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Recent advances in catalytic asymmetric dihydroxylation of olefins

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Asymmetric dihydroxylation of olefinic groups is an extremely important synthetic transformation which has been widely utilized to obtain optically pure pharmaceuticals and other fine chemical products. In recent years, catalyst systems for the asymmetric C=C dihydroxylations have attracted significant interest, the major research efforts being focused on designing environmentally benign catalyst systems. This mini-review summarizes recent progress in the field, surveying both novel, less toxic modifications of the classical osmium-based catalysts, and the highly efficient and enantioselective non-osmium catalyst systems.
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1. Introduction

Catalytic asymmetric reactions are highly desirable and challenging processes in organic synthesis. The ability of a single chiral catalyst molecule to induce the chirality on the multitude of chiral product molecules is a key for obtaining enantiomerically pure compounds. The latter are strongly demanded in production of various natural products, pharmaceuticals and agricultural agents. Owing to its extreme synthetic power, the asymmetric *cis*-dihydroxylation (AD) of olefins in the presence of osmium compounds has been one of the cornerstones of fine organic synthesis. The first catalytic AD process was reported by Sharpless and coworkers,[1,2] who discovered that the use of chiral cinchona alkaloid derived ligand allowed reducing the loading of toxic and volatile osmium tetroxide, previously used in stoichiometric amounts, to catalytic quantities. Since then, numerous improvements and developments were endeavored, resulting in widespread application of the Sharpless AD catalyst system. This catalytic reaction was employed in a number of total syntheses of enantiopure biologically active compounds, including approved drugs.[3,4] The topic has been attracting considerable research interest over the years, being inherent part of recent comprehensive reviews on catalytic asymmetric processes.[5–10] Meanwhile, non-osmium dihydroxylations were also in focus of studies as far as growing ecological restrictions induced the development of more environmentally benign catalysts.[11,12] However, the latest review entirely dedicated to enantioselective dihydroxylations came more than a decade ago.[13] This mini-review summarizes the progress in asymmetric dihydroxylations, mediated by osmium and non-osmium metal based catalysts, achieved since 2005; in addition, the advancements in organo- and biocatalytic AD reactions are overviewed, too.

The following abbreviations are used in the review:
AD — asymmetric *cis*-dihydroxylation,
AD-mixα — a commercially available catalyst containing $K_2OsO_2(OH)_4$ and $(DHQ)_2$-PHAL,
AD-mixβ — a commercially available catalyst containing $K_2OsO_2(OH)_4$ and $(DHQD)_2$-PHAL,
B_2cat_2 — bis(catecholato)diboron,
B_2neo_2 — bis(neopentylglycolato)diboron,
B_2pin_2 — bis(pinacolato)diboron,
BMMs — bimodal mesoporous silicas,
CAP-OsO_4 — osmate-exchanged chloroapatite,

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$(DHQ)_2$-PHAL — hydroquinine 1,4-phthalazinediyl diether,

$(DHQD)_2$-PHAL — hydroquinidine 1,4-phthalazinediyl diether,

nbd — norbornadiene,

NMM — *N*-methyl-morpholine,

NMO — *N*-methyl-morpholine *N*-oxide,

OsNPs – binaphthyl-osmium nanoparticles,

PI Os — polymer-incarcerated osmium,

PMP — *p*-methoxyphenyl,

TON — turnover number,

TBME — *tert*-butyl methyl ether.

2. Osmium catalysts

The Sharpless catalyst system for asymmetric dihydroxylation (Fig. 1) has inherent drawbacks (including contamination of reaction product with highly toxic osmium species and relatively high cost of the catalyst components) that hampered its wide application on industrial scale. In the late 2000s, studies on this system, aimed at overcoming these limitations, were reported.

Following this improvement paradigm, Afonso and co-workers [14] presented a modified and arguably more environmentally benign approach, based on using water/surfactant reaction media. The AD of a series of olefins afforded high yields and enantioselectivities (up to 99% *ee*, Fig. 2), which were higher than or comparable to those obtained in conventional media (*tert*-butanol/water). Also, the novel system did not require a slow substrate addition to the reaction mixture to achieve high *ee*'s. The separation of the product from osmium catalyst was performed by nanofiltration technique, thus enabling reducing the product contamination with osmium to 5 ppm. This methodology was based on a previous study in which the authors examined organic solvent nanofiltration membranes in AD reaction-nanofiltration cycles under 20 bar N_2 pressure, using 1-hexene as a model substrate.[15]

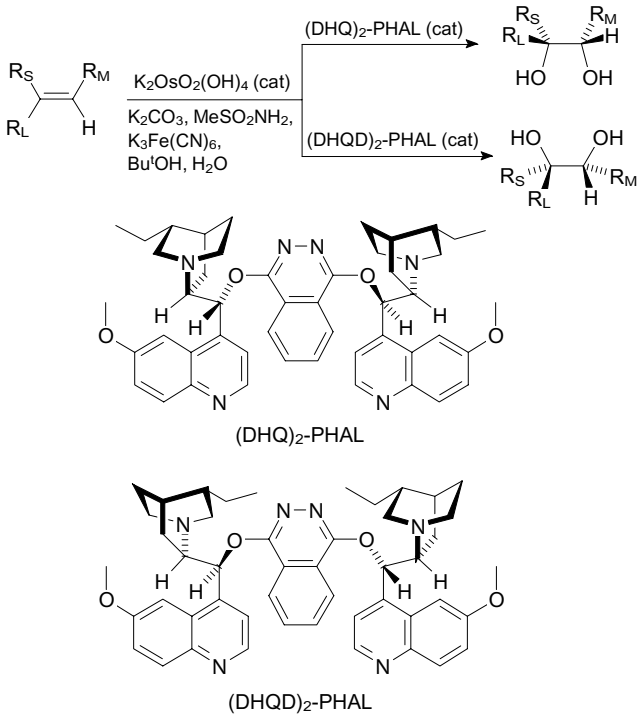


Figure 1. Sharpless AD.
R_L is the largest substituent, R_M is medium-sized substituent, R_S is the smallest substituent.

