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Highly asymmetric Henry reaction catalyzed by chiral copper(II) complexes

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ABSTRACT

Two chiral pyridinylmethyl diphenylprolinolsilyl ether derivatives have been synthesized from N-alkylation of (*S*)-diphenylprolinolsilyl ether in a single step. They were successfully applied as ligands in the Cu(II)-catalyzed enantioselective Henry reaction between aldehydes and nitromethane in ethanol at room temperature. A variety of chiral Henry products β-nitroalcohols were obtained in good to high yields (up to 94%) with high to excellent enantioselectivities (up to 94% ee) under the optimized reaction conditions. The results indicate that the bulky substituent diphenylprolinolsilyl ether of ligand **2** plays an important role to induce the high stereoselectivity of the process.

The asymmetric Henry or nitroaldol reaction is without question one of the most useful methods for the formation of C–C bonds in organic synthesis.[1] The resulting optically active β-nitroalcohols are versatile building blocks for further transformations into, for example, chiral β-amino alcohols, 1,2-diamines, α-hydroxy acids, or other invaluable precursors of biologically active compounds.[2] Thus, it is not surprising that the development of efficient asymmetric catalytic protocols for this cornerstone reaction has received much attention.[3] Since the pioneering work by Shibasaki and co-workers in 1992,[4] a great deal of effort has been devoted to the development of more selective and catalytic systems for this transformation, and significant progress has been made in recent years.[3] Both organocatalysts and metal-containing catalyst complexes for this reaction have been described to give good to excellent enantioselectivities.[5,6] Among those that have been successfully applied, copper complexes with chiral ligands (e.g. aminoalcohols, diamines, and Schiff bases) are, in particular, highly efficient catalysts for the asymmetric Henry reaction, and in some cases providing β-nitroalcohols with excellent enantioselectivities.[7] Despite significant advances in this field, there are some catalytic systems that show critical shortcomings, these include substrate specificity limitation, anhydrous reaction conditions, low reaction temperatures, high catalyst loading, and some of the reactions require the use of activated silyl nitronates and tetrabutylammonium triphenylsilyldifluorosilicate (TBAT).[8] Therefore, the design and development of new chiral ligands aimed at overcoming these limitations have proven to be a significant challenging task and limited success has been achieved to date. Herein, we report the synthesis of a new and novel diamine and its chiral copper (II) complex as catalyst to promote highly asymmetric Henry reactions of nitromethane to aldehydes in ethanol at room temperature. High yields (up to 94%) and ee values (up to 94%) were achieved for a wide range of aldehydes.

According to the analogous procedure reported in the literature,[7k] the ligand **2** was readily prepared by a single step from both commercially available (*S*)-diphenylprolinolsilyl ether **1** and 2-(bromomethyl)pyridine hydrobromide using K_2CO_3 and KI in ethanol (Scheme 1, eq. 1). Ligand **2** was conceived based on an intuition that the diphenylsiloxymethyl group would act as an effective steric controller due to these bulky groups near the catalytic site of the catalyst. Similarly, chiral ligand **3** was prepared from **1** and 2,6-bis(bromomethyl)pyridine in 74% yield (Scheme 1, eq. 2).

With the chiral ligands **2**–**3** in hand, we examined their asymmetric induction abilities in the Cu catalyzed enantioselective Henry reaction between nitromethane and benzaldehyde, and the results are summarized in Table 1. Initially, 5 mol % of $Cu(OAc)_2$ was used as catalyst and 5 mol % of chiral diamine **2** was used as ligand. When toluene was used as solvent, the reaction resulted in low yield (entry 1). Using THF as solvent, the reaction gave the desired Henry product **4a** in 68% yield with 84% ee (entry 2). When the protic solvents such as *i*-PrOH, EtOH, and MeOH were used as solvents, all the reactions proceeded smoothly to afford the desired product **4a** in good yields (65–75%) and high enantioselectivities (up to 87% ee) (entry 3–5). However, the use of triamine **3** as chiral ligand gave product **4a** with only 47% ee (entry 6). Other catalysts $Cu(OTf)_2$ and $CuCl_2$ were tested and only resulted in either low ee value or no reaction (entries 7 and 8). From these results, it was

