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Hydrogen-Bond-Mediated Enantio- and Regioselectivity in a Ru-Catalyzed Epoxidation Reaction

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Abstract: A chiral epoxidation catalyst based on a tricyclic octahydro-1*H*-4,7-methanoisoindol-1-one scaffold, in which a hydrogen bonding site and the catalytically active ruthenium center are spatially separated, was synthesized. It was shown that epoxidation reactions in such a supramolecular catalyst occur with high enantio- and regioselectivity because the hydrogen bonds expose the substrate to the ruthenium porphyrin complex with a clear conformational preference. The epoxidation of 3-vinylquinolone proceeded in up to 95% ee (71% yield).

Nature has mastered the use of hydrogen bonds to selectively process substrates in enzyme-catalyzed reactions. Along with other noncovalent interactions, hydrogen bonds can serve to display a substrate for regio- and stereoselective transformations in the active site of an enzyme. Model systems to mimic this mode of action have attracted significant scientific interest and continue to be developed.[1] With regard to oxidation chemistry, extensive attention has been paid to the development of mimics of cytochrome P 450,[2] an enzyme that plays a pivotal role in biological oxidation chemistry.[3] Through the combination of a noncovalent binding site with a catalytically oxidative metal, selective oxidation reactions have become possible.[4] While hydrogen bonds have frequently been used for substrate activation in organocatalysis,[5] the use of a remote hydrogen-bonding motif[6,7] for directing the enantioselective approach of a transition-metal catalyst has not yet been investigated. We have now found that highly enantio- and regioselective oxidation reactions are feasible with a ruthenium porphyrin complex that is fused to a stereodirecting lactam unit, and we report on our results in preliminary form.

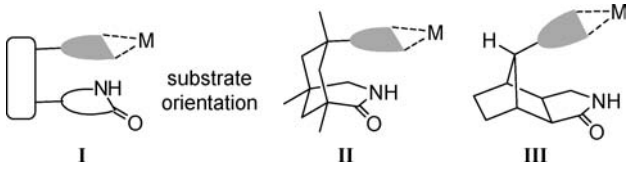
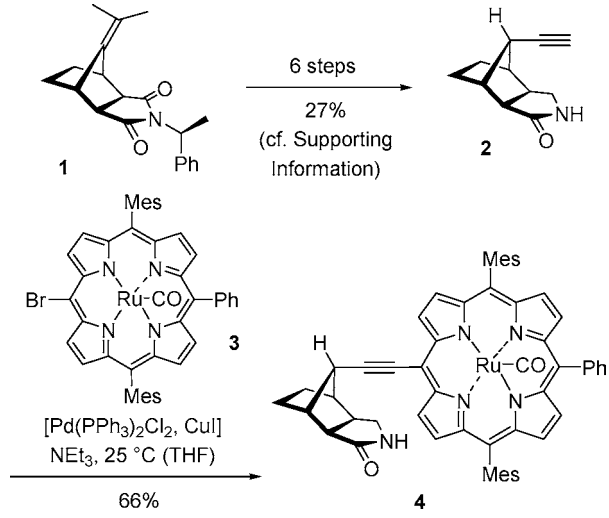


Figure 1. Hydrogen bonds as directing devices in transition-metal-catalyzed reactions (M = metal center; gray shaded region = ligand).

The ability of hydrogen bonds to display the enantiotopic face of a substrate to a transition-metal catalyst was probed in the present study by combining a hydrogen-bonding motif with a catalytically active metal center. In such a catalyst, the hydrogen bonds provide the orientation of a given substrate with respect to a ligand-bound metal center, as schematically depicted by **I** in Figure 1. The known 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-one scaffold[8] (**II** in Figure 1) was considered to be less suited for the desired approach because the spatial proximity of the ligand-bound metal appeared to prevent the substrate from binding to the δ-lactam in motif **II**. The two entities are oriented almost parallel at a relatively short distance (ca. 400 pm). Inspired by the pioneering work of Deslongchamps and co-workers,[9] we investigated hydrogen-bonding scaffold **III**, which can be connected to a transition metal via an appropriate ligand and provides a reasonable open space for a substrate in the presence of a ligand-bound metal because of its V-shaped structure. In addition, it offers the significant advantage of easy synthetic accessibility (Scheme 1).

