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Fluorous chiral bis(oxazolines): Synthesis and application in asymmetric Henry reaction

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ABSTRACT

A fluorous bis(oxazolines) was synthesized by a facile two-step process using malononitrile as the starting material. The compound was tested as a chiral ligand in copper-catalyzed Henry reactions of nitromethane with different aldehydes to afford the corresponding β-nitroalcohols in 61–75% yield with enantioselectivities up to 99%. Furthermore, the fluorous ligand can be easily recovered and reused without significant loss in its activity.

1. Introduction

There is increasing interest in developing catalytic asymmetric C–C formation processes [1,2]. The Henry reaction which can be used to create a new chiral carbon center at the β-position of a nitro group is a powerful and atom-economical carbon–carbon formation reaction [3–5]. The resulting β-nitro alcohols can be transformed into various important building blocks of natural products and pharmaceuticals, such as β-amino alcohols, α-hydroxy ketones, aldehydes, carboxylic acids, azides, and sulfides [6]. Consequently, increasing attention has recently been focused on the development of novel catalytic, asymmetric versions of the Henry reaction [7,8].

Since 1992, asymmetric catalytic Henry reactions have been gained particular attention. For example, Shibasaki and co-workers have reported that rare-earth-metal complex $La_3(O\text{-}t\text{-}Bu)_9$ can be applied as a catalyst for the enantioselective reaction of aldehydes with nitroalkanes [9]. Jørgensen and co-workers reported the catalytic asymmetric Henry reaction of α-keto esters with nitromethane in the presence of chiral ligands [10]. Trost et al. have disclosed a catalytic enantioselective Henry reaction employing a bimetallic zinc complex [11]. Evans et al. successfully developed the asymmetric Henry reaction of aldehydes using a bis(oxazoline) complex [12].

As one of the most popular classes of chiral ligands, C_2-bis(oxazolines) has received a great deal of attention in coordination chemistry and asymmetric catalysis [13]. Bis-oxazoline-based complexes have been successfully used as chiral ligands for the enantioselective Henry reaction, either with concurrent or independent activation of both reagents [14,15]. However, this kind of ligands is always expensive and difficult to recycle during the reactions. An alternative strategy is to design recyclable and subsequently reusable versions of ligands by fluorous technology. Curran's group reported the first example of application of solid–liquid separations based on fluorous silica gel in 1997 [16]. Then, fluorous techniques have been applied to many chemical transformations, replacing standard polymer-supported methods in the production of recyclable and reusable reagents. Recently, some fluorous chiral ligands have been designed for a variety of reactions including Michael addition, Diels–Alder and Aldol reactions.

However, there are few reports describing the recoverability of fluorous bis(oxazolines) for the asymmetric catalysis [17]. Along this line, we tried to introduce a fluorous tail C_6F_{13}- to bis(oxazolines) and studied the activity of the designed fluorous bis(oxazolines) (Fig. 1) which was synthesized by an easy method from malononitrile (Scheme 1) as a ligand in the Cu(II)-catalyzed asymmetric Henry reaction (Scheme 2). Compared to traditional recyclable supported ligands, the fluorous ligands are soluble in common reaction solvents, yet they can be easily separated and recovered from the reaction mixture by fluorous solid-phase extraction (F-SPE).

2. Results and discussion

We first carried out the reaction of 4-nitrobenzaldehyde and nitromethane as a model to optimize the reaction conditions.

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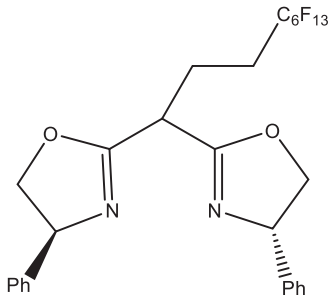
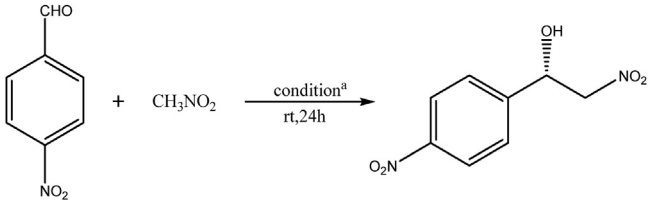


Fig. 1. Fluorous bis(oxazolines).

Table 1
Effect of different copper sources on Henry reaction.