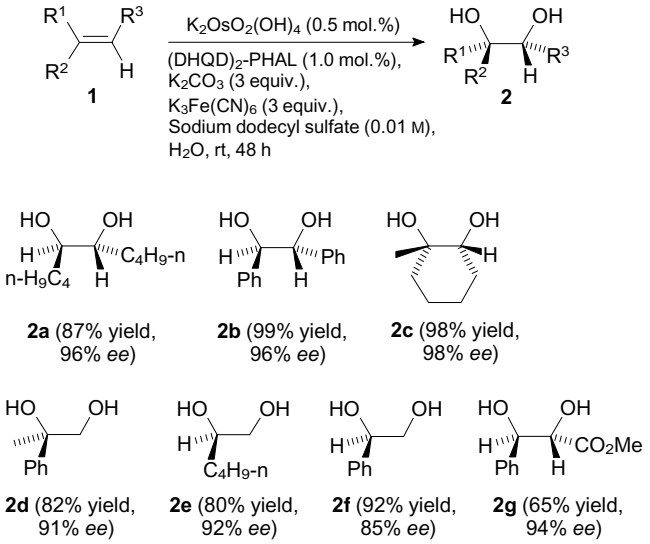


Figure 2. AD of olefins in water/surfactant reaction media.[14]

Sun and co-workers [16] prepared bimodal mesoporous silicas (BMMs), modified by 1-methyl-3-(trimethoxysilyl)-propylimidazolium chloride ($MTMSPIm^+Cl^-$) ionic liquid, bearing immobilized osmium-chiral ligand catalyst. In AD catalytic tests, *trans*-stilbene was chosen as a model substrate, with *N*-methylmorpholine *N*-oxide (NMO) as the terminal oxidant. As low as 0.001 mol.% (based on Os) loading of the solid catalyst was sufficient to obtain the diol in 99% yield and 99% *ee* (Fig. 3). The reusability of the catalyst was quite low, the second run giving only 33% diol yield, indicative of catalyst leaching from the matrix of the functionalized BMMs.

Richardson and co-workers reported the osmium catalyzed AD of olefins using CO_2/H_2O_2 oxidant in the presence

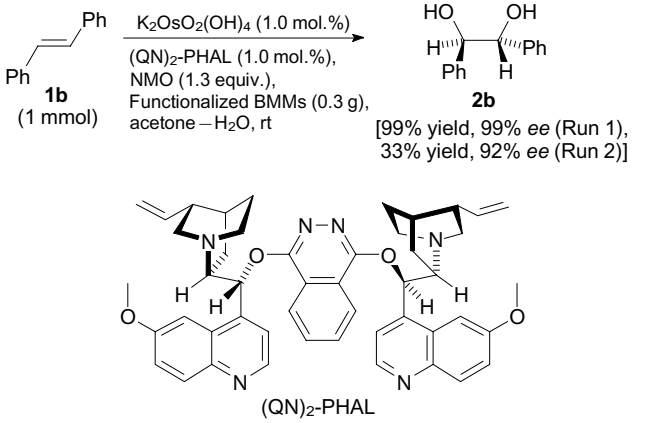


Figure 3. AD of *trans*-stilbene using bimodal mesoporous silicas modified by ionic liquid.[16]

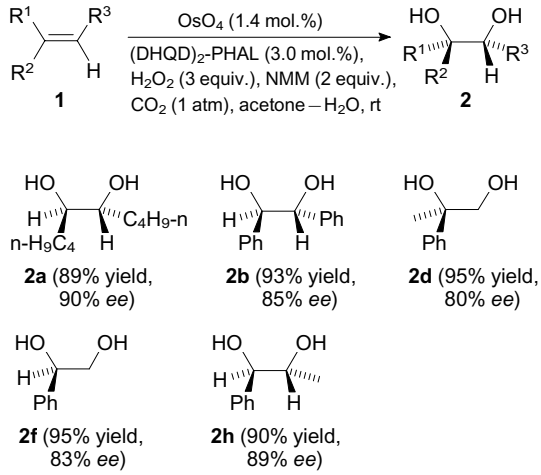


Figure 4. AD of olefins with CO_2/H_2O_2 oxidant.[17]

of *N*-methylmorpholine (NMM).[17] The latter was *in situ* oxidized to NMO, which, in turn, was responsible for the regeneration of OsO_4 species during the catalytic cycle. The AD reactions were probed on 5 substrates with the addition of the chiral $(DHQD)_2$-PHAL ligand (3 mol.%), and 1.4 mol.% OsO_4 loadings. The documented yields (89% – 95%) and enantioselectivities (80% – 90% *ee*, Fig. 4) were fairly high and comparable with the classical version of the AD reaction. From the environmental perspective, unquestionable advancement of this catalyst system was the use of hydrogen peroxide, a safe, low-cost, and green oxidant, with high active oxygen content.

The mechanism of osmium catalyzed AD was also in focus of research interest. Periasamy and co-workers studied the AD of substituted *trans*-stilbene derivatives using 9-*O*-acetyldihydrocinchonidine chiral ligand (**3**, Fig. 5).[18] The distinctive feature of the catalyst system was that both electron-donating and electron-withdrawing 4,4′-substituents in *trans*-stilbenes had adverse effect on enantioselectivity of the diol formation, while the highest *ee* of 90% was documented for unsubstituted *trans*-stilbene. These observations were interpreted as an indication that efficient (L)-OsO_4 1,3-dipole in [3 + 2] transition state is vital for achieving high enantioinduction (**4**, Fig. 5); electron-rich or electron-poor stilbenes would more effectively compensate such 1,3-dipole, resulting in enantioselectivity deterioration.

Junttila and Hormi[19] observed similar regularities in the AD of *para*-substituted styrenes with $NaClO_2$ and

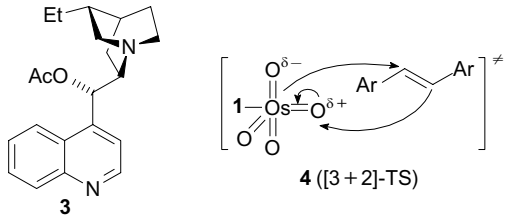


Figure 5. Chiral ligand (**3**) and proposed TS (**4**) in osmium-catalyzed AD of alkenes.[18]

$K_3[Fe(CN)_6]$ as oxidants. A concave-type shape of the Hammett plot, together with solvent kinetic isotope effects, were explained by the change of hydrolysis mechanism of the intermediate osmium (mono)glycolates when going from substrates with electron-withdrawing to those with electron-donating substituents. For the former substrates, a stepwise attack of the nucleophile on the electrophilic osmium centre, with subsequent protonation of the alkaline intermediate were hypothesized. For the latter substrates, reaction mechanism with specific acid catalysis was proposed (Fig. 6). It was found that the rate of the hydrolysis step influenced the enantioselectivity of the AD: if this rate was slow, the *ee* was deteriorated by competitive bis(glycolation). In subsequent paper,[20] the authors studied the effect of methanesulfonamide on the AD. It was revealed that weakly acidic methanesulfonamide acts like a general acid catalyst, protonating the intermediate esters of conjugated aromatic olefins during the hydrolysis step. However, methanesulfonamide had no accelerating effect on the AD of short-chain terminal aliphatic olefins. Non-terminal aliphatic substrates exhibited the dependence on the electronic properties of the intermediate osmate ester: with increasing polarity of the latter, the accelerating effect of methanesulfonamide was attenuated.

