C_1-Symmetric Aminosulfoximines as Ligands in Copper-Catalyzed Carbonyl-Ene Reactions

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Abstract: Highly modular C_1-symmetric aminosulfoximines were prepared and applied as chiral ligands in copper-catalyzed enantioselective carbonyl-ene reactions. The optimized system catalyzed the conversion of pyruvates and 1,1-disubstituted olefins yielding the corresponding hydroxy esters with high enantiomeric excesses (up to 91% ee) in moderate yields.

Key words: asymmetric catalysis, α-hydroxy esters, carbonyl-ene reactions, copper, sulfoximines

Within the last decades, sulfoximines[1] have successfully been applied in various fields of modern organic chemistry. Their use ranges from building blocks for bioactive molecules[2] and pseudopeptides[3] to chiral auxiliaries[4] for asymmetric synthesis and ligands[5] for enantioselective metal catalysis. In the latter context, the first generation of chiral sulfoximine ligands included C_1-symmetric hydroxysulfoximines which led to high enantiomeric excesses in 1,2-additions of diethyl zinc and TMSCN to aldehydes,[6,7] for example.[8] Later, we and others developed C_2-symmetric bissulfoximines which were found to be highly effective in enantioselective copper and palladium catalyses.[9,10] Guided by the discovery that C_1-symmetric *N*-quinolyl-sulfoximines served as powerful ligands in Cu-catalyzed hetero-Diels–Alder reactions as well,[11] we recently began to focus our attention on the design and preparation of aminosulfoximines **1**, which constitute a new class of electron-rich aryl-bridged sulfoximine ligands (Figure 1).[12]

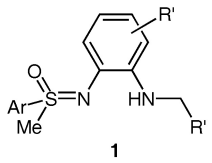

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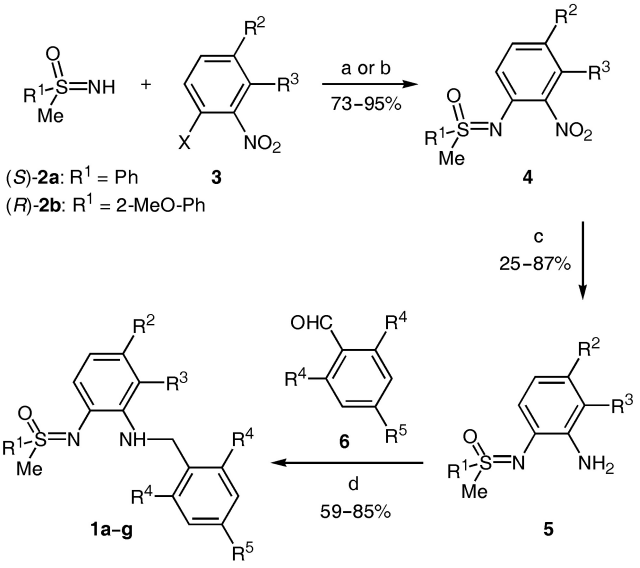
Figure 1

Starting from enantiomerically pure sulfoximines **2**, aminosulfoximines **1** are easily accessible in an efficient three-step reaction sequence including first Pd- or Cu-catalyzed coupling reactions,[13,14] second reductions of the resulting nitro compounds **4**, and finally reductive aminations of anilines **5** with aldehydes **6** (Scheme 1). This highly modular approach allows a rapid generation of a compound library by utilizing various sulfoximines [here (*S*)-**2a** and (*R*)-**2b**], nitro benzenes **3**, and carbonyl compounds **6**.



