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The domino way to heterocycles

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Contents

1. Introduction

Molecules containing heterocyclic substructures continue to be attractive targets for synthesis since they often exhibit diverse and important biological properties.[1] Accordingly, novel strategies for the stereoselective synthesis of heteropolycyclic ring systems continue to receive considerable attention in the field of synthetic organic chemistry.[2–8] The

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efficiency with which heterocycles can be constructed is important not only because it affects the production costs for the desired material, but also the environmental impact associated with waste disposal, conservation of source materials like petroleum stocks, and energy consumption. The rate of increase in molecular intricacy as one progresses from simple starting materials to the final product can serve as a measure of efficiency.[9] On one end of the continuum, a single synthetic step could convert an inexpensive material into a highly complex heterocyclic product. On the other end lies a linear series of transformations, wherein a single atom or group is added in each step to build complexity. As a prerequisite for an ideally proceeding one-pot sequential transformation, the reactivity pattern of all participating components has to be such that each building block gets involved in a reaction only when it is supposed to do so. The reality of chemical synthesis is somewhere between these extremes, with the one-step process held as the ideal.

Domino reactions (reactions in which several bonds are formed in one sequence without the isolation of intermediates, the changing of reaction conditions, or the addition of reagents),[10] multi-component reactions, and the so-called 'telescoping' of reactions (the sequencing of multiple transformations in a single reaction vessel through the changing of conditions and/or adding of reagents at appropriate times) allow for a rapid increase in molecular complexity in a single chemical operation. The terms '*tandem*' and '*cascade*' have been applied to all three of these reaction types and are thus used as general descriptors in this work.[11–16] Because of the rate at which they increase molecular intricacy, cascade reactions have received considerable attention from the synthetic organic community. The development of sequences that combine transformations of differing fundamental mechanism broadens the scope of such procedures in synthetic chemistry.

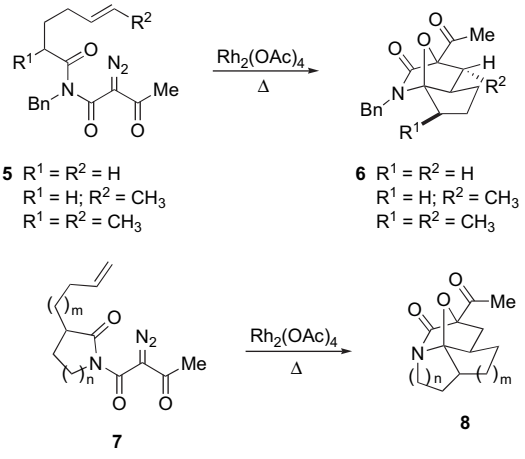
This review contains a representative sampling from the last 15 years of the kinds of reactions that have been sequenced into cascades to produce heterocyclic molecules. The fact that multiple reactions give rise to a cascade sequence makes the categorization of these processes difficult. The structure we have imposed, therefore, is somewhat arbitrary but is loosely based upon what, in our judgment, is the key reaction in the cascade sequence. This mini review is not intended to be a critical or comprehensive coverage, but rather provides an overview of the field and thus some cascade processes are covered in more detail than others.

2. [4π+2π]-Cycloadditions

2.1. [1,3]-Dipolar cycloadditions

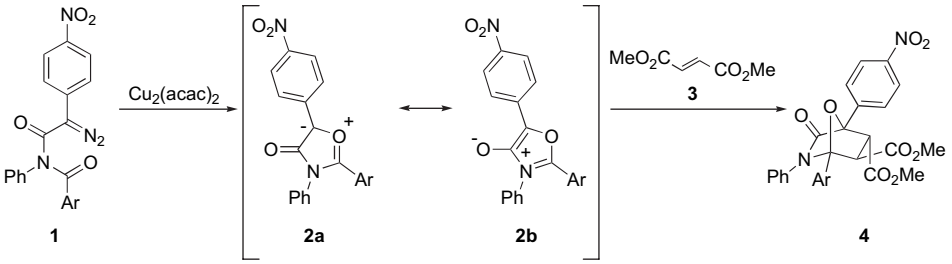
2.1.1. Metallo-carbenoid initiated cascades. Many different examples of cascade processes that employ 1,3-dipoles as reactive intermediates have been described in the literature. The transition metal-catalyzed decomposition of diazoimides results in the formation of isomünchnone dipoles, a class of mesoionic betaines[17] that are known to undergo 1,3-dipolar cycloaddition chemistry. Ibata and Hamaguchi were the first to report that diazoimide **1** formed isomünchnone **2** upon heating in the presence of $Cu_2(acac)_2$,[18] and that this reactive dipole could be trapped with various dipolarophiles such as **3** to give the oxabicyclic product **4** (Scheme 1).[19]

Rhodium(II) catalysts initiate a similar reaction.[20] By including the dipolarophile moiety within the diazoimide, complex polycyclic compounds can be formed in a single step.[21] Thus, heating compounds such as **5** with catalytic $Rh_2(OAc)_4$ produced cycloadduct **6** as a single diastereomer in 73–91% yield (Scheme 2). Over a period of years, Padwa and coworkers demonstrated that this cascade sequence is quite general. Diazoimides with the general structure **7** (n=1, 2, 3; m=1, 2) were readily converted into the corresponding polycyclic system **8**.[22]

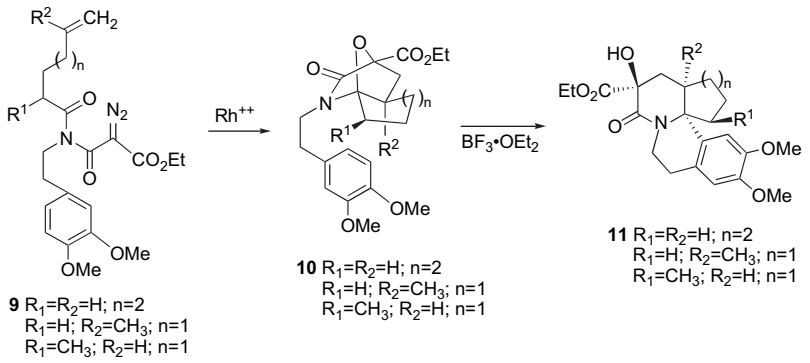


Scheme 2.

Compounds of type **6** and **8** contain an *N*,*O*-acetal functional group and have been used as precursors to *N*-acyliminium ions. This method was exploited for the synthesis of B-ring homologs of the erythrinane family of alkaloids.[23] In these studies, diazoimides of type **9** were exposed to



Scheme 1.



Scheme 3.

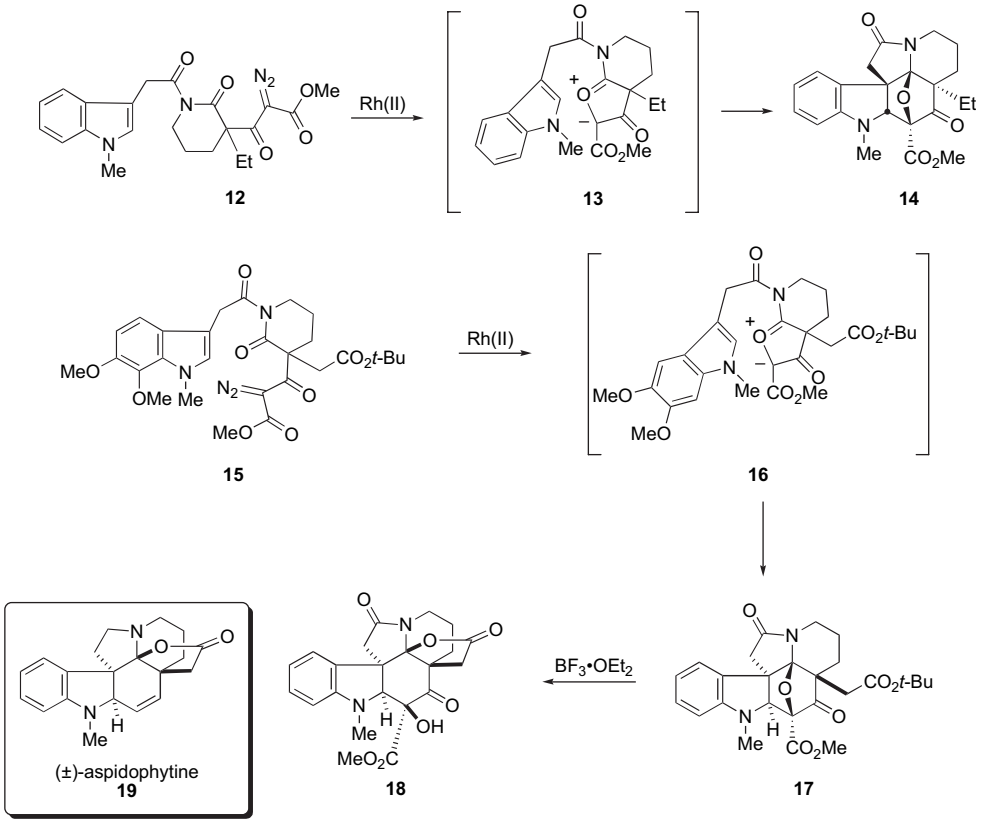
catalytic amounts of rhodium(II) and oxabicycles **10** are formed in 90–98% yield (Scheme 3). Treating **10** with $BF_3 \cdot OEt_2$ provided the ring-opened products **11** in 85–95% yield as single diastereomers.

Isomünchnone dipoles generated by the cyclization of rhodium carbenoid intermediates with adjacent amido groups undergo cycloaddition with both electron-rich and certain heteroaromatic π-bonds. For example, the catalytic decomposition of diazoimide **12** provided dipole **13**, which subsequently added across the indole π-bond to give a cycloadduct possessing the aspidosperma skeleton (Scheme 4).[24]

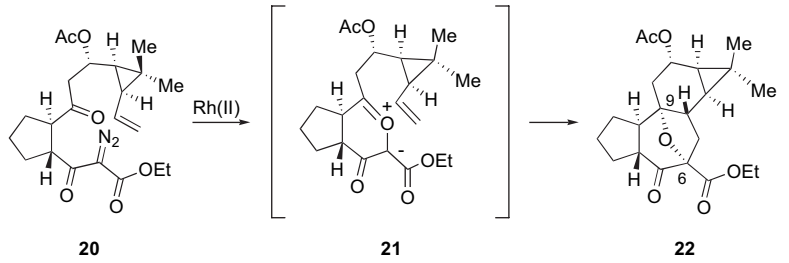
This sequence was recently used for the synthesis of the alkaloid (±)-aspidophytine (**19**). The key sequence of reactions began with the treatment of diazo ketoester **15** with $Rh_2(OAc)_4$ to generate a transient metallocarbene that reacted with the proximal imido carbonyl group to form dipole **16**.[25] A subsequent 1,3-dipolar cycloaddition across the tethered indole π-bond gave cycloadduct **17** in 97% yield. Oxabicycle **17** was then converted into **18** by the action of $BF_3 \cdot OEt_2$ in 70% yield and this compound was eventually converted into (±)-aspidophytine (**19**).

Dauben used a related cyclization/cycloaddition approach for the synthesis of tigliane **22**. Carbonyl ylide **21**, derived from the diazo ketoester **20**, underwent intramolecular cycloaddition to form **22**, a molecule which contains the C(6), C(9)-oxido bridge of the tigliane ring system (Scheme 5).[26]

2.1.2. Pummerer-initiated cascade. A Pummerer-initiated cascade reaction was also used as a method for generating isomünchnones for further use in cycloaddition chemistry. For example, treatment of sulfoxide **23** with acetic anhydride first

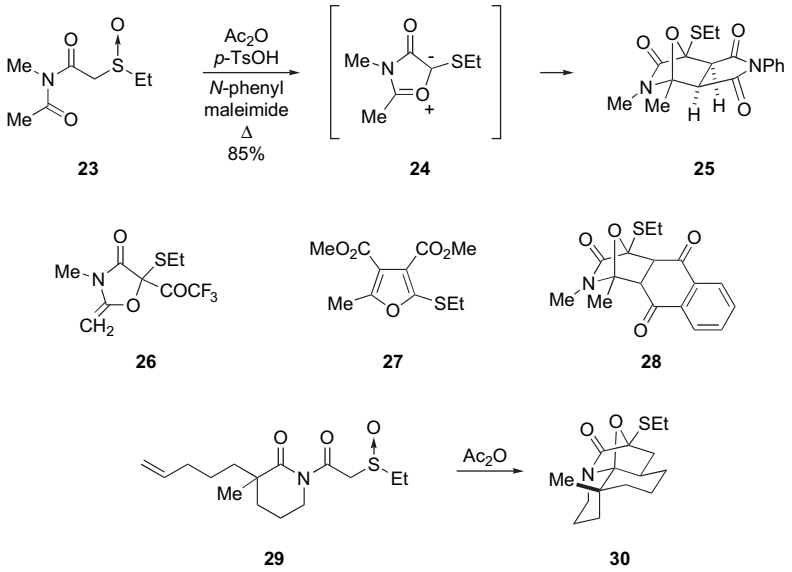


Scheme 4.



20 21 22

Scheme 5.



23 24 25 26 27 28 29 30

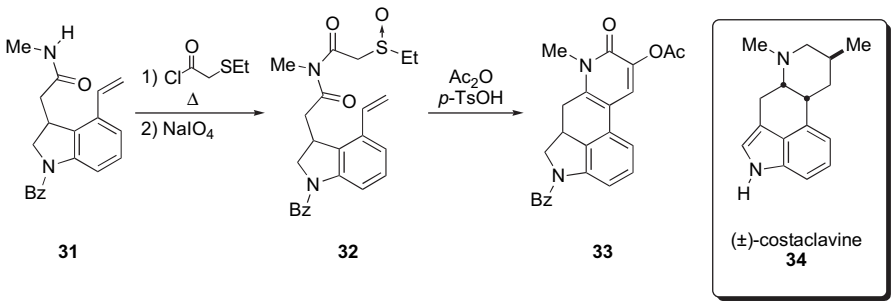
Scheme 6.

resulted in the formation of a reactive thionium ion that reacted with the distal amide carbonyl group to produce isomünchnone **24** (Scheme 6).[27] Further exposure of **24** to a dipolarophile, such as *N*-phenylmaleimide, resulted in 1,3-dipolar cycloaddition to give **25** as a single diastereomer in 85% yield.

The specific conditions required to successfully effect this transformation were important and warrant comment. The initial attempts to form the isomünchnone intermediate, employing TFAA to promote the cyclization and Et_3N to deprotonate the oxonium ion intermediate, failed to produce the isomünchnone dipole. Rather, cyclic ketene acetal **26** was obtained. After considerable experimentation, it was found that the slow addition of **23** to a mixture of acetic anhydride, a catalytic amount of *p*-TsOH, and the appropriate dipolarophile at 120 °C in toluene gave consistently good yields of the 1,3-cycloadduct. A variety of dipolarophiles were found to participate in these cycloadditions. When **24** was allowed to react with DMAD, the initially formed oxabicycle underwent a rapid fragmentation reaction to produce furan **27** (41% yield) and methyl isocyanate. The reaction of isomünchnone **24** with 1,4-naphthoquinone afforded cycloadduct **28** in 73% yield. Other suitable dipolarophiles include vinyl sulfones, maleic anhydride, and acrylate derivatives. Unactivated olefins also participated in the cycloaddition reaction when they were tethered to the isomünchnone dipole. For example, when sulfoxide **29** was treated with acetic anhydride, azapolycycle **30** was isolated as a single diastereomer in 73% yield.

The synthesis of the ergot alkaloid (±)-costaclavine **34** demonstrates the utility of this methodology for the synthesis of natural products (Scheme 7).[28] Construction of the ergot skeleton began by acylation of the methyl amide functionality of **31** with (ethylsulfanyl)acetyl chloride and this was followed by a subsequent oxidation of the sulfide with $NaIO_4$ to provide sulfoxide **32**. A tandem Pummerer cyclization/cycloaddition cascade, initiated by exposing **32** to acetic anhydride and catalytic quantities of *p*-TsOH, gave tetracycle **33** in 64% yield. Several functional group interconversions of **33** then delivered (±)-costaclavine **34**. The synthesis of several other alkaloids, including onychine, dielsiquinone, (±)-lupinine, and pumiliotoxin C, was also accomplished using this methodology.[28]

2.1.3. Nitrones. The intramolecular 1,3-dipolar cycloaddition of nitrones is a well precedented reaction for the formation of cyclic isoxazolidines. An interesting method that has been used for the generation of N−H nitrones from readily available starting materials is through the 1,2-prototropic shift of oximes. Although it is unusual to observe cycloadditions using these N−H nitrones, a few examples have been reported. For example, while studying the synthesis of a series of Amaryllidaceae alkaloids, Wildman observed that the reaction of 6-hydroxybuphanidrine (**35**) with hydroxylamine produced cycloadduct **38** in good yield (Scheme 8).[29] This reaction presumably occurs by formation of the intermediate oxime **36** that undergoes a subsequent 1,2-prototropic shift to give nitrone **37**. Cycloaddition of the nitrone



31 32 33 **34**

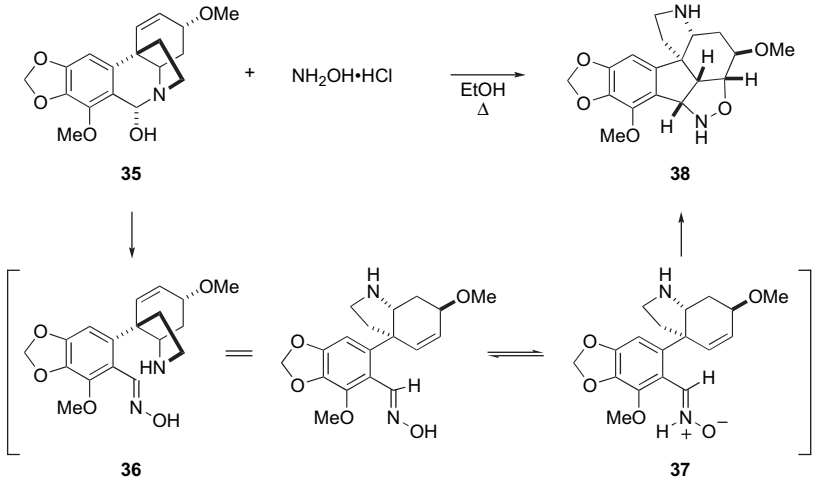
Scheme 7.

dipole across the adjacent alkene moiety furnished cycloadduct **38**.

Christy and co-workers observed a similar cyclization upon condensing ketone **39** with hydroxylamine in hot ethanol, which provided compound **41** (Scheme 9).[30] Oxime **40** was prepared under milder conditions and was found to undergo a 1,2-prototropic shift followed by intramolecular cycloaddition to provide **41** upon warming to 75 °C in toluene.

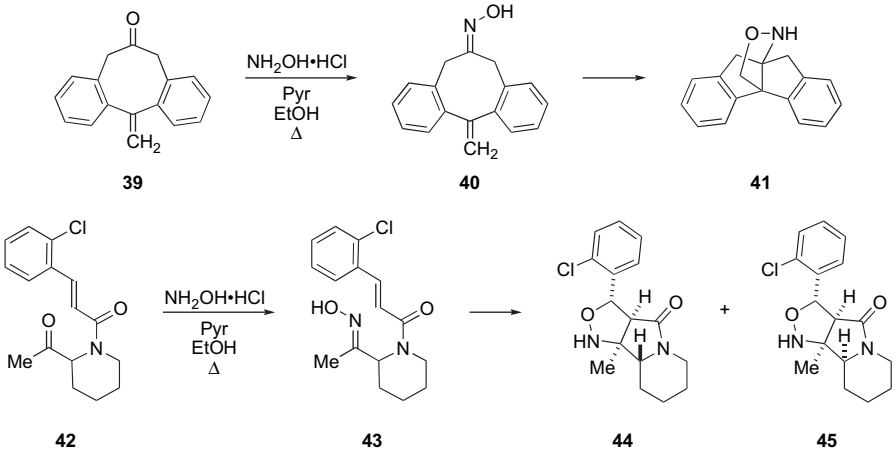
In a related study, Heathcock reported that ketone **42** reacted with hydroxylamine hydrochloride under similar conditions to produce **44**.[31] The intermediate oxime **43** that was first formed could be isolated under milder conditions. Whereas heating oxime **43** at reflux in acetonitrile for 30 h gave **44** in 92% yield, heating **43** in DMF solvent produced a 1:1 mixture of the diastereomeric cycloadducts **44** and **45**.

While exploring the chemistry of α-brominated aldoxime derivatives, Padwa and Hassner observed the cycloaddition of oximes that contained pendant olefins. For example, the reaction of **46** with fluoride ion in the presence of allyl alcohol produced oxime **47** (Scheme 10).[32] Heating a benzene



35 36 37 38

Scheme 8.

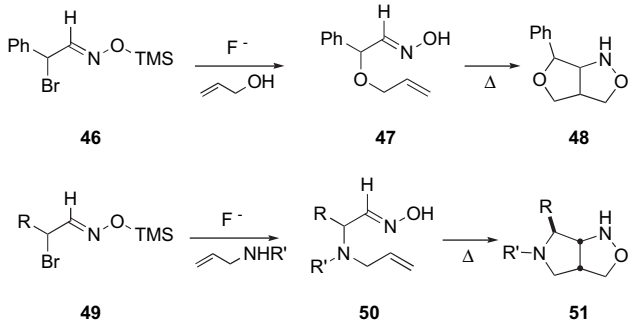


39 40 41

42 43 44 45

Scheme 9.

solution of **47** at 80 °C led to the formation of **48** as a single diastereomer, though only in 25% yield. The Hassner group later expanded the method to include the fluoride-mediated reaction of aldoxime **49** with various allyl amines to generate oximes **50** in 70–80% yield.[33] Heating toluene solutions of these oximes at reflux temperatures led to the formation of pyrrolidines **51**.

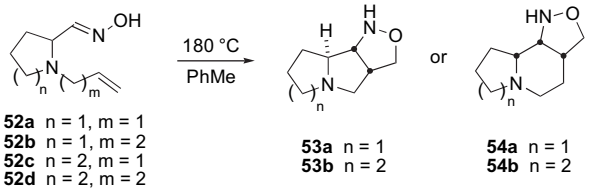


46 **47** **48**

49 **50** **51**

Scheme 10.