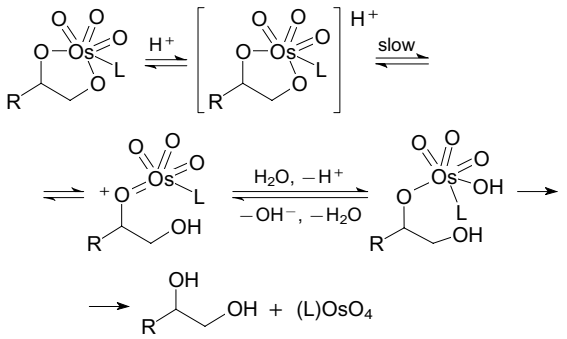


Figure 6. Mechanism of osmium (mono)glycolate hydrolysis in the AD of styrenes.[19]

Brückner and co-workers[21] investigated stereochemical peculiarities of the AD of (*E*)- and (*Z*)-pentenynyl chlorides and pentenyne-based ester and ethers (Fig. 7). It was shown that olefins (*E*)-**5b** and (*Z*)-**7c** had the same stereochemical preference under analogous conditions, thus correcting previous reports on the contrary. For all studied substrates, the stereochemical outcome was rationalized using the Sharpless-mnemonic transition state[2,22] which presumes catalyst – substrate orientation with minimized steric hindrance in the zone of the most repulsive interaction.

Later, Weber and Brückner[23] performed a systematic study of the Sharpless AD of esters and amides of methacrylic (**9a**), tiglic (**9b**) and angelic acids (**9c**, Fig. 8). The derivatives of tiglic acid demonstrated the best results, affording diols in over 80% yields with up to 97% – 99% *ee*. Esters and amides of angelic acid reacted with lower enantioselectivities (up to 77% – 90% *ee*). *N*-Methoxy-*N*-methylmethacrylamide was converted with the highest enantioinduction (up to 95% – 98% *ee*), as compared with other methacrylic acid derivatives. It was found that both ester and amide of the same acid furnished

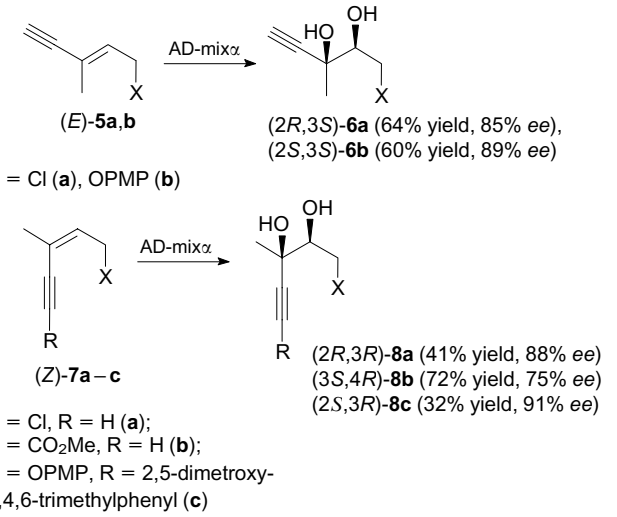
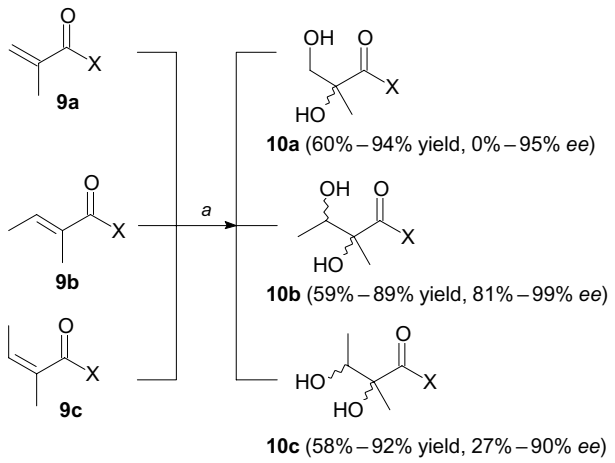


Figure 7. AD of pentenyne-based substrates.[21]
AD-mixα is a commercially available catalyst containing $K_2OsO_2(OH)_4$ and $(DHQ)_2$-PHAL.



(*a*) $K_2OsO_2(OH)_4$ (1.0 mol.%), K_2CO_3 (3 equiv.), $K_3Fe(CN)_6$ (3 equiv.), $MeSO_2NH_2$ (1 equiv.), $(DHQ)_2$-PHAL or $(DHQD)_2$-PHAL (2.0 mol.%), Bu^tOH, H_2O, 0 °C, 1 – 6 days; X = OMe, OBu^i, OPMB, N(OMe)Me, $N(CH_2)_4$

Figure 8. AD of esters and amides of methacrylic, tiglic and angelic acids.[23]

the same enantiomer. Again, the stereoselectivity of the AD was established to obey the Sharpless mnemonic.[2, 22]

Dehury and Hariharakrishnan [24] synthesized an osmate-exchanged chloroapatite (CAP-OsO_4) catalyst by a simple ion-exchange technique and screened its activity in the AD of olefins. The corresponding diols were obtained in good to high yields (71% – 96%) and high *ee*'s (90% – 97%, some examples are presented in Fig. 9). Catalyst recycling and reuse up to 5 times resulted in a minor loss of activity and stereoselectivity, no osmium leaching was detected. The catalytic procedure was not straightforward, requiring very slow (during 12 hours) addition of the olefin.

Kobayashi and co-workers [25] developed polymer-incarcerated osmium (PI Os) catalysts. The system was tested in

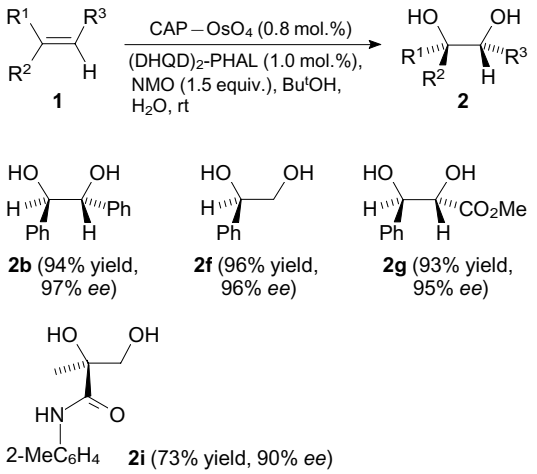


Figure 9. AD of olefins using osmate-exchanged chloroapatite catalyst.[24]

the AD of model olefins, demonstrating high activity and enantioselectivity (82% – 99% *ee*, some examples are presented in Fig. 10). Also, it was employed for the preparation of a key intermediate for camptothecin, an anticancer drug. The PI Os catalyst could be recovered; osmium leaching was detected to be rather small (1% – 3%).

