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Synthesis of tetrahydropyrans and related heterocycles via prins cyclization; extension to aza-prins cyclization

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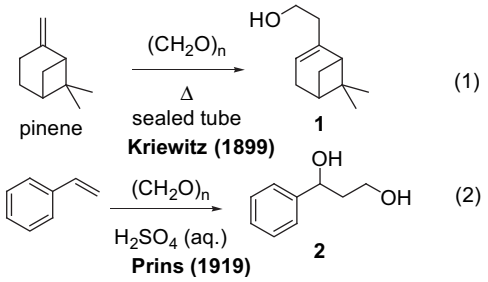
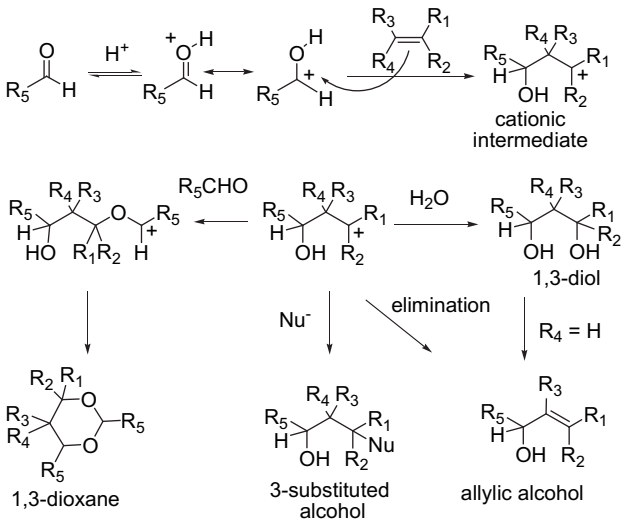
1. Introduction

The Prins reaction[1] is often related to the Kriewitz reaction.[2] The latter leads to unsaturated alcohol **1** from α-pinene and formaldehyde through a thermal 'ene-rearrangement' (Eq. 1). When the reaction between an alkene and formaldehyde is conducted in the presence of an acid catalyst, it is called the Prins reaction. As an example, in the presence of aqueous sulfuric acid (Eq. 2), styrene reacts with paraformaldehyde to give diol **2** (Scheme 1). Numerous protonic acids and Lewis acids are known to catalyze the reaction, and excellent reviews have been published on the earliest work.[3,4]



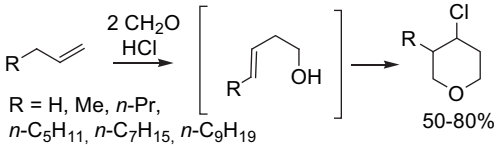
Scheme 1.

The Prins reaction is one of the fundamental methods for C–C bond formation. However, it is necessary to exert an accurate control of the experimental conditions, since several types of products can formally be formed, and mixtures are often isolated (Scheme 2).



Scheme 2.

Modifications brought successively by Hanschke and Gendorf,[5] and by Stapp[6] have led to the ready synthesis of 3-alkyl-4-chloro-tetrahydropyrans (Scheme 3).



Scheme 3.

The demonstration that homoallylic alcohols were intermediates on the reaction pathway has induced the development of 'Prins cyclization', which provides a powerful access to tetrahydropyran derivatives. Tetrahydropyrans (THP) are structural subunits frequently encountered in natural products.[7]

It is somewhat astonishing that the number of applications of a reaction that has been known for more than fifty years is still showing an exponential increase at the beginning of the 21st century.

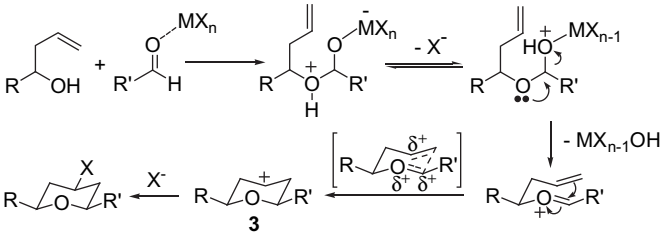
This comprehensive review is devoted specifically to Prins cyclizations leading to tetrahydropyrans or dihydropyrans, and to their extension to aza-Prins cyclization. Both mechanistic and synthetic studies will be discussed, covering the most recent literature up to 2009. A much larger field of applications (including both the classical Prins reaction, and Prins cyclization leading to five-, seven-, eight- and nine- membered ring carbocycles and heterocycles) has been covered by Yus and Pastor in 2007.[8]

2. Mechanistic aspects and strategies

2.1. General mechanism

In the simplest case, the reaction involves a homoallylic alcohol, an aldehyde and a Lewis acid. The latter plays the role of the catalyst and, depending on the experimental conditions, it can act as a source of nucleophilic anion.

A general mechanism is shown in Scheme 4. The key intermediate, i.e., an oxocarbenium ion, is generated from a hemiacetal and undergoes 6-*endo* cyclization to give selectively a secondary tetrahydropyranyl carbocation **3** that can be trapped by various nucleophiles.



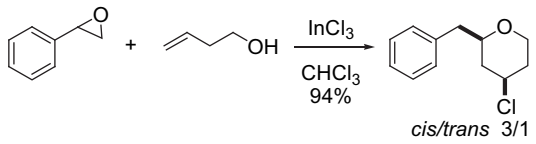
Scheme 4.

2.2. Strategies

2.2.1. Two-component reactions. Several strategies have been designed to form the oxocarbenium ion intermediate. As reported

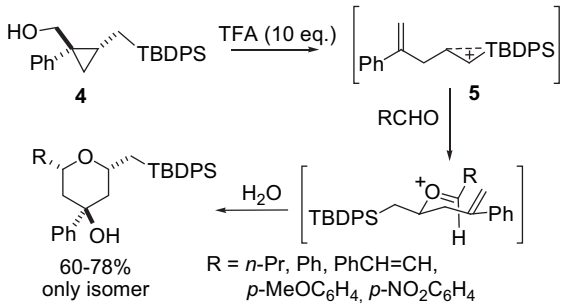
in Scheme 4, the addition of a homoallylic alcohol to the aldehyde carbonyl group activated by a Lewis acid can be used.

Alternatively, the aldehyde can be replaced by an acetal, or an epoxide. As an example, Li et al. have used epoxystyrene to prepare 2-benzyl-4-chlorotetrahydropyran from 3-buten-1-ol in the presence of indium trichloride (Scheme 5).[9]



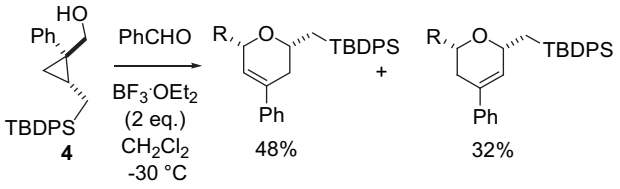
Scheme 5.

One of the most sophisticated methods to induce the formation of the oxocarbenium ion consists of treating a silylated cyclopropylmethylcarbinol **4** (as an equivalent of homoallyl alcohol) with trifluoroacetic acid in the presence of an aldehyde. Ring opening generates the corresponding unsaturated β-silylated carbenium ion **5**, which is trapped by the aldehyde basic oxygen atom. Three stereogenic centers are introduced in one step in the final tetrahydropyranol, isolated as a unique isomer (Scheme 6).[10] The bulky silylmethyl group occupies the equatorial position in the chair-like six-membered cyclic transition state. The cyclization is followed by selective axial trapping of the resulting benzylic carbocation by water.



Scheme 6.

The same protocol can be applied to ketones (acetone, cyclohexanone or pentan-2-one). When BF_3•OEt_2 was used to promote the reaction in dichloromethane, the tetrahydropyranyl carbocation was deprotonated. The reaction led to a mixture of regioisomeric alkenes (Scheme 7).

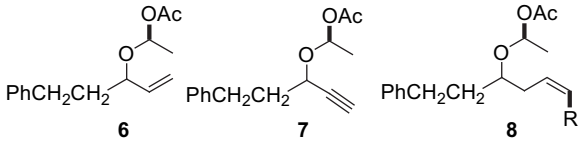


Scheme 7.

2.2.2. One-component reactions. Instead of using two components, it is also possible to generate the oxocarbenium intermediate from a 'masked aldehyde' already covalently linked to the homoallylic alcohol moiety.

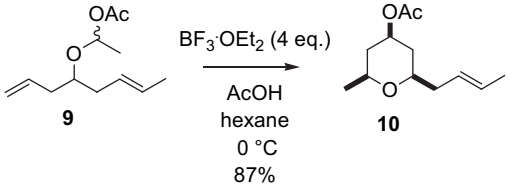
Thus, the key oxocarbenium ion can be formed via Lewis acid-catalyzed cleavage of an α-acetoxyether prepared in a preliminary step. The regio- and the stereo- selectivity of Prins cyclizations starting from α-acetoxyethers have been throroughly investigated by Rychnovsky.[11] Depending on the nature of the Lewis acid, different functionalities can be incorporated at C4, like halides, acetoxy groups, etc. (masked aldehydes such as cyclic acetals can also be used as precursors for oxocarbenium ions).

Starting materials prepared from either allylic- (**6**) or propargylic (**7**) alcohols did not lead to cyclization products (Scheme 8).



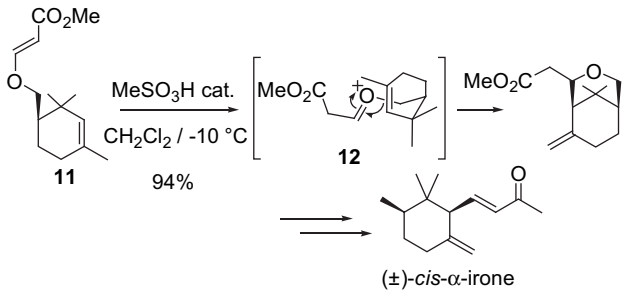
Scheme 8.

Substrates like (**8**) derived from homoallylic alcohols led to tetrahydropyran derivatives in yields ranging from 62 to 74%. The following order of reactivity was established: terminal alkene>*Z*-alkene>*E*-alkene. As exemplified in Scheme 9, acetoxyether **9** led to acetate **10** in 87% yield in the presence of acetic acid and BF_3•OEt_2 as the catalyst.



Scheme 9.

A closely related procedure was used by Nussbaumer and Fráter. In the following example, the aldehyde unit was introduced as an enoxyester (Scheme 10). The oxocarbenium ion was formed via protonation of the double bond of the homoallylic alcohol-derived enol ether **11**. This one-component protocol has scarcely been used. Nussbaumer and Fráter applied it to the synthesis of (±)-*cis*-α-irone.[12,13] The relay of Prins cyclization leading to a bridged bicyclic heterocycle enables control of the stereochemistry in the key precursor of the natural product. As shown in Scheme 10, the oxocarbenium ion **12** undergoes 6-*endo* cyclization via a chair transition state where the carbomethoxymethyl substituent occupies an equatorial position in order to minimize 1,3-diaxial interactions.

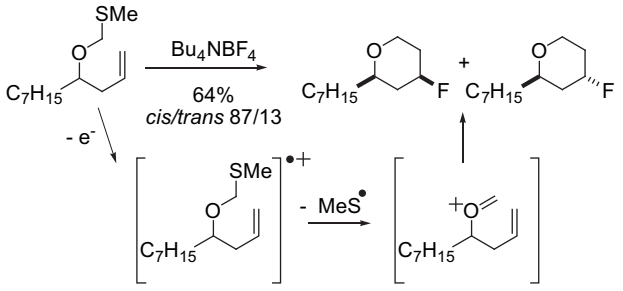


Scheme 10.

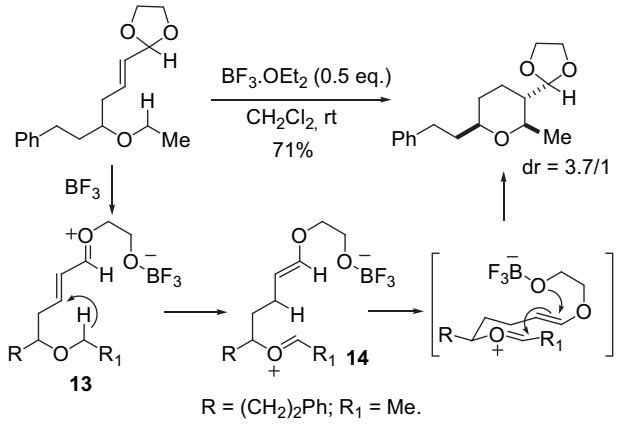
The one-component procedure may also imply prior preparation of a precursor where the masked aldehyde is introduced as an α-thioether, or even as an α-stannyl-, or an α-silylether.[14] Anodic oxidation of the latter leads to tetrahydropyranyl ring closure (Scheme 11).

The reaction might proceed through the formation of a substrate radical cation that would fragment by elimination of a methylsulfanyl radical to give the key cationic intermediate. Other mechanistic hypotheses have been discussed by the authors.

The reactive oxocarbenium intermediates were recently generated via hydride migration by Sames and co-worker.[15] High yields were obtained from alkenyl acetals when the reaction was catalyzed by BF_3. Alternatively, ethylene glycol can serve as organocatalyst. An example and a rationale are given in Scheme 12.



Scheme 11.

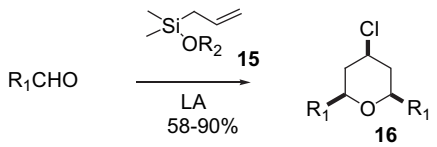


Scheme 12.

The first oxocarbenium species **13** is generated via boron trifluoride-mediated opening of the cyclic acetal. Translocation of the positive charge via hydride transfer gives rise to the second oxocarbenium species **14**, which undergoes 6-*exo* ring closure, with concomitant regeneration of the acetal.

2.2.3. Tandem procedures. Some examples are now discussed involving various strategies where the homoallylic alcohol moiety is generated in situ. These strategies consists of using Sakurai allylation or Keck allylation (for other examples, see Refs. 136,138). Another possibility is to proceed under indium-mediated Barbier conditions.

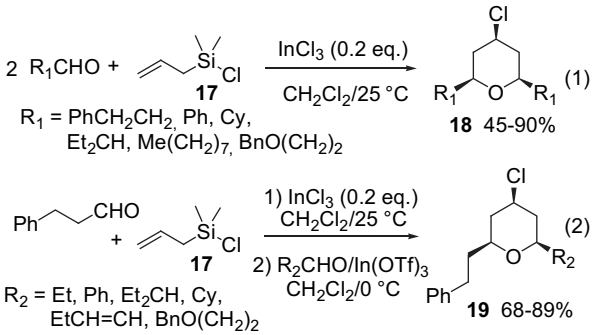
The first example was described by Chan and co-workers.[16] Alkoxyallylsilanes **15** led to symmetrical *cis* 4-chlorotetrahydropyrans **16** by reacting with 2 equiv of aldehydes (Scheme 13).



Scheme 13.

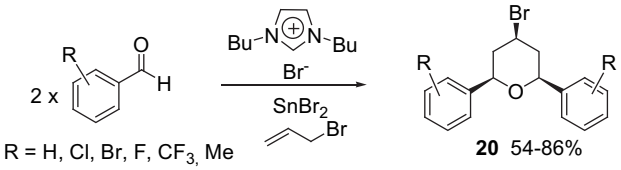
The same reaction catalyzed by In(III) was achieved by Loh and coworker with chloroallylsilane **17**.[17] Good yields of **18** were obtained by slowly adding a mixture of allysilane and aldehyde to a diluted solution of Lewis acid. The reaction was instantaneous (Scheme 14, Eq. 1).

It is also possible to prepare dissymmetrical THP **19** via the successive addition of two different aldehydes. No cyclization could be observed with conjugated aldehydes like cinnamaldehyde or *trans*-2-pentenal used as the first partner (this is likely to be due to prior conjugate allylation). The latter could only be used as the second partner (Scheme 14, Eq. 2).



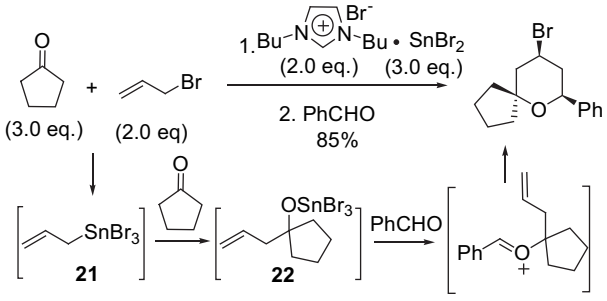
Scheme 14.

An original pathway, based on the use of allyl halides in ionic liquids generated from imidazolium or pyridinium halides and the corresponding Sn(II) halides, has been developed by Wang and coworkers.[18] Both aromatic and aliphatic aldehydes led to 4-halotetrahydropyrans **20** in yields ranging from 54 to 86% (Scheme 15). Again, the method associates in a tandem process the Barbier reaction (to form the homoallylic alcohol) and Prins cyclization.



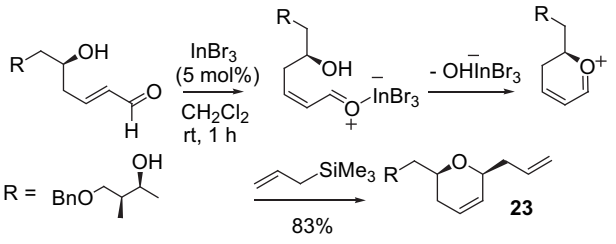
Scheme 15.

Cross reactions were achieved for the synthesis of spirocyclic derivatives from ketones (Scheme 16). The authors propose the in situ formation of an allyltin **21**, which reacts with the ketone to give the tin alkanoate **22**. The latter is reactive enough in the anhydrous medium to give rise to Prins cyclization with benzaldehyde.



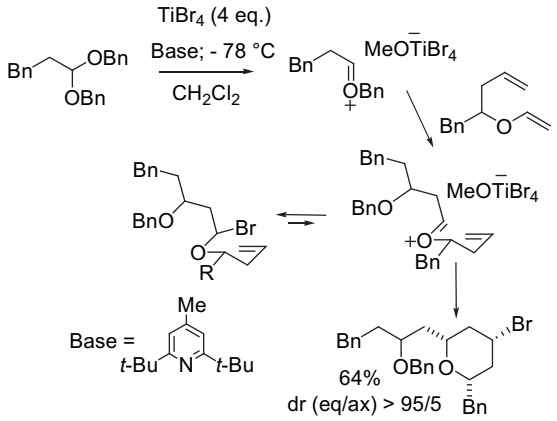
Scheme 16.

The reverse sequence, i.e., $InBr_3$-catalyzed tandem Prins cyclization/Sakurai allylation, was applied to the synthesis of the C6–C18 fragment (**23**) of scytophycin C.[19] The proposed mechanism is given in Scheme 17. Instead of an allyl group, a cyanide can be introduced in good yield, by using TMSCN as the cyanation reagent.[19a]



Scheme 17.

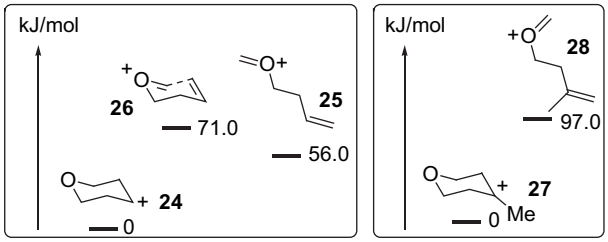
A clever strategy, named Mukaiyama–Aldol–Prins (MAP) cyclization, starting from homoallylic vinyl ethers allows the introduction of functionalized side chains in position 2 at the tetrahydropyranic product.[20] In the Mukaiyama aldol step, the vinyl ether moiety can react with aldehydes, acetals, α-acetoxyacetals, or orthoformates. The mechanism is illustrated in Scheme 18 (the control of diasteroselectivity will be discussed in Section 2.3).



Scheme 18.

2.3. Mechanistic studies-stereoselectivity

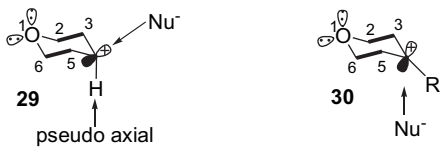
2.3.1. Alder's model: equatorial trapping. DFT calculations on different plausible reaction intermediates have been performed by Alder.[21] Carbocation **24** in its chair conformation is more stable by 56.0 kJ/mol than cation **25** in its most stable staggered conformation. It is plausible that the reaction proceeds through a chair transition state very close to **26** (Scheme 19). Cross-boat conformers would lead to more energetic transition states.



Scheme 19.

Subtituents on the carbon chain and more particularly at C4 influence the stability of the cyclic carbocation. Thus, the tertiary carbocation **27** is more stable than the most stable open-chain conformation **28** by 97 kJ/mol.

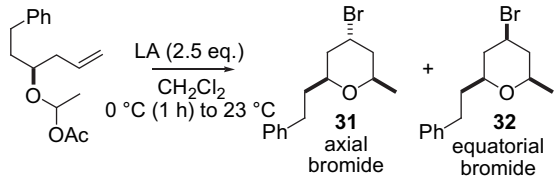
There are several reports that the Prins cyclization exhibits modest selectivity in favour of equatorial trapping of the cyclic carbocation by the nucleophile (most often a halide). According to DFT calculations, in the case of secondary carbocations the chair conformation **29** is stabilized by stereoelectronic effects. The C2–C3 and C5–C6 σ* and σ orbitals overlap both the equatorial lone pair of the oxygen atom and the vacant p orbital at C4. Optimal overlap is reached when the hydrogen atom at C4 is pseudo-axial.



Scheme 20.

This stabilization favours equatorial attack by the nucleophile (Scheme 20). Converse to the secondary carbocation, but still for stereoelectronic reasons, the tertiary cation **30** is planar, and, in this case, axial trapping, which is less hindered, would be favoured.

2.3.2. Rychnovsky's model: axial trapping. In apparent contradiction with the above-cited equatorial trapping of secondary tetrahydropyranyl cations, Rychnovsky has observed that, depending on the experimental conditions, 4-bromo-tetrahydropyrans bearing either an axial or an equatorial bromine atom could be favoured. The data are summarized in Scheme 21.[22]

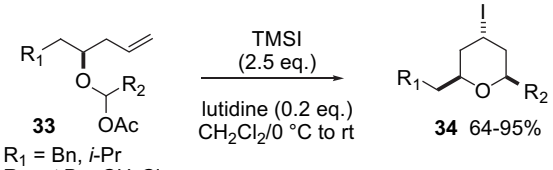


Entry	Lewis acid	Additive	Solvent	**31** Yield (%)	**32** Yield (%)
1	$SnBr_4$	lutidine	CH_2Cl_2	9	79
2	TMSBr	none	CH_2Cl_2	71	7
3	TMSBr	lutidine	CH_2Cl_2	98	0
4	TMSBr	lutidine	hexanes	0	0
5	HBr	none	CH_2Cl_2	60	27
6	AcBr	lutidine	CH_2Cl_2	96	0

Scheme 21.

In the presence of $SnBr_4$ (entry 1), the equatorial bromide (**32**) predominated, whereas when TMSBr was used (entry 2) the selectivity was reversed in favour of the axial epimer (**31**). The addition of lutidine increased this selectivity (entry 3). Other Lewis acids also favoured axial trapping in the presence of lutidine in dichloromethane (entries 5,6). No reaction was observed in low-polarity solvents (entry 4).

