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Catalytic asymmetric oxidations using molecular oxygen

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Catalytic enantioselective oxygen transfer reactions have been a long-standing goal of synthetic chemistry. The use of molecular oxygen in these oxidations has engaged significant research efforts for decades. The present review considers the state of the art of aerobic asymmetric oxidations mediated by chiral organocatalysts and transition metal catalysts, occurring with formation of new C – O bonds, *i.e.* oxygenations. The milestones and limitations of existing approaches are discussed, with focus on catalyst design and catalytic performance.
The bibliography includes 41 references.

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1. Introduction

Continuously toughening environmental constraints dictate the need in novel, environmentally benign catalytic processes and reagents. Molecular oxygen is an attractive green reagent for oxidation processes: it is nontoxic and does not produce noxious by-products, and is readily available at virtually no cost. The use of molecular oxygen as oxidant in asymmetric transformations has been attracting great attention for decades.[1] In this area, catalyzed asymmetric oxygenations of organic substrates hold a privileged position, such reactions affording plenty of molecules with new C – O asymmetric centre(s) per molecule of a chiral catalyst. The resultant optically active compounds are in demand as pharmaceuticals, agrochemicals, cosmetics, fragrances, *etc*.[2] The search for catalyst systems capable of conducting asymmetric aerobic oxygen transfer reactions under mild conditions with high efficiency and stereoselectivity is a challenging objective.

Generally, the catalysts of aerobic asymmetric oxidations fall into two classes: organocatalysts and transition metal complex catalysts. The scope of the former catalysts is generally limited with C – H hydroxylations of carbonyl compounds,[3] while the latter have broader applicability, namely in asymmetric epoxidations, sulfoxidations and Baeyer – Villiger oxidations. The present review covers the progress of catalysts of both classes, paying particular attention to the catalyst design and catalytic characteristics of the reactions, such as substrate scope, yield, enantioselectivity and efficiency (typically reflected by the catalyst loadings). The oxidation mechanisms, mostly remaining controversial, are given limited consideration.

So far, focus reviews related to this area, have been rather scarce. In 2002, Sigman *et al*. published a brief survey of catalytic enantioselective oxidations using molecular oxygen.[1] Three years later, Iqbal and co-workers contributed a review on transition metal-catalyzed oxidations with molecular oxygen, including several examples of asymmetric oxidation reactions.[4] Ten years ago, Piera and Bäckvall overviewed the catalytic biomimetic oxidations with hydrogen peroxide and molecular oxygen proceeding *via* multistep electron transfer, yet leaving enantioselective reactions beyond the scope.[5] More recently, Laschat and co-workers considered the selective, but not stereoselective, catalytic C – H oxidations with molecular oxygen.[6]

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2. Organocatalyzed oxidations

The first report on the enantioselective α-hydroxylation of carbonyl compounds was contributed by Shiori and co-workers[7] in 1988. The authors studied a series of quaternary ammonium salts derived from cinchona alkaloids (cinchonine and cinchonidine) as well as ephedrine and cyclohexanediamine as chiral phase-transfer catalysts (CPTCs) in the asymmetric hydroxylation of 2-methyltetralone **1a**. Compounds **Ia – d** (Fig. 1) were identified as the best catalysts in this series (36% – 70% *ee*, 48% – 95% yield). Among them, catalyst **Ia** demonstrated the highest results and was used in the oxidation of substituted tetralones **1a – d** and indanone **1e** (Table 1, entries 1, 3, 5, 8, 9). The reaction required 50% aqueous NaOH to deprotonate the substrate and thus initiate molecular oxygen capture, and also triethyl phosphite $(EtO)_3P$ for the reduction of the intermediate hydroperoxide.[7] The products **2a – e** were isolated in high yields (59% – 98%) and moderate to good enantioselectivities (72% – 79% *ee*) using 5 mol.% CPTC loadings. It was proposed that the asymmetric induction originated from ion pairing between the CPTC and the substrate.

Later, Lian *et al.*[10] reported the results of screening of a broadened series of CPTCs in the aerobic C – H hydroxylation of indane-based adamantyl β-keto esters wherein CPTC **Ie** proved to be the most effective catalyst (Table 1, entry 12). Instead of alkali, K_2HPO_4 solution was employed, and the reaction took place under visible light irradiation with 100-W halogen lamp, using tetraphenylporphine (TPP) as a sensitizer. The involvement of singlet oxygen $^1O_2$ in the reaction was assumed. In the subsequent paper,[11] the authors disclosed catalyst **If** (Fig. 1) bearing an aryl substituent at quinoline C(2) atom,[9] demonstrating enhanced asymmetric induction in the same reaction (90% *ee vs* 75% *ee*) and nearly quantitative yield (Table 1, entry 13). The improvements included the use of 3W-LED-yellow light and lower catalyst loadings (2.5 mol.%). Later, Wang *et al.*[12] applied cinchona-derived CPTC **II** containing quinoline N-oxide moiety instead of traditional quinoline substituent (Fig. 1), which was applied in the aerobic asymmetric oxygenation of the same class of substrates.[12] Chiral phase-transfer catalyst **II** showed efficiency comparable to that of CPTC **If** though coming short of enatioselectivity (Table 1, entry 14). Nevertheless, the catalyst **II** performed 20 turnover numbers (TON) (which required 5 mol.% loadings), and the authors claimed that CPTC of this type can be easily separated and reused with only a minor loss of reactivity and enantioselectivity. It should be noted that using CPTC **II** in the asymmetric C – H hydroxylation of β-keto amides demostrated more moderate asymmetric induction (37% – 71% *ee*).[12] Thus, for CPTCs **Ie**,**f**, **II** the reaction scope is limited mostly to indanone-derived β-keto esters.

