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Developing asymmetric variants for enantioselective oxidations: A review

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Abstract
Asymmetric oxidation reactions are pivotal in modern organic chemistry, facilitating the synthesis of enantiomerically enriched molecules with significant synthetic and industrial relevance. This review encapsulates advancements in asymmetric oxidation methodologies, emphasizing catalytic systems, ligand design strategies, notable breakthroughs recently, and mechanistic insights. The focus is on metal-catalyzed, organocatalytic, and emerging electrochemical techniques, illustrated through examples such as allylic oxidations, sulfoxidations, epoxidations, and innovative C-H oxidation strategies. It also addresses the challenges and future prospects aimed at enhancing stereoselectivity and substrate versatility in asymmetric oxidations. The significance of enantioselective oxidation reactions is underscored as they are essential for introducing oxygen-containing functional groups in organic molecules. The review discusses effective strategies for achieving enantioselectivity through various methods, including metal-catalyzed, organocatalytic, and biocatalytic approaches that provide high enantiocontrol. Transformations highlighted include asymmetric epoxidation, dihydroxylation, Baeyer-Villiger oxidation, sulfoxidation, and allylic oxidation, focusing on catalyst design, reaction mechanisms, and practical synthetic applications. Additionally, emerging trends in photoredox catalysis, enzymatic oxidation, and electrochemical methods reflect the dynamic progress in asymmetric oxidation, showcasing its crucial role in the stereoselective synthesis of complex molecules.

Keywords: Asymmetric oxidation, methodologies, catalytic systems, ligand design, stereoselective synthesis, complex molecules

1. Introduction
Asymmetric oxidations introduce stereogenic centers into achiral or prochiral substrates using chiral catalysts, with predictably high enantioselectivity. These transformations have broad applications across pharmaceuticals, agrochemicals, natural product synthesis, and materials science. Historically, methods like Sharpless epoxidation (a landmark asymmetric oxidation reaction) laid the foundation by enabling reliable enantioselective epoxide formation using chiral titanium-diethyl tartrate catalysts with tert-butyl hydroperoxide as oxidant. Such pioneering work demonstrated the power of chiral catalysts to control stereochemistry in oxidation reactions a principle extended to multiple contemporary methodologies. A landmark reaction, Sharpless epoxidation, demonstrates this principle by using chiral titanium-diethyl tartrate catalysts with tert-butyl hydroperoxide to form 2,3-epoxyalcohols from allylic alcohols shown in figure 1. This established the effectiveness of chiral catalysts in controlling stereochemistry in oxidation reactions [1-3].

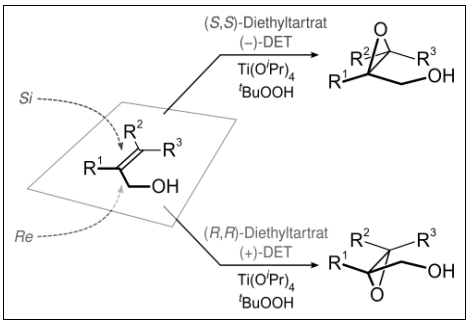

Fig 1: Sharpless asymmetric epoxidation of allylic alcohols to enantioenriched 2,3-epoxyalcohols using chiral titanium catalysts.

2. Catalytic Systems in Asymmetric Oxidations

2.1 Transition-Metal Catalysis

Transition metals such as copper, iron, manganese, molybdenum, and vanadium, combined with chiral ligands, have been central to asymmetric oxidations. Chiral transition-metal complexes activate oxygen donors (e.g., H_2O_2, peracids) and control substrate approach to generate enantiomerically enriched products.

Chiral salen and related ligands: Chiral salen complexes, particularly those of Mn and Co, have emerged as essential tools in asymmetric catalysis, especially for sulfoxidations and oxidative kinetic resolution, owing to their high enantiocontrol shown in figure 2. These complexes utilize tetradentate coordination to precisely orient substrates during oxidation, enhancing reaction efficiency.

