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A Highly Effective Bis(sulfonamide)–Diamine Ligand: A Unique Chiral Skeleton for the Enantioselective Cu-Catalyzed Henry Reaction

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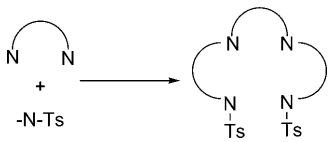
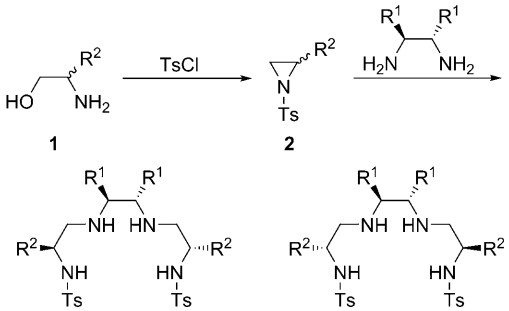
The nitroaldol (Henry) reaction constitutes an atom-economic approach to β-hydroxynitroalkanes[1] that provides efficient access to valuable bifunctional compounds, such as 1,2-amino alcohols and α-hydroxy carboxylic acids.[2] Since the pioneering work on a BINOL-derived heterometallic complex (BINOL = 1,1′-bi-2-naphthol) was disclosed by Shibasaki in 1992[3] for the Henry reaction, various types of catalyst systems, containing chiral ligands with metal atoms (such as Zn,[4] Co,[5] Cu,[6] Mg,[7] or Cr[8]), and organocatalysts[9] have been studied. However, most of these methods suffer from some limitations, such as relatively high catalyst loading, low reaction temperatures, multistep synthetic procedures for ligand preparation, or demanding the use of additives, for example molecular sieves. To solve the problem of reacting aliphatic aldehydes, one of the key strategies is to develop new chiral ligands, since ligand design has played a pivotal role in the development of efficient metal-catalyzed asymmetric reactions.

In the past few decades, a large number of chiral diamines[10] and chiral sulfonamides[11] have been used as ligands for numerous enantioselective reactions. However, there is no precedent for the combination of both diamine and bis(sulfonamide) moieties in a single chiral ligand for the Henry reaction. The objective of this work is to explore the viability of integrating diamine and sulfonamide fragments into a unique bis(sulfonamide)–diamine chiral ligand for the asymmetric Henry reaction of aliphatic aldehydes (Scheme 1). Herein, we report our preliminary results on the development of this bis(sulfonamide)–diamine-type ligand for the Cu-catalyzed asymmetric Henry reaction. The catalyst system that we developed demonstrates excellent performance, providing up to 99% *ee* for the synthesis of β-hydroxynitroalkanes with aliphatic aldehydes.



Scheme 1. Ligand design.

The bis(sulfonamide)–diamines were easily prepared from commercially available chiral α-amino alcohols and diamines in two steps (Scheme 2). Initially, α-amino alcohols **1** were cyclized by sulfonylation to generate the corresponding aziridines **2** in high yields.[12] Aziridines **2** were then treated with a 1,2-diamine to form compounds **3** and **4** in satisfactory yields.



Scheme 2. Synthesis of the bis(sulfonamide)-diamines.

The efficiency of ligands **3** and **4** was then evaluated by the use of a $Cu(OAc)_2 \cdot H_2O$-catalyzed asymmetric Henry reaction between hexanal (**5a**) and nitromethane (**6**); the results are summarized in Table 1. The reaction was carried out at room temperature, in the presence of a low catalyst

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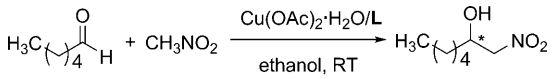
Table 1. Ligand evaluation in the Henry reaction.[a]



5a 6 7a

Entry	Ligand	Yield [%]	*ee* [%][b]
1	3	9	35
2	4a	85	95
3	4b	14	65
4	4c	45	84
5	4d	99	97

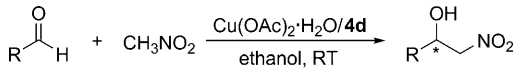
[a] Reactions were carried out with hexanal (0.5 mmol), CH_3NO_2 (5.0 mmol), $Cu(OAc)_2{\cdot}H_2O$ (2.5 mol%), and ligand (2.5 mol%) in ethanol (1.0 mL) at room temperature for 48 h. [b] Enantiomeric excesses were determined by HPLC on a Chiral OD-H column.

loading of $Cu(OAc)_2{\cdot}H_2O$ (2.5 mol%) and of the ligand (2.5 mol%) in ethanol. The ligand screening results showed that the reactivity and enantioselectivity are dependent upon both the chiral diamine fragment and the substituents of the side chain which were derived from the α-amino alcohol (R^2). In comparison with **3**, **4a** provided a better yield and higher enantioselectivity. Replacing the R^2 substituents with methyl or benzyl (Bn) groups did not improve the enantioselectivity. Compared with ligand **4a**, with a cyclohexyl fragment, ligand **4d**, containing a 1,2-diphenylethylenediamine backbone, gave a better enantioselectivity (97% *ee*). Moreover, since all diamine ligands only provide racemic products (see the Supporting Information), this proves the validity of the bis(sulfonamide)–diamine ligand design. The bis(sulfonamide)–diamine ligands have significant advantages over the traditional chiral diamines and sulfonamides used for the Henry reaction.

