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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 104

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

Louis Pasteur

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

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

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

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

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

I would be remiss if I did not acknowledge the entire *Organic Reactions* Editorial Board for their collective efforts in steering this chapter through the various stages of the editorial process. I would like particularly to thank Gary A. Molander (Chapter 1) and Steven M. Weinreb (Chapter 2), who each served as the Responsible Editor for the first two chapters and I was responsible for marshalling Chapter 3 through the

various phases of development. I am also deeply indebted to Dr. Danielle Soenen for her 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 Weinreb (Executive Editor), Dr. Engelbert Ciganek (Editorial Advisor), Dr. Landy Blasdel (Processing Editor), and Dr. Debra Dolliver (Processing Editor). I would also like to acknowledge Dr. Barry Snider (Secretary) and Dr. Jeffery Press (Treasurer) for their efforts to keep everyone on task and make sure that we are fiscally solvent!

I am indebted to all the individuals that are dedicated to ensuring the quality of *Organic Reactions*. The unique format of the chapters, in conjunction with the collated tables of examples, make 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

KINETIC RESOLUTION AND DESYMMETRIZATION OF ALCOHOLS AND AMINES BY NONENZYMATIC, ENANTIOSELECTIVE ACYLATION

AILEEN B. FROST, ELIZABETH S. MUNDAY, STEFANIA F. MUSOLINO, AND ANDREW D. SMITH

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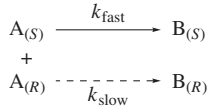
INTRODUCTION

Enantiomerically pure alcohols and amines are ubiquitous throughout Nature and are found within numerous biologically active compounds. Alcohol and amine functional groups are also synthetically versatile and can be incorporated within a diverse array of synthetic strategies. Consequently, significant efforts have been made toward the development of new methods that permit the preparation of enantiomerically pure alcohols and amines. In this regard, resolution methods in which the two enantiomers of a racemic mixture are separated are still widely used to obtain enantiomerically enriched alcohols and amines.

Kinetic resolution (KR) is a process by which enantiomeric enrichment of a racemic mixture is achieved through manufacturing a difference in the rate of reaction of the two enantiomers (Scheme 1). This is inherently challenging given that in the absence of a chiral environment the rate of reaction of two enantiomers

is identical. Since the pioneering studies of Pasteur in the 19th century relating to resolution and stereochemistry,[1] the field of KR progressed at a modest rate until the early 1980s when landmark discoveries in enantioselective catalysis provided the platform for the development of new KR methods. A wide range of KR processes have subsequently been reported that employ a variety of transformations with different functional groups to facilitate the resolution and thereby enantiomerically enrich a racemic starting material. A number of comprehensive reviews and books are available that detail progress in the many different aspects of KR.[2–8]



Scheme 1

The efficiency of a KR process is often characterized by its selectivity factor (s), which is defined as the ratio of the rate constant for the fast-reacting enantiomer (k_{fast}) to the rate constant for the slow-reacting enantiomer (k_{slow}) (Eq. 1).

$$s = k_{fast}/k_{slow} \qquad \text{(Eq. 1)}$$

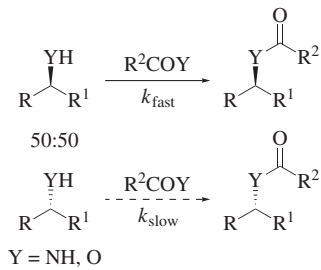
In practice, the selectivity factor cannot be easily obtained by directly measuring the individual rate constants. Consequently, Kagan developed an equation (Eq. 2)[1,9,10] based on the theoretical aspects of KR processes, which links the reaction conversion (C) to the enantiomeric excess of the recovered substrate (ee_A), both of which are easily measured. This equation is valid for a set of homocompetitive reactions in which the reaction is first-order with respect to the substrate. Alternative equations have also been derived for reactions using either scalemic catalysts and/or nonracemic substrates.[11] In some cases, the selectivity factor of a given KR process may vary with reaction conversion because of nonlinear effects associated with the kinetic partitioning of catalytic species.[12]

$$s = \ln[(1 - C)(1 - ee_A)]/\ln[(1 - C)(1 + ee_A)] \qquad \text{(Eq. 2)}$$

For a completely selective KR, in which only one enantiomer of a racemate reacts, the maximum theoretical yield of the recovered substrate is 50% (ca. $s > 500$). Nevertheless, reactions with lower selectivity can also be used to obtain enantiomerically pure recovered substrate by increasing the reaction conversion beyond 50%. For example, a reaction must proceed to 70% conversion with $s = 10$ to recover the unreacted substrate in 99:1 er, while a reaction with $s = 20$ requires 60% conversion to achieve the same result. Consequently, KR processes with $s > 10$ are considered synthetically useful, while reactions with $s > 50$ allow the isolation of highly enantiomerically enriched substrate (and product, if applicable) at 50% conversion.

