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# Recent advances in the synthesis of piperidones and piperidines

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## 1. Introduction

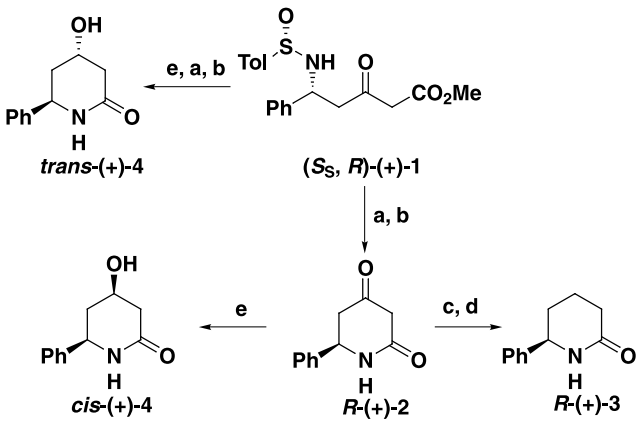
The piperidine ring is an ubiquitous structural feature of many alkaloid natural products and drug candidates. Watson et al. asserted that during a recent 10-year period there were thousands of piperidine compounds mentioned in clinical and preclinical studies.[1] Piperidones are somewhat less prominent, but often they serve a role as advanced intermediates prior to their conversion to piperidines. Reviews updating progress in the stereoselective syntheses of substituted piperidines have appeared recently.[2] The purpose of this review is to compile stereocontrolled approaches to piperidone and piperidine heterocycles, focusing on the published literature from 1999 to present. The review is organized by bond formation or process leading to the heterocyclic ring. Piperidone syntheses are reviewed first and are categorized by the position of the carbonyl group. Next, follow methodologies used to convert piperidones to piperidines. Lastly, piperidine syntheses are discussed. The large volume of published literature over the past three years precludes a comprehensive review. Methodologies were selected on the basis of diversity and stereocontrol, with the intent of providing the reader with a variety of options for the synthesis of these useful heterocycles.

## 2. Synthesis of 2-piperidones

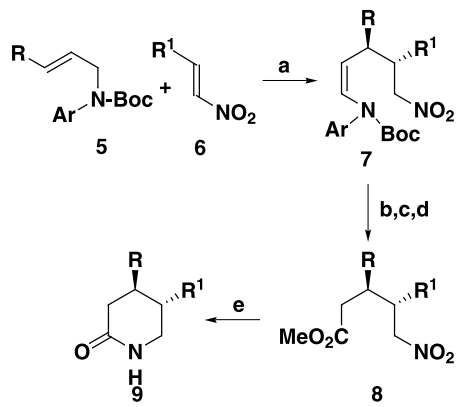
### 2.1. Intramolecular N–C processes

**2.1.1. Lactam formation from acyclic δ-amino carboxylates.** Recent reports from the Davis laboratories highlight the versatility of *N*-sulfinyl-δ-amino-β-ketoesters as designed polyfunctional chiral building blocks (Scheme 1). Enantiopure sulfinimines are prepared readily by the condensation of commercially available (*R*)- or (*S*)-*p*-toluenesulfinimides with aromatic and aliphatic aldehydes and serve as versatile intermediates in the asymmetric synthesis of amine derivatives. For example, β-keto ester (+)-**1** was prepared in one pot by treatment of (*S*)-(+)-*N*-benzylidene-*p*-toluenesulfinamide[3] with excess sodium enolate of methyl acetate. Deprotection and cyclization provided keto lactam **2** which was deoxygenated to 6-phenyl-2-piperidone (**3**) en route to a synthesis of (*R*)-(+)-2-phenylpiperidine.[4] Hydride reduction of **1** was *syn* selective and deprotection/cyclization gave *trans*-(+)-**4**. The synthesis of *cis*-(+)-**4** was achieved by hydride reduction of **2**. Piperidones **4** were advanced intermediates in the asymmetric synthesis of 4-hydroxypipecolic acid stereoisomers[5] where the phenyl group served as a $CO_2H$ surrogate. The utility of *N*-sulfinyl-δ-amino-β-ketoesters in the stereoselective synthesis of the quinolizidine alkaloid (−)-lasubine II was reported,[6] and another application will be highlighted in Section 4.2.1. This methodology provides convenient access to polysubstituted nitrogen heterocycles with minimal protecting group chemistry.

Methodology from the Beak laboratories[7] provides a route to enantiopure, substituted δ-lactams and piperidines (Scheme 2). Enecarbamate **7** was prepared by the enantio- and diastereoselective conjugate addition of lithiated *N*-Boc-allylamine **5** to nitroalkene **6**, easily allowing the introduction of aliphatic, aromatic and heterocyclic




**Scheme 1.** (a) TFA, MeOH; (b) $NaHCO_3$ [90–92%]; (c) $(CH_2SH)_2$, $BF_3{\cdot}OEt_2$, room temperature [85%]; (d) W2 Raney Ni [75%]; (e) $Zn(BH_4)_2$, THF, −78°C.

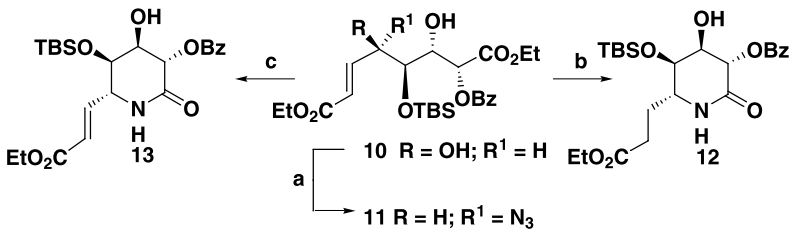


**Scheme 2.** (a) BuLi, (−)-sparteine, PhMe, −78°C, then **6** [73–90%]; (b) HCl, $CHCl_3$; (c) $NaClO_2$, $NaH_2PO_2$; (d) HCl, MeOH; (e) $H_2$, Raney Ni [58–71%].

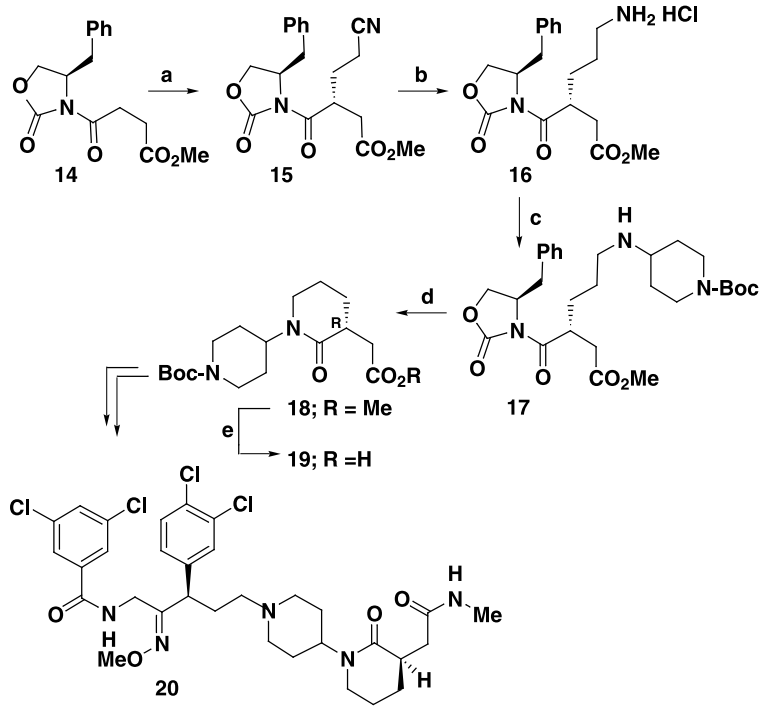
substituents. Hydrolysis of enecarbamate **7** to the aldehyde was followed by oxidation and esterification to nitroester **8**. Reduction and cyclization to lactam **9** afforded single diastereomers in >94% ee. Additionally, reduction of lactam **9** gave 3,4-disubstituted piperidines that could be functionalized at positions adjacent to the nitrogen atom by lithiation/substitution methodology.[8] Enolate alkylation of *N*-protected **9** provided trisubstituted δ-lactams that could be reduced to 3,4,5-trisubstituted piperidines.

A recently reported chiral acyclic building block was useful for syntheses of glycosidase inhibitors such as polyhydroxylated piperidine and indolizidine alkaloids (Scheme 3).[9a] Allylic alcohol **10**[10] underwent selective Mitsunobu inversion to azide **11**. Catalytic hydrogenation and cyclization of **11** gave 2-piperidone **12** while Staudinger reduction/cyclization retained the double bond affording **13**. This chemistry enabled the chemoselective manipulation of the hydroxyl groups and provided a route to highly functionalized 2-piperidones. Additional strategies to glycosidase inhibitors utilizing δ-lactams as advanced intermediates were reported.[9b–e]

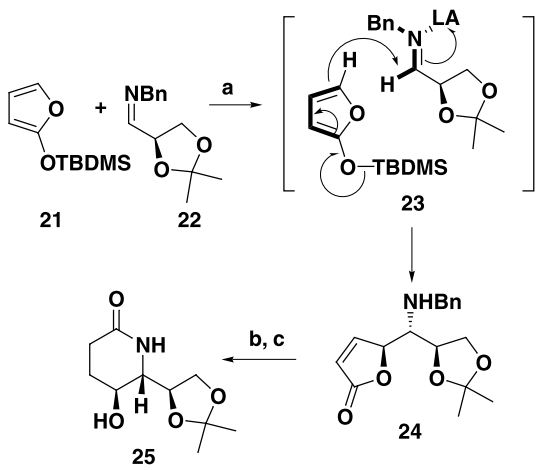
A diastereoselective Michael addition was the key step of a large-scale asymmetric synthesis of the functionalized δ-lactam found in the core fragment of the potent dual $NK_1/NK_2$ antagonist **20** (Scheme 4).[11] Conjugate addition of the enolate of acyl oxazolidinone **14** to acrylonitrile afforded nitrile **15** (de >99%). Hydrogenation of **15** to amine hydrochloride **16** was followed by reductive amination to secondary amine **17**. Thermal cyclization of **17** with extrusion of the oxazolidinone chiral auxiliary



**Scheme 3.** (a) $HN_3$, TPP, DEAD, THF [77%]; (b) $H_2$, 10% Pd/C [62%]; (c) TPP, THF, $H_2O$, reflux [62%].



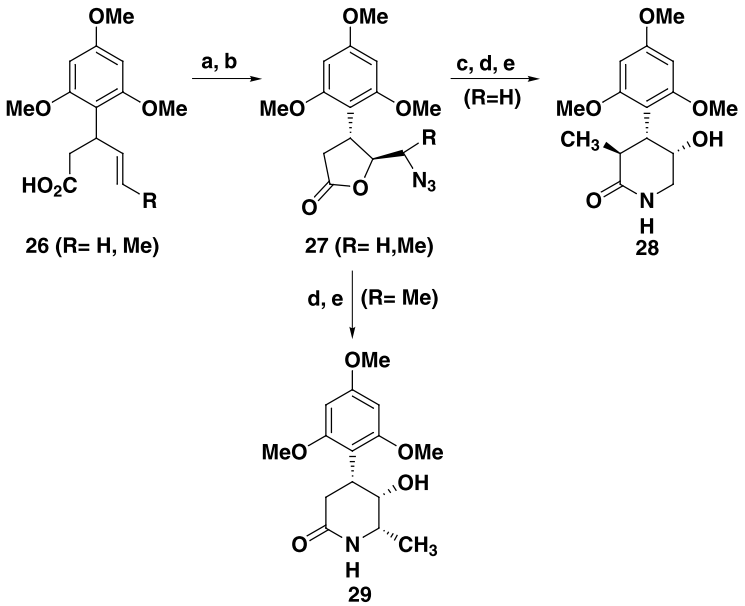
**Scheme 4.** (a) $Ti(O^iPr)Cl_3$, $^iPr_2NEt$, 0°C, then acrylonitrile, 0°C [60%]; (b) $H_2$, Pt/C, TsOH; (c) *N*-Boc-4-piperidone, $NaB(OAc)_3H$, THF; (d) Ph–Me, 110°C; (e) NaOH, PhMe, room temperature [51–67% from **16**].




**Scheme 5.** (a) TBS–OTf, $CH_2Cl_2$, −80°C [83%, dr=9:1]; (b) $H_2$, Pd/C, THF; (c) DBU, 80°C [62%].

provided the δ-amino-γ-lactone that underwent ring rearrangement to δ-lactam **25** upon treatment with DBU at 80°C. Additional functionality was introduced at C-3 by alkylation of the corresponding lactam enolate.

A similar rearrangement was used in a short, stereocontrolled approach to D-ring analogs of flavopiridol,[17] a cyclin-dependent kinase inhibitor in phase II clinical trials (Scheme 6). The iodocyclization[18] of unsaturated carboxylic acid **26** was completely stereoselective. Subsequent treatment with sodium azide afforded multigram quantities of γ-lactones **27**. The enolate of **27** (R=H) was stereoselectively alkylated to a *trans*,*trans* lactone that was converted to **28** by azide reduction and cyclization with base. Direct conversion of **27** (R=Me) to **29** was carried out in a similar manner. This approach provided flexible access to 2-piperidones with contiguous arrays of stereocenters.

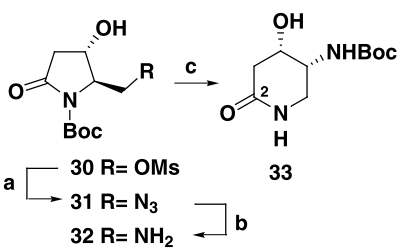



**Scheme 6.** (a) $I_2$, MeCN, 0°C [75–80%]; (b) $NaN_3$ DMF, 100°C [88–95%]; (c) LiHMDS, THF, −70°C, then MeI [60%]; (d) $H_2$ (60 psi), EtOH, 10% Pd/C [100%]; (e) MeONa, MeOH, 65°C [57–75%].

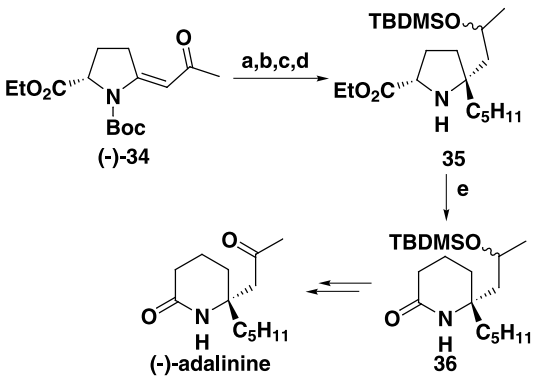
afforded carboxylate **18**, which was saponified to enantiopure carboxylic acid **19** (>99% ee). This process was used to prepare multikilogram quantities of **19** with minimal chromatographic purification.

**2.1.2. Ring rearrangements.** The rearrangement of δ-amino-γ-lactones to δ-lactams is well precedented,[12] and recent applications of this procedure were used to prepare glycosidase inhibitors,[13,14] that were designed as aza-analogs of natural glycosides. In an approach to the synthesis of cyclic inhibitors of HIV protease,[15] a vinylogous Mannich reaction[16] was used to construct a δ-amino-γ-butenolide scaffold with high diastereoselectivity (Scheme 5). The addition of 2-(*tert*-butyldimethylsilyloxy)furan **21** to *N*-benzylimine **22** was carried out in the presence of a Lewis acid catalyst producing butenolide **24**. Felkin model **23** accounted for the observed diastereoselectivity by addition of the nucleophile to the more accessible *Si* face. Hydrogenation of **24** with concomitant removal of the benzyl group

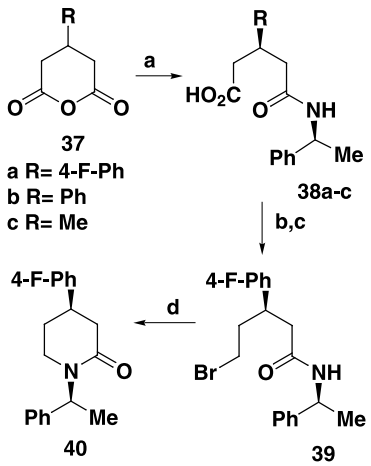
An analogous intramolecular transamidation was used in a stereoselective, formal synthesis of the piperidine alkaloid pseudodistomin C (Scheme 7).[19a] Thus, mesylate **30** was prepared from (*S*)-pyroglutaminol and converted via azide **31** into amine **32**. Translactamization occurred quantitatively to δ-lactam **33**. An alternate synthesis of **33**, using an intramolecular Mitsunobu reaction was reported.[19b]




**Scheme 7.** (a) $NaN_3$, DMF [90%]; (b) $H_2$, MeOH, 10% Pd/C [100%]; (c) MeOH, 65°C [100%].




**Scheme 8.** (a) $^{n}C_5H_{11}MgBr$, $CuBr{\cdot}SMe_2$, $BF_3{\cdot}OEt_2$, THF, −78°C [100%]; (c) TFA, $CH_2Cl_2$ [95%]; (d) TBDMS Cl, DMAP, $CH_2Cl_2$ [91%]; (c) $SmI_2$, $^{t}BuCO_2H$, THF, HMPA, 0°C→room temperature [70%].

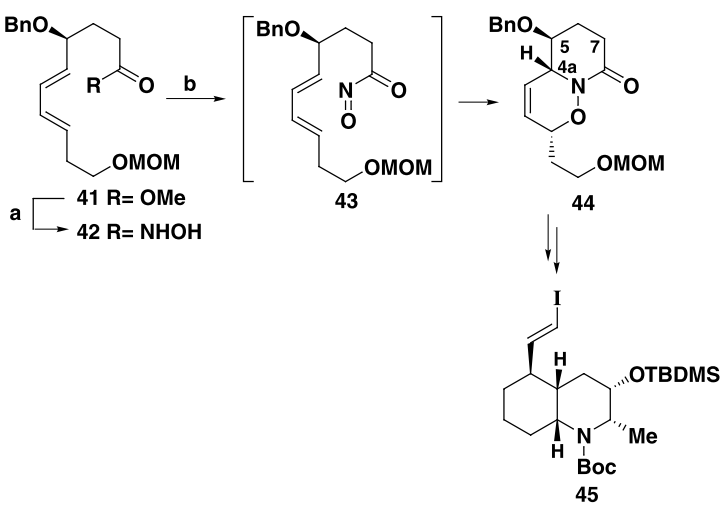



**Scheme 9.** (a) (*S*)-Methylbenzylamine, $Et_3N$, PhMe, −78°C→room temperature [**38a**, 70, 95% de; **38b**, 67, 94% dec; **38c**, 76, 99% de]; (b) $Et_3N$, $^{t}BuO_2CCl$, THF, −78→0°C, then $NaBH_4$, $H_2O$, 0°C→room temperature [86%]; (c) $PBr_3$, conc HBr [70%]; (d) NaH, THF, reflux [85%].

An enantiospecific synthesis of (−)-adalinine, a piperidine alkaloid containing a chiral quaternary center, utilized a ring expansion promoted by samarium iodide regioselective carbon–nitrogen bond cleavage.[20] Enaminone **34** (Scheme 8) was prepared from ethyl (*S*)-(−)-pyroglutamate by an established procedure,[21] and the stereochemistry at the quaternary center was introduced by copper-promoted Michael addition of pentylmagnesium bromide to the less hindered face of **34**. Further manipulation to pyrrolidine **35** was followed by samarium iodide induced[22] reductive carbon–nitrogen bond cleavage and simultaneous cyclization to furnish δ-lactam **36**. Removal of the silyl protecting group and oxidation of the corresponding secondary alcohol completed the total synthesis of (−)-adalinine.

**2.1.3. Amide alkylations.** A convenient asymmetric synthesis of 4-substituted and *trans*-3,4-disubstituted 2-piperidones and piperidines commenced with the desymmetrization[23] of *meso*-3-substituted glutaric anhydrides **37a–c** with (*S*)-methylbenzylamine (Scheme 9).[24] The amido acids **38a–c** were formed in good yields with excellent diastereoselectivities after single recrystallizations. Facile conversion of **38a** to **39** was followed by an intramolecular amide alkylation producing 2-piperidone **40** in >99% diastereomeric purity. Lactam enolate alkylation of **40** afforded chiral *trans*-3,4-disubstituted 2-piperidones. This methodology was applied successfully to the synthesis of paroxetine, a clinically used antidepressant agent. An asymmetric synthesis of (−)-paroxetine using a porcine liver esterase mediated asymmetric desymmetrization as the key step was reported.[25]

**2.1.4. Acylnitroso Diels–Alder reactions.** The acylnitroso Diels–Alder reaction is a powerful tool for the stereoselective synthesis of piperidine, indolizidine, and decahydroquinoline alkaloids.[26] This methodology was used as a key step in the enantioselective syntheses of the decahydroquinoline alkaloids (−)-lepadin A, B and C (Scheme 10).[27] Ester **41** was prepared from (*S*)-malic acid and converted to hydroxamic acid **42**, whereupon oxidation with tetrapropylammonium periodate generated acyl nitroso intermediate **43** that underwent intramolecular [4+2] cycloaddition to oxazino lactam **44**. The *endo* boat-like transition state **43** was proposed as most favored and use of aqueous media effected optimum *trans* selectivity (with respect to C-4a and C-5) in the cycloaddition as a result of secondary orbital interactions and hydrophobic packing of reactants.[28] Oxazino lactam **44** was a useful scaffold for the

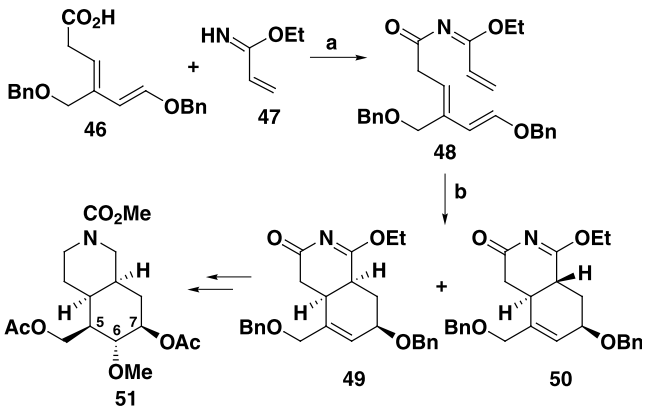



**Scheme 10.** (a) $NH_2OH{\cdot}HCl$, KOH, MeOH, 0°C [80%]; (b) $Pr_4NIO_4$, $H_2O$–DMF, 0°C [90%, 6.6:1].

stereocontrolled introduction of additional substituents. Enolate hydroxylation[29] was used to oxidize the C-7 position diastereoselectively, and a tandem process of Grignard addition followed by stereoselective hydride reduction converted the lactam carbonyl group of **44** to an (8*S*)-methyl group.[30] Reductive cleavage of the N–O bond was followed by annulation of the side chain and elaboration to *cis*-fused decahydroquinoline **45**. Application of this methodology to the synthesis of (±)-fasicularin and (±)-lepadiformine was reported recently.[31] The elegance of this methodology is highlighted by the efficient construction of a substituted bicyclic oxazino lactam and its utility for stereocontrolled functionalization.

