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Highly Enantioselective Hetero-Diels−Alder Reactions Catalyzed by a C_2-Symmetric Bis(sulfoximine) Copper(II) Complex

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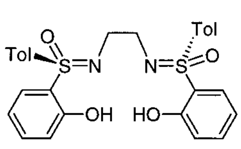
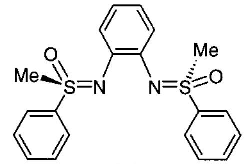
Asymmetric metal catalysis represents one of the most active areas in modern organic chemistry, and the number of novel chiral ligands for catalytic asymmetric transformations is growing rapidly.[1] Although a few thousand chiral ligands have been described, those which deliver enantioselectivities above 90% are still quite rare.[1c] Among these compounds, C_2-symmetric ones[2] are of immense importance, and some of them have already been applied in industry, for example, in the Takasago and Monsanto processes.[3] Whereas early on the use of C_2-symmetric diphosphine ligands dominated, more and more chelating compounds with sp^2-nitrogens have been found to serve the same purpose, leading to high enantioselectivities in metal catalyses.[4] Representative examples in this area are the semicorrins,[5] bis(oxazolines),[6] and salens,[7] which all have been applied in numerous catalyzed asymmetric transformations including C−C-bond forming reactions and oxidations. A few years ago we reported on the synthesis of C_2-symmetric bis(sulfoximine) (*S*,*S*)-**1**, which we regarded as unusual tetradentate salen-type ligand having chiral (sulfur) atoms at positions which inevitably are achiral in the original salen structures.[8] Tests in sulfide oxidations with cumyl hydroperoxide as oxidant and the oxovanadium(IV) complex of (*S*,*S*)-**1** as catalyst proved successful, giving sulfoxides in high yields, although as racemates. We now synthesized related bis(sulfoximine) (*S*,*S*)-**2** and were pleased to note that its copper complex showed both high activity and enantioselectivity in catalyzed asymmetric hetero-Diels−Alder (HDA) reactions.[9]

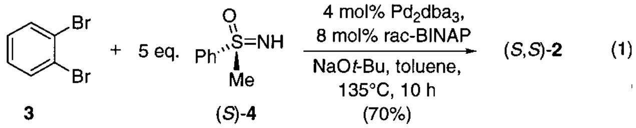
The synthesis of (*S*,*S*)-**2** starts from (*S*)-*S*-methyl-*S*-phenylsulfoximine [(*S*)-**4**] which is readily available on a 100-g scale by oxidation of thioanisole followed by imination of the intermediate sulfoxide with sodium azide and subsequent resolution of the resulting racemic sulfoximine with (*S*)-camphor-10-sulfonic acid.[10,11] Our earlier attempts to prepare bis(sulfoximine) (*S*,*S*)-**2** from 1,2-dibromobenzene (**3**) and (*S*)-**4** using palladium-catalyzed *N*-aryl imination methodology,[12] which worked well with other halobenzenes bearing electron-withdrawing substituents, failed under the usual reaction conditions with Pd(OAc)$_2$ as metal source and Cs$_2$CO$_3$ as base. However, when employing a slightly modified protocol, which was recently developed by Diver et al. for the bisamination of *o*-dibromobenzene using 4 mol % of Pd$_2$dba$_3$, 8 mol % of rac-BINAP and an excess of reagents at 135 °C,[13] the desired transformation occurred smoothly, yielding bis(sulfoximine) (*S*,*S*)-**2** as a crystalline solid, which is stable to air, light, and moisture in 70% yield (eq 1).[14]



(*S*,*S*)-**1**



(*S*,*S*)-**2**



3 (*S*)-**4** (1)

Asymmetric HDA reactions between electron-rich dienes and activated aldehydes have intensively been studied by Jørgensen et al., who found cationic bis(oxazolinyl) (box) copper(II) complexes to catalyze these transformations with high diastereo- and enantioselectivity.[9,15] On the basis of results of our previous studies on the coordination behavior of sulfoximine copper complexes,[16] we began to explore the catalytic potential of (*S*,*S*)-**2**

