ORGANIC REACTIONS

Volume 114

Organic Reactions

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Organic Reactions

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INTRODUCTION TO THE SERIES BY ROGER ADAMS, 1942

In the course of nearly every program of research in organic chemistry, the investigator finds it necessary to use several of the better-known synthetic reactions. To discover the optimum conditions for the application of even the most familiar one to a compound not previously subjected to the reaction often requires an extensive search of the literature; even then a series of experiments may be necessary. When the results of the investigation are published, the synthesis, which may have required months of work, is usually described without comment. The background of knowledge and experience gained in the literature search and experimentation is thus lost to those who subsequently have occasion to apply the general method. The student of preparative organic chemistry faces similar difficulties. The textbooks and laboratory manuals furnish numerous examples of the application of various syntheses, but only rarely do they convey an accurate conception of the scope and usefulness of the processes.

For many years American organic chemists have discussed these problems. The plan of compiling critical discussions of the more important reactions thus was evolved. The volumes of *Organic Reactions* are collections of chapters each devoted to a single reaction, or a definite phase of a reaction, of wide applicability. The authors have had experience with the processes surveyed. The subjects are presented from the preparative viewpoint, and particular attention is given to limitations, interfering influences, effects of structure, and the selection of experimental techniques. Each chapter includes several detailed procedures illustrating the significant modifications of the method. Most of these procedures have been found satisfactory by the author or one of the editors, but unlike those in *Organic Syntheses*, they have not been subjected to careful testing in two or more laboratories. Each chapter contains tables that include all the examples of the reaction under consideration that the author has been able to find. It is inevitable, however, that in the search of the literature some examples will be missed, especially when the reaction is used as one step in an extended synthesis. Nevertheless, the investigator will be able to use the tables and their accompanying bibliographies in place of most or all of the literature search so often required. Because of the systematic arrangement of the material in the chapters and the entries in the tables, users of the books will be able to find information desired by reference to the table of contents of the appropriate chapter. In the interest of economy, the entries in the indices have been kept to a minimum, and, in particular, the compounds listed in the tables are not repeated in the indices.

The success of this publication, which will appear periodically, depends upon the cooperation of organic chemists and their willingness to devote time and effort to the preparation of the chapters. They have manifested their interest already by the almost unanimous acceptance of invitations to contribute to the work. The editors will welcome their continued interest and their suggestions for improvements in *Organic Reactions*.

INTRODUCTION TO THE SERIES
BY SCOTT E. DENMARK, 2008

In the intervening years since "The Chief" wrote this introduction to the second of his publishing creations, much in the world of chemistry has changed. In particular, the last decade has witnessed a revolution in the generation, dissemination, and availability of the chemical literature with the advent of electronic publication and abstracting services. Although the exponential growth in the chemical literature was one of the motivations for the creation of *Organic Reactions*, Adams could never have anticipated the impact of electronic access to the literature. Yet, as often happens with visionary advances, the value of this critical resource is now even greater than at its inception.

From 1942 to the 1980's the challenge that *Organic Reactions* successfully addressed was the difficulty in compiling an authoritative summary of a preparatively useful organic reaction from the primary literature. Practitioners interested in executing such a reaction (or simply learning about the features, advantages, and limitations of this process) would have a valuable resource to guide their experimentation. As abstracting services, in particular *Chemical Abstracts* and later *Beilstein*, entered the electronic age, the challenge for the practitioner was no longer to locate all of the literature on the subject. However, *Organic Reactions* chapters are much more than a surfeit of primary references; they constitute a distillation of this avalanche of information into the knowledge needed to correctly implement a reaction. It is in this capacity, namely to provide focused, scholarly, and comprehensive overviews of a given transformation, that *Organic Reactions* takes on even greater significance for the practice of chemical experimentation in the 21st century.

Adams' description of the content of the intended chapters is still remarkably relevant today. The development of new chemical reactions over the past decades has greatly accelerated and has embraced more sophisticated reagents derived from elements representing all reaches of the Periodic Table. Accordingly, the successful implementation of these transformations requires more stringent adherence to important experimental details and conditions. The suitability of a given reaction for an unknown application is best judged from the informed vantage point provided by precedent and guidelines offered by a knowledgeable author.

As Adams clearly understood, the ultimate success of the enterprise depends on the willingness of organic chemists to devote their time and efforts to the preparation of chapters. The fact that, at the dawn of the 21st century, the series continues to thrive is fitting testimony to those chemists whose contributions serve as the foundation of this edifice. Chemists who are considering the preparation of a manuscript for submission to *Organic Reactions* are urged to contact the Editor-in-Chief.

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, Liher 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 Huigsen 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 nitrone 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 nitrone, 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 nitrone 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.