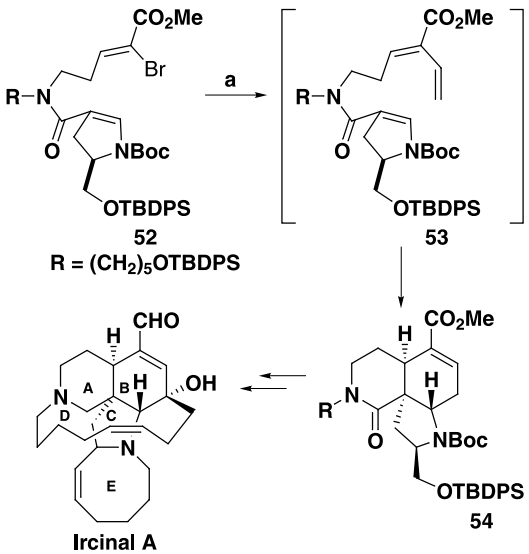
## 2.2. Intramolecular C–C processes

**2.2.1. Acylvinylimidate Diels–Alder reaction.** An application of the intramolecular *N*-acylvinylimidate Diels–Alder[32] reaction provided an efficient route to the yohimbine alkaloid *cis*-fused decahydroisoquinoline ring system (Scheme 11). Diels–Alder precursor **48** was assembled by coupling carboxylic acid **46** with 2-ethoxy-1-aza-1,3-butadiene **47**.[33] Intramolecular cycloaddition proceeded through an *endo* transition state affording cycloadducts **49** and **50**, with the major cycloadduct **49** possessing three of the five stereocenters required for the synthesis of decahydroisoquinoline **51**. After reduction of the acylimidate and *N*-protection, the remaining two stereocenters were introduced by olefin hydroboration. Installation of the C-6 methyl ether and transposition of the benzyl groups for acetates completed the synthesis of **51**, an intermediate previously reported in a total synthesis of reserpine.[34] This methodology provided a facile stereocontrolled approach to *cis*-fused hexahydroisoquinolines, with potential for elaboration to complex isoquinoline ring systems.




**Scheme 11.** (a) 2-Chloro-1-methylpyridinium iodide, $Et_3N$, $CH_2Cl_2$, 0°C (85%); (b) $CHCl_3$, 60°C [95%, **49**/**50**=6:1].

**2.2.2. Domino Stille coupling/vinylogous imide Diels–Alder reaction.** A domino Stille coupling/Diels–Alder reaction provided the foundation of a clever strategy culminating in the total syntheses of ircinal A[35,36a] and manzamine A (Scheme 12).[36b] The key intermediate **52** was assembled by coupling an unsaturated amino ester with a chiral dienophile derived from D-pyroglutamic acid. Stille coupling[37] produced diene **53** that underwent a spontaneous intramolecular Diels–Alder reaction with the vinylogous



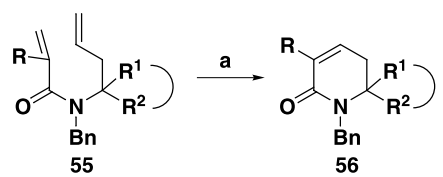

**Scheme 12.** (a) $CH_2$=CHSnBu$_3$, Pd(PPh$_3$)$_4$, PhMe, reflux [68%].

imide furnishing tricycle **54**, the ABC ring core of ircinal A. Most noteworthy was the fact that the lone stereocenter in **53** was used to establish the relative stereochemistry and absolute configuration of the three new chiral centers of **54**.

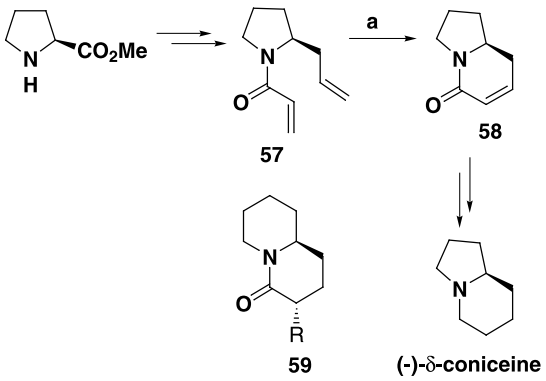
The intramolecular Diels–Alder strategies outlined in Schemes 10–12 provide efficient approaches to polycyclic δ-lactams, and serve to highlight their utility in complex alkaloid synthesis.

**2.2.3. Ring closing metatheses.** Ring closing metathesis (RCM) is one of the most powerful and useful procedures for producing medium to large rings.[38] RCM reactions are reversible and driven primarily by favorable entropic factors (DS>0) that are related to the extrusion of a volatile group usually ethylene. Furthermore, RCM reaction rates also depend on both steric and electronic factors. RCM reactions are believed to proceed via a metallacyclobutane-forming mechanism through the catalytic cycle.[39] The first carbene–olefin [2+2] cycloaddition is assumed to be the rate-determining step and takes place on the electronically least deactivated and/or least sterically substituted C=C bond. The faster second cycloaddition is less sensitive to steric hindrance.

Simple α,β-unsaturated lactams **56** (Scheme 13) were prepared starting from unsaturated amides **55** using Grubbs' catalyst.[40] The authors also synthesized trisubstituted 2-piperidones using methacryloylamides. These compounds were prepared in good yield provided Ti(O$^i$Pr)$_4$ was added to the reaction. However, if substituents were on the homoallylic double bond no reaction was observed, even when second generation catalysts were employed.

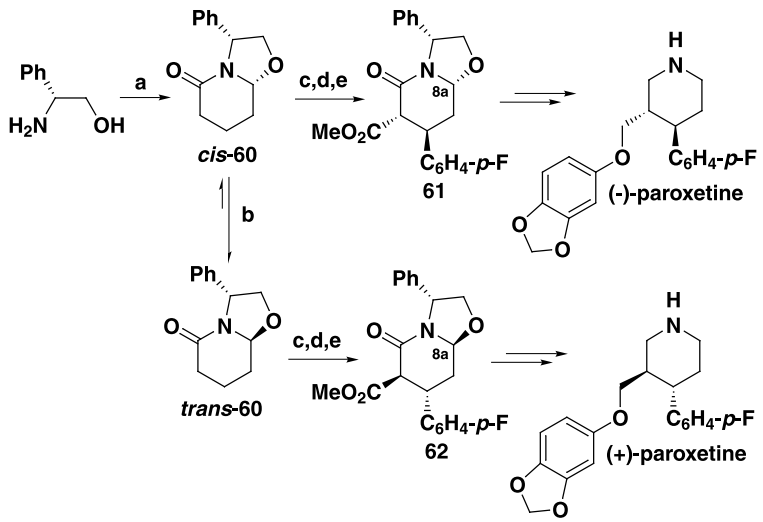



**Scheme 13.** (a) PhCH=Rh(PCy$_3$)$_2$Cl$_2$, Ti(O$^i$Pr)$_4$, $CH_2Cl_2$.




**Scheme 14.** (a) PhCh=$RuCy_3Cl_2(Im)$, $CH_2CI_2$, room temperature, 3 h [74%].

*cis*-**60** and *trans*-**60** (Scheme 15).[45] Treatment of *cis*-**60** with TFA afforded multigram quantities of a chromatographically separable mixture favoring *trans*-**60**. After lactam *cis*-**60** was converted into an activated Michael acceptor, diastereofacial cuprate addition afforded **61** with excellent facial selectivity (97:3 at the β-dicarbonyl center). The same sequence was used to transform *trans*-**60** to **62** with similar yield and facial selectivity. It is important to note that the configuration of H-8a is responsible for the facial selectivity in the conjugate addition. Diastereomers **61** and **62** were converted into the (−)- and (+)-enantiomers of the antidepressant agent paroxetine (see Section 2.1.3 for an alternate synthesis). Recent publications reported the functionalizations of γ-substituted-α,β-unsaturated bicyclic lactams by stereocontrolled conjugate additions.[46]

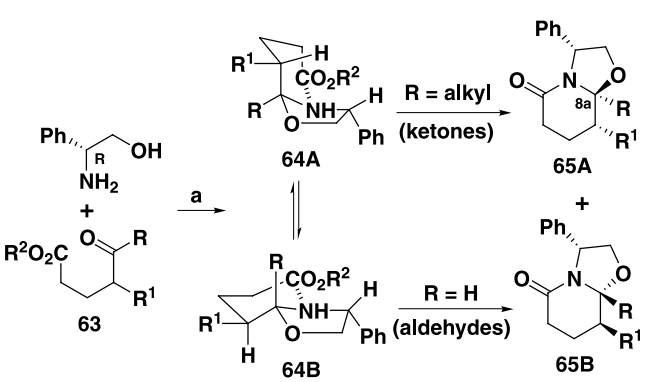



**Scheme 15.** (a) Ph–Me, $OHC(CH_2)_3CO_2Me$, reflux, [86%, *cis*-**60**/*trans*-**60**=85:15]; (b) TFA, $CH_2Cl_2$, room temperature [100%, *cis*-**60**/*trans*-**60**=14:86]; (c) LHMDS, $ClCO_2Me$, PhSeBr, THF, −78°C; (d) $O_3$, $CH_2Cl_2$, −78°C, then $O_2$, room temperature; (e) 4-$FC_6H_4Cu(CN)Li$, THF, −78°C [*cis*-**60**→**61**, 54%; *cis*-**60**→**62**, 77%].

A formal synthesis of the indolizidine alkaloid (−)-δ-coniceine was reported recently (Scheme 14).[41] (2*S*)-2-(2-Propenyl)pyrrolidine was prepared in 3-steps from L-proline methyl ester hydrochloride and reacted with acryloyl chloride to give bisolefin **57**. The resulting diolefin underwent RCM reaction using PhCH=$Ru(PCy_3)Cl_2(Im)$ to afford indolizidin-5-one **58** that can be converted to (−)-δ-coniciene by known methods.[42] Similarly, the RCM with Grubbs' catalyst was used in a diastereoselective synthesis of 3-substituted octahydroquinolizin-4-ones **59**.[43]

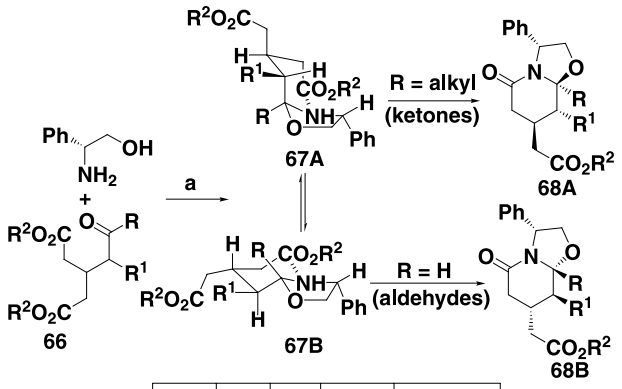
## 2.3. Intermolecular processes

**2.3.1. Chiral bicyclic lactams.** The use of chiral bicyclic lactams for the asymmetric synthesis of functionalized carbocycles and nitrogen heterocycles has proven to be a highly useful and practical strategy.[44] Bicyclic lactams can be prepared through the cyclodehydration of amino acid derived (*R*)- or (*S*)-β-amino alcohols with γ- or δ-oxoacid derivatives. An enantiodivergent synthesis of (+)- and (−)-paroxetine commenced with the cyclodehydration of (*R*)-phenylglycinol and methyl 5-oxopentanoate affording a chromatographically separable mixture of bicyclic lactams



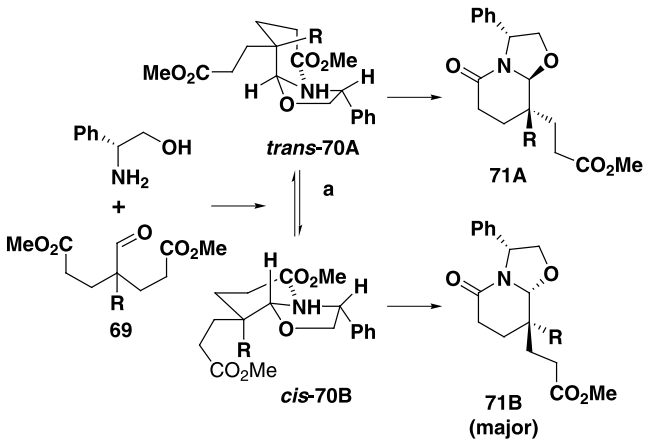

| Entry | R | $R^1$ | $R^2$ | yield | 65A:65B |
|---|---|---|---|---|---|
| a | H | Et | Me | 80 | 20:80 |
| b | H | $CH_2CH_2C(S_2C_3H_6)Me$ | Me | 70 | 17:83 |
| c | H | Ph | Me | 58 | 16:84 |
| d | Me | Et | H | 60 | 78:22 |
| e | Me | 4-MeOPh | Me | 76 | 80:20 |
| f | $-CH_2CH_2CH_2CH_2-$ | | H | 70 | 79:21 |

**Scheme 16.** (a) PhMe, reflux.




| R | $R^1$ | $R^2$ | yield | 68A:68B |
|---|---|---|---|---|
| H | H | Me | 95 | 20:80 |
| Me | H | Et | 77 | 82:18 |
| H | Et | Et | 77 | 20:80 |
| Me | Pr | Et | 54 | 85:15 |

**Scheme 17.** (a) PhMe, reflux.




| entry | R | yield % | 71B:71A |
|---|---|---|---|
| a | H | 67 | 90:10 |
| b | Et | 50 | 90:10 |

**Scheme 18.** (a) PhMe, reflux.

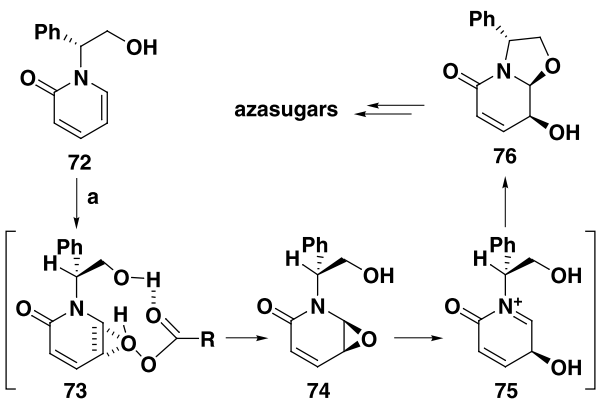
The introduction of substituents during cyclodehydration focused on the reaction of (*R*)-phenylglycinol with racemic substituted δ-oxoacid derivatives and examined the diastereoselectivity in bicyclic lactam formation through the processes of dynamic kinetic resolution (DKR) and desymmetrization.[47] A series of racemic δ-oxoacid derivatives **63** having an epimerizable α-stereocenter afforded either bicyclic lactams **65A** or **65B** as major products (Scheme 16). The stereoselectivity was attributed to lactamization through chair-like transition states **64A** and **64B** in which the $R^1$-substituent occupied an equatorial position, with approach of the carboxylate group to the more accessible face of the oxazolidine nitrogen atom. The diastereoselectivities for **65A** or **65B** were 4:1 indicating that a DKR had occurred. The stereocontrolled reduction of the C-8a bond of **65A** (R=Me) provided a route to *cis*- or *trans*-2,3-disubstituted piperidines.[47d]

Prochiral δ-oxodiesters **66** were used in cyclodehydrations with (*R*)-phenylglycinol to study enantioselective desymmetrization for $R^1$=H and tandem desymmetrization-DKR processes for $R^1$=alkyl (Scheme 17). Transition states **67A** or **67B** place $R^1$ and an acetyl chain in equatorial positions with the stereochemical outcome of the cyclodehydration favoring bicyclic lactam **68A** for R=alkyl or **68B** for R=H (drs=4–5:1) in examples studied with R=H or Me. The desymmetrization of prochiral 4-formylpimelic diesters **69** by cyclodehydration with (*R*)-phenylglycinol also was studied (Scheme 18). Preferential formation of bicyclic lactam **71B** (dr=9:1) was a consequence of lactamization through *cis*-oxazolidine transition state **70B**.

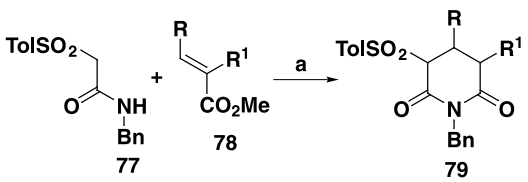
The oxidation of a phenylglycinol derived 2-pyridone **72** with *m*-CPBA provided a one-step synthesis of a chiral bicyclic lactam (Scheme 19).[48] The interactions between the phenyl ring and the carbonyl group of pyridone **72**[49] favor the hydroxyl assisted epoxidation taking place through conformation **73**. Ring cleavage of epoxide **74** by the nitrogen lone pair and intramolecular hydroxyl group attack produced unsaturated hydroxylactam **76** as a single stereoisomer. Lactam **76** is potentially useful for the synthesis of azasugars.

The methodologies highlighted in this section expand the utility of chiral bicyclic lactams. A diverse array of polysubstituted chiral bicyclic lactams are available by taking advantage of diastereotopic differentiation during the cyclodehydration of racemic δ-oxoacid derivatives with a chiral inductor. These substituted chiral bicyclic lactams are useful substrates for additional stereocontrolled functionalization en route to enantiopure δ-lactams and piperidines.

**2.3.2. [3+3] Annulations.** Recent reports describe the syntheses of functionalized δ-lactams using [3+3] annulation procedures that combine [C–C–C] and [N–C–C] moieties.[50,51] An efficient synthesis of *N*-benzyl-3-sulfonyl glutarimides **79** was accomplished by reaction of the dianion of α-toluenesulfonyl acetamide **77** with α,β-unsaturated esters **78** (Scheme 20).[50a] A useful feature of this approach is the utility of a sulfonyl group to control subsequent regioselective functionalizations that led to a variety of δ-lactams with diverse substitution patterns (Scheme 21). A dianion alkylation of **80** was used to produce the quaternary center in glutarimide **81**.




**Scheme 19.** (a) *m*-CPBA, $CH_2Cl_2$, room temperature (35–40%).



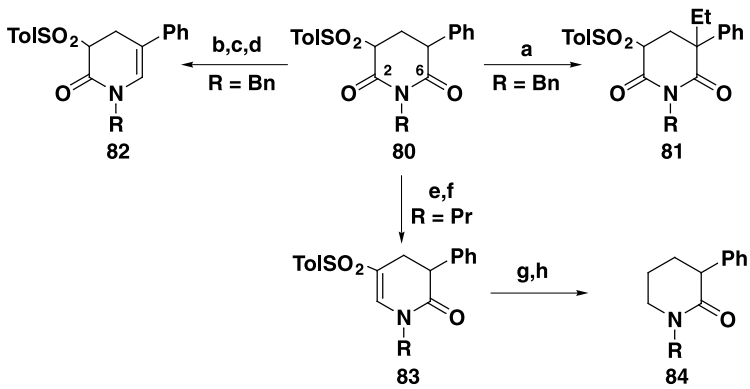

| R | $R^1$ | yield (%) |
|---|---|---|
| H | H | 90 |
| Me | H | 86 |
| H | Me | 82 |
| $(MeO)_2CH$ | H | 95 |
| 2-furyl | H | 75 |
| Ph | H | 72 |
| H | Ph | 74 |
| 4-$NO_2$-Ph | H | 73 |

**Scheme 20.** (a) NaH, THF, room temperature.

both the α-sulfonyl and C-2 carbonyl.[50d] The intermediate hydroxy piperidone was dehydrated to unsaturated lactam **83** and then converted to piperidone **84** by olefin hydrogenation and reductive desulfonylation with sodium amalgam. A slight modification of this glutarimide-based strategy yielded γ-substituted-α,β-unsaturated δ-lactams **88** from α-sulfinyl acetamides **85** (Scheme 22).[50b] This efficient three-step preparation of **88** provides access to *cis*- and *trans*-3,4-disubstituted piperidines through the conjugate addition of stabilized anions and organocuprates. A formal synthesis of racemic protoemetinol was also reported.

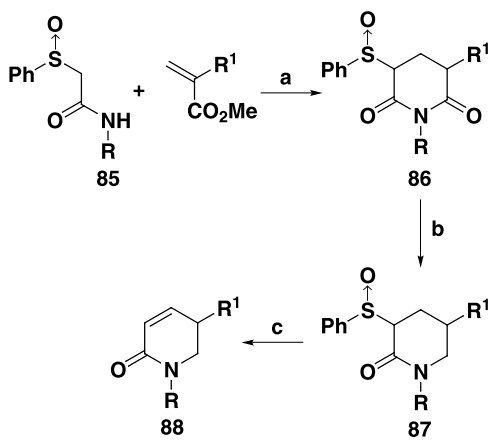
The [3+3] aza-annulation of chiral non-racemic β-enamino esters with acryloyl chloride provided oxazolo-δ-lactams that were used in a synthesis of enantiopure *cis*- and *trans*-2,3-disubstituted piperidines.[52]

**2.3.3. 2-Azadiene Diels–Alder reaction.** The aza Diels–Alder reaction is an established procedure for the synthesis of nitrogen-containing six-membered rings. The Diels–




**Scheme 21.** (a) NaH, THF, EtBr, reflux (92%); (b) NaH, THF, room temperature; (c) LAH, THF, room temperature; (d) $BF_3{\cdot}Et_2O$, $CH_2Cl_2$, room temperature [80%, for 3 steps; (e) $NaBH_4$, MeOH, THF, 4–7°C; (f) $BF_3{\cdot}Et_2O$, $CH_2Cl_2$, room temperature [80%, for 2 steps]; (g) $H_2$, $Pd(OH)_2$, AcOH, room temperature; (h) Na(Hg), MeOH, room temperature [80%, for 2 steps].

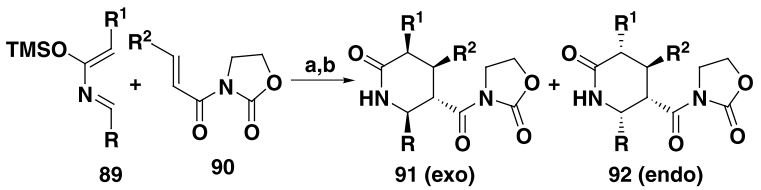
Regioselective reduction of the C-6 carbonyl of glutarimide **80** was accomplished by protection of the C-2 carbonyl as an enolate. The resultant hydroxy piperidone, an *N*-acyliminium ion precursor, was then dehydrated to unsaturated lactam **82**.[50c,f] Regioselective reduction of the C-2 carbonyl of **80**, was best accomplished with $NaBH_4$. This was attributed to chelation of the reducing agent with




**Scheme 22.** (a) NaH, THF, room temperature; (b) LAH, THF, reflux; (c) PhMe, reflux [40–46%, for 3 steps].

Alder reaction of electron rich 2-azadienes[53] **89** with acyl oxazolidinones **90** catalyzed by $C_2$-symmetric chiral bis(oxazoline)-metal complexes[54] was used to synthesize enantiopure polysubstituted δ-lactams (Scheme 23).[55] The reaction was run at either −45°C or room temperature and yields, diastereoselectivities and enantioselectivities were excellent, the lone exception being a 4-unsubstituted azadiene. An Evans transition state model, proposed for related Diels–Alder reactions catalyzed by $C_2$-bis(oxazoline)–metal complexes, predicted the stereochemical outcome (Scheme 24).[56] The relative stereochemistry and absolute configuration of the stereocenters of **91** were attributed to *exo*-approach of the diene to the less hindered face of the square planar dienophile–chiral catalyst complex. In addition, functional group transformations of **91** are possible without loss of enantiomeric purity.

