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Synthesis of six-membered oxygenated heterocycles through carbon–oxygen bond-forming reactions

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Contents

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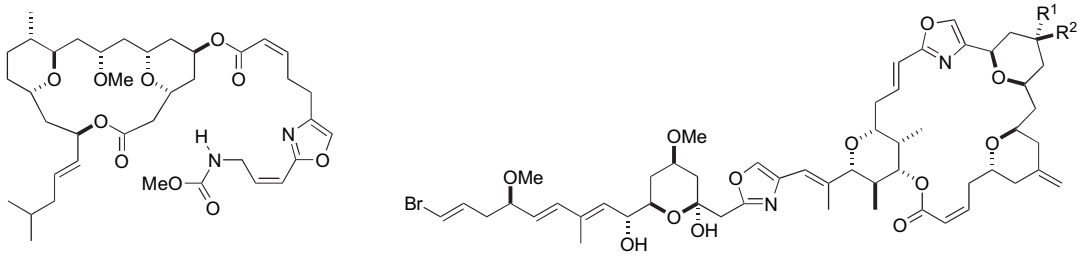


1 leucascandrolide A

2a phorboxazole A, R^1 = OH, R^2 = H
2b phorboxazole B, R^1 = H, R^2 = OH

Figure 1.

1. Introduction and scope

Six-membered oxygenated heterocycles, or pyrans, are probably one of the most common structural motifs spread across natural products, from simple glucose to structurally complex metabolites such as leucascandrolide A (**1**),[1] phorboxazole A (**2a**) and B (**2b**),[2–4] and the even more elaborated architectures present in palytoxin, maitotoxin, and other marine natural products (Fig. 1).[5]

Due to the remarkably rich array of functionalities and chiral centers that these heterocycles can incorporate, their stereoselective preparation has become a continuous challenge for organic synthesis practitioners.[6–10] They can be synthesized by means of five-membered ring expansions (e.g., Baeyer–Villiger oxidation of cyclopentanones[11]), cycloaddition processes (e.g., Hetero-Diels–Alder reactions[12]), or intramolecular cyclizations.[13] Classical examples of these cyclizations are the lactonisation of δ-hydroxy acids or the thermodynamically favorable conversion of δ-hydroxy aldehydes into the corresponding hemiacetals, which, in turn, can be easily modified (e.g., C-glycosidation reactions[14]) to provide other pyran-based structures. In addition to these processes, there is a set of important methodologies based on the cyclization of an oxygenated precursor that affords pyran structures in a highly efficient and straightforward manner.

Considering the crucial ring-forming step (or the parallel *transform* in the retrosynthetic sense), the cyclization methodologies can be classified into three types, represented in Figure 2. Type 1 gathers those methodologies based on O1–C2 bond formation[15] (or disconnection in the retrosynthetic sense), which encompass S_N2- and S_N1-mediated cyclizations, metal-promoted processes, and Michael-like reactions. Likewise, Type 2 and 3 methodologies affect C2–C3 and C3–C4 bond formation, respectively, which include Prins sequences, Petasis–Ferrier rearrangements, or ring-closing metathesis reactions.

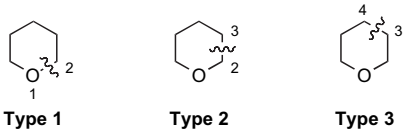
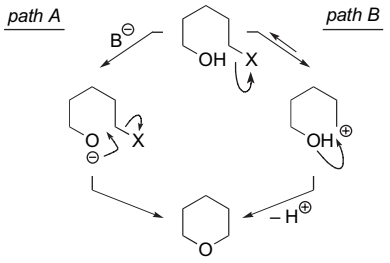


Figure 2.

The aim of this report is to highlight Type 1 methodologies addressed to the stereoselective construction of di- and tetrahydropyrans and their application to the synthesis of natural products, with special attention being paid to the most recent contributions.

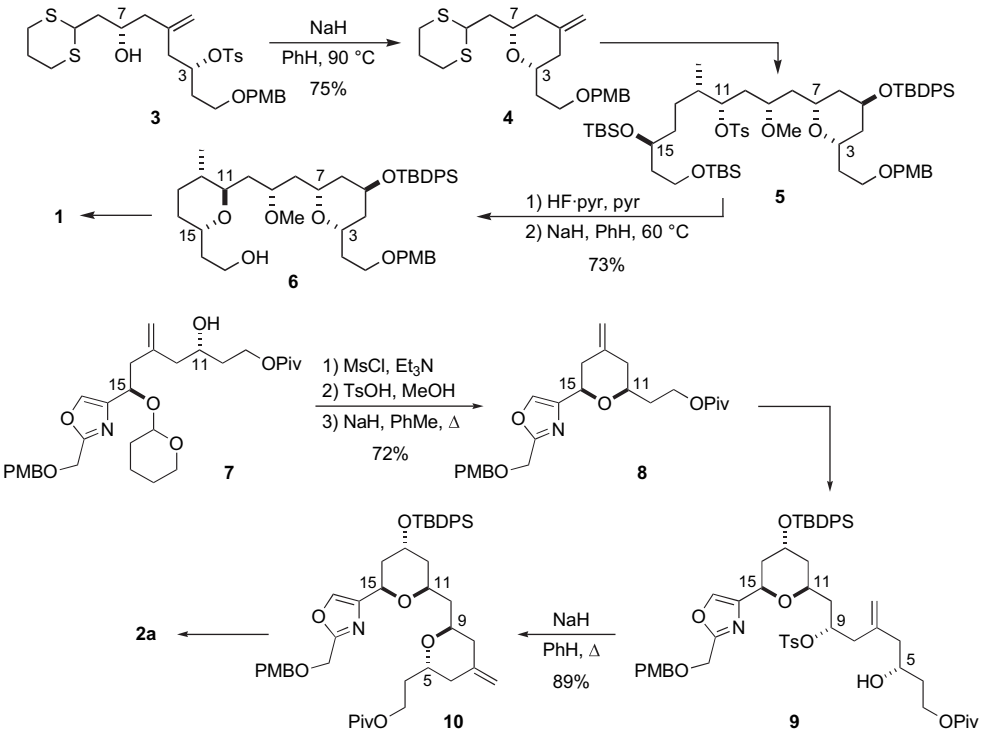
2. S_N2-Mediated cyclizations

Transformations based on an S_N2-mediated cyclization of a hydroxy precursor represent the simplest strategy leading to di- and tetrahydropyran. They only require a suitable combination of base (B: tertiary amine, alkoxide, hydride; see Scheme 1) and leaving group (X: sulfonate, halide; see Scheme 1) to promote a 6-*exo-tet* process[16] with inversion of the configuration at the C–X center in accordance with the pattern dictated by the Williamson reaction (see path A in Scheme 1). Thus, the stereochemistry of the resulting tetrahydropyran relies exclusively on the configuration of the acyclic precursor.



Scheme 1.

