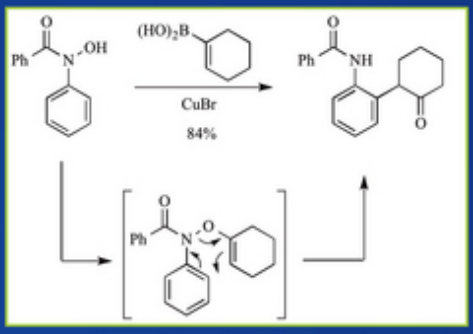
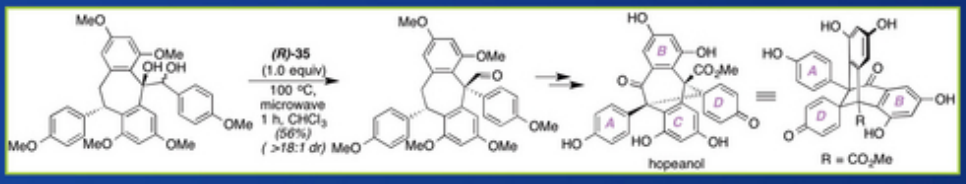
Edited by **Christian M. Rojas**

MOLECULAR REARRANGEMENTS in Organic Synthesis





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Edited by

CHRISTIAN M. ROJAS
Barnard College, New York, NY, USA

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CONTENTS

LIST OF CONTRIBUTORS

Laura L. Anderson, Department of Chemistry, University of Illinois at Chicago, Chicago, IL, USA

Martin G. Banwell, Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, Australia

Hongli Bao, Key Laboratory of Coal to Ethylene Glycol and Its Related Technology, Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences, Fuzhou, Fujian, China

David J.-Y. D. Bon, Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, Australia

Noritaka Chida, Department of Applied Chemistry, Keio University, Kohoku-ku, Yokohama, Japan

Yoann Coquerel, Aix Marseille Université, Centrale Marseille, CNRS, iSm2 UMR 7313, Marseille, France

Donald Craig, Department of Chemistry, Imperial College London, South Kensington Campus, London, UK

Laurent El Kaim, Laboratoire de Synthèse Organique, CNRS, Ecole Polytechnique, ENSTA ParisTech – UMR 7652, Universtité Paris-Saclay, Palaiseau, France

Xiaoming Feng, Key Laboratory of Green Chemistry and Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu, P.R. China

Diego Gamba-Sánchez, Laboratory of Organic Synthesis, Bio and Organocatalysis, Chemistry Department, Universidad de los Andes, Bogotá, Colombia

Alison Xiang Gao, Department of Chemistry, The Scripps Research Institute, Jupiter, FL, USA

Fabián Garzón-Posse, Laboratory of Organic Synthesis, Bio and Organocatalysis, Chemistry Department, Universidad de los Andes, Bogotá, Colombia

Gunda I. Georg, University of Minnesota, Department of Medicinal Chemistry and Institute for Therapeutics Discovery and Development, Minneapolis, MN, USA

Nicolas Gigant, Institut de Chimie Organique et Analytique, UMR 7311 CNRS, Université d'Orléans, rue de Chartres, Orléans Cedex 2, France

Isabelle Gillaizeau, Institut de Chimie Organique et Analytique, UMR 7311 CNRS, Université d'Orléans, rue de Chartres, Orléans Cedex 2, France

Laurence Grimaud, Département de Chimie, Ecole Normale Supérieure-PSL Research University, Paris, France; CNRS, UMR 8640, PASTEUR, Sorbonne Universités, UPMC Univ Paris 06, Paris, France

Michael Harmata, Department of Chemistry, University of Missouri-Columbia, Columbia, MO, USA

Joanne E. Harvey, School of Chemical and Physical Sciences, Victoria University of Wellington, Wellington, New Zealand

Trinh A. D. Holth, University of Minnesota, Department of Medicinal Chemistry and Institute for Therapeutics Discovery and Development, Minneapolis, MN, USA

Oliver E. Hutt, CSIRO, Industrial Chemistry and Biotechnology, Clayton South, Australia

Minoru Isobe, Department of Chemistry, National Tsing Hua University, Hsinchu, Taiwan, ROC

Lili Lin, Key Laboratory of Green Chemistry and Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu, P.R. China

