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A Medicinal Chemist's Guide to Asymmetric Organocatalysis

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Abstract

The majority of drugs work by interacting with chiral counterparts, such as proteins, and we are all too aware of how chirality can have a negative impact on the outcome of a therapeutic regimen. The market for chiral, non-racemic drugs is growing, and it is becoming increasingly important to prepare these compounds in a safe, cost-effective, and environmentally sustainable manner. Asymmetric organocatalysis has a long history, but its renaissance period began only in the first millennium. Since then, this field has advanced to an extraordinary level, as evidenced by the awarding of the 2021 Nobel Prize in Chemistry. We would like to highlight the use of organocatalysis in the synthesis of enantio-enriched molecules that may be of interest to the pharmaceutical industry and the medicinal chemistry community in this review.

Keywords: Asymmetric organocatalysis • Chiral drugs • Drug discovery • Drug synthesis

Introduction

The majority of prescribed drugs work by interacting with a biochemical counterpart that is chiral due to its spatially defined three-dimensional shape. As a result, this recognition process is highly stereotypical. This simple word has had a massive impact on all phases of today's drug discovery process, from hit discovery to manufacturing process fine-tuning. Despite the infamous thalidomide case involving the chirality and stereospecificity of the drug-biological counterpart interaction, pharmacopoeias were still dominated by racemic drugs until 20 years ago, and it was only in 1992 that regulatory agencies began to set some guidelines for commercialising chiral drugs. The Food and Drug Administration document titled "Development of new stereoisomeric drugs" was critical in this context.

The drug discovery industry has reached a point of no return. Indeed, according to Agranat et al., 108 of the 195 new molecular entities approved by the FDA between 2001 and 2010 were single enantiomers. Importantly, such a significant shift was made possible by the development of appropriate technological platforms that allowed for the large-scale synthesis and/or separation of a given chiral compound, as well as the identification of the chiral compounds. There are three approaches to preparing enantiopure compounds: resolution of racemates, synthesis from the chiral pool, and synthesis from prochiral substrates. The chiral information is primarily transferred from an enantiopure catalyst to a non-chiral compound in the latter case.

Literature Review

Asymmetric organocatalysis is the use of small organic molecules to speed up reactions and induce stereochemical information. It represented a paradigm shift in the minds of chemists who had previously dealt with metal compounds or biomolecules as catalytic systems. The success of organocatalysis is due to the numerous advantages it has over enzymes and metal catalysts. Indeed, while enzymes are safe to use and perform admirably in a physiological environment, they are prohibitively expensive, do not perform well under normal organic conditions of solvent, temperature, and so on, and can be highly specific with respect to substrate, resulting in a very limited scope.

List and Barbas' and MacMillan's simultaneous and independent publications represented the breakthrough that finally conceptualised the field and triggered the explosion of asymmetric organocatalysis. Organocatalysis has since become the third pillar of asymmetric catalysis, providing chemists with a phenomenally powerful tool for the synthesis of enantio-enriched compounds. We would like to highlight the use of organocatalysis in the synthesis of enantio-enriched molecules that may be of interest to the pharmaceutical industry and the medicinal chemistry community in this review. In this review, we will look at the various activation modes for organocatalytic asymmetric carbon-carbon bond forming reactions, examining the general mechanisms, the most important reactions, and their applications in medicinal chemistry by using examples from academic and industrial research.

Discussion

Covalent activation modes rely on the formation of a reactive intermediate as a result of a covalent reversible interaction between a catalyst and a substrate. Covalent activation is primarily dependent on aminocatalysis. Other important activation modes for forming a C-C bond rely on the use of catalysts such as nitrogen heterocyclic carbenes (NHC), phosphines, carbonyl compounds, and iodine derivatives. Despite their intriguing properties, aminocatalysis is the primary activation mode in organocatalysis due to the possibility of recycling the catalyst, scaling up the reaction, and so on. Importantly, chiral secondary amines can activate a carbonyl compound, such as saturated or unsaturated aldehydes or ketones, by forming a nucleophilic enamine, which is an electrophilic iminium ion.

This potent synthetic strategy is widely used in nature because a small number of enzymes, such as serine proteases, catalyse their functions via hydrogen-bond activation. The asymmetric alkylation methodology developed at Merck in 1984 pioneered phase-transfer catalysis, which allows carbon-carbon and heteroatom-carbon bond formation under mild biphasic conditions. Several substrates can be activated via H-bonding catalysis, and this is not limited to carbonyl compounds; thus, different reaction types, such as rearrangements and cyclizations, have been established. Because of the versatility of these activation modes, several classes of catalysts, including thioureas and diols, have been developed over the years. In ion-pairing catalysis, the catalyst donates hydrogen to an electronegative acceptor, resulting in the formation of a counterion pair.

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Soon after the re-discovery of enamine catalysis by List,Lerner, and Barbas III, MacMillan and colleagues reported the discovery of iminium-ion catalysis, which used the secondary amine 48 as a Diels-Alder-mediated catalyst for performing the aforementioned cycloaddition, in this case between an,-unsaturated aldehyde and a diene. This discovery established the concept of "iminium-ion" as a general activation mode in asymmetric synthesis. The catalytically generated dienophile in this reaction is an unsaturated iminium-ion. The catalyst structure regulates the approach of the diene from the less hindered face, resulting in nearly complete control of the enantioselectivity in the formed adduct [1-5].

Conclusion

Asymmetric organocatalysis has experienced a meteoric rise in the last two decades, from its discovery to global recognition with the awarding of the Nobel Prize. This advancement has elevated this technique to the same level as enzymatic and metal catalysis for the synthesis of enantiopure molecules. As a result, general interest in asymmetric organocatalysis has shifted from "methodology" development to a much more "applied" field, such as use as a key step in the synthesis of various biologically active or medicinally relevant molecules. Indeed, the absence of metal contaminants, operational simplicity, the availability of catalysts, and the possibility of a wide range of possible reactions make this methodology very appealing to medicinal chemists.

As discussed in this review, there are numerous methods for activating organic molecules, and numerous organocatalytic reactions have been developed. Simultaneously, academic and industrial applications of organocatalysis in the synthesis of natural products, drugs, and drug candidates have grown year after year. We only covered a small portion of the available literature in this review, but we believe that asymmetric organocatalysis will be increasingly used by medicinal chemists in the coming years to access enantiopure molecules in an easy, cheap, and environmentally friendly manner. This process will be aided and facilitated by numerous developments in organocatalysis, which will broaden the range of applications for this incredible technique.

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Conflict of Interest

There are no conflicts of interest by author.

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