ORGANIC LETTERS

2006
Vol. 8, No. 6
1209−1211

Sulfoximines as Ligands in Copper-Catalyzed Asymmetric Vinylogous Mukaiyama-Type Aldol Reactions

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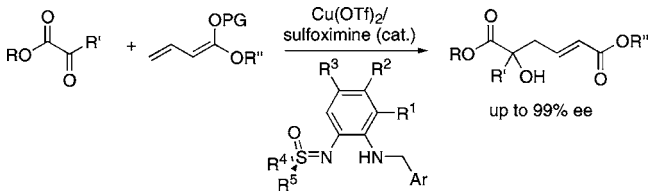
Received January 11, 2006

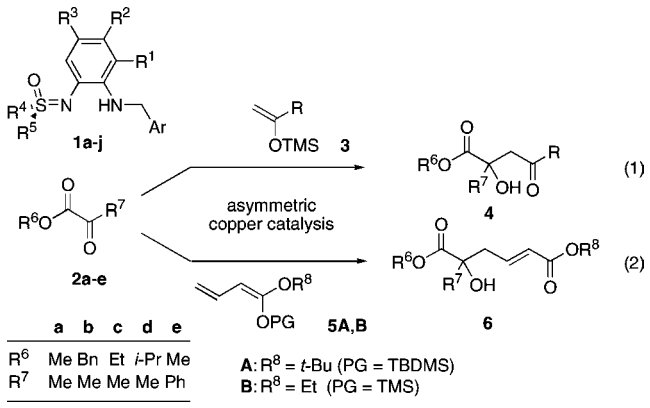
ABSTRACT



γ,δ-Unsaturated α-hydroxy diesters with quaternary centers have been obtained with up to 99% ee in high yields using catalysts prepared from copper(II) triflate and C_1-symmetric aminosulfoximines.

During the past two decades, the enantioselective metal-catalyzed Mukaiyama-type aldol reaction has become a powerful tool in organic synthesis.[1] Mostly, enolsilanes and aldehydes have been employed as substrates. In contrast, addition reactions to activated ketones are still rather rare, despite the fact that synthetically valuable products with quaternary stereogenic centers can be obtained. Recently, we reported that copper(II) complexes bearing C_1-symmetric aminosulfoximines **1** are efficient catalysts for this type of reaction (Scheme 1, eq 1), affording aldol products **4** in high yields with excellent enantioselectivities (up to 99% ee).[2−4] We wondered about the use of this catalyst system in *vinylogous* asymmetric Mukaiyama-type aldol reactions (Scheme 1, eq 2),[5,6] which to the best of our knowledge have never been described with combinations of pyruvate esters **2** and silyl vinyl ketene acetals **5**.[7,8] In a single step, γ,δ-unsaturated α-hydroxy diesters **6** with quaternary stereogenic centers would result, which are useful building blocks for the synthesis of natural products.[9]

Scheme 1



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(2) (a) Langner, M.; Bolm, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 5984−5987. (b) Langner, M.; Rémy, P.; Bolm, C. *Chem. Eur. J.* **2005**, *11*, 6254−6265.

(3) (a) For the use of **1** in copper(II)-catalyzed asymmetric carbonyl ene reactions, see: Langner, M.; Rémy, P.; Bolm, C. *Synlett* **2005**, *5*, 781−784. (b) for a recent review summarizing syntheses and applications of sulfoximines in asymmetric catalysis, see: Okamura, H.; Bolm, C. *Chem. Lett.* **2004**, *33*, 482−487.

10.1021/ol060077d CCC: $33.50
Published on Web 02/18/2006

First, the effect of the ligand structure in the reaction between methyl pyruvate (**2a**) and 1-[(*tert*-butyldimethylsilyl)oxy]-1-(*tert*-butyloxy)-1,3-butadiene (**5A**) affording unsaturated hydroxydiester **6aA** was studied. These experiments were performed in THF at room temperature using a catalyst composed of 10 mol % of copper(II) triflate and 10 mol % of the ligand. Table 1 summarizes the results.

