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Ethylene-Bridged Bissulfoximines in Copper-Catalyzed Enantioselective Hetero-Diels–Alder Reactions

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Dedicated to Professor Steven V. Ley on the occasion of his 60th birthday.

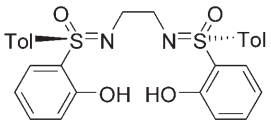
Abstract: Ethylene-bridged bissulfoximines were applied as chiral ligands in copper-catalyzed enantioselective hetero-Diels–Alder reactions. After optimization of the reaction conditions, products with up to 99% ee were obtained.

Keywords: asymmetric catalysis; C–C bond formation; hetero-Diels–Alder reactions; sulfoximines

Introduction

Since the early 1990s, chiral sulfoximines[1] have been the subject of extensive research focused on the development of new ligands for asymmetric catalysis.[2] In the last few years, considerable success has been achieved in this field, mainly due to the introduction of C_1- and C_2-symmetrical compounds, which served as ligands in copper- or palladium-catalyzed reactions affording products with excellent enantioselectivities.[3,4]

At the outset of our studies, we had synthesized the C_2-symmetrical ethylene-bridged bissulfoximine **1**, which is structurally reminiscent of chiral salens **2**, and investigated its potential in vanadium-catalyzed sulfide oxidation.[5]



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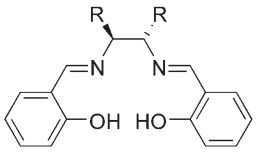

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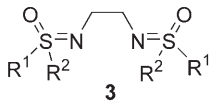
The corresponding structurally well-characterized oxo-vanadium(IV) complex of **1** showed high catalytic activity, giving sulfoxides in very good yields,[6] albeit as racemates. Through the development of a straightforward and low-cost acylation-reduction procedure of general applicability, a wide range of bissulfoximines **3** with different alkyl and aryl substituents could be prepared under mild conditions and in good yield.[7] Their application in various catalytic transformations resulted in high levels of enantioselectivity. For example, it was found that palladium(II) complexes of bissulfoximines **3**, used in allylic substitutions, led to products with up to 98% ee.[4a] Such bissulfoximines **3**, with ethylene as the bridging unit, were regarded as flexible analogues of the well-established aryl-bridged bissulfoximines **4**, which proved to be excellent ligands in copper(II)-catalyzed asymmetric cycloadditions.[3a, b]



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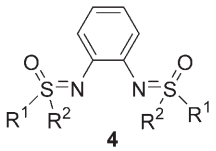

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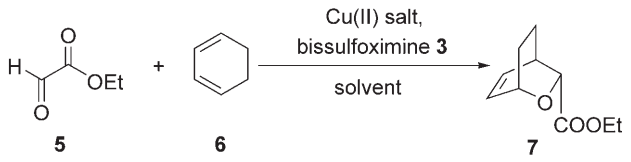
3a: R^1 = Me, R^2 = Ph
3b: R^1 = *i*-Pr, R^2 = Ph
3c: R^1 = Me, R^2 = Biphen
3d: R^1 = Me, R^2 = 3,5-di-*t*-Bu-C_6H_3
3e: R^1 = 2-MeO-C_6H_4, R^2 = Me
3f: R^1 = 2-MeO-Naph, R^2 = Me

Results and Discussion

We have already reported the application of bissulfoximines **3** and their aryl-bridged analogues **4** in Cu(II)-catalyzed Diels–Alder cycloadditions, and demonstrated their ability to serve as highly enantioselective li-

gands for these reactions.[3b] With the intention of extending this comparison between flexible and rigid structures, and to further investigate the potential of ethylene-bridged bissulfoximines **3**, we examined their application in copper-catalyzed asymmetric hetero-Diels–Alder reaction of ethyl glyoxalate (**5**) with 1,3-cyclohexadiene (**6**).[8]



Copper(II) complexes of bissulfoximines **3a**–**f** were screened and evaluated on their ability to provide enantiomerically enriched **7**. At this early stage, all catalytic reactions were performed at room temperature for 15 h, with CH_2Cl_2 as solvent and with 5 mol % catalyst prepared from a 1:1 mixture of bissulfoximine **3** and $Cu(OTf)_2$. The results of this screening are reported in Table 1.

In all catalyses the hetero-Diels–Alder adduct **7** was obtained in good yields and isolated as only the *endo* diastereomer. Very good enantioselectivities were achieved with methyl phenyl bissulfoximine **3a** (93% ee, entry 1) and bissulfoximines **3c** and **3e**, bearing *para*- and *ortho*-substituents on the phenyl group, respectively (93% and 91% ee, entries 3 and 5). Increasing the steric demand of the aliphatic or aromatic-substituents R^1 or R^2, as in bissulfoximines **3b** and **3d**, reduced the enantioselectivity in the product formation (79 and 84% ee, respectively, entries 2 and 4). The best result was obtained with bissulfoximine **3f**, which possesses an *ortho*-methoxynaphthyl group as aromatic substituent at sulfur (95% ee, entry 5). (*S,S*)-Bissulfoximines **3a**–**d** afforded cycloadduct **7** with the (1*R*,3*S*,4*S*) configuration, and accordingly (*R,R*)-**3e** and (*R,R*)-**3f** gave (1*S*,3*R*,4*R*)-**7**.

