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Epoxidation

Iron-Catalyzed Asymmetric Epoxidation of Aromatic Alkenes Using Hydrogen Peroxide

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Dedicated to Süd-Chemie on the occasion of its 150th anniversary

Optically active oxiranes are key building blocks for the synthesis of fine chemicals and pharmaceuticals.[1] They are available from resolution processes[2] and more interestingly from catalytic asymmetric epoxidations. State-of-the-art protocols are the Sharpless epoxidation of allylic alcohols,[3] the Katsuki–Jacobsen epoxidation of unfunctionalized alkenes using chiral Mn(salen) catalysts (salen = *N*,*N*′-bis(salicylidene)ethylenediamine),[4] and organocatalytic methods using chiral ketones and oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$).[5] Despite the usefulness of the known procedures, the development of less expensive and environmentally more benign catalysts and oxidant systems is a major goal for organic synthesis.

Among the various oxidants, hydrogen peroxide is one of the most practical reagents (second only to air) in terms of cost and atom efficiency. In recent years hydrogen peroxide has become increasingly important not only for bulk epoxidations but also for asymmetric catalyis.[6] In this respect the work of Katsuki and co-workers, who developed convenient Ti catalysts for asymmetric alkene epoxidation with hydrogen peroxide, is most notable.[7] In addition, also Pt[8] and Ru catalysts[9] have been reported for asymmetric epoxidations of olefins. While these systems give high enantioselectivity, the catalysts involved are relatively expensive.

Nature relies on various iron-containing enzymes for the oxidative degradation of a number of xenobiotics often with exceptional selectivities. Iron is not only ubiquitous but also one of the most versatile transition metals.[10] Hence, it is surprising that research on epoxidations using iron-based catalysts has largely been neglected. Only recently, a successful biomimetic approach was reported with iron porphyrin complexes for the epoxidation of styrene derivatives applying iodosobenzene as oxidant.[11] Unfortunately, the synthesis of the required chiral porphyrin ligands is notoriously difficult,[12] and the oxidant is not environmentally friendly. Moreover, Cheng et al. reported recently the aerobic epoxidation of styrene derivatives catalyzed by tris(*d*,*d*-dicamphorylmethanato) iron(III) complex, $[Fe(dcm)_3]$.[13] Although encouraging results were achieved, a drawback of this method is the need to employ an excess of aldehyde as sacrificial reductant and dichloroethane as the solvent.

To the best of our knowledge there is no Fe-based asymmetric epoxidation catalyst known that gives more than 20% enantiomeric excess when hydrogen peroxide is used as the oxidant. This currently highest *ee* value was reported by Francis and Jacobsen, who used an elaborate combinatorial screening of 5760 metal–ligand combinations to identify three Fe complexes with peptide-like ligands suitable for asymmetric epoxidation of *trans*-β-methylstyrene.[14] Using biomimetic non-porphyrin Fe catalysts, Costas et al. reported the $[Fe(bpmcn)(CF_3SO_3)_2]$-catalyzed dihydroxylation of of *trans*-2-heptene with hydrogen peroxide which gave the epoxide as a by-product with 12% *ee* (bpmcn = *N*,*N*′-bis(2-pyridylmethyl)-*N*,*N*′-dimethyl-1,2-cyclohexanediamine).[15] Clearly, it has not yet been possible to replace the established epoxidation catalysts with iron complexes.

For some time we have been interested in Ru-catalyzed epoxidations with hydrogen peroxide in the presence of nitrogen ligands such as 2,6-di(4,5-dihydro-1,3-oxazol-2-yl)pyridine (pybox),[16a] 2,2′-(pyridine-2,6-diyl)bis(5,6-dihydro-4*H*-1,3-oxazine) (pyboxazine),[16b] terpyridines,[16c] and pyridinebisimidazolines (pybims)[16d] together with the coligand pyridine-2,6-dicarboxylic acid (H_2pydic). Our initial approach to extend these Ru systems to Fe failed in terms of the stereoselectivity of the epoxidation. Nevertheless, a general racemic epoxidation of aromatic alkenes with hydrogen peroxide is possible with a convenient in situ catalyst consisting of ferric chloride hexahydrate ($FeCl_3 \cdot 6H_2O$), H_2pydic, and organic bases such as pyrrolidine.[17] Herein, we report the first genuinely promising iron-catalyzed asymmetric epoxidation of aromatic alkenes without porphyrin ligands and using hydrogen peroxide. This method not only gives good to excellent yields of isolated epoxides but also *ee* values up to 97%.