Xiaohua Liu, Key Laboratory of Green Chemistry and Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu, P.R. China

Janis Louie, Department of Chemistry, University of Utah, Salt Lake City, UT, USA

Graham K. Murphy, Department of Chemistry, University of Waterloo, Waterloo, ON, Canada

Chatchawan Ploysuk, Department of Chemistry, National Tsing Hua University, Hsinchu, Taiwan, ROC

Jean Rodriguez, Aix Marseille Université, Centrale Marseille, CNRS, iSm2 UMR 7313, Marseille, France

Christian M. Rojas, Department of Chemistry, Barnard College, New York, NY, USA

Michiko Sasaki, Department of Synthetic Organic Chemistry, Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan

Scott A. Snyder, Department of Chemistry, The Scripps Research Institute, Jupiter, FL, USA; Department of Chemistry, Columbia University, New York, NY, USA

Kei Takeda, Department of Synthetic Organic Chemistry, Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan

Uttam K. Tambar, Department of Biochemistry, The University of Texas Southwestern Medical Center at Dallas, Dallas, TX, USA

Ashish Thakur, Department of Chemistry, University of Utah, Salt Lake City, UT, USA

Stephen B. Thomas, Department of Chemistry, Columbia University, New York, NY, USA

F. G. West, Department of Chemistry, University of Alberta, E3-43 Gunning-Lemieux Chemistry Centre, Edmonton, AB, Canada

Takashi Yamazaki, Division of Applied Chemistry, Institute of Engineering, Tokyo University of Agriculture and Technology, Tokyo, Japan

Lin Zhou, Key Laboratory of Green Chemistry and Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu, P.R. China

PREFACE

There is an aesthetically pleasing quality – a Kekuléan snake-seizing-its-tail appeal – to molecular rearrangements. A chemist using the arrow-pushing formalism to outline a rearrangement reaction feels a certain tactile satisfaction in charting the electron flow, an aspect that makes these reactions fun for instructors to teach or for students to work through at the blackboard. Rearrangements often have perfect atom economy, satisfying the frugal: bonds reorganized and nothing wasted. In some cases, a small molecule or other appropriate leaving group is extruded, initiating the rearrangement; sometimes, a catalyst is involved. Whatever the details, molecular rearrangements possess an inherent elegance that makes them especially appealing to students and practitioners of organic chemistry.

But molecular rearrangements do not just satisfy the intellect; they are irreplaceable tools in getting the work of organic chemical synthesis done. Different types of rearrangements enable synthetically useful operations, including ring expansions as in certain Beckmann rearrangements, ring-contracting reactions (e.g., the quasi-Favorskii and Ramberg–Bäcklund rearrangements), and functional group transpositions as occur in Payne and Mislow–Evans rearrangements. Another synthetically essential hallmark of many rearrangements is their stereospecificity, providing, as in the Claisen rearrangement, a means to parlay more readily established stereochemical features of the starting material into product stereochemistry that might otherwise be difficult to access.

How to group different molecular rearrangements? There is an understandable desire to classify and categorize, to find common themes, but there are many possible points of comparison. One could focus on functionality within the starting material, the type of product accessible via the rearrangement, or the reaction mechanism. To a certain extent, however, any categorization scheme is idiosyncratic and

imperfect. For example, mechanistic categorization can be difficult for certain reactions, such as the vinylcyclopropane–cyclopentene rearrangement, which may have mechanistic variants, including radical, ionic, or metal-catalyzed versions. In this book, rearrangements are sorted mainly by changes in connectivity during the reaction: 1,2-migrations, 1,3-transpositions, or ipso rearrangements. However, sigmatropic rearrangements of differing order, [3,3] versus [2,3], are grouped together as a mechanistic category so as to hew to tradition and not confound the reader.

The purpose of this book is to provide readers with a clear and interesting point of departure for thought and further investigation. There is a clear focus on synthetic utility, analyzing how rearrangement reactions can meet challenges in the synthesis of complex molecular structures, including biologically active natural products. Importantly, the chapters are not intended as comprehensive reviews, and each is rendered in a distinctive voice. Some chapters take a broad outlook, while others concentrate on the authors' own contributions. Some chapters are more limited to the recent literature, while others provide historical context and discuss seminal studies in addition to current examples. By highlighting key examples and describing recent progress in the field, this book aims to help stimulate creative rearrangement-mediated solutions to contemporary challenges in synthetic organic chemistry.

