chemistry

MDPI

Review

Chiral Hydroxamic Acid Ligands in the Asymmetric Synthesis of Natural Products

Tushar Janardan Pawar [1], Karla Irazu Ventura-Hernández [1,2], Fernando Rafael Ramos-Morales [2] and José Luis Olivares-Romero [1,*]

[1] Red de Estudios Moleculares Avanzados, Clúster Científico y Tecnológico BioMimic del Instituto de Ecología, A.C. Carretera Antigua a Coatepec 351, Xalapa 91073, Mexico; tushar.janardan@inecol.mx (T.J.P.); irazuhdez1995@gmail.com (K.I.V.-H.)
[2] Instituto de Química Aplicada, Universidad Veracruzana, Xalapa 91073, Mexico; framos@uv.mx
* Correspondence: jose.olivares@inecol.mx

Abstract: Chiral hydroxamic acid (HA) and bis-hydroxamic acid (BHA) ligands have made significant contributions to the field of asymmetric synthesis, particularly in the synthesis of natural products. These ligands possess unique molecular structures that allow for exceptional stereochemical control, leading to their widespread use in catalytic systems. This review highlights the advancements made in asymmetric synthesis using chiral hydroxamic acid and bis-hydroxamic acid ligands and their impact on the synthesis of complex natural products. This discussion encompasses their role in enantioselective C–C bond formation, the functionalization of C–H bonds, the asymmetric transformations involving heteroatoms, and their application in the total synthesis of natural products. The versatility and efficiency of chiral hydroxamic acid ligands and bis-hydroxamic acid ligands make them invaluable tools for synthetic chemists working towards the efficient and selective synthesis of natural products. This review provides a comprehensive overview of their contributions, showcasing their potential to expand the boundaries of chemical synthesis and access the diverse array of natural product scaffolds.

Keywords: chiral hydroxamic acid ligands; chiral bishydroxamic acid ligands; asymmetric synthesis; natural products

Citation: Pawar, T.J.; Ventura-Hernández, K.I.; Ramos-Morales, F.R.; Olivares-Romero, J.L. Chiral Hydroxamic Acid Ligands in the Asymmetric Synthesis of Natural Products. *Chemistry* **2023**, *5*, 2700–2712. https://doi.org/10.3390/chemistry5040174

Academic Editors: Maria Luisa Di Gioia, Luísa Margarida Martins, Isidro M. Pastor and George O'Doherty

Received: 7 October 2023
Revised: 15 November 2023
Accepted: 22 November 2023
Published: 1 December 2023

1. Introduction

The synthesis of natural products has long been a captivating pursuit in organic chemistry, spurred by the remarkable structural complexity and diverse array of biological activities exhibited by these compounds. Serving as a wellspring of inspiration, natural products are integral to the development of novel drugs, agrochemicals, and materials [1]. Asymmetric synthesis, geared toward accessing enantiomerically pure compounds, plays a pivotal role in constructing complex natural product scaffolds with the desired stereochemistry crucial for their biological activities. Over the years, the evolution of efficient chiral ligands has revolutionized asymmetric synthesis, enabling chemists to achieve high selectivity and efficiency in their synthetic endeavors [2]. These ligands act as molecular tools influencing the stereochemical outcome of reactions, facilitating the precise control of stereocenters. This breakthrough not only facilitates the synthesis of natural products, but also opens new avenues for the design and creation of chiral molecules tailored for diverse applications, emphasizing the profound impact of asymmetric synthesis and chiral ligand development on the continued exploration and utilization of natural products in various scientific and industrial domains.

Among the various classes of chiral ligands, hydroxamic acids have emerged as versatile tools for asymmetric synthesis. Hydroxamic acids possess a distinctive molecular structure characterized by a hydroxylamine (–NOH) functional group attached to a carbonyl group. This arrangement imparts them with a unique set of properties that make them

highly effective ligands in coordination chemistry. The hydroxamic acid moiety can form coordination complexes with transition metal catalysts, leading to the formation of chiral catalysts that are capable of inducing asymmetric transformations [3].

Chiral hydroxamic acid (HA) and bis-hydroxamic acid (BHA) ligands have gained significant attention and found widespread application in asymmetric synthesis due to their ability to provide exceptional stereochemical control. The design and development of these ligands have been driven by the need to achieve high enantioselectivity, regioselectivity, and stereoselectivity in a variety of synthetic transformations. The inherent flexibility and modifiability of hydroxamic acid ligands allow for the fine-tuning of their properties, enabling chemists to tailor them to specific reactions and target molecules [4,5].

In the realm of natural product synthesis, chiral hydroxamic acid ligands have made remarkable contributions, offering elegant solutions to challenging synthetic problems. Their effectiveness in accessing enantiopure compounds has enabled chemists to construct complex natural product architectures, reproduce their biological activities, and explore structure–activity relationships. By harnessing the power of these ligands, synthetic chemists have achieved impressive advancements in various aspects of asymmetric synthesis pertaining to natural products [6,7].

One area where chiral hydroxamic acid ligands have demonstrated exceptional utility is in enantioselective carbon-carbon (C–C) bond formation. The formation of C–C bonds is a key step in constructing the carbon framework of natural products [6]. Chiral hydroxamic acid ligands have been successfully employed in asymmetric allylation reactions, aldol reactions, Mannich reactions, and other important C–C bond-forming transformations. Through careful ligand design and optimization, chemists have achieved high levels of enantioselectivity, enabling the synthesis of complex natural product motifs with precise stereochemistry [7].

In addition to C–C bond formation, the functionalization of carbon-hydrogen (C–H) bonds represents an important strategy in natural product synthesis. Direct C–H functionalization allows chemists to access molecular complexity efficiently by utilizing unactivated carbon-hydrogen bonds as functional handles. Chiral hydroxamic acid ligands have been instrumental in developing transition metal-catalyzed C–H activation reactions with high enantioselectivity. These reactions have enabled the selective formation of chiral centers in the target molecules, thus providing access to diverse natural products that were previously challenging to synthesize [3]. Furthermore, chiral hydroxamic acid ligands have demonstrated their efficacy in asymmetric transformations involving heteroatoms. Natural products frequently contain heterocyclic motifs that contribute to their biological activities. Chiral hydroxamic acid ligands have been successfully employed in asymmetric amination reactions, amidation reactions, and epoxidations, enabling the controlled formation of chiral heterocycles with high enantioselectivity. The ability to selectively introduce heteroatoms into complex natural product scaffolds expands the synthetic possibilities and provides access to a broader range of natural product structures (Figure 1).

Moreover, the impact of chiral HA and BHA ligands extends beyond their application in specific transformations. These ligands have played a pivotal role in the total synthesis of numerous natural products, showcasing their versatility and efficiency. By strategically incorporating chiral hydroxamic acid ligands in key steps, synthetic chemists have successfully achieved the total synthesis of complex alkaloids, polyketides, terpenoids, and other structurally intricate natural products. These achievements not only facilitate the acquisition of biologically active compounds but also deepen our understanding of complex relationships [8,9].