Itoh and co-workers[13] modified the structure of the parent CPTC **I** not only by introducing the bulky 9-anthracenylmethyl substituent to the quaternized nitrogen atom but also replacing the bromide counter-ion for chloride (Fig. 1, catalyst **III**), which enabled the aerobic asymmetric oxidation of 3-substituted-2-oxindoles **1h**,**i** to the corresponding 3-hydroxy-derivatives **2h**,**i** in high yields and with high enantioselectivity (Table 1, entries 16, 18).[13] The reaction proceeded at −20 °C with 50% KOH_{aq} and $(EtO)_3P$ (4 equiv. *vs* substrate). The major drawback of the catalytic system was the need for high catalyst loadings (20 mol.%).[13]

Later, Tan and co-workers[14] discovered that pentanidium CPTC **IV** (Fig. 1) is no less effective in this reaction in as low as 5 mol.% catalyst loading providing 20 TON (Table 1, entries 17, 19). Moreover, contrary to all previously reported studies, the catalyst system required no co-reductant. It was demonstrated that the catalytic reaction occured in two steps, the initial formation of the optically active hydroperoxide oxindole being followed by its kinetic resolution.

Zhao and co-workers[8] designed a dimeric cinchona-derived chiral phase-transfer catalyst **V** (Fig. 1) for the asymmetric α-hydroxylation of both cyclic and acyclic ketones with molecular oxygen. However, in contrast to cyclic (tetralone and indanone) substrates **1a – c**,**e** (Table 1,

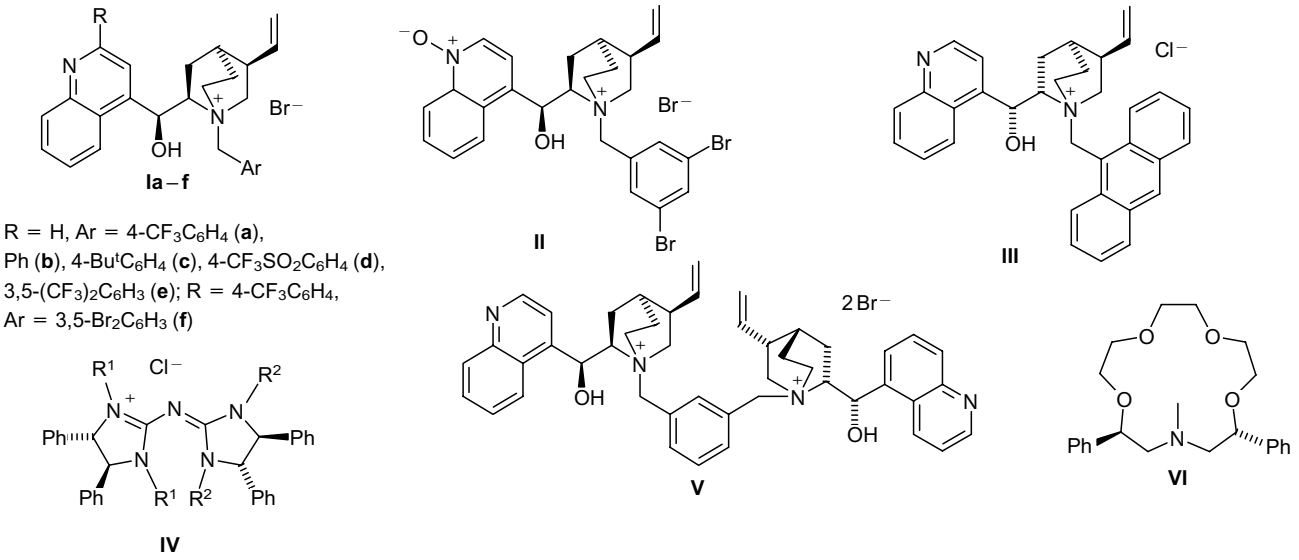
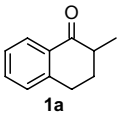
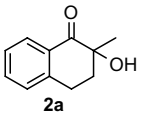
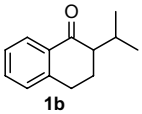
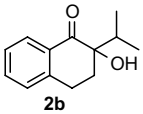
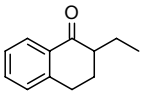
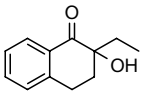
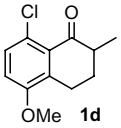
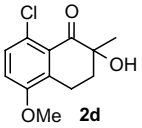
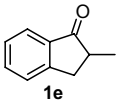
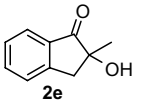
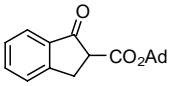
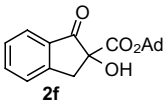
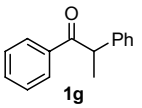
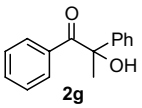
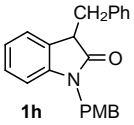
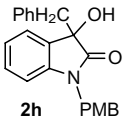
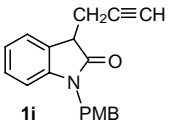
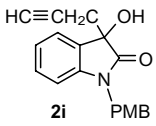
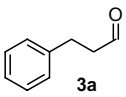
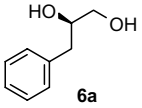
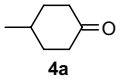
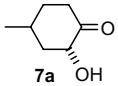


Figure 1. Phase-transfer catalysts employed for the asymmetric α-hydroxylation of carbonyl compounds.

Table 1. Organocatalyzed enantioselective aerobic hydroxylation of α-carbonyl compounds.

Entry	Substrate	Product	Catalyst (mol.%)	Oxidizing agent	Yield (%)	*ee* (%)	Ref.
1	 **1a**	 **2a**	**Ia** (5)	O_2	95	70	7
2			**V** (5)	O_2	98	98	8
3	 **1b**	 **2b**	**Ia** (5)	O_2	59	77	7
4			**V** (5)	O_2	96	92	8
5	 **1c**	 **2c**	**Ia** (10)	O_2	98	72	7
6			**V** (5)	O_2	78	86	8
7			**VI** (5)	Air	95	67	9
8	 **1d**	 **2d**	**Ia** (5)	O_2	95	79	7
9	 **1e**	 **2e**	**Ia** (5)	O_2	94	73	7
10			**V** (5)	O_2	98	94	8
11			**VI** (10)	Air	93	52	9
12	 **1f**	 **2f**	**Ie** (5)	Air	87	75	10
13			**If** (2.5)	Air	99	90	11
14			**II** (5)	Air	99	82	12
15	 **1g**	 **2g**	**V** (5)	O_2	75	88	8
16	 **1h**	 **2h**	**III** (20)	Air	95	86	13
17			**IV** (5)	Air	92	92	14
18	 **1i**	 **2i**	**III** (20)	Air	92	93	13
19			**IV** (5)	Air	83	94	14
20	 **3a**	 **6a**	L-α-Me-Proline (20)	O_2	77	66	15
21			**VIIa** (20)	O_2	70	87	17
22	 **4a**	 **7a**	L-Alanine (20)	O_2	67	72	16
23			L-Valine (20)	O_2	75	69	16

