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RING-SUBSTITUTION, ENLARGEMENT, AND CONTRACTION BY BASE-INDUCED REARRANGEMENTS OF *N*-HETEROCYCLIC AMMONIUM SALTS

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Abstract – An overview of the utility of base-induced Stevens, Sommelet–Hauser, and related sigmatropic rearrangements of *N*-heterocyclic ammonium salts into various types of *N*-heterocycles reported after 1970 will be described. The synthetic transformations are classified as *N*-heterocyclic ring-substitution, ring-enlargement, and ring-contraction.

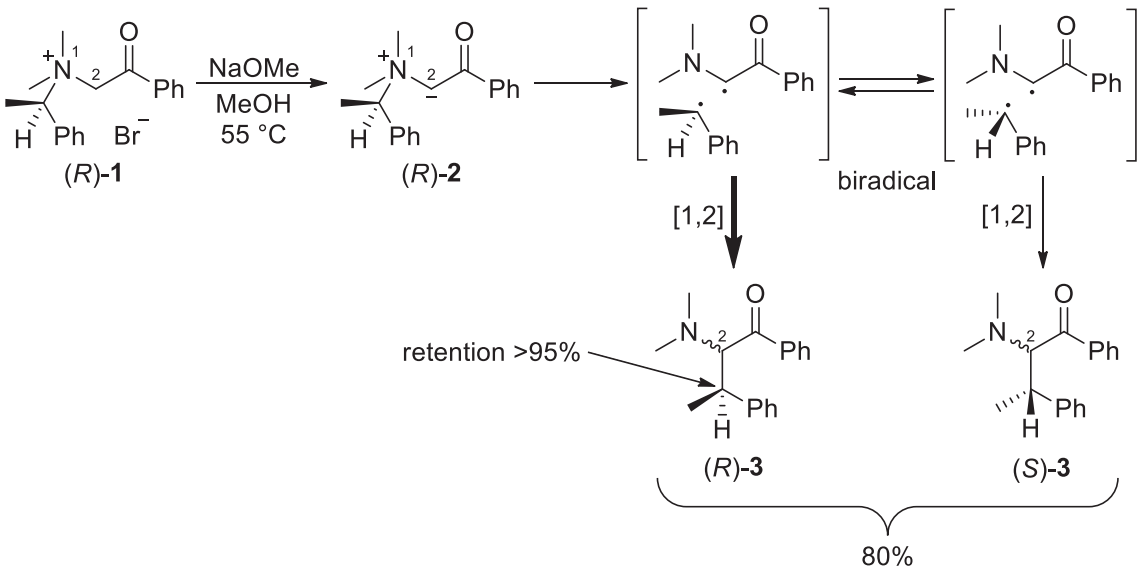
CONTENTS

1. INTRODUCTION

1-1. Definitions

Ammonium ylide ($R_3N^+C^-R_2$) rearrangements, for example, [1,2] Stevens,[1] [2,3] sigmatropic (Stevens),[2] and Sommelet–Hauser[3,4] (S–H) rearrangements are useful synthetic transformations because they convert a readily accessible C–N bond into a new C–C bond under mild and simple conditions to produce various types of nitrogen-containing compounds.[5-8] As the representative synthetic application, the rearrangements of amino acid-derived ammonium ylides into unnatural amino acid analogs have been well-studied.

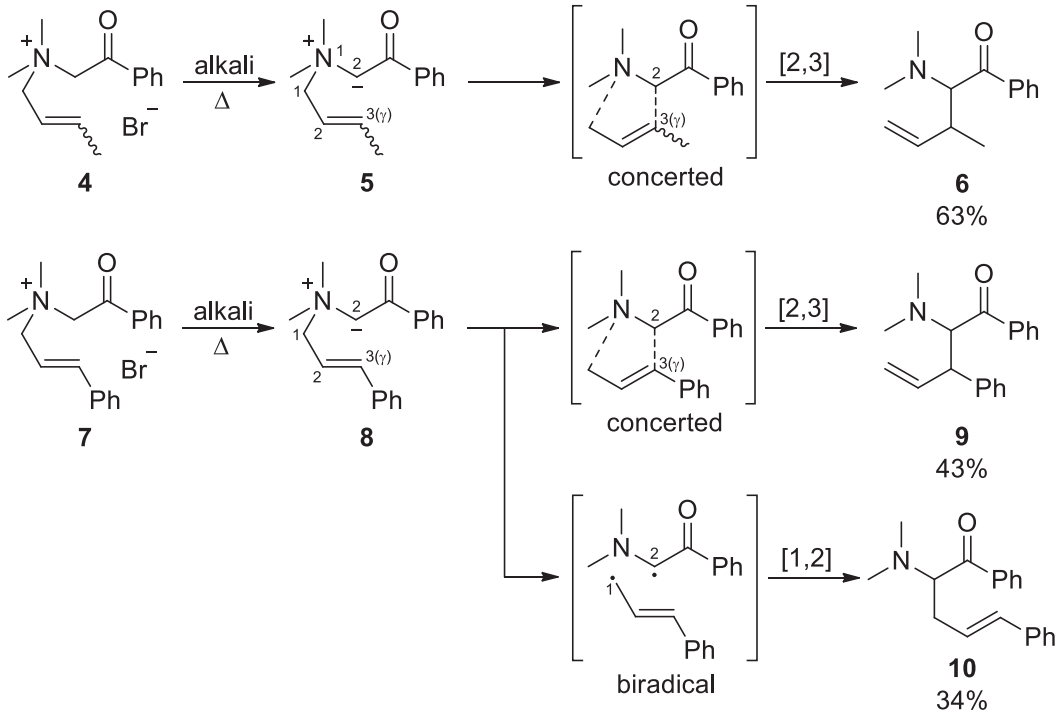
A [1,2] Stevens rearrangement is the [1,2] shift of an *N*-migrating group into a ylide carbon involving C–N bond cleavage followed by C–C bond formation to afford the corresponding α-substituted tertiary amine. A representative example is shown in Scheme 1.[9] Based on depth studies, researchers believe that the [1,2] Stevens rearrangement mainly proceeds via a radical cleavage–recombination process. The preferred *N*-migrating group is benzylic, which stabilizes and generates the biradical intermediate. When a chiral *N*-benzylic migrating group is used, such as *N*-(*R*)-(α-methylbenzyl), as in salt (*R*)-**1**, the ylide (*R*)-**2** generated with sodium methoxide in methanol was rearranged into product **3** in 80% yield, and the chirality was retained (>95%) at the carbon migrating center. A [1,2] rearrangement of non-benzylic migrating group is also possible; however, successful examples are limited unless the rearrangement is intramolecular.



Scheme 1. Representative example of a [1,2] Stevens rearrangement

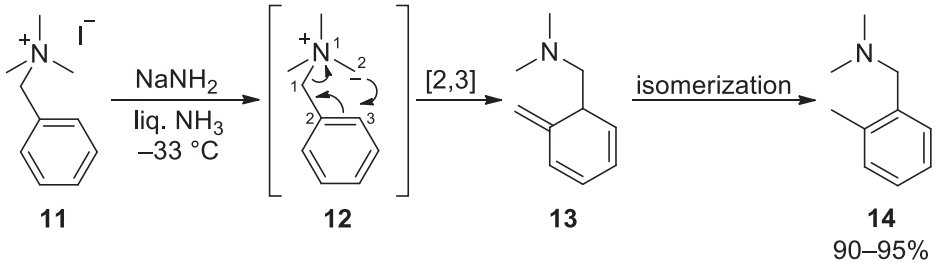
A [2,3] sigmatropic (Stevens) rearrangement is performed using *N*-allylic ammonium ylides and proceeds via C–N bond cleavage and C–C bond formation at the *N*-allylic migrating group γ-carbon. A

representative example is shown in Scheme 2.[2] The rearrangement of *N*-crotyl ammonium ylide **5** generated from ammonium salt **4** afforded the α-(but-3-en-2-yl)derivative **6** in 63% yield. The [2,3] rearrangement mainly proceeds via a concerted pathway; however, when *N*-cinnamyl ammonium salt **7** was subjected to the same conditions, the generated ylide **8** provided the corresponding [2,3] rearrangement product **9** in 43% yield and the [1,2] Stevens rearrangement product **10** in 34 % yield. This result indicates that radical cleavage–recombination process is also possible for *N*-allylic ammonium ylide rearrangements because the allylic moieties stabilize the biradical intermediate.



Scheme 2. Representative example of a [2,3] sigmatropic (Stevens) rearrangement

An S–H rearrangements is a [2,3] sigmatropic rearrangement with an aromatic double bond in the *N*-benzylic migrating group. The representative example includes transformation of benzyltrimethylammonium iodide **11** into (2-methylbenzyl)dimethylamine **14**, which is depicted in Scheme 3.[10] When treating **11** with sodium amide in liquid ammonia to generate ylide **12**, a [2,3] sigmatropic rearrangement with an aromatic double bond occurred to afford the corresponding dearomatized **13**. Finally, the isomerization of **13** leads to **14**. This reaction resulted in enabling the conversion of a readily accessible C–N bond into a new C–C bond in an aromatic ring. This S–H rearrangement frequently competes with the [1,2] Stevens rearrangement.

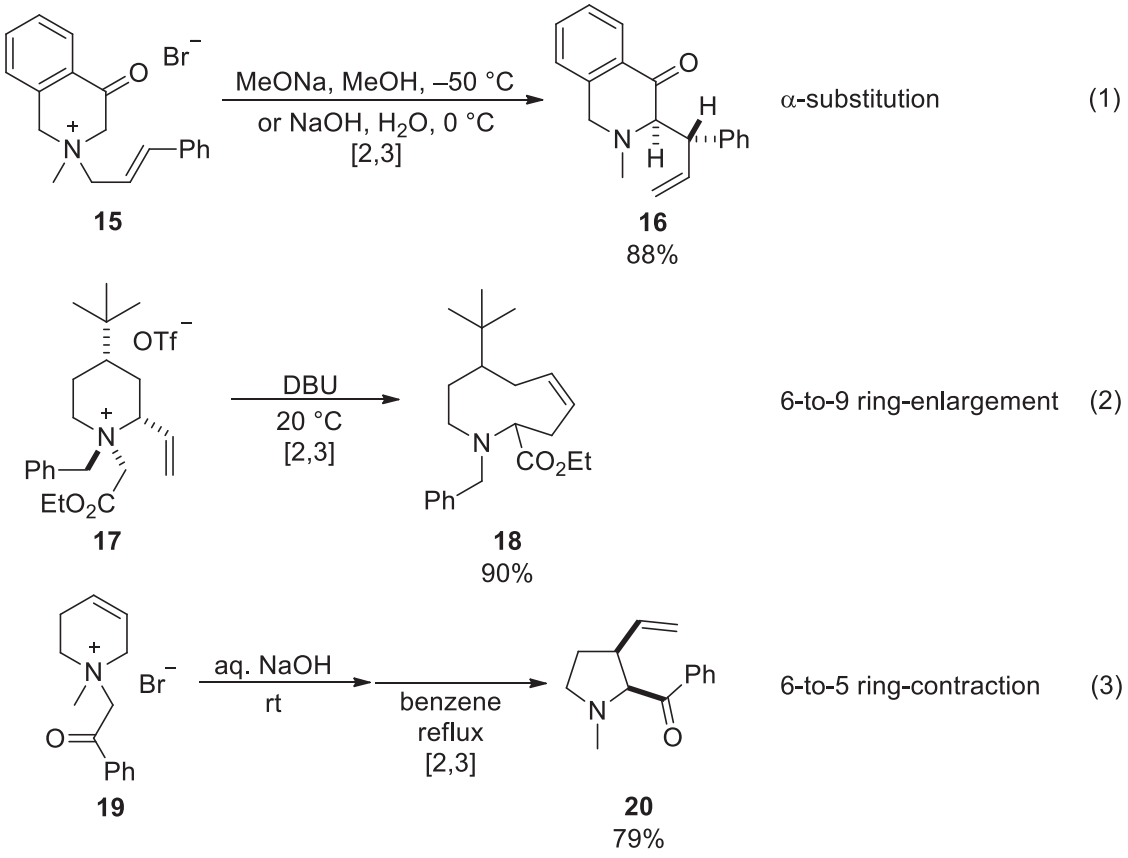


Scheme 3. Representative example of an S–H rearrangement

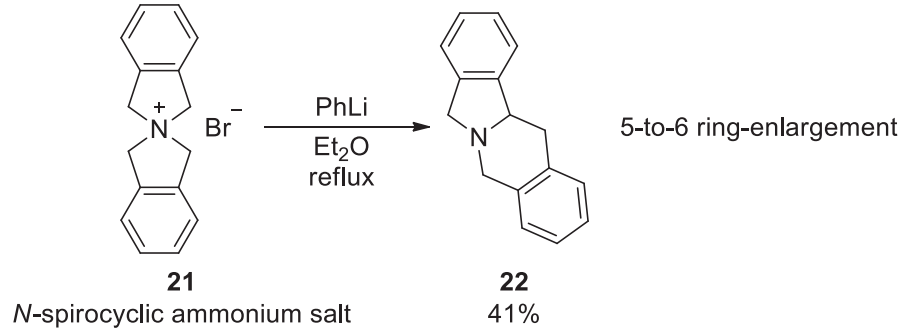
1-2. Rearrangements of *N*-heterocyclic ammonium ylides

Rrearrangements of *N*-heterocyclic ammonium ylides into other *N*-heterocycles are notable because the rearrangements not only facilitate *N*-heterocyclic ring-substitution but also ring-enlargement or ring-contraction; these transformations provide key building blocks for the synthesizing biologically active compounds, such as alkaloids. For example, the [2,3] sigmatropic rearrangement of *N*-allylic piperidinium ylide generated from salt **15** with a base afforded the α-substituted derivative **16** (Scheme 4, Eq. 1);[11] however, 2-vinylpiperidinium salt **17** reacted to produce the 6-to-9 ring-enlarged **18** (Eq. 2).[12] In another reaction, 1,2,3,6-tetrahydropyridinium salt **19** was rearranged into the 6-to-5 ring-contracted **20** (Eq. 3).[13] The transformations depicted in Scheme 4 were successful due to the substrate ammonium salt structure design. In many cases, *N*-heterocyclic ammonium salts, such as **15**, **17**, and **19** are used as substrates; however, *N*-spirocyclic salts also have been employed for ring-enlarged rearrangements. For example, the [1,2] Stevens rearrangement of *N*-spiro ammonium salt **21** afforded a 5-to-6 ring-enlarged **22** in 41% yield (Scheme 5).[14]

For these rearrangements, the desired ammonium ylide must be generated from the precursor.[5,6,15-17] One of the standard methods used includes forming a base-induced ylide from a tetraalkylammonium salt; however, this method involves undesirable side reactions.[7] When the *N*,*N*-dialkylpiperidinium salt **23** is used as a model ammonium salt (Scheme 6), the ylide **24** is generated through deprotonating the α-proton on the piperidine ring (Eq. 1). The ylide anion located on the *N*-heterocyclic ring is an 'internal ylide'. However, ylide **25** is also formed under the same conditions through deprotonating the α-proton at the external *N*-alkyl substituent (Eq. 2). The ylide anion located outside of the *N*-heterocyclic ring is an 'external ylide'. Furthermore, a Hoffmann elimination into **26** can also occur and is caused by deprotonation of the β-proton at the piperidine ring (Eq. 3).