**2.3.4. Metal catalyzed cyclocarbonylations.** Pd-catalyzed decarboxylative-carbonylation of vinyloxazolidinones (Scheme 25) provided a useful approach to the enantioselective synthesis of unsaturated δ-lactams.[57] Treatment of amino acid derived aldehydes and ketones **93** with vinyl Grignard reagents gave alcohols **94** having low diastereoselectivities (dr=1–5:1). Cyclization to 5-vinyloxazolidin-2-ones **95** was followed by Pd-catalyzed decarboxylative

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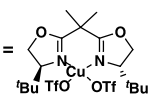
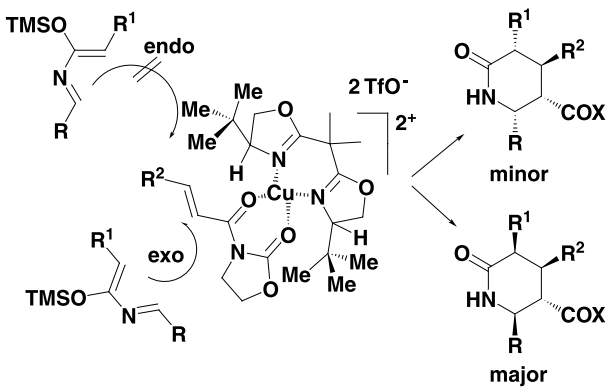
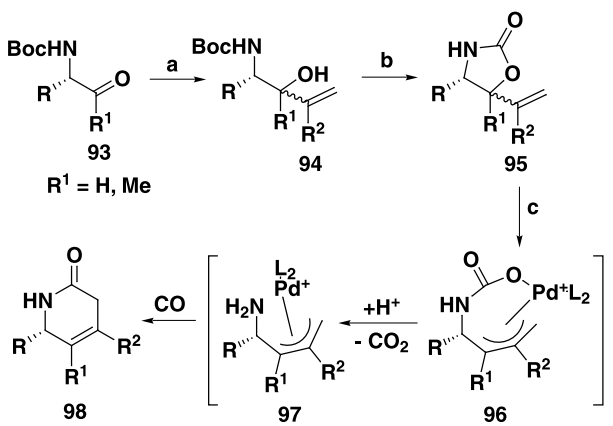



| R | $R^1$ | $R^2$ | temp (°C) | product (exo:endo) | yield (%) | ee (%) |
|---|---|---|---|---|---|---|
| Ph | Me | Me | -45 | >99:1 | 80 | 95.1 |
| Ph | Me | Me | rt | >99:1 | 96 | 94 |
| Ph | H | H | -45 | 6.1:1 | 83 | 98.3 |
|  | Me | Me | rt | >99:1 | 98 | 90 |

**Scheme 23.** (a) Catalyst, $CH_2Cl_2$, 4 Å, MS, −45°C or room temperature; (b) MeOH.




**Scheme 24.**



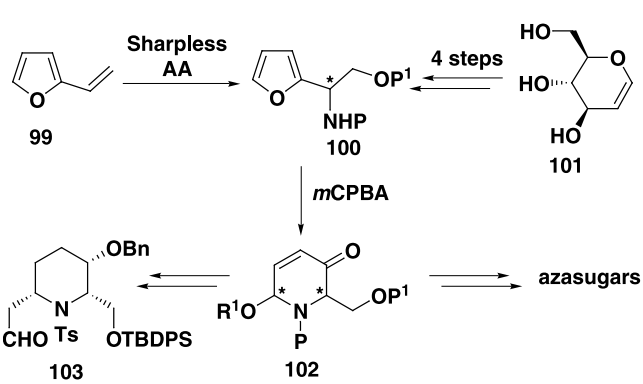

**Scheme 25.** (a) $BrMg(R^2)C{=}CH_2$, THF, −78°C→room temperature; (b) NaH, THF, −78°C→room temperature; (c) $Pd(PPh_3)_2(OAc)_2$, EtOH, CO (65 atm), 65–70°C [57–87% for step c].

carbonylation to enantio-enriched δ-lactams **98**. The authors proposed transition states **96** and **97** for the decarboxylation and carbonylation steps, respectively. Citing the similar Pd-catalyzed decarboxylation of *N*-tosyl vinyloxazolidinones to *N*-tosyl vinylaziridines, the authors treated **95** (R=$^i$Pr, $R^1$, $R^2$=H) under similar conditions and recovered **95** as a single *trans* diastereomer.[58] It was proposed that ring opening of **95** to form the π-allyl palladium species was reversible, and was not accompanied by fast decarboxylation. This enantioselective process provides access to substituted, unsaturated δ-lactones with the potential for elaboration to more complex nitrogen heterocycles. This procedure also was used to prepare 3,6-disubstituted-3,6-dihydro-1*H*-pyridin-2-ones.[57b]

## 3. Synthesis of 3-piperidones

### 3.1. Oxidative cyclization (aza-Achmatowicz reaction)

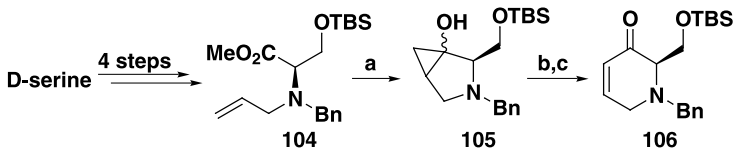
Two excellent reviews[59] provide good background information for this section. The aza-Achmatowicz reaction (Scheme 26) is exemplified by the oxidative rearrangement of furylamides **100** to 1,6-dihydro-2*H*-pyridin-3-ones **102**. Chiral, non-racemic furylamides **100** were obtained by the Sharpless catalytic, asymmetric aminohydroxylation (AA) of 2-vinylfuran **99**[60] or by transformation of D-glucal **101**.[61] 3-Piperidone **102** was used in the synthesis of azasugars,[60a] and in the stereoselective preparation of aldehyde **103**, an intermediate for the synthesis of 2,3,6-trisubstituted piperidine alkaloids.[62] The aza-Achmatowicz reaction also was used in the stereoselective synthesis of 2,5,6-trisubstituted 3-piperidones.[63] Additional applications of this oxidative cyclization were used in the asymmetric synthesis of 3-hydroxypipecolic acid δ-lactams[64] and polyhydroxylated 6-oxa-*nor*-tropanes.[65]



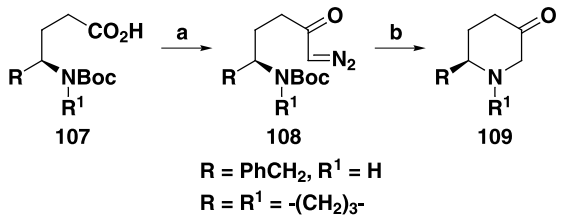

**Scheme 26.**

### 3.2. From amino acids

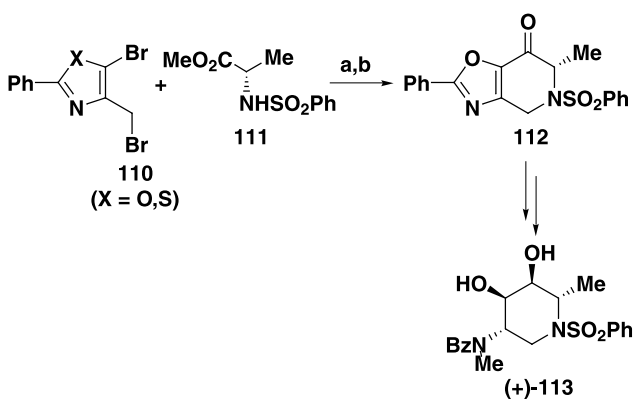
An intramolecular nucleophilic acyl substitution (INAS)[66] and ring expansion were used to prepare 3-piperidone **106**, a




**Scheme 27.** (a) $Ti(O^iPr)_4$, $^iPrMgCl$, $Et_2O$ [86%]; (b) $FeCl_3$, $Et_2O$; (c) NaOAc, MeOH [94%, 2 steps].




**Scheme 28.** (a) $^t$BuOCOCl, TEA, THF, −10°C, then $CH_2N_2$, $Et_2O$ [27–56%]; (b) TFA, $CH_2Cl_2$, −78°C [62–88%].




**Scheme 29.** (a) $K_2CO_3$, MeCN, reflux [90%]; (b) BuLi, THF, −100°C [74%].

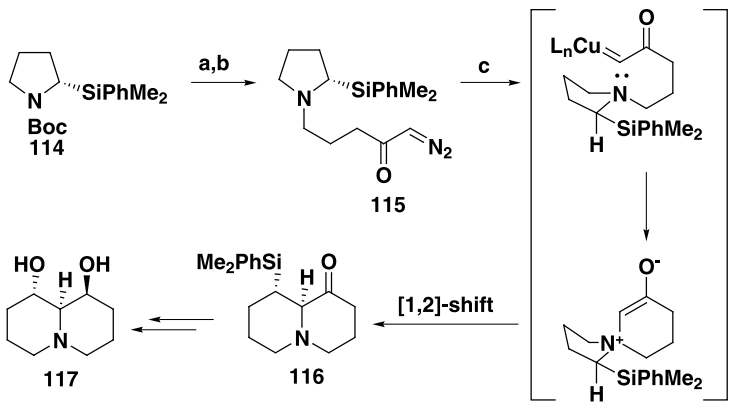
versatile chiral building block for the preparation of 1-deoxyazasugars (Scheme 27).[67] Thus, D-serine was converted to N-allylated ester **104**, and Ti(II)-mediated INAS produced bicyclic cyclopropanol **105**. A $FeCl_3$-mediated ring expansion of bicyclic cyclopropanols to conjugated cycloalkenones[68] was used to convert **105** into enantiopure **106**.

An efficient route to optically active 3-piperidones utilized a trifluoroacetic acid (TFA)-promoted intramolecular N–H insertion as the key C–N bond forming process (Scheme 28).[69] *N*-Boc-γ-amino acid **107** was prepared efficiently from commercially available *N*-Boc-α-amino acids and its conversion to *N*-Boc-γ′-amino-α-diazoketone **108** was accomplished through mixed anhydride formation and diazomethane coupling. The TFA-mediated intramolecular N–H insertion process then afforded 3-piperidone **109** with concomitant removal of the Boc group. A nitronium species might be involved in this transformation. The reaction was fast (<5 min) and clean provided low substrate concentrations (0.5 μM) were used. Enantiopure 3-piperidones and azabicycles were accessible from D- or L-amino acids with retention of chirality.

The synthesis of annulated dihydropyridin-3-ones was the cornerstone of a novel strategy for the enantioselective synthesis of polyhydroxypiperidines (Scheme 29).[70] Alkylation of *N*-benzenesulfonyl amino ester **111** with 5-bromo-4-(bromomethyl)-2-phenyloxazole (**110**, X=O), followed by low temperature bromine–lithium exchange and intramolecular Barbier-type cyclization provided access to oxazolopyridin-3-one **112**. In this efficient approach, the azole ring contributed three carbon ring atoms and two heteroatoms which were liberated late in the synthesis. Other salient features of this strategy were the stereocontrolled introduction of three additional stereocenters and the inclusion of a Mitsunobu step for inversion of configuration or the introduction of additional heterosubstituents. A further extension of this azasugar strategy started with thiazoles as starting materials enabling the preparation of 5-amino-4-thiohydroxypiperidines.

### 3.3. Ring expansion

The first example of a stereoselective silyl-directed Stevens rearrangement of ammonium ylides was the key step in a short, enantioselective route to hydroxylated quinolizidines (Scheme 30).[71] Asymmetric lithiation and silylation were used to prepare (*S*)-*N*-Boc-2-phenyldimethylsilylpyrrolidine **114** in 92% yield and 85% ee. Removal of the



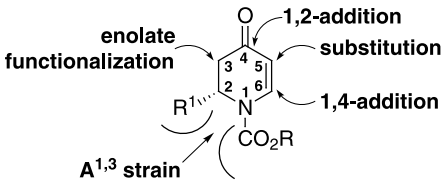

**Scheme 30.** (a) AcCl, EtOH, EtOAc; (b) $K_2CO_3$, $Et_3N$, MeCN, $Br(CH_2)_3C(O)CHN_2$, (47%); (c) $Cu(acac)_2$, PhMe, 85°C (58%).

protecting group and alkylation furnished diazoketone **115**. Copper-catalyzed rearrangement afforded quinolizidine **116** in 58% yield and 77% ee as a single diastereomer, a result attributed to the conformational rigidity of the pyrrolidine ring due to the steric bulk of the phenyldimethylsilyl group. A stereoselective ketone reduction and a Fleming–Tamao oxidation provided diol **117**.

## 4. Synthesis of 4-piperidones

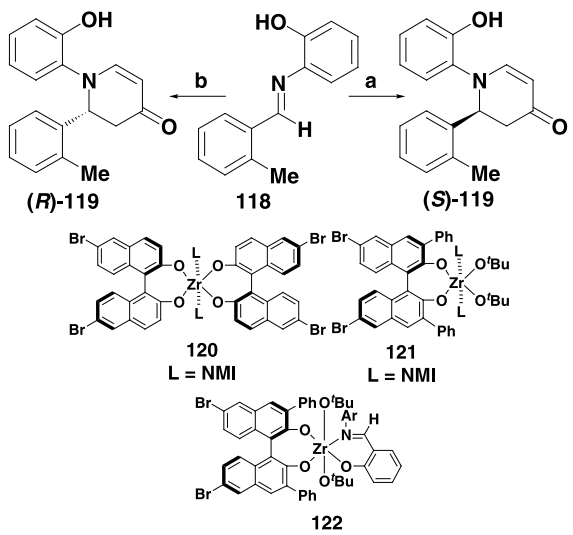
### 4.1. Intermolecular processes

**4.1.1. From 1-acylpyridinium salts.** 2,3-Dihydro-4-pyridones are utilized in the syntheses of numerous alkaloids due to the variety of stereocontrolled functionalizations that are possible (Scheme 31).[72] 2-Substituted-*N*-acyl-2,3-dihydro-4-pyridones were prepared enantiomerically pure by the stereoselective addition of organometallic reagents and metalloenolates to chiral 1-acylpyridinium salts.[73] Also, a resin activation/capture approach (RECAP technology) was used for the synthesis and elaboration of 2,3-dihydro-4-pyridones on solid support.[74] $A^{1,3}$ strain[75] causes the C-2 substituent to occupy an axial position thereby influencing the stereochemical outcome of subsequent transformations. Iodocyclocarbamation of *N*-acyl-2-alkenyl-4-piperidones produced bicyclic carbamates in a highly stereoselective manner.[76] Enolate alkylations were used to functionalize C-3,[72] and C-3 α-acetoxylations afforded *trans*-2,3-disubstituted products.[77] Organocerium reagents added to C-4 from the face opposite the axial C-2 substituent, while reduction with sodium borohydride/cerium chloride provided C-4 equatorial alcohols.[72] Substitution at C-5 was achieved via the corresponding vinyl iodide (prepared using iodine monochloride).[78] Functionalizations at C-6 were achieved by Mukaiyama–Michael[73c] and copper catalyzed Grignard conjugate additions,[78b] intramolecular Heck reactions[72] and conjugate reduction.[79] The intramolecular [2+2] photocycloaddition of a nitrogen tethered terminal olefin was a key reaction in the total synthesis of plumerinine.[80]




**Scheme 31.**

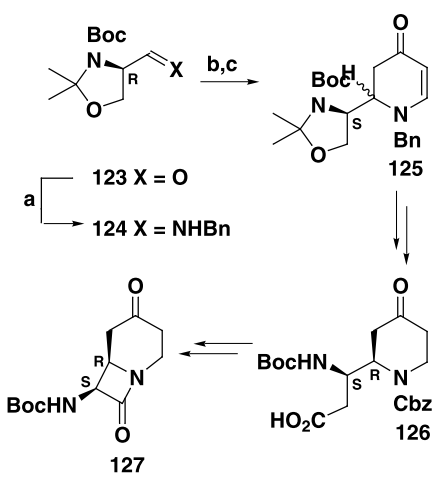
**4.1.2. Imino Diels–Alder reactions.** The hetero Diels–Alder (HDA) reaction of imines with Danishefsky's diene (1-methoxy-3-trimethylsiloxy-1,3-butadiene) is an efficient method for construction of functionalized 2,3-dihydro-4-pyridones with control of regio-, diastereo- and enantioselectivity.[81] Recently, Nafion-H,[82] bismuth(III) chloride and triflate,[83] and samarium diiodide[84] were used as achiral catalysts in these reactions. Kobayashi et al. reported a switch of enantiofacial selectivity when using either (*R*)-6,6′-dibromo-1,1′-binaphthol or (*R*)-6,6′-dibromo-3,3′diphenyl-1,1′-binaphthol as the ligand in chiral zirconium catalyst systems (Scheme 32).[85a] Initial studies from the Kobayashi laboratories reported the use of catalyst system **120** in the enantioselective HDA reaction of



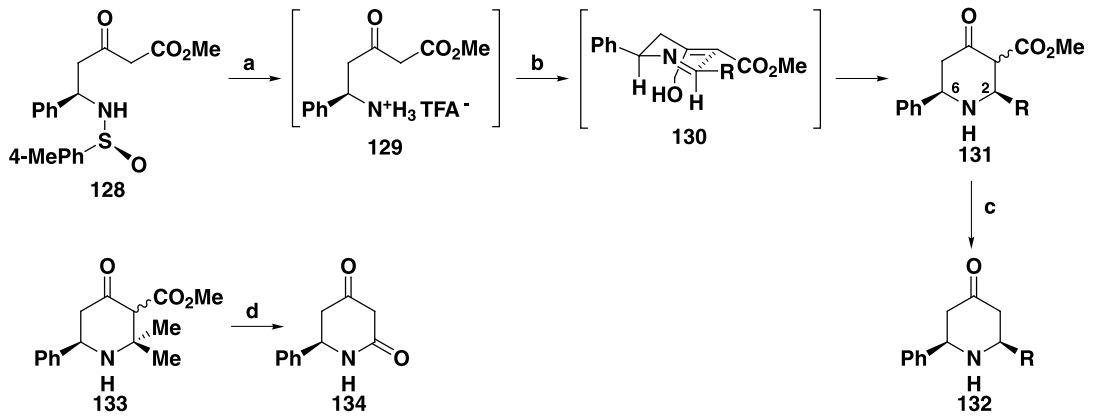

**Scheme 32.** (a) $Zr(O^tBu)_4$, (*R*)-6,6′-dibromo-1,1′-binaphthol; *N*-methylimidazole (NMI), Ph–Me, 45°C [83%, ee=82%]; (b) $Zr(O^tBu)_4$, (*R*)-6,6′-dibromo-3,3′-diphenyl-1,1′-binaphthol, NMI, Ph–H, 3 Å, MS, 23°C [93%, ee=91%].

Danishefsky's diene with *ortho*-hydroxyphenyl imine **118** that produced 2,3-dihydro-4-pyridone (*S*)-**119**.[86] Use of a similar chiral catalyst **121** with substituents on the 3,3′-positions, caused a reversal in the absolute configuration of the product yielding (*R*)-**119**. The observed enantioselectivity was rationalized by approach of the diene to the *Re*-face of complex **122**, with shielding provided by one of the phenyl groups and possibly one of the axial *tert*-butoxy groups. Kobayashi also used polymer-supported (*R*)-1,1′-binaphthols as chiral catalysts in aza Diels–Alder reactions of aldimines with Danishefsky's diene. High yields, high enantioselectivities and low catalyst loadings were achieved.[85b]

The HDA reaction of Danishefsky's diene with the benzylimine derived from Garner's aldehyde was used as the key step in an efficient approach to the asymmetric synthesis of carbacepham **127** (Scheme 33).[87] Imine **124** was prepared under non-epimerizable conditions,[88] and HDA reaction with Danishefsky's diene catalyzed by




**Scheme 33.** (a) $BnNH_2$, $CH_2Cl_2$ $MgSO_4$, room temperature; (b) Danishefsky's diene, $Et_2AlCl$, $CH_2Cl_2$, −40°C; (c) 1N HCl, then chromatography [65%, *S*,*S*/*S*,*R*=1:4].




**Scheme 34.** (a) TFA, MeOH; (b) RCHO, $CH_2CI_2$, room temperature, then aq. $NaHCO_3$ [70–84%, 2 steps]; (c) 48% HBr [62–66%] (d) LiOH, MeOH, reflux [70%].

diethylaluminum chloride gave the best diastereoselectivity for dihydro-4-pyridone **125**. Subsequent transformations provided **127** via β-amino acid **126**.[89] Use of Danishefsky's diene in the HDA reaction was central in the asymmetric synthesis of functionalized indolizidines,[90] indolo[2,3-*a*]quinolizidine,[91] tetracyclic alkaloid phyllanthine[92] and enantiopure pipecolic acids.[93]

Similarly, the HDA reaction of *E*-1-dimethylamino-3-*tert*-butyldimethylsiloxy-1,3-butadiene[94] with activated imines proceeded at room temperature in the absence of Lewis acid catalysts providing a simple, one-pot synthesis of dihydro-4-pyridone derivatives.[95]

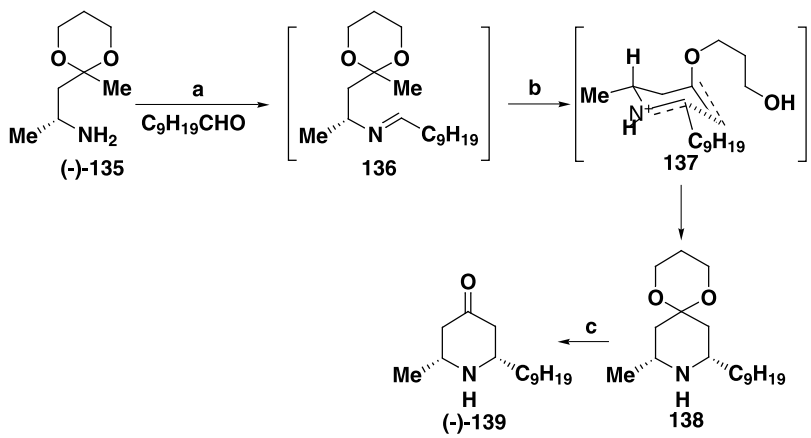
A convenient, large-scale synthesis of chiral 4-oxo-pipecolates was achieved by HDA reaction of 2-trimethylsilyloxy-1,3-butadiene with activated imines derived from condensation of ethyl glyoxalate with (*R*)- or (*S*)-α-methylbenzylamine.[96] Diastereomerically pure 4-oxo-piperidine-2-carboxylates were obtained by crystallization and were converted to a variety of protected 2-substituted 4-oxo-piperidine derivatives.