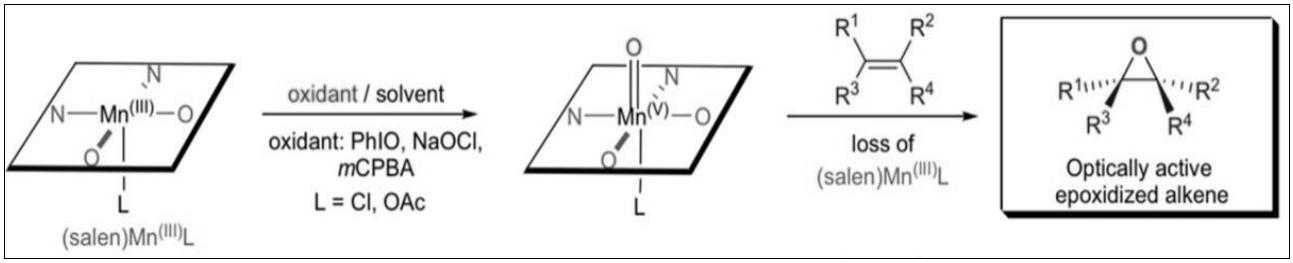

Fig 2: Chiral Mn- and Co-salen complexes enabling highly enantioselective sulfoxidation and oxidative kinetic resolution.

Over the past two decades, significant advancements have been made in the field, leading to diverse synthetic, structural, and catalytic developments, including Ti-, Co-, and Mn-salen systems. Innovations in this area have emphasized sustainability and recyclability, contributing to more environmentally friendly catalysis. Furthermore, ongoing research is exploring new frontiers, such as machine learning, redox tuning, and deeper mechanistic insights, which promise to expand the utility and efficiency of chiral salen ligands in asymmetric catalysis [4].

Vanadium catalysis: Chiral vanadium complexes have garnered significant attention for their role in enantioselective oxidations, including epoxidation and sulfoxide formation, showcasing the versatility of vanadium in asymmetric oxidation chemistry. Asymmetric vanadium catalysis has seen resurgence in recent years due to its broad applicability in organic transformations and its lesser moisture sensitivity compared to other metals. Historically underutilized, vanadium's significance was amplified following its introduction in asymmetric epoxidation by Sharpless as shown in figure 3.

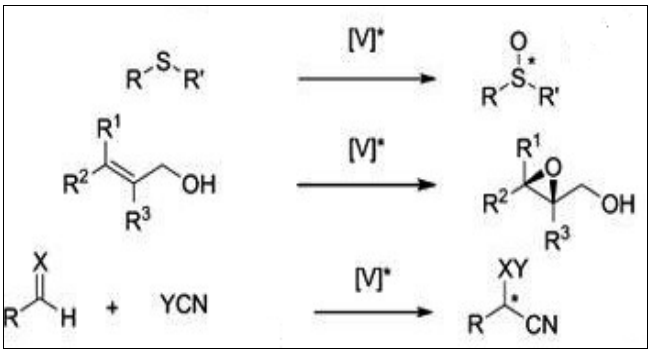

Fig 3: Chiral vanadium complexes in asymmetric epoxidation and sulfoxide formation reactions.

Recent advancements in this field include asymmetric oxidative couplings, Sulfoxidations, and domino reactions, primarily utilizing mononuclear and bifunctional dinuclear catalysts based on Schiff base ligands [5].

Novel ligand design: Modern rational ligand designs increasingly exploit ligand-substrate noncovalent interactions to enhance stereo control and catalytic efficiency across asymmetric transformations, including oxidation reactions. Enantioselective transition metal catalysis is a crucial area in chemistry, pivotal for both academia and the pharmaceutical industry. This field relies on noncovalent interactions such as hydrogen bonding, ion pairing, and π-system engagements, which facilitate asymmetric synthesis and stereo chemical control in transition metal reactions. Recent breakthroughs have led to new ligands designed to harness these noncovalent interactions, becoming essential for stereo controlled synthesis and advancing ligand engineering [6]. The general model of ligand-substrate noncovalent interactions are engaged enantioselective transition metal catalysis is shown in Figure 4.

