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The Jacobsen catalyst in asymmetric synthesis: Structure, mechanism, and applications

El catalizador de Jacobsen en síntesis asimétrica: estructura, mecanismo y aplicaciones

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Abstract

The Jacobsen catalyst has become a benchmark in asymmetric synthesis over the past three decades, particularly in the enantioselective epoxidation of unfunctionalized alkenes. This work provides a critical overview of the structural features, mechanistic insights, and synthetic applications of the (R,R)-Jacobsen catalyst and its analogues. Particular emphasis is placed on its ability to achieve high enantiomeric excess, its commercial availability, and its broad substrate scope. Recent advancements, including metal substitution, heterogeneous immobilization, and the integration of computational approaches, have further expanded the catalyst's utility and improved its sustainability profile. Representative examples from the total synthesis of natural products and pharmacologically active compounds underscore the continued relevance of Jacobsen-type systems in contemporary chemistry. Overall, the catalyst stands as a paradigmatic model of selectivity, efficiency, and adaptability in modern stereoselective catalysis, in accordance with the principles of green chemistry.

Keywords: Catalysis, Jacobsen catalyst, manganese, olefins, epoxidation, asymmetric synthesis.

Resumen

El catalizador de Jacobsen se ha convertido en un referente en la síntesis asimétrica durante las últimas tres décadas, en particular en la epoxidación enantioselectiva de alquenos no funcionalizados. Este trabajo ofrece una revisión crítica de las características estructurales, los aspectos mecanísticos y las aplicaciones sintéticas del catalizador (R,R)-Jacobsen y sus análogos. Se hace especial énfasis en su capacidad para lograr altos excesos enantioméricos, su disponibilidad comercial y su amplio espectro de sustratos. Los avances recientes, como la sustitución metálica, la inmovilización heterogénea y la integración de enfoques computacionales, han ampliado aún más la utilidad del catalizador y mejorado su perfil de sostenibilidad. Ejemplos representativos de síntesis total de productos naturales y compuestos con actividad farmacológica destacan la vigencia de los sistemas tipo Jacobsen en la química contemporánea. En conjunto, el catalizador se erige como un modelo paradigmático de selectividad, eficiencia y adaptabilidad en la catálisis estereoselectiva moderna, de acuerdo con los principios de la química verde.

***Palabras clave**: Catálisis, catalizador de Jacobsen, manganeso, olefinas, epoxidación, síntesis asimétrica.*

1 Introduction

A significant advance in modern chemistry has been the development of enantioselective (or asymmetric) synthesis (Brown et al., 1989). This progress is particularly relevant considering that most naturally occurring compounds are chiral, possessing one or more stereogenic carbon centres and exhibiting optical activity. The impact of this field has been so profound that it was acknowledged with the 2001 Nobel Prize in Chemistry, awarded to K. Barry Sharpless, William S. Knowles, and Ryoji Noyori for their pioneering contributions to asymmetric catalysis (Periasamy, 2002; Noyori, 2002). Two decades later, the 2021 Nobel Prize in Chemistry was awarded to Benjamin List and David W. C. MacMillan, whose contributions to chiral organocatalysis further expanded the scope of asymmetric synthesis (Hargittai, 2022).

Asymmetric synthesis can be defined as the field of chemistry focused on the development of molecules con-

taining chiral centres, employing strategies that enable stereoselective control to generate specific enantiomers or diastereomers. This process typically involves the selective formation of one or more stereogenic centres, most commonly achieved through the use of asymmetric catalysts (Behera et al., 2023), chiral reagents (Wang et al., 2018), or kinetic resolution techniques (Imayoshi et al., 2021). A central objective is to maximize the enantiomeric excess (e.e.) of the resulting products, a key parameter in the design and synthesis of bioactive molecules and pharmaceutical agents.

