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Biomimetic and organocatalytic approaches to oxidation catalysis*

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Abstract: The lecture summarized our recent work in the fields of (i) catalytic asymmetric epoxidation and cyclopropanation, (ii) C–C coupling reactions, and (iii) dynamic kinetic resolution (DKR). The first section describes the use of chiral Ru-porphyrins as catalysts for the asymmetric epoxidation and cyclopropanation of nonfunctionalized olefins, and of peptides and alkaloid-based phase-transfer catalysts for the asymmetric epoxidation of enones. The second section highlights the application of the DIANANE-salen ligands (DIANANE: *endo,endo*-2,5-diamino-norbornane) to the asymmetric Nozaki–Hiyama–Kishi coupling of aldehydes with allylic and vinylic electrophiles, and of *N*-tosyl proline amides for asymmetric aldol additions. In the final section, bifunctional urea-based organocatalysts for the DKR of azlactones to provide enantiomerically enriched amino acid esters are presented.

Keywords: Biomimetic oxidation catalysis; organocatalysis; amino acids; asymmetric epoxidation; cyclopropanation; C–C coupling; dynamic kinetic resolution; Ru-porphyrins; DIANANE; Nozaki–Hiyama–Kishi coupling.

CATALYTIC ASYMMETRIC EPOXIDATION AND CYCLOPROPANATION

Biomimetic oxidation catalysis aims at achieving the efficiencies and selectivities of enzymes such as monooxygenases or peroxidases with low-molecular-weight compounds. The design of biomimetic oxidation catalysts is based on the active-site structure and function of oxidative enzymes. In 1997, we reported the use of the chiral Ru-porphyrin **1a** for the asymmetric epoxidation [1] and cyclopropanation [2] of olefins (Scheme 1). For the electronic fine-tuning of the porphyrin ligand [3], electron-donating and -withdrawing substituents were attached to the dimethanoctahydroanthracene substituents present at the four *meso*-positions of the porphyrin ligand. We found that the introduction of the CF_3 substituent led to a particularly improved performance of the Ru-porphyrin catalyst **1b**. As shown in Scheme 1, high enantioselectivity was achieved in both epoxidation and cyclopropanation. At the same time, remarkable catalyst stabilities resulted (>14.000 total turnovers in the asymmetric epoxidation of olefins under *Hirobe* conditions [4], and >7.500 total turnovers in the asymmetric cyclopropanation of olefins with diazo compounds).

The epoxidation of olefins such as styrene (Scheme 1) requires electrophilic oxidants. On the other hand, the asymmetric epoxidation of, for example, enones calls for nucleophilic oxygen donors. The well-known Juliá–Colonna epoxidation of enones makes use of poly-amino acids as catalysts and of hydrogen peroxide as oxidant, and is a method of high practical utility [5]. Unfortunately, the sub-