Scheme 4. Ring-substitution, enlargement, and contraction through base-induced [2,3] rearrangements

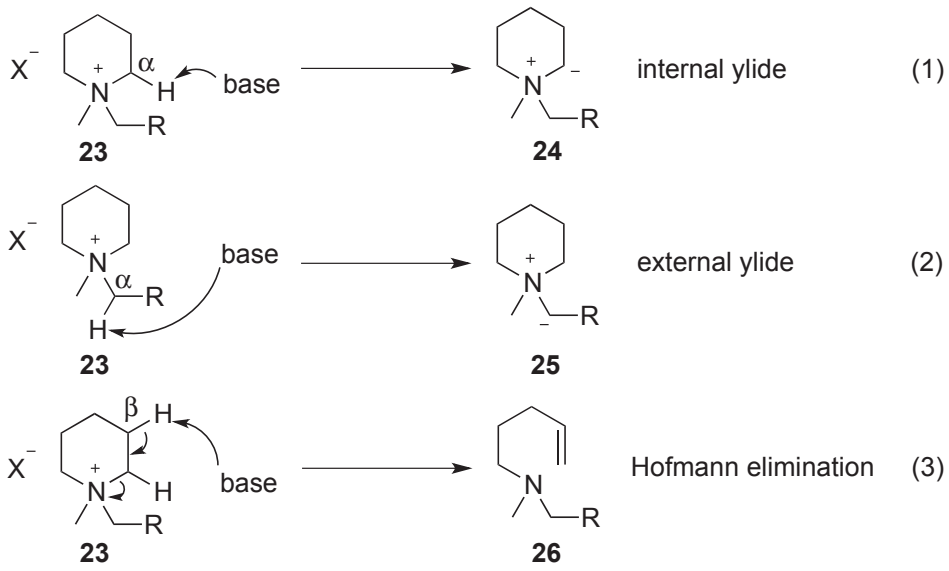


Scheme 5. Base-induced [1,2] rearrangement of an *N*-spirocyclic ammonium salt

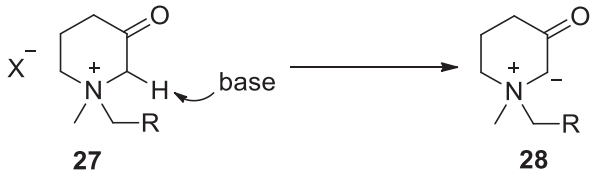
To achieve regioselective deprotonation, an acidic proton at the α-position of an ammonium nitrogen activated by carbonyl, benzylic, or allylic substituents is essential. For example, treatment of a model ammonium salt having a carbonyl substituent **27** with base gives exclusively the stabilized ammonium ylide **28** (Scheme 7).

Deprotonation of ammonium salts followed by the rearrangements of ammonium ylides is defined as the base-induced (or promoted) rearrangement of ammonium salts. The earlier works (prior to 1970) on the

rearrangements were fully summarized by Pine in *Organic Reactions*.[7] For the purpose of this review, only the rearrangements of *N*-heterocyclic ammonium salts reported after 1970 will be described with the origin of each rearrangement.



Scheme 6. Possible reactions during base-induced generation of an ylide from an ammonium salt



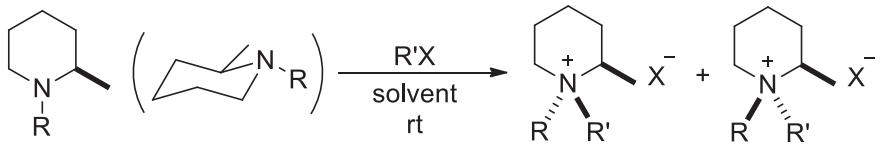
Scheme 7. An example of stabilized ylide formation by regioselective deprotonation

1-3. Diastereoselective *N*-quaternization of *N*-heterocyclic tertiary amines

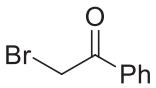
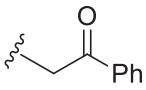
In base-induced rearrangements of *N*-heterocyclic ammonium ylides, a diastereoselective tetraalkylammonium salt preparation may be necessary to control the rearrangement pathway or the stereoselective product formation. In many cases, the pure diastereomeric salts could be obtained by diastereoselective *N*-quaternization of *N*-heterocyclic amines with alkyl electrophiles followed by fractional recrystallization of the resulting ammonium salts. In 1970, Mckenna summarized stereochemistry studies on *N*-quaternization of *N*-heterocyclic amines.[18] Several examples were reported thereafter; however, the results have not been summarized. In 2015, Dumbar and West reviewed diastereoselective *N*-quaternization of *N*-substituted piperidines (Table 1).[19] The diastereoselectivity of *N*-quaternization can be partially controlled by adjacent substituents or alkylating reagents. Focusing on *N*-alkyl-2-methylpiperidines **29** as substrates, *N*-quaternization preferentially

gives the axial alkylated salts **30** over the equatorial alkylated salts **31**; however, occasionally, the selectivity is turned over.[20] The precise basis is difficult to explain; the conformational mobility of the piperidine rings may affect diastereoselective *N*-quaternization. In fact, *N*-quaternization of five- and four-membered *N*-heterocycles, such as *N*-substituted pyrrolidines or azetidines, proceeds with better to high diastereoselectivity due to less conformational mobility.

Table 1. Diastereoselectivity in 2-methylpiperidine *N*-alkylation



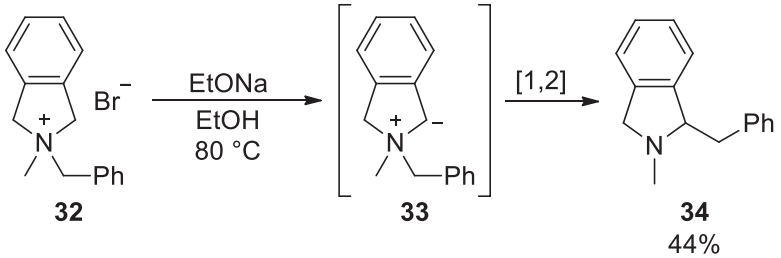
29 **30** axial alkylation **31** equatorial alkylation

R	R'X	solvent	% axial	% equatrial
Me	Et_3OBF_4	CH_2Cl_2	62	38
Me	EtI	acetone	43–50	57–50
Me	CD_3I	acetone	66	34
Me		MeCN	19	81
	MeI	MeCN	62	38

2. RING-SUBSTITUTION

2-1. [1,2] Stevens rearrangement

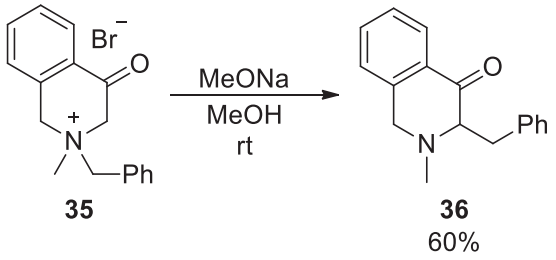
The first example of ring-substitution of *N*-heterocycles by a base-induced [1,2] Stevens rearrangement of ammonium salts was reported by Wittig and Streib in 1953 (Scheme 8).[21] Treatment of *N*-benzyl isoindolinium salt **32** with sodium ethoxide to generate the semi-stabilized ylide **33** followed by a [1,2] rearrangement of the benzyl migrating group afforded 1-benzylated isoindolin **34** in 44% yield.



32 **33** **34** 44%

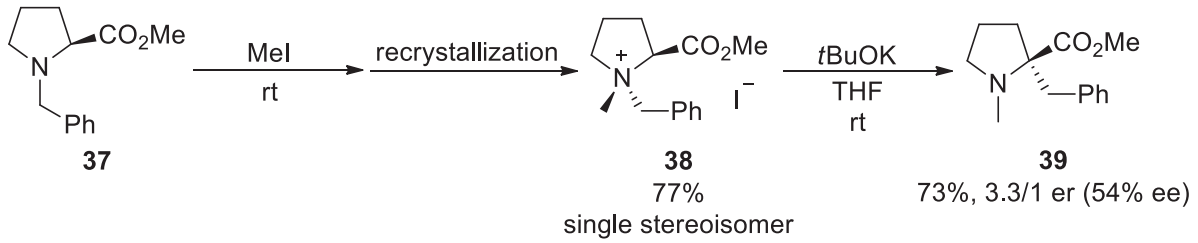
Scheme 8. Ring-substitution by a base-induced [1,2] Stevens rearrangement of an ammonium salt

In 1971, Mageswaran et al. examined the base-induced [1,2] Stevens rearrangement of a stabilized ammonium ylide generated from *N*-benzyl isoquinolinium salt **35** and obtained 3-benzylated **36** in 60% yield (Scheme 9).[11] In the ylide formation step, regioselective deprotonation at an acidic α-proton of the carbonyl minimized undesirable side reactions.



Scheme 9. Regioselective deprotonation followed by a [1,2] Stevens rearrangement

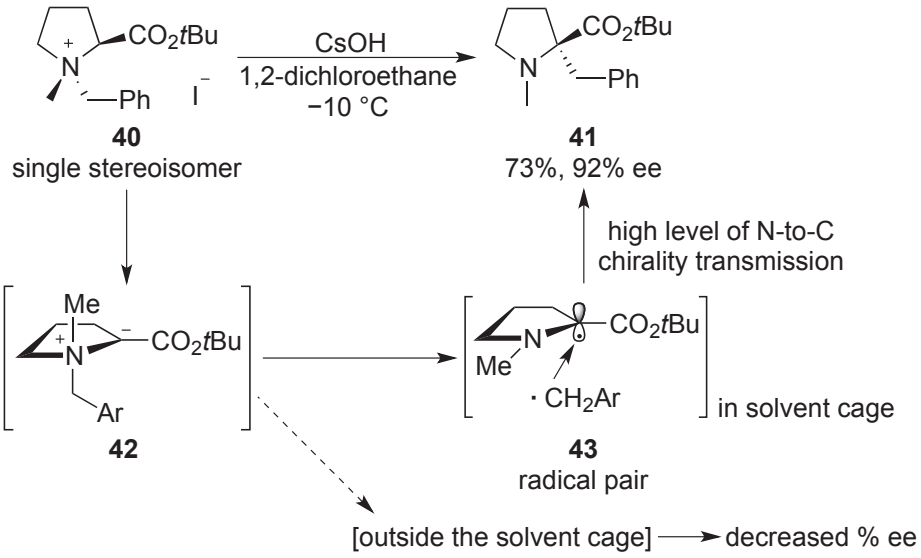
This result was applied to the synthesis of α-quaternary amino acid derivatives. In 1999, Glaeske and West reported the asymmetric base-induced [1,2] Stevens rearrangement of L-proline-derived ammonium salt **38** prepared by diastereoselective quaternization of *N*-benzyl-L-proline ester **37** with methyl iodide (Scheme 10).[22] Diastereoselective *N*-methylation is controlled by the adjacent ester moiety as in **37**. The [1,2] rearrangement of the single diastereomer **38** proceeded with a moderate level of N-to-C chirality transmission to yield the α-benzylated proline **39** with a 3.3/1 enantiomeric ratio (54% ee). The lack of the stereoisomeric ratio (100% de to 54% ee) could be explained that this [1,2] Stevens rearrangement proceeded via a radical cleavage–recombination mechanism.



Scheme 10. Asymmetric base-induced [1,2] Stevens rearrangement via N-to-C chirality transmission

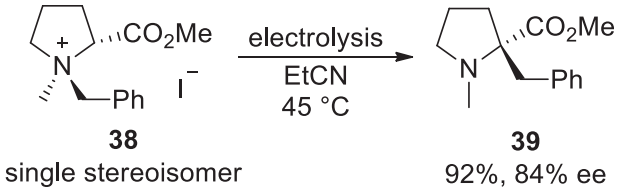
The rate of chirality transmission for this rearrangement improved under solid–liquid biphasic conditions using a halogenated solvent as the liquid phase. When the rearrangement of *tert*-butyl ester derivative **40** was performed with cesium hydroxide monohydrate in 1,2-dichloroethane, 92% ee of α-benzylated **41** was obtained (Scheme 11).[23] Under these biphasic conditions, recombination of the radical pair **43** initially formed from the *N*-ylide **42** occurs more rapidly in a solvent cage and preferentially in a retentive

fashion (on the bottom side) to give **41** with high N-to-C chirality transmission. Recombination outside the solvent cage that decreases the % ee would be suppressed.



Scheme 11. Asymmetric [1,2] Stevens rearrangement under solid–liquid biphasic conditions

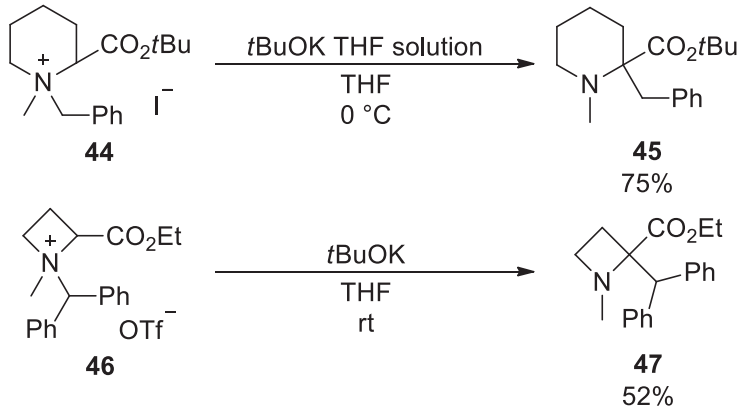
Although not a base-induced rearrangement, the author would like to introduce a closely related work developed by Palombi (Scheme 12).[24] The rearrangement described in Scheme 10 was applied to an electrochemically promoted version. Ylide generation by electrolysis of **38** in propionitrile at 45 °C followed by a [1,2] Stevens rearrangement yielded the α-benzylated **39** in 92% yield with 84% ee.