In this context, one of the most successful catalysts in asymmetric synthesis emerged: the Jacobsen catalyst, named after the American chemist Eric N. Jacobsen, whose pioneering contributions to the asymmetric epoxidation of alkenes are widely recognized. In this system, the active centre consists of a Mn(III) ion coordinated by a *salen*-type ligand that provides the chiral environment required for enantioselectivity (Contreras et al., 2018). The Jacobsen catalyst, formally designated as *N,N'*-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride (see Fig. 1), was first reported in 1991 as an effective enantioselective system for the epoxidation of a representative range of unfunctionalized alkenes (Jacobsen et al., 1991). This seminal publication was preceded by earlier studies on related analogues (Zhang et al., 1990; Zhang et al., 1991), conducted as part of a broader research program at the Roger Adams Laboratory, Department of Chemistry, University of Illinois (USA).

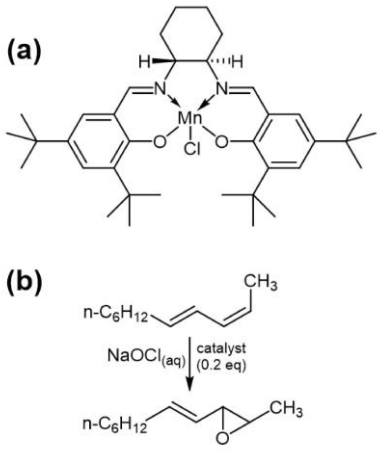

Fig. 1. (a) Structure of the (R,R)-Jacobsen catalyst. (b) Example of a reaction involving a pharmaceutically relevant substrate catalyzed by Jacobsen's catalyst (Chang et al., 1993).

Since the publication of Jacobsen's initial results (Lee et al., 1991; Deng et al., 1992; Palucki et al., 1992; Jacobsen et al., 1994), the catalyst rapidly gained widespread recognition as a powerful tool in asymmetric synthesis (Chang et al., 1994). In recognition of its remarkable efficiency in producing highly enantiomerically enriched epoxides from unfunctionalized olefins, the (R,R)-Jacobsen catalyst was designated "Reagent of the Year" by *Fluka* in 1994 (Hanson, 2001). Furthermore, Eric N. Jacobsen received two prestigious honors for his pioneering contributions: the 2016 Arthur C. Cope Award (Wang, 2016), "for his contributions, both fundamental and practical, to the fields of asymmetric catalysis and organic synthesis," and the 2024 Willard Gibbs Medal (Cottle, 2024).

In this regard, it is important to emphasize the strategic relevance of transition metal catalysis (Contreras, 2021a), both in homogeneous and heterogeneous phases, in advancing research and development, particularly due to its broad applicability in organic synthesis (Wang, 2015). Along these lines, a wide range of homogeneous catalysts have been developed, many of which, like the Jacobsen catalyst, have become indispensable tools for the chemical transformation of structurally diverse substrates. Notable examples that have received considerable recognition in recent decades include Wilkinson's catalyst (Contreras et al., 2017a), Vaska's complex (Contreras et al., 2020a), Grubbs' catalyst (Contreras et al., 2020b), Crabtree's catalyst (Contreras et al., 2020c), Stryker's reagent (Contreras, 2021b), Schwartz's reagent (Contreras et al., 2021c), and the Lindlar catalyst (Contreras, 2023), among others.

Given the significance of asymmetric epoxidation reactions and in commemoration of nearly thirty-five years since Eric N. Jacobsen's seminal publication introducing the catalytic activity of his Mn(III)-based system, this article presents a concise review of the Jacobsen catalyst and its most relevant applications, highlighting the fundamental role of catalysis within the framework of the twelve principles of green chemistry (Contreras, 2017b).

