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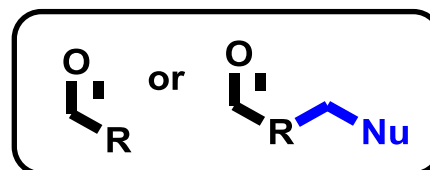
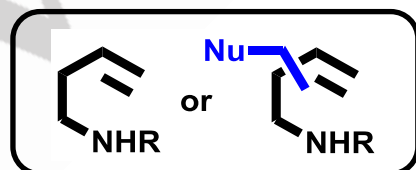
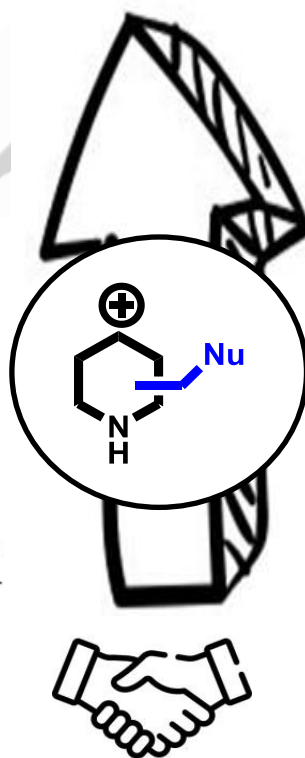
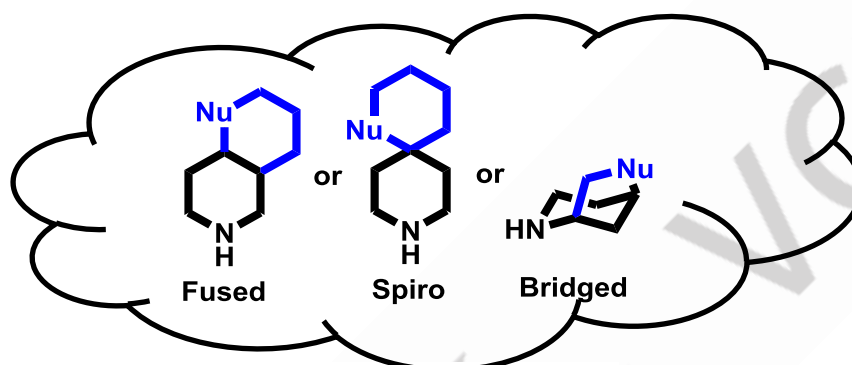
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One-Pot Double Cyclizations Involving an Aza-Prins Process

Nicolas Gouault,^[a] Maxence Roydor,^[a] Jacques Renault,^[a] Swarnayu Banik,^[b] B. V. Subba Reddy,^[b] and Claudia Lalli^{*,[a]}

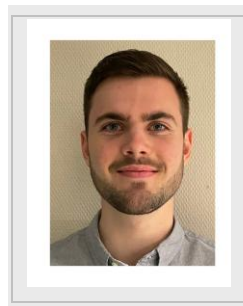


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Dr Nicolas Gouault studied chemistry at the University of Rennes 1, France. He obtained his PhD from the University of Rennes 1 in 2002 under the supervision of Dr M. David. He was then appointed as Research Assistant Professor in the same group in 2002 and promoted to lecturer in 2004. His research interests include heterocyclic chemistry, organic chemistry at the interface with biology, and medicinal chemistry.



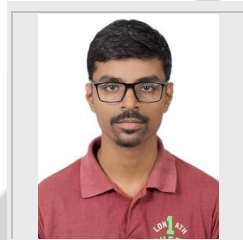
Maxence Roydor completed his M.Sc degree in molecular chemistry in the year 2024 from University of Rennes, France. In 2023, he joined the ISCR in Rennes (France) and University of Florence (Italy) under the supervision of Dr. C. Lalli, Dr. N. Gouault, and Pr. A. Trabocchi. His work was mainly focused on the syntheses of novel polysubstituted piperidines by aza-Prins cyclization.



Dr. Jacques Renault received his diploma of doctor of pharmacy in 1989 then PhD from the University of Caen (France) in 1994. He has been appointed as assistant professor in 1995 then associate professor in 2001, at the University of Rennes. His research interests cover new methods in heterocyclic chemistry for medicinal chemistry.



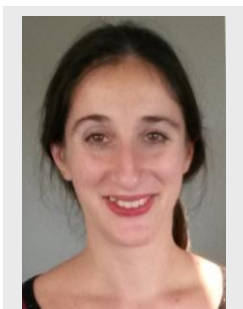
Swarnayu Banik started his PhD under the guidance of Dr. B. V. Subba Reddy at CSIR-IICT, Hyderabad, India in the year 2019. Later on, he worked under the supervision of Dr. Claudia Lalli as a Raman-Charpak Fellow at ISCR, University of Rennes, France (Feb'23-Jul'23). His research is mainly focused on asymmetric synthesis, photoredox organic transformations and cascade aza-Prins spirocyclization.



Dr. B. V. Subba Reddy obtained his PhD in 2003 from CSIR-IICT, Hyderabad under the supervision of Dr. J. S. Yadav. After completion of his post-doc study with Pr. E. J. Corey at Harvard University, he returned to India and joined as a scientist at CSIR-IICT in 2006 and currently occupies the position of chief scientist. He has made significant contributions in the field of Prins cyclization. His other areas of expertise include asymmetric synthesis, carbohydrate chemistry, and the synthesis of biologically active natural products.



Dr. Claudia Lalli received her PhD from the University of Florence (Italy) in 2009. After a post-doctoral experience at the Institut de Chimie des Substances Naturelles in Gif-sur-Yvette (France) in Pr. J. Zhu and Dr. G. Masson's groups on multicomponent reactions and new chiral phosphoric acid catalyzed enantioselective transformations, she has been appointed as Researcher CNRS in 2012, at the University of Rennes. Her research interests cover new methods in (asymmetric) Prins processes, enantioselective organocatalytic transformations and heterocyclic synthesis for medicinal chemistry.



Abstract: Piperidine derivatives are highly abundant in natural products and pharmaceutically relevant compounds. Aza-Prins cyclization has emerged as a step-atom-economical and stereoselective method for the preparation of such azacycles. The possibility of coupling aza-Prins process with the formation of a second cycle in a one-pot manner is even more powerful and makes the object of this review. Cascade/domino/tandem *bis*-cyclizations involving an aza-Prins process, for the rapid construction of complex small molecules, are discussed in detail.

1. Introduction

Nitrogen containing heterocycles are widespread in both natural products and modern pharmaceuticals. The piperidine ring in particular, is widely found in alkaloids and it is the most abundant aza-cycle in FDA approved drugs, being present in 72 drugs following a recent survey.^[1] Aza-Prins processes are particularly appealing for the synthesis of piperidine derivatives, as from homoallylic or homopropargylic amines and aldehydes, at least three new bonds, including C-C and C-N, and two new carbon stereogenic centers are formed, with only a removal of water molecule (**Figure 1**). As already been discussed in a previous review by us,^[2] the modern aza-Prins cyclization can be classified in four processes, the aza-Prins cyclization itself (**Figure 1, a**), the alkynyl aza-Prins annulation (**Figure 1, b**), the aza-silyl-Prins reaction (**Figure 1, c**) and the aza-acyliminium-Prins variant (**Figure 1, d**), all of them are terminated by the nucleophilic trapping of the transient carbocation on the C-4 or loss of the Si atom. The increasing number of papers published, describing a variety of Brønsted and Lewis acids, even in catalytic amounts, together with nucleophiles compatible with the reaction conditions, testify of the recent success and significant progress in the field of aza-Prins cyclization.^[3]

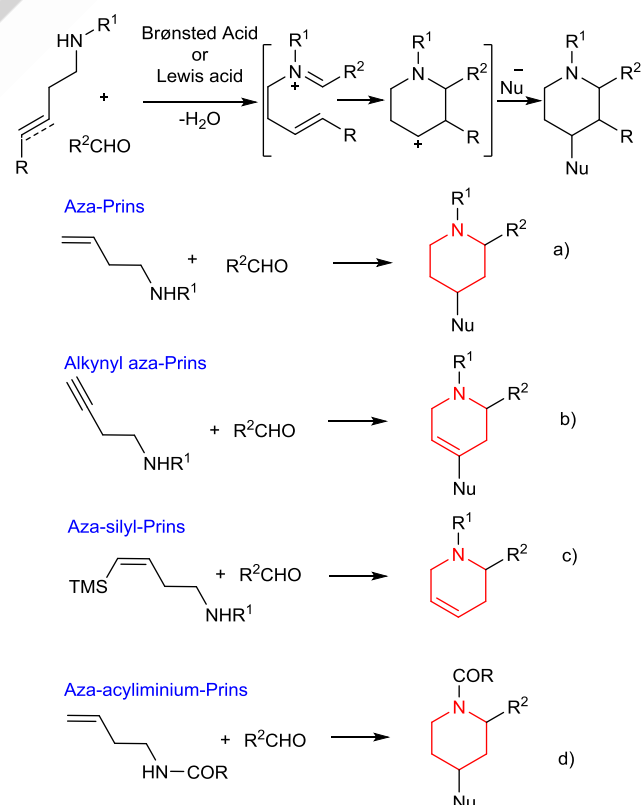


Figure 1. Different aza-Prins processes.