The cascade sequence was also used to synthesize indolizidine, pyrrolizidine, and quinolizidine structures. Thus, heating oximes **52** at 180 °C in a sealed tube provided cycloadducts **53** or **54** in 60–76% yields (Scheme 11).[34] Each of the products was isolated as single diastereomers. When five-membered rings were obtained from the cycloaddition, cis–*anti* isomers (i.e., **53a**,**b**) were formed, whereas formation of a six-membered ring led only to the cis–*syn* isomer (i.e., **54a**,**b**).



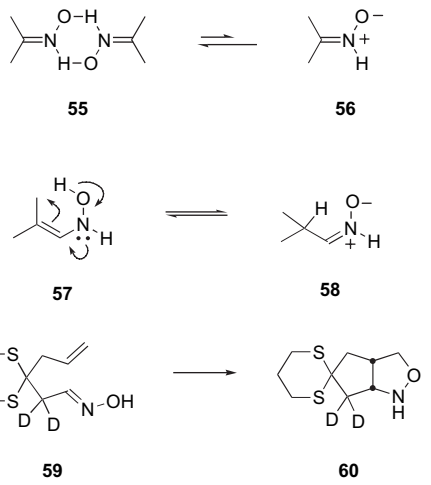
52a n = 1, m = 1
52b n = 1, m = 2
52c n = 2, m = 1
52d n = 2, m = 2

53a n = 1
53b n = 2

54a n = 1
54b n = 2

Scheme 11.

The Grigg group also studied the tautomerization of oximes to N−H nitrones followed by a dipolar cycloaddition reaction. The well-known H-bonding dimeric association of oximes, in both solution and the solid states, allows for a concerted proton switch to occur and provides nitrone **56** (Scheme 12).[35] Another possible pathway involves tautomerization of the oxime to an ene-hydroxylamine (i.e., **57**) followed by a 1,4-hydride shift to give nitrone **58**. To probe the ene-hydroxylamine mechanism, deuterated oxime **59** was prepared and heated at 140 °C in xylene. The physical characteristics of the isolated product, however, were consistent with compound **60**, suggesting that the 1,2-prototropic reaction does not proceed via the ene-hydroxylamine. Grigg postulated that while the tautomerization between an oxime and a N−H nitrone is facile, dipolar cycloadditions involving these types of nitrones are relatively rare because (a) unactivated or electron-rich dipolarophiles have too large HOMO/LUMO gap, although intramolecular cycloadditions to form five-membered rings can overcome this gap, and (b) electron-deficient dipolarophiles preferentially undergo Michael-type reactions with oximes.



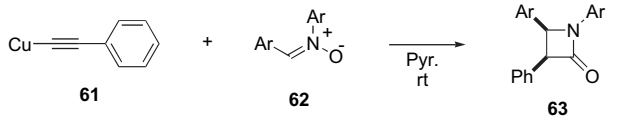
55 **56**

57 **58**

59 **60**

Scheme 12.

Another interesting cascade involving nitrones is the copper catalyzed reaction with alkynes to produce β-lactams that was originally reported by Kinugasa and Hashimoto.[36] Stoichiometric amounts of copper(I) phenylacetylide (**61**) react with various aryl nitrones **62** in pyridine solvent and gave β-lactams **63** in 50–60% yield (Scheme 13). In each case, only the *cis*-lactams were isolated.



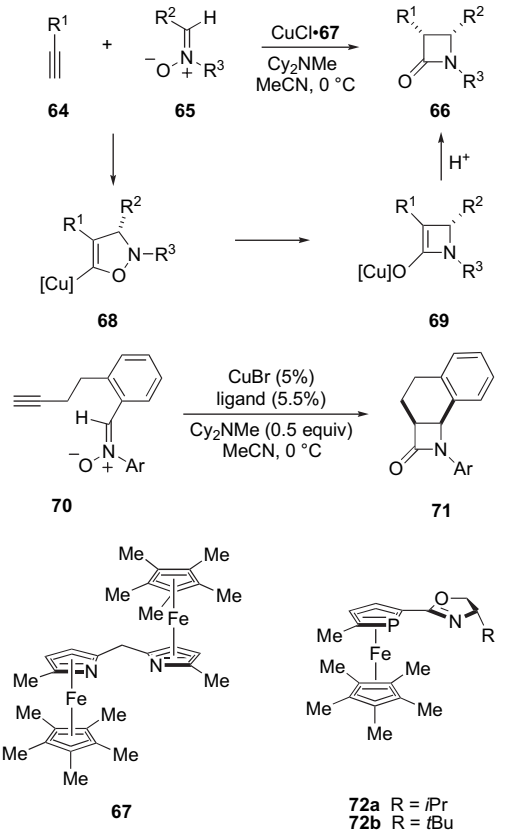
61 **62** **63**

Scheme 13.

Miura and co-workers showed that the reaction could also be carried out using catalytic amounts of CuI in the presence of pyridine.[37] Asymmetric reactions were reported to occur with chiral bisoxazoline ligands producing β-lactams with moderate (40–68%) enantiomeric excess. Use of an oxazolidinone with a chiral auxiliary attached to the alkyne did provide enantiomerically pure products.[38] In all of these latter reports, mixture of *cis*- and *trans*-lactam isomers was obtained in which the trans-product predominates. It was also shown that the cis isomer could easily be converted into the trans product when exposed to base.

The Fu group recently reported the use of *C*2-symmetric planar-chiral bis(azaferrocene) ligands for the catalytic enantioselective Kinugasa reaction. A variety of terminal alkynes **64** (R^1=Ar, Bn, 1-cyclohexenyl) were allowed to react with nitrones **65** (R^2=Ar, Cy, PhCO; R^3=Ar) in the presence of catalytic amounts of the CuCl·**67** complex to give diastereomeric mixture (>90:10) predominating in cis-substituted β-lactams **66** in moderate to good yields (45–90%) and with good enantiomeric excess (67–92%, Scheme 14).[39] With regard to the R^3 group on nitrone **65**, electron-rich

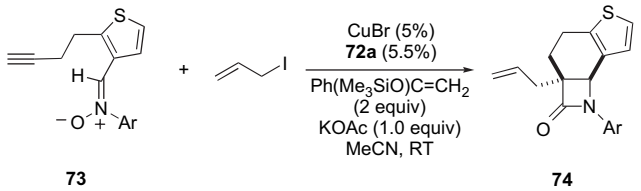
aromatic groups increased the enantioselectivity, though the yields were somewhat lower.



Scheme 14.

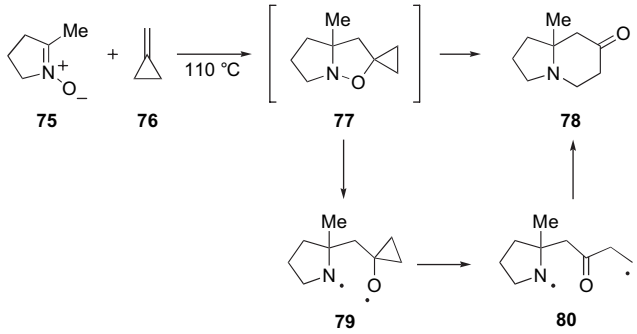
An intramolecular variant of this catalytic enantioselective process was recently reported. Nitrone **70** was converted into azetidinone **71** in the presence of the CuBr·**72a** complex in 74% yield and with 88% ee.[40] Ligand **72b** was also quite effective, providing **71** with 90% ee, though the yield was only 47%.

The mechanism for the Kinugasa reaction is thought to involve a [3+2]-cycloaddition of the nitrone with the copper-acetylide to give isoxazolidine **68**. Rearrangement of **68** then provides the copper enolate of the corresponding β-lactam (i.e., **69**), which is subsequently protonated to provide the observed product. The proton source for this last step is most likely the conjugate acid of the base used to generate the copper-acetylide. Through considerable experimentation, the Fu group developed conditions that allowed for the reaction of the enolate with added electrophiles. Thus, exposing **73** to CuBr·**72a** in the presence of KOAc, allyl iodide, and the silyl enol ether of acetophenone gave rise to β-lactam **74** in 70% yield and with 90% ee (Scheme 15).[27]



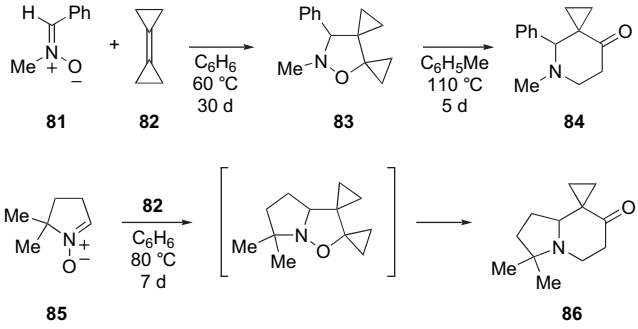
Scheme 15.

Brandi and co-workers developed an interesting tandem cycloaddition/thermal rearrangement cascade involving nitrones and methylenecyclopropane derivatives to produce 4-pyridones. For example, heating nitrone **75** with **76** at 110 °C for 7 days afforded pyridone **78** in 63% yield (Scheme 16).[41] The intermediate isoxazolidine **77** was suggested to undergo homolytic cleavage of the weak N−O bond to give diradical **79** that underwent fragmentation to provide diradical **80**.[42] Cyclization of **80** then gave rise to 4-pyridone **78**.



Scheme 16.

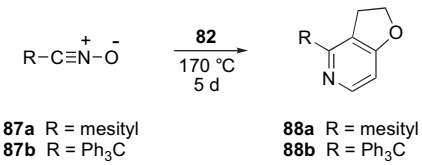
Nitrone **81** underwent a dipolar cycloaddition reaction with bicyclopropylidene (**82**) at 60 °C over a 30-day period to give isoxazolidine **83** in 93% yield (Scheme 17).[43] Further heating of **83** in toluene at reflux for 5 days produced pyridone **84** in 63% yield. When a toluene solution of **81** and **82** was heated at reflux for several days, pyridone **84** was isolated in 61% yield. Nitrone **85** produced indolizidine **86** when heated with **82** in benzene at reflux temperatures for 7 days.



Scheme 17.

2.1.4. Nitrile oxides. Brandi also examined the subsequent thermal behavior of the dipolar cycloadducts that arise from the reaction of nitrile oxides with methylenecyclopropanes. In general, the isoxazoline intermediates require much higher temperatures than their isoxazolidine counterparts for the rearrangement to occur, and the yields obtained from single pot cascades are somewhat low. In part, this is because some nitrile oxides rearrange to the corresponding isocyanates at elevated temperatures. Another complication is that the intermediate isoxazolines can act as dipolarophiles in [3+2]-cycloadditions with the starting nitrile oxides. For example, nitrile oxide **87a** undergoes the

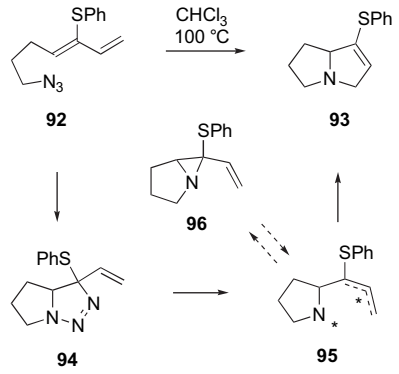
cycloaddition/rearrangement cascade with **82** at 170 °C over 5 days to provide dihydrofuropyridine **88a** in only 7% yield (Scheme 18).[30] Similarly, nitrile oxide **87b** reacted with **82** under the same conditions to give **88b** in 21% yield.



Scheme 18.

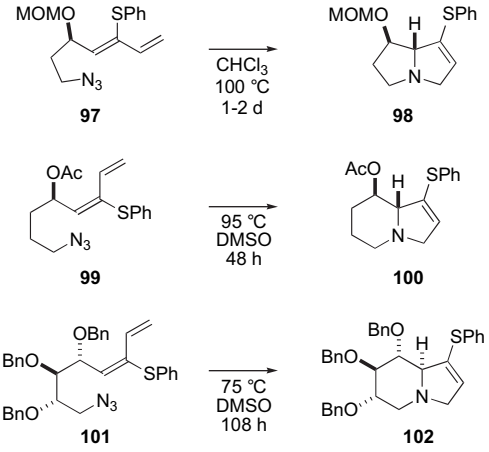
Other cascade sequences have also been observed to occur from the thermolysis of isoxazolines, thereby increasing the utility of the nitrile oxide cycloaddition reaction. For example, in the context of synthesizing testosterone derivatives, Guarna and co-workers reported that the reaction of a nitrile oxide derived from oxime **89** with **76** gave isoxazoline **90** (Scheme 19).[44] Hydrolysis of the ketal moiety provided cycloadduct **91**, which was heated at reflux in DMF to furnish **92** in 30% yield.

2.1.5. Azides. The Pearson group studied a synthetically useful cascade in which azides undergo dipolar cycloaddition with dienes followed by a thermal rearrangement to produce pyrrolidine-containing products. Thus, heating azido diene **92** to 100 °C in $CHCl_3$ for 15 h afforded the pyrrolizidine derivative **93** in 90% yield (Scheme 20).[45] The phenylsulfanyl substituent was critical both in terms of the products isolated and the rates of the reaction. The mechanism for this cascade was suggested to involve an initial dipolar cycloaddition to provide an intermediate triazole **94** in the rate-determining step. Triazole **94** then fragments by loss of nitrogen to produce either a diradical or a zwitterionic intermediate **95**. The resulting intermediate could cyclize either to **93** directly or alternatively give vinylaziridine **96**. The formation of **96** would likely be reversible, and some products isolated with other substrates suggest its involvement as an intermediate. Formally, this process can be considered as a [4+1]-cycloaddition of a nitrene with a 1,3-diene.

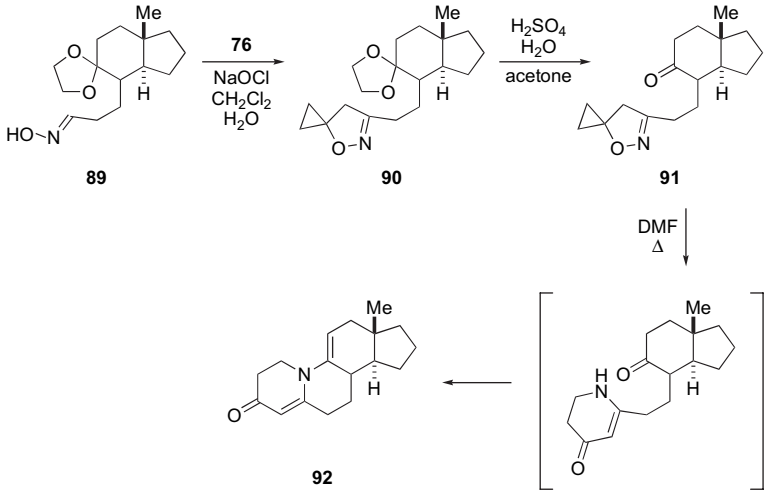


Scheme 20.

The stereoselectivity of the azide-diene cascade was examined using substrates bearing chiral centers. Choosing azido dienes that could lead to natural product precursors, Pearson group prepared azides **97**, **99**, and **101** (Scheme 21).[32] Thermolysis of **97** at 100 °C in $CHCl_3$ for 2 days provided **98** in 74% yield. Diene **99** produced **100** in 62% yield on heating at 95 °C in DMSO for 48 h, and the polyoxygenated azide **101** furnished **102** in 55% yield on heating at 75 °C in DMSO.

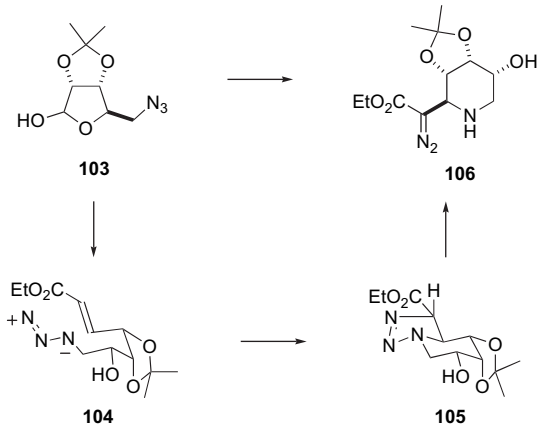


Scheme 21.



Scheme 19.

An unusual tandem Wittig/[3+2]-cycloaddition sequence of an azide was used for the synthesis of azasugars. Thus, acetal **103** was allowed to react with $Ph_3P{=}CHCO_2Et$ to provide diazoamine **106** (Scheme 22).[46] The Wittig reagent presumably underwent reaction with the ring-opened form of ketal **103** to provide the intermediate enoate **104**. Dipolar cycloaddition of the pendant azide across the π-bond then produces triazole **105** that undergoes a subsequent dipolar cycloreversion reaction to give diazoamine **106**.



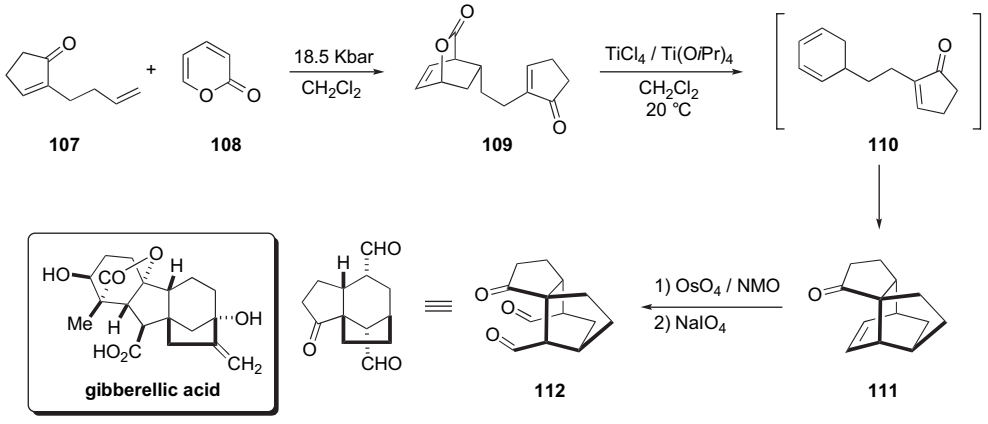
Scheme 22.

2.2. Diels–Alder and related processes

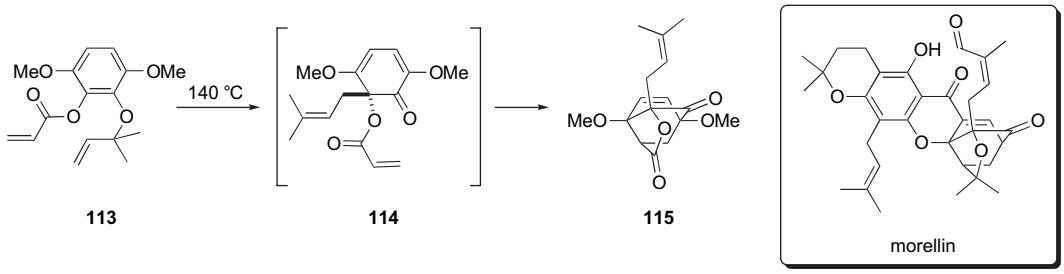
2.2.1. Diels–Alder. Diels–Alder cycloaddition chemistry has also been extensively exploited for many cascade reactions. A tandem Diels–Alder approach[47] toward tricyclic molecules was used by Markó group as an approach toward gibberellic acid. Enone **107** was reacted with 2-pyrone (**108**) under high pressure to provide the Diels–Alder bicycle **109** in 33% yield (Scheme 23).[48] Exposure of **109** to $TiCl_4$ effected the extrusion of CO_2 to give the intermediate cyclohexadiene **110** that underwent cycloaddition to afford **111** in 69% yield. Dihydroxylation followed by a periodate-mediated ring cleavage produced **112**, which contains the core of gibberellic acid, in 80% yield.

A tandem Claisen/Diels–Alder sequence was recently used to construct the tricyclic structure found in a series of *Garcinia* natural products, represented by morellin. Upon heating at 140 °C, acrylate ester **113** underwent an initial [3,3]-sigmatropic rearrangement to provide intermediate **114** (Scheme 24).[49] A subsequent intramolecular Diels–Alder cycloaddition then produced **115** in 92% yield.

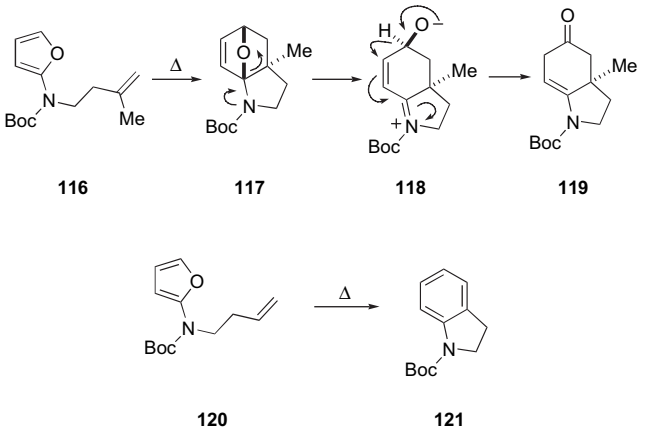
Several reaction cascades where amidofurans act as 4π components in Diels–Alder chemistry have recently been examined as a strategy for alkaloid synthesis.[50] For example, the thermolysis of amidofuran **116** led to the formation of **119** in 71% yield (Scheme 25).[51] In this reaction, an intramolecular [4+2]-cycloaddition of **116** first provides oxabicycle **117**. Nitrogen-assisted opening of the oxygen bridge then leads to zwitterionic **118**. A 1,2-hydride shift of **118**, driven by the formation of a strong C=O double bond, results in the formation of **119**. Interestingly, if the 2π reaction partner was not geminally substituted (as in **120**), a deprotonation/dehydration cascade proceeds at a faster rate than the 1,2-hydride shift. This reaction sequence constitutes a de novo synthesis of the carbocyclic ring of an indole.



Scheme 23.



Scheme 24.