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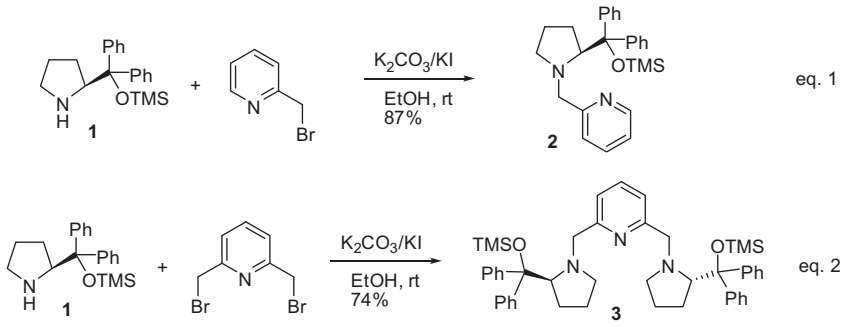
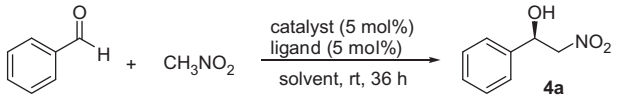


Scheme 1. The synthesis of chiral ligands **2** and **3**.

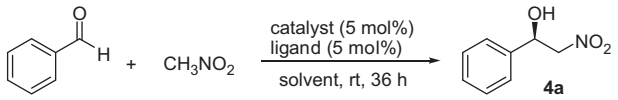
Table 1
Optimization of the Henry reaction condition



Entry	Ligand	Catalyst	Solvent	Yield[a] (%)	ee[b] (%)
1	**2**	$Cu(OAc)_2$	Toluene	<10	—
2	**2**	$Cu(OAc)_2$	THF	68	84
3	**2**	$Cu(OAc)_2$	*i*-PrOH	65	75
4	**2**	**$Cu(OAc)_2$**	**EtOH**	**75**	**87**
5	**2**	$Cu(OAc)_2$	MeOH	72	73
6	**3**	$Cu(OAc)_2$	EtOH	65	47
7	**2**	$Cu(OTf)_2$	EtOH	66	25
8	**2**	$CuCl_2$	EtOH	—	—

[a] Isolated yield.
[b] Determined by chiral HPLC of the product.

Table 2
Scope of aldehydes in the catalytic enantioselective Henry reaction



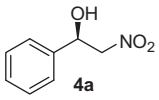
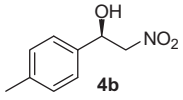
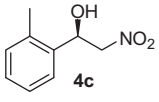
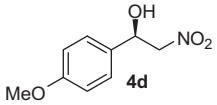
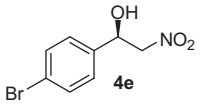
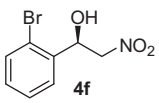
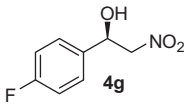
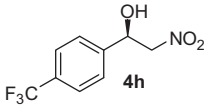
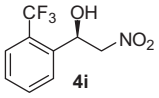
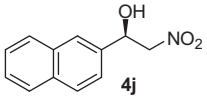
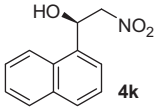
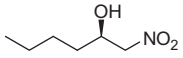
Entry	Product	Yield[a] (%)	ee[b] (%)
1	 **4a**	75	87
2	 **4b**	66	89
3	 **4c**	65	94
4	 **4d**	62	90
5	 **4e**	85	87
6	 **4f**	88	92

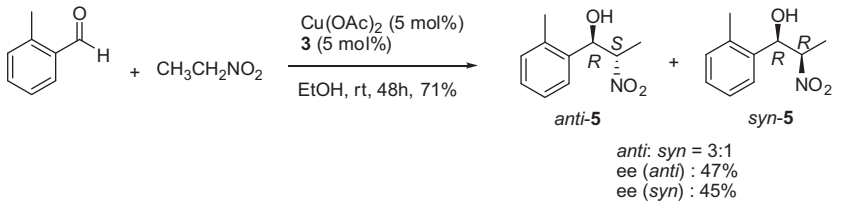
Table 2 (*continued*)

Entry	Product	Yield[a] (%)	ee[b] (%)
7	 **4g**	70	87
8	 **4h**	94	89
9	 **4i**	85	92
10	 **4j**	80	87
11	 **4k**	75	93
12	 **4l**	50	80

[a] Isolated yield.
[b] Determined by chiral HPLC of the product.

demonstrated that ligand **2** in combination with $Cu(OAc)_2$ in EtOH, is the optimal reaction condition to give the product **4a** in 75% yield and 87% ee (entry 4).