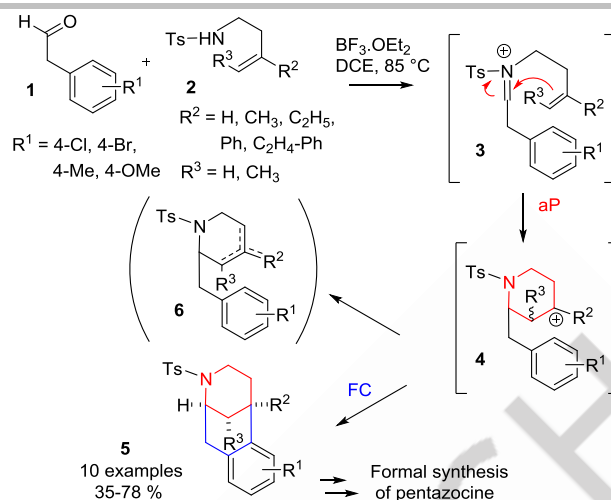
Nevertheless, the examples of cascade/domino/tandem reactions involving an aza-Prins process for the construction of polycycles piperidines remain limited compared to the well documented oxo version, namely the Prins cyclization,^[4] and makes the subject of this review. In particular, cascade reaction starting with an aza-Prins cyclization followed by a nucleophilic trapping with an embedded carbon (intramolecular Friedel-Crafts reaction) or heteroatom will be discussed in a first section. The second part will be devoted to tandem processes involving a first cyclization, mainly cyclic acyliminium formation, followed by domino aza-Prins cyclization. In each case the aza-Prins process and its stereochemical outcome will be highlighted. Examples of stepwise synthesis of two new rings, i.e. whenever the intermediate formed are isolated, are not covered/considered in this review.

2. Cascades Initiated by Aza-Prins

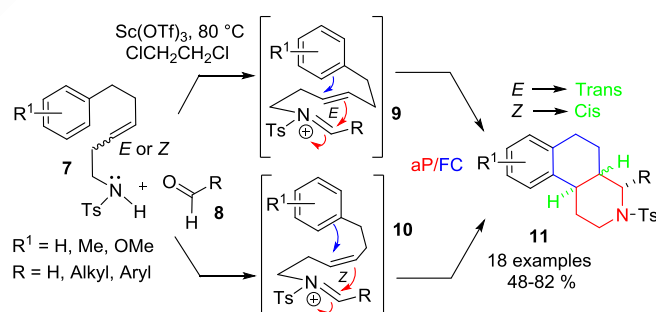
In the first section, the examples of tandem reactions starting with an aza-Prins cyclization, followed by an internal nucleophilic trapping, to form the second cycle, are listed. The discussion begins with the presentation of the synthetic efforts towards the trapping with a carbon nucleophile, therefore the domino Prins/Friedel-Crafts will be detailed. Follows a second section devoted to intramolecular trapping with heteroatoms, oxygen and nitrogen.

2.1. Tandem Aza-Prins/Friedel-Crafts Cyclizations

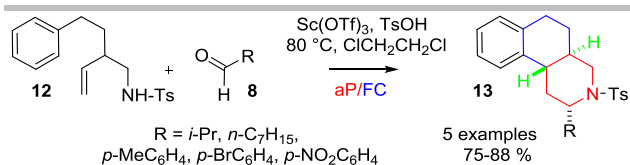
Domino aza-Prins/Friedel-Crafts bis-cyclization, leading to fused aza-tricycles, has been extensively studied. Following a seminal report on a Prins/Friedel-Crafts tandem reaction leading to oxabicyclononanes,^[5] Maison's group performed the extension to aza-Prins/Friedel-Crafts (aP/FC) reaction from readily available aromatic aldehydes **1** and tosylated homoallylamines **2** (**Scheme 1**).^[6] Amongst the possible targets of this aza-extension, the authors envisioned the synthesis of pentazocine, a potent analgesic that had been previously obtained by a "one-pot" procedure. The postulated mechanism goes through an iminium species **3** that could cyclize to give the intermediate carbocations **4** then benzomorphans **5**. The authors carefully optimized the reaction conditions, Lewis acids, solvents, temperature and reaction time, to achieve the formation of desired compounds **5** rather than competing tetrahydropyridines **6**. They finally reported 10 examples of enantiomer pairs of benzomorphans in moderate to good yields (35-78 %). Of note is the fact that some compounds **5** were obtained in better yields in a "one-pot" procedure using TMSOTf then TfOH.

**Scheme 1.** Maison's synthesis of benzomorphans.

A second work from Reddy's group showed the efficient synthesis of heterotricyclic systems with stereoselective control (**Scheme 2**).^[7] The scope of this work included Prins/, aza-Prins/ and also thia-Prins/FC cyclizations. The use of Sc(OTf)₃ in the presence of TsOH had led to good results for Prins/Friedel-Crafts reactions at room temperature. For aP/FC transformations, a rapid screening of catalysts led to the unique use of the same Brønsted acid. Thus, (*E*) or (*Z*)-homoallylic amine **7** were used in the presence of various aldehydes **8**. Unlike Prins/FC examples, the reaction proceeded at 80 °C to yield benzo-isoquinolines **11** according to the plausible intermediates **9** and **10**. The reaction resulted in enantiomeric pairs of benzo-isoquinolines that were purified by chromatography. The authors also describe the reaction either with phenyl acetaldehyde or styrene oxide leading to the same compounds even if the yields were a little better from the aldehyde.

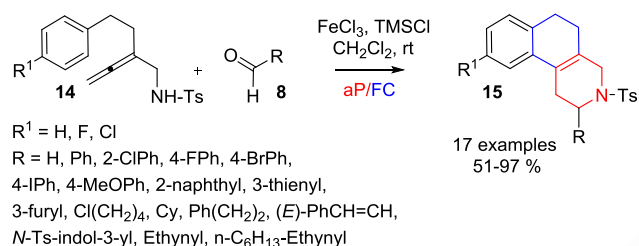
**Scheme 2.** Benzo-isoquinolines obtained from linear alkenes.

Two years later, the same authors slightly extended the scope of their previous work.^[8] Starting from the ramified alkene **12** and five aldehydes **8** (**Scheme 3**), they reported *trans*-fused benzo-isoquinolines **13** as racemic pairs, substituted on a different position compared to **11**. One of these isoquinolines successfully underwent deprotection of *N*-tosyl group.



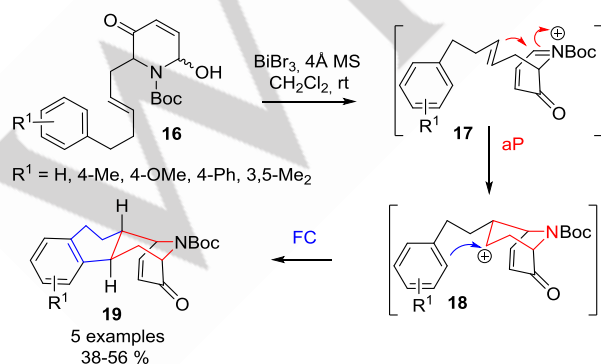
Scheme 3. Benzo-isoquinolines obtained from ramified alkenes.

More recently, an additional extension to allene substrates **14** was brought by the group of Ma^[9] who described the efficient synthesis of 17 examples of racemic benzo-isoquinolines **15** (**Scheme 4**). The reaction was catalyzed by FeCl₃ in the presence of TMSCl and revealed very efficient in most cases and successfully applied to the gram scale synthesis of one of these compounds.



Scheme 4. Benzo-isoquinolines obtained from allenes.

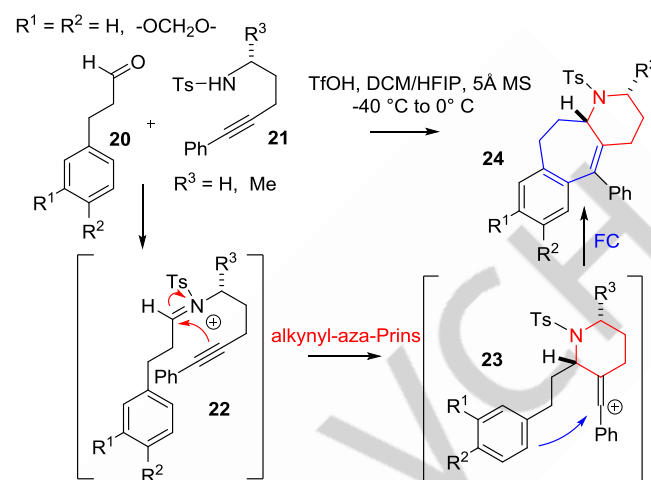
The next example of aP/FC cascade reaction was reported by Tong and coworkers who designed the synthesis of azabicyclononanes as valuable starting blocks for the synthesis of natural alkaloids by aza-Prins cyclization.^[10] Among their precursors resulting of an aza-Achmatowicz rearrangement, some substrates **16** contained a tethered phenyl group (**Scheme 5**). In these cases, the Lewis acid BiBr₃ generated the intermediate **17** that underwent a first aP cyclization to **18**. The second one occurred through a FC intramolecular reaction. This cascade transformation efficiently led to a tetracyclic compound **19** that was obtained as racemic pairs. The procedure was extended to other substrates for the construction of polycyclic alkaloids.



