

PREFACE TO VOLUME 114

The precision of naming takes away from the uniqueness of seeing.

Pierre Bonnard, Painter

An eponym honors and acknowledges a significant accomplishment by naming it after a person, object, or location. Today, we use eponyms for all manner of things and even to navigate – specific landmarks make something instantly recognizable and thus simplify directions (e.g., the Eiffel Tower, the Taj Mahal, Summer Palace, London Bridge, etc). Every aspect of modern life is now replete with examples, including science, medicine, technology, politics, literature, etc. The eponym is particularly important as a shorthand in many aspects of science, albeit there is often a primary and secondary hierarchy to enable scientists to precisely identify the relevant research more efficiently. Indeed, eponyms have become a so-called second language and are often a major component of the jargon that is so pervasive in many scientific fields. In organic chemistry, the naming of organic reactions has become a central theme that can be traced back to the nineteenth century, although the assignment of names can be controversial because, unlike the science it represents, it is based on many factors and is often subjective because the name(s) can reflect a different stage in a reaction's development! For instance, the first name reaction is the 1870 Lieben Haloform Reaction, although it was first reported by Georges-Simon Serullas in 1822. Nevertheless, the name reaction is now a central part of the language of organic chemistry in which the reaction type is sometimes added to further identify the process (e.g., Cope Rearrangement, Friedel-Crafts Acylation, Stille Cross-Coupling, etc.). In some cases, multiple names are used because of concurrent contributions (e.g., Buchwald-Hartwig Amination) or to recognize further developments of a specific process (e.g., Horner-Wadsworth-Emmons Wittig Olefination). The name reaction thus describes a kind of prototypical process in the context of the changes in bonding; however, the specific context is dramatically different and, as such, aligns with Bonnard's vision that the *precision of naming* is not a substitute for the *uniqueness of seeing*. Although the name can provide instant recognition, some of the more obscure processes are not as easily identified. Furthermore, the names can often be misleading and thereby lead to the amplification of a misconception about the origin of a process. Despite the pros and cons of *name reactions*, they have become a critical aspect of the language of organic chemistry and represent the essence of *Organic Reactions*, a preeminent reference work for the synthetic organic chemistry community that curates all the examples of a particular reaction to illustrate the breadth of the process. This volume contains three chapters on name reactions: the Cloke–Wilson Rearrangement, the Kinugasa reaction, and the Pictet–Spengler reaction.

The first chapter by Efraím Reyes, Lihier Prieto, Rubén Manzano, Luisa Carrillo, Uxue Uria, and Jose L. Vicario provides a detailed account of the Cloke–Wilson Rearrangement, which is the heteroatom equivalent of the vinylcyclopropane–cyclopentene rearrangement to afford heterocycles. The reaction is named after the seminal reports by Cloke and Wilson in 1929 and 1947, respectively. The former reported the rearrangement of the imine of cyclopropyl phenyl ketone at 200 °C to afford 2-phenylpyrroline, whereas the latter described the preparation of 2,3-dihydrofuran through the thermal rearrangement of cyclopropanecarboxaldehyde at 375–500 °C. These examples illustrate that the rearrangement of cyclopropanes requires high temperatures despite their inherent ring and torsional strain, which has prompted the examination of the factors that permit milder reaction conditions. To this end, the addition of substituents that either increase ring strain or the polarity of the C-C bond (e.g., donor-acceptor cyclopropanes) has been examined. Alternatively, activating the cyclopropane with various reagents and catalysts has further broadened the scope to permit the rearrangement to proceed under milder conditions.

The Mechanism and Stereochemistry section outlines thermal and photochemical rearrangements that proceed through either a concerted or a biradical process depending on the cyclopropane structure, making this aspect challenging to control. For instance, adding donor and acceptor substituents lowers the barrier for the rearrangements, which are stereoselective rather than stereospecific, because of the biradical character of the reactive intermediate. The photochemical reactions proceed at room temperature and have been theoretically corroborated to involve biradical intermediates. This section also describes a series of Lewis acid- or Brønsted acid-catalyzed reactions that proceed in a stepwise manner through zwitterionic intermediates. Notably, the formation of an achiral intermediate enables a chiral Brønsted acid catalyst to facilitate the only enantioselective variant of this process. The Lewis base mediated reactions utilizing a stoichiometric promoter or catalyst have also been explored to facilitate stereospecific rearrangements. The Scope and Limitations section describes using the Cloke–Wilson Rearrangement to prepare dihydrofurans, dihydropyrroles, dihydrothiophenes, and dihydroisoxazole-2-oxides. The first two sections are further subdivided into the type of carbonyl functionality employed (e.g., aldehydes, ketones, carboxylates, carboxamides, etc.), including variations in substitution on these substrates. The section is completed with the sulfa- and nitro-variants of the Cloke–Wilson rearrangement, which are rare and thus may well provide future opportunities for reaction development.

