

Synthetic Methods for the Construction of Chiral Molecules: Enantioselective Catalysis and Asymmetric Synthesis

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Abstract

Chiral molecules, which possess non-superimposable mirror images or enantiomers, play a pivotal role in various fields, including pharmaceuticals, agrochemicals, and materials science. The unique properties of chiral compounds often make them essential components of life-saving drugs and advanced materials. Consequently, the development of efficient and selective methods for the synthesis of chiral molecules is of paramount importance. Two of the most powerful strategies in this realm are enantioselective catalysis and asymmetric synthesis. Enantioselective catalysis is a specialized branch of catalysis that focuses on the selective production of a single enantiomer (chiral molecule) from a racemic mixture (a 50:50 mixture of two mirror-image isomers known as enantiomers). This field has had a profound impact on chemistry and various industries, especially pharmaceuticals, where the chirality of molecules can significantly affect their biological activity and safety.

Keywords: Chiral molecules • Enantioselective catalysis • Pharmaceuticals

Introduction

Enantioselective catalysis represents a groundbreaking approach to chiral molecule synthesis, allowing chemists to control the absolute stereochemistry of a molecule with precision. This method is based on the use of chiral catalysts, which are molecules that can differentiate between the two enantiomers of a substrate and selectively promote the formation of one enantiomer over the other. One of the most prominent examples of enantioselective catalysis involves chiral transition metal complexes. These complexes, often containing chiral ligands, can catalyze a wide range of reactions with high selectivity. For instance, the Sharpless epoxidation and asymmetric hydrogenation reactions employ chiral catalysts to generate chiral epoxides and enantiomerically enriched alcohols, respectively.

Chirality refers to the property of molecules that cannot be superimposed onto their mirror images, much like left and right hands. Chiral molecules exist as enantiomers, which are non-superimposable mirror images of each other. Understanding and controlling chirality are essential in enantioselective catalysis. Enantioselective catalysis relies on the use of chiral catalysts, which are molecules or complexes that possess chirality themselves and can differentiate between the two enantiomers of a substrate. Chiral catalysts play a critical role in controlling the stereochemistry of the reaction. Enantioselective catalysis can be applied to a wide range of chemical reactions, including asymmetric transformations such as asymmetric hydrogenation, asymmetric epoxidation, asymmetric allylic substitution, and more. The choice of catalyst and reaction conditions depends on the specific transformation being pursued.

Description

The primary goal of enantioselective catalysis is to control the stereochemistry

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of a chemical reaction so that it selectively produces one enantiomer while minimizing or eliminating the formation of the other enantiomer. This high level of selectivity is crucial in industries like pharmaceuticals, where the efficacy and safety of drugs are often dependent on the absolute configuration of chiral molecules. Sharpless Asymmetric Epoxidation is a reaction, developed by K. Barry Sharpless, involves the asymmetric epoxidation of alkenes using a chiral titanium complex. It is widely used in the synthesis of chiral epoxides, which are valuable intermediates in organic synthesis. Asymmetric hydrogenation reactions use chiral transition metal catalysts to selectively convert prochiral ketones or olefins into chiral alcohols or amines. This method is vital for the synthesis of chiral pharmaceuticals and agrochemicals.

Organocatalysis employs small organic molecules as chiral catalysts to facilitate various asymmetric transformations. One notable example is the use of proline derivatives in the Hajos-Parrish-Eder-Sauer-Wiechert reaction for the synthesis of chiral cyclic compounds. Enzymes are highly selective biocatalysts that can catalyze a wide range of enantioselective reactions. Enzymatic enantioselective catalysis is employed in the production of chiral pharmaceutical intermediates and natural product synthesis. Organocatalysis, which uses small organic molecules as chiral catalysts, has gained significant attention in recent years. Examples include the use of proline derivatives in the Hajos-Parrish-Eder-Sauer-Wiechert reaction to synthesize chiral cyclic compounds and the use of bifunctional thiourea catalysts in the aza-Michael reaction for the synthesis of chiral amines. Asymmetric synthesis is another powerful method for the construction of chiral molecules, offering a broad toolkit for chiral compound preparation. Unlike enantioselective catalysis, asymmetric synthesis does not rely on the use of a chiral catalyst but rather on the creation of chiral intermediates or substrates.

Chiral auxiliaries are temporary chiral groups that are attached to a substrate to impart chirality to a specific position. After the reaction is complete, the auxiliary can be removed, yielding the desired chiral compound. This method has been used successfully in the synthesis of various chiral compounds, such as amino acids. Resolution techniques involve separating a racemic mixture of enantiomers into their individual components. One common method is crystallization resolution, where diastereomeric salt formation is used to separate the enantiomers based on their different solubilities. Enzymes are highly selective catalysts that can promote reactions with exceptional enantioselectivity. Enzymatic methods, such as kinetic resolution and dynamic kinetic resolution, have been employed to prepare chiral molecules in both laboratory and industrial settings.

While enantioselective catalysis and asymmetric synthesis have revolutionized chiral molecule synthesis, challenges remain. These include

the development of more efficient catalysts, a broader substrate scope, and sustainability concerns. The development of enantioselective catalysis has had a profound impact on several industries, most notably the pharmaceutical industry. The ability to produce single enantiomers of drug molecules has improved drug efficacy and safety while reducing production costs. Additionally, enantioselective catalysis plays a crucial role in the synthesis of agrochemicals, flavors, fragrances, and fine chemicals [1-5].

Conclusion

The construction of chiral molecules through enantioselective catalysis and asymmetric synthesis is a dynamic and evolving field of research. These methods provide powerful tools for chemists to access a wide range of chiral compounds with high selectivity. As research continues, we can expect to see even more efficient and sustainable processes emerge, further expanding the possibilities for chiral molecule synthesis and its applications in various industries. Enantioselective catalysis continues to be an active area of research, with ongoing efforts to discover new chiral catalysts, expands the range of applicable reactions, and improve catalytic efficiency. As our understanding of chiral chemistry and catalysis deepens, enantioselective catalysis is poised to play an even more significant role in the synthesis of chiral molecules and the development of novel materials and compounds.

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Conflict of Interest

None.

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