%)				
	2a	**2b**	**2c**	**2d**	**2e**	**2a**	**2b**	**2c**	**2d**	**2e**
PhCOMe	80.6	89.2	81.6	85.6	88.6	75.5	71.1	72.5	69.8	59.8
PhCOEt	85.3	90.2	87.9	86.3	86.7	81.7	69.5	73.6	70.0	52.3
PhCOPr-n	88.4	89.5	94.3	87.4	90.5	86.2	72.6	71.9	72.6	41.6
p-MeOPhCOMe	87.6	86.7	91.2	89.2	82.3	71.3	65.4	64.8	63.8	39.8

It can be seen that (*S*)-ferrocenyl amino alcohol **2a-e** combined with reagent $NaBH_4/I_2$ are efficient chiral catalysts for reducing ketones to obtain the corresponding chiral alcohols. We find that the bulkiness of R_1 in **2a-e** do affect the enantioselectivity of these compounds. The larger R_1 are, the higher enantioselectivity of the catalysts show. This *in situ* procedure can avoid the toxic borane complex, exclusion of moisture sensitive B-H oxazaborolidines, and provides an effective and simple method for enantioselective reduction of ketones.

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