PREFACE TO VOLUME 118

The world is so constructed, that the balance of attraction and repulsion, affinity and antagonism, is continually being preserved.

Johann Wolfgang von Goethe

In Goethe's philosophy, life and the cosmos are sustained by a dynamic equilibrium between opposing forces. Human relationships evolve through conflict and cooperation. In nature, growth and decay work cooperatively to allow ecosystems to thrive. In chemistry, the equilibrium state achieves a kinetic balance between reactants and products.

The chapters in this volume describe catalytic processes in which chemical equilibria are applied or controlled to promote a desired chemical outcome. The first chapter reviews copper-catalyzed enantioselective conjugate addition of organometallic reagents to Michael acceptors. In these reactions chiral copper catalysts bind preferentially to one face of the alkene leading to enantioenriched addition products. The second chapter provides an overview of the alkylation of nitrogen nucleophiles using alcohols as direct alkylating agents through a hydrogen-borrowing mechanism. In the hydrogen-borrowing mechanism, the catalyst equilibrates reactants between dehydrogenated (oxidized) and hydrogenated (reduced) states to achieve this transformation. In the final chapter, dynamic kinetic resolution (DKR) of secondary alcohols using a combination of enzyme and metal-based catalysts to convert racemic secondary alcohols to enantiomerically enriched ester products in high yield is described. As in the hydrogen-borrowing reaction, the DKR process uses a metal catalyst to equilibrate alcohols and ketones resulting in racemization of the alcohol to continuously provide the desired alcohol enantiomer for the enzyme catalyst to process.

Chapter 1 by Simon Woodward, Raja Rit, Montserrat Diéguez, Oscar Pàmies, Jèssica Margalef Pallarès, Maria Biosca, José Antonio García Alcázar, Pol de la Cruz-Sánchez, and Jorge Faiges provides a detailed overview of the copper-catalyzed enantioselective conjugate addition of organometallic nucleophiles to electron-deficient alkenes (Michael acceptors). This methodology provides an important route for the enantioselective synthesis of carbonyl compounds with β-chiral centers. The Mechanism and Stereochemistry section describes the main mechanisms for this reaction, which include 1) selective coordination of the catalyst to one face of the activated alkene followed enantioselective oxidative addition of the organocopper(I) active species to the Michael acceptor and then reductive elimination and 2) direct transfer of the carbon nucleophile from copper to the β-carbon of the Michael acceptor after an enantioselective coordination of the catalyst to one face of the activated alkene. This section also describes some general trends that are useful

in predicting enantioselectivity in these reactions, as well as highlighting substrate classes known to give poor selectivity.

The Scope and Limitation section is organized first by different classes of organometallic reagents used in these copper-catalyzed reactions, including organoaluminum, organomagnesium, organozinc, and organozirconium reagents. The scope of Michael acceptors is then reviewed. Finally, tandem reactions where the metal enolate intermediate is trapped in situ with electrophiles are described. The Application to Synthesis section highlights the use of copper-catalyzed asymmetric conjugate addition to the syntheses of several natural-product targets. The Comparison with Other Methods section discusses alternative methods for the introduction of chiral centers at β-carbons of carbonyl compounds, including conjugate reduction of β,β-disubstituted enones and asymmetric metal-catalyzed additions of carbon nucleophiles using metal catalysts other than copper. Situations in which these alternative methods overcome limitations of copper-catalyzed conjugate additions are highlighted. Table 1 contains examples of 1,4-addition of carbon nucleophiles to Michael acceptors and is further subdivided based on the type of Michael acceptor. Table 2 provides examples of 1,6- and higher additions to electron-deficient conjugated systems. Table 3 highlights tandem processes where the enolate intermediate is trapped by various electrophiles. This chapter provides a comprehensive and critical review of an increasingly important route to enantioselective conjugate addition reactions.