Scheme 5. Tong's obtaining of polycyclic compounds **19**.

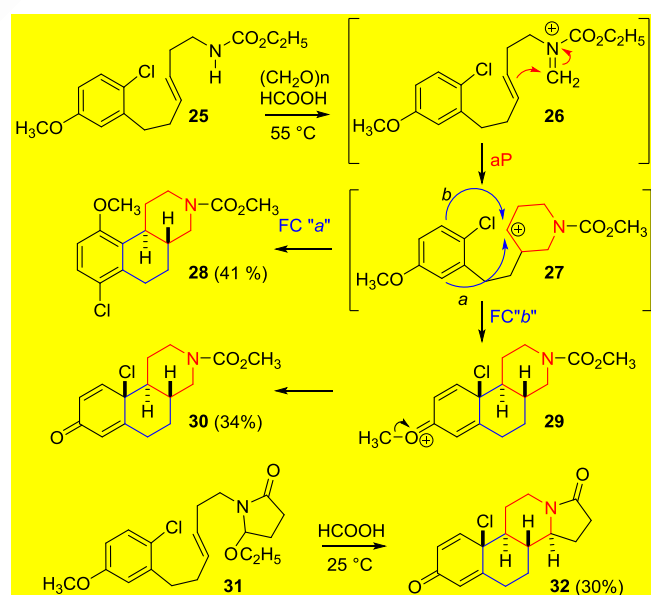
In 2022, the group of Frontier described a Brønsted acid catalyzed sequence of Prins carbocyclization cascade enabling the synthesis of a wide range of fused heterotricycles from

sulfonamides **21** and two aldehydes **20** (**Scheme 6**). After the formation of the iminium intermediate **22**, the alkynyl-aza-Prins followed by a FC reaction gave the final compounds **24** in 54 and 56 % and good diastereomeric ratios (for R³ = Me).^[11]



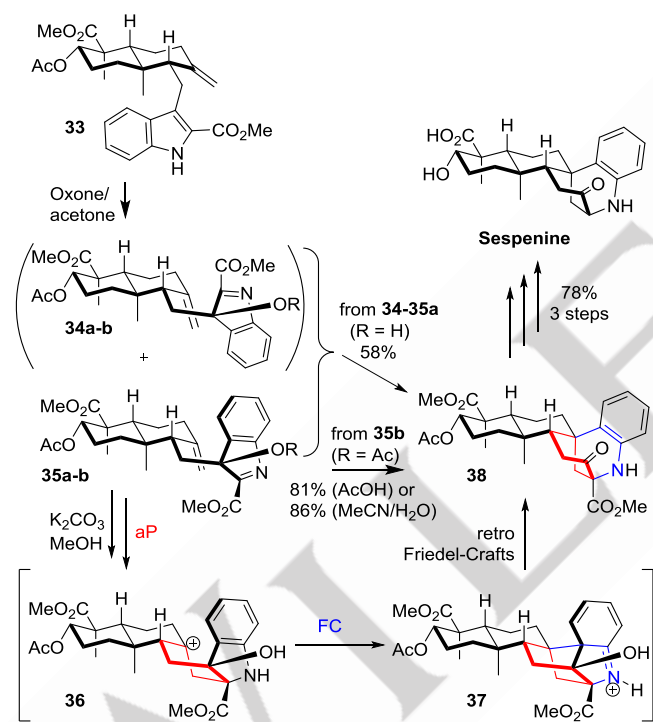
Scheme 6. Alkynyl-aza-Prins/carbocyclization to deliver tricyclic piperidines.

Even if the authors do not mention the term “aza-Prins”, the tandem aP/FC cyclization has been initially described by Romero *et al.* in 1996 for the synthesis of azasteroids.^[12] In this work, the precursor **25**, previously synthesized in eight steps, underwent a reaction with paraformaldehyde to give the compound **26** in formic acid. The intermediate carbocation **27** that resulted from an aP mechanism, was likely to furnish two FC products, **28** and **30**, whose partitioning is discussed. The authors applied the reaction to **31** to obtain the azasteroid **32**. In this application, the intermediate acyl iminium ion formed from **31**, would initiate an aP reaction then a “pseudo FC” to generate the azasteroid skeleton **32** in very good selectivity (**Scheme 7**).



Scheme 7. Tandem cyclisation towards azasteroids.

In 2014, Li's group reported the first synthesis of sespenine, an indole terpenoid initially isolated from a *Streptomyces* in 2011.^[13] Its complex structure displays a spiro-tetrahydroquinoline scaffold attached to a cyclic ketone bridge. The authors initially obtained the intermediate **33** as a pure stereoisomer in 8 steps and 12% yield (**Scheme 8**). The next key steps include an oxidation to **35** (and **34**) then, via an intermediate **36**, aP/FC to **37**, which re-aromatizes through a retro-Friedel-Crafts fragmentation to give the compound **38**. This sequence was achieved by a "one-pot" procedure during which the aP/FC sequence occurred as a cascade reaction. In a first attempt, the authors conducted this sequence on the mixture of inseparable epimers **34a** and **35a** ($R = H$, 1/2.5 ratio) and obtained **38** with a 58% yield from **33**. This procedure was successfully amplified on multiple hundred milligram scale. On the other hand, the acetylation of **34a** and **35a** furnished **34b** and **35b** and allowed for their HPLC separation. After removal of acetyl group, the reaction sequence was repeated and, under two separate conditions, allowed a better synthesis of **38**. Three more steps – demethoxycarbonylation, hydrolysis, and deacetylation– yielded the sespenine in 78% overall yield.



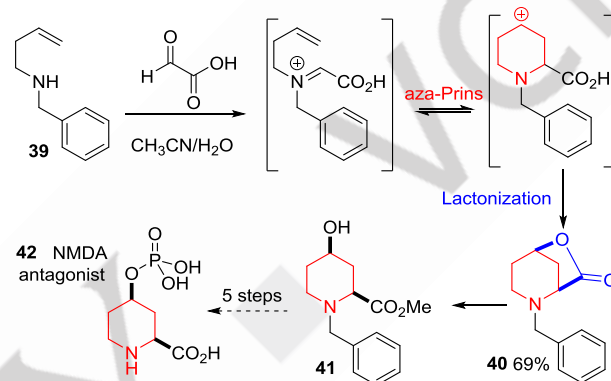
Scheme 8. Total synthesis of Sespenine using a tandem aza-Prins/FC double cyclization.

2.2. Tandem Aza-Prins/Lactonization Reactions

The synthesis of bridged piperidine- γ -butyrolactone core in concise routes attracts great attention since the γ -butyrolactone moiety is a valuable intermediate towards 2,6-disubstituted piperidines like 4-hydroxypipicolic acid and derivatives. In this section, the methodological developments for the construction of bridged piperidine- γ -butyrolactone skeletons in one-step will be described, and then their applications in medicinal chemistry programs will be illustrated.

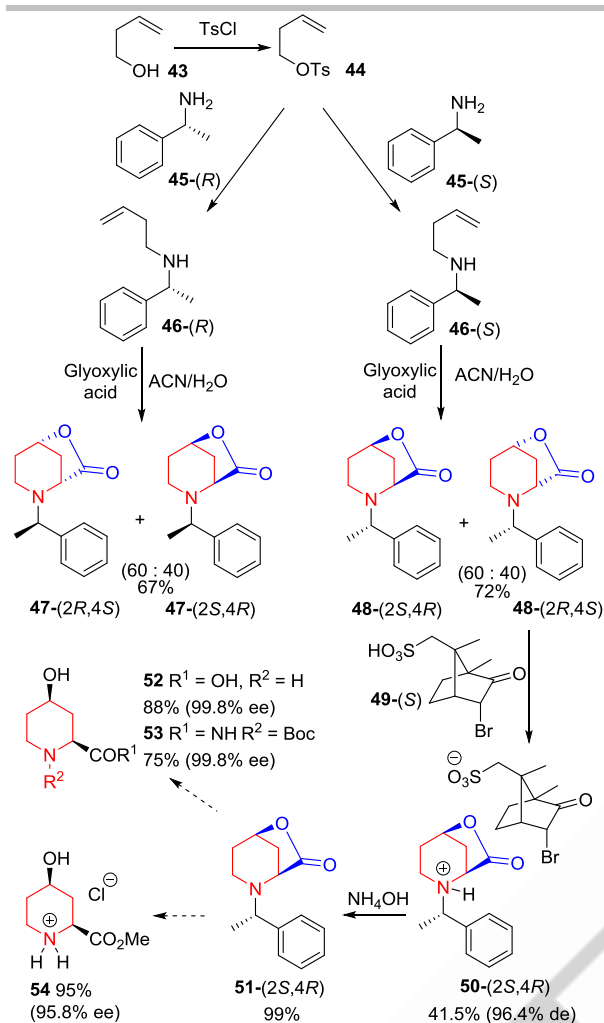
Hays' group reported a first strategy involving a tandem aza-Prins/lactonization sequence for the synthesis of racemic

lactone **40** as a valuable intermediate for the synthesis of *cis*-4-(phosphonoxy)-2-piperidinecarboxylic acid, an *N*-methyl-*D*-aspartate (NMDA) antagonist (**Scheme 9**).^[14] The reaction of homoallylic amine **39** with glyoxylic acid in aqueous acetonitrile resulted in the formation of an iminium that underwent cyclization to give the piperidine via an aza-Prins reaction and finally trapping the carbocation by the carboxylic acid function (lactonization) lead to racemic lactone **40** as a unique *cis* isomer -with substituents at 1,3-diaxial position of the piperidine ring- in 69% yield. Subsequent debenzoylation and lactone cleavage occurred under hydrogenolysis conditions in methanol to afford the racemic *cis*-4-hydroxypipicolic derivative **41** that was further transformed into final phosphate **42** in an overall yield of 48% from the starting homoallyl amine **39**.



