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Catalyzed Vinylogous Mukaiyama Aldol Reactions with Controlled Enantioand Diastereoselectivities

Marcus Frings, Iuliana Atodiresei, Jan Runsink, Gerhard Raabe, and Carsten Bolm^{*[a]}

Dedicated to Professor Dr. Peter Luger on the occasion of his 65th birthday

The Mukaiyama aldol reaction is an important and valuable carbon–carbon bond-forming reaction, and its enantioselective metal-catalyzed version has attracted much attention.^[1] By using chiral Lewis acids, enantiomerically enriched alcohols are accessible that frequently occur in natural or bioactive compounds.^[2] By applying the concept of vinylogy,^[3] δ -hydroxy α,β -unsaturated carbonyl compounds can be prepared in a highly stereoselective manner.^[4] The vinylogous Mukaiyama aldol reaction (VMAR), which involves the use of *O*-silylated dienolates, is of particular interest in that respect, and much progress has been made in controlling its regio- and stereoselectivity.^[5,6]

As part of our ongoing studies on the use of sulfoximines in metal catalysis,^[7] we recently reported that C_1 -symmetric amino sulfoximines **1** and oxazolinyl sulfoximines **2** were effective ligands in asymmetric copper catalyses.^[8–10]



We now describe the use of sulfoximine **1a** in copper-catalyzed VMARs between various cyclic dienol silanes and

[a] M. Frings, Dr. I. Atodiresei, Dr. J. Runsink, Prof. Dr. G. Raabe, Prof. Dr. C. Bolm Institut für Organische Chemie der RWTH Aachen University Landoltweg 1, 52056 Aachen (Germany) Fax: (+49)241-8092391 E-mail: carsten.bolm@oc.rwth-aachen.de

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ketonic electrophiles. In contrast to the large number of studies with aldehydes as carbonylic substrates,^[11] reports on reactions with ketones are relatively rare,^[13] and only a few of those include pyruvates as starting materials.^[12b,c,13] Pre-sumably the additional demand for diastereoselectivity in the simultaneous formation of two stereogenic centers (including one with a fully substituted carbon) in conjunction with the general requirement of top-level regio- and enantioselectivities have posed additional challenges, which have not allowed rapid progress in this area.

For the initial adjustment of the reaction conditions, commercially available 2-(trimethylsilyloxy)furan (TMSOF, 3a) and methyl pyruvate (4a) were chosen as starting materials (Scheme 1). After a brief optimization, we found that with a



Scheme 1. Synthesis of γ -butenolide **5a** by VMAR with TMSOF (**3a**) and methyl pyruvate (**4a**).

catalyst loading of 10 mol%, a Cu(OTf)₂ to sulfoximine **1a** ratio of 1:1 and 2,2,2-trifluoroethanol (1.2 equiv) as additive in dry diethyl ether, γ -butenolide **5a** could be obtained in 88% yield after only 5 h at room temperature. No α -substitution product was observed, and both the *de* and *ee* values were remarkably high (94 and 95%, respectively). At a temperature of -68°C neither the yield (88%) nor the stereose-lectivities (95% *de*, 94% *ee*) were significantly affected, but the reaction time had to be extended (to 16 h) to achieve a high conversion.

To evaluate the substrate scope of the VMAR, the applicability of various cyclic dienol silanes **3** in combination with other ketonic substrates **4** was examined. All catalyses were performed under the reaction conditions summarized

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above (unless otherwise noted). The results are presented in Table 1.

Table 1. Effect of the substrates in reactions between 3 and 4 to give 5.^[a]

perature to 0° C or -30° C had no beneficial effect on the enantioselectivity. Control experiments showed that a rapid

	() X 39: X	+ R ¹ `OTMS	$O = R^2$	asymme copper cat (for conditio Table foot	etric alysis ons see note a)			
	3b: X 3c: X	= (CH ₂) ₂ = S Me	o ⊖O OMe 4n			MeO OMe O 5p O		
Entry	Dienol silane	Electro- phile	\mathbf{R}^1	\mathbf{R}^2	Prod.	Yield [%] ^[b]	<i>de</i> [%] ^[c]	ee [%] ^[d]
1	3a	4a	Me	Me	5a	88	94 (94)	95/n.d.
2	3a	4b	Me	Bn	5 b	20	92 (92)	93/n.d.
3	3a	4 c	Me	Ph	5c	99	94 (99)	97/70
4	3a	4 d	Me	CF ₃	5 d	75	92 (99)	4/3
5	3a	4e	Me	Et	5e	79	98 (99)	97/n.d.
6	3a	4 f	Et	Me	5 f	92	96 (96)	96/n.d.
7	3a	4 g	Et	Ph	5 g	95	96 (99)	98/n.d.
8	3a	4 h	Et	CH ₂ Bn	5 h	91	99 (99)	98/n.d.
9	3a	4i	Et	iPr	5i	99	99 (99)	99/n.d.
10	3a	4j	Et	4-NO ₂ -Ph	5j	96	85 (99)	91/95
11	3a	4 k	Et	C(O)OEt	5 k	91	—	28
12	3a	41	iPr	Me	51	84	94 (99)	98/n.d.
13	3a	4 m	Bn	Me	5m	84	96 (96)	95/n.d.
14	3 b	4 c	Me	Ph	5n	38	16 (99) ^[e]	92/50
15	3c	4 a	Me	Me	50	52	7 (7)	82/80
16	3a	4n		—	5 p	87	99 (99)	94