In this review, we aim to provide a comprehensive overview of the remarkable contributions of chiral hydroxamic acid and bis-hydroxamic acid ligands in the asymmetric synthesis of natural products. Natural products have long captivated the attention of organic chemists due to their intricate structural complexity and diverse biological activities. Asymmetric synthesis, which enables access to enantiomerically pure compounds, has played a pivotal role in the construction of complex natural product scaffolds with

precise stereochemistry. Within this context, chiral hydroxamic acid and bis-hydroxamic acid ligands have emerged as versatile tools, offering unique properties that facilitate high selectivity and efficiency in synthetic endeavors. By examining key examples from the literature, we aim to explore the pivotal role of these ligands in the synthesis of natural products, highlighting their impact on enantioselective carbon–carbon bond formation, the functionalization of carbon-hydrogen bonds, heteroatom-based transformations, and their contribution to total synthesis efforts. Through this review, we aim to shed light on the versatility and potential of chiral HA and BHA ligands as valuable tools in the asymmetric synthesis of natural products.

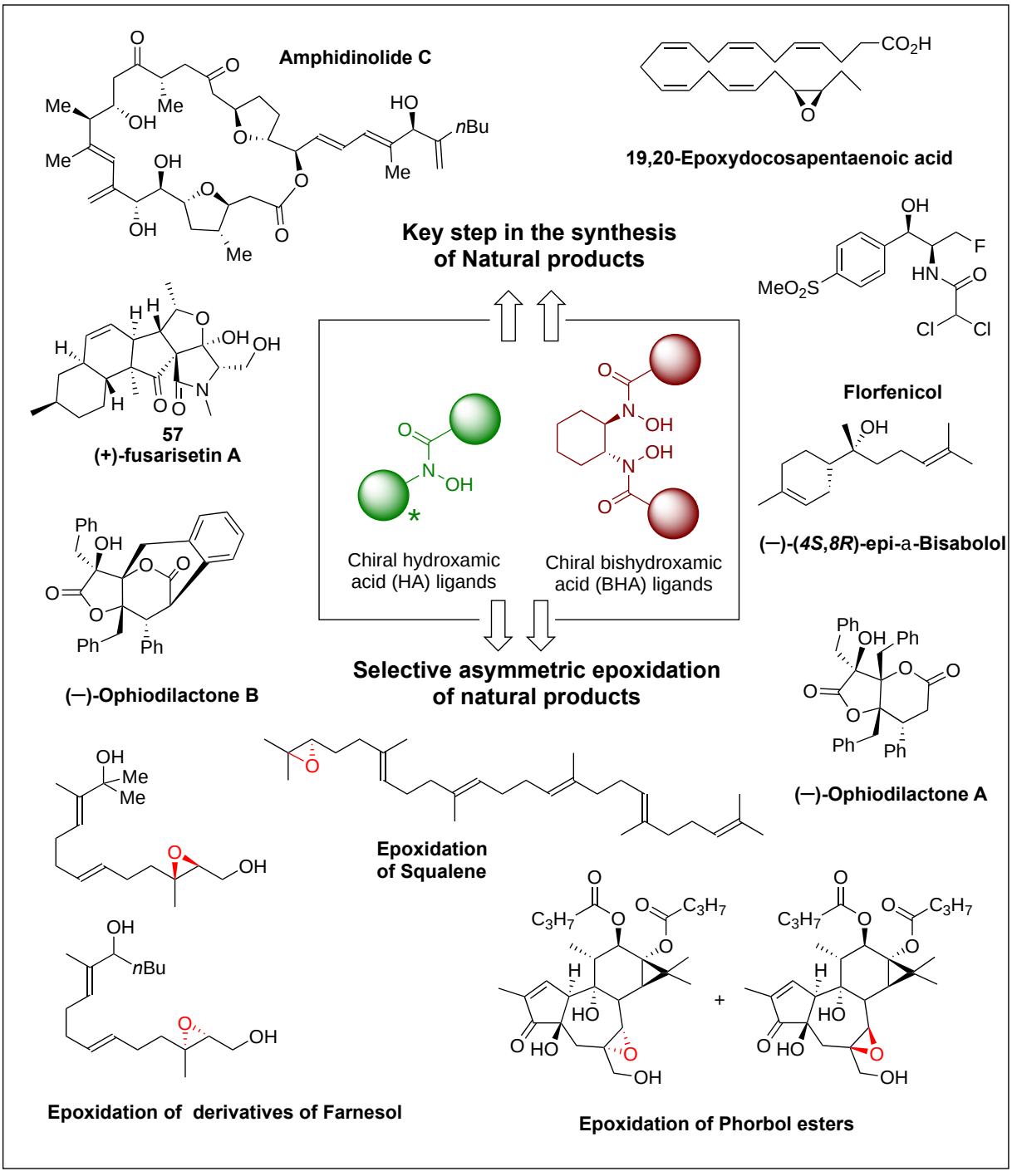


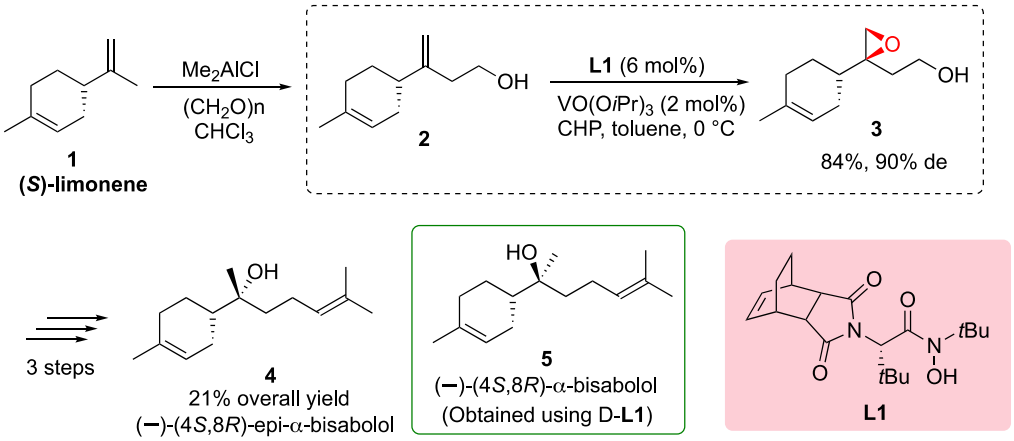
Figure 1. The remarkable contributions of chiral hydroxamic acid ligands in the asymmetric synthesis of natural products.

2. Total Synthesis of Natural Compounds

In this section, we explore the meticulous craft of total synthesis, a pursuit that entails the precise recreation of intricate molecular structures inherent in natural compounds. This endeavor serves as an intellectual challenge, offering profound insights into the strategic arrangement of chemical transformations. Notably, we focus on the noteworthy contributions of HA and BHA ligands, highlighting their pivotal role as a key step in various total synthesis projects. Our investigation will unveil strategic synthetic approaches, showcasing how HA and BHA ligands have been instrumental in achieving high selectivity and efficiency, thereby contributing significantly to the construction of natural product scaffolds. Through a detailed examination of specific examples, we aim to unravel breakthroughs in total synthesis, illuminating the symbiotic relationship between chemistry and the nuanced world of natural products.