116 117 118 119

120 121

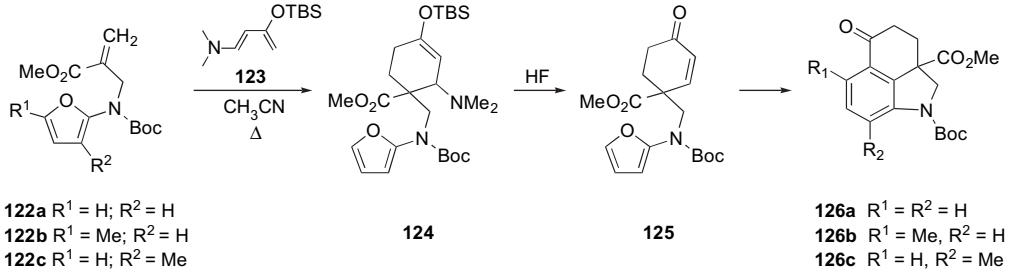
Scheme 25.

Coupling of this indole methodology with Rawal's azadiene work[52] led to a synthesis of Kornfeld ketone analogs with substitution patterns that are difficult to otherwise obtain. Heating a mixture of **122a** and Rawal's diene (**123**) in CH_3CN at reflux for 2 h furnished a 2:1 mixture of diastereomeric amines **124** that was immediately treated with HF at room temperature to unmask the enone **125** (Scheme 26).[53]

The crude reaction mixture was then heated at reflux in toluene for 30 min to effect an IMDAF cycloaddition. Ring opening of the resulting Diels–Alder cycloadduct followed by dehydration provides the tricyclic ketone **126a** in 60% yield from **122a**. In a similar manner, amidofurans **122b**,**c** were converted into dihydroindoles **126b**,**c**.

Furans are also useful 4π components for tandem Ugi condensation/intramolecular Diels–Alder cascade reactions. For example, stirring a methanolic mixture of compounds **127**–**129** and benzylamine at room temperature provided the Ugi condensation product **130** that underwent a subsequent intramolecular Diels–Alder cycloaddition to furnish **131** in 70–90% yield (Scheme 27).[54] This methodology also allowed for a solid phase synthesis by using an ArgoGel-Rink resin as the amine component, providing cycloadducts **131** (after cleavage from the resin) in ca. 90–95% yields.

In a related sequence, pyrrole was found to act as a 4π reaction partner leading to the formation of aza-bridged derivatives. Propionic acid (**132**) was used in the Ugi condensation with **128** and **133** to provide alkyne **134** (Scheme 28).[55] Heating **134** at reflux temperature in toluene promoted a somewhat rare intramolecular Diels–Alder reaction of a pyrrole, giving rise to the formation of intermediate **135**.

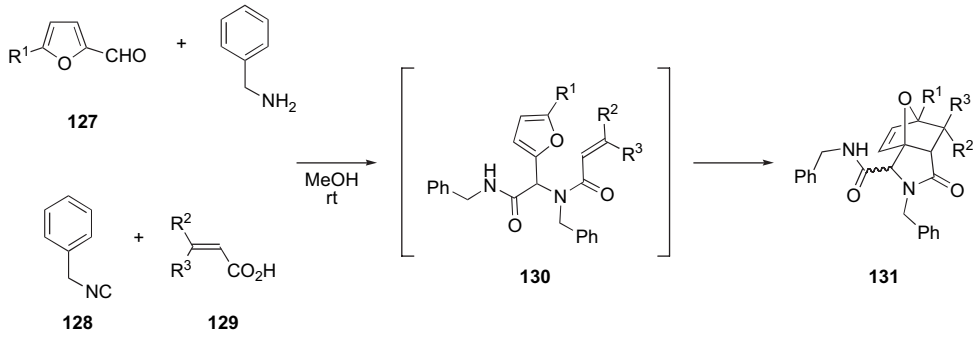


122a R^1 = H; R^2 = H
122b R^1 = Me; R^2 = H
122c R^1 = H; R^2 = Me

124 125

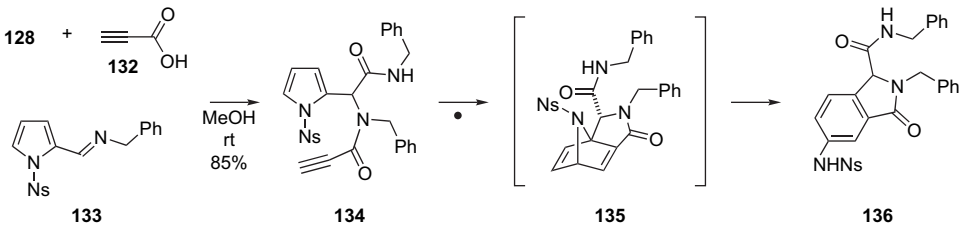
126a R^1 = R^2 = H
126b R^1 = Me, R^2 = H
126c R^1 = H, R^2 = Me

Scheme 26.



127 128 129 130 131

Scheme 27.



133 134 135 136

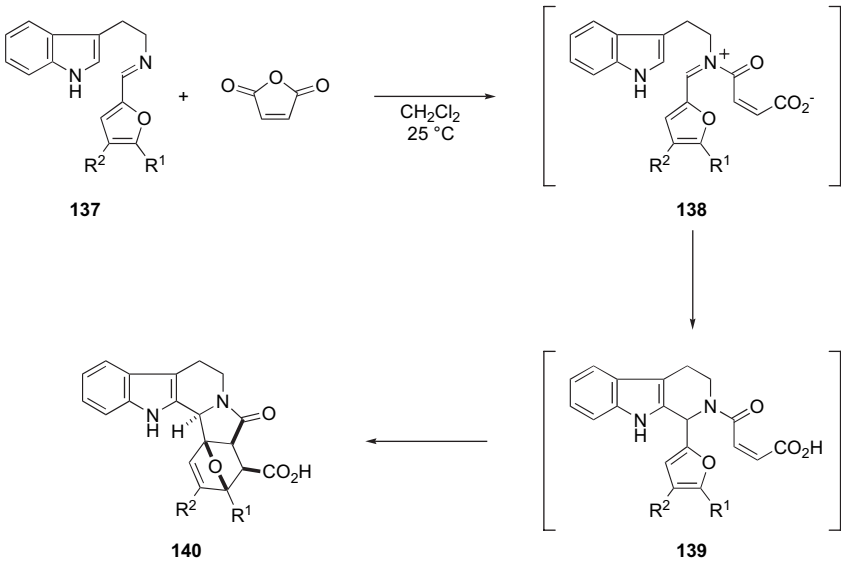
Scheme 28.

Ring opening of the nitrogen bridge in **135** produced isoindolone **136** in 65% yield.

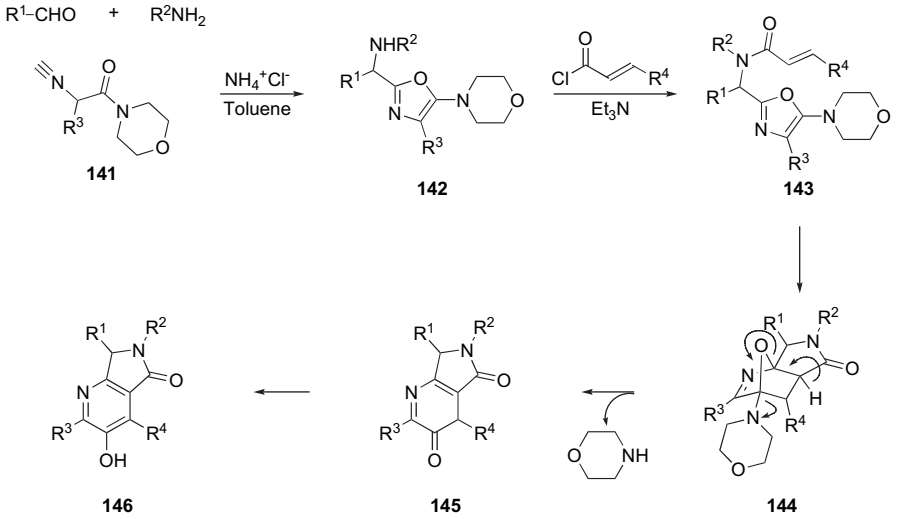
A novel tandem Pictet–Spengler/intramolecular Diels–Alder sequence has been used to prepare carboline derivatives. Reaction of imine **137** with maleic anhydride in CH_2Cl_2 provided cycloadduct **140** in 60–80% yields (Scheme 29).[56] The reaction proceeds by acylation of the imine with the available anhydride to first produce iminium ion **138** that then cyclizes with the indole ring to give **139**. An intramolecular Diels–Alder reaction of the furan with the proximal π-bond ultimately provides **140**.

In another example of multi-component reactions involving Diels–Alder cycloadducts, Zhu and co-workers found that a mixture of an amine, an aldehyde, and isonitrile **141** led to oxazole **142** when the reaction was carried out in the presence of a mild acid catalyst (Scheme 30).[57] The further reaction of **142** with a variety of α,β-unsaturated acid chlorides produced Diels–Alder substrates **143** that underwent cyclization to give bridged ethers **144**. Ring opening with concomitant loss of morpholine afforded **145** that rapidly tautomerized to give **146** in 32–75% yield.

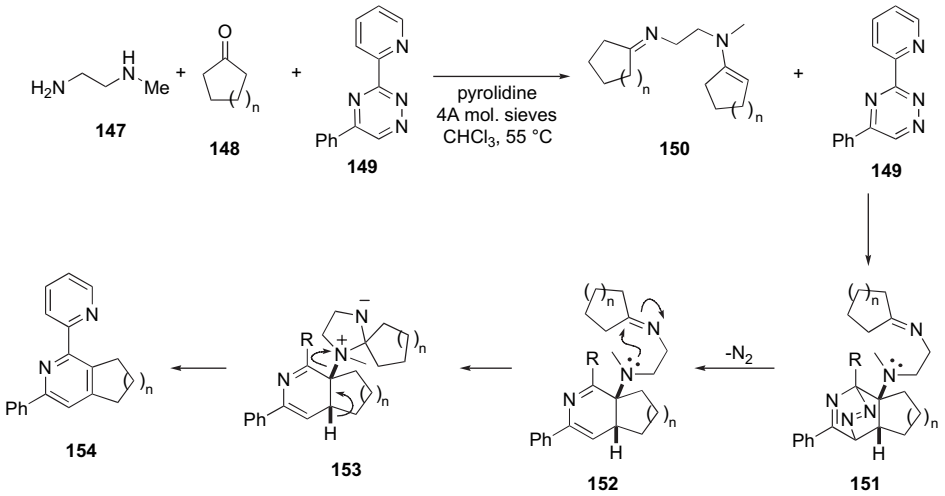
Taylor and Raw recently designed a tethered imine-enamine cascade sequence that converts 1,2,4-triazenes into substituted pyridines. In the presence of molecular sieves, *N*-methylethylenediamine (**147**) underwent condensation with excess cyclic ketone **148** (n=1–4) to give imine-enamine **150** (Scheme 31).[58] The enamine portion of the molecule then participated in an inverse-demand Diels–Alder cycloaddition reaction with **149** to provide intermediate **151**. Cycloreversion of **151** with loss of N_2 then gave **152** in which the tertiary resulting amino group added to the adjacent imine functionality to afford zwitterionic **153**. Finally, an intramolecular Cope elimination produced **154** in 74–100% yield. Several other triazines were also shown to participate in this novel cascade.



Scheme 29.



Scheme 30.

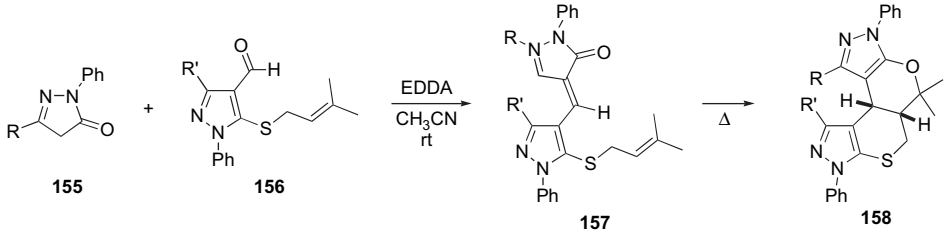


Scheme 31.

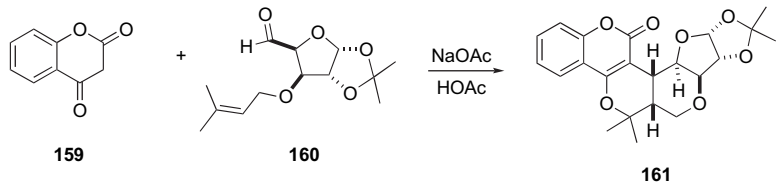
2.2.2. Hetero Diels–Alder. A domino Knoevenagel/hetero-Diels–Alder cycloaddition cascade was developed by Tietze[10,11] and has continued to attract considerable attention. For example, variously substituted pyrazolones **155** and thio substituted heterocycles of type **156** were condensed to furnish novel heterocyclic structures (Scheme 32).[59] The reaction of **155** and **156** in the presence of EDDA (ethylene diammonium diacetate) at room temperature in CH_3CN gave **157**. Upon heating the reaction mixture at reflux, hetero-Diels–Alder cycloadducts such as **158** could be isolated in good yields (81–87%).

A related domino process was used for the synthesis of coumarin derivatives that contain sugar-fused moieties. In the presence of NaOAc and HOAc, the reaction of coumarin **159** with prenylated sugar aldehyde **160** produced **161** in 82% yield (Scheme 33).[60] A variety of 1,3-dicarbonyl compounds also participated in the reaction and provided tandem condensation/cycloaddition products in good yields (70–80%).

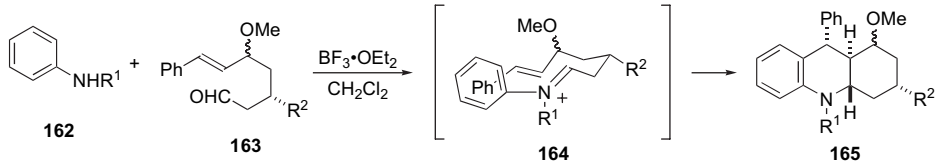
An interesting example of a formal [4+2]-cycloaddition has been found to occur upon condensing *N*-substituted anilines with ω-unsaturated aldehydes in the presence of Lewis acids. In this study, *N*-phenylamines **162** underwent condensation with **163** to provide acridine products **165** in ca. 60–75% yields (Scheme 34). The intermediate iminium ions **164** that are first formed either participate in a concerted



Scheme 32.



Scheme 33.



Scheme 34.

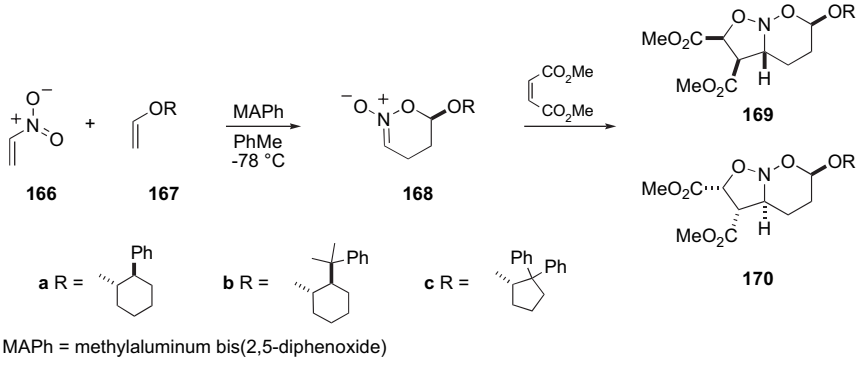
[4+2]-cycloaddition (followed by proton transfer) or else undergo polar addition to the pendant alkene by addition of the resultant benzylic carbocation onto the aniline ring.

2.2.3. Nitroalkene [4+2]/[3+2]-cycloadditions. The Denmark laboratory has developed an elegant tandem [4+2]/[3+2]-cycloaddition strategy for the synthesis of a variety of alkaloid natural products.[61] Nitroethylene (**166**) undergoes a ready Lewis acid-promoted cycloaddition with vinyl ethers that contain a chiral auxiliary group to give nitronates **168** with good stereoselectivity (Scheme 35).[62] For example, vinyl ether **167a** provided **168a** with a 20:1 diastereoselectivity, whereas **167c** afforded **168c** with >50:1 selectivity. The initially formed nitronates **168** were unstable to silica gel chromatography, but the crude products underwent a ready [3+2]-cycloaddition reaction with electron-deficient dipolarophiles. In these reactions, dimethyl maleate reacted with **168** to provide a 6:1 mixture of **169** and **170** in 84–89% yield.

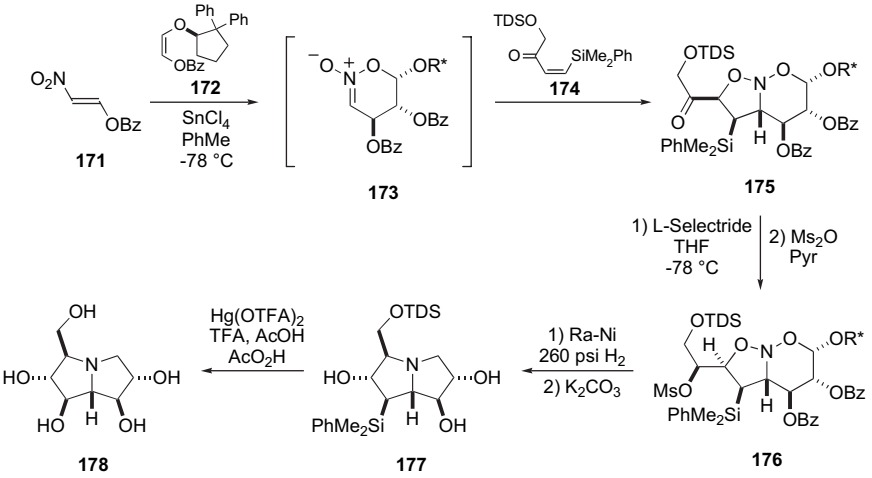
This tandem intermolecular [4+2]/intermolecular [3+2]-cycloaddition strategy was successfully applied to the synthesis of (+)-casuarine. In this synthesis, nitroalkene **171** was allowed to react with enol ether **172** in the presence of $SnCl_4$ at −78 °C to give intermediate nitronate **173** (Scheme 36).[63] A dipolar cycloaddition of **173** with **174** provided **175** in 76% yield as a mixture predominating in the stereoisomer shown in Scheme 36. Stereoselective reduction of the ketone moiety in **175**, followed by conversion to the corresponding mesylate, gave **176** in 84% yield. Exposure of **176** to Raney nickel under high pressure afforded pyrrolizidine **177** in 64% yield and with 98% ee. Oxidative removal of the silyl group produced (+)-casuarine (**178**) in 84% yield.

The Denmark group has developed several interesting variants of this sequence. For example, the intermolecular [4+2]/intramolecular [3+2]-cycloaddition cascade[64] was used to construct several natural products, such as (−)-rosmarinecine.[65] For this particular natural product, the Lewis acid-promoted reaction of nitroalkene **179** with chiral enol ether **180** produced nitroso acetal **181** in 94% yield and with excellent stereoselectivity (25:1 *exo*/*endo*) as shown in Scheme 37. Reduction of the lactone moiety afforded lactol **182** in 91% yield. Exposing **182** to Raney nickel under H_2 (160 psi) gave the bicyclic lactam **183** in 64% yield. The chiral auxiliary could be recovered in 98% yield. Protection of the lactol followed by reaction with *p*-NO_2-benzoic acid, Ph_3P, and DEAD provided benzoate ester **184** in 69% yield from **183**. Finally, deprotection of the lactol in compound **184** followed by exposure to Red-Al produced rosmarinecine (**185**) in 57% yield for the two-step procedure.

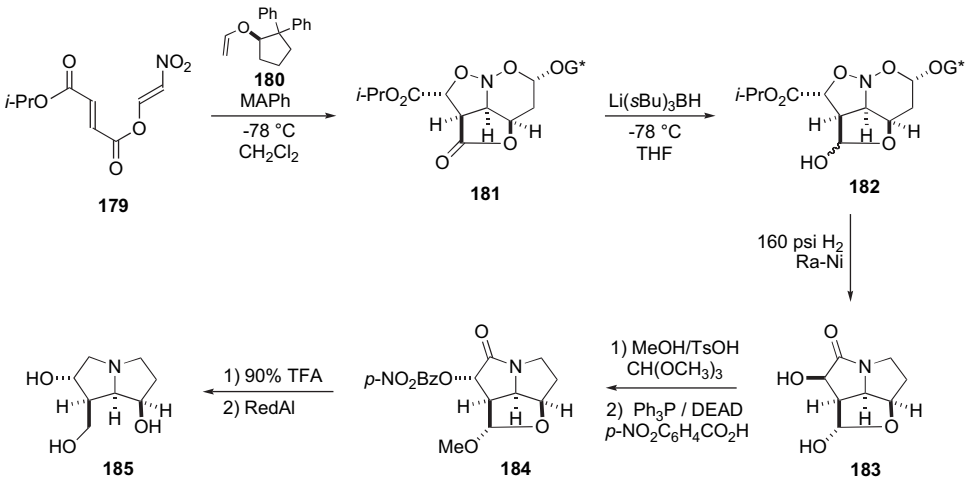
More recently, the Denmark group reported on the tandem intramolecular [4+2]/intramolecular [3+2]-cycloaddition of nitroalkenes. Exposure of nitrone **186a**,**b** to $SnCl_4$ produced nitronate **187a**,**b** (Scheme 38).[66] Warming the crude reaction



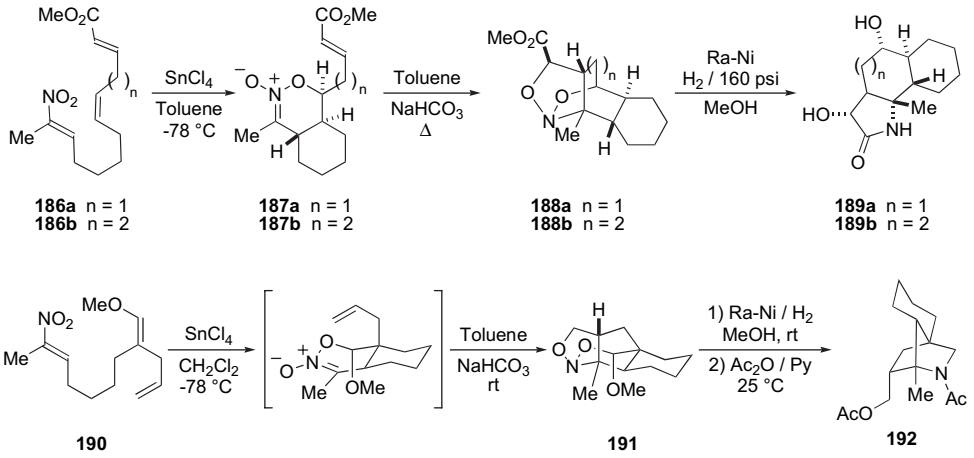
Scheme 35.