Table 1. Influence of Ligand Structure on the Vinylogous Mukaiyama-Type Aldol Reaction between **2a** and **5A** To Give **6aA**[a]

entry	sulfoximine	R^1	R^2	R^3	R^4	R^5	Ar	yield (%)[b]	ee (%)[c]
1	(*S*)-**1a**	H	H	H	Ph	Me	Mes	50	82
2	(*S*)-**1b**	H	CF_3	H	Ph	Me	Mes	48	75
3	(*S*)-**1c**	H	F	H	Ph	Me	Mes	38	78
4	(*S*)-**1d**	H	Me	Me	Ph	Me	Mes	43	79
5	(*S*)-**1e**	Me	H	H	Ph	Me	Mes	43	79
6	(*S*)-**1f**	H	OMe	H	Ph	Me	Mes	35	80
7	(*S*)-**1g**	H	Me	H	Ph	Me	Mes	39	82
8	(*R*)-**1h**	H	H	H	Me	2-MeO-Ph	Mes	31	76
9	(*S*)-**1i**	H	H	H	Ph	Me	2,4,6-Et_3-Ph	59	83
10	(*S*)-**1j**	H	H	H	Ph	Me	2,4,6-*i*-Pr_3-Ph	48	85

[a] Reaction conditions: **2a** (0.50 mmol), **5A** (0.55 mmol), $Cu(OTf)_2$ (0.05 mmol), aminosulfoximine **1** (0.05 mmol), THF, rt, 24 h. [b] After column chromatography. [c] The enantiomer ratios were determined by HPLC using a chiral stationary phase (Chiralcel AD). For the assignment of the absolute configuration of **6aA**, see text and ref 10. Except in entry 8, *R*-configurated **6aA** was formed in preference.

The initial experiments with the least substituted aminosulfoximine **1a** led to **6aA** with a promising ee of 82% (Table 1, entry 1). As determined by correlation with known 2-acetocitromalate, the *R* enantiomer of **6aA** was formed in preference when (*S*)-**1a** was used as the ligand (for details see Supporting Information).[10] Neither the introduction of substituents in the aromatic backbone nor the presence of an *o*-methoxy group on the sulfoximine part resulted in higher enantioselectivities with this type of ligand (having Ar = Mes; entries 1−8).[11] However, variations of the *N*-benzyl group showed positive effects (entries 9 and 10), and finally, aminosulfoximine **1j** having a 2,4,6-triisopropylphenyl group at that position gave the best result, affording **6aA** with 85% ee. This improvement in enantioselectivity was in accord with previous observations made in Mukaiyama-type aldol reactions with simple enolsilanes (eq 1) and this catalyst system.[2]

Assuming that under catalysis conditions at ambient temperature the stability of both substrate **5A** and product **6aA** was a critical factor, the reaction time was shortened. Confirming this hypothesis, the yield of **6aA** increased from 48% to 66%, when the reaction was stopped after 12 h instead of the previously used 24 h.

A variation of the solvent revealed that weakly coordinating or aromatic solvents such as THF, Et_2O, dioxane, or toluene were crucial for achieving good enantioselectivities (Table 2). Interestingly, only traces of product were observed when the reaction was performed in dichloromethane. This is in contrast to previous results with the same catalyst system,[2] where in this solvent the best yields were achieved. In the copper catalysis reported here, diethyl ether proved to be the most suitable solvent, affording diester **6aA** with 92% ee in 76% yield (Table 2, entry 3).

Table 2. Solvent and Additive Effects on the Vinylogous Mukaiyama-Type Aldol Reaction between **2a** and **5A** To Give **6aA**[a]

entry	solvent	additive	yield (%)[b]	ee (%)[c]
1	THF	−	66	85
2	THF	+	92	85
3	Et_2O	−	76	92
4	Et_2O	+	75	92
5	CH_2Cl_2	−	trace	nd[d]
6	dioxane	−	47	85
7	toluene	−	30	91

[a] Reaction conditions as described in footnote of Table 1 with aminosulfoximine **1j** as ligand and a reaction time of 12 h (instead of 24 h). In entries 2 and 4, 2,2,2-trifluoroethanol (0.6 mmol) was used as additive. [b] After column chromatography. [c] The enantiomer ratios were determined by HPLC using a chiral stationary phase (Chiralcel AD). The *R*-configured **6aA** was formed in preference. For the assignment of the absolute configuration of **6aA**, see text and ref 10. [d] nd = not determined.