P. Andrew Evans
Kingston
Ontario, Canada

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ORGANIC REACTIONS

CHAPTER 1

THE CLOKE–WILSON REARRANGEMENT

EFRAÍM REYES, LIHER PRIETO, RUBÉN MANZANO, LUISA CARRILLO, UXUE URIA, AND JOSE L. VICARIO

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Edited by CHRIS VANDERWAL

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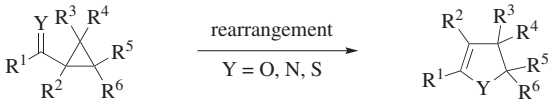
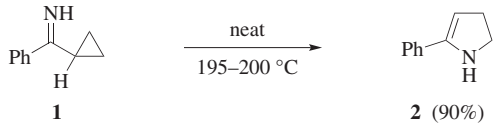
INTRODUCTION

Cyclopropanes that are directly substituted with carbonyl, thiocarbonyl, or imino groups undergo Cloke–Wilson rearrangement under diverse reaction conditions to provide dihydrofurans, dihydrothiophenes, or dihydropyrroles, respectively (Scheme 1). This reaction can also be regarded as the heteroatom equivalent of the vinylcyclopropane rearrangement[1,2] that relies on the release of ring strain to facilitate ring opening, which ultimately leads to the formation of significantly less-strained five-membered heterocyclic compounds.



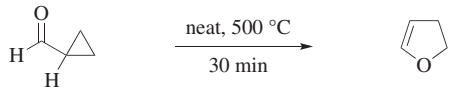
Scheme 1

The reaction is named after the authors who published the first two seminal reports: in 1929, Cloke reported the formation of 2-phenylpyrroline (**2**) by heating cyclopropyl phenyl ketimine (**1**) at 195–200 °C (Scheme 2);[3] some years later, the thermal rearrangement of cyclopropanecarbaldehyde (**3**) to 2,3-dihydrofuran (**4**) was described by Wilson (Scheme 3).[4]



1 **2** (90%)

Scheme 2



3 **4** (7%)

Scheme 3

Despite their inherent high ring and torsional strain, cyclopropanes are kinetically rather inert, as seen by the harsh reaction conditions that are required to facilitate the rearrangement. Consequently, most studies of this reaction have focused upon identifying milder reaction conditions. One approach has been to incorporate additional substituents into the cyclopropane scaffold that could facilitate the rearrangement process, either by increasing the ring strain (e.g., using alkylidenecyclopropanes as substrates)[5–9] or by increasing the polarity of the C–C bond undergoing cleavage during the rearrangement process (Fig. 1). One of the best examples of this strategy involves using cyclopropanes with an electron-withdrawing and an electron-donating substituent at vicinal positions, which results in donor-acceptor cyclopropanes.[10] The second approach involves the use of external reagents able to activate the cyclopropane and thereby facilitate the rearrangement process. This concept has led to the identification of suitable catalysts or promoters for this reaction, which are, in the broadest sense, either Brønsted acids, Lewis acids, Lewis bases, or organometallic complexes. All these advances have contributed to broadening the scope of this transformation and to demonstrating its potential applicability as a general tool for the synthesis of densely functionalized dihydrofurans, dihydrothiophenes, dihydropyrroles, and related scaffolds.

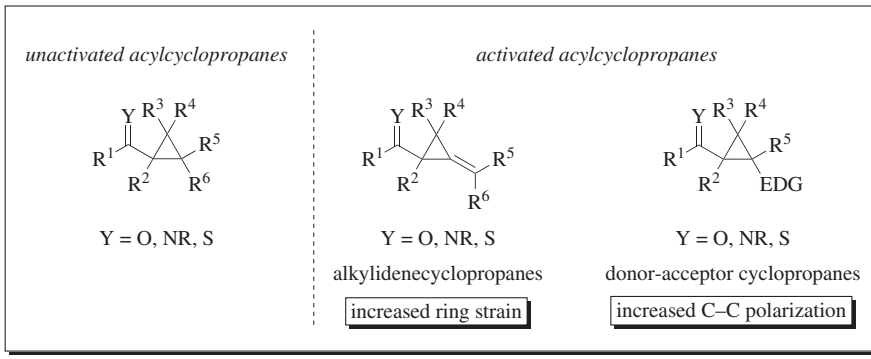


Figure 1. Modulating the reactivity of cyclopropanes.