2.1. Total Synthesis of α-Bisabolol

The total synthesis of (−)-α-bisabolol, a fragrance compound derived from (*S*)-limonene **1**, was successfully achieved through the utilization of hydroxamic acid ligands **L1**, as demonstrated by Yamamoto in 2003. The synthetic route involved several key steps starting with the hydroxymethylation of (*S*)-limonene **1**, resulting in the formation of (*S*)-alcohol **2**. Diastereoselective epoxidation utilizing hydroxamic acid ligand **L1** proved highly effective, yielding epoxy alcohol **3** with a good overall yield of 84% and a high diastereomeric excess of 90% (de). A subsequent reduction in epoxy alcohol **3** produced diol, which was further subjected to tosylation and coupling with isopropenyl magnesium bromide, ultimately leading to the synthesis of (−)-(*4S*,*8S*)-α-bisabolol **4**. The overall yield from (*S*)-limonene was reported to be 21%. Additionally, this study explored the use of hydroxamic acid ligand **L1**, resulting in the synthesis of (−)-(*4S*,*8R*)-epi-α-Bisabolol **5** (Scheme 1). These findings underscore the remarkable efficiency of hydroxamic acid ligands in controlling diastereoselectivity and achieving high yields in the synthesis of complex molecules, thereby providing a practical and promising approach for accessing natural products such as (−)-α-bisabolol [10]. α-Bisabolol is a significant monocyclic sesquiterpene derived from essential oils of various edible and ornamental plants. It possesses diverse biological activities, including anticancer, antimicrobial, and anti-inflammatory properties. Its therapeutic potential and natural occurrence in essential oils make α-bisabolol an intriguing target for total synthesis and the development of synthetic strategies using hydroxamic acid ligands. The utilization of hydroxamic acid ligands offers a practical approach to accessing natural products like α-bisabolol, further enabling the exploration of its therapeutic applications, and expanding our knowledge of its biological activities [11].

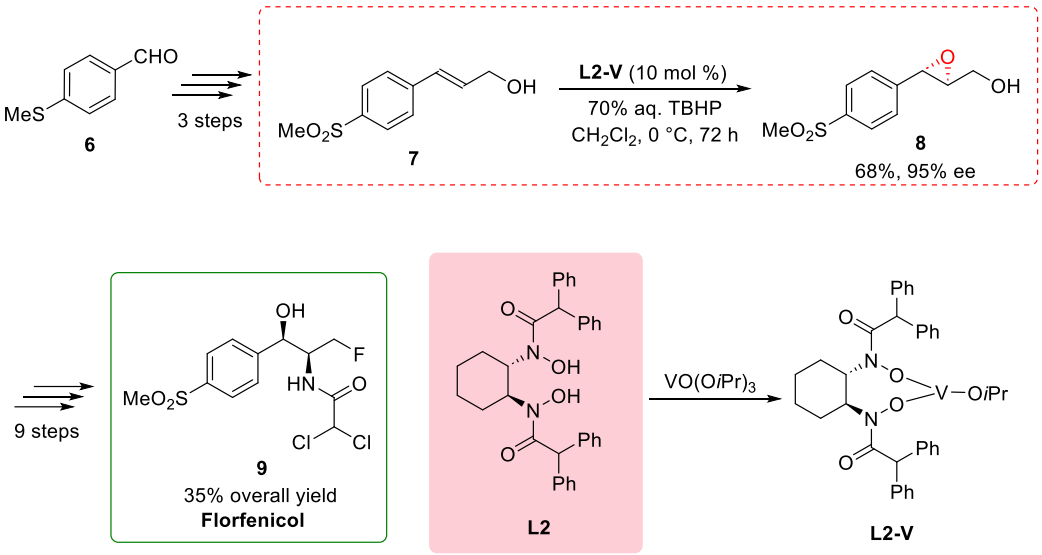


Scheme 1. Concise and stereoselective total synthesis of (−)-(*4S*,*8S*)-α- and (−)-(*4S*,*8R*)-epi-α-bisabolol.

2.2. Total Synthesis of Florfenicol

The total synthesis of Florfenicol **9**, as reported by Chen in 2011, involved a concise and efficient route with a significant emphasis on the utilization of a chiral bishydroxamic acid (BHA) ligand **L2** [12]. Florfenicol, a fluorinated analog of thiamphenicol, is a broad-spectrum antibiotic widely used in aquaculture species as well as various livestock species, including bovine, porcine, and chicken, for the treatment of infections.

The synthetic pathway commenced with the transformation of 4-methylthiobenzaldehyde 6, leading to the formation of allylic alcohol **7** in three sequential steps. The subsequent critical focus was directed toward the synthesis of the pivotal intermediate (*2S*,*3S*)-epoxide **8**. While the initial consideration was the Sharpless epoxidation protocol employing anhydrous tert-butyl hydroperoxide (TBHP), its limitations for scale-up necessitated an alternative strategy. Consequently, the authors employed a modified procedure involving 1.5 equivalents of 70% aqueous TBHP and Yamamoto's vanadium catalyst **L2**-V at 0 °C for 72 h [8]. This innovative approach successfully furnished (*2S*,*3S*)-epoxide **8** with a yield of 75% and an enantiomeric excess of 90%. Recrystallization enhanced further the enantiomeric excess to 95%. Subsequently, an additional nine steps were executed to achieve the desired product, Florfenicol **9**, with an overall yield of 37% [12]. The successful total synthesis of Florfenicol demonstrates the significant contribution of chiral BHA ligands in the synthesis of important pharmaceutical compounds. The broad-spectrum antibiotic properties and widespread applications of Florfenicol highlight the importance of efficient synthetic methodologies to access such valuable compounds (Scheme 2) [13].

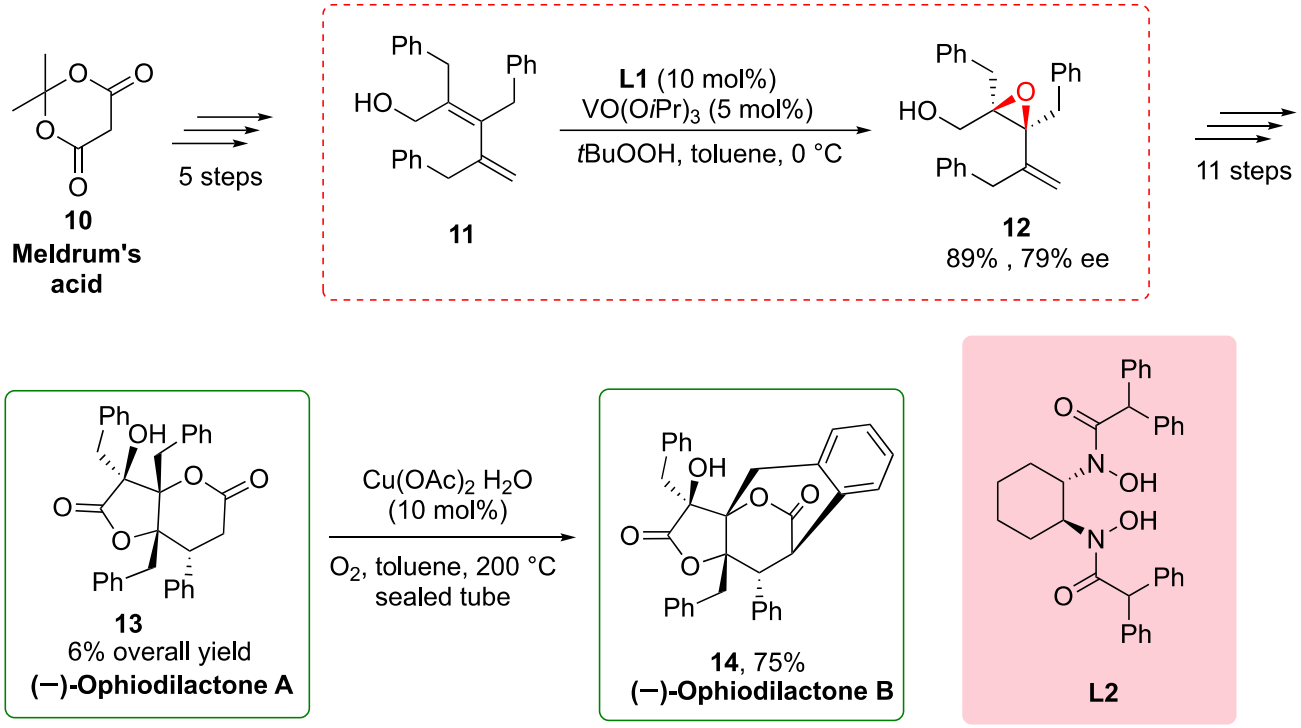


Scheme 2. Chiral BHA ligand-enabled key step in the total synthesis of Florfenicol.