entries 2, 4, 6, 10), acyclic ketones, *e.g.* compound **1g**, proved to be less active in this reaction (Table 1, entry 15). To explain this distinction between cyclic and acyclic ketones, the mechanism was proposed, involving α-cleavage of the peroxide intermediate in the presence of a base. Like in the earlier works of Itoh [13] and Lian,[10] it was shown that the introduction of a substituent at the hydroxyl group of the catalyst resulted in dramatic deterioration of the asymmetric induction.[8] This observation agrees with the initial assumption by Shioiri [7] that the hydroxyl group participates in the ion-pair formation with the substrate and therefore is vital for the generation of asymmetric induction.

Chiral phase-transfer catalysts of other types were also investigated. De Vies *et al.*[9] described the application of chiral monoaza-15-crown-5 ether **VI** (Fig. 1) in catalysis of the aerobic asymmetric C – H hydroxylation of 2-alkyl-indanones and 2-alkyl-tetralones with moderate (43% – 72%) *ee*'s (Table 1, entries 7, 11). The reaction was carried out in the presence of 50% $NaOH_{aq}$ and $(EtO)_3P$ (10 equiv.) at −20 °C, with 10 mol.% catalyst loadings.

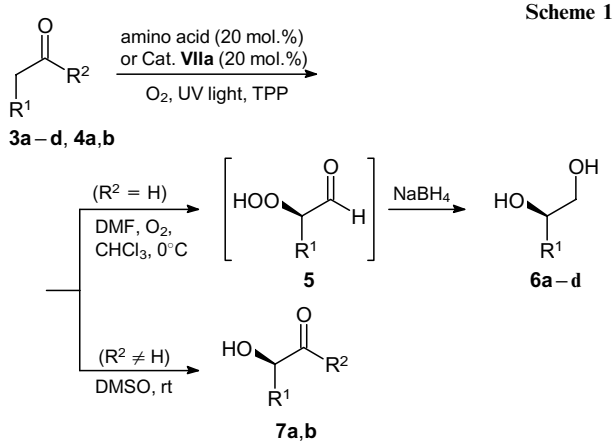
It should be noted that though providing high yields of the corresponding alcohols **2c**,**e**, CPTC **VI** ensured lower enantioselectivities compared to CPTCs **Ia** and **V** (Table 1, entries 7, 11 *vs* 5, 6, 9, 10). Moreover, the reaction scope is rather limited since unsubstituted 1-indanone as well as tetralone-derived β-keto esters appeared to be inert under the reaction conditions.

Cordova and co-workers reported the direct amino acid-catalyzed asymmetric incorporation of molecular oxygen into aldehydes[15] (**3a** – **d**) and ketones[16] **4a**,**b** (Ref. 17) (Scheme 1). The intermediate products of the reaction — α-carbonyl hydroperoxides **5** — were *in situ* reduced by $NaBH_4$ to afford optically active diols **6a** – **d**. The oxidation of aldehydes **3a** – **d** was conducted in DMF under UV-light, using TPP as a sensitizer.[15] The oxidation of ketones **4a**,**b** was performed under similar conditions, but using DMSO.[16] Various amino acids were tested, with best results being achieved with L-α-methyl-proline for the oxidation of aldehydes **3a** – **d** (66% *ee*, Table 1, entry 20) and with L-alanine and L-valine for ketones (69% – 72% *ee*, Table 1, entries 22, 23). The loadings of the amino acid catalysts were as high as 20 mol.%. In a subsequent paper, Cordova and co-workers reported novel proline-derived catalysts (**VIIa** – **d**, Scheme 1).[17] The latter ones were also studied in the asymmetric α-oxygenation of aldehydes **3a** – **d** with O_2, according to the previously developed protocol.[15] Among catalysts **VIIa** – **d**, the best results were observed for compound **VIIa** providing *ee*'s which were 17% – 28% higher than those for L-α-Me-proline (Table 1, entry 21). As in the previous cases, high catalyst loadings (20 mol.%) were required to ensure acceptable yields (50% – 71%).[17]

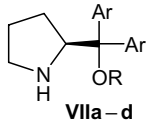
At present, aerobic organocatalyzed α-hydroxylations of carbonyl compounds afford chiral products with high enantioselectivity. However, critical drawbacks such as low catalytic efficiencies, narrow substrate scope, and (in most cases) the need for the external co-reductant substantially limit their utility so far. The authors hope that further studies, encouraged by the unfading interest in the field, will bring about technical solutions for problems outlined above.

Asymmetric aerobic organocatalytic oxidations other than carbonyl α-hydroxylations are scarce. In 2013, Shibata and co-workers reported the highly enantioselective epoxidation of 3-trifluoromethyl chalcones **8** with ambient air in the presence of cinchona-derived CPTCs **VIIIa** – **d** (Scheme 2).[18] The reaction was promoted by the addition of a base (Cs_2CO_3) and methyl hydrazine. The epoxide products **9** were isolated in high yields (90% – 99%) and had excellent optical purity (96% – 99% *ee*).