Tiller and co-workers [26] utilized conjugates of enzymes and poly(2-methyloxazoline) as organosoluble amphiphilic polymer nanocontainers for dissolving the osmium precursor, thus transforming the enzymes into organosoluble artificial metalloenzymes. The catalyst prepared from copper-containing laccase enzyme showed good to high enantioselectivity (up to 93% *ee* for styrene) in the AD of alkenes, yet the activity, measured as pseudo first-order rate constant, was 2 – 3 orders of magnitude lower than that for the traditional Sharpless AD.

Wu and co-workerss [27] reported the AD catalyzed by binaphthyl-osmium nanoparticles (OsNPs) with

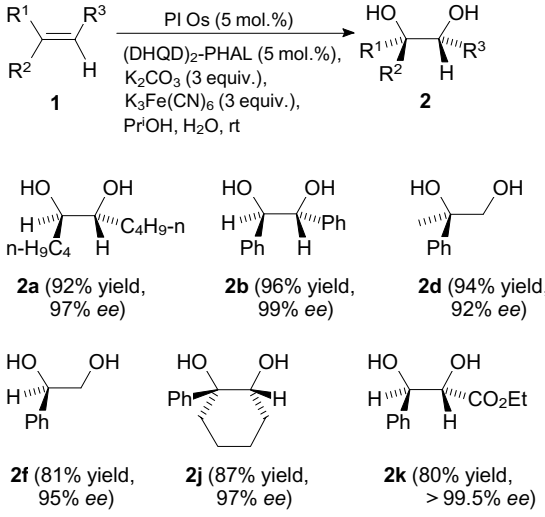


Figure 10. AD of olefins using polymer-incarcerated osmium catalyst.[25]

$(DHQD)_2PHAL$ as the chiral modifier. The authors documented a significant size effect of the OsNPs, depending on the density of the covalent organic shells. The catalyst with balanced metal/ligand ratio exhibited high activity and enantioselectivity (up to >95% *ee*, some examples are presented in Fig. 11), performing better than Os^0 black, $OsCl_3$ and $K_2OsO_2(OH)_4$, taken for comparison. The AD reaction tolerated different functional groups, including halogens, aromatic moieties, alicycles, amides and esters. The reusability of the catalyst was tested in 5 successive cycles, revealing no loss in activity or enantioselectivity.

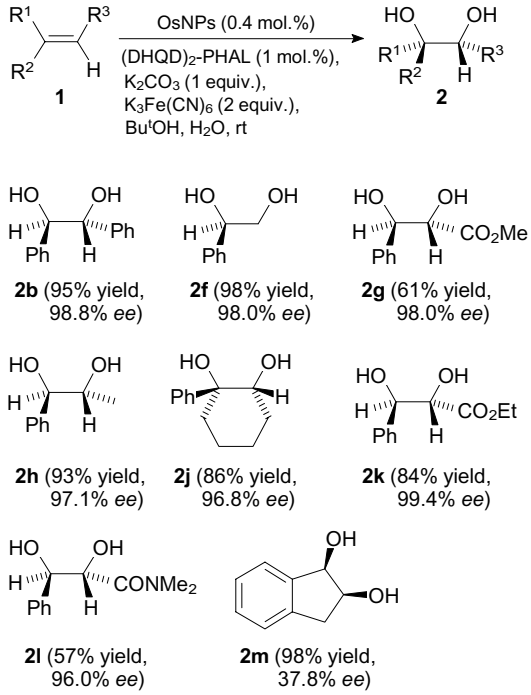
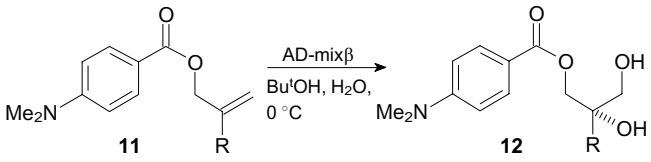


Figure 11. AD of olefins using binaphthyl-osmium nanoparticles as the catalyst.[27]

Another heterogeneous system was reported by Rana and co-workers,[28] who synthesized a robust and reusable catalyst of a hierarchical polyamine-silica with encased osmate ions. The catalyst was capable of mediating the AD of olefins utilizing NMO as oxidant with up to 700 turnover numbers (TON) and 96% – 99% *ee* [9 alkenes were tested, including stilbene, styrene, 1-hexene and (2-methylpropenyl)benzene].

Contributions focused on revealing optimal conditions for the AD of some traditionally challenging substrates were also reported. Wang and co-workers[29] studied the AD of *N*,*N*-dimethylaminobenzoate derivatives as a route to the chiral diols of 1,1-disubstituted alkenes. The authors screened various substituents at the benzoate moiety tethered to the alkene, and revealed that *N*,*N*-dimethylamino group provided the best results. The corresponding diols were obtained in good yields and moderate to high enantioselectivities (Fig. 12). The authors successfully exploited the design concept aimed at maximizing the catalyst – substrate

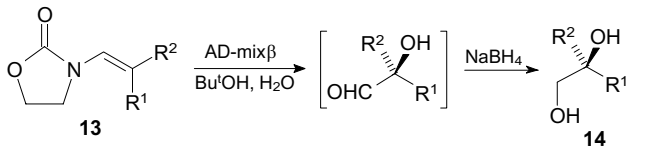


R = Alk (70% – 90% yield, 72% – 94% *ee*),
CH_2OR^1 (70% – 90% yield, 96% – 98% *ee*),
$(CH_2)_2OR^2$ (69% – 88% yield, 96% – 99% *ee*),
$(CH_2)_2$Hal (70% – 73% yield, 88% *ee*),
Ph (65% yield, 43% *ee*)

Figure 12. AD of *N*,*N*-dimethylaminobenzoate derivatives.[29] Ad-mixβ is a commercially available catalyst containing $K_2OsO_2(OH)_4$ and $(DHQD)_2$-PHAL.

electronic interactions, developed in an earlier study on kinetic resolutions by the Sharpless AD reactions.[30]

Lam and Gourdet[31] presented another approach to enantio enriched diols of 1,1-disubstituted alkenes, *via* the AD of the corresponding enamides **13** and subsequent reduction with sodium borohydride (Fig. 13). The method afforded the diols **14** in 61% – 86% isolated yields and 87% – 97% *ee*. Practical synthetic utility of this technique was demonstrated by applying it as the key step in the syntheses of (*S*)-oxybutynin pharmaceutical and (+)-tanikolide natural product.



