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

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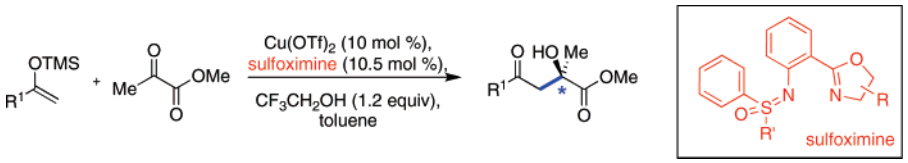
ABSTRACT



Aryl-bridged C_1-symmetric oxazolinyl sulfoximines are applicable in copper-catalyzed asymmetric Mukaiyama aldol reactions with methyl pyruvate. The resulting α-hydroxy esters have been obtained with up to 94% ee in good yields. They contain a quaternary stereogenic center and represent valuable precursors for biologically active molecules.

The enantioselective metal-catalyzed Mukaiyama aldol reaction has become an important synthetic tool for C−C bond formations.[1] It allows the preparation of enantiomerically enriched alcohols, which often represent useful building blocks for biologically active molecules.[2] Most catalytic systems have been applied in additions of enol silanes to aldehydes, resulting in secondary alcohols. However, for reactions involving pyruvates as electrophiles, the number of efficient systems is rather limited.[3] Recently, we reported that copper complexes with C_1-symmetric amino sulfoximines are efficient catalysts for asymmetric Mukaiyama and vinylogous Mukaiyama-type aldol reactions.[4] Inspired by these results, we decided to test the applicability of newly designed oxazolinyl sulfoximines **4** in such transformations.

Sulfoximines of this type can be prepared in a two-step synthesis using readily accessible, commercially available starting materials.[5] Following the reaction sequence depicted in Scheme 1, sulfoximines **4a**−**j** were prepared in overall yields of 65−78%.[6]

For the optimization of the Mukaiyama-type aldol reaction, the solvent, temperature, metal source, and catalyst structure were varied. In the coupling reaction between ketoester **5** and enol silyl ether **6a** to give **7a**, toluene proved superior to DCE, DCM, 1,4-dioxane, Et_2O, THF, and EtOH. This variation also revealed that use of a weakly coordinating

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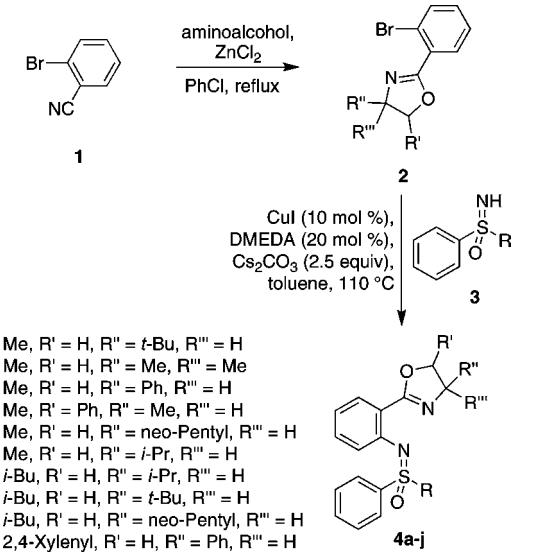
Scheme 1



1 **2** **3** **4a-j**

solvent was crucial for achieving high enantioselectivities. Strongly coordinating solvents such as ethanol hampered the reaction. Table 1 summarizes the results. Furthermore, the effect of 2,2,2-trifluorethanol was investigated. As observed in previous studies,[5,7] the reaction rate increased immensely in the presence of this additive. The enantioselectivity remained unaffected by 2,2,2-trifluorethanol.