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(6) For vinylogous Mukaiyama-type aldol reactions with dienolsilanes and aldehydes and their relevance in natural product synthesis, see: (a) Hassfeld, J.; Eggert, U.; Kalesse, M. *Synthesis* **2005**, 1183−1199. (b) Lepicidin A: Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497−4513. (c) Swinholide A: Paterson, I.; Smith, J. D.; Ward, R. A. *Tetrahedron* **1995**, *51*, 9413−9436. (d) Ratjadone: Christmann, M.; Bhatt, U.; Quitschalle, M.; Claus, E.; Kalesse, M. *Angew. Chem., Int. Ed.* **2000**, 39, 4364−4366. (e) Oleandolide: Hassfeld, J.; Kalesse, M. *Tetrahedron Lett.* **2002**, *43*, 5093−5095. (f) Group A streptogramin: Brennan, C. J.; Campagne, J.-M. *Tetrahedron Lett.* **2001**, *42*, 5195−5197. (g) Dactylolide: Aubele, D. L.; Wan, S.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2005**, *44*, 3485−3488

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(8) Recently, it was demonstrated that combinations of Binol and $Ti(iPrO)_4$ as well as tol-Binap and CuF catalyze addition reactions of ketene acetals such as **5** to aldehydes, affording products with moderate to good enantioselectivities. (a) Bluet, G.; Campagne, J.-M. *Tetrahedron Lett.* **1999**, *40*, 5507−5509. (b) Bluet, G.; Campagne, J.-M. *J. Org. Chem.* **2001**, *66*, 4293−4298. (c) Bluet, G.; Bazan-Tejeda, B.; Campagne, J.-M. *Org. Lett.* **2001**, *3*, 3807−3810. (d) Moreau, X.; Bazan-Tejeda, B.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, *20*, 7288−7289.

(9) For a recent example showing the importance of a γ,δ-unsaturated α-hydroxy ester with a quaternary center as intermediate in the synthesis of natural products, see: Kingsbury, J. S.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 13813−13815.

(10) Only *E*-configured products have been observed. If minor quantities of *Z*-olefins are formed, those must be lost during the isolation and purification of the main products.

Inspired by the previous finding that the presence of 2,2,2-trifluoroethanol facilitated the turnover in catalytic Mukaiyama-aldol reactions,[2,12] its effect in the copper catalysis described here was studied, too. Indeed, when the reaction was performed in THF in the presence of this additive, the yield of **6aA** increased from 66% to 92% (Table 2, entries 1 and 2). In contrast, this positive effect was not observed with diethyl ether as solvent. In both cases the enantioselectivity remained unaffected. Thus here, THF proved superior to other solvents in terms of the yield. Diethyl ether, however, led to the highest enantioselectivity, giving **6aA** with 92% ee.

Further studies focused on the optimization of the copper source, the reaction temperature, and the catalyst loading. As test reaction, the addition of **5A** to **2a** affording **6aA** in the presence of a catalyst prepared in situ from copper(II) triflate and aminosulfoximine **1j** in diethyl ether with 2,2,2-trifluoroethanol as additive was chosen. Among various copper(II) salts, including $Cu(ClO_4)_2$, $Cu(OAc)_2$, and $CuSO_4$, copper(II) triflate was the only one that gave **6aA** with high ee and in good yield (92% ee, 75% yield). All other copper reagents gave less active catalysts, leading to both low yields and reduced (if any) enantioselectivities (for details see Supporting Information).

Lowering the reaction temperature (from ambient temperature) to −78 °C or shortening the reaction time (from 12 h) to 5 h did not affect the ee (92%) but to our delight increased the yield of **6aA** (from 75%) to 80% and 85%, respectively. Catalyst loadings of 5 and 1 mol % (instead of the commonly used 10 mol %) led to lower product yields (64% and 60%, respectively, at room temperature after 5 h compared to 85% with 10 mol %). However, even under those conditions the ee of **6aA** was still remarkably high (90% and 86%, respectively).

To evaluate the substrate scope of the vinylogous asymmetric Mukaiyama-type aldol reaction, we finally examined the applicability of other pyruvate esters and another silyl vinyl ketene acetal.[13] All catalyses were performed at both room temperature and −78 °C using a catalyst derived from copper(II) triflate and aminosulfoximine **1j** (10 mol % each). The results of this study are summarized in Table 3.

