Wiley Series on Comprehensive Name Reactions
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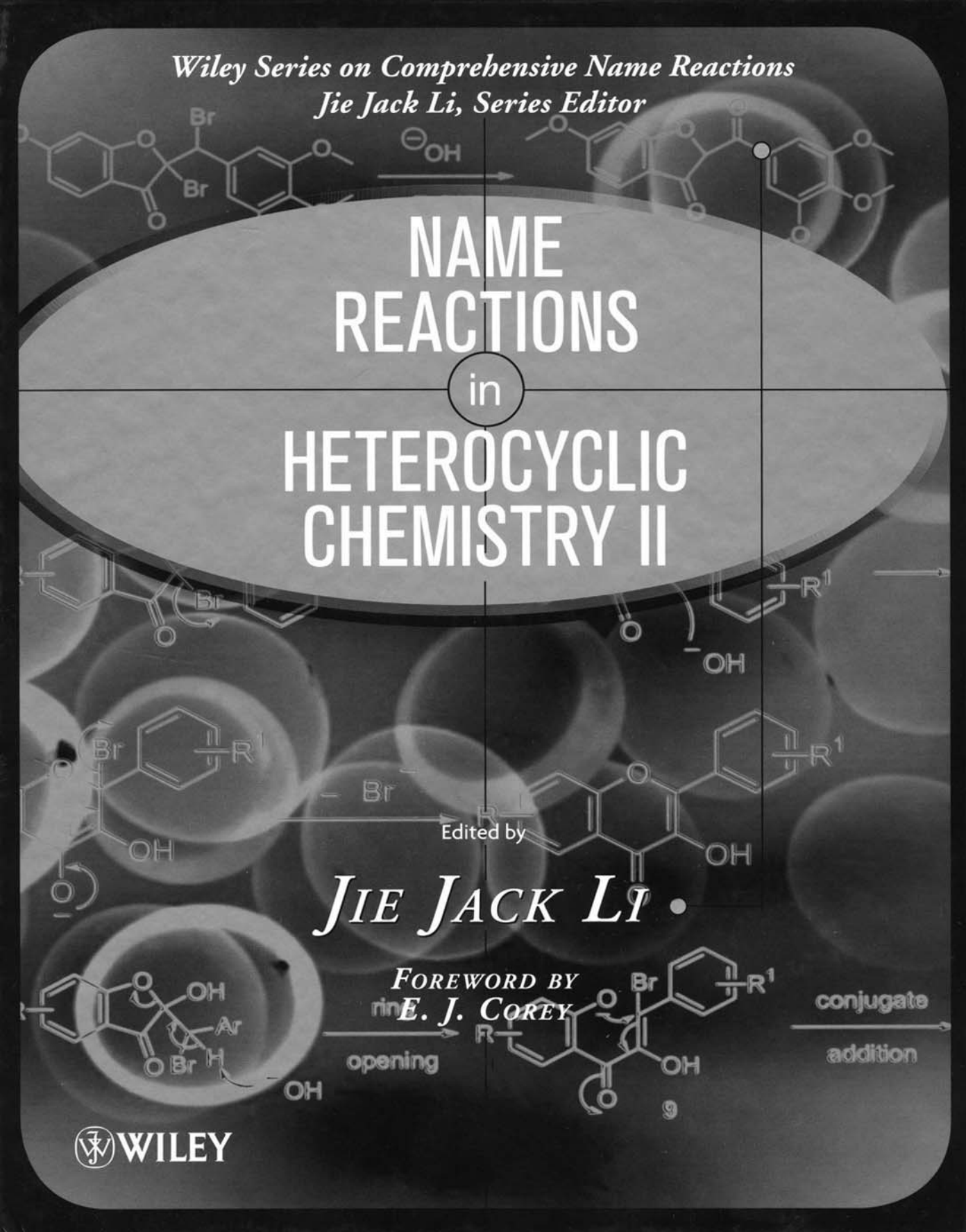

NAME REACTIONS in HETEROCYCLIC CHEMISTRY II

Edited by

Jie Jack Li

Foreword by
E. J. Corey

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Name Reactions in Heterocyclic Chemistry II

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Name Reactions in Heterocyclic Chemistry
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Name Reactions of Functional Group Transformations
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Bristol-Myers Squibb Company

Foreword by

E. J. Corey

Harvard University

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Foreword

Part of the charm of synthetic organic chemistry derives from the vastness of the intellectual landscape along several dimensions. First, there is the almost infinite variety and number of possible target structures that lurk in the darkness waiting to be made. Then, there is the vast body of organic reactions that serve to transform one substance into another, now so large in number as to be beyond credibility to a nonchemist. There is the staggering range of reagents, reaction conditions, catalysts, elements, and techniques that must be mobilized to tame these reactions for synthetic purposes. Finally, it seems that new information is being added to that landscape at a rate that exceeds the ability of a normal person to keep up with it. In such a troubled setting any author, or group of authors, must be regarded as heroic if through their efforts, the task of the synthetic chemist is eased.

This last volume on heterocyclic chemistry fills the holes left behind in Volume 1 and brings to the attention of practicing synthetic chemists and students of chemistry a wide array of tools for the synthesis of new and useful molecules. It is a valuable addition to the literature by any measure and surely will prove its merit in years to come. The new knowledge that arises with its help will be impressive and of great benefit to humankind.