Scheme 36.



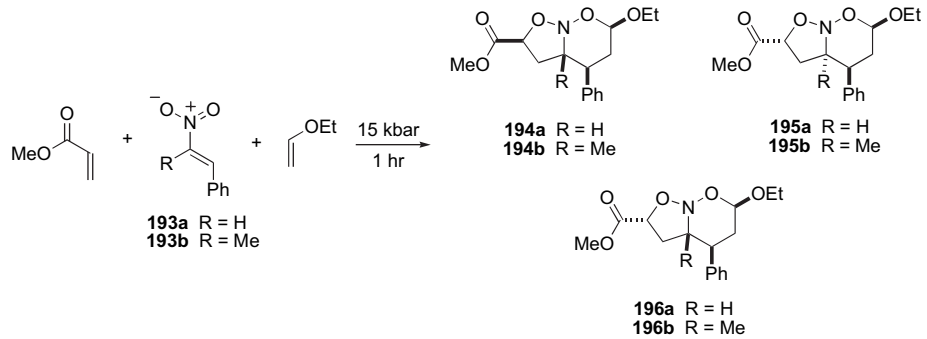
Scheme 37.



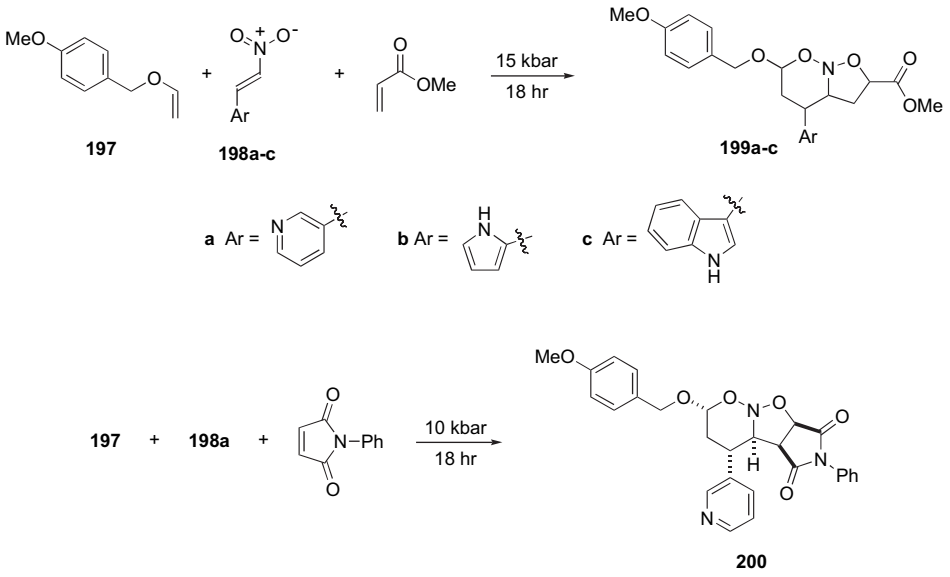
Scheme 38.

mixture containing **187a** in toluene at 80 °C for 90 min afforded **188a** as a single diastereomer in 82% overall yield. Nitronate **187b** required heating at 100 °C in toluene for 3 days in order to give **188b** as a single diastereomer, though in only 44% yield (along with 40% of **187b**). Reduction of **188a**,**b** with Raney nickel under a hydrogen atmosphere (160 psi) provided the fused tricycles **189a**,**b** in 71 and 78% yield, respectively. The selectivity of this tandem sequence is remarkable considering that the compounds formed (i.e., **189a**,**b**) each contain six contiguous stereogenic centers. Similarly, nitroalkene **190** produced **191** in 87% yield when exposed to a Lewis acid. The reaction of **191** with Raney nickel in the presence of hydrogen provided the bridged tricycle **192** in 81% yield.

In these cited examples, Denmark employed a Lewis acid (often in 2–3 fold excess) to effect the tandem cycloaddition reaction. In an alternate approach, Scheeren promoted the tandem [4+2]/[3+2]-cycloadditions by using high pressure. For example, nitroalkene **193a** reacted with methyl acrylate and ethyl vinyl ether under 15 kbar pressure to produce the bicyclic nitroso acetals **195a** and **196a** in 17 and 45% yield,



Scheme 39.

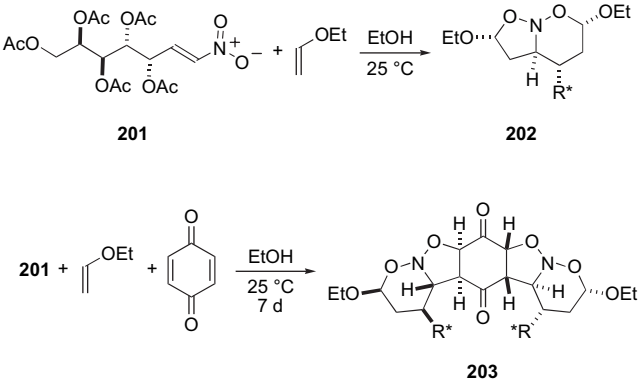


Scheme 40.

respectively, after heating for 1 h (Scheme 39).[67] Nitrone **193b** reacted under similar conditions to produce **194b**, **195b**, and **196b** in 29, 18, and 29% yields, respectively.

Heteroaromatic substituted nitroalkenes also participate in this high-pressure reaction sequence. For example, the reaction of **198a–c** with **197** and methyl acrylate afforded diastereomeric mixture of **199a–c** in 53–74% yields (Scheme 40).[68] In contrast, **198a** reacted with **197** and *N*-phenyl maleimide to provide **200** as a single diastereomer.

A tandem cycloaddition sequence involving nitroalkenes derived from carbohydrates was recently investigated. In this study, nitroalkene **201** reacted with ethyl vinyl ether in EtOH at 25 °C to produce **202** as a single diastereomer in 89% yield (Scheme 41).[69] A subsequent reaction of **201** with ethyl vinyl ether and 1,4-benzoquinone gave rise to a single diastereomer, whose structure was tentatively assigned as **203**, in 41% yield.[70]



Scheme 41.

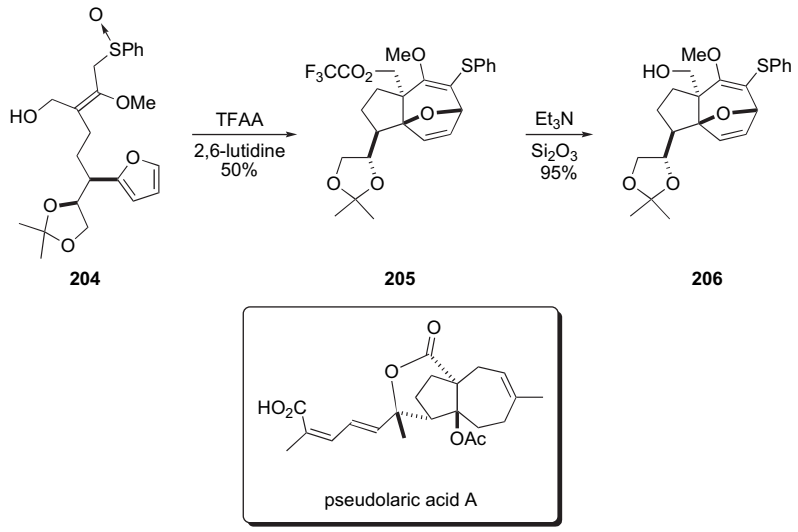
2.2.4. [4+3]-Cycloadditions. Based upon the Harmata group's earlier work using alkoxyallyl sulfone[71] and vinyl sulfoxide[72] substrates, Bai and co-workers applied a Pummerer rearrangement/intramolecular [4+3]-cycloaddition cascade toward the synthesis of pseudolaric acid A (Scheme 42).[73] In their studies, sulfoxide **204** was allowed to react with TFAA in the presence of 2,6-lutidine to give cycloadduct **205** in 50% yield and with a remarkably high diastereoselectivity (>95% de). Hydrolysis of the trifluoroacetyl group delivered an advanced intermediate (**206**) that was used for the synthesis of pseudolaric acid A.

3. Rearrangements and electrocyclizations

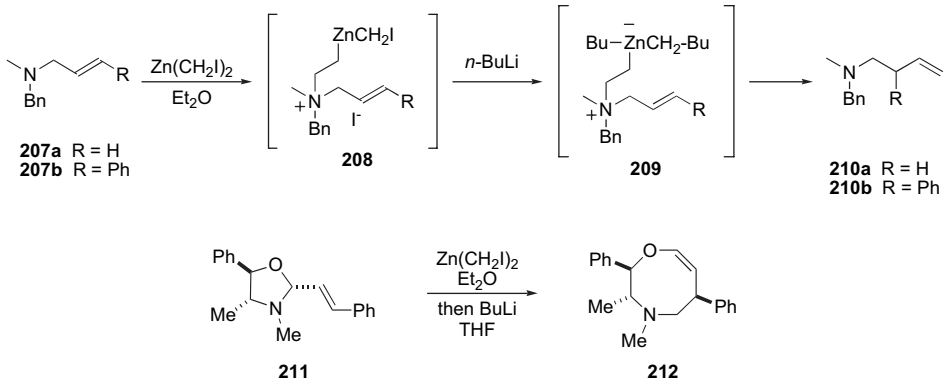
3.1. [2,3]-Sigmatropic shifts

The [2,3]-sigmatropic rearrangement of ammonium ylides can lead to interesting heterocycles. Although it has been known for some time that the Simmons–Smith reagent $(ClCH_2)_2Zn$ reacts with tertiary amines to provide quaternary ammonium salts, the chemistry of the intermediate ammonium ylide had received little attention. More recently, Aggarwal reported that the reaction of $(ICH_2)_2Zn$ with allyl amine **207a** produced the unreactive ylide **208**.[74] Treatment of **208** with BuLi, however, generated an activated zincate complex **209** that rearranged to give homoallyl amine **210a** in 70% yield (Scheme 43). That a [2,3]-sigmatropic rearrangement occurs, as opposed to a Stevens rearrangement, was established by treating **207b** with $(ICH_2)_2Zn$ followed by *n*-BuLi to produce **210b** in 76% yield. This reaction was also applied to oxazolidine **211**, furnishing the eight-membered ring **212** in 72% yield and with a >98% diastereoselectivity.

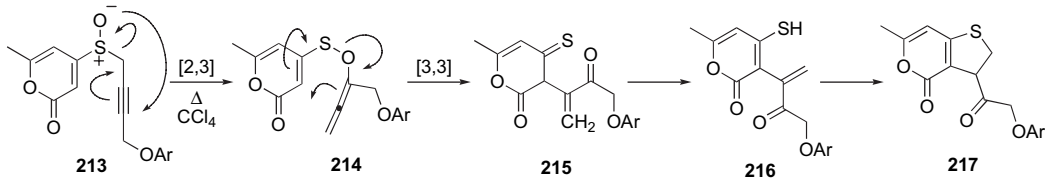
A novel cascade sequence was encountered during a study of the thermolysis of propargylic sulfoxide **213**, which gave the rearranged structure **217** in 60–70% yield (Scheme 44).[75] The cascade was initiated by a [2,3]-rearrangement of the sulfoxide, which first produced the allene intermediate **214**. A subsequent [3,3]-rearrangement of the transient allene then gave enone **215**. Tautomerization of the thione functionality afforded **216** and this was followed by intramolecular Michael addition to give the observed product **217**.



Scheme 42.



Scheme 43.

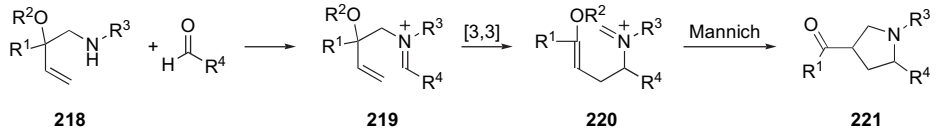


Scheme 44.

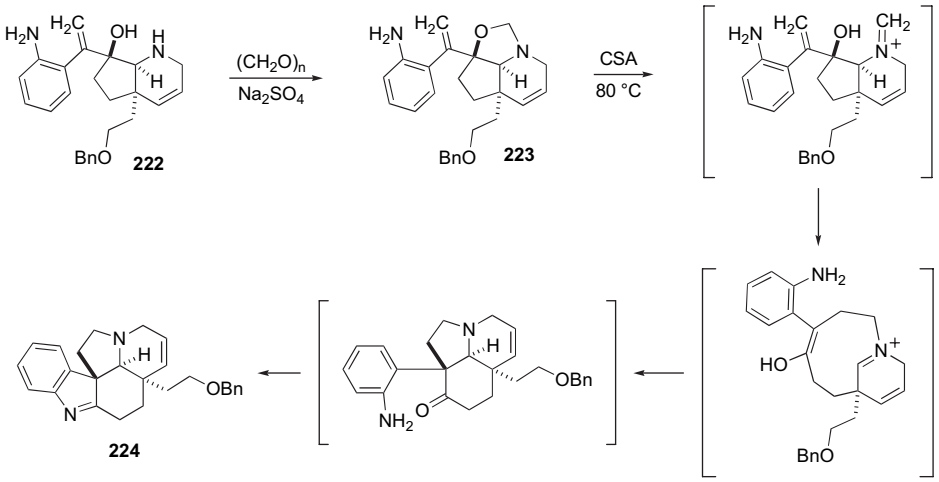
3.2. [3,3]-Sigmatropic rearrangements

Of the various heterocycle-forming cascade reactions involving [3,3]-rearrangements, Overman's use of the Aza-Cope rearrangement/Mannich cyclization sequence certainly represents the best known example of this methodology.[76] Condensation of a secondary homoallylic amine containing an allylic alcohol or ether such as **218** with aldehydes produces the intermediate iminium ion **219** (Scheme 45).[77] A Cope rearrangement then provides a new iminium ion (**220**) that contains a transient enol, which attacks the cationic center in a Mannich fashion to deliver pyrrolidines of type **221**.[78]

This methodology has been the strategic core of several clever synthetic endeavors carried out by the Overman group. For example, amine **222** was converted into the pentacyclic core of the aspidosperma alkaloid family (Scheme 46).[79]



Scheme 45.



Scheme 46.

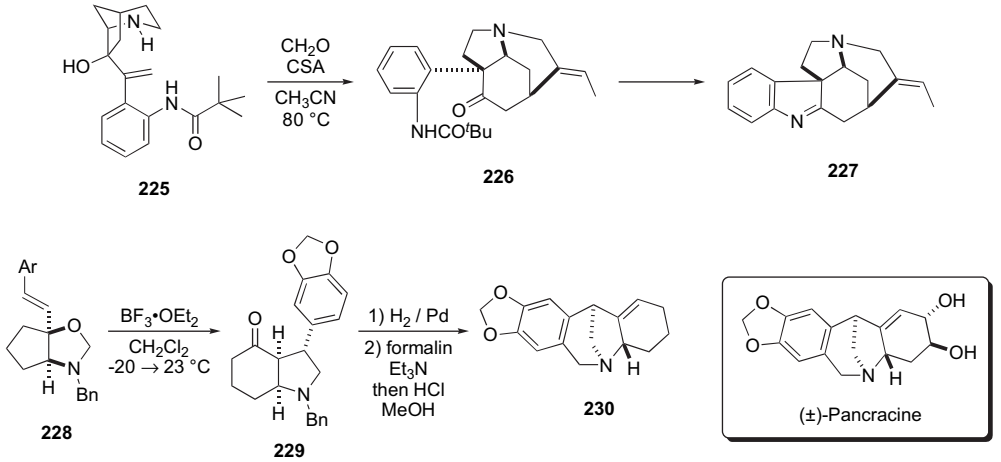
Condensation of **222** with paraformaldehyde produced oxazoline **223**. Heating **223** with excess camphorsulfonic acid (CSA) effected the aza-Cope/Mannich cyclization cascade to furnish **224** in nearly quantitative yield.

An efficient synthesis of the strychnos alkaloid skeleton was also achieved using this novel cascade process. The key transformation in this sequence occurs by heating bicyclic amine **225** with formaldehyde and CSA in CH_3CN to give **226** as a single diastereomer in 88% yield (Scheme 47).[80] Hydrolysis of the amide and subsequent condensation of the ketone with the aniline derivative provided dehydrotubifoline (**227**).

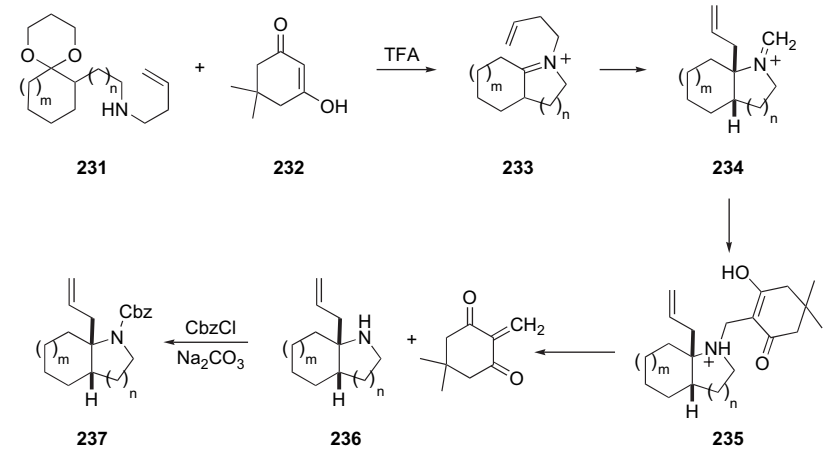
Overman also used his aza-Cope/Mannich cascade for a total synthesis of (±)-pancracine. In this particular synthesis, *N*,*O*-acetal **228** was allowed to react with $BF_3 \cdot OEt_2$, which resulted in the eventual formation of amine **229** in 97% yield.[81] Hydrogenolysis removed the *N*-benzyl group, and the resulting amine was then heated with formaline in the presence of catalytic amounts of CSA to effect a Pictet–Spengler reaction, the product of which (**230**) contains the pancracine skeleton.

More recently, Overman designed a variant of this process for the construction of angularly substituted bicyclic amines. Heating ketal **231** with TFA and dimedone (**232**) resulted in condensation with the pendant amine group to give iminium ion **233** (Scheme 48).[82] The [3,3]-rearrangement resulted in the formation of a second iminium ion **234** that was intercepted by enol **232** to give the Mannich adduct **235**. Finally, elimination of the α-methylene 1,3-dione afforded amine **236**. For ease of isolation, the crude reaction mixture was subjected to the action of benzyl chloroformate. Several examples demonstrated the versatility of this sequence in that the original ring size could be varied (m=1–3) as well as the annulated ring size (n=1, 2) to produce predominantly cis-fused bicycles **237** in ca. 65–95% yields.

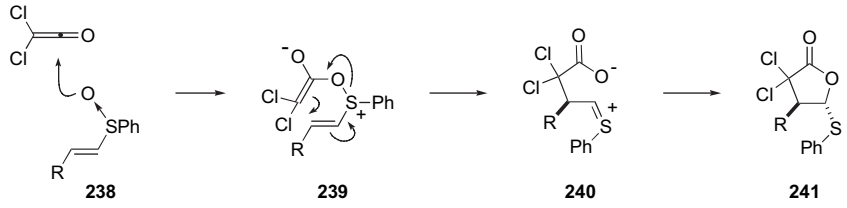
A novel [3,3]-sigmatropic process that involves an additive-Pummerer reaction that produces γ-butyrolactones by the reaction of dichloroketene with vinyl sulfoxides was developed by the Marino and Neisser.[83] The oxygen atom of vinyl sulfoxide **238** first attacks dichloroketene to produce an internal salt **239** (Scheme 49). The resulting enolate present in **239** then undergoes a [3,3]-sigmatropic rearrangement to provide thionium ion intermediate **240**. Finally, the



Scheme 47.



Scheme 48.



Scheme 49.

resulting carboxylate adds to the neighboring thionium ion to furnish butyrolactone **241** whose stereochemistry depends upon the geometry of the starting olefin. The use of chiral sulfoxides **238** led to the enantiospecific formation of butyrolactones **241**.[84]

This novel strategy was applied to a synthesis of (+)-aspidospermidine. In this approach, enantiomerically pure sulfoxide **242** was treated with trichloroacetyl chloride in the presence of zinc–copper couple (Zn−Cu) to give lactone **243** in 78% yield (Scheme 50).[85] Removal of the chloro substituents followed by the deprotection of the ketal afforded **244** in 96% yield. Reaction of **244** with pyrrolidine effected an O- to N-transacylation with a subsequent elimination of thiolate to furnish the amido aldehyde **245** in 86% yield. Further exposure of **245** to pyrrolidine in the presence of 33% aqueous AcOH and 2-propanol promoted an intramolecular aldol reaction and simultaneously hydrolyzed the amide group to furnish an intermediate carboxylic acid. Conversion of the carboxylic acid to a mixed anhydride followed by the addition of 3-chloropropylamine gave **246** in 64% yield from **245**. Exposure of **246** to NaH initiated a tandem intramolecular conjugate addition/alkylation to provide **247** in 86% yield. Subjection of the silyl enol ether of **247** to modified Saegusa oxidation conditions delivered **248** (85%), which was subsequently carried on to (+)-aspidospermidine.

