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Asymmetric Catalysis by a Chiral Ruthenium Porphyrin: Epoxidation, Hydroxylation, and Partial Kinetic Resolution of Hydrocarbons

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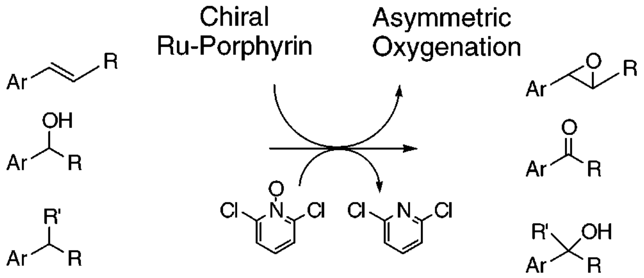
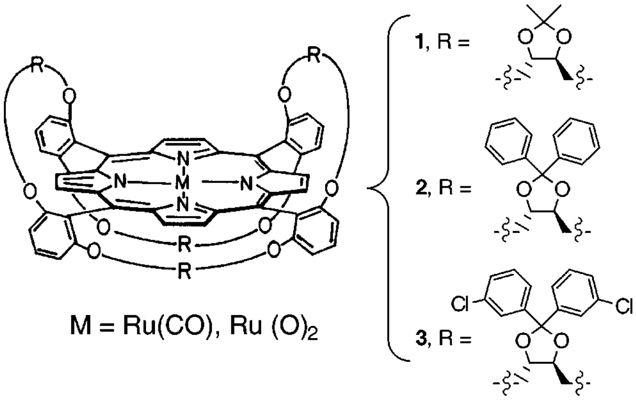
ABSTRACT



A new member of our D_2 symmetry ruthenium porphyrins is shown to be a most selective catalyst for asymmetric epoxidation of terminal and *trans*-disubstituted olefins. The same catalyst displays some selectivity in kinetic resolution of secondary alcohols and in what appears to be the first example of catalytic enantioselective hydroxylation of tertiary alkanes.

The first utilization of a chiral iron porphyrin as catalyst for catalytic asymmetric epoxidation of nonactivated olefins has initiated the preparation of many chiral porphyrins.[1,2] We have contributed to this field by reporting the facile synthesis of double-side protected porphyrins with D_2 symmetry (**1** in Scheme 1).[3] This led to the first utilization of a chiral ruthenium porphyrin (**1**−Ru(O)$_2$, Scheme 1) as oxidation catalyst, which was found to be outstandingly active in the epoxidation of olefins by aromatic *N*-oxides.[4] Subsequently, similar results were obtained with D_4 symmetry ruthenium porphyrin complexes,[5,6] and both types of complexes were also later found to be excellent cyclopropanation catalysts.[7] Most important, in both catalytic processes it was found that for identical chiral porphyrins the ruthenium complexes are

Scheme 1 Structures of the Catalysts



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much better at inducing asymmetry than the more commonly used iron, manganese, or rhodium derivatives.[4,7−9] For example, the **1**−Ru(O)$_2$- and **2**−Ru(O)$_2$-catalyzed epoxidations of olefins proceed with higher enantioselectivities than the same reactions in the presence of the iron and manganese complexes of the same porphyrins.[4,9] The enantiomeric enrichments (ee's) of the epoxides obtained from the reactions of ring-substituted styrenes with *N*-oxides under **2**−Ru(O)$_2$ catalysis are in the range of 74−80% ee, record values at that time.[10]

Another intriguing result with both the iron and the ruthenium complexes of porphyrins **1** and **2** is that the ee's obtained from epoxidation of *cis*-olefins such as *cis*-β-methylstryrene and 1,2-dihydronaphthalene are much lower than those obtained for styrene.[9] This is in sharp contrast to most other chiral metalloporphyrins,[2,11] as well as for chiral manganese salen complexes.[12] Furthermore, Che and coworkers have most recently found a novel *trans*-selectivity for **1**−Ru(O)$_2$.[13] The epoxidation of *trans*- and *cis*-β-methylstryrene displayed a very large difference in enantioselectivity in favor of the *trans*-isomer (stoichiometric, 67% vs 40% ee; catalytic, 50% vs 7% ee), which is in sharp contrast to all other metal complexes.