Table 1. Solvent Effect on the Mukaiyama Aldol Reaction between Ketoester **5** and Enol Silyl Ether **6a** to give **7a**[a]

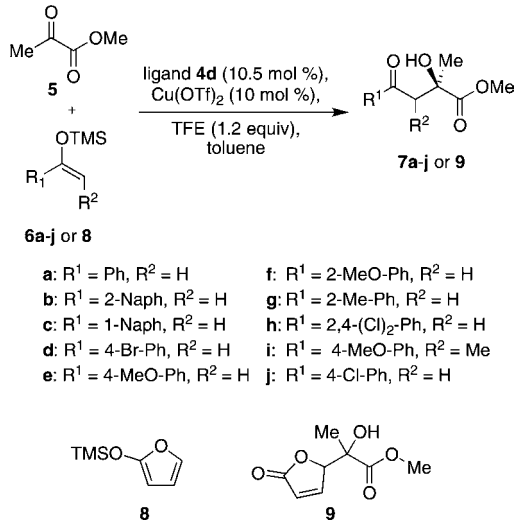
entry	solvent	yield[b] (%)[b]	ee[c] (%)
1	Et_2O	67	40
2	THF	49	17
3	DCM	83	37
4	DCE	85	47
5	1,4-dioxane	69	23
6	EtOH	trace	5
7	toluene	84	67

[a] Reaction conditions: **5** (0.25 mmol), **6a** (0.30 mmol), CF_3CH_2OH (0.30 mmol), $Cu(OTf)_2$ (0.025 mmol), (*S*,*S*)-oxazolinyl sulfoximine **4a** (0.026 mmol), solvent (1.5 mL) at rt for 14 h. [b] Yield after column chromatography. [c] The enantiomer ratios were determined by HPLC using a chiral stationary phase (Chiracel ODH). The (*R*)-configured product **7a** was formed in preference.

Further studies focused on the variation of the copper source and catalyst loading. Among various copper salts, including $Cu(ClO_4)_2$, $Cu(OAc)_2$, $CuCl_2$, Cu(OTf), and Cu(OAc), copper(II) triflate was the most efficient salt concerning yield and ee. Copper(I) salts did not catalyze the reaction at all. Lowering the catalyst loading from 10 to 5 mol % led to reduced product yields and lower enantioselectivities.

Next, the effect of ligand structure in the reaction depicted in Scheme 2 was investigated. Again, the catalytic conversion of **5** and **6a** to give **7a** served as a test reaction. From the behavior of the two diastereomeric oxazolinyl sulfoximine (*S*,*S*)-**4a** and (*S*,*R*)-**4a**, it was concluded that the former was superior with respect to yield and enantioselectivity (Table 2, entries 1 and 2). Thus, the subsequent ligand screening focused on the use of homochiral oxazolinyl sulfoximine derivatives.

Scheme 2



5 **6a-j or 8** **7a-j or 9**

8 **9**

Table 2. Influence of Ligand Structure in the Mukaiyama Aldol Reaction between Ketoester **5** and Enol Silyl Ether **6a** to give **7a**[a]

entry	sulfoximine[b]	yield[c] (%)	ee[d] (%)
1	(*S*,*S*)-**4a**	95	84
2	(*S*,*R*)-**4a**[e]	92	23
3	(*S*)-**4b**	68	9
4	(*S*,*S*)-**4c**	74	57
5	(*S*,1*R*,2*S*)-**4d**[f]	94	91
6[g]	(*S*,1*R*,2*S*)-**4d**[f]	94	94
7	(*S*,*S*)-**4e**	56	46
8	(*S*,*S*)-**4f**	79	66
9	(*S*,*S*)-**4g**	46	21
10	(*S*,*S*)-**4h**	51	16
11	(*S*,*S*)-**4i**	33	32
12	(*S*,*S*)-**4j**	71	11

[a] Reaction conditions: **5** (0.25 mmol), **6a** (0.30 mmol), CF_3CH_2OH (0.30 mmol), $Cu(OTf)_2$ (0.025 mmol), sulfoximine **4** (0.026 mmol), toluene (1.5 mL), rt, 20 h. [b] All sulfoximidoyl units have (*S*)-configuration at sulfur. [c] Yield after column chromatography. [d] The enantiomer ratios were determined by HPLC using a chiral stationary phase (Chiracel ODH). The (*R*)-configured product **7a** was preferentially formed. [e] Oxazolinyl moiety derived from (*R*)-configured *tert*-leucinol. [f] Oxazolinyl moiety derived from L-(−)-norephedrine. [g] Performed at −20 °C.