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[14] Experimental procedure for the preparation of (*S*,*S*)-**2**: An oven-dried 100-ml-three neck flask equipped with a magnetic stirbar and a reflux condenser was cooled under argon and charged with Pd$_2$dba$_3$ (72 mg, 0.08 mmol, 4 mol %) and rac-BINAP (100 mg, 0.16 mmol, 8 mol %). Toluene (30 mL) was added, and the mixture was then heated to 135 °C for 20 min. After cooling to ambient temperature, (*S*)-*S*-methyl-*S*-phenylsulfoximine [(*S*)-**4**, 1.55 g, 10.0 mmol, 5 equiv], NaO*t*-Bu (768 mg, 8.1 mmol, 4 equiv) and 1,2-dibromobenzene (**3**, 0.24 mL, 2.0 mmol, 1 equiv) were added into the reaction vessel. The mixture was then heated in an oil bath to 135 °C and stirred at that temperature for 5 h. After cooling to ambient temperature, the solution was diluted with dichloromethane, filtered through a pad of Celite, and concentrated in vacuo, to give a dark brown oil. The product was isolated by flash chromatography ($R_f = 0.28$, ethyl acetate), and (*S*,*S*)-**2** (0.55 g, 70%) was obtained as a colorless solid.

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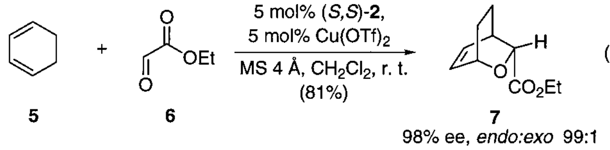
Table 1. Effects of Catalyst Amount and Temperature on the Reaction between 1,3-Cyclohexadiene (**5**) and Ethyl Glyoxalate (**6**) to Give HDA Adduct 7

entry	cat (*S,S*)-**2** (mol %)	temp (°C)	time (h)	yield[a] (%)	ee[b] (%)	*endo/exo* ratio[b]
1	10	r.t.	6	62	99	99:1
2	5	r.t.	6	61	98	99:1
3	5	−5	10	61	99	99:1
4[c]	1	−5	15	98	98	99:1
5[c]	0.5	r.t.	6	96	98	99:1

[a] Yield referring to isolated amount of product. [b] Determined by GC. For exact separation conditions see Supporting Information. [c] Use of freshly prepared ethyl glyoxalate according to ref 15b.

in the copper-catalyzed asymmetric HDA reaction between 1,3-cyclohexadiene (**5**) and ethyl glyoxalate (**6**) (eq 2). The chiral metal catalyst was prepared by simple mixing of equimolar amounts of bis(sulfoximine) (*S,S*)-**2** and Cu(OTf)$_2$ in dichloromethane at room temperature. To our delight we found that using 5 mol % of this in situ catalyst, diene **5** and glyoxylate ester **6** underwent smooth cycloaddition to afford HDA adduct **7** in 81% yield with exceptionally high stereoselectivity (98% ee; isolated as as a single diastereomer).



(2)

This promising result led us to further optimize the reaction conditions in terms of temperature and catalyst loading. Table 1 illustrates some significant aspects of this study.

The reaction of 1,3-cyclohexadiene (**5**) and ethyl glyoxalate (**6**) catalyzed by 10 mol % of the MePh-BiSOX[17] copper(II) triflate complex in dichloromethane at ambient temperature provided the HDA-adduct **7** with 99% ee in 62% yield (entry 1).[18] To the best of our knowledge this is the highest asymmetric induction that has ever been observed in this reaction. An increase in enantioselectivity also occurred when the reaction temperature was lowered to −5 °C (entry 3). The catalyst loading can be reduced to 1 mol % without significant loss of enantioselectivity. Under these conditions the reaction rate is slightly diminished, and the reaction time is prolonged. Even with only 0.5 mol % of the BiSOX Cu(II) catalyst the HDA reaction proceeds well, giving **7** with 98% ee in excellent yield (entry 4). Since the quality of the substrates can affect the product yield,[15b] freshly prepared ethyl glyoxalate instead of the commercially available 50% toluene solution should be used.[19] The absolute configuration of product **7**, which was obtained from a catalysis with (*S,S*)-**2** as ligand, was determined to be 1*S*,3*R*,4*R* by comparison of the value of optical rotation with the one given in the literature.[15a]

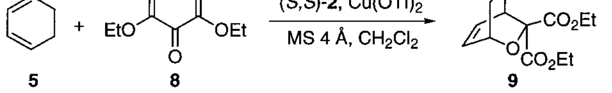
Table 2. Effects of Catalyst Amount and Temperature on the Reaction between 1,3-Cyclohexadiene (**5**) and Diethylketomalonate (**8**) to Give HDA Adduct **9**

entry	cat (*S,S*)-**2** (mol %)	temp (°C)	time (h)	yield[a] (%)	ee[b] (%)
1	5	r.t.	8	95	92
2	10	−5	12	98	94
3	10	−20	18	93	96
4	5	−40	30	92	98

[a] Yield referring to isolated amount of product. [b] Determined by HPLC. For exact separation conditions see Supporting Information.