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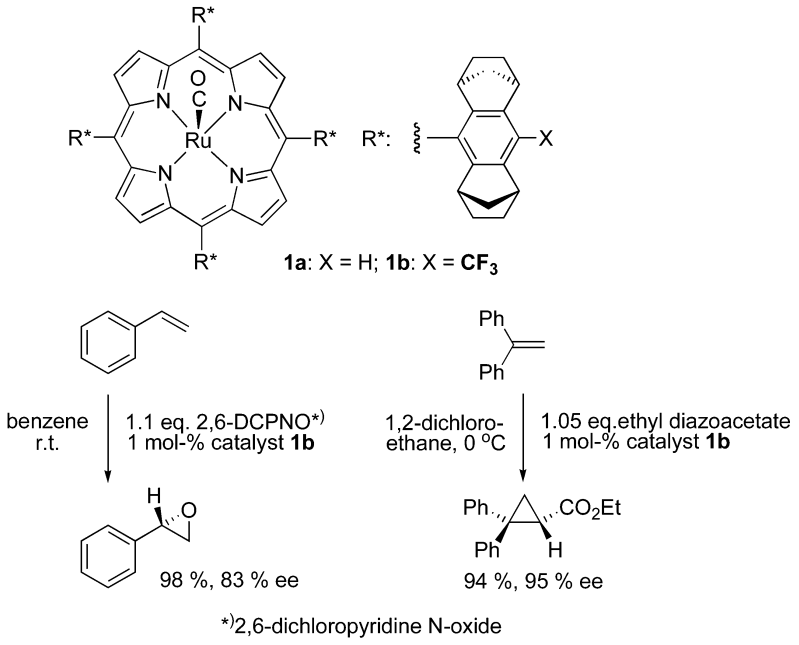
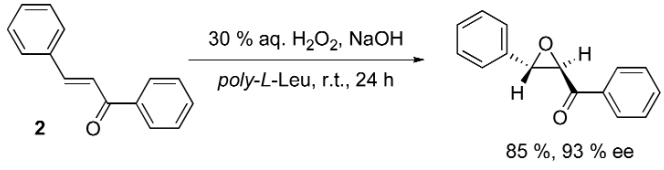
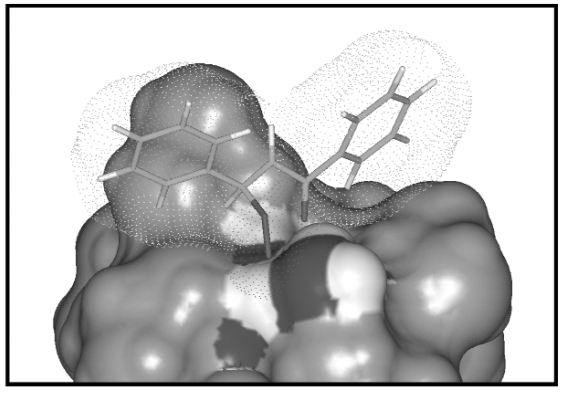


Scheme 1

strate spectrum is fairly narrow, with chalcone (**2**) and derivatives affording the best yields and enantiomeric excesses (Scheme 2, top) [6]. On the other hand, cyclic enones and quinones are much less suitable substrates. Our recent studies on the mechanism of the Juliá–Colonna epoxidation revealed that this epoxidation is catalyzed by the *N*-terminus of the amino acid α-helix [7]. The most important feature in this respect is the presence of three amide NH groups that are not involved in intra-helix hydrogen bonding, but protrude into the solution [7,8]. Two of these NH moieties form hydrogen bonds to the oxygen atom of the enone carbonyl group, whereas the third one binds the hydroperoxide anion in

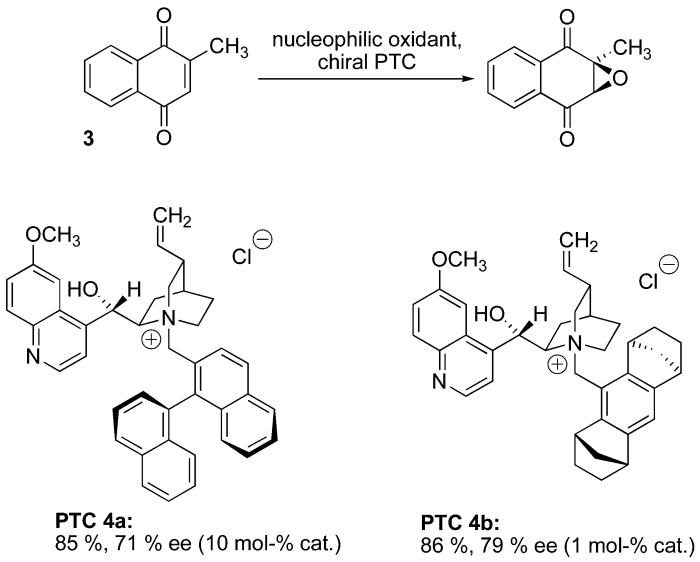




Scheme 2

the intermediate peroxyenolate (Scheme 2, bottom). The induction of asymmetry thus rests on the helical chirality of the peptide backbone.