With regard to the reactivity of such systems, cyclizations that involve leaving groups placed on a primary position take place smoothly,[17] whereas those located on a secondary position often require a more accurate control of the reaction conditions.[18] Even in such a challenging situation, this strategy enjoys an interesting synthetic potentiality, as has been clearly proved in the successful construction of tetrahydropyrans embedded in leucascandrolide A (**1**),[1f] and phorboxazole A (**2a**)[2d] and B (**2b**).[3b] Noteworthy, either 2,6-*cis*-tetrahydropyran (see **4** and **8** in Scheme 2) or 2,6-*trans*-tetrahydropyran (see **6** and **10** in Scheme 2) is obtained by simple application of the same experimental conditions. Thus, both stereochemistries



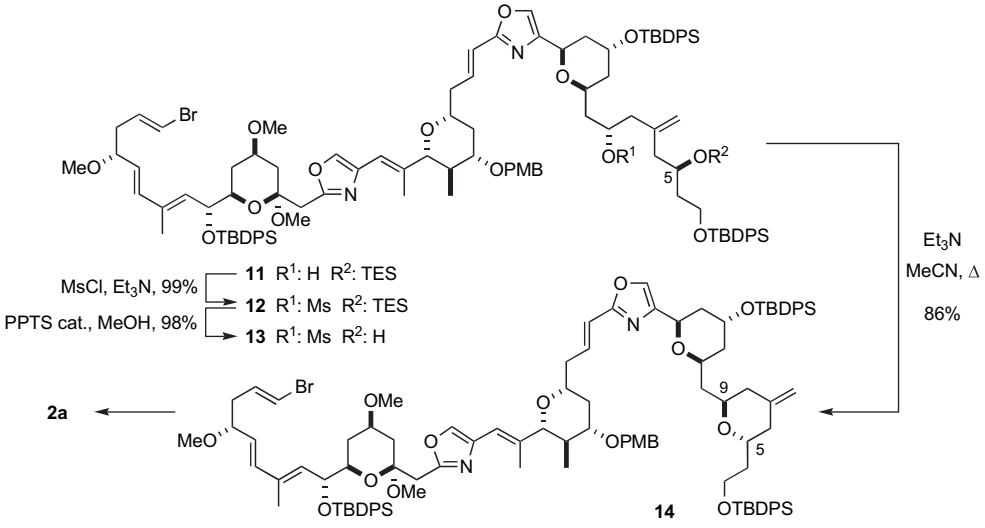
Scheme 2.

are available, depending on the configuration of the reacting center.

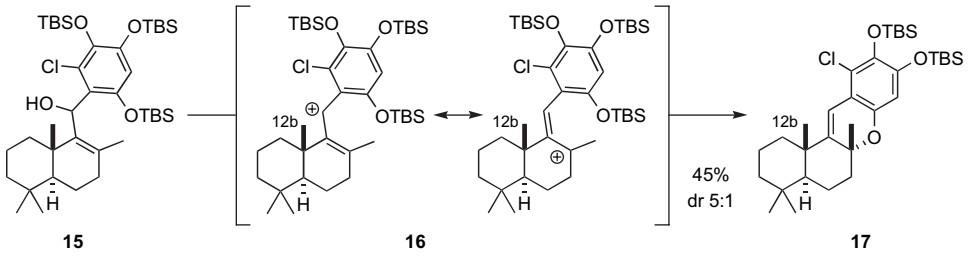
Remarkably, an S_N2-mediated cyclization has also been used for the assemblage of C5–C9 tetrahydropyran of phorboxazole A (**2a**) in the final stages of the synthesis.[2h] Thereby, alcohol **11** is easily converted into its mesylate **12**, the silicon protecting group at C5 is selectively removed and the simple exposure of the resulting hydroxy mesylate **13** to Et_3N affords the desired 2,6-*trans*-tetrahydropyran **14** in an excellent yield (Scheme 3).

3. S_N1-Mediated cyclizations

In contrast to the above-mentioned methodologies, S_N1-mediated cyclizations take advantage of the stability of allylic and benzylic carbocations to drain the process represented in Scheme 1 along path B.[19,20] Now, the planarity of the carbocationic intermediate does not exert any control on the configuration of the new stereocenter and the stereochemical outcome of the cyclization relies on the stereogenic elements of the substrate and the experimental conditions.



Scheme 3.



Scheme 4.

Thereby, cyclization of benzylic allylic alcohol **15** during an aqueous work-up is supposed to proceed through cationic intermediate **16**, which undergoes ring closure followed by the release of the silicon protecting group (Scheme 4).[19d] The stereochemistry of the major diastereomer **17** arises from the preferential attack of the OTBS oxygen from the opposite side of C12b methyl.

Better results are typically obtained for 2,6-*cis*-tetrahydropyrans, which are usually the most stable diastereomers. For instance, construction of the C22–C26 2,6-*cis*-tetrahydropyran of phorboxazole A (**2a**) has been achieved through an intramolecular S_N1-mediated cyclization of alcohol **18**, as shown in Scheme 5. Actually, the stereochemical outcome of this transformation is consistent with the internal capture of a transoid allylic cation at C26 by the C22 β-methoxymethyl ether and dealkylation of the resulting oxonium species.[2d,21]

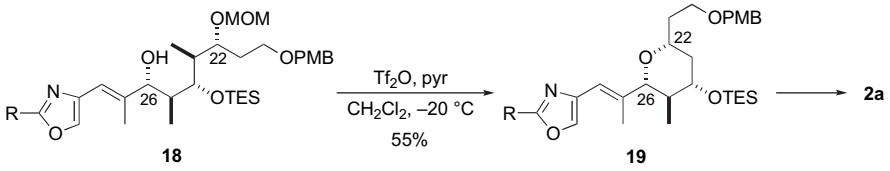
Propargylic carbocations can also participate in these cyclizations, since they are easily generated by treatment of $Co_2(CO)_6$–alkynol complexes with either Brønsted or Lewis acid[22] and are stable enough to be intramolecularly trapped by oxygenated nucleophiles. Indeed, ring closure of diol **20** affords tetrahydropyrans **21** in excellent overall yield (Scheme 6).[23] Remarkably, the thermodynamically more stable 2,3-*trans* derivative is increasingly obtained with long reaction times or higher temperatures.

Furthermore, epoxides can also act as nucleophiles and, in particular, precursors containing a protected epoxy alcohol moiety participate in highly regio- and stereoselective cyclizations. For instance, treatment of carbonates **22a** or **b** (Scheme 7) with $BF_3{\cdot}OEt_2$ followed by protecting group transformations furnishes 2,6-*cis*-tetrahydropyran **23a** or **b** as a sole diastereomer through a putative propargylic carbocation,[24] which has provided a new entry to a formal synthesis of (+)-muconin **24**.[25]

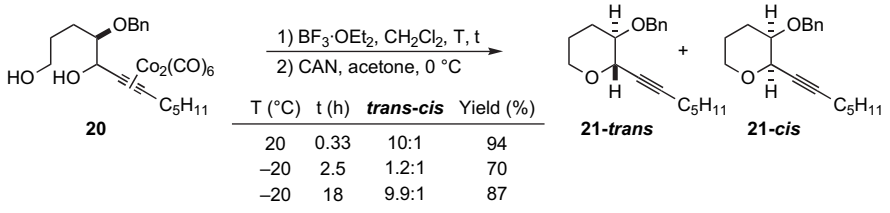
4. Epoxide-mediated cyclizations

Since the seminal studies on the intramolecular epoxide opening carried out by Nicolaou et al.[26] established the structural criteria required for the regio- and stereocontrolled synthesis of six-membered oxygenated heterocycles overriding the competitive formation of the corresponding five- or seven-membered counterparts, acid-catalyzed cyclizations of hydroxy epoxides have become a common approach to the stereoselective construction of tetrahydropyrans.[27]