[[]a] Reaction conditions for entries 1—14 and 16: Cyclic dienol silane **3** (0.22 mmol), electrophile **4** (0.2 mmol), Cu(OTf)₂ (10 mol%), amino sulfoximine **1a** (10 mol%), CF₃CH₂OH (0.24 mmol), Et₂O (2 mL), RT, 2–6 h; for entry 15: as before, but at -15 °C, overnight. [b] Yield of all stereoisomers after column chromatography. [c] Determined by ¹H NMR analysis of the crude reaction mixture; in parentheses, *de* (referring to the *anti:syn* ratio) of the product after column chromatography. [d] Determined by CSP-HPLC; given for *anti* and *syn* isomers. [e] Diastereomers were separated by preparative HPLC.

Most substrate combinations afforded Mukaiyama aldol products **5** with excellent stereoselectivities in high yields. The best result was achieved in the reaction between α -ketoester **3a** (TMSOF) and 3-methyl-2-oxobutyrate (**4i**), which gave **5i** with a *de* and an *ee* of 99% in essentially quantitative yield (99%) (Table 1, entry 9). α -Substitution products were not observed. In most cases it was possible to isolate the major diastereomer of **5** by column chromatography or preparative HPLC to give a diastereomerically pure product.^[14] Increasing the steric bulk at the ester functionality of **4** (Table 1, compare entries 1, 6, 12, and 13) had almost no effect on the stereoselectivity (93–98% *ee*). Only the yields were slightly lower in the reactions with the isopropyl or benzyl esters (84% yield for both compared to 88% and 92% yield for the methyl and the ethyl ester, respectively).

The catalysis was more sensitive with respect to the ketonic substituent of **4**. Thus, when activated methyl 3,3,3-trifluoropyruvate (**4d**) was used in combination with TMSOF (**3a**, entry 4), product **5d** was isolated in good yield (75%) but, albeit the diastereoselectivity was high, the *ee* of the major isomer was low (4%). Decreasing the reaction tem-

uncatalyzed background reaction (leading to the racemate) could be responsible for this result. γ-Butenolide 5b (entry 2), formed from phenylpyruvic acid methyl ester (4b) and TMSOF (3a), was obtained in low yield (20%) but very good stereoselectivity (92% de and 93% ee). A considerable amount of the corresponding furan-2(5H)-one was formed as a by-product. With 4-nitrophenylglyoxylate (4j) as substrate, the product had a comparably moderate de (85%, entry 10), and noteworthy, the syn product, which was formed as a minor diastereomer, had a higher ee than the (major) anti product (95 and 91% ee, respectively). Ketodiester 4k also reacted well with TMSOF (3a) affording 5k in high yield (entry 11), but the ee was low (28%). Also in this case the uncatalyzed background reaction was fast as shown by a reaction in the absence of the catalyst.

Changing the nucleophile in the reaction with 4c from 3a to cyclic dienol silane 3b(entry 14) led to the γ -product 5n in moderate yield (38%).

While the diastereoselectivity was low (16% de), the enantioselectivity was respectable (92% ee). Use of **3c** having a sulfur (instead of an oxygen as in **3a**) in the heterocyclic ring system had a strong influence on the reaction as well (entry 15). While at room temperature the product **5o** was isolated in only trace amounts, performing the catalysis at -15 °C led to **5o** in moderate yield (52%). Although the *de* was rather low (7%), the *ee* values of 80 and 82% were acceptable for both diastereomers.

Interestingly, pyruvic aldehyde dimethyl acetal (**4n**) could also be applied (Table 1, entry 16), and from its reaction with TMSOF (**3a**) the product **5p** was obtained in very good yield (87%) with excellent stereoselectivity (99% *de* and 94% *ee*). This is most noteworthy because of the masked aldehyde functionality in **5p**, which offers possibilities for further transformations.