Although various strategies for the KR of alcohols and amines are available, this chapter focuses on the use of nonenzymatic, acylative KR methods. In this case, one

enantiomer of the racemic alcohol or amine selectively reacts with a suitable acylating agent to form the corresponding ester or amide, respectively (Scheme 2). Throughout this review, stoichiometric KRs are defined as those in which the enantioselectivity of the acylation is controlled using a chiral acylating agent, while catalytic KRs generally employ achiral acylating agents, and stereocontrol originates from the chiral catalyst.



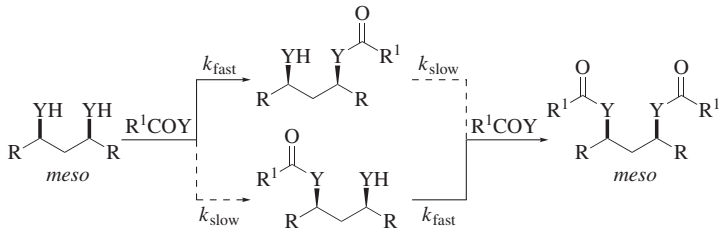
Scheme 2

Enantioselective acylation is a particularly attractive strategy for the KR of both alcohols and amines and has several advantages compared with other techniques. For example, the ester or amide products are often readily separable from the unreacted substrates, allowing the purification of the desired enantiomer. Furthermore, acylative KR allows both enantiomers of the substrate to be recovered, unlike some alternative methods in which one enantiomer is destroyed to perform the resolution. Once isolated from the initial KR, the product ester or amide can often be hydrolyzed to its parent alcohol or amine, giving access to both enantiomers of the substrate from a single KR process. Finally, the acylation of alcohols and amines is a well-studied field, and as such an array of acylating agents, catalysts, and conditions is available, that can act as a starting point for the development of a specific KR process.

Despite their similarities, the acylative KR of alcohols and amines presents distinctly different challenges. For example, the uncatalyzed acylation of amines with common reagents such as acid chlorides or anhydrides is often extremely rapid in comparison with the corresponding background acylation process for alcohols. Therefore, it is more challenging to develop a selective catalytic acylative KR for amines compared with alcohols. This difference is reflected in the literature to date, with many more methods and a broader substrate scope accessible for the acylative KR of alcohols than for amines, although recent advances in the latter suggest that further developments in this important process will be possible. Advances in acylative KR can also impact other areas of enantioselective synthesis. For example, the development of highly selective acyl transfer catalysts for the KR of alcohols preceded the renaissance in organocatalysis, and many of the catalysts explored in the context of KR have found broader utility in other areas.

Acylative desymmetrization processes of prochiral diols and diamines are also possible using either stoichiometric chiral acylating agents, or achiral acylating agents in combination with a chiral catalyst. Selective monoacylation of the prochiral

starting material results in desymmetrization, with quantitative conversion into a single enantiomer of product theoretically possible. In many cases, the enantiomeric excess of the monoacylated desymmetrization product can be enhanced by a further in situ KR process to form the corresponding *meso* bisacylated product (Scheme 3).