Next, we focused our attention on the optimization of the reaction conditions by performing the catalysis with bissulfoximine (*R,R*)-**3f** as ligand in the presence of var-

Table 1. Influence of the ligand structure on the hetero-Diels–Alder reaction between ethyl glyoxalate (**5**) and 1,3-cyclohexadiene (**6**).[a]

Entry	Bissulfoximine	Yield [%][b]	*endo*:*exo* Ratio[c]	ee [%][c]	Configuration[d]
1	(*S,S*)-**3a**	73	99:1	93	1*R*,3*S*,4*S*
2	(*S,S*)-**3b**	61	99:1	79	1*R*,3*S*,4*S*
3	(*S,S*)-**3c**	82	99:1	93	1*R*,3*S*,4*S*
4	(*S,S*)-**3d**	70	99:1	84	1*R*,3*S*,4*S*
5	(*R,R*)-**3e**	62	99:1	91	1*S*,3*R*,4*R*
6	(*R,R*)-**3f**	81	99:1	95	1*S*,3*R*,4*R*

[a] Reaction conditions: **5** (1 equiv.), **6** (2 equivs.), $Cu(OTf)_2$ (5 mol %), bissulfoximine **3** (5 mol %), CH_2Cl_2, room temperature, 15 h.[9]
[b] After column chromatography.
[c] Determined by GC analysis.[9]
[d] Determined by comparison of the optical rotations.[10]

Table 2. Effect of the solvent, counterion and temperature on the reaction between ethyl glyoxalate (**5**) and 1,3-cyclohexadiene (**6**).[a]

Entry	Copper salt	Solvent	Temperature	Yield [%][c]	*endo*:*exo* Ratio[d]	ee [%][d]
1	$Cu(OTf)_2$	CH_2Cl_2	rt	81	99:1	95
2	$Cu(ClO_4)_2$[b]	CH_2Cl_2	rt	85	99:1	95
3	$Cu(PF_6)_2$[b]	CH_2Cl_2	rt	88	99:1	92
4	$Cu(SbF_6)_2$[b]	CH_2Cl_2	rt	65	99:1	90
5	$Cu(OTf)_2$	CH_3NO_2	rt	89	99:1	86
6	$Cu(OTf)_2$	THF	rt	82	99:1	97
7	$Cu(OTf)_2$	$CHCl_3$	rt	85	99:1	98
8	$Cu(OTf)_2$	$CHCl_3$	0 °C	83	99:1	99
9[e]	$Cu(OTf)_2$	$CHCl_3$	0 °C	14	99:1	97

[a] Reaction conditions: **5** (1 equiv.), **6** (2 equivs.), copper(II) salt (5 mol %), bissulfoximine (*R,R*)-**3f** (5 mol %), 15 h.[9]
[b] Prepared *in situ* from $CuCl_2$ (5 mol %) and AgX (10 mol %).[9]
[c] After column chromatography.
[d] Determined by GC analysis.[9]
[e] Reaction conducted over 48 h using 1 mol % of catalyst [1:1 mixture of $Cu(OTf)_2$ and bissulfoximine (*R,R*)-**3f**].

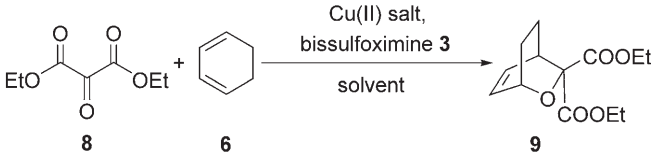
Table 3. Influence of the ligand structure on the hetero-Diels–Alder reaction between diethyl ketomalonate (**8**) and 1,3-cyclohexadiene (**6**).[a]

Entry	Bissulfoximine	Solvent	Temperature	Yield [%][b]	ee [%][c]	Configuration[d]
1	(*S,S*)-**3a**	CH_2Cl_2	rt	95	88	1*S*,4*R*
2	(*S,S*)-**3b**	CH_2Cl_2	Rt	52	76	1*S*,4*R*
3	(*S,S*)-**3c**	CH_2Cl_2	Rt	94	88	1*S*,4*R*
4[e]	(*S,S*)-**3c**	CH_2Cl_2	Rt	68	85	1*S*,4*R*
5	(*S,S*)-**3d**	CH_2Cl_2	Rt	57	78	1*S*,4*R*
6	(*R,R*)-**3e**	CH_2Cl_2	rt	79	90	1*R*,4*S*
7	(*R,R*)-**3f**	CH_2Cl_2	rt	75	91	1*R*,4*S*
8[e]	(*R,R*)-**3e**	CH_2Cl_2	rt	65	83	1*R*,4*S*
9	(*R,R*)-**3e**	$CHCl_3$	0	68	93	1*R*,4*S*

