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A new class of C_1-symmetric monosulfoximine ligands for enantioselective hetero Diels–Alder reactions†

Carsten Bolm,*[a] Marinella Verrucci,[a] Oliver Simic‡,[a] Pier Giorgio Cozzi,[b] Gerhard Raabe[a] and Hiroaki Okamura[a]

[a] *Institute of Organic Chemistry, RWTH Aachen Professor-Pirlet-Strasse 1, D-52056 Aachen, Germany. E-mail: Carsten.Bolm@oc.rwth-aachen.de; Fax: +49 241 809 2391; Tel: +49 241 809 4675*

[b] *Dipartimento di Chimica, G. Ciamician, Via Selmi 2, 40126 Bologna, Italy*

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Quinoline-based C_1-symmetric sulfoximines have been used as chiral ligands in copper-catalyzed asymmetric hetero Diels–Alder reactions leading to cycloadducts with up to 96% ee.

Over the last thirty years, optically active sulfoximines have successfully been applied as versatile reagents in various fields of organic synthesis.[1] Due to the proximity of the donor sites to the stereogenic sulfur atom, sulfoximines were expected to be promising ligands for asymmetric catalysis. Along these lines, we recently introduced C_2-symmetric bissulfoximines **1** and **2** (Fig. 1),[2] which led to very high enantiomeric excesses in Pd-catalyzed allylic alkylations[3] and Cu-catalyzed cycloaddition reactions.[4]

ESR and EXAFS measurements of the ligand/metal/substrate assembly in a Cu(II)-catalyzed Diels–Alder reaction with sulfoximine **2** as ligand revealed a distorted, nonsymmetric square pyramidal geometry at copper.[5] Most interestingly, in this arrangement the two coordinating sulfoximine nitrogens occupy non-equivalent positions. We therefore wondered if the C_2-symmetry of the ligands was really essential or if C_1-symmetric monosulfoximine derivatives could also be applied in asymmetric reactions and lead to high enantioselectivities. On this basis, sulfoximines **5**, in which the second donor atom is a quinolyl nitrogen, became prime targets. A wide range of these compounds were easily synthesized by palladium-catalyzed *N*-arylations of enantiopure sulfoximines **3** with 8-bromoquinoline derivatives **4** affording the products in good yields (Table 1).[6]

The potential of monosulfoximines **5** to serve as chiral ligands was evaluated in the asymmetric Cu(II)-catalyzed hetero Diels–Alder reaction[7] between 1,3-cyclohexadiene (**6**) and ethyl glyoxylate (**7**)[8] or diethyl ketomalonate (**8**).[9] In order to specify a standard for a preliminary screening of sulfoximines **5a–l**, all catalytic reactions were performed at room temperature for 18 h, in CH_2Cl_2 as solvent and with 10 mol% of a catalyst prepared from a 1 : 1 mixture of sulfoximine **5** with $Cu(OTf)_2$. The influence of the ligand structure on the enantioselectivity of the HDA reaction is summarized in Table 2.

First, sulfoximine **5a** was tested and cycloadduct **9** was obtained in excellent yield (97%) with an enantiomeric excess of 75% and an *endo*/*exo* ratio of 97 : 3 (entry 1). Starting from this promising result we made some structural changes in **5** in order to find the most effective ligand. We proceeded in two directions: 1) modification of the quinolyl backbone and 2) modification of the sulfoximine moiety by varying the alkyl and aryl substituent. The results of this optimization studies are presented in Table 2.

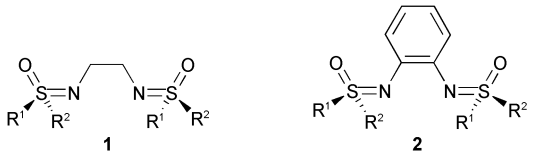


Fig. 1

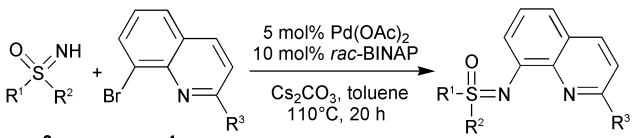
The high enantiomeric excess obtained with sulfoximine **5h** encouraged us to optimize the reaction conditions in terms of temperature, catalyst loading, solvent and counterion. By lowering the temperature to −10 °C, adduct **9** could be obtained in 98% yield and 93% ee. With a reduced catalyst loading of 1 mol% neither enantioselectivity (91% ee) nor conversion (98% yield) was affected under standard conditions. To our delight, *we observed that even upon reducing the amount of catalyst to 0.05 mol% the selectivity remained invariably high (91% ee).* Unfortunately, in this case the conversion was incomplete during the standard reaction time, and therefore the yield of the isolated product dropped to 68%.