For our investigations we chose *trans*-stilbene (**1a**) as the model substrate because of its nonvolatility and the stability of the product epoxide for reliable determination of conversion, yield, and selectivity by gas chromatography. In testing a large number of commercially available optically pure amines we often obtained high conversions and excellent chemoselectivities. However, we could not obtain the corresponding epoxide **2a** with enantioselectivities anywhere close to 10% *ee*. Among the ligands that gave small but reproducible enantioselectivities, we identified 2,2-diphenylprolinol (**3d**). A closer look at the effect of different chiral pyrrolidine derivatives **3** revealed a relationship between the type and

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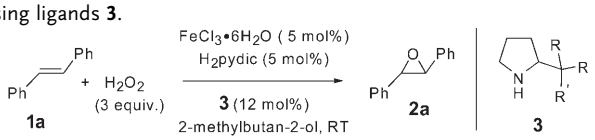
size of substituents adjacent to the chiral center and the *ee* values (Table 1). While prolinol (**3a**) gave the racemic product (Table 1, entry 1), the diphenyl-substituted **3d** led

Table 1: Iron-catalyzed asymmetric epoxidation of *trans*-stilbene (**1a**) using ligands **3**.



Entry	Ligand, abs. config.	R	R′	*t* [h]	Conv.[a] [%]	Yield[a] [%]	*ee*(**2a**) [%],[b] abs. config.[c]
1	**3a**, (*S*)	H	OH	1	95	73	0
2	**3b**, (*S*)	H	NH_2	36	60	58	1, (−)-(2*S*,3*S*)
3	**3c**, (*S*)	Ph	H	60	61	45	0
4	**3d**, (*S*)	Ph	OH	36	78	53	10, (+)-(2*R*,3*R*)
5	**3e**, (*R*)	Ph	F	1	100	90	16, (−)-(2*S*,3*S*)
6[d]	**3e**, (*R*)	Ph	F	14	100	98	17, (−)-(2*S*,3*S*)
7	**3f**, (*S*)	F	F	1	100	93	2, (+)-(2*R*,3*R*)

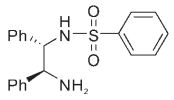
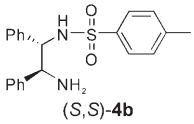
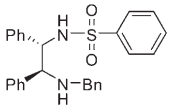
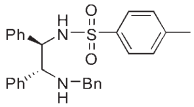
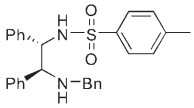
[a] Determined by gas chromatography using dodecane as the internal standard. [b] Determined by HPLC on a chiral column. [c] Determined by comparing the sign of the optical rotation of the major enantiomer on a chiral detector coupled to a chiral HPLC, with known data.[19] [d] Reaction at 0 °C.

to 10% *ee* (Table 1, entry 4). Interestingly, maintaining the phenyl substituents and replacing the hydroxy group by fluoride led to a much more active catalyst (complete substrate conversion in less than 1 h at room temperature) and increased the *ee* value to 17% (Table 1, entries 5 and 6). This suggested the importance of H-bonding in addition to steric factors in the enantioselectivity-determining step. Although, H-bonding has also been implicated in asymmetric oxidations catalyzed by **3e** using oxone,[18] under our reaction conditions no epoxide is formed when the ligand is used without Fe.

Next, we extended our search to chiral amine ligands with a neighboring group capable of intramolecular H-bonding such as carbonyl and sulfonyl groups. The required ligands are easily accessible by monoamidation or -sulfonylation of optically pure C_2-symmetrical 1,2-diamines such as (−)-(*S*,*S*)-1,2-diphenylethylenediamine and N-alkylation of the resulting products where necessary. In Table 2 the influence of ligands **4a**,**b** and **5a**,**b** on the enantioselectivity of the model reaction is summarized.