It is noteworthy that Jørgensen increased the enantioselectivity in his catalysis with box Cu(II) complexes up to 97% ee by changing the counterion from triflate (TfO$^-$) to hexafluoroantimonate (SbF$_6^-$) and by performing the reaction in more polar solvents such as nitromethane instead of dichloromethane.[15,20] With the BiSOX Cu(II) system described here these additional modifications are not necessary for achieving both excellent ee and yield.[21]

Next, we examined the use of activated ketone **8** in the HDA reaction with diene **5** (eq 3). As is compound **7**, cycloaddition product **9** is also a particularly attractive synthetic target, because it can serve as key intermediate in the synthesis of natural products and related compounds.[22] The results of catalyses with the copper complex of (*S,S*)-**2** under various reaction conditions are summarized in Table 2.



(3)

After a reaction time of 8 h at ambient temperature, use of 5 mol % of the BiSOX Cu(OTf)$_2$ catalyst led to the formation of **9** with 92% ee in 95% yield. By increasing the catalyst amount to 10 mol % and lowering the reaction temperature to −5 and −20 °C the enantioselectivity of the reaction was improved to 94% and 96% ee, respectively. The highest enantiomeric excess was found when the catalysis was performed at −40 °C for 30 h. Under these conditions **9** was isolated in 92% yield having 98% ee. The absolute configuration of the product was determined to be 1*S*,4*R* [in a catalysis with (*S,S*)-**2** as ligand]. Compared to the other catalyst systems employed in this transformation the copper catalyst developed here, bearing the BiSOX ligand, proved superior again.

Further studies are directed toward the expansion of the substrate scope and the use of other chiral sulfoximines as ligands in asymmetric metal catalysis.

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Supporting Information Available: Experimental procedures, data of NMR spectra, and characterization information for (*S,S*)-**2** as well as a detailed description of the HDA reactions and separation conditions for the HDA adducts **7** and **9** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The term MePh-BiSOX stands for the *bis*(sulfoximine) with methyl and phenyl substituents at sulfur [here (*S,S*)-**2**].

(18) A detailed experimental procedure is given in the Supporting Information.

(19) As observed in copper-catalyzed enantioselective carbonyl-ene reactions with glyoxylate, (box) Cu(II) complexes are able to depolymerize the glyoxylate. Thus, with an increased reaction time comparable yields and enantioselecitivies could be realized even with polymeric undistilled ethyl glyoxylate solutions. Evans, D. A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T. *J. Am. Chem. Soc.* **2000**, *122*, 7936. It still needs to be established if the BiSOX Cu(II) system described here behaves similarly.

(20) Positive effects of noncoordinating counterions in box Cu(II) catalyses are well-known. For an early study see: Evans, D. E.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem.* **1995**, *107*, 864; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798.

(21) The reaction between 2,3-dimethylbutadiene and ethyl glyoxalate (**6**) catalyzed by 10 mol % of (*S,S*)-**2**/Cu(OTf)$_2$ (in CH$_2$Cl$_2$ at −5 °C in the presence of MS 4 Å) afforded a 93:7 mixture of HDA and carbonyl-ene reaction products. This result is remarkable because previous studies with these substrates under Ti, Al, and Cu catalysis had revealed either a much lower preference for the HDA product or even a dominance of the ene reaction pathway. For leading references, see: (a) Mikami, K.; Terada, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; p 1143. (b) Oi, S.; Terada, E.; Ohuchi, K.; Kato, T.; Tachibana, Y.; Inoue, Y. *J. Org. Chem.* **1999**, *64*, 8660. (c) Reference 9. (d) Reference 19.

(22) (a) For the converison of cycloaddition product **7** to a synthetically interesting bicyclic lactone, see: Yao, S.; Johannsen, M.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1998**, *63*, 118. (b) For the use of HDA adduct **9** in synthetic approaches towards anticapsine see the related discussion in ref 9a.