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Introduction

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1.1 Molecular Chirality and Atropisomerism

1.1.1 Molecular Chirality

The exploration of stereochemistry has captivated the chemical community since Pasteur's groundbreaking revelation of molecular chirality in 1848 [1], followed by van 't Hoff and Le Bel's influential introduction of tetrahedral carbon in 1874 [2, 3]. The International Union of Pure and Applied Chemistry (IUPAC) defines **chirality**, derived from the Greek word χείρ (kheir) meaning hand, as *the geometric property of a rigid object (or spatial arrangement of points or atoms) being nonsuperposable on its mirror image. Such an object lacks symmetry elements of the second kind, including a mirror plane, a center of inversion, or a rotation-reflection axis* [4]. Chiral molecules typically possess at least one stereogenic element, giving rise to their chirality. The most prevalent type of stereogenic element is a stereogenic center or **chirality center**, which is *an atom holding a set of ligands in a spatial arrangement which is not superposable on its mirror image* (IUPAC) [5]. A chirality center is thus a generalized extension of the concept of the asymmetric carbon atom to the central atoms of any element, for example, nitrogen N or phosphorus P. There are other types of stereogenic elements that can give rise to chirality, including a stereogenic axis (axial chirality), a stereogenic plane (planar chirality), and a screw axis (helical chirality) (Figure 1.1) [5].

Chirality axis: *An axis around which a set of ligands is held so that it results in a spatial arrangement that is not superposable on its mirror image.*

Chirality plane: *A planar unit connected to an adjacent part of the structure by a bond, which results in restricted torsion so that the plane cannot lie in a symmetry plane.*

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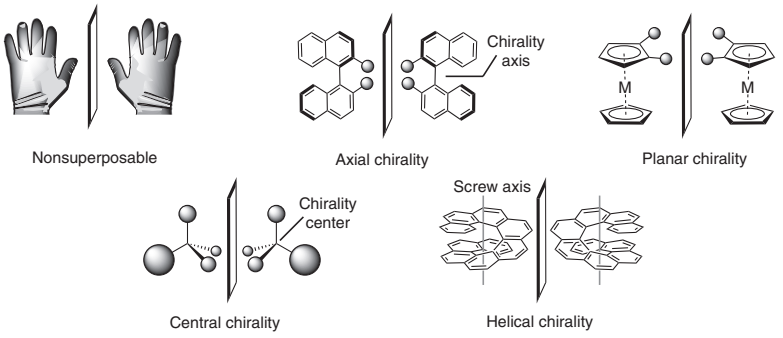


Figure 1.1 Different types of molecular chiralities and stereogenic elements.

Screw axis: *An axis around which the atoms are held in a screw-shaped arrangement that is not superposable on its mirror image. While certain sources categorize helical chirality as a form of axial chirality, IUPAC does not acknowledge helicity as a subtype of axial chirality.*

Chirality is a ubiquitous phenomenon observed in various disciplines, mainly in the realms of biology, pharmaceuticals, organic chemistry, and materials science [6]. Biological homochirality of essential molecules such as L-amino acids in proteins and D-sugars in nucleic acids is vital for the proper functioning of living organisms [7]. The thing is reflected in the drug industry, as often only one enantiomer of a chiral drug exhibits therapeutic efficacy, leading to the development and production of single-enantiomer drugs to enhance their efficacy and minimize associated side effects [8]. Chirality extends its impact to materials science, where certain chiral molecules exhibit unique chiroptical features, such as circularly polarized luminescence (CPL) and circular dichroism (CD), facilitating the design of advanced materials and devices [9–12]. Chiral catalysts in organic chemistry have a key role in asymmetric synthesis, contributing to the selective production of enantioenriched chiral compounds, especially in the synthesis of pharmaceuticals and functionalized materials [13–16].

1.1.2 Axial Chirality and Atropisomerism

Earlier investigations primarily focused on central chirality, with the pioneering works of Pasteur, van't Hoff, and Lebel centered on chiral tetrahedral carbon with four distinct substituents [1–3]. However, a milestone was achieved a century ago in 1922 when George Christie and James Kenner first identified atropisomerism in a tetra-substituted biphenyl diacid **1** [17]. After this groundbreaking discovery, some efforts were exerted to explore this new type of chirality, but a quantum leap transpired with the advent of asymmetric catalysis. Ligands exhibiting axial chirality, such as derivatives of 1,1′-bi-2-naphthols (BINOLs), 2,2′-bis(di-phenylphosphino)-1,1′-binaphthyls (BINAPs), and 2,2′-diamino-1,1′-binaphthalenes (BINAMs) (refer to Chapters 7 and 8 for detailed insights), demonstrated superior efficacy in controlling asymmetric metal-based reactions, as elucidated by Ryoji Nyori [18].