Combining these influences and performing also solvent and counterion optimization we further improved the reaction conditions and were able to obtain product **9** with 96% ee in 65% yield and with an *endo*/*exo* ratio of 99 : 1 by using 1 mol% of $Cu(ClO_4)_2$ and (*R*)-**5h** in $CHCl_3$ at −10 °C for 18 h (entry 9).

A comparable trend concerning selectivities and yields was observed for substrate **8** as well (Table 2, entries 14–20), but in general the ee values were slightly lower.

The absolute configurations of the products **9** and **10** were confirmed by comparison of their optical rotations with those reported in the literature.[8a,9] Uniformly (*R*)-**5** afforded product **9** with configuration (1*S*,3*R*,4*R*), whereas (*S*)-**5** gave the

Table 1 Synthesis of quinolyl- and acridinyl-sulfoximines **5a–l** by Pd-catalyzed coupling reaction[a]



3 **4** **5**

Entry	Sulfoximine	R^1	R^2	R^3	Yield[b] (%)
1	**5a**	CH_3	Ph	H	90
2	**5b**	CH_3	Ph	*n*-Bu	75
3	**5c**	CH_3	Ph	$-C_4H_4-$[c]	68
4	**5d**	*i*-Pr	Ph	H	75
5	**5e**	*t*-Bu	Ph	H	72
6	**5f**	CH_3	biphenyl	H	84
7	**5g**	CH_3	3,5-di-*t*-Bu-Ph	H	81
8	**5h**	CH_3	2-MeO-Ph	H	87
9	**5i**	*n*-pentyl	2-MeO-Ph	H	85
10	**5j**	phenethyl	2-MeO-Ph	H	73
11	**5k**	*t*-Bu	2-MeO-Ph	H	55
12	**5l**	CH_3	2-MeO-Naph	H	81

[a] Reaction conditions: sulfoximine **3** (1 equiv.), bromoquinoline **4** (1 equiv.), $Pd(OAc)_2$ (5 mol%), *rac*-BINAP (10 mol%) and Cs_2CO_3 (2 equiv.) in toluene at 110 °C for 24 h. [b] Yields refer to product amounts after flash chromatography. [c] 4-Bromoacridine was used.

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‡ *Present address*: Novartis Pharma AG, Postfach, CH-4002 Basel, Switzerland.

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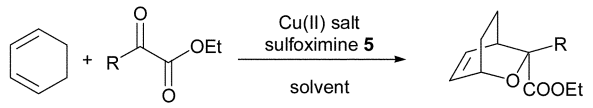
opposite HDA-adduct enantiomer *ent*-**9**. In case of substrate **8**, we observed inverse selectivity and (*R*)-ligands led to (1*R*,4*S*)-product *ent*-**10**.

In order to gain a deeper mechanistic insight into the origin of the efficiency of ligand **5h**, we focussed our efforts on obtaining structural data of compounds in the solid state. The X-ray structure of complex (*R*)-**5h**/$CuCl_2$ is outlined in Fig. 2.[10] In the complex **5h** acts as a *N*,*N*-bidentate ligand, the chloride counterions coordinate to the copper center and the complex exhibits a distorted tetrahedral coordination geometry.

Its structure in the solid state and the absolute configuration of adduct **9** allowed us to propose a mechanistic model, which explains the stereochemical outcome of the reaction (Fig. 2).

Table 2 Effect of the ligand structure on the enantioselectivity of the hetero Diels–Alder reactions[a]



6 **7** R = H, **8** R = COOEt → **9** R = H (1*S*,3*R*,4*R*), **10** R = COOEt (1*S*,4*R*)

