1

PINACOL AND SEMIPINACOL REARRANGEMENTS IN TOTAL SYNTHESIS

Alison Xiang Gao

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

Stephen B. Thomas

Department of Chemistry, Columbia University, NY, USA

Scott A. Snyder

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

1.1 INTRODUCTION

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

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

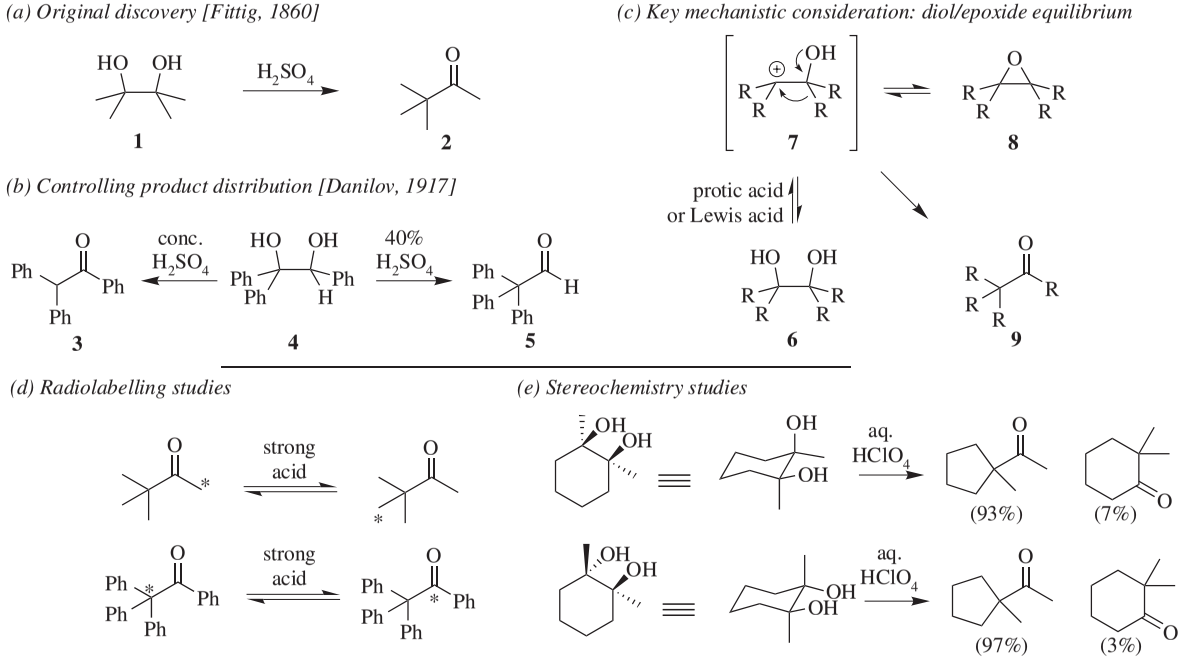
1.2 PINACOL REACTION

1.2.1 Background and Introduction

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

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

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



Scheme 1.1 The pinacol rearrangement: discovery and key considerations.

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

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

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

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

Equally important is the following additional observation:

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

1.2.2 Stereochemistry of the Pinacol Rearrangement

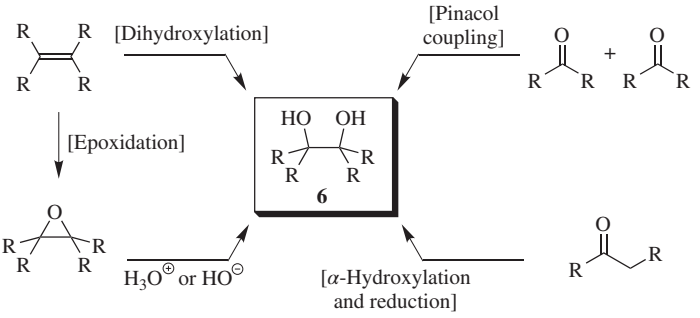
The alignment of orbitals as part of the bond migration itself ensures that stereochemical information encoded in the starting material can be expressed with high fidelity in the rearrangement if the substrate is designed appropriately. Again, however, it is critical to note that substrate-specific subtleties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

1.2.3 Preparation of Substrates for the Pinacol Rearrangement

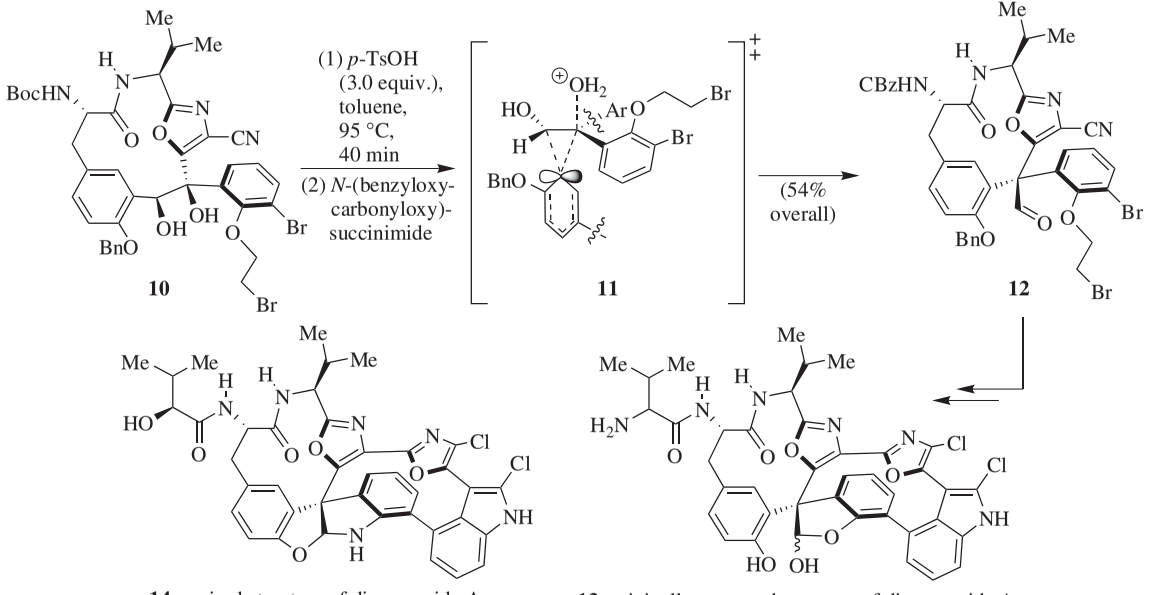
The diol substrates needed for the pinacol rearrangement are readily constructed through a variety of procedures as denoted in Scheme 1.2. Though the overall diversity of methods is not as numerous as for some functional groups, the potential advantage, at least from a strategic perspective, is that there are only a select number of choices, streamlining synthetic planning. Critically, if the stereospecific, or chiral, preparation of these materials is necessary from achiral precursors, then only dihydroxylation, epoxidation, or α-functionalization of carbonyls are reasonable approaches.

1.2.4 Applications of the Pinacol Reaction in Complex Molecule Synthesis

1.2.4.1 Two Key Case Studies To see the general precepts of the preceding sections in action, we begin our discussion of specific examples with an elegant application of the pinacol rearrangement as part of a synthesis of the originally proposed structure of diazonamide A (**13**, Scheme 1.3), a marine natural product with antitumor activities originally harvested from the colonial ascidian *Diazona angulata*. This work, published in 2000 by the Harran group, highlights a number of the critical features in substrate design needed to render a pinacol rearrangement having high levels of regio- and stereocontrol, especially in a complex context.[9] Seeking to forge the all-carbon quaternary center linking the two 12-membered rings of the target, the Harran team designed 13-membered intermediate **10** in hopes that it could undergo a regio- and stereospecific pinacol rearrangement (and ring contraction) by way of a bridging phenonium intermediate that would communicate the original stereochemistry to forge the needed isomer of the quaternary center. Pleasingly, exposure of a 5:1 mixture of diols (favoring **10** as drawn and whose structure was confirmed by X-ray) to *p*-TsOH at elevated temperature afforded compound **12** in 54% overall yield following a terminal protection of the free amine unveiled during the acid-initiated rearrangement. Complete stereochemical fidelity was achieved in this process, with **12** arising only from the drawn epimer of **10**; the alternate, minor stereochemical diol isomer gave the alternate chirality at the newly formed quaternary carbon. Apart from providing the means to ultimately



Scheme 1.2 Generic methods for the preparation of key starting materials.