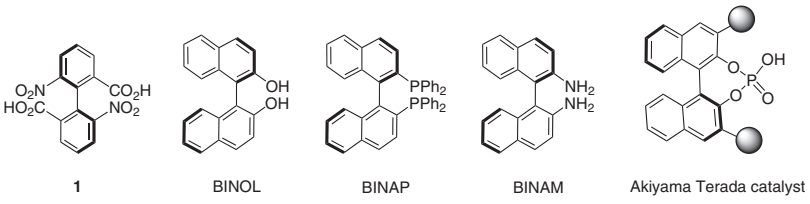


Figure 1.2 Atropisomerism in privileged chiral ligands and organocatalysts.

The prevalence of axial-to-central chirality transfer became evident in the realm of asymmetric catalysis. Over the past two decades, these ligands have additionally proven their superiority in various organocatalysts, such as chiral phosphoric acid catalysts, independently developed by Akiyama and Terada (Figure 1.2). These advancements captivated researchers, prompting them to delve deeper into the study and exploration of axial chirality and atropisomerism [19, 20].

While some may mistakenly conflate axial chirality and atropisomerism concepts considering them synonymous, it is imperative to recognize that axial chirality encompasses broader forms. According to IUPAC, **axial chirality** is precisely defined as a *stereoisomerism resulting from the nonplanar arrangement of four groups in pairs about a chirality axis* [5]. In essence, these frameworks possess a **chiral axis**, imposing restrictions on the rotation of two pairs of groups. As per the IUPAC definition, this concept encompasses diverse families of organic molecules featuring noncoplanar arrangement of two pairs of substituents in the parent backbone. The most prominent class of axially chiral compounds falling under this definition is **atropisomers**, including biaryls, heterobiaryls, aryl alkenes, anilides, and diaryl ethers, whose *axial chirality arises from the restricted rotation about single bonds* [5]. Allenes, spiro compounds, spiranes, and alkylidene-cyclic compounds are other examples of axially chiral compounds, wherein their chirality comes from the perpendicular geometry of two pairs of substituents (Figure 1.3) [21].

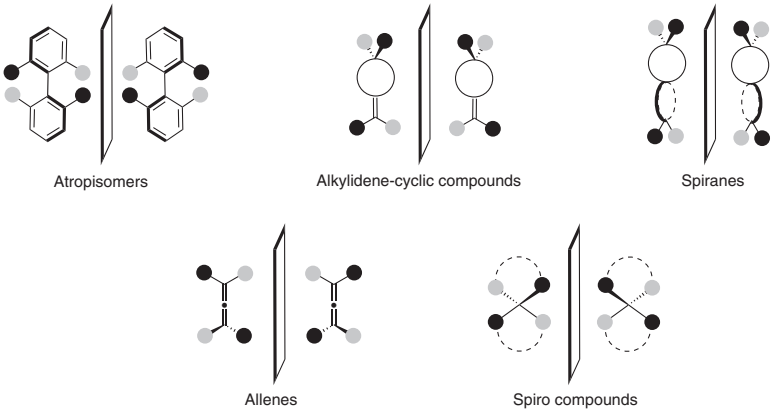


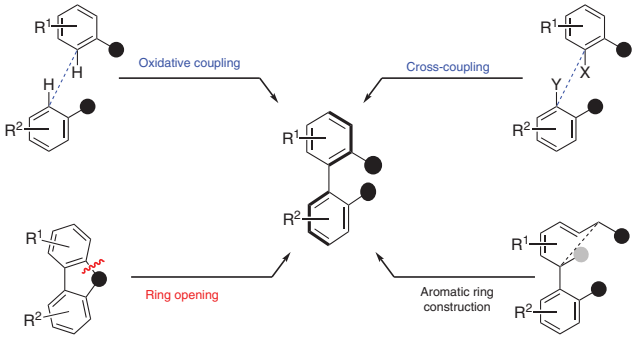
Figure 1.3 The most prominent classes of axially chiral compounds.

The recent surge in literature addressing atropisomerism has significantly impacted the field, capturing attention with its exploration of naturally occurring molecules that exhibit this chirality element [22]. These molecules play a pivotal role in advancing various scientific domains, addressing not only physical organic issues related to structure and stability but also inspiring the development of innovative reaction concepts [23]. The design and synthesis of novel scaffolds showcasing atropisomerism contribute to the ongoing expansion of this interdisciplinary field, which seamlessly integrates chemistry, biology, and physics, finding applications in both medicinal chemistry and materials science [24–28]. Atropisomers, as a fundamental chirality element in nature, exhibit diverse biological activities and functions, rendering them indispensable in asymmetric catalysis. Numerous atropisomers serve as privileged chiral ligands, demonstrating their critical role in catalytic processes [29, 30]. However, despite their immense potential, challenges persist, exemplified by the varying biological activities observed in stable atropisomeric Food and Drug Administration (FDA)-approved drugs and experimental compounds. The phenomenon of rapidly interconverting atropisomerism adds complexity, as these compounds, while conventionally considered achiral, exhibit atroposelective binding to protein targets [31, 32].