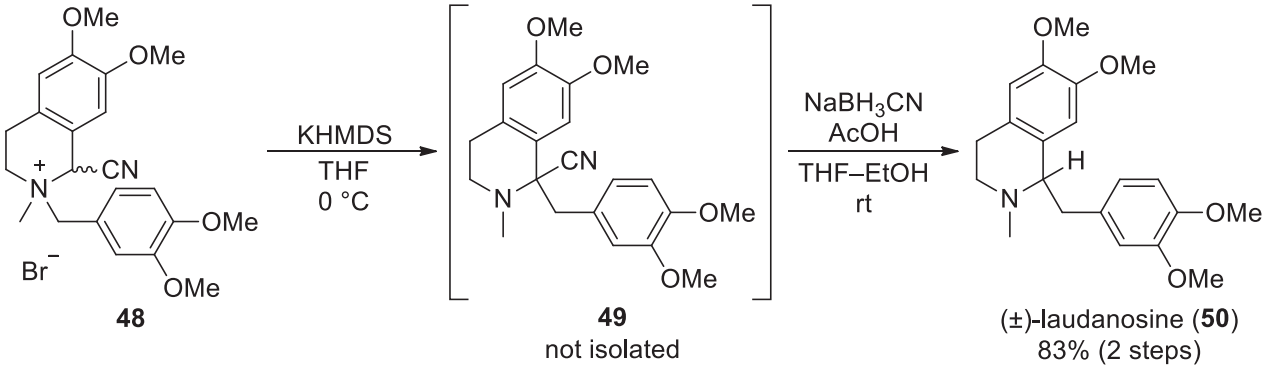
Scheme 12. Electrochemically promoted asymmetric [1,2] Stevens rearrangement

The rearrangements of six- and four-membered cyclic amino acid-derived ammonium salts were also reported (Scheme 13). *N*-Benzylic pipecolinic and azetidinic acid-derived ammonium salts **44** and **46** were rearranged into the corresponding α-substituted **45** and **47** in moderate yields.[25,26]

Pacheco et al. employed the ring-substitution for the synthesis of alkaloid derivatives (Scheme 14).[27] Deprotonation of α-cyano ammonium salt **48** with potassium bis(trimethylsilyl)amide followed by a [1,2] rearrangement afforded a solution of α-aminonitrile **49**. The nitrile substituent, as in **49**, was eliminated *in situ* by treatment with sodium cyanoborohydride to produce (±)-laudanosine (**50**).

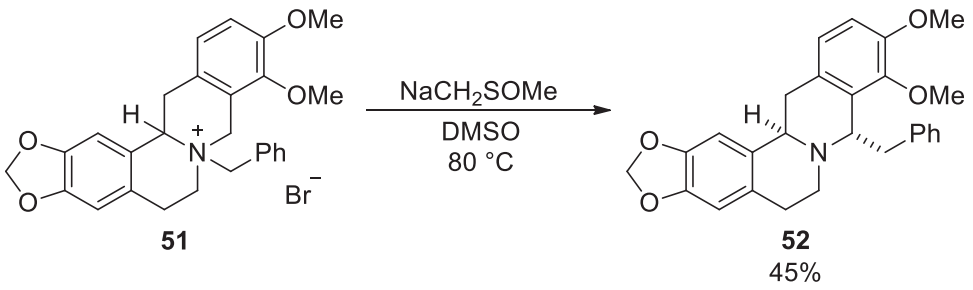


Scheme 13. Rearrangement of six- and four-membered cyclic amino acid-derived ammonium salts



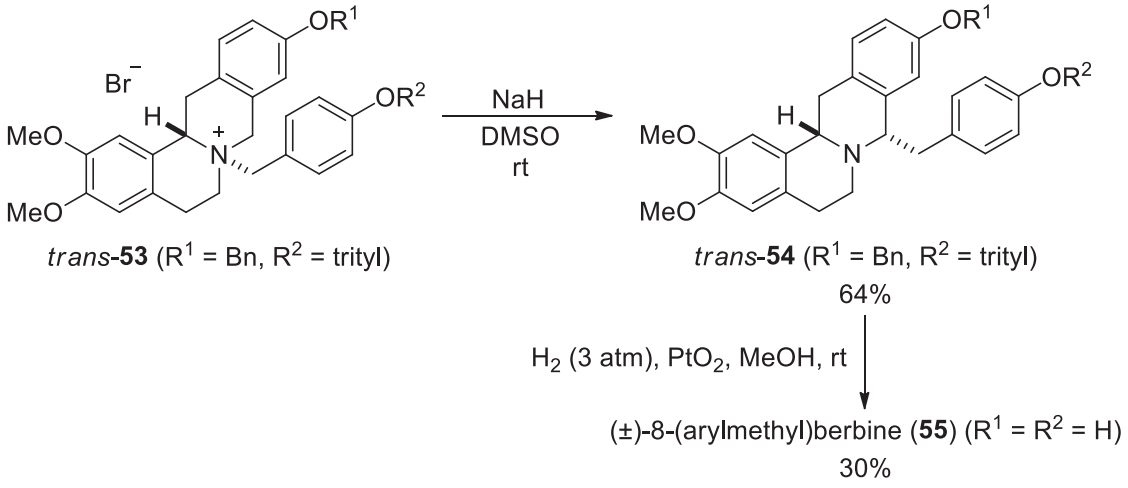
Scheme 14. Synthesis of (±)-laudanosine (**50**)

Valpuesta et al. succeeded with a regioselective deprotonation of ammonium salt **51** without an efficient electron-withdrawing group (EWG) followed by a [1,2] Stevens rearrangement (Scheme 15).[28] Their group tested various bases and solvents and found that the use of dimsylsodium in DMSO afforded the desired polycyclic **52** in 45% yield.

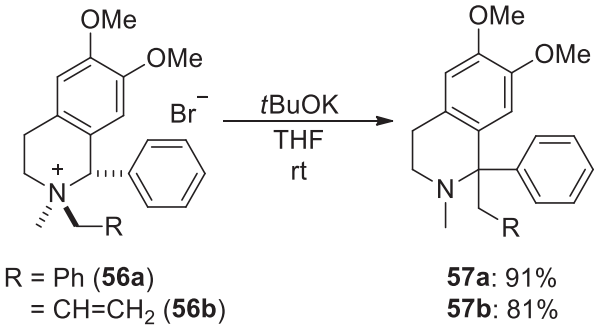


Scheme 15. Regioselective deprotonation with dimsylsodium followed by a [1,2] Stevens rearrangement

This results was applied to a total synthesis of an alkaloid natural product (Scheme 16).[29] The reactions of diastereomerically pure berbinium salt *trans*-**53** stereoselectively yielded 8-(arylmethyl)derivative *trans*-**54**. Hydrogenation of *trans*-**54** provided (±)-8-(arylmethyl)berbine (**55**), which has been isolated from the aerial part of *Aristolochia constria*. Later, their group reported a regioselective deprotonation of a dibenzylic methine proton, as in salts **56**, followed by a rearrangement to give 1,1-disubstituted isoquinolines **57** in good yields (Scheme 17).[30]



Scheme 16. Synthesis of (±)-8-(arylmethyl)berbine (**55**)



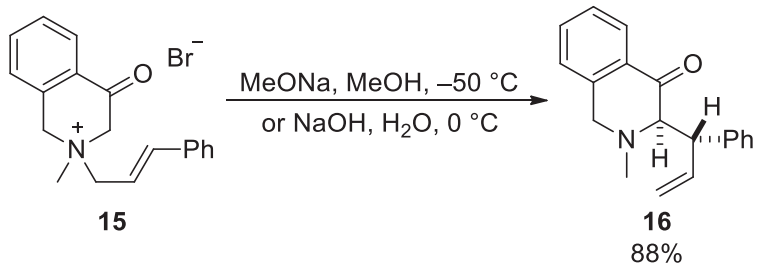
Scheme 17. Deprotonation of a dibenzylic methine proton followed by a rearrangement

2-2. [2,3] Sigmatropic (Stevens) rearrangement

When allyl ($CH_2CH=CH_2$) or methallyl ($CH_2C(Me)=CH_2$) substituents are used as a migrating group, the exact pathway of [2,3] or [1,2] cannot be identified from the products; however, the rearrangements are summarized in this section.

As already mentioned in introduction, the ring-substitution of *N*-heterocycles by base-induced [2,3] rearrangement were employed by Ollis's group in 1971 using amino ketone-derived ammonium salts **15**

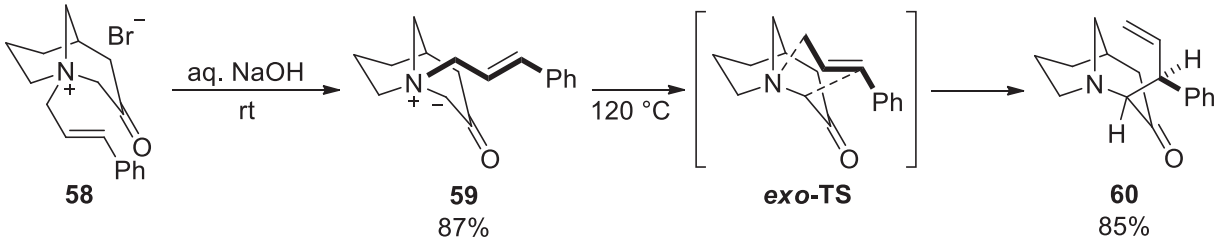
as the substrate (Scheme 18).[11] α-Substituted **16** was obtained in 88% yield as a single diastereomer.



15 **16** 88%

Scheme 18. Ring-substitution by a [2,3] rearrangement of an amino ketone-derived ammonium salt

Their group investigated the rearrangement of *N*-cinnamyl-1-azabicyclo[3.3.1]nonanium salt **58** to clarify the stereochemical mechanism (Scheme 19). The [2,3] rearrangement proceeded on the sterically less hindered face of the ylide **59** through an *exo* transition state (***exo*-TS**) to afford the diastereomerically pure rearranged product **60**.



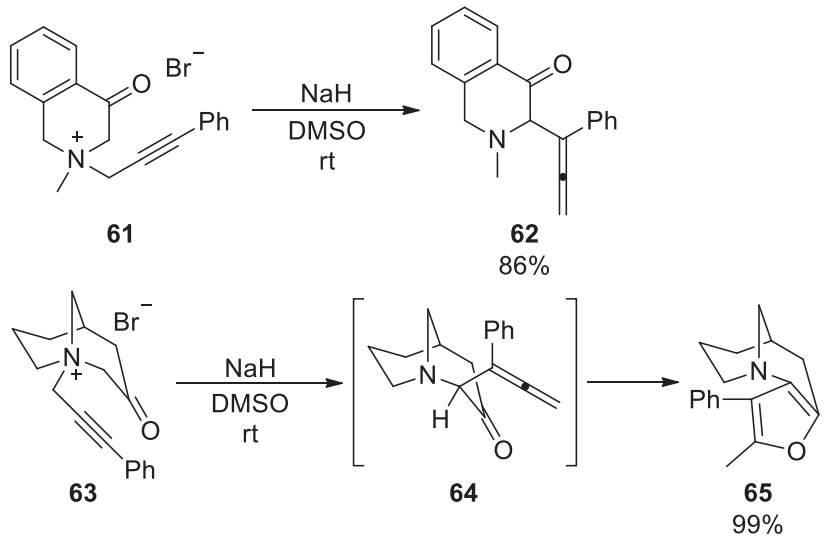
58 **59** 87% ***exo*-TS** **60** 85%

Scheme 19. Ring-substitution by a [2,3] rearrangement of 1-azabicyclo[3.3.1]nonanium salt

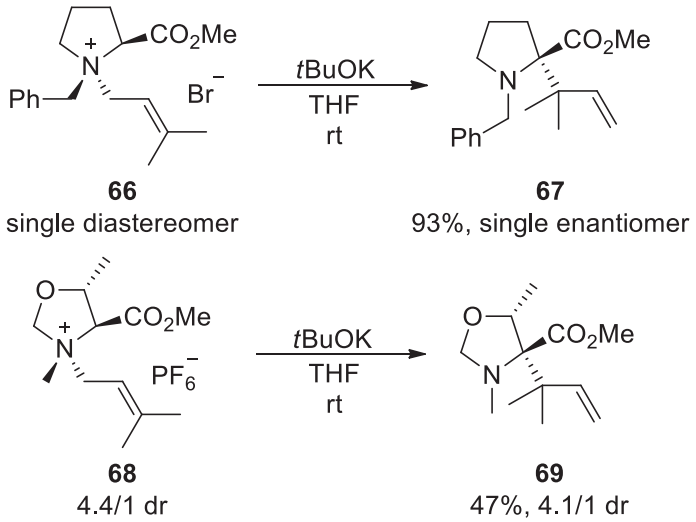
Later, the [2,3] rearrangement of *N*-propargyl ammonium ylides was also examined to expand the scope and highlight its limitations (Scheme 20).[31] On treatment of *N*-3-phenylpropargyl salt **61** with sodium hydride in DMSO provided the α-allenyl derivative **62** in 86% yield. In contrast, the reaction of 1-azabicyclo[3.3.1]nonanium salt **63** under similar conditions afforded the furan derivative **65** in 99% yield via formation of the α-allenyl derivative **64** followed by adding an enolate *O*-anion generated by excess base to a central allenyl carbon. The product **62** was unreacted under the same conditions at room temperature because an enolate *O*-anion derived from aromatic ketone **62** is less nucleophilic than aliphatic ketone **64**.

The asymmetric [2,3] rearrangement via N-to-C chirality transmission was demonstrated by Glaeske and West as well as the [1,2] rearrangement described in Scheme 10.[22] The concerted [2,3] rearrangement from the single diastereomer of chiral cyclic amino acid-derived ammonium salts **66** and **68** proceeded with excellent levels of N-to-C chirality transmission (Scheme 21). The diastereomeric ratios of **66** or

68 were converted into the enantiomeric ratios of rearrangement products **67** or **69**, respectively. This method provides efficient access to the optically active α-quaternary amino acid derivatives.