The Applications to Synthesis section provides excellent examples that showcase the various adaptations of the rearrangement in the total synthesis of natural products to prepare an array of oxygen and nitrogen heterocycles. The Comparison with Other Methods section delineates several alternative approaches to unsaturated five-membered heterocycles, including dihydrofurans, pyrrolines, and dihydrothiophenes. There is also an extensive discussion of cycloadditions and sequential processes that afford similar heterocycles. The Tabular Survey is primarily organized in terms of the heterocyclic product formed and then by the nature of the starting cyclopropane substrate. Overall, this is an excellent chapter on an important reaction that will be invaluable to anyone interested in this transformation.

The second chapter by Marek Chmielewski, Rafał Kutaszewicz, Artur Ulikowski, Michał Michalak, Karol Wołosewicz, Sebastian Stecko, and Bartłomiej Furman provides a detailed account of the historical development of the Kinugasa reaction, which is the union of copper acetylides with nitrones to afford β -lactams. Kinugasa and Hashimoto described the first example of this process in 1972 using copper phenyl acetylide and several diaryl nitrones to afford *cis*-disubstituted β -lactams. Even though the reaction affords the appropriate stereochemistry for preparing a wide range of clinically important antibiotics, has excellent atom-economy, and employs stable starting materials, the reaction lay dormant for nearly three decades! Although copper acetylides were widely utilized in Sonogashira and Glaser couplings that were prevalent at the same time, they were ignored as coupling partners for nitrones in 1,3-dipolar cycloadditions. The renaissance of this transformation has been ascribed to the independent development of the copper-catalyzed Huisgen cycloaddition (CuAAC) by Meldal and Sharpless. Notably, the Sonogashira reaction is the subject of an upcoming chapter in *Organic Reactions*.

The Mechanism and Stereochemistry section outlines several possible mechanistic pathways that involve a 1,3-dipolar cycloaddition followed by a rearrangement. Although theoretical and experimental studies support a ketene-based pathway, two mechanistic variants for this process are presented. A third mechanistic possibility is also outlined, which involves an initial [3+2] cycloaddition (to form an isoxazoline), followed by a [3+2] cycloreversion and a Staudinger-type [2+2] cycloaddition, albeit this model does not explain the stereochemical outcome. The section on stereochemistry and constitutional isomerism delineates the origin of stereocontrol and the influence of substituents, including their effect on enantioselectivity. The section is further subdivided into the impact of a stereocenter in either the alkyne or nitron fragments, including the influence of stereochemistry in both components in the context of matched and mismatched combinations. The section is completed with a discussion of several enantioselective variants that deliver both *cis*- and *trans*-cycloadducts. A very attractive aspect of this chapter is that the authors have meticulously delineated the origin of stereocontrol in every aspect of this process, which will be invaluable to the reader. The Scope and Limitations section is subdivided by the type of nitron, namely diaryl nitrones (achiral- and chiral-based substituents), other acyclic variants, and five- and six-membered cyclic nitrones. The section on five-membered derivatives is further split into achiral and chiral nitrones reacting with achiral and chiral alkynes, which provides a guide to the stereochemical possibilities. This chapter section also extensively discusses enantioselective and intermolecular Kinugasa reactions.

The section on Applications to Synthesis provides examples of using the methodology to prepare some important natural products and pharmaceutically relevant targets. The Comparison with Other Methods section describes the most widely used alternative methods for assembling β -lactams, including cycloaddition, cyclization, carbenoid insertion, and ring expansion reactions. The Tabular Survey mirrors the Scope and Limitations section in that the primary rubric is based on the type of nitron employed, followed by the corresponding alkyne, which makes analyzing the tables effortless for the reader. Overall, this is a very important

chapter that I believe will be of significant interest to heterocyclic and medicinal chemists.