2.3. Total Synthesis of (−)-Ophiodilactones A and B

In a study conducted by Hatakeyama in 2014 [14], the total synthesis of (−)-ophiodilactones A and B was achieved using a chiral bishydroxamic acid (BHA) ligand. The synthesis involved several key steps, including Stille coupling and asymmetric epoxidation. Previous reports have shown low enantioselectivity in the epoxidation step, prompting the researchers to employ a method developed by Yamamoto and co-workers [8]. By utilizing tert-butyl hydroperoxide and a vanadium catalyst in the presence of a BHA ligand, they successfully obtained epoxy alcohol **12** with an improved enantioselectivity of 79%. Subsequently, a sequence of 11 steps led to the synthesis of ophiodilactone A **13**. The synthesis involved various transformations, including Swern oxidation, a Grignard reaction, and hydrogenation, culminating in the desired compound **13**. Furthermore, ophiodilactone B **14** was obtained via the direct oxidative coupling reactions of C–H and Ar–H bonds of ophiodilactone A. The strategic use of the BHA ligand in the asymmetric epoxidation step played a pivotal role in improving the enantioselectivity and enabling the synthesis

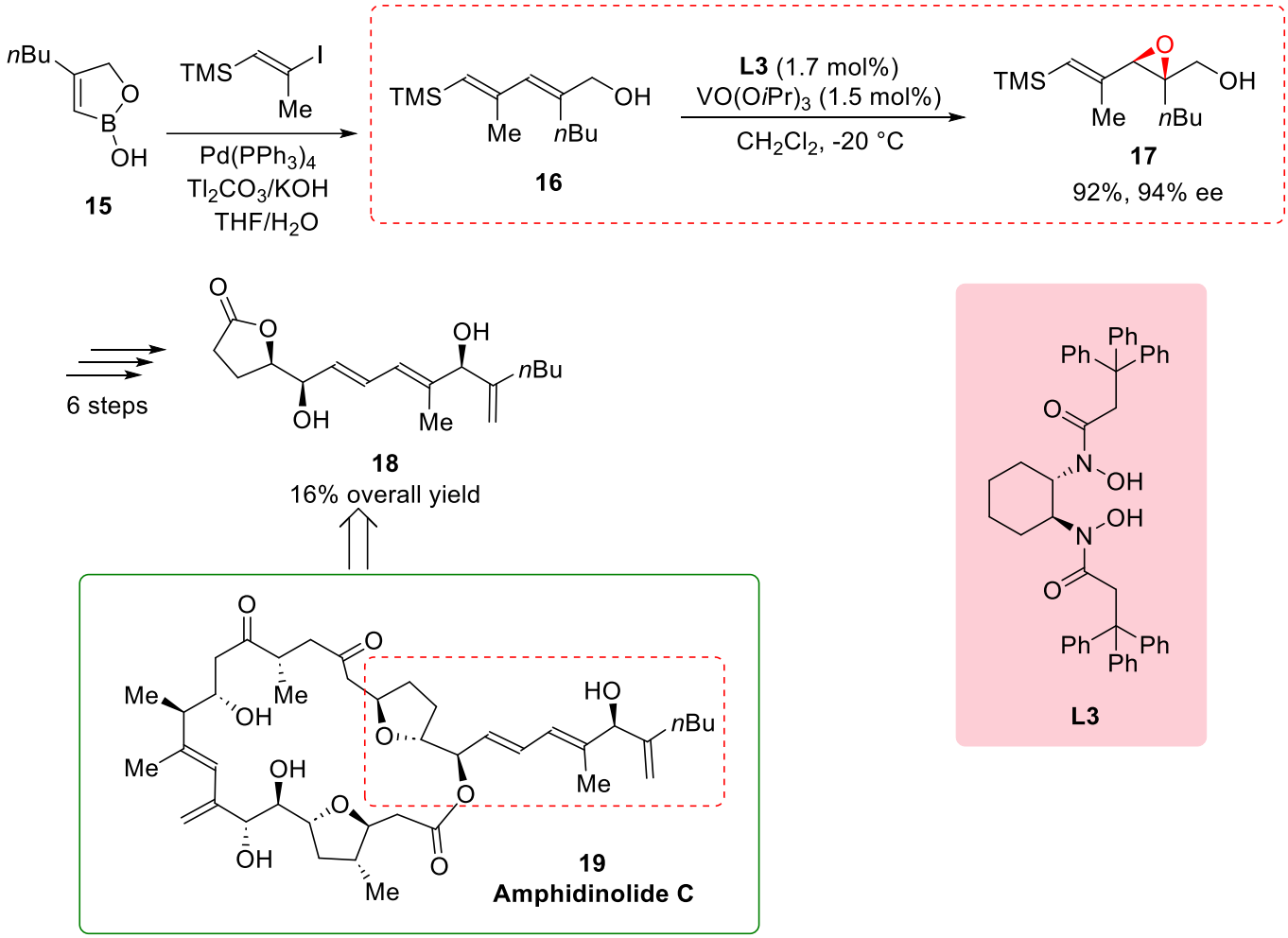
of ophiodilactones A and B. The use of the BHA ligand in the asymmetric epoxidation step played a crucial role in improving the enantioselectivity of the synthesis. By implementing the method developed by Yamamoto and co-workers, the researchers achieved higher enantioselectivity in the formation of epoxy alcohol **12**. This success enabled the subsequent transformations, leading to the synthesis of γ-lactones **13** and **14** and ultimately facilitating the synthesis of ophiodilactone A **13** (Scheme 3) [15].



Scheme 3. Chiral BHA in total synthesis of (−)-Ophiodilactone A and (−)-Ophiodilactone B.

