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Hydrogen bond induced enantioselectivity in Mn(salen)-catalysed sulfoxidaton reactions†

Felix Voss, Eberhardt Herdtweck and Thorsten Bach*

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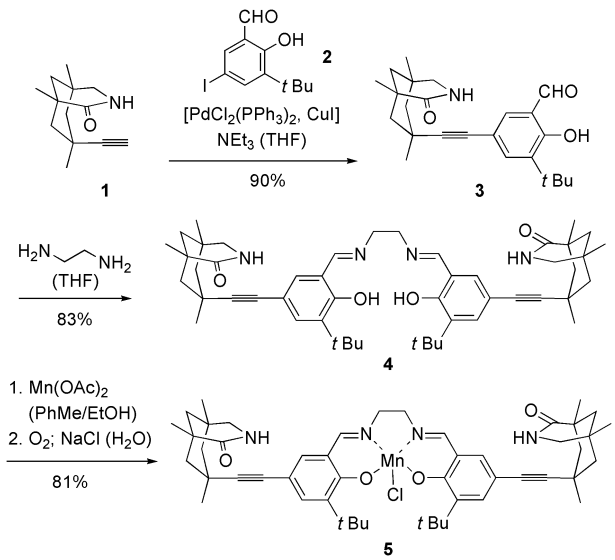
A chiral Mn(salen) complex exhibiting two lactam binding sites at two rigid 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-one skeletons is capable of enantioselective sulfoxidation due to spatially remote substrate hydrogen bonding.

The enantioselective oxidation of sulfides (sulfoxidation) has over the last two decades been established as the most straightforward access to enantiomerically enriched sulfoxides.[1] Pioneering work on the Ti-catalysed sulfoxidation[2] was followed by further studies, in which the catalytically active metal centre has been broadly varied.[3] In most cases enantioselectivity relies on a size differentiation between the two different substituents at a given sulfide. Although hydrogen bonding has been invoked to explain high enantioselectivities in certain sulfoxidation reactions[4] hydrogen bonds have so far not been used as a design principle for exposing a prochiral sulfide to a spatially remote catalytically active metal centre. In the study, which we herein present in preliminary form, the well established oxidation properties of manganese salen complexes[5,6] were combined with a chiral hydrogen bonding scaffold.[7] Enantioselective sulfoxidation reactions were achieved (up to 71% *ee*), the success of which relied exclusively on the hydrogen bonding properties of the scaffold.[8–10]

It was shown recently that a chemical modification of 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-ones, which were used previously as chiral auxiliaries,[11] as chiral templates[12] and as chiral sensitisers,[13] is possible at the 7-position *via* an alkyne unit. Alkyne **1**,[7b] which can be readily synthesised from Kemp's triacid was in the present study connected to the salicylic aldehyde **2**[14] by a Sonogashira cross-coupling reaction (Scheme 1).[15] Salen formation was achieved from aldehyde **3** following a procedure by Hong *et al.*[16] Salen **4** was subsequently converted into the manganese complex **5** following established procedures.[17] Oxidation of Mn(II) to Mn(III) was achieved by purging oxygen through the crude reaction mixture in toluene. Subsequent treatment with sodium chloride



Scheme 1 Synthesis of catalyst **5** starting from enantiomerically pure, chiral alkyne **1**.

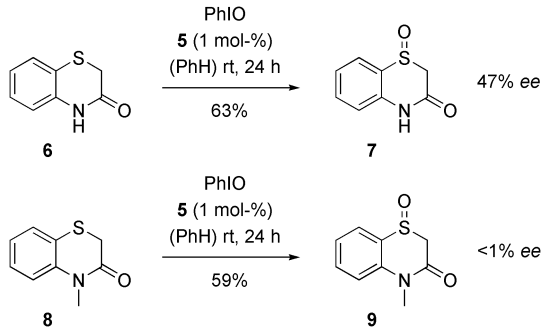
delivered after recrystallisation a light-brown solid, the analytical data of which (see ESI†) are in agreement with the structure **5** depicted in Scheme 1.