Scheme 20. Ring-substitution through a [2,3] rearrangement of *N*-propargyl ammonium salts

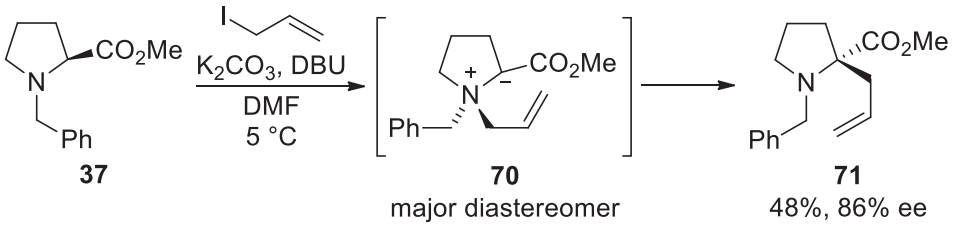


Scheme 21. Asymmetric [2,3] rearrangement via N-to-C chirality transmission

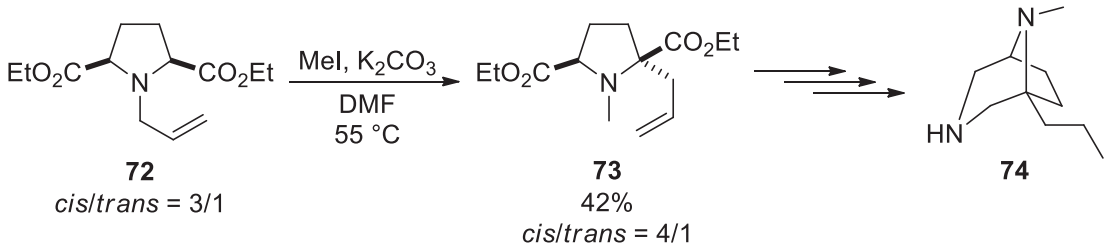
Arboré et al. reported a similar rearrangement without isolation of the ammonium salt derived from *N*-benzyl L-proline ester **37** (Scheme 22).[32] Diastereoselective quaternization of **37** with allyl iodide followed by generation of the ylide **70** in a one-pot synthetic approach gave α-allylated proline ester **71** in 48% yield with 86% ee.

Smith and Bentley applied this protocol for the diastereoselective synthesis of 5-disubstituted proline analog **73** (Scheme 23).[33] One-pot quaternization and [2,3] rearrangement of 5-substituted proline ester

72 (*cis*/*trans* = 3/1) afforded α-allylated **73** in 42% yield (*cis*/*trans* = 4/1). The product **73** was successfully converted into diazabicyclo[3.2.1]octane **74**, which acts as a key building block for alkaloid synthesis.



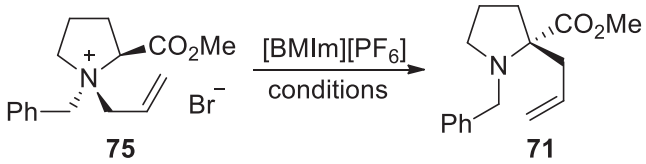
Scheme 22. One-pot diastereoselective quaternization and asymmetric [2,3] rearrangement



Scheme 23. Diastereoselective synthesis of a trisubstituted proline analog

In the base-induced [2,3] rearrangement of **75**, the use of [BMIm][PF_6] (1-butyl-3-methylimidazolium hexafluorophosphate) as an additive improved the yields of the rearrangement product **71**, as proposed by Duran-Lara et al. (Table 2).[34] This effect was observed under various reaction conditions.

Table 2. Effect of [BMIm][PF_6] as an additive in base-induced [2,3] rearrangements

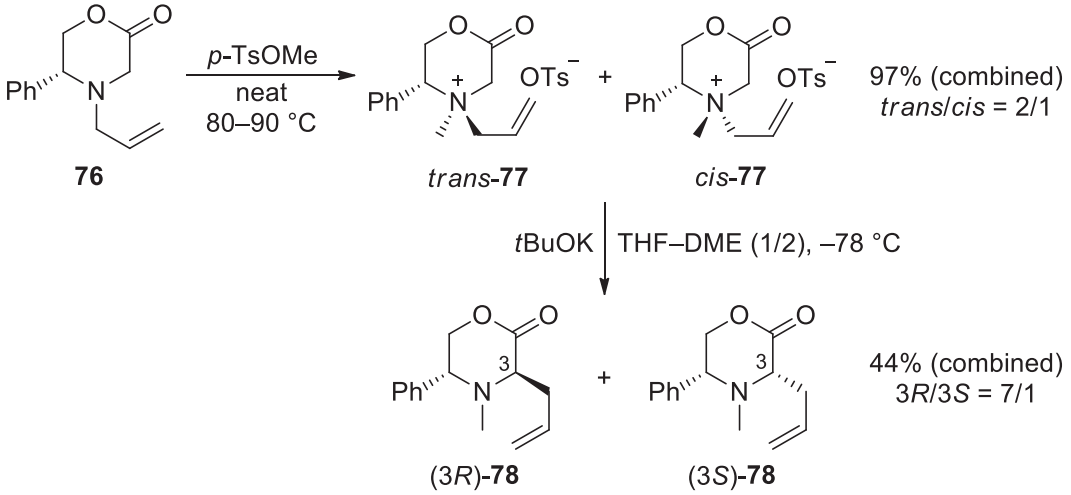


conditions	with [BMIm][PF_6]	without [BMIm][PF_6]
K_2CO_3, DMF, rt	50%, 85% ee	40%, 85% ee
*t*BuOK, DMF, rt	50%, 85% ee	40%, 85% ee
DBU, MeCN, 0 °C	80%, 65% ee	55%, 50% ee

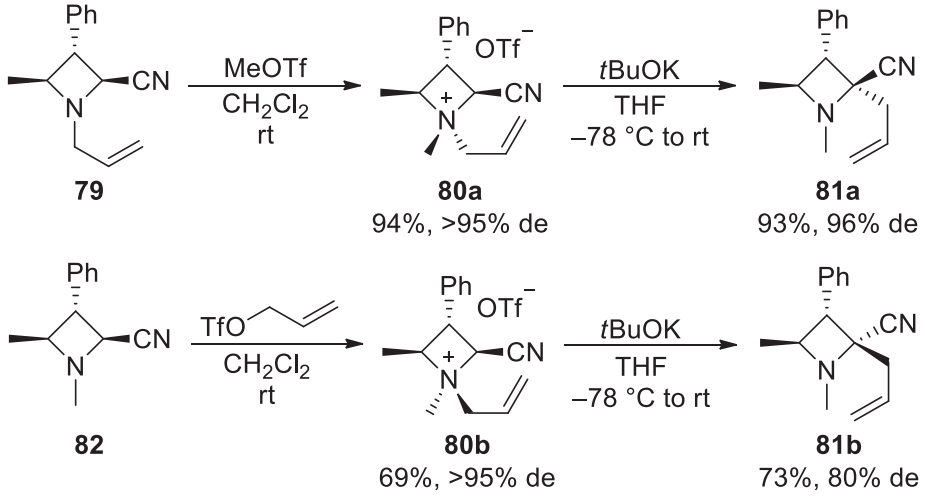
The asymmetric [2,3] rearrangement involving N-to-C chirality transmission was applied to other cyclic amino acid-derived ammonium ylides. Quaternization of (*R*)-5-phenylmorpholin-2-one **76** with methyl

tosylate gave the salt **77** as a *trans*/*cis* = 2/1 mixture of diastereomers (Scheme 24).[35] The [2,3] rearrangement of diastereomixture salts **77** with potassium *tert*-butoxide in THF–DME at –78 °C afforded 3-allylated (3*R*)-**78** and (3*S*)-**78** in 44% combined yield with 3*R*/3*S* = 7/1 ratio. During this rearrangement, kinetic resolution occurs to improve the diastereomeric ratio from 2/1 to 7/1.

Couty's group demonstrated the successive diastereoselective transformations from substituted azetidine derivatives (Scheme 25).[36] Quaternization of *N*-allyl azetidinic nitrile **79** with methyl triflate proceeded with high diastereoselectivity to yield the salt **80a** as a single isomer. The [2,3] rearrangements of **80a** gave α-allylated **81a** in 93% yield with 96% de via N-to-C chirality transmission. When *N*-methyl azetidinic nitriles **82** and allyl triflate were used as the starting materials, the other diastereomers **80b** and **81b** were obtained.

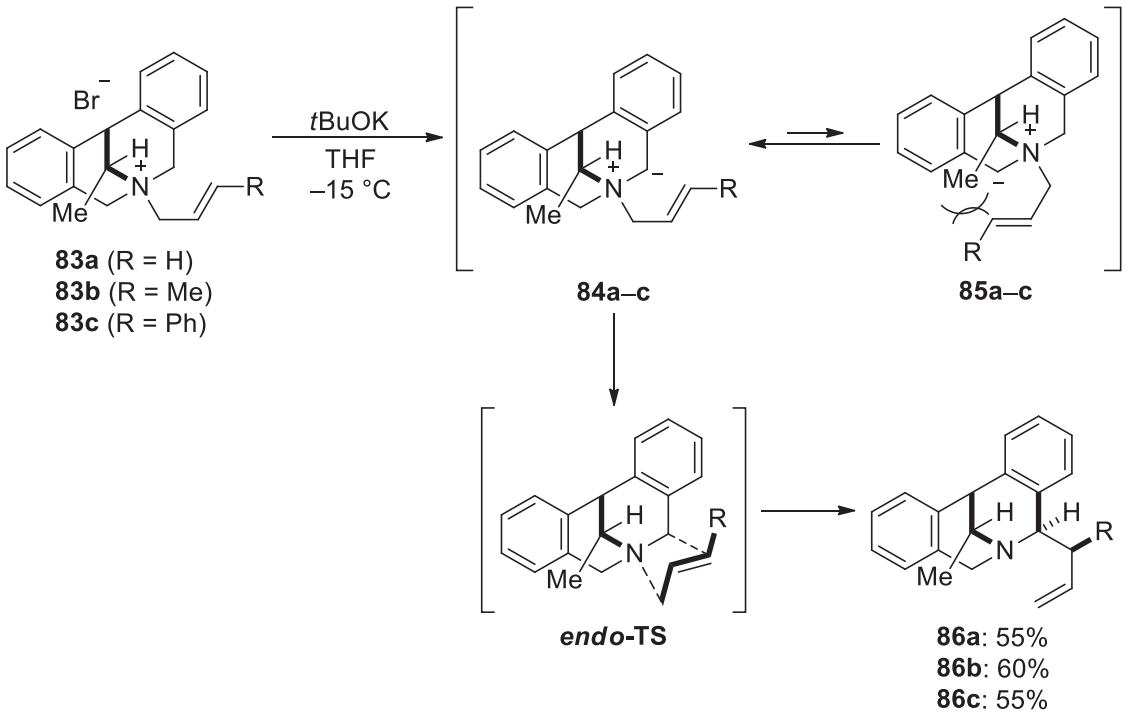


Scheme 24. Kinetic resolution via a [2,3] rearrangement



Scheme 25. Successive diastereoselective quaternization and [2,3] rearrangements

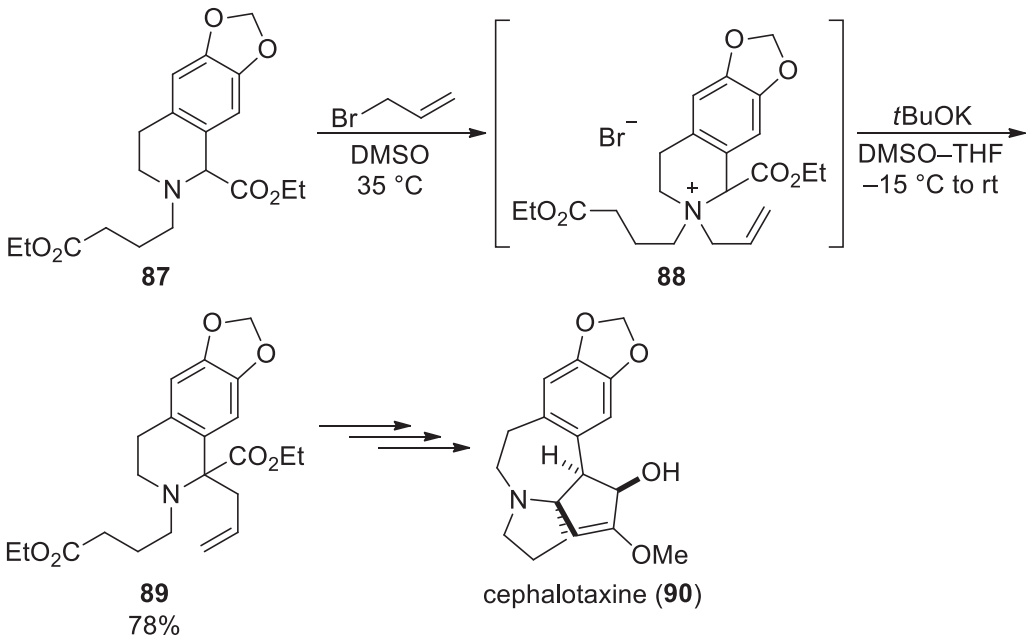
An example of bicyclic ring-substitution through a base-induced [2,3] rearrangement was reported by Hanessian et al. (Scheme 26).[37] Treating the *N*-allylic-1-azabicyclo[3.3.1]nonanium salts **83** with potassium *tert*-butoxide generated ylide **84** or **85** as a [2,3] rearrangement intermediate. The rearrangement proceeded preferentially from less sterically hindered site and face of the ylide **84** via an *endo* transition state (***endo*-TS**) to give α-substituted **86** in moderate yields.



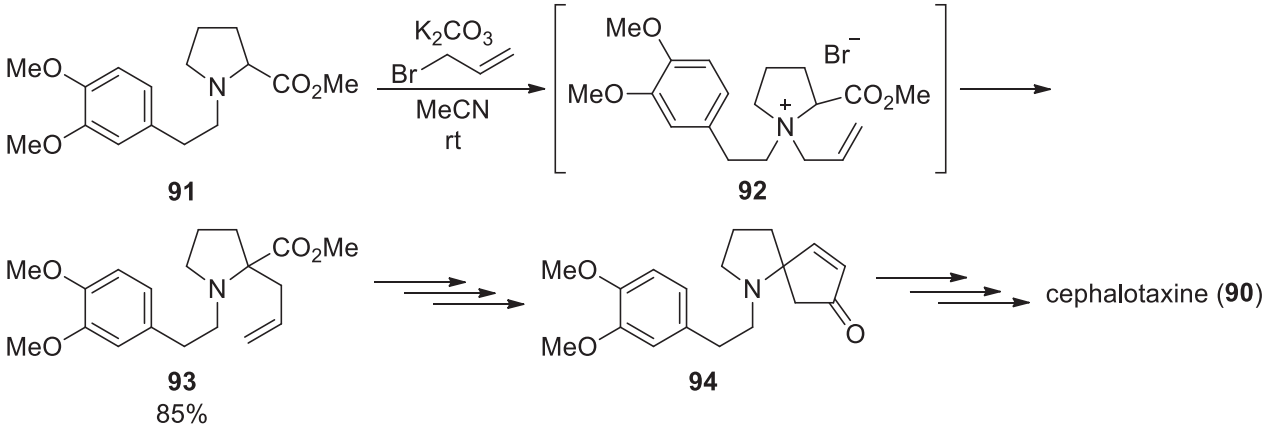
Scheme 26. Bicyclic ring-substitution through a base-induced [2,3] rearrangement

The synthesis of alkaloid natural products or their key building blocks has been investigated by Li and Wang in 2003 (Scheme 27).[38] Quaternization of 1,2,3,4-tetrahydroisoquinoline derivative **87** with allyl bromide followed by [2,3] rearrangement of the salt **88** in one-pot produced 1-allylated **89**. The product **89** was successfully converted into cephalotaxine (**90**), which is the parent member of cephalotaxus alkaloids.

