Synthesis, Utility, and Structure of Novel Bis(sulfinyl)imidoamidine Ligands for Asymmetric Lewis Acid Catalysis

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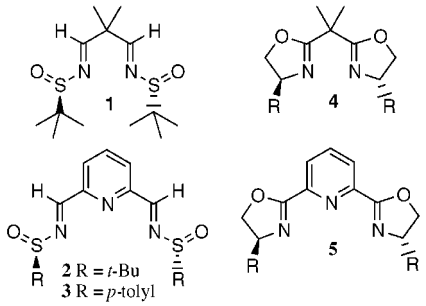
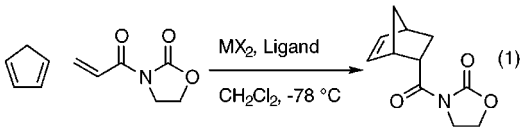
The vast majority of chiral ligands utilized in asymmetric catalysis rely on chiral carbon centers for stereochemical induction.[1] In contrast, ligands incorporating chirality solely at sulfur have been much less well developed.[2] Further, despite the ready availability of enantiomerically pure sulfinamides,[3] the preparation of metal complexes of sulfinamide derivatives and catalysis by these complexes have not been explored. Herein, we report on a novel bis(sulfinyl)imidoamidine (siam) ligand **8** that is prepared by a straightforward, modular synthesis. The Cu(II) complex of **8** catalyzes the Diels−Alder reaction with exceptional levels of enantio- and diastereoselectivity. Furthermore, the complex exhibits a unique mode of binding in the solid state, self-assembling to form a rarely observed M_2L_4 quadruple-stranded helicate.[4]



Chiral sulfinamides are commercially available, optically stable compounds that are readily transformed into sulfinyl imines through condensation with aldehydes and ketones.[5] Sulfinyl imines are widely used, stable intermediates in the asymmetric synthesis of a variety of amine-containing compounds.[6] These derivatives should serve as versatile donor ligands for asymmetric catalysis due to their ease of synthesis, chirality about sulfur, and the potential for metal coordination through the N, S, and O atoms. To evaluate sulfinyl imine ligands in asymmetric catalysis, C_2-symmetric ligands **1**−**3** were first prepared in analogy to the highly successful bisoxazoline ligands **4** and **5**, which have provided high levels of stereoselectivity in numerous Lewis Acid-catalyzed reactions.[7] However, while the Cu(II) complex of ligand **1** (entry 1, Table 1) displayed good catalytic activity for the Diels−Alder reaction (eq 1), the asymmetric induction was disappointing. The Cu(II) complex of ligand **2** was less active, but afforded the Diels−Alder adduct in moderate selectivity. In contrast, the Cu(II) complex of the *p*-tolyl substituted ligand **3** (entry 3) led to lower enantioselectivity than the bulkier *tert*-butyl substituted **2**. In accordance with Evans' work, use of the noncoordinating hexafluoroantimonate (SbF_6) counterion greatly accelerated the reaction but with a concomitant loss of selectivity (entry 4).

Table 1. C_2-Symmetric Sulfinyl Imines as Diels−Alder Catalysts[a]

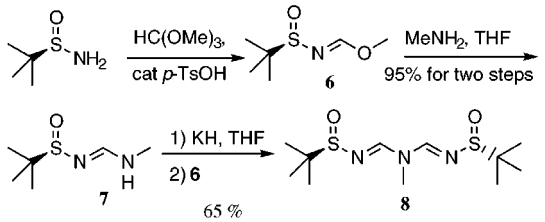


entry	ligand	metal	% conv[b]	ee[c]	dr[b]
1	**1**	$Cu(OTf)_2$	100	6	90:10
2	**2**	$Cu(OTf)_2$	60	72	94:6
3	**3**	$Cu(OTf)_2$	50	37	94:6
4	**2**	$Cu(SbF_6)_2$	100	39	94:6
5	**2**	$Zn(OTf)_2$[d]	35	30	94:6
6	**8**	$Cu(SbF_6)_2$	100	98	>99:1
7	**8**	$Zn(SbF_6)_2$	90	36	92:8

[a] All reactions performed using 10 mol % catalyst and 11 mol % ligand. [b] All reactions stopped at 6 h, conversion and dr determined by ^{1}H NMR. [c] Determined by chiral HPLC. [d] Reaction run at −40 °C.