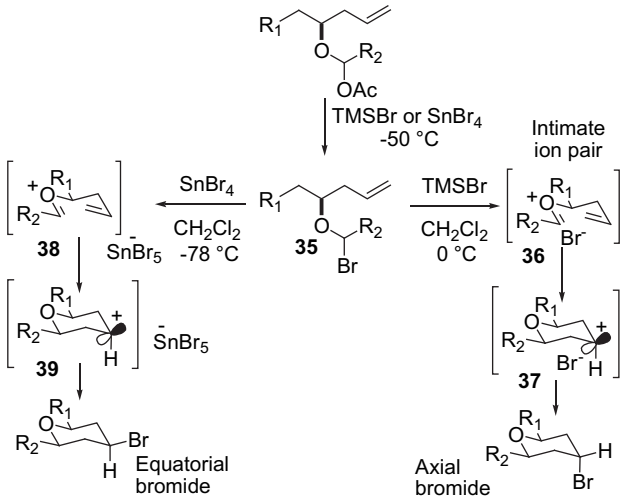
The same preference for axial trapping was registered with TMSI. Axial iodides **34** were the unique isomers isolated in the cyclization of α-acetoxyethers **33** (Scheme 22).



R_1 = Bn, *i*-Pr
R_2 = *t*-Bu, CH_2Cl, Me, CH_2CH_2OTIPS

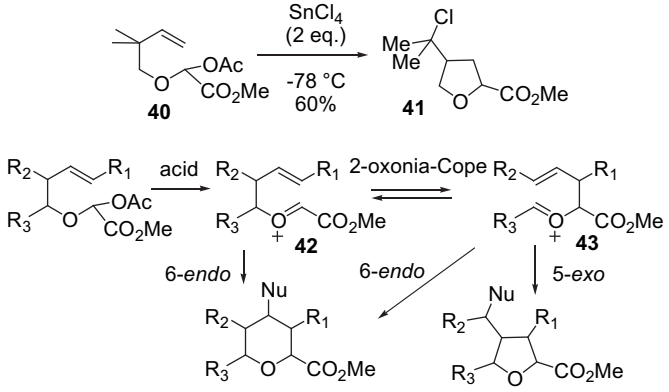
Scheme 22.

In the case of TMSBr, an intermediate α-bromoether **35** was identified by NMR. As shown in Scheme 23, the solvolysis of **35** would lead to an intimate ion pair **36**. Cyclization through a chair transition state, as proposed by Alder, would lead to tetrahydropyranyl carbocation **37** associated to Br^-, still in a contact ion pair. According to the principle of the least motion pathway, axial bromide attack would occur. In the case of $SnBr_4$, the counter anion, $SnBr_5^-$, more crowded and less nucleophilic, would lead to a solvent-separated ion pair **38**. Preferential equatorial attack of the nucleophile on the 4-tetrahydropyranyl carbocation **39** would therefore occur.



Scheme 23.

2.3.3. Competitive 2-oxonia-Cope rearrangement. Products resulting from the 2-oxonia-Cope rearrangement are not detected in 'standard' Prins cyclizations. The involvement of this competitive pathway was first suggested to rationalize the cyclisation of α-acetoxyester **40** (Scheme 24).[23]



Scheme 24.

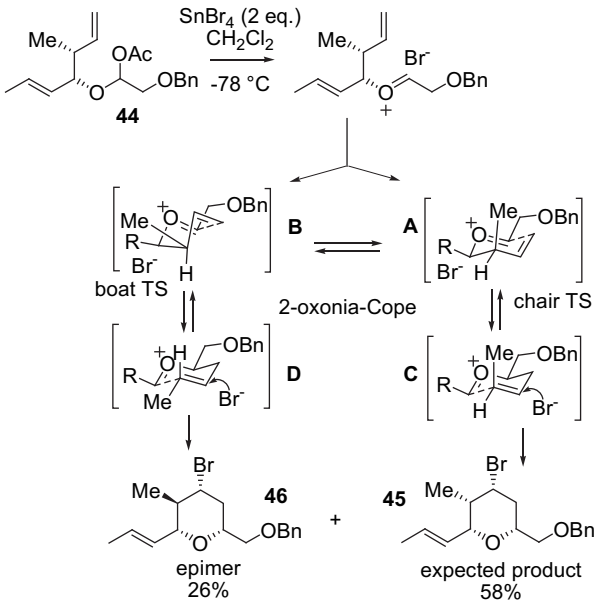
According to Speckamp, only a [3,3]-sigmatropic rearrangement of the intermediate oxocarbenium ion **42** into **43** could explain the total chemoselectivity observed in the cyclization of **40**, which led exclusively to **41** via the 5-*exo* cyclization mode.

Later on, an unexpected epimerization at C3 was oberved by Rychnovsky and co-workers in the cyclization of **44** (Scheme 25).[24]

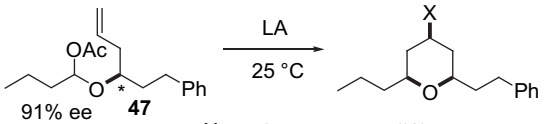
The stereochemical balance of epimers **45** and **46** was rationalized by the possible equilibration of transition states **A** and **D** via [3,3]-sigmatropic C–C bond migration, i.e., 2-oxonia-Cope rearrangement. Chair transition state **A** and chair transition state **C**, resulting from **A** via sigmatropic rearrangement, lead to the expected product **45**, while 2-oxonia-Cope rearrangement, via boat transition state **B**, leads to the rearranged oxocarbenium ion (with an *E*-double bond) that undergoes Prins cyclization via chair transition state **D**, and thus leads to the minor epimer **46**.

Jasti and Rychnovsky have demonstrated that experimental conditions (temperature, solvent) and structural parameters had an impact on the ratio of racemization in the cyclization of an optically pure acetoxyester **47** (Scheme 26).[25] Racemization resulted from the competitive [3,3]-sigmatropic rearrangement. The latter could be minimized by using $SnBr_4$ as Lewis acid in dichloromethane.

Rychnovsky and co-workers have taken advantage of the occurrence of a 2-oxonia-Cope rearrangement prior to Prins cyclization in the synthesis of lasonolide A subunit **48** (Scheme 27).[26] Only



Scheme 25.

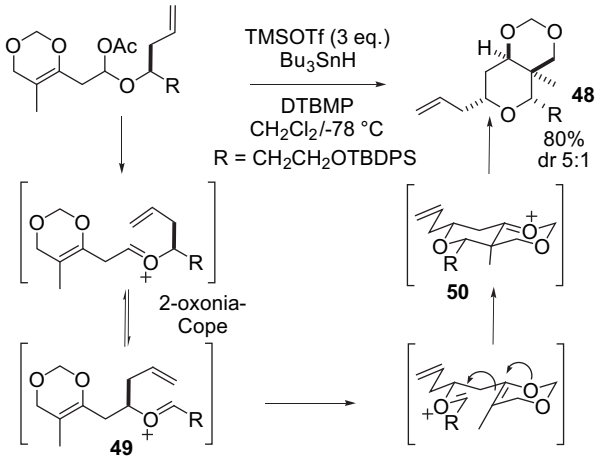


LA	X	Solvent	Yield (%)	% ee
$SnBr_4$[a]	Br	CH_2Cl_2	75	91
$BF_3.OEt_2$[a]	O_2CCH_3	CH_2Cl_2	86	77
TFA	O_2CCF_3	TFA	74	66

[a] 3 eq.

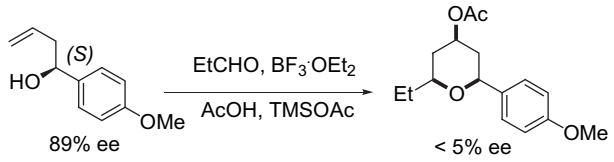
Scheme 26.

the rearranged oxocarbenium ion **49** can be trapped by the electron-enriched alkene, i.e., the enol ether. After reduction of the resulting carbocation (**50**), the bicyclic protected tetrahydropyran **48** was isolated in high yield with an attractive diastereoselectivity.



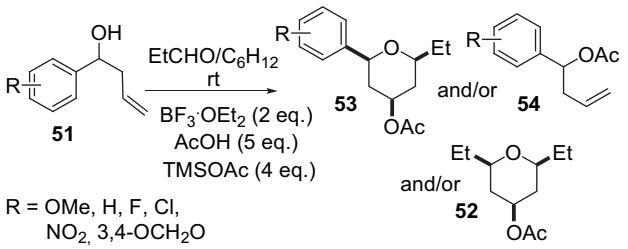
Scheme 27.

As exemplified in Scheme 28, an extensive loss in enantiomeric excess can also occur by way of a solvolytic mechanism when an achiral stabilized benzylic cation can be formed.[25b,27]



Scheme 28.

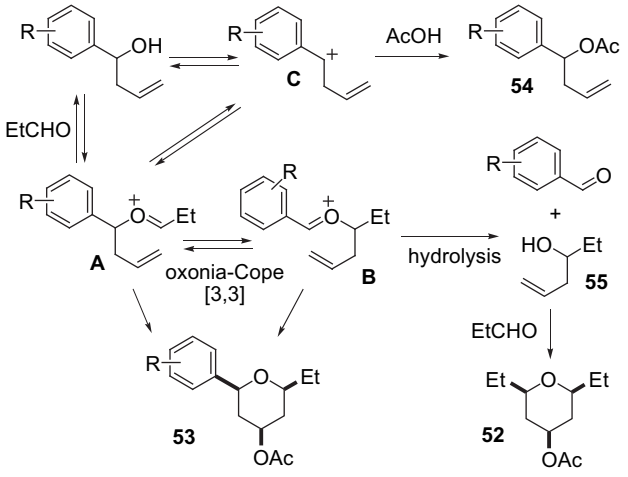
This was well demonstrated by Willis and co-workers, who have shown that the fate of the reaction and, thus, the nature of the product, were greatly influenced by the substituent on the aromatic ring in the reaction of benzylic homoallylic alcohols **51** with propanal (Scheme 29).[27]



Scheme 29.

Electron-rich aromatics favour an oxonia-Cope rearrangement leading to the symmetrical tetrahydropyran **52**. Conversely, the presence of electron-withdrawing substituents favours the formation of **53** via a direct Prins cyclization, which in this case is likely to be faster than the migration of the C–C bond along the π systems.

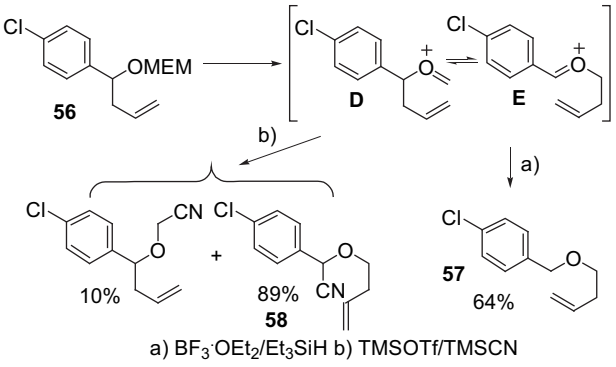
A rationale is given in Scheme 30. The formation of **54** results from direct trapping of the benzylic cation **C**, particularly stabilized by electron-donating substituents, with acetic acid. The formation of **53** can result from **A** or **B**, which are interconverted via a sigmatropic rearrangement. In situ hydrolysis of **B** generates **55**, which is the precursor of **52** (Scheme 30).



Scheme 30.

The aromatic ring substituted by a chlorine atom in **56** does not stabilize by that much the benzylic cation **C**. As shown in Scheme 31, the reaction proceeds via **D**, which undergoes rearrangement into the oxocarbenium ion **E**, stabilized both by the aromatic ring and the oxygen atom lone pair.

The trapping of the intermediates was achieved in the presence of selected traps. Carbocation intermediates could be reduced by Et_3SiH or Bu_3SnH. Alternatively, they could be trapped by nucleophiles like allyltrimethylsilane, TMSCN or $AlMe_3$.[28,29]

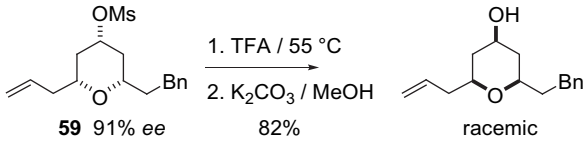


Scheme 31.

The formation of **57** in the presence of Et_3SiH, and the formation of **58** in the presence of TMSCN gave evidence for the involvement of an oxonia-Cope rearrangement (Scheme 31). These reactions were not observed when the aromatic ring carried a methoxy group.

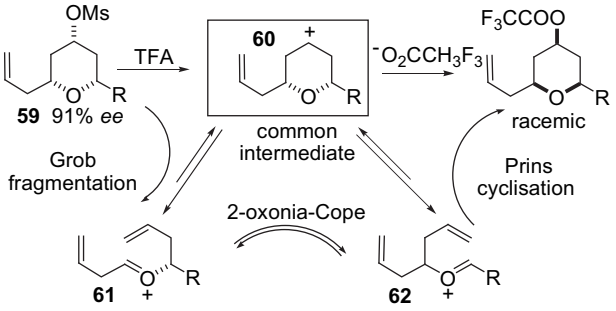
Therefore, it is possible to favour or suppress oxonia-Cope rearrangement by changing the nature of the substituent on the aromatic ring.

Oxocarbenium ions, key intermediates in Prins cyclization in equilibrium via oxonia-Cope sigmatropic migration, can be generated through Grob fragmentation of 4-substituted tetrahydropyrans.[30] This was demonstrated by the racemization observed during the solvolysis of the optically pure mesylate **59** in trifluoroacetic acid (Scheme 32).[31]



Scheme 32.

Racemisation indicates that ring opening of the tetrahydropyranyl carbocation **60**, leading to both oxocarbenium ions **61** and **62**, is faster than trapping by trifluoroacetic acid, which is a poor nucleophile. The results can be rationalized according to the equilibriums shown in Scheme 33.



Scheme 33.

3. Synthetic applications of Prins cyclisation

As already stated, synthetic applications have shown an exponential increase over the last ten years. In the following, the adopted framework is based essentially on two discussions. The first is the nature of the π system that traps the oxocarbenium ion (alkene, alkyne, allene…). In each case, the subdivision is organized according to the nature of the nucleophile used to trap the 4-tetrahydropyranyl carbocation (mentioning as far as possible the experimental conditions, i.e., temperature, solvent, time of reaction),

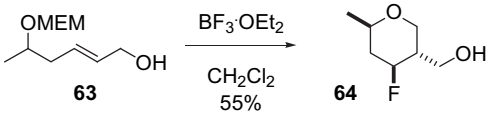
and, finally applications of each type of methodology to the synthesis of natural products are presented.

3.1. Cyclization involving alkenes

Prins cyclization involving alkenes is the method of choice to prepare 4-halogeno-tetrahydropyrans. By adapting the nature of the Lewis acid and that of the nucleophile, however, oxygenated functions like alcohols, ethers, or esters, and even nitrogen-containing functional groups like amides or azides can be introduced into position 4.

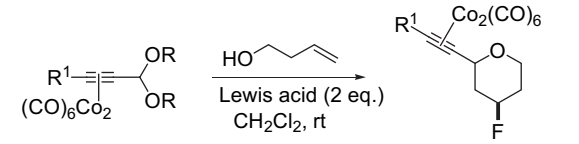
3.1.1. Halo–Prins cyclization

3.1.1.1. Syntheses of 4-fluoro-tetrahydropyrans. Trapping by F^- is not frequently encountered in the literature. Only one example was reported by Rychnovsky in the previously mentioned mechanistic studies of α-acetoxyester cyclization.[11] Using BF_3•OEt_2 as the Lewis acid, Willis and co-workers have prepared 2,6-substituted 4-fluoro-tetrahydropyrans.[32] As exemplified in Scheme 34, **64** was obtained as a unique stereoisomer in 55% yield from the acetal **63**. Two new stereogenic centers were created with an excellent control of the diastereoselectivity.



Scheme 34.

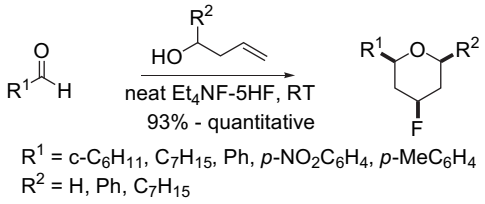
There are very few examples of 2-alkynyl-tetrahydropyrans synthesis.[73] This is likely to be due to the instability of conjugated alkynyl aldehydes. The Nicholas–Prins procedure enables the synthesis of 2-alkynyl-4-fluoro-tetrahydropyrans from dicobalt hexacarbonyl complexes of propargylic acetals. Yields ranging from 52 to 85% were obtained using either HBF_4 or BF_3•OEt_2 as mediator (Scheme 35).[33] The highest diastereomeric ratio was registered with the latter. The diastereoselectivity is much lower than expected for this type of cyclization, probably because the stabilization of the Nicholas cations by cobalt complexes enables epimerization via reversible ring opening.



Scheme 35.

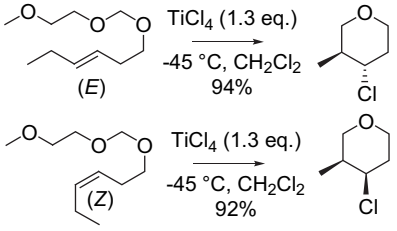
Although the above-mentioned catalysts are the most frequently encountered in the synthesis of 4-fluoro-THP, in some cases hydroxylated by-products are concomitantly formed.[34] An easy and high-yielding procedure using ionic liquid hydrogen fluoride salts has been recently reported by Fugichami and co-workers.[35] The salt plays the role of both the medium and the catalyst. Quantitative yields have been reported when using Et_4NF·5HF, with reaction times varying from 10 min to 2 h (Scheme 36). An excess of HF was necessary to completely prohibit competitive attack by contaminating water.

It must be noted that ketones either reacted very slowly or were totally unreactive. The method was extended to the preparation of fluorinated thiacyclohexanes and piperidines, by using homoallylic thiols and homoallylic protected amines (tosylamides or carbamates), respectively.



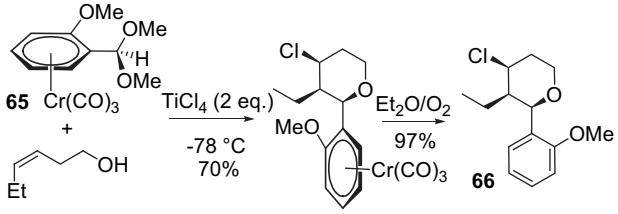
Scheme 36.

3.1.1.2. Syntheses of 4-chloro-tetrahydropyrans. Titanium tetrachloride was used by Thompson[36] in the cyclization of ethylenic acetals.[37] Yields were excellent. *Z*-Alkenes led to *cis* isomers, whereas *E*-alkenes led to *trans* isomers (Scheme 37).



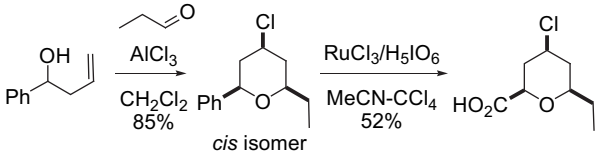
Scheme 37.

The reaction of an arenechromium tricarbonyl with a homoallylic alcohol was achieved by Davies and co-workers.[38] The use of optically active complexes enabled the asymmetric synthesis of optically pure 4-chloro-tetrahydropyrans. An example is given in Scheme 38. Only one optically pure stereoisomer of **66** was isolated from **65** in the presence of $TiCl_4$ and *Z*-hex-3-en-1-ol.



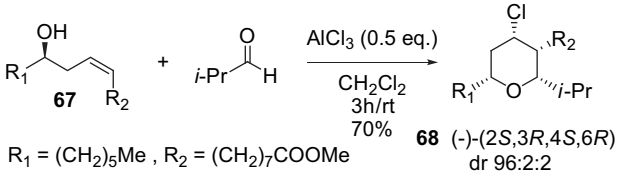
Scheme 38.

Vasconcellos has reported the ruthenium-catalyzed chemoselective oxidation of 2-aryl-4-chloro-tetrahydropyrans.[39] In this case the chloride was stereoselectively introduced via $AlCl_3$-mediated cyclization (Scheme 39).



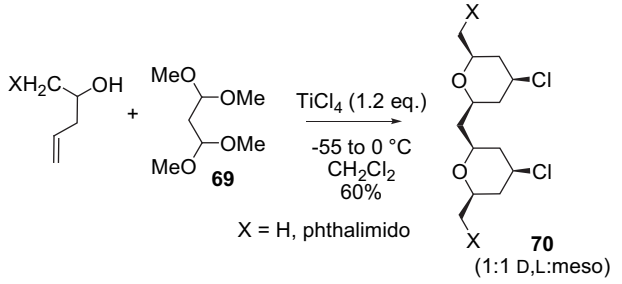
Scheme 39.

The $AlCl_3$-mediated enantioselective synthesis of tetrahydropyrans **68** was achieved in good yields by Metzger and co-workers from methyl ricinoleate (**67**) and various aldehydes. An example is given in Scheme 40.[40]



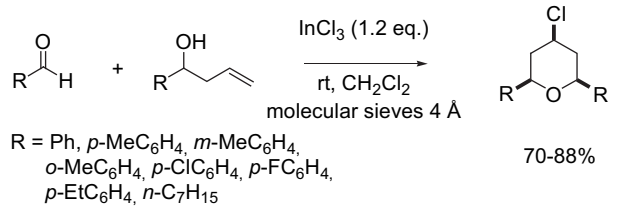
Scheme 40.

Gross and co-workers have selected $TiCl_4$ and $SnCl_4$ to prepare bis-(2-tetrahydropyranyl)-methanes **70** from diacetals **69** (Scheme 41).[41,42]



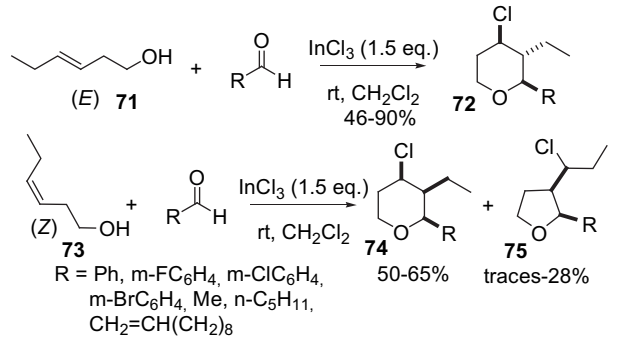
Scheme 41.

The use of Ti(IV) and Al(III) chorides often generates experimental difficulties owing to their highly hygroscopic character. In(III) chloride avoids the use of an inert atmosphere and carefully dried solvents. It constitutes an alternative of choice to prepare 4-chloro-tetrahydropyrans via Prins cyclization. The synthesis of symmetrical 2,6-dialkyl-4-chloro-tetrahydropyrans, in the presence of a slight excess of indium trichloride, has been reported by Li and co-workers (Scheme 42).[43]



Scheme 42.

The synthesis of 2,3,4-trisubstituted tetrahydropyrans has also been investigated by Li.[44] Again the diastereoselectivity was influenced by the stereochemistry of the C=C double dond. The *E*-homoallylic alcohol **71** led to *trans*,*trans*-tetrahydropyrans **72** in good yields (except for R=CH_2=$CH(CH_2)_8$, where the yield was only 46%) (Scheme 43).