In 2009, a formal synthesis of cephalotaxine (**90**) via the [2,3] rearrangement was reported by Sun et al. (Scheme 28).[39] One-pot quaternization and ylide generation from *N*-substituted proline ester **91** followed by a [2,3] rearrangement of the ylide **92** yielded the α-allylproline ester derivative **93**. Further synthetic transformation produced spirocyclopentenone **94**, which is a known intermediate leading to **90**.



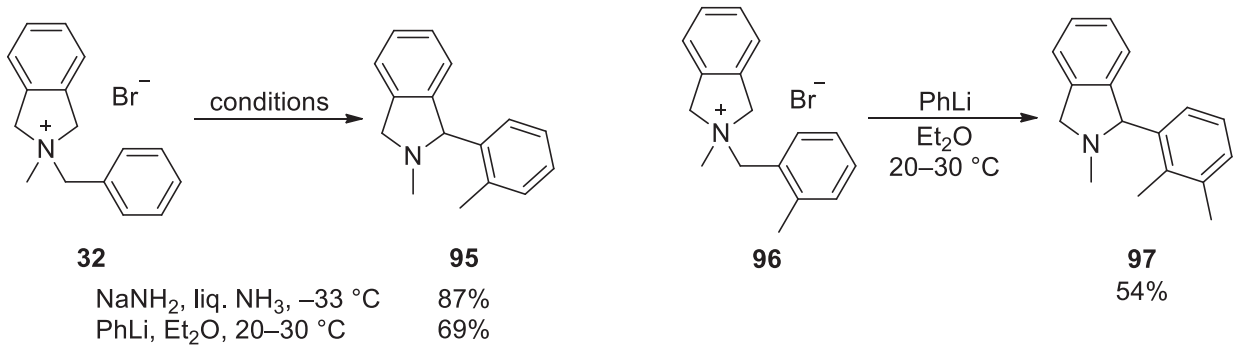
Scheme 27. Synthesis of cephalotaxine (**90**)



Scheme 28. A formal synthesis of cephalotaxine (**90**)

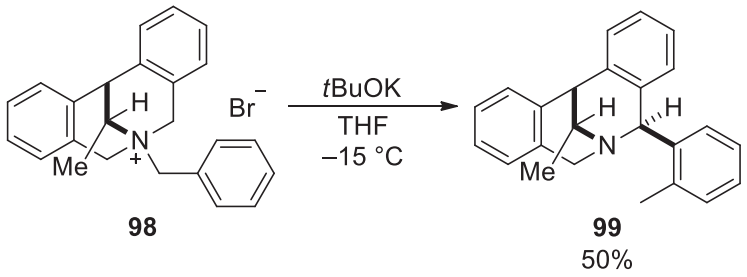
2-3. Sommelet–Hauser rearrangement

The first example of ring-substitution of *N*-heterocycles by base-induced S–H rearrangement was reported by Wittig and Streib in 1953 (Scheme 29).[21] Treatment of *N*-benzylic-1-isoindolinium salts **32** or **96** with sodium amide in liquid ammonia or phenyllithium in diethyl ether gave 1-(*o*-tolylic)isoindolines **95** or **97** in acceptable yields without formation of competitive [1,2] Stevens rearrangement products.



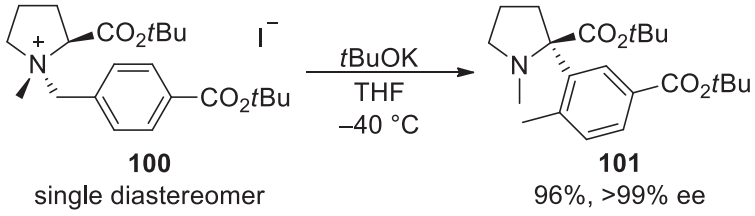
Scheme 29. Ring-substitution of *N*-heterocycles by a base-induced S–H rearrangement

In 2006, Hanessian et al. reported the rearrangement of *N*-benzyl-1-azabicyclo[3.3.1]nonanium salt **98** into *o*-tolyl substituted **99** (Scheme 30).[37] Their group examined additional reactions to investigate the substituent effect on the migrating aromatic ring; however, the maximum yield of the S–H rearrangement product was 50%.



Scheme 30. Ring-substitution of azabicyclo ammonium salt by a base-induced S–H rearrangement

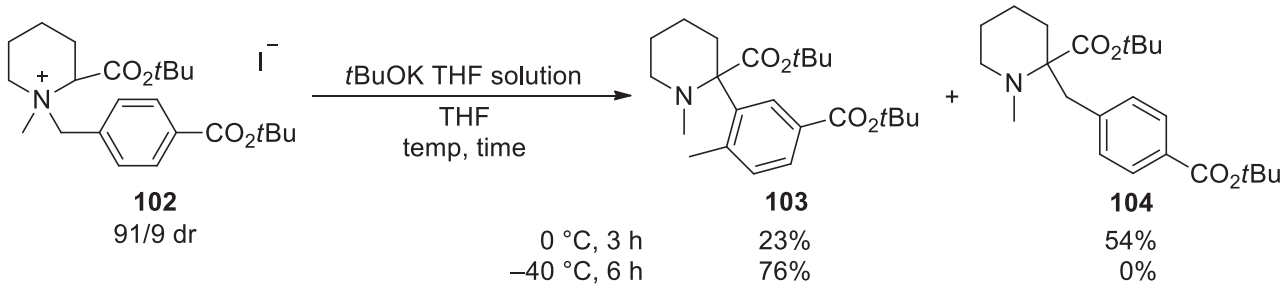
Although only one example, the successful demonstration of ring-substitution by base-induced asymmetric S–H rearrangement was reported in 2007 (Scheme 31).[40] On treatment of diastereomerically pure L-proline ester-derived ammonium salt **100** with potassium *tert*-butoxide in THF at –40 °C, S–H rearrangement proceeded exclusively with a perfect level of N-to-C chirality transmission to give α-arylated **101** in 96% yield with >99% ee. An EWG, such as *para*-*tert*-butoxycarbonyl, on the aromatic ring improved the yield of S–H rearrangement product.



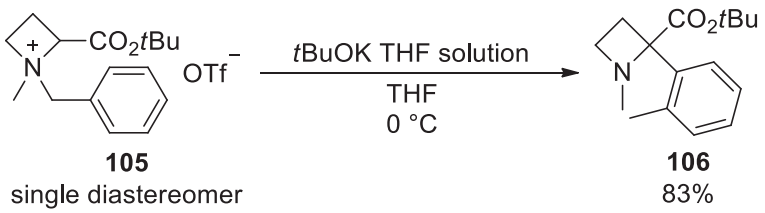
Scheme 31. Ring-substitution of L-proline ester-derived ammonium salt

Similarly, a reaction of *N*-benzylpipecolinic acid-derived ammonium salt **102** (racemic, 91/9 diastereomeric mixture) also gave the S–H rearrangement product **103** (Scheme 32).[8] An EWG on the *N*-benzylic aromatic ring and a lower reaction temperature (–40 °C) were necessary for sufficient yield (76%) of **103**. These conditions minimized competitive [1,2] Stevens rearrangements that would lead to α-benzylated **104**.

Although the cause was not identified, on treatment of diastereomerically pure *N*-benzylazetidine-2-carboxylic acid ester-derived ammonium salt **105** with potassium *tert*-butoxide, a S–H rearrangement occurred exclusively to afford **106** as the sole product, even at 0 °C, without an EWG on the aromatic ring (Scheme 33).



Scheme 32. Ring-substitution of pipecolinic acid ester-derived ammonium salt

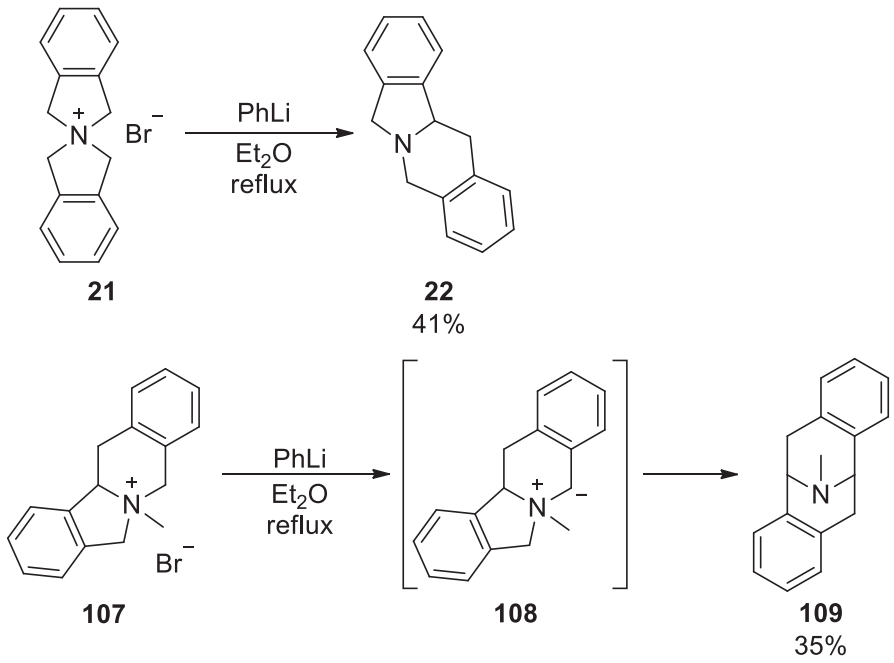


Scheme 33. Ring-substitution of azetidinic acid derivative by a base-induced S–H rearrangement

3. RING-ENLARGEMENT

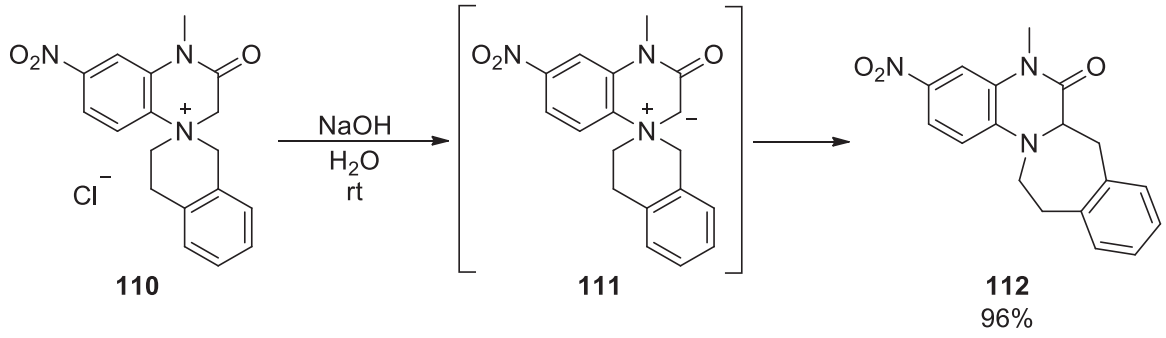
3-1. [1,2] Stevens rearrangement

The first example of ring-enlargement of *N*-heterocycles by base-induced [1,2] Stevens rearrangement was reported by Wittig et al. in 1951 (Scheme 34).[14] As already mentioned in Scheme 5, when *N*-spiro ammonium salt **21** was treated with phenyllithium in diethyl ether, a 5-to-6 ring-enlargement by a [1,2] shift gave [5,6]-fused *N*-heterocycle **22** in 41% yield. Similarly, polycyclic ammonium salt **107** rearranged into dibenzo-9-azabicyclo[3.3.1]nonane derivative **109** in 35% yield via the formation of the internal ylide **108**.



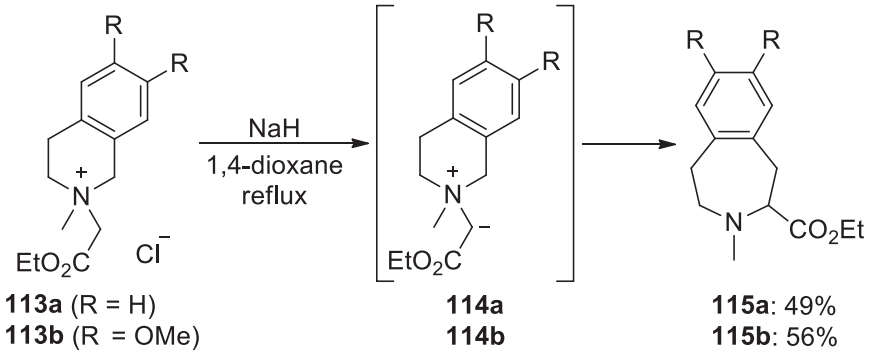
Scheme 34. Ring-enlargement of *N*-heterocycles by a base-induced [1,2] Stevens rearrangement

Chicharro et al. examined the ring-enlarged rearrangement of *N*-spiro ammonium salt **110** via the formation of the stabilized ammonium ylide **111** to afford a 6-to-7 ring-enlarged polycyclic quinoxaline-2-one **112** in 96% yield (Scheme 35).[41]



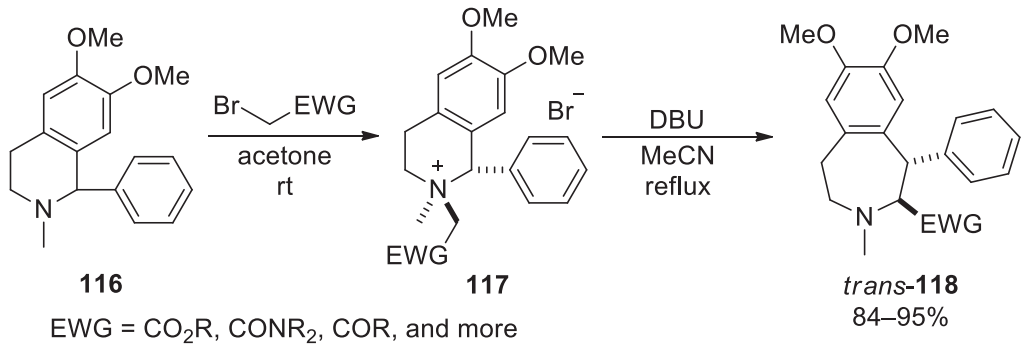
Scheme 35. 6-to-7 Ring-enlarged [1,2] Stevens rearrangement of a stabilized internal ylide

Ring-enlargement via the formation of an external ylide **114** were reported by Gimranova et al. (Scheme 36).[42] Treatment of 1,2,3,4-tetrahydroisoquinolinium salts **113** with sodium hydride in boiling 1,4-dioxane gave benzo-fused azepane-2-carboxylic acid esters **115** in moderate yields.