E. J. Corey
February 1, 2011

Preface

This book is the sixth and the last volume of the *Comprehensive Name Reactions* series, an ambitious project conceived by Professor E. J. Corey of Harvard University in the summer of 2002. Volume 1, *Name Reactions in Heterocyclic Chemistry*, was published in 2005. Volume 2, *Name Reactions for Functional Group Transformations came out in* 2007. Volumes 3 and 4 *Name Reactions for Homologations Part I and Part II* were published in 2009. And Volume 5, *Name Reactions on Ring Formations* came out in 2010. Continuing the traditions of the first five volumes, each name reaction in Volume 6 is also reviewed in seven sections:

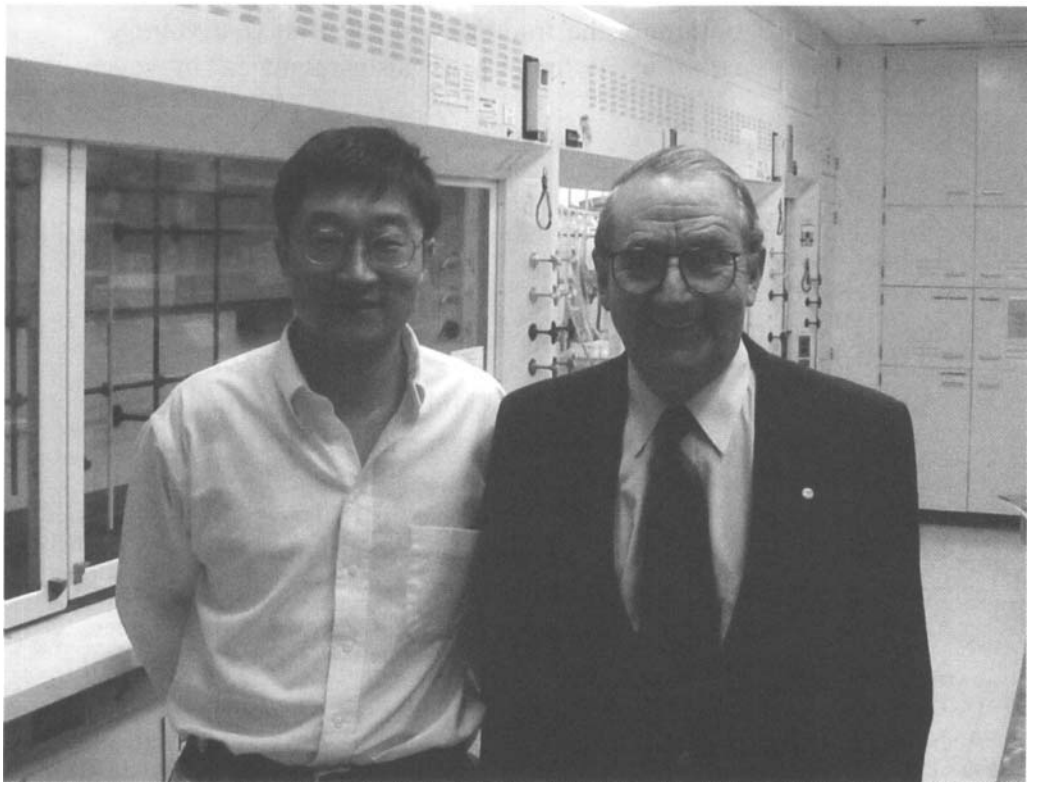
1. Description
2. Historical Perspective
3. Mechanism
4. Variations and Improvements
5. Synthetic Utility
6. Experimental
7. References.

I also introduce a symbol [R] to highlight review articles, book chapters, and books dedicated to the respective name reactions.

I have incurred many debts of gratitude to Professor E. J. Corey. He once told me "The desire to learn is the greatest gift from God," which has been a true inspiration. Furthermore, it has been my great privilege and a pleasure to work with a collection of stellar contributing authors from both academia and industry. Some of them are world-renowned scholars in the field; some of them have worked intimately with the name reactions that they have reviewed; some of them even discovered the name reactions that they authored in this series. As a consequence, this book truly represents the state-of-the-art for name reactions in heterocyclic chemistry.

I welcome your critique.

Jack Li
February 1, 2011



Jie Jack Li and E. J. Corey, circa 2000.

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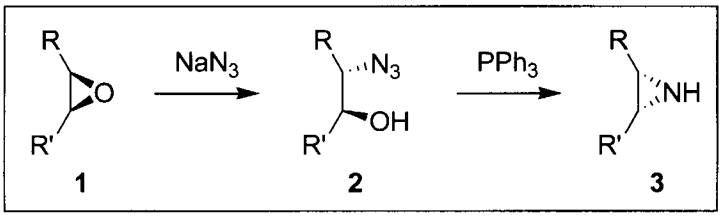
1.1 Blum Aziridine Synthesis

Jeremy M. Richter

1.1.1 Description

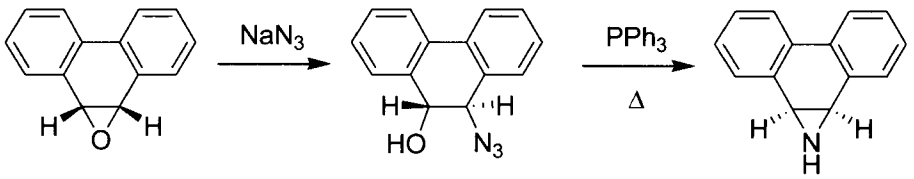


1 2 3

The Blum aziridine isomerization describes the net coversion of epoxides **1** into N–H aziridines **3** *via* an intermediate azido–alcohol **2**. The reaction proceeds by opening of the epoxide with an azide source followed by the Staudinger reduction and cyclization of the intermediate azido–alcohol to give the aziridine.[1] The reaction proceeds with net inversion of stereochemistry around the epoxide.