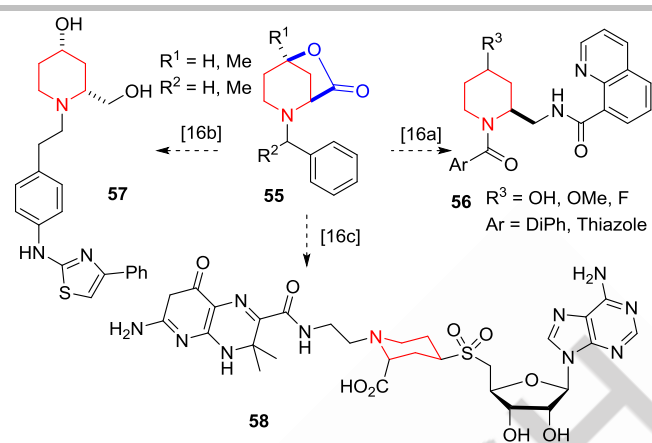
Scheme 9. Bridged piperidine- γ -butyrolactone synthesis from *N*-benzyl homoallylamine **39** and glyoxylic acid.

This approach was extended to an asymmetric version few years later by the group of Beaulieu.^[15] This group developed a process that used (*S*)- or (*R*)- α -methylbenzylamine **45** as a readily available and inexpensive chiral auxiliary in a way to induce diastereoselectivity in the iminium cyclization with glyoxylic acid (**Scheme 10**). Lactones **47**-(2*R*,4*S*), **47**-(2*S*,4*R*) and **48**-(2*S*,4*R*), **48**-(2*R*,4*S*) were obtained with low levels of diastereoselectivity (60:40 mixture of diastereomers as determined by ¹H NMR) and in 67 and 72% overall yield respectively from **43**. In order to perform the separation of those diastereomers on a large scale, the amine **49**-(*S*) was used as a resolving agent to efficiently obtain the crystalline adduct **50**-(2*S*,4*R*) in 41.5% yield and 96.4% de. After neutralization with ammonia, the lactone **51**-(2*S*,4*R*) was prepared from homoallylic alcohol **43** in 30% overall yield and with 93.9% de. This lactone **51** was finally used as a versatile intermediate for the synthesis of *cis*-4-substituted piperidic acid derivatives (**52-54**) in high enantiomeric purity.



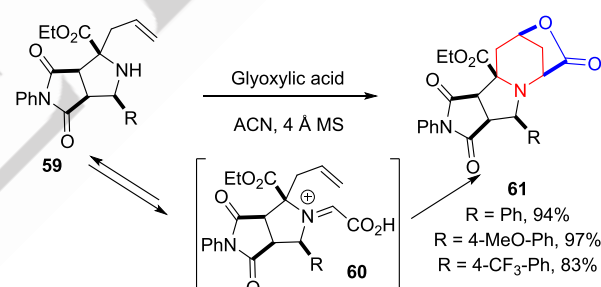
Scheme 10. Asymmetric synthesis of bridged piperidine- γ -butyrolactone using (S)- or (R)- α -methylbenzylamine as a chiral auxiliary. Access to *cis*-4-substituted pipercolic acid derivatives in high enantiomeric excess.

Synthetic usefulness of this methodology was demonstrated in medicinal chemistry programs for which the bridged piperidine- γ -butyrolactone **55** was used as a valuable intermediate towards biologically active 2,6-disubstituted piperidine derivatives **56-58** (**Scheme 11**).^[16] Compounds **56** were reported as potent orexin receptor antagonists for the treatment of sleep disorders,^[16a] compound **57** was synthesized in a SAR study dedicated to the optimization of sphingosine kinase inhibitors^[16b] and compound **58** is a potent bisubstrate inhibitor of 6-hydroxymethyl-7,8-dihydropterin pyrophosphokinase (HPPK), a key enzyme in the folate biosynthesis pathway and therefore a target of choice for developing antimicrobial agents.^[16c]



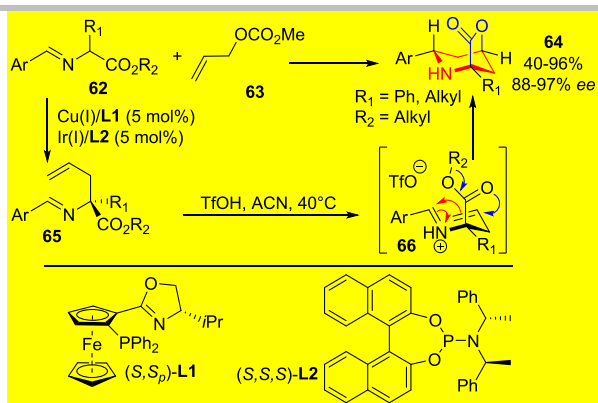
Scheme 11. Synthetic usefulness of bridged piperidine- γ -butyrolactone intermediate for the synthesis of biologically active compounds.

An application in the field of natural products was also realized by Waters's group who described the stereoselective synthesis of functionalized indolizidines **61** from 2-allylpyrrolidines **59**.^[17] The reaction of endocyclic amine with glyoxylic acid in ACN led to the formation of iminium ion **60** followed by the nucleophilic attack from the embedded allyl substituent. Finally, the carbocation was trapped by the carboxylic acid and therefore an extra lactone ring **61** was formed with substituents in 1,3-diaxial position of the piperidine ring (**Scheme 12**). Thus, the reaction proceeded with a complete diastereoselectivity.



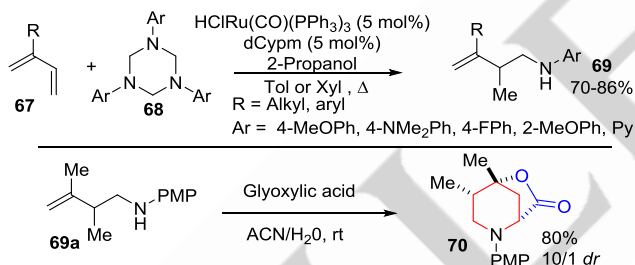
Scheme 12. Indolizidine synthesis from allylpyrrolidines.

Very recently, Fu et al. reported a catalytic allylation/aza-Prins cyclization/lactonization sequence from imines **62** and allyl carbonate **63** for the synthesis of enantioenriched bridged piperidine- γ -butyrolactones **64** (**Scheme 13**).^[18] This approach combines a synergistic Cu/Ir catalyzed allylation of imines **62** with simple allylic precursor **63** that occurs in high yields and excellent enantioselectivity. Enantiopure products **65** were treated with TfOH, to promote the aza-Prins cyclization/lactonization through intermediate **66**. This process facilitates the sequential construction of 2,4,6-three skipped stereogenic carbon centers with exclusive stereocontrol.



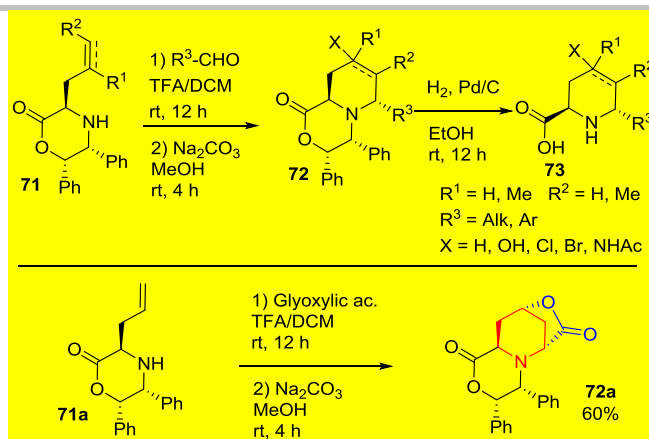
Scheme 13. Catalytic asymmetric allylation/aza-Prins cyclization/lactonization sequences towards chiral bridged piperidine- γ -butyrolactones.