Product	R^1	R^2	R^3	R^4	R^5
(*S*)-**1a**	Ph	H	H	Me	Me
(*S*)-**1b**	Ph	H	H	*i*-Pr	*i*-Pr
(*S*)-**1c**	Ph	H	H	Cl	H
(*R*)-**1d**	2-MeO-Ph	H	H	Me	Me
(*S*)-**1e**	Ph	H	Me	Me	Me
(*S*)-**1f**	Ph	F	H	Me	Me
(*S*)-**1g**	Ph	Me	H	Me	Me

Scheme 1 *Reagents and conditions*: (a) Ar-Br (1 equiv), $Pd(OAc)_2$ (5 mol%), *rac*-BINAP (7.5 mol%), Cs_2CO_3 (1.4 equiv), toluene, reflux, 24 h; (b) Ar-I (2 equiv), CuI (1 equiv), CsOAc (2.5 equiv), DMSO, 90 °C, 12 h; (c) Fe, HOAc, EtOH, H_2O, reflux, 3–5 h; (d) $NaBH_3CN$ [or $NaBH_4$ for (*S*)-**1b**; 2.5 equiv], MeOH, HOAc, 0 °C to r.t., 3–12 h.

Aminosulfoximines **1** with unsubstituted aromatic core units have recently been employed in Cu-catalyzed Mukaiyama-type aldol reactions of pyruvate esters and silylenolethers. There, compounds **1a**,**b** having *ortho*-disubstituted *N*-benzyl groups proved particularly effective leading to aldol products with excellent enantiomeric excesses in very good yields.[12] Encouraged by these results, we decided to assess the use of the aminosulfoximines as

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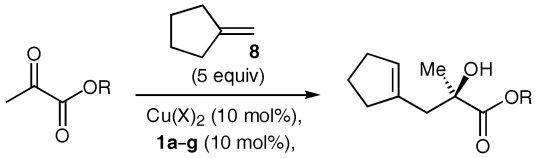
ligands in Cu-catalyzed carbonyl-ene reactions between activated carbonyl compounds as enophiles and 1,1-disubstituted olefins.[15] This important C-C bond forming process yields allylic α-hydroxy esters, which are useful building blocks in organic synthesis,[16] and so far only one catalytic system is known, which is capable of mediating the intermolecular addition of olefins to activated ketones.[15d] As model reaction, the addition of methylenecyclopentane (**8**, 5 equiv) to methyl pyruvate (**7a**) was chosen. The catalyst was prepared in situ by mixing 10 mol% of $Cu(OTf)_2$ and 10 mol% of the chiral ligand in dry CH_2Cl_2. The results of this initial investigation confirmed our assumption, as in presence of the mesityl ligand **1a**, product **9a** was obtained with promising 86% ee (Table 1, entry 1). Unfortunately, however, the yield was rather low (29%) under those conditions. Based on results of previous studies by us[17] and others,[15b,d] we expected an enhanced catalytic activity after the exchange of the triflate anion by other weakly coordinating counterions. Indeed, the application of $Cu(ClO_4)_2$ (formed in situ from $CuCl_2$ and 2 $AgClO_4$) led to a significantly higher yield (63%), whereas the enantioselectivity remained essentially unaffected (87% ee; Table 1, entry 2). In contrast, other counterions such as SbF_6^-, BF_4^-, or PF_6^- lowered both the yield and the enantioselectivity.

Apart from dichloromethane, dichloroethane proved to be a suitable solvent, although the yield and the enantioselectivity decreased to 52% and 82%, respectively. By performing the test reaction in chloroform, an even higher ee (89%) was achieved, but the yield dropped significantly to 18%. Other chlorinated solvents such as 1,1,1-trichloroethane or 1,1,2-trichloroethane and weakly coordinating ethers (THF, MTBE) were inappropriate for this catalytic application.