Scheme 1



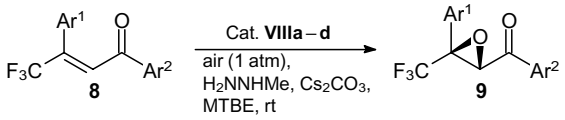
3: R^2 = H: R^1 = Bn (**a**), Pr^i (**b**), n-Pent (**c**), Bu^n (**d**);
4: $R^1 - R^2 = CH_2CH(CH_3)(CH_2)_2$ (**a**), $(CH_2)_4$ (**b**)



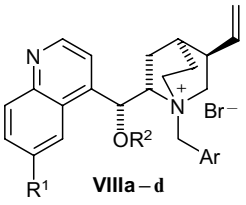
VIIa – **d**

R = TMS, Ar = Ph (**a**), 2-Naph (**b**),
Ar = 3,5-di-$CF_3C_6H_3$ (**c**); R = H, Ar = Ph (**d**)

Scheme 2



Ar^1, Ar^2 = Ph, 3-MeC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 2-Naph



VIIIa – **d**

Compound **VIII**	R^1	R^2	Ar
a	MeO	H	3,5-$(CF_3)_2C_6H_3$
b	H	H	3,5-$(CF_3)_2C_6H_3$
c	MeO	H	3,5-$(Bu^t)_2C_6H_3$
d	MeO	Me	2,5-$(CF_3)_2C_6H_3$

3. Transition-metal-catalyzed oxidations

In this section, several types of aerobic oxygenations in the presence of transition metal-based catalysts will be considered in the following order: epoxidations, the Baeyer – Villiger oxidation and others.

3.1. Asymmetric epoxidations

In 1992, Mukaiyama and co-workers[19] reported the enantioselective epoxidations of alkenes with molecular oxygen in the presence of manganese complexes with chiral salen ligands. Using pivaldehyde as a sacrificial co-reductant, complexes **IX** and **X** (Fig. 2) were tested as catalysts in fluorobenzene in the presence of N-methylimidazole (NMI) as a catalytic additive (Scheme 3). Unfunctionalized alkenes (**10a**,**b**) were epoxidized with moderate to good enantioselectivities (52% – 77% *ee*; Table 2, entries 1, 3, 6) with 12 mol.% catalyst loading. It was noticed that in the absence of NMI, the optical yield decreased significantly (down to 40% *ee*, Table 2, entry 2), and epoxide **11a** with reversed absolute configuration was formed. It was proposed that NMI additive acted as an axial ligand. The

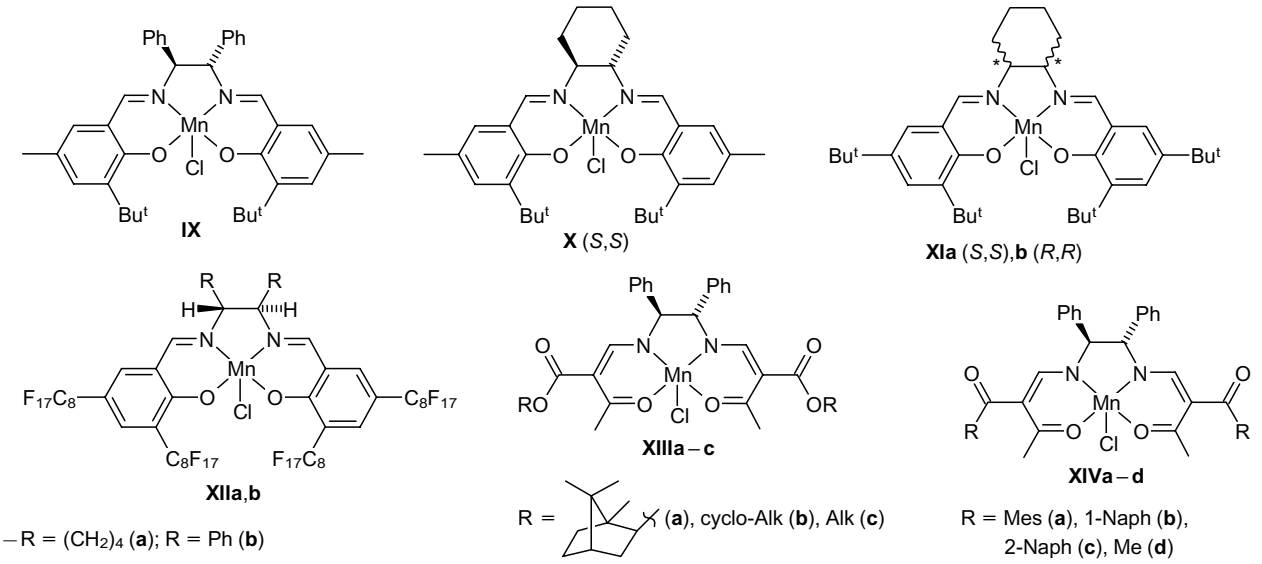
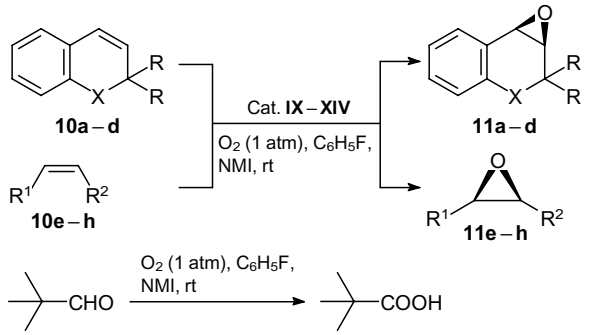


Figure 2. Structures of chiral manganese(III) complexes **IX** – **XIV**.

Scheme 3

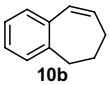
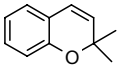
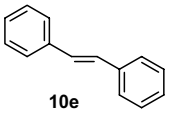
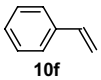
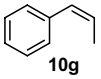
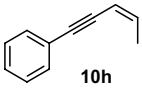


R = H: X = CH_2 (**a**), $(CH_2)_2$ (**b**), absent (**c**); R^1 = Me, X = O (**d**);
R^2 = Ph (**e**), H (**f**), Me (**g**), Ph—≡— (**h**)

elongation of N-alkyl substituent in imidazole was found to increase the epoxide yield though had no effect on enantioselectivity (Table 2, entries 11, 12).[24] Highly enantioselective epoxidation of chromene **10d** (90% – 92% *ee*, Table 2, entry 11) with O_2 in the presence of complex **XIa** (Fig. 2) was documented.[20] It is interesting to note that its (*R*,*R*)-enantiomer **XIb** provides as low as 60% *ee* for the same substrate and requires as high as 20 mol.% catalyst loading and 2-oxocyclopentanecarboxylates as co-reductants instead of aldehydes (Table 2, entry 14).[25] Other substrates, such as *trans*-stilbene (**10e**) and styrene (**10f**), were converted into the corresponding epoxides **11e**,**f** in poor optical yields (5% – 12% *ee*) (Table 2, entries 15, 16). Pozzi *et al.*[23] reported the syntheses of chiral complexes **XIIa**,**b** (Fig. 2), which were selectively soluble in perfluorocarbons. These complexes were tested as catalysts for the aerobic asymmetric epoxidation of alkenes under fluorous biphasic conditions. Epoxidation of only indene **10c** appeared to be highly enantioselective (92% *ee*, Table 2, entries 9, 10), while other substrates demonstrated inferior results.