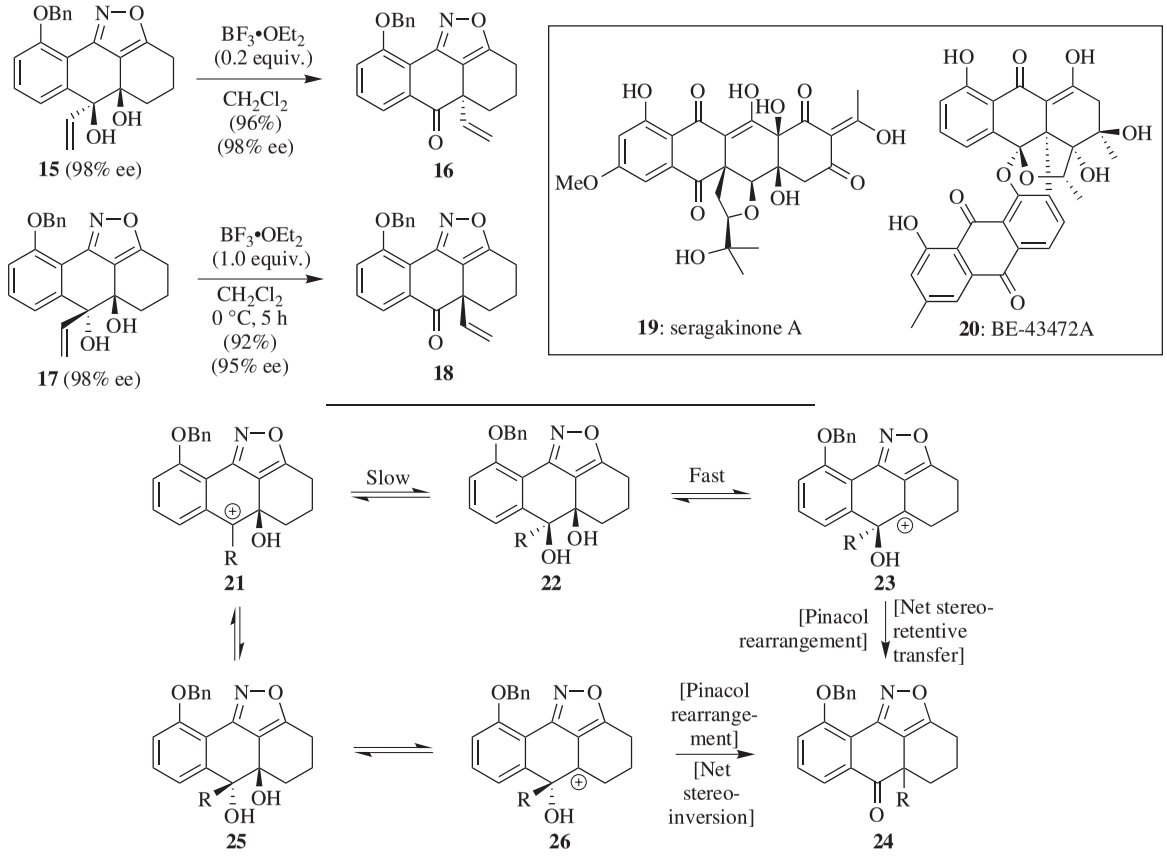


Scheme 1.3 Use of a pinacol rearrangement as part of the total synthesis of the original structure of diazonamide A (**13**).[9a]

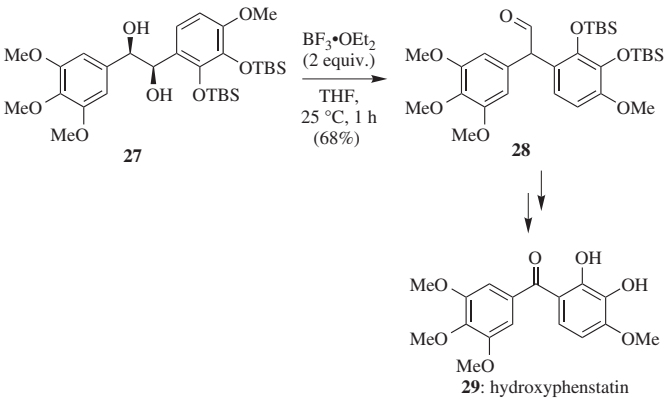
determine that the originally assigned structure of diazonamide A was incorrect (the Harran group revised it correctly to structure **14**), this work highlights how positional carbocation control, migrating group control, and stereocontrol can be merged together to accomplish a beautiful ring contraction, leading to a highly strained final product.

A more recent example which similarly displays key components of regio- and stereocontrol in a pinacol rearrangement process, with some additional critical twists, derives from the Suzuki group's approach to seragakinone A and BE-43472A (**19** and **20**, Scheme 1.4).[10] In their pursuit of these, and several other related polyketide targets, the Suzuki team required a general and effective method for establishing quaternary stereogenic centers at the angular position in these polycycles, a challenge that could not be addressed successfully by more conventional approaches such as enolate alkylation or nucleophilic displacement. Their more indirect solution utilizing the pinacol rearrangement is shown in Scheme 1.4, an approach that hinged upon the ability to access the requisite diol in stereodefined form (either **15** or **17**) and achieve regiospecific carbocation formation at the desired migration terminus with a subsequent stereospecific 1,2-shift (to generate **16** and **18**). The regiochemical requirement was the critical challenge, and its solution was the installation of the isoxazole ring within the substrates that afforded the stabilization necessary to render cation formation at the requisite site preferable over its mutually reinforcing tertiary allylic and benzylic alternative. As shown in the lower part of Scheme 1.4, the induced stabilization is so significant that the formation of **21** from generalized starting material **22** is effectively prevented, allowing for the desired 1,2-suprafacial shift to occur, with the cyclic constraints of the system driving stereoselectivity. Worth noting is that varying degrees of enantioselectivity were observed based on the migratory aptitude of the alkyl group, with better migrating groups affording enhanced enantioselectivities and highlighting the critical contribution of this component in the final, successful synthesis design.

1.2.4.2 Stereocontrol with Acyclic Diols In the absence of a preexisting cyclic system, achieving similar levels of stereocontrol with chiral diols can be difficult. An instructive example along these lines derives from the Pettit group in work targeting the antitumor natural product hydroxyphenstatin (**29**, Scheme 1.5).[11a] In this case, enantiomerically pure diol **27** was obtained through a Sharpless asymmetric dihydroxylation of the precursor olefin. Subsequent exposure to $BF_3 \cdot OEt_2$ in tetrahydrofuran (THF) at ambient temperature for 1 h afforded aldehyde **28** in 68% yield, but as a racemate (as determined by optical rotation experiments and X-ray crystallography). That absence of chiral control could be the result of racemization of the product given that the aldehyde is bis-benzylic, though it is worth noting that in other cases involving such aldehydes, that process has not been observed[11b]; alternatively, a stepwise mechanism through the intermediacy of two possible carbocationic intermediates could also be the cause for the loss of chiral information. Although in this case that outcome was fine in regard to the final benzophenone target, where stereochemistry was of no consequence, the fact that the chiral diol led to racemic product



Scheme 1.4 An isoxazole-directed pinacol rearrangement as part of total syntheses of seragakinone A and BE-43472A (**19** and **20**).[10]



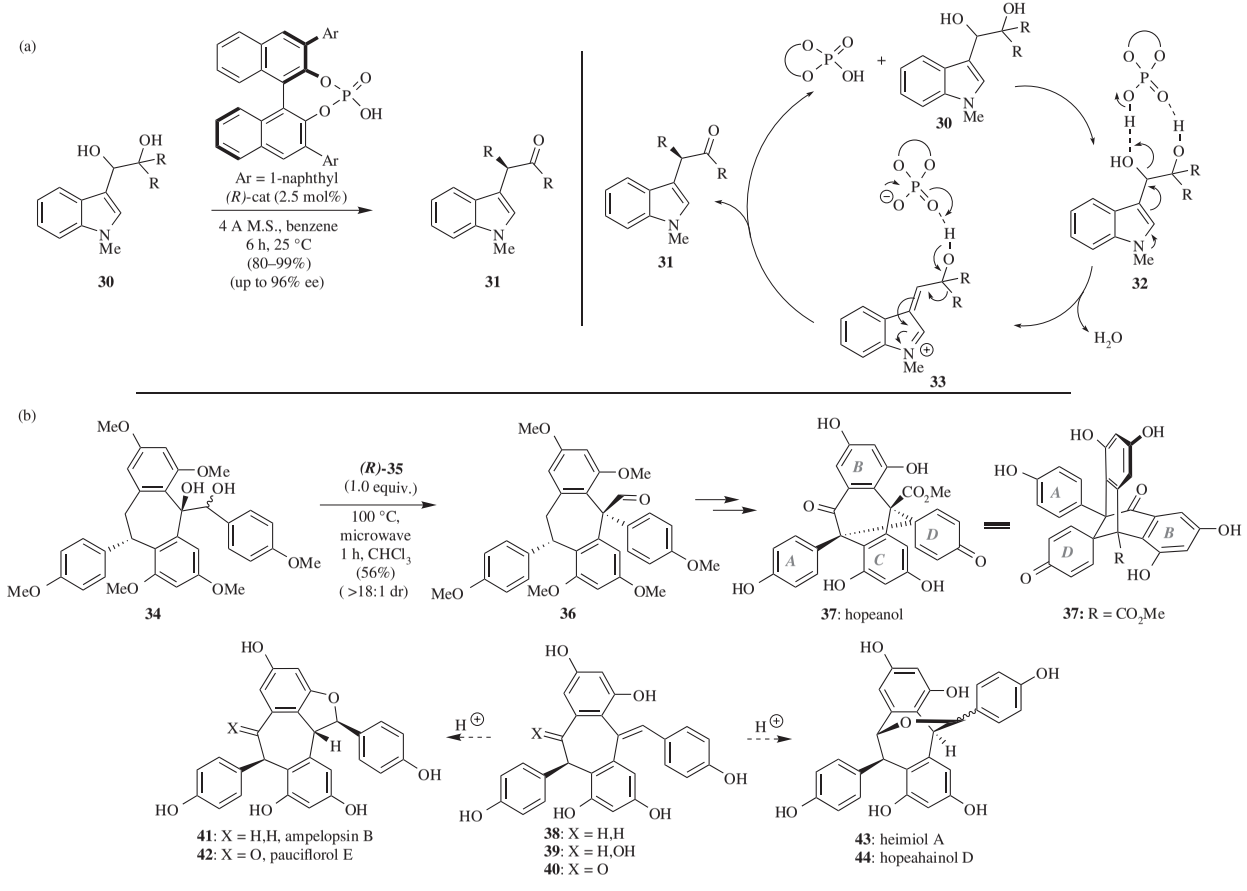
Scheme 1.5 Use of a pinacol rearrangement as part of the total synthesis of hydroxyphenstatin (**29**).[11a]

in this pinacol rearrangement highlights that in acyclic cases, absolute stereocontrol can be very difficult (if not sometimes impossible) to achieve.