Next, the effect of the ligand structure on the product ee and the yield in the test reaction using (mostly) $Cu(ClO_4)_2$ as metal source was studied. Taking into account that *ortho*-disubstituted *N*-benzyl aminosulfoximine **1a** had led to a product with high ee in good yield, we were surprised to note that the catalyst system with ligand **1b** bearing three isopropyl substituents in the 2-, 4-, and 6-position was catalytically much less effective affording **9a** with decreased ee in lower yield (Table 1, entry 3). Presumably, the increased steric bulk of the isopropyl groups reduced the activity as well as the asymmetric induction of the catalytically active species. Use of dichloro derivative **1c** and ligand **1d** with a modified sulfoximine unit[18] gave similar results as with **1a** (entries 4 and 5). In the latter catalysis, *R*-configured **1d** was used leading to predominant formation of the *S*-enantiomer of **9a**. In all other cases, the applied aminosulfoximines had *S*-configuration affording preferentially the *R*-enantiomer of the product.

For further ligand optimization, the aryl backbone of the ligand was modified by the introduction of various substituents on the bridging benzene core (Figure 1, $R' \neq H$). Depending on their position as well as their steric and electronic properties, the course of the catalysis varied. A methyl group in the *ortho*- or a fluoro substituent in the *meta*-position to the amino substituent of the ligand as in **1e** and **1f**, respectively, affected the ee and the yield of hydroxy ester **9a** only to a minor degree (entries 6 and 7). Although both values were slightly lower than those obtained in catalyses with the unsubstituted mesityl analogue **1a** (entry 2), satisfying results were still obtained. Gratifyingly, we then found that an electron-donating methyl substituent in the *meta*-position to the aryl amino group had a positive effect on the enantioselectivity. Thus, aminosulfoximine **1g** proved to be the best ligand for this catalysis, and its application provided **9a** with 91% ee in 50% yield (entry 8).[19]

Table 1 Use of Aminosulfoximines **1a**–**g** in Cu(II)-Catalyzed Carbonyl-Ene Reactions[a]



7a: R = Me
7b: R = Bn

9a: R = Me
9b: R = Bn

Entry	Sulfoximine	Educt → Product	$Cu(X)_2$[b]	Yield (%)	ee (%)[c]
1	(*S*)-**1a**	**7a** → (*R*)-**9a**	$Cu(OTf)_2$	29	86
2	(*S*)-**1a**	**7a** → (*R*)-**9a**	$Cu(ClO_4)_2$	63	87
3	(*S*)-**1b**	**7a** → (*R*)-**9a**	$Cu(ClO_4)_2$	25	79
4	(*S*)-**1c**	**7a** → (*R*)-**9a**	$Cu(ClO_4)_2$	58	85
5	(*R*)-**1d**	**7a** → (*S*)-**9a**	$Cu(OTf)_2$	23	86
6	(*S*)-**1e**	**7a** → (*R*)-**9a**	$Cu(ClO_4)_2$	44	80
7	(*S*)-**1f**	**7a** → (*R*)-**9a**	$Cu(ClO_4)_2$	62	84
8	(*S*)-**1g**	**7a** → (*R*)-**9a**	$Cu(ClO_4)_2$	50	91
9[d]	(*S*)-**1a**	**7b** → (*R*)-**9b**	$Cu(ClO_4)_2$	44	80

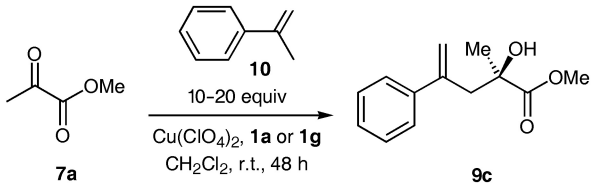
[a] *Reaction conditions*: Pyruvate (0.5 mmol), olefin **8** (2.5 mmol), $Cu(X)_2$ (10 mol%), sulfoximine (10 mol%), CH_2Cl_2 (2 mL), r.t., 48 h.
[b] $Cu(ClO_4)_2$ was prepared in situ from $CuCl_2$ and 2 $AgClO_4$.
[c] Determined by HPLC or GC using chiral columns (Chiralcel OB-H or Cyclodex B, respectively). The absolute configuration of **9a** was assigned by comparison to the known GC data (ref.[15d]), that of **9b** in analogy to **9a**.
[d] See ref. 20.