Scheme 3

This review aims to provide a comprehensive overview of the range of stoichiometric and catalytic methods available for the acylative KR of both alcohols and amines, highlighting the scope of substrates applicable to each process. The review covers relevant literature up until the end of 2019. Previous literature reviews on various aspects of acylative KR are also available.[1−8] Methods for the acylative desymmetrization of prochiral diols and diamines are also discussed and have been previously reviewed.[13,14] Although many enzyme-catalyzed, acylative KRs have been developed, these are outside the scope of this review and are covered elsewhere.[15−17] Related methods such as dynamic KR and parallel KR that often rely on enantioselective acylation are also not discussed but have been previously reviewed.[18−24]

MECHANISM AND STEREOCHEMISTRY

General Considerations

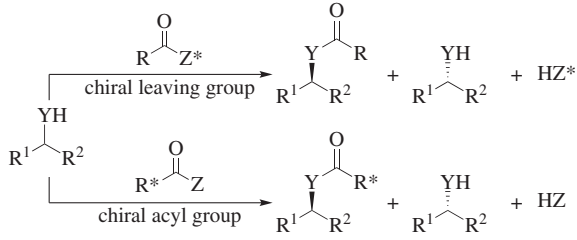
Many methods have been developed for KR and desymmetrization that vary in terms of reaction mechanism and the origin of stereoselectivity. For an effective KR, the two enantiomers of a starting material must be differentiated, with reliance upon diastereomeric interactions with either a chiral reagent or a chiral catalytic species, allowing reactions at different rates. For desymmetrization, a similar distinction must be made between either side of the mirror plane within the substrate to achieve enantiodiscrimination.

The choice of chiral reagent or chiral catalyst is key to the success of a given KR or desymmetrization process. Further details of the key interactions most commonly employed to achieve enantiodiscrimination in such processes are outlined in more detail in the following sections. The acylating agent selection is also crucial in many instances as it can have a dramatic effect on both the stereoselectivity and overall reactivity. The nature of KR dictates that a substoichiometric amount of acylating agent relative to the racemic substrate is often employed (0.5–1 equiv), whereas

desymmetrization may require an excess of the reagent to reach completion. Many methods also require the addition of base to facilitate acylation and to sequester acidic byproducts, which typically involves organic tertiary amine bases. The reaction solvent can also influence the stereoselectivity of KR and desymmetrization reactions, albeit such effects are catalyst- and substrate-dependent and can be difficult to predict. Although there are many examples of KR and desymmetrization that work well at room temperature, lower temperatures are also commonly used to improve reaction stereoselectivity.

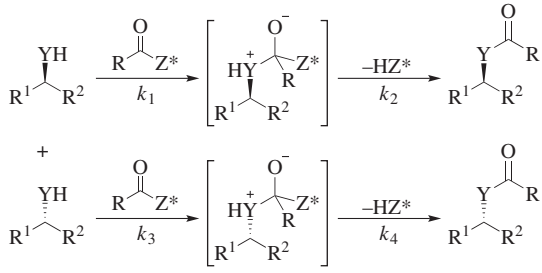
Stoichiometric KR and Desymmetrization

A stoichiometric acylative KR requires a chiral acylating agent to provide selectivity in the reaction. Stoichiometric acylative KRs have been reported in which the stereochemical control element is present within either the leaving group or the acyl group (Scheme 4), although the latter leads to diastereomeric products that have different physical properties and could, therefore, be considered a classical resolution.



Scheme 4

For KRs in which the stereochemical control element resides in the leaving group, two potential steps could be stereodifferentiating (Scheme 5). The initial addition of the racemic starting material into the acylating agent may proceed at different rates ($k_1 \neq k_3$). Alternatively, the collapse of the diastereomeric, tetrahedral intermediate may be the stereodetermining step ($k_2 \neq k_4$), albeit this process would need to be reversible for the mismatched diastereoisomer.



Scheme 5

There are relatively few examples of stoichiometric acylative KR and desymmetrization of alcohols, which may be ascribed to the many efficient catalytic methods that exist for these processes. In contrast, the stoichiometric acylative KR and desymmetrization of amines have been more widely studied, and several effective acylating agents for these substrates have been reported (Fig. 1).

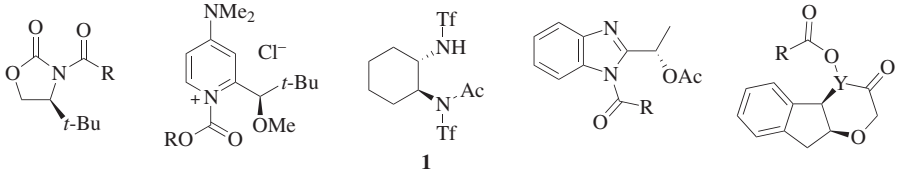
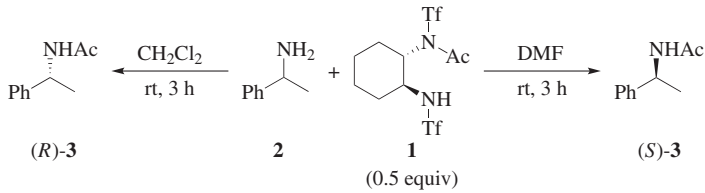


Figure 1. Examples of stoichiometric acylating agents used for KR.