[a] Reaction conditions: **8** (1 equiv.), **6** (2 equivs.), $Cu(OTf)_2$ (10 mol %), bissulfoximine **3** (10 mol %).[9]
[b] After column chromatography.
[c] Determined by HPLC analysis using a chiral column (Chiralcel AD).[9]
[d] Determined by comparison of the optical rotations.[15]
[e] Reaction performed using 5 mol % of catalyst [1:1 mixture of $Cu(OTf)_2$ and bissulfoximine **3**].

ious solvents and counterions at different temperatures (Table 2).

With the notion in mind that less coordinating counterions could positively affect the enantioselectivity of the catalysis,[11] we first tested different copper(II) salts. Contrary to our expectations, use of PF_6^- and SbF_6^- resulted in a slight decrease in the ee of the product (92 and 90% ee, respectively, entries 3 and 4), whereas copper(II) perchlorate led to no variation in the enantioselectivity from that obtained with triflate (95% ee, entry 2). Thus, keeping $Cu(OTf)_2$ as copper(II) source, several solvents were tested. It was found that the ee of **7** increased from 95 to 97 and 98% by simply switching from CH_2Cl_2 to THF or $CHCl_3$ (*cf.* entries 1, 6 and 7). By lowering the temperature to 0 °C a further increase in enantioselectivity was observed, and cycloadduct **7** was obtained in 83% yield and 99% ee. It was also found that the catalyst loading could be reduced to 1 mol % without significant loss of enantioselectivity (97% ee, entry 9), although the yield of **7** was considerably reduced even after a prolonged reaction time. These results show that ethylene-bridged bissulfoximines **3** serve as excellent ligands in the copper-catalyzed hetero-Diels–Alder reaction between ethyl glyoxalate (**5**) and 1,3-cyclohexadiene (**6**) and provide one of the highest asymmetric inductions ever observed for this reaction.[12] Subsequently, we examined the reaction of 1,3-cyclohexadiene (**6**) with the activated ketone **8**.[13] Hetero-Diels–Alder adduct **9** is a particularly attractive target, as it serves as a key intermediate in synthetic approaches towards biologically active compounds.[14]



The results of catalyses with copper(II) complexes of bissulfoximines **3a**–**f** under various reaction conditions are summarized in Table 3.

The entire screening of bissulfoximines **3a**–**f** was performed with 10 mol % of catalyst. Reducing the catalyst loading to 5 mol % in the case of bissulfoximine (*S,S*)-**3c** resulted in a decrease in the ee of the product from 88% to 85% (entries 3 and 4). The best results were obtained with bissulfoximines (*R,R*)-**3e** and (*R,R*)-**3f**, bearing *ortho*-methoxy substituents on the aromatic system (90 and 91% ee, respectively; entries 6 and 7). Performing the reaction with bissulfoximine (*R,R*)-**3e** under the same optimized conditions as found for aldehyde **5** [at 0 °C, with $CHCl_3$ as solvent and with $Cu(OTf)_2$ as copper source], it was possible to improve the enantioselectivity of the reaction to 93% ee without affecting significantly the yield (entry 9).

These results are only slightly inferior to that obtained with aryl-bissulfoximines **4**,[16] which renders ethylene-bridged bissulfoximines **3** a new class of highly enantioselective ligands for the hetero-Diels–Alder reaction of ketones, one of the most interesting challenges in synthetic organic chemistry.[17]

Conclusion

In summary, we have described a new application of ethylene-bridged bissulfoximines as ligands in copper-catalyzed hetero-Diels–Alder reactions. These compounds are easily accessible by a well established, low-cost synthetic procedure and compare well with the structurally related aryl-bissulfoximines, leading to cycloaddition products in good yield and with up to 99% ee.

Experimental Section

Materials

All chemicals were commercially available and have been used as provided. Dichloromethane was distilled from calcium hydride prior to use. Representative procedures for the syntheses of bissulfoximines **3**[18] and the HDA reactions are given below. For further details and product analyses see, respectively, ref.[7] and ref.[3]

Representative Procedure for the Synthesis of Ethylene-Bridged Bissulfoximines 3: Preparation of (*R,R*)-3f[7]

Step 1: Acylation of the sulfoximine: To a solution of the (*R*)-*S*-(2-methoxynaphthyl)-*S*-methyl sulfoximine[19] (2.0 g, 8.5 mmol) in CH_2Cl_2 (50 mL), was added triethylamine (1.4 mL, 10 mmol) and a catalytic amount of dimethylaminopyridine at 0 °C, followed by dropwise addition of a solution of oxalyl chloride (0.52 g, 4.2 mmol) in CH_2Cl_2 (15 mL). After stirring for about 1 h the mixture was warmed to room temperature and stirred overnight. Then, the solution was partitioned between saturated aqueous $NaHCO_3$ (20 mL) and CH_2Cl_2 (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (5×20 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The solid was washed with EtOAc and after filtration the pure acylated bissulfoximine was obtained as colorless solid; yield: 1.9 g (3.6 mmol, 85%).

