Asymmetric Catalysis

C_1-Symmetric Sulfoximines as Ligands in Copper-Catalyzed Asymmetric Mukaiyama-Type Aldol Reactions**

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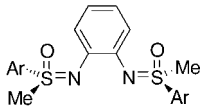
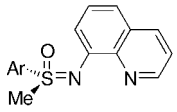
Since the report of the discovery of sulfoximines by Whitehead and Bentley in 1952,[1] they have found numerous applications in organic synthesis.[2] For example, they have been used as building blocks in bioactive molecules[3] and pseudopeptides,[4] chiral auxiliaries for asymmetric synthesis,[5] and ligands for enantioselective metal catalysis.[6] In the latter context we and others have prepared sulfoximines, such as **1** and **2**, which lead to products with up to 99% *ee* by palladium and copper catalysis.[7,8]



1a: R = Ph
1b: R = 2-MeO-Ph



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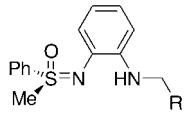


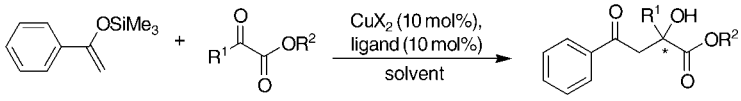
3

3a: R = Ph
3b: R = 1-Naph
3c: R = 2-MeO-Ph
3d: R = Mes
3e: R = 2,4,6-iPr$_3$-Ph

Relevant intermediates in copper-catalyzed cycloaddition reactions were recently identified by spectroscopic means.[9] We have now investigated the use of sulfoximines in Mukaiyama-type aldol reactions and found novel benzene-bridged aminobenzyl-substituted sulfoximines **3** (Mes = mesityl) to be excellent ligands for this synthetically important C–C bond-forming reaction.

We chose the reaction between 1-phenyl-1-(trimethylsilyloxy)ethene (**4**) and methyl pyruvate (**5a**, Scheme 1) as a model reaction to allow meaningful comparisons to be made with well-established systems such as [Cu(*t*Bubox)]$^{2+}$ or [Sn(pybox)]$^{2+}$ (box = bis(oxazoline), pybox = pyridylbis(oxazoline)) catalysts.[10] The initial experiments were performed in THF with copper(II) triflate as the metal source.

To our disappointment complexes based on C_2-symmetric bissulfoximines **1** and *N*-quinolyl-substituted sulfoximine **2**, which previously had been successfully applied in copper-catalyzed cycloaddition reactions,[8] led to rather unsatisfying results and gave products with low or moderate enantioselectivities.[11] On the basis of the hypothesis that an amino group would improve the metal-binding properties of the ligands, novel C_1-symmetric benzene-bridged benzylaminosulfoximines **3** were designed. Their syntheses are summarized in Scheme 2. Starting from 2-bromonitrobenzene (**7**) and enantiopure (*S*)-*S*-methyl-*S*-phenylsulfoximine (**8**),[12] the desired sulfoximines **3** were readily available by a three-step reaction sequence involving first a Buchwald–Hartwig-type



4 **5** **6**

a: $R^1 = R^2 = Me$
b: $R^1 = Me$, $R^2 = Bn$
c: $R^1 = Me$, $R^2 = i$Pr
d: $R^1 = Et$, $R^2 = Me$
e: $R^1 = CH_2Bn$, $R^2 = Et$

Scheme 1. Mukaiyama-type aldol reaction. Bn = benzyl.

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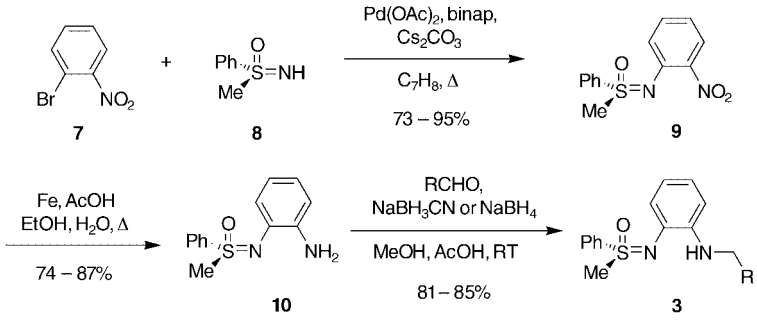


Scheme 2. Synthesis of benzene-bridged aminosulfoximines **3**. Binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl.

coupling reaction,[13] followed by reduction of the nitro group and a reductive amination. Aniline **10** reacted readily with a wide variety of aldehydes, and thus a library of sulfoximine analogues became easily accessible. The high modularity of this synthetic approach becomes apparent when it is considered that other aromatic core units, various sulfoximines, and a number of aldehydes could be combined in the synthetic scheme.