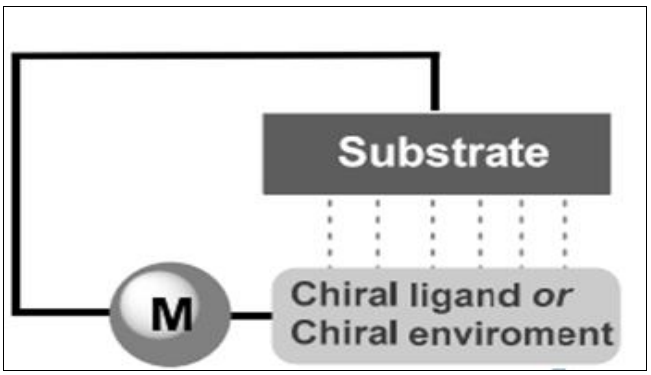

Fig 4: General model of ligand-substrate noncovalent interactions governing enantioselective transition metal catalysis.

2.2 Organocatalytic Oxidations

Organocatalysis avoids the use of metal catalysts, instead employing chiral small molecules to induce enantioselectivity in oxidations. Among the advancements in this field, chiral iodine catalysts (I(I/III) systems) have surfaced as efficient mediators for oxidative transformations, enabling the stereoselective formation of C-O and C-C bonds under mild conditions [7]. These developments extend to various stereoselective bonds, including C-N and C-X, showcasing the versatility of chiral iodine catalysis in asymmetric synthesis shown in Figure 5.

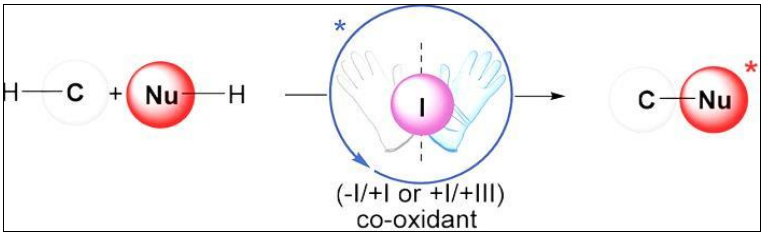

Fig 5: Chiral iodine(I/III) catalysts enabling stereoselective C-O, C-C, C-N, and C-X bond formations.

Iodine compounds present significant advantages over traditional metal-catalyzed methods, such as low toxicity and straightforward handling. The use of chiral aryliodine or ammonium iodide in conjunction with oxidants has facilitated high enantioselectivity in numerous oxidative transformations. This includes processes like α-functionalization of carbonyl compounds, dearomatization of phenol derivatives, and difunctionalization of alkenes, underscoring the pivotal role of iodine catalysis in the realm of asymmetric organocatalysis [8].

Recent breakthroughs in organocatalytic strategies have demonstrated the power of organocatalysis in asymmetric oxidation, particularly in the construction of axially chiral sulfoxides, which are critical compounds in medicinal chemistry and organic synthesis [9] shown in Figure 6.