In the realization of this volume, I am indebted foremost to the chapter authors for their willingness to participate in the project and their insightful, thorough treatment of the rearrangement topics. I am also grateful to Jonathan Rose, my editor at Wiley, for his patient guidance in completion of the book. Finally, I thank Ms. Jenny Lam for her invaluable assistance in compiling the manuscript components.

Christian M. Rojas
Barnard College
New York, NY
March 2015

PART I

1,2-MIGRATIONS

1

PINACOL AND SEMIPINACOL REARRANGEMENTS IN TOTAL SYNTHESIS

Alison Xiang Gao

Department of Chemistry, The Scripps Research Institute, Jupiter, FL, USA

Stephen B. Thomas

Department of Chemistry, Columbia University, NY, USA

Scott A. Snyder

Department of Chemistry, The Scripps Research Institute, Jupiter, FL, USA;
Department of Chemistry, Columbia University, NY, USA

1.1 INTRODUCTION

Among the array of reactions available to alter molecular complexity, pinacol and semipinacol rearrangements have a particularly long history, constituting among the very first (if not the first) rearrangement reactions discovered by synthetic chemists.[1] However, despite being known for over a century and a half, their use in complex natural product synthesis has only recently come of age. Indeed, with a clearer understanding of the factors governing their regio- and stereoselectivity, as well as more powerful variants (including asymmetric) that can induce the rearrangement under mild conditions, these processes have a number of specific, but highly valuable, applications whose wealth is beginning to be tapped with ever greater frequency. This chapter seeks to provide a sense of the current state of the art of both pinacol and semipinacol processes, discussing each separately under the rubric of recent applications.

Molecular Rearrangements in Organic Synthesis, First Edition. Edited by Christian M. Rojas.

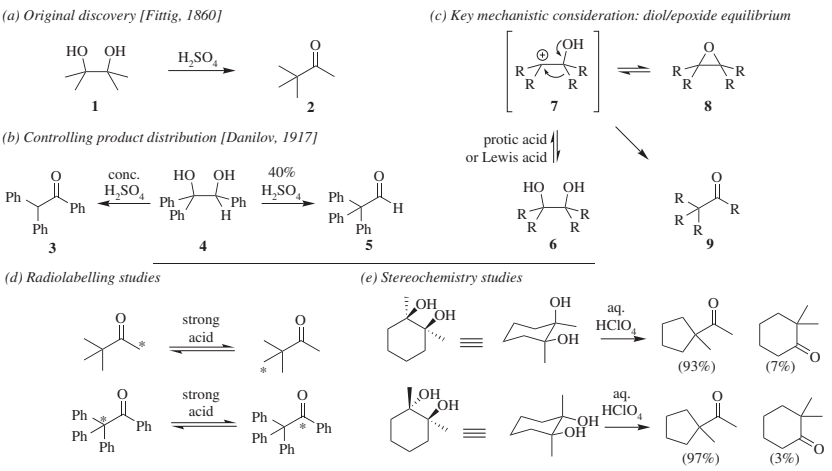
1.2 PINACOL REACTION

1.2.1 Background and Introduction

We begin with the pinacol rearrangement, a reaction process whose name derives from the starting material used in the earliest known example of the transformation. That event, the exposure of pinacol (**1**, 2,3-dimethylbutane-2,3-diol; Scheme 1.1) to sulfuric acid, produced pinacolone (**2**, 3,3-dimethylbutane-2-one). Although this reaction was first performed by Fittig in 1860,[2] it was not until the early 1870s that the actual structure of the product was confirmed by Butlerov[3]; this lapse not only reflects the challenges of determining structure in that era but also the fact that rearrangements were effectively unknown. In fact, a contemporary publication by Kekulé (his seminal paper on representing organic structures) included rules which suggested that carbon skeletal rearrangements could not occur.[4] In any event, by the end of the 19th century, the overall process depicted for the conversion of **1** to **2** was clear in terms of starting material and product. As additional substrates proved amenable to the process, the term pinacol rearrangement has since been used more broadly to define the conversion of any acyclic or cyclic vicinal diol into an aldehyde or ketone under acidic (proton or Lewis) conditions.[5]