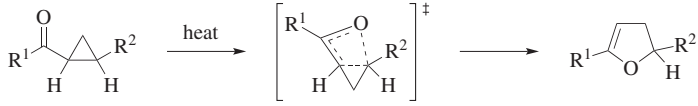
This chapter covers the entire range of reaction manifolds for the Cloke–Wilson rearrangement that have been developed since the first examples of the reaction were reported. Heteroatom variants such as the analogous aza- and sulfa-Cloke–Wilson rearrangement are also included. Although a range of reviews have been published in related areas, no review has focused completely on the Cloke–Wilson reaction and all of its variants. Several general reviews have been published covering the chemistry of cyclopropanes[11–17] and their use in synthesis.[18–22] In addition, the reactivity of electrophilic[23] or nucleophilic[24] cyclopropanes has also been highlighted and the particular behavior of donor-acceptor cyclopropanes has received special attention in recent years.[25–37] More focused reviews of the chemistry of acyl-substituted cyclopropanes or the corresponding imines have also been published,[38,39] and the most relevant advances regarding the reactivity of vinylcyclopropanes[40–42] and the vinylcyclopropane rearrangement[2] have also been reviewed.

MECHANISM AND STEREOCHEMISTRY

The mechanism of the Cloke–Wilson rearrangement varies depending on the reaction conditions employed for the activation of the starting material. Nevertheless, the number of detailed studies directed towards the elucidation of the mechanism of this reaction is very limited and are focused on explaining the outcome of the reaction, based on the particular structure of the starting cyclopropane substrate and the influence of the substitution pattern, rather than the elucidation of the mechanistic pathway for the reaction.

Thermal and Photochemical Cloke–Wilson Rearrangements: Concerted or Biradical Processes

For reactions occurring under thermal activation, a concerted mechanism is typically proposed. The C–C bond cleavage of the cyclopropane ring-opening event is proposed to take place simultaneously with formation of the C–O bond, wherein one of the carbonyl electron lone-pairs is involved, leading to the final five-membered heterocyclic product (Scheme 4). The overall process is thermodynamically favored due to the release of ring strain from the conversion of the starting three-membered carbocycle to the five-membered heterocyclic adduct.



Scheme 4

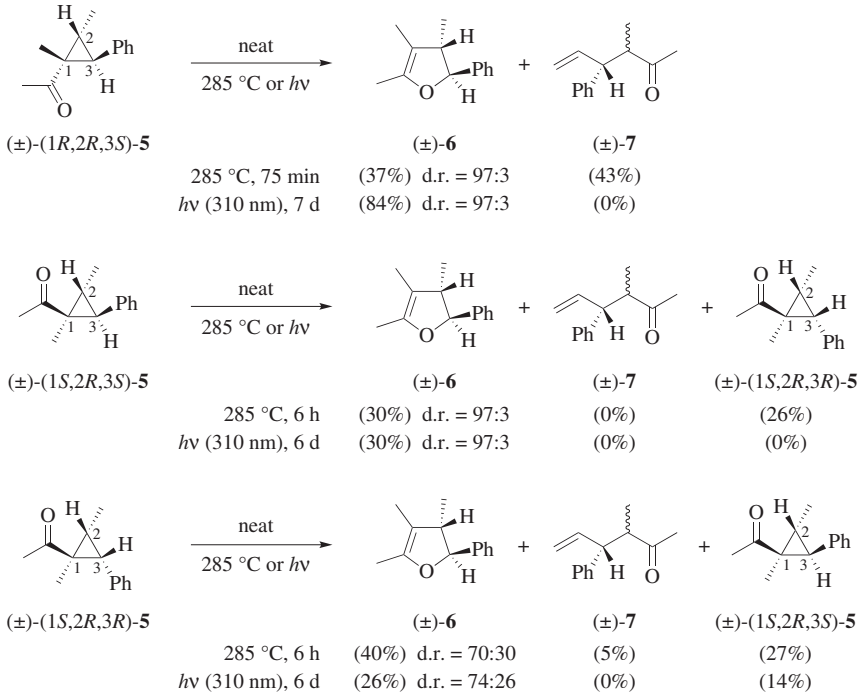
The high kinetic stability of simple unsubstituted cyclopropyl ketones and imines generally requires harsh reaction conditions for the rearrangement, such as those employed initially by Cloke and Wilson in their seminal studies (Schemes 2 and 3).

A critical development in this process stemmed from recognizing that placing an electron-donating substituent R^2 vicinal to the electron-withdrawing acyl substituent on the cyclopropane creates a push-pull effect, which leads to increased polarization of the C–C bond that undergoes ring cleavage, thus facilitating the rearrangement process.

The key role played by the electron-donating substituent in accelerating the Cloke–Wilson rearrangement has been studied by computational methods.[43,44] These studies indicate a clear trend, in which increasing the electron-donating nature of the R^2 group and the electron-withdrawing nature of the acyl group leads to a kinetically more-favored process. Incorporating additional donor or acceptor substituents further lowers the calculated activation energies for the rearrangement process.[44] This study also points towards the fact that simple phenyl or methyl substituents provide enough electron donation for a reaction to be feasible under relatively mild reaction conditions.

