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From determination of enantiopurity to the construction of complex molecules: The Horeau principle and its application in synthesis

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Dedicated to the memory of Prof. Kurt M. Mislow.

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ABSTRACT

In 1973, Horeau and co-workers reported a technique capable of upgrading the enantiopurity of a scalemic mixture (for example, [(*R*)-enantiomer] > [(*S*)-enantiomer]). This method involved coupling the compound of interest to a simple, bifunctional reagent in order to form a statistical mixture of (*R*,*R*)-, (*S*,*S*)-, and (*R*,*S*)-stereoisomers. Separation of the two diastereomers and cleavage of the incorporated coupling agent effectively removes the minor, (*S*)-enantiomer from the major, (*R*)-enantiomer; thereby increasing the enantiopurity of the starting compound. Since that time, this concept of removing a minor enantiomer through the statistical formation of diastereomeric compounds (the Horeau principle) has also been applied when sequential enantioselective reactions are performed on a substrate, when multiple enantioenriched fragments are coupled together, and for determining the enantiopurity of the initial scalemic mixture. Under the right circumstances, the Horeau principle can be deployed in an iterative fashion in order to access material with extremely high enantiopurity (>99.999% ee). This review provides comprehensive coverage of the underlying theory behind the Horeau principle and its application in organic synthesis.

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1. Introduction

The selective formation of one stereoisomer of a compound over another continues to be of central importance in complex molecule synthesis. This issue is most commonly experienced in natural product synthesis. Some synthetic targets represent such a challenge that even their preparation in racemic form is heralded as a significant achievement.[1] However, the story is never complete until the target is prepared in optically active form.[2] Arguably, achieving high stereoisomeric purity, especially enantiopurity, is more of a concern in the pharmaceutical industry where different stereoisomers may display different biological effects (good or bad).[3] Not surprisingly, the U.S. FDA has developed strict guidelines regarding the development of chiral drugs.[4] Recently, the pharmaceutical industry has shown renewed interest in chiral molecules.[5] Consequently, the production of molecules as single enantiomers is a problem that will occupy the thoughts of synthetic chemists for the foreseeable future.

Given the importance of chiral molecules, and the numerous structural elements that can give rise to chirality, it should come as no surprise that synthetic chemists have devised several strategies for accessing enantioenriched materials.[6] Not all of these strategies are applicable to every class of molecule. These strategies also have different economic and time considerations that must be weighed at different stages of project development. Nevertheless, it will be useful to discuss these different strategies in order to see how they relate to the topic of this review.

First, let's consider a scenario in which the product that is needed contains a single stereocenter: for example the *S*-enantiomer of alcohol **2**. The most direct approach to (*S*)-**2** would be to use a chiral reagent or catalyst to reduce achiral ketone **1** (Fig. 1A). If $k_S > k_R$, then alcohol (*S*)-**2** will be produced with high enantiopurity.[7] Another way to access alcohol (*S*)-**2** is to perform a kinetic resolution on the racemate.[8] This is represented in its simplest form by using a catalyst or reagent to acylate (*R*)-**2** in preference to (*S*)-**2** (Fig. 1B). If $k_R > k_S$, then alcohol (*S*)-**2** will be produced with high enantiopurity.[9] Because a racemate is used as the starting material

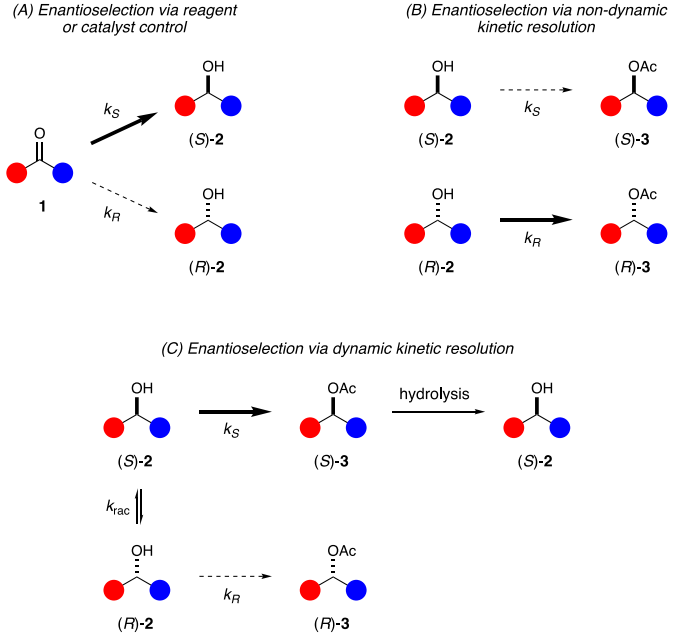

Fig. 1. Strategies for accessing enantioenriched product (*S*)-**2**. Legend: bold arrow = major pathway (faster kinetics), dashed arrow = minor pathway (slower kinetics), red circles have higher CIP priority than blue circles, k_X = overall rate constant for the pathway that generates product with configuration *X*.

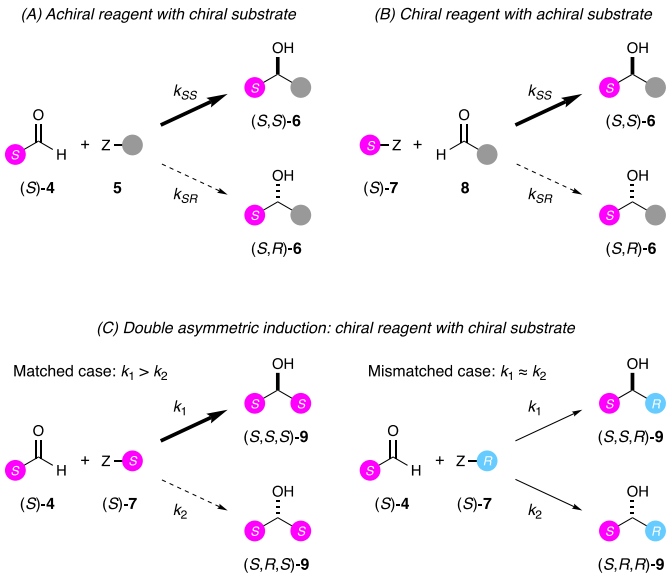

Fig. 2. Strategies for stereocontrol involving multiple stereocenters. Legend: pink and light blue circles represent a stereogenic group with indicated configuration, grey circles represent a nonstereogenic group.