Recognizing the need for a comprehensive resource addressing the opportunities and challenges in this field, we present this handbook, focusing on recent advances in atroposelective synthesis and their different applications. This book explores diverse atroposelective synthetic approaches, including cross-coupling reactions, ring-opening reactions, formation of aromatic rings, and desymmetrization *via* functional group transformation, utilizing different metal and organocatalysts [33, 34]. By showcasing the impact of these advances on asymmetric catalysis, the synthesis of natural products, functionalized materials, and drug industry, this book contributes to a deeper understanding of the current state of atropisomerism and highlights unresolved challenges. In alignment with the broader context, this book integrates and complements existing literature, particularly *Axially Chiral Compounds: Asymmetric Synthesis and Applications* by Bin Tan (WILEY-VCH GmbH, **2021**) [35] and *Atropisomerism and Axial Chirality* by José M Lassaletta (World Scientific Publishing Europe Ltd, **2019**) [36]. By collating and discussing recent advances, we aim to provide valuable insights for researchers working in this dynamic field.

1.2 Atropisomerism in Asymmetric Organic Synthesis

The pursuit of atroposelective synthesis of various atropisomers, mainly biaryls [37] and heterobiaryls [38] holds significant relevance due to its applications across various domains, including polymers, ligands, natural products, and pharmaceuticals. One of the most straightforward methods is based on oxidative coupling reactions, a methodology presenting a direct pathway that, while having a restricted substrate scope, obviates the need for prefunctionalization of starting materials (Scheme 1.1) [39]. A second strategy entails the direct establishment of chirality



Scheme 1.1 Straightforward strategies for enantioselective synthesis of atropisomers.

axes through C—C bond-forming asymmetric cross-coupling reactions. This approach necessitates highly efficient catalysts capable of imparting the requisite stereocontrol, especially in the context of coupling hindered *ortho*-substituted substrates [40–42]. A third alternative is based on the *de novo* formation of one or more aromatic rings by cycloaddition or cyclization reactions [43]. Additionally, a noteworthy strategy, stemming from the seminal work of Bringmann et al. in 1986 [44], focuses on atroposelective ring opening, incorporating the enantioselective cleavage of diverse bonds [45]. Great advances have been introduced in this domain, especially with the expansion of their applications. A diverse array of metal-based and organocatalysts alongside enzymatic transformations have proven their efficiency in the highly controlled and selective construction of atropisomers [46]. While numerous enduring challenges have been recently addressed, the field still confronts unresolved issues and offers multiple opportunities that can propel it further [47]. The ongoing interplay between challenges and opportunities underscores the dynamic nature of atroposelective synthesis and presents avenues for continued advancement.

Recognizing the need for a comprehensive resource addressing the opportunities and challenges in this field, we present this handbook, focusing on recent advances in atroposelective synthesis. This book is structured into two parts: Part I, titled "Atroposelective Synthesis", and Part II, titled "Challenges and Applications". Part I primarily focuses on recent advancements and challenges in atroposelective synthesis, employing diverse approaches. Chapters 2–4 delve into various metal-catalyzed atroposelective coupling strategies, specifically targeting the construction of biaryls and heterobiaryls, which are prevalent in this context. Chapter 2 concentrates on group 8 transition-metal complexes, mainly iron and ruthenium, as catalysts for atroposelective oxidation of different arenols. Within this chapter, **Prof. Uchida** extensively discusses the key role played by iron and ruthenium complexes in achieving stereoselective oxidative homo- and hetero-coupling reactions of arenols. The author emphasizes recent breakthroughs, showcasing how the design of innovative ligands has overcome long-standing challenges in hetero-coupling methodologies. Notable examples include Pappo's recent work in 2022, illustrating the cross-selective synthesis of NOBIN through the introduction

of a chiral iron disulfonate complex as the catalyst [48]. Additionally, Smith's 2023 findings highlight the efficiency of an iron Pybox complex as a catalyst in the cross-coupling of 3-hydroxynaphthoates with indole derivatives as coupling partners, utilizing bis(*tert*-butyl) peroxide as the oxidant [49]. Uchida's work is also discussed, demonstrating the cross-coupling of arenols with similar structures and electronic natures using (H_2O)Ru-Salen complexes [50].

Chapter 3 delves into recent advancements in the catalytic oxidative coupling of arenols utilizing vanadium complexes, with a particular focus on its application in the preparation of polycyclic heteroaromatics (PHAs). Notably, optically active vanadium complexes, featuring a Schiff base ligand and a tetravalent or pentavalent vanadium metal center, have garnered attention as environmentally benign catalysts facilitating the generation of axially chiral molecules [51]. **Prof. Salem** and **Prof. Takizawa** discuss with many mechanistic insights why these complexes exhibited noteworthy characteristics, serving as active catalysts in diverse regio- and enantioselective C—C bond formation reactions. Importantly, the inherent selectivity and distinctive catalytic activity of vanadium not only mitigate undesirable side reactions and peroxidation but also confer broad functional group tolerances in various organic syntheses [51]. Therefore, the applications of this chemistry extend beyond their catalytic role, finding utility in the atroposelective synthesis of heterocyclic nanographenes endowed with favorable optical properties, such as helicenes and dehydrohelicenes [12, 52]. Furthermore, these vanadium complexes have been instrumental in synthesizing various naturally occurring substrates (also refer to Chapter 10).