Under the optimized conditions, the aliphatic aldehyde substrate scope of the Henry reaction was explored (Table 2). To our surprise, the reactions proceeded very well; excellent yields accompanied with excellent enantioselectivities were achieved in most cases. It is notable that neither the length of the carbon chain, nor its steric bulk has an obvious effect on the enantioselectivity. Importantly, α-branched aliphatic aldehydes, such as isobutyraldehyde, pivalaldehyde, and cyclohexanecarboxaldehyde, resulted in the formation of the β-nitroalcohol with excellent enantioselectivities of up to 99% *ee* (Table 1, entries 4–7). Furthermore, the optimized catalyst was also used for the Henry reaction of aromatic aldehydes (Table 2, entries 9–18). In general, all of the investigated aromatic aldehydes provided the corresponding adducts in excellent enantioselectivities. The aromatic substrates containing electron-donating groups tended to afford better results than those with electron-withdrawing groups (Table 2, entries 11–16). Even for the bulkier 2-naphthaldehyde and 2-furylaldehyde, high enantioselectivities still remained (Table 2, entries 17–18).

To further demonstrate the applicability of the new bis(sulfonamide)–diamine ligand, the transformation of the nitroaldol adduct **7d** was performed as shown in Scheme 3. Initially, **7d** was reduced to furnish (*R*)-(−)-3-methyl-1-aminobutan-2-ol (**8**).[13] Then, **8** was cyclized by sulfonylation to

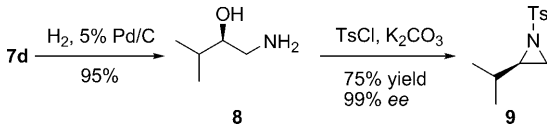
Table 2. Aldehyde scope of the $Cu(OAc)_2$/**4d** system.[a]



5 6 7

Entry	R	Product	*t* [h]	Yield [%]	*ee* [%][b]
1	$CH_3(CH_2)_4$	7a	48	99	97 (*R*)
2	$CH_3(CH_2)_6$	7b	48	99	97 (*R*)
3	$CH_3(CH_2)_8$	7c	48	99	97 (*R*)
4	$(CH_3)_2CH$	7d	48	91	99 (*R*)
5	$(CH_3CH_2)_2CH$	7e	48	89	98 (*R*)
6	$(CH_3)_3C$	7f	48	98	98 (*R*)
7	Cyclohexyl	7g	48	99	98 (*R*)
8	$C_6H_5(CH_2)_2$	7h	24	99	95 (*R*)
9	PhCH=CH	7i	30	74	94 (*R*)
10	Ph	7j	86	99	96 (*R*)
11	4-$NO_2C_6H_4$	7k	24	99	92 (*R*)
12	2-$MeOC_6H_4$	7l	96	99	95 (*R*)
13	4-PhC_6H_4	7m	48	76	97 (*R*)
14	4-FC_6H_4	7n	60	87	96 (*R*)
15	4-ClC_6H_4	7o	60	99	96 (*R*)
16	4-BrC_6H_4	7p	60	88	96 (*R*)
17	2-naphthyl	7q	48	81	96 (*R*)
18	2-furyl	7r	60	95	97 (*R*)

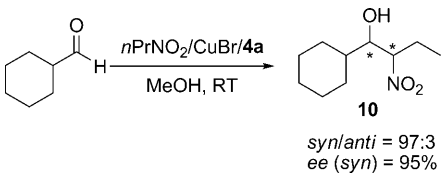
[a] Reactions were carried out with aldehyde (0.5 mmol), CH_3NO_2 (5.0 mmol), $Cu(OAc)_2{\cdot}H_2O$ (2.5 mol%), and ligand **4d** (2.5 mol%) in ethanol (1.0 mL) at room temperature. [b] Enantiomeric excesses were determined by HPLC and the absolute configurations (*R*) were established by comparison to literature data.



Scheme 3. An application of a nitroaldol adduct.

generate the corresponding aziridine **9** without any loss of stereochemical information. Aziridines constitute the fundamental synthetic tool for the generation of some N-containing natural products and also serve as chiral building blocks, auxiliaries, and ligands in organic synthesis.[14] They are also a key intermediate in the synthesis of our bis(sulfonamide)–diamine ligand.

The bis(sulfonamide)–diamine ligands were also preliminarily examined in Henry reactions in which other nitroalkanes were used. We found that the catalyst system of ligand **4a** with CuBr was highly effective for the Henry reaction between 1-nitropropane and cyclohexanecarboxaldehyde (Scheme 4). Excellent stereocontrol and the apparently favorable formation of the *syn* diastereomer were observed in this reaction. The ratio of the *syn* to *anti* isomers was determined to be 97:3. The *syn* diastereoisomer was produced



Scheme 4. A Henry reaction of 1-nitropropane.

with an excellent enantiomeric excess of 95% *ee*. These results, together with those of reactions with **4d**, have shown that the new bis(sulfonamide)–diamine backbone is a useful chiral skeleton for the Henry reaction of aliphatic aldehydes.

In summary, a unique chiral skeleton, the bis(sulfonamide)–diamine, containing both diamine and bis(sulfonamide) moieties has been developed. This new type of ligand has been demonstrated to be highly effective for the asymmetric Cu-catalyzed Henry reaction of both aliphatic and aromatic aldehydes with low catalyst loading, at room temperature. Both aliphatic and aromatic aldehydes gave excellent enantioselectivities of up to 99% *ee*. Since the bis(sulfonamide)–diamine ligands have significant advantages over the traditional chiral diamines and sulfonamides, they are expected to be further investigated in the near future, for instance, by replacing the Ts with acyl, aryl, alkyl, and so forth. These features may allow this chiral skeleton to achieve extensive application in other asymmetric catalysis reactions. The reaction mechanism of the bis(sulfonamide)–diamine ligands will be the subject of future investigations in our group.

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Keywords: asymmetric catalysis · copper · N ligands · sulfonamides · Henry reaction

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