In fact, there were no effective solutions to this general challenge with acyclic diols prior to 2010 when Antilla and coworkers provided an example of an asymmetric pinacol rearrangement involving racemic substrates of general flavor **30** (Scheme 1.6a, R = aryl).[12] These starting materials were very carefully designed, noting that it was expected that upon complexation with a chiral phosphoric acid (to afford **32**), acid-mediated dehydration could lead to iminium species **33**, a reactive intermediate previously shown to be compatible to chiral phosphoric acids for asymmetric nucleophile addition. Here, that nucleophile would be the internal migrating group in the pinacol rearrangement to forge chiral **31**. A variety of BINOL-derived phosphoric acids worked well in the process, with backbone variation directly correlating with enhancements in enantiospecificity. Chiral selectivity is postulated overall to arise via favorable electrostatic and hydrogen bonding interactions which constrain the 1,2-aryl shift to proceed with stereocontrol.

Inspired by this unique precedent, members of our group used the concept of a chiral phosphoric acid initiator to convert the diol diastereomers of **34** into the quaternary carbon of aldehyde **36**, a key precursor toward a total synthesis of the resveratrol dimer hopeanol (**37**, Scheme 1.6b).[13] The key ideas here hinge upon the ionization ability of the bis-benzylic tertiary alcohol versus the secondary benzylic alcohol affording requisite regiocontrol, while the chiral phosphoric acid could potentially impart some exogenous stereocontrol to enhance throughput to the desired diastereomer.

In initial probes of the process, traditional acid sources such as *p*-TsOH did indeed furnish pinacol rearrangement product **36** in moderate yield and diastereoselectivity along with a small amount of an epoxide side-product (which could not be converted to pinacol-rearranged material). However, the critical observation was that one diastereomer of the starting material reacted more quickly and under milder conditions than the other, suggesting that this diastereomer had a more favorable



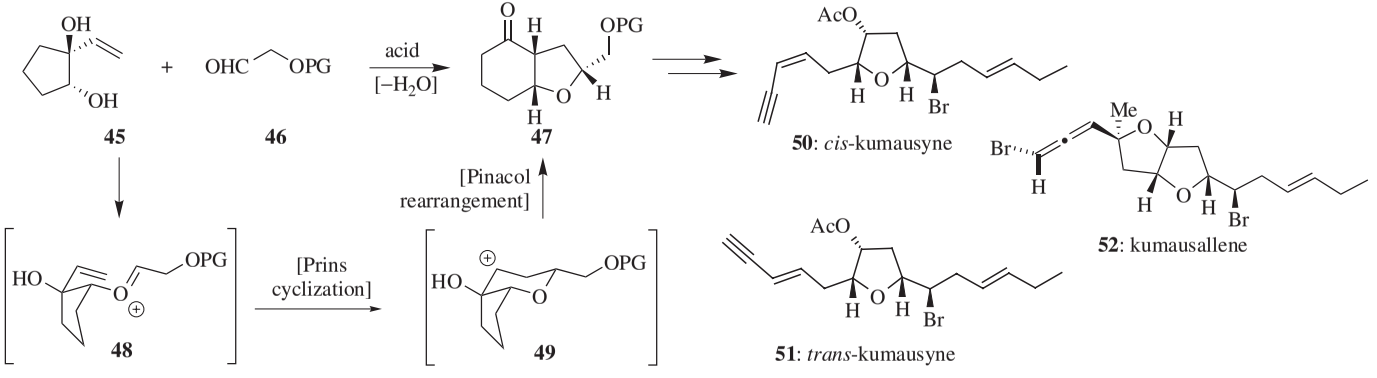
Scheme 1.6 Development of an asymmetric pinacol rearrangement by Antilla and coworkers[12] and related application to a total synthesis of hopeanol (**37**).[13]

stereochemical alignment than the other with facilitated transposition of the migrating aryl group due to advantageous orbital alignment with the departing alcohol. Intriguingly, when chiral phosphoric acids of BINOL flavor were instead employed to induce the rearrangement, the overall diastereoselectivity and yield were dramatically enhanced. Thus far, there is no evidence that the chiral phosphoric acids overturned the initial ratio of diastereomers of **34** that entered the reaction; however, it did indeed promote a rapid and clean reaction of the more reactive isomer such that it funneled toward desired product, while the less reactive isomer remained largely unaffected.

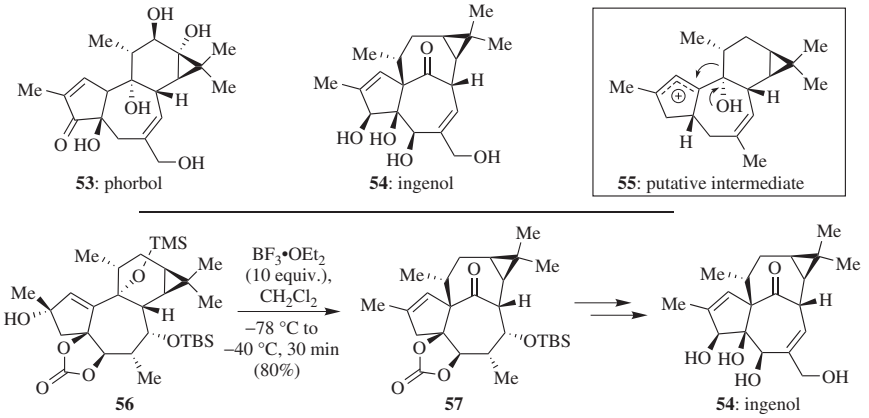
Thus, it would seem that the chiral phosphoric acid's reinforcement (and potential acceleration) of this preferential reactivity profile ensured that virtually none of the undesired diastereomer of **36** was formed under the reaction conditions. It seems appropriate, therefore, in an empirical sense to conclude that this increase in selectivity can be attributed to specific interactions between the diol moiety of the substrate and the chiral acid. Significantly, this notion may be applicable to other systems where such opportunities may exist. And, as a side note, the pinacol reaction process here may have biogenetic relevance as well, considering the structures of related natural products that are presumed to arise via acid-catalyzed processes from various oxidized forms of **38–40**. In this case, starting diol **34** is the fully oxidized version of these substrates (**38–40**) in terms of the double bond.

1.2.4.3 Pinacol Rearrangements in a Cascade Process We conclude this section with two final examples, each of which highlights two additional, and critical, components of pinacol rearrangement chemistry. What is emphasized here is the power of pinacol rearrangements when coupled with additional transformations in a cascade, or domino, set of processes where those events are promoted through a different intermediate other than the traditional carbocation generated directly by ionization of a diol. The first is slightly older work than the examples already described, and issued from the Overman group in 2003 where that key initiating event is a Prins cyclization.[14] As shown in a generic format (based on the protecting group used), the sequence afforded expedient and highly stereoselective constructions of the THF ring systems at the heart of several *Laurencia* sesquiterpenes (**50–52**, Scheme 1.7) through the mechanistic process delineated. Critically, enantiopure starting material (as in **45**) translated smoothly into enantiopure **47**, a material amenable for elaboration to several targets in the family.

The second example is more recent and was a critical part of a 14-step, gram-scale synthesis of ingenol (**54**, Scheme 1.8) by the Baran research group.[15] This case illustrates that the starting material for a successful pinacol rearrangement does not necessarily have to be a vicinal diol. Inspired by the structural similarities of this natural product with the related antitumor compound phorbol (**53**), these researchers postulated that perhaps the phorbol skeleton, in the form of a less oxidized intermediate such as **55**, could undergo a pinacol rearrangement using a stabilized vinylic carbocation to create the ingenol core. Only ring expansion to a seven-membered ring, not the nine-membered alternative, was expected even though the cycloheptanone is intramolecularly transfused onto the established scaffold. In practice, Baran and coworkers found that the TMS-protected vinylic alcohol **56**, when



Scheme 1.7 Development of a Prins–pinacol rearrangement strategy for *Laurencia* sesquiterpenes (**50–52**).[14]



Scheme 1.8 Use of a vinylogous pinacol rearrangement as part of the total synthesis of ingenol (**54**).[15]

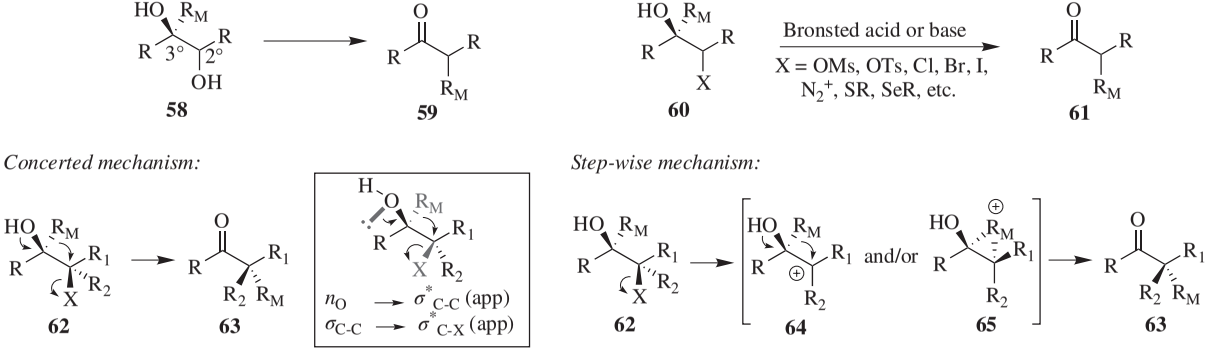
exposed to $BF_3{\cdot}OEt_2$, rearranged to the desired framework in 80% yield. Intriguingly, use of the unprotected alcohol variant of **56** and a variety of other alternatives failed to deliver the needed pinacol-rearranged target. Although formally this process can only be called a pinacol-type rearrangement, or more accurately a semipinacol rearrangement since the starting material is not explicitly a vicinal diol, it highlights additional variations of the process of high value in complex contexts, adds to the substrate scope and versatility of the pinacol rearrangement, and serves as a wonderful introduction to the seemingly more predictable, and controllable, rearrangement processes which will consume the remaining pages of this chapter.