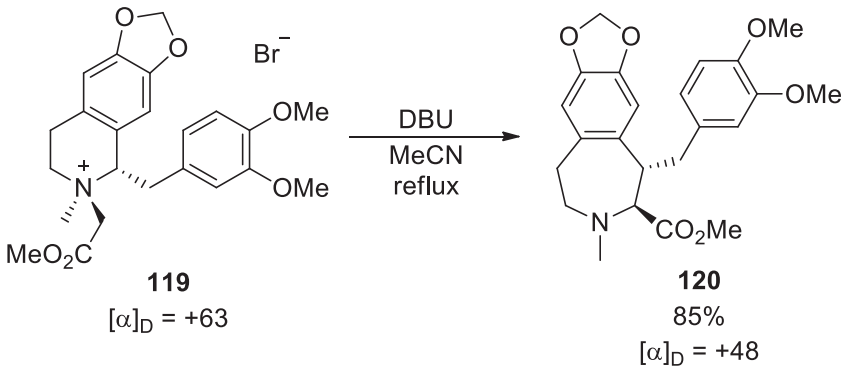
Scheme 36. 6-to-7 Ring-enlarged [1,2] Stevens rearrangement of external ylides

Valpuesta et al. applied this protocol to diastereoselective transformations (Scheme 37).[30] Diastereoselective quaternization of 1-phenylisoindonin derivative **116** controlled by the adjacent 1-phenyl substituent produced 1-phenyl-1,2,3,4-tetrahydroisoquinolinium salt **117** as a single stereoisomer. The rearrangement of **117** afforded ring-enlarged *trans*-**118** in good yields.



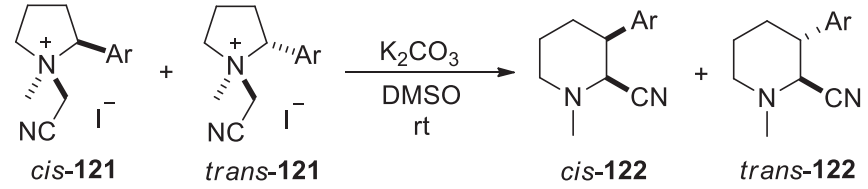
Scheme 37. Successive diastereoselective quaternization followed by a 6-to-7 ring-enlargement

Their group investigated the reaction using various types of 1-substituted-1,2,3,4-tetrahydroisoquinolinium salts to clarify its scope and limitations (Scheme 38).[43] As an example of an asymmetric reaction, an enantiomerically pure salt **119** prepared from chiral tertiary amine rearranged into optically active azepanyl derivative **120** in 85% yield. The enantiopurity of the ring-enlarged product **120** was not determined.



Scheme 38. Asymmetric 6-to-7 ring-enlargement

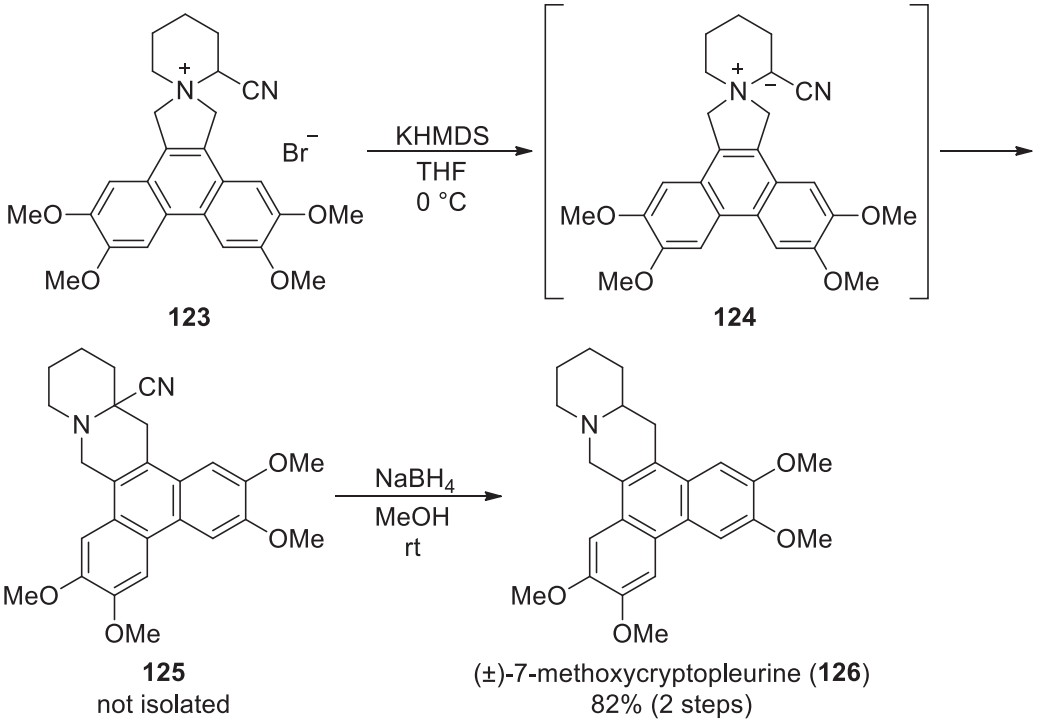
Kowalkowska and Jończyk examined a similar transformation using five-membered *N*-heterocyclic ammonium salts (Scheme 39).[44] A *cis*/*trans* mixture of *N*-cyanomethyl-2-arylpyrrolidinium salts **121** were transferred into the 5-to-6 ring-enlarged piperidinyl derivatives **122** as a mixture of *cis*/*trans* diastereomers.



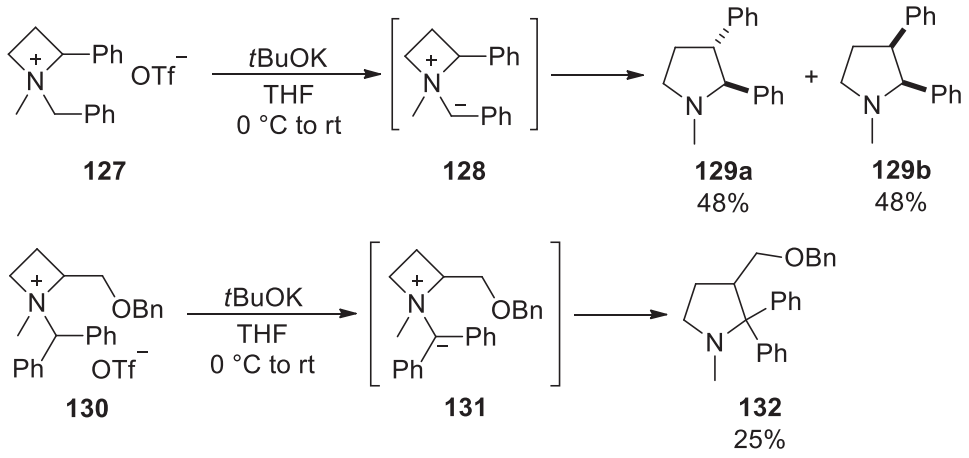
Scheme 39. 5-to-6 Ring-enlarged [1,2] Stevens rearrangement of 2-arylpyrrolidinium salts

The synthesis of polycyclic alkaloids via ring-enlarged [1,2] Stevens rearrangements were demonstrated by Pacheco et al. (Scheme 40).[27] The rearrangement of *N*-spiro-α-cyanopiperidinium salt **123** via the formation of nitrile ylide **124** gave the 5-to-6 ring-enlarged **125**. One-pot reductive elimination of the nitrile substituent, as in **125**, afforded (±)-7-methoxycryptopleurine (**126**).

Couty's group examined the ring-enlargement of four-membered *N*-heterocyclic ammonium ylides. Deprotonation of the sterically less hindered benzylic methylene proton, as in salt **127**, to generate the external ylide **128** followed by a [1,2] shift afforded the 4-to-5 ring-enlarged 2,3-diphenylpyrrolidines **129a** and **129b** in 48% yields (Scheme 41).[26] Similarly, deprotonation of a diphenylmethine proton, as in salt **130**, to generate ylide **131** followed by a [1,2] shift gave the ring-enlarged **132** in 25% yield. The ring-enlarged base-induced [1,2] Stevens rearrangement occurs not only for the benzylic migrating group but also the alkyl migrating group.



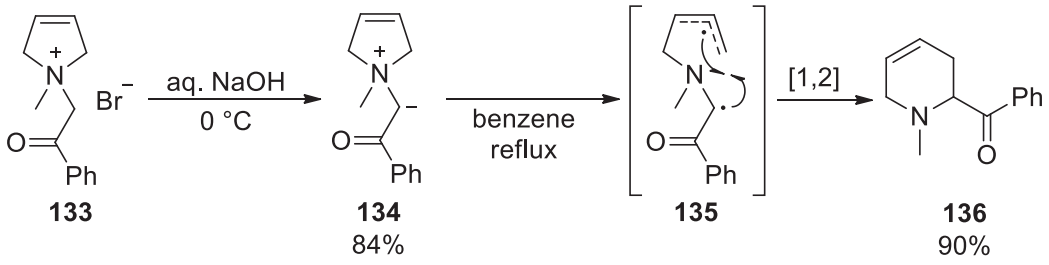
Scheme 40. Synthesis of (±)-7-methoxycryptopleurine (**126**)



Scheme 41. 4-to-5 Ring-enlarged [1,2] Stevens rearrangement of azetidinic ammonium salts

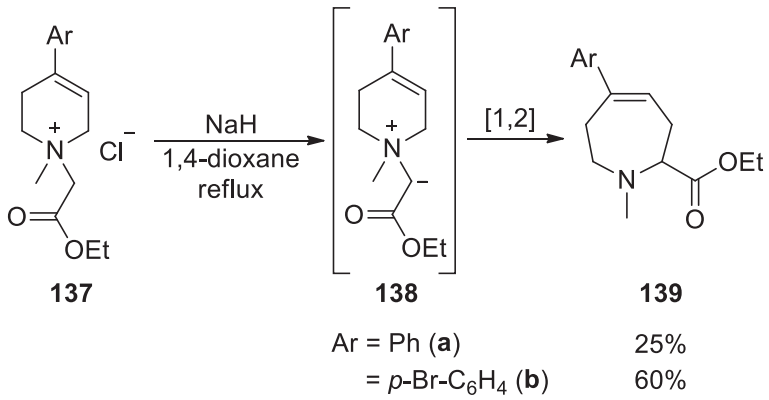
An allylic migrating group also undergoes a ring-enlarged [1,2] Stevens rearrangement depending on the structure of the ammonium ylides or the electronic effect of the substituents. 2,5-Dihydro-1*H*-pyrrolidinium ylide **134**, which has an internal *N*-allylic migrating group, was generated from the salt **133** (Scheme 42).[13] The C–N bond cleavage of **134** to form the biradical intermediate **135** followed by recombination between the α-carbonyl radical and the allylic radical afforded the 5-to-6 ring-enlarged **136**. The [2,3] rearrangement from **134** between the external ylide anion and the internal

N-allylic double bond (ring-contraction) did not proceed because of strain in the four-membered heterocycle.



Scheme 42. 5-to-6 Ring-enlarged [1,2] Stevens rearrangement involving an internal *N*-allylic group

Soldatova et al. reported similar ring-enlarged [1,2] Stevens rearrangements involving an internal *N*-allylic migrating group (Scheme 43).[45] A reaction of 4-aryl-1,2,3,6-tetrahydropyridinium salt **137** proceeded via the formation of ylide **138** followed by a [1,2] shift to give 6-to-7 ring-enlarged **139**. In this reaction, the [2,3] rearrangement toward the internal double bond was accompanied. An electron-deficient aryl group attached at the 4-position preferred the ring-enlarged [1,2] Stevens rearrangement. The details are described in section 4 (Table 3).

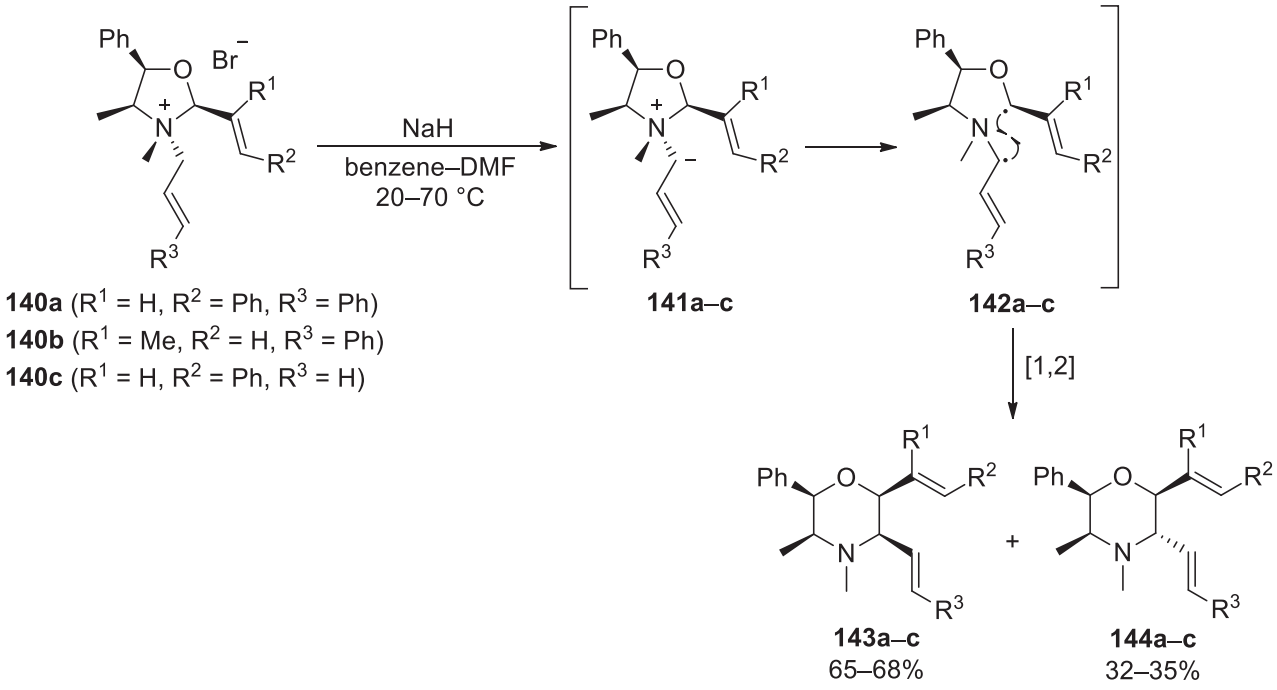


Scheme 43. 6-to-7 Ring-enlarged [1,2] Stevens rearrangement involving an internal *N*-allylic group

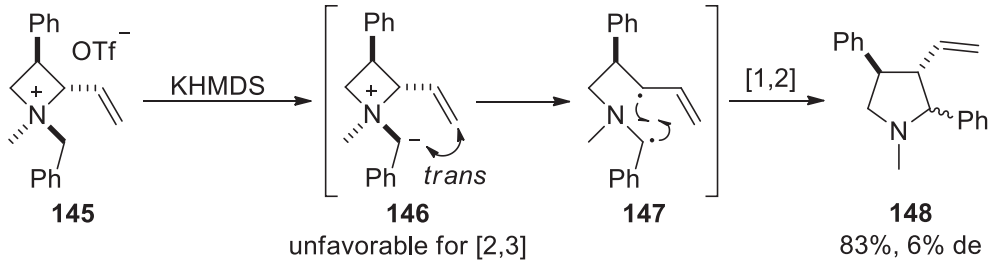
Rearrangement of 1,3-oxazolidinium salts **140** via forming external ylides **141** was followed by the biradical intermediate **142**, which afforded 5-to-6 ring-enlarged **143** and **144** through [1,2] shifts with chirality retained at the 2-position carbon migrating center, as in **140** (Scheme 44).[46] The corresponding [2,3] rearrangement products derived through C–C bond formation between the ylide anion and external double bond, as in **141**, were not obtained.

