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# Enantioselective nitroaldol (Henry) reaction catalyzed by chiral Schiff-base ligands

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**Abstract**—Chiral Schiff-bases **2**, **3**, **4** and **5** were designed for the enantioselective nitroaldol (Henry) reaction. The highest enantioselectivity was observed for ligand **4** (82% ee) when $CH_2Cl_2$ was used as a solvent.

## 1. Introduction

The nitroaldol or Henry reaction is one of the classical named reactions in organic synthesis. Essentially the coupling of the nucleophile generated from a nitroalkane with a carbonyl electrophile, it is a widely used transformation, since its discovery in 1895.[1] The resulting product of this reaction is a β-nitroalcohol, which is a versatile intermediate in synthetic organic chemistry. However, until recently, the wide applicability of this transformation was impaired due to the non-availability of suitable catalysts for imparting a definite stereochemistry onto the newly generated stereogenic centres. The first asymmetric version of the Henry reaction was reported by Shibasaki in 1992.[2] Since then, interest in this area has been expanded upon considerably and various reports have been continuously appearing in the literature with regard to the development of various metal and non-metal based catalysts for the asymmetric Henry reaction.

In these processes, different chiral catalysts were developed, such as those based upon BINOL by Shibasaki,[2] bis(oxazolines) by Evans and Jørgensen,[3] cinchona alkaloid by Corey,[4] dinuclear zinc complexes by Trost,[5] salen–cocomplexes by Yamada[6] and amino alcohols by Palomo.[7,8] A chiral Schiff-base is one of the most frequently used catalysts, especially in asymmetric cyclopropanation.[9,10] The first asymmetric Henry (nitroaldol) reaction catalyzed by chiral copper Schiff-base complexes was first reported by Zhou.[11] Two reviews have already been appeared in the literature on recent advances in the asymmetric nitroaldol (Henry) reaction.[12,13] In addition, various reports have been continuously appearing in the literature.[14–23] We have previously reported the novel synthesis of a chiral Schiff-base and enantioselective nitroaldol reactions.[24] In the previous study, the observed enantioselectivities were low. As a result, we decided to improve the catalyst and began with the synthesis of a simple chiral Schiff-base with a phenol group. Finally, to explore the effect of a spacer group, we linked a simple chiral Schiff-base with a spacer group 1,3-bis(bromomethyl) benzene.

## 2. Results and discussion

To synthesize structurally simple, chiral Schiff-base, *o*-hydroxybenzaldehyde was chosen as an aldehyde part of the Schiff-base. To synthesize the desired simple chiral Schiff-base ligands, the three commercially available chiral amino alcohols (1*S*,2*R*)-2-amino-1,2-diphenylethanol, (*S*)-(+)-phenylglycinol and (*R*)-(+)-2-amino-1,1,3-triphenylpropanol were used as chiral sources. The amino alcohols were chosen to create a steric effect on the carbinol carbon. The reaction of *o*-hydroxybenzaldehyde with three chiral amino alcohols in EtOH gave chiral Schiff-base compounds. To explore the effect of a spacer group, the *o*-hydroxy benzaldehyde was reacted with 1,3-bis(bromomethyl) benzene in the presence of $K_2CO_3$ in $CH_3CN$. All reactions were simple and straightforward. All compounds were characterized with $^1H$ NMR, $^{13}C$ NMR and elemental analysis (Schemes 1–3).