Krische's group described a Ruthenium-catalyzed hydroaminomethylation of dienes to deliver homoallylic amines in good yields and total regioselectivity (**Scheme 14**).^[19] The catalytic pathway involves a reductive C-C coupling between 1,3-diene **67** and formaldimines generated *in situ* from 1,3,5-tris(aryl)-hexahydro-1,3,5-triazine **68** via transfer hydrogenation mediated by 2-propanol as terminal reductant. This study also included an enantioselective variant of the reaction using chiral phosphine ligands. To illustrate the synthetic utility of their methodology, **69a** was engaged in a tandem aza-Prins/lactonization sequence in the presence of glyoxylic acid in aqueous acetonitrile to afford a bridged piperidine- γ -butyrolactone **70** in good yield and diastereoselectivity.



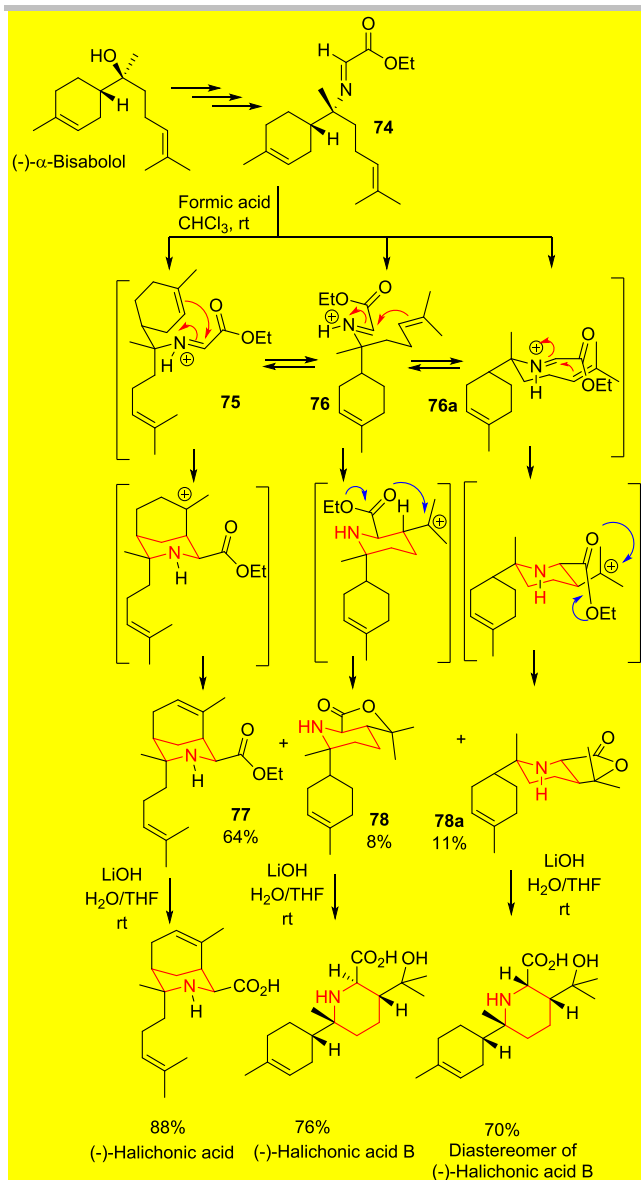
Scheme 14. Ruthenium-catalyzed hydroaminomethylation of 1,3-dienes with 1,3,5-tris(aryl)-hexahydro-1,3,5-triazines to form homoallylic amines. Illustration of their synthetic utility towards chiral bridged piperidine- γ -butyrolactones.

More recently, in a work dedicated to the synthesis of enantiopure piperidines **72** and pipercolic acid derivatives **73** via an aza-Prins reaction, Dobbs and coworkers reported the synthesis of bridged piperidine-lactone **72a** from (*R*)-diphenyl allylmorpholin-2-one **71a** and glyoxylic acid in a single step (**Scheme 15**).^[20] The reaction proceeded smoothly at room temperature in the presence of TFA to afford piperidine-lactone **72a** in 60% yield as a single enantiomer and diastereomer.



Scheme 15. Stereoselective aza-Prins reaction to access enantiopure piperidines. Use of glyoxylic acid in a tandem aza-Prins/lactonization process for the synthesis of bridged piperidine- γ -butyrolactone **72a**.

The synthesis of fused piperidine- γ -butyrolactone core via tandem aza-Prins/lactonization sequence was less documented compared to their bridged analogs. Only one example was reported for the total synthesis of (-)-halichonic acid B along with (-)-halichonic acid by the group of Reber (**Scheme 16**).^[21] Their synthesis has been achieved in ten steps starting from commercially available (-)- α -bisabolol and a key imine intermediate **74**. Upon activation under acidic conditions, imine **74** undergoes an iminium formation with different conformations (**75**, **76** and **76a**). In each case, the chair-like transition state of aza-Prins reaction is controlled by the stereocenter bearing a methyl group in α position of the nitrogen. Two nucleophilic attacks are possible on the iminium electrophilic site, one by the trisubstituted alkene within the cyclohexene ring leading to compound **77**, the other one by the prenyl group leading to compounds **78** and **78a**. Products **77**, **78** and **78a** were obtained in 64, 8 and 11% yield respectively.



Scheme 16. Total synthesis of (-)-halichonic acid B using tandem aza-Prins/lactonization as key reactions.

2.3. Trapping by Other Nucleophiles

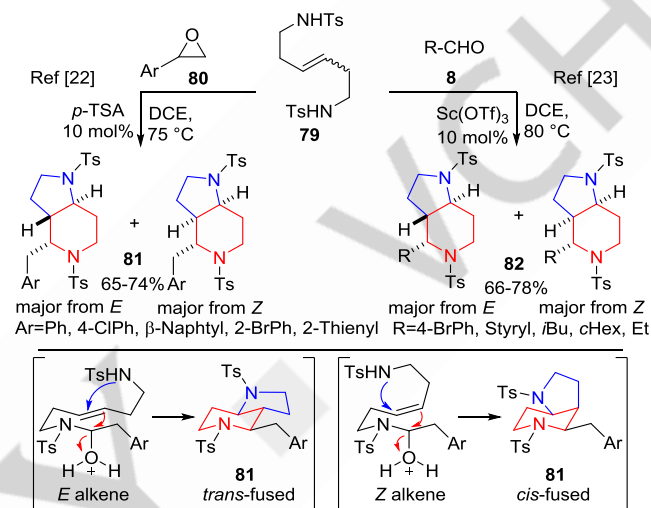
The use of heteroatoms like oxygen or nitrogen as nucleophile to trap the carbocation generated during the aza-Prins cyclization reaction and to achieve one more heterocyclic ring was also envisioned. Depending on the position of the nucleophilic heteroatom, fused-, bridged- or spiro- bicyclic privileged structures based on the piperidine core can be obtained.

2.3.1. Fused-Bicyclic Piperidines

Yadav and Subba Reddy reported as a first example, a study dedicated to the synthesis of fused-pyrrolidino-piperidine skeleton **81** using 10 mol% of *p*-TSA-catalyzed through an intramolecular aza-Prins cyclization between styrene epoxides **80**, as phenyl acetaldehyde equivalents, and homoallylic amines containing a tethered amine nucleophile **79** (**Scheme 17**).^[22] The reaction proceeded smoothly with the *E*-alkene to give the *trans*-

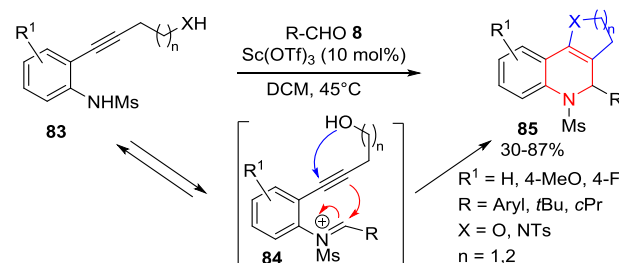
fused azabicycles **81** while *cis* selectivity was observed with the *Z*-olefin, thus demonstrating the importance of the double bond geometry of the homoallylic bis-*N*-tosylamides **79** in the diastereoselectivity of the reaction.

As a continuation, the same group proposed a Lewis acid catalyzed extension of this work to aldehydes **8** instead of epoxydes.^[23] Upon activation with catalytic amount of Scandium(III) triflate, **79** reacted with various aliphatic or aromatic aldehydes **8** to give the corresponding *trans*- and *cis*-fused pyrrolidino-piperidines **82** respectively in good yields, depending on the geometry of the alkene.



Scheme 17. Synthesis of pyrrolidino-piperidine skeleton via aza-Prins cyclization with epoxides or aldehydes.