Scheme 1. Preparation of Chiral Ruthenium Porphyrin Complex **4** from Substrate **1**



For the synthesis of alkyne **2** (Scheme 1), the Diels−Alder product of 6,6-dimethylfulvene and maleic anhydride[10] was converted into imide **1**. Straightforward separation and functional-group operations delivered alkyne **2** and its enantiomer *ent*-**2** (not depicted in Scheme 1) in an overall yield of 27%. The absolute configuration of compound **2** was established by a reported procedure.[11] Alkyne **2** can be coupled to a variety of potential ligands by Sonogashira cross-coupling reactions.[12] On the basis of the well-documented oxidation properties of metalloporphyrins,[13,14] the porphyrin-based transition-metal complex **3** (Mes = 2,4,6-trimethylphenyl),[15,16] which does not carry an element of chirality for itself, was chosen for the coupling. Chiral ruthenium porphyrin complexes have previously been employed in enantioselective epoxidations of alkenes.[17] In the present case, however, the element of chirality in catalyst **4** is spatially remote from the ruthenium center and acts exclusively by hydrogen bonding.

The epoxidation of 3-vinylquinolone (**5a**) was established as a test reaction and conducted in the presence of ruthenium catalyst **4** (Scheme 2, Table 1). 2,6-Dichloropyridine-*N*-oxide was employed as the stoichiometric oxidant.[18] With as little as 1 mol % catalyst

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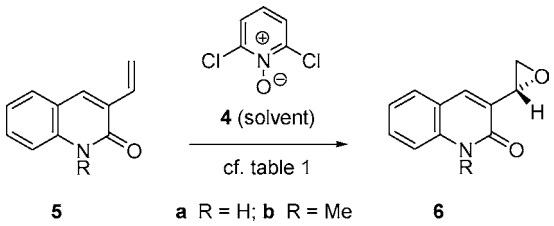
Scheme 2. Enantioselective Oxidation of Olefin **5a** to Epoxide **6a** by Chiral Catalyst **4** and Unselective Oxidation of Olefin **5b** (cf. Table 1 and the Text)



5 **a** R = H; **b** R = Me **6**

Table 1. Enantioselective Epoxidation Reactions Catalyzed by Complex **4** (cf. Schemes 1 and 2)

entry[a]	substrate	*c* (mM)	solvent	Θ (°C)	product	yield (%)[b]	ee (%)[c]
1	**5a**	20	CH_2Cl_2	25	**6a**	54	85
2	**5a**	20	toluene	25	**6a**	60	91
3	**5a**	20	$PhCF_3$	25	**6a**	53	94
4	**5a**	20	benzene	25	**6a**	71	95
5	**5b**	20	benzene	25	**6b**	55	≤5
6[d]	**5a**	20	benzene	25	**6a**	68	14
7[e]	**5a**	20	benzene	25	*ent*-**6a**	71	95
8	**5a**	100	benzene	25	**6a**	78	92
9	**5a**	20	benzene	50	**6a**	86	89

[a] The reactions were carried out on a 29 μmol scale in the given solvent at the given temperature Θ and substrate concentration *c* using 2,6-dichloropyridine-*N*-oxide (32 μmol) as a stoichiometric oxidant and 1 mol % catalyst **4** (see the Supporting Information). [b] Yield of isolated product. [c] The enantiomeric excess (ee) was determined by chiral HPLC (Chiralpak AS-H). [d] The N-methylated derivative of catalyst **4** was used in this experiment. [e] The enantiomer *ent*-**4** of catalyst **4** was used in this experiment.

4, a sufficiently fast epoxidation reaction could be initiated at ambient temperature (25 °C) in a variety of solvents (entries 1−4).

Even in the relatively polar solvent CH_2Cl_2, a high enantiomeric excess (ee) of 85% was recorded (entry 1), and the ee was further improved in nonpolar solvents in the order toluene < trifluorotoluene < benzene (entries 2−4). While conversion was complete in all cases and no side products were detected in the crude reaction mixture, facile epoxide ring opening/rearrangement may lead to a loss of material upon purification by column chromatography. Yields varied between 53 and 71% (entries 1−4) The absolute configuration of product **6a** was determined by the Mosher method[19] upon reductive ring opening to a secondary alcohol (see the Supporting Information).

Experiment to prove the directing ability of the remote hydrogen bonds were performed with *N*-methylquinolone (**5b**) (entry 5) and the N-methylated analogue of catalyst **4** (entry 6). In both cases, the substrate−catalyst interaction was restricted to a single hydrogen bond, and the reactions were expected to be significantly less enantioselective than entry 4. Indeed, product **6b** (entry 5) was obtained with ≤5% ee and product **6a** (entry 6) with 14% ee. Moreover, the reaction of substrate **5b** (entry 5) was slower than the reaction of substrate **5a**. The olefin was still present in detectable amounts after a reaction time of 40 h, at which point the transformation **5a** → **6a** had in all instances reached completion (entries 1−4). This observation suggests that hydrogen bonding exerts not only a stereodirecting effect but also an activating effect. As expected, the enantiomer of catalyst **4**, catalyst *ent*-**4**, delivered the same enantioselectivity as catalyst **4** under identical conditions (entries 4 and 7) but with opposite face selection. An increase in the substrate concentration[20] led to an increase in yield, but the enantioselectivity dropped slightly (entry 8). The reaction rate increased when the oxidation was conducted at elevated temperature. At 50 °C, the reaction went to completion within 4 h (entry 9). Again, however, the lower enantioselectivity in comparison with entry 4 was undesirable.

