

Separation of Enantiomers

During the past thirty to thirty five years remarkable advances have been made in the separation of enantiomers by means of the difference in rates of reaction of the enantiomers with a chiral non-racemic agent. The basis of discrimination is kinetic. These related methodologies form the subject matter of this book. (Chiral) high pressure liquid chromatography (HPLC), which has developed concurrently, has been an enabling technology. The scope of this book is more confined than suggested by “synthetic methods” in the title. Separations by means of diastereomer formation and resolutions of conglomerates by preferential crystallization, also a kinetic method based on rates of crystallization of enantiomers, are discussed only in brief terms of definition and reference to other reviews.

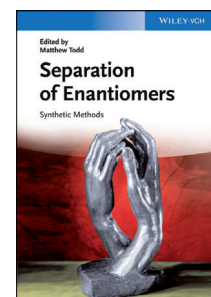
However, the coverage of the chosen methods is excellent and each subject is discussed professionally. Stoichiometric kinetic resolutions are treated by Maddani, Fiaud, and Kagan, catalytic kinetic resolutions by Pellissier, enzymes in kinetic resolutions by Humphrey, Ahmed, Ghanem, and Turner, dynamic kinetic resolutions by Nakano and Kitamura, and parallel kinetic resolutions by Russell and Vedejs. Introductory and closing chapters have been written by the editor. The quality of each chapter is uniformly good. Historical background is given, the necessary mathematics, if needed, are given in understandable form and thereafter illustrative examples are provided usually with analysis. The style of writing is on the whole uniform and pleasing. The chapters are generously illustrated and all structures appear to have been made according to the same format. The result is an easy to read, informative, and useful book.

Although not a stated goal, the book also provides histories of rapid transition from academic curiosity to, in many cases, broad application also in industry. In my view these are not stories of competing technologies but rather of complementary methods that increase the size of the toolbox of methods available to separate enantiomers. The methods link smoothly into rapid advances in catalytic transition metal chemistry, application and engineering of enzymes and clever applications of long known chemical reactions.

Transition metal catalysts serve as the basis of highly successful dynamic kinetic resolutions, play a key role in some stoichiometric kinetic resolutions and have, of course, also been combined with the use of enzymes to effect kinetic resolutions. These methodologies are discussed in depth in the relevant chapters by Nakano and Kitamura, by Turner

et al. and Kagan et al. The latter chapter forms about a third of the book. The authors of this chapter carefully refer to previous reviews and avoid unnecessary repetition. Kinetic resolutions form a good part of the chapter by Russell and Vedejs although the examples and analysis nicely complement the chapter by Kagan et al. Parallel kinetic resolutions wherein two chiral reagents are used simultaneously also discussed in this chapter. This sophisticated methodology represents an area under promising development.

A chapter-by-chapter analysis reveals the breadth of coverage. The chapter by Kagan et al begins with mathematical analysis and turns to general examples of the reaction of chiral (usually non-racemic) reagents with racemic substrates. Esterifications, amidations, cycloadditions, conjugate additions, borane reductions of ketones, and related reactions are discussed. The general theory of enantiodivergent reactions—reactions of a chiral non-racemic reagent with a chiral substrate whereby a new chiral center is formed—is discussed together with examples including special techniques. The chapter by Pellissier on catalytic kinetic resolution includes discussion of catalysts for acylation, oxidation (generally ligands with transition metals), the broadly explored kinetic resolution of alkenes by dihydroxylation (Sharpless reactions) and of the very successful catalytic kinetic resolution of epoxides with Jacobsen’s catalyst, and finally kinetic resolutions of amines. Turner and colleagues discuss the use of lipases and esterases for resolution of alcohols and amines, cover epoxide hydrolases and go briefly into techniques such as solvent engineering and directed evolution. Examples of dynamic kinetic resolution using enzymes or enzymes combined with metal catalysts are given and finally enzyme-catalyzed racemization processes are discussed. Enzyme-catalyzed reactions form also part of the chapter by Nakano and Kitamura on dynamic kinetic resolutions although there is little overlap with the chapter by Turner et al. The use of hydantoins for the preparation of enantiomerically pure amino acids is discussed. Further examples include the use of monooxygenases for Baeyer–Villiger reactions. Finally the authors turn to synthetic ligands coupled to transition metal catalysts as used for a variety of dynamic kinetic resolutions. The chapter on enantiodivergent reactions by Russell and Vedejs begins with a discussion of parallel kinetic resolution using two chiral reagents. Examples of this elegant process are still rather limited. Reactions of racemic mixtures with a single chiral non-racemic reagent are, of course, more common. Examples of such processes with reduction and oxidation are given (including applications of enzymes), the specifics of application of chiral organometallic reagents are discussed, and last



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clever applications of parallel kinetic resolution are given including the fascinating combination of a chiral phosphine with a crystalline, cross-linked lipase.

An introductory chapter by the editor gives a short overview of the various techniques. The suggestion that conglomerates “can be resolved with ease” by preferential crystallization is a bit overoptimistic. The closing chapter on rare, neglected and promising methods provides a quick view of interesting developments in the areas of polymerization, photochemistry, dynamic combinatorial chemistry, crystallization (including Ostwald ripening), and autocatalysis.

I discovered only a few minor typographical errors. The literature citations are very complete although it is curious that in some cases the title of the publication is given and in other cases not. The

chapter by Kagan et al. is sometimes more difficult to follow because the many schemes are not numbered.

This book will serve as an excellent guide to all types of kinetic resolutions. Scientists in laboratories, both academic and industrial, should have access to it particularly if they desire to undertake any type of resolution of enantiomers. This book could also serve as very complete text material for a special topics course. In summary this is a short, thoughtfully constructed, and well-written book full of useful information.

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