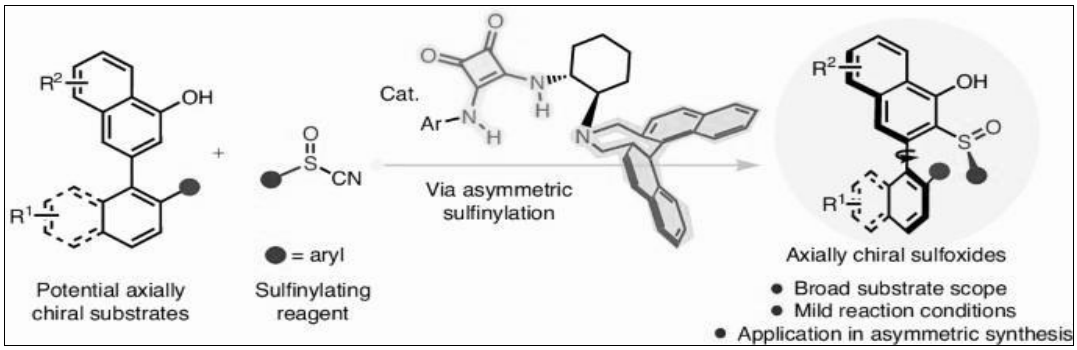

Fig 6: Organocatalytic asymmetric oxidation enabling synthesis of axially chiral sulfoxides.

A streamlined synthetic strategy has been developed that utilizes specially designed reagents and catalytic systems, enabling the establishment of both chiral sulfoxides and axial chirality in a single step. This method has been successfully applied to diverse substrates, showcasing its versatility. Additionally, mechanistic experiments were conducted to explore the sulfinylation reaction, highlighting the potential for creating chiral sulfoxides with unique functionalities for future applications, thus advancing the field beyond traditional metal catalysis [10].

2.3 Electrochemical and Photoredox Approaches

Electrochemical methods have gained significant interest due to their sustainability and green credentials, particularly in the realm of organic synthesis. Enantioselective electrochemical oxidations, though still in the early stages of development, show promise for efficient enantioinduction through controlled redox potentials and unique mechanistic pathways [11]. Recent contributions have highlighted various approaches to stereoselective electrochemical synthesis, focusing on the challenges associated with developing general strategies for enantiocontrol [12]. This review categorizes the advancements in asymmetric electrochemical catalysis into three main types: metal-based catalysis, organocatalysis, and biocatalysis, showcasing notable strides in each area. Additionally, photoredox catalysis presents an exciting avenue for oxidative processes under light activation, with potential enantioselective control enabled by engineered chiral photosensitizers or dual catalytic systems. Together, these developments underline the growing importance of electrochemical techniques in advancing enantioselective processes while addressing sustainability in chemical synthesis [13] shown in Figure 7.

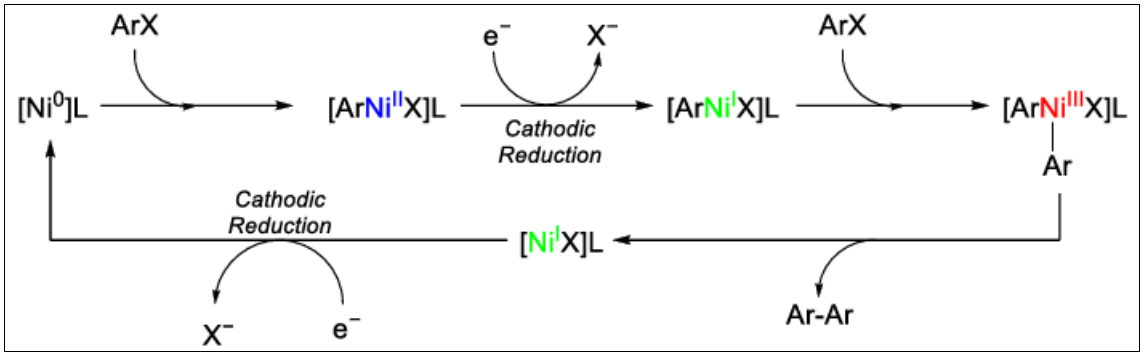

Fig 7: Overview of asymmetric electrochemical catalysis: metal-based, organocatalytic, biocatalytic, and photoredox approaches.