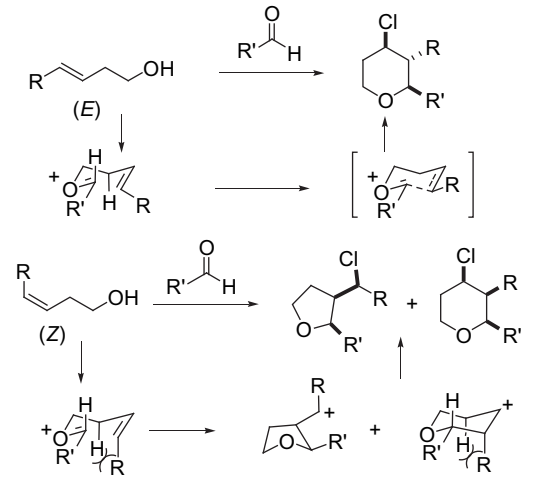


Scheme 43.

The *Z*-homoallylic-alcohol **73** led to *cis*,*cis* tetrahydropyrans **74**. However, in this case, it can be underlined that the reaction was not chemoselective, and a significant amount of the chloro-tetrahydrofurans **75** was also isolated. According to the authors, the formation of the latter can be rationalized by repulsive 1,3-diaxial interactions in the chair transition state, leading to six-membered rings (Scheme 44).[45]

The same conditions were also applied to the synthesis of 4-chloro-thiacyclohexanes from homoallylic thiols.[44]

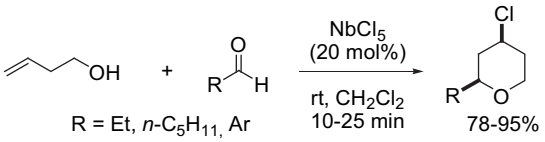
Other metal chlorides have been used to mediate the reaction. Martín has investigated the structure/activity relationships of chloro-tetrahydropyrans very close to natural products, which



Scheme 44.

show a high toxicity with regard to human cancer cells.[46] The targeted chlorides were obtained by using anhydrous ferric chloride.

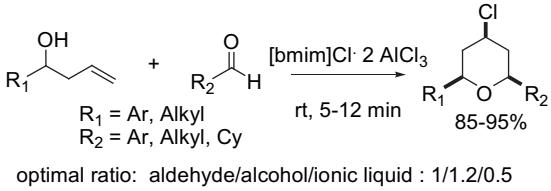
Interestingly, $NbCl_5$ and $GaBr_3$ (or GaI_3) were pointed out as being the most effective catalysts for Prins cyclization leading to 4-halo-THPs. They were used in 20 and 35% molar amounts, respectively (Scheme 45).[47]



Scheme 45.

Indium triflate can also be used in a catalytic amount (20 mol %) in the presence of TMSCl as the source of chloride anion.[48]

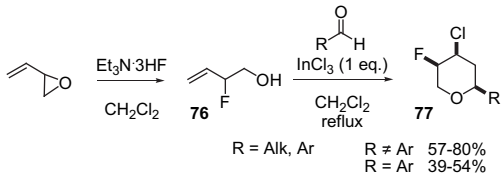
Yadav and co-workers have investigated the use of ionic liquids as solvents to achieve Prins cyclization.[49] Imidazolium chloroaluminates, formed via the reaction of 1-*n*-butyl-3-methylimidazolinium chloride with $AlCl_3$, play at the same time the role of solvent and that of reactant to prepare 4-chloro-THPs (Scheme 46).



Scheme 46.

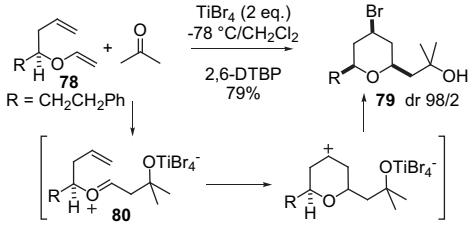
Even though the presence of fluorine atoms is not frequently encountered in natural products, the introduction of fluorine is known to influence biological properties. Dobbs has reported the highly stereoselective synthesis of 4-halo-5-fluoro-tetrahydropyrans via Prins cyclization, starting with homoallyl alcohol **76** bearing a fluorine atom in the allylic position (Scheme 47).[50] The reactions led exclusively to *cis*,*cis* isomers **77** where fluorine is axial in the most stable conformer. Yields were lower with aromatic aldehydes. The highest yields were obtained with $InCl_3$.

These reactions had to be carried out at reflux of dichloromethane instead of room temperature. The fluorine atom in position 3 destabilizes the positive charge in the intermediate 4-tetrahydropyranyl carbocation. It can be noted that the introduction of two geminal fluorine atoms in the allylic position inhibits the cyclization.



Scheme 47.

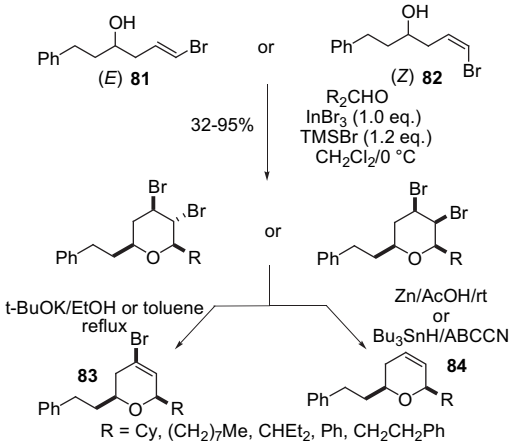
3.1.1.3. Syntheses of 4-bromo-tetrahydropyrans. Titanium tetrabromide was used by Rychnovsky to introduce a bromine atom in position 4 on THP units.[51] The tandem reaction between diene **78** (where the masked acetaldehyde is introduced as an enol ether) and acetone led to **79** in 79% yield with a high diastereomeric ratio in favour of the all-*cis* isomers (Scheme 48). The oxocarbenium ion **80** was generated via a Mukaiyama-like aldol condensation.



Scheme 48.

As previously mentioned, the formation of 4-bromo-tetrahydropyrans can also be mediated with $SnBr_4$.[22,25] Indium tribromide was also proposed as the mediator of choice for these syntheses, allowing the reaction to be carried out under less drastic experimental conditions than with the previous reagents.

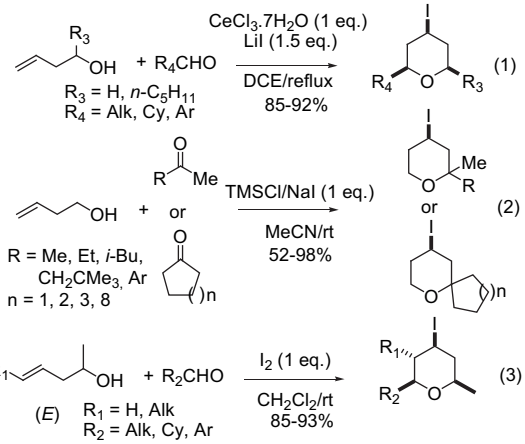
Liu and Loh have recently developed an efficient $InBr_3$-mediated route leading to 2,6-*cis*-dialkyl-3,4-dibromo-tetrahydropyrans from terminal vinyl bromides **81** and **82**, where TMSBr was used as the source of bromide anion. The best experimental conditions are reported in Scheme 49.[52] These dibromides were further transformed via dehydrobromation or debromination. The relative configuration at C3 was controlled by the introduction of *E*- or *Z*-vinylic bromide units in the starting homoallylic alcohol, in both cases preferential equatorial trapping being observed at C4.



Scheme 49.

Regioselective dehydrobromination led to the vinylic bromides **83**. Debromination leading to **84** could be achieved with Zn/AcOH or by classical radical methodology.

3.1.1.4. Syntheses of 4-iodo-tetrahydropyrans. According to Yadav and co-workers, the synthesis of 4-iodo-tetrahydropyrans via Prins cyclization can be performed in the presence of any of the following systems: $CeCl_3.7H_2O$/LiI (Eq. 1),[53] TMSCl/NaI (Eq. 2),[54] or even iodine alone (Eq. 3)[55] (Scheme 50).



Scheme 50.

The first methodology (Eq. 1) necessitates a higher temperature (reflux of dichloroethane) than the two others. It can be applied to both aldehydes and ketones. The best results were obtained with 1 equiv of $CeCl_3$, while CAN and $Ce(OTf)_3$ proved to have little efficiency, and led to hydroxylated side products. As previously mentioned, gallium triiodide, used in a catalytic amount, was also shown to be valuable for the synthesis of 4-iodo-tetrahydropyrans.[47]

Reactions conducted in the presence of TMSI (generated in situ from TMSCl and NaI)[22] were only applied to ketones (Eq. 2). It must be underlined that in the presence of iodide anion, no trapping of the intermediate 4-tetrahydropyranyl carbocation by acetonitrile was detected.

In the case of iodine used alone (Eq. 3), HI, generated in situ, would be responsible for the formation of the hemiacetal precursor of the oxocarbenium ion.

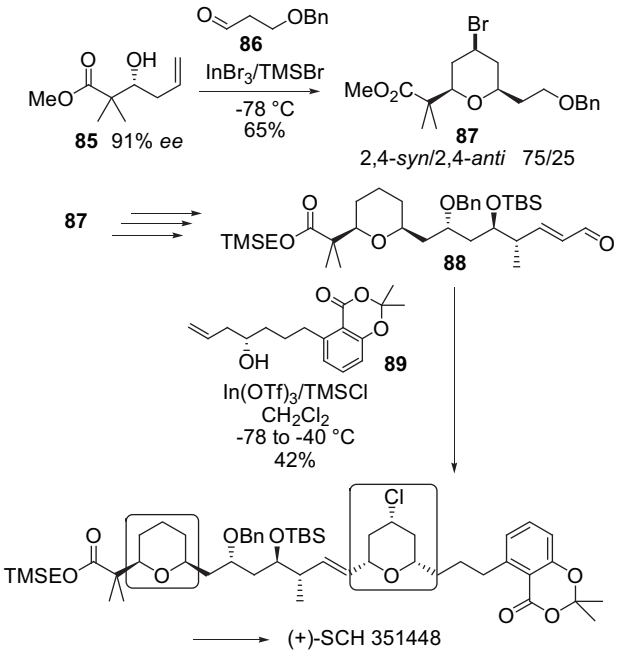
3.1.1.5. Application to the synthesis of natural products. THP units are frequently encountered in natural products. Two Prins cyclizations were used by Loh[56] to form the two tetrahydropyranic subunits of (+)-SCH 351448, which is the first small molecule, isolated from *Micromonospora sp.*, able to activate the receptors of LDL-cholesterol. The target was obtained through the coupling of two identical substructures by an ester linkage. Each half structure contains two tetrahydropyran units having opposite configurations at C2 and C6. The first THP ring **87** was obtained from alcohol **85** and aldehyde **86.** The Prins reaction of alcohol **89** with aldehyde **88** proceeded without deprotecting the acetonide function when an $In(OTf)_3$/TMSCl couple was used (which was not the case for an $InBr_3$/TMSBr couple) (Scheme 51).

Several syntheses proceeding via the intermediacy of Prins cyclization key steps have been reported for centroboline, an antibiotic isolated from *Centrobolium robustum*.

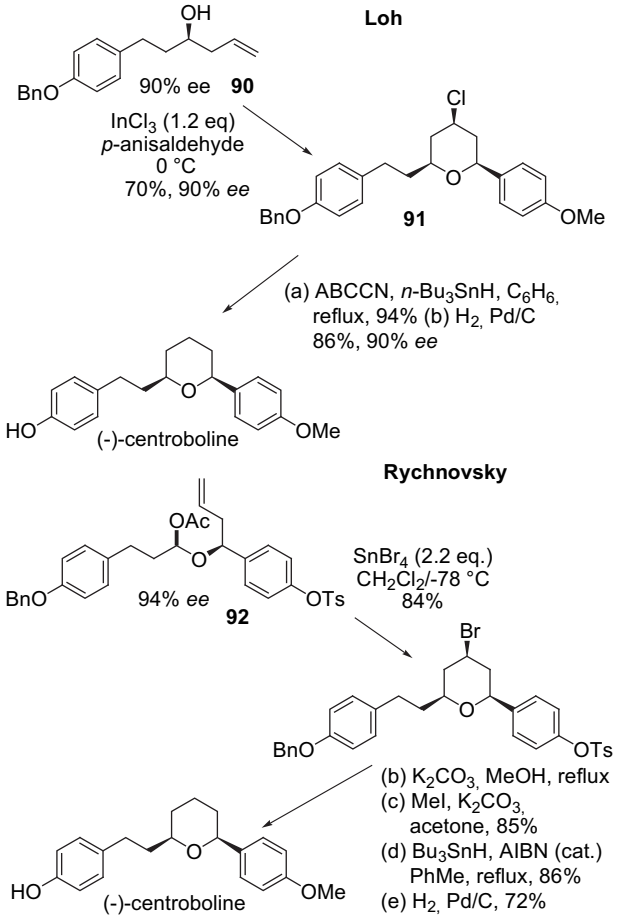
The Loh[57] and Rychnovsky[58] groups have further achieved independently the synthesis of (−)-centroboline. In Loh's strategy, 4-chloro-tetrahydropyran **91** was obtained via the reaction of enantiopure alcohol **90** with *p*-anisaldehyde in the presence of an excess of indium trichloride.[59] (−)-Centroboline was obtained in 90% ee (Scheme 52).

α-Acetoxyether **92** (prepared from the corresponding enantiomerically pure alcohol) was selected as precursor by Rychnovsky, (Scheme 52).[58] This strategy enabled the classical problem encountered in Prins cyclization, i.e., racemization due to competitive 2-oxonia-Cope rearrangement, to be avoided. However, it was necessary to introduce temporarily a tosylate function on the aromatic ring, since the methoxy group is a good electron donor, that it

favoured the unwanted [3,3]-sigmatropic migration by stabilizing the rearranged oxocarbenium ion. The stereoselectivity was total, no epimerization was observed, and the target was isolated after classical group interconversions.



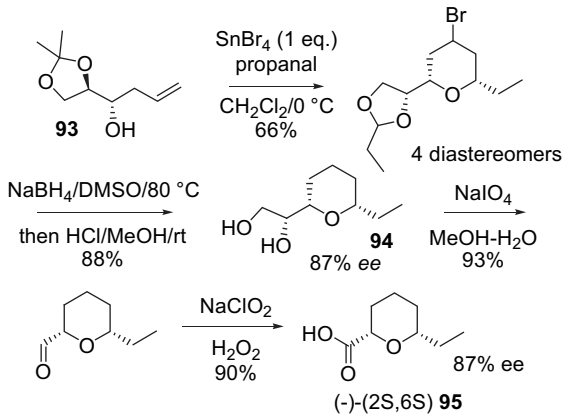
Scheme 51.



Scheme 52.

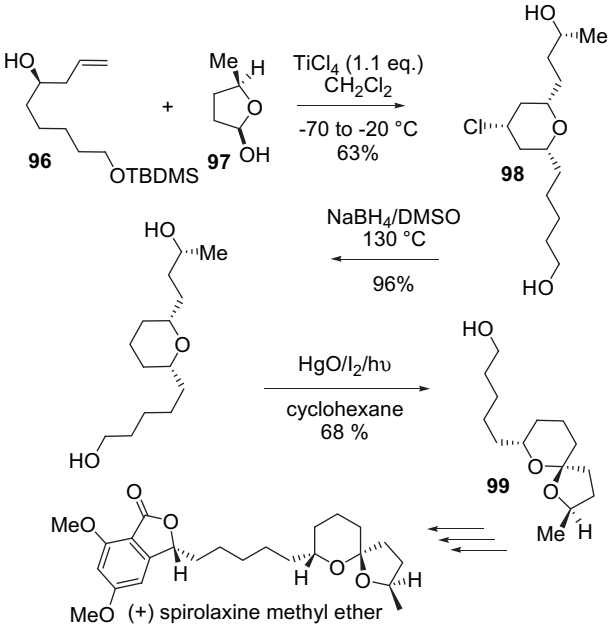
Yadav has prepared the target molecule in racemic form by using TMSI, generated in situ from TMSCl and NaI. The methodology led diastereoselectively to the all *cis* 4-iodo-tetrahydropyran that was subsequently reduced by Bu_3SnH/AIBN to give (±)-centroboline.[60]

(−)-(2*S*,6*S*)-(6-Ethyltetrahydropyran-2-yl) formic acid (**95**), which is an analgesic, was prepared by Vasconcellos.[61] The optically pure starting material **93** was prepared via stereocontrolled allylation of glyceraldehyde isopropylidene acetal. Subsequent Prins cyclization was mediated with $SnBr_4$ (Scheme 53). Due to concomitant transacetalization with propanal, the reaction resulted in a mixture of four diastereomers. Reduction of the latter, followed by oxidative cleavage of diol **94**, led to the levo enantiomer of **95** in 87% *ee*.



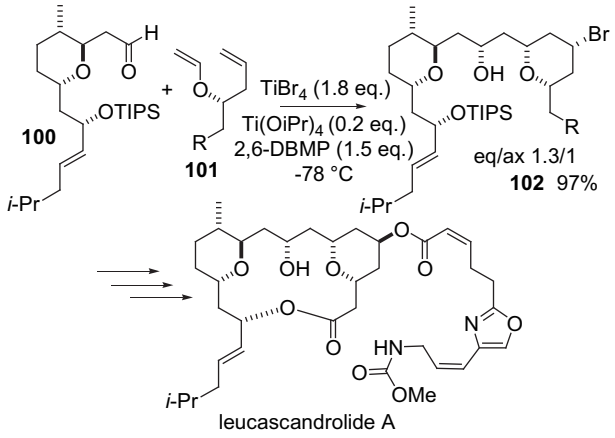
Scheme 53.

Prins cyclization was also a key step in Nasini and co-workers' total synthesis of the methyl ether of (+)-spirolaxine, a metabolite of *Sporotrichum laxum*, active against *Helicobacter pylori*.[62] The reaction between optically pure alcohol **96** and lactol **97** in the presence of $TiCl_4$ led stereoselectively to 4-chloro-tetrahydropyran **98** (Scheme 54). Subsequent reduction of the chloride, followed by radical spiroacetalization, led to **99**, a precursor of (+)-spirolaxine.



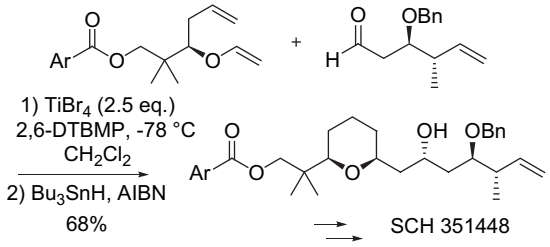
Scheme 54.

In the total synthesis of leucascandrolide A, Rychnovsky has again applied a tandem Mukaiyama reaction/Prins cyclization to introduce the second THP unit. The oxocarbenium ion, precursor of 4-bromo-THP **102**, resulted from the condensation of enol ether **101** with aldehyde **100** (Scheme 55).[63]



Scheme 55.

The same strategy, implying subsequent reduction by tributyltin hydride of the bromide resulting from Prins cyclization, was also applied to the synthesis of a key intermediate in the synthesis of SCH 351448 (Scheme 56).[64]

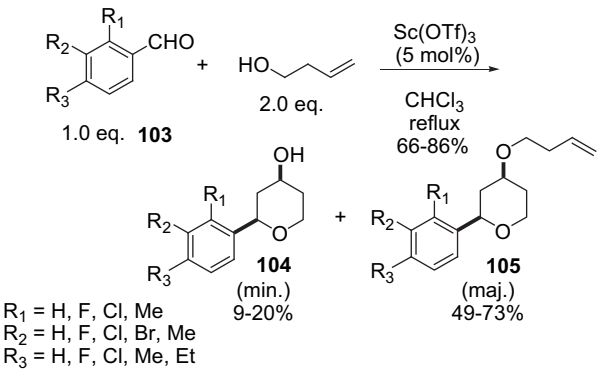


Scheme 56.

3.1.2. Trapping by oxygenated nucleophiles. Many examples of Prins cyclization are concerned with the trapping of the tetrahydropyranyl cation by oxygen-centered nucleophiles. The formation of THP bearing an oxygen atom in position 4 is conditioned by the replacement of halide ligands in the Lewis acid by ligands of lower nucleophilicity, most often triflates. Methodologies leading to 4-hydroxy, 4-alkoxy, and 4-alkoxycarbonyl derivatives are now discussed.

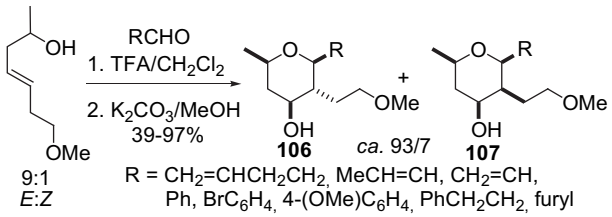
Most examples in this field concern the synthesis of 4-hydroxy-tetrahydropyrans. However, hydroxylated derivatives are often obtained as by-products when other functional groups need to be introduced.

Li and Zhang[65] have reported the diastereoselective synthesis of mixtures of 4-hydroxy-tetrahydropyrans **104** and the corresponding ethers **105** via scandium triflate-catalyzed Prins cyclization. Aromatic aldehydes **103** reacted with 3-buten-1-ol, to give *cis* isomers in overall yields ranging between 66 and 86% (Scheme 57). Ethers **105** were the major products. They resulted from the trapping of the 4-tetrahydropyranyl carbocation by the homoallyl alcohol in excess.



Scheme 57.

A two step procedure reported by Willis and co-workers enabled the introduction of a large variety of R substituents at C2. However, aldehydes leading to strongly stabilized oxocarbenium ions, such as crotonaldehyde or 4-methoxybenzaldehyde, gave lower yields (Scheme 58).[66]



Scheme 58.

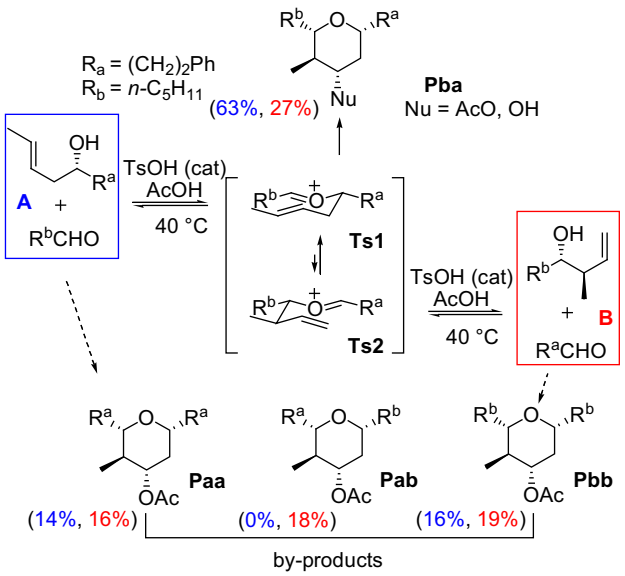
When the double bond was *E*, the diasteroselectivity was in favour of **106** bearing an equatorial substituent at C3, and the diastereomeric ratios were very high (Scheme 58). An axial substituent at C3 (**107**) was favoured when the double bond was *Z*, but in this case the diastereomeric ratio was lower. The authors have reported that racemization was not observed when starting from an optically pure homoallylic alcohol with an *E*-double bond, even for reactions involving aromatic aldehydes, susceptible to favouring the competitive oxonia-Cope rearrangement.