Notably, the stereodetermining step is often the initial acylation of the racemic substrate, which in some cases is governed by the conformation of the acylating agent[25,26] and/or by noncovalent interactions such as H-bonding[27] and π-cation stacking[28] with the substrate. The stoichiometric, acylative KR of secondary benzylic amines such as 1-phenylethylamine (**2**) using chiral diamine **1** undergoes an interesting switch in stereoselectivity depending on the solvent used, with basic solvents such as DMF, DMPU, and ionic liquids giving amide (*S*)-**3**, whereas more acidic solvents such as CH_2Cl_2 furnish amide (*R*)-**3** selectively (Scheme 6).[29,30] The switch is rationalized by a change in the stereodetermining step in different solvents. In acidic solvents, reversible hemiaminal formation is nonselective, with subsequent collapse of the diastereomeric, tetrahedral intermediates determining the reaction selectivity. In more basic solvents, this initial equilibrium is proposed to be disfavored, and the selectivity determined by the initial enantioselective acylation of the racemic substrate.



Scheme 6

Catalytic KR and Desymmetrization

A wide range of catalytic KR and desymmetrization reactions has been reported that permit the resolution of many classes of substrates. These processes employ achiral acylating agents and often require the addition of base to facilitate the acylation. The reaction solvent is highly dependent on the catalytic system, with reactions typically conducted at room temperature or below to achieve optimal selectivity.

Lewis acid and Lewis base catalysts have been the most widely explored for acylative KR and desymmetrization processes, with more details on the different modes of activation and origins of enantiodiscrimination provided below.

Acylating Agents. A key consideration in catalytic, acylative KR and desymmetrization processes is the choice of achiral acylating agent, with the steric demand of the acyl group often having an impact on the reaction selectivity. The rate of the noncatalyzed reaction between the acylating agent and the racemic substrate must be significantly slower than the catalytic, enantioselective process. For the KR and desymmetrization of alcohols, such noncatalyzed reactions are rarely problematic, and consequently, a wide range of acylating agents can be employed (Fig. 2). Readily available acid chlorides and symmetrical anhydrides are by far the most commonly used *O*-acylating agents and are compatible with many different catalysts under a variety of conditions. In particular, aryl-substituted acid chlorides (e.g., benzoyl chloride) and short-chain alkyl acid anhydrides (e.g., acetic, propanoic, and isobutyric anhydrides) are the most widely reported.

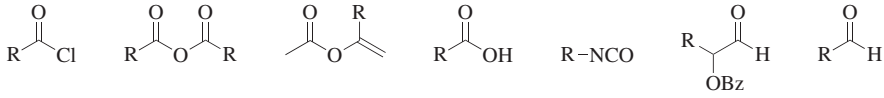
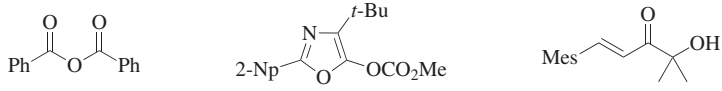


Figure 2. Examples of acylating agents used for the KR and desymmetrization of alcohols.

The use of vinyl esters as *O*-acylating agents for KR has also been reported, and carboxylic acids require the in situ formation of a reactive mixed anhydride using a sterically demanding anhydride (e.g., pivaloyl anhydride) that is unreactive to the catalytic *O*-acylation. Isocyanates have also been used to form carbamate products instead of esters in both KR and desymmetrization processes. Acylating agents that are not at the carboxylic acid oxidation level can also be used in conjunction with an *N*-heterocyclic carbene (NHC) catalyst. For example, α-benzoyloxy aldehydes undergo a redox reaction in the presence of a suitable NHC to form an active *O*-acylating agent in situ, and unsubstituted aldehydes can also be used in the presence of an NHC with external oxidant.