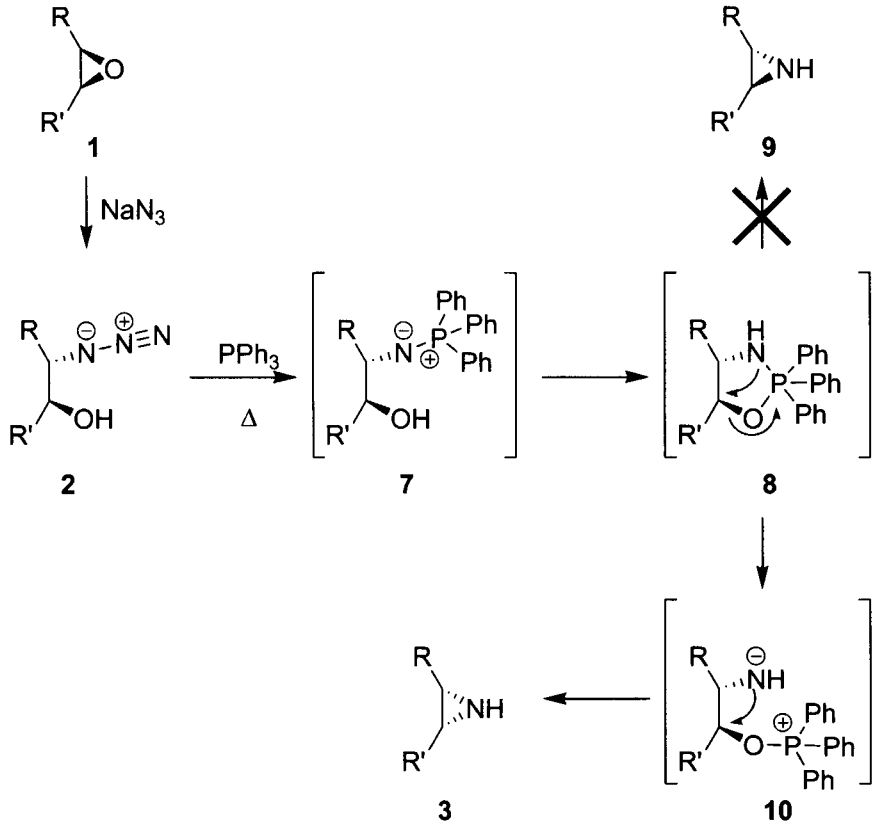
1.1.2 Historical Perspective

While investigating chemical carcinogens, Jonathan Blum and co-workers[1] hypothesized that arene imines were chemical intermediates in carcinogenesis and therefore sought to prepare several phenanthrene imines to test this hypothesis. However, they found that unsubstituted arene imines could not be prepared by the current methods and required alternate means by which to access these structures. Starting from the stable arene oxides (**4**), Blum and co-workers discovered that these epoxides could be opened by the action of sodium azide, forming the intermediate azido–alcohol **5**. They then found that further heating with triphenylphosphine provided the desired N–H aziridine **6** in good yield.



4 5 6

1.1.3 Mechanism

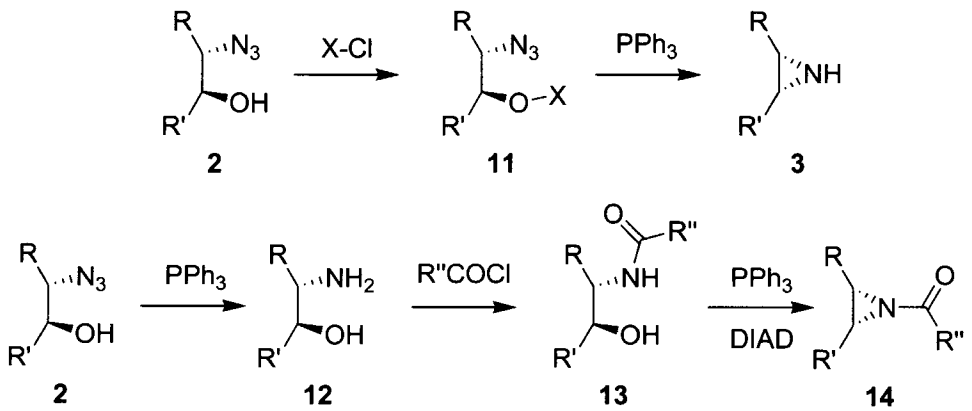


In Blum's original publication on the reaction that bears his name, he postulated a mechanistic interpretation of this process.[1] While investigating sterically flexible systems, he astutely noticed that the *cis/trans* nature of the double bond is conserved during the course of the reaction. That is, the reaction proceeds with complete inversion of stereochemistry but no *cis/trans* isomerisation is observed. In spite of this observation, two mechanistic interpretations could be put forth to explain the overall transformation. Little controversy exists surrounding the initial reaction intermediates and the preparation of the isolable azido–alcohol **2**. Good evidence also exists for the azide reduction proceeding through a standard Staudinger sequence, as the amino-alcohol can be easily isolated if no heat is applied to the system.[2] From this point, the mechanism can be explained by two competing pathways, diverging from the cyclic intermediate **8**. It would certainly seem reasonable to propose that the cyclization occurs in a concerted fashion (*cf.* Wittig Reaction), leading to direct expulsion of triphenylphosphine oxide from intermediate **8** (as shown by the arrows below). However, this reaction would proceed with retention of stereochemistry at the oxygen-containing