It is possible to trap the cyclic carbocation by an acetate anion. The methodology consists of using $BF_3{\cdot}OEt_2$ as Lewis acid in the presence of TMSOAc. Fluoride anion is trapped by TMSOAc, which delivers the nucleophilic carboxylate in the reaction medium. Unfortunately, these conditions are racemizing.[27,32]

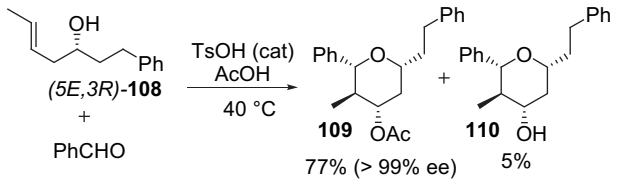
It has been reported for the synthesis of 2,3,4,6-tetrasubstituted tetrahydropyrans from optically active alcohols that less scrambling at C2 and C6, and thereby less side products, were observed when starting from the reactants pair **A** than from pair **B**.[67] As an example (Scheme 59), acetate **Pba** was largely predominant from pair **A** (63%). It was isolated together with 16% of **Pbb** and 14% of **Paa**. Comparatively, all four products were obtained in nearly equal amounts from pair **B** (**Pba**: 27%, **Pbb**: 19%, **Pab**: 18% and **Paa**: 16%) (for the mechanism of formation of side products, see Scheme 30). This was ascribed to the greater stability of transition state **Ts1**, compared to transition state **Ts2**.

As an application, the acetate **109** was isolated in 77% yield (>99% *ee*) from benzaldehyde and alcohol **108**, the corresponding hydroxylated derivative **110** being formed in 5% yield (Scheme 60).

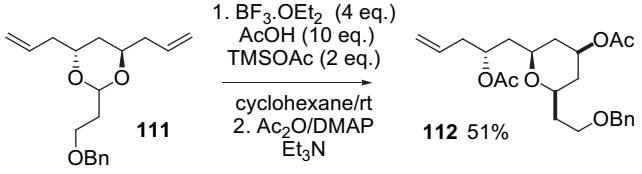
Desymmetrization of C_2-symmetrical 1,3-diols was achieved by Rychnovsky via Prins cyclization of acetal **111**.[68] The use of $BF_3{\cdot}OEt_2$ in acetic acid led to acetoxy-tetrahydropyrans **112** (Scheme 61).



Scheme 59.

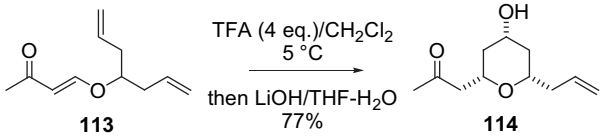


Scheme 60.



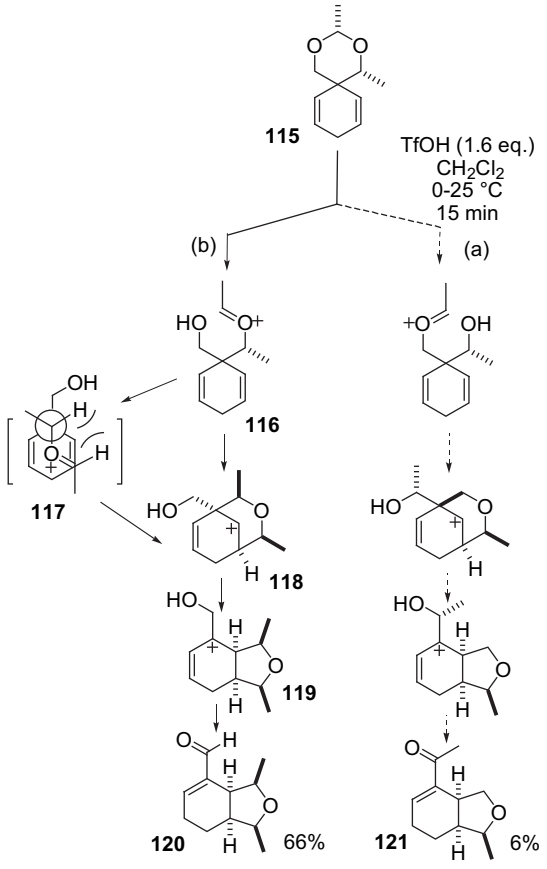
Scheme 61.

Prins cyclization was also used for desymmetrization by Kozmin.[69] In that case, the substrate was enol ether **113** derived from bis-allylcarbinol. Tetrahydropyran **114**, a subunit of leucascandrolide A, where three stereogenic centers were introduced in one single step, was isolated in 77% yield (Scheme 62).



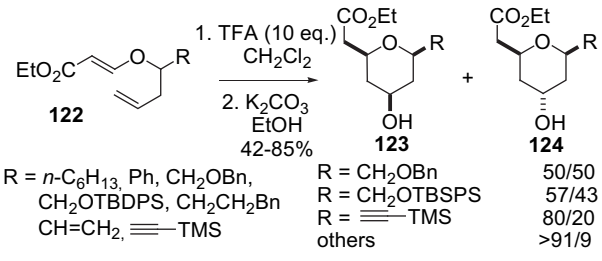
Scheme 62.

The use of triflic acid enabled an improvement in the desymmetrization of 1,4-cyclohexadienes via the Prins–Pinacol sequence (Scheme 63).[70,71] Acetal **115** underwent preferential opening according to path b. This led to the oxocarbenium ion **116**, which cyclized via transition state **117**, in order to minimize $A^{1,3}$ strain. The resulting cation **118** led to **119** a precursor of **120** that was isolated in a 10–1 ratio together with **121** resulting from path a.



Scheme 63.

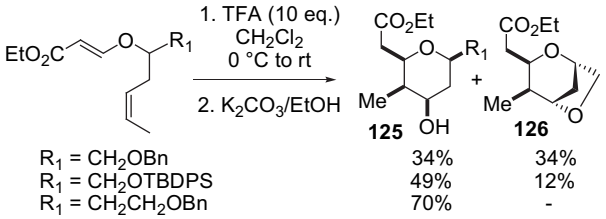
Enol ethers **122** have been cyclized into the corresponding 4-hydroxy-tetrahydropyrans by Hart[72,73] and by Fráter.[12b] The cyclization, carried out in an acidic medium, led after basic work-up to pyranols **123** and **124** in yields ranging from 42 to 85%. Diastereoselectivities ranged from 91/9 to 50/50 depending on the nature of the R substituent (Scheme 64).[73]



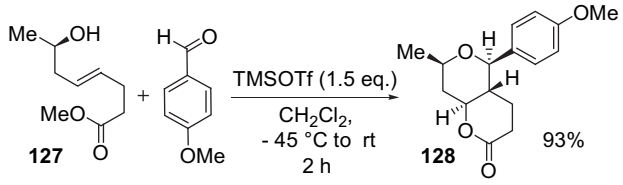
Scheme 64.

As shown in Scheme 65, the introduction of a substituent at the terminal carbon of the *Z* double bond enabled the control of an additional stereogenic center at C3 in tetrasubstituted pyranols **125**. However, sterocontrol at C4 was influenced by the nature of R_1. When R_1=CH_2OBn or R_1=$CH_2OTBDPS$, the participation of the ether group oxygen atoms led to the competitive formation of bicyclic compounds **126** (Scheme 65).

Intramolecular trapping has been exploited by Willis and coworkers to prepare fused-bicyclic tetrahydropyrans.[74] Ester groups were used as internal traps for tetrahydropyranyl cations. Homoallylic alcohol **127** was converted into lactone **128** in 93% yield when reacting with *para*-anisaldehyde in the presence of TMSOTf in dichloromethane (Scheme 66).

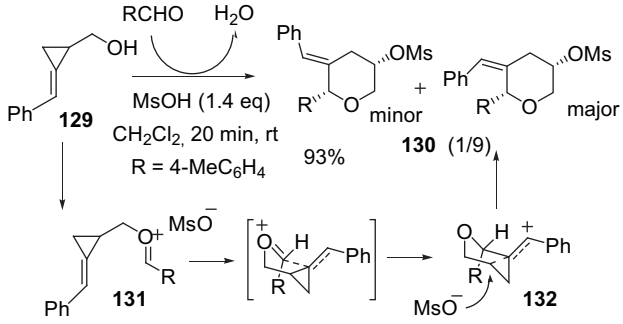


Scheme 65.



Scheme 66.

Sulfonic acids (MsOH or TsOH) were used in the approach to 3-methylene-tetrahydropyrans developed by Shi and co-workers.[75] In the presence of these Brönsted acids and aromatic aldehydes (acetaldehyde also proved to be a good partner), 2-(arylmethylene)cyclopropylcarbinol **129** was converted into **130,** isolated as a mixture of isomers. The highest yields were obtained when using MsOH in dichloromethane at room temperature (Scheme 67).

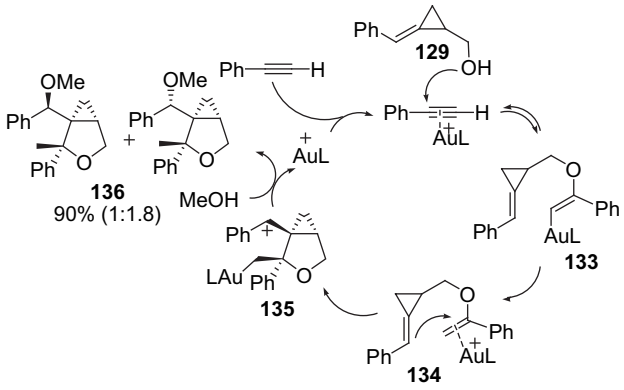


Scheme 67.

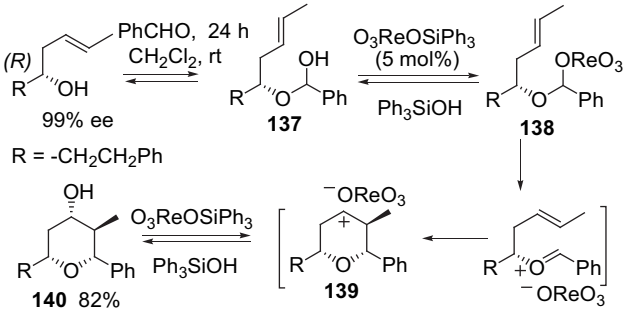
A plausible mechanism implies 5-*exo* cyclization[76] of the oxocarbenium ion **131**, leading to a benzylic cyclopropylmethyl cation **132** that would open through trapping by sulfonate counterion.

An original extension was devised by replacing the protonic acid by $Ph_3PAu(I)Cl$, used in a catalytic amount in the presence of silver triflate.[77] In this multicomponent process the aldehyde was replaced by an alkyne. A rationale is given in Scheme 68. Upon Au(I) activation, cyclopropylcarbinol **129** adds to the triple bond. Protodemetalation of the intermediate **133**, followed by Prins-type cyclization of **134**, leads to the bicyclic cationic complex **135**. The trapping of the cation by methanol and the concomitant protodemetalation explain the formation of **136** as a mixture of diastereomers.

Other catalysts have been used in different media. As shown previously, trapping the 4-tetrahydropyranyl cation by carboxylic acids led to esters that had to be hydrolyzed to form the 4-hydroxy derivatives. Re(VII) catalysts are known to isomerize allylic alcohols via ionization. Prins cyclization mediated with $O_3ReOSiPh_3$ is very mild. The reaction proceeds with good selectivity in favour of the formation of equatorial 4-hydroxy-tetrahydropyrans **140** in low-polarity solvents (Scheme 69).[78] Activation is supposed to involve the formation of a perrhenate ester **138**, from the hemiacetal **137**. The solvolysis of **138** generates a contact ion pair that rearranges into **139** according to the least motion principle. Exchange with Ph_3SiOH would regenerate the catalyst.



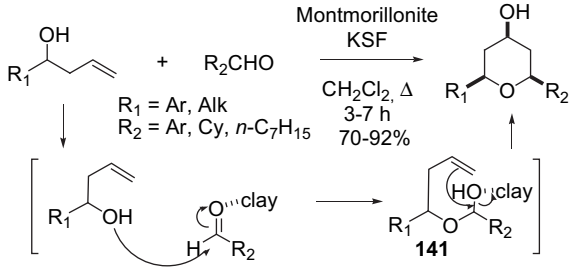
Scheme 68.



Scheme 69.

Phosphomolybdic acid is also an efficient catalyst for Prins cyclization.[78,79] The reaction of homoallylic alcohols with aldehydes and ketones proceeds in water, in high yield and with a high selectivity to give all-*cis* 4-hydroxy-tetrahydropyrans.

Heterogeneous media were investigated by Yadav for the synthesis of the very same targets. Solid catalysts present several advantages such as eco-compatibility, ready recycling, absence of corrosion, low cost, and easy purification of products. Montmorillonite KSF was shown to catalyze Prins cyclization.[80] According to the authors, the formation of tetrahydropyranols could be rationalized via the formation of hemi-acetal **141** (Scheme 70). The reaction under thermodynamic control is totally stereoselective.

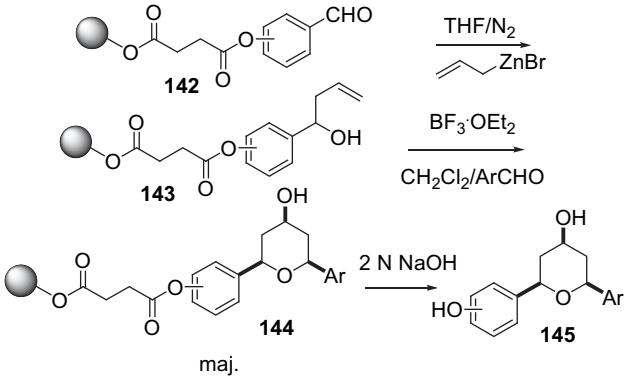


Scheme 70.

The use of zeolites or ion-exchange resins in ionic liquids offers an alternative to the use of chlorinated solvents, which are not recommended for environmental reasons.[81] These solvents can be recycled after washing by ether. However, the yields were shown to decrease from 90 to 79% after four cycles. In order to avoid this drawback, it is necessary to eliminate water by drying the ionic liquid under vacuum before recycling (no reaction takes place in non dried solvents).[82] It must be noted that quaternary ammonium salts ionic liquids could not be used to perform Prins cyclization.

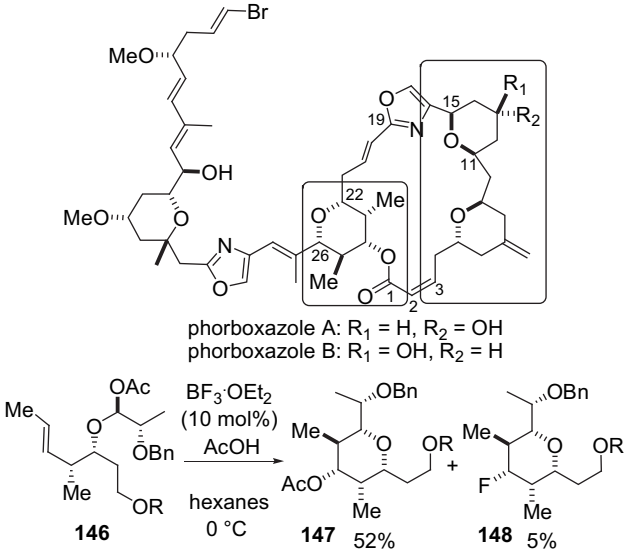
The association of [bmim]PF_6 with a $Ce(OTf)_3$ catalyst was investigated by Li.[83] Under these experimental conditions, tetrahydropyranols were isolated in yields ranging from 42 to 69%. Catalysis by $Bi(OTf)_3$ in [bmim]PF_6 generated the same product in even superior yields and higher diastereoselectivity.[84]

A sequential procedure can be carried on solid support.[85] PEG-supported aldehydes **142** react first with allylzinc bromide to give supported homoallylic alcohols **143**. Prins cyclization, mediated with BF_3•OEt_2, leads under thermodynamic control to *cis*,*cis*-2,6-diaryl-4-hydroxy-tetrahydropyrans **144** (Scheme 71). Hydroxylation competes with fluorination of the intermediate 4-tetrahydropyranyl carbocation (the hydroxy/fluoride ratio ranges from 78/22 to 85/15). Saponification releases **145** from the resin.



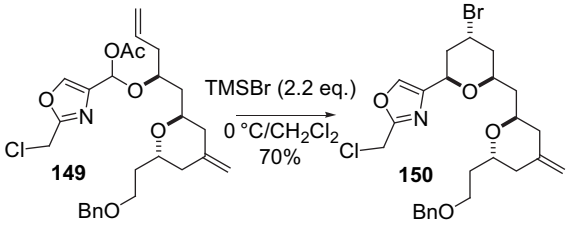
Scheme 71.

3.1.2.1. Application to the synthesis of natural products. The key steps in Rychnovsky's synthesis of phorboxazoles A and B[86] are stereoselective Prins cyclizations, the first of which was used to build the C22–C26 tetrahydropyranic fragment from α-acetoxy-ether **146**. In the presence of BF_3•OEt_2 and acetic acid, acetate **147**, including five stereogenic centers, was obtained as a single isomer in 52% yield together with 5% of the fluoride **148** (Scheme 72).



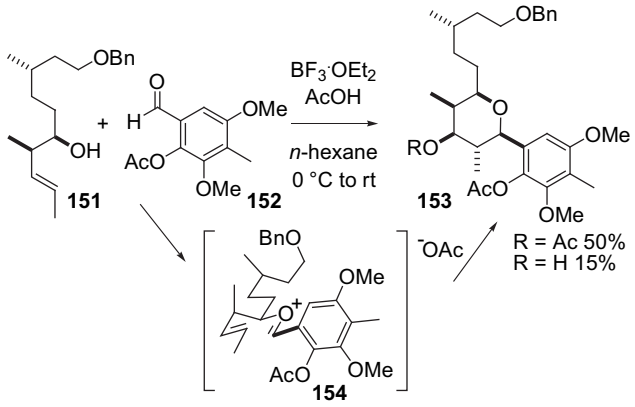
Scheme 72.

The C3–C19 fragment in phorboxazole B was obtained via another Prins cyclization. The stereoselective temporary introduction of an axial bromine atom in position 4 was achieved via TMSBr-mediated cyclization of **149** (Scheme 73).[87] The axial bromide **150** was further converted into an equatorial acetoxy group with CsOAc.



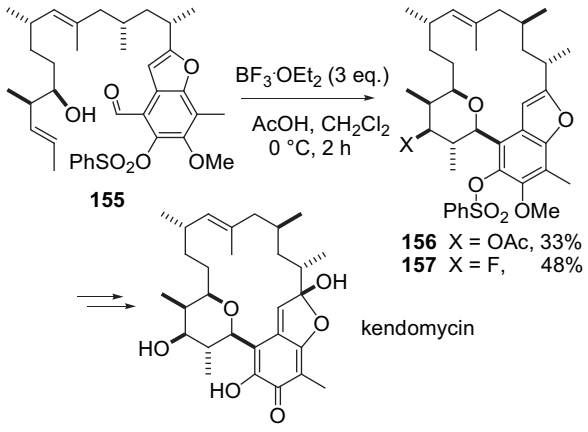
Scheme 73.

In the field of anticancer agents, the pentasubstituted tetrahydropyranyl fragment of kendomycin **153** was first prepared by Rychnovsky via reaction of alcohol **151** with electron-rich aldehyde **152**.[88] As shown in Scheme 74, Prins cyclization introduced three new stereogenic centers, which were totally controlled via equatorial attack of the nucleophile onto the 4-tetrahydropyranyl cation resulting from the cyclization of oxocarbenium ion **154** via a chair transition state. Acetylation of the phenol group in **152** was necessary to suppress any interference of the competitive oxonia-Cope rearrangement. Minimization of [3,3]-sigmatropic C–C bond migration was reinforced by the use of AcOH, a better nucleophile than CF_3CO_2H. The reaction was mediated with BF_3•OEt_2 in a heterogeneous apolar medium (*n*-hexane).



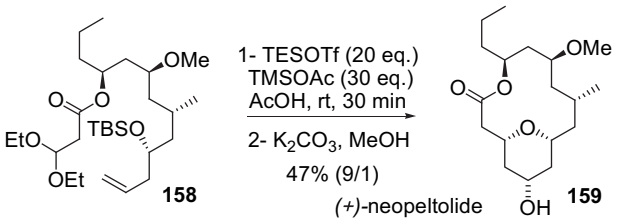
Scheme 74.

In their final strategy to the natural product, Rychnovsky and coworker have used Prins cyclization to achieve the macrocyclization (Scheme 75).[89] Due to the favourable preferred conformation of hydroxyaldehyde **155**, the macrocyclization was highly efficient. However, it led to a mixture of 4-fluorinated-tetrahydropyran **157** and to the corresponding 4-acetoxy-tetrahydropyran **156** in a 48:33 ratio. Attempts to achieve the cyclization with TFA or TMSOAc were unsuccessful.



Scheme 75.

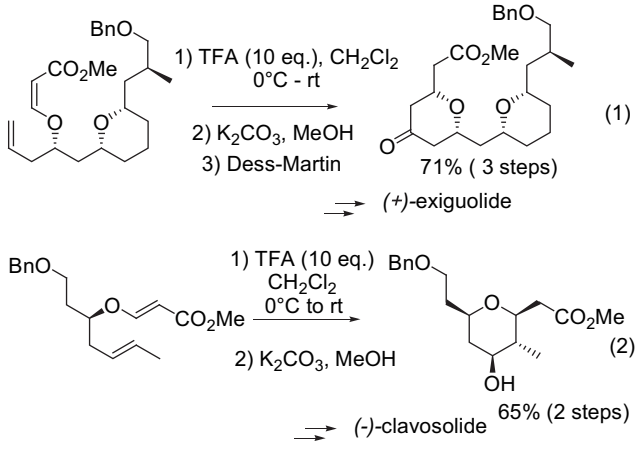
A related strategy was selected by Lee and co-workers to obtain selectively the hydroxyl derivative.[90] In their synthesis of (+)-neopeltolide, the macrocyclization of **158** was also achieved via Prins cyclization, but under the mediation of TESOTf and TMSOAc in AcOH. The resulting acetate was then saponified to give the corresponding alcohol **159** (Scheme 76).



Scheme 76.

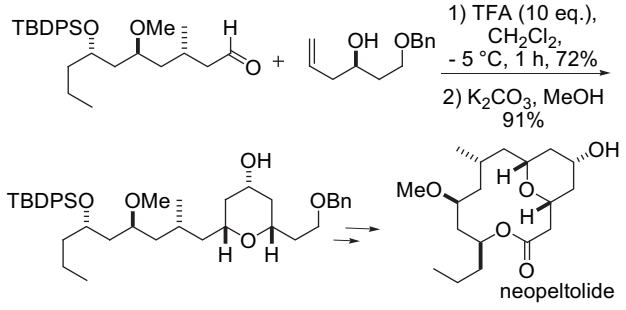
The use of trifluoroacetic acid-mediated Prins cyclization followed by subsequent hydrolysis of the trifluoroacetate, has been widely applied in natural product syntheses.[91,92] Some selected examples are now discussed.