Varying the size of carbonyl compound **2** by using methyl, benzyl, ethyl, or isopropyl esters in reactions with **5A** had only a minor effect. All products **6aA**−**6dA** were obtained with 91−92% ee in good yields after 5 h at room temperature (entries 1−8). Performing the catalyses at −78 °C for 12 h increased the enantioselectivies to a remarkable 96−99% ee. Similarly, compound **2e** bearing an enlarged acyl moiety (phenyl instead of methyl) reacted smoothly with **5A**, providing diester **6eA** with up to 93% ee (entries 9 and 10). Use of trimethylsilyl vinyl ketene acetal **5B** derived from the ethyl crotonate gave the best results (Table 3, entries 11 and 12). In this case, the resulting γ,δ-unsaturated α-hydroxy diester **6aB** had 97% ee at room temperature and 99% ee at −78 °C after 5 and 12 h, respectively.

Table 3. Substrate Scope of the Vinylogous Mukaiyama-Type Aldol Reaction between **2** and **5** To Give **6**[a]

entry	keto ester	ketene acetal	product	temp (°C)	t (h)	yield (%)[b]	ee (%)[c]
1	**2a**	**5A**	**6aA**	rt	5	85	92 (*R*)
2	**2a**	**5A**	**6aA**	−78	12	80	96 (*R*)
3	**2b**	**5A**	**6bA**	rt	5	83	91 (*R*)
4	**2b**	**5A**	**6bA**	−78	12	72	97 (*R*)
5	**2c**	**5A**	**6cA**	rt	5	81	91 (*R*)
6	**2c**	**5A**	**6cA**	−78	12	77	97 (*R*)
7	**2d**	**5A**	**6dA**	rt	5	58	91 (*R*)
8	**2d**	**5A**	**6dA**	−78	12	69	99 (*R*)
9	**2e**	**5A**	**6eA**	rt	5	88	89 (*S*)
10	**2e**	**5A**	**6eA**	−78	12	72	93 (*S*)
11	**2a**	**5B**	**6aB**	rt	5	68[d]	97 (*R*)
12	**2a**	**5B**	**6aB**	−78	12	81	99 (*R*)

[a] Reaction conditions: **2** (0.50 mmol), **5** (0.55 mmol), CF_3CH_2OH (0.6 mmol), $Cu(OTf)_2$ (0.05 mmol), aminosulfoximine **1j** (0.05 mmol), Et_2O. [b] After column chromatography. [c] The enantiomer ratios were determined by HPLC using a chiral stationary phase (entries 1−10, Chiralcel AD; entries 11 and 12, Chiralcel OJ). For the assignment of the absolute configuration of **6aA**, see text and ref 10. The absolute configurations of the other products were assigned in analogy to **6aA**. [d] After 12 h, 73% yield.

In summary, we have demonstrated that copper complexes bearing C_1-symmetric aminosulfoximines are capable of catalyzing asymmetric vinylogous Mukaiyama-type aldol reactions. Various γ,δ-unsaturated α-hydroxy diesters with quaternary stereogenic centers have been obtained in good yields with enantioselectivities of up to 99% ee. Current studies are focused on further elucidating the substrate scope and identifying potential intermediates.

Acknowledgment. We are grateful to the Fonds der Chemischen Industrie and to the DFG within the SFB 380 'Asymmetric Synthesis by Chemical and Biological Methods' for financial support. We also thank Dr. L. Hintermann and Dr. M. Christmann, both RWTH Aachen University, for stimulating discussions and the former for the donation of a sample of **5A**.

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.

OL060077D

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(13) **General Procedure for the Vinylogous Asymmetric 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 aminosulfoximine **1** (0.05 mmol). Then, dry Et_2O (2 mL) was added, and the resulting deep green solution was stirred for 30 min at room temperature. Subsequently, pyruvate ester **2** (0.5 mmol), vinyl ketene acetal **5** (0.55 mmol), and 2,2,2-trifluoroethanol (0.6 mmol, 44 μL) were added. After stirring for the indicated period of time, trifluoroacetic acid (0.2 mL) was added, and the solution was stirred for 30 min. The reaction mixture was then diluted with Et_2O, and a saturated aqueous solution of $NaHCO_3$ was added slowly. The aqueous layer was extracted three times with Et_2O, and the combined organic layers were dried over $MgSO_4$. The solvent was removed, and the product was purified by flash chromatography. For details of the ee determination, see Supporting Information.