The catalytic KR of amines is significantly more challenging compared with the KR of alcohols because of the increased nucleophilicity of amines, which results in faster rates of noncatalyzed *N*-acylation using common reagents such as acid chlorides and acid anhydrides, even at low temperature. Consequently, choosing an appropriate *N*-acylating agent that avoids unwanted background reactivity is crucial for success (Fig. 3). Benzoic anhydride (**4**) is unreactive toward secondary amines at low temperatures in toluene and has been used for the KR and desymmetrization of amines using a suitable chiral H-bonding catalyst in the presence of 4-(dimethylamino)pyridine (DMAP).[31,32] The KR of amines has also been reported using *O*-acyl azlactone **5**, which preferentially reacts with the planar-chiral DMAP catalyst rather than the racemic amine.[33] An alternative approach is to employ a

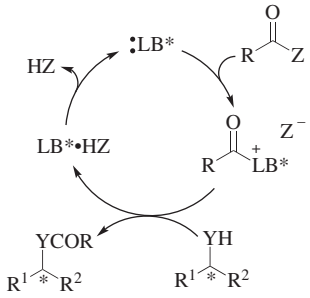
masked acylating agent that can only be revealed in the presence of a catalyst. For example, α′-hydroxyenone **6** undergoes a retro-benzoin reaction in the presence of an NHC catalyst, releasing acetone as the byproduct.[34] The resulting unsaturated Breslow intermediate undergoes protonation followed by tautomerization to form an acyl azolium ion, which undergoes preferential transesterification with a chiral hydroxylamine catalyst to form the key chiral *N*-acylating agent. Importantly, the intermediate acyl azolium ion reacts slowly with secondary amines, and therefore the undesired racemic *N*-acylation is minimized.



4 **5** **6**

Figure 3. Examples of acylating agents used for the KR of amines.

Lewis Base Catalysis. Chiral Lewis bases are the most commonly used class of catalysts for the acylative KR and desymmetrization of alcohols and amines. In these cases, the Lewis base first reacts with the achiral acylating agent to form a more reactive chiral acylating agent (Scheme 7). Stereoselective acylation of one enantiomer of the substrate generates the product, with the associated counterion (Z^-) often crucial for concomitant proton transfer during this selectivity-determining step. In many protocols, an additional base is necessary to aid the dissociation of the resulting Lewis base-acid adduct to regenerate the catalyst. Many different classes of Lewis bases have been used for acylative KRs and desymmetrizations, but within each class, there are some common interactions and/or modes of recognition that allow the catalyst to discriminate between the two substrate enantiomers.



Scheme 7

Pyridine Analogues. Pyridine and analogues such as 4-dimethylaminopyridine (DMAP) are widely used as acyl transfer agents in many different reactions, including the acylation of both alcohols and amines.[35] As such, the investigation of chiral pyridine analogues was a logical step for the development of enantioselective acyl transfer

agents for KR, and consequently, this class of catalyst has been the most widely explored to date. Mechanistic studies on the catalytic cycle in such processes are predominantly focused on the origins of stereoselectivity; however, details regarding the other steps in the catalytic cycle can be inferred from investigations into related (achiral) acyl transfer reactions.

The acylation of pyridine analogues to form the key *N*-acylpyridium intermediates is highly dependent upon the catalyst structure, the achiral acylating agent, and the solvent. For example, 4-pyrrolidinopyridine (PPY) readily reacts with acetyl chloride to form the corresponding *N*-acetylpyridium chloride quantitatively, whereas the analogous reaction with acetic anhydride results in <10% of the *N*-acetylpyridinium acetate at equilibrium.[35,36] Despite this difference, the rate of acylation of a tertiary alcohol is three times faster using acetic anhydride compared with acetyl chloride. These experiments highlight the importance of the *N*-acylpyridinium counterion,[37] in which computational studies suggest that the acetate counterion assists proton transfer in the turnover-limiting acylation step (Fig. 4).[38]

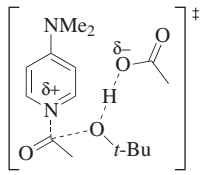
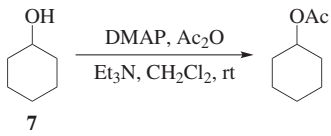


Figure 4. Computationally predicted role of acetate counterion in DMAP-catalyzed *O*-acylation using acetic anhydride.