2 Methodology

The methodology employed consisted of a systematic review of the specialized scientific literature aimed at examining the Jacobsen catalyst in the context of its relevance to asymmetric synthesis. For this purpose, the following databases were consulted: ACS Publications, ScienceDirect, Scopus, Google Scholar, and the digital catalogs of Strem Chemicals and Sigma-Aldrich (Merck KGaA®). The search strategy utilized the keywords "Jacobsen catalyst," "epoxidation," and "catalysis," in combination with terms such as "manganese catalyst," "asymmetric catalysis," and "enantioselective epoxidation." The review covered the period from 1991 to 2024, taking as its starting point the seminal article by Eric N. Jacobsen published in the *Journal of the American Chemical Society* in 1991 (Jacobsen et al., 1991). Additionally, a keyword co-occurrence analysis was performed using the VOSviewer software (version 1.6.20) (Van Eck et al., 2010) based on a Scopus® database search with "Jacobsen catalyst" as the primary keyword. The dataset was filtered by relevance, and the records were clustered using the program's algorithm. The resulting bibliometric map revealed color-coded thematic clusters, highlighting the main research areas associated with Jacobsen-type catalysts.

3 Results and Discussion

3.1 Synthesis of (R,R)-Jacobsen Catalyst

The synthetic route to the (R,R)-Jacobsen catalyst, as originally described by Eric N. Jacobsen, involves at least four steps (Larrow et al., 2003), beginning with the preparation of the ligand (1R,2R)-(–)-1,2-cyclohexane-*N*,*N'*-bis(3,5-di-tert-butylsalicylidene), which is obtained through the condensation of (R,R)-1,2-diaminocyclohexane mono-(+)-tartrate with 3,5-di-tert-butylsalicylaldehyde. Both the (R,R)-Jacobsen ligand (CAS 135616-40-9; Sigma-Aldrich: 40,441-1; Strem Chemicals: 07-0316) and the catalyst itself (CAS 138124-32-0; Sigma-Aldrich: 40,444-6; Strem Chemicals: 25-0300) are now commercially available. For illustrative purposes, the final two steps of the synthesis were selected and are shown in Fig. 2.

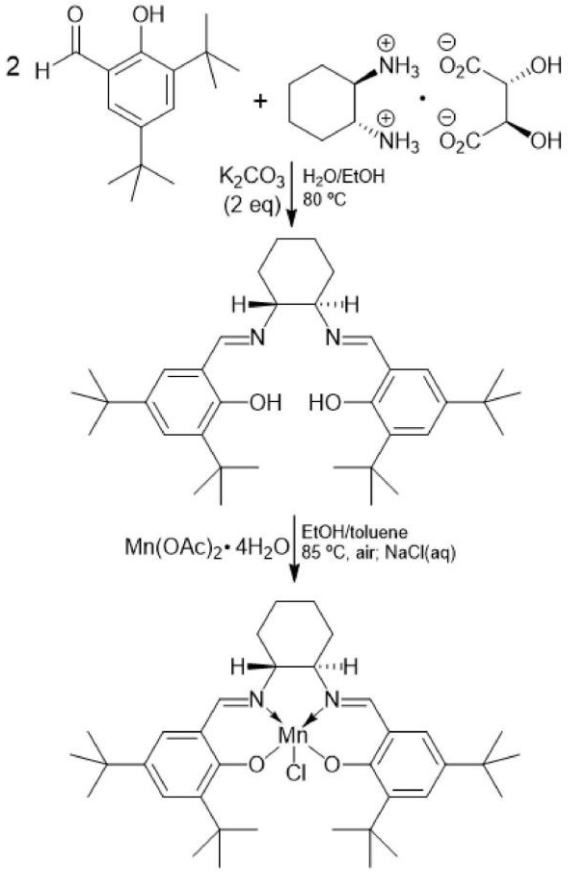

Fig. 2. Synthesis of Jacobsen's catalyst, adapted from the Organic Syntheses database (Larrow et al., 2003).