In the context of cross-coupling reactions for synthesizing biaryl and heterobiaryls, particular attention is directed toward the Suzuki–Miyaura coupling (SMC) – an indispensable transformation in contemporary synthetic chemistry [53]. This reaction holds paramount significance in the synthesis of functionalized materials, various ligands, natural products, and biologically active molecules [54–56]. Consequently, we dedicated Chapter 4 to explore the atroposelective SMC for the production of axially chiral biaryls. In this comprehensive chapter, **Prof. Korenaga** systematically reviews numerous successful examples of atroposelective SMC toward biaryl synthesis, emphasizing the pivotal role played by directing groups in the enantioinduction. Furthermore, it delves into recent studies that have reconsidered established mechanisms, exemplified by the work of Patel et al. [57]. Their theoretical considerations and density functional theory (DFT) calculations shed light on the importance of weak interactions in the asymmetric induction of aryls lacking directing groups. The chapter also addresses the challenges prevailing in the field and highlights issues such as the necessity for high catalyst loading and the limited substrate scope. It also assesses potential avenues for overcoming these challenges, including the utilization of Buchwald ligands with preliminary efforts by the Korenaga group to implement this approach.

In contrast to the preceding chapters, which discussed the metal-based methodologies for atroposelective synthesis, Chapter 5 delves into the diverse array of

organocatalysts and their pivotal role in the enantioselective synthesis of atropisomers. **Prof. Bencivenni** introduces an array of organocatalytic approaches, encompassing aminocatalysis, base catalysis, phase-transfer catalysis (PTC), and phosphoric acid catalysis (PAC). The inherent adaptability of these catalytic modalities to various synthetic strategies, coupled with the orthogonality of their modes of action, renders them invaluable for the enantioselective construction of a broad spectrum of atropisomers exhibiting diverse scaffolds. The chapter discusses selected examples of structurally diverse atropisomers, including C–C (biaryls and non-biaryls) and C–N as well as C–O, C–B, and N–N atropisomers [33]. The chapter also highlights various recent advancements, including Sparr's work on the *de novo* construction of one or two aromatic rings and his key achievement in the diasterodivergent synthesis of arenes with two stereogenic axes [58–60]. In the evolution of organocatalysts, crowned with the Nobel Prize in Chemistry to Benjamin List and David MacMillan in 2021 [61], a large variety of atropisomers have found substantial utilities for catalyzing atroposelective transformations themselves, suggesting that further breakthroughs can still be expected from today's research in expanding fields like organocatalysis and atropisomers.

Enantioselective ring-opening reactions of fused biaryl compounds represent another powerful strategy for constructing axially chiral products. This approach offers practical advantages, including the broad substrate applicability, excellent selectivity control, and high atom efficiency. Experimental observations indicate that inert chemical bonds within tensegrity structures can be selectively cleaved under mild conditions through the ring opening of these structures, attributed to the torsional strain induced by their twisted conformation [45, 62]. In recent years, significant progress has been made in this field, extensively reviewed in existing literature. However, a comprehensive discussion specifically focusing on the synthesis of atropisomers *via* enantioselective ring-opening reactions has been notably absent. In Chapter 6, **Dr. Duan** and **Prof. Gu** provide an insightful historical overview of the asymmetric ring-opening strategy, commencing with the pioneering work of Bringmann [44] and encompassing subsequent key advancements in this domain. The chapter is organized into six sections corresponding to different types of bond cleavage, including the CO—O bond of "Bringmann's Lactone" as well as C—X (X = group 14, 15, 16, and 17 elements) bonds. The final section briefly addresses the ring-opening reactions of transient pentacyclic metal species. The authors elucidate the structural prerequisites of various substrates for effective implementation of this strategy, incorporating dynamic kinetic resolution (DKR), and discuss the impact of torsional strain in bridged biaryls on their efficiency. Within this framework, Chapter 6 systematically explores the use of various metal-based catalysts, including iridium, cobalt, nickel, copper, rhodium, and palladium, along with different ligands and organocatalysts. This structured organization facilitates an understanding of the advancements and challenges in a good context mainly revolving around the synthetic approach rather than the substrate or the obtained product.

1.3 Atropisomerism: Challenges and Applications

Part II of this book delves into the multifaceted applications of scaffolds exhibiting atropisomerism, spanning across diverse realms such as asymmetric catalysis, the total synthesis of natural compounds, medicinal chemistry, and material-oriented applications. By elucidating recent strides in these areas, alongside the obstacles impeding their integration, particularly in domains like drug industry [31, 32], researchers can gain insight into the current situation of the field and discern avenues for prospective advancements.