Lee *et al.*[20] described the application of a system based on complex **XIa**, $CHCl_3$, aq. NaOH and Bu_4NBr for the

Table 2. Enantioselective epoxidations of alkenes with O_2 catalyzed by Schiff-base Mn(III) complexes.

Entry	Substrate	Catalyst (mol.%)	Yield (%)	*ee* (%)	Ref.
1		**IX** (12)	62	52	19
2		**IX** (12)	42	12 [a]	19
3	**10a**	**X** (12)	78	63	19
4		**XIa** (10)	12	53	20
5		**XIIIa** (13)	70	64	21
6		**X** (12)	52	77	19
7		**XIIIa** (13)	52	83	21
8	**10b**	**XIVa** (13)	57	79	22
9		**XIIa** (1.5)	83	92	23
10		**XIIb** (1.5)	77	90	23
	10c				
11		**XIa** (12)	12	91	24
12		**XIa** (12)	37	92 [b]	24
13	**10d**	**XIa** (10)	15	81	20
14		**XIb** (20)	52	60	25
15		**XIb** (10)	44	< 5	25
	10e				
16		**XIb** (10)	38	12	25
	10f				
17		**XIa** (10)	6	80	20
18		**XIVa** (13)	28	80	26
	10g				
19		**XIVa** (13)	28	80	26
	10h				

[a] In the absence of NMI, [b] N-(n-C_8H_{17})imidazole was used.

asymmetric epoxidation of alkenes (**10a**,**d**) by O_2 without a co-reductant (Table 2, entries 4, 13, 17). It was assumed that oxygen capture was implemented by the *in situ* generated $:CCl_2$ to produce dichlorocarbonyl peroxide, the actual terminal oxidant. The addition of NMI was necessary for at least partial formation of epoxide, otherwise only dichlorocyclopropanes were found among the reaction products.

Also, other structurally similar manganese(III) complexes were studied. Mukaiyama *et al.*[21,23,26,27] published a series of papers introducing β-ketoiminato manganese complexes (**XIII** and **XIV**, Fig. 2) as catalysts of enantioselective alkene epoxidation with O_2. The reaction conditions were analogous to those used in Mukaiyama's Mn-salen epoxidation system.[19] Catalyst **XIIIa** displayed moderate to good enantioselectivity (64% – 83% *ee*, Table 2, entries 5, 7) in the epoxidation of substrates **10a**,**b**.[21,27] The enantioselective epoxidation of *cis*-alkenes catalyzed by **XIIIa** was accompanied by partial loss of stereoselectivity, resulting in formation of *trans*-epoxides as side products.[26] For *cis*-epoxides **11g**,**h**, the main epoxidation products, optical yields of 80% *ee* (Table 2, entries 18, 19) were documented.

Besides manganese complexes, some other metal-based catalysts were investigated in asymmetric aerobic epoxidations. Nickel(II) chiral Schiff base complexes (**XV** – **XX**, Fig. 3) were synthesized by Kureshy *et al.*[28] These complexes catalyzed the asymmetric epoxidation of non-functionalized olefins (1-hexene, 1-octene, *trans*-4-octene and indene) with molecular oxygen in the presence of sacrificial reductant isobutyraldehyde. The chemical yields were generally high (70% – 90%) using only 0.33 mol.% catalyst loadings, but the reaction enantioselectivity was at best moderate (20% – 30% *ee* in most cases, with the highest value of 41% *ee* for indene and catalyst **XVI**).

Recently, the highly enantioselective epoxidation of terminal aliphatic alkenes catalyzed by magnetite nanoparticles (NPs) has been reported.[29] The catalyst was obtained by heating diethylene glycol solution of $FeCl_3 \cdot 6H_2O$, L-(+)-tartaric acid and urea at 200 °C. The resultant Fe_3O_4/tart-NPs were reported to promote the epoxidation of 1-octene and 1-decene by molecular oxygen (2 atm) in the presence of isobutyraldehyde with exceptionally high enantioselectivity (99% *ee*). For styrene and 1-methylcyclohexene, somewhat lower enantioselectivities (67% and 62% *ee*, respectively) were reported. α-Methylstyrene and *trans*-β-methylstyrene demonstrated poor results (33% *ee*).

Chiral ruthenium complexes were also examined in asymmetric epoxidation reactions. Kureshy with co-workers[30] reported Ru(III) complexes **XXI** – **XXIII** (Fig. 4) active in the asymmetric epoxidations of substituted styrenes with O_2 in the presence of isobutyraldehyde as a co-reductant. However, compared to Ni(II)-complexes **XV** – **XIX**,[28] a series of Ru(II) complexes demonstrated both lower *ee* values (11% – 30%) and more moderate yields (50% – 80%) with the same catalyst loadings (0.33 mol.%). The addition of pyridine *N*-oxide improved the conversion and enantioselectivity; however, the latter still did not exceed 30%. Ruthenium(VI) porphyrin complex **XXIV** (Fig. 4) was disclosed by Che and co-workers[31] to provide both stoichiometric and catalytic aerobic epoxidation of alkenes. This catalytic version did not require any co-reductant, performing up to 21 TON under 8 atm pressure of O_2. The enantioselectivity varied in the range of 52% – 73% *ee*. More recently, Katsuki and co-workers[32,33] developed a family of Ru-salen complexes **XXV** (Fig. 4). Complexes **XXVa** – **c**, containing NO axial ligand, were capable of catalyzing asymmetric epoxidation of conjugated olefins with O_2 under visible light irradiation in the presence of water.[32] The latter presumably served as a proton transfer mediator for the oxygen activation process in the catalyst system, whilst visible light was necessary for NO dissociation. Complex **XXVc** (5 mol.%) demonstrated high enantioselectivities, affording epoxides in 76% – 92% *ee*. Next-generation complexes **XXVd**,**e** contained water molecule as an axial ligand instead of NO, and thus required no irradiation for the epoxidation reaction to proceed.[33] Conjugated olefins were epoxidized with air at 25 °C or with O_2 at 0 °C in the presence of **XXVe** (5 mol.%), in high optical yields (up to 95% *ee*). It is worth mentioning that no sacrificial reductant was required in this Ru-salen catalyst systems.[32,33]