Calculations also reveal similar activation energies for the reaction with either the *cis*- or *trans*-substituted donor-acceptor cyclopropanes. Despite these computational studies, there is no definitive experimental evidence demonstrating that chiral information is transferred from the starting material to the final product under thermal conditions. However, the employment of an enantioenriched cyclopropane substrate has been used in many cases to confirm or disprove whether a particular Cloke–Wilson rearrangement has proceeded through a concerted reaction pathway.

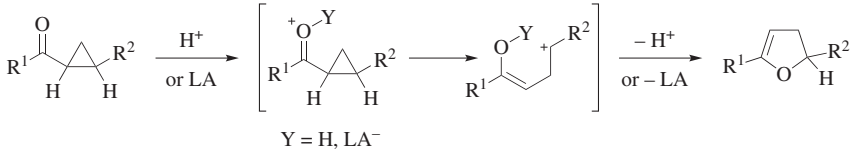
Other studies have proposed that the transition-state structures have biradical character in the concerted rearrangement process, which parallels the mechanism considered for the related vinylcyclopropane–cyclopentene rearrangement.[2,45,46] In particular, the rearrangement of a variety of diastereomerically pure, racemic polysubstituted cyclopropyl methyl ketones **5** containing a phenyl group as the electron-donating substituent, in addition to a methyl group as a stereochemical marker, indicate that the reaction is not stereospecific, as the same diastereoisomer of dihydrofuran **6** is obtained regardless of the *cis* or *trans* relative configuration of the donor phenyl group and the acceptor acyl moiety (Scheme 5).[47] The Cloke–Wilson rearrangement of these substrates also takes place with complete regioselectivities, to provide the products from the cleavage of the more polarized cyclopropane C–C bond. The formation of the observed mixture of diastereoisomers is explained by the participation of a biradical intermediate species that is long-lived enough to permit C–C bond rotation prior to cyclization. In fact, the rearrangement product is formed together with either the acyclic γ,δ-unsaturated ketone **7** byproduct and/or with some amount of the C3 epimerized cyclopropane **5**. These findings also support the formation of the proposed ring-opened biradical intermediate. In addition, the fact that the reaction can also be carried out at room temperature under photochemical irradiation is also consistent with the proposed radical pathway versus the potential formation of a zwitterionic ring-opened intermediate. More specifically, computational studies also support the biradical mechanism for the Cloke–Wilson rearrangement of 2-vinylcyclopropane-1-carbaldehyde.[48]



Scheme 5

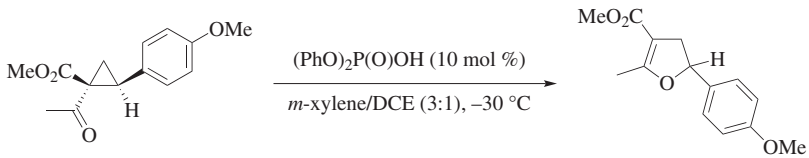
Lewis or Brønsted Acid Promoted Cloke–Wilson Rearrangement: Stepwise Processes

Another approach to the Cloke–Wilson reaction involves activating the substrate with a Brønsted or Lewis acid. In each case a stepwise mechanism is proposed for the reaction,[49,50] which is proposed to involve the formation of either a carbocationic enol or a carbocationic metal enolate intermediate after ring-opening (Scheme 6).[51–54] A critical consideration for this approach is the nature of the carbocationic moiety, since the formation of a primary carbocation from an unsubstituted cyclopropyl ketone is unlikely.[51] In contrast, cyclopropanes bearing two geminally positioned electron-withdrawing carbonyl moieties have an increased tendency to undergo the Cloke–Wilson rearrangement as a result of enhanced polarization of the C–C bond compared to simple monoacyl-substituted cyclopropanes.[55]



Scheme 6

From a kinetic point of view, the C–C bond cleavage event is the proposed rate-determining step and once the zwitterionic intermediate has been formed, the cyclization is usually fast. In fact, computational studies have been unable to find a minimum in the reaction coordinate that corresponds to a ring-opened intermediate, and only detect the possibility for the formation of a hidden intermediate (a shoulder on the IRC analysis plot) that would evolve without a barrier to the final product.[56] However, the electron distribution along the reaction coordinate is consistent with participation of the ring-opened carbocationic enol intermediate. Hence, the possibility of this intermediate also operating in other reactions with thermal activation cannot be discounted. In addition, experimental evidence for the stepwise mechanism has been provided using the enantioenriched substrate **8** that undergoes Cloke–Wilson rearrangement catalyzed by diphenylphosphoric acid, to provide the final dihydrofuran **9** in racemic form (Scheme 7).[56] This experiment shows that the reaction is not stereospecific and provides solid support for the formation of the proposed achiral zwitterionic carbocationic enol intermediate for this reaction manifold.