Critically, as with many other skeletal rearrangements, there are subtleties that define both its mechanism as well as the products that can be generated from a given substrate under a specific set of reaction conditions. One early clue to that complexity derived from the observation by Danilov in 1917 that a single diol substrate (**4**) could yield different carbonyl-containing products (**3** or **5**) based solely on the strength of the acid deployed (Scheme 1.1b).[6] Although these outcomes reflect kinetic control, that analysis, in and of itself, is insufficient given that separate study has shown that both **4** and **5** can interconvert, suggesting the prospect of reversibility as part of the pinacol rearrangement process itself. Indeed, that concept was beautifully illustrated by Fry in a subsequent series of elegant ^{14}C-labeling studies which showed the transposition of carbon atoms of an array of pinacol "products" exposed to strongly acidic conditions (Scheme 1.1d).[7] A second critical observation resides in the fact that a number of pinacol rearrangements produce epoxides in addition to the standard carbonyl-containing adduct. In some cases, these materials can be induced to rearrange to standard pinacol products, while in others, they are inert to the reaction conditions. Finally, there is a wide range of contexts, employing both protic acids and Lewis acids under varying reaction conditions, that can induce the rearrangement to occur for most individual substrates (with expected variations in yield).

Collectively, these findings indicate that very few mechanistic conclusions can be drawn in general terms for all diols under all conditions. However, what is reasonable to presume, and/or consider, is participation of a substrate along the generalized mechanistic process shown in Scheme 1.1 while concurrently taking into account what is reasonable to occur under a given set of conditions. For instance, in strongly acidic aqueous media, diol substrate **6** is likely in equilibrium with epoxide **8**, with the more stabilized cation (**7**) being both the connecting intermediate and the active species for rearrangement (Scheme 1.1c). In this mechanistic paradigm, either **6** or



Scheme 1.1 The pinacol rearrangement: discovery and key considerations.

8 could be viewed as a reasonable starting material for the pinacol rearrangement, with the two substrates being effectively equivalent from a product-determining perspective. Under milder conditions, particularly as promoted by Lewis acids and/or when a good nucleophile is present, alternate pathways may proceed from **6**, **7**, and/or **8** to afford isolable intermediates and/or side products in addition to the desired pinacol adduct.

To put these thoughts, and the dozens of successful examples of the process, in more specific terms, the following generalizations can be made about pinacol rearrangements:

- Virtually any cyclic or acyclic vicinal diol can undergo the rearrangement, with aldehydes or ketones formed based solely on the substitution pattern of the diol.
- The reaction occurs in an exclusively intramolecular fashion. As such, symmetrical diols will yield a single product, while unsymmetrical diols may lead to product mixtures.
- The product is formed via the more stable carbocation intermediate, with the final product determined by the migratory aptitude of the substituents at the neighboring alcohol-bearing carbon.

What the pinacol rearrangement provides from a strategic perspective is the ability to generate carbonyl compounds with a high degree of substitution at the alpha position (particularly tertiary and quaternary systems), as well as to effect ring contraction and/or expansion with a high degree of regiocontrol in appropriate systems. Few other, if any, methods provide access to such products as readily.

Equally important is the following additional observation:

- The reaction can proceed with a high degree of stereoselectivity with appropriate substrates, especially cyclic diols.

1.2.2 Stereochemistry of the Pinacol Rearrangement

The alignment of orbitals as part of the bond migration itself ensures that stereochemical information encoded in the starting material can be expressed with high fidelity in the rearrangement if the substrate is designed appropriately. Again, however, it is critical to note that substrate-specific subtleties can also play a role. One representative example along these lines rounds out the presentation in Scheme 1.1. In this work by Bunton and Carr, exposure of two different diastereomers of 1,2-dimethyl-1,2-cyclohexanediol to aqueous $HClO_4$ at 60 °C afforded nearly indistinguishable distributions of two products, favoring the expected ring-contracted adduct (Scheme 1.1e).[8] This outcome suggests the intermediacy of the same carbocation intermediate. However, because the final product distributions are not exactly identical, there must be a slight stereochemical memory effect that contributes to (but clearly does not dominate) the reaction process. Intriguingly, even larger differences are found with analogous five-membered systems. This key component of effecting stereocontrol will be a critical point of discussion in the case studies that follow in later sections.