1.3 SEMIPINACOL REARRANGEMENT

1.3.1 Background and Introduction

Semipinacol rearrangement events were first defined as a special type of pinacol rearrangement by Tiffeneau in 1923.[16] In Tiffeneau's original conception, these reactions involved migration toward the secondary carbon center on a tertiary/secondary diol as shown in Scheme 1.9 (**58** → **59**), the reverse regiochemistry of the typical pinacol rearrangement. Currently, however, this definition no longer applies, with the term semipinacol rearrangement referring to any process reminiscent of a pinacol rearrangement that utilizes a nondiol-based starting material.[14,17] Hence, the Baran ingenol example shown in Scheme 1.8 is technically a semipinacol rearrangement since it is a vinylogous diol, not a 1,2-diol, which served as the starting material. More formally, the key defining feature of a semipinacol rearrangement with these alternate starting materials is:

- 1,2-Migration of a C—C or C—H bond that is centered on the oxygen-bearing carbon and that occurs toward a vicinal electrophilic carbon center, generating a carbonyl group at the end of the process.



Scheme 1.9 General features and possible mechanisms of the semipinacol rearrangement.

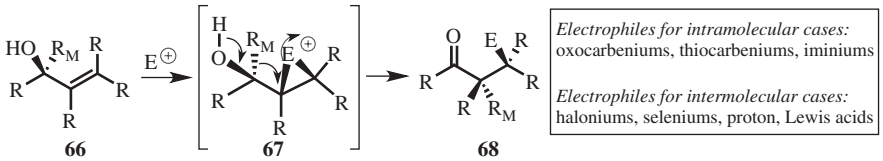
This concept is represented by the generalized conversion of **60** into **61** (Scheme 1.9), highlighting the large variety of species that can serve as the departing group in the process. Among these, sulfonates, halides, N_2, thiolates, and selenolates are the most common.

1.3.2 Mechanism of the Semipinacol Rearrangement

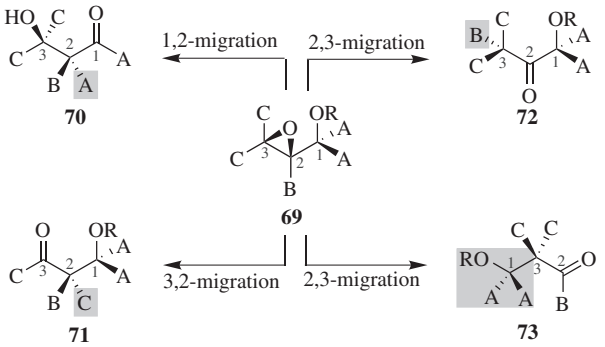
Once activated by an appropriate Lewis acid, metal species, or even base (as we will see shortly in the examples that follow), the semipinacol rearrangement readily proceeds in a concerted manner. Stereoelectronically, the most favorable orbital alignment for the process is *anti*periplanar (as highlighted schematically). That concertedness translates into high stereospecificity, irrespective of whether the semipinacol rearrangement leads to ring expansion, ring contraction, and/or carbonyl homologation. A less common but possible mechanistic alternative is the stepwise process shown in Scheme 1.9 invoking the intermediacy of carbocation **64** or its migrating group-stabilized variant **65**. This pathway, too, can afford stereospecificity but can also account for possible erosion in stereocontrol. Critical, though, is that these semipinacol processes have far more mechanistic harmony than their pinacol counterparts, affording greater assurance of selective and predictable product formation, as we will see.

1.3.3 Selected Variants of Semipinacol Rearrangements

1.3.3.1 Electrophilic Activation of Allylic Alcohols Outside of the specific manifold illustrated in Scheme 1.9, the semipinacol rearrangement is also broad enough in scope to include a number of substrate types in addition to 1,2-difunctionalized systems. One of the most common variants involves electrophilic activation of the C═C double bond within allylic alcohols and their derivatives. Scheme 1.10 shows this overall process and indicates which electrophiles typically promote the process; activation conditions are dependent on the intra- or intermolecular nature of the rearrangement event. The intramolecular variant, achievable via oxocarbenium, thiocarbenium, and iminium ions, is also known as the Prins–pinacol rearrangement, an example of which was shown in Scheme 1.7. Critical to note, however, is that with these substrates, following activation of the double bond, the migrating group undergoes a 1,2-shift to the electrophilic carbon center, driven exclusively by ring opening of the cyclic cationic intermediate; the migratory aptitude of the shifting group is not a dominant factor. As before, however, the robust stereoselectivity of rearrangements



Scheme 1.10 Semipinacol rearrangements via electrophile activation of allylic alcohols.



Scheme 1.11 Possible rearrangements of hydroxyepoxide derivatives in semipinacol processes; migrating group is highlighted in each product.

with these starting materials relies on the *anti*periplanar orientation of the C—R_M and C—E bonds (cf. **67**).

1.3.3.2 Epoxy Alcohol Rearrangements Similarly, epoxy alcohols and their derivatives can also undergo semipinacol rearrangements. The difference here from the examples in Scheme 1.10 just denoted is the ability to isolate the starting material (epoxide **69** in Scheme 1.11 vs. transient intermediate **67** in Scheme 1.10). Because both the C-2 and C-3 positions are highly electrophilic (in accordance with the numbering shown for the generalized 2,3-epoxy alcohol **69** within Scheme 1.11), a range of migrations are possible, including 1,2-, 2,3-, and 3,2-shifts to produce **70–73**. As a result, application of semipinacol rearrangements with these materials allows direct access to many synthetically useful functionalities such as β-halo and β-amino ketones as well as aldol-type products. And, with careful design, the resulting electrophilic carbon centers in the product can also be used for further chemistry, including tandem reactions. The mechanism for these transformations is analogous to the rearrangement of allylic alcohols, where the migrating group generally travels *anti* to the epoxide, accounting for the excellent stereospecificity observed in most cases. Of particular note, aldol-type products bearing a stereogenic quaternary carbon at C-1 can be generated from the rearrangement with excellent diastereoselectivity; this outcome remains a challenge using classical aldol strategies, highlighting a key use for semipinacol processes within a variety of synthetic contexts.

1.3.4 Key Features of the Semipinacol Rearrangement

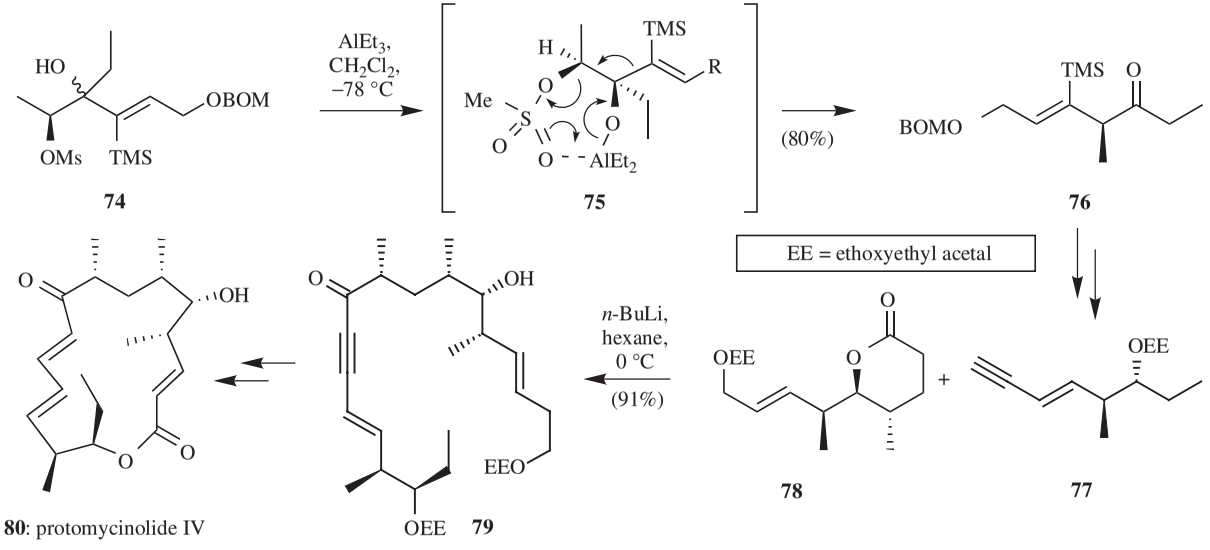
To summarize this introduction to semipinacol processes, this variant of the rearrangement has several distinguishing features compared to its pinacol cousin that make it particularly well suited to applications in synthesis. First, semipinacol reactions typically proceed under much milder conditions. Whereas the classical pinacol rearrangement usually requires a strong acid to form the reactive carbocation, less drastic conditions, including basic ones, work in the semipinacol manifold, thereby greatly enhancing the overall array of functional and protecting groups compatible