3. Major Classes of Asymmetric Oxidation Reactions

3.1 Allylic and Propargylic Oxidations

Enantioselective variants of classical allylic oxidations, such as the Kharasch-Sosnovsky reaction, have been developed using chiral copper catalysts to install chiral acyloxyl motifs in allylic/propargylic positions [14]. This advancement not only enhances regio- and stereo control across a broader substrate scope but also marks the evolution of copper-catalyzed enantioselective allylic/propargylic acyloxylation as a versatile strategy for the stereo controlled synthesis of chiral esters [15] shown in Figure 8. A recent review comprehensively summarizes these developments, highlighting asymmetric variants of the Kharasch-Sosnovsky reaction across three primary substrate categories with particular emphasis on substrate scope and mechanistic insights [16].

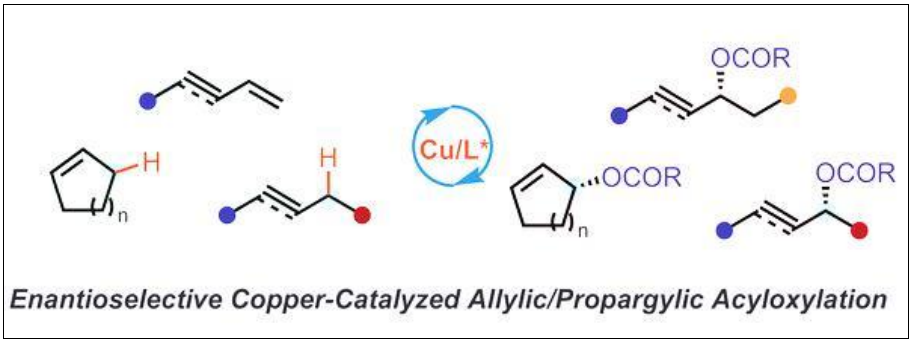

Fig 8: Copper-catalyzed enantioselective allylic and propargylic acyloxylation for chiral ester synthesis.

3.2 Sulfoxidation and Sulfoxide Formation

Oxidative transformations of sulfides to sulfoxides and the formation of N-oxides from amines are both classic asymmetric oxidations that hold significant value in fields such as natural product chemistry and drug design. Sulfoxides are particularly notable for their roles as chiral auxiliaries and bioactive motifs, while N-oxides have emerged as important compounds in medicinal chemistry [17]. Recent advancements utilizing metal complexes and organocatalysts have demonstrated high enantiomeric excess in these reactions, which have also extended to the oxidation of tertiary amine N-oxides [18]. This study introduces a highly enantioselective N-oxidation method for both cyclic and acyclic amines, employing a chiral bisguanidinium ion-pair catalyst in conjunction with an achiral oxodiperoxomolybdosulfate anion as shown in figure 9.