In the test reaction shown in Scheme 1, the use of aminosulfoximine **3a**, which was prepared by reductive amination of **10** and benzaldehyde in 81% yield, yielded aldol product **6a** with a promising *ee* value of 70% (Table 1, entry 1). Aminosulfoximines **3b** and **3c** were prepared (in 85 and 81% yield, respectively) for the conversion of **10**, with the expectation that the introduction of an electron-donating substituent on the *N*-benzyl arene group would provide a sterically more demanding environment at the metal center and further increase the metal–ligand interaction.[14] Confirmation of this hypothesis was obtained when **6a** was generated with higher enantioselectivties in both cases (83% and 86% *ee* for catalysis with **3b** and **3c**, respectively; Table 1, entries 2 and 3) than when **3a** was used. The introduction of a substituent with two *ortho* groups improved the enantioselectivity even further, and the use of mesitylene derivative **3d** (prepared in 81% yield) led to aldol product **6a** with 93% *ee*. Finally, the best result in terms of both enantioselectivity and yield was obtained with triisopropyl-substituted analogue **3e** (prepared in 82% yield), which gave **6a** with 93% *ee* in >99% yield (Table 1, entry 5).

Table 1: Influence of the ligand structure on the Mukaiyama-aldol reaction shown in Scheme 1.[a]

Entry	Aminosulfoximine	R of **3**	Yield [%][b]	*ee* [%][c]
1	**3a**	Ph	64	70
2	**3b**	1-Naph	77	83
3	**3c**	2-MeO-Ph	72	86
4	**3d**	Mes	88	93
5	**3e**	2,4,6-*i*Pr$_3$-Ph	>99	93

[a] Reaction conditions: **4** (0.6 mmol), **5a** (0.5 mmol), Cu(OTf)$_2$ (0.05 mmol), aminosulfoximine (0.05 mmol), THF, RT, 24 h. [b] After column chromatography. [c] Determined by HPLC on a column with a chiral stationary phase (Chiralcel OD).

Next, we focused our attention on the optimization of the reaction conditions. First the effect of the solvent was investigated. It was deduced from studies with **3d** in various solvents (such as THF, diethyl ether, dioxane, toluene, dichloromethane, and chloroform) that weakly coordinating or aromatic solvents were important for achieving high enantioselectivity. THF proved to be the most suitable solvent in terms of catalytic activity.[15]

Additional optimizations (with **3d**) in regard to the copper(II) salt and the reaction temperature were also performed. In general, the application of counterions other than triflate (for example, PF_6, BF_4, SbF_6, or ClO_4) resulted in a significant decrease in the *ee* value of the product.[15] In terms of product yield, Cu(ClO$_4$)$_2$ was superior to all other metal sources (>99%). With this copper salt, however, the enantioselectivity (81% *ee* for **6a**) was always lower than that obtained with the catalyst based on copper(II) triflate (93% *ee*). The enantioselectivity of the reaction was improved to 98% *ee* by performing the reaction at −55 °C instead of ambient temperature. However, long reaction times (>9 days) were necessary under those reaction conditions to obtain the product in acceptable yields. Since 2,2,2-trifluoroethanol had been reported to facilitate the turnover in catalytic Mukaiyama-type reactions,[16] its capability to accelerate the copper(II)–sulfoximine catalysis at low temperature was studied. To our delight we found that in the presence of this additive (1.2 equiv) the catalysis proceeded smoothly even at −30 °C to afford **6a** with 98% *ee* in 89% yield after only 15 h (Table 2, entry 1). This result clearly confirmed the acceleration effect, which occurred without affecting the enantioselectivity.

Table 2: Effect of the substrate in reactions between **4** and **5** to give **6** (Scheme 1).[a]

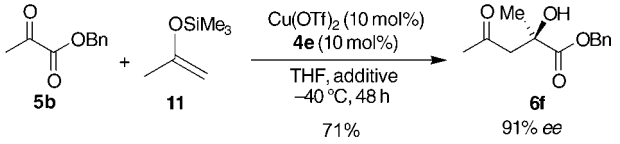
Entry	Product	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**6a**	−30	15	89	98
2	**6b**	−50	47	86	98
3	**6c**	−40	28	90	99
4	**6d**	RT	24	78	89
5	**6e**	−20	40	86	96

[a] Reaction conditions: **4** (0.6 mmol), **5a–e** (0.5 mmol), CF_3CH_2OH (0.6 mmol), Cu(OTf)$_2$ (0.05 mmol), aminosulfoximine **3e** (0.05 mmol). [b] After column chromatography. [c] Determined by HPLC.