1.3.1 Axially Chiral Ligands and Organocatalysts

The revolution in asymmetric catalysis, particularly with the pioneering work of Nyori in 1980 utilizing BINAP as a ligand in the rhodium-catalyzed asymmetric hydrogenation, has significantly propelled the field of atropisomerism [18]. This progress underscores the profound significance of scaffolds featuring axial chirality, with predictable spatial projection of functionalities, thereby yielding remarkable organocatalysts, ligands, or auxiliaries [63, 64]. Notably, a considerable array of chiral ligands and organocatalysts stems from a few privileged chiral structures, among which the atropisomeric 1,1′-binaphthyl structure occupies a prominent position. The atropisomerism of the 1,1′-binaphthyl moiety offers several advantages in catalysis. First, both enantiomers of the 1,1′-binaphthyl moiety can be easily accessed from commercially available (*R*)- or (*S*)-BINOL. Second, the atropisomerism of the 1,1′-binaphthyl is notably stable and does not undergo racemization under most reaction conditions. Third, the electronic and steric properties of the 1,1′-binaphthyl moiety can be finely tuned by introducing various substituents at the 3,3′ or 7,7′ positions. Additionally, the solubility of the catalyst can be improved by incorporating lipophilic substituents. Last, the 1,1′-binaphthyl moiety with its C^2-symmetric skeleton reduces the number of potential competing diastereomeric transition states and thereby simplifying the understanding of reaction mechanisms. The axially chiral BINOL, BINAM, and NOBIN represent exemplary binaphthyl molecules, from which a multitude of chiral ligands (Figure 1.4) and organocatalysts (Figure 1.5), including the well-regarded BINAP and phosphoric acids, are derived. In Chapter 7, **Dr. Cen** and **Prof. Zhang** meticulously introduce around 150 representative chiral ligands and organocatalysts derived from axially chiral binaphthyl structures, particularly emphasizing BINOL, BINAM, and NOBIN. Spanning from phosphine and phosphoramidite ligands to Schiff base ligands and from Brønsted acids to Lewis bases and phase-transfer organocatalysts, these privileged axially chiral binaphthyl structures underpin the majority of widely utilized chiral catalytic systems. While it may be impractical to encompass all binaphthyl chiral catalysts within a single chapter, the selected examples by the authors underscore the remarkable enantioinductive capability of these privileged atropisomeric binaphthyl structures. Symbolized by BINOL, BINAM, and NOBIN, axially chiral binaphthyl structures have furnished an exceptional chiral environment for numerous asymmetric transformations [29].

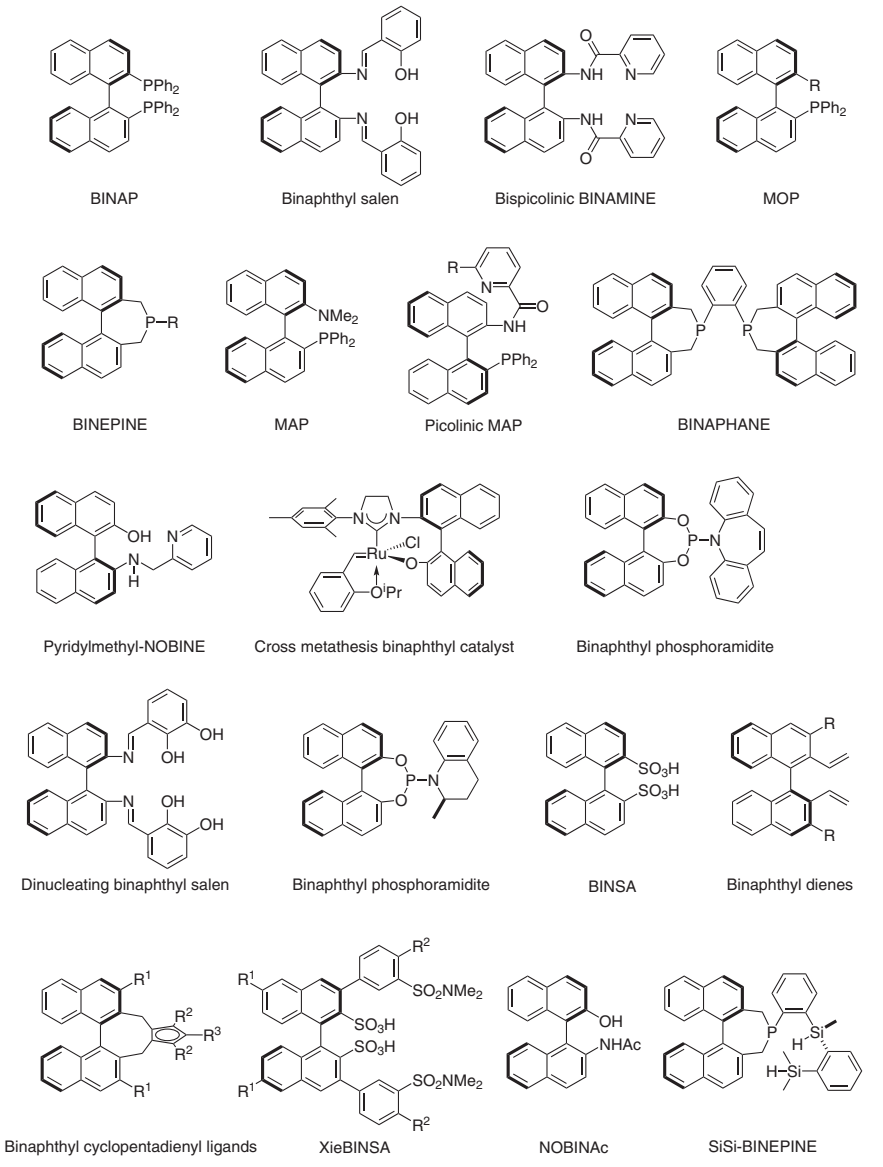


Figure 1.4 Representative chiral ligands derived from atropisomeric binaphthyl structures.