A one-pot, three-component synthesis of 2-substituted 2,3-dihydro-4-pyridones was accomplished by a highly efficient aza Diels–Alder reaction.[97] The reaction was carried out in methanol in the absence of acid and likely proceeded through a Mannich-type pathway. The solid-phase HDA reaction of 2-amino-1,3-butadienes with nitrogen-bound imines (BOBA resin) and carbon- bound imines (Wang resin) furnished 4-piperidones with 4 points of diversity.[98]

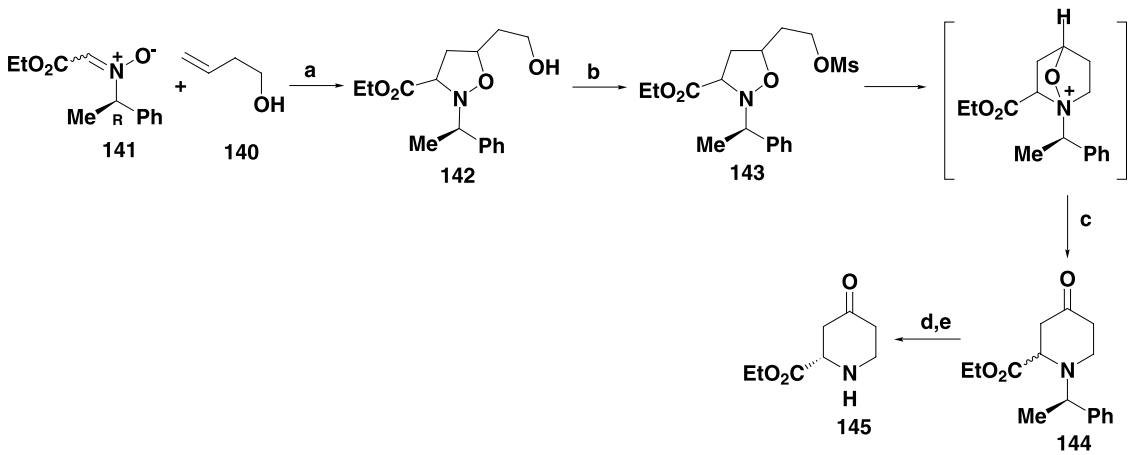
## 4.2. Intramolecular processes

**4.2.1. Mannich reactions.** The intramolecular Mannich reaction is a powerful tool for the rapid, efficient, highly stereoselective assembly of polysubstituted piperidones. Sulfinyl amines **128** served as asymmetric precursors to δ-amino-β-ketoesters (Scheme 34).[99] Treatment with excess trifluoroacetic acid removed the sulfinyl group and the released chiral amine salt **129** was then reacted with an aldehyde or ketone giving polysubstituted piperidone **131**. The major isomer was shown to have the C-2 and C-6 substituents in a *cis*-orientation with the C-2- and C-3-substituents *trans*. For aldehydes, the nearly exclusive formation of the 2,6-*cis*-disubstituted piperidone **131** was consistent with transition state **130**. Decarboxylation to **132** was best effected with 48% HBr in methanol. Some erosion of chirality was noted and was attributed to a retro-Mannich reaction. The authors demonstrated a base-induced retro-Mannich reaction of **133** giving 6-phenylpiperidine-2,4-dione (**134**). 2,6-Disubstituted-4-piperidones serve as important building blocks for piperidine alkaloid synthesis.

Another approach to 4-piperidones using an intramolecular Mannich-type reaction was described by Troin and




**Scheme 35.** (a) $MgSO_4$, $CH_2CI_2$, relfux, [100%]; (b) TsOH, Ph–Me, 70°C [90%]; (c) 6% HCl, $Me_2CO$, 20°C [92%].



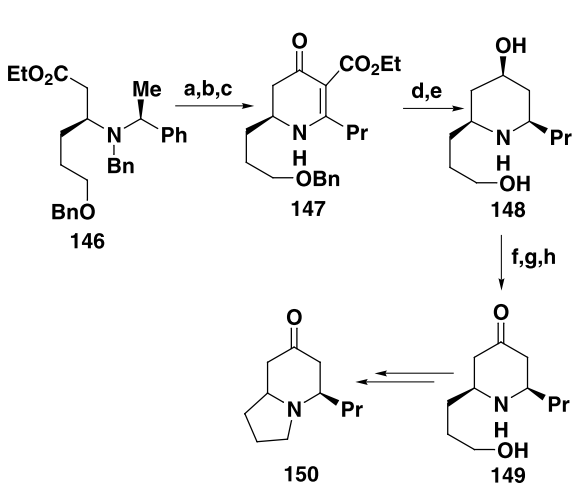

**Scheme 36.** (a) $CHCl_3$, reflux, [98%]; (b) MsCl, pyridine, 0°C; (c) DABCO, MeCN, reflux [44%, 2 steps]; (d) $SiO_2$ chromatography (e) $H_2$, $Pd(OH)_2/C$ [94%].

co-workers in a series of papers utilizing chiral β-amino ketals as starting materials (Scheme 35).[100] Enantiopure amine **135** was condensed with decylaldehyde to form imine **136**. Subsequent treatment with *p*-toluenesulfonic acid afforded **138** with the diastereoselectivity of >95% accounted for by transition state **137**. Removal of the ketal protecting group afforded piperidone **139**.[100b] Using this intramolecular Mannich-type reaction, Troin and co-workers rapidly assembled 2,2′-spiro-4-piperidone skeletons[101] that are present in a variety of natural products.

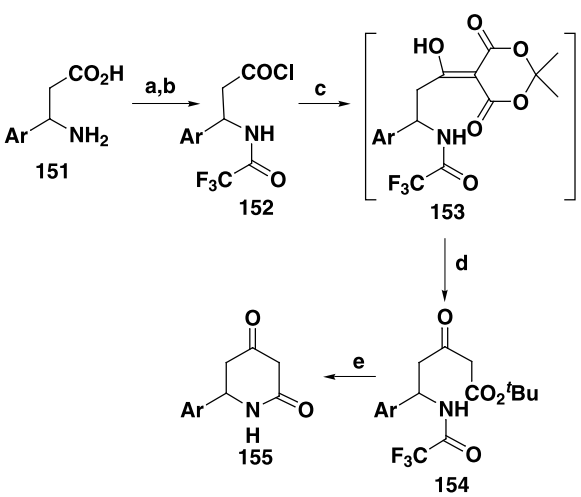
**4.2.2. Cycloadditions.** A short, practical, multigram synthesis of both isomers of ethyl 4-oxopipecolate (**145**) was achieved utilizing a 1,3-dipolar cycloaddition as the key step (Scheme 36).[102] Reaction of nitrone **141** with 3-butenol (**140**) gave isoxazoline **142** as an equimolar mixture of four diastereomers. Reaction of the mixture with mesyl chloride and treatment of the resulting mesylates **143** with DABCO in refluxing acetonitrile gave a 1:1 mixture of **144** epimeric at C-2. Deprotection of the separated epimers led to (*R*)- and (*S*)-4-oxopipecolic acid.

**4.2.3. From β-amino carboxylates.** Enantiopure β-amino esters are readily available[103] and served as starting points for a simple, efficient synthesis of enantiopure 4-oxo- and 4-hydroxy-2,6-disubstituted-piperidines.[104] Their utility in the syntheses of dendrobate alkaloid (+)-241D and (−)-indolizidine 167B are highlighted in a formal synthesis of the latter (Scheme 37). *N*-Deprotection of **146** gave a β-amino ester that was transformed to 2,3-dihydropyridone **147**. After conversion to diol **148** and selective protection of the amine and primary alcohol with benzyl chloroformate, the secondary alcohol was oxidized. Removal of the protecting groups from the resulting ketone gave **149** which could be converted to **150** by a known procedure.[105]

3-Trifluoroacetylamino-3-arylpropionyl chloride **152** was prepared in two steps from the corresponding β-aryl-β-amino acid **151** and condensed with Meldrum's acid to afford the chain homologated intermediate **153** (Scheme 38). Ring opening hydrolysis of **153** with refluxing *tert*-butanol gave the δ-aryl-δ-trifluoroacetylamino-β-ketoester **154** that was cyclized with aqueous NaOH in tetrahydrofuran to **155**. This represents an easy, versatile preparation of 6-arylpiperidine-2,4-diones.[106] See Scheme 1 for an alternate preparation.




**Scheme 37.** (a) $H_2$, Pd/C, room temperature; (b) AcOH, then $PrCOCH_2CO_2Et$; (c) Na, EtOH [79%, 3 steps]; (d) aq NaOH, EtOH; (e) $H_2$, Pd/C; (f) Cbz-Cl; (g) Dess–Martin oxidation; (h) $H_2$, Pd/C [82%, 5 steps].

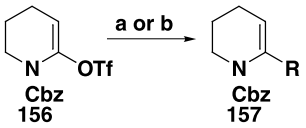



**Scheme 38.** (a) TFAA, TFA; (b) $(COCl)_2$, $CH_2Cl_2$, [74–91%]; (c) Meldrum's acid, pyridine, $CH_2CI_2$; (d) $^tBuOH$ [71–79%]; (e) aq NaOH, THF [79–88%].

## 5. Synthesis of piperidines

### 5.1. From 2-piperidones

**5.1.1. From *N*-alkoxycarbonyl enol derivatives.** There is a growing interest in the utility of lactam-derived vinyl triflates in Pd(0)-catalyzed C–C bond forming processes. Palladium-mediated displacement of the triflate group with nucleophiles such as cuprates, organotin and organozinc derivatives and methoxycarbonylations were reported.[107] Sonogashira cross-coupling reactions with monosubstituted acetylenes were done also.[108] A recent paper highlighted methodology for the efficient introduction of aryl, alkenyl, allyl and alkyl groups onto piperidine rings by Suzuki couplings[109] with lactam-derived vinyl triflate **156** (Scheme 39).[110a] Substituents were introduced under mild conditions in THF–water, whereas coupling with an alkylboronic acid (entry b) required anhydrous conditions and Pd(dppf)$Cl_2$ as a catalyst in the presence of $Ag_2O$ to facilitate transmetalation. Suzuki couplings of *N*-$CO_2$Ph δ-lactam-derived vinyl phosphates with aryl and heteroaryl boronic acids have been reported.[111] The vinyl phosphates were used as stable, cost effective alternatives to vinyl triflates, and couplings proceeded under mild conditions providing C-2 substituted enecarbamates in good yields.

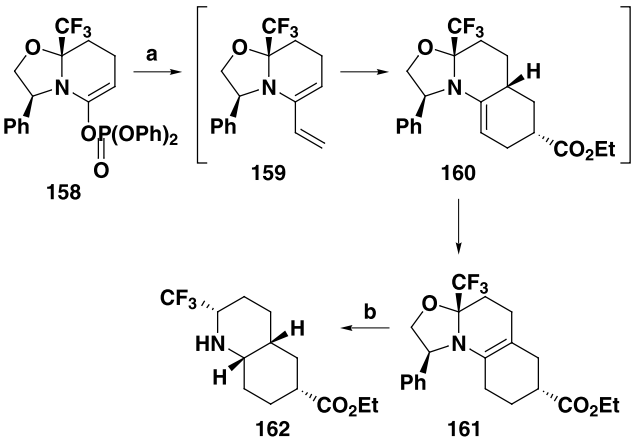



| 156 | boronic acid or ester | R | Yield % |
|---|---|---|---|
| a | $PhB(OH)_2$ | Ph | 84 |
| b | $BuB(OH)_2$ | Bu | 93 |
| c | BuCH=CH-catechol borane | BuCH=CH | 86 |
| d | allyl-pinacol borane | allyl | 65 |

**Scheme 39.** (a) Aq $Na_2CO_3$, THF, Pd$(PPh_3)_2Cl_2$, 40–80°C; (b) for b, $Ag_2O$, $K_2CO_3$, Pd(dppf)$Cl_2$, PhMe, 80°C.

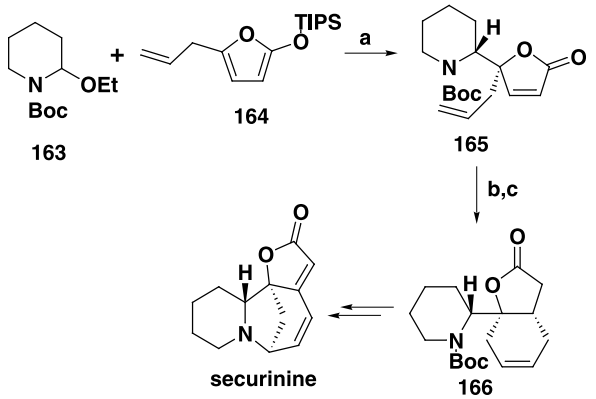
Enol triflates and phosphates derived from chiral bicyclic lactams were used in the asymmetric synthesis of trifluoromethyl-substituted piperidines and decahydroquinolines (Scheme 40).[112] Enamine phosphate **158** was converted to diene **159** and trapped as the *endo* α-face Diels–Alder adduct **160** that isomerized to **161** during workup and silica gel chromatography. Hydrogenation of the double bond of **161** occurred with concomitant cleavage of the oxazolidine ring and nitrogen deprotection to produce enantiopure decahydroquinoline **162**. An *N*-*p*-toluenesulfonyl δ-lactam enol triflate was converted to a vinylstannane by Pd(0)-catalyzed cross-coupling with hexamethyldistannane. Tin–lithium exchange followed by addition of cyclobutanone afforded cyclobutanols that were used in a study on the utility of semipinacol type rearrangements for the construction of azaspirocyclic ketones.[113]

**5.1.2. From cyclic *N*-acyliminium intermediates.** *N*-Acyl-δ-lactams are readily converted to *N*-acyl-2-alkoxypiperidines by treatment with sodium borohydride in the presence



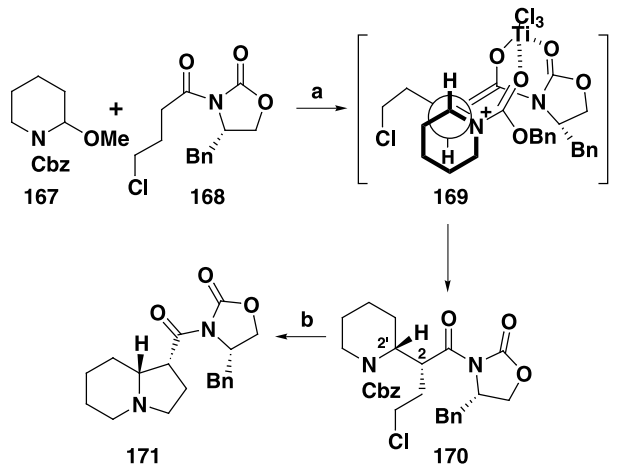

**Scheme 40.** (a) $Bu_3$(vinyl)Sn, Pd$(PPh_3)_4$, LiCl, THF, reflux, then ethyl acrylate [68%]; (b) $H_2$, Pd$(OH)_2$ [80%].

of hydrochloric acid and a recent review by Speckamp highlighted their utility in C–C bond forming reactions.[114] A total synthesis of securinine used a stereoselective addition of a siloxyfuran to an *N*-acyliminium ion as the key step (Scheme 41).[115] The vinylogous Mannich reaction[16a] of 2-ethoxypiperidine **163** and siloxy furan **164**[116] provided adduct **165**, which possessed the requisite stereochemical relationship of the piperidine and butenolide moieties found in securinine. Conjugate addition of the anion of allyl phenyl sulfoxide afforded a single diastereomer and utilization of a full equivalent of Grubbs' reagent was necessary to effect a novel, ring closing metathesis to **166**. Similar applications of the vinylogous Mannich reaction were reported.[117]




**Scheme 41.** (a) TIPSOTf, heptane, −78°C [78%]; (b) allyl phenyl sulfoxide, LiHMDS, THF, −78→−45°C (71%); (c) PhCH=Ru$(PCy_3)_2Cl_2$, DCE, 70°C [79%].

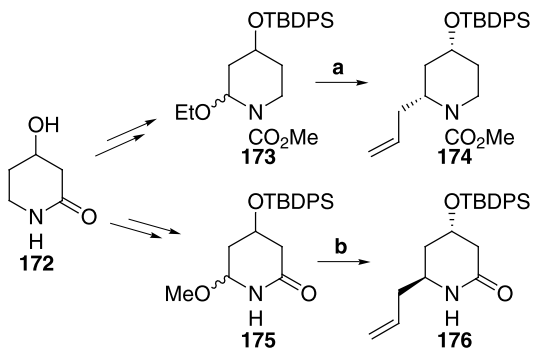
Strategies for asymmetric C–C bond forming reactions at C-2 of the piperidine ring involving additions to *N*-acyliminium ions derived from 2-alkoxy piperidine were reported. Addition of the titanium(IV) enolate derived from (*S*)-oxazolidinone **168** to a piperidine-derived *N*-acyliminium ion was the key step in an approach to the indolizidine core of stelletamide alkaloids (Scheme 42).[118] The reaction proceeded through coordinated intermediate **169** with preferential addition of the *Si* face of a chelated *Z*-enolate to the *Si* face of the *N*-acyliminium ion resulting in a preference for *threo*-(2*R*,2*R*′)-**170**. Hydrogenolysis of




**Scheme 42.** (a) $TiCl_4$, DIPEA, $CH_2Cl_2$, −23°C [62%, dr=5:1]; (b) $H_2$, $Pd(OH)_2$, EtOH, room temperature [73%].

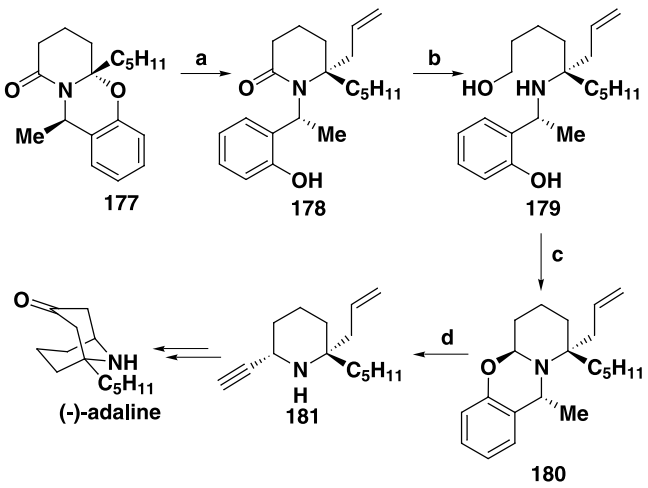
**170** was accompanied by intramolecular alkylation to provide indolizidine **171**. A similar strategy was used in a synthesis of *d-threo*-methylphenidate.[119] Asymmetric nucleophilic substitution at the 2-position of an *N*-acyl-3,4-didehydro-2-methoxypiperidine with dimethylmalonate was catalyzed by chiral Cu(II) bis-oxazoline ligands, and 2-substituted piperidines were produced with moderate enantioselectivity.[120]

A stereodivergent approach to substituted 4-hydroxypiperidines was accomplished by the selective formation of regioisomeric *N*-acyliminium ion precursors from a common intermediate (Scheme 43).[121] The most significant difference between the acyliminium ions is the position of the acyl group. Racemic 4-hydroxy-2-piperidone **172** was prepared in four steps from vinyl acetic acid, whereas enantiopure **172** was obtained from the biocatalytic desymmetrization of 3-benzoyloxypentanedinitrile. Allylation of the exocyclic acyliminium ion generated from **173** showed a preference for *cis*-**174** due to axial attack by the nucleophile, a result attributed to a transition state conformation in which the oxygen substituent is pseudo-axial thereby enabling its lone pair electrons to partially stabilize the acyliminium cation. By contrast, allylation of the endocyclic acyliminium ion from **175** favored *trans*-**176** due to axial attack of the nucleophile on a transition state conformation with the substituent pseudo-equatorial.




**Scheme 43.** (a) Allyltrimethylsilane, $BF_3{\cdot}Et_2O$, MeCN, −50°C→room temperature [92%, *cis*/*trans*=72:28]; (b) allyltrimethylsilane, $BF_3{\cdot}Et_2O$, MeCN, 0°C→room temperature [100%, *cis*/*trans*=11:89].

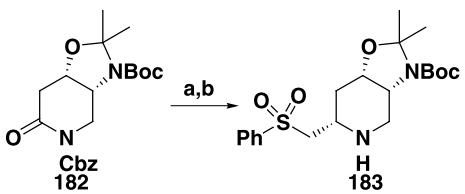
In an asymmetric synthesis of (−)-adaline,[122] chiral *N*,*O*-acetals were used to stereoselectively functionalize both the C-2 and C-6 positions of the piperidine ring. *N*,*O*-Acetal **177** was used for stereoselective introduction of an allyl substituent onto the C-6 position of lactam **178** (Scheme 44). Reduction to primary alcohol **179** and oxidation to the corresponding aldehyde resulted in ring closure to *N*,*O*-acetal **180** that was stereospecifically functionalized to 2,2,6-trisubstituted piperidine **181**. Subsequent transformations afforded (−)-adaline.




**Scheme 44.** (a) $TiCl_4$, $H_2C{=}CHCH_2TMS$; (b) $LiH_2NBH_3$, THF, 40°C [88%]; (c) TPAP, NMO, MeCN, 4 Å MS, room temperature [80%]; (d) $HC{\equiv}CLi{\cdot}H_2NCH_2CH_2NH_2$, THF, 40°C [88%].

Stereoselective nucleophilic substitution reactions of *N*-acyl-2-methoxypiperidine with silyl enol ethers and ketene silyl acetals catalyzed by $Sc(OTf)_3$[123] and $BF_3{\cdot}Et_2O$[124] were carried out. A coupling of a bicyclic *N*-acyliminium ion with 3-trimethylsilyl-1-decene was used in a synthesis of piclavines A1 and A2.[125]

**5.1.3. From ring opening of *N*-alkoxycarbonyl-δ-lactams.** Another feature that δ-lactams afford is the option to replace the lactam carbonyl with a substituent. The process involves regioselective ring opening of an activated lactam with a nucleophile followed by recyclization with dehydration and stereoselective reduction. This and related procedures are well-documented with pyroglutamate derivatives,[126] and the utility of this sequence in the synthesis of an all *cis*-2,4,5-trisubstituted piperidine was reported (Scheme 45).[19a] Treatment of activated δ-lactam **182** with (benzenesulfonyl)methyllithium afforded a ring opened product in modest yield. Subsequent hydrogenation resulted in *N*-deprotection, cyclization and reduction affording the all *cis*-trisubstituted piperidine **183**, an

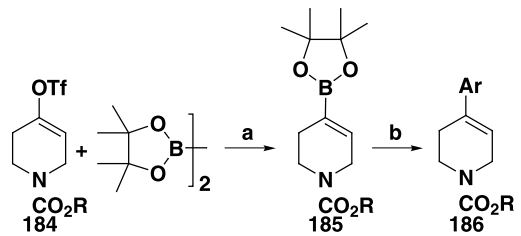



**Scheme 45.** (a) $PhSO_2CH_2Li$, THF, −78°C [41%]; (b) $H_2$, $Pd(OH)_2$, MeOH, room temperature [76%].

advanced intermediate in a formal synthesis of the alkaloid pseudodistomin C.[127]

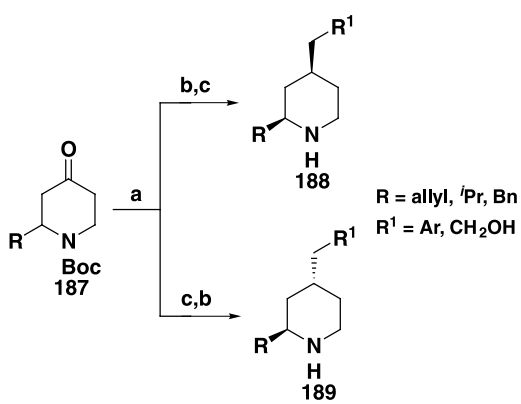
## 5.2. From 4-piperidones

**5.2.1. From *N*-alkoxycarbonyl vinyl triflates.** 4-Aryl-piperidines are useful therapeutic entities synthesized through palladium-mediated vinyl tin–aryl bromide[128] and vinyl triflate–aryl boronate[129] cross-couplings. However, the toxicity of the tin compounds and the limited availability of aryl boronates may restrict their utility in synthetic strategies. A versatile synthesis of 4-aryl-tetrahydropyridines was accomplished by the Suzuki coupling of 4-piperidone derived cyclic vinyl boronates with aryl bromides, iodides and triflates (Scheme 46).[130] Palladium-mediated cross-coupling of *N*-protected vinyl triflates **184** with bis(pinacolato)diboron furnished cyclic boronates **185** and cross-coupling with aromatic substrates afforded 4-aryl-tetrahydropyridines **186** in good to excellent yields. A variety of substituents were tolerated, as well as *o*-substitution and heteroaromatic coupling partners. *N*-Deprotection enabled additional functionalization.