8
d.r. = 10:1
e.r. = 90.0:10.0

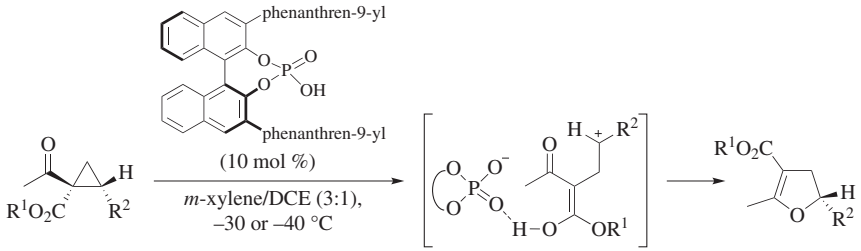
9 (92%)
e.r. = 50.0:50.0

Scheme 7

In fact, the formation of an achiral acyclic intermediate using a Brønsted acid was exploited in the development of the only example to date of a catalytic and enantioselective Cloke–Wilson rearrangement that makes use of a BINOL-based chiral phosphoric acid as a chiral catalyst. Under the optimized reaction conditions, a variety of racemic donor-acceptor cyclopropanes **10** rearrange to the corresponding dihydrofurans **12** in highly enantioenriched form (Scheme 8).[56] The enantiocontrol is believed to stem from the stabilizing cation-π interactions between the benzylic carbocation and the π-extended phenanthren-9-yl substituent on the BINOL core of the catalyst in the transition state that connects intermediate **11** with the rearrangement product.

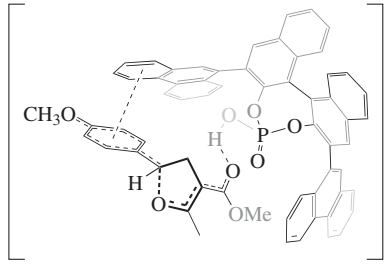
Lewis Base Promoted Cloke–Wilson Rearrangement: Stepwise Processes

The third possibility for activating cyclopropyl ketones to undergo Cloke–Wilson rearrangement employs a Lewis base as either a catalyst or stoichiometric promoter. The mechanism proposed in these cases generally involves the reaction of the Lewis base with the electrophilic carbon of the cyclopropane scaffold, which triggers a ring-opening process to generate a functionalized intermediate. This intermediate



(±)-**10** **11** **12**

R^1	R^2	Temp (°C)	Time (h)	Yield (%)	e.r.
Me	4-$MeOC_6H_4$	–40	84	95	95:5
Et	4-$MeOC_6H_4$	–40	84	92	93:7
Bn	thien-2-yl	–30	88	91	85:15
Bn	4-$MeOC_6H_4$	–30	48	90	95:5
Bn	4-(BnO)C_6H_4	–30	80	91	90:10

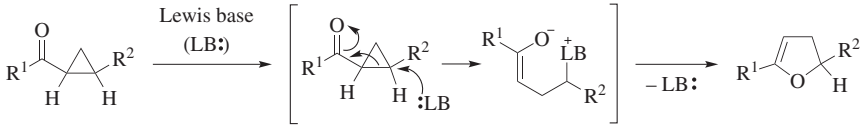


11 ⟶ **12**

R^1 = Me, R^2 = 4-$MeOC_6H_4$

Scheme 8

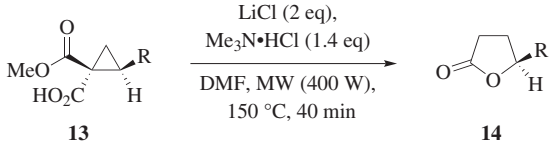
then undergoes cyclization by intramolecular nucleophilic substitution to expel the Lewis base as a leaving group (Scheme 9). A Brønsted or a Lewis acid additive or cocatalyst is commonly employed to enhance the reactivity of the cyclopropane scaffold towards the nucleophilic ring-opening process.