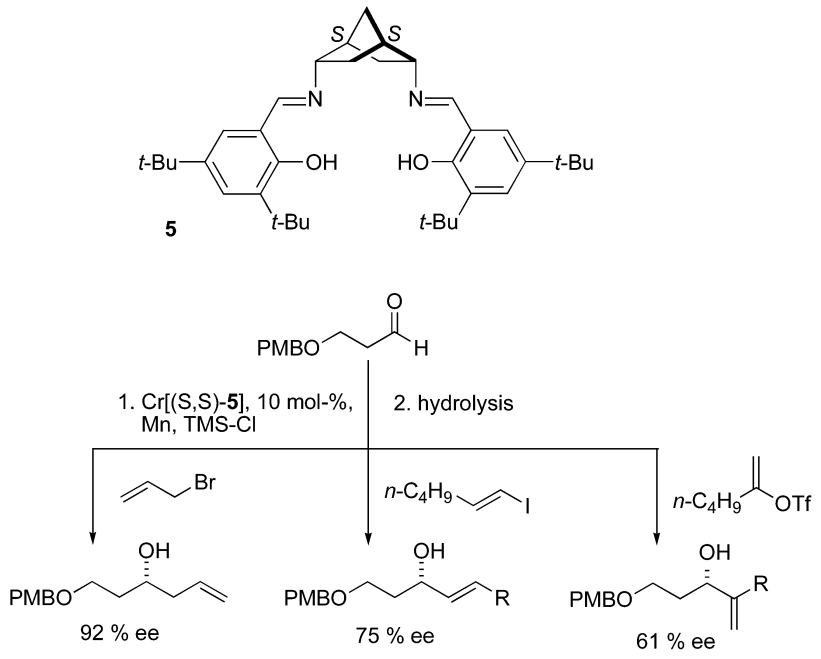
Our mechanistic model explains why poly-amino acids do not efficiently catalyze the asymmetric epoxidation of cyclic *Z*-enones: Apparently, the binding site for the hydroperoxide anion is well positioned for *E*-enones, but not for *Z*-enones. One solution to the problem may be seen in the development of nonpeptidic cationic phase-transfer catalysts (PTCs) that deliver the nucleophilic oxidant in an enantioface-selective manner. Quaternary ammonium ions derived from *cinchona*-alkaloids have proven their potential in this respect, but enantiomeric excesses, for example, in the epoxidation of vitamin K_3 (**3**, Scheme 3), still need improvement [9]. We found that introducing an additional element of chirality into *cinchona*-based PTCs significantly enhances their performance in the asymmetric epoxidation of, for example, vitamin K_3 (**3**, Scheme 3). The novel (+)-quinidine-based PTCs **4a** and **4b** shown in Scheme 3 represent the "matched pairs" and afford the best enantioselectivities reported to date for the catalytic asymmetric epoxidation of vitamin K_3 (**3**) [10]. The corresponding "mismatched" diastereomers effect significantly lower enantioselection.