Kinetic analysis of the DMAP-catalyzed acylation of cyclohexanol (**7**) with acetic anhydride and triethylamine shows that the reaction is first-order in the substrate, DMAP, and the anhydride, but zero-order in triethylamine (Scheme 8).[38] This provides evidence that substrate acylation is turnover-limiting and that the role of added base is to sequester acidic byproducts formed during this step.



Component	Order
7	first
DMAP	first
Ac_2O	first
Et_3N	zero

Scheme 8

Various approaches for generating chiral analogues of the planar DMAP core have been explored in attempts to make efficient catalysts for acylative KR and desymmetrization (Fig. 5). The enantioselective acylation requires differentiation of the two faces of the intermediate *N*-acylpyridinium, and the two enantiomers of the racemic substrate must interact differently with the accessible face. One strategy is to introduce a substituent that contains a stereocenter onto the pyridine ring in either the

2- or 3-position; however, substitution in the 2-position generally leads to a significant decrease in reactivity because of the increased steric demand around the reactive nitrogen atom, and therefore such catalysts are often unsuitable for acyl transfer reactions.[39] Conversely, substitution in the 3-position retains the catalytic activity, but any stereocenter present is now further away from the reactive site of the *N*-acylpyridinium intermediate. A tactic for improving selectivity in these cases is to introduce substituents that may have stacking interactions with the *N*-acylpyridinium core.[40] For example, the *N*-acylpyridinium intermediates formed from 3-substituted DMAP analogues **8** and **9** are proposed to be stabilized by π–π and n_S–π interactions, respectively.[39,41] Such interactions restrict the conformation of the intermediate, providing enhanced differentiation between the two faces of the pyridinium core and enhancing the selectivity of the acylation step. Despite these advances in acylative KRs and desymmetrizations, catalysts that employ point chirality to facilitate enantiodiscrimination generally afford lower selectivity in contrast to those that use other forms of chirality.

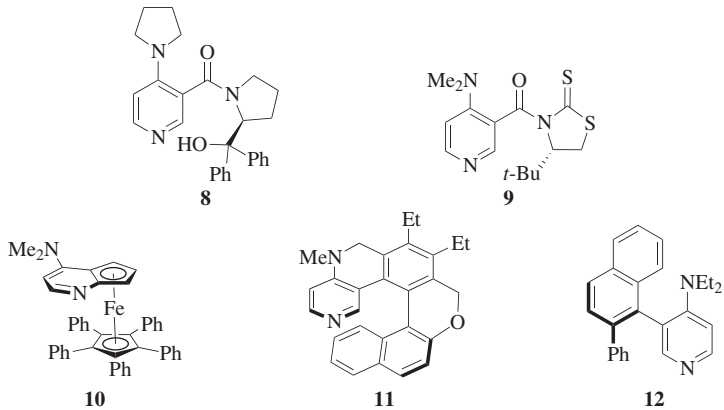
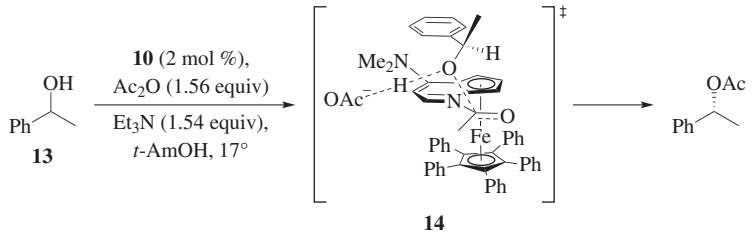


Figure 5. Examples of chiral DMAP-derived catalysts.