To obtain a ligand containing a rigid backbone that incorporates more basic donor atoms, bis(sulfinyl)imidoamidine **8** was prepared in three straightforward steps (Scheme 1).[8] The modular nature of the ligand synthesis should enable steric and electronic fine-tuning of the ligand structure by the introduction of different sulfinamides, ortho esters, and amine nucleophiles. While a complex of **8** with $Cu(OTf)_2$ did not catalyze the Diels−Alder reaction, the use of the SbF_6 counterion resulted in a greatly accelerated reaction that proceeded with exceptional levels of enantio- and diastereoselectivity (entry 6). The $Zn(SbF_6)_2$ complex showed reduced catalytic activity and greatly reduced stereoselectivity (entry 7). In accordance with the trend for sulfinyl imine ligands (entries 2 and 3, Table 1), the corresponding bis(*p*-tolylsulfinyl)imidoamidine gave reduced selectivities (17% ee).[9] In contrast, different nitrogen substituents are well tolerated, suggesting a convenient site for the preparation of support-bound catalysts.[10]

Scheme 1



Several dienophiles were employed for a preliminary determination of substrate generality (Table 2). Reactions of the less electrophilic crotyl and cinnamoyl dienophiles require higher temperatures and longer reaction times but afford good yields and high stereoselectivities (entries 2 and 3). Not surprisingly, the highly activated β-carboxy-substituted dienophile reacts

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Table 2. Substrate Generality in the Diels−Alder Reaction Using Ligand 8[a]

entry	n	substrate (R =)	time (h)	temp (°C)	yield	ee[b]	dr[c]
1	1	H	0.1	−78	96	>98	>99:1
2	1	CH_3	8	−40	76	97	98:2
3	1	Ph	16	0	58	94	95:5
4	1	CO_2Et	2	−78	85	96	97:3
5	1	acrolein	2	−78	65	32	96:4
6	2	H	16	0	50	90	98:2
7[d]	1	H	0.1	−78	95	>98	>99:1

[a] Reactions run with 10 mol % catalyst and 11 mol % ligand. [b] Determined by chiral HPLC or GC (see Supporting Information). [c] Determined by ^{1}H NMR spectroscopy. [d] 2-to-1 stoichiometry of ligand-to-Cu(II) employed.

rapidly and with high levels of stereoselectivity (entry 4). Use of the monodentate substrate acrolein showed markedly decreased selectivity consistent with previous reports on Cu(II) complexes of bis(oxazoline)-based ligands. Finally, cyclohexadiene reacts only at higher temperatures yet retains excellent selectivities (entry 6).

While we envisioned that the sulfinyl nitrogens of ligand **1** would coordinate to Cu(II) in accordance with mechanisms proposed by the Evans and Pfaltz groups for Cu(II)-bis(oxazoline) catalysts, there also existed the possibility of coordination at either sulfur or oxygen. We were intrigued by the observation that in contrast to Evans' oxazoline system, the use of excess ligand relative to Cu(II) did not slow reaction rates for the Diels−Alder reaction (entry 6).[11] Furthermore, correlation of enantioselectivity versus ligand enantiopurity revealed a negative slope, indicating that the catalyst system involves more than a simple monomeric species. Interestingly, in the solid state, the free ligand exists in an extended, linear conformation, which would require a conformational change for bidentate binding via nitrogen.[12]