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Increasing the steric bulk of the substituents at the sulfur atom [by changing methyl to *iso*-butyl or xylenyl (Table 2, entries 8 vs 9 and 4 vs 12, respectively)] led to a decrease in yield and enantioselectivity. For further ligand optimization, the methyl phenyl combination at the sulfonimidoyl moiety was kept constant and the oxazolinyl substituents were varied.

Use of sulfoximine **4b** having no stereogenic center at the heterocycle led to **7a** with poor ee in moderate yield (Table 2, entry 3). The testing of other oxazolinyl sulfoximine derivatives revealed that the substitution pattern at the oxazoline ring was of major importance, and finally, compound **4d** derived from L-(−)-norephedrine and (*S*)-configured methyl phenyl sulfoximine was identified as the best ligand yielding **7a** with 91% ee in 94% yield (Table 2, entry 5). Lowering the reaction temperature to −20 °C increased the enantioselectivity to remarkable 94% ee without affecting the yield (Table 2, entry 6). Consequently, the optimal conditions for the catalytic reaction between methyl pyruvate (**5**) and silyl enol ether **6** (1.2 equiv) involved the use of 10.5 mol % of (*S*,*S*)-oxazolyl sulfoximine **4a**, 10.0 mol % of $Cu(OTf)_2$, and 1.2 equiv of 2,2,2-trifluorethanol, and the reaction had to be performed in a temperature range of 0 to −20 °C (Scheme 2).

In order to evaluate the substrate scope of the asymmetric Mukaiyama aldol reaction, the applicability of various silyl enol ethers and pyruvate esters was examined. To our delight, several substrate combinations reacted well, affording products with enantioselectivities in the 80−90% ee range (Table 3). The highest enantiomeric excesses (94%) were achieved in reactions with enol silyl ethers **6a**, **6b**, and **6e** derived from aryl methyl ketones (Table 3, entries 2, 3, and 7). In general, catalyses with methyl pyruvate (**5**) and enol silyl ethers derived from acetophenones proceeded smoothly, whereas other pyruvate esters and donor substrates with aliphatic R^1 groups did not react at all. Enol silyl ethers bearing aryl groups with electron-donating substituents were good substrates. If the presence of electron-withdrawing groups reduced electron density of the enol silyl ether (Table 3, entries 6, 10, and 13), the reaction temperature had to be increased to room temperature to obtain acceptable yields.

Silyl enol ethers with sterically more demanding groups resulted in somewhat lower enantioselectivities and reduced yields. Nevertheless, 90% ee was still achieved in conversions of *ortho*-substituted compounds **6g** and **6h** (Table 3, entries 9 and 10).

In a vinylogous Mukaiyama aldol reaction 2-(trimethylsilyloxy)furan (**8**) underwent facile reaction with pyruvate **5** to afford *anti*-aldol adduct **9** in high yield with excellent diastereoselectivity, albeit with low ee (Table 3, entry 12). This transformation is particularly interesting since it provides a highly functionalized γ-lactone which represents a versatile precursor for natural product synthesis.[8]

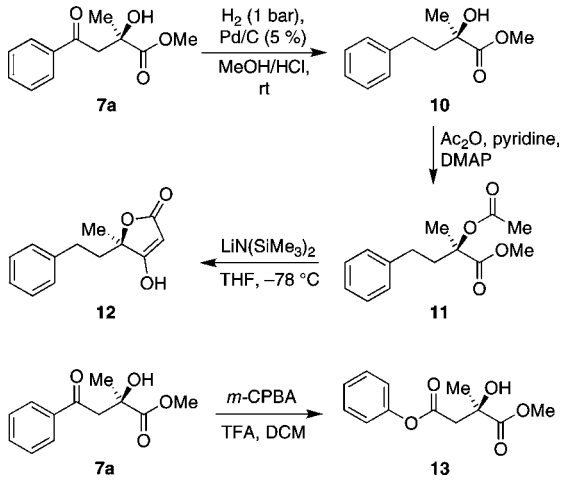
In order to further demonstrate the synthetic value of the newly developed Mukaiyama aldol catalyst system, conversions of **7** into tetronic and malic acid derivatives were established (Scheme 3). Tetronic acids and their metabolites are common in nature,[9] and optically active derivatives are of immense interest due to their versatile pharmacological applications.[10] Tetronic acid derivative **12**, for example, can be used in the treatment and prevention of diseases modulated by a β-secretase inhibitor, such as Alzheimer's disease,[11] or can be applied for the inhibition of the HIV protease enzyme.[12]