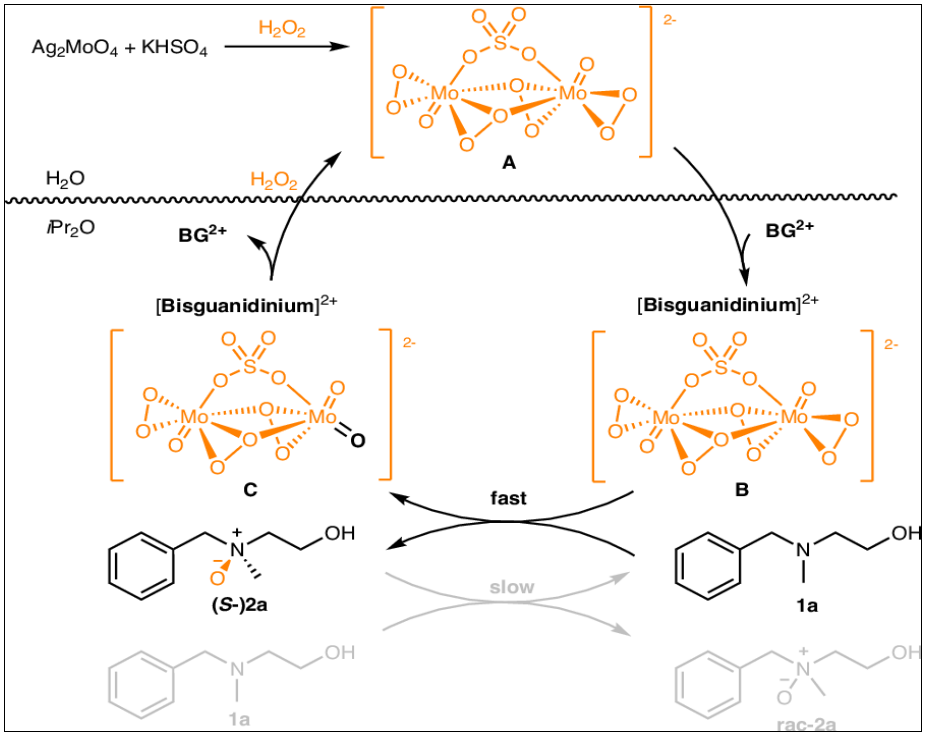

Fig 9: Chiral bisguanidinium ion-pair catalyzed enantioselective N-oxidation of cyclic and acyclic amines.

The bisguanidinium structure, which has been modified with silyl groups, is characterized through X-ray crystallography [19]. The research emphasizes the critical influence of side chain configurations on the sizes of chiral pockets, thereby facilitating the oxidation of various tertiary amines with notable enantioselectivity. Detailed mechanistic studies further elucidate the system's effectiveness, showcasing its capability to achieve dynamic kinetic resolution efficiently. Together, these advancements underscore the ongoing significance of asymmetric oxidations in enhancing the synthesis of valuable chiral compounds.

3.3 Epoxidation and Oxygen-Atom Transfer

Asymmetric epoxidations remain a cornerstone of oxidation chemistry, with classic systems such as the Sharpless epoxidation paving the way for newer organocatalytic and metal-catalyzed protocols capable of transforming diverse olefins with high enantioselectivity and improved functional group tolerance of divinyl carbinol [20] as shown in figure 10.

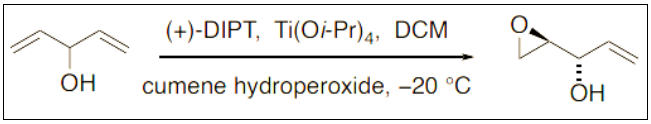

Fig 10: Asymmetric epoxidation of divinyl carbinol via classical and modern catalytic systems.

In parallel, epoxidation reactions based on oxygen atom transfer have advanced organic synthesis by enabling selective oxidation using mild oxygen donors like peracids or high-valent metal-oxo species, minimizing over-oxidation and preserving sensitive functionalities such as alcohols and aldehydes. Metal-catalyzed oxygen atom transfer systems employing titanium, manganese, or ruthenium complexes offer fine control over chemo-, regio-, and stereoselectivity through ligand design, making these refined epoxidation strategies highly valuable for the synthesis of complex molecules in pharmaceutical and natural product chemistry [21].

3.4 C-H Oxidation Strategies

Direct enantioselective C-H oxidation represents an ambitious and highly valuable target because of its potential for late-stage functionalization. In particular, enantioselective C(sp^3)-H bond oxidation offers a powerful strategy for installing functionality in C(sp^3)-H-rich molecules [22]. Recent advances in catalyst frameworks and mechanistic understanding are enabling site- and stereoselective oxidation of otherwise inert C-H bonds, thereby expanding the scope of asymmetric oxidation chemistry.

Notably, site- and enantioselective oxidation of strong C-H bonds in monosubstituted cyclohexanes using hydrogen peroxide, catalyzed by aminopyridine manganese complexes in combination with alkanoic acids, has been recently described as shown in figure 11.