To summarize, the asymmetric transition metal-catalyzed epoxidations with O_2 were extensively studied by Mukaiyama's group in the 1990s. Important contributions were done relatively recently by Katsuki and co-workers, who suggested highly enantioselective alkene epoxidation using Ru-salen complexes. The major shortcomings of

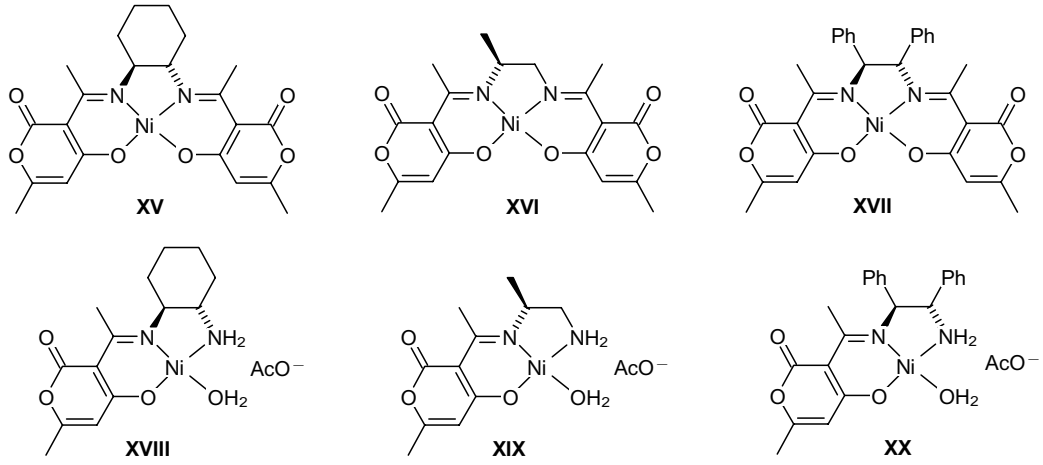
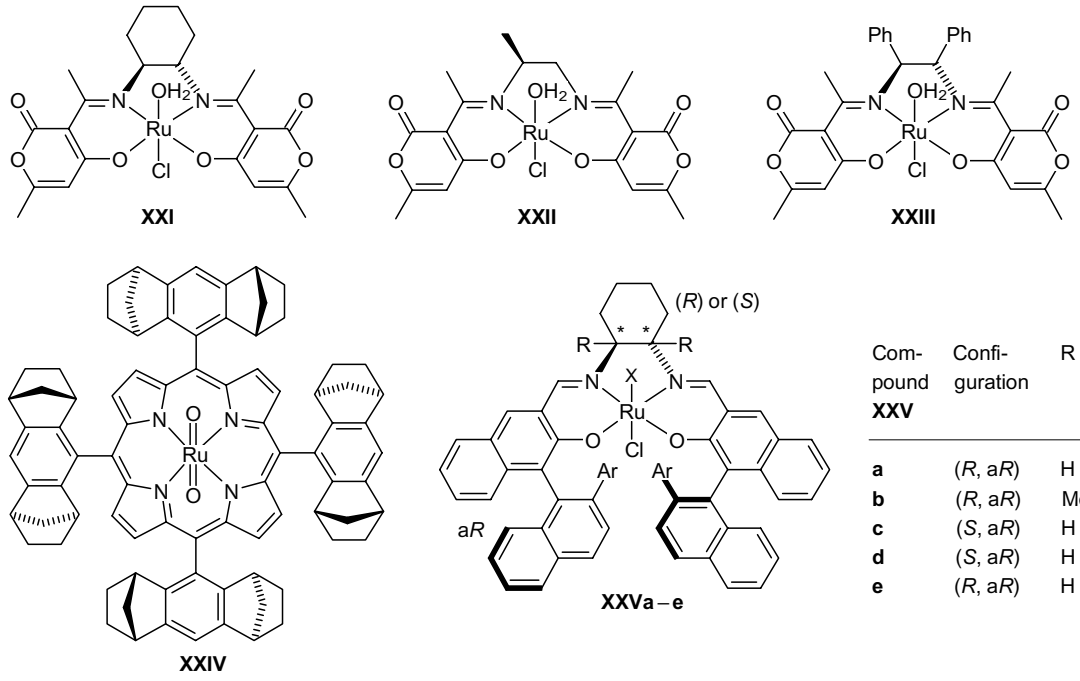


Figure 3. Structures of chiral nickel(II) complexes.



Compound XXV	Configuration	R	Ar	X
a	(*R*, a*R*)	H	Ph	NO
b	(*R*, a*R*)	Me	Ph	NO
c	(*S*, a*R*)	H	Ph	NO
d	(*S*, a*R*)	H	Ph	H_2O
e	(*R*, a*R*)	H	3,5-$Cl_2C_6H_3$	H_2O

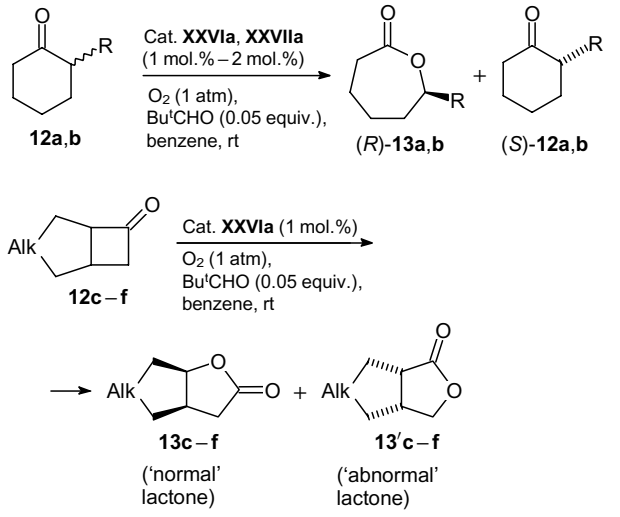
Figure 4. Structures of chiral ruthenium complexes.

transition-metal based systems are (1) in most cases the need in several equivalents of an external co-reductant, which entails the formation of high-molecular-weight organic by-products, and (2) typically relatively low catalytic efficiencies; in the case of catalysts based on precious metals and elaborated chiral ligands (such as complexes of the type **XXV**), the second issue substantially restricts the practical perspectives.