R^1 = Ar, R^2 = Alk (61% – 86% yield, 87% – 97% *ee*)

Figure 13. AD of enamides and subsequent reduction.[31]

Schirmer, Ward and co-workers[32] designed a tunable hybrid catalyst, with Os^{VIII} centres anchored within a protein to afford an artificial metalloenzyme for the AD of olefins. Five proteins were tested and streptavidin demonstrated the best results in terms of both activity and enantioselectivity on a test substrate α-methylstyrene (27 TON, 95% *ee*). The reaction conditions included potassium osmate salt, protein monomer, and potassium ferricyanide as conventional oxidant. The catalyst system demonstrated good performance in the AD of some challenging substrates including *cis*-β-methylstyrene (26 TON, 90% *ee*). It was shown that the hybrid catalyst provided rich opportunities for genetic optimization to improve the enantioselectivity and even achieve inverse enantiopreference. The major drawback of this system was modest efficiency as compared to the traditional Sharpless AD.

Recently, Talero and Burtoloso[33] extended the substrate scope of the Sharpless AD to the α,β-unsaturated diazoketones **15** (Fig. 14). Subsequent Wolff rearrangement of diols **16** furnished enantiomerically pure 4,5-disubstituted 2-furanones **17** (see Fig. 14), an important class of biologically active compounds.

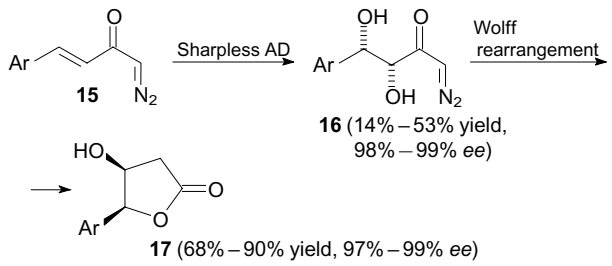


Figure 14. AD of α,β-unsaturated diazoketones.[33]

3. Non-osmium catalysts

Complexes of iron, an analogue of osmium, have also been examined as catalysts in the asymmetric dihydroxylation of olefins. Que and co-workers [34, 35] explored non-heme iron complexes **18** and **19** (Fig. 15) in the asymmetric *cis*-dihydroxylation of olefins by hydrogen peroxide. Unlike in osmium-based systems, significant amount of epoxide by-product was formed in these catalytic reactions. The highest *ee* of 97% was achieved for *trans*-2-heptene using complex **19**, although the catalytic efficiency was rather low (3.4 – 7.5 TON). Besides, the efficiency of H_2O_2 consumption did not exceed 10%, thereby making this system fairly distant from synthetic application.

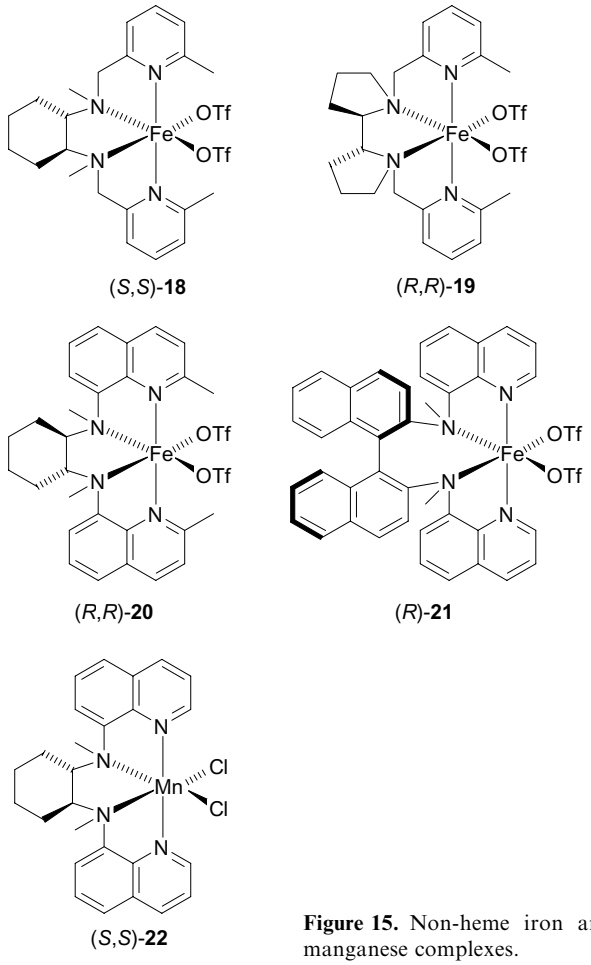


Figure 15. Non-heme iron and manganese complexes.

Recently, Che and co-workers [36] reported a more practically attractive catalyst system, based on non-heme iron complexes. The authors screened seven iron complexes in the AD with H_2O_2 as oxidant in different solvents. Under optimized catalytic conditions, catalyst **20** (see Fig. 15) was used at 3 mol% loadings in methanol with 3-fold excess of H_2O_2 relative to olefin. The enantioselectivity was excellent for (*E*)-alkenes (87% – 99% *ee*, Fig. 16). In addition, good

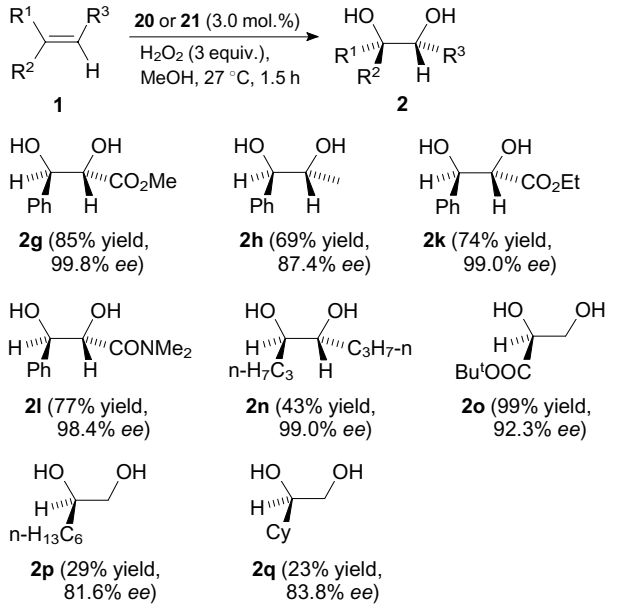
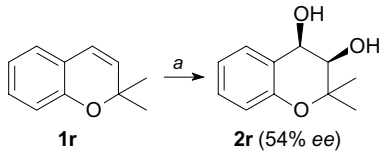