In Chapter 2, Anju Nalikezhathu, Alexander Maertens, Carlos Navarro, Adriane Tam, Van Do, Long Zhang, and Travis J. Williams describe the formation of C–N bonds through the hydrogen-borrowing approach. These reactions are an alternative to the classic reductive amination process of an aldehyde or ketone with an amine, which requires a stoichiometric hydride source. In the hydrogen-borrowing approach, an alcohol is used as the alkylating agent and is first dehydrogenated to a carbonyl group by a metal catalyst followed by condensation with the nitrogen nucleophile. The resulting imine is then reduced to an amine using the hydrogen that was removed from the original alcohol. Thus, the hydrogen was "borrowed" from the alcohol and then delivered back to the imine intermediate to form the desired amine.

The Mechanism section of this chapter describes key mechanistic steps involved in this process: alcohol dehydrogenation, amine condensation with the resulting carbonyl moiety, and imine reduction. The hydrogen-transfer steps are catalyzed by late-transition metals, such as ruthenium, palladium, or copper. This section highlights both experimental and computational studies of the mechanisms of these processes. Examples of *N*-alkylation by hydrogen-borrowing methods that lead to enantioenriched chiral amines are highlighted in the Stereochemistry section. Asymmetric products can be obtained starting from chiral amines, using amines bearing chiral auxiliaries, or using asymmetric catalysts to effect enantioselective reduction of the imine intermediate.

The Scope and Limitations section is organized based on the structure of the nitrogen nucleophile. A separate section deals with hydrogen-borrowing C–N bond-forming reactions that produce nitrogen heterocycles. A third section describes

examples of tandem reactions where the *N*-alkylation step is followed by subsequent reactions leading to *N*-heterocyclic compounds in many cases. The Application to Synthesis section demonstrates the use of the hydrogen-borrowing C-N coupling strategy in the synthesis of pharmaceutical targets and natural products. In the Comparison with Other Methods section, the hydrogen-borrowing *N*-alkylation process is compared to traditional routes to *N*-alkylation, such as reductive amination and alkylation with alkyl (pseudo)halides. Metal-catalyzed C-N coupling and alkene hydroamination and hydroaminoalkylation are also discussed as alternative routes to effect *N*-alkylation. The Tables are organized first by the substitution pattern of the nitrogen nucleophile and then further subdivided based on the substitution at the alcohol carbon. Tables 17–19 provide examples of intramolecular *N*-alkylations leading to *N*-heterocycles, whereas Table 20 highlights tandem processes involving hydrogen-borrowing *N*-alkylation. This chapter highlights a relatively new advance in C-N bond formation that is becoming a widely used synthetic methodology.

Chapter 3 by Mahn-Joo Kim, Jaiwook Park, Yoon Kyung Choi, Inyeol Yun, and Jin Yong Park reviews dynamic kinetic resolution (DKR) of secondary alcohols to give enantiomerically enriched esters, which can be hydrolyzed to the very useful enantiomerically-enriched secondary alcohols. Chiral alcohols are useful chiral building blocks and methods for their synthesis have been widely studied. The major approaches to enantioselective alcohol synthesis include asymmetric reduction of carbonyls, asymmetric nucleophilic addition to carbonyls, and kinetic resolution (KR) of racemic alcohols. Enzymatic KR is a widely used alternative technique to convert one enantiomer of a racemic secondary alcohol mixture into an ester, while leaving the other enantiomer unreacted, and is thus limited to a maximum yield of 50%. The DKR process couples enantioselective kinetic resolution of alcohols with an alcohol racemization catalyst. In this process, the racemization catalyst reversibly oxidizes the unreacted alcohol enantiomer to a ketone and then back to a racemic mixture of alcohols that can be further resolved. In this way, high yields of chiral ester products are obtained with high enantioselectivity.