3.2 (R,R)-Jacobsen Catalyst structure and molecular architecture

Structurally, the Jacobsen catalyst exemplifies the application of molecular architecture in the design of catalysts capable of directing chemical transformations and, in this case, facilitating enantioselective reactions. The proposed mechanistic model considers the presence of a *salen*-type ligand containing highly sterically demanding groups, such as tert-butyl substituents, which promote a lateral or "side-on" approach for the stereoselective transfer of oxygen to the substrate (Fig. 3a). This model was originally introduced in the context of asymmetric epoxidation catalyzed by metal–porphyrin complexes (Groves et al., 1983). According to this interpretation, the alkene is sterically constrained by the bulky ligand environment, forcing a lateral approach to the metal–oxo intermediate, an interaction that accounts for the high levels of enantioselectivity observed. Although the exact sequence of bond formation remains a matter of debate, there is clear consensus that steric effects play a critical role in the reaction. This mechanistic model has become a widely accepted paradigm for the epoxidation of olefins using tetradentate metal complexes, particularly those featuring *salen*-based ligands. Moreover, it has been proposed that the same *salen*-type ligands responsible for enantioselectivity in epoxidation also create a chiral environment favourable for the nucleophilic ring-opening of epoxides through Lewis acid–base activation (Jacobsen, 2000) (Fig. 3b).

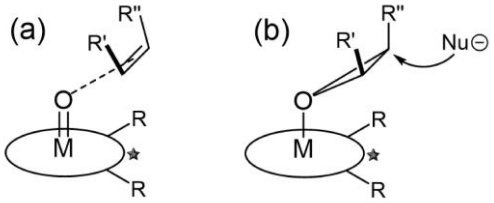

Fig. 3. Fig. 3. (a) Schematic representation of the side-on approach model for the epoxidation of alkenes by chiral metal–*salen* complexes. (b) Possible mode of Lewis acid–base activation of epoxides.

3.3 El (R,R)-Jacobsen Catalyst en la literatura especializada

The number of publications related to the Jacobsen catalyst has shown an upward trend over time, as illustrated in Fig. 5. The graph, based on data from Google Scholar, ScienceDirect, ACS Publications, and Scopus, reflects a steady increase in research activity beginning in 1991 and peaking between 2005 and 2015. This surge in publications coincides with the widespread recognition of the Jacobsen catalyst in the field of enantioselective epoxidation. Google Scholar reports the highest number of entries due to its broader coverage, which includes journal articles, books, theses, patents, and preprints. ScienceDirect and Scopus display a similar trend, although with comparatively fewer publications, while ACS Publications shows a more limited representation but follows the same general pattern of growth. The decline in the number of studies published after 2015 suggests that the topic has reached a stage of maturity, with ongoing research increasingly focused on specific applications. These findings highlight the Jacobsen catalyst as a topic of sustained scientific interest, particularly in the development of asymmetric epoxidation methodologies. The

overall trend, together with the continued presence of references in databases such as Google Scholar, underscores the catalyst's enduring relevance in contemporary scientific literature.

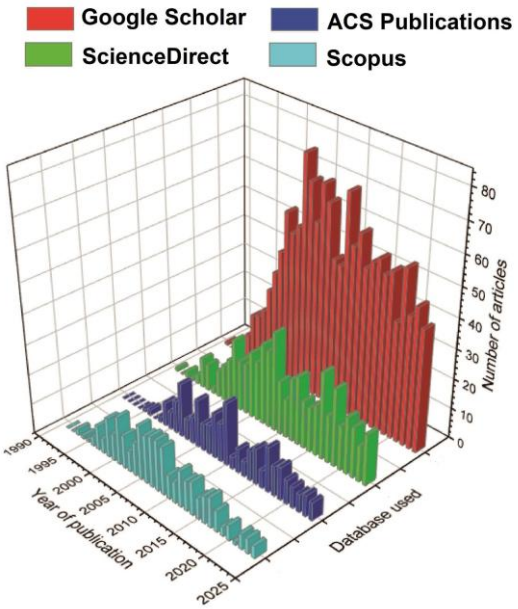

Fig. 4. Annual distribution of published articles on the Jacobsen catalyst during the period 1991–2024. The search was refined to exclude duplicate results, yielding 1232 entries in Google Scholar, 458 in ScienceDirect, 275 in Scopus, and 263 in ACS Publications. Keyword used: "Jacobsen catalyst".

