ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 5596–5598

www.rsc.org/chemcomm

COMMUNICATION

Design of chiral sulfoxide–Schiff base hybrids and their application in Cu-catalyzed asymmetric Henry reactions†

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Received 15th March 2012, Accepted 16th April 2012
DOI: 10.1039/c2cc31907a

A new class of chiral sulfoxide–Schiff base ligands has been developed by the rational combination of two privileged chiral backbones. These sulfoxide–Schiff base ligands were found to be highly efficient for Cu-catalyzed asymmetric Henry reactions (up to 98% yield and 96% ee).

Asymmetric metal catalysis as an efficient and powerful method for obtaining enantiopure compounds has seen tremendous advances in the past decades, and a great number of chiral ligands have been successfully developed.[1] A literature survey reveals that the overwhelming majority are still limited to phosphorus and nitrogen ligands, which usually involve multistep synthesis or tedious separation procedures. Therefore, the design of highly efficient and selective ligands and catalytic systems for metal-catalyzed asymmetric reactions remains an intriguing but challenging research topic in the chemical community.[1] Recently, sulfoxides have emerged as potentially ideal ligand candidates for catalytic asymmetric transformations due to their ready availability, moisture and air stability, and well-defined coordination features.[2] Since the pioneering work from the Dorta group on the successful application of a new sulfur-based *p*-tol-BINASO ligand to the Rh-catalyzed 1,4-addition of boronic acids to α,β-unsaturated ketones,[3] the development of novel and efficient sulfoxide ligands has received intensive research interest. For example, Liao and co-workers developed a C_2-symmetric chiral bis-sulfoxide ligand and also successfully applied it to Rh-catalyzed asymmetric 1,4-addition reactions.[4] Inspired by these works, Zhou and Li *et al.* recently described an efficient oxidative coupling reaction for the synthesis of a series of bis-sulfoxide ligands containing a stereogenic axis.[5] In addition to these chiral bis-sulfoxide ligands, other types of hybrid ligands based on chiral sulfoxide have also been elegantly developed. Representative examples include olefin-sulfoxide,[6] phosphine sulfoxide,[7] oxazoline sulfoxide,[8] hydroxysulfoxide,[9] and ferrocenyl sulfoxide ligands.[10] Nevertheless, despite these impressive advances, there is still great room for the development of new sulfoxide-based ligands with high stereoselectivity and broad reaction scope.

On the other hand, catalytic asymmetric reactions employing Schiff base derivatives, such as privileged salen ligands, have been intensively investigated in recent years.[11] However, to the best of our knowledge, the Schiff base moiety has never been incorporated into the sulfoxide scaffold as an additional binding site. Moreover, as a further application of our previously developed concept of catalyst development,[12] the combination of two privileged chiral backbones into one molecule for the design of new types of ligands and catalysts,[13] we envision that a rational assembly of the sulfoxide and Schiff base moieties with a suitable chiral backbone may provide a new type of ligand (Fig. 1). Herein, we describe the design and synthesis of such sulfoxide–Schiff hybrids as efficient chiral ligands for highly enantioselective Henry reactions.

Starting from commercially available (1*R*,2*S*)-2-amino-1,2-diphenylethanol, the target chiral sulfoxide–Schiff base ligand **1a** could be synthesized in four steps in good overall yield (see ESI†). We then evaluated its performances in the benchmark asymmetric Henry reaction of 4-nitrobenzaldehyde with nitromethane.[14,15] To our delight, with 10 mol% of $Cu(OAc)_2 \cdot H_2O$ and **1a** in *t*-BuOH, the reaction proceeded smoothly to provide the corresponding product in 94% yield and 85% ee (Scheme 1). To examine the roles of the sulfoxide group and Schiff base moiety on the catalytic efficiency, we designed analogous

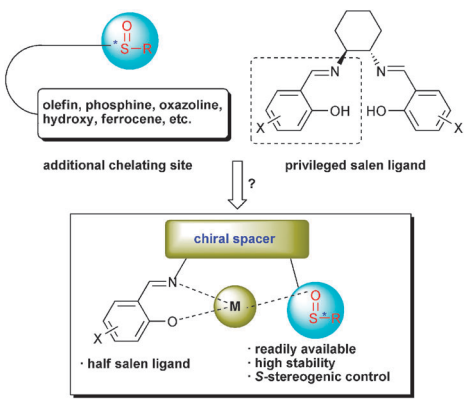

Fig. 1 Design of chiral sulfoxide–Schiff base ligand.