After a comprehensive scope of the role played by axially chiral scaffolds in general, particularly those derived from binaphthyl, the subsequent two chapters delve into a more in-depth and detailed discussion of the role played by two specific families of ligands and organocatalysts that were previously not discussed in depth. Chapter 8 introduces a comprehensive review of various reactions catalyzed by zinc complexes in conjunction with axially chiral ligands, particularly derivatives of BINOL. **Prof. Arai** elucidates in his chapter the significance of specific positions

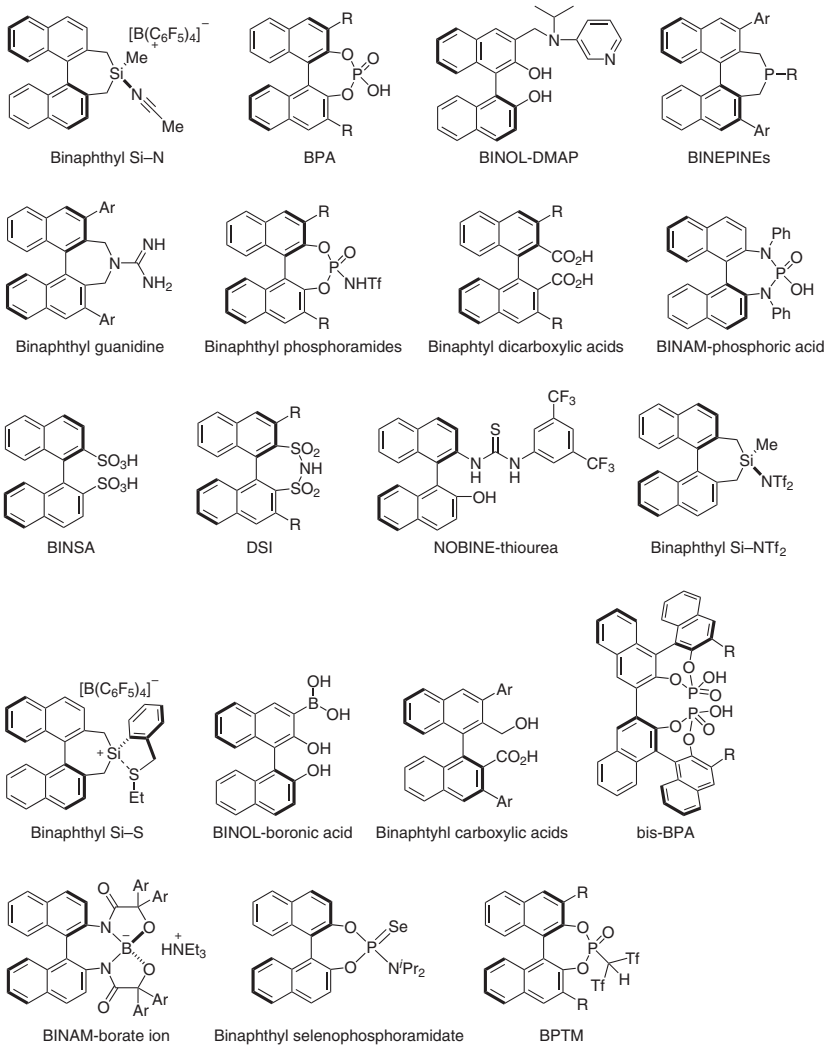


Figure 1.5 Representative chiral organocatalysts derived from atropisomeric binaphthyl structures.

on the ligands, notably the 3,3′ positions, and examines how substituents at these sites influence the overall activity of the zinc catalysts. Furthermore, the chapter expands its scope to encompass other metals, such as lanthanum and barium, which were not extensively discussed in the previous sections of this book. The chapter highlights the significant contributions facilitated by the development of multinuclear zinc catalysts with axial chirality, marking numerous milestones in asymmetric catalysis. Throughout the discussion, mechanisms are scrutinized, providing valuable insights into the underlying processes driving these catalytic transformations.

Chapter 9 covers one of the most rare examples in the domain of atropisomeric organocatalysts, which is nucleophilic catalysis exemplified by binaphthyl-based chiral *N*,*N*-4-dimethyl-4-aminopyridine (DMAP) derivatives [65]. In their chapter, **Prof. Mandai** and **Prof. Suga** explore a range of binaphthyl-based DMAP derivatives and their significant impact on accelerating nucleophilic catalytic reactions. The discussion underscores the favorable outcomes resulting from the incorporation of polar functional groups into the skeleton of the optically active DMAP derivatives. These modifications lead to enhanced catalytic activity and improved enantioselectively, primarily attributed to hydrogen bonding interactions. The chapter delves into the utilization of these derivatives in both intra- and intermolecular enantioselective acylation reactions, highlighting their remarkable efficacy in promoting desired chemical transformations, including different strategies such as kinetic resolution, desymmetrization of alcohols, and DKR.