In addition, based on data retrieved from Scopus using "Jacobsen catalyst" as the search keyword and processed with the VOSviewer software (Van Eck et al., 2010), a network visualisation was generated (Fig. 5). The resulting map illustrates the interconnections among key concepts emerging from the literature on the Jacobsen catalyst, particularly those related to the catalytic epoxidation of alkenes and their association with enantioselective synthesis, highlighting the central role of this catalytic system. The structure displayed in the network reveals three main clusters: (1) a red cluster, where terms such as *catalysis*, *epoxidation*, *enantioselectivity*, and *manganese compounds* emphasise the relevance of manganese complexes in alkene epoxidation; (2) a green cluster, which reflects the connection to enantioselective synthesis and pharmaceutical applications, represented by terms such as *stereochemistry*, *drug synthesis*, and *epoxide*; and (3) a blue cluster, which associates epoxidation with the use of prochiral ligands and oxidising agents, reinforcing the role of metal complexes in modulating catalytic activity. The strong interconnection between the Jacobsen catalyst and enantioselective epoxidation processes highlights its ongoing relevance in the field and reaffirms its status as a foundational system for asymmetric transformations with broad impact across modern chemistry.

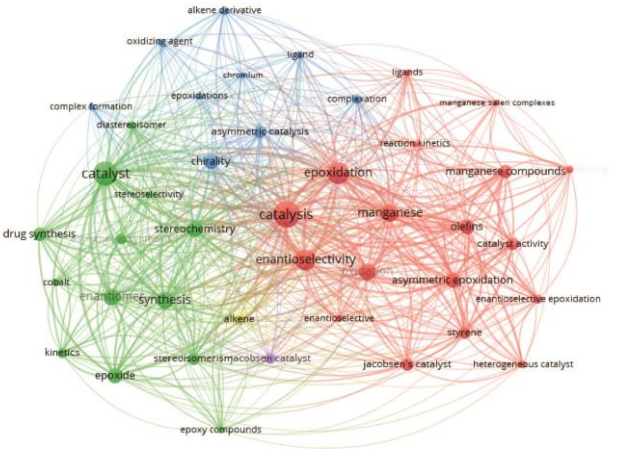

Fig. 5. Network visualization generated with VOSviewer (version 1.6.20) using data retrieved from Scopus with "Jacobsen catalyst" as the search keyword. The resulting map reveals three main thematic clusters: (1) manganese complexes and enantioselective epoxidation (red), (2) enantioselective synthesis and pharmaceutical chemistry (green), and (3) prochiral ligands and oxidising agents (blue). Jacobsen's catalyst appears as a central node in the network.

Considering its relevance, the review of the primary literature reveals a substantial number of studies devoted to specific applications of the Jacobsen catalyst, together with numerous investigations employing Mn(III) complexes bearing various *salen*-type ligands (Sasaki et al., 1994; Hosoya et al., 1994) for the epoxidation of alkenes with a wide range of molecular substituents. These substrates include heterocyclic rings such as chromones (Yang et al., 2019; Adam et al., 1996), isoflavones (McGarrigle et al., 2005; Adam et al., 1998), indene and styrene derivatives, as well as long-chain saturated and polyunsaturated alkenes, among other functionalised groups. Notably, from around 1995, these complexes began to be referred to in the literature as "Jacobsen-type" *salen* complexes (Pietikäinen, 1995) or as Jacobsen's Mn(III) *salen* catalysts (Adam et al., 1995).

In this context, the Jacobsen catalyst has been applied in a variety of emerging areas, including the structural modification of carbohydrates (Wang et al., 2018) and the development of novel methodologies such as its immobilisation on organic and inorganic supports, for example ZnPS–PVPA (Huang et al., 2019). Although such immobilisation strategies had already been reported (Silva et al., 2004), recent innovations have focused on the incorporation of new types of support materials. Moreover, several recent studies have highlighted its role in the total synthesis of pharmacologically relevant compounds, including centrolobine and other molecules exhibiting antitubercular activity (Kumar et al., 2021).