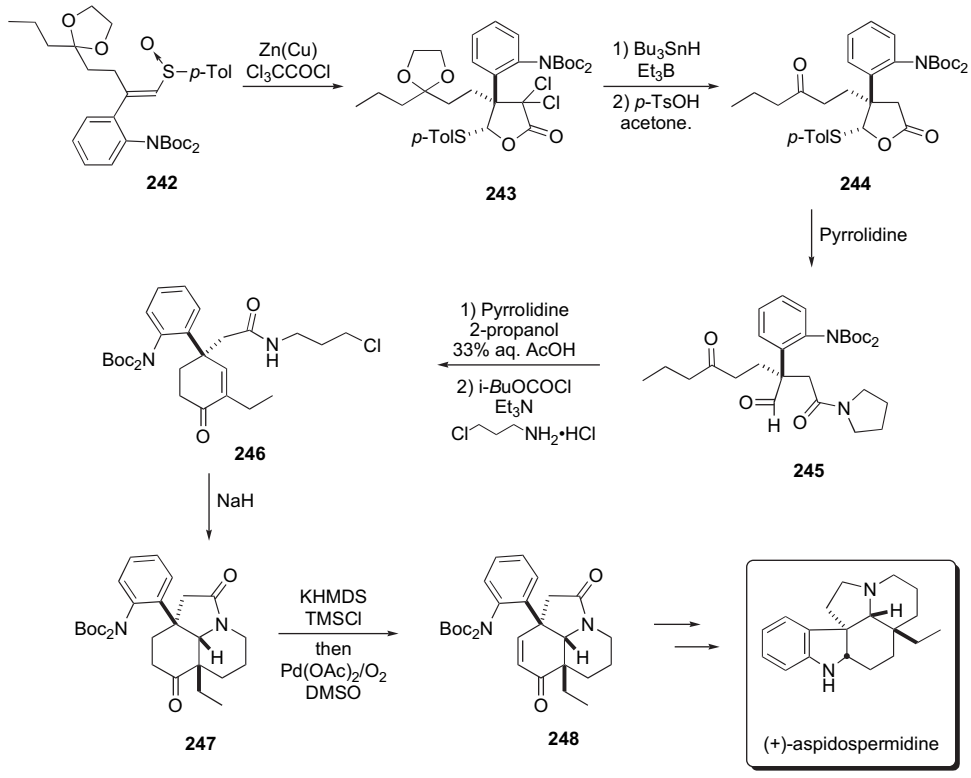
Kawasaki and Sakamoto developed a [3,3]-sigmatropic rearrangement cascade to introduce angular substituents found in several indole alkaloids. In one of the cases studied, the Claisen rearrangement was first preceded by a Horner–Emmons olefination of indolinone **249** to give **250** (Scheme 51).[86] Isomerization of **250** provided indole **251** that then underwent a [3,3]-rearrangement to furnish **252** in 73% yield. Reduction of the nitrile by the action of Red-Al gave **253** in 89% yield. Methylation of the imine nitrogen in the presence of $NaHCO_3$ then afforded flustramine C (**254**) in 38% yield. A more complete study on the scope of this cascade sequence has been reported,[87] and the application of domino Wittig-pericyclic reactions to bioactive heterocycles has recently been reviewed.[88]

The stereoselective formation of imidazolidine thiones via the rearrangement of chiral thiocyanates has recently been reported. Heating allylic thiocyanates such as **254a** at 80 °C for 3 h produced 1:1 mixture of diastereomeric isothiocyanates **255** in 92% yield (Scheme 52).[89] Prolonged heating, however, led to the isolation of the cyclic thiourea **256** as a single stereoisomer in 89% yield. Several other examples, differing in the nature of the alkyl substituent, were also reported.

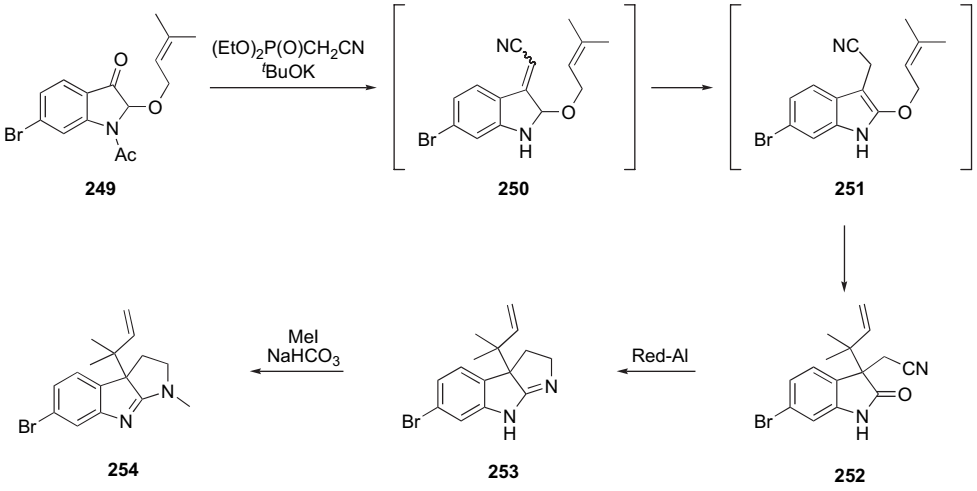
3.3. Other rearrangements

In the context of developing rapid access to thioaurone structures, De and co-workers observed an interesting 6π-electrocyclization/isomerization cascade. The reaction of sulfanyl amide **257** with an excess of LDA and cinnamaldehyde produced thioaurone **258** in 83% yield (Scheme 53).[90] Upon heating at 210 °C, compound **258** isomerized to give **259**, which underwent a subsequent electrocyclization reaction to produce **260**. A formal [1,3]-hydride shift then furnished the observed product **261**.

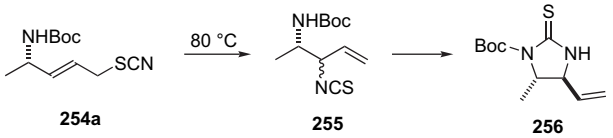
A tandem Wolff rearrangement/cyclization process has been used to synthesize benzopyran derivatives. In this sequence, α-diazo ketones **262a**,**b** were heated to effect a Wolff rearrangement, giving rise to ketenes **263** (Scheme 54).[91] The



Scheme 50.



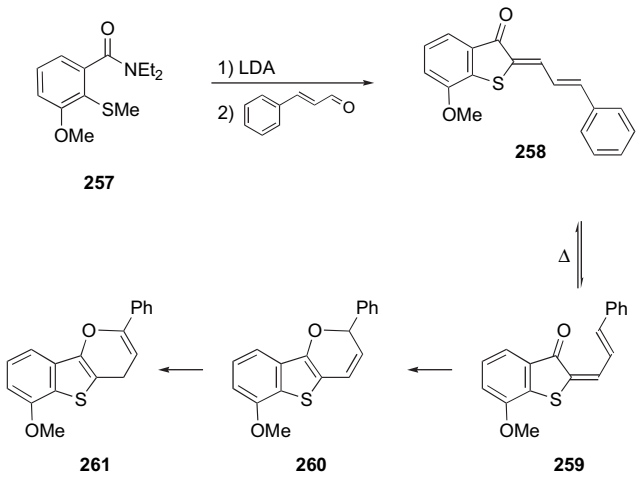
Scheme 51.



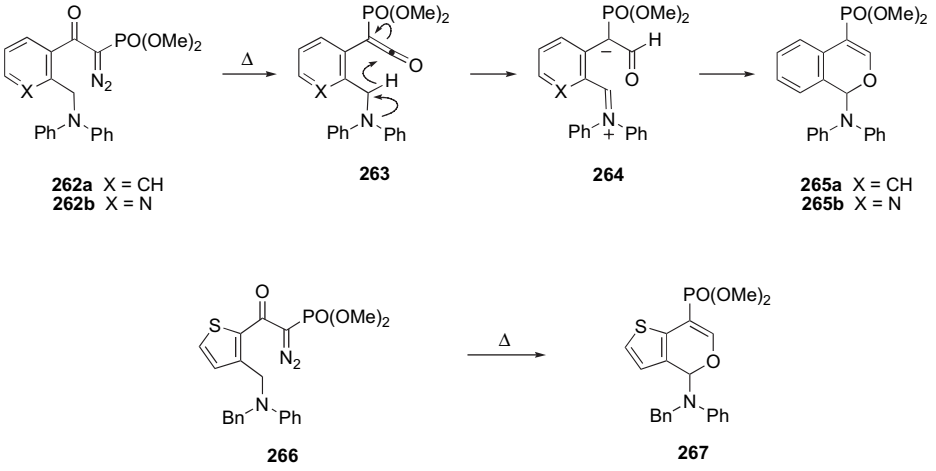
Scheme 52.

authors propose that a [1,5]-hydride shift then provided **264**, and a subsequent cyclization gave **265a**,**b** in 88 and 75% yields, respectively. Thiophene derivative **266** was also found to rearrange to **267** in 75% yield. However, the reaction of a related furan derivative led to extensive decomposition.

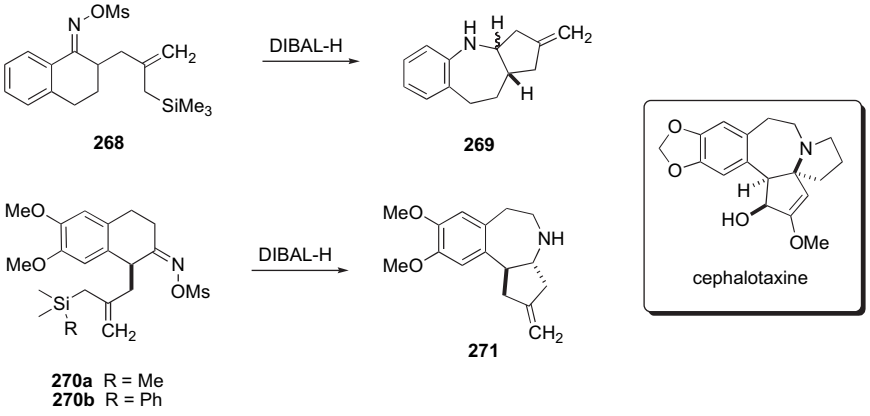
A clever synthetic approach toward the synthesis of cephalotaxine relies on an asymmetric Beckman rearrangement/allylsilane-terminated cation-cyclization cascade. In these studies, Schinzer and co-workers found that the reaction of racemic **268** with DIBAL-H produced **269** in 36% yield (Scheme 55).[92] The racemic oxime ether **270a** was converted into **271** in 23% yield under similar conditions. By changing the size of the silicon group (i.e., **270b**), the yield was increased to 41%. Non-racemic (*S*)-**270b** was synthesized using a chiral chromium–arene complex and afforded



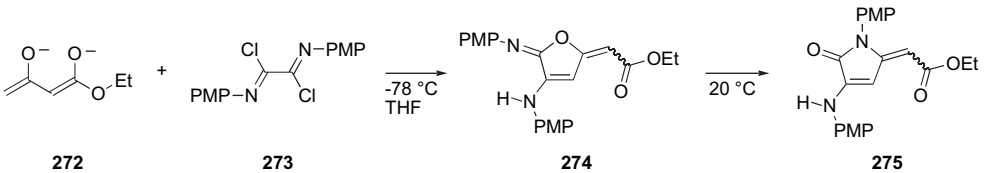
Scheme 53.



Scheme 54.



Scheme 55.



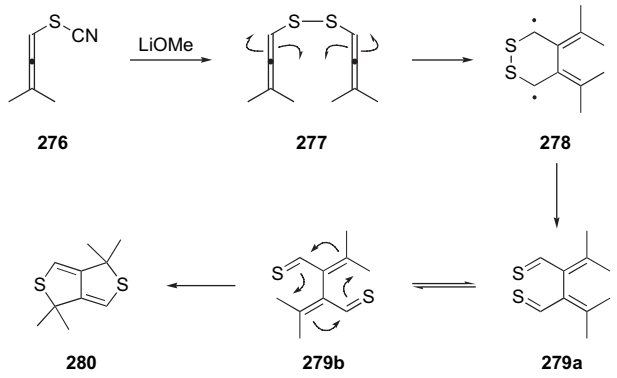
Scheme 56.

(*S*,*R*)-**271** in 55% yield and with 81% ee upon exposure to excess DIBAL-H.[93]

A tandem anionic cyclization/Dimroth rearrangement was employed for the preparation of γ-lactams containing alkylidene substituents.[94] In this cascade sequence, the dianion of ethyl acetoacetate (**272**) reacted with **273** to provide furan derivative **274** (Scheme 56), which underwent a subsequent rearrangement to give **275** in 56% yield.[95]

The rearrangement of bis-allenyl disulfides provides an interesting route to prepare fused thieno[3,4-*c*]thiophenes. Thus, Braverman reported that **276** reacted with lithium methoxide to give **280** in 70% yield (Scheme 57).[96] Presumably, allene **276** first dimerized under the reaction conditions to generate disulfide **277**. Cyclization of **277** would then produce a diradical **278** that fragments into **279a**. A further

cyclization of the *E*-isomer **279b** nicely accounts for the formation of **280**. The analogous diselenide underwent a related reaction to give the corresponding selenophene derivative.

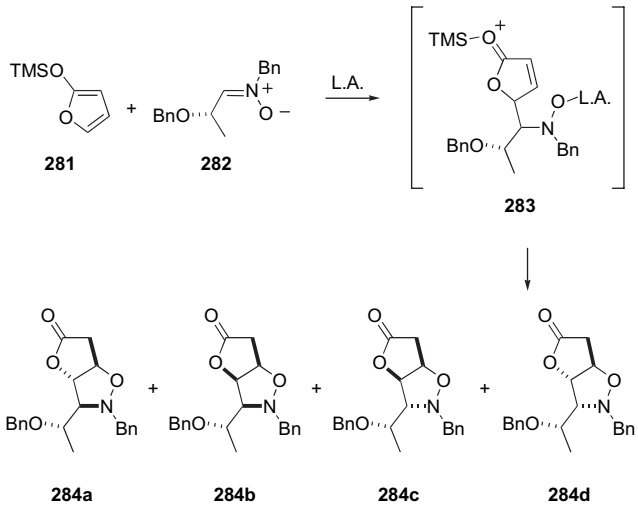


Scheme 57.

4. Cation-promoted cyclization cascades

4.1. Nitrogen stabilized carbocations

The Mannich reaction is a very common process that occurs in many tandem reaction sequences. For example, the Overman aza-Cope cascade sequence is terminated by a Mannich reaction (cf. Scheme 45). Several groups have used variants of the Mannich reaction to initiate cascades that lead to the formation of heterocyclic molecules. Thus, the Lewis acid catalyzed intermolecular vinylogous Mannich reaction[97] of silyloxy furan **281** with nitrone **282** produced a diastereomeric mixture (49:3:42:6) of azabicycles **284a–d** in 97% combined yield (Scheme 58).[98] These products arose from an intramolecular Michael addition of the initially formed oxonium ion **283**.



Scheme 58.

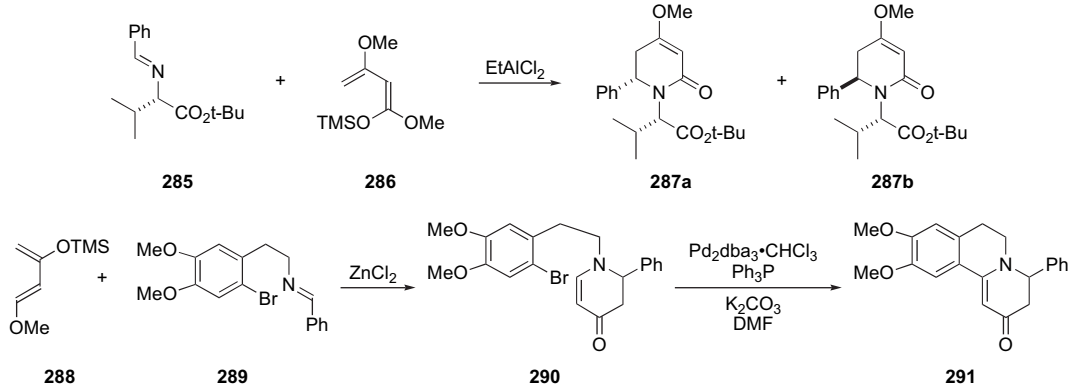
A Mannich/Michael reaction sequence was used by Waldman for the formation of several piperidone derivatives. The reaction of **285** with **286** in the presence of a variety of Lewis acids produced a mixture of **287a**,**b** in 84% yield (Scheme 59).[99]

Using diene **288** and imine **289**, the tandem Mannich/Michael reaction sequence afforded the vinylogous amide **290** in 66% yield.[100] Imines derived from other aldehydes were also studied, providing derivatives of **290** in moderate yields (ca. 40–65%). The palladium catalyzed cyclization of **290** furnished tricyclic benzoquinolizine **291** in 76% yield.

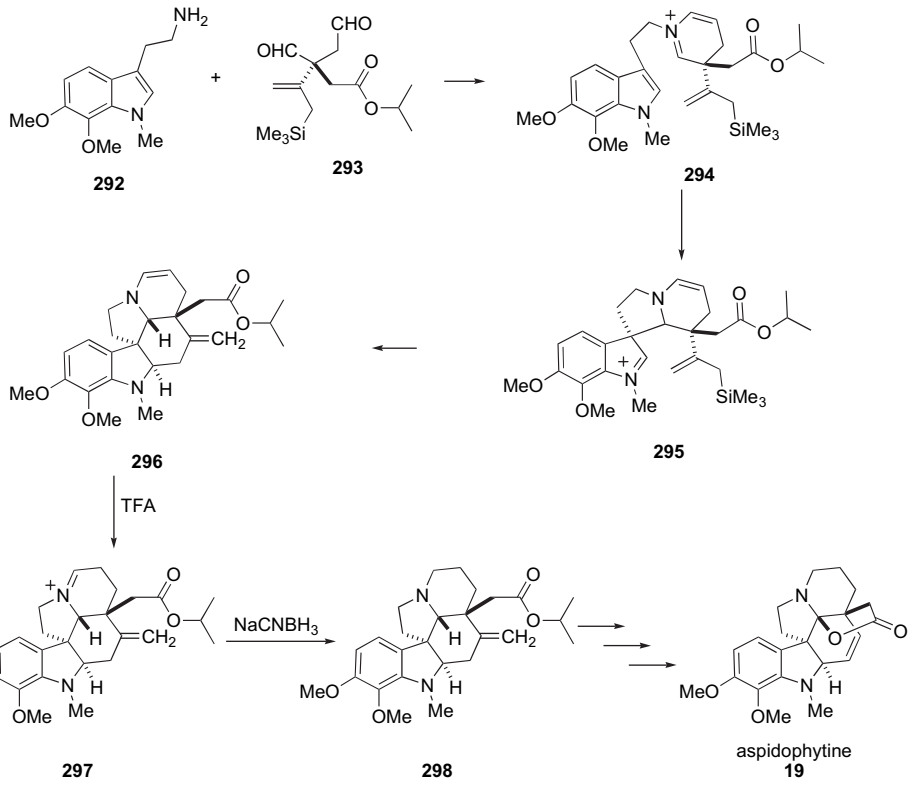
In addition to their use in Mannich (and variant) reactions, iminium ions are useful for other cationic type cyclizations. Corey employed a novel tandem iminium ion cyclization as part of an elegant cascade used for the synthesis of aspidophytine. The reaction of the tryptamine **292** and dialdehyde **293** in CH_3CN at ambient temperature afforded the pentacyclic skeleton of the alkaloid (**296**, Scheme 60).[101] Condensation of the free amino functionality of **292** with the dialdehyde produced a dihydropyridinium intermediate **294** that then cyclized onto the indole π-bond to give **295**. The iminium ion so produced underwent a second cyclization with the tethered allylsilane moiety to give **296**. Protonation of the enamine in **296** provided still another iminium ion (**297**) that was then reduced with $NaCNBH_3$ to furnish **298** in 66% yield. All of the above reactions could be made to occur in a single pot.

4.2. Pummerer cascade reactions

The combination of a Pummerer-based reaction[102] followed by an *N*-acyliminium ion cyclization in tandem to form pyrrolidine-containing ring systems represents a unique method

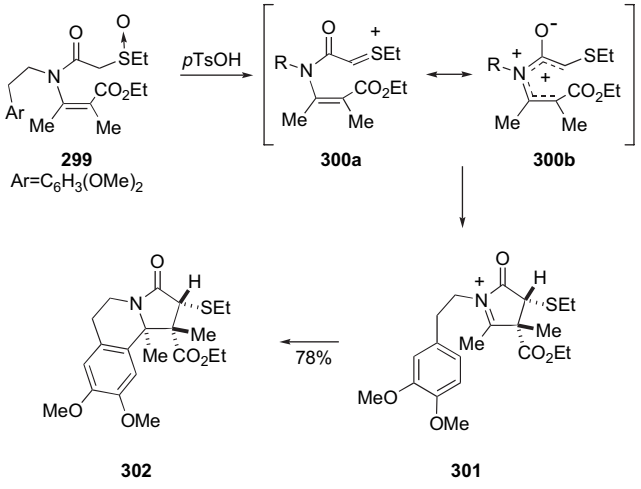


Scheme 59.



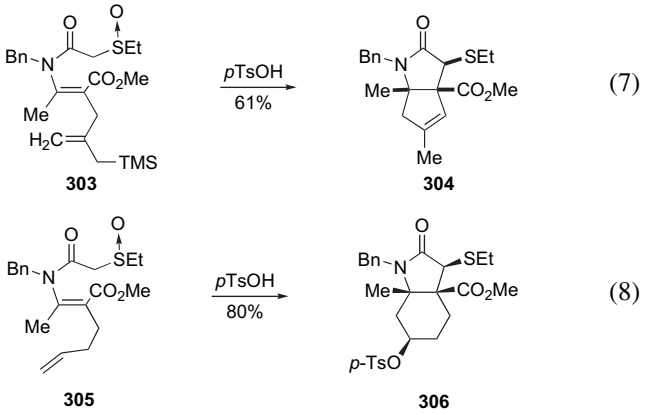
Scheme 60.

to synthesize heterocycles. In a typical example from the Padwa laboratory, enamide **299** was treated with *p*-TsOH in boiling benzene to produce thionium ion **300**. A subsequent Nazarov-like ring closure of **300** furnished iminium ion **301**. Finally, an intramolecular Pictet–Spengler reaction with the pendant aromatic ring of **301** provided **302** as a single diastereomer in 78% yield (Scheme 61).[103] The stereochemistry of **302** was established by X-ray crystallographic analysis and is compatible with a *conrotatory* ring closure.