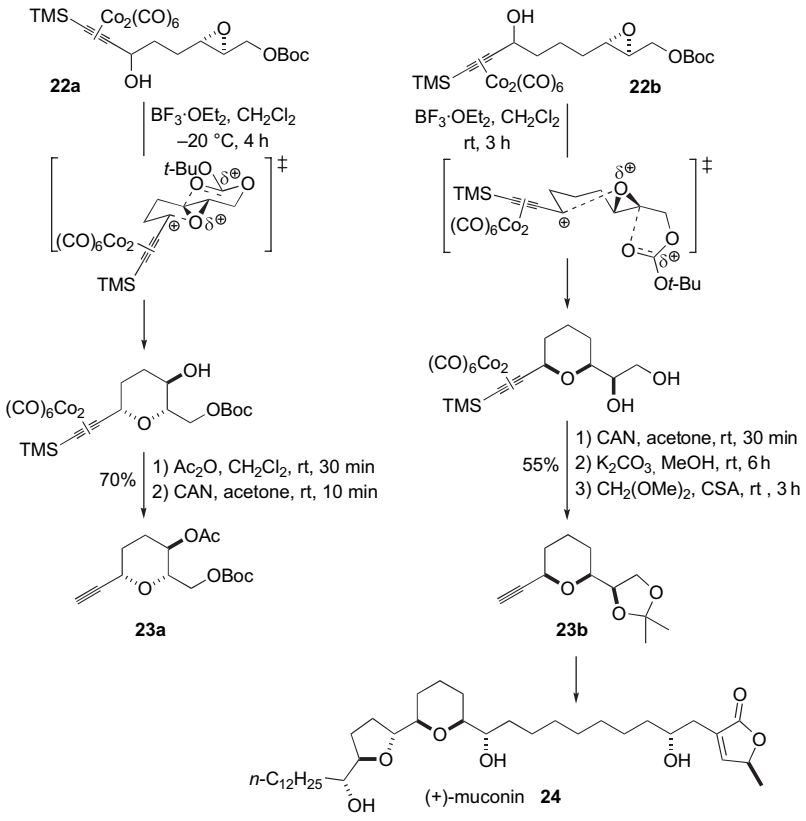
The regioselectivity of the cyclization for γ-hydroxy epoxides greatly depends on the geometry of the epoxide. Indeed, *cis*-epoxides reliably afford the 5-*exo* ring closure probably because these systems do not easily assume the planar arrangements necessary for maximum stabilization in the transition states leading to six-membered rings (Eq. 1 in Scheme 8). On the other hand, *trans*-epoxides enable the desired 6-*endo* process provided that a π-orbital adjacent to the epoxide unit activates the C–O bond close to it and stabilizes the developing positive charge in the transition state (Eq. 2 in Scheme 8). In both cases, these cyclizations are accompanied



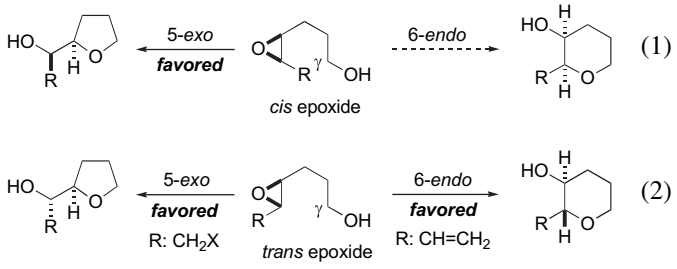
Scheme 5.



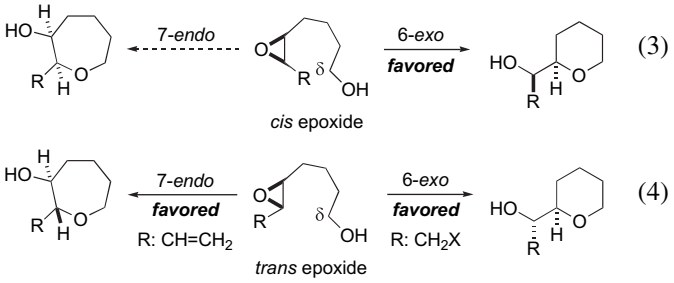
Scheme 6.



Scheme 7.



Scheme 8.



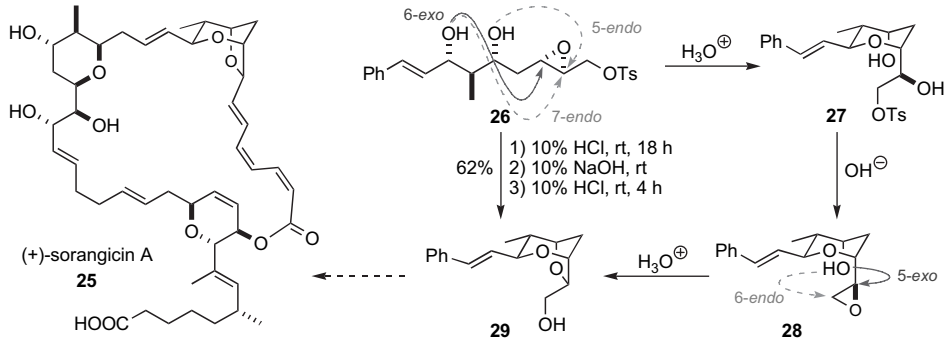
Scheme 9.

by inversion of the stereochemistry at the carbon undergoing nucleophilic attack.

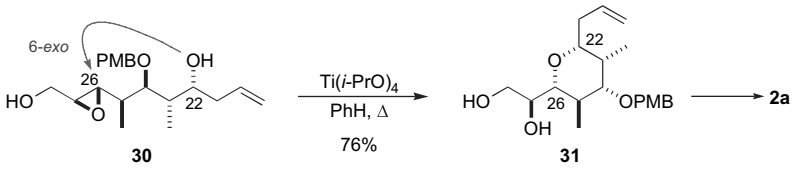
A similar analysis was performed for δ-hydroxy epoxides. In these systems, *cis*-epoxides exhibit low selectivity for the 7-*endo* ring closure irrespective of the R substituent, preferentially forming the corresponding tetrahydropyran (Eq. 3 in Scheme 9). Conversely, the R substituent plays a crucial role in the case of *trans*-epoxides. As expected on kinetic grounds, any saturated substituent favors the 6-*exo* process and yields almost exclusively the six-membered ring, whereas, once again, a π-orbital close to the epoxide directs the attack to the allylic position and produces the oxepane ring (Eq. 4 in Scheme 9).