The Mechanism and Stereochemistry section of this chapter describes the pathways for the key classes of metal racemization catalysts. Rhodium and ruthenium catalysts perform the racemization by reversible transfer hydrogenation between the secondary alcohol and ketone forms of the substrate. Aluminum-catalyzed racemization occurs via the Meerwein-Ponndorf-Verley-Oppenauer reaction in which a hydride is directly transferred from the secondary alcohol to the ketone within the aluminum coordination sphere. The mechanism and stereoselectivity of the enzymatic asymmetric acylation reaction is then discussed. The enzymes used for these transesterification reactions are typically lipases, esterases, and proteases, and generally provide high enantioselectivity if there is a sufficient difference in size of the substituents on the secondary alcohol carbon.

The Scope and Limitations section describes the DKR of different classes of secondary alcohols and is organized by the type of carbon substituents attached to the secondary alcohol carbon. This section concludes with examples where the initial substrate is a ketone or enol ester that is converted under the reaction conditions to a racemic secondary alcohol, which is then resolved via the DKR process to an

enantioenriched ester. The Applications to Synthesis section highlights the utility of DKR in the synthesis of some bioactive molecules and chiral polymers. The Comparison with Other Methods section discusses alternative methods for enantioselective synthesis of secondary alcohols, including traditional KR, asymmetric hydrogenation of ketones, and asymmetric nucleophile addition to aldehydes. The Tables are organized in the same manner as the Scope and Limitations with tables highlighting examples of DKR of different classes of secondary alcohols based on the substitution pattern at the alcohol carbon. This chapter highlights a beautiful example of the synergistic application of enzymatic and metal-based catalysts to convert racemic alcohols to enantioenriched products in high chemical yield.

I would like to take this opportunity to acknowledge the entire *Organic Reactions* Editorial Board for their collective efforts in steering these chapters through the various stages of the editorial process. I would particularly like to thank Prof. Jeffrey Johnson and Prof. David Berkowitz who, along with myself, served as Responsible Editors for the chapters in this volume and who worked closely with authors to ensure that these chapters came to fruition. I am also deeply indebted to Dr. Danielle Soenen for her invaluable efforts as the Editorial Coordinator. Her knowledge of *Organic Reactions* is critical to maintaining the quality and consistency of the series. Dr. Dena Lindsay (Secretary to the Editorial Board) is thanked for coordinating the contributions of the authors, editors, and publisher. In addition, the *Organic Reactions* enterprise could not maintain the quality of production without the meticulous efforts of Prof. Steven Weinreb (Executive Editor), Dr. Landy Blasdel (Processing Editor), and Dr. Tina Grant (Processing Editor). I would also like to thank Dr. Michael Evans and Dr. Joseph Ward for maintaining our web presence (organicreactions.org). Thank you to Prof. Barry Snider (Secretary) for keeping everyone on task and Prof. Robert Maleczka (Treasurer) for ensuring *Organic Reactions* continues to remain fiscally viable.

Finally, I would like to recognize Dr. Engelbert "Bert" Ciganek for his long and distinguished association with *Organic Reactions*. Bert recently announced his retirement at the age of 95 after more than 40 years of dedicated service to *Organic Reactions*. Bert is the most prolific *Organic Reactions* author over the 85-year course of the series, serving as author or co-author on eight chapters. Bert was the sole author for three of these chapters (Volumes 32, 51, and 72), and a co-author for an additional five chapters (Volumes 62, 81, 85, 95, and 105). He was invited to join the *Organic Reactions* Board of Editors in 1983 and served until 2000. Since 2000, Bert has been very involved as an Editorial Advisor, carefully reviewing every chapter submitted to *Organic Reactions* thus ensuring that published chapters maintain the high standards of accuracy and consistency for which *Organic Reactions* is known. Bert's contributions have been invaluable to the success of the series as he is the ultimate authority on *Organic Reactions* style, formatting, and table organization. His contributions will be difficult to replace. Dr. Ciganek passed away on November 19, 2025 as this volume was going to press; a full obituary appears elsewhere in this volume and on the *Organic Reactions* website.

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