These experimental conditions were applied by Lee in the total synthesis of (+)-exiguolide (Eq. 1),[93] and by Willis in her synthesis of (−)-clavosolide D (Eq. 2).[94] As shown in Scheme 77, in both cases the aldehyde was introduced as an enol ether in the precursor, as in the previously cited approach developed by Nussbaumer and Fráter.[12]



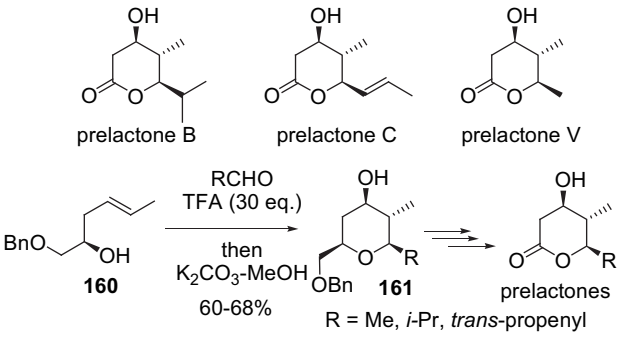
Scheme 77.

The pyran ring in the core structure of neopeltolide was also fashioned, by Maier, via Prins cyclization in the presence of TFA followed by hydrolysis of the resulting trifluoroacetate (Scheme 78).[95]



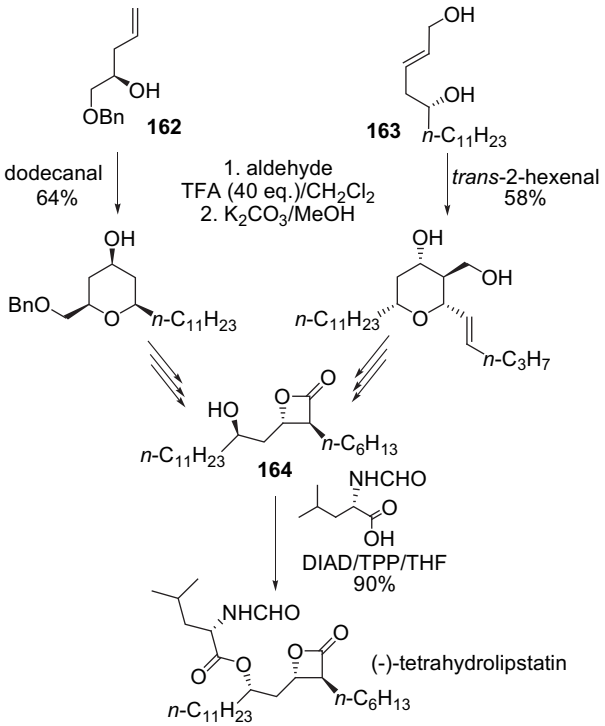
Scheme 78.

Yadav and co-workers have shown that δ-lactones, such as prelactones B, C and V, are available via Prins cyclization followed by oxidation.[96] Homoallylic diol **160**, monoprotected as a benzyl ether, was treated with the appropriate aldehyde in the presence of trifluoroacetic acid. The reaction led to trifluoroacetates that were saponified into the corresponding 4-hydroxy-tetrahydropyrans **161** (Scheme 79).



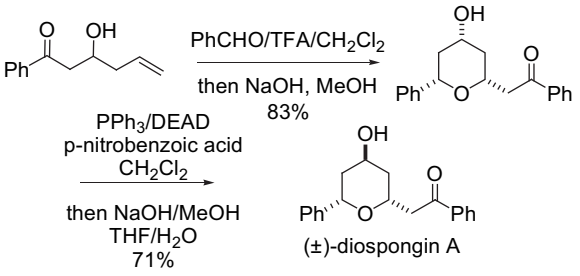
Scheme 79.

The very same methodology was applied to the synthesis of (−)-tetrahydrolipstatin, an inhibitor of pancreatic lipase used in obesity treatment.[97] Two strategies starting from two different enantiopure diols **162** and **163** were investigated to prepare lactone **164**. The introduction of (*S*)-*N*-formyl leucine was achieved in the very last step via a Mitsunobu reaction selected to invert the configuration of the secondary alcohol (Scheme 80).



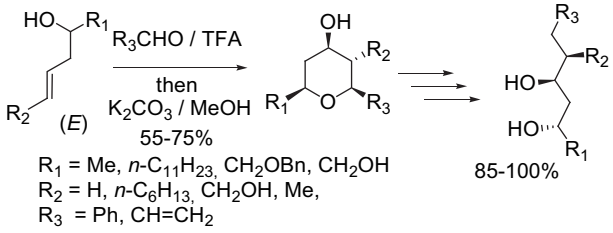
Scheme 80.

In Piva's synthesis of (±)-diospongin A, Prins cyclization enabled control of the relative configuration of the three stereogenic centers contained in the natural product (Scheme 81).[98] Many compounds in the diarylheptanoids family exhibit promising biological activities, and diospongin A is active against osteoporosis. The equatorial hydroxyl group at C4 had to be inverted to obtain the racemic target.



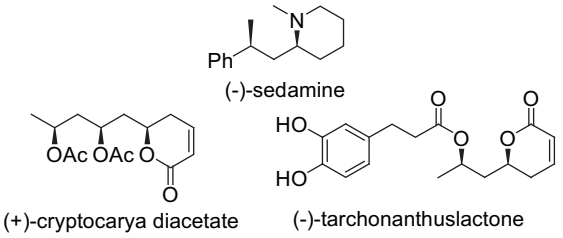
Scheme 81.

Yadav has developed a route to *anti*-1,3-diols from 4-hydroxy-tetrahydropyrans via functional-group interconversions, including ring opening via dealkoxyhalogenation or by dissolving-metal reduction (Scheme 82).[99,100]



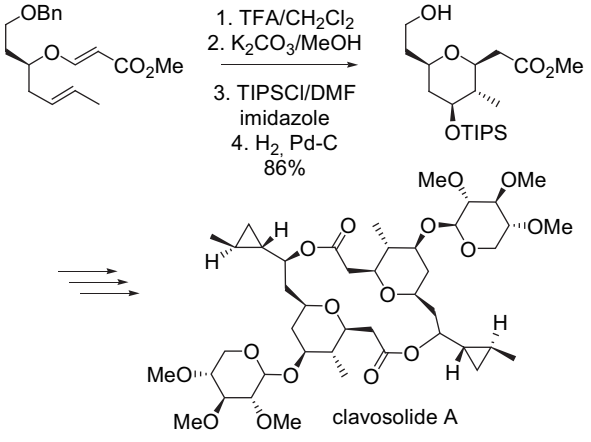
Scheme 82.

These methodologies leading to *anti*-1,3-diols were then applied to the syntheses of (−)-sedamine,[99a] (+)-cryptocarya diacetate,[101] and (−)-tarchonanthuslactone (Scheme 83).[102]



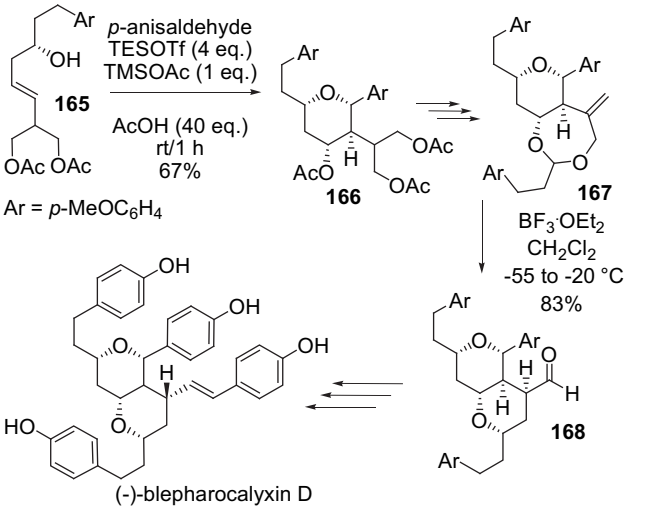
Scheme 83.

The first total synthesis of clavosolide A, isolated from *Myriastra clavosa* marine sponge, was reported by Willis and co-workers.[103] Their strategy was based on the construction of the central tetrahydropyranic unit via Prins cyclization. The latter proved again to be highly effective to introduce three additional stereogenic centers with complete stereocontrol. After functional-group interconversions to set up the lateral chains, the key subunit was dimerized (Scheme 84).



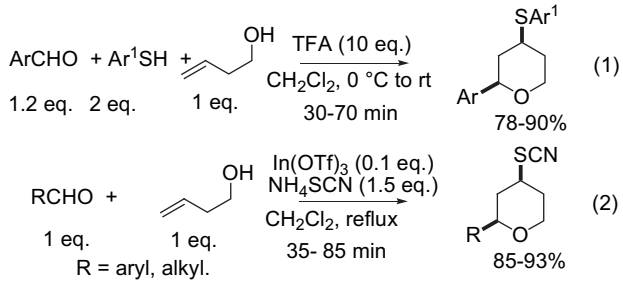
Scheme 84.

(−)-Blepharocalyxin D exhibits interesting activity against colon cancer. Two Prins cyclizations were involved in the synthetic strategy developed by Lee and co-workers (Scheme 85).[104] The reaction of enantiopure homoallylic alcohol **165** with *p*-anisaldehyde led to 4-acetoxy-tetrahydropyran **166** in 67% yield after optimizing Willis's experimental conditions.[66] No racemization was detected. The second Prins cyclization using acetal **167** as the starting material was mediated with $BF_3{\cdot}OEt_2$. It led to an intermediate diol that underwent pinacolic rearrangement to give **168**, a precursor of the natural product.



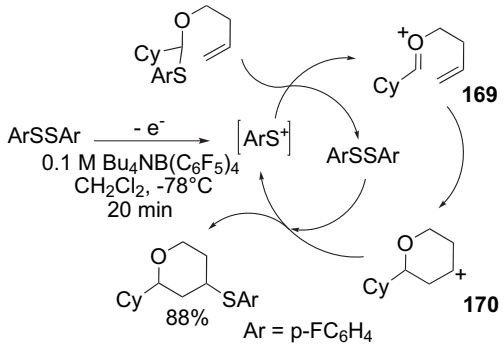
Scheme 85.

3.1.3. Trapping by sulfur-centered nucleophiles. The synthesis of 4-arylthio-tetrahydropyrans has been reported very recently.[105a] A three-component procedure involving an aromatic aldehyde, a homoallylic alcohol and an aromatic or heteroaromatic thiol was developed using trifluoroacetic acid to catalyze the reaction at room temperature. Good yields and all-*cis*-selectivity were reported (Scheme 86, Eq. 1). Other Lewis acids including acetic acid, $BF_3{\cdot}OEt_2$, metal halides, metal triflates, and heterogeneous catalysts such as Montmorillonite KSF clay were found to be ineffective or did not lead to the expected sulfide. This methodology complements previous work from Yadav concerning the introduction of a thiocyanate group in position 4 (Scheme 86, Eq. 2).[105b]



Scheme 86.

An original approach has been proposed by Yoshida and co-workers.[106] The oxocarbenium ion **169** is generated from an *S*,*O*-acetal. According to the author, anodic oxidation would initiate the formation of an ArS^+ cation that reacts with the starting material to generate the disulfide and the oxocarbenium species. After cyclization, the latter would transfer a thiolate to the 4-tetrahydropyranyl cation **170** and regenerate ArS^+, thus promoting a cation chain reaction (Scheme 87).

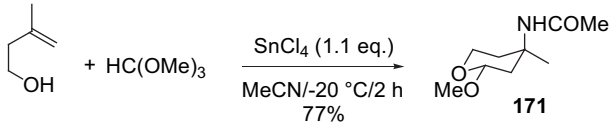


Scheme 87.

3.1.4. Trapping by nitrogen-centered nucleophiles

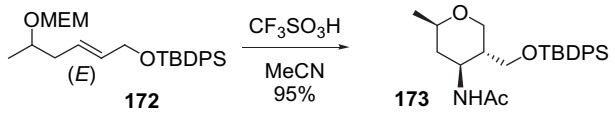
3.1.4.1. Tandem Prins–Ritter reaction: amide formation. There are rather few examples of 4-tetrahydropyranyl carbocation trapping by nitrogen-centered nucleophiles in the literature. Owing to their basicity, most of them are incompatible with the presence of strong Lewis acids. The most frequently encountered examples of C–N bond formation following on from Prins cyclization involve the Ritter reaction.

Perron and Albizati were the first to develop a tandem Prins–Ritter sequence.[107] They have prepared 4-acetamido-pyranosides through $SnCl_4$– mediated reaction of orthoesters with homoallylic alcohols in acetonitrile. As an example, 3-methylbut-3-en-1-ol led to *trans* pyranoside **171** in 77% yield, via reaction with trimethyl orthoformate at −20 °C (Scheme 88). In agreement with Alder's model,[21] the planar tertiary carbocation intermediate led to the *trans* thermodynamic product via axial attack at C4.



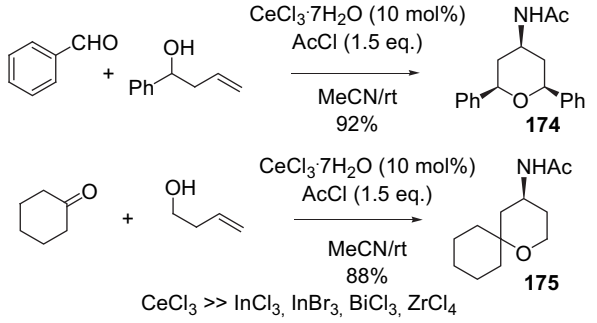
Scheme 88.

Willis[32] and co-workers have cyclized acetal **172** in the presence of triflic acid in acetonitrile. Acetamide **173** was isolated in 95% yield with total control of the diastereoselectivity (Scheme 89). It must be noted that, in the very same article, the authors have amply demonstrated the versatility of Prins cyclization, which can also lead selectively to the 4-halo-tetrahydropyran, or to the corresponding tetrahydropyranols by selecting the appropriate reaction conditions.



Scheme 89.

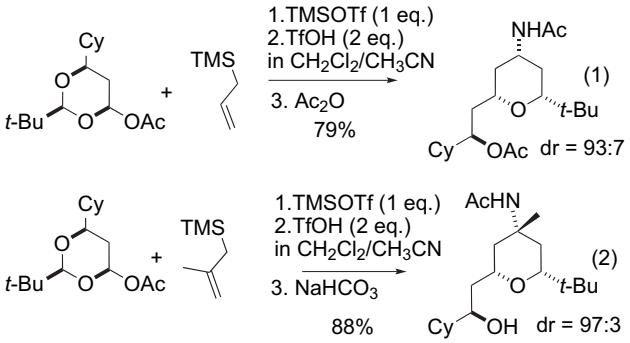
The tandem Prins–Ritter reaction can be promoted by $CeCl_3$ that was shown to be clearly superior to other Lewis acids like $InCl_3$, $InBr_3$, $BiCl_3$, or $ZrCl_4$. However, no reaction occurred with this mediator in the absence of AcCl.[108a,109] Different aromatic aldehydes and ketones were allowed to react with primary or secondary homoallylic alcohols. All led to all-*cis* tetrahydropyrans in yields ranging from 82 to 94%. Examples are given in Scheme 90, e.g., the reaction of benzaldehyde with 1-phenylbut-3-en-1-ol led to **174** in 92% yield. Under the same experimental conditions, cyclohexanone led to the spiranic THP **175** in 88% yield.



Scheme 90.

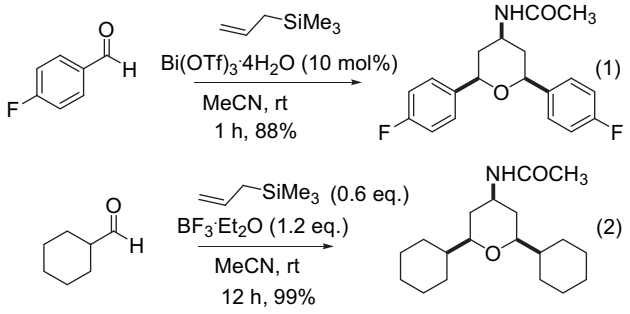
The three-component reaction was recently carried out using 20 mol % of phosphomolybdic acid at ambient temperature.[108b] Bismuth triflate also proved to be an efficient mediator for the Prins–Ritter reaction.[110]

The Sakurai–Prins–Ritter sequence developed by Rovis also led to a variety of 4-acetamido-tetrahydropyrans with high diastereomeric ratios (≥93/7) (Scheme 91, Eq. 1).[111] This multicomponent reaction enables the introduction of structural diversity at C4. A large number of nitriles were tested. Yields ranged between 42 and 89%. As shown in Eq. 2, it is possible to control the stereoselective formation of tetrasubstituted derivatives.



Scheme 91.

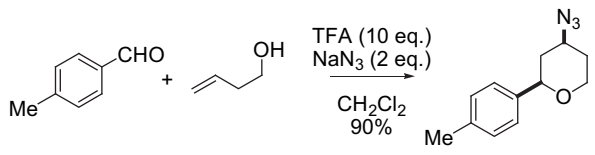
As exemplified in Scheme 92, the multicomponent domino reaction involving allyltrimethylsilane, and an aldehyde in the presence of a variety of nitriles, led to symmetrical 2,6-dialkyl- or to 2,6-diaryl-4-amido-tetrahydropyrans. The catalyst could be either bismuth triflate (Eq. 1)[112a] or boron trifluoride (Eq. 2).[112b]



Scheme 92.

3.1.4.2. Trapping with azides. Yadav has recently reported a multicomponent procedure involving an aldehyde, a homoallylic alcohol and sodium azide.[113] Yields are high and diastereoselectivity is total (Scheme 93). According to the authors, under these experimental conditions, HN_3 is generated in situ from trifluoroacetic acid and NaN_3. Trifluoroacetic acid is absolutely

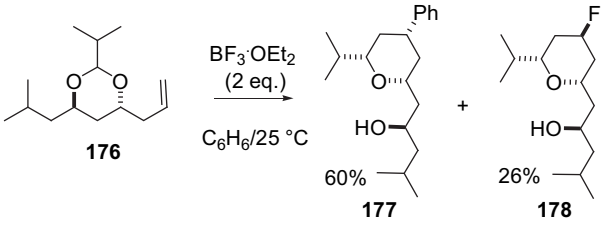
necessary, since non-protonic Lewis acids like $InCl_3$, $BiCl_3$, $ZrCl_4$, or even $Sc(OTf)_3$ do not mediate this cyclization.



Scheme 93.

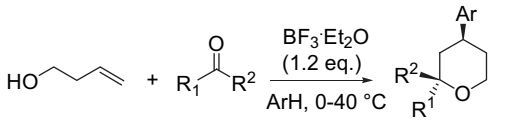
The methodology was recently improved by avoiding the use of strongly acidic conditions and explosive sodium azide. Trimethylsilyl azide and 10 mol % phosphomolybdic acid in dichloromethane gave high yields of the expected 4-azido-tetrahydropyrans at room temperature.[114]

3.1.5. Trapping with carbon-centered nucleophiles: Tandem Prins–Friedel–Crafts reaction. While studying the reactivity of 4-allyl-1,3-dioxan **176** in benzene, Rychnovsky and co-workers have isolated, besides the fluoride **178**, an unexpected product: 4-phenyl-tetrahydropyran **177** resulting from a Friedel–Crafts reaction between the intermediate cyclic carbocation and benzene (Scheme 94).[115] As encountered previously in this strategy, the 'masked aldehyde' was covalently linked to the homoallylic alcohol moiety via an acetal function.



Scheme 94.

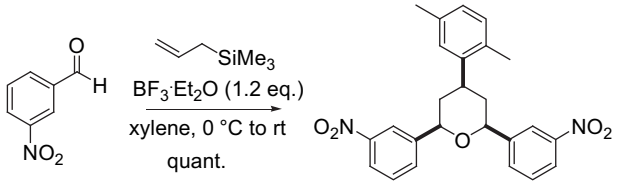
The scope of the one-pot three-component procedure was investigated at 0 °C with BF_3•OEt_2 as the catalyst. Yields ranged from 63 to 95% with aldehydes, while lower yields ranging from 40 to 56% were obtained with ketones.[116a] Selected examples are given in Scheme 95.



R^1	R^2	ArH	Yield (%)
H	*p*-$O_2NC_6H_4$	benzene	90
H	*p*-$MeOC_6H_4$	benzene	65
H	*m*-$O_2NC_6H_4$	*p*-xylene	80
CH_2Cl	CH_2Cl	benzene	50

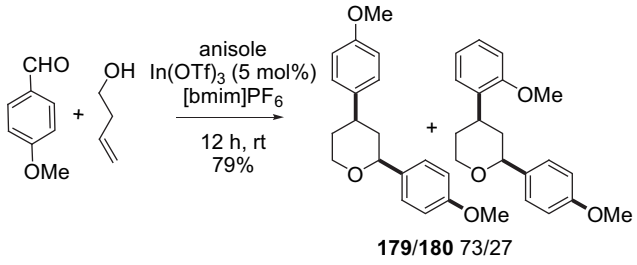
Scheme 95.

The multicomponent domino process involving Sakurai–Prins cyclization-Friedel–Crafts reactions was designed under similar conditions (Scheme 96).[116b]



Scheme 96.

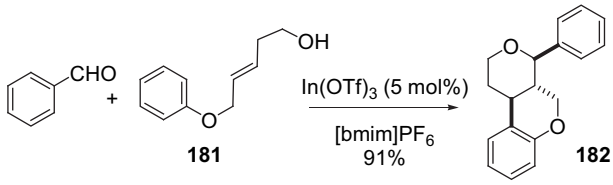
Tandem Prins–Friedel–Crafts reaction was also investigated in ionic liquids by Li in view of the synthesis of 2,4-diaryl-tetrahydropyrans.[117] As shown in Scheme 97, in this reaction mediated with indium(III) triflate, a 4-tetrahydropyranyl carbocation was trapped by anisole. When the reaction was achieved in $[bmim]PF_6$, in the presence of 5 equiv of anisole, it led to *para*- and *ortho*-regioisomers **179** and **180** in a 73/27 ratio in 79% overall yield. It is important to point out that the anion associated with the Lewis acid must be a poor nucleophile.



Scheme 97.

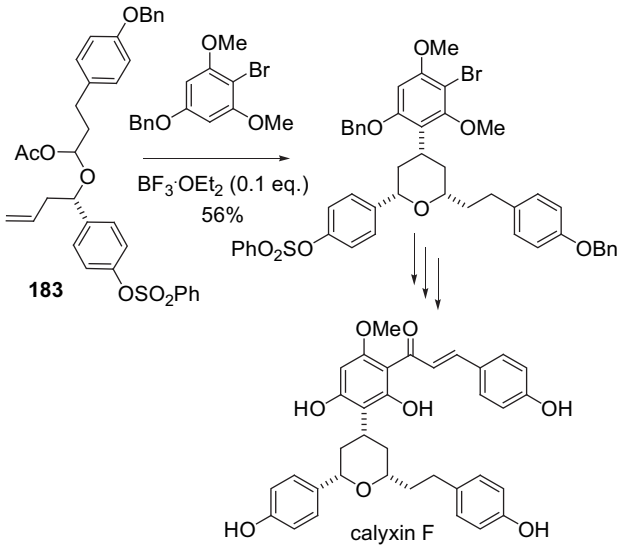
The use of the imidazolium salt as solvent, completely suppressed the competitive trapping of the intermediate cyclic carbocation by the homoallyl alcohol, that was even observed when the reaction was carried out in methanol.

An intramolecular Friedel–Crafts reaction was used to prepare the tricyclic compound **182** (a subunit present in the structure of calyxin I) from the alcohol **181** and benzaldehyde (Scheme 98).[117]



Scheme 98.