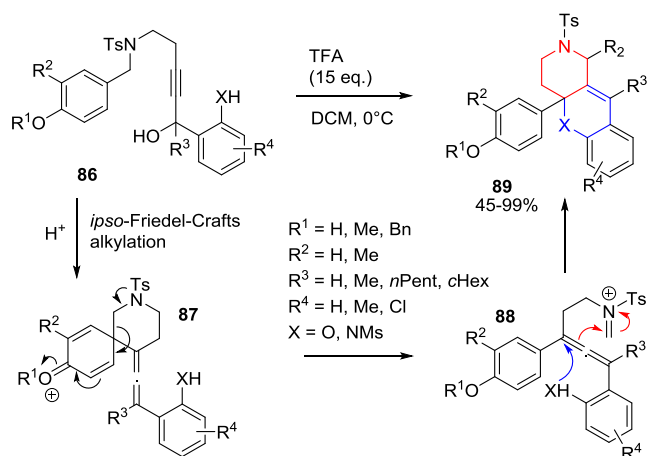
Zhu et al. described a $\text{Sc}(\text{OTf})_3$ -catalyzed reaction to build fused tricyclic derivatives **85** bearing useful 1,2-dihydroquinoline moiety from *o*-alkynylanilines **83** (**Scheme 18**).^[24] The cascade aza-Prins cyclization of *o*-alkynylanilines bearing a hydroxy or amine side-chain, was initiated by iminium **84** formation in the presence of an aldehyde and catalytic amount of $\text{Sc}(\text{OTf})_3$ followed by aza-Prins cyclization, allowing the formation of 1,2-dihydroquinoline core and a concomitant trapping of the carbocation by the hydroxy or amine function to afford the final tricyclic derivatives **85** in moderate to good yields.



Scheme 18. $\text{Sc}(\text{OTf})_3$ -catalyzed bicyclization of *o*-alkynylanilines to afford fused 1,2-dihydroquinolines.

Hamada's group reported the synthesis of fused-tricyclic dihydroquinolines **89** via a cascade cyclization process from propargyl alcohol derivatives **86** (**Scheme 19**).^[25] An

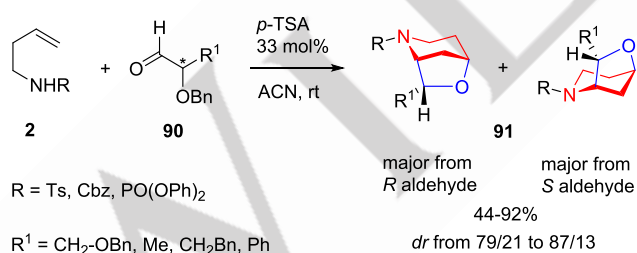
intramolecular *ipso*-Friedel-Crafts alkylation of phenol derivatives **87** proceeds through a TFA-promoted rearomatization-induced C-C bond cleavage, that allowed the formation of iminium **88**. This latter underwent a smooth aza-Prins reaction followed by a 6-membered ring formation.



Scheme 19. Acid-promoted synthesis of fused-tricyclic dihydroquinoline derivatives from propargylic alcohols.

2.3.2. Bridged-Bicyclic Piperidines

Diaz-de-Villegas's group studied the use of protected glyceraldehyde derivatives **90** as simultaneously carbonyl counterpart and intramolecular nucleophile in the *p*-toluenesulfonic acid promoted aza-Prins reaction of simple homoallylic amine **2**. This a versatile methodology allowed to prepare 6-oxa-2-azabicyclo[3.2.1]octanes **91** in a one step process (**Scheme 20**).^[26a] Reaction proceeded smoothly and in a high diastereoselective manner to afford bicycles except for Cbz and diphenylphosphoryl as *N*-protecting groups of **2** for which yields were moderate (50 and 44% respectively).

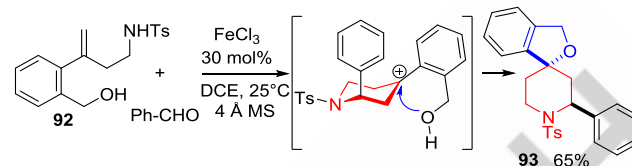


Scheme 20. Diastereoselective synthesis of the bridged furano-piperidines via aza-Prins cyclization with chiral α -benzyloxyacetaldehydes.

As an extension, the same authors showed that **91** can be obtained in slightly different reaction conditions, namely in the presence of 22 mol% of $\text{Bi}(\text{OTf})_3$ and when R_1 are aryl groups are valuable intermediates towards enantiomerically pure benzomorphan derivatives via hydrogenolysis followed by an intramolecular Friedel-Crafts cyclization.^[26b]

2.3.3. Spiro-bicyclic piperidines

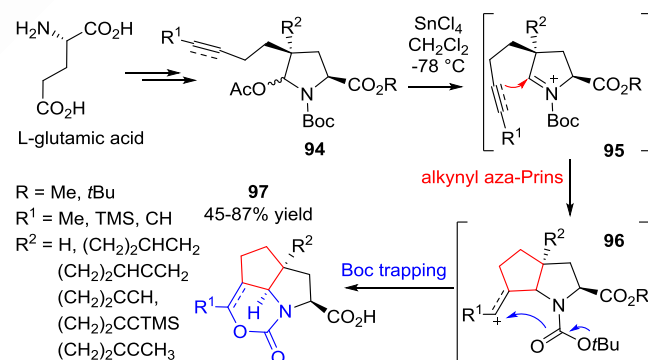
In an unprecedented work dedicated to Prins spirocyclization to access spiro[isobenzofuran-pyran] derivatives, Subba Reddy et al. demonstrated that this process can be extended to aza-Prins reaction starting from homoallylic amine **92** (**Scheme 21**).^[27] The reaction was successful with benzaldehyde and iron(III) chloride as the catalyst in DCE at room temperature to afford the spiro-piperidine **93** in 65% yield with high diastereoselectivity.



Scheme 21. Only example of intramolecular spirocyclization.

2.4. Miscellaneous Domino Reactions Starting with an Aza-Prins Process

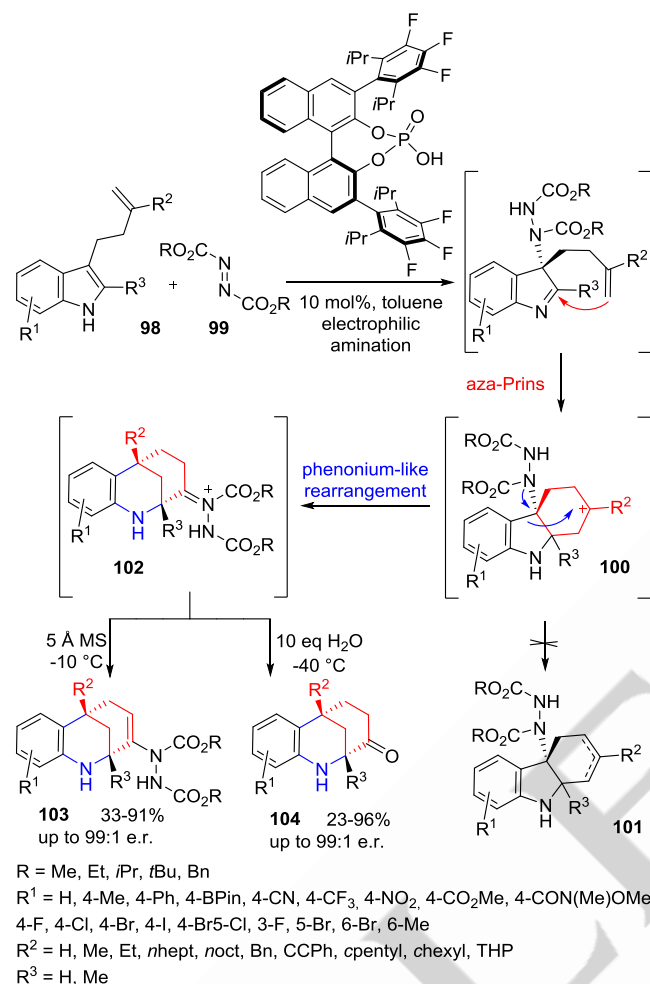
During their studies towards the total synthesis of Oscillarin, an antithrombotic marine natural product, Hanessian and coworkers established an efficient route to 4-substituted L-pyroglutamic esters with an embedded alkene, alkyne and allene function **94**, from L-glutamic acid and they reported a systematic study about their Lewis acid mediated intramolecular carbocyclizations.^[28] In particular, they observed a different reactivity as a function of the unsaturation, and typically, whenever the tethered moiety was an allene or an alkyne substituted with TMS and Me, a cascade SnCl_4 -promoted *N*-acyliminium ion **95** formation, followed by alkynyl aza-Prins annulation (intermediate **96**) and intramolecular trapping of the Boc protecting group as terminal nucleophile was observed. As consequence, tricyclic oxazinones derivatives **97** were formed in a yield range of 45-87% and in a stereocontrolled manner (**Scheme 22**).^[28c]



Scheme 22. Tandem *N*-acyliminium/alkynyl aza-Prins/intramolecular trapping for tricyclic oxazinones synthesis.