with the process. Second, excellent stereochemical control can be achieved for both cyclic and acyclic systems because of the generally concerted semipinacol mechanism, one where the migrating group is *anti*periplanar to the leaving group, reliably leading to inversion of configuration. This remarkable feature allows for the generation of highly substituted contiguous stereogenic centers and the diastereospecific construction of complex structural motifs such as spirocycles and sterically hindered fused ring junctions. Third, migratory aptitude is not the dominant factor controlling the product in a semipinacol rearrangement. Instead, factors such as release of ring strain or the stereoelectronic preference for *anti*periplanar alignment play a more important role in determining which bond will migrate. Lastly, given the versatility of the precursors to the semipinacol rearrangement, it is unsurprising that a variety of methods exist to prepare these substrates enantioselectively, including the Sharpless asymmetric epoxidation of allylic alcohols. For these reasons, the semipinacol rearrangement has proven far more applicable to challenging synthetic endeavors, and the following case studies provide specific examples of the generic strategies outlined previously. We have chosen these select applications to highlight the diversity of substrates, conditions, and complex high-value products accessible through semipinacol rearrangement processes.

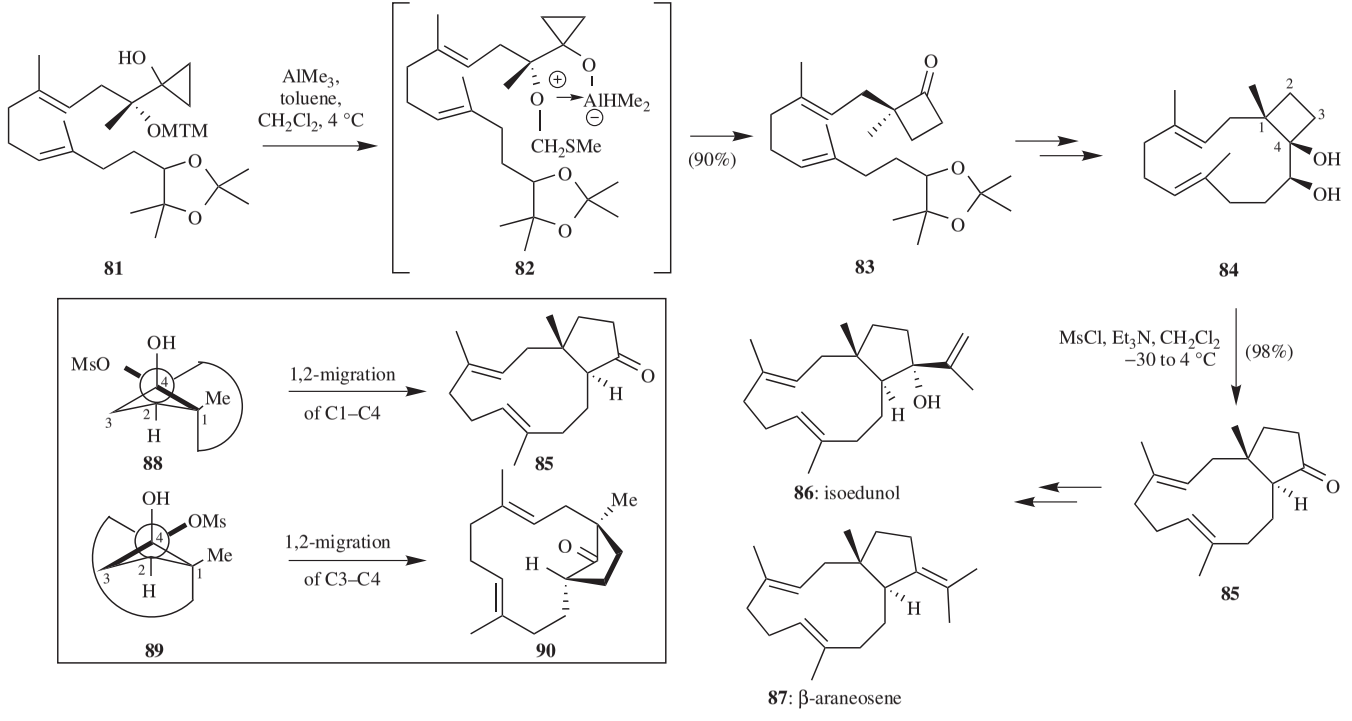
1.3.5 Examples of Semipinacol Rearrangements in Total Synthesis

We begin these case studies with a total synthesis of the macrolide natural product protomycinolide IV (**80**, Scheme 1.12) as accomplished by Tsuchihashi and coworkers in 1985.[18] This work, although older than many of the examples we will present in this chapter, is significant in that it highlights how very mild conditions, namely, exposure to trialkylaluminum species, can be extremely effective in imposing a concerted semipinacol rearrangement as a result of the electron-deficient metal center coordinating oxygen atoms on both the alcohol and a vicinal sulfonate leaving group. Indeed, as shown, exposure of **74** to $AlEt_3$ in CH_2Cl_2 at $-78\,^{\circ}C$ effected the desired event leading to **76** in 80% yield, with complete stereocontrol (i.e., conservation) of the alkene stereochemistry in the vinyl migration achieved via the intermediacy of **75**, leading to the final inversion of configuration at the sulfonate-bearing center. Here, aluminum activation facilitated the ability of the sulfonate to serve as a leaving group, with the TMS group on the alkene increasing the ability of the hydroxylated carbon to electronically support δ^+ and facilitating the final migration. Similar chemistry was also used to prepare chiral lactone **78**, affording facile and rapid access to the needed pieces to complete an effective total synthesis of the target molecule (**80**).

A more recent, but similar, deployment of such mild conditions for effecting a semipinacol rearrangement can be found in the opening steps of the Corey and Kingsbury synthesis of isoeudunol (**86**) and related terpenes such as β-araneosene (**87**, Scheme 1.13).[19] Here, in an effort to construct the transfused 5,11-membered ring system found in these and a number of other targets, these researchers began by effecting a ring expansion of cyclopropyl carbinol **81** (prepared from a Kulinkovich cyclopropanation), using $AlMe_3$ to induce a concerted rearrangement. As shown with the



Scheme 1.12 Development of a mesylate-assisted semipinacol rearrangement for protomycinolide IV (**80**).[18a]



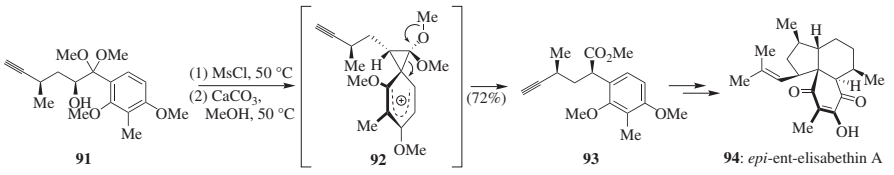
Scheme 1.13 Application of a ring-expanding semipinacol rearrangement to the total synthesis of isoedunol (**86**) and *β*-araneosene (**87**).[19]

structure of intermediate **82**, the Lewis acid played a bis-coordinating role in ensuring that the desired cyclobutanone could arise with high stereospecificity. If Brønsted acids such as catalytic PPTS were used instead to initiate the process (species without such a bis-coordination capability), significant loss of enantiopurity was observed due to partial racemization of the lone chiral center, presumably via a nonconcerted semipinacol rearrangement.

However, this event would not be the only semipinacol rearrangement of the sequence. Indeed, once **83** was elaborated to diol **84** (using a SmI_2-mediated pinacol coupling to create this key motif), a second semipinacol variant, this time promoted under basic conditions by the formation of a secondary mesylate, effected another ring expansion. As long as the diol was cis, the desired migration to **85** occurred smoothly through transition state **88** with migration of C1—C4 bond; however, for the trans-diol variant of **84** (drawn here as mesylate derivative **89**), migration occurred instead through the C3—C4 bond to afford the undesired bridged 5,12-bicyclopentanone (i.e., **90**). The conformational rigidity of the adjoining 12-membered ring is presumed to play a critical role in this process, making extensions of this exact reaction to other systems difficult to predict. Nevertheless, the more global lesson of this work is that semipinacol chemistry can be readily used to effect a number of critical ring expanding bond constructions with high stereocontrol under very mild conditions.

As one final example of a mild semipinacol rearrangement using diol derivatives as starting materials, and to highlight that stepwise versions can also be quite effective when properly deployed, we present Rawal's synthesis of *epi*-ent-elisabethin A (**94**, Scheme 1.14).[20] In this example, the displacement of a mesylate group formed from substrate **91** was induced by the *ortho*- and *para*-disposed electron-donating OMe groups on the aromatic ring upon heating in MeOH in the presence of $CaCO_3$ at 50 °C, forming a bridged quinone methide intermediate (**92**). The culmination of this stepwise semipinacol rearrangement involved 1,2-aryl migration from the ketal, driven by rearomatization, and afforded ester **93** in 72% yield. Further elaboration featuring an *endo*selective intramolecular Diels–Alder reaction and oxidative cyclization then furnished the target molecule. This synthesis strategy highlights an extremely clever and nonobvious use of a semipinacol process, in that few direct traces of the original substrate are present in the final product except for the critical chiral centers established with the formation of **93**.