2.4. Synthesis of the Side Chain of Amphidinolide C

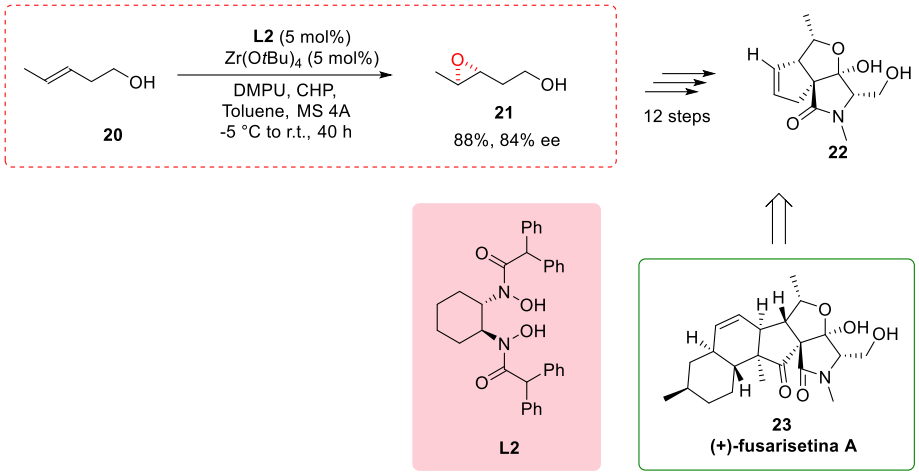
In the synthesis of the side chain of amphidinolide C, a complex natural product with potent antineoplastic activity, the epoxidation of allylic alcohol **16** played a crucial role in achieving the desired structure and functionality. However, the commonly used Sharpless epoxidation method did not provide the required enantioselectivity for the formation of epoxy alcohol **17**. To overcome this challenge, Fenneteau et al. (2015) turned to the use of a BHA ligand, specifically the **L3**-Vanadium complex, which is known for its ability to control stereoselectivity in reactions. By incorporating the BHA ligand into the epoxidation reaction, the researchers aimed to enhance the enantioselectivity and obtain the desired epoxy alcohol **17** with the desired stereochemistry. The BHA ligand, in conjunction with the Vanadium catalyst, proved highly effective in improving the enantioselectivity of the epoxidation reaction, resulting in a remarkable enantiomeric excess of 94% and a yield of 92%. This successful application of the BHA ligand demonstrates its versatility and effectiveness in achieving challenging synthetic goals, particularly in the synthesis of complex natural products. The synthesis of the side chain of amphidinolide C continued with six additional steps, ultimately yielding the desired side chain **18** (Scheme 4) [16]. Amphidinolide C is, the first twenty-five-membered macrocyclic lactone with potent antineoplastic activity. Its complex structure and biological activity make it an intriguing target for synthesis. The utilization of the BHA ligand in the synthesis of the side chain of amphidinolide C highlights its importance in controlling the stereochemistry and achieving the desired structural features [17].



Scheme 4. Synthesis of the side chain of amphidinolide C.

2.5. Partial Synthesis of (+)-Fusarisetin A

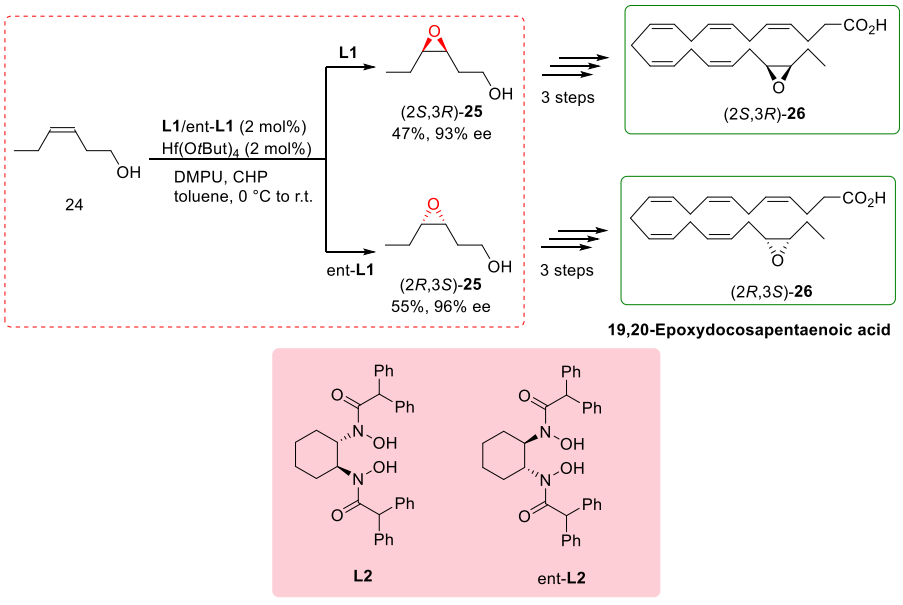
In their study, Kohyama et al. (2015) utilized a novel methodology in the partial synthesis of (+)-fusarisetin A, a pentacyclic fungal metabolite known for its intriguing biological properties, including its role as an acinar morphogenesis inhibitor [18]. The researchers specifically focused on the transformation of homoallylic alcohol 20, employing the conditions described by Yamamoto and coworkers [8]. By utilizing chiral bishydroxamic acid ligand **L2**, Zn(O*t*Bu)$_4$, and DMPU, they successfully formed the corresponding epoxide **21** with an impressive enantiomeric excess of 84% and a yield of 88%. Furthermore, through an additional twelve steps, the desired compound **22** was obtained, representing a significant milestone in the synthesis of (+)-fusarisetin A. These steps involved various transformations, including functional group manipulations, ring formations, and stereochemical control, enabling the construction of the intricate pentacyclic structure of (+)-fusarisetin A. Notably, this study revealed the critical role of the metal core in controlling the enantioselectivity of the reaction, with chiral BHA ligands **L2** and hafnium catalyst leading to improved enantiomeric excesses (Scheme 5) [19]. The successful application of this methodology in the partial synthesis of (+)-fusarisetin A not only enhanced our understanding of the compound's synthetic pathway but also highlighteds its potential for the efficient synthesis of complex natural products and other valuable compounds.



Scheme 5. Partial synthesis of (+)-Fusarisetin A.

2.6. Total Synthesis of 19,20-Epoxydocosapentanoic Acid

The total synthesis of fatty acids is a challenging task, especially when large quantities of materials are required for biological assays. Within this context, the synthesis of specific unsaturated fatty acids containing an epoxide group is of particular importance as they play crucial roles as endogenous lipids [20]. To address this challenge, Cinelli et al. reported the total synthesis of 19,20-epoxydocosapentanoic acid (19,20-EDP), which is a significant compound with biological relevance. Previous synthetic routes for fatty acids do not offer a direct method for the epoxidation of alcohols, resulting in poor outcomes. In their study, the researchers focused on the transformation of homoallylic alcohol **24** into the corresponding epoxy alcohols (*S*,*R*) and (*R*,*S*)-**25**. They employed **L2** and ent-**L2** ligands in conjunction with Hf(O*t*Bu)$_4$ as the catalyst. Although the yield and enantioselectivity achieved were modest and lower than the reported values, this study represented the first report of utilizing BHA ligands in the total synthesis of these exciting compounds. Scheme 6 illustrates the key steps involved in the total synthesis of 19,20-EDP. Despite the challenges faced in achieving high yields and enantioselectivity, this work showcased the potential of BHA ligands in the total synthesis of complex fatty acids, expanding the synthetic scope and paving the way for the efficient synthesis of important bioactive compounds (Scheme 6) [21].



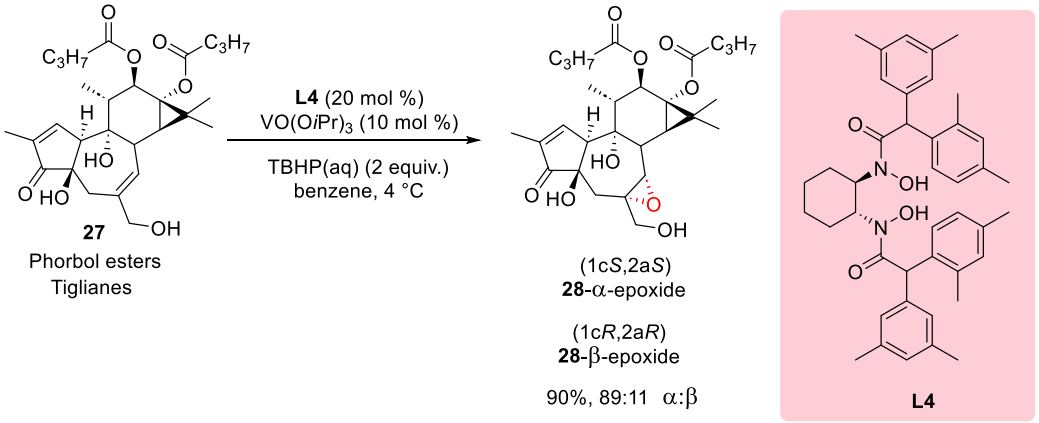
Scheme 6. Hf(IV) in the total synthesis of 19,20-Epoxydocosapentanoic acid.