Table 3. Substrate Scope of the Mukaiyama Aldol Reaction between Ketoester **5** and Enol Silyl Ethers **6** to give **7**[a]

entry	product	temp (°C)	yield[b] (%)	de[c] (%)	ee[d] (%)
1	**7a**	rt	94		91
2	**7a**	−20	85		94
3	**7b**	−20	89		94
4	**7c**	rt	70		90
5	**7c**	0	67		82
6	**7d**	rt	58		86
7	**7e**	−20	98		94
8	**7f**	−20	74		85
9	**7g**	−20	81		90
10	**7h**	rt	21		90
11	**7h**	0	17		88
12	**7i**	rt	65	20	72/40[e]
13	**7j**	rt	46		90
14	**9**	−20	95	98	22[f]

[a] Reaction conditions: **5** (0.25 mmol), **6** (0.30 mmol), CF_3CH_2OH (0.30 mmol), $Cu(OTf)_2$ (0.025 mmol), sulfoximine **4d** (0.026 mmol), toluene (1.5 mL), 16 h. [b] After column chromatography. [c] Diastereomer ratio was determined by ^1H NMR. [d] The enantiomer ratios were determined by HPLC using a chiral stationary phase (Chiracel ODH, OBH, ADH, OJ). The (*R*)-configured product **7** was preferentially formed. The absolute configurations of the products were assigned in analogy to **7a**. [e] The relative configuration has not been determined. [f] Absolute and relative configurations have been determined by comparison with literature data (see ref 3c).

Scheme 3



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The preparation of 5,5-disubstituted (*R*)-tetronic acid derivative **12** started from 2-hydroxyester **7a**. The deoxygenation step from **7a** to methyl ester **10** proceeded smoothly, but traces of the corresponding acid were formed as byproduct. In order to obtain a quantitative yield of **10**, the reaction mixture was evaporated to dryness and the resulting oil was dissolved in MeOH/HCl. After 2 h at 50 °C, all acid was converted into ester **10**, which could then be isolated with 94% ee in 99% yield.[13] Subsequent acylation with acetic anhydride/pyridine and DMAP led to the corresponding 2-acetoxycarboxylate **11** in 90% yield. Finally, tetronic acid derivative (*R*)-**12** was obtained in excellent yield (94%) by cyclization of (*R*)-**11** using $LiN(SiMe_3)_2$ (2.2 equiv) in THF at −78 °C.[14] As expected, no racemization occurred during the described reaction sequence providing **12**.

Malic acid derivatives represent valuable building blocks for peptides[15] and are potential precursors for natural product synthesis. Citramalic acid derivative (*R*)-**13**, containing a stereogenic quaternary center and two different ester moieties, was obtained in 95% yield by Baeyer−Villiger oxidation of **7a** using *m*-CPBA and TFA in DCM at room temperature (Scheme 3).

In summary, we have described the synthesis of novel C_1-symmetric aryl-bridged oxazolinyl sulfoximines and demonstrated their applicability as ligands in copper-catalyzed enantioselective Mukaiyama-type aldol reactions. Various α-hydroxy esters with quaternary stereogenic centers have been obtained in good yields with enantioselectivities of up to 94% ee. Furthermore, we have shown that the newly developed catalytic system can be used for the synthesis of synthetically and pharmacologically interesting compounds, such as γ-lactone **9**, tetronic acid derivative **12**, and the malic acid ester derivative **13**.

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Supporting Information Available: Experimental procedures and full characterization (^1H and ^{13}C NMR data and spectra, MS, IR, and CHN analyses) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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