A second example comes from the Zheng and You group. The authors developed a chiral phosphoric acid catalyzed dearomatization of indoles bearing an embedded alkene moiety in C3 position **98**, by electrophilic amination with azodicarboxylates **99**, followed by the intramolecular aza-Prins. Surprisingly, the reaction didn't undergo elimination to give the expected indolines **101**, from intermediate **100**, it was terminated instead by a phenonium-like rearrangement to give the

intermediate **102**. This latter delivered tricyclic benzoazocines **103**, bearing controlled tertiary and quaternary carbons, in 33-91% yield and up to 99:1 e.r. Interestingly, when 10 equiv. of water were present in the medium, from **102**, ketones **104**, were recovered in 23-96% yield and with up to 99:1 e.r. (Scheme 23).^[29]



Scheme 23. Cascade enantioselective electrophilic amination/aza-Prins cyclization/Phenonium-like rearrangement.

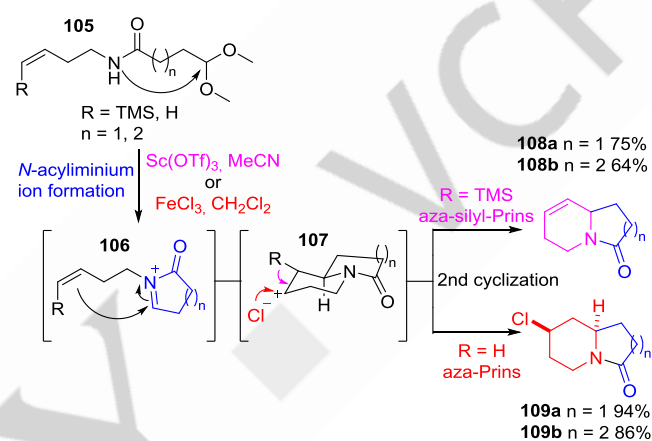
3. Cascades Terminated by Aza-Prins

In the next sections, the examples of tandem reactions involving a first cyclization followed by aza-Prins process are listed. In particular, the formation of cyclic iminium ions as first annulation step will be detailed. An example of S_N2 alkylation for the generation of the first cycle is also presented.

3.1. *N*-Acylium Ion Formation/Aza-Prins Cyclization

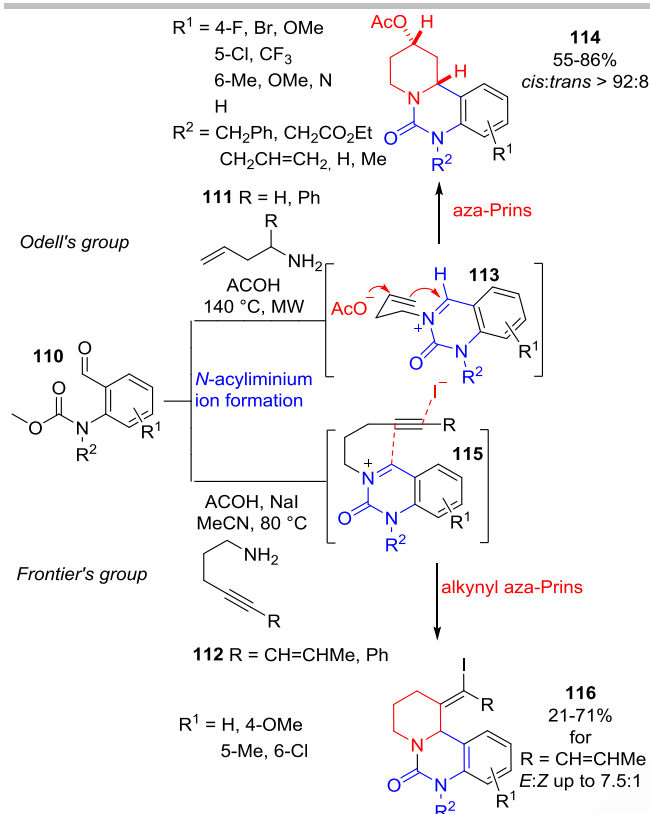
Herein four examples of *N*-acylium ion formation, followed by an aza-Prins type process will be discussed. Dobbs group has been pioneering in describing an intramolecular one-pot bis-cyclization, forming the bicyclic indolizidine and quinolizidine cores in a single transformation.^[30] The amide precursor **105**, bringing both the homoallyl amine and the aldehyde masked as acetal, underwent first cyclization with concomitant acyl iminium **106** formation upon treatment with 1 equiv. of appropriate Lewis

acid, Sc(OTf)₃ or FeCl₃ (Scheme 24). An intramolecular Prins process gave rise to the second cyclization, leading to the pyridinyl carbocation **107**, which evolved into products **108** or **109** depending on the nature of the substituent R on the double bond. When the amide **105** was a *Z*-vinyl silane, the aza-Silyl-Prins took place, by elimination of TMS group and alkene formation, to give the indolizidine **108a** and quinolizidine **108b** in 75 and 64% yields respectively. In the absence of substituent on the terminal position of the double bond, the external chlorine, anion of the Lewis acid employed, provided the nucleophilic attack on the equatorial position. As the result, the *cis*-fused indolizidine **109a** and quinolizidine **109b** were obtained in 94% and 86% yields respectively.



Scheme 24. Cascade *N*-acylium/aza-(silyl)-Prins cyclization for indolizidines and quinolizidines core synthesis.

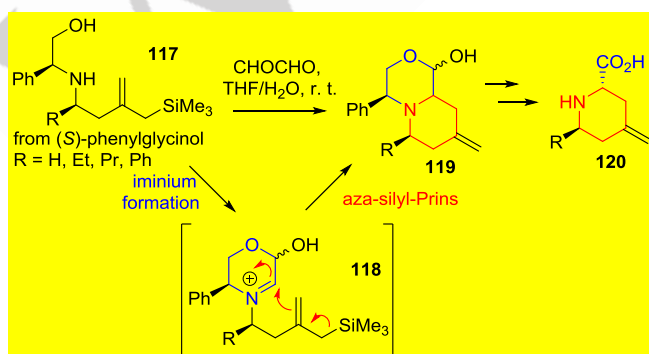
Fused tricyclic piperidines could be obtained by a cascade of *N*-acylium/aza-Prins bis-cyclization of *o*-formyl carbamates **110** with primary homoallyl **111** or homopropargyl **112** amines (Scheme 25). Odell group worked on substrates **111** and demonstrated the feasibility of the cascade cyclization in acetic acid under MW irradiation. After the imine formation, the first cyclization delivered the acylium **113**, which underwent aza-Prins cyclization leading to the formation of quinazolinones **114** in a 55-86% yield range in favor of the *cis*-fused diastereomer.^[31] Frontier group established a route to products **116** in 21-71% yield, from amines **104** under similar conditions. Because in AcOH the yields were noticeably lower than described with homoallyl amines, the reactions conditions were reoptimized. Notably, NaI was added as halide nucleophilic source, which reacted with the electrophilic intermediate **115** and completed the second cyclization. Of note, enyne (R = CH=CHMe) was employed as a mixture of *E*:*Z* = 4.6:1 isomers and both reacted in the aza-Prins cascade, delivering products in a range of 3.1:1 to 7.5:1 depending on the isomerization degree in the reaction conditions.^[32]



Scheme 25. Cascade *N*-acyliminium/(alkynyl) aza-Prins cyclization for quinazolinone products.

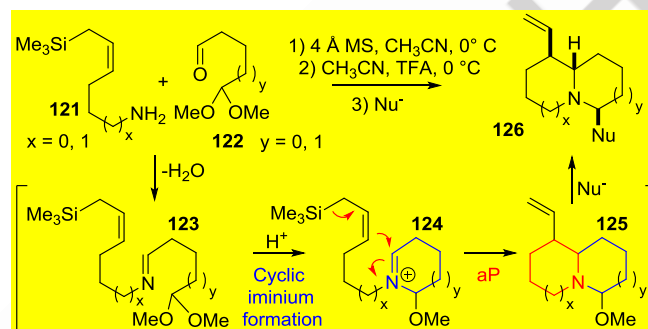
3.2. Miscellaneous Cascades Terminated by an Aza-Prins Process

Other transformations have been explored to generate cyclic iminium ions which underwent aza-Prins annulation to end up to complex aza-bicycles. The Kadouri-Puchot group has been pioneering in describing this type of domino process.^[33] Their cascade consists in a condensation between *N*-substituted (*S*) or (*R*)-phenylglycinols derivatives **117** and glyoxal to give the intermediate cyclic iminium ion **118**, followed by aza-silyl-Prins to deliver quinolizidines **119** in excellent yields with very good stereoselectivities. This methodology represents an attractive access to enantioenriched heterocycles of biological interest, such as pipercolic acids **120**, after oxidation of the hydroxyl group and hydrogenolysis (**Scheme 26**).