The substrate scope was evaluated under the conditions optimized for the reaction between **4** and **5a** (use of **3e** as the ligand, THF as the solvent, Cu(OTf)$_2$ as the copper source, and 2,2,2-trifluoroethanol as the additive at low temperature). Gratifyingly, we found that other α-keto esters also reacted well with enolsilyl ether **4**. Thus, the reaction between benzyl pyruvate (**5b**) and **4** at −50 °C yielded the corresponding aldol product **6b** with 98% *ee*, and use of isopropyl pyruvate (**5c**) furnished **6c** with 99% *ee* (Table 2, entries 2 and 3, respectively). These results showed that the efficiency of the catalyst was independent of the size of the ester moiety. Substrates

bearing more bulky acyl substituents were also investigated. The reaction between methyl α-keto butyrate (**5d**) and **4** gave **6d** with 89% *ee* at room temperature (Table 2, entry 4). No conversion was observed at lower temperatures. The sterically more-demanding ethyl 2-oxo-4-phenyl butyrate (**5e**) yielded **6e** with 96% *ee* at −20°C (Table 2, entry 5). Apparently, the catalyst tolerates an enlarged alkyl chain adjacent to the acyl function, although in some cases higher temperatures are required.

To test the applicability of another enolsilane, benzyl pyruvate (**5b**) was treated with 1-methyl-1-(trimethylsilyloxy)ethane (**11**) to afford the corresponding product **6f** with 91% *ee* in 71% yield (Scheme 3).



Scheme 3. Synthesis of **6f**. Tf = trifluoromethanesulfanyl.

In summary, we have described the synthesis of new C_1-symmetric benzene-bridged aminosulfoximines, which are capable of serving as efficient ligands in copper-catalyzed enantioselective Mukaiyama-type aldol reactions. Aldol products with quarternary centers, which are commonly difficult to prepare in enantiomerically enriched form,[17] have been obtained with up to 99% *ee* in high yields. In terms of *ee* values and yield, the new catalysts compare well with the established $[Cu(t\text{Bubox})]^{2+}$ or $[Sn(pybox)]^{2+}$ systems.[10,18] Ongoing studies are directed to further expand the substrate scope and to demonstrate the applicability of the novel aminosulfoximines in other enantioselective catalyses.

Experimental Section

Representative example for the syntheses of aminosulfoximines **3a–e**: Preparation of **3e**: Glacial acetic acid (172 μL, 3.00 mmol) was added to a solution of aniline **10** (3.00 mmol, 739 mg) and 2,4,6-triisopropylbenzaldehyde (3.60 mmol, 837 mg) in MeOH (20 mL) at RT. The solution was stirred for 3 h and then cooled to 0°C. Subsequently, $NaBH_4$ (7.50 mmol, 284 mg) was added over 20 min, and the mixture was stirred at RT overnight. The solution was partitioned between 10% aqueous K_2CO_3 (20 mL) and CH_2Cl_2 (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated. The product was purified by flash chromatography on silica gel (pentane/EtOAc 10:1) to afford 1.14 g (2.46 mmol, 82%) of **3e** as a colorless solid. For analytical data see the Supporting Information.

General procedure for the Mukaiyama-type aldol reaction: A flame-dried Schlenk flask under Ar atmosphere was charged with $Cu(OTf)_2$ (18.1 mg, 0.05 mmol) and the aminosulfoximine **3a–e** (0.05 mmol). Dry THF (2 mL) was then added and the resulting deep green solution was stirred for 30 min at RT. The mixture was subsequently cooled to the selected temperature, and the α-keto ester **5a–e** (0.5 mmol), silylenol ether **4** (0.6 mmol, 123 μL), and 2,2,2-trifluoroethanol (0.6 mmol, 44 μL) were added. After stirring the reaction mixture for the indicated period of time, it was warmed to RT, diluted with diethyl ether (50 mL) and filtered through a plug of silica gel. The solvent was evaporated, and the product was purified by flash chromatography. For analytical data and determinations of the *ee* values see the Supporting Information.

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[18] Compound **6a** was obtained with a comparable *ee* value (98 versus 99%) but in higher yield (89 versus 77%) with respect to the previously reported results obtained with [M(box)] complexes. In the case of **6f**, the *ee* value and the yield were similar with both systems (91 versus 93% *ee* and 71 versus 76% yield). To the best of our knowledge, **6b–e** have not yet been prepared.