Couty's group reported a similar result with a sufficient explanation using azetidinium salt as the

substrate (Scheme 45).[47] When a diastereomerically pure *N*-benzyl-2-vinylazetidinium salt **145** was treated with KHMDS, the 4-to-5 ring-enlarged [1,2] rearrangement product **148** was obtained in 83% yield via the formation of the biradical intermediate **147**. The [2,3] rearrangement between the external ylide anion and the external *N*-allylic double bond, as in **146**, did not proceed because the two reacting centers adopt a *trans*-relationship and did not overlap for the [2,3] rearrangement.



Scheme 44. 5-to-6 ring-enlarged [1,2] Stevens rearrangement involving an external double bond



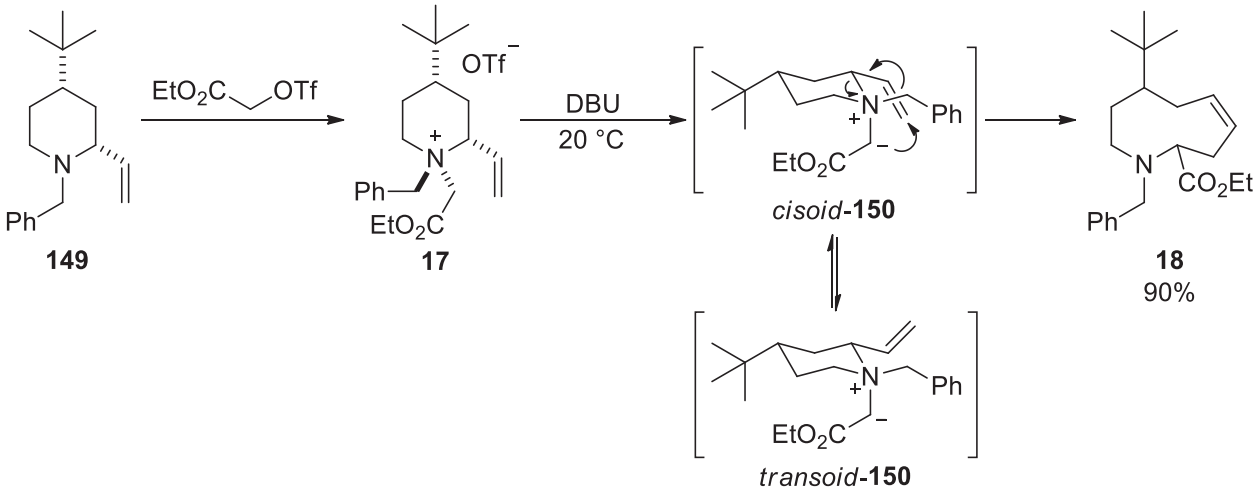
Scheme 45. 4-to-5 Ring-enlarged [1,2] Stevens rearrangement involving an external *N*-allylic group

3-2. [2,3] Sigmatropic (Stevens) rearrangement

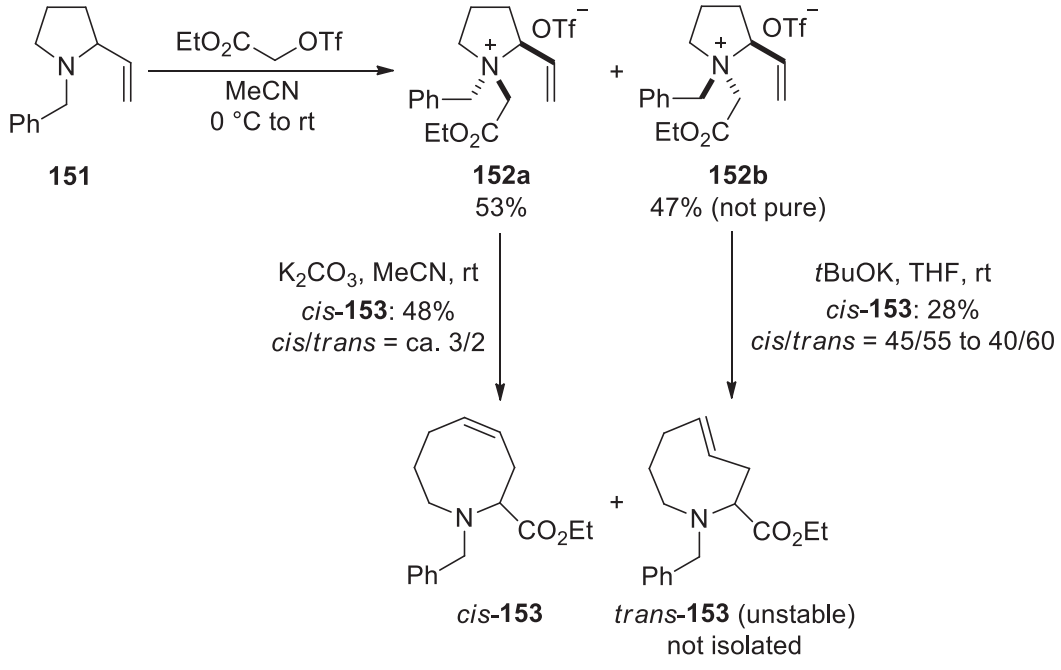
The ring-enlarged [2,3] rearrangement of *N*-heterocyclic ammonium ylides has been achieved by a C–C bond formation between an external ammonium ylide anion and an external allylic double bond, which enables the reaction of *N*-heterocycles with three carbons. Earlier studies on this transformation were investigated by Vedejs et al. in 1978 (Scheme 46).[12] Diastereoselective quaternization of

2-vinylpiperidine **149** followed by deprotonation of piperidinium salt **17** generated ylide **150**. The *cisoid* ylide **150** underwent a 6-to-9 ring-enlarged [2,3] rearrangement to produce the nine-membered *N*-heterocycle **18** in 90% yield as a single isomer.

Their group also examined a similar reaction of five-membered *N*-heterocyclic ammonium salts prepared from tertiary amine **151** (Scheme 47).[48] The rearrangement of 2-vinylpyrrolidinium salts **152a** or **152b** yielded the 5-to-8 ring-enlarged *cis*-**153** as the only isolatable product (48% yield from **152a**, 28% from **152b**). As an unstable product, *trans*-**153** was observed by ^{1}H NMR analysis of the crude product.

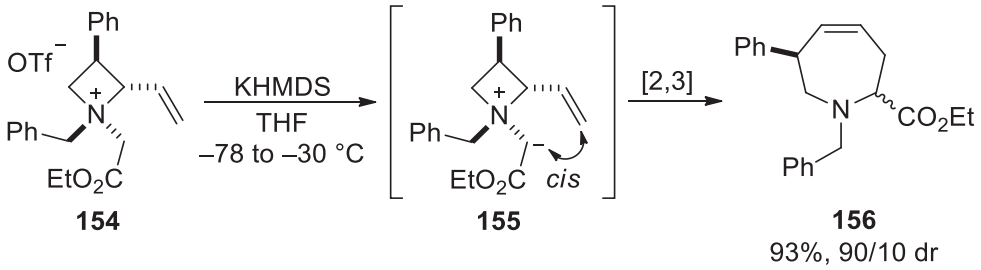


Scheme 46. 6-to-9 Ring-enlargement of *N*-heterocycle by a base-induced [2,3] rearrangement



Scheme 47. 5-to-8 Ring-enlarged base-induced [2,3] rearrangement

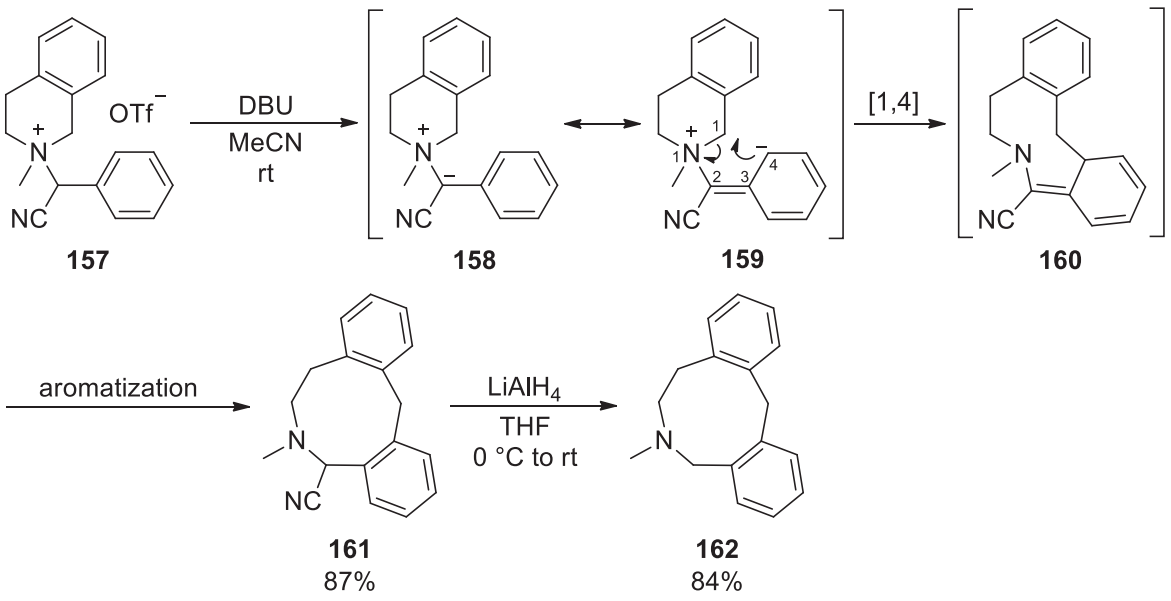
Couty's group reported a 4-to-7 ring-enlargement (Scheme 48).[49] Deprotonation of diastereomerically pure 2-vinylazetidinium salt **154** followed by a [2,3] rearrangement of the ylide **155** produced azepanyl derivative **156** in 93% yield. A *cis*-relationship between the external ylide anion and the external alkenyl substituent, as in **155**, is favored for this transformation because the two reacting centers can overlap for the [2,3] rearrangement.



Scheme 48. 4-to-7 Ring-enlarged [2,3] rearrangement of azetidinic ammonium salt

3-3. [1,4] Sigmatropic rearrangement

In the ammonium ylide rearrangement, a [1,4] rearrangement is one possible pathway; however, previous examples and synthetic applications have been limited. Recently, Pacheco and Opatz successfully demonstrated the first example of a 6-to-9 ring-enlarged base-induced [1,4] rearrangement of *N*-cyano(phenyl)methyl isoquinolinium salt **157** into dibenzo[*c*,*f*]azonine **161** (Scheme 49).[50,51]

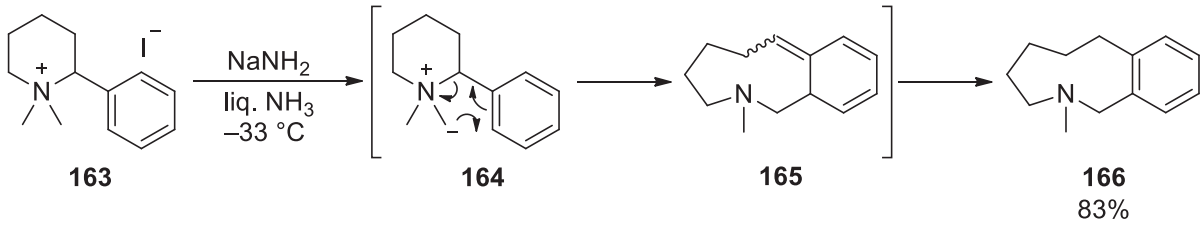


Scheme 49. Ring-enlargement of an *N*-heterocycle by a base-induced [1,4] sigmatropic rearrangement

They proposed that the reaction proceeds as follows: (i) ammonium ylide **158** formation, (ii) isomerization to the zwitterionic intermediate **159**, (iii) ring-enlarged concerted [1,4] rearrangement into the dearomatized **160** involving a six-electron aromatic transition state with suprafacial–suprafacial characteristics,[52] and (iv) aromatization to **161**. Finally, hydride reduction of the product **161** yielded decyanated dibenzo[*c*,*f*]azonine **162**. The [1,2] Stevens rearrangement from **158** did not proceed because of strong stabilization by an electron-withdrawing cyano group. In addition, the substituent would aid in forming dearomatized **159**.