1.3.2 Natural Product Synthesis

Atropisomeric molecules, imposing a restricted rotational barrier, are not only prevalent in catalysis as chiral ligands or organocatalysts but are also a recurring motif in numerous natural products (Figure 1.6) [22]. The captivating structures and unique features associated with this motif have significantly increased its importance within the synthetic community. The advancement of atroposelective coupling methods, employing various strategies, has contributed to the synthesis of complex molecules [66, 67].

Chapter 10 explores various success stories in the total synthesis of atropisomeric natural products, employing a range of transition-metal-catalyzed asymmetric oxidative coupling reactions coupled with diverse oxidants to augment reactivity and selectivity. **Dr. Kang** and **Prof. Kozlowski**'s contribution to this chapter focuses particularly on copper- and vanadium-catalyzed methodologies. Notably, copper-mediated asymmetric oxidative couplings have utilized poly-substituted naphthols as coupling monomers, while vanadium-catalyzed approaches have expanded the scope to include monocyclic phenols for axial chirality construction in natural product synthesis. The chapter delves into the stereoselectivity of these processes, highlighting the intricate interplay between asymmetric catalysts and the innate stereochemistry of substrates. Additionally, it explores how both catalysts and substrates impact stereochemical outcomes, ultimately enhancing atroposelectivity. The authors shed light on enzyme-based strategies for constructing natural products with chirality axes, encompassing both symmetrical dimers and unsymmetrical coupling products – a feat challenging to achieve *via* conventional chemical means.

1.3.3 Atropisomerism in Drug Discovery and Development

Atropisomerism has garnered an increasing interest in drug design and development within both academia and the pharmaceutical industry over recent decades [68]. The effectiveness of drug action relies heavily on the specific binding