Scheme 9

From a stereochemical point of view, the reaction is comprised of two consecutive S_N2 processes and therefore results in net retention of configuration, in line with other intermolecular reactions involving substituted electrophilic cyclopropanes.[57–64] This process has also been demonstrated experimentally for the Cloke–Wilson

rearrangement using the enantioenriched cyclopropane hemimalonate **13** as starting material. This compound undergoes LiCl-promoted rearrangement/decarboxylation with microwave heating, in which the stereochemical configuration is predominantly transferred to the final product **14** with only minor erosion (Scheme 10).[65]

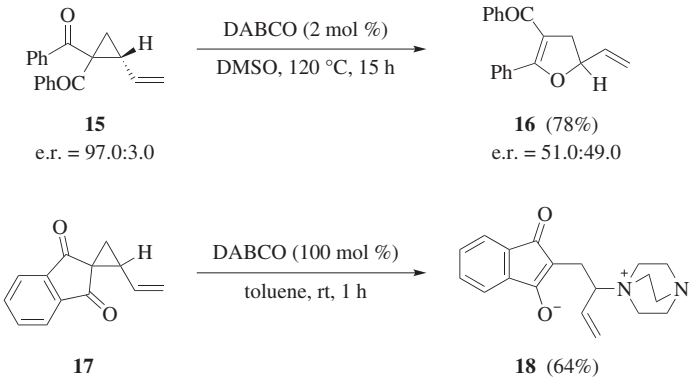


13 **14**

R	e.r. **13**	Yield (%)	(*E*)/(*Z*) **14**	e.r. **14**
Ph	95.0:5.0	82	—	90.0:10.0
(*E*)-*n*-C_6H_{13}CH=CH	97.5:2.5	82	7:1	97.0:3.0

Scheme 10

The reaction conditions determine the level of chirality transfer in conjunction with the nucleophilic promoter and its leaving-group ability. The loss of stereospecificity occurs when there is an S_N1-type substitution in the ring-opening/cyclization process, or an additional intermolecular S_N2-type reaction with excess Lewis base promoter takes place before the ring-closing event. For example, the DABCO-catalyzed Cloke–Wilson rearrangement of the enantioenriched 1,1-dibenzoyl-2-vinylcyclopropane (**15**, Scheme 11) in DMSO at 120 °C results in the rearrangement product **16** as essentially a racemate.[66] Nucleophilic attack of the related diketone **17** (Scheme 11) affords the ring-opened product **18**, which could be isolated and fully characterized; however, the zwitterion **18** does not undergo a subsequent ring closing to generate a furan product upon heating at reflux. This result may indicate the possibility of an alternative mechanistic pathway, such as a reversible S_N2' pathway occurring in the ring-opening event, in which the terminal alkene moiety could be involved to form an achiral intermediate after addition of the catalyst.



15
e.r. = 97.0:3.0

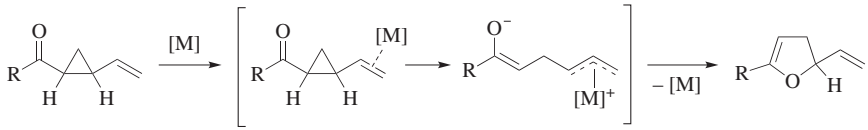
16 (78%)
e.r. = 51.0:49.0

17

18 (64%)

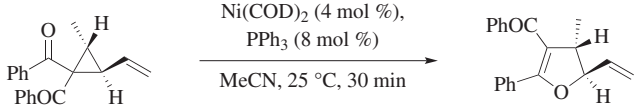
Scheme 11

Organometallic activation of vinylcyclopropanes can also be used to trigger the Cloke–Wilson rearrangement. The most straightforward approach relies on activation of the substrate through the formation of a π-allyl organometallic intermediate (Scheme 12).[27] In this case, the transition-metal catalyst is believed to first coordinate with the alkene moiety, which promotes the formation of a π-allyl metal complex with concomitant cyclopropane ring opening and formation of an enolate. The intramolecular addition of the nucleophilic enolate oxygen to the proximal electrophilic π-allyl metal site leads to the formation of the final dihydrofuran rearrangement product and the regeneration of the low-valent transition-metal complex.



Scheme 12

The reaction has also been reported to be enantiospecific and proceeds with retention of configuration using the enantioenriched vinylcyclopropane substrate **19**, which is consistent with an overall double S_N2-type process to form dihydrofuran **20** (Scheme 13).[67]



