PREFACE TO VOLUME 104

The universe is asymmetric and I am persuaded that life, as it is known to us, is a direct result of the asymmetry of the universe or of its indirect consequences.

Louis Pasteur

The term *chirality* was originally coined by Lord Kelvin, and this concept now plays a central role in nearly every aspect of modern-day life. This phenomenon's impact on biological systems is immense and arguably, the most vital force for sustaining life on the planet. Louis Pasteur appreciated the implications of chirality after he inadvertently discovered molecular chirality in the spontaneous resolution of an aqueous solution of racemic sodium ammonium tartrate tetrahydrate in 1848. Although enantiomers primarily differ in their ability to rotate plane-polarized light, this definition is a gross oversimplification of the importance of homochirality. For example, Nature produces amino acids as single enantiomers, which provide the building blocks for proteins that recognize and differentiate between molecules with complementary shape and chirality. The origin of this preference for one-handedness remains a subject of significant debate and speculation. Pasteur also described the first chiral resolution, which involved the addition of the chiral base, cinchonine, to *rac*-tartaric acid to form diastereoisomers and thus established the basis for the classical chiral resolution process that is still widely employed today, particularly in the pharmaceutical industry. Based on these important discoveries, the idea that enantiomerically pure chiral molecules can only be formed in the presence of a chiral influence was formulated, which now forms the very basis of modern asymmetric catalysis. The following three chapters delineate the historical development of three entirely different transformations that, to varying degrees, incorporate the principles of chiral resolution and induction. Hence, the first chapter outlines non-enzymatic resolution reactions, while the second two chapters provide examples of challenging enantioselective and desymmetrization reactions.

The first chapter by Aileen B. Frost, Mark D. Greenhalgh, Elizabeth S. Munday, Stefania F. Musolino, James E. Taylor, and Andrew D. Smith provides an outstanding treatise on the desymmetrization and kinetic resolution of alcohols and amines by non-enzymatic enantioselective acylation reactions. The chapter aligns beautifully with the notion of efficiently separating enantiomers, which remains a stalwart approach in organic synthesis. Notably, the chapter describes the evolution of small molecules that emulate the efficiency and selectivity exhibited by enzymes. The discussion is organized in the context of stoichiometric and catalytic processes for the desymmetrization and kinetic resolution reactions of alcohols and amines in the context of mechanism, selectivity, scope and limitations, which illustrate the

transition from the stoichiometric to the catalytic reaction manifold. The Mechanism and Stereochemistry section further subdivides the catalytic processes into the type of acylating agent and catalyst employed for a specific resolution. The Scope and Limitations component is categorized in the context of the substrate, namely, diols, alcohols, amines, diamines, amides, etc., which permits the reader to appreciate the expansive scope of this approach. The Applications to Synthesis illustrates how these methods have been implemented in the construction of some important pharmaceuticals and natural products, and the Comparison with Other Methods section provides a direct comparison with acylative and hydrolytic enzymatic kinetic resolution methods. The Tabular Survey summarizes the types of stoichiometric acylating agents and the various catalysts that have been employed to date, including oxidants and additives. The tables systematically provide examples of the types of substrates in the context of the associated approach and the organization mirrors the Scope and Limitations to permit the identification of suitable reaction conditions for a specific substrate. Overall, this is an excellent chapter on a particularly important and useful process, which will be an invaluable resource to anyone wishing to facilitate either a desymmetrization or kinetic resolution reaction of alcohol and amine derivatives.