These models account for most of the synthetic approaches found across the most recent literature.[28] For instance, construction of the bicyclic ether core of (+)-sorangicin A (**25** in Scheme 10) illustrates some of the aforementioned trends. Exposure of epoxide **26** to aqueous acid produces tetrahydropyran **27** through a 6-*exo* ring closure (see Eq. 4 in Scheme 9), without observing alternative 7-*endo* or even 5-*endo* cyclizations. Furthermore, **27** can be easily converted into epoxy alcohol **28**, which is subjected to an acid-mediated cyclization that follows a 5-*exo* pathway (see Eq. 1 in Scheme 8). Interestingly, three steps can be combined in a one-pot, three-step sequence that delivers the bicyclic ether **29** in a 62% overall yield.[29,30]

Similarly, a parallel set of experimental conditions based on the use of a Lewis acid (Ti(*i*-PrO)$_4$ activation in hot benzene) have been devised for the assemblage of the C22–C26 2,6-*cis*-tetrahydropyran **31** from **30** in a route to phorboxazole A (**2a**) (Scheme 11).[2c]



Scheme 10.



Scheme 11.

As pointed out in Scheme 8, alkenes adjacent to epoxides override the common bias favoring the 5-*exo* ring-closure mode. This is the behavior observed in the intramolecular cyclization of α,β-unsaturated epoxide **33**, which permits the regio- and stereoselective preparation of a densely substituted C8–C12 tetrahydropyran directed toward the synthesis of brevenal (**32** in Scheme 12).[31] Indeed, removal of the PMB group on **33** triggers a 6-*endo* cyclization to a tetrahydropyran, which is subsequently converted into TES ether **34**.[32]

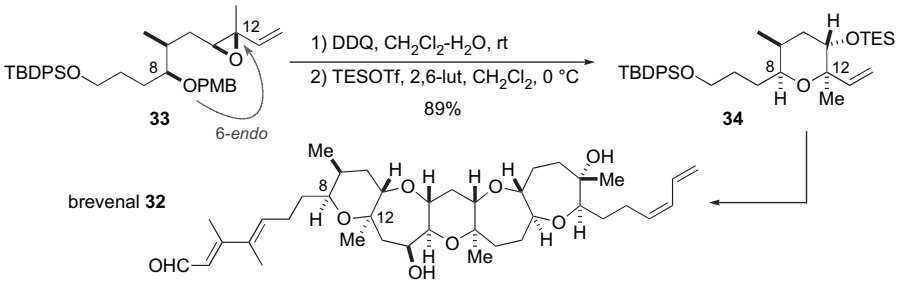
Occasionally, these methodologies are combined in a synthetic sequence. For instance, the tristetrahydropyran substructure of diol **35**, an advanced intermediate toward the synthesis of thyrsiferol and venustatriol (**36a** and **36b**, respectively, in Scheme 13), has been regio- and stereoselectively prepared through three intramolecular cyclizations of γ- and δ-hydroxy epoxides.[33] The first acid-catalyzed ring closure of hydroxy epoxide **37** proceeds quantitatively to form **38** with complete 6-*exo* regioselectivity,[†] and no competitive 7-*endo* cyclization is observed. Next, the construction of tetrahydropyran B takes advantage of the allylic character of a *trans*-epoxide. Indeed, cyclization of hydroxy diepoxide **39** affords the desired six-membered heterocycle **40** under very mild conditions with excellent 6-*endo* regioselectivity. Eventually, Ti(*i*-PrO)$_4$ activation of hydroxy epoxide **41** produces the third ring in 58% yield.

In spite of these accomplishments, it was soon realized that new methodologies able to switch 5-*exo* to 6-*endo* processes irrespective of the substituent R (see Eqs. 1 and 2 in Scheme 8) were highly desirable. In this context, it has been recently reported that epoxide openings triggered by bulky silyl triflates in nitromethane yield the desired tetrahydropyrans regioselectively.[34] In addition to these observations, the regioselective tenet summarized in Scheme 8 favoring 5-*exo* over 6-*endo* ring closures of γ-hydroxy epoxides has recently been challenged in vanadium-catalyzed mediated processes.[35] As outlined in Scheme 14, the asymmetric oxidation of unsaturated α-hydroxy esters followed by an epoxidation/cyclization sequence using the same chiral catalyst provide regio- (6-*endo*/5-*exo* ratio ca. 4:1) and stereoselectively (dr>88:12, ee>95%) 2,5-*trans*-tetrahydropyrans in 20–35% yield (the highest theoretical yield is 50%).

Hence, this process is divided into two steps. The first step involves the oxidative resolution (acetone/O_2) of a racemic mixture of α-hydroxy esters (R^1, $R^2 \neq H$) using a vanadium catalyst prepared from VO(*i*-PrO)$_3$ and the chiral Schiff base **42**. Once the alcohol has been chemo- and stereoselectively oxidized, change of solvent and oxidant to $CHCl_3$/*t*-BuOOH promotes a stereoselective epoxidation followed by a fast cyclization of the resultant hydroxy epoxide. The mechanistic model that accounts for the stereochemical outcome of the overall process emphasizes the coordination of the ester carbonyl to the metal. Such a coordination places the ester in the pseudoaxial position, which allows an efficient π-facial discrimination of the carbon–carbon double bond. Finally, the resultant short-lived epoxide undergoes a backside attack of the hydroxyl to the corresponding 2,5-*trans* tetrahydropyran.[36]

The pursuit for regioselective 6-*endo* cyclizations has found its own Holy Grail in the synthesis of fused polycyclic ethers, a family of marine metabolites with remarkable biological activity.[9] As partly suggested by the name, their molecular architectures contain large and highly rigid polycyclic frameworks of all fused six- to nine-membered oxygenated rings in a well-defined stereochemical arrangement, as shown in Figure 3.

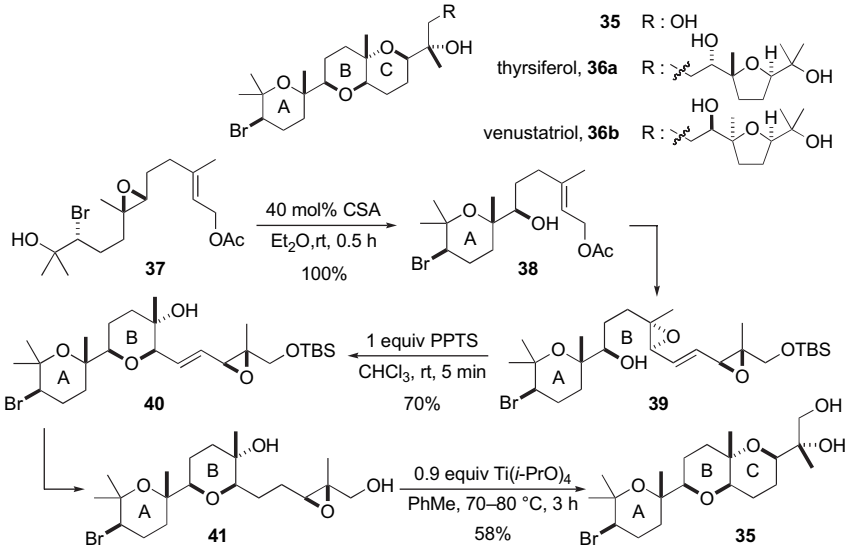
[†] Actually ring closure to tetrahydropyran A is carried out on a 1:1 epimeric mixture of 3-bromo derivatives. Interestingly, the experimental conditions provide a highly efficient kinetic resolution and just hydroxy epoxide **37** undergoes the desired cyclization.