Single crystals of the Cu(II)−siam complex **9** were obtained by vapor diffusion of ether into a solution of the ligand and $CuCl_2$ in CH_2Cl_2. The complex exists as a rare M_2L_4 quadruple-stranded helicate in which the two Cu atoms are coordinated to the sulfinyl oxygen in a square pyramidal array (Figure 1).[13] Of particular note, a naked chlorine ion is trapped within the shell of the helicate. The solid-state structure proved invaluable for determining the predominant binding mode of **8** in solution. In both the crystalline Cu(II) complex and in a freshly prepared CH_2Cl_2 solution of the catalyst, the sulfinyl S=O stretch is shifted to longer wavelength (969 cm^{-1} vs 1077 cm^{-1} in the free ligand, Figure 2), in accordance with the observed shifts for oxygen-bound sulfoxide Cu(II) complexes.[14] It appears that the predominant binding mode in the catalyst solution is via oxygen. Further studies to elucidate the active species are ongoing.

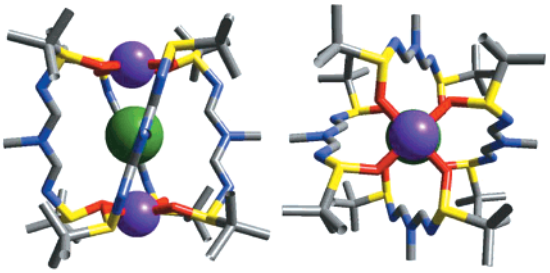

Figure 1. Two views of the $CuCl_2$·siam complex **9** in solid state showing helical twist (Cu in purple, Cl in green, other counterions omitted).

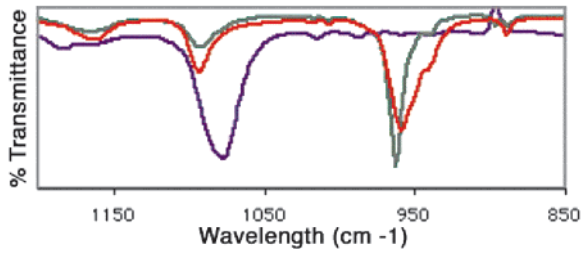

Figure 2. IR overlay of siam in solution (purple), $Cu(SbF_6)_2$·siam in solid state (green), and $Cu(SbF_6)_2$·siam in solution (red).

In conclusion, a previously unexplored ligand class has been developed for asymmetric Lewis acid catalysis. In addition to providing high levels of asymmetric induction in the Lewis acid-catalyzed Diels−Alder reaction, the ligand class is straightforward to prepare using a modular synthesis from readily available building blocks. Notably, the Cu(II) ligand complex exists as a unique M_2L_4 helicate in the solid state, and in solution **8** predominately coordinates through the sulfinyl oxygen. The further application of bis(sulfinyl)imidoamidines and other *N*-sulfinyl-based ligands in asymmetric catalysis are under active investigation.

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Supporting Information Available: Synthetic details and crystallographic data for **8** and helicate **9** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The *p*-tolyl derivative was prepared in analogy to ligand **8**. See Supporting Information.

(10) The *N*-benzyl derivative of **1** was prepared in the same fashion but employing benzylamine in place of methylamine and afforded the Diels−Alder adduct in 96% ee and >99:1 dr.

(11) Evans and co-workers have shown that complexes derived from 2 equiv of bis(oxazoline) are catalytically inactive for this reaction. Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460−6461.

(12) The solid-state structure of **8** and relevant data are reported in the Supporting Information. For X-ray structures of sulfinyl imines, see: (a) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Reddy, G. V.; Portonovo, P. V.; Zhang, H.; Fanelli, D.; Thimma Reddy, R.; Zhou, P.; Carrol, P. J. *J. Org. Chem.* **1997**, *62*, 2555−2563. (b) Robinson, P. D.; Hua, D. H.; Shan, J. S.; Saha, S. *Acta Crystallogr.* **1991**, *C47*, 594−596.

(13) **9** forms orange prisms, orthorhombic, space group $P2_12_12_1$(No. 19). a = 17.9275(5) Å, b = 18.2786(3) Å, c = 27.4798(8) Å, Z = 4. R = 0.082. GOF = 2.16. With the SbF_6 counterion, the same helical structure is observed; however, the data was insufficient to resolve the counterions.

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