Encouraged by these results, we next investigated the scope of the reaction with nitromethane and a variety of aldehydes (Table 2). All reactions were conducted in denatured EtOH at room temperature in the presence of 5 mol % of chiral ligand **2** and $Cu(OAc)_2$. In each case, a smooth reaction occurred to generate desired Henry products **4a–l** in good to high yields (50–94%) and high enantioselectivities (80–94% ee). The results in Table 2 also show that the nature of substituents on aryl groups influences the yields and enantioselectivities. For benzaldehydes substituted with electron-donating groups, the reactions afforded the Henry products **4b–c** in lower yields than **4a** (entries 2–4 vs entry 1). Conversely, benzaldehydes with electron-withdrawing substituents resulted in higher yields (entries 5–9 vs entries 1–4). Although the electronic nature of the substituents on the aromatic ring affected the yields, they had little influence on the enantioselectivity. Next, the effect of steric hindrance of the aromatic ring was also investigated. It was found that the aromatic aldehydes with *ortho* substituents (entries 3, 6, and 9) showed better enantioselectivity than those



Scheme 2. The Henry reaction of 2-methylbenzaldehyde and nitroethane.

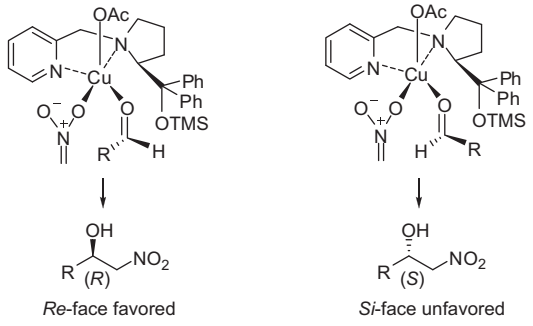


Figure 1. A plausible transition state model.

with *para* substituents (entries 2, 5, and 8). Other aromatic aldehydes, 2-naphthaldehyde and 1-naphthaldehydes, were also suitable substrates, the reaction afforded the desired Henry products **4j–k** in high yields (75–80%) and enantioselectivities (87–93% ee) (entries 10–11). Under the same reaction conditions, the reaction of aliphatic aldehyde pentanal with nitromethane afforded the Henry product **4l** in relative low yield (50%) and enantioselectivity (80% ee) (entry 12).

The reaction of 2-methylbenzaldehyde and nitroethane was also examined under standard reaction conditions and gave the desired product **5** in 71% yield with moderate diastereoselectivity (*anti*:*syn* = 3:1) and enantioselectivities (47% and 45% ee for the *anti*- and *syn*-isomers, respectively) (Scheme 2).[7m]

On the basis of the reported mechanistic studies on the asymmetric Henry reaction catalyzed by Cu–diamine complexes,[7g] the high enantioselectivity can be rationalized by the transition model as shown in Figure 1. The reaction would involve Cu(II) complex dual activation of both the aldehyde and nitromethane reactants. The substituent diphenylsiloxymethyl group of **2** sterically shielded one side. The aldehyde molecule coordinates to the copper ion with the bulky R group oriented away from the diphenylsiloxymethyl group, whereas the corresponding nitromethane approaches from the *Re* face of the aldehyde to afford the (*R*)-enantiomer as a major product. *Si* face attack is not favorable due to the steric interaction between the bulky R group and the diphenylsiloxymethyl group.

In conclusion, a new type of diamine, pyridinylmethyl diphenylprolinolsilyl ether, has been synthesized and was found to be very effective chiral ligand for the Cu(II)-catalyzed asymmetric Henry reaction in EtOH proving the Henry products β-nitroalcohols in good to high yields (up to 94%) with high to excellent enantioselectivities (up to 94% ee). There are several other advantages in the present reaction: (a) the diamine ligand **2** is readily available; (b) a broad range of aldehydes, including aromatic and aliphatic aldehydes, are employed; (c) the reaction can be conducted under mild conditions using only 5 mol % of ligand and $Cu(OAc)_2$. These remarkable advantages make this approach very suitable for practical use. Further studies focusing on the modification of ligand **2** and their use as chiral ligands for other asymmetric reactions are currently under investigation and will be reported in due course.

Experimental section

Typical procedure for the asymmetric Henry reaction

To a 10 mL vial was added ligand **2** (10.4 mg, 0.025 mmol), $Cu(OAc)_2$ (4.5 mg, 0.025 mmol), and 96% denatured EtOH (0.5 mL), the mixture was stirred for 1 h at room temperature. Then the aldehyde (0.5 mmol) and nitromethane (2.5 mmol) were added and the resulting mixture was stirred at room temperature for 24–48 h (monitored by TLC plate). After completion, the solvent was removed and the resulting residue was purified by column chromatography on silica gel to give the Henry product **4**.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.053.

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