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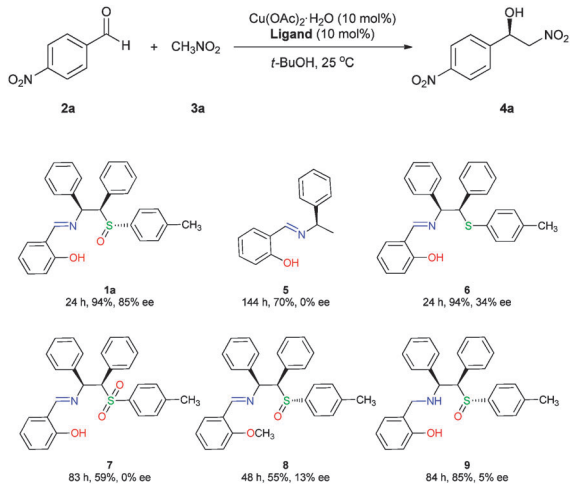
† Electronic supplementary information (ESI) available: Experimental procedures and compound characterisation data, including X-ray crystal data for **1g** (CCDC 852993). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc31907a



Scheme 1 Control experiments.

ligands **5–9** for control experiments. Comparison studies using ligands **1a** and **5–7** revealed that the presence of chiral sulfoxide groups is critical for the reaction efficiency and enantioselectivity. Notably, either protection of the hydroxyl group or reduction of the imine group resulted in diminished yield and ee, which indeed highlighted the importance of these two binding sites.

These results have shown that both the sulfoxide group and the Schiff base moiety are indispensable for the high catalytic efficiency and enantioselectivity.

Encouraged by these preliminary results, we prepared an array of other chiral sulfoxide–Schiff base ligands bearing different substituents (Fig. 2) and explored their catalytic efficiency in the Henry reaction. As summarized in Table 1, all the sulfoxide–Schiff base ligands were effective for the model reaction (90–96% yield, 80–90% ee), except for the sterically bulky ligand **1e** (53% yield, 24% ee) (Table 1, entry 5). Moreover, it was found that the electronic properties of the sulfoxide group had little influence on this reaction (Table 1, entries 1–3, 6). Then, we continued to investigate the effect of substituents on the benzene ring of the Schiff-base moiety (Table 1, entries 7–10). Generally, electron-withdrawing groups resulted in higher enantioselectivity but with longer reaction time, while electron-donating ones displayed better catalytic reactivity with lower enantioselectivity. Finally, **1f** was found to be the ligand of choice with respect to the yield

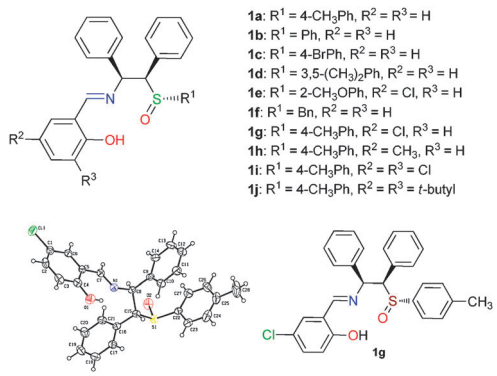
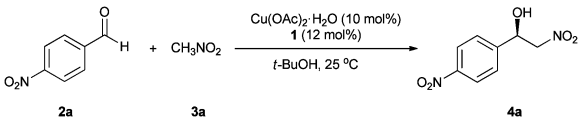


Fig. 2 Chiral sulfoxide–Schiff base ligands explored in this study and X-ray structure of ligand **1g**.

Table 1 Ligand screening[a]



Entry	Ligand	Time (h)	Yield (%)[b]	Ee (%)[c]
1	**1a**	24	95	88
2	**1b**	24	92	88
3	**1c**	24	91	87
4	**1d**	24	94	80
5	**1e**	108	53	24
6	**1f**	20	96	90
7	**1g**	32	92	90
8	**1h**	24	93	86
9	**1i**	48	90	90
10	**1j**	24	94	80
11[d]	**1f**	30	94	93

[a] Unless otherwise noted, reactions were carried out with **2a** (0.4 mmol), **3a** (1.0 mL), $Cu(OAc)_2{\cdot}H_2O$ (10 mol%) and **1** (12 mol%) in *t*-BuOH (4.0 mL) at 25 °C. [b] Isolated yield. [c] Determined by chiral HPLC, the absolute configuration was established as *R* by comparison with literature data. [d] 2.5 mol% of $Cu(OAc)_2{\cdot}H_2O$ and 3 mol% of **1f** were used.