Outside of diol derivatives, a number of other substrate types with alternative leaving groups work well as semipinacol substrates. Next, we present an example using a

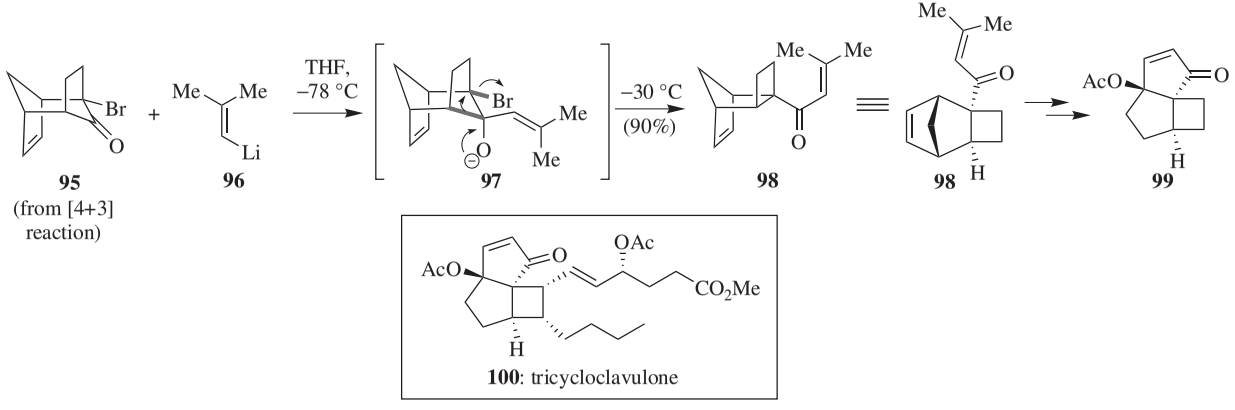


Scheme 1.14 Use of a base-mediated semipinacol rearrangement as part of the total synthesis of *epi*-ent-elisabethin A (**94**).[20]

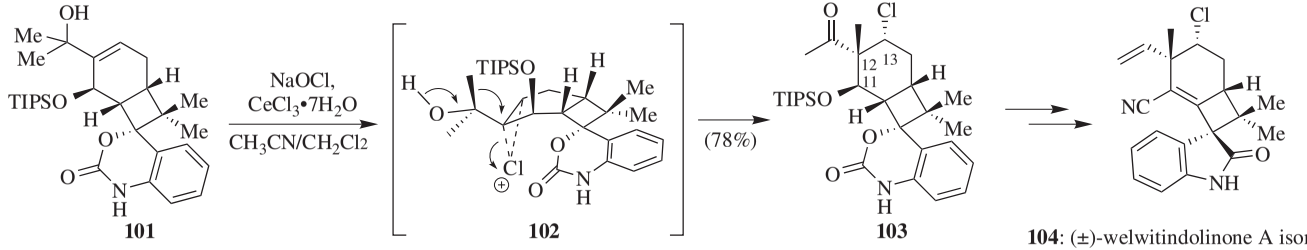
halide leaving group, where the generation of a halohydrin intermediate is critical for effecting the semipinacol rearrangement step. In these events, the halogen is typically removed (and thus the semipinacol process is initiated) by the addition of a metal salt which has a high affinity for a halide (such as Ag(I)). Classically, these events are also known as "quasi-Favorskii" rearrangements because either steric hindrance or the absence of an appropriate α-proton prevents the formation of a cyclopropanone through a standard Favorskii process, instead allowing for migration of a C—C bond through a semipinacol event. One recent use of this chemistry derives from the Harmata group's synthesis of the core of tricycloclavulone (**100**, Scheme 1.15).[21] Here, after forming **95** through a [4+3] cycloaddition, treatment with vinyl lithium species **96** in THF at −78 °C effected the formation of halohydrin anion **97**. Despite the inability to generate a cyclopropanone from **95** through a Favorskii-type process due to the rigidity of the system, the semipinacol alternative proceeded instead to deliver **98** in 90% yield upon warming to −30 °C. As expected, this ring-contracted product reflects a stereospecific transfer in which the migrating C—C bond is *anti*periplanar to the leaving group in the more favorable chair conformation (as drawn within **97**). The resultant enone (**98**) was elaborated into the tricycloclavulone core (**99**) through a series of steps including a ring-closing metathesis reaction.

Halogen atoms, besides serving as leaving groups in their halide form, can also activate substrates for semipinacol rearrangements in their halonium form, affording β-halocarbonyl products from allylic alcohol starting materials. One recent and highly illustrative application of such a process to generate a chlorinated motif as found directly in a natural product derives from the Wood group's total synthesis of welwitindolinone A isonitrile (**104**, Scheme 1.16).[22] Here, exposure of allylic alcohol **101** to NaOCl and $CeCl_3 \cdot 7H_2O$ effected chloronium generation *in situ* to form intermediate **102** via electrophile addition on the concave face. Critical to controlling this addition from the seemingly more hindered face of the substrate was the large TIPS-protected alcohol, which is presumed to reside in a pseudoaxial position as drawn within **102** and thus blocks the less hindered convex face. Stereospecific alkyl migration *anti* to the chloronium ion via a concerted mechanism afforded **103** as a single stereoisomer in which both the C-12 quaternary carbon and the adjoining C-13 stereocenter were fashioned as needed for the final target.

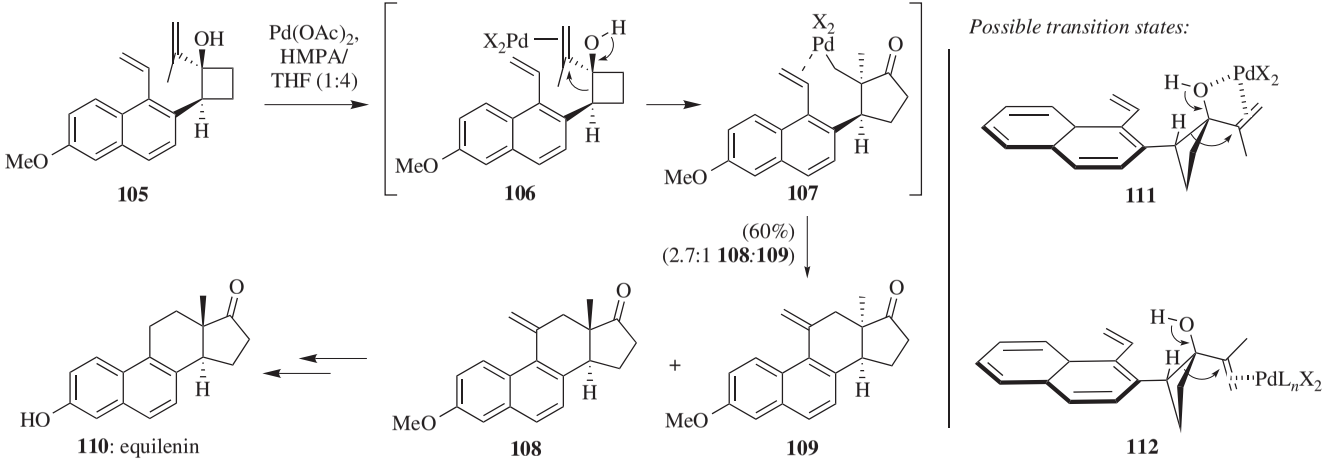
An even wider array of substrates can be induced to participate in semipinacol processes, and often additional cascades, if metals are used to initiate the rearrangement. As one recent example, Nemoto, Ihara, and coworkers developed a palladium-promoted cascade involving semipinacol ring expansion/intramolecular insertion of an isopropenylcyclobutanol as part of an asymmetric total synthesis of (+)-equilenin (**110**, Scheme 1.17).[23] As shown, coordination of the palladium onto the isopropenyl group of **105** activated its double bond in the form of complex **106**, generating the electrophilic carbon center necessary to induce carbonyl bond formation and concomitant alkyl migration to **107**. The subsequent olefin insertion and β-hydride elimination then afforded the complete steroid core, favoring the trans-isomer (**108**) needed for the target molecule. Of note, the diastereoselectivity of this ring expansion process was governed by the conformation of the isopropenyl group in the cascade process (**111** vs. **112**). In nonpolar or noncoordinating solvents,



Scheme 1.15 Development of a [4+3]-cycloaddition-Favorskii sequence and its application in the synthesis of tricycloclavulone core (**99**).[21]



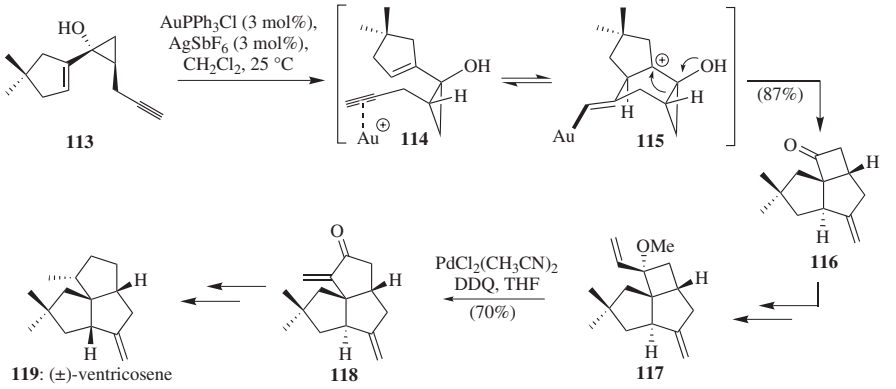
Scheme 1.16 Use of a chloronium ion-mediated semipinacol rearrangement in the total synthesis of (±)-welwitindolinone A isonitrile (**104**).[22a]



Scheme 1.17 Semipinacol rearrangement as part of the asymmetric total synthesis of (+)-equilenin (**110**).[23]

ring expansion gave predominantly the *cis*-product (**109**) via transition state **111**, where the hydroxy group occupies a coordination site on palladium. In polar or coordinating solvents such as HMPA, the rearrangement could proceed instead through transition state **112** with only palladium bound to the olefin, preferentially affording **108**. On a more general level, this ring expansion process is driven by release of ring strain, and though an extra carbon atom not needed for equilenin (**110**) was installed as a result of the requirements of completing the reaction cascade, that atom could be easily cleaved making its presence more than worthwhile for what the tandem semipinacol process was able to accomplish overall.