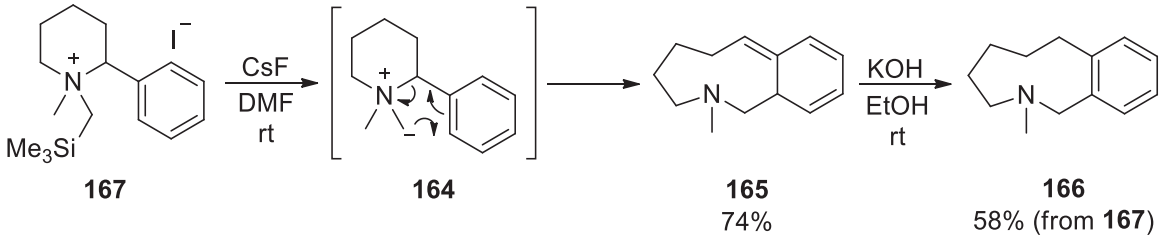
3-4. Sommelet–Hauser rearrangement

The first example of a ring-enlarged S–H rearrangement was reported by Lednicer and Hauser in 1957 (Scheme 50).[53] Treatment of 2-phenylpiperidinium salt **163** with sodium amide in liquid ammonia gave a nine-membered *N*-heterocycle **166** via the formation of unstabilized ammonium ylide **164** followed by dearomatized **165**. However, further studies on this transformation have not been advanced because of the difficulty of regioselective deprotonation to generate the unstabilized ammonium ylide.[8]



Scheme 50. Ring-enlargement of an *N*-heterocycle by a base-induced S–H rearrangement

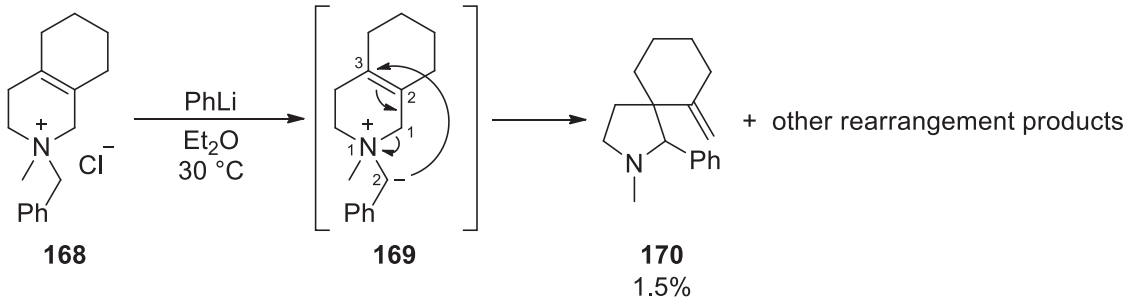
Although not a base-induced rearrangement, the author would like to introduce a closely related work reported by Sato and Shirai's group. In 1979, Vedejs et al. developed the fluoride-induced regioselective formation of an ammonium ylide from *N*-silylmethylammonium salts.[15] This method enables the formation of the desired ammonium ylide at the silylated carbon without base. Nakano and Sato focused on this method and developed the fluoride-induced S–H rearrangement[54] and reported ring-enlargement of *N*-heterocycles (Scheme 51).[55] For example, treatment of 2-phenyl-*N*-silylmethylpiperidinium salt **167** with cesium fluoride in DMF generated ylide **164**. Subsequent S–H rearrangement afforded the dearomatized **165** in 74% yield. Aromatization to benzo-fused **166** proceeded by treatment with potassium hydroxide in ethanol. Their further investigation on this fluoride-induced S–H rearrangement produced various types of benzo-fused *N*-heterocycles.[56]



Scheme 51. Ring-enlargement of an *N*-heterocycle by a fluoride-induced S–H rearrangement

4. RING-CONTRACTION

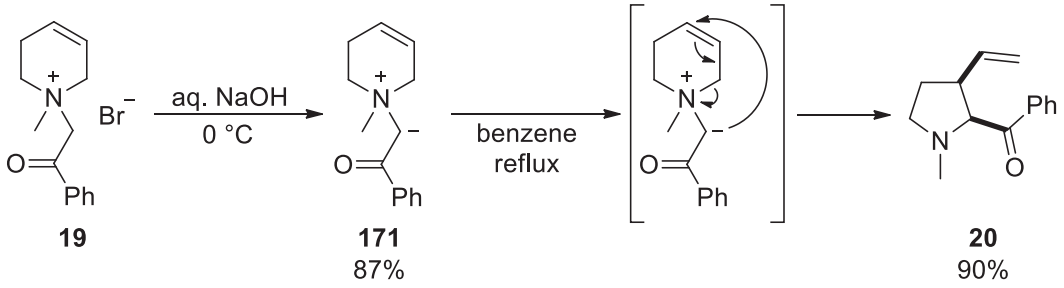
The ring-contractive rearrangement of *N*-heterocyclic ammonium ylides have been achieved by a C–C bond formation between an external ylide anion and an internal allylic migrating group. To the best of my knowledge, the first observation of a ring-contraction by base-induced rearrangements of ammonium salts was reported by Maeda and Ohsugi in 1968 (Scheme 52).[57] A reaction of *N*-benzyl-1,2,3,6-tetrahydropyridinium salt **168** with phenyllithium in diethyl ether generated ylide **169** and that produced various rearrangement products. As a minor product, the 6-to-5 ring-contracted spiro-pyrrolidine **170** derived by a [2,3] rearrangement was isolated in 1.5% yield.



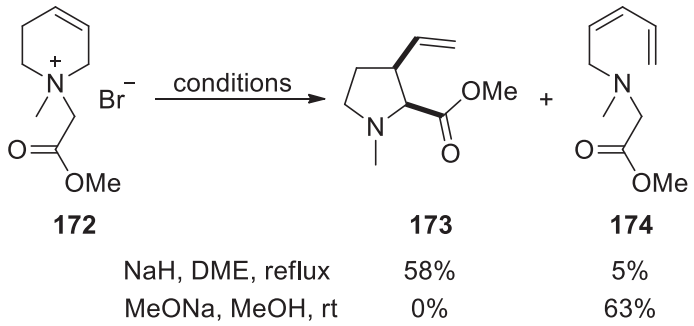
Scheme 52. The first observation of a ring-contractive ammonium ylide rearrangement

In 1973, Ollis's group demonstrated a successful example of a 6-to-5 ring-contraction from *N*-benzoylmethyl tetrahydropyridinium ylide **171** prepared from salt **19** (Scheme 53).[13] The 2,3-disubstituted pyrrolidinyl derivative **20** was obtained in 90% yield via a [2,3] rearrangement.

Sweeney's group applied this method to the synthesis of 3-substituted proline ester **173** from salt **172** (Scheme 54).[58] The use of sodium hydride in DME minimized the potential for a competing Hofmann elimination to lead to diene **174**. The same reaction was performed in sodium methoxide in methanol, and the formation of the undesiread **174** product proceeded exclusively. Later, their group attempted an asymmetric version of this rearrangement using chiral auxiliaries, as in the *N*-alkoxycarbonylmethyl substituent; however, the reaction resulted in almost no stereocontrol.[59]

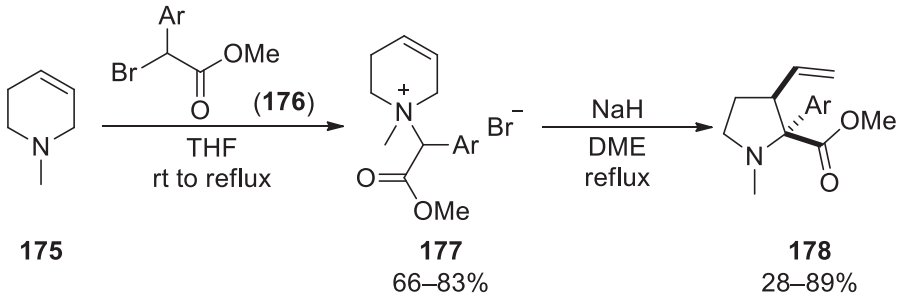


Scheme 53. 6-to-5 Ring-contraction of an *N*-heterocycle by a [2,3] rearrangement



Scheme 54. Effects of base and solvent in a 6-to-5 ring-contractive [2,3] rearrangement

Notably, α-arylproline ester derivatives **178** could be prepared by this protocol (Scheme 55).[60] Quaternization of *N*-methyl-1,2,3,6-tetrahydropyridine **175** with α-bromoacetate **176** followed by a ring-contractive base-induced [2,3] rearrangement of the resulting salts **177** produced 2-aryl-3-vinylproline esters **178** as the main product.



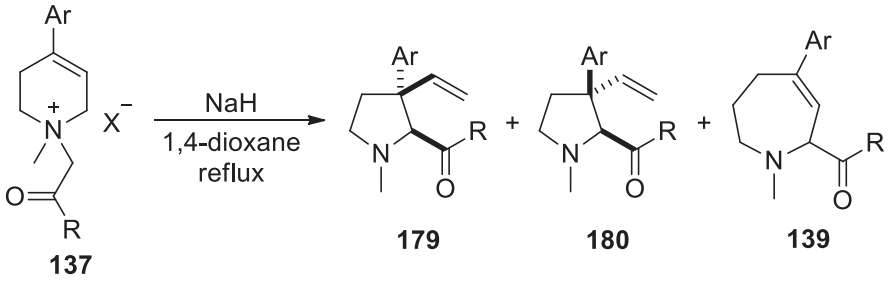
Ar = Ph, 1-Naphthyl, 4-MeO-C_6H_4, 4-NO_2-C_6H_4, 4-Cl-C_6H_4, 3-Cl-C_6H_4, 4-F-C_6H_4, 3-F-C_6H_4

Scheme 55. Synthesis of 2-aryl-3-vinylproline esters by a 6-to-5 ring-contraction

Soldatova et al. studied the substituent effect in ring-contractive [2,3] rearrangements. A reaction of 4-arylpiperidinium salts **137** afforded the ring-contracted **179** and **180** or the ring-enlarged **139** (Table 3).[45] As already mentioned in section 3-1 (Scheme 43), when an electron-deficient aryl group such as

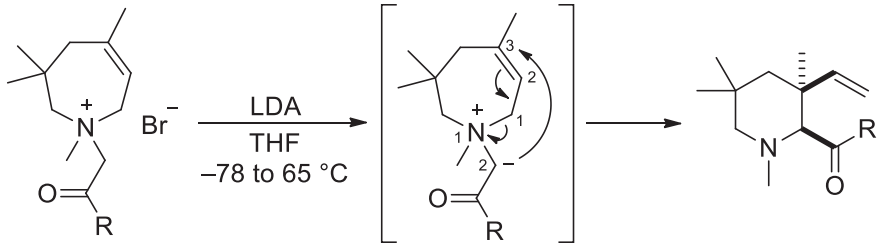
p-bromophenyl was attached at the 4-position (**137b**), a cooperative ring-enlarged [1,2] Stevens rearrangement proceeded to afford **139**.

Table 3. Substituents effects for ring-enlargement and contraction reactions



R = OEt, Ar = Ph, X = Cl (**a**)	31%	8%	25%
R = OEt, Ar = *p*-Br-C_6H_4, X = Cl (**b**)	–	–	60%
R = OEt, Ar = *p*-tolyl, X = Cl (**c**)	58%	–	5%
R = Ph, Ar = Ph, X = Br (**d**)	18%	18%	–
R = Ph, Ar = *p*-tolyl, X = Br (**e**)	9%	6%	–

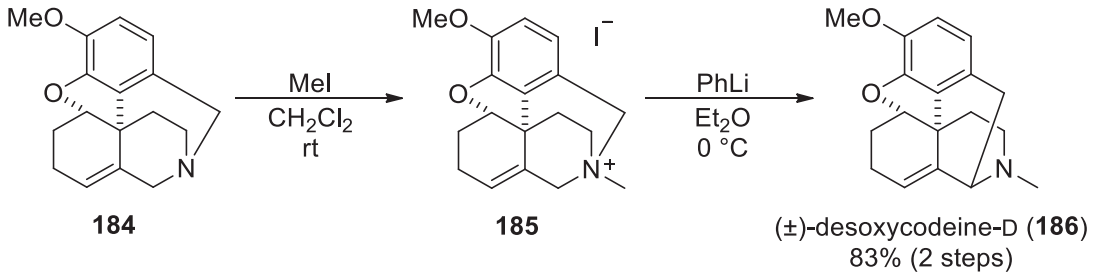
Additionally, Neeson and Stevenson demonstrated a 7-to-6 ring-contraction by a [2,3] rearrangement (Scheme 56).[61] Treatment of azepinium salt **181** with LDA to generate ylide **182** followed by a [2,3] Stevens rearrangement afforded substituted pipecolinic acid analogs **183**.



Scheme 56. 7-to-6 Ring-contraction of *N*-heterocycles by a [2,3] rearrangement

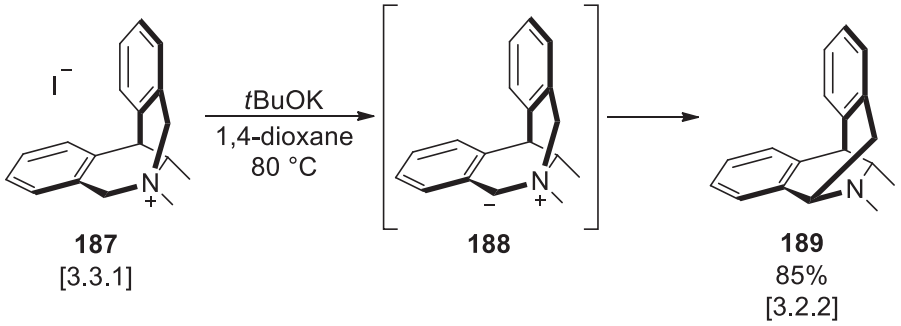
5. RING SYSTEM TRANSFORMATION OF BICYCLIC COMPOUNDS

Ammonium ylides derived from azabicyclic compounds enable the transformation of ring systems by simultaneous ring-enlargement/contraction. In 2000, Liou and Cheng applied this protocol to the total synthesis of (±)-desoxycodeine-D (**186**) (Scheme 57).[62] Quaternization of tertiary amine **184** followed by a base-induced [1,2] Stevens rearrangement of azabicyclo ammonium salt **185** provided the desired **186** in 83% yield.



Scheme 57. Total synthesis of (±)-desoxycodeine-D (**186**)

In addition, Hanessian et al. reported a similar transformation in 2001. A reaction of 1-azabicyclo[3.3.1]nonanium salt **187** proceeded via the formation of ylide **188** to afford 2-azabicyclo[3.2.2]nonane derivative **189** in 85% yield (Scheme 58).[63]



Scheme 58. Ring system transformation of a bicyclic compound by a [1,2] Stevens rearrangement

6. CONCLUSION

The present review has focused on base-induced rearrangements of ammonium salts for the synthesis of *N*-heterocycles reported after 1970. The representative Stevens, Sommelet–Hauser, related sigmatropic rearrangements composed by ring-substitution, ring-enlargement, and ring-contraction are unique and powerful synthetic tools for the synthesis of various types of *N*-heterocycles. By judicious design of the substrate structure, highly substituted *N*-heterocycles have been produced and used as key building blocks for the synthesis of biologically active compounds such as alkaloids. The increasing interest of these rearrangements will advance this area of research and enable the development of new synthetic methods. In 2014, Smith's group reported an asymmetric ammonium ylide rearrangement using a chiral isothiourea as the Lewis base catalyst. This is the first example of a catalytic asymmetric base-induced rearrangement of acyclic ammonium salts.[64] This method may be applicable to the synthesis of optically active *N*-heterocycles. Furthermore, studies on ammonium ylide rearrangements may expand the synthetic scope and utility of analogous sigmatropic rearrangements such as aza-Wittig

rearrangements,[65,66] or Lewis acid-mediated rearrangements[67] of tertiary amines. New synthetic transformations into *N*-heterocycles by these rearrangements will be demonstrated in the future.

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