Entry	Sulfoximine	HDA adduct	Yield [%][b]	ee [%][c]	*endo* : *exo* ratio[d]	Configuration
1	(*R*)-**5a**	**9**	97	75	97 : 3	1*S*,3*R*,4*R*
2	(*S*)-**5b**	*ent*-**9**	93	63	99 : 1	1*R*,3*S*,4*S*
3	(*S*)-**5c**	*ent*-**9**	95	56	99 : 1	1*R*,3*S*,4*S*
4	(*S*)-**5d**	*ent*-**9**	22	38	96 : 4	1*R*,3*S*,4*S*
5	(*S*)-**5e**	*ent*-**9**	18	0	88 : 12	1*R*,3*S*,4*S*
6	(*S*)-**5f**	*ent*-**9**	92	73	98 : 2	1*R*,3*S*,4*S*
7	(*S*)-**5g**	*ent*-**9**	81	73	97 : 3	1*R*,3*S*,4*S*
8	(*R*)-**5h**	**9**	98	91	98 : 2	1*S*,3*R*,4*R*
9[e]	(*R*)-**5h**	**9**	65	96	99 : 1	1*S*,3*R*,4*R*
10	(*R*)-**5i**	**9**	92	90	98 : 2	1*S*,3*R*,4*R*
11	(*R*)-**5j**	**9**	93	86	97 : 3	1*S*,3*R*,4*R*
12	(*R*)-**5k**	**9**	41	0	92 : 8	1*S*,3*R*,4*R*
13	(*S*)-**5l**	*ent*-**9**	88	91	98 : 2	1*R*,3*S*,4*S*
14	(*R*)-**5a**	*ent*-**10**	80	73	—	1*R*,4*S*
15	(*S*)-**5c**	**10**	60	57	—	1*S*,4*R*
16	(*S*)-**5d**	**10**	28	38	—	1*S*,4*R*
17	(*S*)-**5e**	**10**	26	0	—	1*S*,4*R*
18	(*S*)-**5f**	**10**	86	63	—	1*S*,4*R*
19	(*S*)-**5g**	**10**	82	70	—	1*S*,4*R*
20	(*R*)-**5h**	*ent*-**10**	86	89	—	1*R*,4*S*

[a] Reaction conditions (except for entry 9): **6** (2 equiv.), **7** or **8** (1 equiv.), $Cu(OTf)_2$ (10 mol%), sulfoximine **5a–l** (10 mol%), CH_2Cl_2, rt, 24 h. [b] Yields refer to product amounts after flash chromatography. [c] Determined by GC or HPLC analysis using a chiral column. [d] Determined by GC analysis. [e] For conditions see text.

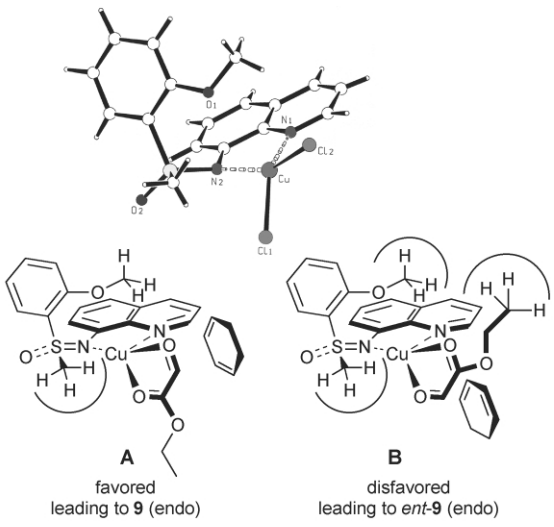


Fig. 2 Structure of (*R*)-**5h**/$CuCl_2$ in the solid state (top) and proposed transition-state models for the HDA reaction between **6** and **7** (bottom).

The peculiar structure of the ligand reduces the number of possible transition states by shielding one region and forcing the diene **6** to approach only from the sterically less hindered side. As a consequence, the enantioselectivity of the reaction is determined by the coordination mode of the substrate. Due to the steric hindrance of the methoxy group, the substrate coordinates preferentially with the ethoxy substituent under the quinoline plan (Fig. 2, **A**) leading to cycloadduct **9** as the major enantiomer. The proposed model also explains the different ligand influences indicated in Table 2. In the case of the reaction catalyzed by **5a**, the absence of an *ortho*-substitutent on the phenyl ring makes the transition state **B** less disfavored and thus the enantioselectivity is reduced (Table 2, entry 1). For the same reason, substituents in the *meta*- and *para*-positions (sulfoximines **5f** and **5g**) have no significant influence on the stereochemical outcome of the reaction (entries 6, 7). A sterically more demanding group R^1 gives rise to an enhanced interaction with the ethyl chain of the substrate **7** in the transition state **A**, thus reducing the energy difference between the two diastereomeric transition states.

On the basis of these results we proposed that the optimal ligand should bear a sulfoximine unit with a small alkyl substituent and an aryl moiety having a bulky group in the *ortho*-position. As a first confirmation of this prediction we demonstrated that use of (*R*)-*N*-(8-quinolyl)-*S*-(2-isopropoxyphenyl)-*S*-methylsulfoximine afforded product **9** in 94% yield and 93% ee. This was indeed the highest enantioselectivity achieved in this reaction under standard conditions.

In conclusion, we have reported the first example of a copper catalyzed HDA reaction in the presence of a C_1-symmetric sulfoximine ligand, leading to cycloadducts in good yield and with up to 96% ee.

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