Another example of the synthetic value of transition metals in initiating cascades that include semipinacol processes derives from the Toste group. In this case, shown in Scheme 1.18, a gold(I)-catalyzed cycloisomerization/semipinacol ring expansion was followed by a similar shift as in **106** → **107** to assemble the entire polycyclic core of the target.[24] Just as in the Corey work described in Scheme 1.13, the cyclopropanol framework was prepared by the Kulinkovich reaction, and after installation of the alkyne by a Seyferth–Gilbert homologation using the Ohira–Bestmann reagent to afford **113**, the stage was set for the critical operation. In the event, exposure of this substrate to the complex formed from $AuPPh_3Cl$ and $AgSbF_6$ generated the Au(I)-activated cationic intermediate **115**, which rearranged to give cyclobutanone **116** as a single diastereomer in 87% yield. The high stereoselectivity of this process can be understood by considering the drawn intermediates (**114** and **115**) presumed to account for the observed product. The only other alternative (not drawn) would be of much higher energy since it would possess a *trans*-diquinane motif, one that would have led instead to a high-energy *trans*-cyclobutanone if it was product determining. Overall, this powerful strategy allowed for rapid construction of the angular triquinane ring system with the methyl-bearing stereocenter; after elaboration of **116** into **117**, a palladium-catalyzed ring expansion effected in the presence of DDQ or benzoquinone afforded a 4:1 mixture of products favoring migration of the more substituted C—C bond. Oxidation state adjustments and removal of the



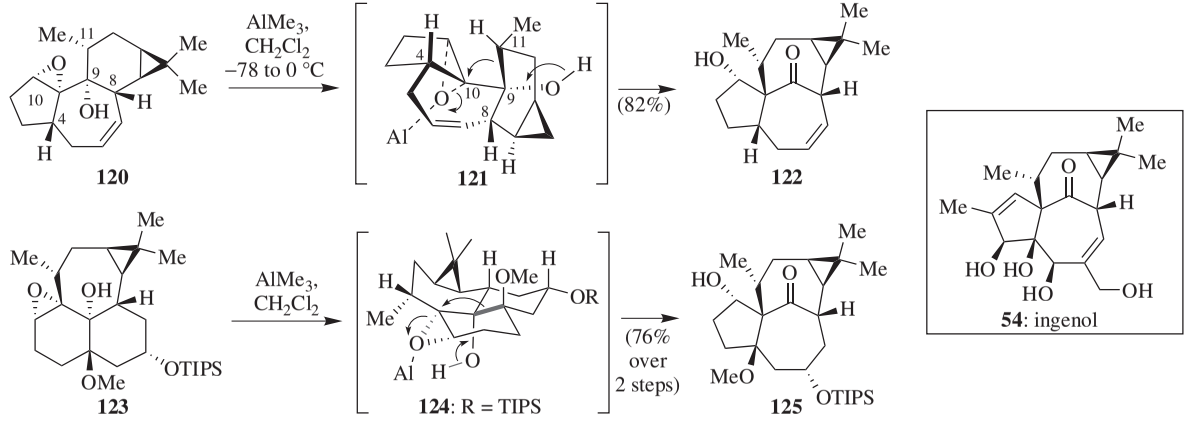
Scheme 1.18 Use of a double ring expansion strategy in the total synthesis of (±)-ventricosene (**119**).[24]

heteroatom critical to both rearrangements then completed the total synthesis of ventricosene (**119**).

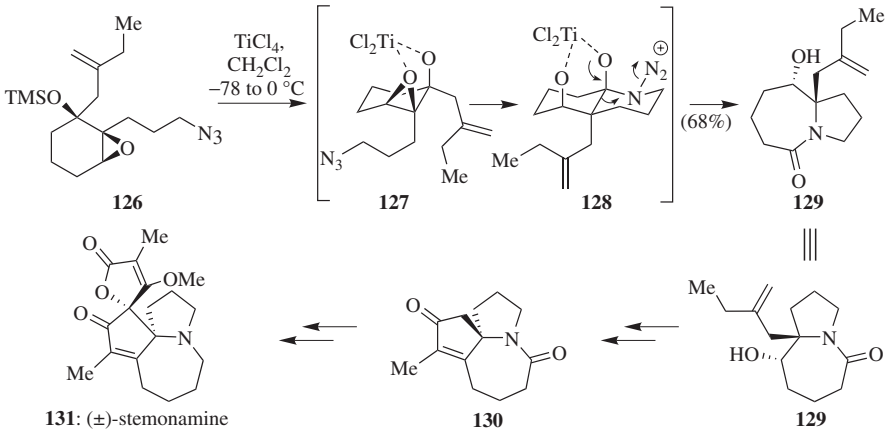
Finally, we will round out our presentation of semipinacol rearrangements with a number of examples using 2,3-epoxy alcohols and their derivatives as substrates. We begin with two different approaches to ingenol (**54**), a target mentioned earlier in the context of Scheme 1.8 as likely arising in nature from a pinacol-like rearrangement of an appropriate terpene precursor. Here, we show two different approaches, one from the Cha group and the other from Tanino and Kuwajima, which used very different epoxy alcohols to accomplish the same general conversion, affording a highly strained transfused architecture. In the Cha case, treatment of **120** with $AlMe_3$ at −78 °C activated the epoxide and induced the alkyl shift to give the carbocyclic core of **122** in 82% yield.[25] Of note, the stereochemistry of the alcohol group at C-4 is crucial in ensuring the migrating group is the requisite C9—C11 bond. As modeled in the presumed transition state with the alcohol group properly in place (**121**), the C9—C11 bond is *anti*periplanar to the epoxide C10—O bond, providing the orbital alignment required for the desired rearrangement to **122**. On the other hand, with the alternate C4-alcohol stereochemistry (not shown), the C8—C9 bond can migrate as well. In the Tanino and Kuwajima work, a different epoxy alcohol (**123**) underwent stereospecific 1,2-migration upon treatment with $AlMe_3$ to afford a similar framework (**125**) in 76% yield.[26] Globally, these powerful approaches allow for facile ring size manipulation to access fused 5,7,7-ring systems without the loss of any stereochemical information. They highlight, in combination with the Baran case presented earlier, the variety of pinacol and semipinacol processes that can be deployed creatively to solve the challenging synthetic problem of the ingenol core, showing the true versatility of these rearrangements (Scheme 1.19).

Next, we consider a creative semipinacol approach leading to a total synthesis of stemonamine (**131**, Scheme 1.20) from Tu and coworkers.[27] In this case, a tandem semipinacol rearrangement/Schmidt reaction was deployed to construct the functionalized aza-quaternary carbon center of the target, using $TiCl_4$ to activate the two oxygen groups of substrate **126**. The cascade began with the semipinacol rearrangement in which alkyl group migrated to the adjacent quaternary carbon to open up the epoxide. The carbonyl group generated from this event was then attacked by the nucleophilic nitrogen of the azide, forming a favorable chair, chair hetero-decalin system. This event presumably afforded an intermediate (**128**) that readily underwent a stereospecific 1,2-migration, driven by loss of N_2, to furnish 5,7-bicyclic lactam **129** in 68% yield. The rapid access to this bicyclic system underscores the power of the approach, with subsequent operations including ozonolysis of the pendant alkene, alcohol oxidation, and aldol condensation yielding a tricyclic core (**130**) that was then elaborated smoothly into stemonamine (**131**).