In recent years, research has increasingly centred on modifying the Jacobsen catalyst to develop a new generation of catalytic systems (Martines et al., 2005; Fig. 6), thereby opening a promising and rapidly evolving area of investigation.

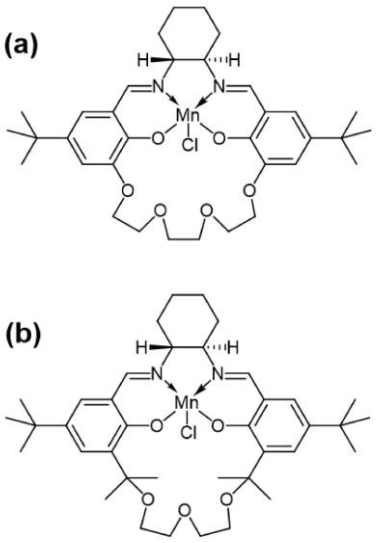

Fig. 6. Jacobsen catalysts of the first (a) and second (b) generations.

3.4 The Jacobsen catalyst in the total synthesis of complex molecules and natural products

A review of the Jacobsen catalyst's role in the total synthesis of natural products demonstrates its relevance as a key tool in organic chemistry, particularly for enabling direct asymmetric epoxidation of alkene functionalities and for performing kinetic resolution strategies such as hydrolytic kinetic resolution (HKR), in which the catalyst selectively differentiates between enantiomers in racemic mixtures. These transformations often represent crucial steps in synthetic strategies designed to achieve products with the desired enantioselectivity. In this regard, the Jacobsen catalyst has been employed in the synthesis of numerous pharmacologically relevant compounds, including S-atenolol, a β-adrenergic receptor antagonist used to treat cardiovascular conditions (Subhas et al., 2005); 7(S),17(S)-resolvin D5, a potent anti-inflammatory agent (Rodríguez et al., 2005); divergolides E and H, compounds investigated for anti-inflammatory, antioxidant, and antineoplastic properties (Caplan et al., 2018); (–)-galantinic acid, with therapeutic potential for cognitive and neurological disorders (Rahman et al., 2020); dendrodolide L, a medium-sized cyclic compound with antibacterial and anticancer potential (Regalla et al., 2017); relgro and 10′-oxorelgro, macrolides of interest due to their antibiotic, immunomodulatory, anti-inflammatory, and antitumour properties (Mohapatra et al., 2019); (2E)-macrolactin 3, known for its broad-spectrum biological activity, including antibacterial, antifungal, antiviral, anticancer, and anti-inflammatory effects (Reddy et al., 2023); chromanol 293B, studied for its pharmacological applications in arrhythmia, hypertension, and other cardiovascular conditions (Ma et al., 2020); and bistramide A, which interacts with actin and contributes to antitumour effects (Hanna et al., 2018).

Other noteworthy applications include (+)-desmethylxestospongin B, an IP3R inhibitor relevant to cancer therapy development (Borum et al., 2024); diphosphatidyltrehalose, a component of the *Mycobacterium tuberculosis* cell wall targeted for diagnostic and therapeutic purposes (Mishra et al., 2019); pyrenophorol, exhibiting antifungal and antimicrobial activity against a variety of organisms (Anusha et al., 2024); (+)-muconin, showing cytotoxicity towards human tumour cells (Srinivas et al., 2018); greensporone F and dechlorogreensporone F, fungal metabolites with antimicrobial and anticancer properties (Gaddam et al., 2020); cryptorigidifoliol K, a diterpenoid from cryptocarya rigidifolia with antimycobacterial, antiparasitic, and antitumour activity (Reddy et al., 2017); berkeleylactone A, a macrolide displaying promising antibiotic potential (Schmidt et al., 2023); crispine A, a pyrroloisoquinoline alkaloid with potential applications in oncology (Mohan et al., 2021); combretastatins D-1, a natural product with anti-inflammatory and anticancer activity (de Lima et al., 2023); methoxylated ether lipids, intermediates in the synthesis of anti-inflammatory and anticancer drugs (Sigurjónsson et al., 2022); and miyakolide, madeirolide A, lasonolide A, polycavernoside A, and clavosolides, marine natural products containing a 4-O-2,3,4,6-tetrasubstituted tetrahydropyran moiety and exhibiting diverse biological activities, particularly anti-inflammatory and anticancer effects (Fariñas-Ramos et al., 2021).