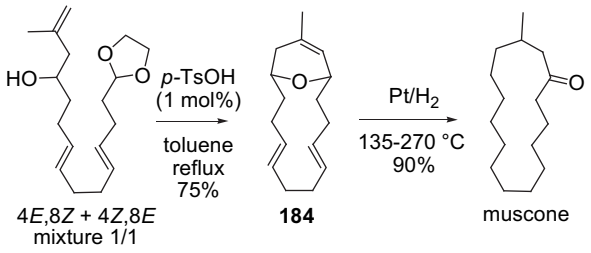
As exemplified in Scheme 99, the Prins-Friedel–Crafts strategy was recently applied by Rychnovsky to the syntheses of calyxins F and L from α-acetoxyether **183**.[118]



Scheme 99.

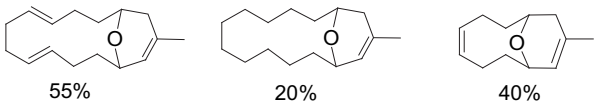
3.1.6. Intramolecular Prins cyclization leading to bridged bicyclic ethers. There are few examples of 'intramolecular' reactions leading to bridged bicyclic tetrahydropyrans.

This type of process was used by Ohloff for the synthesis of muscone via the bridged bicyclic ether **184** (Scheme 100).[119]



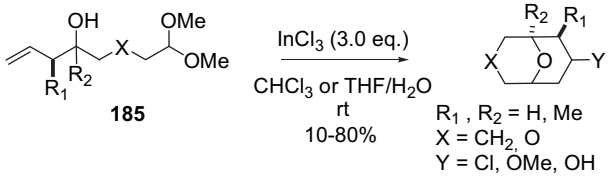
Scheme 100.

The same procedure was extended to the preparation of the bridged macrocycles shown in Scheme 101, but the yields were modest. The presence of the methyl group on the double bond proximal carbon atom is required for the cyclization to proceed.



Scheme 101.

9-Oxabicyclo[3.3.1]nonanes and 3,9-dioxabicyclo[3.3.1]nonanes were similarly obtained via $InCl_3$-mediated Prins cyclization of hydroxy-acetals **185** (Scheme 102).[120]



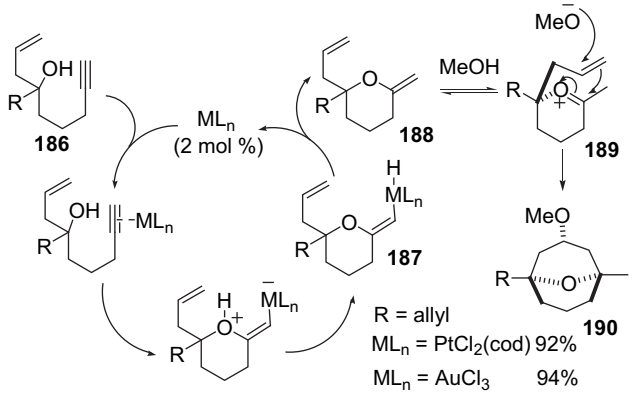
Scheme 102.

Tandem gold- or platinum-promoted cycloisomerization/Prins cyclization leading to bridged bicyclic tetrahydropyrans has been devised by Barluenga and co-workers.[121] As an example, homoallylic alkynol **186** led to bicylic ether **190,** via enol ether **188**, in 92–94% yield (based on recovered starting material). A mechanism involving activation of the triple bond, through coordination with gold or platinum, followed by intramolecular addition of the hydroxy group leads to metal hydride **187** after proton transfer. Reductive elimination regenerates the catalytic species and produces **188** precursor of the oxocarbenium ion **189** (Scheme 103). The corresponding acetate was isolated in similar yields when replacing methanol by acetic acid in the presence of a Pt(II) catalyst.[122]

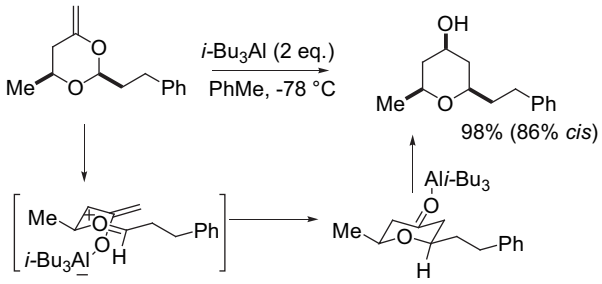
3.2. Cyclization involving electron-rich double bonds

More nucleophilic than simple alkenes, functionalized double bonds like enol ethers, ene-carbamates, allylsilanes and vinylsilanes have also been involved in Prins cyclizations. Depending on the nature of the double bond, the reaction can lead to pyranones, dihydropyrans, or methylenetetrahydropyrans.

3.2.1. Cyclization involving enol ethers and ene-carbamates. Petasis has shown that, after methylenation, 1,3-dioxan-4-ones reacted with triisobutylaluminum to generate an oxocarbenium intermediate that cyclized onto the aluminum enolate formed concomitantly. The alternative possible pathway proceeding through an oxonia-Cope rearrangement was discarded. The reaction afforded substituted tetrahydropyranols in high yields (Scheme 104).[123]

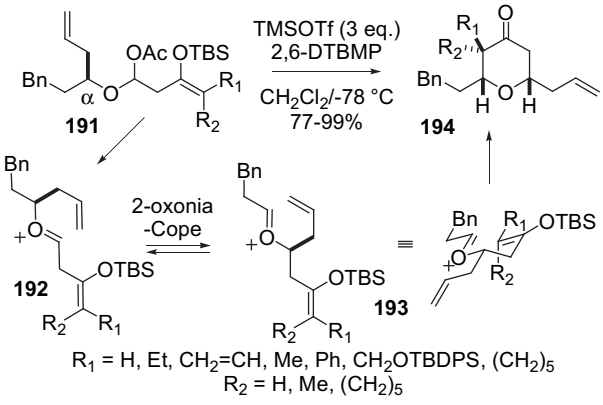


Scheme 103.



Scheme 104.

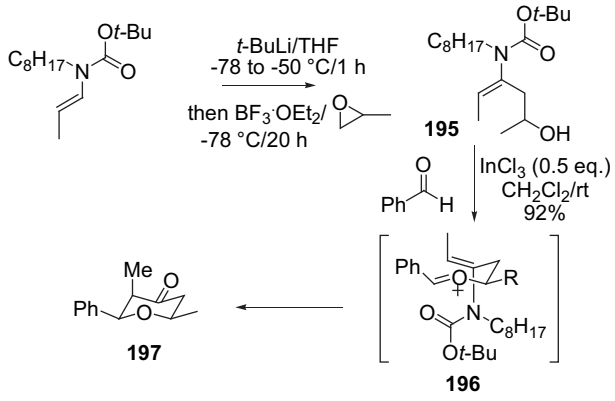
A general route to tetrahydropyranones using enol ethers was devised by Rychnovsky.[124] Owing to an oxonia-Cope rearrangement, the carbocations **192** generated from acetoxyethers **191** are in equilibrium with the cations **193** (Scheme 105). The Prins cyclisation process involving the enol ether moiety is much faster than that involving the terminal alkene. The reaction proceeds, via the former, to give the pyranone **194** (for related example, see Ref. 26). It must be emphasized that the tandem oxonia-Cope–Prins cyclization pathway implies inversion of the stereogenic center (Cα).



Scheme 105.

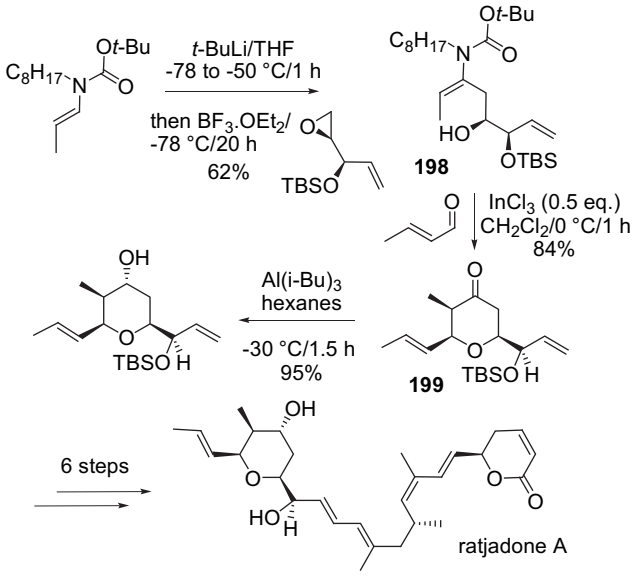
Ene-carbamates such as **195** can participate in a Prins cyclization process. The synthesis of these carbamates can be achieved in two steps. As exemplified in Scheme 106, the reaction of **195** with benzaldehyde led to trisubstituted 2,3,6-*cis*,*cis*-tetrahydropyran-4-

one **197**.[125] The diastereoselectivity resulted from the preferred *E* configuration of the double bond and from the favoured chair transition state for the cyclization of the oxocarbenium ion **196**.



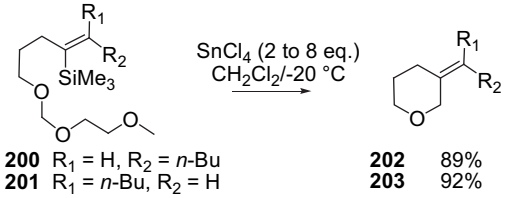
Scheme 106.

Funk and co-workers have proposed a formal synthesis of (+)-ratjadone A, via **198** that was prepared according to the above methodology. Again, two different double bonds could trap the oxocarbenium ion. The ene-carbamate reacted much faster to give chemoselectively **199** (Scheme 107).[125]



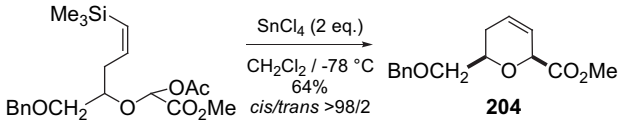
Scheme 107.

3.2.2. Cyclization involving vinylsilanes and vinylstannanes. Overman was the first to investigate the cyclization of MEM acetal-derived oxocarbenium ions onto vinylsilanes. According to Scheme 108, treatment of **200** and **201** by $SnCl_4$ led stereospecifically to **202** and **203** in 89 and 92% yield, respectively.[126]



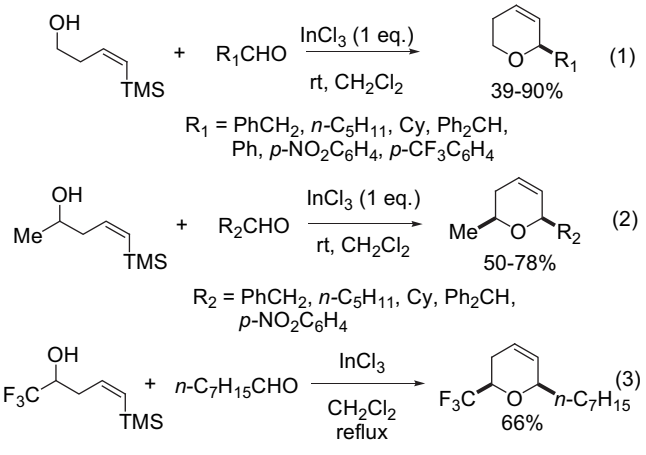
Scheme 108.

Speckamp and co-workers have reported the cyclization of a vinyl silane onto an oxocarbenium ion. The carbocations were generated from α-acetoxyethers, prepared from glyoxal and homoallyl alcohol bearing a TMS group on the terminal carbon of the *Z* or *E* double bond.[127] As shown in Scheme 109, the reaction led to dihydropyran **204**. The diastereoselectivity was remarkably high when starting from the *Z*-isomers.



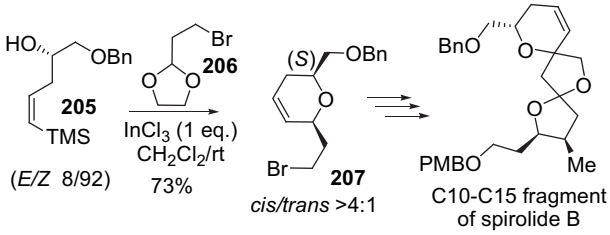
Scheme 109.

Dobbs and Martinović have extended the silyl-Prins methodology to various aldehydes (Scheme 110, Eq. 1).[128] The reaction can be carried out at room temperature, in the presence of indium trichloride that can be used either in a stoichiometric or catalytic amount. It should be noted that other Lewis acids, like $BF_3{\cdot}OEt_2$ or TMSOTf, also led to high yields but these reactions had to be carried out at −78 °C. As in the previously cited Li's report,[9] these authors have shown that the use of an epoxide as starting material is an alternative to the use of an aldehyde (Eq. 2). The procedure was recently extended to the preparation of trifluoromethylated heterocycles. However, owing to the reduced nucleophilicity of the homoallylic alcohol, elevation of the reaction temperature up to reflux of dichloromethane, and longer reaction times (on average 48 h), were necessary to reach acceptable yields (Eq. 3).[129]



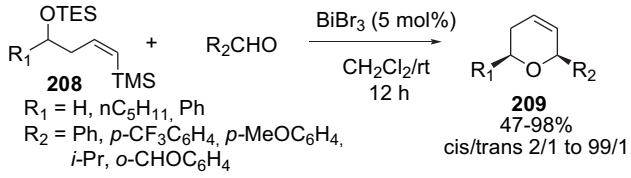
Scheme 110.

Brimble has prepared the dihydropyran unit present in spirolides B and D via this modification of the Prins cyclization.[130] *Z*-Alcohol **205**, bearing a TMS group in the terminal position, was allowed to react with acetal **206** to obtain **207** as a mixture of *cis* and *trans* isomers in a ratio exceeding 4/1 (Scheme 111).



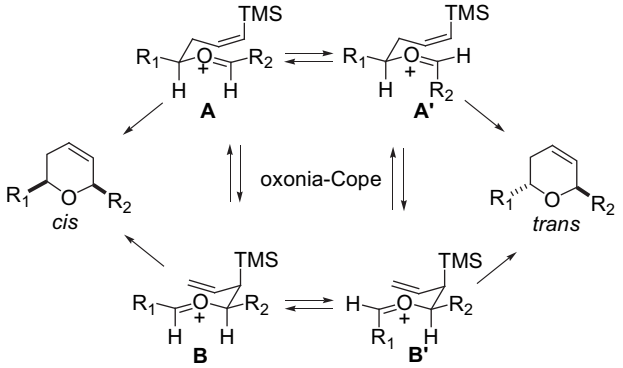
Scheme 111.

The silyl-Prins methodology was also adapted by Hinkle to the cyclization of δ-triethylsilyloxy-vinyltrimethylsilanes **208**, using $BiBr_3$ as catalyst.[131] The silylated alcohol was deprotected in situ. 2,6-Disubstituted dihydropyrans **209** were isolated in yields ranging from 47 to 98% (Scheme 112). Both the diastereoselectivity and yield depended strongly on the structure of the aldehyde. These were good to high as far as aliphatic aldehydes were involved. Conversely, with aromatic aldehydes the reactivity was influenced by the subtituents on the aromatic ring. *cis/trans* ratios varied from 2/1 to 99/1, depending on whether the aromatic was electron rich or poor.



Scheme 112.

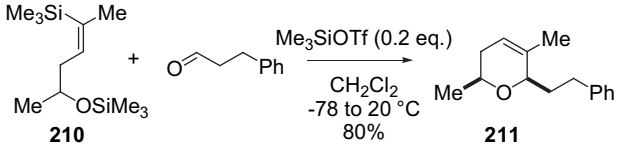
The data were rationalized taking again into account chair-like transition states for the cyclization of the oxocarbenium ion, where the TMS group is axial due to stereoelectronic factors. In this orientation, the electrons of the C–Si σ bond bring an optimal stabilization to the incoming positive charge on the carbon atom β to silicon.[132] These transition states equilibrate via an oxonia-Cope rearrangement and partially restricted rotations around the C–O bonds (Scheme 113). Transition states **A** and **B**, where 1,3-diaxial interactions are minimized since both alkyl groups are equatorial, are favoured.



Scheme 113.

In the presence of electron-donating substituents, the cyclization of **A** is slowed down and isomerization can occur, which opens up routes to *trans* isomers. Interconversions of **A** into **A′**, and of **B** into **B′**, are promoted by steric decompression, since the TMS group and R^2 are no more in a *cis* relationship. The balance between electronic and steric effects determines the diastereomeric ratio.

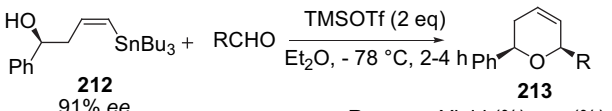
Dihydropyrans **211** bearing a trisubstituted double bond were prepared by Markó from the protected alcohol **210** (Scheme 114).[133]



Scheme 114.

A similar approach was applied to the synthesis of bicyclic ethers from *C*-glycosides.[134]

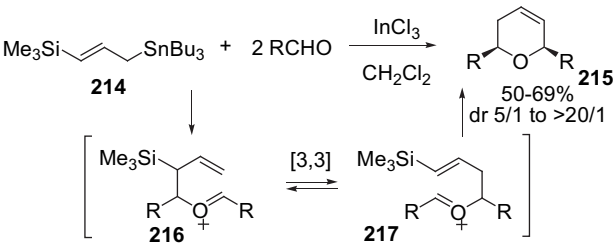
As shown in Scheme 115, *Z*-vinylstannane **212** led similarly to 2,6-disubstituted-dihydropyrans **213**, in high yield and without racemization, by reacting with both aliphatic and aromatic aldehydes in the presence of TMSOTf.[135]



R	Yield (%)	*ee* (%)
Ph	95	91
$Ph(CH_2)_2$	80	87

Scheme 115.

3.2.3. Cyclization involving allylsilanes. A multicomponent procedure involving tandem allylation-Prins cyclization was designed by Li for the synthesis of symmetrical *cis*-2,6-dialkyl-dihydropyrans **215**.[136] The reaction was promoted by indium trichloride, and the allylating agent **214** was used to generate in situ the silylated homoallylic alcohol. Only aliphatic aldehydes gave satisfactory results (Scheme 116).

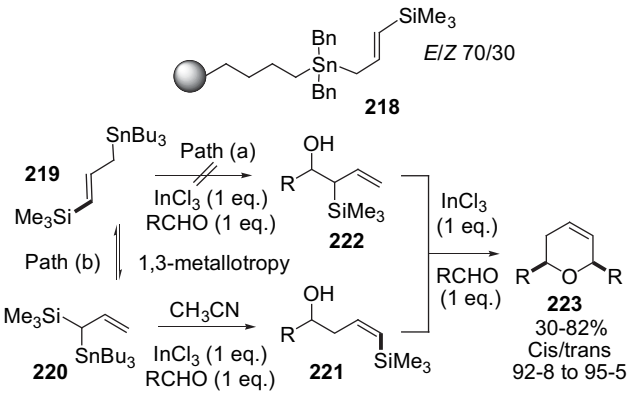


Scheme 116.

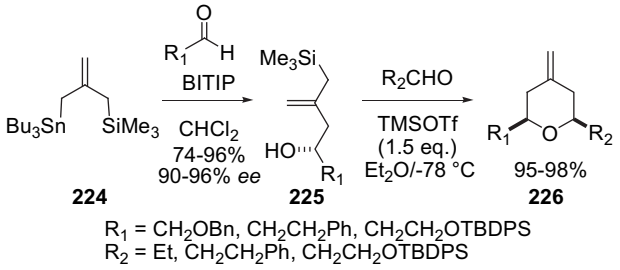
It must be underlined that the oxocarbenium intermediate **216** containing the allylsilane moiety can be converted into **217** containing a vinylsilane moiety via a sigmatropic [3,3]-rearrangement. Thus, the cyclization might as well proceed via the latter.

The synthesis of γ-trimethysilyldibutylallylstannane **218** grafted on an insoluble macroporous polymer has recently been reported.[137] This bimetallic reagent afforded both symmetrical and unsymmetrical *cis*-2,6-tetrahydropyrans in moderate yields, when reacting with aldehydes in the presence of indium trichloride. Mechanistic studies performed on the ungrafted reactant have shown that the reaction proceeded via 1,3-metallotropy leading to **220**, precursor of the alcohol **221**, from **219** (path (b)). Alcohol **222** that would result from path (a) was not detected. Subsequent reaction of **221** with a second equivalent of aldehyde led to **223** (Scheme 117). The reaction proceeded within 2–5 h in CH_2Cl_2 at room temperature or in acetonitrile at 60 °C. The product contained less than 20 ppm of organotin residues. The recovered resin could be re-used without significant loss of activity.

Asymmetric Keck allylation using silyl-allylstannane **224** and a BINOL/Ti(O*i*Pr)$_4$ (BITIP) catalyst was applied to prepare homoallylic alcohols **225** in high enantiomeric excess. The latter were allowed to react with another aldehyde in the presence of TMSOTf to prepare 4-*exo*-methylene-2,6-dialkyltetrahydropyrans **226** (Scheme 118).[138] It must be noted that the choice of the proper solvent is very important, and when dichloromethane was replaced by diethyl ether, by-products with endocyclic double bonds were formed.

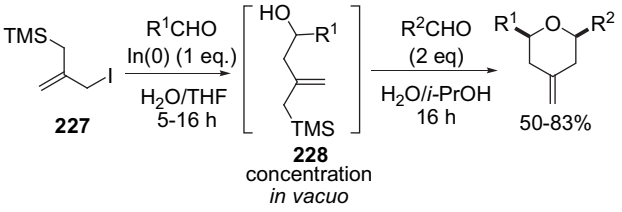


Scheme 117.



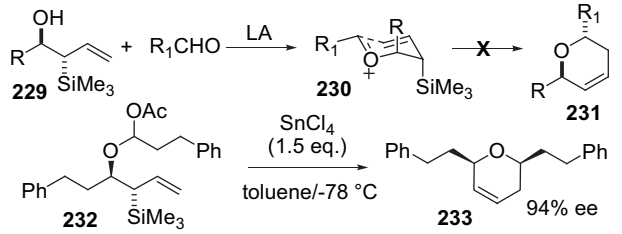
Scheme 118.

A strategy involving indium-mediated Barbier allylation to generate in situ homoallylic alcohol **228** from **227**, and subsequent, one-pot InI-mediated silyl-Prins cyclization to give 4-methylene-2,6-di-substituted-tetrahydropyrans, has been reported recently (Scheme 119).[139] The reaction was extended to the preparation of unsymmetrical derivatives, by changing the solvent between the two steps, in order to avoid incomplete consumption of the first added aldehyde.



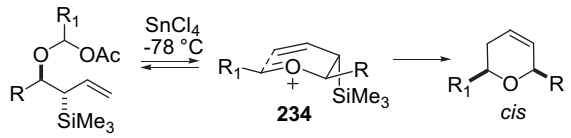
Scheme 119.

The control of diastereoselectivity is of prime importance for any application to total synthesis. Despite predictions based on the stereoelectronic effects of the TMS group,[132] the reaction of alcohol **229** with aldehydes did not proceed via transition state **230** where the silicon atom is axial, and therefore did not lead to dihydropyran **231** (Scheme 120).[140] Roush and co-workers have shown that the $SnCl_4$-mediated cyclization of α-acetoxyether **232** led to the *cis* isomer of dihydropyran **233** with retention of configuration.



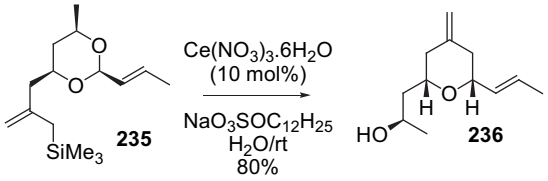
Scheme 120.