**Scheme 46.** (a) Pd(dppf)$Cl_2$, dppf, KOAc, dioxane, 80°C [85–87%]; (b) ArX (X=I, Br, OTf), Pd(dppf)$CI_2$, $K_2CO_3$, DMF, 80°C [60–92%].

**5.2.2. From Wittig olefinations.** A highly diastereoselective synthesis of 2,4-disubstituted piperidines was developed that provided access to either diastereomer simply by changing the reaction order (Scheme 47).[1] 2-Substituted 4-piperidones **187** were prepared using Comins' methodology (see Section 4.1.1) and Wittig olefination subsequently provided styrenes and α,β-unsaturated esters in good yields. $A^{1,3}$ strain was used as a control element for the dissolving metal reduction of the 2-substituted *N*-acyl-α,β-unsaturated esters and styrenes, and *cis*-2,4-disubstituted piperidines **188** were produced in good yield and excellent diastereoselectivity (*cis*/*trans*=10–30:1) after *N*-deprotection. Removal of the control element prior to conjugate reduction reversed the diastereochemical outcome in favor of the *trans*-2,4-disubstituted piperidines **189** (*cis*/*trans*=1:4–88). An adaptation of this methodology was used by the authors to synthesize 8-substituted-quinolizin-4-ones.

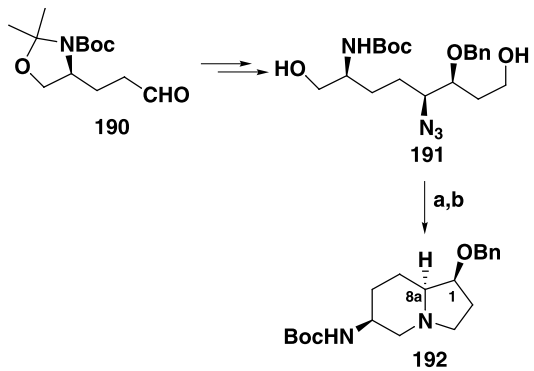



**Scheme 47.** (a) $^tBuOK$, $PhCH_2PPh_3Cl$, THF, room temperature or $Ph_3P{=}CHCO_2Et$, PhMe, reflux, or $^tBuOK$, 4-ZHN-$PhCH_2PPh_3Cl$, THF, −78°C→room temperature [89–95%]; (b) Li, $NH_3$, THF, −78→−28°C; (c) TFA, $CH_2CI_2$ [44–100%, for 2 steps].

Wittig olefination of *N*-Boc-4-piperidone afforded *N*-Boc-4-methylene piperidine that was used as a substrate for β-alkyl Suzuki–Miyaura couplings[131] with aryl halides in a synthesis of 4-arylmethylpiperidines.[132] A wide range of functional groups were tolerated. The intramolecular Pauson–Khand reaction of *N*-Cbz-4-methylene-3-prop-2-ynylpiperidine was used as a key step to prepare *N*-Cbz-3-oxo-8-aza-tricyclo[5.3.1.$0^{1,5}$]undec-4-ene.[133]

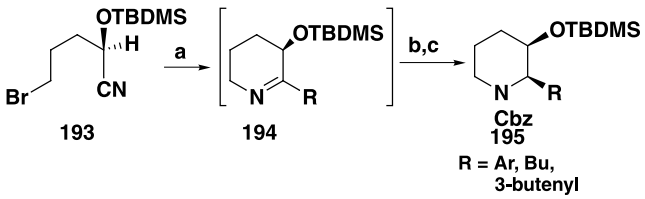
## 5.3. Intramolecular N–C processes

**5.3.1. Nucleophilic substitutions.** The intramolecular $S_N2$ displacement of a halide or activated alcohol by a nitrogen nucleophile is a well established method for forming piperidine rings, and this section will highlight several recent novel applications of this process. A double, reductive cyclization was used to form the indolizidine skeleton of (−)-slaframine (Scheme 48).[134] The key azido diol **191** was derived from aldehyde **190** using an enantioselective allyltitanation and a Mitsunobu reaction to introduce functionality and control the C-1 and C-8a stereocenters. Mesylation of the alcohols followed by reduction of the azide resulted in bis-cyclization to indolizidine **192**, with a separate hydrogenation step needed to remove the benzyl protecting group en route to (−)-slaframine. An alternate synthesis of (−)-slaframine using an intramolecular displacement to form the piperidine ring also was reported.[135]




**Scheme 48.** (a) MsCl, DMAP, pyr; (b) $H_2$, Pd/C, $Et_3N$, MeOH, room temperature→reflux [67%, for 2 steps].

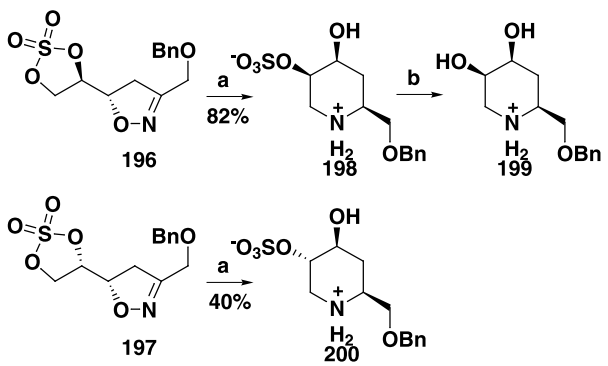
Optically active ω-bromocyanohydrins were used as starting materials in a synthesis of enantiopure 2,3-*cis*-disubstituted piperidines **195** (Scheme 49).[136] Protected cyanohydrin **193** (91% ee) was prepared using an enantioselective (*R*)-oxynitrilase-catalyzed transcyanation. A one-pot procedure consisting of an initial Grignard addition proceeded through an intermediate cyclic imine **194**, and sodium borohydride reduction followed by *N*-protection afforded *cis*-(*R*,*R*)-piperidine **195** as a single diastereomer. Aromatic Grignard reagents gave higher




**Scheme 49.** (a) RMgX, THF, reflux; (b) $NaBH_4$, $MeBH_4$, MeOH, room temperature; (c) CbzCl, $Na_2CO_3$, $H_2O$, $CH_2Cl_2$, 0°C [22–92%, 91% ee].

yields than aliphatic Grignards in this useful, tandem process.

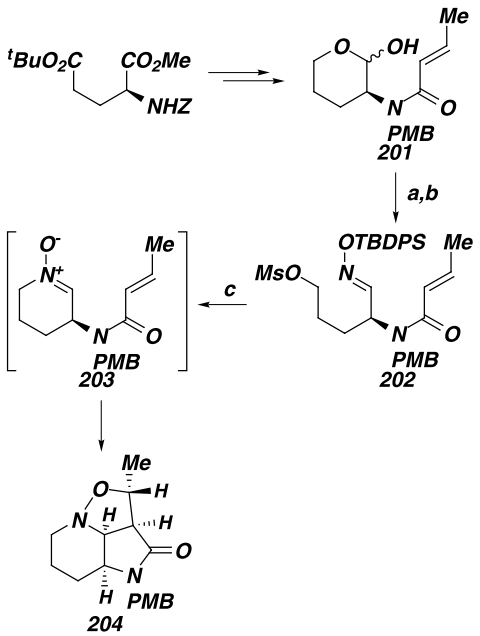
Aminosugars, potent inhibitors of glycosidase and glycoprotein-processing enzymes, were prepared conveniently by a one-pot reduction-alkylation of isoxazoline derivatives (Scheme 50).[137] Cyclic sulfates[138] **196** and **197** were derived from the 1,3-dipolar cycloaddition reaction of the nitrile *N*-oxide prepared from 1-benzyloxy-2-nitroethane with 2,2-dimethyl-4-vinyl-1,3-dioxolane. Reduction of **196** and **197** was accompanied by hydrogenolysis of the N–O bond. Cyclization of the resulting amine was completely regioselective affording piperidines **198** and **200**. Interestingly, reduction of the isoxazoline delivered hydrogen to the more hindered face. Sulfate group removal afforded piperidine **199**. A similar approach to functionalized indolizidines proceeded through an isoxazolidine scaffold.[139]




**Scheme 50.** (a) $H_2$, Pd/C, $Na_2CO_3$, MeOH, room temperature; (b) $H_2SO_4$, $H_2O$, dioxane, room temperature.

The facile synthesis of cyclic nitrone **203** derived from hemiacetal **201** by a fluoride mediated intramolecular desilylative oxime *N*-alkylation was key to the synthesis of tricycle **204** (Scheme 51).[140] Hemiacetal **201**, prepared from an L-glutamate, was converted to ω-mesyloxy-*O*-*tert*-butyldiphenylsilyloxime **202**. Treatment with tetrabutylammonium triphenyldifluorosiliconate (TBAT) subsequently afforded cycloadduct **204** via desilylation and intramolecular cycloaddition of the resulting nitrone **203**. The authors also presented examples of chiral, cyclic nitrones prepared from sugar hemiacetals that should be useful for the synthesis of polyhydroxylated alkaloids and aza-sugars. A similar nitrone preparation was used for a 1,3-dipolar cycloaddition to allyl alcohol in an enantioselective synthesis of the alkaloids (+)-febrifugine and (+)-isofebrifugine.[141]

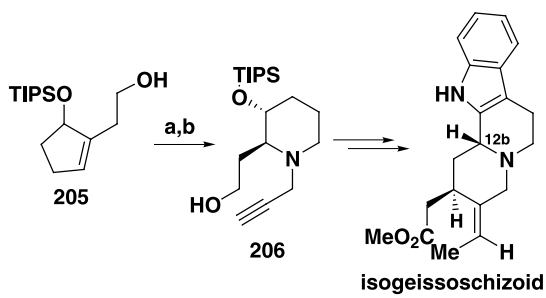
A regioselective, intramolecular nucleophilic substitution of an azido epoxide was the key step in a synthesis of *trans*-




**Scheme 51.** (a) $NH_2OTBDPS$, PPTS, $MgSO_4$, $Et_2O$, reflux; (b) MsCl, $Et_3N$, $CH_2CI_2$, 0°C [96%, for 2 steps]; (c) TBAT, 4 Å MS, THF, reflux [84%].

(2*R*,3*R*)-3-hydroxypipecolic acid.[142] Additional examples of piperidine syntheses utilizing intramolecular *N*-alkylations were reported.[143]

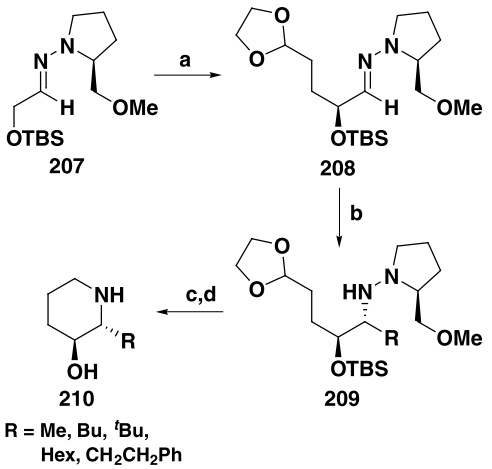
**5.3.2. Reductive aminations and imine reductions.** Intramolecular reductive ring closures are employed often in the synthesis of piperidines and substrates are required in which either the carbonyl or amino component is masked to avoid premature interactions. Ozonolysis of protected cyclopentenol **205** followed by double reductive amination gave *trans*-disubstituted piperidine **206**, the piperidine core of the polycyclic indole alkaloid isogeissoschizoid (Scheme 52).[144] The *N*-propargyl substituent was used later as a component of an intramolecular nickel-catalyzed cyclization, and the protected alcohol functionality was used as a handle for stereocontrol at C-12b, and for a late-stage Fischer indole synthesis. Additional examples of double[145] and triple[146] reductive aminations were reported.




**Scheme 52.** (a) $O_3$, MeOH, $Me_2S$; (b) $NaBH_3CN$, $HC{\equiv}CCH_2NH_2{\cdot}HCl$, MeOH [54%, for 2 steps; dr=88:12].

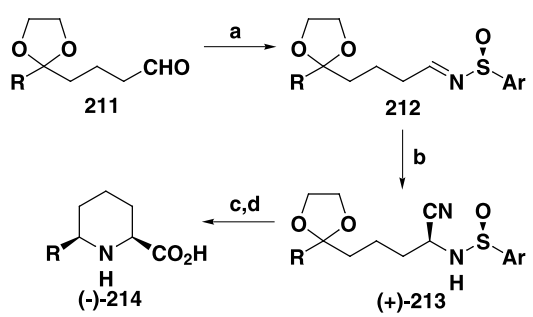
A flexible asymmetric synthesis of 2-substituted 3-piperidinols **210** used a versatile chiral synthon for the synthesis of a substituted 1,2-amino alcohol prior to a reductive ring closure (Scheme 53).[147] The enolate of SAMP hydrazone **207**,[148] prepared by aldehyde condensation with an (*S*)-1-amino-2-methoxymethylpyrrolidine chiral auxiliary was

α-alkylated with an acetal protected β-iodopropanal to afford SAMP-hydrazone **208** with excellent stereocontrol. Hydrazine **209** was produced in moderate to excellent yields and excellent diastereoselectivity (de >96%) by treatment of **208** with a variety of alkyllithiums. Cleavage of the N–N bond with borane was followed by aqueous HCl release of the aldehyde and spontaneous cyclization to an imine. Sodium borohydride was added to complete the reductive amination. Additional applications of SAMP/RAMP hydrazone methodology[149] in the asymmetric synthesis of piperidines were reported.[150]




**Scheme 53.** (a) LDA, THF, −78°C, then 2-(2-iodoethyl)-1,3-dioxolane, −78°C [42%]; (b) RLi, THF, −78°C [42%]; (b) RLi, THF, −78°C, then aq $NaHCO_3$ [45–91%, de >96%]; (c) $BH_3$·THF, THF, reflux, then 3 M HCl, $CH_2Cl_2$, room temperature; (d) $NaBH_4$, EtOH, room temperature [51–76%, de, ee >96%].

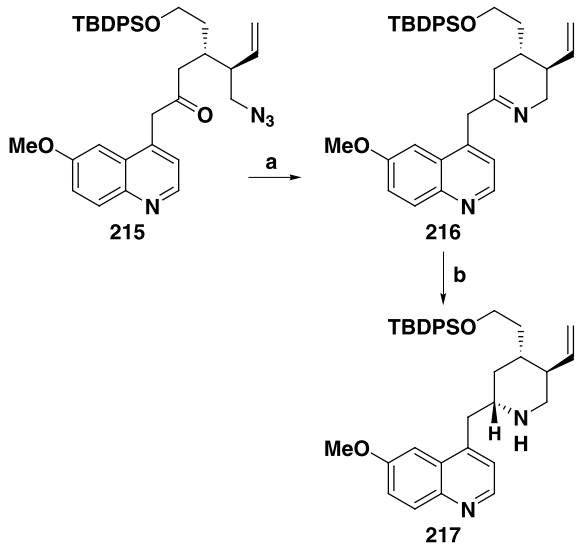
Another application of polyfunctionalized chiral building blocks from the Davis laboratories (see Schemes 1 and 34) led to the synthesis of pipecolic acid derivatives by the intramolecular cyclization/reduction of masked *N*-sulfinyl imines (Scheme 54).[151] The masked oxo-aldehyde **211** was converted readily to sulfinime **212** and a sulfinimine-mediated asymmetric Strecker synthesis using ethylaluminium cyanoisopropoxide was carried out. The sulfinyl group controlled the stereochemistry of cyanide addition and amino nitrile **213** was predicted to have the ($S_s$-*S*)-configuration. Hydrolysis of the diastereochemically pure amino nitriles removed the *N*-sulfinyl auxiliary and converted the nitrile to an acid, in addition to unmasking the oxo group and promoting cyclization to an iminium ion.




**Scheme 54.** (a) (1*S*,2*S*,5*R*)-(−)-Methyl (*S*)-*p*-toluenesulfinate, LHMDS, −78°C or (*S*)-(+)-*p*-toluenesulfinamide, $Ti(OEt)_4$, $CH_2Cl_2$ [57–80%]; (b) $Et_2AlCN$, $^i$PrOH, THF, −78°C [61–80%, de=93–95%]; (c) HCl, reflux; (d) $H_2$, Pd/C, MeOH [48–95%, ee=95–97%].

Hydrogenation then delivered hydrogen from the less hindered face forming exclusively *cis* amino acids **214**.

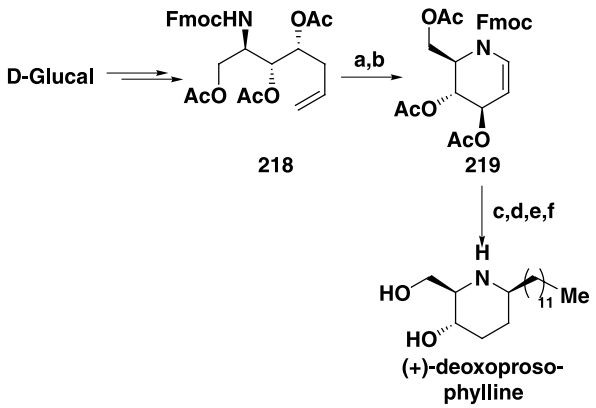
A brilliant strategy for the stereospecific synthesis of deoxyquinine used a hydride reduction of a tetrahydropyridine as the key step in the first stereoselective total synthesis of quinine (Scheme 55).[152] (*S*)-4-Vinylbutyrolactone was the starting material for acyclic stereocontrol in the synthesis of keto-azide **215**. Intramolecular Staudinger reaction and cyclization afforded tetrahydropyridine **216**. Assuming a half-chair conformation with the vinyl group and the protected hydroxyethyl chain in equatorial positions, axial delivery of hydride to the imine produced 2,4,5-trisubstituted piperidine **217** having the correct stereochemistry for further conversion to deoxyquinine and completion of the quinine synthesis.




**Scheme 55.** (a) $PPh_3$, THF, reflux [81%]; (b) $NaBH_4$, MeOH, THF [91%].

Additional examples of intramolecular reductive aminations in piperidine syntheses proceeded by catalytic hydrogenation of oxo-azides,[153] oxo-Cbz amines,[154] oxo-benzylamines[155] and amino-lactols,[156] and hydride reduction of imines.[157]

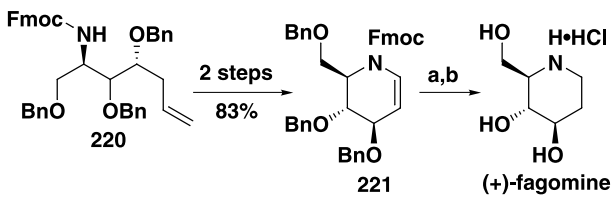
**5.3.3. Cyclization–dehydration to imino glucals.** Imino glucals have been utilized as building blocks for the synthesis of nitrogen containing heterocycles.[158] Amino sugars, for example, have gained prominence in their utility as inhibitors of glycosidase enzymes.[159] A novel imino glucal building block was developed for the synthesis of highly oxygenated amino sugar *C*-glycosides (Scheme 56). The acyclic precursor **218** was derived from D-glucal, with the key step being introduction of the amine by a stereocontrolled oxime reduction. Ozonolysis of the double bond and dehydration of the resulting hemiaminal with oxalyl chloride completed the synthesis of imino glucal **219**. The latter underwent Lewis acid mediated C–C bond formation by allylic displacement of the C-3 acetoxy group. The addition showed a preference for the β-anomer, which is the reverse of the facial selectivity seen in reactions of the same nucleophiles with 3,4,6-tri-*O*-acetyl-D-glucal under comparable conditions. This result might be attributed to $A^{1,3}$ strain which biases axial attack of the nucleophile onto




**Scheme 56.** (a) $O_3$, $CH_2Cl_2$, −78°C, then $Me_2S$; (b) $(COCl)_2$, $Et_3N$, DMF [53%, 2 steps]; (c) $BF_3{\cdot}Et_2O$, $CH_2Cl_2$, $H_2C{=}CHCH(TMS)(CH_2)_8Me$, −60→0°C [β/α=9:1]; (d) piperidine, $CH_2Cl_2$, room temperature [78%, 2 steps]; (e) $H_2$, Pt/C, EtOH; (f) LiOH, $THF/H_2O$ [51%, 2 steps].

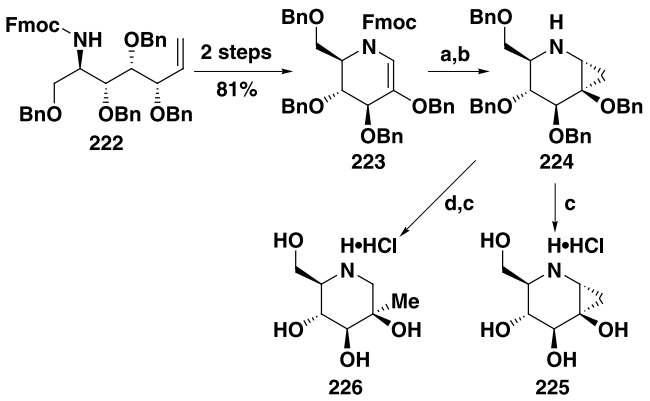
a chair-like conformer of **219**. Application of this stereocontrolled *C*-glycoside procedure resulted in a synthesis of (+)-deoxoprosophylline. Also, by combining this methodology with dihydroxylation chemistry, the synthesis of more highly oxygenated amino sugar *C*-glycosides was possible.[160]

A reported synthesis of the naturally occurring amino sugar (+)-fagomine (Scheme 57) was based on imino glucal formation.[161] Diastereomerically pure **220** was prepared from tri-*O*-benzyl-D-glucal. Double bond ozonolysis followed by cyclization–dehydration then produced imino glucal **221**. Hydrogenation of **221** in the presence of morpholine reduced the double bond and facilitated chromatographic purification. An additional hydrogenation in the presence of hydrochloric acid removed the benzyl protecting groups furnishing (+)-fagomine as a hydrochloride salt.