carbon, leading to *cis/trans* isomerization. Experimental observations are in contrast to this mechanistic explanation (*vide supra*). Alternatively, the cyclic intermediate **8** could decompose to the linear intermediate **10**. The nitrogen would then be free to participate in an S_N2 displacement of triphenylphosphine oxide, preserving the *cis* configuration of the starting material, albeit with net inversion of stereochemistry. This mechanistic interpretation has been generally accepted and is widely used in the literature.[3]

1.1.4 Variations and Improvements

Few variations or improvements have been reported for the Blum aziridine synthesis. The major modification to the procedure concerns the method of ring closure to form the aziridine from the azido–alcohol. Several groups have reported variations in which the azido–alcohol **2** is activated for displacement (X = Ms, Ts, *etc.*) before reduction of the azide. This alternate sequence then allows for a milder and potentially higher efficiency cyclization to occur.[4,5] Alternatively, the Staudinger can be performed first to generate amino-alcohol **12**, followed by acylation of the nitrogen to give intermediate **13**. The alcohol can then be activated for displacement (*e.g.*, PPh_3/DIAD) to form aziridine **14**.[6,7] This method is especially useful if acylated aziridines are desired, although it does not satisfy the strict definition of a Blum aziridine synthesis.

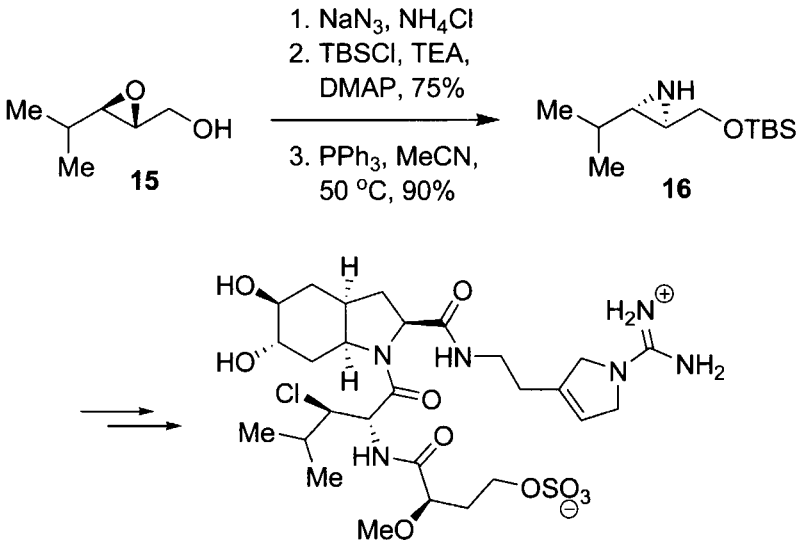


1.1.5 Synthetic Utility

Total Synthesis

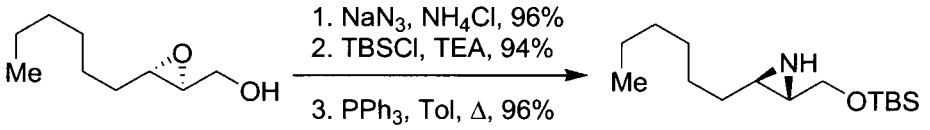
The Blum aziridine synthesis has found widespread utility in the synthetic community. The field of total synthesis has especially benefited from the

power of this transformation. In one example of how this reaction can be applied in complex natural product synthesis, Hanessian and co-workers applied a Blum reaction in the total synthesis of chlorodysinosin A (**17**).[8] In this sequence, epoxide **15** was opened with sodium azide and the primary alcohol protected as the silyl ether. The azide was then treated with triphenylphosphine and heat, resulting in concomitant reduction and aziridine formation to give intermediate **16**. Aziridine **16** was eventually processed to chlorodysinosin A (**17**).

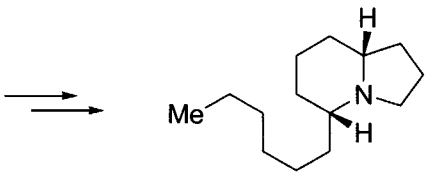


chlorodysinosin A (**17**)

Somfai and Åhman have applied the Blum aziridine synthesis to the total synthesis of indolizidine 209D (**20**).[9,10] Epoxide **18** was opened with sodium azide and the primary alcohol protected as the silyl ether. The azide was then treated with triphenylphosphine and heat, resulting in concomitant reduction and cyclization to give intermediate **19**. Aziridine **19** was eventually processed to indolizidine 209D (**20**).