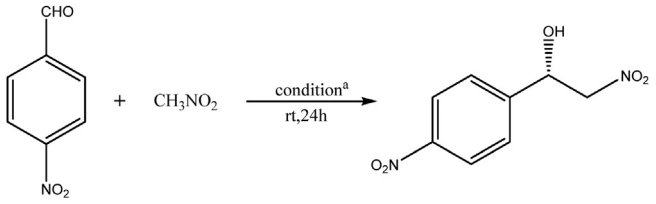


Entry	Copper source	Base (mol%)	Yield[b] (%)	ee[c] (%)
1	None	Et_3N(10)	12	–
2	$CuCl_2$	Et_3N(10)	63	98
3	CuCl	Et_3N(10)	59	98
4	$CuSO_4$	Et_3N(10)	61	96
5	Cu	Et_3N(10)	58	98
6	$Cu(OAc)_2$	Et_3N(10)	75	99
7	$Cu(OAc)_2$	–	32	67
8	$Cu(OAc)_2$	Et_3N(5)	36	70
9[d]	$Cu(OAc)_2$	Et_3N(15)	54	99
10	$Cu(OAc)_2$	Pyridine(10)	–	–
11	$Cu(OAc)_2$	DBU(10)	6	–

[a]Reaction condition: 1 mmol of 4-nitrobenzaldehyde, 10 mmol of nitromethane, 0.05 mmol of ligand and 0.1 mmol metal salt in 1 mL of EtOH.
[b] Determined by HPLC.
[c] Determined by chiral HPLC using a Ultron ES-OVM column. Reported values are the average of two runs.
[d] 15 mol% of ligand was added.

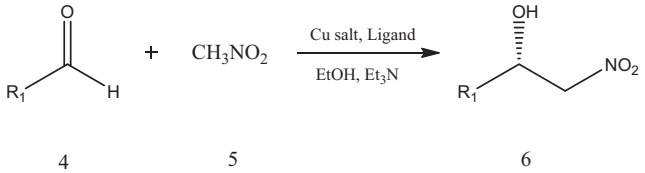
Table 1 summarizes the results obtained with various copper salts under the different reaction conditions. $Cu(OAc)_2$ gave a high yield and good enantioselectivity (Table 1, entry 6). It was found that the amount of base had significant influence to the conversion and enantioselectivity. The yield dropped from 75 to 32% in the absence of Et_3N with a low enantioselectivity (Table 1, entry 7). An increase of the amount of Et_3N to 15 mol% relative to the ligand (5 mol%) gave the same enantioselectivity but low yield, while a decrease in the amount of Et_3N to 5 mol% resulted in an obvious reduction in both conversion and enantioselectivity (Table 1, entries 8 and 9).

Table 2
Effect of solvent on Henry reaction of 4-nitrobenzaldehyde with nitromethane.



Entry	Solvent	Yield[b] (%)	ee[c] (%)
1	Tetrahydrofuran	41	68
2	Ethanol	75	99
3	Methanol	62	89
4	Acetonitrile	35	66
5	Dichloromethane	38	43

[a]Reaction condition: 1 mmol of 4-nitrobenzaldehyde, 10 mmol of nitromethane, 0.1 mmol of Et_3N, 0.05 mmol of ligand and 0.1 mmol $Cu(OAc)_2$in 1 mL of solvent.
[b] Determined by HPLC.
[c] Determined by chiral HPLC using a Ultron ES-OVM column. Reported values are the average of two runs.

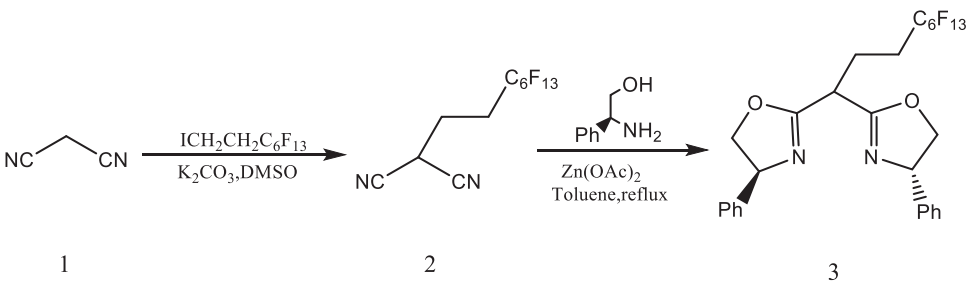


Scheme 2. Cu-catalyzed Henry reaction.

Other bases such as pyridine, DBU were also tested in the reaction. However, no better results were obtained than Et_3N (Table 1, entries 10 and 11).

Different solvents were tested in the asymmetric Henry reaction between 4-nitro-benzaldehyde and nitromethane. With $Cu(OAc)_2$ as a catalyst and Et_3N as a base, the protonic solvents were superior to the aprotonic ones (Table 2, entries 1–5). As a result, ethanol was the best solvent for this reaction (Table 2, entry 2).

With the optimized conditions in hand, the scope of the substrate was extended. A variety of aldehydes were employed as substrates to react with nitromethane, giving the corresponding products with high yields and ee values, as shown in Table 3. The data clearly showed that ligand 3 and the optimized reaction conditions can be applied in a wide scope of substrates. The aromatic aldehydes could undergo an asymmetric Henry reaction smoothly with good yields and ee values. The steric hindrance had little influence on this reaction (Table 3, entries 1–11). The aldehydes with electron-withdrawing group gave higher yields (entries 1–7 vs. entries 9–11).



Scheme 1. Preparation of fluorous bis(oxazolines).