To our delight, application of this basic concept led to the identification of the commercially available ligand **4b**, which gave *trans*-stilbene oxide (−)-(2*S*,3*S*)-**2a** in 28% *ee* under the standard reaction conditions (Table 2, entry 2). Interestingly this starkly contrasts with the nearly racemic product obtained when the unsubstituted (−)-(*S*,*S*)-1,2-diphenylethylenediamine is used as the ligand. Among the modified ligands **5** the N-benzyl-substituted derivative (*S*,*S*)-**5b** led to the most significant increase in *ee* values, giving (+)-(2*R*,3*R*)-**2a** in 42% *ee* (Table 2, entry 5) at room temperature which improved to 47% *ee* when the temperature was lowered to −8 °C (Table 2, entry 6). It is also striking that in the oxidation

Table 2: Iron-catalyzed asymmetric epoxidation of *trans*-stilbene (**1a**) using ligands **4** and **5**.[a]

Entry	Ligand	Conv.[b] [%]	Yield[b] [%]	*ee*(**2a**) [%][c], abs. conf.[d]
1	 (*S*,*S*)-**4a**	100	88	26, (−)-(2*S*,3*S*)
2	 (*S*,*S*)-**4b**	100	86	28, (−)-(2*S*,3*S*)
3	 (*S*,*S*)-**5a**	100	98	36, (+)-(2*R*,3*R*)
4	 (*R*,*R*)-**5b**	100	92	41, (−)-(2*S*,3*S*)
5	 (*S*,*S*)-**5b**	100	87	42, (+)-(2*R*,3*R*)
6[e]	(*S*,*S*)-**5b**	100	97	47, (+)-(2*R*,3*R*)

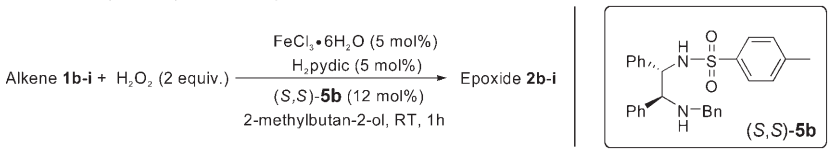
[a] Conditions: 0.5 mmol **1a**, 1 mmol H_2O_2, 5 mol%, $FeCl_3 \cdot 6H_2O$, 5 mol% H_2pydic, 12 mol% **4a**,**b**/**5a**,**b**, 2-methylbutane-2-ol, RT, 1 h. [b] Determined by gas chromatography using dodecane as the internal standard. [c] Determined by HPLC on a chiral column. [d] Determined by comparing the sign of the optical rotation of the major enantiomer on a chiral detector coupled with a chiral HPLC, with known data.[19] [e] Reaction at −8 to −10 °C, 24 h.

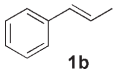
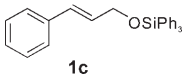
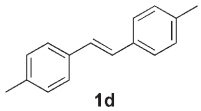
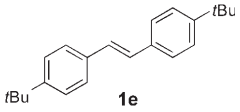
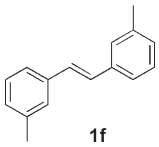
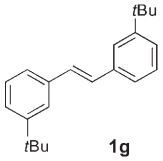
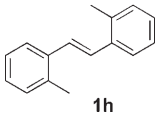
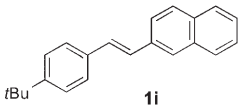
of *trans*-stilbene, use of the mono(arenesulfonyl)-protected ligands **4a**,**b** and the N-benzylated ligands **5a**,**b** resulted in selectivity for enantiomers of **2a** with opposite absolute configurations (Table 2, entries 1 and 3). In general, manipulations of the N-benzyl substituent led to decreased reactivity in the epoxidation reaction and did not improve results.

To explore the scope of the reaction, we epoxidized different aromatic olefins in the presence of **5b**, which was the best ligand in the model reaction in terms of costs, selectivity, and product yields (Table 3). The reaction performed well for β-methylstyrene (**1b**), a cinnamyl alcohol derivative (**1c**), and various *trans*-stilbenes (**1d**–**h**). While **1b** furnished (+)-(2*R*,3*R*)-**2b** with 28% *ee*, substrate **1c** was oxidized to (+)-(2*R*,3*R*)-**2c** with 35% *ee* (Table 3, entries 1 and 2).

In reactions of *trans*-stilbenes **1d**–**h**, the substrates with substituents in the *para* position were more reactive than the analogous *ortho*- or *meta*-substituted compounds, presumably on steric grounds (Table 3, entries 3–7). Best enantioselectivities were obtained with sterically demanding 4,4′-dialkyl-substituted stilbenes. Here, the enantioselectivity increases with steric bulk of the substituents, H < Me < *t*Bu, and reaches a maximum value for **1e**, which gave the corresponding oxirane **2e** in 82% yield and 81% *ee* at room temperature within one hour (Table 3, entry 4). On the other hand, for 3,3′-

Table 3: Fe-catalyzed asymmetric epoxidation of different aromatic alkenes.