Scheme 3

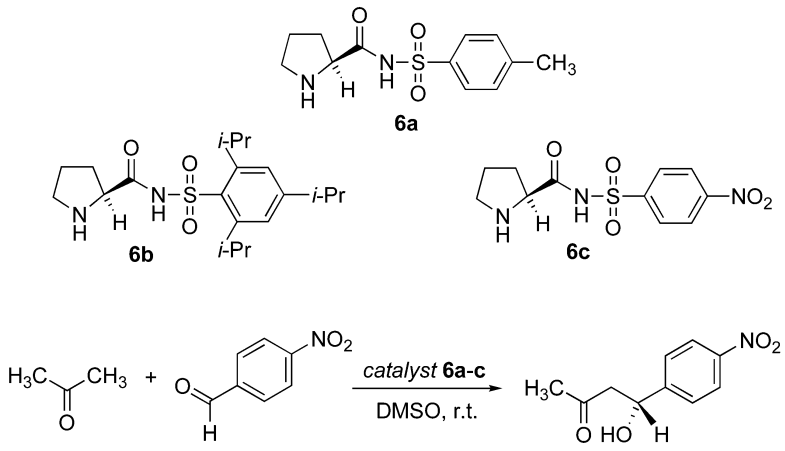
ASYMMETRIC C–C COUPLING

In 2003, we published the synthesis of the DIANANE-salen ligand **5** (DIANANE: *endo,endo*-2,5-diamino-norbornane) and its application in the catalytic asymmetric Nozaki–Hiyama–Kishi coupling (Scheme 4) [11]. As summarized in Scheme 4, the ligand **5** affords up to 92 % ee in the addition of allylic electrophiles to aldehydes. Furthermore, we could show that vinylic iodides and triflates can be employed as well: In the addition to the PMB-protected 3-hydroxypropionic aldehyde, the resulting allylic alcohols were obtained with up to 75 % ee. Our improved synthesis furnishes the DIANANE ligand **5** in large quantities [12]. See ref. [13] for a recent application of the ligand **5** by Paterson et al. in the enantioselective total synthesis of the 11-desmethyl analog of the marine natural product (+)-laulimalide.



Scheme 4

Aldol additions undoubtedly belong to the most important C–C coupling reactions in organic synthesis. The recent years have seen the development of a number of proline-catalyzed asymmetric intermolecular aldol reactions [14]. Proline is readily available at low cost and is thus an attractive and economic organocatalyst. However, one of its disadvantages is its poor solubility in organic solvents of low polarity. To overcome this hurdle, we synthesized the *N*-sulfonyl proline amides **6a–c** (Scheme 5) [15]. These amino acid derivatives are of similar acidity as the amino acids themselves. In fact, the sulfonyl proline amides **6a–c** turned out to be quite enantioselective catalysts: As shown in Scheme 5, enantiomeric excesses >95 % ee were achieved for all three catalysts, with the nitro-compound **6c** giving an optimum ee of 98 %. Proline gave a maximum ee of 80 % under the reaction conditions. Besides better enantioselectivity, catalyst loadings could be reduced from 30 mol % (typical for proline) to 5 mol % without significant loss in yield or enantioselectivity, in particular in the case of the tris-*iso*-propyl catalyst **6b** (Scheme 5).

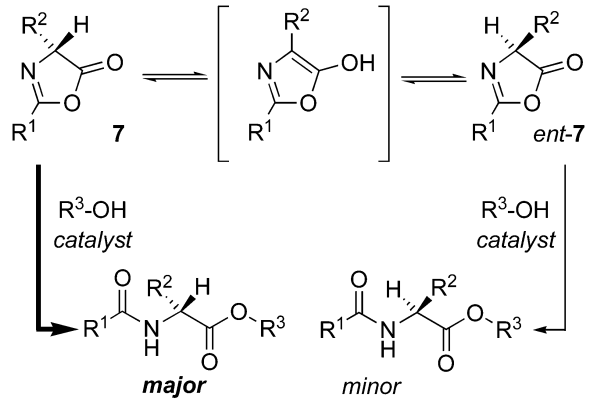


catalyst loading [mol-%]	reaction time [h]	ee (yield) [%] of the aldol product, catalyst:			
		6a	**6b**	**6c**	*L*-proline
30	24	93 (98)	92 (98)	92 (73)	72 (98)
10	24	95 (29)	95 (70)	□97 (8)	75 (41)
10	48	96 (69)	**97 (96)**	98 (15)	73 (42)
10	72	94 (96)	95 (99)	**98 (25)**	76 (43)
5	24	94 (15)	95 (39)	□97 (3)	80 (14)
5	48	94 (30)	94 (72)	□97 (5)	77 (17)
5	72	95 (45)	**95 (91)**	**98 (10)**	76 (17)