3.2. Asymmetric Baeyer – Villiger oxidations

Catalytic asymmetric Baeyer – Villiger oxidations with molecular oxygen were first reported in 1994 by Bolm *et at*.,[34] who using chiral oxazoline copper catalysts **XXVI** (Scheme 4). 2-Phenylcycloalkanes (**12a**,**b**) were tested as model substrates; the oxidation protocol required a co-reducing agent, capable of activating molecular oxygen. Several aldehydes were tested as co-reductants; the best results were achieved with pivaldehyde (0.5 equiv.) and catalyst **XXVIa** (1 mol.%). Moderate yields (47% – 53%) were accompanied by moderate to good *ee* values of 65% – 69% (Table 3, entries 1 and 3).[34] The residual unreacted ketones were enantio-enriched, thus formally suggesting kinetic resolution type of reaction. In the subsequent paper,[36] the authors found that **XXVIa** catalyzed Baeyer – Villiger oxidation of bicyclic cyclobutanones **12c** – **f** with O_2. Formation of two isomeric γ-lactones was detected ('normal' and 'abnormal', Scheme 4), the latter being produced with higher enantioselectivity (92% – 95% *ee*), albeit in lower chemical yield (Table 3, entries 4 – 7). Additionally, prochiral 3-substituted cyclobutanone **12e** was explored as a substrate in the Baeyer – Villiger oxidations (*i.e.*, oxidative desymmetrizations) with O_2 in the presence of **XXVIa**.[37] In most cases, moderate enantioselectivities were documented (47% *ee*, Table 3, entry 8). The highest optical yield was achieved in the oxidation of the tricyclic ring-strained ketone **12f** (Table 3, entry 9, 91% *ee*).

Scheme 4



Structures XXVI, XXVII

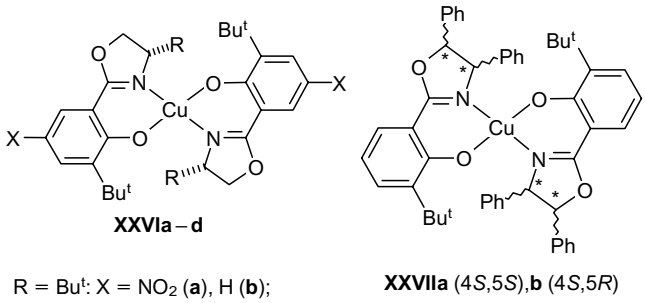
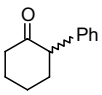
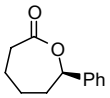
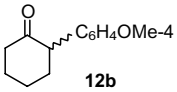
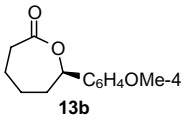
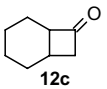
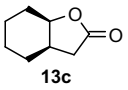
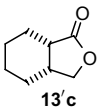
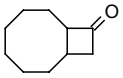
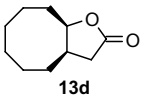
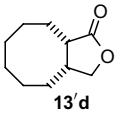
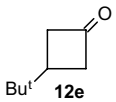
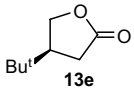
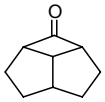
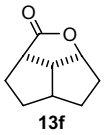


Table 3. Enantioselective copper-catalyzed Baeyer – Villger oxidations with O_2.

Entry	Substrate	Product	Catalyst (mol.%)	Yield (%)	*ee* (%)	Ref.
1	 **12a**	 **13a**	**XXVIa** (1)	47	69	34
2			**XXVIIa** (2)	62	26	35
3	 **12b**	 **13b**	**XXVIa** (1)	53	65	34
4	 **12c**	 **13c**	**XXVIa** (1)	45	67	36
5		 **13′c**	**XXVIa** (1)	15	92	36
6	 **12d**	 **13d**	**XXVIa** (1)	49	61	36
7		 **13′d**	**XXVIa** (1)	25	94	36
8	 **12e**	 **13e**	**XXVIa** (1)	85	47	37
9	 **12f**	 **13f**	**XXVIa** (1)	62	91	37

Peng *et al.*[35] tested modified oxazoline copper complexes **XXVIIa**,**b** (Scheme 4) as catalysts in Baeyer – Villiger oxidations of 2-phenylcyclohexane with molecular oxygen. Various sacrificial aldehydes were tested as additives, yet none of them afforded decent optical yield: the highest value of 26% *ee* was attained using catalyst **XXVIIa** and pivaldehyde (Table 3, entry 2).

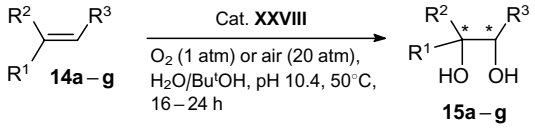
So far, Baeyer – Villiger type asymmetric oxidations with O_2 have not been numerous, the existing examples being restricted to copper-based catalysts. High optical yields have only been reported for the oxidation of a handful of 'good' substrates, such as a few bicyclic and tricyclic ketones.