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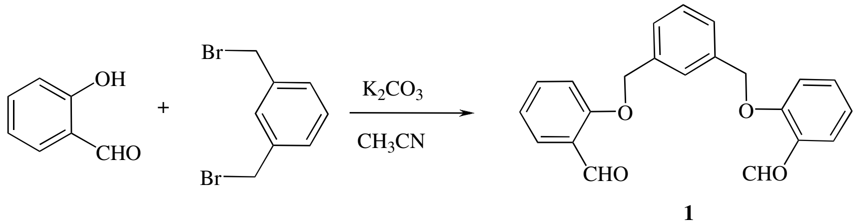
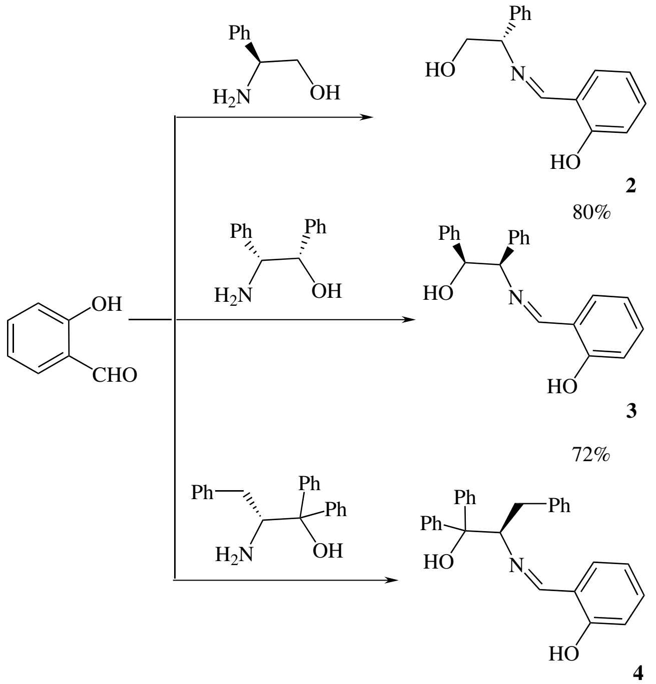


**1**

97%

Scheme 1.



**2** 80%

**3** 72%

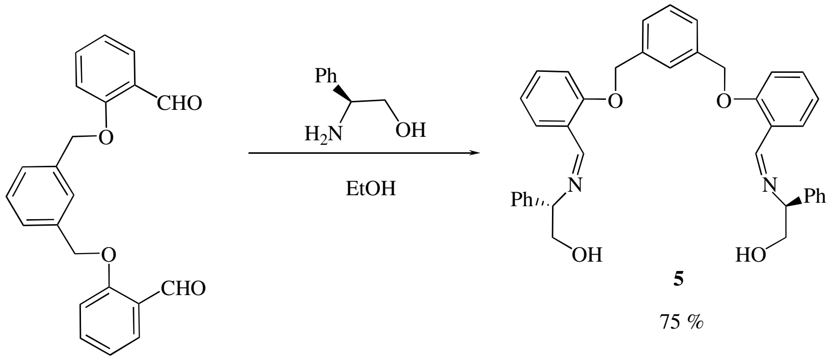
**4** 94 %

Scheme 2.

Under our previous reaction conditions,[24] the reaction was initially carried out at room temperature using 10 mol % catalyst and triflate as the source for metal ion and triethylamine as a promoter for 40 h. We used chiral Schiff-base ligands **2**, **3**, **4** and **5** under the above mentioned conditions to examine the solvent effect using solvents such as ethanol, dichloromethane and toluene. Under the first experimental conditions, 10 mol % triethyl amine was added as an organic base in all the reactions (Table 1). The first experimental results show that the reaction yields were higher in all the cases when triethylamine was added to the reaction medium as a promoter. Next, $CH_2Cl_2$ proved to be the best solvent for the enantioselective nitroaldol reaction catalyzed by chiral Schiff-base ligands. The organic base triethylamine increased the reaction yield in all entries (Table 1); however, it caused a slight decrease in ee. The effect of organic base was shown dramatically in catalyst **4.** The enantioselectivity observed increased from 17 up to 82 ee when triethylamine was not used as a promoter. In general, the organic base increased the reaction yield, but decreased enantioselectivity. The best catalyst proved to be **3** when the organic base, triethylamine, was not added to the reaction medium. Whenever triethylamine was added to the reaction medium the best catalyst was **4**. The spacer group did not have a profound effect on selectivity but it did change the configuration of adduct meaning that it may be useful in applications for obtaining the desired configuration (Table 2).

## 3. Conclusion

In conclusion we have synthesized simple chiral Schiff-base ligands, which can be used in enantioselective metal-catalyzed reactions. The experimental results show that simple chiral Schiff-base ligands catalyze the enantioselective nitroaldol reaction. The spacer group has the potential to alter the configuration of the adduct which may be useful for that application.



**5**

75 %

Scheme 3.