Since we found that the enantioselectivities obtained with **2**−Ru(O)$_2$ are much larger than with **1**−Ru(O)$_2$, we decided to explore the ruthenium complex of porphyrin **3**. This choice is based on the X-ray crystal structures of **1** and its ruthenium complex[3,4] and on the molecular modeling investigation of **2**. This suggested that *meta*-substitution of the phenyl groups of porphyrin **2** will be beneficial for the selective recognition of the *re* and *si* faces of the alkene substrates (Figure 1).

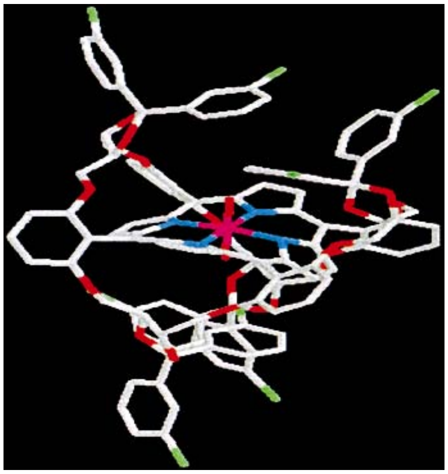
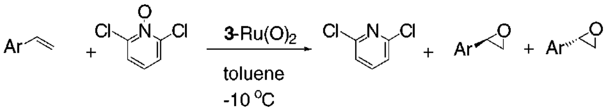
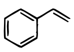
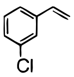
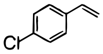
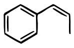
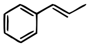
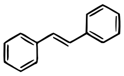


Figure 1. Computer model (MM2) of the new porphyrin.

The new porphyrin and its ruthenium complexes were prepared by analogy to the published procedures for **1** and **2**.[3,4,9,10] The chiral moiety was prepared from tartaric acid and 3,3′-dichlorobenzophenone and connected to 5,10,15,-20-tetrakis(2,6-dihydroxyphenyl)porphyrin via etherfication, to afford **3**−H$_2$.[14] The catalytic reactions were performed with equimolar amounts of olefin and 2,6-dichloropyridine *N*-oxide, with as low as 0.1 mol % of catalyst (note that the standard procedures with metal salen complexes call for 2 mol %, limiting the system to a maximum of 50 catalytic turnovers). The data in Table 1 show that **3**−Ru(O)$_2$ is a very good catalyst indeed. The epoxidation of styrene and its *m*- and *p*-chloro-substituted derivatives proceed with a 79−83% ee, practically identical to the most recently

Table 1. Asymmetric Epoxidation of Olefins[a]



Substrate	%ee	TON
	79[a]	551
	81[a]	226
	83	191
	57	244[b]
	69	487[c]
	38	242[c]

[a] Reactions were performed at −10 °C with 0.165 μmol of catalyst, 165 μmol of oxidant, and 165 μmol of olefin in 1 mL of toluene under Ar for 48 h. Yields were determined by GC analysis relative to an internal standard, and the enantiomeric excesses were determined by capillary GC, using a Cyclodex-B column for the ring-substituted styrenes and Chiraldex A-TA for *trans*-β-methylstyrene, and by HPLC, using (s,s)-whelk-01 (5 μm), for *trans*-stilbene oxide. [a]The absolute configuration of the enantiomer in excess is (*R*)-(+). [b]The *cis*:*trans* ratio is 15:1, and the TON and ee are for the *cis*-olefin. [c]Only the *trans*-olefin is obtained.