**Scheme 57.** (a) $H_2$, Pd/C, morpholine, EtOH [70%]; (b) $H_2$, Pd/C, HCl, EtOH [85%].

Novel deoxymannojirimycin analogs were prepared from imino glucals (Scheme 58).[162] Olefin **222** was prepared from tetra-benzoyl-D-glucopyranose and converted to imino glucal **223** as described in the previous paragraph. Cyclopropanation[163] using excess diiodomethane and diethyl zinc was highly stereoselective and removal of the Fmoc group with morpholine provided secondary amine **224** as a single diastereomer. Hydrogenation of **224** in the presence of hydrochloric acid resulted in debenzylation without cyclopropane ring fission and the conformationally constrained analog **225** was isolated in quantitative yield as a hydrochloride salt. In addition, it was possible to regioselectively cleave the cyclopropane ring without concomitant debenzylation by hydrogenation over

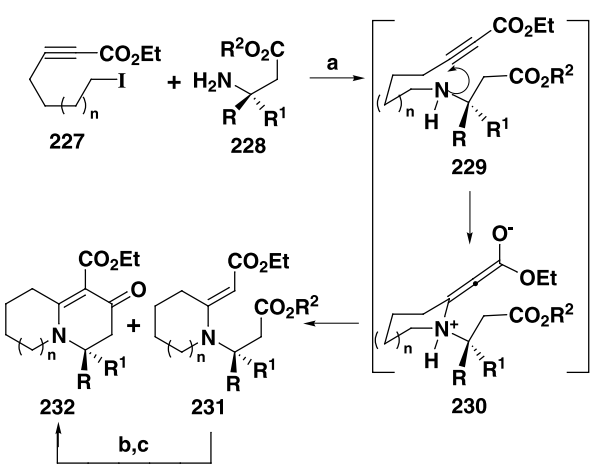



**Scheme 58.** (a) $Et_2Zn$, $CH_2I_2$, PhMe; (b) morpholine [64%, 2 steps]; (c) $H_2$, Pd/C, HCl, EtOH [100%]; (d) $H_2$, $Pd(OH)_2$/C, EtOH [79%].

palladium hydroxide on carbon in the absence of acid. Further hydrogenation effected debenzylation affording **226**. The versatile strategies highlighted in this section were very useful for preparing novel amino sugars to probe the binding specificity of the glycosidase family of enzymes.

A facile synthesis of functionalized imino glucals from ω-hydroxycarbamates via tandem oxidative cyclization–dehydration was achieved using Dess–Martin periodinane in methylene chloride.[164] This procedure afforded Boc-protected imino glucals in excellent yields. Interestingly, the reaction did not work for the formation of five- and seven-membered ring analogs.

**5.3.4. Michael additions.** Intramolecular Michael additions are a well-established method for piperidine ring formation and the versatility of this process will be highlighted in this section. An additional application for β-amino carboxylates (see also Section 4.2.3) led to methodology for the synthesis of enantiopure quinolizidinones and indolizidinones (Scheme 59).[165] The amino group of enantiopure β-amino ester **228**[103a] was alkylated first by iodide **227** to form secondary amine **229** that underwent an intramolecular Michael addition generating enolate **230** followed by protonation to **231** or intramolecular condensation to **232**. As an added feature, all monocyclic products **231** were

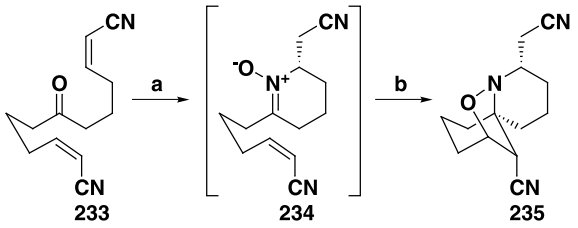



**Scheme 59.** (a) $K_2CO_3$, MeCN, 65°C [**231**/**232**=1.25–2.27:1]; (b) NaOH, EtOH, room temperature; (c) $Ac_2O$, $Et_3N$, THF [72–89%, 2 steps].

converted to quinolizidinones ($n$=1) or indolizidinones ($n$=0) **232** in high yields by a convenient two-step procedure. This methodology was used for the total synthesis of the quinolizidine alkaloid (−)-lasubine II.

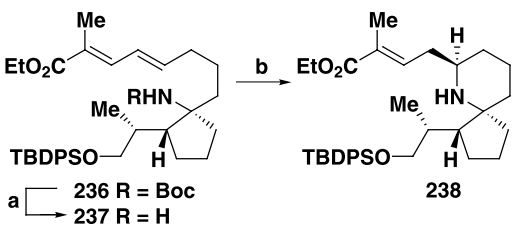
Another route to the quinolizidine skeleton used a two-directional synthesis strategy and a tandem deprotection/double intramolecular Michael addition as the key step.[166] Also, an intramolecular amine conjugate addition was used to form the piperidine A-ring of cylindrospermopsin.[167]

A synthesis of the azaspiro[5.5]undecane skeleton **235** required two operations from an acyclic symmetrical precursor (Scheme 60).[168] Treatment of ketone **233** with hydroxylamine hydrochloride afforded six-membered cyclic nitrone **234** by way of oxime formation and subsequent Michael addition. Intramolecular [3+2] dipolar cycloaddition produced dinitrile **235** as a single regioisomer. Dinitrile **235** was an advanced intermediate in a recent formal synthesis of histrionicotoxin and histrionicotoxin 235A.[169] Additional applications of this strategy for the synthesis of the azaspiro core unit of alkaloids were disclosed recently.[170]



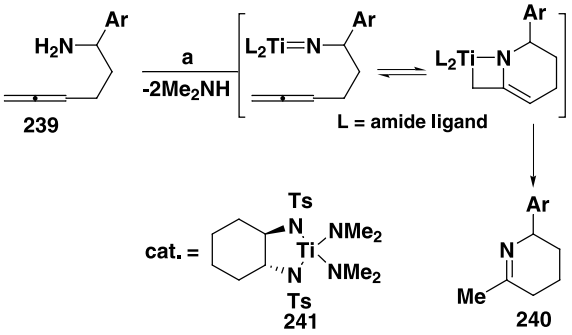

**Scheme 60.** (a) $NH_2OH{\cdot}HCl$, NaOAc, MeOH, room temperature; (b) PhMe, 160°C [47%, 2 steps].

The synthesis of the azaspiro core of pinnaic acid utilized a stereoselective intramolecular vinylogous (1,6-addition) Michael addition to form the piperidine ring (Scheme 61).[171] A chiral bicyclic lactam was used for the synthesis of amine **236**. Removal of the Boc protecting group and base-induced cyclization proceeded with excellent diastereoselectivity, generating piperidine **238** exclusively as the *E*-isomer. Intramolecular 1,6-addition of an amine was used also as a key step for piperidine ring formation in the total synthesis of the erythrina alkaloid cocculolidine.[172]



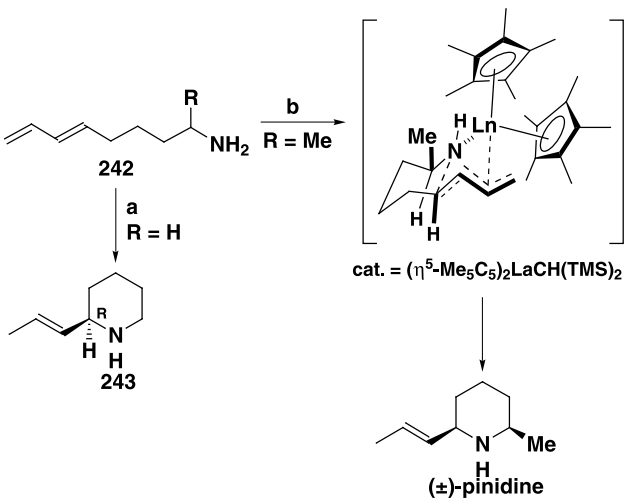

**Scheme 61.** (a) TFA, $CH_2Cl_2$, room temperature; (b) DBU, room temperature [81%, 2 steps].

**5.3.5. Hydroamination/cyclization.** The catalytic intramolecular addition of an N–H bond across an unactivated C–C multiple bond is a useful, atom-economical transformation and progress in this area will be highlighted. Titanium bis-sulfonamide catalysts were useful for the efficient intramolecular hydroamination/cyclization of aminoallenes (Scheme 62).[173] For α-aryl amines **239**, catalyst **241** was optimal in terms of reactivity and regioselectivity, favoring cyclic imines **240** exclusively. This was due to the sterically demanding bis(sulfonamide) ligand that disfavored cycloaddition of the titanium imido species with the internal double bond of the allene. This catalyst system tolerated fluoride, chloride (both *o*- and *p*-), methoxy, and methyl substituents on the aryl ring, and was used also to form seven-membered cyclic imines. A related strategy from aminoalkynes[174] was reported, as well as procedures for the Bronsted acid catalyzed intramolecular hydroamination of protected alkenylamines,[175] and the intramolecular radical cyclization of allenic sulfonamides in the presence of AIBN and *p*-toluenesulfonyl bromide or iodide.[176]




**Scheme 62.** (a) Catalyst, PhMe, 75°C [79–95%].

Progress in the cyclization of amines tethered to 1,2-disubstituted alkenes was realized with conjugated aminodienes **242** as substrates and organolanthanide catalysts (Scheme 63).[177] Excellent diastereoselectivity was observed in the formation of *cis*-2,6-disubstituted piperidine (±)-pinidine due to a chair-like transition state in which the diene and methyl group occupy equatorial positions. In addition, a catalytic enantioselective cyclization afforded piperidine **243** in 69% ee.

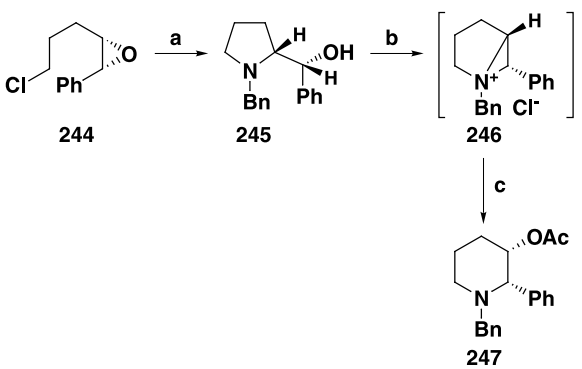



**Scheme 63.** (a) Chiral catalyst, $C_6D_{12}$, 0°C [*E*/*Z*=95:5, 69% ee]; (b) catalyst, $C_6D_6$, room temperature [95%, *cis*/*trans*=178:1, *E*/*Z*=94:1.5].

Palladium-catalyzed cyclizations leading to azasugars,[178a] six-membered heterocycles,[178b] and a palladium-catalyzed carbonylation–coupling–cyclization of allenic sulfonamides

with aryl iodides and carbon monoxide[179] were reported recently.

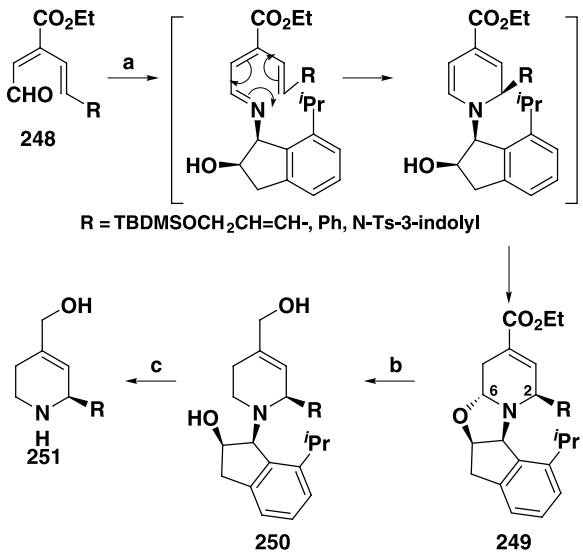
**5.3.6. Ring expansions.** An asymmetric synthesis of (2*S*,3*S*)-3-hydroxy-2-phenylpiperidine was accomplished using a prolinol ring expansion as the key step (Scheme 64).[180] *cis*-Epoxide **244** was derived from an acetylene precursor by hydrogenation with Lindlar's catalyst followed by catalytic enantioselective epoxidation with Jabobsen's catalyst.[181] Treatment with benzylamine in refluxing acetonitrile afforded prolinol **245**, presumably the product of a 5-*exo-tet* cyclization. After conversion to a mesylate, the reaction proceeded through bicyclic aziridinium intermediate **246**, and treatment with *tetra-n*-butylammonium acetate afforded *cis*-α-phenyl-β-acetoxypiperidine (**247**). Chiral pool starting materials were used to prepare prolinols for ring expansions to enantiomerically pure *trans*-3,4-disubstituted[182] and 3,3,5-trisubstituted piperidines.[183]



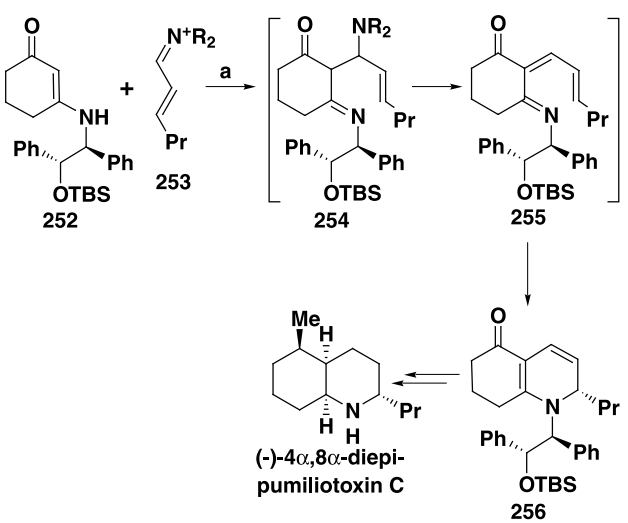

**Scheme 64.** (a) $PhCH_2NH_2$, $NaHCO_3$, NaI, MeCN, reflux [65%]; (b) MsCl, $Et_3N$, THF, −20°C; (c) $Bu_4NOAc$, THF, −20°C→room temperature [85, 99% ee].

**5.3.7. 6π-Azaelectrocyclizations.** Thermal 6π-azaelectrocyclization of 1-azatrienes to 1,2-dihydropiperidines is a well known pericyclic reaction that proceeds in a disrotatory mode.[184] Significant progress in accelerating the azaelectrocyclization was achieved by a combination of C-4 ester and C-6 alkenyl or aryl substituents on the linear 1-azatriene that enhanced HOMO and LUMO orbital interactions. Utilizing 7-alkyl substituted *cis*-aminoindanols to control diastereoselectivity resulted in the first highly stereoselective asymmetric 6π-azaelectrocyclization (Scheme 65).[185] Optimum conditions for this facile azaelectrocyclization utilized a C-7 isopropyl substituted aminoindanol affording aminoacetal **249**. Removal of the chiral auxiliary was initiated with lithium aluminum hydride reduction producing diols **250**. Subsequent treatment with manganese dioxide and silica gel chromatography provided piperidine **251**. The authors postulated that manganese dioxide affected *N*-oxide formation with auxiliary removal by an acid catalyzed Polonovski reaction. These authors also reported a formal synthesis of 20-epiuleine.

The synthesis of substituted piperidines from the alkylations of vinylogous amides with α,β-unsaturated iminium salts was reported by the Hsung group.[186] To illustrate, reaction of vinylogous amide **252** and α,β-unsaturated iminium salt **253** (Scheme 66) afforded the dihydropyridine **256** as a >96:4 mixture of diastereomers.[186d] The reaction was



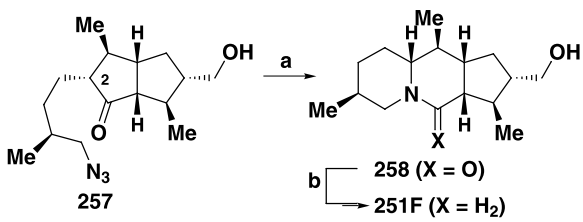

**Scheme 65.** (a) 7-Isopropyl-(1*S*,2*R*)-(−)-*cis*-1-amino-2-indanol, $CHCl_3$, room temperature [96–100%, dr (2-position)=10–>40:1]; (b) LAH, $Et_2O$, [76–100%]; (c) $MnO_2$, $CH_2Cl_2$, then $SiO_2$ [55–69%].




**Scheme 66.** (a) PhH/EtOH, reflux [85–91%].

suggested to proceed via Knoevenagel-like condensation product **254**. β-Elimination afforded 1-azatriene **255** and electrocyclic ring closure produced **256** that was transformed further to (−)-4α,8α-*diepi*-pumiliotoxin C.

**5.3.8. Schmidt reaction.** An intramolecular Schmidt reaction[187] was the key step in the synthesis of the piperidine ring of dendrobatid alkaloid 251F (Scheme 67).[188] The azide **257** was prepared from the corresponding alcohol using an

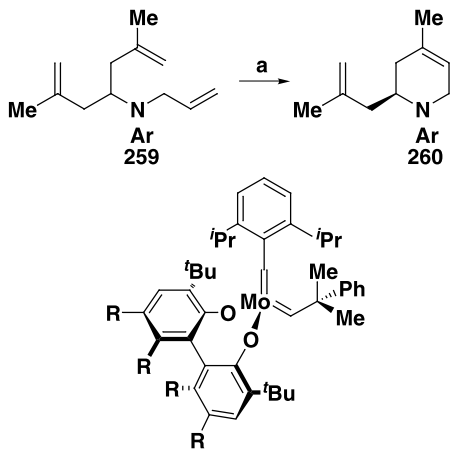



**Scheme 67.** (a) TfOH, $CH_2Cl_2$, 0°C [79%]; (b) $LiAlH_4$, $Et_2O$, 0°C [86%].

azide-modified Mitsunobu reaction.[189] Triflic acid promoted rearrangement proceeded with migration of C-2 to afford **258** as a single diastereomer. Subsequent reduction completed the asymmetric total synthesis of 251F. The intramolecular Schmidt reaction was used also as the key step in the first asymmetric, total synthesis of (+)-sparteine.[190]

### 5.4. Intramolecular C–C processes

**5.4.1. Ring closing metatheses.** The utility of ring closing metathesis (RCM) as a tool for the synthesis of substituted piperidines will be highlighted in this section (see also Section 2.2.3). Progress in catalyst development has greatly expanded the scope of this reaction to the extent that retrosynthetic planning incorporating a RCM reaction has become relatively routine. Recent reviews on olefin metathesis reported on the current status of catalyst design, mechanistic understanding and preparative utility.[191] The application of this methodology to the synthesis of enantiopure piperidines normally required non-racemic substrates derived from chiral pool sources or available by asymmetric methodologies. Recent advances in olefin metathesis led to the development of chiral Mo-based catalysts that promoted asymmetric ring closing metathesis (ARCM) reactions and provided access to optically enriched carbocycles and oxygen heterocycles.[192] The first catalytic ARCM method for the synthesis of non-racemic, small and medium ring, unsaturated *N*-heterocycles was accomplished by kinetic resolution or desymmetrization of unsaturated amines (Scheme 68).[193] Piperidine **260** was prepared efficiently and with excellent enantioselectivity by Mo-catalyzed desymmetrization of acyclic aminodiene **259**. The reactivity and selectivity of catalytic desymmetrizations were sensitive to the amine substituents. For amines bearing phenyl and *p*-substituted phenyl groups (entries a–c), catalyst **261a** proved most efficient. For amines with *o*-substituted phenyl groups (entries d and e), catalyst **261a** proved ineffective. The importance of a modular chiral catalyst for screening resulted in the identification of **261b** for efficient ARCM of these substrates. Some practical aspects that highlight the utility of this methodology should be mentioned. The Mo-catalysts were prepared from commercially available materials and used in situ.[194] Reactions were carried out in the absence of solvent in an efficient and environmentally friendly manner. Amine **260** (entry a) was prepared in 78% yield and >98% ee under solvent-free conditions (2.5 mol% **261a**, 22°C, 10 min). This methodology was used also for the enantioselective synthesis of seven and eight-membered ring amines.

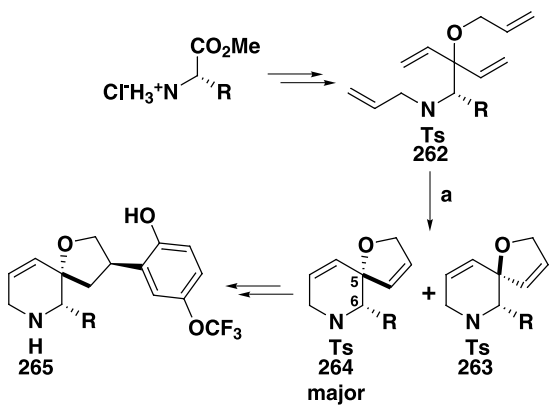



261
a R = Me
b R = -(CH$_2$)$_4$-

| Entry | Ar | 5.4.1-03 | yield | ee % |
|---|---|---|---|---|
| a | Ph | a | 78 | 98 |
| b | 4-MeOPh | a | 81 | 97 |
| c | 4-BrPh | a | 81 | 98 |
| d | 2-MeOPh | b | 77 | 84 |
| e | 2-BrPh | b | 90 | 82 |

**Scheme 68.** (a) Catalyst, PhH, 22°C.

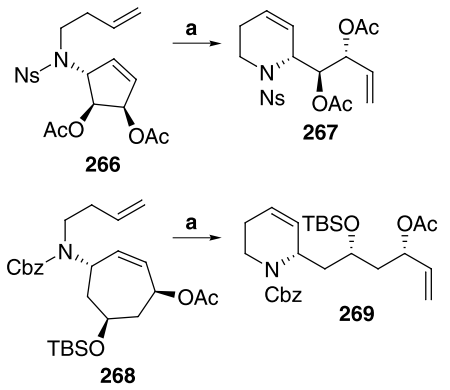
A stereoselective double RCM was useful for the synthesis of spirocyclic compounds, resulting in the enantioselective synthesis of the selective NK-1 receptor antagonist **265** (Scheme 69).[195] The *N*-tosyl protected tetraene **262** was prepared from commercially available amino acid esters. The key double RCM reaction with Grubbs' catalyst proceeded at room temperature affording chromatographically separable spirocycles favoring 5*R*,6*S* diastereomers **264**. Mechanistic studies determined the predominant pathway involved initial formation of the dihydrofuran ring. A regio- and stereoselective reductive Heck reaction on diene **264** introduced the aryl group in the synthesis of NK-1 receptor antagonist **265**. This strategy also was used for the synthesis of functionalized spiropiperidines.[196]




| R | % yield 263 + 264 | % ds |
|---|---|---|
| Me | 74 | 92 |
| iPr | 84 | 92 |
| iBu | 76 | 92 |
| Bn | 87 | 92 |
| Ph | 86 | 70 |

**Scheme 69.** (a) PhCH=Ru(PCy$_3$)$_2$Cl$_2$, CHCl$_3$, 20°C.

The ruthenium-catalyzed ring rearrangement emerged as a useful complement to RCM. Rapid access to a variety of aza- and oxacycles was achieved using a process in which a carbocycle was transformed into a heterocycle by an intramolecular ring opening–ring closing domino metathesis. Starting with enantiomerically pure carbocycles, the

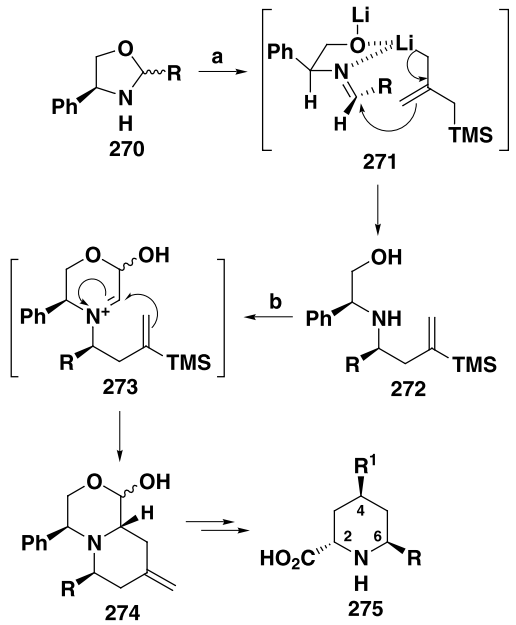



**Scheme 70.** (a) PhCH=Ru(PCy$_3$)$_2$Cl$_2$, CH$_2$=CH$_2$, CH$_2$Cl$_2$, room temperature [100%]; (b) PhCH=Ru(PCy$_3$)$_2$Cl$_2$, CH$_2$Cl$_2$, reflux [92%].

metathesis rearrangement transferred chirality into the heterocycle and the formed side chain. Enantiopure piperidines were available from this rearrangement (Scheme 70).[197] All reactions were carried out in methylene chloride using Grubbs' catalyst. To accelerate the reaction and to avoid formation of side products, the reactions were performed in the presence of ethylene. Piperidines **267** and **269** were produced in excellent yields, with the side chain length being controlled by the size of the carbocyclic ring. This tandem ring rearrangement process was used also to prepare seven-membered heterocycles.