Entry	Alkene	Conv.[a] [%]	Yield[b] [%]	*ee*(**2**) [%],[c] abs. config.
1	 **1b**	100[d]	94[d]	28, (+)-(2*R*,3*R*)[e]
2	 **1c**	100	67	35, (+)-(2*R*,3*R*)[f]
3	 **1d**	100	92	64, (+)-(2*R*,3*R*)[g]
4	 **1e**	100	82	81, (+)-(2*R*,3*R*)[g]
5	 **1f**	> 95	88	27, (+)-(2*R*,3*R*)[h]
6	 **1g**	> 95	66	10, (−)-(2*S*,3*S*)[h]
7	 **1h**	60[i]	57[i]	55, (−)-(2*S*,3*S*)[h]
8[j]	 **1i**	100	46	91, (+)-(2*R*,3*R*)[h]
9[j,k]	**1i**	100	40	97, (+)-(2*R*,3*R*)[h]

[a] Estimated by GC-MS and/or TLC which indicated absence of substrate. [b] Yield of isolated pure product. [c] Determined by HPLC on chiral columns. [d] Determined by GC. [e] Assigned by comparing the retention times of the two enantiomers on a chiral HPLC with that of an authentic sample of the *S*,*S* enantiomer; [f] Assigned by desilylation to the corresponding epoxy alcohol by analogy with literature protocol[20] and comparing the sign of optical rotation of the resulting product with that of an authentic sample. [g] Determined by comparing the sign of the optical rotation of the major enantiomer on a chiral detector coupled with a chiral HPLC, with known data; the CD spectra of these products are positive, opposite to those reported for the *S*,*S* enantiomers.[19a] [h] Tentatively assigned by comparing the CD spectrum with those of **2a**,**d**,**e**. [i] Determined after 24 h by ^{1}H NMR spectrum of crude product using an internal standard. [j] 4 equiv H_2O_2, 10 mol% H_2pydic, 10 mol% $FeCl_3{\cdot}6H_2O$, 24 mol% (*S*,*S*)-**5b**. [k] Reaction at 10°C.

dialkyl-substituted stilbenes the *ee* values decrease with increasing size of the substituent. The highest *ee* value was achieved with **1i** as the substrate in the presence of 10 mol% of the iron catalyst (Table 3, entry 8). In this case oxirane **2i** was obtained with 91% *ee* and 46% yield. When the the reaction temperature was lowered slightly to 10°C, the *ee* value increased to 97% with complete substrate conversion within one hour (Table 3, entry 9).

In summary, we have demonstrated for the first time that high enantioselectivity can be achieved in Fe-catalyzed epoxidations with hydrogen peroxide. This long-standing goal in oxidation catalysis was realized by combining $FeCl_3$ with appropriately chosen chiral diamine ligands and pyridine-2,6-dicarboxylic acid. Clearly the catalyst system has to be improved with respect to generality. Further work to extend the substrate scope and towards a mechanistic understanding of this new catalyst are underway.

Experimental Section

General: Alkenes **1a**,**b**,**d**, ligands **3**, **4b**, (*S*,*S*)-(−)-1,2-diphenylethylenediamine, H_2pydic, $FeCl_3{\cdot}6H_2O$, and 2-methylbutan-2-ol are commercially available. Monosufonylated ligand **4a** was prepared by analogy with known protocols.[21] Alkenes **1e**–**h** were synthesized by McMurry[22] coupling of the corresponding alkyl-substituted benzaldehydes in high yields and purities. Analytical data are in accord with literature values. Alkene **1i** was synthesized by the Heck reaction of 4-*tert*-butylbromobenzene with 2-vinylnaphthalene by modification of the method of Chandrasekhar et al.[23] Alkene **1c** was synthesized by silylation of *trans*-cinamyl alcohol with triphenylsilylchloride in the presence of pyridine in 87% yield. All racemic epoxides **2** required as references for chiral HPLC data were synthesized by epoxidation with *meta*-chloroperbenzoic acid (*m*CPBA): Typically 1–2 equivalents of a solution of *m*CPBA were added dropwise to an ice-cooled solution of the alkene in CH_2Cl_2. After stirring overnight at room temperature the solvent was removed and the residue purified by flash chromatography to furnish high yields (80–92%) of the corresponding epoxides.