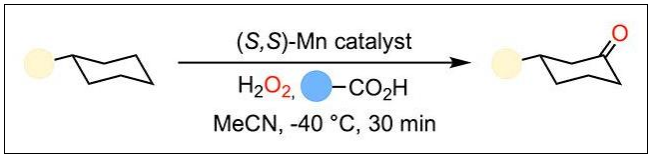

Fig 11: Site- and enantioselective C-H oxidation of monosubstituted cyclohexanes using manganese catalysts.

Despite this progress, mechanistic uncertainties and non-intuitive enantioselectivity trends continue to limit the full synthetic potential of this transformation. Herein, we apply predictive statistical analysis to identify mechanistically informative correlations that provide deeper reaction insight and guide the future development and optimization of enantioselective C-H oxidation reactions [23].

4. Mechanistic Considerations and Ligand Design

Efficient asymmetric oxidation reactions depend on catalyst design that dictates selective oxygen insertion into prochiral substrates. A mechanism often involves the formation of high-valent metal-oxo intermediates capable of transferring oxygen in a stereo controlled fashion, Strategic placement of chiral ligands to enforce asymmetric induction through steric and electronic steering and Emerging use of noncovalent interactions between ligand environments and substrates to enhance enantioselection [24] shown in figure 12.

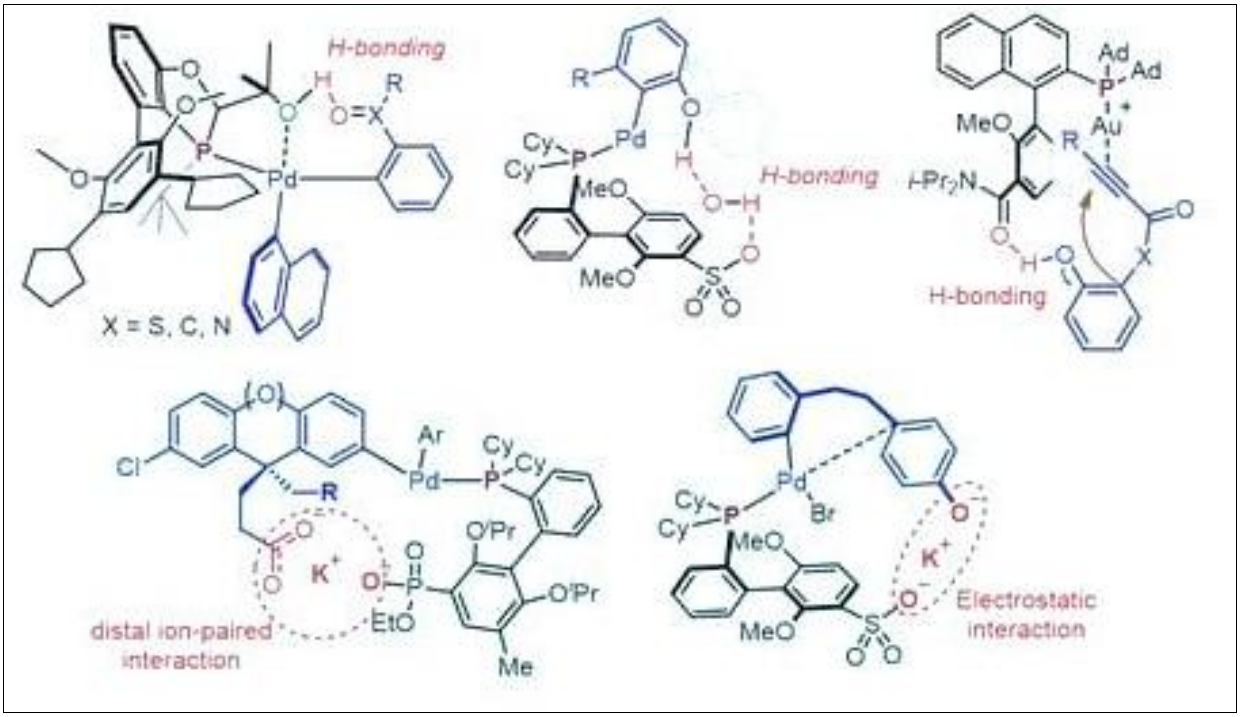

Fig 12: General mechanism of asymmetric oxidation via chiral metal-oxo intermediates and noncovalent interactions.