3. Asymmetric Epoxidation of Natural Products

In this section, we explore the role of hydroxamic acid (HA) and bis hydroxamic acid (BHA) ligands, not only in the synthesis of natural products, but also in the enantioselective epoxidation of key natural compounds. The application of HA and BHA ligands extends beyond mere synthesis; it offers a strategic avenue for modifying the structures of essential natural products. Through enantioselective epoxidation, these ligands enable precise structural modifications, presenting opportunities to tailor the biological activities of the resulting molecules. By examining three examples reported until now, we highlight how HA and BHA ligands contribute not only to the construction of natural product scaffolds, but also to the nuanced modification of their structures, thereby influencing their biological properties.

3.1. Epoxidation of Phorbol Esters

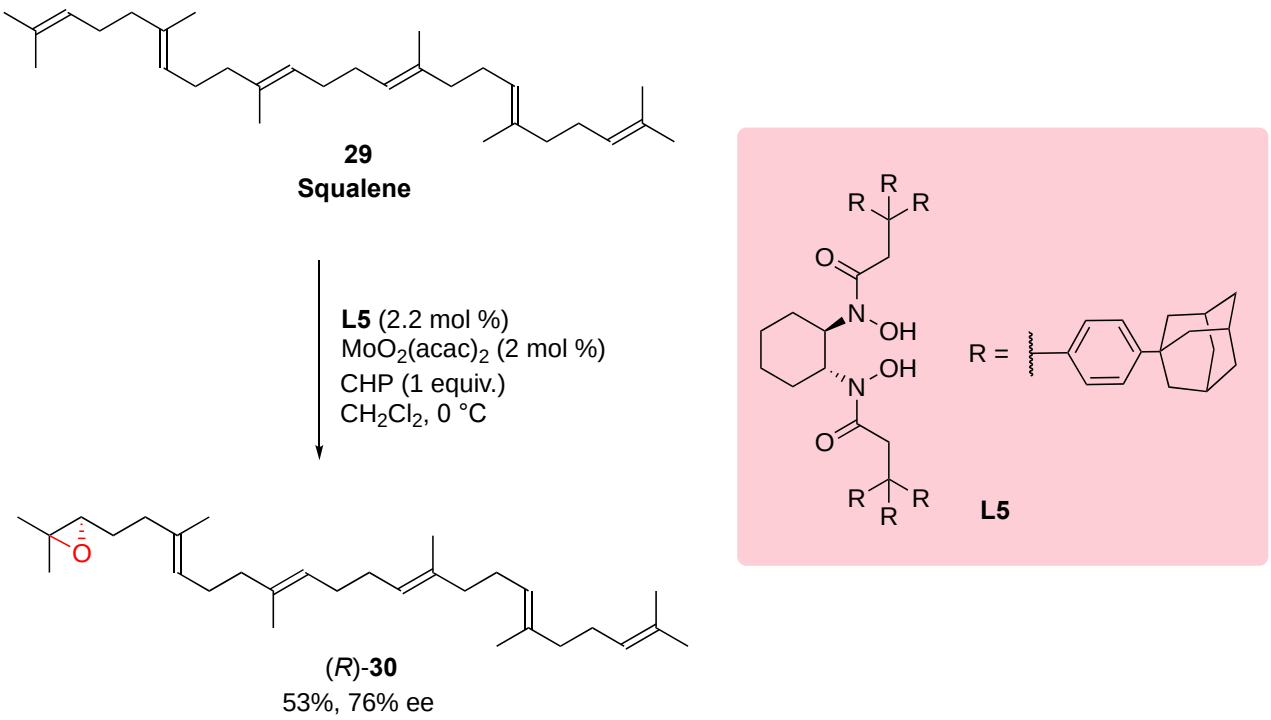
In a pivotal study conducted in 2015, Wender et al. delved into the intricate realm of diterpene epoxidation, focusing specifically on daphnanes and tiglianes at the C_6–C_7 position. The investigation meticulously probed the diastereoselectivity of the reaction, strategically manipulating the steric size of the ligand to unveil its impact. The researchers chose phorbol ester **27** as a test substrate, and the outcomes underscored the profound influence of ligand selection on diastereoselectivity. Scheme 7 visually encapsulates this influence, revealing that the utilization of V(V)-ligand L4 resulted in a diastereoselectivity ratio of 89:11, favoring the formation of the **28**-α-epoxide. This compelling observation serves as a testament to the adept modulation of diastereoselectivity achieved by judiciously varying the steric size of the ligand. In essence, this study contributes significantly to the understanding of ligand design's pivotal role in dictating the stereochemistry of epoxidation reactions, particularly in the synthesis of diterpenes (Scheme 7) [22].



Scheme 7. Ligand effect on Yamamoto epoxidation with Phorbol esters.

3.2. Epoxidation of Squalene

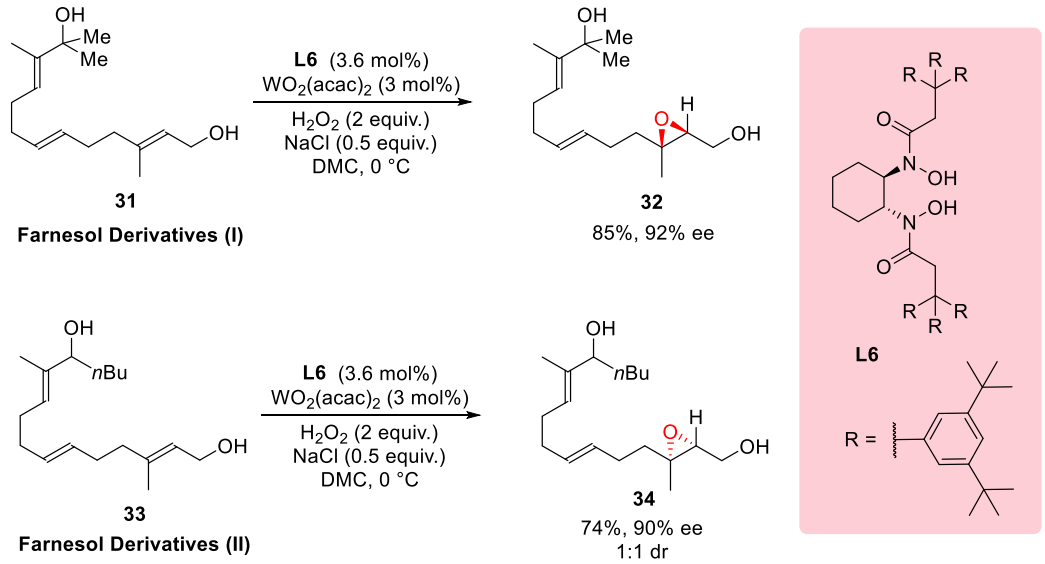
In the intricate synthetic pathway illustrated in Scheme 8, the foundational biogenetic precursor squalene **29**, integral in the synthesis of steroids and polycyclic terpenoids, underwent a transformation under specified conditions. This synthetic experiment culminated in the formation of 2,3-epoxysqualene **30**, showcasing a remarkable enantioselectivity of 76%. Squalene, classified as a triterpene hydrocarbon, plays a pivotal role as an intermediate in the biosynthesis of diverse biologically active molecules. To strategically introduce an epoxide group at a specific position within the squalene molecule, the researchers meticulously tailored reaction conditions conducive to this transformation. The optimization of these conditions yielded the desired 2,3-epoxysqualene **30**, demonstrating a substantial enantioselectivity of 76%. This heightened enantioselectivity serves as a clear indicator of the successful application of the chosen ligand or catalyst system in precisely controlling the stereochemistry of the reaction (Scheme 8) [23].