The second chapter by Lucile Marin, Emmanuelle Schulz, David Lebœuf, and Vincent Gandon provides a scholarly account of the Piancatelli reaction or rearrangement, which is a useful process for the construction of 4-hydroxy-5-substituted-cyclopent-2-enones from 2-furylcarbinols. Piancatelli and coworkers reported this process in the course of studying acid-mediated reactions with heterocyclic steroid analogs in 1976. Notably, the rearrangement represents a rare example of a reaction that directly transforms a heterocycle into a carbocycle. The transformation is envisioned to proceed via an electrocyclic ring closure in a similar manner to the related Nazarov cyclization. Hence, while the preferred mechanism is a conrotatory 4π-electrocyclization of a transient pentadienyl carbocation, the Mechanism and Stereochemistry section also outlines some other possibilities, namely, ionic stepwise and aldol-type condensations. The Scope and Limitations portion is organized by the three variations of this process, namely, the oxa-, aza-, and carba-Piancatelli reactions, which each include sections on cascade processes. Interestingly, the enantio-determining step in this process, namely, a 4π-electrocyclization of a transient pentadienyl carbocation, makes the asymmetric version challenging. Nevertheless, the ability to employ chiral phosphoric acids to generate enantiomerically enriched substituted cyclopentenones (albeit limited to the aza-Piancatelli variant using anilines) represents a significant breakthrough for this process. The Applications to Synthesis describes the applications of this methodology to prostaglandin synthesis and some related natural products, and the Comparison with Other Methods section provides a relatively comprehensive assessment of other methods commonly deployed for the construction of this structural motif. The Tabular Survey incorporates reactions reported up to December 2019. The tables are uniquely organized based on the product framework with different substitutions to permit the identification of a suitable product. Overall, this is an important chapter on a remarkably useful reaction that has not been fully exploited in comparison with some of its related counterparts.

The third chapter by Constanze N. Neumann and Tobias Ritter outlines transition-metal-mediated and metal-catalyzed carbon-fluorine bond formation. The exponential growth in the development of methods that permit a late-stage fluorination can be ascribed to the unique physical properties that fluorine bestows on functional organic molecules, such as pharmaceuticals, agrochemicals, and materials. For instance, fluorine forms the strongest bond to carbon, which results in a highly polarized bond that has significant ionic character. Hence the large dipole moment provides a weak hydrogen bond acceptor that infers unique conformational behavior. The Mechanism and Stereochemistry component of this chapter categorizes the fluorination process in the context of nucleophilic and electrophilic fluorine sources, which are subdivided into the type of catalyst employed. Notably, the authors have devised an excellent classification system highlighting the knowledge gaps in this important and rapidly developing area that should stimulate further work in this field. The mechanistic classifications are then used throughout the remainder of the chapter to make cross-referencing a specific type of mechanism effortless for the reader. The Scope and Limitations part is organized by the substrate type, namely aryl, alkyl, and aliphatic substrates in the context of the aforementioned mechanistic variations, which permit one to identify the optimal approach for a particular substrate class. The substrates also address the critical challenges with site-selectivity (aryl) and stereocontrol (alkenyl and aliphatic) that are encountered with these substrate classes. A key and striking feature is the realization that the C-F bond can be introduced in a chemo-, regio-, and stereoselective manner. Consequently, several chiral catalysts have been developed that permit the asymmetric construction of carbon-fluorine bonds through desymmetrization and enantioselective reactions, which have proven particularly important in medicinal chemistry. The Applications to Synthesis section delineates the incorporation of fluorine into unnatural functionalized molecules, given the relatively few natural products that contain this motif. Fluorine in natural molecules is rare because of the difficulties that a haloperoxidase has to oxidize fluorine anion compared with other halide ions. Hence, this section outlines several successful applications to fluorine-18 positron-emission tomography (^{18}F-PET) tracer synthesis, an important and challenging aspect of late-stage fluorination given the relatively short half-life of the ^{18}F isotope. The Comparison with Other Methods portion describes some of the more classical fluorination methods, including nucleophilic aromatic substitution and displacement reactions with both nucleophilic and electrophilic fluorine sources. The Tabular Survey parallels the Scope and Limitations part in the context of aryl, alkenyl, and aliphatic fluorination reactions using both electrophilic and nucleophilic reaction conditions. Overall, this chapter provides the reader with an outstanding perspective on the recent developments of this important transformation, and represents a very important resource for the community.

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