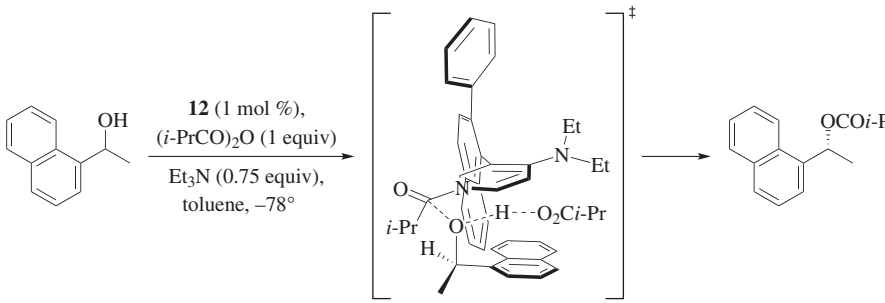
Consequently, the DMAP analogues **10** and **11** that possess planar chirality and helical chirality, respectively, provide high selectivity in acylative KR.[42,43] In these cases, the two faces of the intermediate *N*-acylpyridinium are clearly differentiated. These catalysts are particularly effective for the KR of benzylic secondary alcohols, as the two enantiomers of the alcohol have different stacking interactions with the *N*-acylpyridinium intermediate, leading to effective enantiodiscrimination. For example, π–π stacking in the proposed acylation transition state **14** between the aryl ring of the fast-reacting enantiomer of 1-phenylethanol (**13**) and the pyridinium ring, as well as minimization of steric interactions between the remaining substituents and the catalyst, provide selectivity (Scheme 9).[43] A similar model for enantiodiscrimination is proposed for helical catalyst **11** in the corresponding KR of secondary benzylic alcohols.[42]



Scheme 9

Reaction progress kinetic analysis of the KR of 1-phenylethanol (**13**) using planar-chiral DMAP catalyst **10** and acetic anhydride suggests the process is first-order with respect to catalyst **10** but has fractional orders with respect to acetic anhydride and the racemic alcohol.[43] The fractional orders are attributed to the equilibrium between the free catalyst **10** and its *N*-acetylpyridinium ion. In contrast, the KR of secondary benzylic amines using a related planar-chiral DMAP analogue and *O*-acyl azlactone **5** is first-order in both catalyst and amine and zero-order in acylating agent, which is consistent with the corresponding *N*-acylpyridinium being the catalyst resting state in this case.[33]

The mechanism of KR using enantiomerically pure, axially chiral, atropisomeric DMAP analogues such as **12** has also been studied computationally.[44,45] The Lewis base mode of reaction is again favored, with the steric interactions between the substrate and the catalyst minimized during nucleophilic attack of the fast-reacting enantiomer on the *N*-acylpyridinium intermediate (Scheme 9a).



Scheme 9a

Amidines, Guanidines, and Isothioureas. Several Lewis basic amidines, guanidines, and isothioureas have been explored as catalysts for the KR of various alcohols, typically using acid anhydrides as the acylating agents.[46] The catalysts usually contain a stereocenter adjacent to the nucleophilic nitrogen atom that controls the facial selectivity of the acylation step. The catalysts often contain an extended aromatic π-system within the backbone that may provide additional stabilization through

stacking interactions in the acylation transition state of the fast-reacting enantiomer of certain substrate classes.

Enantiomerically pure amidines such as **15**–**17** (Fig. 6) provide high selectivity for the KR of a wide range of alcohol substrates. Secondary alcohols bearing one sp^2-hybridized substituent on the stereogenic carbinol carbon tend to afford the highest selectivities because of the presence of cation-π interactions within the favored transition state of the fast-reacting enantiomer.

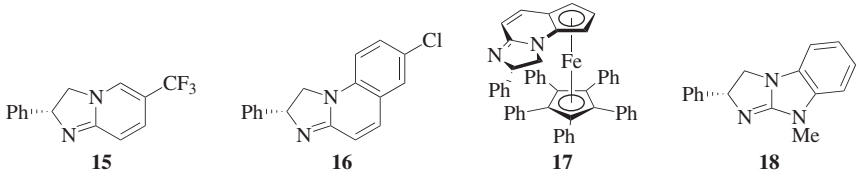
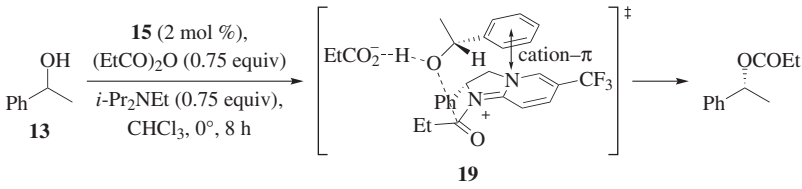


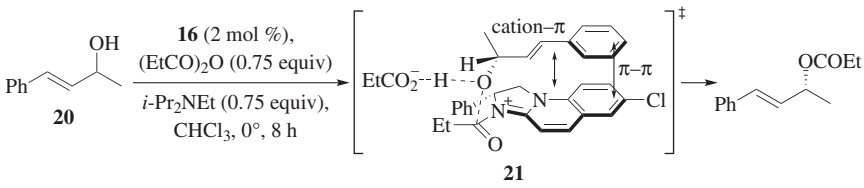
Figure 6. Examples of amidine and guanidine catalysts.