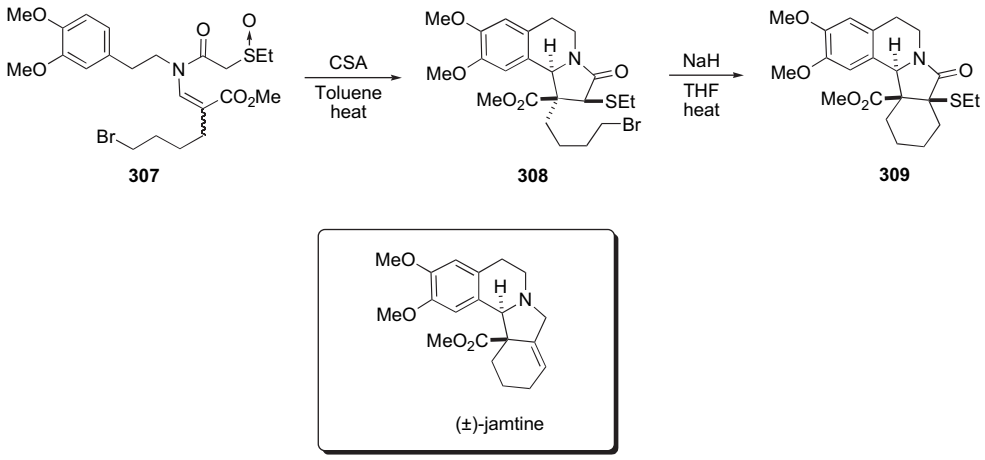
Scheme 61.

Other π-bonds were also found to efficiently participate in the Pummerer/Mannich ion cascade. For example, allylsilane **303** gave bicycle **304** in 61% yield when heated with *p*-TsOH (Scheme 62). The terminal alkene present in **305** cyclized to give **306**, wherein the resultant secondary carbocation was captured by the sulfonate anion in 80% yield. In each case, only one diastereomer was isolated, suggesting that a concerted 4π-electrocyclization reaction occurs from the intermediate thionium ion.



Scheme 62.

This methodology was employed for the synthesis of the reported structure of the alkaloid jamtine.[104] The key sulfoxide intermediate **307** was heated with CSA to produce several tricyclic products (98% yield) as a mixture (5:2:1:1) of diastereomers in which **308** predominated (Scheme 63). The stereochemistry of **308** was secured by X-ray crystallographic analysis and is consistent with a Nazarov-type *conrotatory* 4π-electrocyclization followed by attack of the nucleophilically disposed aromatic ring from the least



Scheme 63.

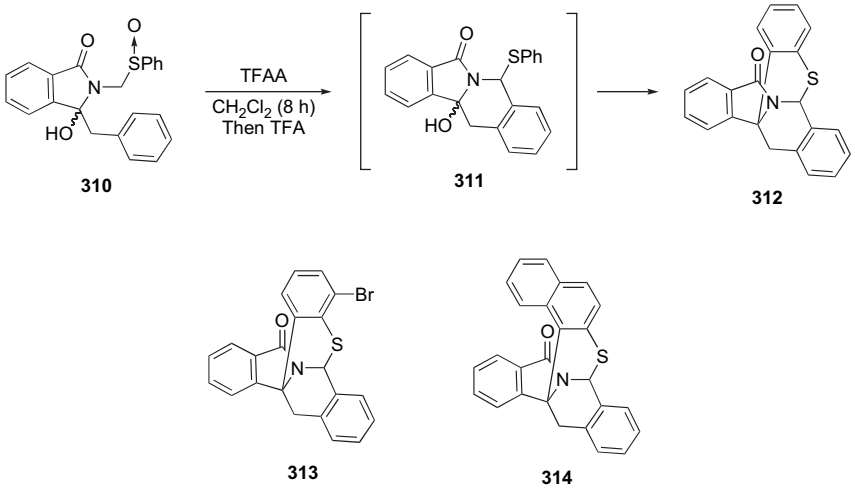
hindered side of the intermediate iminium ion. Reaction of α-ethylthio amide **308** with NaH effected an intramolecular alkylation to provide tetracycle **309**.

As part of their investigations dealing with *N*,*S*-fused polycyclic ring systems, Daich and co-workers reported the use of a tandem Pummerer/*N*-acyliminium ion cyclization to construct interesting isoquinolinone structures. Thus, treatment of sulfoxide **310** with TFAA in CH_2Cl_2 at room temperature for 8 h followed by the addition of TFA produced **312** in 42% yield through the intermediacy of **311** (Scheme 64).[105] By conducting the reaction under buffered conditions (TFAA and pyridine), compound **311** could be isolated in 56% yield. An *N*-acyliminium ion intermediate was then generated by treating **311** with neat TFA and a subsequent cyclization of the resulting cationic intermediate gave **312** in 58% yield. Other arylthio groups were also studied, with compounds **313** and **314** being obtained from the TFAA/TFA conditions in 62 and 41% yield, respectively.

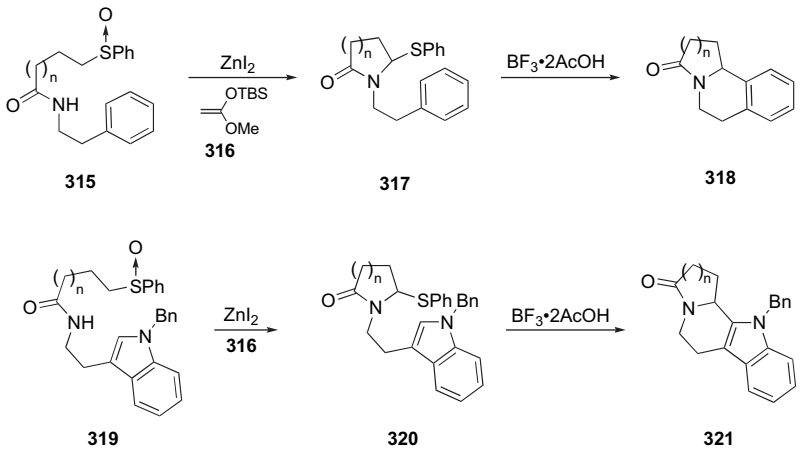
α-Thiophenylamides were also employed as precursors for the formation of *N*-acyliminium ions, which were then used as intermediates for subsequent cyclization chemistry. For example, treatment of amido sulfoxide **315** with silylketene acetal **316** in the presence of ZnI_2 gave lactam **317** in excellent yield (>90%, Scheme 65).[106] The action of $BF_3 \cdot 2AcOH$ on **317** led to further ionization of the phenylthio group and cyclization of the resultant iminium ion onto the aromatic ring furnished **318** in 98 (n=1) and 79% (n=2) yields. The indole-substituted amido sulfoxide **319** gave compound **321** via the intermediacy of **320** in good overall yield, when subjected to these reaction conditions.

The above tandem Pummerer/Mannich cyclization cascade was modified to allow the use of dithioketals rather than sulfoxides as thionium ion precursors.[107] This change in thionium ion precursor allowed the Pummerer cyclization to produce the requisite iminium ion in a single reaction vessel. An efficient synthesis of the erythrina alkaloid core demonstrated the utility of this cascade. Keto acid **322** was transformed into the thioketal **323** (Scheme 66). Coupling of **323** with 3,4-dimethoxyphenethylamine using carbonyl diimidazole (CDI) gave **324**. Treatment of **324** with dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) in CH_2Cl_2 at reflux temperatures delivered the indolo-isoquinoline **325** in 71% yield.

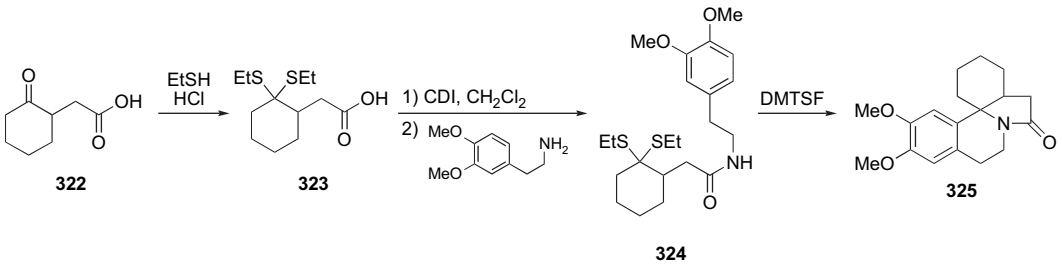
The Padwa group has also made extensive use of a Pummerer-based cyclization cascade for the formation of amidofurans.[108] For example, the lithium enolate of cyclic amides



Scheme 64.



Scheme 65.

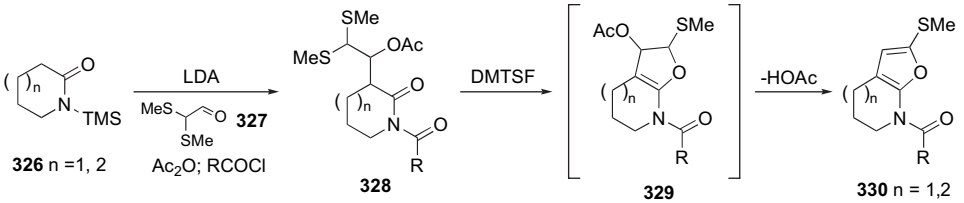


Scheme 66.

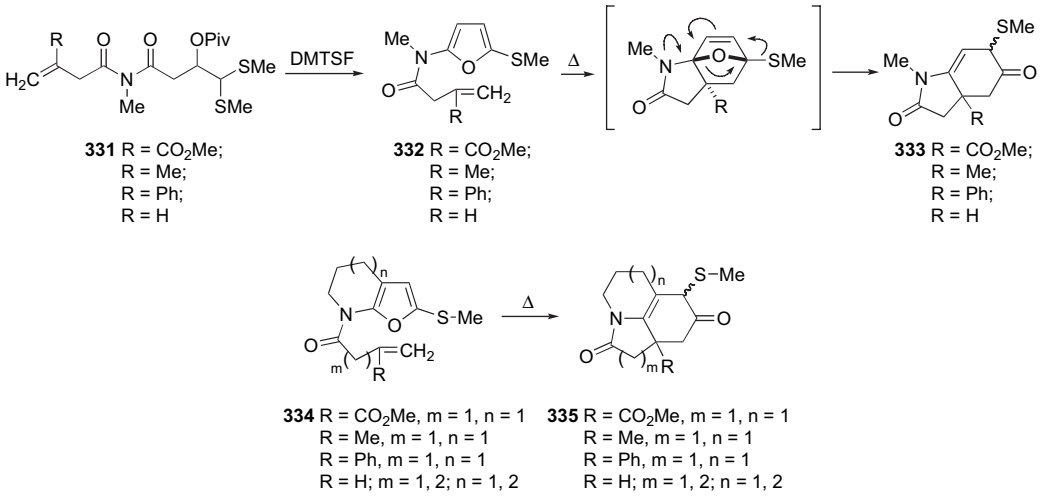
such as **326** added cleanly to bis-(methylsulfanyl)acetaldehyde (**327**) to furnish aldol products of type **328** (Scheme 67).[109] Reaction of **328** with DMTSF triggered a Pummerer cascade process by first inducing the loss of a methylthio group in **328**, which provided a reactive thionium ion intermediate. This cation reacts with the proximal carbonyl group to give the dihydrofuran derivative **329**. Elimination of acetic acid under the reaction conditions furnished amidofurans **330** in 70–80% isolated yields.

A variety of 2-methylthio-5-amidofuran systems containing a tethered π-bond on the amido nitrogen were prepared and utilized for a subsequent intramolecular Diels–Alder reaction.[110] Thus, exposure of imides **331** to DMTSF resulted in the formation of furans **332** in 40–70% yields (Scheme 68). Thermolysis of these furans in toluene at reflux initiated an intramolecular Diels–Alder reaction to first produce an intermediate oxabicyclo adduct. A subsequent fragmentation of the intermediate cycloadduct followed by a 1,2-thio shift provided the bicyclic amides **333** in good yields (ca. 70%). In an analogous manner, the cycloaddition chemistry of amidofurans **334** provided the azatricyclic products **335**. Apparently, the rate of the 1,2-thio shift of the initially formed cycloadduct is much faster than the deprotonation/dehydration pathway previously described in Scheme 25.

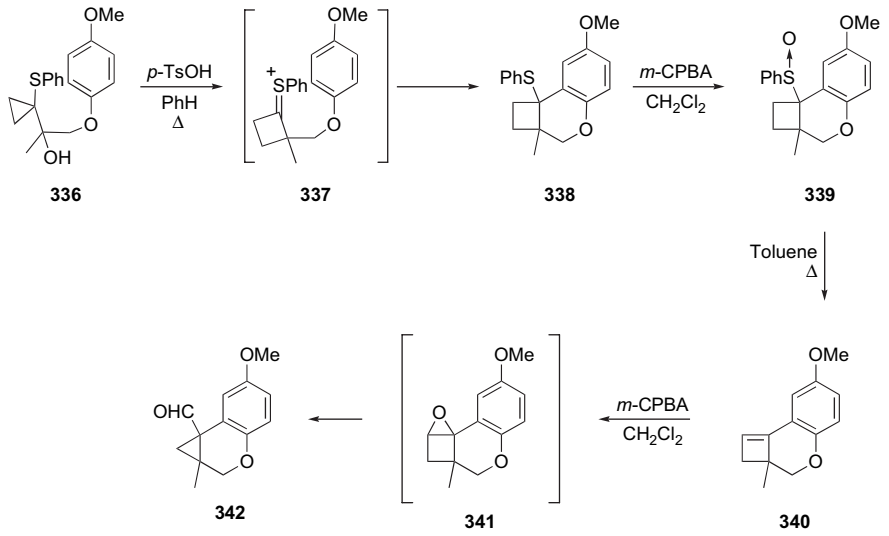
An interesting example of a Wagner–Meerwein-type rearrangement that triggers a subsequent Pummerer cyclization has recently been reported.[111] Phenylsulfanyl-cyclopropane **336** was heated with *p*-TsOH in dry benzene at reflux. Ionization of the hydroxyl group occurred with concomitant ring expansion to give the transient cyclobutyl thionium **337** ion that was subsequently captured by the pendant aryl group to furnish **338** in 77% yield (Scheme 69). Other aryl groups, such as those containing a *p*-Me or a *p*-Cl substituent, also participated in this reaction, as did the unsubstituted analog (67–80% yield). Chromene **338** could be converted into the core structure of the radulanins by treatment with *m*-CPBA, which gave sulfoxide **339** in 70% yield. Thermolysis of **339** in toluene resulted in the elimination of PhSOH producing **340** in 83% yield. Further exposure of **340** to *m*-CPBA induced a ring contraction reaction. This reaction presumably



Scheme 67.



Scheme 68.



Scheme 69.

proceeds through the intermediacy of epoxide **341** and provides **342** whose carbon skeleton is found in the radulanin family of natural products.

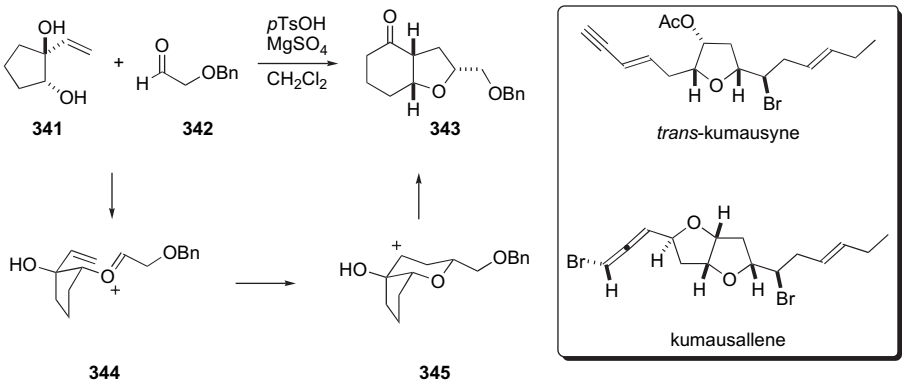
4.3. Prins-pinacol cascades

The Overman group has made effective use of a pinacol-terminated Prins cyclization cascade for the synthesis of oxygen-containing heterocycles.[112] His synthetic strategy for the synthesis of several *Laurencia* sesquiterpenes, such as kumausyne and kumausallene, focused on the acid-mediated reaction of (1*S*,2*R*)-1-vinylcyclopentane-1,2-diol with 2-(benzyloxy)acetaldehyde. This reaction led to tetrahydrofuran **343**, which contains the requisite stereochemistry for these natural products (Scheme 70). In this reaction, the *p*-TsOH-mediated condensation first generated oxonium ion **344**. A Prins cyclization then afforded carbocation **345**, which underwent a pinacol rearrangement to furnish racemic **343** in 69% yield. Enantiomerically enriched starting (1*S*,2*R*)-diol (84% ee) gave (−)-**343** in 57% yield under similar conditions.

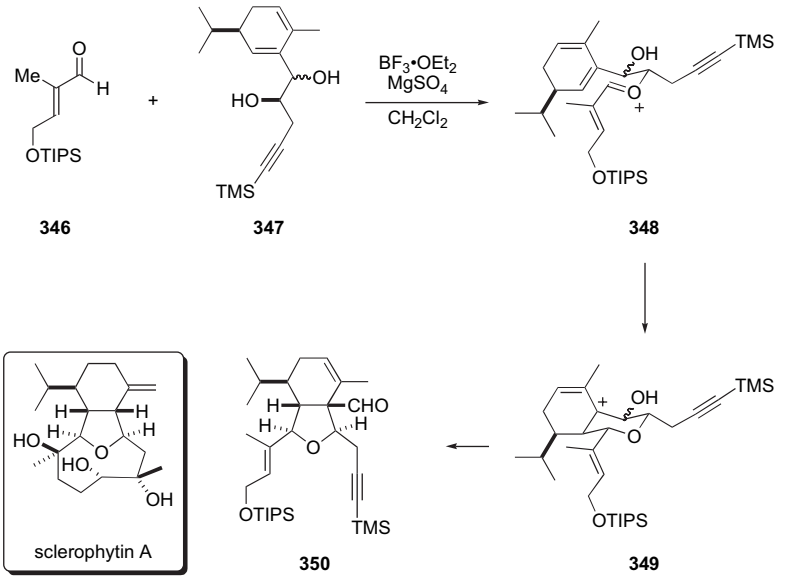
Application of the Prins-pinacol strategy also led to the synthesis of several cembranoid diterpenes. In these syntheses, $BF_3 \cdot OEt_2$ promoted the condensation of aldehyde **346** with diol **347**, which generated oxonium ion **348** that underwent a subsequent Prins cyclization to provide **349** (Scheme 71). The Pinacol rearrangement of **349** then afforded tetrahydrofuran **350** in 79% yield. This compound was employed for the construction of several natural products, including sclerophytin A.

4.4. Other cationic cyclizations

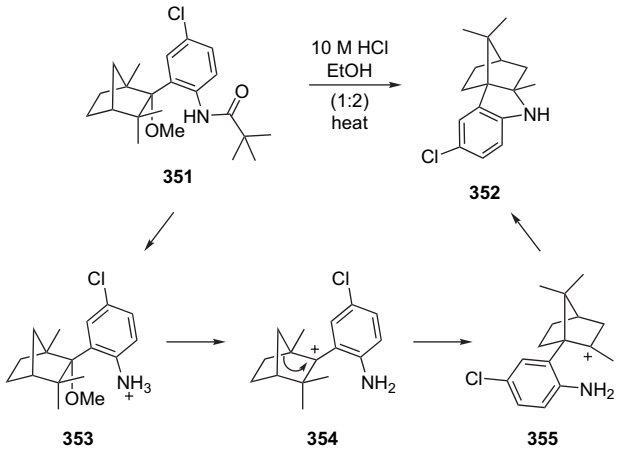
A tandem Wagner–Meerwein rearrangement/carbocation cyclization was used to synthesize several fenchone-derived systems.[113] Heating a mixture of HCl and amide **351** at reflux temperature in aqueous ethanol for 24 h produced the indole derivative **352** in 60% yield (Scheme 72). Presumably, this reaction involves hydrolysis of amide **351** to initially produce compound **353**. Solvolysis of **353** then provided carbocation **354**, which undergoes a rearrangement



Scheme 70.



Scheme 71.



Scheme 72.

to give **355**. Carbocation capture by the adjacent nitrogen ultimately affords the ammonium salt of **352**.

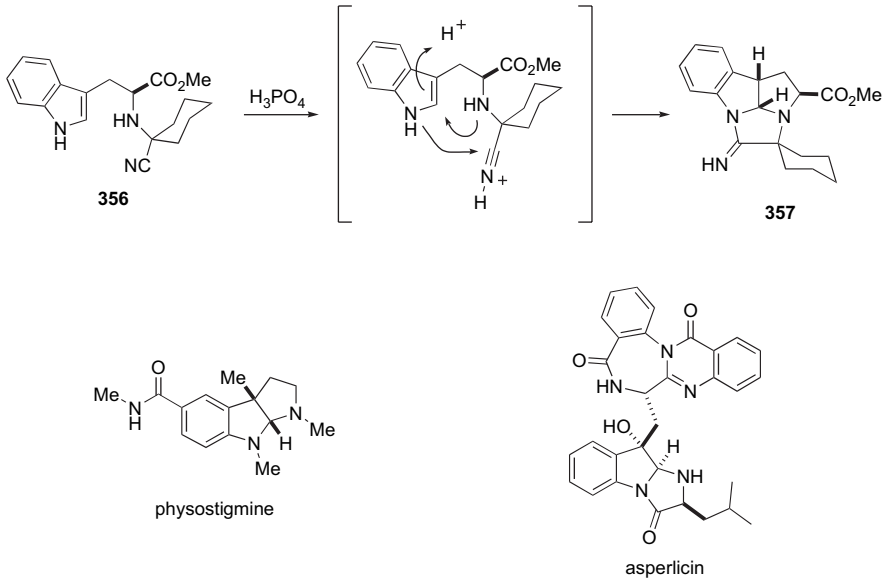
When stirred in 85% H_3PO_4, the tryptophan derived α-amino nitrile **356** underwent a stereospecific cyclization cascade to give **357** in nearly quantitative yield (Scheme 73).[114] The formation of tetracyclic **357** is interesting because this compound incorporates both the tetrahydropyrrolo[2,3-*b*]indole structure, which is found in physostigmine and related alkaloids, and the tetrahydroimidazo[1,2-*a*]indole skeleton, which is present in asperlicin and related natural products.