As illustrated by the examples above, the Jacobsen catalyst has found broad application in the total synthesis of natural products and other bioactive compounds. Its use continues to expand, particularly in the design of synthetic strategies for novel pharmaceutical agents and fine chemicals.

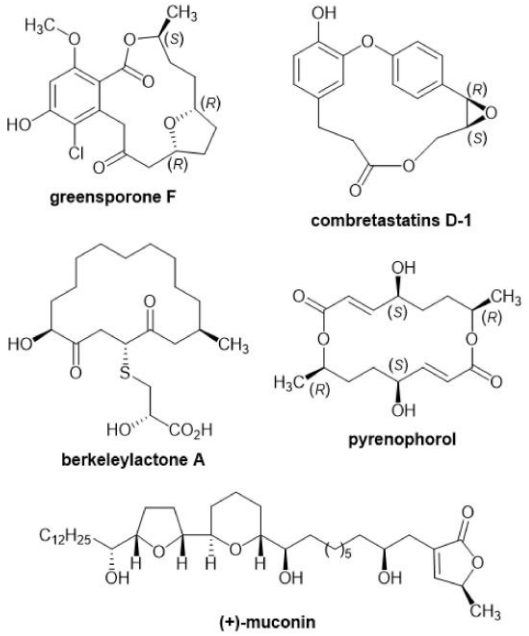

Fig. 7. Structures of selected natural products whose total syntheses involve the use of the Jacobsen catalyst.

3.5 Current trends in the use and application of the Jacobsen catalyst

Over the past three decades, the Jacobsen catalyst has undergone a series of modifications aimed at broadening its applications in asymmetric epoxidation and in the kinetic resolution of racemic mixtures, thereby consolidating its status as a powerful tool in stereoselective chemical synthesis. One of the earliest and most influential developments was the substitution of the Mn(III) ion with other transition metals, significantly expanding the scope and efficiency of asymmetric catalytic transformations. Among these, Cr(III) complexes [Cr(*salen*)] have shown excellent performance in the enantioselective epoxidation of alkenes, offering notable improvements in both catalytic activity and selectivity (Shaw et al., 2019; McGarrigle et al., 2005). In particular, such complexes have been encapsulated within catalytic nanoreactors employing thermoresponsive polymer matrices formed through the folding of amphiphilic random copolymers, namely poly(N-isopropylacrylamide-co-IL/Cr(*salen*)) [poly(NIPAAM-co-IL/Cr(*salen*))], which exhibit superior performance compared to conventional [Cr(*salen*)] systems in aqueous asymmetric epoxidation (Wang et al., 2019). In parallel, Co(III) complexes [Co(*salen*)] have been widely employed in the hydrolytic kinetic resolution of terminal epoxides, affording enantiomerically pure epoxides and diols with excellent yields and minimal environmental impact (Kang et al., 2023; Vyas et al., 2021). Furthermore, the incorporation of alternative transition metals such as aluminium, iron, ruthenium, and vanadium has led to the development of new and valuable catalytic transformations, thereby enhancing the synthetic versatility of these systems (Gualandi et al., 2019; Cozzi, 2004). These advances have not only improved the reactivity of [M(*salen*)] complexes but have also enabled their application under more sustainable catalytic conditions, including aqueous media, ionic liquids, and heterogeneous supports (silica or functionalised polymers), in full accordance with the principles of green chemistry (Guo et al., 2023; Freire et al., 2019; Kaur, 2018; Guedes et al., 2005) (Fig. 8).