Scheme 8. Regio- and enantioselective oxidation of squalene.

3.3. Epoxidation of Farnesol Derivatives

The regioselective synthesis of compounds featuring multiple olefin and alcohol moieties stands as a formidable challenge in organic chemistry. In a seminal study by Wang et al. in 2014, the potential of two farnesol derivatives, 31 and 33, as precursors for such intricate compounds was systematically explored using a meticulously designed catalyst system. Through the application of this catalyst system, the desired products were obtained with striking regioselectivity. The synthetic approach involved the strategic functionalization of specific positions on the farnesol derivatives, resulting in the creation of compounds adorned with multiple olefin and alcohol moieties. The notable regioselectivity achieved in this transformation underscores the efficiency and precision of the catalyst system, unveiling novel avenues for the synthesis of complex molecules characterized by diverse functionalities (Scheme 9) [24].



Scheme 9. Regioselective epoxidation of farnesol derivatives.

4. Discussion

The application of hydroxamic acid (HA) and bishydroxamic acid (BHA) ligands in total natural product synthesis signifies a realm teeming with possibilities for advancing efficient synthetic methodologies. Ongoing research places a pronounced emphasis on the design and refinement of BHA ligands, seeking to enhance catalytic properties and broaden substrate scope. Structural modifications and the incorporation of diverse functional groups stand as avenues for exploration, offering valuable insights into the factors influencing reactivity and selectivity. These progressive strides aim to enrich the synthetic toolbox, empowering chemists to access a broader array of natural product scaffolds with heightened efficiency.

A promising trajectory for future research involves the exploration of alternative metal catalysts in tandem with BHA ligands. While current attention revolves around vanadium-based catalysts, delving into other transition metals holds the potential for manipulating stereochemistry and achieving distinctive reactivity profiles. Initiatives to develop more sustainable and readily available metal catalysts are underway, aligning with the overarching objective of augmenting the practicality and scalability of BHA-mediated transformations [5].

Beyond the realms of ligand and catalyst development, overcoming challenges associated with scalability and practicality is imperative for the widespread industrial adoption of BHA ligands. Directing efforts towards formulating scalable and cost-effective synthetic methodologies compatible with large-scale production is paramount. This involves meticulous optimization of reaction conditions, catalyst loading, and purification strategies to ensure consistently high yields and product purity.

An equally crucial avenue for future exploration involves the integration of BHA ligands into multistep syntheses, applying them in the total synthesis of complex natural products. Streamlining synthetic routes becomes pivotal, enabling the construction of intricate natural product structures with precise stereochemical control. The synergistic utilization of BHA ligands alongside other potent synthetic tools, such as Organocatalysis [25,26] and other transition metal-catalyzed enantioselective epoxidations [27], holds substantial potential for unveiling novel synthetic strategies and expanding the horizons of chemical synthesis.

Furthermore, the continuous pursuit of novel BHA designs aligns with the overarching goal of adapting these ligands to alternative metal catalysts and sustainable synthetic methodologies [5,28]. By fine-tuning ligand structures, researchers aspire to enhance metal–ligand interactions, influencing catalytic outcomes and opening avenues for the use of different transition metals. This evolution in ligand design not only broadens the scope of potential applications, but also contributes to the development of more environmentally friendly and economically viable synthetic processes.

The outlook for BHA ligands in total natural product synthesis is promising, presenting opportunities for advancements in ligand design, the exploration of alternative metal catalysts, scalability optimization, and integration into multistep syntheses. Addressing these challenges remains pivotal for propelling synthetic methodologies forward, facilitating the efficient and sustainable synthesis of complex natural products with significant biological activities. The evolving landscape of BHA ligands continues to carve a path toward innovative synthetic strategies, promising a future marked by breakthroughs in total natural product synthesis.

5. Conclusions

In conclusion, the exceptional contributions of chiral hydroxamic acid (HA) ligands, especially bis-hydroxamic acid (BHA) ligands, have emerged as indispensable catalysts in the field of asymmetric synthesis, particularly in the synthesis of natural products. Their significance lies in their unique ability to act as catalysts for enantioselective epoxidation, a key step in the synthesis of complex molecules found in nature. Enantioselective epoxidation is pivotal as it introduces oxygen functionality with precise stereochemistry, a critical feature

often present in biologically active compounds. BHA ligands, with their distinctive molecular structures and exceptional stereochemical control, provide a powerful tool for organic chemists to achieve high levels of enantioselectivity, contributing to the synthesis of natural products with well-defined stereochemical architectures. The versatility of BHA ligands extends beyond their catalytic role in enantioselective epoxidation. Through numerous case studies, it has become evident that these ligands play a multifaceted role, catalyzing a range of transformations crucial for natural product synthesis. Their impact includes improved reaction yields, heightened enantioselectivity, and more streamlined synthetic routes. As research and development in this field progress, BHA ligands are poised to continue shaping the landscape of asymmetric synthesis, with their role in facilitating enantioselective epoxidation remaining central to the pursuit of efficient and selective synthesis of natural products. The enduring importance of BHA ligands underscores their potential for further innovations and groundbreaking contributions to the synthesis of complex molecular architectures.

Author Contributions: Conceptualization, T.J.P. and J.L.O.-R.; methodology, T.J.P.; software, T.J.P.; validation, T.J.P., F.R.R.-M. and J.L.O.-R.; formal analysis, T.J.P. and J.L.O.-R.; investigation, T.J.P. and K.I.V.-H.; resources, J.L.O.-R.; data curation, T.J.P. and K.I.V.-H.; writing—original draft preparation, T.J.P. and K.I.V.-H.; writing—review and editing, T.J.P., K.I.V.-H., F.R.R.-M. and J.L.O.-R.; visualization, T.J.P. and J.L.O.-R.; supervision, J.L.O.-R.; project administration, T.J.P. and J.L.O.-R.; funding acquisition, T.J.P. and J.L.O.-R. All authors have read and agreed to the published version of the manuscript.

Funding: CONAHCYT postdoctoral fellowship of T.J.P. (grant number I1200/331/2023-MOD. ORD./10/2023) and CONAHCYT postgraduate scholarship of K.I.V.H (Application number 651dc8c33e4b0f172641d2cb-1301333).