Figure 16. AD of olefins catalyzed by non-heme iron complexes **20** and **21**.[36]

cis-diol selectivity (over epoxide) was demonstrated. Terminal aliphatic alkenes showed somewhat inferior results under these conditions (82% – 92% *ee*, Figure 16). In the AD of (*Z*)-alkenes, complex **21** (see Fig. 15) demonstrated the best results, affording *cis*-diols with 83% *ee* for coumarin and 67% *ee* for indene. Using various techniques, including ^{18}O-labelling and ESI-MS, the authors obtained evidence for the direct involvement of iron(III)-hydroperoxo (L)$Fe^{III}-OOH$ active species in the enantioselective oxygen transfer to olefin. This picture is strikingly different from the widely accepted mechanism of oxidation by the oxo-iron complexes (L)$Fe^{V}=O(OH)$ in analogous non-heme systems.[37]

Another 1st row transition metal, manganese, was also engaged in the AD catalysis. Feringa and co-workers [38] studied a well-known manganese complex with *N*,*N*′,*N*″-trimethyl-1,4,7-triazacyclononane (tmtacn) $[Mn_2^{IV}(\mu\text{-}O)_3(tmtacn)_2]^{2+}$, using additives of optically pure chiral carboxylic acids. Screening 24 different additives revealed *N*-acetyl-D-phenylglycine as the best one, ensuring the AD of 2,2-dimethyl chromene with high conversion towards *cis*-diol with moderate enantioselectivity (54% *ee*, Fig. 17). The catalyst performed up to 250 TON.

Che and co-workers [39] developed a non-heme manganese(II) complex **22** (see Fig. 15) with chiral linear N_4-tetradentate ligand. It was tested in the AD of olefins with Oxone as oxidant; the most suitable substrates for this catalyst system appeared to be (*E*)-α,β-unsaturated esters



(*a*) $[Mn_2^{IV}(\mu\text{-}O)_3(tmtacn)_2]$ (0.4 mol.%), *N*-acetyl-D-Ph-Glycine (4 mol.%), H_2O_2 (1.7 equiv.), MeCN/H_2O (19 : 1), −20 °C, 5 h

Figure 17. AD of 2,2-dimethylchromene in the presence of manganese catalyst.[38]

(82% – 96% *ee*) and amides (72% – 89% *ee*, some examples are presented in Fig. 18), whilst terminal olefins, such as styrene and benzyl acrylate, demonstrated much lower enantioinduction (24% and 47% *ee*, respectively). As a rule, the catalyst performed 20 – 50 TON. Considerable amount of epoxide by-product (8% – 30%) was formed in most cases.

Tan with co-workers[40] reported the use of potassium permanganate as the stoichiometric oxidant in the catalytic AD of α-aryl acrylates. The general concept of the research was the development of chiral cation-controlled ion-paring catalysis, which was realized by applying chiral dicationic bisguanidinium **26** (Fig. 19). The catalytic reaction was conducted at −60 °C in *tert*-butyl methyl ether (TBME), with 20 wt.% aqueous KI solution as additive. 2 mol.% loadings of the bisguanidinium catalyst were enough to afford the diols **24** in 60% – 72% yields with high enantioselectivity (84% – 96% *ee*). Formation of by-products **25**, resulting from the C=C bond cleavage, was reported.

Hua with co-workers[41] synthesized bimetallic Pd/Au nanoclusters stabilized with chiral-substituted poly-*N*-vinylpyrrolidinones and probed it in the AD catalysis using molecular oxygen as oxidant in aqueous media. Besides the major reaction products *cis*-diols (67% – 90% yields), small amounts of *trans*-diols (3% – 11%) were isolated. The optical yields were generally high for both types of diols (93% – 99% *ee*). The proposed mechanism of the catalytic reaction invoked η^2-peroxido Pd^{II} active species, which

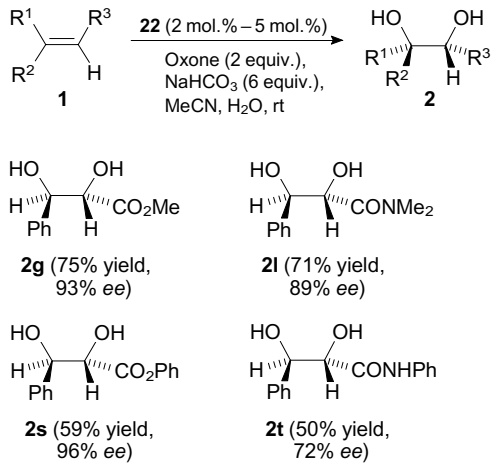
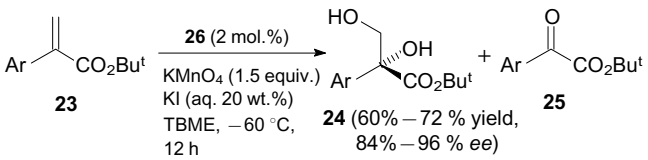


Figure 18. AD of olefins catalyzed by non-heme manganese complexes **22**.[39]



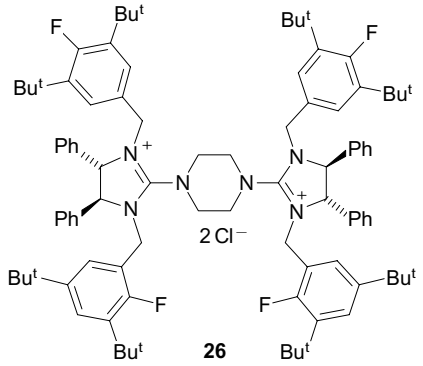


Figure 19. AD of olefins in the presence of dicationic bisguanidinium catalyst.[40]

underwent *syn*-addition to alkene, yielding metallo-1,2-dioxolane intermediate.

An alternative synthetic approach to *cis*-diols consists in diboration of an alkene, with subsequent oxidation with H_2O_2 or $NaBO_3$. Asymmetric catalytic version of this reaction was reported by Morken and co-workers.[42] They studied diboration of terminal alkenes with bis(pinacolato)-diboron (B_2pin_2) in the presence of *in situ* prepared platinum complex with ligand **27** as chiral catalyst (Fig. 20), followed by oxidation with H_2O_2 to obtain the 1,2-diols with 86% – 94% *ee*. The authors also explored rhodium-catalyzed asymmetric diboration – oxidation sequence using diboration agent bis(catecholato)diboron (B_2cat_2).[43] In the presence of (*S*)-Quinap ligand (**28**, Fig. 20), the reaction proceeded with excellent enantioinduction for (*E*)-alkenes (97% – 98% *ee*), albeit generally moderate optical yields were achieved for (*Z*)-alkenes and terminal alkenes.