It was anticipated that binding of a sulfide-containing lactam to one of the δ-lactam units in catalyst **5** would place the substrate in a chiral environment, in which an enantioselective oxidation was possible. Initial experiments were performed with commercially available 2*H*-benzo[*e*][1,4]thiazin-3-one (**6**), which was oxidised under typical conditions (c = 0.06 M) with iodosobenzene (1.3 equiv.) in benzene at ambient temperature (Scheme 2).[3a] In the presence of 1 mol% of catalyst **5** the reaction proceeded smoothly delivering the desired enantiomerically enriched (47% *ee*) sulfoxide **7** in 63% yield, together with 8% re-isolated starting material and 5% of the respective sulfone (product of overoxidation). *N*-Methylated 2*H*-benzo[*e*][1,4]thiazin-3-one (**8**) reacted under identical conditions to yield sulfoxide **9**, which was formed as a racemate (Scheme 2). The latter result strongly supports the hypothesis that the enantioselectivity in the former reaction was due to hydrogen bonding.

The absolute configuration of the major enantiomer of compound **7** was elucidated by single crystal X-ray crystallography.[18] Derivatisation of the enantiomerically enriched

Department Chemie and Catalysis Research Center (CRC), Technische Universität München, 85747 Garching, Germany. E-mail: thorsten.bach@ch.tum.de; Fax: +49 89 28913315; Tel: +49 89 28913330

† Electronic supplementary information (ESI) available: Preparation and analytical data for all new compounds, selected HPLC traces. CCDC 798187 (**10**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc04636a



Scheme 2 Catalytic oxidation of sulfides **6** and **8**.

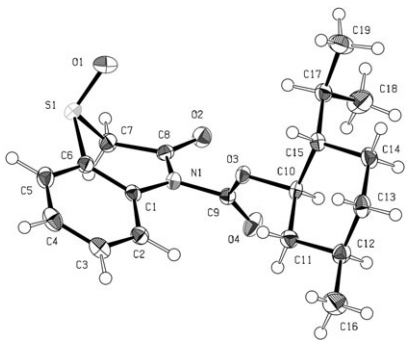


Fig. 1 Single crystal structure analysis of the *N*-menthyloxycarbonyl derivative **10** of chiral sulfoxide **7**.

product **7** (90% *ee*) with (−)-(1*R*,2*S*,5*R*)-menthyl chloroformate delivered a major diastereoisomer **10** (Fig. 2), which was isolated by column chromatography. From the crystal structure depicted in Fig. 1 and from the known absolute configuration of the menthyl substituent it can be concluded that the stereogenic sulfur atom in the sulfoxide is (*S*)-configured.

The outcome of the reaction can be understood by assuming a coordination of the substrate to one of the δ-lactam units in the active catalyst and by formation of complex **11**, the relevant features of which are depicted in Fig. 2. Oxygen transfer to the sulfide occurs intramolecularly to provide the observed (*S*)-enantiomer. Kinetic resolution of the sulfoxide by a preferred further oxidation of one enantiomer to the respective sulfone is not relevant as proven by the reaction of racemic sulfoxide **7** under prolonged reaction conditions.[19] The recovered sulfoxide was not enantiomerically enriched.

Optimisation experiments were conducted with sulfide **6** varying the oxidation conditions. Regarding the solvent, CH_2Cl_2 (65%, 43% *ee*) and iodobenzene (56%, 46% *ee*) delivered under otherwise unchanged conditions similar results as benzene. Lowering the concentration resulted in a significant *ee* increase if iodobenzene was used as the solvent

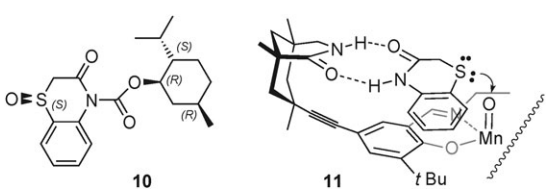
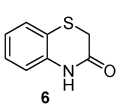
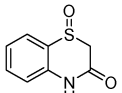
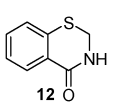
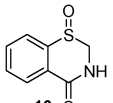
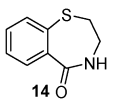
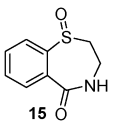
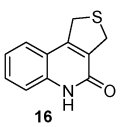
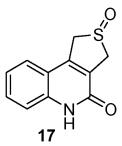
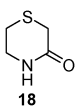
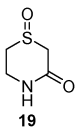
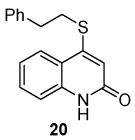
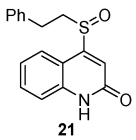


Fig. 2 Structure and configuration of *N*-menthyloxycarbonyl derivative **10**; possible mechanism for the oxygen transfer in the complex **11** of sulfide **6** with the catalytically active Mn(salen) species.

while the enantioselectivity was not concentration dependent in benzene. Through employing an extended reaction time of 72 h and a substrate concentration of 0.02 M in iodobenzene it was possible to obtain product **7** in 67% *ee* and with a yield of 76% (based on conversion). The influence of other parameters was less pronounced. At lower temperature (0 °C) the enantioselectivity was slightly higher (70% *ee*) than at room temperature. The enantioselectivity also increased if more catalyst was employed. With 5 mol% of catalyst an *ee* of 71% was recorded. The use of other oxidants or the use of varying amounts of iodosobenzene had no effect. As a result of the optimisation studies further experiments with different substrates were performed at ambient temperature in iodobenzene as the solvent (Table 1).