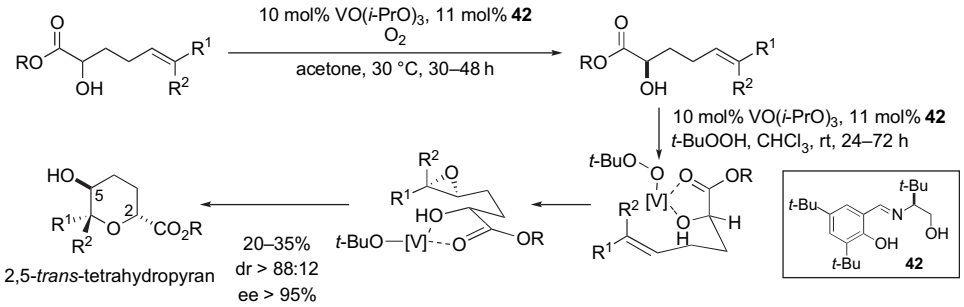
Scheme 12.

The synthesis of these large and complex structures has raised much interest in strategies rooted on biogenetic grounds. Unfortunately, the biosynthesis of these metabolites is not well understood and current working hypotheses are rather speculative. In this context, the Cane–Celmer–Westley model, originally proposed for the synthesis of polyether antibiotics,[37] has inspired most of those hypotheses, which envisage that the fused polycyclic ether frameworks might arise from the cyclization of a polyepoxide precursor through a cascade of S_N2 ring openings.[38] Therefore, any biomimetic strategy must be able to provide a synthetic route to a chiral polyepoxide with the structural elements to allow for the regio- and stereoselective 6-*endo* ring closures required for the fused tetrahydropyran arrays. Otherwise, alternative pathways based on 5-*exo* cyclizations leading to tetrahydrofurans would predominate (Scheme 15).[39]

In this context, a biomimetic approach takes advantage of *endo*-selective cyclizations of methoxymethyl epoxy alcohols controlled by chelation with a suitable Lewis acid. Indeed, the asymmetric epoxidation of polyene **43** leads to **44** in 56% isolated yield, and removal of the silicon protecting group provides quantitatively triepoxide alcohol **45** (Scheme 16). Then,



Scheme 13.



Scheme 14.

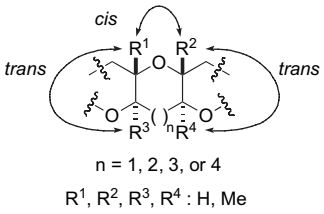
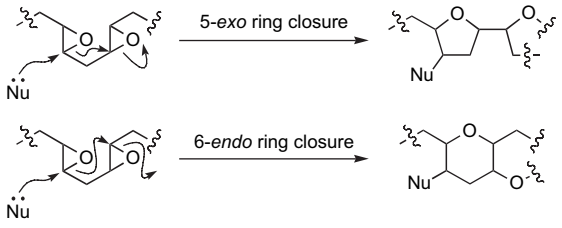


Figure 3.

a cascade cyclization catalyzed by $La(OTf)_3$ proceeds in a stepwise mechanism to afford the desired tricyclic ether **46** in 9% yield.[40]

Lewis acid-mediated *endo* oxacyclization of polyepoxides affords *cis*- or *trans*-fused polyethers depending on the nature of the terminal nucleophile. The rationale for such dependence relies on the mechanism depicted in Scheme 17. Initially, Lewis acid activation of a first epoxide triggers the generation of a bridged onium intermediate, which can evolve through a tight ion pair to a tertiary carbocation. Therefore, the terminal nucleophile may intercept different species. It has been proposed that the *cis*-fused products arise by trapping of an intermediate close to the carbocation, whereas the *trans*-fused derivatives are mainly obtained with a better nucleophile (i.e., a tertiary carbamate) by adding to an intermediate structurally close to the epoxonium ion. This is the case for dimethylcarbamate epoxide **47** prepared through stereoselective Sharpless and Shi epoxidations of the corresponding alkenes. Then, $BF_3 \cdot OEt_2$-promoted oxacyclization of **47** produces the desired polyether **48** in 31% isolated yield.[41]



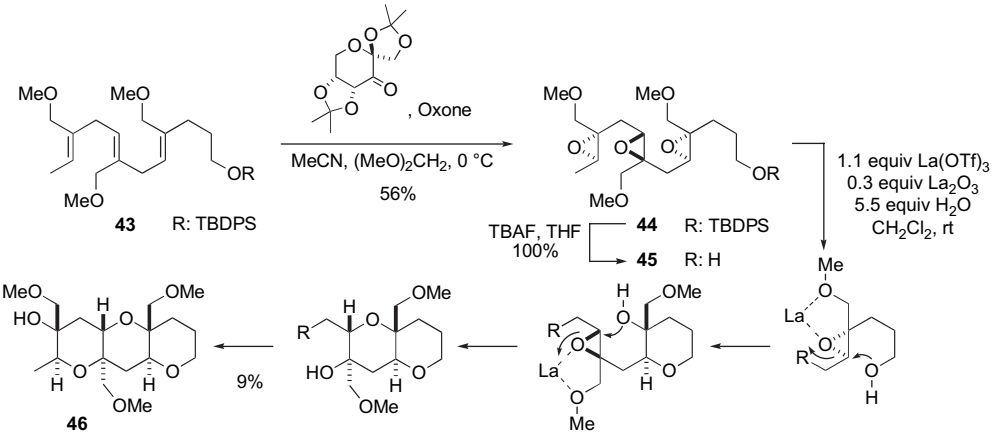
Scheme 15.

A different strategy employs epoxysilanes as starting materials for the cyclizations. It takes advantage of trimethylsilyl groups to achieve highly regioselective openings of the epoxides, and, immediately after the ring closure, the silicon group is removed by fluoride-promoted protodesilylation.[42] As outlined in Scheme 18, this approach allows for the straightforward conversion of triepoxysilane **49** into the large tetrahydropyran array **50**. Indeed, chiral epoxide **49**, prepared from a reagent-controlled Shi epoxidation (dr 90:10), undergoes a cascade of ring openings mediated by a Brønsted base and a fluoride source in a hydroxylic solvent. Finally, the resultant alcohol is acylated to furnish **50** in 20% overall yield.