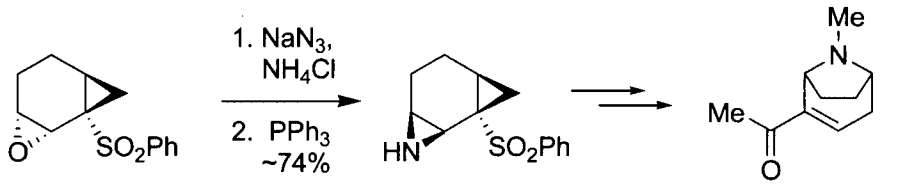


18 **19**



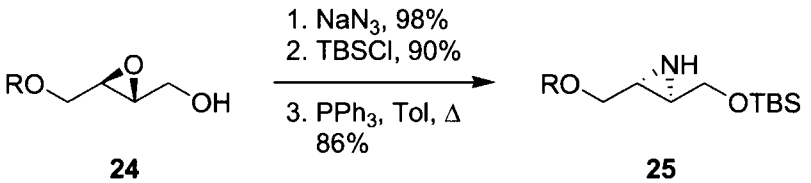
indolizidine 209D (**20**)

Bäckvall and co-workers used the Blum reaction in the total synthesis of ferruginine (**23**).[11] Epoxide **21** was opened with sodium azide and the resultant azido–alcohol was reduced and cyclized with triphenylphosphine in good yield to give aziridine **22**. Intermediate **22** was eventually processed to ferruginine (**23**).

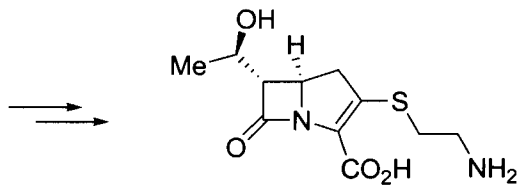


21 **22** ferruginine (**23**)

Finally, Tanner and Somfai completed a formal total synthesis of thienamycin (**26**) using the Blum aziridine synthesis as a key step.[12] As in the previous examples, epoxide **24** was converted to aziridine **25** in good yield using a Blum aziridine synthesis. Intermediate **25** was eventually processed to thienamycin (**26**).



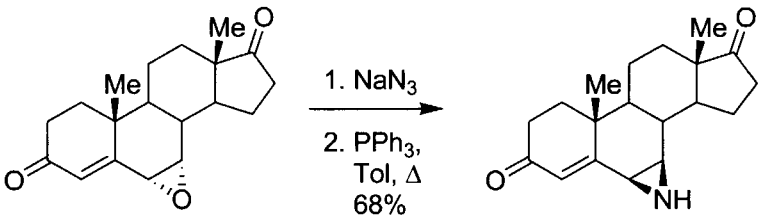
24 **25**



thienamycin (**26**)

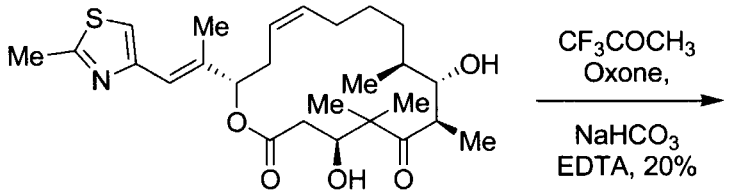
Medicinal and Process Chemistry

Robinson and co-workers reported the preparation of aromatase inhibitors that used the Blum aziridine synthesis as a key step.[13] Epoxy–steroid **27** was opened with sodium azide to form the azido-alcohol, which was then reductively cyclized with triphenylphosphine and heat to provide the desired aziridine **28**. Analog **28** exhibited modest inhibitory activity toward human placental aromatase.

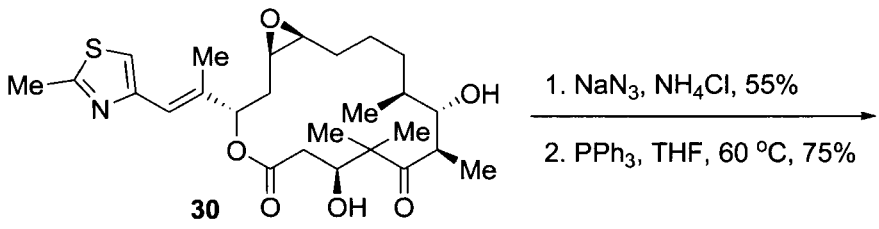


27 **28**

Researchers at Bristol-Myers Squibb reported the preparation of an epothilone analog using the Blum aziridine synthesis as a key step.[14] Epothilone C (**29**) was epoxidized to provide intermediate **30**. Opening of the epoxide with sodium azide followed by reductive cyclization forged the desired N–H aziridine analogue **31** in good yield, especially in light of the complex setting for this transformation.



epothilone C (**29**)