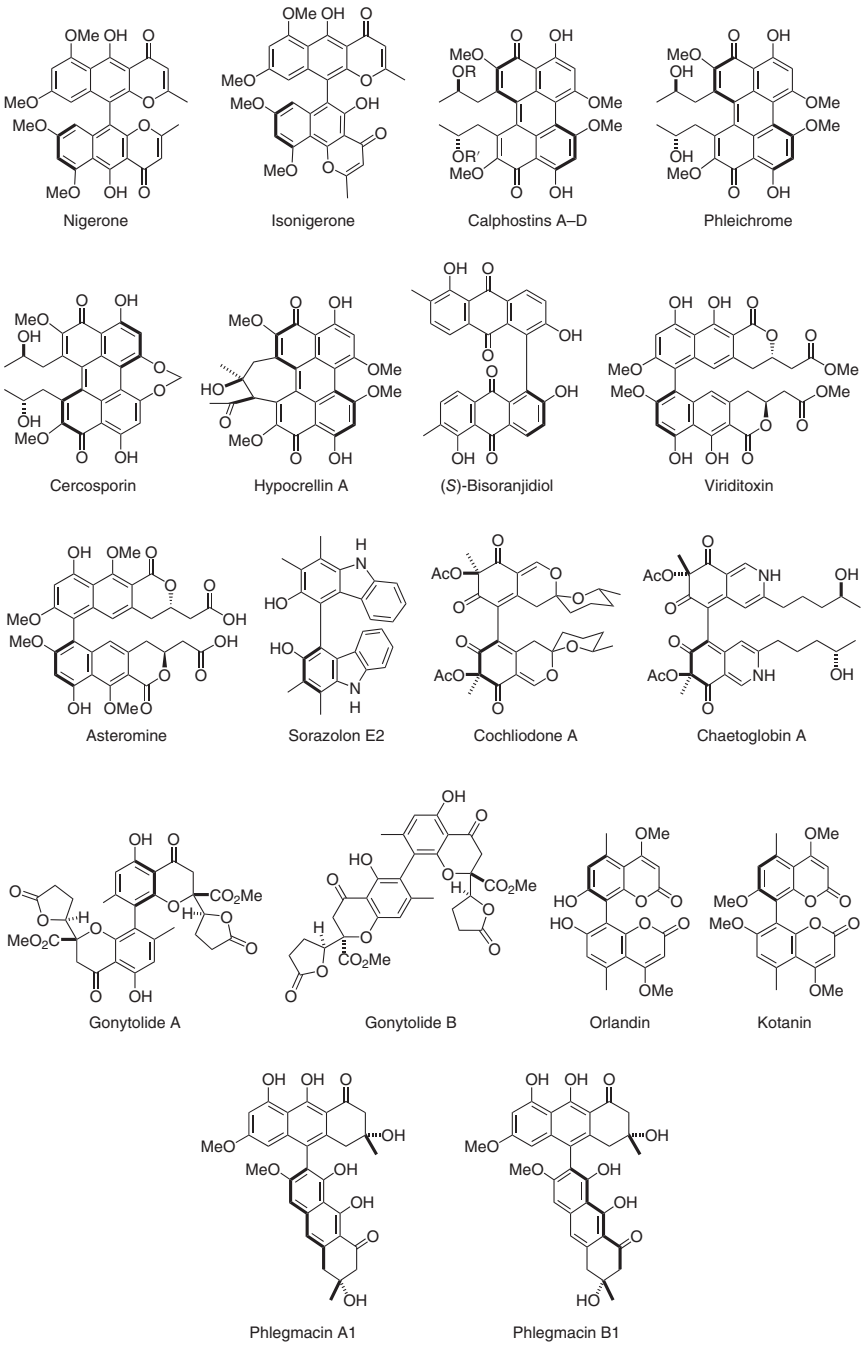


Figure 1.6 Representative natural products featuring chirality axis.

of the bioactive molecule to its protein target, facilitating the formation of crucial chemical interactions that trigger a cascade of biological events culminating in desired bioactivity [8]. Consequently, the influence of axial chirality is anticipated and should be meticulously considered early in the drug design process. It is widely acknowledged that the activity toward a particular target is predominantly dictated by a single atropisomer, with minimal or no contribution from the other enantiomer [69]. "Locking" the molecule in the bioactive atropisomeric form not only enhances activity but also improves selectivity toward the intended biological target. So far, a few FDA-approved drugs stand out as **class III** stable atropisomers, characterized by a high rotational energy barrier (ΔE rotation ≥ 30 Kcal/mol) and slow interconversion between atropisomers ($t_{1/2} > 4.5$ years) [69]. These drugs, including **lesinurad** (urate transporter inhibitor for gout), **telenzepine** (selective M1 receptor blocker for peptic ulcers), **colchicine** (anti-inflammatory/gout agent), and **sotorasib** (KRASG12C covalent inhibitor for non-small cell lung cancer), are either marketed as racemates, single diastereoisomers, or even separated as single atropisomers (Figure 1.7) [24].

In Chapter 11, **Prof. Helal** and his team provide an overview of atropisomerism's utilization in drug discovery, accompanied by examples from recent literature and FDA-approved drugs. These compounds are classified based on their chemical classes into biaryls/heterobiaryls, diaryl ethers or amines, benzamides, and macrocycles. The chapter also discusses the key advantages of controlling atropisomerism in the drug industry and how singular atropisomers offer safer profiles, higher/selective bioactivity, lower administration doses, and reduced off-target activities. Additionally, the authors discuss the main challenges hindering the manufacture of pure atropisomeric drugs, including cost increases and the rapid interconversion of **class I** atropisomers. These compounds, characterized by low ΔE rotation (< 20 Kcal/mol) and quick interconversion at room temperature ($t_{1/2} < 60$ seconds), represent the majority of atropisomeric drug molecules. The chapter concludes by discussing potential opportunities, such as introducing bulkier, sterically hindered scaffolds, which facilitate the switch from **class I** atropisomeric racemates to **class III** atropisomers, easily separable *via* SFC chiral separation [70].

It is worth noting that while this book's structure into two parts facilitates content organization and accessibility for readers, there is a high degree of integration

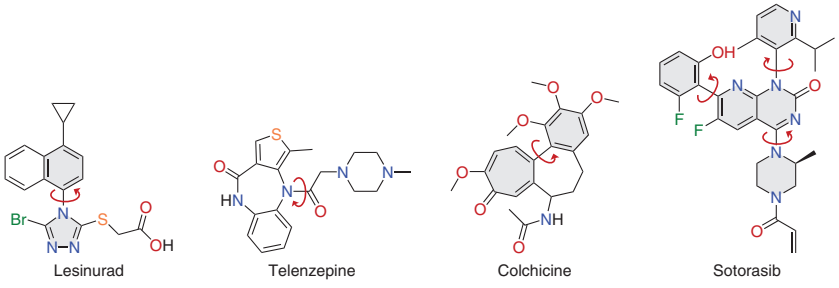


Figure 1.7 Representative FDA-approved drugs featuring class III stable atropisomeric scaffolds.

between the contents and context among the two parts and in each chapter. This book consistently explores different atroposelective synthetic approaches and highlights interconnected parts, whether discussing applications or challenges. For instance, Chapter 3 initiates the first part by delving into vanadium-catalyzed atroposelective synthesis and extends this discussion to the application of this approach in creating functionalized materials such as helicenes and dehydrohelicenes *via* axial-to-helical chirality transfer. These material-based applications are not addressed in other parts of the book. Similarly, some chapters in Part II, dedicated to applications, discuss atroposelective synthetic strategies not previously highlighted in Part I. For example, Chapter 10 delves into copper-catalyzed and enzymatically based atroposelective oxidative coupling of atropisomeric natural products, presenting novel synthetic methodologies not previously discussed in Part I. This integrated context ensures a comprehensive discussion of atropisomerism from various angles, providing readers with a holistic understanding of its applications and implications.

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