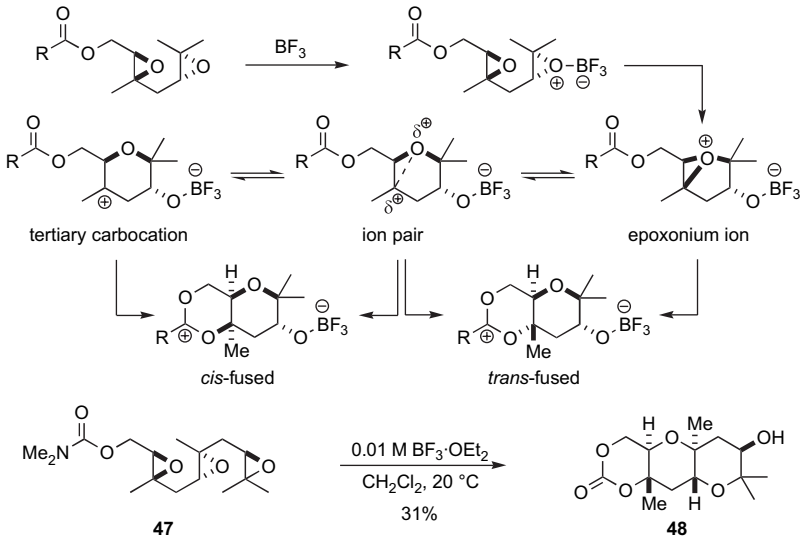
5. Alkene-mediated cyclizations

Closely related to the epoxide-mediated cyclizations, there is an important number of methodologies based on the intramolecular attack of an oxygenated nucleophile on an olefin activated by electrophiles. The most common precursors are δ-hydroxy alkenes, which afford the corresponding pyrans through highly regioselective 6-*exo* ring closures (Scheme 19). The rationale for these cyclizations assumes the reversible formation of a π-complex, which can proceed either directly to the corresponding heterocycle by reaction with the nucleophile or indirectly by first collapsing to an onium intermediate before undergoing nucleophilic attack.[43] In any case, cyclization involves the attack of the oxygenated nucleophile on the opposite face of the electrophile. Therefore, the success of this strategy mostly relies on the stereocontrolled electrophilic addition to the alkene.

These cyclizations can be classified as stoichiometric or catalytic, according to the amount of electrophile engaged in the process. The stoichiometric electrophile-induced cyclizations routinely involve mercury(II) salts and iodo or seleno reagents as activators of the carbon–carbon double bond. Otherwise, palladium chemistry dominates the catalytic counterparts, although other metals are being increasingly employed.



Scheme 16.



Scheme 17.

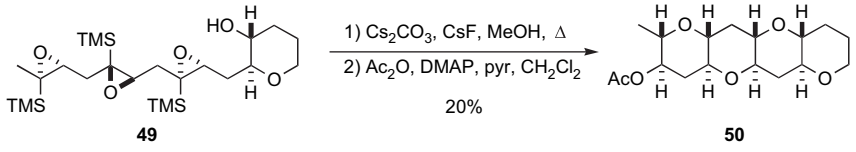
5.1. Stoichiometric cyclizations

5.1.1. Mercury-mediated cyclizations

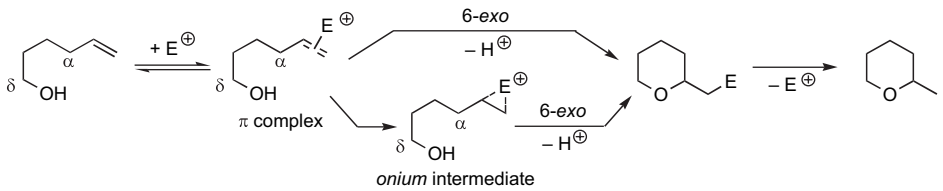
The electrophiles employed in these processes are mercury(II) salts and the resultant carbon–mercury bonds are usually reduced with $NaBH_4$ or *n*-Bu_3SnH.[44] The course of these intramolecular oxymercuriations depends on the stability of the cationic intermediates and, with the exception of one example,[45] they are substrate-controlled processes that usually lead to the thermodynamically more stable tetrahydropyran. Thus, the hydroxy alkene must contain the structural elements required to achieve the desired π-facial discrimination of the carbon–carbon double bond. This is the case for the δ-hydroxy alkene **52**, an intermediate in the total synthesis of the antibiotic X-206 (**51** in Scheme 20).[44a] Indeed, steric and conformational arguments would be responsible for the outstanding stereocontrolled electrophilic addition of $Hg(OAc)_2$ to the olefin in such a way that the resulting onium intermediate **53** is suitably prepared for the intramolecular cyclization leading to 2,6-*cis*-tetrahydropyran **54** quantitatively. Eventually, treatment of **54** with *n*-Bu_3SnH effects the desired demercuriation to **55** in excellent yield.

The intramolecular oxymercuriation has also been applied to the assemblage of the C22–C26 tetrahydropyran of phorboxazole B (**2b**). As shown in Scheme 21, treatment of diol **56** with $Hg(OAc)_2$ followed by reaction of the resultant organomercuriate with iodine furnishes a 5:1 mixture of the 2,6-*cis*-tetrahydropyran **57-*cis*** and the corresponding 2,6-*trans* isomer. Then, chromatographic purification of the mixture permits the isolation of the desired **57-*cis*** in 71% yield.

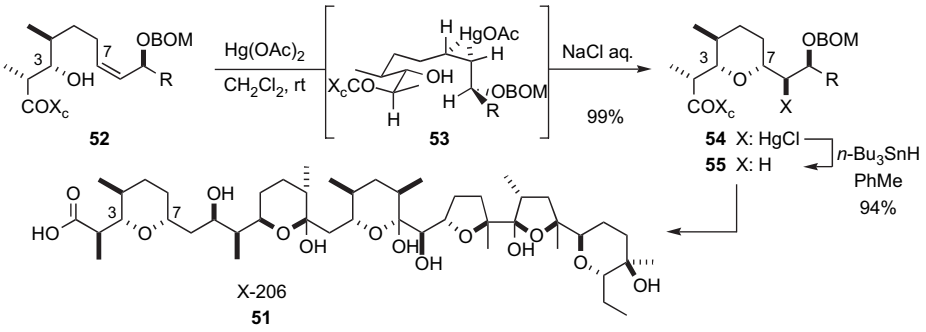
Given that the success of such a strategy relies on the π-facial discrimination of an alkene, any methodology able to fulfill this requirement should allow for a complete stereochemical control. In this context, mercury(II)-mediated electrophilic ring-opening reactions of δ-hydroxy cyclopropylcarbinol derivatives represent an appealing entry into the asymmetric synthesis of tetrahydropyrans. In this approach, the cyclopropane unit plays the role of an activated olefin. These highly diastereoselective processes usually occur with anchimeric assistance by the closest alcohol and subsequent nucleophilic backside



Scheme 18.



Scheme 19.



Scheme 20.

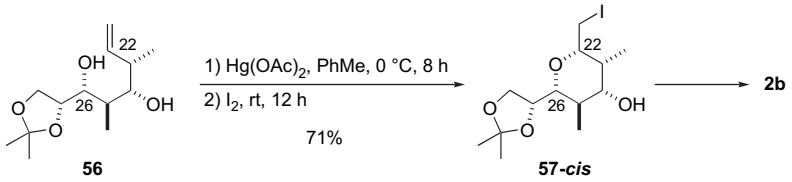
attack of the δ-OH, which causes an inversion in the configuration of the reacting center (Scheme 22). Hence, the stereochemical outcome of these cyclizations mostly depends upon the configuration of the cyclopropane ring.[46]

This strategy has been applied to the construction of the C3–C7 tetrahydropyran of zincophorin (**58** in Scheme 23).[47] The cyclopropane ring of the advanced intermediate **59** is installed at the beginning of the synthesis by means of the catalytic asymmetric cyclopropanation of an allylic diazoacetate. Then, simple treatment of **59** with $Hg(OCOCF_3)_2$ followed by aqueous work-up cleanly produces 2,6-*trans*-tetrahydropyran **60**. In turn, this organomercuric bromide is subjected to a reductive demercuriation, which eventually provides **61** in 85% yield and 93:7 dr.