The third chapter by Daniel Seidel outlines the development of the enantioselective Pictet–Spengler reaction, which involves the condensation of a ketone or aldehyde with an amine that is tethered to an aryl group to promote intramolecular addition to the iminium ion with concomitant rearomatization. Hence, the reaction is often envisioned as an intramolecular variant of the Mannich and Friedel–Crafts reactions that represents an important method for preparing a variety of alkaloids. The first Pictet–Spengler reaction was reported in 1911 by Amé Pictet and Theodor Spengler and involved the acid-promoted condensation of β -phenylethylamine and dimethoxymethane to form tetrahydroisoquinoline. This process is also feasible with electron-rich heteroaromatic derivatives, such as indoles and pyrroles, which proceed under milder reaction conditions. An early example of the heteroaromatic variant involved the condensation of tryptamine and paraldehyde to afford 1-methyltryptoline. More recently, the enzyme-catalyzed variant that proceeds under relatively mild reaction conditions has been reported, which extends the scope of this venerable process.

The Mechanism and Stereochemistry section delineates two convergent pathways: a 6-*endo-trig* ring-closure followed by elimination or an alternative 5-*endo-trig* with a 1,2-alkyl shift. Although theoretical studies support the former process, recent work provides insight into factors that can switch the process to favor the latter pathway. The section is then split by Lewis Acid promoters based on BINOL and pseudoephedrine, in addition to a section on Brønsted acid variants. The latter section includes Brønsted acid catalysts derived from chiral ureas that have been successfully implemented in this process. It also describes the enantioselective acyl-Pictet Spengler reaction, which involves the intermediacy of an *N*-acyliminium ion using chiral ureas and chiral phosphoric acid as organocatalysts. A model for asymmetric induction accompanies each method to guide the reader and thus provide insight into developing new variants. The Scope and Limitations section is organized in the context of stoichiometric Lewis acid-promoted reactions followed by catalytic methods. Notably, the latter section is more extensive and further subdivided by the substrate and the type of catalyst (*vide supra*). For instance, the section is split into the asymmetric reactions of tryptamines, β -phenethylamines and related reactions with the various organocatalysts, including dual catalysis. The chapter also has a section on catalytic cascade reactions that feature an enantioselective Pictet–Spengler reaction.

The Applications to Synthesis section illustrates the breadth of this process in complex alkaloid synthesis to provide the reader with an appreciation of the synthetic utility of this transformation. The Comparison with Other Methods section describes the related enantioselective methods, which involve the asymmetric reduction and addition to cyclic imines, in which the latter are either preformed or generated *in situ* through oxidation. The Tabular Survey parallels the Scope and Limitations section in the context of substrates to facilitate identifying a specific process of interest. This chapter gives the reader an excellent perspective on the development of enantioselective variants of this venerable reaction.

I want to take this opportunity to thank Dr. Joseph S. Ward for the creation of the new *Organic Reactions* website (<https://www.organicreactions.org>) and Dr. Michael J. Evans for transferring and maintaining the content. We hope the new site will make it easier to find content and provide a better interface with the *Organic Reactions* readership. I also want to acknowledge Dr. Angie R. Angeles for her continued outreach efforts to promote *Organic Reactions*, including the new website. Her efforts have improved our visibility with younger members of the community who may not be acquainted with this venerable publication. I am sure Roger Adams would approve of the recent changes and be proud that after 80+ years, the publication he initiated is still an essential resource for practicing synthetic organic chemists in academia and industry.

I would be remiss if I did not acknowledge the entire *Organic Reactions* Editorial Board for their collective efforts in steering this volume through the various stages of the editorial process. I thank Christopher D. Vanderwal (Chapter 1), Jeffrey B. Johnson (Chapter 2), and Paul R. Blakemore (Chapter 3), who served as the Responsible Editors to marshal the chapters through the various phases of development. I am also deeply indebted to Dr. Danielle Soenen for her continued and heroic efforts as the Editorial Coordinator; her knowledge of *Organic Reactions* is critical to maintaining consistency in the series. Dr. Dena Lindsay (Secretary to the Editorial Board) is thanked for coordinating the contributions of the authors, editors, and publishers. In addition, the *Organic Reactions* enterprise could not maintain the quality of production without the efforts of Dr. Steven M. Weinreb (Executive Editor), Dr. Engelbert Ciganek (Editorial Advisor), Dr. Landy Blasdel (Processing Editor), and Dr. Tina Grant (Processing Editor). I would also like to acknowledge Dr. Barry B. Snider (Secretary) for keeping everyone on task and Dr. Jeffery Press (Treasurer) for ensuring we remain fiscally solvent!

I am also indebted to past and present members of the Board of Editors and Board of Directors for ensuring the enduring quality of *Organic Reactions*. The distinctive format of the chapters, in conjunction with the curated tables of examples, makes this series of reviews both unique and exceptionally valuable to the practicing synthetic organic chemist.

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