Understanding reaction mechanisms remains essential to rational catalyst development, enabling the translation of empirical observations into predictable design principles.

Enantioselective C(sp3)-H bond oxidation is a notable method for adding functionality to C(sp3)-H rich molecules [25]. Recent studies have shown site- and enantioselective oxidation of strong C-H bonds in cyclohexanes using aminopyridine manganese catalysts and hydrogen peroxide. However, mechanistic uncertainties and unclear enantioselectivity trends limit the potential of this reaction. This study utilizes predictive statistical analysis to uncover correlations that enhance understanding of the reaction and inform future enantioselective C-H oxidation developments [26].

5. Recent Developments

Recent literature highlights continued evolution in asymmetric oxidations as follows

Chiral ligand scaffolds: Chiral ligand scaffolds, especially next-generation salen derivatives and bisguanidinium frameworks, have significantly improved oxidation reactions. Novel salen ligands enhance metal-ligand cooperation and improve enantioselectivity and catalyst stability. Bisguanidinium frameworks, through strong hydrogen bonding and ion-pairing, offer precise organization of oxidants and substrates, leading to high asymmetric induction in various oxidations.

Copper-mediated allylic/propargylic oxidations: These are effective methods for selectively functionalizing C-H bonds adjacent to alkenes and alkynes. Recent advancements have broadened the applicability of these techniques, allowing for the oxidation of various substrates, including complex heterocycles and bioactive molecules, under mild conditions with enhanced regio- and chemoselectivity compared to traditional oxidants. Mechanistic studies have revealed copper's role as a redox mediator and its involvement in processes such as hydrogen atom abstraction and the formation of copper-oxo or copper-radical intermediates. These findings aid in the development of more efficient and sustainable C-H oxidation strategies.

Organocatalytic oxidative methods: These methods have evolved, allowing metal-free organic catalysts to effectively promote oxidation reactions with high stereocontrol. This advancement facilitates enantioselective bond formations and functionalizations like asymmetric α-oxidations and C-C bond constructions, previously reliant on transition-metal catalysts. Consequently, organocatalysis provides greener, sustainable alternatives, enhancing asymmetric synthesis in complex molecule construction.

Enantioselective C-H oxidation: The research reveals promising advancements in late-stage functionalization with controlled chirality. New catalyst designs, including chiral metal complexes and organocatalysts, allow for selective oxidation of C-H bonds, overcoming traditional limitations. This enables the modification of complex molecules, such as drug candidates, to install stereocenters and differentiate between enantiotopic bonds, thus providing precise control over their 3D structure.

6. Challenges and Future Directions

Despite progress, challenges persist are generalizing asymmetric C-H oxidations across diverse substrates with predictable selectivity. Expanding green methodologies are electrochemical and photoredox systems and to match efficiency of established metal-catalyzed protocols. Enhanced mechanistic understanding to drive rational design of next-generation chiral catalysts. Future research will likely integrate computational design, advanced ligand frameworks, and sustainable activation methods to unlock new asymmetric oxidation pathways.

7. Conclusion

Asymmetric oxidations have transformed synthetic strategies for accessing enantiopure compounds. From classical metal-catalyzed systems to contemporary organocatalytic and electrochemical methods, the field continues to advance toward broader substrate scopes, higher enantioselectivities, and more sustainable processes. Continued innovation in catalyst design and mechanistic elucidation will propel asymmetric oxidations into increasingly sophisticated and practical applications.

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