Examples of RCM where one of the olefins is directly connected to a heteroatom are rare. Recent papers report the RCM reaction of olefins containing enamides[198] and ynamides[199] that were used to prepare *N*-protected six-membered cyclic enamides. RCM reactions were used as the key step in the preparation of azasugar analogs and recent reports detail the synthesis of hydroxylated indolizidines[200] and oxazolidinyl piperidines.[201] The RCM reaction also was used in the synthesis of pipecolic acids,[202] pipecolic acid analogs,[203] enantiopure bicyclic lactams,[204] bridged bicyclic piperidines[205] and the hexahydroquinoline DE ring system of the aspidosperma alkaloids.[206] The following piperidine alkaloids were synthesized using a RCM reaction as the key step: (*S*)-anabasine and (*S*)-anatabine,[207] (−)-β-conhydrin and analogs,[208] (*R*)-coniine and (2*R*,6*R*)-solenopsin A analogs,[209] (+)-febrifugine,[210] fagomine and analogs,[211] (+)-sedamine[210] and (−)-prosophylline.[212] In addition, publications have appeared that detail RCM on a soluble poly(ethylene glycol) supported substrate[213] and the successful use of polymer supported ruthenium catalysts in RCM reactions.[214]

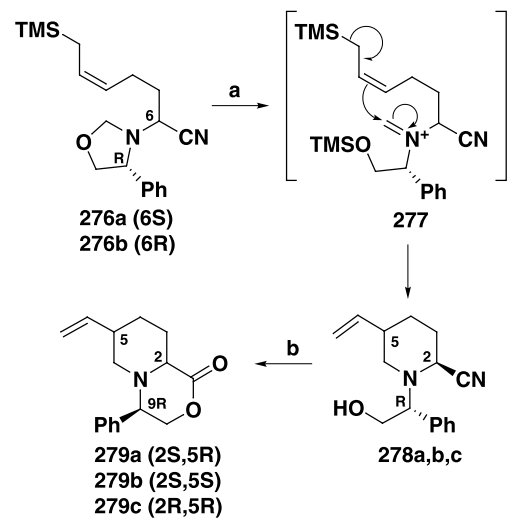
**5.4.2. Iminium ion cyclizations.** Intramolecular cyclizations between iminium ions and allyl or vinyl silanes are an established method for the synthesis of *N*-heterocycles.[215] This intramolecular cyclization, an allylsilane onto an iminium ion, was the key step in a synthesis of enantiopure 6- and 4,6-disubstituted pipecolic acids **275** (Scheme 71).[216] Reaction of chiral oxazolidine **270** with {2-[(trimethylsilyl)methyl]prop-2-enyl}lithium afforded functionalized β-amino alcohol **272**. Addition to oxazoline **270** proceeded through chelated intermediate **271**, with internal nucleophilic attack onto the less hindered *Si* face of the (*E*)-imine tautomer. Reaction of β-amino alcohol **272** with glyoxal




**Scheme 71.** (a) TMSCH$_2$C(=CH$_2$)CH$_2$Li, THF, −78→−20°C [73–80%]; (b) OHCCHO, THF/H$_2$O, room temperature [98%].

generated ene-iminium intermediate **273** that cyclized to bicycle **274** as a single ring-juncture diastereomer. Functional group transformations then were employed to modify the exocyclic methylene group prior to removal of the chiral inductor. Related studies highlighted the intramolecular cyclization of vinylsilane and allylsilane moieties onto iminium ions as the key step in the enantioselective synthesis of pipecolic acid[217] and *trans*-6-alkylpipecolic acid.[218]

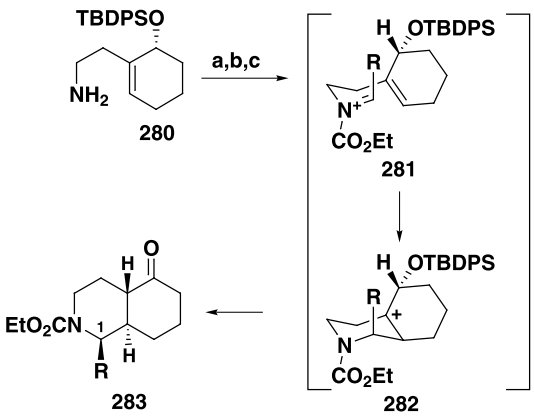
An analogous cyclization was used to synthesize 5-substituted pipecolic acids (Scheme 72).[219] A separable 3:1 mixture of allylsilanes **276a** and **276b** was prepared by alkylation of (*R*)-cyanomethyloxazolidine with a functionalized allylsilane. Treatment of oxazolidine **276a** with TMSOTf generated iminium ion **277**, and intramolecular




**Scheme 72.** (a) TMS−OTf, CH$_2$Cl$_2$, −40°C [96% for **276a→278a** and **b**, **278a**:**b**=9:1; 62% for **276b→278c**]; (b) HCl(g)/EtOAc, room temperature, [77% for **278a** and **b→279a** and **279b**, **279a**:**b**=4:1; 60% for **278c→279c**].

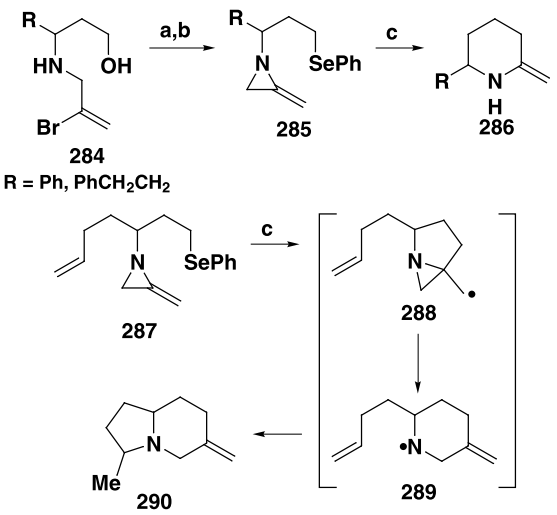
cyclization afforded a 9:1 mixture of diastereomers **278a** and **b**. Similar treatment of **276b** led to formation of cyanopiperidine **278c** as a single diastereomer. The mixture of diastereomers **278a** and **b** was treated with gaseous hydrochloric acid in ethyl acetate affording a chromatographically separable mixture of lactones that were readily characterized by NMR as piperidines **279a** and **279b** with the assigned absolute configurations. Diastereomer **278c** was converted to 2,5-disubstituted piperidine **279c** in similar fashion. The lactones were readily converted to 5-substituted pipecolic acids.

An intramolecular iminium ion cyclization–hydride migration sequence was the salient feature of an asymmetric synthesis of 1-substituted-*trans*-5-oxooctahydroisoquinolines (Scheme 73).[220] Amine **280** was prepared from 2-iodocyclohexenone using a catalytic asymmetric hydride reduction[221] and a Suzuki β-aminoethylation as key steps. An α-ethoxy carbamate was generated from amine **280** following imine formation and treatment with diethyl pyrocarbonate. Reaction of this intermediate with boron trifluoride etherate and a proton scavenger led to generation of the acyl iminium ion **281**. Cyclization to **282** and subsequent hydride migration produced hydroisoquinoline **283**. In this efficient procedure, the lone stereocenter of protected allylic alcohol **280** was used to establish the absolute configuration and relative stereochemistry of the three new chiral centers of **283**. Also, the (*E*)-iminium ion geometry was required to avoid $A^{1,3}$ strain during the cyclization with approach of the iminium ion electrophile to the cyclohexene face opposite the bulky siloxy group. This procedure enabled the synthesis of enantioenriched *trans*-hydroisoquinolones with axial alkyl, aryl or alkenyl substituents at C-1. The ytterbium(III) triflate catalyzed electrophilic cyclization of glyoxalate derived unsaturated imines was used to prepare piperidines fused to δ-lactones[222] that also was adapted to solid-phase synthesis.




**Scheme 73.** (a) RCHO, $MgSO_4$, $CH_2Cl_2$, room temperature; (b) $(EtO_2C)_2O$, EtOH, room temperature; (c) $BF_3{\cdot}Et_2O$, 6,6-di-$^t$butyl-4-methylpyridine, $CH_2Cl_2$, 0°C [15–74%, for 3 steps, 85–90% ee].

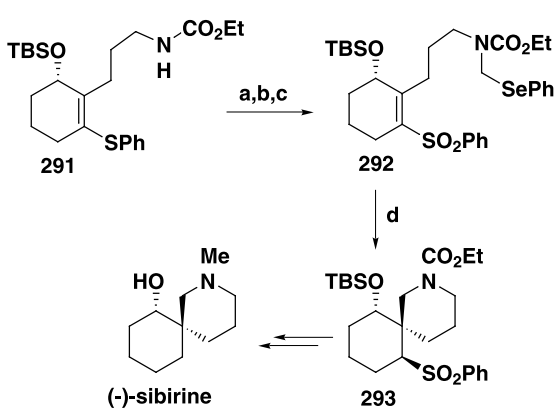
**5.4.3. Radical cyclizations.** Intramolecular radical additions to substituted 2-methyleneaziridines provide a novel route to functionalized piperidines (Scheme 74).[223] Phenylselenide **285** was chosen as the radical source and was available from alcohol **284**. Radical generation was initiated by slow addition of tributyltin hydride and AIBN.




**Scheme 74.** (a) *N*-Phenylselenophthalimide, $PBu_3$, THF, 0°C [75–79%]; (b) $NaNH_2$, $NH_3$ [91–93%]; (c) $Bu_3SnH$, AIBN, PhH, reflux [40–68%].

5-*exo*-Trig cyclization onto the double bond generated an aziridinylcarbinyl radical that then underwent C–N bond cleavage to relieve strain. An acid/base extractive work-up facilitated separation of the product piperidine **286** from tin by-products. A one carbon homolog of **285** failed to yield an azepine. Phenylselenide **287** was synthesized to examine the reactivity of the putative aminyl radical. In this case, cyclization proceeded through radical intermediates **288** and **289** with an additional cyclization producing octahydroindolizine **290** as a single diastereomer. This methodology also was used to prepare a substituted decahydroquinoline. Radical 6-*exo*-trig cyclizations were used in a synthesis of (−)-indolizidine 223AB[224] and the synthesis of enantiopure 3-alkylpiperidines.[225] Photoinduced electron transfer catalyzed radical cyclization reactions of unsaturated *N*-trimethylsilylmethyl amino acid derivatives were used in peptide chemistry for the formation of piperidines.[226]

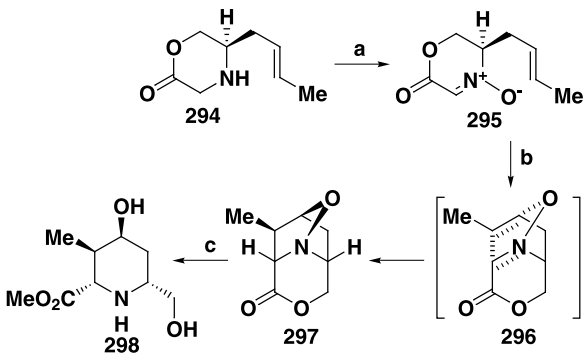
A phenylselenide was used as a radical source for an intramolecular 6-*endo*-trig cyclization in the synthesis of the spirocycle alkaloid (−)-sibirine (Scheme 75).[227] Carbamate **291** was prepared from 3-phenylthio-2-bromo-2-cyclohexen-1-one using a catalytic asymmetric hydride reduction




**Scheme 75.** (a) MCPBA, $CH_2Cl_2$, room temperature [98%]; (b) $^t$BuOK, $(CH_2O)_n$, $^t$BuOH, room temperature [75%]; (c) PhSeH, TsOH, room temperature, [71%]; (d) $Bu_3SnH$, AIBN, PhMe, reflux [60%].

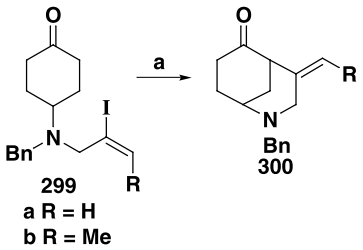
and a β-alkyl Suzuki coupling reaction (see also Scheme 73). Oxidation of the PhS group of **291** to the corresponding sulfone facilitated the preparation of phenylselenide **292** via its *N*-hydroxymethyl derivative. Treatment of phenylselenide **292** with tributyltin hydride in the presence of a catalytic amount of AIBN generated an (alkoxycarbonylamino)methyl radical that underwent 6-*endo*-trig cyclization to spirocycle **293**. Cyclization of **292** lacking the phenylsulfonyl group gave a mixture of 6-*exo* spirocycle and 7-*endo* bicycle. Functional group transformations completed the synthesis of (−)-sibirine.

**5.4.4. 1,3-Dipolar cycloadditions.** The utility of intramolecular 1,3-dipolar cycloadditions in the synthesis of *N*-heterocycles is well documented.[228] Synthesis of the functionalized piperidine A-ring of the marine heptatoxin cylindrospermopsin featured an intramolecular oxazinone *N*-oxide/alkene dipolar cycloaddition (Scheme 76).[229] Oxazin-2-one **294** was prepared from an optically active *N*-Boc-crotylglycine derivative and its oxidation with Davis' oxaziridine yielded the conjugated oxazinone-*N*-oxide **295**. Sealed tube thermolysis of **295** effected cycloaddition to tricyclic isoxazolidine **297** through chair-like *exo*-transition state **296**. Hydrogenolysis of **297** in methanol produced piperidine **298**. *N*-Oxide **295** may be viewed as a constrained α-alkoxycarbonyl nitrone and highly functionalized cycloadducts such as **297** provide opportunities for further elaboration. Additional reports appeared recently that utilize intramolecular 1,3-dipolar cycloaddition strategies to synthesize polysubstituted piperidines.[230]



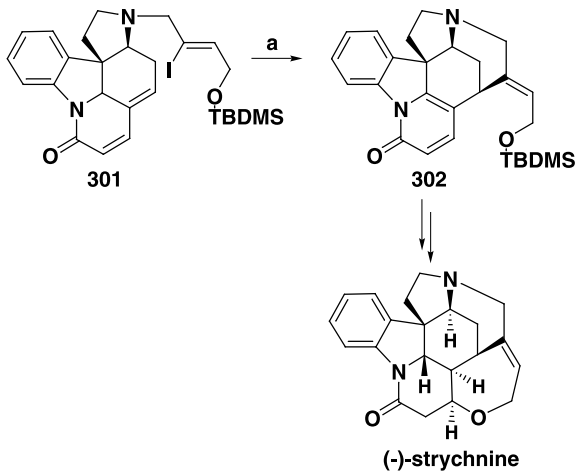

**Scheme 76.** (a) 2-Benzenesulfonyl-3-phenyloxaziridine, THF, 0°C [75%]; (b) PhMe, 200°C [78%]; (c) $H_2$, Pd/C, MeOH [98%].

**5.4.5. Palladium mediated couplings.** A recent review on the intramolecular Heck reaction[231] highlights applications of this procedure for the synthesis of a variety of heterocyclic systems. The palladium-catalyzed intramolecular coupling of amine tethered vinyl iodides and ketone enolates was useful for the synthesis of the 2-azabicyclo[3.3.1]nonane ring system (Scheme 77).[232] Vinyl iodides **299** were available readily by *N*-alkylation of 4-(benzylamino)cyclohexanone. Intramolecular cyclization of **299** to **300** was accomplished with 0.2 equiv. of $Pd(PPh_3)_4$ and potassium *tert*-butoxide as base in refluxing tetrahydrofuran (R=H, Me). The cyclization was achieved also at room temperature in 42% yield (R=H). In contrast, the same reaction run at room temperature with the vinyl bromide of **299a** returned only unreacted starting material.



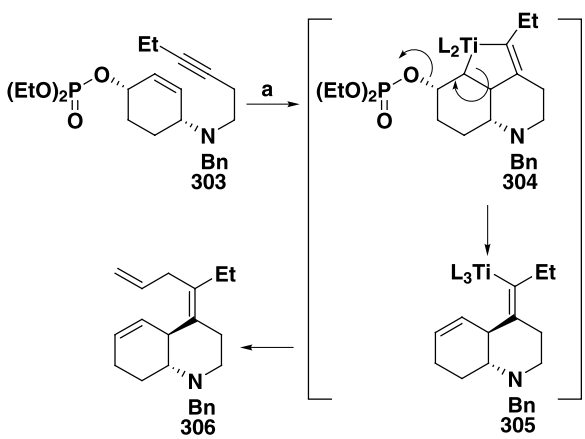

**Scheme 77.** (a) $Pd(PPh_3)_4$, $^t$BuOK, THF, reflux [**299a**=55–60%, **299b**=75%].

This methodology was used also for the synthesis of the 2-azabicyclo[4.3.1]decane ring system and five-membered nitrogen heterocycles. In another report, the intramolecular Heck reaction of vinyl iodide **301** was used to form the piperidine ring of pentacycle **302** as part of a total synthesis of (−)-strychnine (Scheme 78).[233]




**Scheme 78.** (a) $Pd(OAc)_2$, $Bu_4NCl$, $K_2CO_3$, DMF, 70°C [48%].

Palladium-mediated intramolecular cyclizations were used to functionalize piperidines. Halogenated phenols and unsaturated piperidinols were coupled via Mitsunobu condensation and an intramolecular Heck reaction provided hexahydrobenzofuro[2.3-*c*]pyridines.[234] An intramolecular Heck arylation onto a piperidine enamide was the key reaction used in the synthesis of azaspirocycles prepared as conformationally constrained nicotine analogs.[108c] An

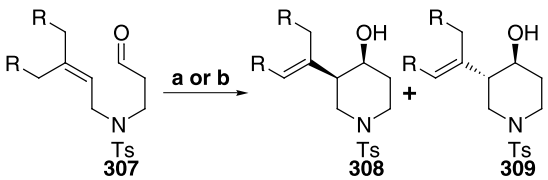



**Scheme 79.** (a) $Ti(O^iPr)_4$, $^i$PrMgCl, $Et_2O$, −78→−50°C, then $Li_2Cu(CN)Cl_2$, $H_2C{=}CHCH_2Br$, −50°C [81%].

*N*-alkyl glutarimide ketene aminal was a substrate for a novel application of an intramolecular Heck cyclization that was used to synthesize the tricyclic carbon skeleton of cytisine.[235]

**5.4.6. Ene cyclizations.** A titanium(II)-mediated intramolecular cyclization of 2,8-bis-unsaturated carbonates was used as the key step in a stereoselective synthesis of enantiopure substituted piperidines.[236] A recent modification of this methodology was used in the synthesis of octahydroquinolines (Scheme 79).[237] Cyclization of enyne **303** proceeded through titanocycle **304** followed by elimination of the diethylphosphoryloxy group to vinyltitanium intermediate **305**. The titanium–carbon bond of **305** was functionalized by a copper-mediated allylation[238] producing triene **306**. Both *cis*- and *trans*-**303** provided only *trans*-octahydroquinolines as products but changing the leaving group to an acetoxy resulted in a lower yield of **306**.

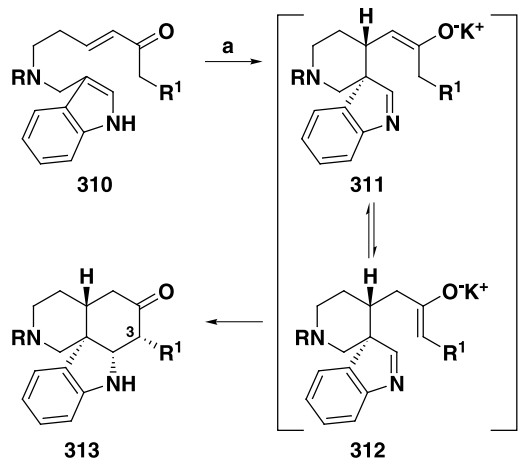
Intramolecular carbonyl cyclizations were used to synthesize *cis*- and *trans*-3,4-disubstituted piperidines. Lewis acid-catalyzed carbonyl ene cyclization of aldehydes **307** produced *trans*-piperidine **309** with diastereomeric ratios of ≤93:7 (Scheme 80).[239] Studies revealed that ene cyclization at −78°C favored *cis*-piperidine **308**. Raising the temperature of the reaction resulted in preferential formation of *trans*-**309** suggesting the carbonyl ene cyclization was reversible and *cis*-**308** was the kinetic product. By contrast, Prins cyclization of **307** catalyzed by a Bronsted acid at −78°C preferentially afforded *cis*-piperidine **308**, but raising the temperature had little effect on the *cis*-diastereoselectivity. Thus, both reactions proceeded initially through the kinetic product **308** with significant conversion to the thermodynamic product *trans*-**309** observed only under Lewis acid catalysis. The switch in diastereoselectivity between Lewis and Bronsted acid catalysis is an intriguing but useful feature of this methodology.




| R | conditions | 308:309 | % yield major (minor) |
|---|---|---|---|
| H | a | 8:92 | 74 (6) |
| | b | 95:5 | 79 (4) |
| Me | a | 22:78 | 55 (15) |
| | b | >98:2 | 86 |
| -$(CH_2)_2$- | a | 30:70 | 53 (22) |
| | b | 90:10 | 71 (7) |
| -$(CH_2)_3$- | a | 7:93 | 74 (4) |
| | b | 89:11 | 72 (9) |
| -$(CH_2)_4$- | a | 25:75 | 61 (20) |
| | b | 80:20 | 60 (14) |

**Scheme 80.** (a) $MeAlCl_2$, $CHCl_3$, 61°C; (b) conc. HCl, $CH_2Cl_2$, −78°C.

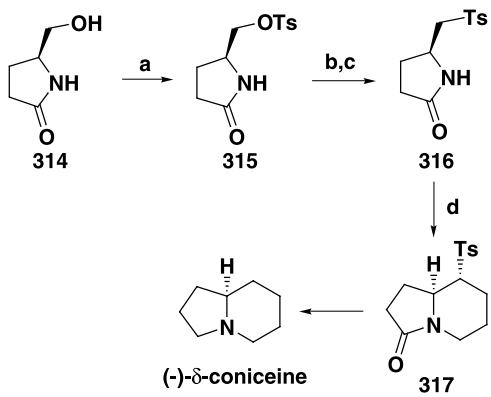
**5.4.7. Anion polycyclization.** The efficient use of a novel anionic polycyclization cascade was the key feature of a rapid, stereocontrolled synthesis of functionalized tetracycles (Scheme 81).[240] In a one-pot sequence, an indol-3-ylmethylamine was reacted sequentially with acrolein and the anion of a β-ketophosphonate. The resulting enone **310** was treated with a catalytic amount of potassium *tert*-butoxide and tetracyclic ketone **313** was produced as the *trans*-diastereomer. The cascade sequence was initiated by proton abstraction from indole **310** and an intramolecular Michael addition afforded **311**. Enolate isomerization of **311** to **312** and an intramolecular iminoaldol cyclization produced an indolenine anion that was quenched by a proton exchange with **310** thereby propagating the cycle. The reaction tolerated a variety of *N*-protecting groups with the newly introduced substituent at C-3 oriented toward the most crowded face of the polycycle. These functionalized polycycles are similar to the core of the manzamine family of indole alkaloids (see also Scheme 12).