19
d.r. = 95:5
e.r. = 94.0:6.0

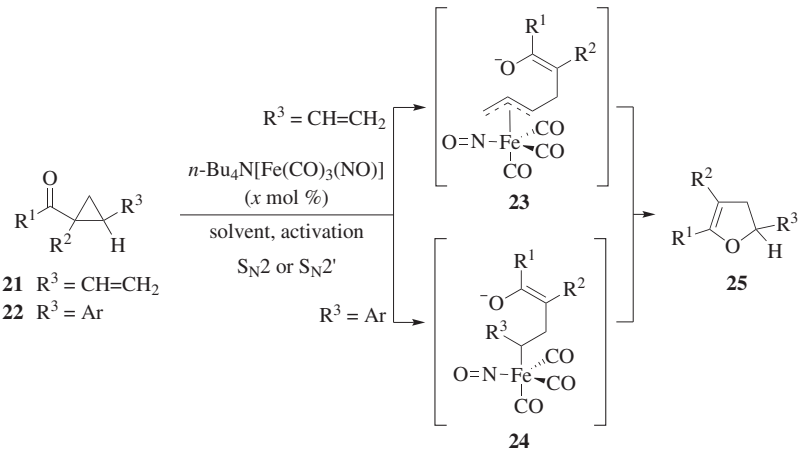
20 (94%)
e.r. = 94.0:6.0

Scheme 13

In a related approach, the ferrate complex *n*-$Bu_4N[Fe(CO)_3(NO)]$ is a superior catalyst for the Cloke–Wilson rearrangement that facilitates the reactions with both vinyl- and aryl-substituted acylcyclopropanes **21** and **22**, respectively, which also incorporate an additional electron-withdrawing substituent geminal to the acyl group.[68,69] The mechanism of this reaction probably involves the participation of the Fe–NO moiety as a nucleophilic counterpart that reacts with the electrophilic cyclopropane substrate through an S_N2-type process (Scheme 14).[70] After the ring-opening event, the intermediates **23** and **24** undergo a subsequent ring closure through an intramolecular S_N2 reaction that forms the final dihydrofuran product **25** and regenerates the iron catalyst. Although the organometallic intermediates **23** and **24** are quite different (π- versus σ-bonding), they effectively result in the same process.

Remarkably, it is proposed that the reaction does not involve metal-centered orbitals but rather the transfer of electrons from the covalent Fe–N π bond, which

results in the formal oxidation of the NO ligand during the process. Therefore, no change in the oxidation state of the iron center takes place during the reaction, with all intermediates being iron(II) species. Further studies demonstrated that since the nonpolar Fe–N bond is involved in the key ring-opening reaction, it can be exploited to develop a photochemical version of this transformation that selectively excites the Fe–N bond upon UV irradiation. Indeed, the photochemical reaction proceeds at room temperature with different light sources, e.g., a 180 W Hg lamp (Scheme 14) or a 75 W Xe lamp.[68]



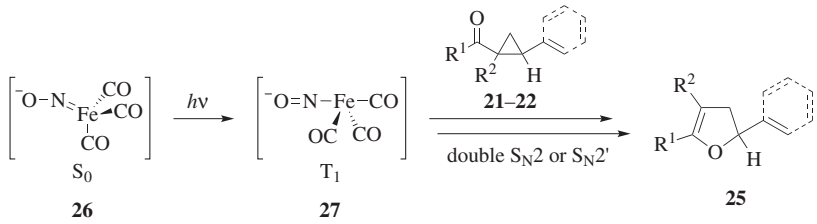
SM	R^1	R^2	R^3	*x*	Solvent	Activation	Temp (°C)	Time (h)	Yield (%)
21	Ph	PhCO	CH_2=CH	1	CH_2Cl_2	heat	45	16	92
21	Ph	PhCO	CH_2=CH	2.5	MeCN	*hν*[a]	20	3	93
22	Me	MeCO	Ph	5	DMF	MW[b]	120	2	99
22	Me	MeCO	Ph	10	DMF	*hν*[a]	20	24	82
22	Me	MeCO	3-BrC_6H_4	5	DMF	MW[b]	120	2	84
22	Me	MeCO	4-BrC_6H_4	10	DMF	*hν*[a]	20	24	97
22	Me	MeCO	4-MeC_6H_4	5	DMF	MW[b]	120	2	99
22	Me	MeCO	4-MeC_6H_4	10	DMF	*hν*[a]	20	24	85
22	Ph	PhCO	Ph	5	DMF	MW[b]	120	2	83
22	Ph	PhCO	Ph	10	DMF	*hν*[a]	20	24	93
22	Ph	MeO_2C	Ph	5	DMF	MW[b]	120	2	74
22	Ph	MeO_2C	Ph	10	DMF	*hν*[a]	20	24	81

[a] 180 W Hg lamp.
[b] 200 W.

Scheme 14

A more detailed study of this process found a maximum conversion/wavelength correlation at 410 nm, which corresponds to a saddle point of the emission spectrum of the iron complex. Spectroscopic and computational studies indicate that the selective irradiation of the Fe–N π bond leads to the excited singlet state **26** in which electron density is shifted from the metal center to the NO ligand, which is followed

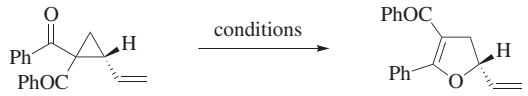
by a fast intersystem crossing (Scheme 15).[68] Subsequent relaxation leads to the triplet state **27** in which the Fe center adopts an almost trigonal bipyramidal arrangement. Structure **27** implies an open and more sterically accessible reaction site for the nucleophilic Fe–NO moiety to react with the electrophilic cyclopropane, thereby initiating the double S_N2 or S_N2' process that facilitates the rearrangement.