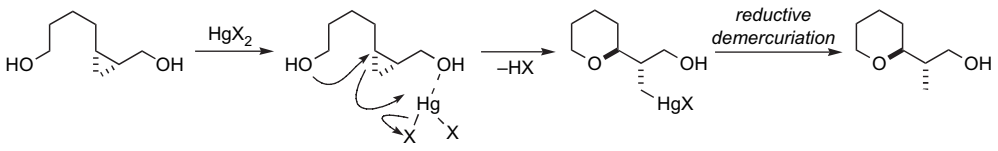
5.1.2. Halo-mediated cyclizations

Halo-mediated cyclizations are similar to the processes based on mercury(II) salts. Most of the intramolecular haloetherification reactions take advantage of the use of iodine or *N*-iodosuccinimide (NIS),[48–50] reagents mild enough to be used on structurally complex substrates. For instance, NIS-mediated iodoetherification plays a crucial role in the assemblage of the G-ring of azaspiracid-1 (**62** in Scheme 24), a prominent member of a family of marine metabolites responsible for human poisoning resulting from the consumption of tainted shellfish. Initially reported in 1998, azaspiracids were shrouded in structural ambiguity that partially arises from the complex and intricate array of sensitive functional groups embedded in their structure and, only in 2004, have Nicolaou et al. reported the correct structure of azaspiracid-1 after considerable synthetic work. It is, then, not surprising that the endeavors applied to the construction of such challenging compounds have spurred the development of new strategies (see also Schemes 57 and 91). As represented in Scheme 24, the intramolecular iodoetherification of the structurally complex alcohol **63** affords iodoether **64**, which is reduced with an excess of *n*-Bu_3SnH in toluene to remove the superfluous iodine at C29. Thus, the highly advanced intermediate **65** is obtained through this two-step sequence in 53% yield.

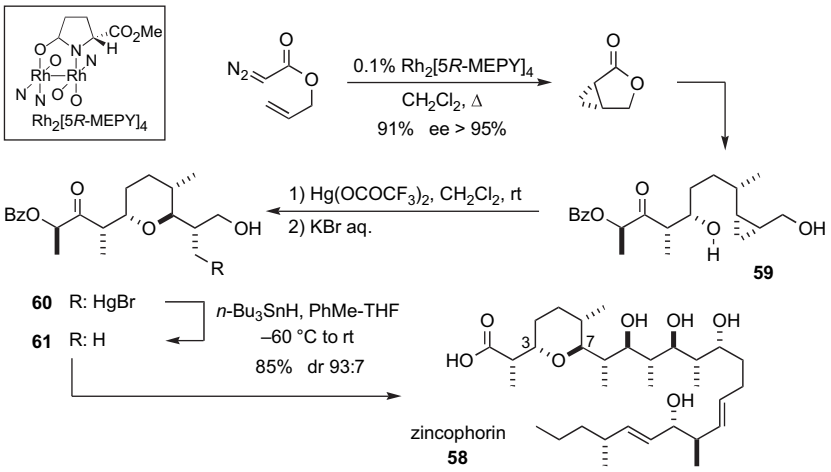
Iodoetherification on substrates containing an allylic alcohol turns out to be highly dependent on conformational issues. Indeed, diol **66a** undergoes a facile cyclization to 2,6-*cis*-tetrahydropyran **67a**, while the diastereomer **66b** fails to give the expected bicyclic system **67b** (Scheme 25).[48e] The rationale for such different behavior relies on the conformational analysis of the allylic moiety. Cyclizations in which the nucleophile is in the R group proceed rapidly (or slowly) through the favored π-complex **68a** (or the disfavored π-complex **68b**) when C–OH (or C–H) eclipses the carbon–carbon double bond. This is the situation for **66a** (or **66b**). Thus, cyclization of **66b** requires a more reactive iodinating agent such as bis(*sym*-collidine)$_2$IPF$_6$, prepared in situ from bis(*sym*-collidine)$_2$AgPF$_6$ and iodine in CH_2Cl_2. This reagent converts **66b** into the desired tetrahydropyran **67b** in 80% yield.



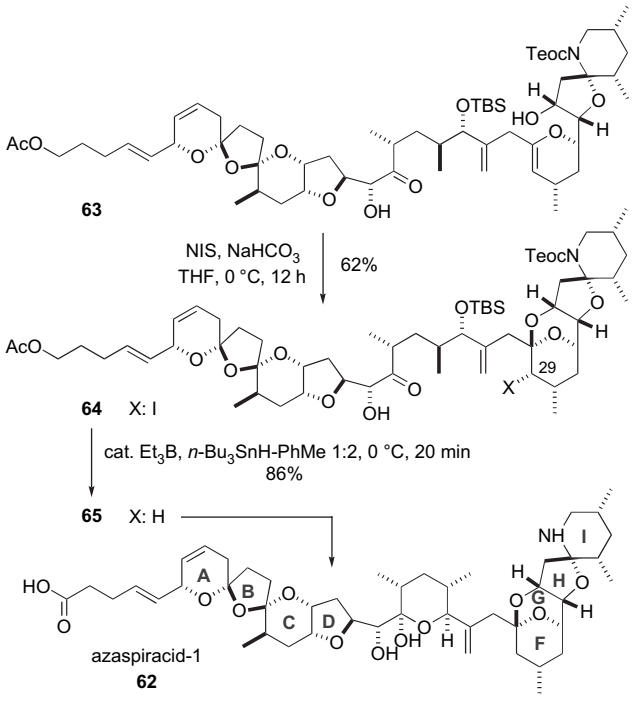
Scheme 21.



Scheme 22.



Scheme 23.



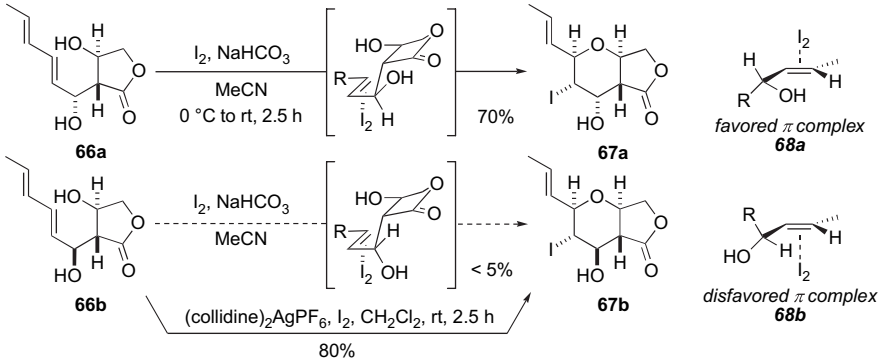
Scheme 24.