Later, Toribatake and Nishiyama[44] reported the synthesis of optically active 1,2-diols through asymmetric diboration, catalyzed by rhodium complex **29** (Fig. 21). The diboration with B_2pin_2, followed by oxidation with $NaBO_3$, furnished 1,2-diols of styrenes and some other terminal alkenes with high to excellent enantioselectivities (88% – 99% *ee*). The rhodium catalyst showed relatively high activity, performing up to 100 TON. The limitation of the method was its inability to catalyze the reaction with 1,2-disubstituted alkenes.

Morken with co-workers[45] developed enantioselective diboration – oxidation reaction mediated by metal-free carbohydrate – derived catalyst **30** (Fig. 21). The reaction required 10 mol.% catalyst loadings with one equivalent of diboration agent bis(neopentylglycolato)diboron (B_2neo_2) to obtain 1,2-diols in 30% – 79% yields with enantioselectivities ranging from 22% up to 94% *ee*.

Biocatalytic approaches to asymmetric dihydroxylations have also been examined. Hauer and co-workers[46] introduced a single-point mutation into Rieske-type cumene dioxygenase to obtain novel whole-cell biocatalyst. Its performance in the AD of alkenes was probed and compared with those of a series of wild-type Rieske oxygenases,

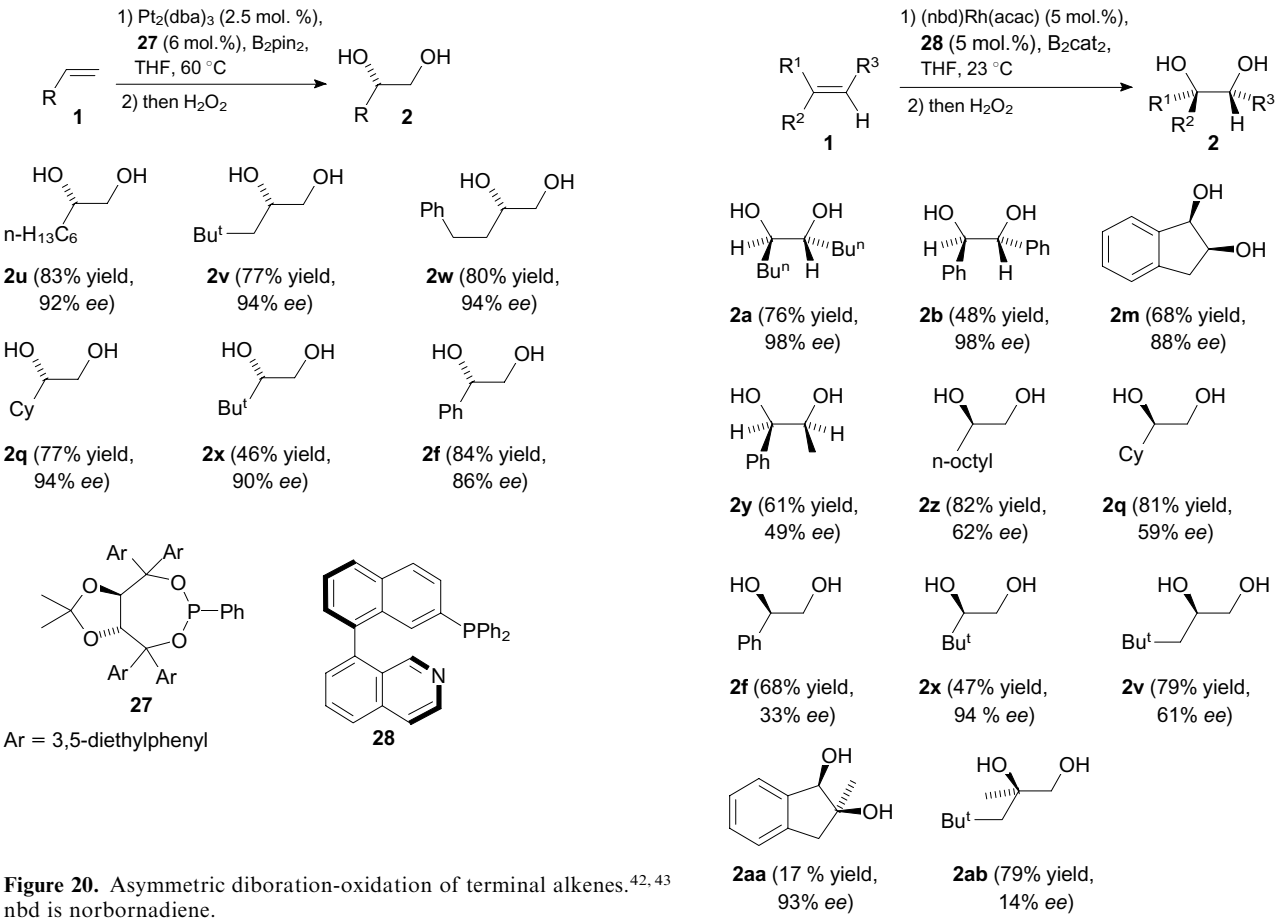


Figure 20. Asymmetric diboration-oxidation of terminal alkenes.[42, 43] nbd is norbornadiene.