26 **27** **25**

Scheme 15

In the case of vinyl-substituted cyclopropanes, the double substitution process might involve S_N2 or S_N2' reactions, with computational studies indicating that both pathways may operate simultaneously.[68] However, for aryl-substituted cyclopropanes, the only reasonable pathway would involve two consecutive S_N2 reactions. Because of this double inversion process, the overall reaction is enantiospecific, which was confirmed using the enantioenriched starting material (2*R*)-**21** in the metal-catalyzed reactions illustrated in Scheme 16.[68] Notably, this reaction proceeds in a stereospecific fashion using either thermal or photochemical activation conditions.



(2*R*)-**21**
e.r. = 98:2

Conditions	Yield (%)	e.r.
n-$Bu_4N[Fe(CO)_3(NO)]$ (1 mol %), CH_2Cl_2, 45 °C, 16 h	92	97.0:3.0
n-$Bu_4N[Fe(CO)_3(NO)]$ (2.5 mol %), *hν* (180 W Hg lamp), MeCN, 20 °C, 3 h	93	97.5:2.5

Scheme 16

SCOPE AND LIMITATIONS

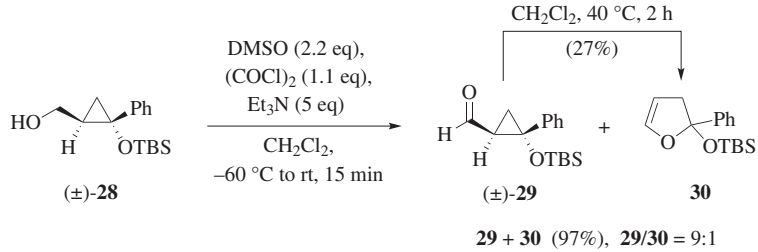
The synthetic utility of the Cloke–Wilson rearrangement or the corresponding heteroatomic variants is generally restricted by the conditions required for the reaction and by the availability of the cyclopropane starting materials. With respect to the first issue, simple acyl-substituted cyclopropanes require harsh reaction conditions that involve prolonged heating at high temperatures, which implies a serious

limitation of the methodology in terms of functional-group compatibility. As an alternative, substrates with a donor-acceptor substitution pattern are far more reactive towards the rearrangement process and the possibility of using more complex and highly functionalized substrates is facilitated by the relatively mild reaction conditions in these cases. Moreover, the synthetic potential of this transformation is directly related to the availability of reliable methods for the construction of cyclopropanes. Although methods for the synthesis of functionalized cyclopropanes were historically limited in scope, recent advances have addressed this limitation, and access to acyl-substituted cyclopropanes with almost any desired substitution pattern is, in principle, feasible. In addition, enantioenriched cyclopropane substrates can be readily prepared, which, in combination with the often stereospecific nature of the Cloke–Wilson rearrangement, presents a powerful tool for the enantioselective synthesis of dihydrofurans that are not readily constructed by other methods.

In particular, most of the reported examples of the Cloke–Wilson rearrangement employ the metal-mediated cyclopropanation of olefins with diazoalkanes, especially those using rhodium catalysis.[71–74] In fact, some reports indicate that once the cyclopropanation is complete, the rearrangement usually takes place rapidly because of the inherent reactivity of the cyclopropane substrate. As alternatives, Simmons–Smith[75] cyclopropanations or Corey–Chaykovsky[76–78] reactions have also been used for the synthesis of certain starting materials.

The Cloke–Wilson Rearrangement for the Synthesis of Dihydrofurans

Rearrangement of Cyclopropanecarbaldehydes. As already shown in Scheme 3, pyrolysis of cyclopropanecarbaldehyde at 500 °C for 30 minutes leads to the direct formation of 2,3-dihydrofuran, albeit in only 7% yield.[4] However, the reaction can be carried out at much lower temperature using an activated donor-acceptor-substituted cyclopropane, as illustrated with the rearrangement of the racemic 2-silyloxy-substituted cyclopropanecarbaldehyde **29** in Scheme 17. Notably, the aldehyde **29** is so reactive and prone to undergo the Cloke–Wilson rearrangement (to dihydrofuran **30**) that it could not be purified after the Swern oxidation of the corresponding primary alcohol **28**.[79]



(±)-**28** (±)-**29** **30**

29 + **30** (97%), **29**/**30** = 9:1

Scheme 17

Using this procedure, a variety of racemic 2-alkenyl-substituted 2-silyloxycyclopropanecarbaldehydes are converted into the dihydrofuran products **32** at room