Table 1 Enantioselective sulfoxidation of various sulfides catalysed by Mn(salen) catalyst **5**

Entry	Substrate[a]	Product[b]	Yield[c] (%)	ee[d] (%)
1[e]	 **6**	 **7**	76	67
2	 **12**	 **13**	90	13
3[e]	 **14**	 **15**	91	20
4	 **16**	 **17**	85	66
5	 **18**	 **19**	72	59
6	 **20**	 **21**	64	64

[a] Catalyst **5** (1 mol%) and iodosobenzene (1.30 eq.) were consecutively added to a solution of the substrate in iodobenzene (c = 0.02 M). The reaction mixture was stirred at room temperature for 72 hours and purified directly by column chromatography over silica gel. [b] The absolute configuration of the major enantiomer of compound **7** was determined as (*S*). Based on the mechanistic model (Fig. 2) the absolute configuration of the other major sulfoxide enantiomers can be deduced. [c] Yield of the isolated product based on the recovered starting material. [d] The enantiomeric excess (*ee*) was determined by chiral HPLC analysis (see ESI†). [e] Minor overoxidation to the corresponding sulfone was observed.

Compared to the quinolone lactam binding motif of 2*H*-benzo[*e*][1,4]thiazin-3-one (**6**) (entry 1) the analogous isoquinolone binding motif in 2*H*-benzo[*e*][1,4]thiazin-4(3*H*)-one (**12**) (entry 2) was less suited for hydrogen bonding and enantioselective sulfoxidation. The resulting sulfoxide **13** was only produced in 13% *ee*. Presumably, a disfavoured steric interaction of the benzo unit in **12** with the *tert*-butyl groups at the salen prevents efficient binding. Consequently, the homologous sulfide **14**[20] suffers from a similar steric clash resulting in a low enantioselectivity for product **15**. In stark contrast, the other substrates **16**,[21] **18**,[20] and **20** reacted with good enantiocontrol. Given the fact that the groups adjacent to the sulfur atom in sulfides **16** and **18** are both methylene groups the enantioselectivities recorded for sulfoxides **17** (entry 4) and **19** (entry 5) are remarkable. As expected from our initial consideration, the selectivity in this hydrogen-bond mediated sulfoxidation relies exclusively on an efficient binding but not on the size difference of the groups around the sulfur atom. Substrate **20** was chosen to probe the reactivity and selectivity in a sulfide, which is not part of a ring. Also in this case (entry 6) formation of the respective sulfoxide **21** proceeded with good enantioselectivity.

In summary, the enantioselective oxidation of sulfides **6**, **12**, **14**, **16**, **18** and **20** containing a lactam binding motif was achieved by the chiral Mn(salen) catalyst **5**, which exhibits a chiral hydrogen bonding pocket. The hydrogen bonding event occurs more than ten carbon–carbon bonds away from the active metal centre. The directing effect of the hydrogen bonds at the spatially remote chiral template is solely responsible for the face differentiation.

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18 Single crystal X-ray structure determination: **10**: colorless fragment, $C_{19}H_{25}NO_4S$, M_r = 363.47; orthorhombic, space group $P2_12_12_1$ (no. 19), a = 9.2813(2), b = 13.9405(3), c = 14.3069(3) Å, V = 1851.11(7) Å^3, Z = 4, $\lambda(Cu_{K\alpha})$ = 1.54180 Å, μ = 1.747 mm^{-1}, ρ_{calcd} = 1.304 g cm^{-3}, T = 123(1) K, $F(000)$ = 776, 0.25 × 0.30 × 0.64 mm, θ_{max}: 66.53°, R_1 = 0.0190 (3130 observed data), wR_2 = 0.0476 (all 3167 data), GOF = 1.069, 327 parameters, $\Delta\rho_{max/min}$ = 0.17/−0.16 eÅ^{-3}; CCDC 798187 (**10**); For more details see ESI†.

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