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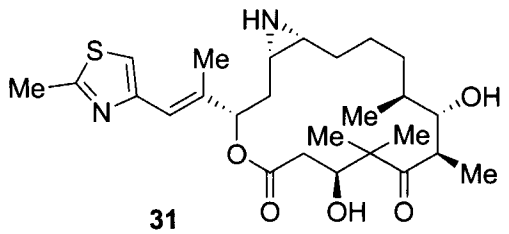
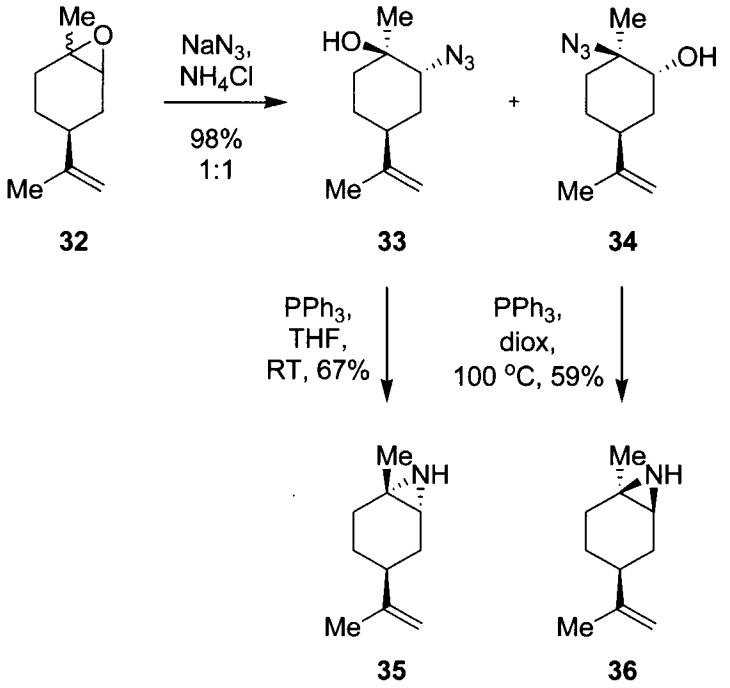


31

Researchers at Lexicon Pharmaceuticals found that limonene aziridines could be efficiently prepared from the corresponding limonene oxides using the Blum aziridine synthesis.[15] Epoxide **32** was opened with sodium azide to produce the regioisomeric azido–alcohols **33** and **34** in an approximate 1 : 1 ratio. The secondary azide was reductively cyclized with triphenylphosphine at ambient temperature, whereas the tertiary azide required heating to effect the same transformation. In this way, the desired aziridines **35** and **36** were prepared in good yield on multigram scale.



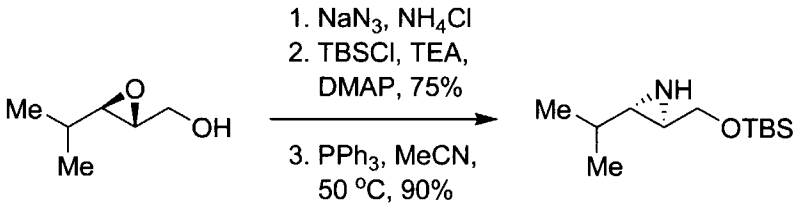
32 **33** **34**

35 **36**

The Blum aziridine synthesis has seen many other uses since its development.[16,17] A common application of the Blum aziridine synthesis is in the preparation of authentic standards while developing novel reactions or synthetic routes.[18–20] The reaction has also found broad utility in the preparation of starting materials or intermediates in novel reaction development.[21–31]

1.1.6 Experimental

Blum aziridine synthesis to prepare a chlorodysinosin A intermediate 16[8]



15 **16**

To a solution of **15** in $CH_3OCH_2CH_2OH$ (0.7 M) was added NaN_3 (10 equiv), NH_4Cl (2 equiv), and water (4 equiv). The mixture was heated to reflux for 24 h, cooled to room temperature, and the solvent removed under vacuum. The residue was then taken up in water, extracted with EtOAc, dried over Na_2SO_4, and concentrated. After drying under reduced pressure for 18 h, the resulting amber oil was taken up in CH_2Cl_2, cooled to 0 °C, and treated sequentially with Et_3N (1.5 equiv), DMAP (cat.), and TBSCl (1.1 equiv). The solution was stirred at 0 °C for 2 h, diluted with CH_2Cl_2, washed with 1 M HCl, dried over Na_2SO_4, and concentrated under vacuum. The crude residue was purified by flash chromatography over silica gel (8% EtOAc/hexanes) to give the azido–alcohol as a 1:1 mixture of regioisomers (75%).

The mixture of azido–alcohols was dissolved in MeCN (0.5 M) and treated with PPh_3 (1.1 equiv). The solution was stirred at RT for 2 h, then heated to 50 °C for 18 h. After removal of MeCN under vacuum, the mixture was taken up in Et_2O, filtered through a pad of Celite, and the filtrate concentrated under vacuum. The crude residue was purified by flash chromatography over silica gel (25% EtOAc/hexanes) to give **16** as a colorless liquid (90% yield).