In order to visualize the outcome of the reaction, we conducted a semiempirical calculation of the presumed intermediate ruthenium complex[21] generated from precursor **4** by decarbonylation and oxidation (see the Supporting Information). Complexation of substrate **5a** in silico delivered a model for the oxygen transfer in which the internal carbon atom of the double bond is perfectly positioned to receive the oxygen atom (Figure 2). On the basis of the outcome of the configuration determination (see above), the double bond of substrate **5a** must be s-cis oriented, as shown.

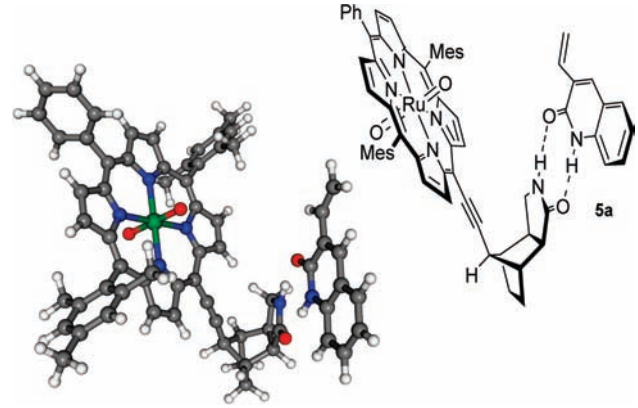
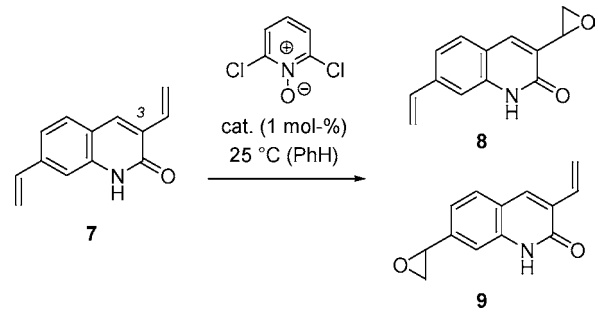


Figure 2. Coordination of substrate **5a** to the dioxoruthenium complex derived from catalyst **4**, visualized by a semiempirical calculation and a chemical structure.

The validity of the proposed model for hydrogen-bond-directed epoxidation was further investigated by studying the regioselectivity of the process. According to Figure 2, coordination by the hydrogen-bonding site should locate only the vinylic double bond at C3 of a quinolone in an ideal position for enantioselective epoxidation but not other double bonds at the heterocyclic scaffold. Reactions at other possible oxidation sites should consequently be disfavored and occur less quickly. Diolefin **7** was prepared in order to verify this hypothesis in an intramolecular competition experiment (Scheme 3). Oxidation of this substrate in benzene in the presence of an achiral Ru complex derived from bromide **3** and *tert*-butylacetylene by Sonogashira cross-coupling (see the Supporting Information) delivered a mixture of the two constitutionally isomeric racemic products **8** and **9** in a 62/38 ratio. The reaction was sluggish, and it was incomplete even after a reaction time of 40 h. In stark contrast to this observation, epoxidation of diolefin **7** with catalyst **4a** or its enantiomer *ent*-**4a** was complete after only 12 h and delivered product **8** as the major isomer (**8**/**9** = 91/9, 71% yield). The enantioselectivity was high (88% ee) for the major product isomer **8**; the minor product **9** was formed in amounts that

Scheme 3. Regio- and Enantioselective Epoxidation of Diolefin **7** to Product **8** (See the Text for Further Explanation)



did not allow for its isolation in pure form or for the determination of its enantiomeric excess.

The last set of experiments demonstrates that the combination of hydrogen bonding and oxidation catalysis enables both a regio- and enantioselective approach to chiral epoxides. As in biological systems, the substrate is presented to the metal in the catalytically active site by hydrogen bonds. This principle should be applicable to other enantioselective reactions and may be further exploited in organic synthesis.

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Supporting Information Available: Synthetic procedures for the preparation of all new compounds; analytical data, including HPLC traces, proving the ee of **6a** and **8**; NMR spectra for new compounds, including **1**, **2**, **6a**, **7**, and **8**; and further information on the computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

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