**Scheme 81.** (a) $^t$BuOK, THF, room temperature [35–60%].

## 5.5. Intermolecular processes

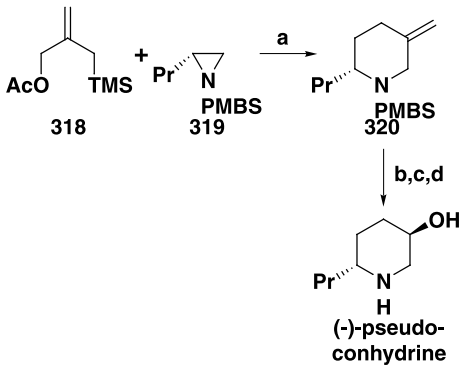
**5.5.1. Formal [3+3] annulations.** A [3+3] bis-alkylation was used to form the piperidine ring in (−)-δ-coniceine.[241] (*S*)-Pyroglutaminol (**314**) afforded tosylate **315** and displacement with 4-methylthiophenol followed by oxidation produced bis-nucleophile precursor **316** (Scheme 82).




**Scheme 82.** (a) TsCl, $Et_3N$, DMAP, $CH_2Cl_2$, room temperature [60%]; (b) MePhSH, NaOH, MeCN, reflux; (c) Oxone®, aq MeOH, room temperature [90%, for 2 steps]; (d) NaH, DMF, room temperature, then $I(CH_2)_3I$, [60%]; (e) Na/Mg, $NaHPO_4$, MeOH [51%]; (f) $LiAlH_4$, $Et_2O$ [85%].

Deprotonation of both acidic sites with sodium hydride and alkylation with diiodopropane afforded piperidine **317**. Reductive cleavage of the tosyl group and amide reduction completed the synthesis of (−)-δ-coniceine.

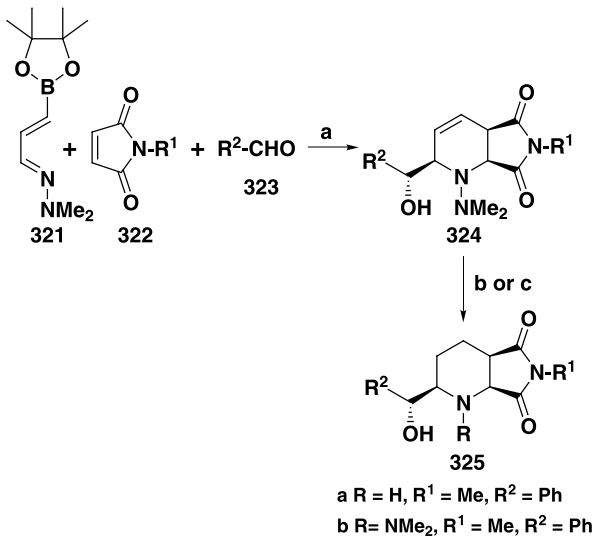
The synthesis of enantiomerically pure piperidines was reported via [3+3] cycloadditions of Pd–trimethylenemethane complexes with aziridines and this approach was parlayed to the total synthesis of (−)-pseudoconhydrine (Scheme 83).[242] Specifically, [3+3] cycloaddition of the Pd–trimethylenemethane complex generated from 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate (**318**) and enantiomerically pure aziridine **319** (PMBS=*p*-methoxybenzenesulfonyl) afforded piperidine **320**. Oxidative cleavage of the double bond followed by reduction with L-selectride® afforded the corresponding carbinol that, following deprotection, gave (−)-pseudoconhydrine.




**Scheme 83.** (a) $Pd(OAc)_2$, $P(O^iPr)_3$, BuLi, PhMe/THF [63%]; (b) $O_3$, DMS; (c) L-Selectride® [77%]; (d) Na-naphthalide [79%].

**5.5.2. Aza Diels–Alder reactions.** The Diels–Alder reaction is arguably one of the most important reactions used to prepare six-membered rings. Its popularity is due to a number of factors which include: formation of the six-membered ring in a single step, toleration of a wide variety of substituents and varying degrees of stereocontrol at as many as four new stereocenters. Given the rather ubiquitous appearance of the piperidine ring in natural products and pharmaceuticals, it is understandable that aza-equivalents of this venerable reaction are utilized as a way to synthesize this heterocycle. In principle, the nitrogen atom of the piperidine may be derived from either the diene (as a 1- or 2-azadiene) or the dienophile (as an imine). Examples of these three motifs are known.

The Diels–Alder reactions of 1-azadienes were reviewed recently.[243] In addition, the mechanism of the reaction of *N*-acyl-1-aza-1,3-butadiene with *N*,*N*-dimethylvinylamine was investigated using density functional theory methods.[244] A tandem 1-aza-Diels–Alder/allylboration reaction has been used to prepare bicyclic piperidine derivatives with a high degree of stereocontrol (Scheme 84).[245] Thus, the three-component reaction of 1-azadiene **321**, substituted maleimides **322** and aldehydes **323** in toluene at 80°C afforded tetrahydropyridines **324** (Scheme 84). High diastereoselectivity was attained by incorporating a chiral auxiliary as the $R^1$-substituent. Reduction of **324** ($R^1$=Me, $R^2$=Ph) with Raney nickel




**Scheme 84.** (a) PhMe, 80°C [47–52%]; (b) $H_2$, Ra Ni, MeOH, 40°C [51%]; (c) $H_2$, Pd/C, EtOH, room temperature [72%].

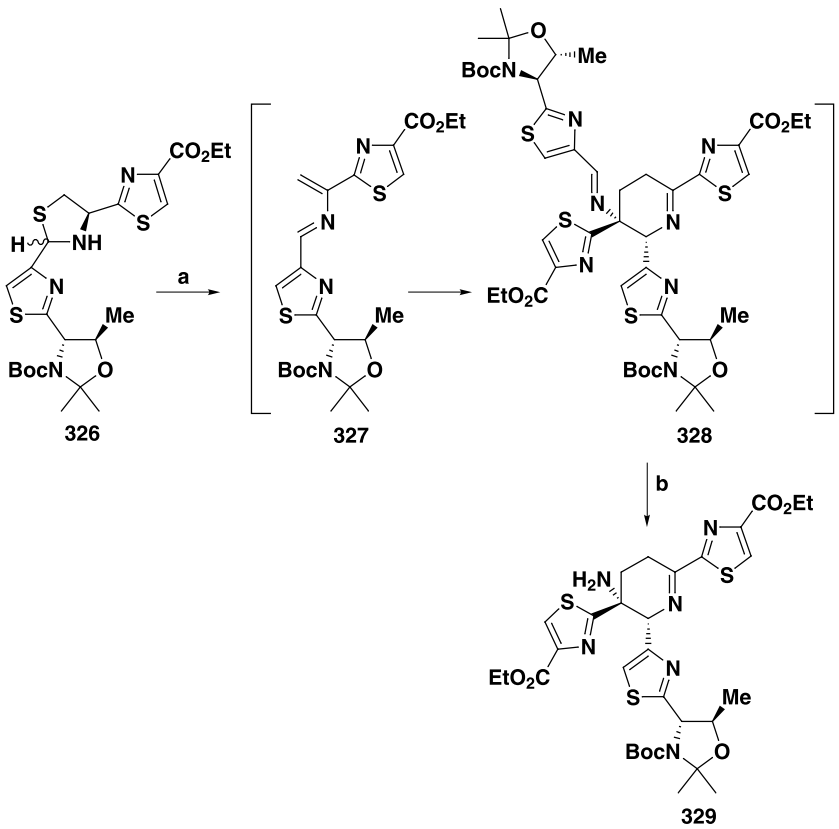
afforded bicyclic piperidine **325a**. Alternatively, hydrogenation over Pd/C produced **325b**.

Syntheses of piperidines derived from the Diels–Alder reactions of 2-azadienes also were reported. For example, the Nicolaou group recently described the synthesis of the tetrahydropyridine core of thiostrepton.[246] Specifically, rupture of the thiazolidine moiety in **326** afforded 2-azadiene **327** that underwent [4+2] dimerization to tetrahydropyridine **328** (Scheme 85). Tautomerization of the tetrahydropyridine to the corresponding enamine and subsequent aza-Mannich cyclization resulted in a significant amount of a [3.2.1]bicyclic impurity. Interestingly, addition of a stoichiometric amount of benzylamine to the reaction almost completely suppressed the formation of this bridged impurity and quenching with water afforded the desired primary amine **329**. Also, this Diels–Alder reaction was regioselective and *endo*-selective but showed no facial selectivity.

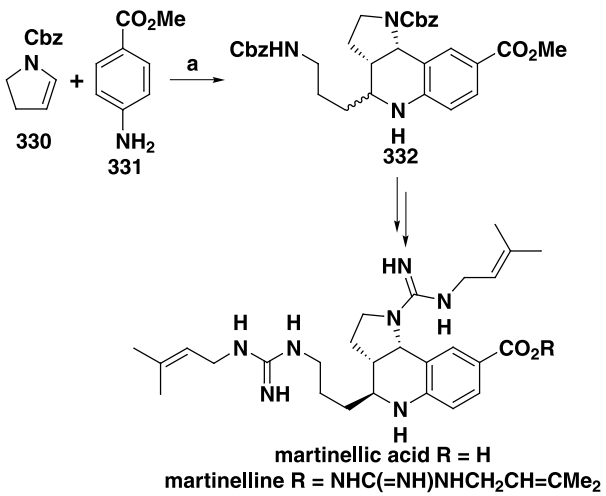
The Diels–Alder reaction of an in situ derived 2-azadiene was employed in the total synthesis of martinellic acid and martinelline.[247] Thus, reaction of two equivalents of Cbz-protected pyrroline **330** and methyl 4-aminobenzoate (**331**) in the presence of a catalytic amount of $Dy(OTf)_3$ gave **332** (*exo*/*endo*=15:85) (Scheme 86). Fortunately for the authors, the stereochemistry of this reaction could be reversed by switching catalysts to CSA (*exo*/*endo*=89:11). *exo*-Isomer **332** was subsequently transformed to martinellic acid and martinelline.

3-Substituted 2*H*-1,4-oxazin-2-ones also were used as 2-azadienes. For example, [4+2] cycloaddition of oxazinones **333** and ethylene afforded bicyclic lactones **334** that were immediately reduced with $LiAlH_4$ in refluxing THF affording piperidines **335** (Scheme 87).[248]

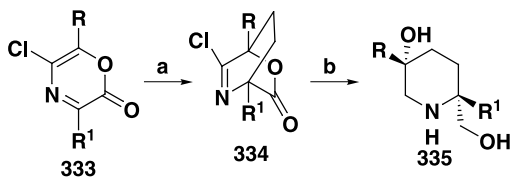
As mentioned above, the nitrogen atom of the piperidine may be derived from the dienophile. The Davis group recently prepared the first examples of enantiopure, quaternary piperidine phosphonates using this concept




**Scheme 85.** (a) $Ag_2CO_3$, DBU, $PhCH_2NH_2$, pyridine, −15°C [42–52%]; (b) $H_2O$ [60%].

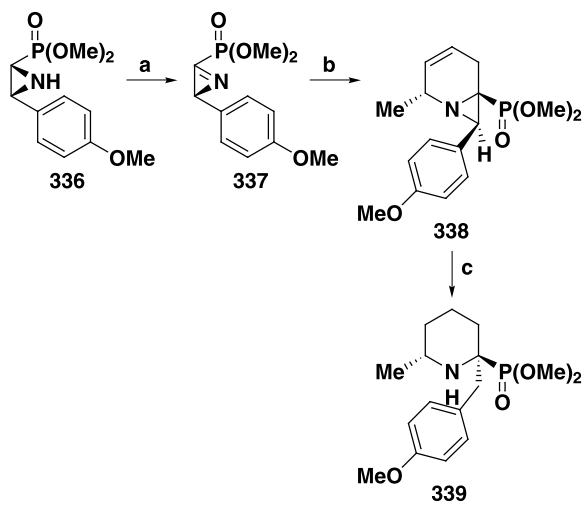



**Scheme 86.** (a) CSA, THF [74%].

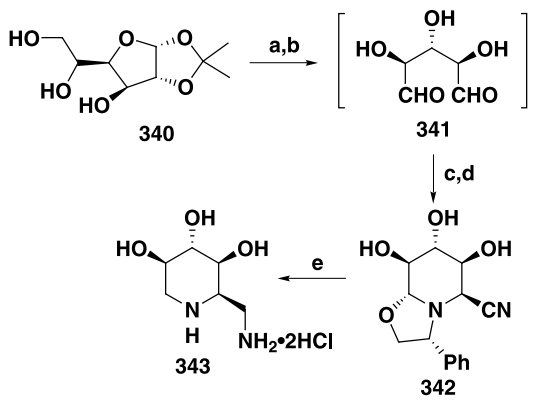



**Scheme 87.** (a) $CH_2{=}CH_2$, PhMe, 110°C (sealed tube); (b) $LiAlH_4$, THF, reflux [60–70%, for 2 steps].

(Scheme 88).[249] More specifically, chiral aziridine phosphonate **336** was prepared using their chiral sulfoximine methodology. Swern oxidation of **336** afforded the 2*H*-azirine 3-phosphonate **337** along with a small amount of the corresponding 2*H*-azirine 2-phosphonate isomer. Diels–Alder cycloaddition of **337** and *trans*-piperylene gave bicyclic piperidine **338** as a single stereoisomer. Hydrogenation of the double bond and concomitant opening of the aziridine ring gave the quaternary piperidine phosphonate **339**. A number of other piperidine syntheses featuring imines as dienophiles were published recently.[250]



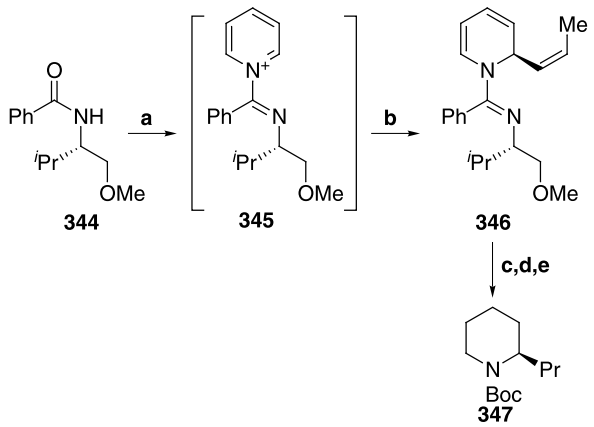

**Scheme 88.** (a) $(COCl)_2$, DMSO, then $Et_3N$, −78°C→room temperature [68%]; (b) *trans*-piperylene, room temperature [89%]; (c) $H_2$, Pd/C, THF [81%].




**Scheme 89.** (a) $NaIO_4$, $NaHCO_3$; (b) DOWEX® $H^+$, $H_2O$; (c) (*R*)-(−)-phenylglycinol, KCN, citric acid buffer, $H_2O$; (d) $ZnBr_2$, MeOH [45%, for 4 steps]; (e) $H_2$, Pd/C, HCl, EtOH [90%].

**5.5.3. CN(*R*,*S*) Methodology.** Husson and co-workers developed CN(*R*,*S*) methodology to prepare substituted piperidines. Using this methodology they reported an expeditious synthesis of 6-amino analogs of 1-deoxynojirimycin and 1-deoxymannonojirimycin.[251] Oxidation and deprotection of D-glucofuranose **340** afforded glutaraldehyde **341** that was immediately condensed with (*R*)-(−)-phenylglycinol in the presence of potassium cyanide and zinc bromide to give piperidine *N*,*O*-acetal **342** (Scheme 89). Subsequent hydrogenation gave primary amine **343**. A review covering this methodology has also appeared.[252] The method also was demonstrated on solid-phase.[253]

**5.5.4. From pyridine reductions.** This section focuses on the synthesis of piperidines by either the complete or sequential reduction of pyridines. For example, substituted piperidines were prepared by hydrogenation of pyridines[254] and their corresponding *N*-oxides.[255] In contrast, the sequential reduction of pyridines allows for further functionalization of the corresponding dihydro and tetrahydro intermediates prior to reduction to the desired piperidine. An interesting application of the latter concept was used to prepare (−)-coniine.[256] Thus, reaction of the triflate of chiral amide **344** and pyridine generated pyridinium amidine **345** that was reacted in situ with *cis*-1-propenyl magnesium bromide giving dihydropyridine **346** (Scheme 90). Hydrogenation of the three double bonds and hydrogenolysis of the chiral auxiliary afforded (−)-coniine which was isolated as its *N*-Boc derivative **347**. Addition of other Grignard reagents to **345** gave yields between 65 and 89%. The C-2 vs C-4 regioselectivity varied between 75:25 and >95:5 while, in all cases, the C-2 diastereoselectivity was >95:5.




**Scheme 90.** (a) $Tf_2O$, pyridine; (b) *cis*-1-propenylmagnesium bromide, −78→−20°C [61%]; (c) $H_2$, $Pd(OH)_2$, EtOH, room temperature; (d) cyclohexane, AcOH, 100°C; (e) $Boc_2O$, THF, aq NaOH [60%].

Other sequential reductions of pyridine derivatives were used to prepare the piperidine moieties found in the azasugar equivalent of L-idose,[257] (±)-dihydropinidine,[258] (±)-tashiromine,[259] the $GABA_c$ antagonist (piperidin-4-yl)methylphosphinic acid,[260] (+)-isofagomine[261] and (±)-catharanthine.[262] The concept also was applied to solid-phase synthesis of vesamicol analogs.[263]

## 6. Conclusion

A plethora of methodologies are available for the stereocontrolled syntheses of piperidones and piperidines. Piperidones, by alkylations and conjugate additions, provide additional opportunity for introduction of substituents α and β to the carbonyl group. Additionally, the carbonyl group may itself be functionalized. In this regard, chiral bicyclic lactams and *N*-acylpyridinium salts often were utilized. Tremendous progress was made in the stereocontrolled assemblage of acyclic precursors to piperidones and piperidines. Also, ring closing metathesis has emerged as a useful strategy. The variety of methods presented in this review and their broad applicability will, hopefully, provide an impetus for additional applications.

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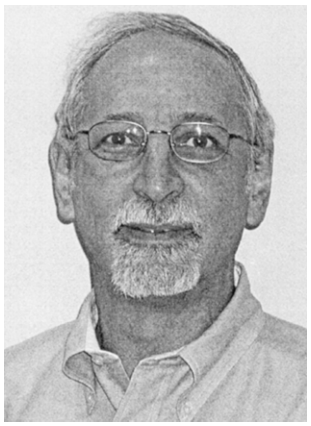
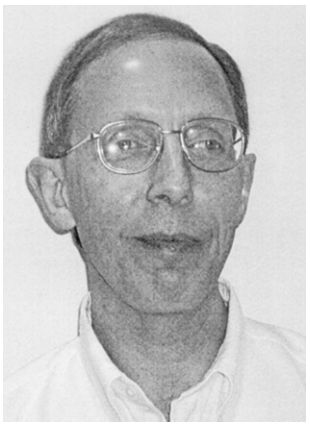
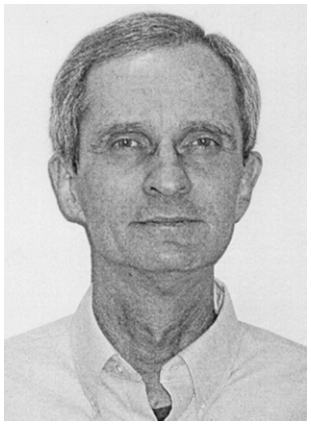
**Biographical sketch**



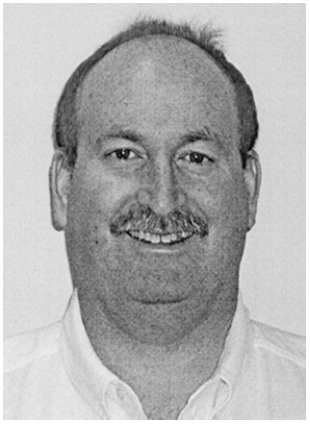
**Philip M. Weintraub** completed his Masters and PhD degrees at The Ohio State University under the direction of Michael P. Cava. After a brief stint at the DuPont experimental station, he moved to Hess & Clark, a vetenary division of Richardson Merrell. In 1970 he was transferred to the Wm S. Merrell Pharmaceutical Co. where he remained through several mergers. In 1998 he was transferred to Aventis in Bridgewater, New Jersey as a member of the medicinal chemistry department. He has been an editor of Annual Reports in Organic Synthesis since 1990.



**Jeffrey S. Sabol** completed his undergraduate work at Purdue University, and then initiated his graduate studies at Columbia University where he received a Masters degree. He completed his graduate work at Northwestern University and received a PhD degree under the guidance of Professor James. A. Marshall. He joined Dow Chemical Co. in Indianapolis, Ind., and was transferred to Merrel Dow Phamaceuticals in 1987. In 1998 he was transferred to the medicinal chemistry department of Aventis Phamaceuticals in Bridgewater, New Jersey. He has been an editor of Annual Reports in Organic Synthesis since 2001.



**John M. Kane** (Mike) completed his PhD at Rensselaer Polytechnic Institute under the direction of Kevin T. Potts. After leaving RPI, he moved to the Colorado State University as a postdoctoral associate of Albert I. Meyers working on the total synthesis of maytansine. Finding gainful employment as a medicinal chemist, he moved to the Richardson Merrel Company in Cincinnati, Ohio where he remained through four mergers. Finally losing his grip on the Midwest, he recently transferred to Aventis in Bridgewater, New Jersey where he is a member of the chemical development department.



**David R. Borcherding** completed his PhD in Medicinal Chemistry at the University of Kansas under the direction of Ronald T. Borchardt. After graduate school he was hired into the Medicinal Chemistry group at Marion Laboratories in 1988. Through a series of mergers and transfers he now works for Aventis Pharmaceuticals in Bridgewater, NJ.