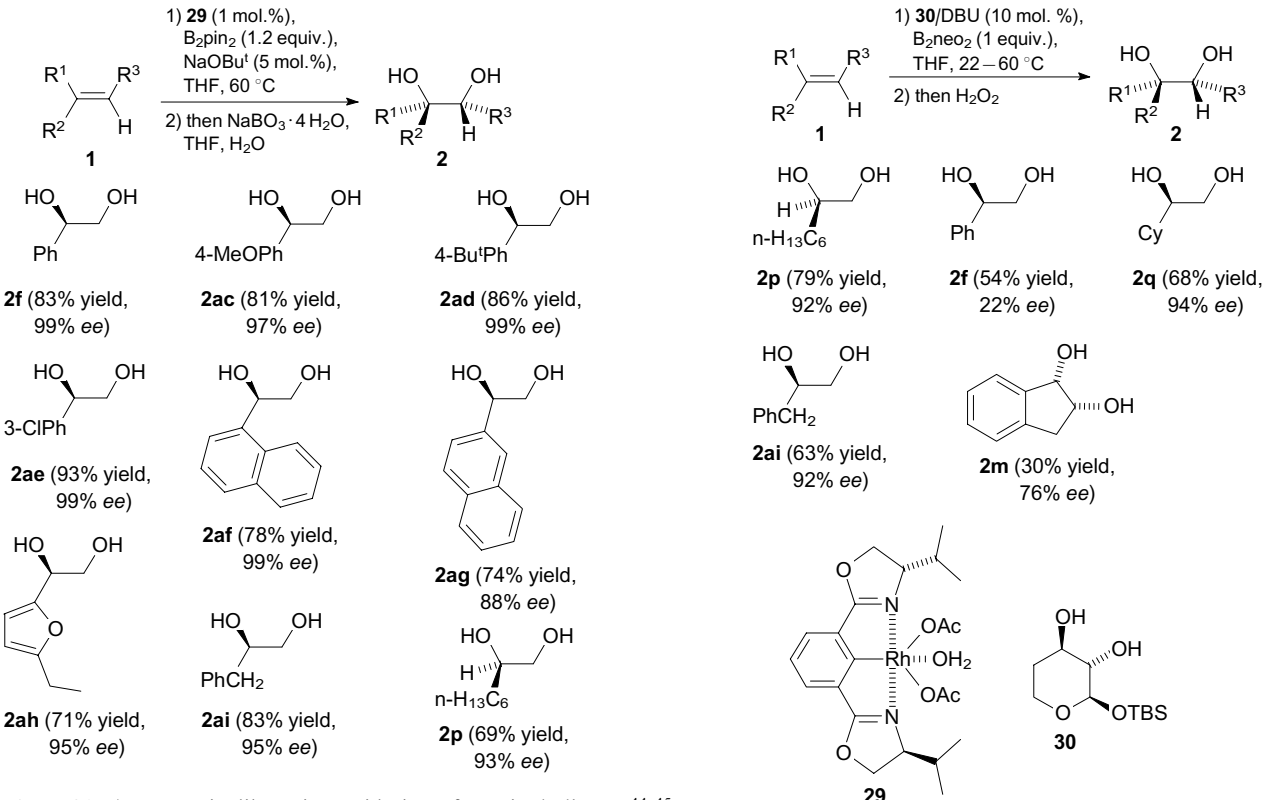


Figure 21. Asymmetric diboration-oxidation of terminal alkenes.[44, 45]

revealing improved activity, chemo- and enantioselectivity; styrene 1,2-diol was obtained in 89% yield and 95% *ee*.

Li and co-workers[47] presented tandem biocatalysts, containing enantioselective styrene monooxygenase and regioselective epoxide hydrolase. The catalyst system was capable of dihydroxylating substituted styrenes with high enantioinduction (up to 99% *ee*). In subsequent contribution, the authors extended the substrate scope of this approach to cyclic olefins.[48] They obtained *trans*-1,2-diols of cyclohexene and *N*-benzyloxycarbonyl-3-pyrroline with 84% and 93% *ee*, respectively. The first step (epoxidation) of the one-pot sequence could be executed either by enzymatic method or with *m*-CPBA as a stoichiometric oxidant. Later, Li and co-workers[49] developed an analogous method for the enantioselective *trans*-1,2-dihydroxylations *via* intracellular epoxidation and hydrolysis. Recombinant *E. coli* cells coexpressing styrene monooxygenase and several epoxide hydrolases were employed to achieve complementary enantiopreference for a series of styrenes, (*E*)- and (*Z*)-conjugated alkenes. With substrates of this type, the enantioselectivity was excellent (up to 99% *ee*). The possibility of preparative hydroxylations was demonstrated.

Jorgensen with co-workers[50] reported the catalytic asymmetric formal *trans*-1,2-dihydroxylation of α,β-unsaturated aldehydes. The system used organocatalyst **33** (Fig. 22) and H_2O_2 as oxidant (1.3 equiv.) to produce an intermediate epoxide. The one-pot procedure involved the NaOMe/MeOH selective ring opening of the epoxide as the second step. Various alkyl- and aryl-type substrates **31** were tested (15 examples) to furnish *trans*-2,3-dihydroxydimethyl acetals **32** in moderate yields (37% – 77%) and high enantioselectivities (90% – 99% *ee*).

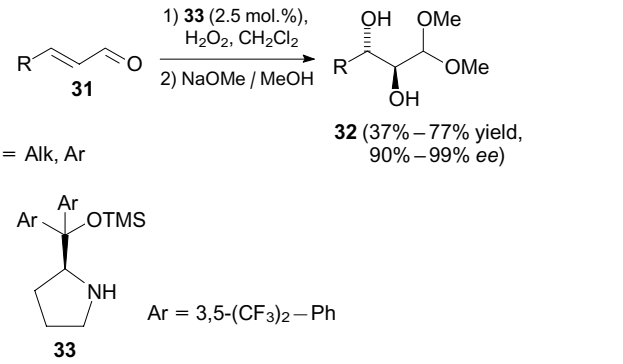


Figure 22. Asymmetric formal *trans*-1,2-dihydroxylation of α,β-unsaturated aldehydes.[50]

4. Conclusion

In the last decade, the catalytic asymmetric dihydroxylation of olefins continued receiving significant research interest. The traditional osmium-based catalysts have continued dominating the field, although the research focus has noticeably shifted towards more environmentally benign protocols. The decrease of highly toxic osmium contamination in the diol products has been targeted by several methods, including: (1) conducting the reaction in alternative reaction media, (2) development of polymer-incarcerated catalysts, (3) synthesis of osmium-containing nanoparticles, (4) immobilization of catalysts on solid supports, (5) creating osmium-containing artificial metalloenzymes. The novel catalysts systems often outperform the traditional Sharpless AD systems in terms of activity and enantioselectivity, ensuring low levels of osmium leaching and high recyclability at the same time.

In parallel, non-osmium catalyst systems have been developed, as part of more environmentally benign synthetic approaches to chiral 1,2-diols. In this regard, non-heme iron and manganese complexes have demonstrated good synthetic promise, exhibiting high enantioselectivities, generally comparable with those of benchmark osmium-based AD systems. Alternative methods of synthesis of optically active 1,2-diols have also been developed, including (1) noble metal-catalyzed asymmetric diboration of alkenes with subsequent oxidation, (2) ion-paring organocatalysis, and (3) biocatalytic epoxidation – epoxide ring opening sequence.

The above achievements bring the asymmetric dihydroxylation catalysis much closer to practical applications than ever before. In this respect, the authors would envision important mainframe developments in the near future.

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