Benzyl pyruvate (**7b**) could also be applied as enophile, and its reaction with methylenecyclopentane (**8**) under catalysis with 10 mol% of the Cu(II)-**1a** complex afforded **9b** with 80% ee (Table 1, entry 9).[20]

When α-methylstyrene (**10**) was reacted with methyl pyruvate (**7a**), a large excess of the olefin and a high catalyst loading was required for achieving an acceptable conversion of the carbonyl compound (Table 2). With 10 equivalents of **10** and in the presence of 10 mol% of the Cu(II)-complex prepared from **1a**, the corresponding α-hydroxyester **9c** was obtained with 86% ee. The yield, however, was very low (11%; Table 2, entry 1). Both,

yield and ee could be improved to 44% and 88%, respectively, by increasing the amount of olefin and ligand to 20 equivalents and 30 mol%, respectively (entry 2). Finally, use of aminosulfoximine **1g** yielded **9c** with even 91% ee. In this case, however, 50 mol% of the catalyst were applied and the product yield was only 53% (Table 2, entry 3).

Table 2 Asymmetric Copper-Catalyzed Reaction between Methyl Puryvate (**7a**) and α-Methylstyrene (**10**)[a]



7a **9c**

Entry	**10** (Equiv)	Sulfoximine (amount)	Yield of **9c** (%)	ee of **9c** (%)[b]
1	10	(*S*)-**1a** (10 mol%)	11	86
2	20	(*S*)-**1a** (30 mol%)	44	88
3	20	(*S*)-**1g** (50 mol%)	53	91

[a] *Reaction conditions*: **7a** (0.5 mmol), olefin **10**, $Cu(ClO_4)_2$ (prepared in situ from $CuCl_2$ and 2 $AgClO_4$), sulfoximine **1a** or **1g**, CH_2Cl_2 (2 mL), r.t., 48 h.
[b] Determined by HPLC using a chiral column (Chiralcel OB-H). The absolute configuration of **9c** was assigned in analogy to **9a**.

In conclusion, the application of aminosulfoximines as ligands in Cu-catalyzed carbonyl-ene reactions was demonstrated. The resulting hydroxy esters **9** have been obtained with high enantiomeric excesses (up to 91% ee) in moderate yields. Those enantioselectivities reach up to the values achieved with Evans' well-established Cu(II)-*t*-Bu-box catalyst system.[15d] Current studies are directed towards an expansion of the substrate scope combined with further process optimizations with the goal of achieving higher product yields.

Acknowledgment

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(18) A pronounced effect of *ortho*-alkoxy groups was observed in hetero-Diels–Alder reactions catalyzed by copper complexes bearing *N*-quinolyl sulfoximines. For details, see ref. 11.

(19) **Experimental Procedure.**
In a dried Schlenk-flask under an argon atmosphere, $CuCl_2$ (6.7 mg, 0.05 mmol) was suspended in dry CH_2Cl_2 (2 mL) and then treated with $AgClO_4$ (20.7 mg, 0.1 mmol). The mixture was stirred for 60 min at r.t. under exclusion of light and subsequently, aminosulfoximine **1a** or **1g** (0.05 mmol) was added. Stirring of the resulting blue suspension was continued for another 30 min followed by the addition of the enophile (0.5 mmol) and the olefin (5–20 equiv). After stirring for 48 h at r.t., the mixture was diluted with Et_2O (50 mL) and filtered through a plug of silica gel. The solvent was removed under reduced pressure, and the corresponding product was purified by column chromatography (pentane–EtOAc, 15:1 for **9a** and **9c**, 10:1 for **9b**) and obtained as colorless oil.

(20) Unfortunately, **9b** was obtained as a mixture with enophile **7b**, which was inseparable by column chromatography. Use of (chiral) HPLC, however, allowed the determination of the enantiomeric ratio of **9b** (80% ee). The 'yield' of **9b** was then estimated from the NMR spectra (44%).