Alternatively, the design of more complex molecular architectures, such as dimeric and trimeric systems, has promoted cooperative interactions between metal centres and enabled catalyst reuse over multiple cycles without significant loss of efficiency (Lv et al., 2011).

Finally, the increasing use of computational tools for theoretical calculations has significantly deepened our understanding of this catalytic system and its role in reaction mechanisms, thereby refining strategies aimed at optimizing its performance (Teixeira et al., 2014; Kemper et al., 2009). For instance, computational studies have provided valuable insight into how the Jacobsen catalyst coordinates with nitrogen-doped graphene (Jang et al., 2020), as well as into the mechanism of imine formation from alcohols and amines, accompanied by the release of molecular hydrogen, in a Jacobsen-type analogue (Samuelsen et al., 2019).

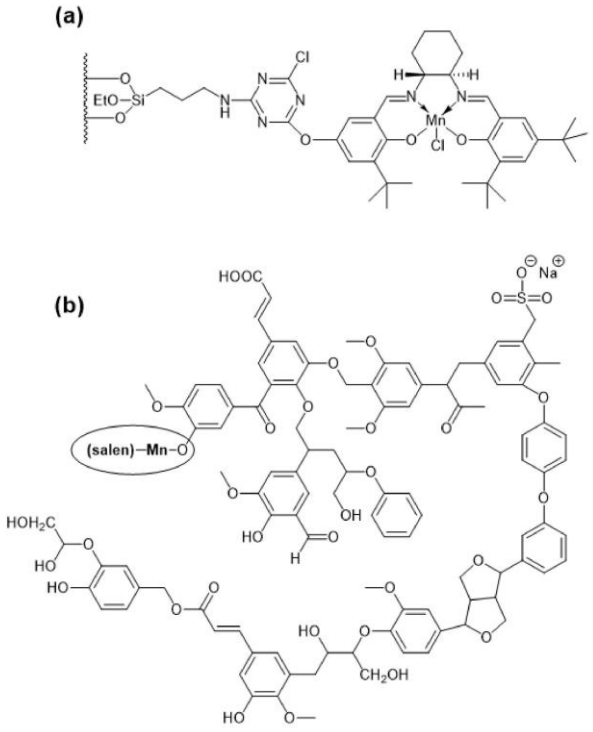

Fig. 8. (a) Representation of the immobilisation of Jacobsen-type complexes onto functionalised mesoporous silica via 3-aminopropyltriethoxysilane (Freire et al., 2019). (b) A Mn(*salen*)@lignin-based catalyst with ultra-low Mn content for the selective epoxidation of olefins under mild conditions (60 °C, 1 bar O_2) (Guo et al., 2023).

These trends position the Jacobsen catalyst as a robust system capable of responding to the demands of modern asymmetric catalysis, with proven relevance in both fundamental research and high-impact industrial applications.

5 Conclusiones

Since its introduction more than thirty years ago, the Jacobsen catalyst has established itself as one of the most versatile and effective systems for asymmetric epoxidation. Its distinctive structural design, centred on a Mn(III) *salen* complex, has enabled the development of highly enantioselective transformations applicable to a wide variety of unfunctionalised alkenes. The catalyst's commercial availability, broad substrate scope, and operational simplicity have all contributed to its widespread adoption in both academic research and industrial applications.

The continuous evolution of the Jacobsen catalyst, including the substitution of manganese with other transition metals and its immobilization on heterogeneous supports, has greatly broadened its synthetic versatility and environmental compatibility. Furthermore, the integration of computational methodologies has deepened mechanistic understanding, facilitating rational design and application in more sustainable catalytic processes.

The extensive number of total syntheses of natural products and pharmacologically active molecules that rely on Jacobsen-type systems attests to their enduring scientific relevance. Asymmetric catalysis remains a cornerstone of modern synthesis, and the Jacobsen catalyst continues to stand as a paradigmatic model of selectivity and adaptability in the field.

Acknowledgment

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