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(14) The full synthetic procedures are provided as Supporting Information.

reported best-ever values.[15] In addition, much to our (pleasant) surprise, despite the increased steric crowding, **3**−Ru(O)$_2$ is more reactive than **2**−Ru(O)$_2$. This is reflected in the high turnover numbers (TON) with **3**−Ru(O)$_2$, 190−550 mol of products/mol of catalyst, as compared to TON = 11, 135, and 150 for the first three alkenes of Table 1 with **2**−Ru(O)$_2$ as catalyst.[10]

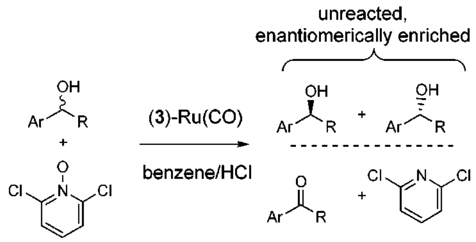
The results for epoxidation of the β-substituted styrenes are also quite intriguing. Similar to the observations of Che et al. with **1**−Ru(O)$_2$,[13] the **3**−Ru(O)$_2$-catalyzed reaction of *trans*-β-methylstyrene was faster, more efficient, and more enantioselective than that of the *cis*-isomer. Actually, the 69% ee of the produced *trans*-epoxide is much higher than that obtained by any other chiral metalloporphyrin catalysis (50% ee with **1**−Ru(O)$_2$ and 25% ee with Collman's catalyst).[13,16] To take the system to its extreme, we have also investigated the epoxidation of *trans*-stilbene. This olefin is known to be a very poor substrate for metalloporphyrin catalysis (0% ee with the D_4 symmetry ruthenium porphyrin),[5] and its enantioselective activation is a remarkable challenge for any system.[17] Still, a 38% ee is obtained, together with 242 catalytic turnovers. Taken together, the chiral induction by **3**−Ru(O)$_2$ is high for terminal and *trans*-olefins but significantly poorer for *cis*-olefins.

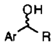
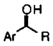
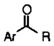
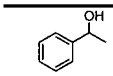
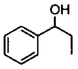
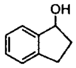
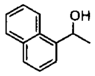
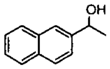
Encouraged by these results, we decided to explore the utilization of our new catalyst in processes that were not previously investigated for chiral metalloporphyrins. Further motivation came from the work of Hirobe and co-workers, who have developed a highly efficient system for hydroxylation of alcohols and alkanes, based on catalytic amounts of (carbonyl)ruthenium porphyrin and HX (X = Cl, Br), with pyridine *N*-oxides as primary oxidants.[18] Accordingly, we investigated the asymmetric version of the Hirobe system with **3**−Ru(CO).

The oxidation of racemic secondary alcohols was allowed to proceed to about 50% conversion, after which the reaction mixture was examined for the amount of kinetic resolution. The results shown in Table 2 show that high conversion is indeed achievable and that the selectivity is quite sensitive to the steric aspects of both the alkyl (entries 1−3) and the aryl groups (entries 4 and 5). The smaller molecules were oxidized with larger selectivity, suggesting that the chiral cavity of the catalyst might be too crowded for large substrates.

Nevertheless, the results obtained were sufficient as a test of a most demanding reaction, the catalytic asymmetric hydroxylation of tertiary alkanes. To our knowledge, there is no system for that transformation, probably because if a free radical intermediate is involved, it is expected to be prone to easy racemization. The examination of racemic 2-phenylbutane and 2-phenylhexane, under a substrate:oxidant:catalyst ratio of 2500:250:1, shows that the reaction is quite efficient (high turnovers) and that the products are formed with significant enantiomeric enrichments (Table 3). The 38% ee in the hydroxylation of 2-phenylbutane is quite remarkable, considering that the chiral discrimination relies

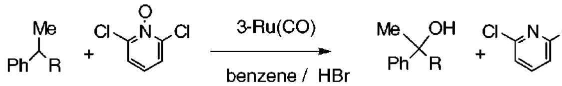
Table 2. Kinetic Resolution of Secondary Alcohols[a]



			
	% unreacted	% ee	%yield
	not determined	24	≈50[a]
	46	10	32
	44	28	34
	50	25	25
	48	2	41

[a] Reactions conditions: 24 h at 20 °C with 0.1 μmol of catalyst, 25 μmol of oxidant, 50 μmol of alcohol, and 5 μL of a HCl-saturated benzene solution in 0.5 mL of benzene under Ar. Chemical yields were determined by GC analysis relative to an internal standard, and the enantiomeric excesses were determined by using a Cyclodex-B chiral capillary column. [a]The GC separation between the alcohol and the ketone was not perfect in this case.