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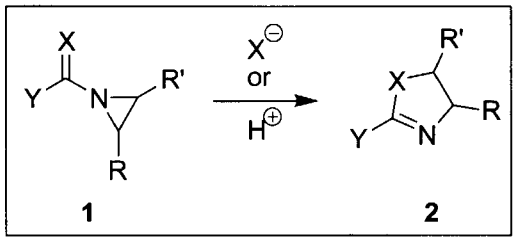
1.2 Gabriel–Heine Aziridine Isomerization

Jeremy M. Richter

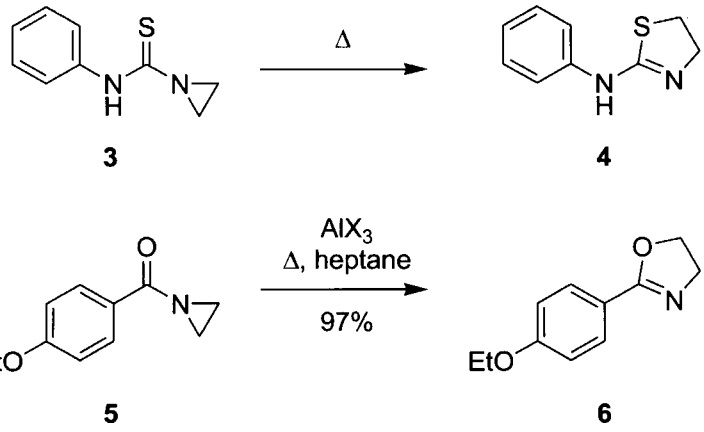
1.2.1 Description



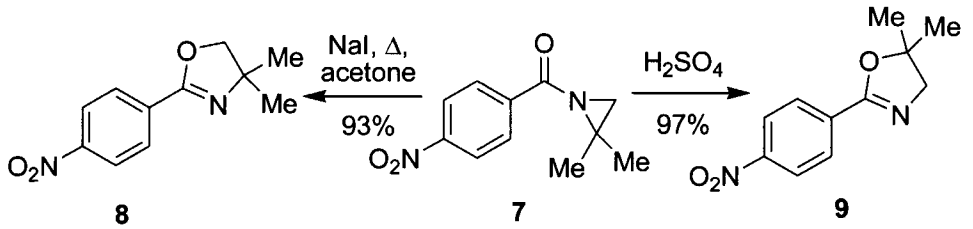
The Gabriel–Heine aziridine isomerization describes the rearrangement of an acylaziridine **1** into an oxazoline **2**.[1–5]

1.2.2 Historical Perspective

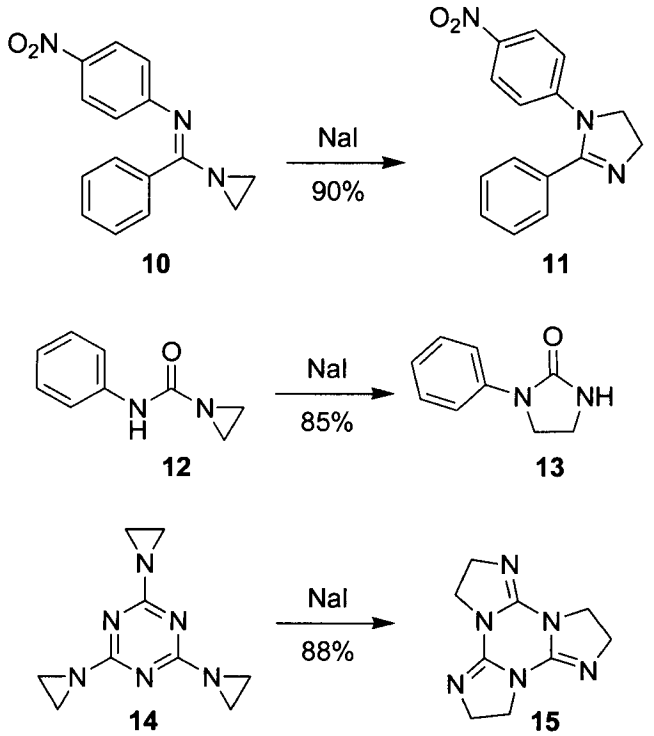
Harold Heine and co-workers were working with ethylenimines, and derivatives thereof, when they became intrigued by the reaction originally reported by Gabriel and coworkers in which thioacyl aziridine **3** was isomerized to thiazoline **4** upon attempted distillation.[1] This report went virtually unnoticed until Heine and co-workers decided to investigate the reaction further.[2] They found that upon exposure of **5** in refluxing heptane to small amounts of aluminum halides, oxazoline **6** was isolated in nearly quantitative yield. They also discovered that the reaction does not occur under purely thermal conditions, but catalysis is required.



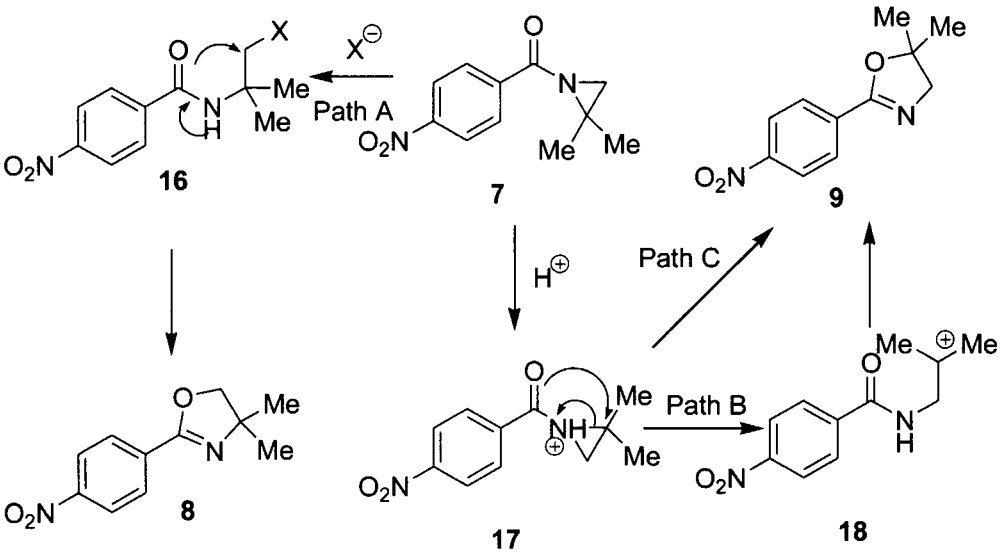
Further work from the Heine group revealed that the reaction could be accomplished under milder conditions and that the choice of catalyst determined the regiochemical outcome of the reaction.[3] For example, in the presence of iodide, **7** rearranges to **8**, wherein the least substituted carbon atom migrates. Alternatively, upon exposure to acid, **7** rearranges to **9**, wherein the most substituted carbon atom migrates. These results suggest that alternate mechanisms may be operable in these two transformations, a point that will be discussed below.