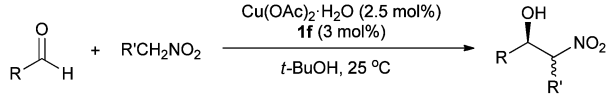
and enantioselectivity (entry 6, 90% ee). Importantly, when the catalyst loading of **1f** was reduced to 2.5 mol%, a slight increase in enantioselectivity was observed (Table 1, entry 11, 93% ee).

Experiments to probe the scope of the asymmetric Henry reaction were performed under optimal reaction conditions. As highlighted in Table 2, a wide range of aldehydes bearing electron-withdrawing (Table 2, entries 1–9), electron-donating (Table 2, entries 11–12), and electron-neutral (Table 2, entry 10) groups can be readily tolerated for the aromatic aldehydes, providing the corresponding products in excellent enantioselectivities (91%–96% ee) and high yields. Moreover, the condensed aromatic aldehyde (2-naphthaldehyde) (Table 2, entry 13), heteroaromatic aldehydes (Table 2, entries 14–15) and cinnamaldehyde (Table 2, entry 16) were also suitable for this reaction, giving the desired products in 61–91% yields and 91–95% ee. Notably, aliphatic aldehydes were also successfully utilized and high enantioselectivities and good yields were obtained (Table 2, entries 17–19). Finally, nitroethane was also investigated and the corresponding adduct **4t** was obtained in good yield and enantioselectivity, albeit with moderate diastereoselectivity (Table 2, entry 20).

In summary, we have developed a new class of chiral sulfoxide–Schiff base ligand by the rational combination of two privileged chiral architectures. These sulfoxide–Schiff base hybrids were found to be highly efficient for the Cu-catalyzed asymmetric Henry reaction, furnishing the corresponding products with excellent yields and enantioselectivities. Studies into the precise reaction mechanism and further applications of this type of ligands in other transition-metal catalyzed asymmetric transformations are currently underway in our laboratory.

We are grateful to the National Science Foundation of China (NO. 21002036) and the National Basic Research Program of China (2011CB808603) for support of this research.

Table 2 Substrate scope examination[a]



2 3 4

Entry	R	R′	Product	Yield (%)[b]	Ee (%)[c]
1	4-NO_2Ph	H	**4a**	94	93
2	3-NO_2Ph	H	**4b**	94	94
3	2-NO_2Ph	H	**4c**	95	96
4	4-CF_3Ph	H	**4d**	96	94
5	4-ClPh	H	**4e**	91	92
6	4-BrPh	H	**4f**	94	92
7	2-FPh	H	**4g**	93	93
8	2,4-Cl_2Ph	H	**4h**	98	95
9	3,4-F_2Ph	H	**4i**	90	94
10	Ph	H	**4j**	85	93
11	2-OCH_3Ph	H	**4k**	92	94
12	2-CH_3Ph	H	**4l**	84	91
13	2-Naphthyl	H	**4m**	75	93
14	2-Furyl	H	**4n**	91	95
15	2-Thiophenyl	H	**4o**	61	92
16	PhCH=CH	H	**4p**	72	91
17[d]	$PhCH_2CH_2$	H	**4q**	90	92
18[d]	$CH_3(CH_2)_3CH_2$	H	**4r**	90	92
19[d]	$(CH_3)_2CH$	H	**4s**	66	92
20	4-ClPh	CH_3	**4t**	87[e]	68/81[f]

[a] Unless otherwise noted, reactions were carried out with **2** (0.4 mmol), **3** (1.0 mL), $Cu(OAc)_2·H_2O$ (2.5 mol%) and **1f** (3 mol%) in *t*-BuOH (4.0 mL) at 25 °C for 30–132 h. [b] Isolated yield. [c] Determined by chiral HPLC. [d] 1.0 mmol of **2** and 2.0 mL of **3** were used. [e] The ratio of *anti*/*syn* was 3 : 2, as determined by chiral HPLC. [f] Ee of *anti* and *syn* isomers.

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