To determine the relative and absolute stereochemistry of the products, a representative example, γ -butenolide **5i**, was analyzed by various experimental and theoretical techniques. First, the relative stereochemistry of **5i** was elucidated by a combination of NMR spectroscopy and quantum-

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chemical calculations. With both (racemic) diastereomers, anti-5i and syn-5i, NOE effects were observed between the olefinic proton (C=OCHCH) and the CH proton of the isopropyl group. To compare their intensities, NOE ratios (of 0.8 and 0.4) were calculated by dividing these NOE values by those observed between the two olefinic protons (C= OCHCH) of each compound. To assign the experimentally found NOE values to the corresponding diastereomers, quantum-chemical geometry optimizations were performed at various levels of theory.^[14,15] A comparison of the energetically lowest conformers of both diastereomers obtained at the highest theoretical level (for graphics see the Supporting Information) revealed that in anti-5i the calculated distance between the olefinic and the isopropylic proton is smaller (2.386 Å) than in syn-5i (4.815 Å). Consequently, the value of 0.8 of the NOE ratio (revealing a stronger interaction between the two protons) was assigned to anti-5i, whereas the value of 0.4 was ascribed to syn-5i.

The relative stereochemistry of *anti*-**5i** was confirmed by single-crystal X-ray analysis (of a racemic sample).^[16] The molecular structure in the solid state (Figure 1) is visually indistinguishable from the most stable structure predicted for this stereoisomer at the MP2/6-31+G** level.



Figure 1. Structure of *anti*-**51** in the solid state obtained from a racemic sample; the (S,S)-enantiomer is shown.^[16]

The NOE ratio was used to identify the enantiomerically pure product, which was obtained in the catalysis with a copper complex bearing (S)-1a as the *anti*-5i diastereomer. Its absolute configuration was then assigned by a comparison of the experimental and calculated CD spectra (shown in Figure 2a and b, respectively).^[14,18]

Both calculated CD spectra showed a strong negative Cotton effect with a minimum between 220 and 240 nm followed by a weaker positive one with a maximum between 200 and 220 nm. The calculated negative Cotton effect was assigned to the positive one observed at 213 nm, and the calculated positive one to the observed weakly negative band with a minimum at about 185 nm. Thus the absolute configuration of *anti*-**5i** stemming from the catalysis with the copper complex bearing the (S)-configured sulfoximine [(S)-**1a**] is most likely opposite to that initially assumed in the calculations, and, therefore R, R.



Figure 2. a) Experimental CD-spectrum of *anti*-**5i**. b) Averaged calculated CD spectra for (*S*,*S*)-**5i**. The relative energies of the included conformers have been obtained at the PCM/MP2/6-31+ $G^{**}/MP2/6-31+G^{**}$ (solid curve) and PCM/B3LYP/6-31+ $G^{**}/MP2/6-31+G^{**}$ (dotted curve) level.

In summary, we have developed a copper-catalyzed vinylogous Mukaiyama aldol reaction that provides products with high diastereo- and enantioselectivities. The relative and absolute stereochemistry of a representative product was rigorously assigned by experimental and theoretical means.

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Keywords: asymmetric catalysis • copper • diastereoselectivity • enantioselectivity • sulfoximines • Mukaiyama aldol reaction

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- 47, 8507–8510.[14] For details, see the Supporting Information.
- [15] As starting point, the (*S*,*S*)-configured enantiomer of *anti*-**5***i* was arbitrarily chosen.
- [16] Suitable crystals were obtained from hexane/EtOAc. The compound (C₁₁H₁₆O₅) crystallizes in the (centrosymmetric) monoclinic space group $P2_1/c$ (no. 14) with cell constants a = 9.913(2), b = 9.594(2), c =12.557(3) Å, and $\beta = 94.060(3)^{\circ}$. At a molecular weight of 228.24, Z=4, and a cell volume of 1191.1(5) Å³ the density and the linear absorption coefficients are 1.273 g cm⁻³ and 0.1 mm⁻¹, respectively. Absorption correction was achieved by using SADABS. Diffraction data were collected at 298 K on a Bruker SMART diffractometer by employing Mo_{Ka} radiation ($\lambda = 0.71073$ Å). A total of 26780 reflections were collected in the range $-13 \le h \le 13$, $-12 \le k \le 12$, and $-16 \le l \le 16$ ($\theta_{\text{max}} = 28.5^{\circ}$), merged to give 2751 independent reflections ($R_{int} = 0.02(2)$). The structure was solved by direct methods as implemented in the XTAL3.7 package of crystallographic routines[17] employing GENSIN^[17] to generate structure-invariant relationships and GENTAN^[17] for the general tangent phasing procedure. A total of 2751 observed reflections $(I > 2\sigma(I))$ were included in a fullmatrix least squares refinement of 209 parameters converging at $R(R_w) = 0.04(0.04; w = 1/\sigma^2 (F))$, and a residual electron density of -0.38/+0.35 eÅ⁻³. Hydrogen atoms were located and refined isotropically. CCDC-697979 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif
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- [18] Experimental CD spectra were recorded in acetonitrile at room temperature using an AVIV 62DS circular dichroism spectrometer. The concentration was $1.011 \times 10^{-3} \text{ mol } \text{L}^{-1}$ and the path length 0.1 cm.

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