According to the authors, the cyclization would proceed through a boat transition state **234** where the vicinal bulky groups are *trans*, while the axial TMS group participates in the stabilization of the incoming positive charge at the β-carbon (Scheme 121).



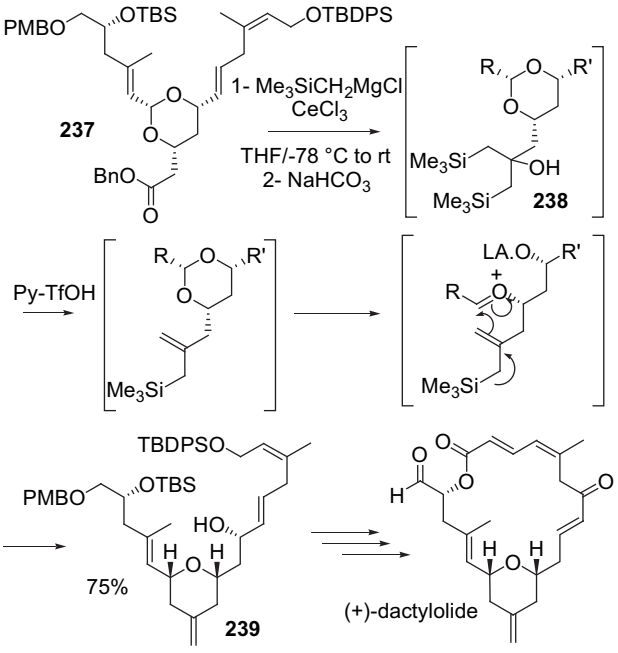
Scheme 121.

Unsaturated 1,3-dioxanes such as **235** derived from α,β-unsaturated aldehydes, and bearing an allylsilane moiety in the appropriate position can also be used as precursors for oxocarbenium ions. They lead to 2-vinyl-4-*exo*-methylene-tetrahydropyrans via Prins cyclization.[141] An original methodology using a micellar Lewis acid in water was developed. The colloidal suspension protects the oxocarbenium ion from hydrolysis, and favours the cyclization. As exemplified in Scheme 122, under these experimental conditions, **235** led to **236** in 80% yield.



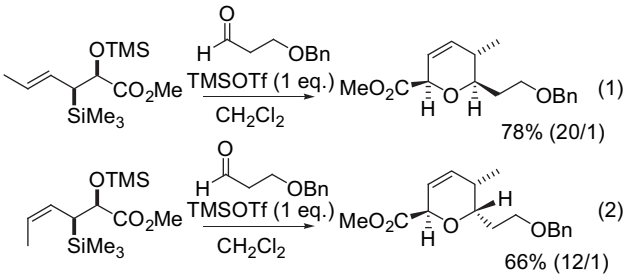
Scheme 122.

Floreancig and co-workers have applied this strategy in their total synthesis of (+)-dactylolide.[142] As reported in Scheme 123, acetal **238** was generated in situ from ester **237** via reaction with Me_3SiCH_2MgCl in the presence of $CeCl_3$. After quenching the reaction with aqueous $NaHCO_3$, the crude tertiary alcohol was subjected to pyridinium triflate and $MgSO_4$ to effect sequential Peterson olefination and Prins cyclization. This led to the 4-*exo*-methylene-tetrahydropyran unit (**239**) of the target molecule.



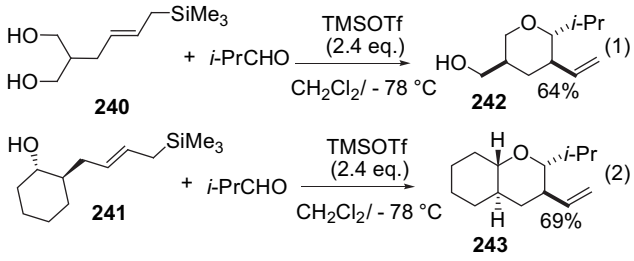
Scheme 123.

Panek and co-workers have also engaged protected homoallylic alcohols containing an allylsilane moiety in Prins cyclizations.[143] This strategy, to prepare 2,5,6-trisubstituted-dihydropyrans, was applied to the synthesis and evaluation of a library of bistramide A stereoisomers (Scheme 124).[143b] The diastereoselectivity of the cyclization step is controlled by the *E* (Eq. 1) or *Z* (Eq. 2) geometry of the crotylsilane moiety.



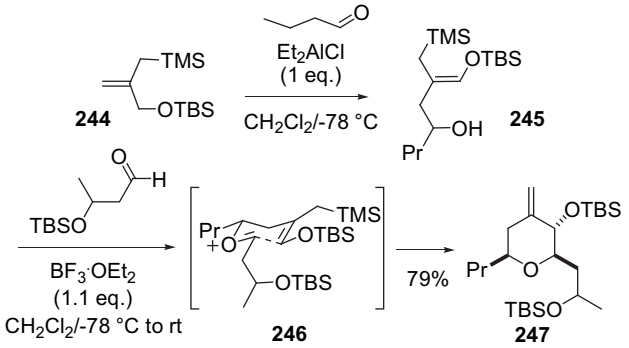
Scheme 124.

Szabó has also taken advantage of the two functionalities in alcohols **240** and **241** for the synthesis of 3-vinyl-tetrahydropyrans **242** and octahydrochromenes **243**, respectively (Scheme 125, Eqs. 1 and 2).[144]



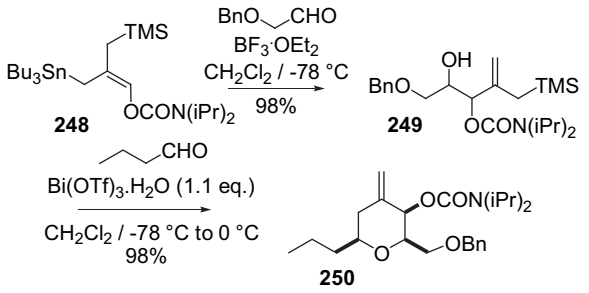
Scheme 125.

Markó has designed a sequence named IMSC (IntraMolecular Sakurai Cyclisation), to prepare *exo*-methylene-tetrahydropyrans bearing a protected hydroxyl group in position 3.[145] Homoallylic alcohol **245** was prepared by an ene reaction between butyraldehyde and allylsilane **244**. The BF_3•OEt_2-mediated Prins cyclization was completely chemo- and diastereo-selective. It proceeded via a chair transition state **246** to afford the exo-methylene-tetrahydropyran **247** in 79% yield (Scheme 126).



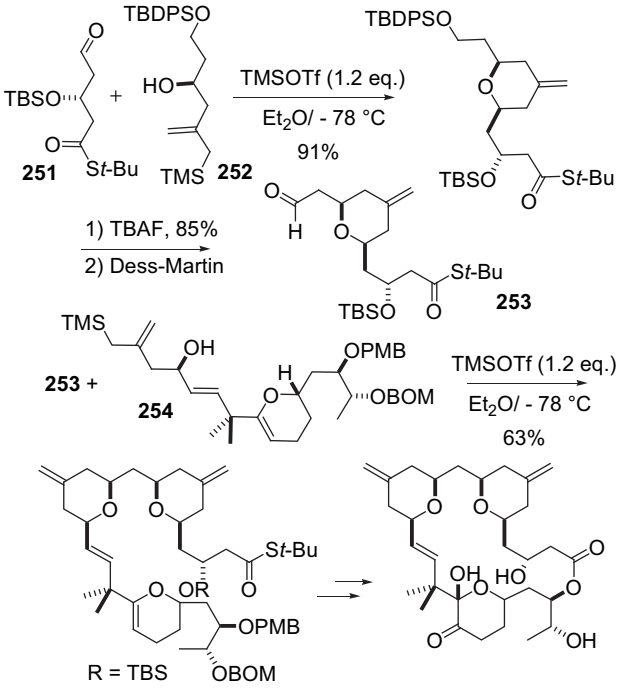
Scheme 126.

Another strategy, from the same research group, involves allylstannation using **248** to form the homoallylic alcohol **249**.[146] Prins cyclization, mediated with bismuth triflate, leading to **250** was again totally stereoselective (Scheme 127).



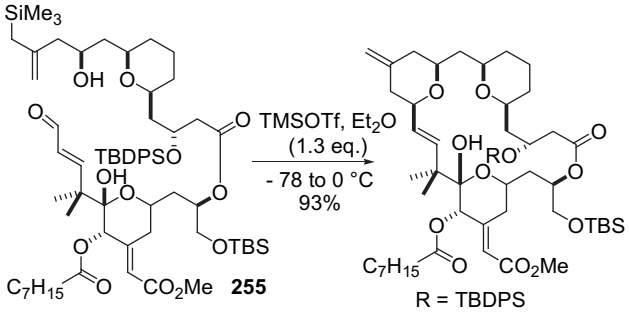
Scheme 127.

Both Keck's,[147] and Wender's[148] groups have used pyran annulation via Prins cyclization to prepare bryostatin analogues. As illustrated in Scheme 128, two successive silyl-Prins annulations were devised by Keck to build rings A and B of the biologically active compound. Ring A was prepared from hydroxysilane **252**, and aldehyde **251**. The second ring was formed from **253** and hydroxysilane **254**.



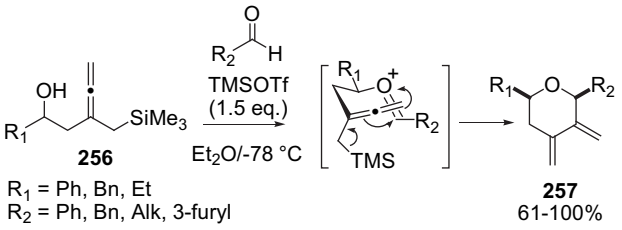
Scheme 128.

In the closely related strategy used by Wender and coworkers,[148] it is the macrocyclization that was achieved via Prins cyclization of **255**, according to Scheme 129.



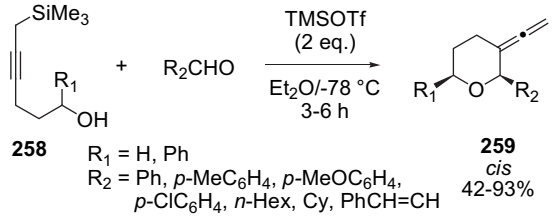
Scheme 129.

3.2.4. Cyclization involving other silylated derivatives. There are very few examples of Prins cyclizations involving allenes, and the case of simple allenes will be discussed in Section 3.3. The reactivity of allenyl silanes was investigated by Chang and co-workers in 2003. Homoallenyl alcohols **256** led to tetrahydropyranyl derivatives **257** with two vicinal *exo*-methylene groups at C3 and C4 (Scheme 130).[149a] The reaction was extended to the synthesis of oxabicycles.[149b]



Scheme 130.

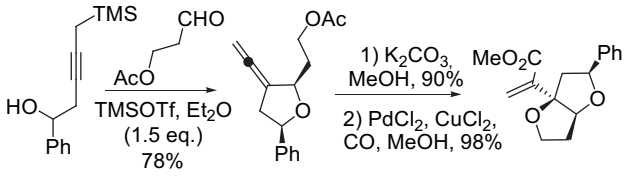
When alcohols **258** containing a propargylsilane moiety were engaged with various aldehydes in a Prins cyclization process, 3-vinylidene-2,6-disubstituted-tetrahydropyrans **259** were formed in yields ranging from 42 to 93% via 6-*exo* ring closure (Scheme 131).[150] In most cases, the diastereomeric ratio was excellent in favour of the *cis* isomer. This is likely to be due to the preferential formation of *E*-oxocarbenium ions.



Scheme 131.

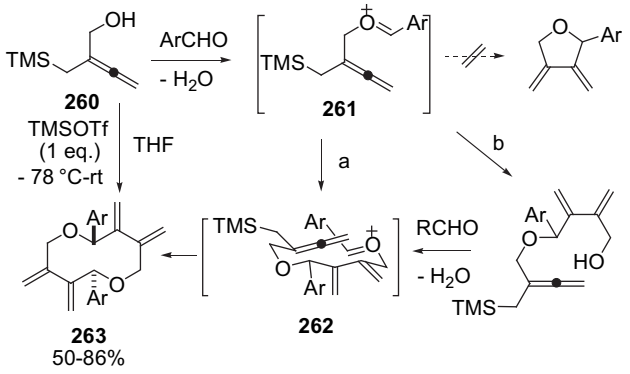
The same experimental conditions were applied to the synthesis of vinylidene-oxepanes from homologous propargylsilanes.[150b]

Although it lies beyond the scope of the present review devoted to six-membered ring closure, it must be noted that homopropargyl alcohols bearing a propargylsilane moiety undergo 5-*exo* ring closure to give 3-allenyl-tetrahydrofurans. Sterically congested bicyclic tetrahydrofurans are available from these synthons via subsequent Pd(II)-mediated cyclization (Scheme 132).[151]



Scheme 132.

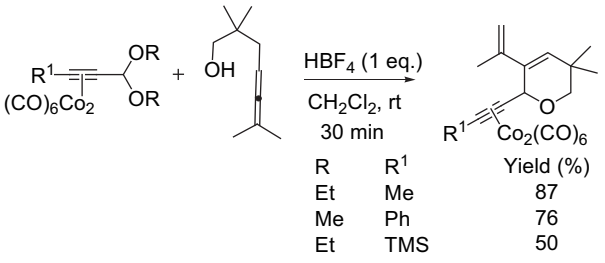
Allenyl alcohols were recently involved in *intermolecular double Prins cyclization* to prepare 1,6-dioxadecanes.[152] As shown in Scheme 133, the 5-*endo-trig* cyclization mode being disfavored, oxocarbenium intermediate **261** underwent either dimerization (path a) or intermolecular addition to **260**, followed by condensation with a second molecule of aldehyde (path b) to give **263** through **262**. The macrocycles were formed in yields ranging from 50 to 85% with a variety of aromatic aldehydes (2- and 4-nitrobenzaldehyde did not react).



Scheme 133.

3.3. Cyclization involving allenes

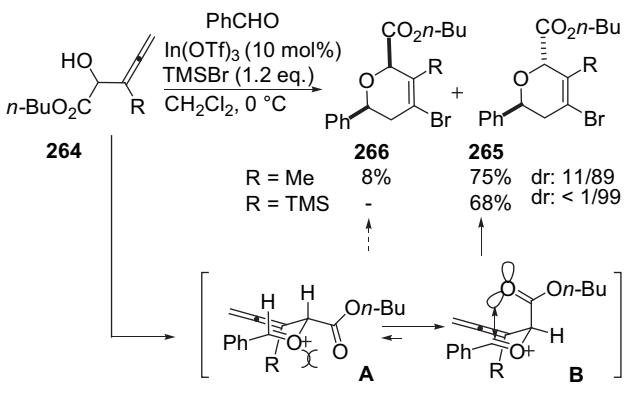
Prins cyclizations involving allenes, were reported in the already mentioned investigation of the reactivity of dicobalt hexacarbonyl complexes of 2-alkynyl acetals.[33] As exemplified in Scheme 134, experiments performed with homoallenyl alcohols led to conjugated dienes in yields ranging from 50 to 87%.



Scheme 134.

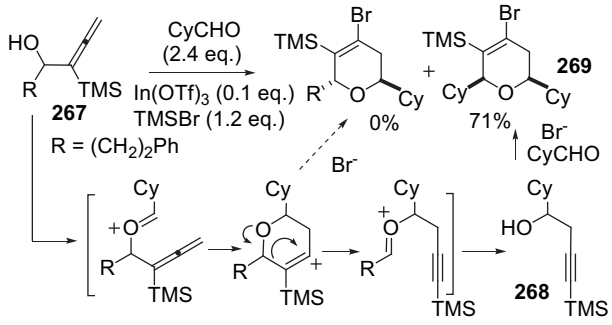
Whereas primary allenyl alcohols did not lead to any cyclization product when reacting with complexed alkynyl acetals, a very recent report by Loh and co-workers established that aliphatic aldehydes and benzaldehyde reacted with secondary gem-disubstituted carboalkoxyl allenic alcohols **264**, in the presence of $In(OTf)_3$ and TMSBr as a source of nucleophilic bromide, to give 2,6-*trans*-dihydropyrans **265** in high yields.[153]

As shown in Scheme 135, the formation of the *cis* isomers **266** is hindered by steric interaction between R and the carboxylate group in transition state **A**. A cyclization through the distorted chair transition state **B** was proposed to rationalize the diastereoselectivity. In the latter, 1,3-diaxial interaction between the carboxylate and the oxocarbenium ion hydrogen atom is counterbalanced by a favourable interaction between the oxygen lone pair and the positive charge.[154]



Scheme 135.

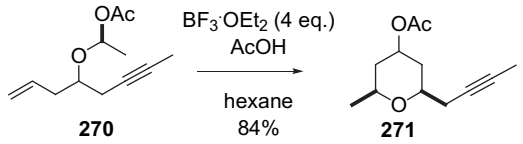
When the alkoxycarbonyl group was replaced by an alkyl chain (alcohol **267**), 2 equiv of cyclohexanecarboxaldehyde were found to lead exclusively to the *cis* derivative **269**.[153] In this case, the formation of the homopropargyl alcohol **268** through an oxonia-Cope rearrangement would occur (Scheme 136).[155] The electron-withdrawing substituent in the alcohol **264** would preclude the rearrangement.



Scheme 136.

3.4. Cyclization involving triple bonds

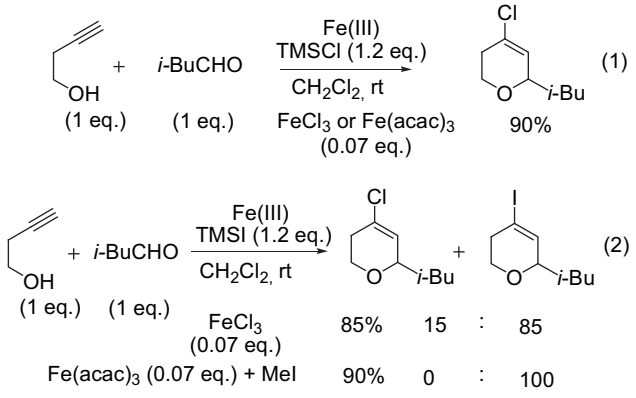
In their very thorough investigation of the Prins cyclization mechanism, Rychnovsky and co-workers have shown that a terminal alkene is more reactive than an alkyne.[11] As exemplified in Scheme 137, 4-acetoxy-tetrahydropyran **271** was the only product isolated, in 84% yield, from the cyclization of acetoxyether **270**.



Scheme 137.

However, when no other trap can compete, the oxocarbenium ion undergoes 6-*endo*-dig cyclization on the terminal triple bond. The very first examples of this type of Prins cyclization were reported by Thompson[36b,c] and by Speckamp.[23a]

More recently, Martin has also explored the synthetic potential of cyclizations involving homopropargylic alcohols (Scheme 138). Reactions mediated with anhydrous $FeCl_3$ or $FeBr_3$ led to 4-halo-2-alkyl-5,6-dihydro-2*H*-pyrans in yields ranging from 30 to 98%.[156,157] Optimization of the experimental conditions have established that the best source of halide anion was TMSX (1.2 equiv) in the presence of 7 mol% of the iron catalyst FeX_3 (Eq. 1). Interestingly, $Fe(acac)_3$, that is less hygroscopic and easier to handle than iron

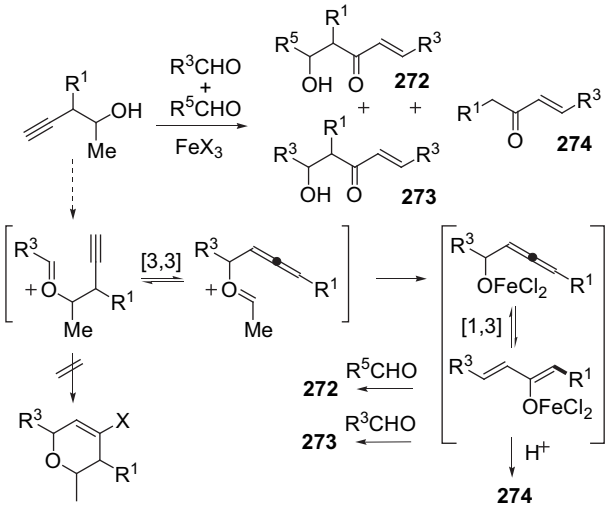


Scheme 138.

trichloride was as efficient as iron(III) halides. Association of the latter with TMSI and MeI, enabled the selective synthesis of the corresponding vinyl iodides (Eq. 2).[158]

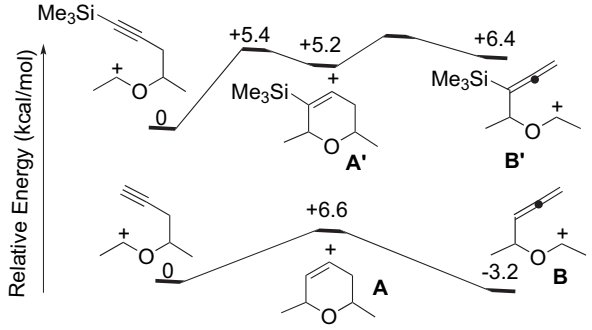
The cyclization could also be mediated with $InCl_3$ and $InBr_3$, but the times of reaction were much longer (a few hours instead of a few minutes) and the yields were slightly lower. The best solvents were shown to be halogenated coumponds, i.e., dichloromethane and 1,2-dichloroethane (or the corresponding bromides). Since halogen exchange was observed, care must be taken to select the solvent appropriate to the nature of the halide.[159] Vinyl iodides were obtained with iodine as mediator.[55b]

A serious drawback was encountered by Martín, Ramírez, Padrón, and co-workers, when they tried to apply Fe(III) catalysis to the synthesis of 2,6-dialkyl derivatives from secondary homopropargylic alcohols. As exemplified in Scheme 139, α,β-unsaturated ketones **272**, **273** and **274** resulting from a competitive 2-oxonia-Cope rearrangement were obtained as the major products. No trace of a Prins-type product was detected.[157e]



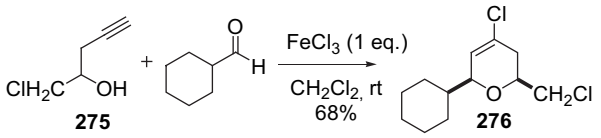
Scheme 139.

The problem could be overcome by silylating the triple bond.[157b] Theoretical DFT calculations established that a TMS group destabilizes allenyloxocarbenium ions (**B'**/**B**) and stabilizes the intermediate dihydropyranyl cation (**A'**/**A**) (Scheme 140). This is in agreement with the result reported in Scheme 136.



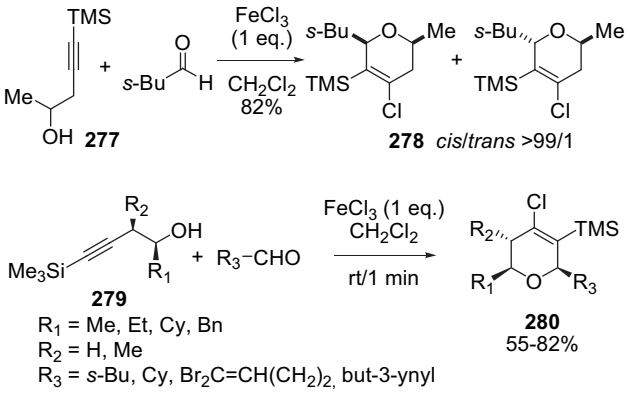
Scheme 140.