Heine also demonstrated that the rearrangement can occur on differentially acylated aziridines to give rise to different heterocycles such as imidazolines (**11**), imidazolones (**13**), and complex heterocycles such as **15**.[4,5] Futhermore, this reaction has been the subject of reviews by Heine and others.[6,7]



1.2.3 Mechanism



In Heine's seminal publications, he astutely noticed that different products are observed under acidic and nucleophilic catalysis.[3] Heine put forth a mechanistic explanation for the formation of both of these products.[6] He proposed that the rearrangement of **7** under nucleophilic catalysis proceeds through aziridine ring opening with the halide followed by displacement with oxygen to form **8** (two sequential S_N2 reactions, Path A). Alternatively, he proposed that the acid-catalyzed rearrangement of **7** to **9** proceeds through protonation of the aziridine nitrogen, formation of a tertiary carbocation, and subsequent attack by the oxygen on this carbocation (Path B). This mechanistic explanation of the nucleophilic catalysis (*i.e.*, **7** to **8**) is still generally accepted and has received further support as more examples have been presented in the literature.[8] His explanation for the acid-catalyzed rearrangement has come under scrutiny, though, and has been modified through further studies. Shortly after Heine put forth his mechanistic interpretation, Nishiguchi and co-workers proposed that the acid catalyzed rearrangement could potentially proceed through an S_Ni reaction (*i.e.*, Path C).[9] Convincing clarity in terms of both nucleophilic and acidic catalysis was not gained until the computational and experimental studies of Hori and co-workers, who concluded that two sequential S_N2 reactions (Path A) were likely operable for nucleophilic catalysis and an S_Ni pathway (Path C) accounted for the observed product under acidic catalysis.[10]

Further evidence exists to support these mechanistic interpretations, in that retention of configuration is observed if the aziridine is chiral in

nature.[11] The mechanism is thus limited to either a double inversion or front-side attack to account for this retention of stereochemistry.

Any mechanistic discussion of reactions of this nature also inherently requires comments on the regioselectivity of the migration. Regioselectivity in the Gabriel–Heine aziridine isomerization is observed under a variety of conditions.[12,13] As mentioned previously (*vide supra*), the most substituted carbon migrates under acidic catalysis and the least substituted carbon migrates under nucleophilic catalysis. This trend holds for acyl shifts, but thioacyl shifts are less regioselective, with more scrambling observed.[14] Finally, Eastwood and co-workers showed that aziridines substituted with electron-donating groups form 2,4-substituted oxazolines upon rearrangement, while those substituted with electron-withdrawing groups form 2,5-substituted oxazolines selectively.[15]

1.2.4 Variations and Improvements

Several variations and improvements of the Gabriel–Heine aziridine isomerization have been reported, primarily surrounding the catalyst selection and/or reaction conditions. An electrochemical rearrangement has been reported, which gave the desired oxazolines in moderate yield.[16] In addition to the catalysts initially reported, several other catalysts have been used in this reaction, including TfOH,[17] Yb(biphenol)OTf, Ti(O*i*-Pr)$_4$, $Zr(Cp)_2(SbF_6)_2$,[18] $Cu(OTf)_2$, $Zn(OTf)_2$, $BF_3{\cdot}OEt_2$, $MgBr_2{\cdot}OEt_2$,[19] $Sn(OTf)_2$,[20,21] Mn(salen),[22] P_2S_5,[23] and TBAI.[24] The reaction has also been performed in the microwave in good yields and rapid reaction times.[25,26] Finally, one major variation of the Gabriel–Heine aziridine isomerization is the use of similar reaction conditions to convert acyl–aziridines into oxazolidinones using $BF_3{\cdot}OEt_2$.[4,27,28]

1.2.5 Synthetic Utility

Total Synthesis

The Gabriel–Heine aziridine isomerization has been used only twice in the context of total synthesis, despite finding widespread utility in alternate contexts. The Vogel group has prepared 3-amino-3-deoxy-L-talose (**21**) using the Gabriel–Heine reaction as a key step.[29–31] The synthesis commences with readily available aziridine **19**, which undergoes a Gabriel–Heine rearrangement under triflic acid catalysis at 80 °C in hexafluoroisopropanol to generate oxazoline **20**. This intermediate was further transformed into 3-amino-3-deoxy-L-talose (**21**).