5. Radical cyclizations

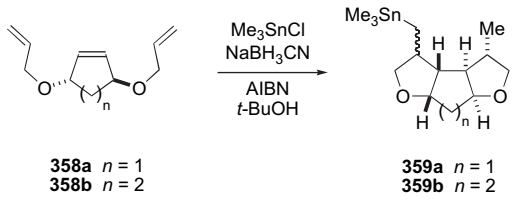
5.1. Polycyclic cascades

Polyethers are readily accessible by tandem radical cyclizations. For example, bis-allylethers **358a**,**b** react with a trimethyl tin radical and then undergoes a sequential radical cyclization to provide **359a**,**b** in 86 and 85% yield, respectively (Scheme 74).[115] A ceric ammonium nitrate oxidation of **359** was carried out in methanol and converted the stannyl moiety into the corresponding dimethylacetal.

Several groups have reported the use of a radical cyclization cascade to form nitrogenous polycyclic structures. In one example, Parsons treated enamide **360** with Ph_3SnH in the

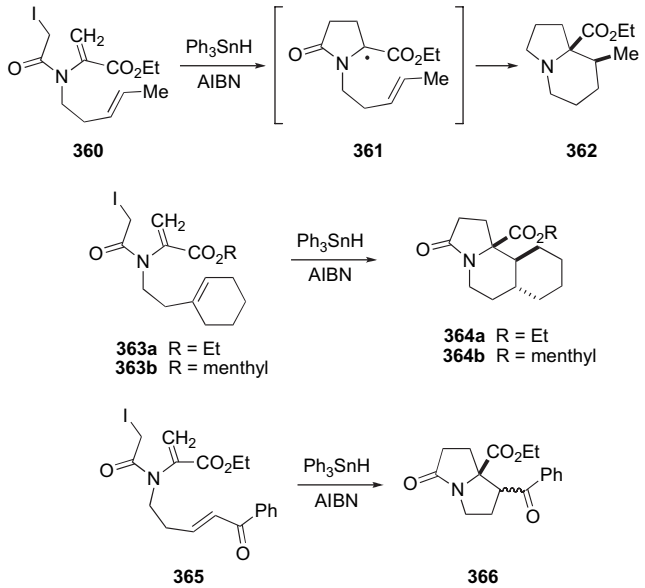


Scheme 73.



Scheme 74.

presence of AIBN to produce **362** in 40% yield (Scheme 75).[116] In this case, cyclization of the intermediate α-amino ester radical proceeded through a 6-*endo-trig* pathway rather than the typically more rapid 5-*exo-trig* closure. The isolation of the 6-*endo-trig* product most likely reflects the reversibility of the ring closure step, thereby allowing thermodynamic product stability to dictate the course of the reaction. When subjected to the same conditions, **363a** produced **364a** as a single diastereomer. Unfortunately, the incorporation of a menthol chiral auxiliary onto the ester group (i.e., **363b**) led to **364b** as mixture of six diastereomers in 38% yield, suggesting that this is not a suitable way to control stereoselectivity in these cyclization reactions.

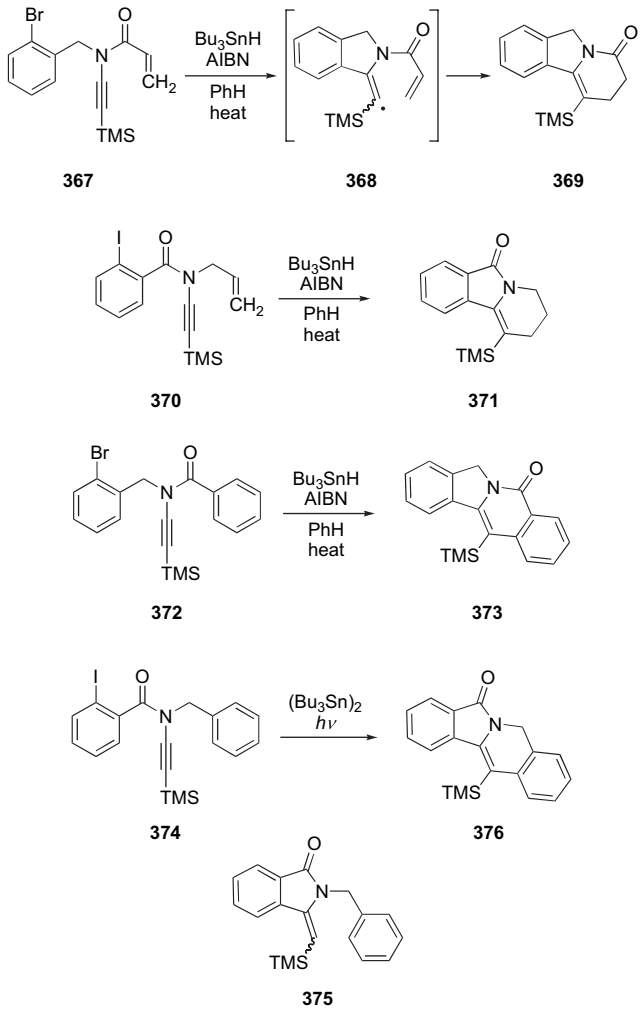


Scheme 75.

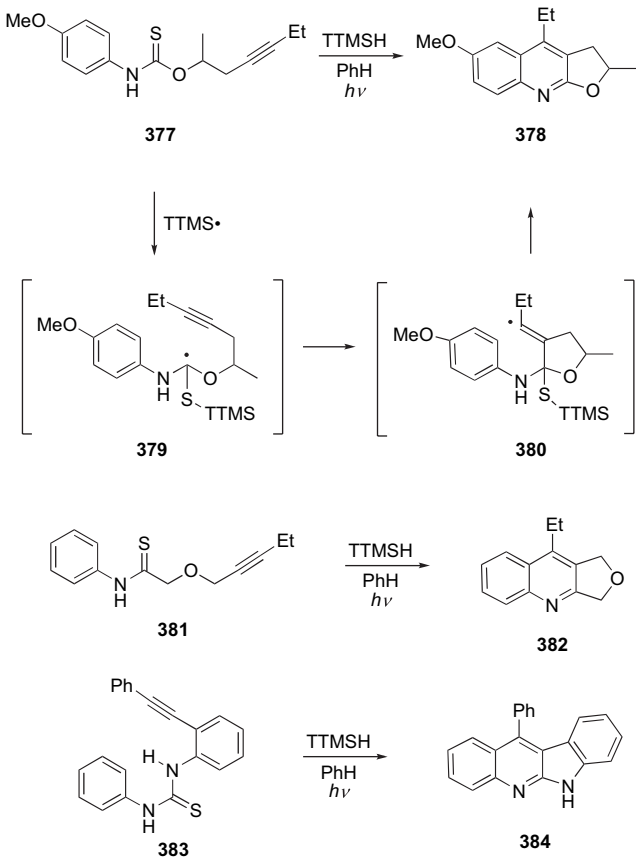
The pyrrolizidinone ring can also be generated using this methodology if the intermediate α-amino ester radical undergoes cyclization onto an appropriately tethered electron-poor double bond. For example, enamide **365** reacted with Ph_3SnH in the presence of AIBN to produce **366** in 52% yield as a 1.6:1 mixture of diastereomers, where the cis-isomer predominates.[128] By incorporating a radical stabilizing group onto the π-bond, the reversibility of the 5-*exo-trig* ring closure was reduced, thereby allowing isolation of the kinetically controlled product.

Ynamides also participate in radical cascade reactions. The Bu_3SnH-mediated cyclization of **367** afforded tricyclic amide **369** in 70% yield via the intermediacy of radical **368** (Scheme 76).[117] Similarly, subjection of ynamide **370**, in which the carbonyl group is no longer part of the radical acceptor, to the same experimental conditions gave **371** in 90% yield. Ynamide **372**, which contains a benzoyl radical acceptor, produced compound **373** in 67% yield, whereas **374** gave only pyrrolidinone **375** in 57% yield under identical conditions. Photolysis of $(Bu_3Sn)_2$, however, promoted the conversion of **374** into **376** in 46% yield.

The Curran group has examined the use of thiocarbonyl derivatives for the radical cyclization cascade and employed this as a method to form quinoline derivatives. Thus, thiocarbamate **377** was allowed to react with tris-trimethylsilyl silane (TTMSH) under irradiation (UV) conditions and this resulted in the formation of **378** in 67% yield (Scheme 77).[118] Tin reagents failed to mediate this reaction. Variously substituted analogs of **377** also participated in this cyclization cascade, affording quinoline derivatives (i.e., **378**) in 44–88% yield. The mechanism of the cyclization is believed



Scheme 76.



Scheme 77.

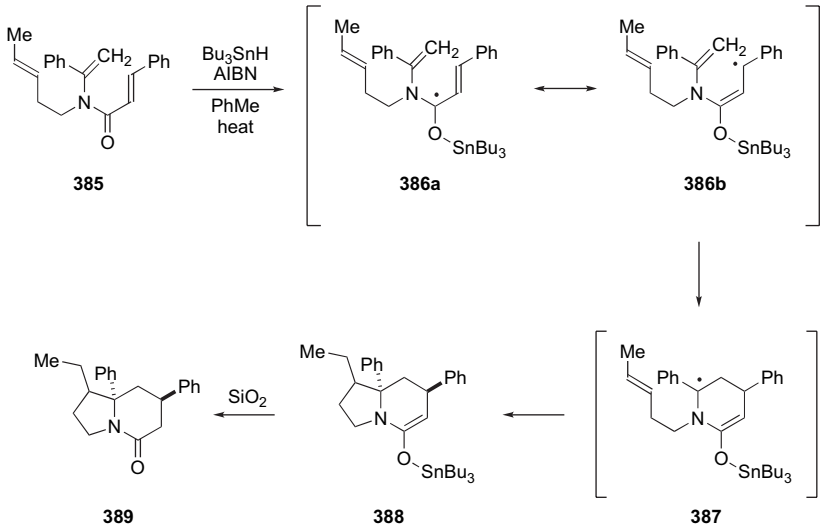
to involve addition of the radical derived from TTMSH onto the sulfur atom to generate an α-thioamino radical **379**, which undergoes a subsequent cyclization onto the pendant alkyne to give vinyl radical **380**. A second cyclization onto the aryl ring then provides **378** (Scheme 77). Substrates possessing substituents in the *meta*-position of the aryl ring afforded 1:1 mixture of regioisomeric products.

Thioamides and thioureas also undergo the silyl-mediated cascade reaction. For example, compound **381** gave **382** in 67% yield, while structural variants generally afforded related cyclized products in 50–87% yield. Thiourea **383** provided **384** in 64% yield, although a related substrate whose alkyne tether was conformationally more flexible failed to produce any cyclized product.

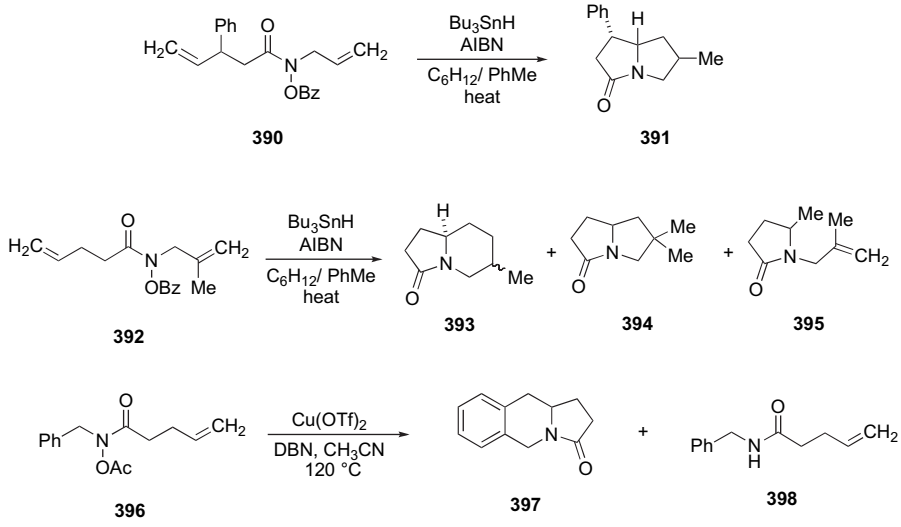
A novel application of the radical cascade for construction of the indolizidinone skeleton focused on the initial formation of *O*-stannyl ketyls. The tributyl tin radical was found to react with the carbonyl group of **385** to give ketyl **386** (Scheme 78).[119] Consecutive 6-*endo* and 5-*exo-trig* cyclizations then furnished stannyl enol ether **388**. Eventual hydrolysis of the enol ether provided indolizidinone **389** in 36% yield as a 1:1 mixture of diastereomers. Again, the predominant isolation of the thermodynamic favored products derived from a 6-*endo-trig* cyclization can be attributed to the stability of **386b**, suggesting that the cyclization to **387** is a reversible process. Without the stabilizing phenyl group, the conditions required to effect the first cyclization were much harsher, and a 5-*exo-trig* product was isolated.

Nitrogen centered radicals have received considerable attention in recent years. In particular, amidyl radicals have been shown to enter into cascade reactions to form pyrrolizidinone and indolizidinone derivatives. Thus, heating the *O*-benzoyl hydroxamic acid derivative **390** with Bu_3SnH in the presence of AIBN produced **391** as a 3:2 mixture of diastereomers (Scheme 79).[120] Separation of compound **391** from the tin residues was difficult, and the isolated yield (17%) was consequently low. When **392** was subjected to identical conditions, a 2:1 mixture of indolizidine **393** and pyrrolizidine **394** was isolated in 42% yield, along with the monocyclic product **395** in 5% yield. Attempts to induce addition of a radical intermediate onto an aromatic ring and thereby form molecules like **397** failed. However, by adding Cu^{2+} salts to the reaction mixture, this permitted the tandem radical cyclization to occur. It was suggested that the intermediate carbon centered radical was first oxidized to a carbocation and this was followed by a Friedel–Craft type reaction. Thus, under high dilution conditions in CH_3CN, compound **396** was converted into **397** in 53% yield. Some reduced starting material (i.e., **398**) was also produced in 40% yield.

The Bowman group investigated different ways to use aminyl radicals for cyclization so as to produce azacycles.



Scheme 78.

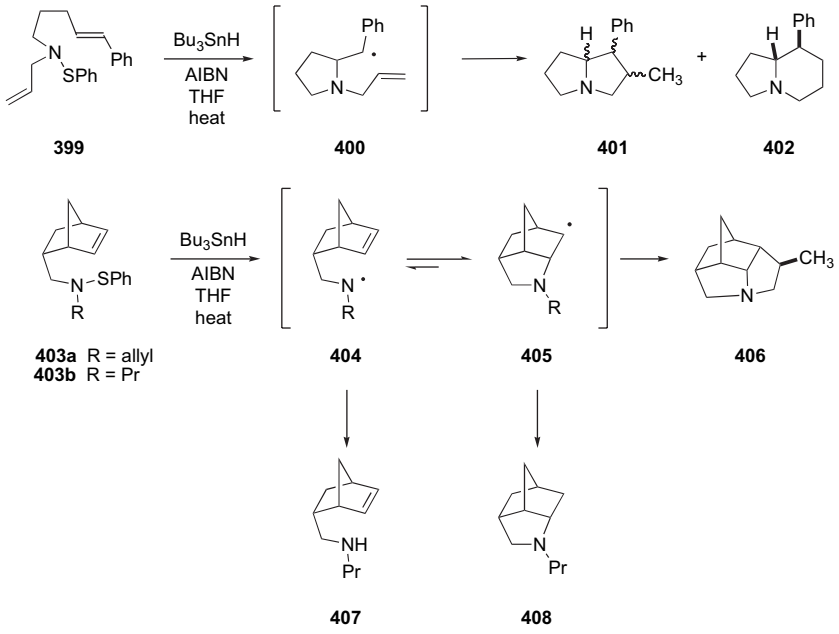


Scheme 79.

Aminyl radicals generally do not react well with alkenes. Bowman found, however, that these radicals will cyclize onto alkenes that are 'activated'. For example, sulfenamide **399** when reacted with Bu_3SnH and AIBN in THF at reflux temperatures delivered pyrrolizidine **401** as a mixture of three diastereomers in 49% yield, as well as indolizidine **402** and 14% yield (Scheme 80).[121] Although the 5-*exo-trig* cyclization pathway is kinetically favored, the 6-*endo-trig* pathway does lead to the thermodynamically more stable radical. The formation of **402** suggests that cyclization of the intermediate radical **400** onto the tethered π-bond is a reversible process.

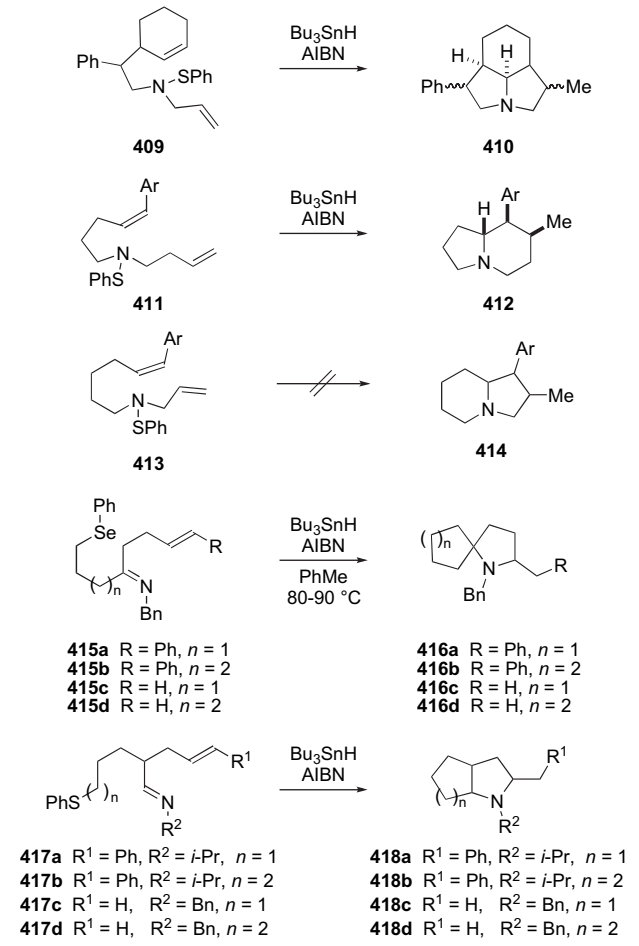
The difficulty associated with cyclization of the aminyl radical onto a π-bond is probably related to a competition between the rate of cyclization versus hydrogen abstraction from the tin hydride. Since the 5-*exo-trig* cyclization of the *endo*-2-(bicyclo[2.2.1]hept-2-en-5-yl)ethyl system is one of the fastest radical reactions known, sulfenamides **403a**,**b** were constructed and then subjected to the cyclization conditions. The course of the reaction was found to depend upon the choice of the substituent group on nitrogen. When **403a** was treated with Bu_3SnH and AIBN, the *N*-allyl group acted as an internal radical trap and gave rise to **406** in 90% yield. Without the presence of the π-bond, products such as **407** were isolated in approximately 6% yield along with the cyclization product **408** (29% yield). The results were interpreted in terms of a fast but reversible cyclization of **404** to give **405**. In the absence of the internal allyl group, hydrogen abstraction by radical **404** becomes competitive with hydrogen abstraction by radical **405**.

Having established that aminyl radicals can undergo cyclization, several different modes of reaction were explored. Allyl sulfenamide **409** was found to participate in a tandem radical cyclization reaction to produce a 2:2:1 mixture of hexahydroindolines **410** in 30% yield (Scheme 81).[122] The cyclization failed when a related substrate lacking the allyl group was subjected to the same reaction conditions. Sulfenamide **411** underwent a tandem 5-*exo*/6-*endo-trig* cyclization to



Scheme 80.

give indolizidine **412** in 64% yield. Substrates that would require a 6-*endo*/5-*exo* cascade to form the indolizidine skeleton (i.e., **413**) failed to cyclize under the radical conditions.



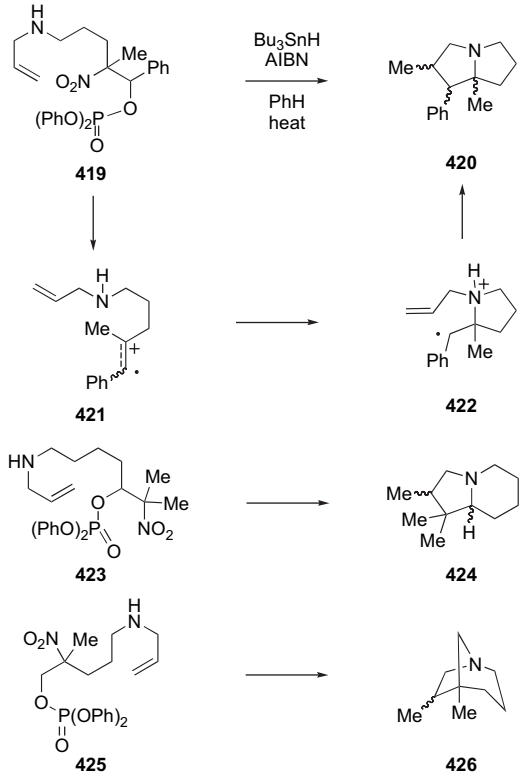
Scheme 81.

Spirocyclic amines can also be formed by using cyclization cascades that involve aminyl radicals. The AIBN promoted reaction of ketimines **415a**,**b** with Bu_3SnH in toluene provided **416a**,**b** in 34 and 30% yields, respectively.[123] Ketimines **415c**,**d** failed to produce spirocycles under these conditions. However, in the presence of $MgBr_2 \cdot Et_2O$, compounds **415c**,**d** underwent the tandem cyclization reaction to give **416c**,**d** in 24 and 33% yield, respectively. Aldimines **417a–d** reacted similarly to afford bicyclic amines **418a–d** in 40, 58, 27, and 33% yield. Again, substrates containing an aromatic group, which provides stabilization for the intermediate radical produced from the cyclization, gave higher yields of bicyclic products. Adding $MgBr_2 \cdot Et_2O$ to the reaction mixture increased the yield of **418c** to 35% yield.