For example, computational modeling of the key acylation step in the KR of secondary benzylic alcohol **13** using **15** and propionic anhydride highlights the importance of a cation-π interaction between the pyridinium nitrogen atom and the phenyl substituent within the substrate transition state **19** for the acylation of the fast-reacting (*R*)-enantiomer (Scheme 10).[47,48] A similar stereochemical model is proposed for KRs of secondary alcohols using planar-chiral amidine catalyst **17**[49] and guanidine **18**.[50]



Scheme 10

For the KR of secondary alcohols bearing a cinnamyl substituent, the presence of an extended π-system in the catalyst leads to higher selectivity. For example, the selectivity in the KR of **20** using amidine **16** is proposed to be enhanced by both cation-π and π-π interactions between the substrate and catalyst in transition state **21** ($s = 27$) for the fast-reacting (*R*)-enantiomer (Scheme 11).[51] Computational modeling of the KR of aryl-substituted secondary amides using amidine **16** also suggests that the cation-π interaction is essential for enantiodiscrimination,[52] whereas alternative functional groups such as enones can also provide the π-system required for selective KR using an amidine catalyst.[53]



Scheme 11

Isothiourea-based catalysts **22**–**25** (Fig. 7) are effective for the acylative KR and desymmetrization of a wide range of substrates. The procedures that use these catalysts generally employ anhydrides as acylating agents. Kinetic analysis of the KR of a cyclic, secondary alcohol using isothiourea **24** suggests that the reaction is first-order with respect to the catalyst, alcohol, and anhydride.[54] KRs using isothiourea catalysts have also been reported using mixed anhydrides generated in situ from a carboxylic acid and a sacrificial anhydride, such as pivaloyl anhydride, which itself does not react with the racemic substrate.[55]

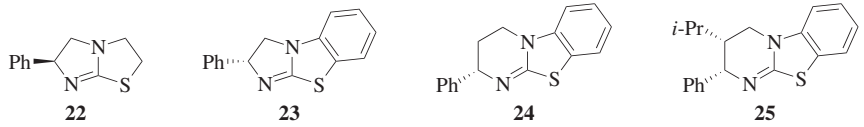


Figure 7. Examples of isothiourea catalysts.

The key acyl ammonium intermediate in isothiourea-catalyzed KRs is stabilized by a nonbonding 1,5-S•••O interaction between the carbonyl oxygen atom and the isothiourea sulfur atom.[56] This interaction serves to lock the conformation of the acyl ammonium intermediate, increasing facial discrimination of the carbonyl. The highest levels of selectivity in isothiourea-catalyzed KRs are obtained when the racemic substrate bears either an sp^2- or sp-hybridized substituent on the stereogenic carbinol center. In these cases, the transition state for the acylation of the fast-reacting enantiomer is stabilized by cation-π interactions, while minimizing steric interactions of the other substituents with the acyl ammonium core.[57−59] For example, the KR of secondary benzylic alcohols using the isothiourea **25** is proposed to proceed through transition state **26** for the fast-reacting enantiomer (Scheme 12).[60] The acyl ammonium intermediate promotes *si* face attack onto the carbonyl opposite to the stereodirecting substituents on the isothiourea core, which is conformationally locked by the 1,5-S•••O interaction. Stabilizing cation-π interactions between the aryl ring and the isothiouronium core provides selectivity during the acylation step. In accord with the amidine-based catalysts, substituents that can participate in π-π interactions with the benzenoid ring of the isothiourea result in higher selectivity. Computational studies suggest that a favorable cation-π interaction is also responsible for the observed selectivity in the KRs of α-hydroxy esters,[61,62] α-hydroxy lactones,[63] and α-hydroxy phosphonate derivatives catalyzed by the isothiourea **23**.[64]