3.3. Miscellaneous asymmetric oxygenations

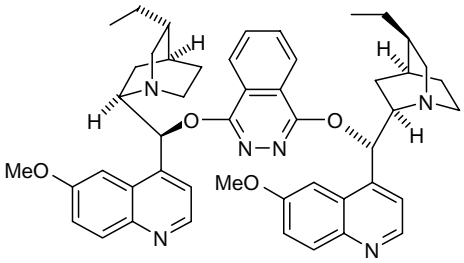
A few other catalytic asymmetric oxygenations with molecular oxygen have been reported. Beller and co-workers[38] reported osmium-catalyzed asymmetric dihydroxylation of alkenes with O_2. The catalyst **XXVIII** was formed *in situ* from $K_2[OsO_2(OH)_4]$ salt (0.5 mol.% – 2.0 mol.%) and $(DHQD)_2PHAL$ chiral ligand (hydroquinidine 1,4-phthalazinediyl diether, Scheme 5) in a mixture of aqueous phosphate buffer solution (pH 10.4) and Bu^{t}OH. The oxidations were conducted at 50 °C under 1 bar O_2 pressure and osmium/ligand ratio of 1/3. Enantioselective dihydroxylation of 1-octene **14a** resulted in almost quantitative yield, with moderate asymmetric induction (65% *ee*). Conjugated olefins **14b** – **e** demonstrated much higher enantioselectivity (80% – 96% *ee*). It was established that both oxygen atoms from the O_2 molecule were incorporated into the product **15** in an atom-efficient manner. In the subsequent paper,[39] the authors extended the substrate scope and adapted the catalyst system for using air (20 bar) instead of oxygen gas. For dihydroxylation of aliphatic terminal olefin **14g** and conjugated olefins **14b** – **d**,**f**, enantioselectivities of 63% – 68% *ee* and up to 98% *ee*, respectively, were reported. Comparing the use of molecular O_2 and air as oxidizing agents, by the example of olefins **14b** – **d**, it can be concluded that air provides higher yields of the corresponding diols **15b** – **d** than O_2 with slightly lower enantioselectivities.

Finally, asymmetric sulfoxidations with molecular oxygen under transition-metal-catalyzed conditions have to be mentioned. Mukaiyama and co-workers[40,41] employed

Scheme 5



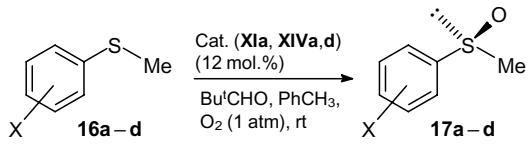
Olefin	R^1	R^2	R^3	Oxidizing agent			
				O_2		air	
				yield (%)	*ee* (%)	yield (%)	*ee* (%)
a	H	$(CH_2)_6$		98	65	–	–
b	1-Naph	H	H	55	96	96	82
c	Ph	H	H	52	90	76	87
d	Ph	$(CH_2)_4$		51	86	88	89
e	Ph	Me	H	96	80	–	–
f	Ph	H	Ph	–	–	89	98
g	C_6H_{13}	H	H	–	–	96	63



$(DHQD)_2PHAL$

manganese-salen and manganese-β-ketoiminato complexes (**XIa**, **XIVa**,**d**, Fig. 2) in the asymmetric oxidations of a series of aryl methyl sulfides **16a** – **d** (Scheme 6). The corresponding sulfoxides **17a** – **d** were obtained in good yields with low to good optical purities (18% – 72% *ee*). The reaction conditions were adapted from analogous epoxidation reactions, including the use of sacrificial aldehyde.[21] Katsuki and co-workers investigated ruthenium complex **XXVb** (Fig. 4) in the enantioselective oxygenation of several aryl methyl sulfides and 2-substituted 1,3-dithianes.[32] The catalyst performed up to 20 catalytic turnovers under oxygen atmosphere and visible light irradiation, demonstrating high enantioselectivity in most cases (72% – 98% *ee*). No external co-reductant was required.

Scheme 6



Sulfide **16**	X	Catalyst	Yield (%)	*ee* (%)
a	2-Br	**XIVd**	73	52
b	2-Br	**XIa**	54	18
c	2-Br	**XIVa**	91	66
d	2-Cl	**XIVa**	72	72
e	4-NO_2	**XIVa**	44	69
d	H	**XIVa**	66	51

4. Conclusions and outlook

The evolution of catalysts for the asymmetric aerobic oxygenations may be contingently divided into two periods. The first wave of progress came in the 1990s when several types of catalytic enantioselective oxygenations with air or O_2 emerged. Mukaiyama's milestone work introduced Mn-salen and related complexes as catalysts for the aerobic asymmetric epoxidations and sulfoxidations, followed by Bolm's copper-oxazoline based catalysts of asymmetric Baeyer – Villiger oxygenations. Beller and co-workers contributed osmium-based catalyst system for the enantioselective dihydroxylation of olefins. Meanwhile, organocatalyzed aerobic asymmetric C – H hydroxylations were also being developed by Shioiri and co-workers. By the end of that period, the common shortcomings of aerobic systems were revealed, in particular the need for several equivalents of sacrificial co-reducing agent for the dioxygen activation, which contaminates the reaction mixture with high-molecular-weight by-products, as well as the need in relatively high catalyst loadings. Such challenges restricted the practical attractiveness and led to temporary extinction of research interest.

In the last decade, the growing demand for optically pure organic compounds and for green and sustainable chemical processes revitalized the research in the field of enantioselective oxygenations with molecular oxygen. Important contributions were made in the organocatalyzed asymmetric C – H hydroxylations of carbonyl compounds. The advancements included the expansion of substrate scope, improvement of catalytic efficiencies and enantioselectivities, as well as activities, which resulted in protocols requiring shorter reaction times. Several examples of highly enantioselective oxidations (> 90% *ee*) were documented by various authors. Of particular fundamental interest are the examples of Ru-catalyzed epoxidation in the absence of co-reducing agent [32, 33] and of Os-catalyzed dihydroxylation of olefins,[40] the catalyst acting in dioxygenase manner: those systems may well supplement our understanding of the dioxygen activation mechanisms.

Future developments in the field, both synthetic and fundamental, are expected, *e.g.* the authors would be eager to see systems capable of conducting the direct enantioselective C – H oxidation of non-activated prochiral substrates with air or dioxygen, so far unprecedented for synthetic catalysts. At the same time, designing highly efficient (performing 100 – 1000 turnovers) and simultaneously highly enantioselective (> 95% *ee*) catalysts for any of the aerobic oxidation reactions considered above would be a potentially highly rewarding trend.

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