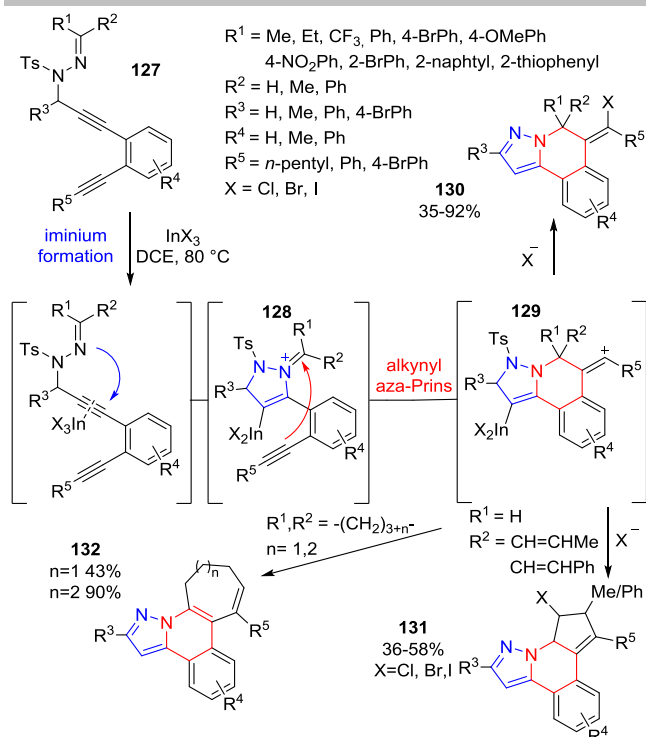
Scheme 26. Access to enantiopure pipercolic acids derivatives by cascade cyclic iminium/aza-silyl-Prins cyclization.

Similarly, Martin and coworkers disclosed a one-pot reaction sequence leading to a number of quinolizidines and indolizidines.^[34] The method relies on the reaction of allylsilyl amines **121** on acetals **122** and was conducted in a three steps-one-pot operation (**Scheme 27**). After the generation of imine **123** the cyclic iminium ion **124** was formed in acidic conditions, followed by aza-silyl-Prins reaction. The resulting cyclic acetal **125** was finally trapped by a nucleophile to lead to the final heterocyclic frame **126**. Even if the yields remained moderate, the stereoselectivity revealed excellent. Due to the possible variation of starting materials or nucleophiles, the authors could obtain several attractive bicyclic natural alkaloids.



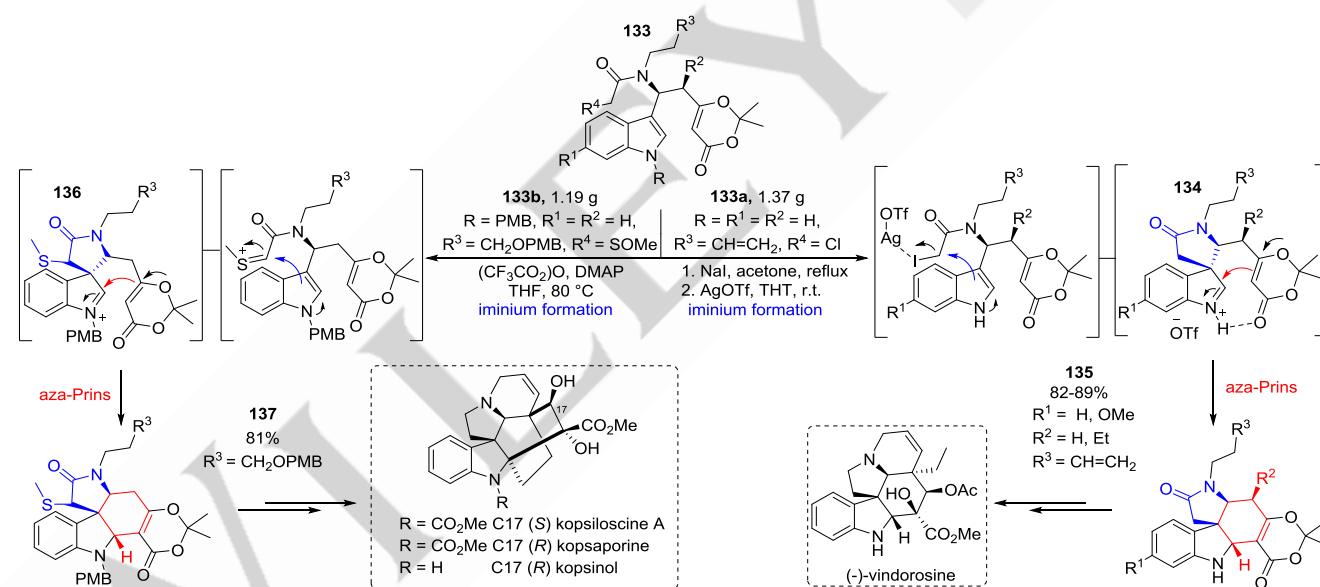
Scheme 27. Cascade cyclic iminium/aza-silyl-Prins cyclization for quinolizidines and indolizidines synthesis.

Zhan and co-workers described the cascade halocyclization of linear *N*-propargylic sulfonylhydrazones **127** to give the pyrazolo-isoquinolines **130-132**.^[35] The reaction started with the activation of alkyne by In(III) towards nucleophilic attack of the imine nitrogen of hydrazone, leading to the cyclic iminium ion **128**. This latter underwent aza-alkynyl-Prins cyclization to give the tricyclic vinyl cation **129**, that is trapped by the halide counterion of the In(III) salt, then proto-demetalation followed by elimination of TsH and consequent aromatization, afforded the products **130** (**Scheme 28**). The reaction scope is broad, hydrazones derived from aliphatic and aromatic aldehydes, with the only exception for electron donating groups- and 2-substituted aryl aldehydes participated to the reaction. Notably, even tetracyclic structures **131** and **132** could be obtained respectively from hydrazones derived from α,β -unsaturated aldehydes and even cyclic ketones and this latter underwent a smooth intramolecular rearrangement and ring expansion.



Scheme 28. Synthesis of pyrazolo-isoquinolines by iminium/aza-alkynyl-Prins annulation.

Zhang's group has reported tandem processes involving an aza-Prins as key step in the synthesis of complex polycyclic natural products such as aspidospermine- and aspidofractine-type alkaloids. The common strategy consists in the design of appropriate S_N2 alkylation/aza-Prins cyclization from a common acyclic indole derivative **133** as shown in **Scheme 29**. In a first report, consecrated to the asymmetric total synthesis of (-)-vindorosine, a new Heathcock annulation have been established by the authors to construct the cyclic iminium, *via* an intramolecular S_N2 promoted by silver salts. Upon treatment of **133a** with NaI and AgOTf, the indolyl iminium is formed together with the spiranic lactam (**134**). The rigidification of the system brought the dioxinone closer to the iminium, favoring the aza-Prins process and leading to **135** in 82-89% yield range, in gram scale.^[36] The strategy towards *Kopsia* alkaloids kopsilosine A, kopsaporine and kopsinol, was based on a domino process including a Pummerer rearrangement of **133b** followed by thionium induced cyclization under modified Magnus conditions (TFAA and DMAP) to form the cyclic iminium **136** in gram scale. Following the same mechanism as just described above, the domino sequence ended with an aza-Prins cyclization to give the compound **137** in 81% yield.^[37]



Scheme 29. Domino S_N2 alkylation/aza-Prins cyclization for alkaloid synthesis.

4. Summary and Outlook

Polycyclic azacycles are ubiquitous among bioactive compounds and have been identified as precious skeletons to build for the advancement of pharmaceutical design, nevertheless their assembly is difficult and requires in general a number of steps. This overview attests the utility of the single step aza-Prins cascade/domino/tandem double cyclizations in the formation of azacycles. Among the methods presented, the diversity and multiplicity of nucleophiles used for carbocation trapping is

important, giving rise mainly to fused piperidines and more complex architectures based on this 6 membered heterocycle. When the cascade ends up with an aza-Prins cyclization or one of the two cycles comes from a rearrangement, other nitrogen-containing heterocycles with different ring size and substitution patterns can be constructed. Despite such achievements, it is surprising to notice that cascade spirocyclization are extremely rare compared to oxonium chemistry^[4a] and represent a great opportunity for further methodological developments and applications in bioactive compounds design. Finally, for natural product and pharmaceutical ingredient synthesis, an asymmetric route has been established in some reported cases, however

the synthetic tool box lacks the enantioselective catalytic pathway, already established for Prins cyclizations.^[38] Therefore, this is still a highly active field and further advances are expected in the future, especially focused on potential application to optically pure drugs synthesis.

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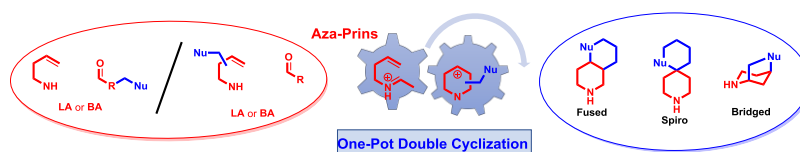
Keywords: aza-Prins • bis-cyclization • cascade reaction • aza-heterocycle • piperidine derivatives

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Entry for the Table of Contents



In this review are discussed one-pot domino/cascade/tandem *bis*-cyclizations involving an aza-Prins process, for poly azacycles synthesis. Those are fused, bridged or spiranic depending on the position of the nucleophile. The mechanism of the two steps together with the stereochemical outcomes are detailed.

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