Step 2: Reduction of the acylated bissulfoximine: At 0 °C in a vacuum-dried Schlenk flask a solution of the acylated bissulfoximine (1.30 g, 2.48 mmol) in freshly distilled CH_2Cl_2 (20 mL) was treated dropwise with catecholborane (1 M in THF, 20 mL). After stirring for 3 h at this temperature, the mixture was warmed to room temperature and stirred overnight. The reaction was carefully quenched with water, and the resulting mixture was extracted with CH_2Cl_2 (5×10 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The product was purified by flash chromatography on silica gel (EtOAc) to afford (*R,R*)-**3f** as yellow crystals; yield: 0.67 g (1.35 mmol, 54%).

General Procedure for the Hetero-Diels–Alder Reactions between Ethyl Glyoxalate (5) or Diethyl Ketomalonate (8) and 1,3-Cyclohexadiene (6)[3a]

A vacuum-dried Schlenk flask under an argon atmosphere was charged with $Cu(OTf)_2$ or $CuCl_2$ (25 μmol, 5 mol %), the bissulfoximine **3** (25 μmol, 5 mol %) and the given solvent (1 mL). The resulting green solution was stirred at room temperature for 1 h. In catalyses with CuX_2 (X = ClO_4, PF_6, SbF_6) as copper source, $CuCl_2$ was applied in combination with AgX (50 μmol, 10 mol %), which was added at this stage. After stirring for 30 min, ethyl glyoxalate (**5**; 0.5 mmol) or diethyl ketomalonate (**8**; 0.5 mmol) and 1,3-cyclohexadiene (**6**; 1.0 mmol) was added at the given temperature. After 15 h, the product was isolated by flash chromatography (pentane/EtOAc 4:1).

The enantiomer ratio of ethyl 2-oxabicyclo[2.2.2]oct-5-ene-3-carboxylate (**7**) was determined by gas chromatography using the β-cylodextrin column {Cyclodex β-I/P: 2,3,6-trimethyl-β-cyclodextrin (25 m × 0.25 mm) with a pre-column FS-Phenyl-Sil (3 m × 0.25 mm); 130 kPa N_2; oven temperature = 90 °C, 5 min; 2 °C/min; 130 °C, 15 min; 2 °C/min; t_{exo} = 40.0 min and 41.3 min, t_{endo} = 42.9 min [(1*S*,3*R*,4*R*)-**7**] and 43.7 min [(1*R*,3*S*,4*S*)-**7**]}.

The enantiomer ratio of 2-oxa-3,3-diethoxycarbonylbicyclo[2.2.2]oct-5-ene (**9**) was determined by HPLC using a Chiralpak AD column {eluent: heptane:*i*-PrOH = 95:5; flow: 0.2 mL/min; 220 nm; t_R = 43.2 min [(1*R*,4*S*)-**9**] and t_R = 48.5 min [(1*S*,4*R*)-**9**]}.

Acknowledgements

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[6] Use of 0.3 mol % of the oxo-vanadium(IV) complex of **1** in the oxidation of methyl phenyl sulfide gave the corresponding sulfoxide in 93% yield, see ref.[5]

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[12] With 5 mol % Cu(II) complex of aryl-bridged bissulfoximine **4** (R^1 = Me, R^2 = Ph) as catalyst, compound **7** was obtained in 61% yield and with 99% ee at –5 °C, see ref.[3a]

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[16] Cu(II) complex of bissulfoximine **4** (R^1 = Me, R^2 = Ph) gave cycloaddition product **9** with 98% ee at –40 °C, see ref.[3a]. Attempts to lower the temperature below 0 °C led in this case to no formation of the reaction product.

[17] For recent reviews on asymmetric synthesis of quaternary carbon centers, see ref.[13] and references cited therein.

[18] For an initial catalyst screening we recommend the use of bissulfoximine **3a**, since both enantiomers of *S*-methyl-*S*-phenyl sulfoximine, which is required as key intermediate in the synthesis of **3a**, are commercially available (Lancaster) or can easily be obtained applying a synthetic protocol reported in J. Brandt, H.-J. Gais, *Tetrahedron: Asymmetry* **1997**, *8*, 909–912.

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