As our final case study, we present the use of a semipinacol rearrangement strategy to generate the spirocyclic core of the potent antitumor natural product fredericamycin A (**135**, Scheme 1.21) using acrylated epoxy alcohols.[28] Following extensive model studies to probe the stereoselectivity of the general process, the Kita group was able to establish that treatment of *cis*-epoxy acylates **136** with $BF_3{\cdot}OEt_2$ led to



Scheme 1.19 Use of a semipinacol rearrangement to access unique core in the total synthesis of ingenol (**54**).[25,26]

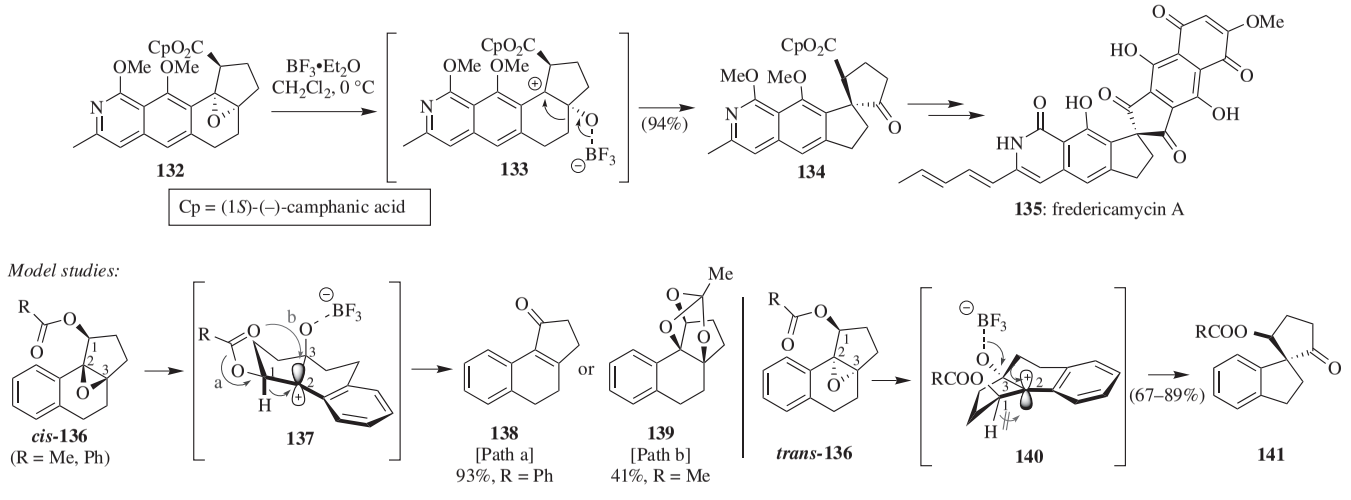


Scheme 1.20 A tandem semipinacol rearrangement/Schmidt reaction in the total synthesis of (±)-stemonamine (**131**).[27]

regioselective epoxide ring opening, generating a benzylic cation **137**. From carbocation **137**, the reaction could proceed along two different pathways dependent on the nature of group R. When that group was large (R = Ph), the intermediate adopted a conformation such that the hydride was properly aligned to undergo 1,2-shift (path a) to give the enone product (**138**) after elimination to form the tetrasubstituted alkene. When R was smaller (R = Me), the formation of orthoester **139** was the predominant process due to the absence of steric hindrance allowing for the methyl group to adopt the requisite conformation for rearrangement. By contrast, when the *trans*-epoxy acetate was used instead (**136**), the same hydride could not align with the adjacent empty orbital, and neighboring group participation from the C—O bond leading to the five-membered ring was unfavorable. Pleasingly, though, the result was that only the desired C—C bond needed for migration was oriented correctly with respect to the empty *p*-orbital, thereby furnishing the desired model spirocycle (**141**). Application of this knowledge to a fully functional case with a related *trans*-epoxy acylate (**132**) worked smoothly to afford spirocycle **134** in 94% yield.

1.4 CONCLUSION

As this chapter has hopefully demonstrated, both pinacol and semipinacol processes have undergone a recent renaissance in their application to complex molecule synthesis, affording a number of highly elegant solutions to challenging problems. And, when combined in tandem with additional chemical events, the rearrangements reach an even greater level of overall power. Further investigation will certainly uncover additional areas of value for these processes in accessing complex molecules. Of special note is that a number of recent explorations into novel, asymmetric variants of pinacol and semipinacol processes have provided and should continue to provide



Scheme 1.21 A semipinacol rearrangement strategy as part of the total synthesis of fredericamycin A (**135**).[28a]

greatly enhanced tools for enantiospecific synthesis.[29] Thus, though these general reactions have been known for many decades, the potential for additional discoveries remains high. We hope this compilation will serve as inspiration for some of those future creative applications.

REFERENCES

1. Rickborn, B. "The pinacol rearrangement" In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, UK, **1991**, Vol. 3, pp. 721–732.
2. Fittig, R. *Justus Liebigs Ann. Chem.* **1860**, *114*, 54–63.
3. Butlerov, A. *Justus Liebigs Ann. Chem.* **1873**, *170*, 151–162.
4. Kekulé, A. *Justus Liebigs Ann. Chem.* **1858**, *106*, 129–159.
5. Kurti, L.; Czako, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Academic Press: Burlington, MA, **2005**, pp. 350–351.
6. Danilov, S. *J. Russ. Phys. Chem. Soc.* **1917**, *49*, 282–289.
7. (a) Rothrock, T. S.; Fry, A. *J. Am. Chem. Soc.* **1958**, *80*, 4349–4354. (b) Fry, A.; Carrick, W. L.; Adams, C. J. *J. Am. Chem. Soc.* **1958**, *80*, 4743–4744.
8. Bunton, C. A.; Carr, M. D. *J. Chem. Soc.* **1963**, 5854–5861 and 5861–5867.
9. (a) Chen, X.; Esser, L.; Harran, P. G. *Angew. Chem. Int. Ed.* **2000**, *39*, 937–940. (b) Li, J.; Jeong, S.; Esser, L.; Harran, P. G. *Angew. Chem. Int. Ed.* **2001**, *40*, 4765–4770.
10. Suzuki, K.; Takikawa, H.; Hachisu, Y.; Bode, J. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3252–3254.
11. (a) Pettit, G. R.; Lippert, J. W.; Herald, D. L. *J. Org. Chem.* **2000**, *65*, 7438–7444. (b) Snyder, S. A.; Gollner, A.; Chiriac, M. I. *Nature* **2011**, *474*, 461–466.
12. Liang, T.; Zhang, Z.; Antilla, J. C. *Angew. Chem. Int. Ed.* **2010**, *49*, 9734–9736.
13. Snyder, S. A.; Thomas, S. B.; Mayer, A. C.; Breazzano, S. P. *Angew. Chem. Int. Ed.* **2012**, *51*, 4080–4084.
14. Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143–7157.
15. Jørgensen, L.; McKerrall, S. J.; Kuttruff, C. A.; Ungeheuer, F.; Felding, J.; Baran, P. S. *Science* **2013**, *341*, 878–882.
16. Coveney, D. J. "The semipinacol and other rearrangements" In Comprehensive Organic Synthesis; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, UK, **1991**, Vol. 3, pp. 777–801.
17. For reviews, see: (a) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352–359. (b) Kurti, L., Czako, B. Strategic Applications of Named Reactions in Organic Synthesis; Elsevier Academic Press: Burlington, MA, **2005**, pp. 366–367. (c) Song, Z. L.; Fan, C. A.; Tu, Y. Q. *Chem. Rev.* **2011**, *111*, 7523–7556.
18. (a) Suzuki, K.; Tomooka, K.; Matsumoto, T.; Katayama, E.; Tsuchihashi, G. *Tetrahedron Lett.* **1985**, *26*, 3711–3714. (b) Suzuki, K.; Tomooka, K.; Katayama, E.; Matsumoto, T.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1986**, *108*, 5221–5229.
19. Kingsbury, J. S.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 13813–13815.
20. Waizumi, N.; Stankovic, A. R.; Rawal, V. H. *J. Am. Chem. Soc.* **2003**, *125*, 13022–13023.
21. Harmata, M.; Wacharasindhu, S. *Org. Lett.* **2005**, *7*, 2563–2565.

22. (a) Reisman, S. E.; Ready, J. M.; Hasuoka, A.; Smith, C. J.; Wood, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 1448–1449. (b) Reisman, S. E.; Ready, J. M.; Weiss, M. M.; Hasuoka, A.; Hirata, M.; Tamaki, K.; Ovaska, T. V.; Smith, C. J.; Wood, J. L. *J. Am. Chem. Soc.* **2008**, *130*, 2087–2100.
23. Yoshida, M.; Ismail, M. A. H.; Nemoto, H.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, *16*, 2629–2635.
24. Sethofer, S. G.; Staben, S. T.; Hung, O. Y.; Toste, F. D. *Org. Lett.* **2008**, *10*, 4315–4318.
25. Epstein, O. L.; Cha, J. K. *Angew. Chem. Int. Ed.* **2005**, *44*, 121–123.
26. Tanino, K.; Onuki, K.; Asano, K.; Miyashita, M.; Nakamura, T.; Takahashi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **2003**, *125*, 1498–1500.
27. Zhao, Y. M.; Gu, P. M.; Tu, Y. Q.; Fan, C. A.; Zhang, Q. W. *Org. Lett.* **2008**, *10*, 1763–1766.
28. (a) Kita, Y.; Higuchi, K.; Yoshida, Y.; Iio, K.; Kitagaki, S.; Akai, S.; Fujioka, H. *Angew. Chem. Int. Ed.* **1999**, *38*, 683–686. (b) Kita, Y.; Higuchi, K.; Yoshida, Y.; Iio, K.; Kitagaki, S.; Ueda, K.; Akai, S.; Fujioka, H. *J. Am. Chem. Soc.* **2001**, *123*, 3214–3222.
29. (a) For a review, see: Hennecke, U. *Chem. Asian. J.* **2012**, *7*, 456–465. For selected examples, see: (b) Chen, Z.-M.; Zhang, Q.-W.; Chen, Z.-H.; Li, H.; Tu, Y.-Q.; Zhang, F.-M.; Tian, J.-M. *J. Am. Chem. Soc.* **2011**, *133*, 8818–8821. (c) Li, H.; Zhang, F.-M.; Tu, Y.-Q.; Zhang, Q.-W.; Chen, Z.-M.; Chen, Z.-H.; Li, J. *Chem. Sci.* **2011**, *2*, 1839–1841.