Scheme 5

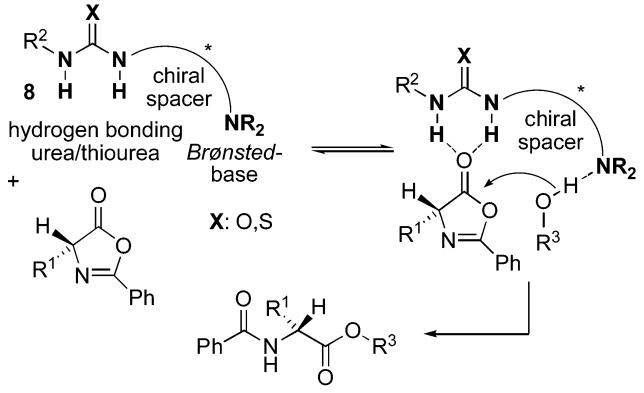
DYNAMIC KINETIC RESOLUTION

The kinetic resolution of racemic mixtures is an alternative for the production of enantiomerically pure substances. Dynamic kinetic resolution (DKR) is a particularly attractive method because it allows the conversion of a racemic mixture to (theoretically) 100 % of the desired enantiomer. The azlactones **7** can be ring-opened with, for example, alcohol nucleophiles, and they readily racemize via enol formation (Scheme 6). Consequently, they are ideal substrates for the production of enantiomerically pure α-amino acids by DKR.



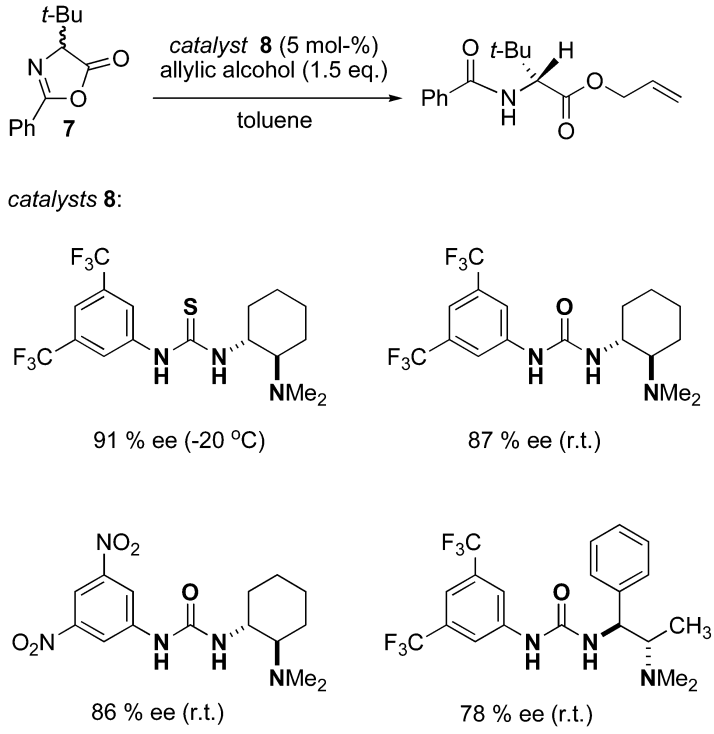
Scheme 6

As catalysts for this type of transformation, we envisaged the bifunctional urea/thiourea–*tert*-amine conjugates **8** (Scheme 7). The latter were used before by Takemoto et al. as catalysts for asymmetric Michael additions to nitro-olefins and for the aza-Henry reaction [17].



Scheme 7

In our hands, the organocatalytsts shown in Scheme 8 provided up to 91 % ee in the alcoholytic DKR of azlactones [18]. Preliminary spectroscopic studies indicate that the catalysts **8** indeed act by hydrogen bonding (of the urea/thioures) to the azlactone and by activating and steering the alcohol nucleophile (by the *tert*-amine group, Scheme 7).



Scheme 8

ACKNOWLEDGMENTS

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