Crich and co-workers developed a novel radical-cation cascade for the construction of azapolycycles. Thermolysis of compound **419** with Bu_3SnH and AIBN in benzene produced pyrrolizidine **420** as a mixture of diastereomers in 85% overall yield (Scheme 82).[124] The reaction was thought to proceed via the formation of radical cation **421**, which was generated by homolytic cleavage of the nitro group and ionization of the phosphate ester moiety. Intramolecular addition of the nitrogen onto the cationic center would then provide radical **422** that could cyclize to give the final product. Depending upon the substitution pattern of the starting nitro compound, a variety of fused and bridged bicyclic amines are possible. For example, allyl amine **423** produced **424** as a 1:1 mixture of diastereomers in 78% yield, whereas **425** afforded **426** as a 2:1 mixture of diastereomers in 78% yield.

6. Metathesis

In recent years, the ring-closing olefin metathesis (RCM) reaction has become one of the more powerful tools for the synthesis of heterocycles,[125] particularly medium-sized

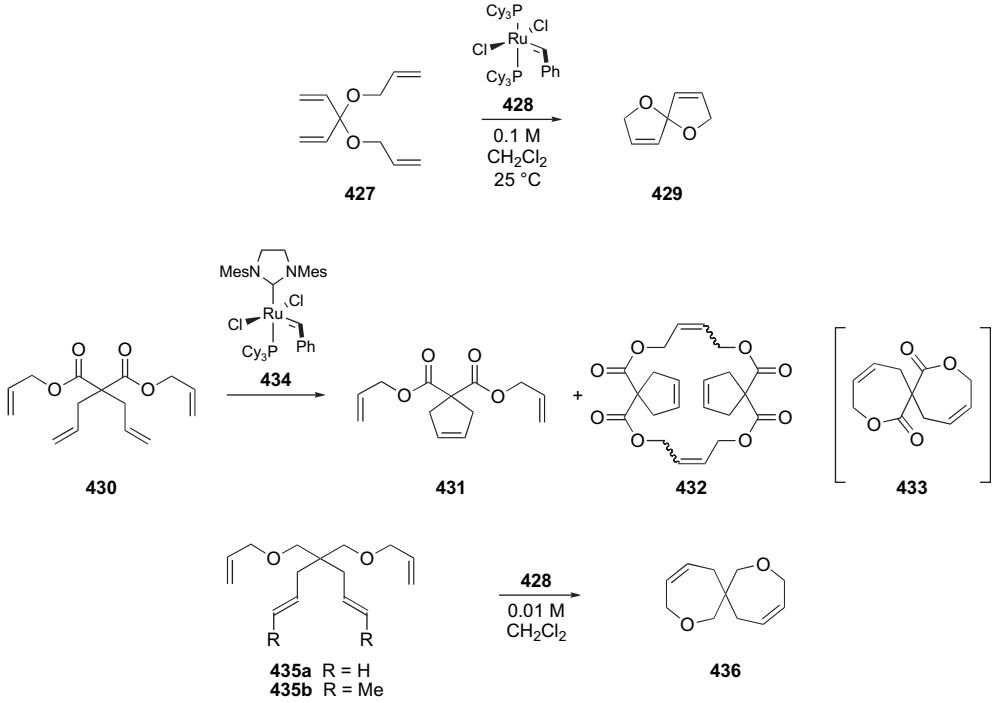


Scheme 82.

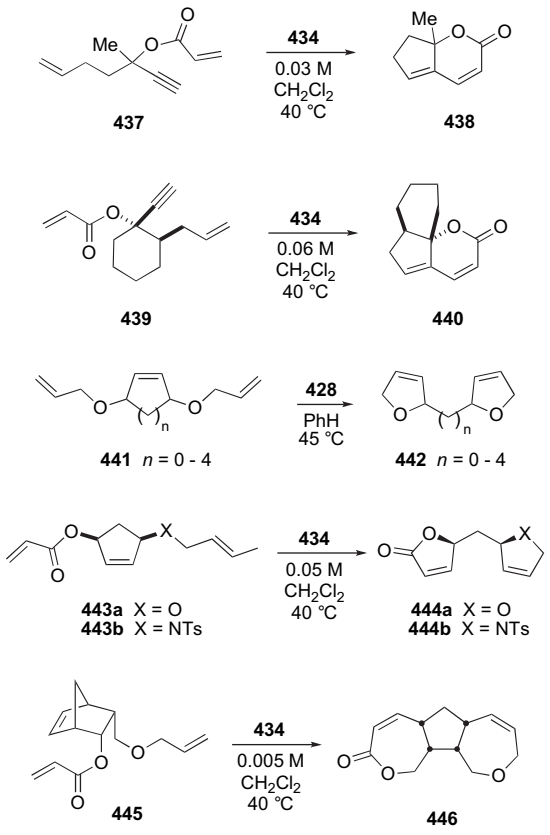
rings that are hard to form by other methods. Of the cascade reactions involving RCM, many are multiple sequential ring closures or involve a tandem ring-opening/ring-closing reaction. Appropriately arrayed polyenes easily undergo multiple ring-closing metathesis reactions. For example, Harrity and co-workers demonstrated that the Grubbs' first generation catalyst **428** catalyzed the conversion of tetraene **427** into the spirocyclic **429** in 90% yield (Scheme 83).[126] None of the corresponding seven-membered ring product was isolated under these conditions. RCM reactions are known to be sensitive to conformational preferences within a molecule as well as substitution on the participating alkene. For example, diester **430** afforded **431** in 50% yield and macrocycle **432** in 19% yield, along with other dimeric material, when exposed to catalytic quantities of **428** at room temperature in CH_2Cl_2.[127] Use of the second-generation Grubbs' catalyst **428** increased the yield of **432** (up to 45% yield), but no detectable amount of **433** was observed. Diether **435a** underwent reaction with **428** to give mixture that contained spirocycle **436**, but only in 21% yield. Formation of five-membered rings continues to be the dominant pathway. To retard the formation of the five-membered ring products, diether **435b** was synthesized and underwent reaction with **428** to produce spirocyclic **436** in 46% yield.

The Grubbs group has made extensive use of the tandem RCM cascade with tethered alkynes to produce heterocyclic compounds. For example, acyclic ester **437** reacted in the presence of 5 mol % of catalyst **434** in CH_2Cl_2 at 40 °C to furnish bicyclic lactone **438** in 95% yield (Scheme 84).[128] The cyclic alkyne **439** reacted under the same conditions to give **440** in 74% yield.

Strained cycloalkenes that contain appropriately tethered olefins can also undergo the tandem ring-opening metathesis/RCM cascade. Using the first generation catalyst **428**, Grubbs transformed a series of diallyloxy-cycloalkenes **441** into bis-furan derivatives **442** in moderate to good yields (57–90%).[129] Likewise, cyclopentenes **443a**,**b** reacted in the presence of catalyst **434** to afford **444a**,**b** in 81 and 89%



Scheme 83.

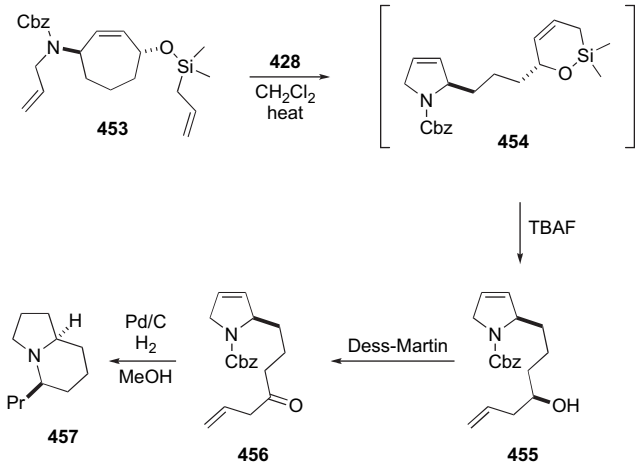


Scheme 84.

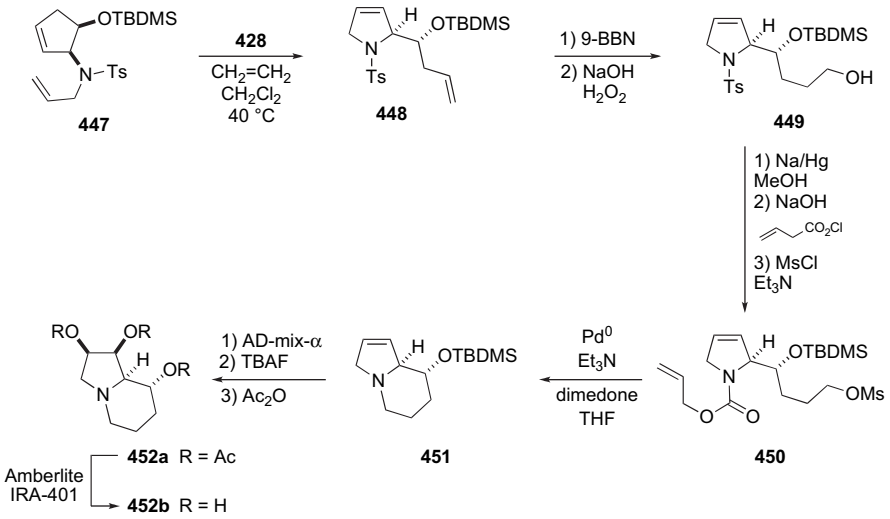
yield, respectively.[128] Bicycloalkene **445** was converted into tricyclic **446** in 47% yield.

The Blechert group exploited the ring-opening/ring-closing cascade for the synthesis of several natural products. In a synthesis of (−)-swainsonine (**452b**), sulfonamide **447** was heated at 40 °C with 5 mol % Grubbs catalyst **428** under an atmosphere of ethene to provide pyrroline derivative **448** in 98% yield.[130] Hydroboration of the terminal alkene in **448** with 9-BBN followed by an oxidative workup under alkaline conditions gave alcohol **449** in 83% yield. The sulfonamide was cleaved by the action of Na/Hg. Acylation of the resulting free amino nitrogen with allyl chloroformate followed by mesylation afforded **450** in 87% yield from **449**. Palladium-mediated removal of the allyl carbamate group liberated a basic nitrogen that subsequently displaced the mesylate group to produce **451** in 95% yield. An asymmetric dihydroxylation of **451** produced an inseparable 20:1 mixture of diastereomeric diols. Separation of these diastereomers required removal of the silyl ether and conversion of the resulting triol into the triacetate occurred in 68% yield and with isomer **452a** predominating. A base promoted hydrolysis then yielded the desired target **452b** in 96% yield (Scheme 85).

Extending this approach, Blechert group reported a particularly efficient synthesis of indolizidine 167B (**457**) (Scheme 86). The cycloheptene derivative **453** was initially converted into silacycle **454** by the action of catalyst **428**.[131] A subsequent addition of TBAF to the reaction mixture promoted cleavage of the silicon group to give **455** in 92% yield from **453**. Oxidation of the alcohol using the Dess–Martin



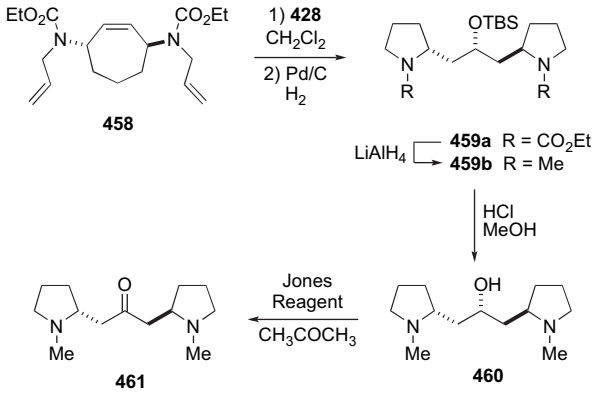
Scheme 86.



Scheme 85.

periodane reagent afforded ketone **456** in 73% yield. A palladium-mediated hydrogenolysis of the benzyl carbamate was accompanied by intramolecular reductive amination of the ketone and this was followed by reduction of the alkene to provide **457** in 79% yield.

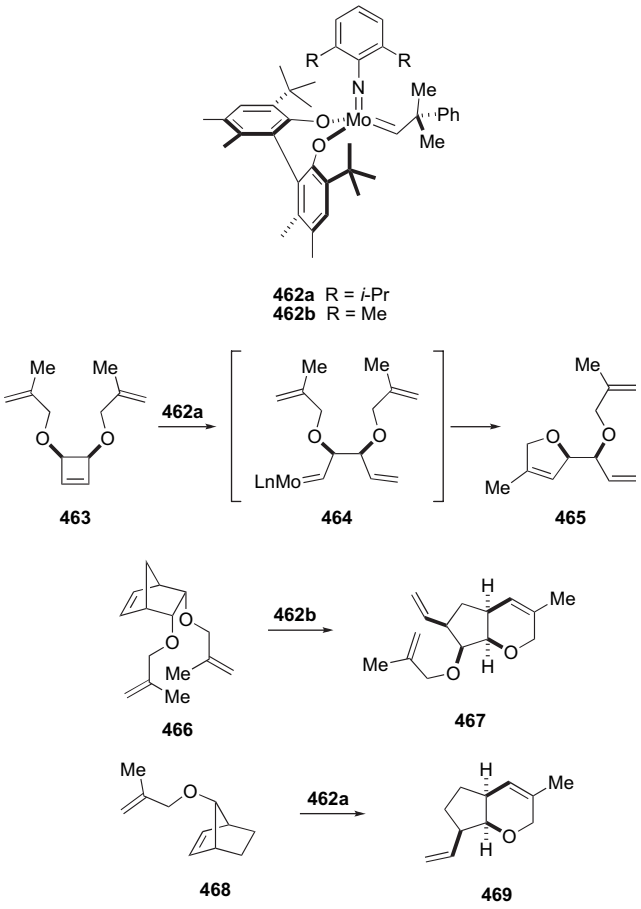
Synthesis of the alkaloid cuscohygrine (**461**) also came about from this methodology (Scheme 87). Exposing bis-carbamate **458** to catalyst **428** in hot CH_2Cl_2 produced a bis-pyrroline derivative whose double bonds proved to be unstable.[132] Accordingly, the crude metathesis reaction mixture was treated with palladium in the presence of a hydrogen atmosphere to give **459a** in 72% yield from **458**. Reduction of the carbamate protecting group by the action of $LiAlH_4$ afforded **459b** in 92% yield. An acid-mediated hydrolysis of the silyl ether provided (+)-dehydrocuscohygrine (**460**) in 89% yield. Further oxidation of the alcohol under Jones conditions produced the desired target **461** in 73% yield.



Scheme 87.

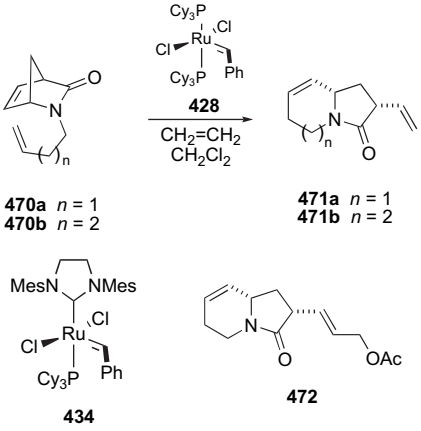
Recently, Hoveyda and Schrock have developed molybdenum-based catalysts (i.e., **462a**,**b**) for an asymmetric ring-opening metathesis (AROM) reaction (Scheme 88).[133] Using a tandem AROM/RCM sequence, they examined the asymmetric synthesis of several heterocyclic compounds. For example, *meso* bis-ether **463** delivered **465** in 69% yield and with a 92% ee upon exposure to 5 mol % of **462a**.[134] In this case, ring opening by the catalyst was faster than the metathesis reaction with one of the pendant alkenes, and alkylidene carbene **464** was enantiospecifically produced as an intermediate. However, the less sterically hindered catalyst **462b** mediated the transformation of **466** into **467** in 84% yield and with greater than 98% ee. Interestingly, **468** could be converted into **469** by the action of catalyst **462b** in 60% yield and with 72% ee, whereas catalyst **462a** did not promote the reaction. By adding diallyl ether to the reaction mixture, **462a** did catalyze the reaction and provided **469** in 54% yield but with 92% ee.

Building on their earlier tandem ring-opening/cross-metathesis studies,[135] Arjona and Plumet have applied the ring-opening/ring-closing/cross-metathesis cascade[136] to the synthesis of various nitrogenous heterocycles. For example, bicyclic amides **470a**,**b** reacted with ethene in the presence of Grubbs catalyst **428** to give **471a**,**b** in 65 and 60% yields, respectively (Scheme 89).[137] Bicyclic lactams **471** were the expected products of a ring-opening/ring-closing metathesis cascade without the initial cross-metathesis with ethylene.



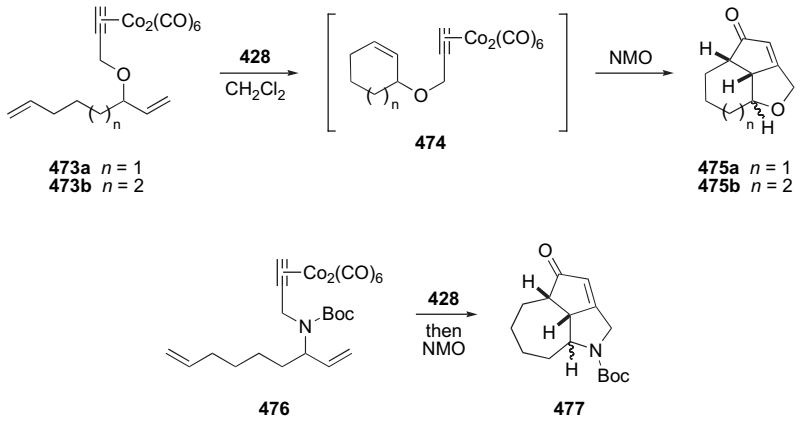
Scheme 88.

To demonstrate the actual cross-metathesis reaction, allyl acetate was used as the partner. In this case, compound **470a** reacted with catalyst **428** and allyl acetate and gave **472** in 40% isolated yield along with **471a** in 30% yield. By changing to catalyst **434**, the yield of **472** was increased to 65% yield, though **471a** was again produced in 30% yield.



Scheme 89.

A one-pot sequential RCM/Pauson–Khand reaction sequence has been used to synthesize nitrogen- and oxygen-containing polycycles. The cobalt–alkyne complexes **473a**,**b** reacted in the presence of Grubbs catalyst **428** to give **474** (Scheme 90).[138] The addition of NMO to the crude reaction



Scheme 90.

mixture promoted the Pauson–Khand reaction and provided **475a**,**b** in 81 and 70% yield as mixture of diastereomers. Similarly, **476** underwent the tandem RCM/Pauson–Khand to produce **477** in 67% yield.

7. Concluding remarks

From the selective sampling of cascade reactions for the synthesis of heterocyclic molecules that has been outlined in this mini review, it is clear that virtually any reaction can be incorporated into a tandem sequence. Some cascade sequences increase molecular complexity more than others, but each seems to provide complex heterocyclic structures in a more efficient manner than the corresponding chemistry wherein each intermediate is isolated. Indeed, many of these cascades rapidly construct hetero-polycyclic systems that are difficult to produce in other ways.

Several domino cascade sequences for heterocyclic synthesis have been well explored; Padwa's rhodium carbenoid-initiated dipolar cycloadditions, Denmark's nitroalkene [4+2]/[3+2]-cycloadditions, Overman's aza-Cope/Mannich cascade, and Grubbs's ring-closing metathesis chemistry have all matured into significant synthetic tools. Familiar multi-component reactions, such as the Ugi reaction, are being used in interesting ways. Others sequences not covered in this mini review show tremendous promise; Fu's asymmetric Kinugasa reaction, indium-initiated radical cascades, Buchwald's copper catalyzed N-arylation reactions, Trost's alkyne heterocyclization, and the Hoveyda and Schrock tandem AROM/RCM reactions all provide improvements in stereoselectivity and involve the use of environmentally benign reagents. Continued development of these domino cascade reactions will have a significant impact on the processes used to make heterocyclic compounds on an industrial scale.

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Biographical sketch

Albert Padwa was born in New York City. He received both his B.A. and Ph.D. degrees from Columbia University. After a NSF postdoctoral position at the University of Wisconsin, he was appointed as Assistant Professor of Chemistry at the Ohio State University in 1963. He moved to SUNY Buffalo in 1966 as Associate Professor and was promoted to Professor in 1969. Since 1979, he has been the William Patterson Timmie Professor of Chemistry at Emory University. He has held visiting positions at University Claude Bernard, France, University of California at Berkeley, The University of Wurzburg, Germany and Imperial College of Chemistry, UK. He has been the recipient of an Alfred P. Sloan Fellowship, John S. Guggenheim Fellowship, Alexander von Humboldt Senior Scientist Award, a Fulbright Hays Scholarship, Senior Award in Heterocyclic Chemistry from the International Society of Heterocyclic Chemists, ACS Arthur C. Cope Scholar Award and is the coauthor of more than 650 publications. He served as the Chairman of the Organic Division of the ACS and as President of the International Society of Heterocyclic Chemistry. He has also served as a member of the editorial boards of the Journal of the American Chemical Society, Journal of Organic Chemistry, Organic Letters, and has been the volume editor of Comprehensive Heterocyclic Chemistry, the Synthesis of Science (Vol 27) and is currently one of the Associate Editors of the Journal of Organic Chemistry. His research interests include heterocyclic chemistry, dipolar cycloadditions, alkaloid synthesis, tandem transformations, organometallic chemistry, and organic photochemistry. Aside from chemistry, his other passion is mountain climbing in various parts of the world.

Scott K. Bur received his B.S. from the University of Michigan in 1994 and worked as an extern with Parke-Davis pharmaceuticals in Ann Arbor for one year. He then earned his Ph.D. from the University of Texas at Austin in 2000 under the supervision of Professor Stephen F. Martin. After an NIH postdoctoral fellowship in the laboratories of Professor Albert Padwa at Emory University, he joined the faculty at Gustavus Adolphus College in 2003 as an Assistant Professor. His research interests include heterocyclic methodology, natural product synthesis, and the application of computational methods to the solution of synthetic organic problems.