Destabilizing the allenyloxocarbenium species could also be achieved by replacing the methyl group at the α-position by CH_2Cl in the secondary carbinol.[160] Unprotected secondary alcohol **275**, bearing an electron-withdrawing group, led to functionalized 3,4-dihydropyran **276** in a satisfying yield with an excellent diastereoselectivity (Scheme 141).



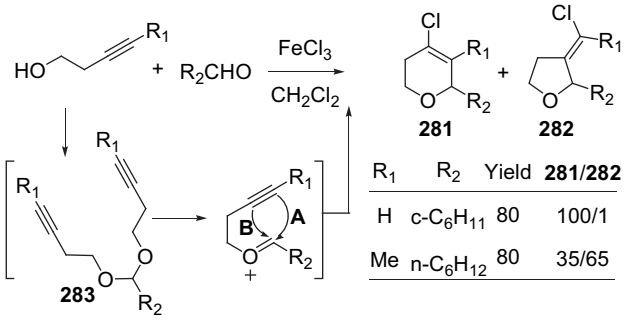
Scheme 141.

Silylated vinyl chlorides **278** and **280** (that exhibit anticancer activities, and enable various further functional-group transformations), could be prepared from the alcohols **277** and **279**, respectively, with a total diastereoselectivity (Scheme 142).[157b,c]



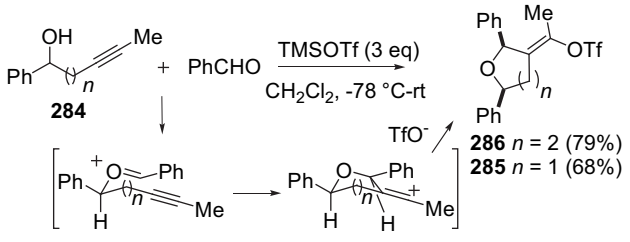
Scheme 142.

Except for the above example of a TMS-protected alkyne, non-terminal alkynes led to mixtures of 5- and 6-membered rings. For instance, when R_1 was a methyl group, vinyltetrahydrofuran **282** became the major product and **281** was the minor component (Scheme 143).[161] The authors proposed a mechanism involving the intermediacy of acetal **283** that was the only isolated product when FeX_3 was used in a catalytic amount.[156]



Scheme 143.

It is worth noting that a high regioselectivity in favour of 5-*exo*- and 6-*exo*-cyclization was reported by Cho and co-workers in TMSOTf-mediated Prins cyclization of terminally substituted benzylic alkynyl alcohols **284** (Scheme 144).[162] Both aliphatic and aromatic aldehydes led to good yields in 2,5-disubstituted-3-methylene-tetrahydrofurans **285** and 2,6-disubstituted-3-methylene-tetrahydropyrans **286**.



Scheme 144.

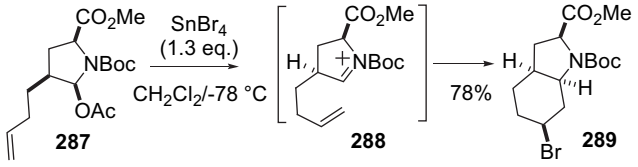
Therefore, modulation of the substituent effect influences significantly the regioselectivity of the cyclization (Schemes 142–144).

4. Aza-Prins cyclization

Compared to classical Prins cyclization, examples of aza-Prins cyclization leading to nitrogen-containing heterocycles have been less developed in the literature. The latter can be divided into two classes: Lewis acid-catalyzed, two-component reactions between homoallylic amines and an aldehyde or a ketone, and reactions involving cyclization onto an iminium ion, but in which the cationic intermediate is formed from a single precursor, generally an α-acetoxy-protected amine. Only the reactions named as 'aza-Prins cyclization' by their authors will be discussed here. The reader can consult the references cited in these articles for related works, and the excellent comprehensive review published in 2000 by Speckamp on the chemistry of *N*-acyliminium ions.[163]

4.1. Cyclization of α-acetoxy-protected amines

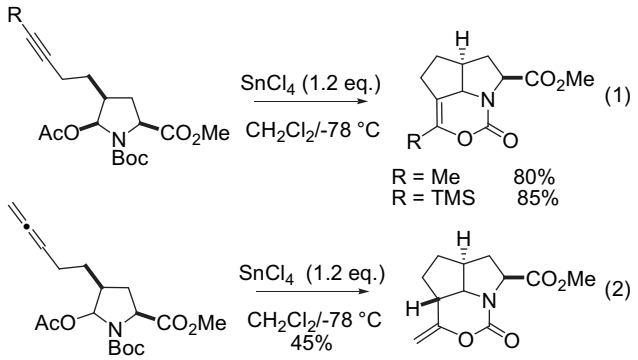
The octahydroindole moiety **289** of oscillarin (a marine natural product exhibiting antithrombotic activity) was prepared by Hanessian and co-workers via aza-Prins cyclization.[164] The precursor **287** generates the *N*-acyloxyiminium intermediate **288** by reacting with $SnBr_4$. Cyclization according to the 6-*endo* mode leads to **289** in 78% yield (Scheme 145).



Scheme 145.

This methodology was developed as a route to bicyclic and tricyclic heterocycles. It must be underlined that the use of the 'aza-Prins cyclization' terminology in these reactions does not refer to piperidine ring closure, but rather to carbocycle formation.

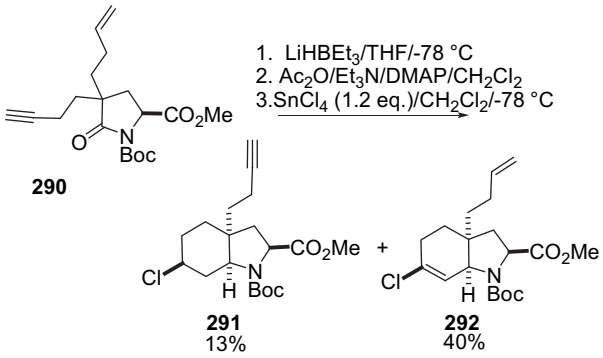
A detailed exploration of the cyclizations involving alkenes, alkynes, and allenes has been reported by the same authors. Examples of cyclization onto an alkyne or an allene are given in Scheme 146 (Eqs. 1 and 2, respectively).[165]



Scheme 146.

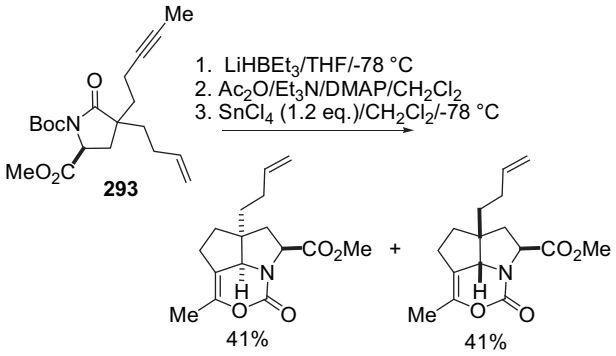
In these cases, the iminium ion intermediate underwent 5-*exo*-ring closure leading to a vinylic cation. The latter was trapped by the basic oxygen atom of the carbamate protective group to give the corresponding tricyclic products.

In fact, the fate of the cyclization with alkynes strongly depends on the substitution at the terminal carbon. When a true alkyne was involved, 6-*endo* ring closure was observed. Hanessian and co-workers have investigated the competition between a terminal alkene and a terminal alkyne (Scheme 147). The acetoxyaminal precursor was prepared in two steps from Boc-protected **290**. When treated with $SnCl_4$, the latter led to a mixture of chloride **292**, resulting from 6-*endo* ring closure onto the triple bond, and chloride **291**, resulting from 6-*endo* ring closure onto the double bond, in a 3:1 ratio.



Scheme 147.

The rate of cyclization onto the alkyne increases when the latter is substituted with an alkyl group, but, as above, the regioselectivity of ring closure favours the formation of a 5-membered ring. As shown in Scheme 148, no stereoinduction was registered, a 1/1 mixture of two diastereomers being isolated from **293**.

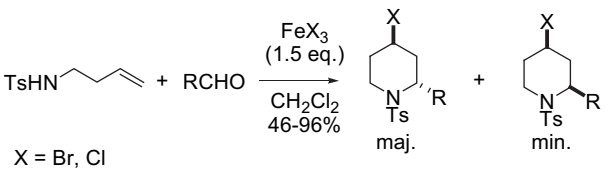


Scheme 148.

It should be noted that, not surprisingly, the cyclization onto an allene is faster than cyclization onto both alkenes and alkynes.

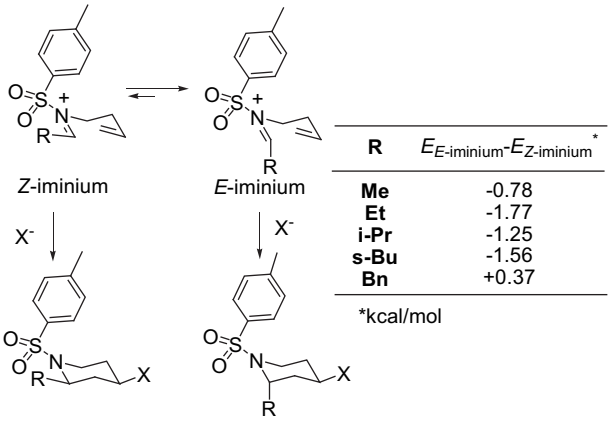
4.2. Two-component aza-Prins cyclizations

The synthesis of piperidines and tetrahydropyridines was investigated by Martín and co-workers.[158–166] Their strategy consisted of allowing homoallylic (or homopropargylic) tosylamides to react with aldehydes in the presence of $FeCl_3$ or $FeBr_3$. As exemplified in Scheme 149, homoallylic tosylamides led preferentially to *trans*-2,4-disubstituted piperidines.



Scheme 149.

The diastereoselectivity is influenced by the geometry of the intermediate iminium cation. DFT calculations indicate that the *E*-iminium ion (precursor of the 2,4-*trans* product through cyclization via a chair transition state followed by equatorial trapping of the resulting carbocation by X^-) is in all cases more stable than the *Z*-iminium ion by 0.78–1.77 kcal mol^{-1}, except when R is a benzyl group (Scheme 150).

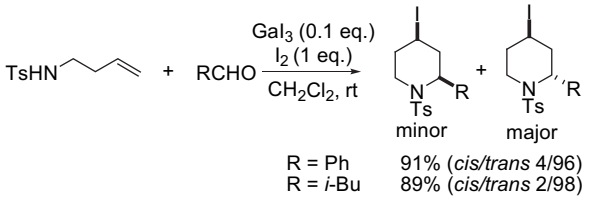


R	$E_{E\text{-iminium}}$-$E_{Z\text{-iminium}}$*
Me	-0.78
Et	-1.77
i-Pr	-1.25
s-Bu	-1.56
Bn	+0.37

*kcal/mol

Scheme 150.

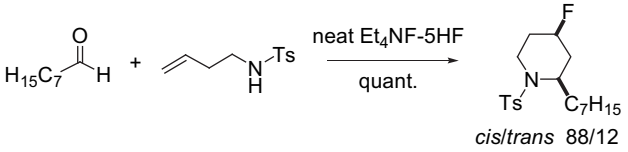
Very good yields of 4-iodopiperidines were obtained from the reaction of *N*-tosyl homoallylamine with aldehydes carried out in the presence of 10% gallium iodide and stoichiometric iodine (Scheme 151).[167]



Scheme 151.

The reaction of homoallylamines (protected as sulfonamides or as Boc-carbamates) with epoxides can also be promoted with $BiCl_3$, a catalyst of low toxicity and low cost, insensitive to atmospheric moisture. Times of reaction are short, compared to those needed for the reactions promoted with $InCl_3$, $ZrCl_4$, or $FeCl_3$ (0.5 h/2–8 h), and the reaction leads to 4-chloropiperidines in high yields (84–93%).[168] The reaction of homoallylic tosylamides with either epoxides or aldehydes, leading to 2-alkyl-4-hydroxy-piperidines, can also be mediated with phosphomolybdic acid.[169]

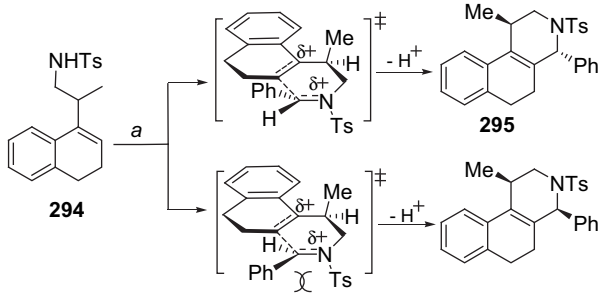
Quantitative yields in 4-fluoropiperidines were obtained from aza-Prins cyclization of *N*-tosyl-homoallylamine with aliphatic aldehydes in an ionic liquid hydrogen fluoride salt (Scheme 152).[35a]



Scheme 152.

A hexahydrobenzo-isoquinoline **295** was prepared in 60% yield from the iodine-catalyzed reaction of tosylamide **294** with benzaldehyde. The cyclic cation loses a proton, rather than being trapped by the nucleophile, to give a tertiary halide (Scheme 153). A similar behaviour was observed by the same authors in their

synthesis of chromenes.[170] The diastereoselectivity can be rationalized by the preferential formation of the *E*-iminium salt intermediate. Owing to steric crowding in the corresponding transition state, the reaction is much longer than the formation of chromenes from aldehydes and ketones from the analoguous homoallylic alcohol.[170]

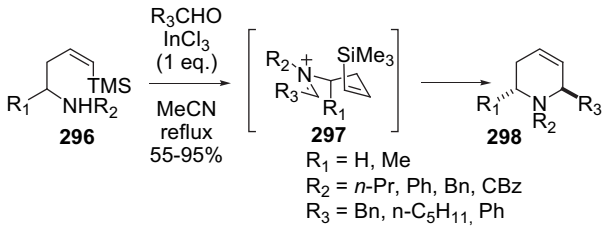


a- PhCHO, I_2 (20 mol%), CH_2Cl_2, rt, 72 h, 60%, (*trans/cis* = 5/1)

Scheme 153.

There is no example of an aza-Prins cyclization involving propynal derivatives. Attempts to react dicobalt hexacarbonyl complexes of propargylic acetals with homoallylic tosylamides failed. In all likelihood, the intermediate cationic species is too stable to undergo cyclization.[171]

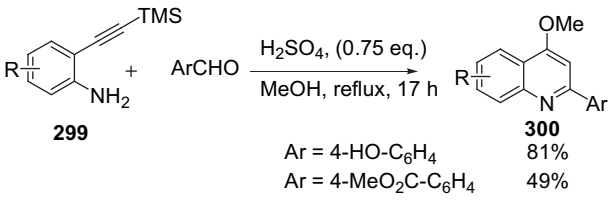
Dobbs has developed indium trichloride-mediated aza-silyl-Prins cyclization.[172] Homoallylic amines **296** are easily available from the corresponding alcohols. Through reaction with either aliphatic or aromatic aldehydes, they led to *trans*-tetrahydropyridines **298** (Scheme 154). Interestingly, the diastereoselectivity is opposite to that reported for the cyclization of the corresponding alcohols.[128] According to the authors, the reaction proceeds through the chair-like transition state **297** involving a *Z*-iminium cation were the R^1 substitutent is axial (only R^1=Me was investigated). The aza-silyl-Prins strategy was also applied to the synthesis of trifluoromethylated pipecolic derivatives.[129]



Scheme 154.

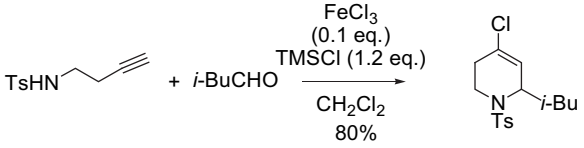
It must be underlined that this is the only example of aza-Prins cyclization involving secondary aliphatic amines, probably because the nucleopilic double bond was a vinylsilane. No cyclization was observed with primary amines. As shown in Scheme 154, their protection as benzyloxycarbonyl carbamates offers wider perspectives than the temporary introduction of a benzyl group on the nitrogen atom. Interestingly, no racemization of the stereogenic center in the position α relative to the nitrogen atom was detected when starting from an enantiopure amine.

4-Alkoxy-2-arylquinolines **300** were isolated in yields ranging from 10 to 81% from the reaction of (2-(2-trimethylsilyl)ethynyl)-anilines **299** with aromatic aldehydes in the presence of sulfuric acid in methanol, ethanol or isopropanol. The best experimental conditions are reported in Scheme 155. The lowest yields were recorded for benzaldehydes bearing electron-withdrawing groups in position 4 (*p*-nitrobenzaldehyde did not react).[173] Since anilines are less basic than aliphatic amines, they need not be protected for the reaction to proceed.



Scheme 155.

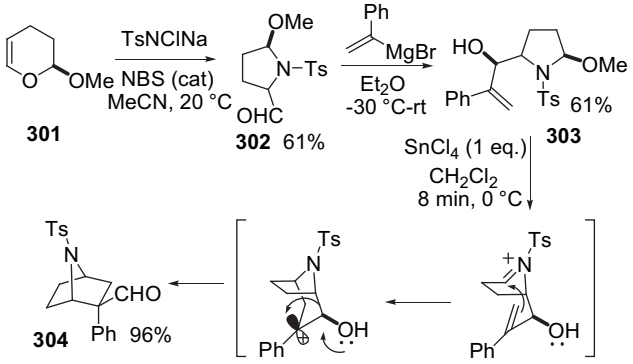
Homopropargylic tosylamides led to tetrahydropyridines, the yields ranging from 67 to 96% with aliphatic aldehydes. Comparatively, the yield obtained with benzaldehyde was very modest (38%). A selected example is given in Scheme 156. As already noted in standard Prins cyclizations, the authors have observed that the solvent could behave as a source of halide anion.[159] Excellent yields were also registered when replacing FeX_3 by $Fe(acac)_3$.[158,160]



Scheme 156.

4.3. Application to natural product synthesis

Azabicyclic targets were shown to be readily available from an aza-Prins pinacol approach.[174] Formyl-pyrrolidine **302**, prepared via the rearrangement of alkoxydihydropyran **301**, led to the homoallylic tosylamide **303**. When treated with $SnCl_4$, the latter underwent tandem aza-Prins cyclization-pinacol rearrangement, leading to 7-azabicyclo[2.2.1]heptane **304** (Scheme 157). The same approach was used to prepare precursors of (±)-epibatidine and its analogue, (±)-epiboxidine.

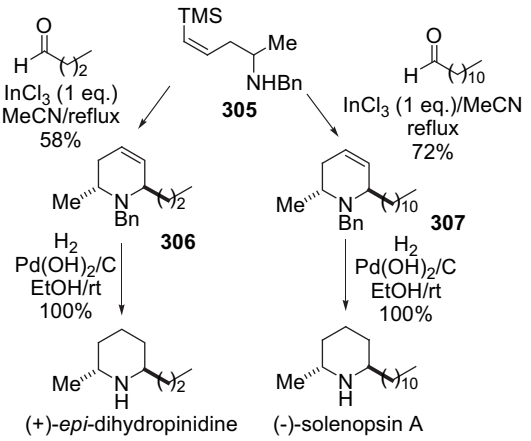


Scheme 157.

The diastereoselective aza-Prins cyclisation was adapted to the total synthesis of (−)-solenopsin A and (+)-*epi*-dihydropinidine from amine **305**.[175] The key cyclization step led to 2,6-*trans*-disubstituted tetrahydropyridine **306** or **307** (epoxides could be used as starting material instead of aldehydes). Subsequent hydrogenation insured both debenzylation and reduction of the double bond (Scheme 158).

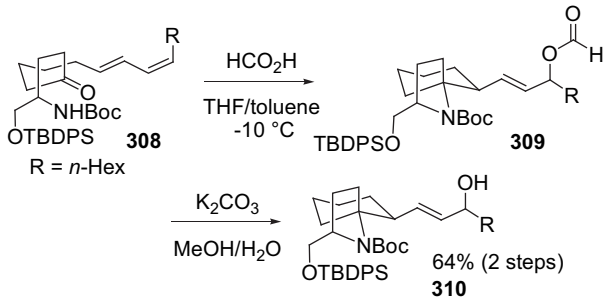
The same method was applied to the preparation of analogous sulfur-containing heterocycles.

In their total synthesis of cylindricines C–E, Hsung and coworkers have devised an elegant application of aza-Prins cyclization to build in one step the spiranic skeleton of **310**.[176] In the key step, formic acid mediated the formation of the reactive iminium salt from **308**, and its cyclization onto the dienic moiety. The resulting allylic carbocation was trapped regioselectively by the



Scheme 158.

carboxylate to give the ester **309**, that was then saponified to release alcohol **310** in 64% overall yield (Scheme 159). It must be noted that this alcohol is also an interesting intermediate for the total synthesis of (−)-lepadiformine.



Scheme 159.

5. Conclusions

Prins cyclization is an old reaction, that is now emerging as one of the most powerful and versatile tools for the highly diastereoselective preparation of functionalized tetrahydropyran skeletons, that are commonly encountered in a wide range of biologically active natural products. Extensive mechanistic studies have led to a clear understanding of the most subtle aspects of the reaction. There are plenty of refinements in the recent literature. These result from an extensive development of new methodologies, including the investigation of new catalysts, and new solvents, the selective introduction of various substituents in position 4 by the trapping of intermediate tetrahydropyranyl cations by appropriate nucleophiles, and the achievement of tandem multicomponent procedures. Progress is such that the building of more and more complex substitution patterns, and the enantioselective synthesis of complex targets may now be achieved.

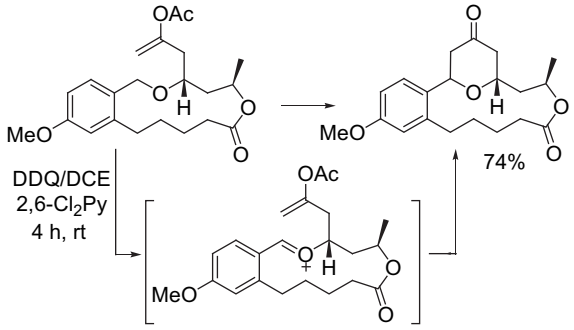
A few examples of the extension to the synthesis of analogous sulfur-containing heterocycles have been reported.

Aza-Prins cyclizations, involving cyclization onto iminium ions less electrophilic than oxocarbenium ions, have received much less attention. However, as exemplified by selected applications, the latter reaction enables access to complex aza-polycyclic skeletons in a single step.

6. Addendum

While this article was being reviewed a few additional examples have been published in the literature. The references are given hereafter, the reader is referred to the relevant Sections.

Section 2.2.2. The oxocarbenium intermediate can be generated through the oxidation of allylic or benzylic C–H bonds with DDQ (Scheme 160).[177]



Scheme 160.

Section 3.1.2. The synthesis of the THP containing fragment of sorangicin A has recently been achieved.[178] The hexahydro-2*H*-furo[3,2-*c*]pyran skeleton is readily available from the coupling of *(Z)*-hex-3ene-1,6-diol with aldehydes.[179]

Section 3.2.2. The three-component one-pot synthesis of dihydropyrans involving a tandem Mukaiyama/Prins sequence can be catalyzed by $BiBr_3$.[180]

Section 3.3.1.5. A new indium-mediated synthesis of (±)-centrobiline and (±)-civet through a one-pot three-step procedure has been reported by Loh et al.[181]

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