Table 3. Catalytic Asymmetric Hydroxylation of Tertiary Alkanes[a]



R	Temp (°C)	%ee	%yield	TON
Bu	25	16	41	103
Et	25	27	54	135
Et	10	38	23	58

[a] Reactions conditions: 0.4 μmol of catalyst were added to a mixture of 100 μmol of oxidant, 1 mmol of alkane, 15 μL of 48% aqueous HBr, and 50 mg of 4A molecular sieves in 1 mL of benzene under Ar. Chemical yields were determined by GC analysis relative to an internal standard. Enantiomeric excesses were determined by GC, using a Cyclodex-B chiral capillary column.

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(17) End, N.; Macko, L.; Zehnder, M.; Pfaltz, A. *Chem. Eur. J.* **1998**, *4*, 818 and references therein.

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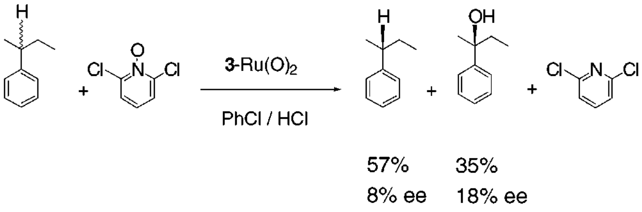
solely on the very small differences between the C–H substituents, methyl vs ethyl.

In principle, as the reaction proceeds, the unreacted substrate also becomes enantiomerically enriched. Obviously, this will only be apparent at high conversions.[19] Accordingly, we tested the hydroxylation of 2-phenylbutane at a substrate:oxidant:catalyst ratio of 500:250:1. Under these conditions, the alcohol was obtained in 35% yield and 18% ee, and the unreacted alkane with 8% ee (Scheme 2).[20]

Scheme 2. Kinetic Resolution of 2-Phenylbutane



In summary, we have introduced an improved version of our D_2 symmetry complexes which is the most selective porphyrin-based catalyst for the asymmetric epoxidation of terminal and *trans*-disubstituted olefins. In the presence of mineral acids, the same catalyst displays moderate selectivity in kinetic resolution of secondary alcohols. In addition, we introduce the first example of catalytic asymmetric hydroxylation of racemic alkanes and their kinetic resolution. We trust that these preliminary results will open the gate for investigations of similar processes with other catalysts. In this respect, we are indeed pleased to note that the previous discoveries from our work[4,9]—the advantages of ruthenium, 2,6-pyridine *N*-oxide, and benzene, in asymmetric epoxidation—have been successfully introduced into catalysis by salen complexes.[21]

Acknowledgment. We thank the S. and N. Grand Research Fund and the Fund for the Promotion of Sponsored Research for financial support and Prof. K. B. Sharpless (Scripps) for a thorough discussion of kinetic resolution processes.

Supporting Information Available: Preparation of the catalysts and their precursors and detailed procedures for the catalytic oxidations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Reactions conditions: 24 h at 0 °C with 0.1 μmol of catalyst, 25 μmol of oxidant, 50 μmol of alkane, and 5 μL of a HCl-saturated benzene solution in 0.5 mL of chlorobenzene under Ar. Chemical yields were determined by GC analysis relative to an internal standard. Enantiomeric excesses were determined by GC, using a Cyclodex-B chiral capillary column for the alcohol and Chiraldex A-TA for the alkane.

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