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Baran, S.P. Natural Product Total Synthesis: As Exciting as Ever and Here to Stay. *J. Am. Chem. Soc.* **2018**, *140*, 4751–4755. [CrossRef] [PubMed]
2. Su, B.; Hartwig, J.F. Development of Chiral Ligands for the Transition-Metal-Catalyzed Enantioselective Silylation and Borylation of C−H Bonds. *Angew. Chem. Int. Ed.* **2021**, *61*, e202113343. [CrossRef] [PubMed]
3. Michaelson, R.C.; Palermo, R.E.; Sharpless, K.B. Chiral hydroxamic acids as ligands in the vanadium catalyzed asymmetric epoxidation of allylic alcohols by tert-butyl hydroperoxide. *J. Am. Chem. Soc.* **1977**, *99*, 1990–1992. [CrossRef]
4. Li, Z.; Yamamoto, H. Hydroxamic Acids in Asymmetric Synthesis. *Acc. Chem. Res.* **2012**, *46*, 506–518. [CrossRef] [PubMed]
5. Pawar, T.J.; Bonilla-Landa, I.; Reyes-Luna, A.; Barrera-Méndez, F.; Enríquez-Medrano, F.J.; Díaz-de-León-Gómez, R.E.; Olivares-Romero, J.L. Chiral Hydroxamic Acid Ligands in Asymmetric Synthesis: The Evolution of Metal-Catalyzed Oxidation Reactions. *ChemistrySelect* **2023**, *8*, e202300555. [CrossRef]
6. Sawano, T.; Yamamoto, H. Substrate-Directed Catalytic Selective Chemical Reactions. *J. Org. Chem.* **2018**, *83*, 4889–4904. [CrossRef] [PubMed]
7. Bhadra, S.; Yamamoto, H. Substrate Directed Asymmetric Reactions. *Chem. Rev.* **2018**, *118*, 3391–3446. [CrossRef]
8. Zhang, W.; Basak, A.; Kosugi, Y.; Hoshino, Y.; Yamamoto, H. Enantioselective Epoxidation of Allylic Alcohols by a Chiral Complex of Vanadium: An Effective Controller System and a Rational Mechanistic Model. *Angew. Chem. Int. Ed.* **2005**, *44*, 4389–4391. [CrossRef]
9. Whitesell, J.K. C_2 symmetry and asymmetric induction. *Chem. Rev.* **1989**, *89*, 1581–1590. [CrossRef]
10. Makita, N.; Hoshino, Y.; Yamamoto, H. Asymmetric Epoxidation of Homoallylic Alcohols and Application in a Concise Total Synthesis of (−)-α-Bisabolol and (−)-8-epi-α-Bisabolol. *Angew. Chem. Int. Ed.* **2003**, *42*, 941–943. [CrossRef]
11. Eddin, L.B.; Jha, N.K.; Goyal, S.N.; Agrawal, Y.O.; Subramanya, S.B.; Bastaki, S.M.A.; Ojha, S. Health Benefits, Pharmacological Effects, Molecular Mechanisms, and Therapeutic Potential of α-Bisabolol. *Nutrients* **2022**, *14*, 1370. [CrossRef]
12. Li, F.; Wang, Z.-H.; Zhao, L.; Xiong, F.-J.; He, Q.-Q.; Chen, F.-E. An efficient enantioselective synthesis of florfenicol via a vanadium-catalyzed asymmetric epoxidation. *Tetrahedron Asymmetry* **2011**, *22*, 1337–1341. [CrossRef]
13. Papich, M.G. Florfenicol. In *Saunders Handbook of Veterinary Drugs*, 4th ed.; Elsevier: Amsterdam, The Netherlands, 2016; pp. 327–329. [CrossRef]
14. Matsubara, T.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. Total synthesis of (−)-ophiodilactone A and (−)-ophiodilactone B. *Angew. Chem. Int. Ed. Engl.* **2014**, *53*, 757–760. [CrossRef]

15. Ueoka, R.; Fujita, T.; Matsunaga, S. Ophiodilactones A and B, Cytotoxic Tetrameric Phenylpropanoids, from the Ophiuroid Ophiocoma scolopendrina. *J. Org. Chem.* **2009**, *74*, 4396–4399. [CrossRef] [PubMed]
16. Fenneteau, J.; Vallerotto, S.; Ferrié, L.; Figadère, B. Liebeskind–Srogl cross-coupling on γ-carboxyl-γ-butyrolactone derivatives: Application to the side chain of amphidinolides C and F. *Tetrahedron Lett.* **2015**, *56*, 3758–3761. [CrossRef]
17. Kobayashi, J.; Ishibashi, M.; Walchli, M.R.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Ohizumi, Y. Amphidinolide C: The first twenty-five membered macrocyclic lactone with potent antineoplastic activity from the cultured dinoflagellate *Amphidinium* sp. *J. Am. Chem. Soc.* **1988**, *110*, 490–494. [CrossRef]
18. Xu, J.; Caro-Diaz, E.J.E.; Trzoss, L.; Theodorakis, E.A. Nature-Inspired Total Synthesis of (–)-Fusarisetin A. *J. Am. Chem. Soc.* **2012**, *134*, 5072–5075. [CrossRef] [PubMed]
19. Kohyama, A.; Kanoh, N.; Kwon, E.; Iwabuchi, Y. An enantiocontrolled entry to the tricyclic polar segment of (+)-fusarisetin. *Tetrahedron Lett.* **2016**, *57*, 517–519. [CrossRef]
20. Morin, C.; Fortin, S.; Rousseau, E. 19,20-EpDPE, a bioactive CYP450 metabolite of DHA monoacyglyceride, decreases Ca^{2+} sensitivity in human pulmonary arteries. *Am. J. Physiol. Heart Circ.* **2011**, *301*, H1311–H1318. [CrossRef] [PubMed]
21. Cinelli, M.A.; Lee, K.S.S. Asymmetric Total Synthesis of 19,20-Epoxydocosapentaenoic Acid, a Bioactive Metabolite of Docosahexaenoic Acid. *J. Org. Chem.* **2019**, *84*, 15362–15372. [CrossRef]
22. Boudreault, P.L.; Mattler, J.K.; Wender, P.A. Studies on the regio- and diastereo-selective epoxidation of daphnanes and tiglianes. *Tetrahedron Lett.* **2015**, *56*, 3423–3427. [CrossRef]
23. Barlan, A.U.; Basak, A.; Yamamoto, H. Enantioselective Oxidation of Olefins Catalyzed by a Chiral Bishydroxamic Acid Complex of Molybdenum. *Angew. Chem. Int. Ed.* **2006**, *45*, 5849–5852. [CrossRef]
24. Wang, C.; Yamamoto, H. Tungsten-Catalyzed Asymmetric Epoxidation of Allylic and Homoallylic Alcohols with Hydrogen Peroxide. *J. Am. Chem. Soc.* **2014**, *136*, 1222–1225. [CrossRef] [PubMed]
25. Pawar, T.J.; Mitkari, S.B.; Peña-Cabrera, E.; Gómez, C.V.; Cruz, D.C. Polyenals and Polyenones in Aminocatalysis: A Decade Building Complex Frameworks from Simple Blocks. *Eur. J. Org. Chem.* **2020**, *2020*, 6044–6061. [CrossRef]
26. Davis, R.L.; Stiller, J.; Naicker, T.; Jiang, H.; Jørgensen, K.A. Asymmetric Organocatalytic Epoxidations: Reactions, Scope, Mechanisms, and Applications. *Angew. Chem. Int. Ed.* **2014**, *53*, 7406–7426. [CrossRef] [PubMed]
27. Heravi, M.M.; Lashaki, T.B.; Nasim Poorahmad, N. Applications of Sharpless asymmetric epoxidation in total synthesis. *Tetrahedron Asymmetry* **2015**, *26*, 405–495. [CrossRef]
28. Pawar, T.J.; Valtierra-Galvan, M.F.; Rodríguez-Hernández, A.; Reyes-Luna, A.; Bonilla-Landa, I.; García-Barradas, O.; Barrera-Méndez, F. Synthesis of Novel C_2 Bishydroxamic Acid Ligands and their Application in Asymmetric Epoxidation Reactions. *Synlett* **2023**, *34*, A–G. [CrossRef]