Synthesis of (*S*,*S*)-**5b**: Amine **4b** (2 g, 5.45 mmol) and freshly distilled benzaldehyde (582 μL, 5.81 mmol) were refluxed in 20 mL anhydrous ethanol for 2 h under Ar. The initially formed precipitate went into solution at 80°C bath temperature. The progress of the reaction was monitored by TLC. After complete consumption of **4b** the reaction vessel was cooled to room temperature. An equal volume of ethanol was added and $NaBH_4$ (186.40 mg, 8.72 mmol) was introduced portionwise. The mixture was stirred at room temperature overnight. After the imine had been consumed completely (TLC), water was added dropwise until no more gas evolved. The gelatinous granules were filtered off and washed with ethanol. The filtrate was dried over $MgSO_4$ and filtered. The solvent

was removed by rotary evaporator and the residue purified by flash chromatography (silicagel 60, *n*-hexane: ethyl acetate 3:1 (v/v), R_f = 0.43) to give **5b** (2.33 g, 93 %). M.p. 139.9 °C; $[\alpha]_D^{25}$ = + 58.0 deg cm^3 g^{-1} dm^{-1} (c = 0.72 g cm^{-3}, CH_2Cl_2); IR (KBr): $\tilde{\nu}$ = 3338, 3305, 3086, 3064, 3028, 2788, 2713, 1599, 1494, 1453, 1348, 1324, 1152; ^{1}H NMR (400.13 MHz, CD_2Cl_2): δ = 1.6 (br s, 1H, N*H*), 2.34 (s, 3H, C*H*$_3$), 3.42 (d, J = 13.16 Hz, 1H, C*H*$_2$), 3.60 (d, J = 13.16 Hz, 1H, C*H*$_2$). 3.74 (d, 7.80 Hz, 1H, C*H*Ph), 4.27 (dd, J = 7.84 Hz, 1H, C*H*Ph), 6.21 (br s, 1H, N*H*), 6.95–7.00 (m, 4H, Ar), 7.05–7.13 (m, 5H, Ar), 7.15–7.19 (m, 5H, Ar), 7.22–7.32 (m, 3H, Ar), 7.37–7.39 ppm (m, 2H, Ar); ^{13}C NMR (75.47 MHz, CD_2Cl_2): δ = 21.56 (*C*H$_3$), 51.16 (*C*H$_2$), 63.45 (*C*HPh), 67.22 (*C*HPh), 127.36, 127.48, 127.69, 127.92, 127.94, 128.04, 128.34, 128.40, 128.76, 128.77, 129.66, 137.21, 139.16, 139.33, 139.90, 143.49 ppm; elemental analysis calcd (%) for $C_{28}H_{28}N_2O_2S$: C 73.65, H 6.18, N 6.14, S 7. 02; found: C 73.60, H 6.44, N 6.01, S 7.24. MS (CI, positive mode, isobutane) *m*/*z*: 457.3 $[M+H]^+$(100), 349(15), 196 (40); HRMS (CI, negative mode, isobutane) *m*/*z*: calcd for $C_{28}H_{27}N_2O_2S$: 455.1788 $[M-H]^+$; found:455.1784.

General protocol for Fe-catalyzed asymmetric epoxidation of alkenes: Pyridine-2,6-dicarboxylic acid (4.24 mg, 0.025 mmol), ferric chloride hexahydrate (6.76 mg, 0.025 mmol), ligand **3**, **4**, or **5** (0.06 mmol), and the corresponding alkene **1** (0.5 mmol) were mixed in 9 mL 2-methylbutane-2-ol and stirred at room temperature for ca. 30 min.[24] The resulting mixture usually assumes pale yellow color. When the yields and conversions were determined by GC, 100 μL dodecane was added as the internal standard. After samples were removed for GC analysis, 1 mmol of aqueous "30 %" hydrogen peroxide[25] dissolved in 1 mL 2-methylbutane-2-ol was added to the reaction mixture over one hour using a syringe pump. In most cases complete conversion was achieved after this time (GC or TLC monitoring). For preparative purposes excess peroxide was destroyed by adding 1 mL of a saturated aqueous solution of sodium sulfite and shaking well. After addition of diethyl ether (10 mL) the organic phase was separated. The aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic phases were dried over anhydrous $MgSO_4$. After filtration and solvent removal by rotary evaporator, the crude product was either directly analyzed by chiral HPLC or purified by silica gel chromatography on a short column (hexane/ethylacetate 20:1, 1 % Et_3N) for full characterization.

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