A conceptually different approach to electrophile-induced cyclizations takes advantage of the nucleophilicity of the carbonyl oxygen of a ketone. As outlined in Scheme 26, if the carbonyl of a δ-alkenyl ketone could trap the π-complex obtained by treatment of the olefin with an electrophile, then the resultant oxocarbenium intermediate would easily lead to the corresponding acetal.

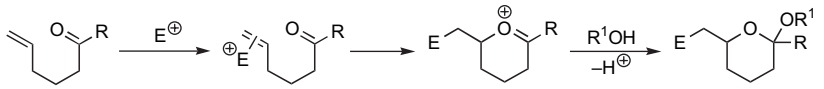
This idea has been put into practice for the stereoselective construction of the C1–C5 ring of a new antitumor agent, FR-901464 (**69** in Scheme 27). With this target in mind, the NBS-mediated cyclizations of two δ-alkenyl ketones, **70** and **71**, have been tested and, in both cases, a sole diastereomer has been isolated in good yield.[51a] Unfortunately, none of the resultant C4–C5 stereochemistries in **72** and **73** match with that in FR-901464 and its final total synthesis has recently been achieved following an alternative strategy.[51b] Despite this failure, the key concept of this methodology maintains a high appeal, as has been proved in a parallel process in the arena of alkynols, which has been commented further upon.[52,53]

5.1.3. Seleno-mediated cyclizations

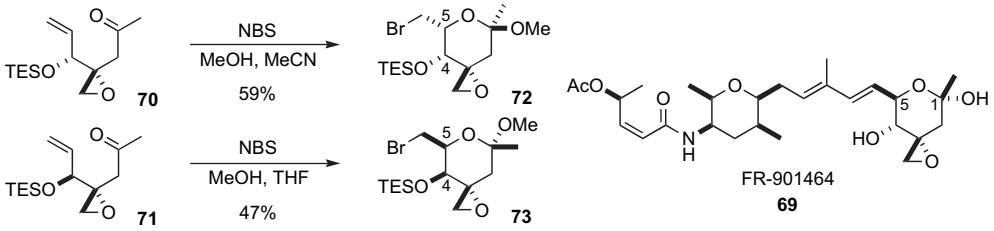
Cyclizations based on selenium reagents are not as common as the mercury(II)- or halo-mediated methodologies.[54,55] Moreover, and contrary to these methods, the stereochemical



Scheme 25.



Scheme 26.



Scheme 27.

outcome of the selenoetherification reactions mostly relies on the coordination of electrophiles such as phenylselenyl chloride (PhSeCl) or *N*-phenylselenophthalimide (NPSP) with the olefin, which is then followed by the ring-closure step. Therefore, the stereoselectivity of these cyclizations reflects the kinetic selectivity for the formation of the onium intermediate, which may give access to 2,6-*trans*-tetrahydropyrans. This is the trend observed for hydroxy alkene **74**. As shown in Scheme 28, 2,6-*trans*-tetrahydropyran **75-*trans*** is only obtained through a selenium-mediated cyclization, whereas **75-*cis*** results from the other methods.[50]

A more selective reagent has been used for the assemblage of the C11–C15 2,6-*trans*-tetrahydropyran of leucascandrolide A (**1**) from diol **76** (Scheme 29).[1d] Unexpectedly, iodine-based electrophiles show little diastereoselectivity, but this is dramatically improved by the use of selenium reagents. Remarkably, the bulky 2,4,6-triisopropylphenylselenyl bromide (TIPPSeBr)[‡] affords 2,6-*trans*-tetrahydropyran **77** in 74% yield and good diastereomeric ratio (dr 88:12). Eventually, a tin-free radical reduction of **77** provides the desired advanced intermediate **78** in 85% yield.

5.2. Catalytic cyclizations

5.2.1. Palladium-mediated cyclizations

In spite of the achievements mentioned above, the use and removal of stoichiometric amounts of often toxic elements have fueled research into alternative activators of olefins that allow the desired intramolecular cyclizations under mild conditions and in a catalytic fashion. In this context, catalytic methodologies based on the activation of olefins are dominated by the palladium chemistry, which has achieved prominent levels of maturity.[13e,56] In this arena, the construction of heterocycles can proceed through carbon–carbon or carbon–heteroatom bond formation, depending upon the nucleophile involved in the ring-closure step. In particular, the synthesis of pyrans relies on the intramolecular cyclization of hydroxy alkenes, which implies the suitable activation of the olefin with a palladium catalyst and the subsequent intramolecular attack by the alcohol.

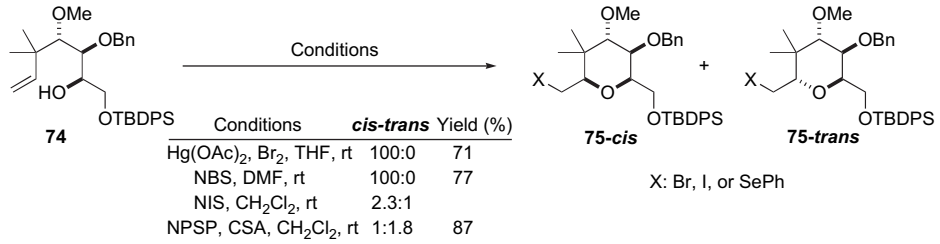
Since the reactivity of palladium catalysts is dominated by their oxidation states, Pd(0) and Pd(II) complexes are considered independently. Indeed, Pd(0) complexes are fairly nucleophilic and the cyclizations of δ-hydroxy alkenes leading to pyrans progress via the π-allylpalladium cations (Tsuji–Trost reaction). Otherwise, parallel processes involving Pd(II) complexes take advantage of their electrophilic character and commonly proceed through the fast and reversible formation of π-complexes with the carbon–carbon double bond, which next undergo an intramolecular attack by the nucleophile.

5.2.1.1. Catalysis by Pd(0). Palladium(0) complexes catalyze the cyclizations of δ-hydroxy alkenes containing allylic leaving groups (X: OAc, OCO_2R, $OPO(OR)_2$, OAr, Cl, Br). As shown in Scheme 30, the initial π-complex evolves through a η^3-complex to a π-allyl cation, a highly reactive intermediate that undergoes intramolecular attack of the hydroxyl to provide the corresponding pyran. The regioselectivity of this cyclization is rarely a problem, since 6-*exo* ring closures are more favored than their competitive 8-*endo* counterparts.

From a stereochemical point of view, substrate-controlled cyclizations usually proceed with retention of configuration at the reacting center. Coordination of the palladium to the carbon–carbon double bond occurs on the less-hindered face opposite to the leaving group and the nucleophile adds to the cationic π-allylpalladium complex on the opposite face to the metal. Thus, a net retention of the stereochemistry is observed.[57] Studies on the assemblage of the tetrahydropyran moiety embedded in zampanolide (**79** in Scheme 31) have demonstrated how highly diastereoselective this strategy can be. Indeed, Pd(0)-mediated cyclizations of both **80a** and **80b** afford, respectively, 2,6-*cis*- and 2,6-*trans*-tetrahydropyrans **81** as a single diastereomer in good yields under very mild conditions.[58]

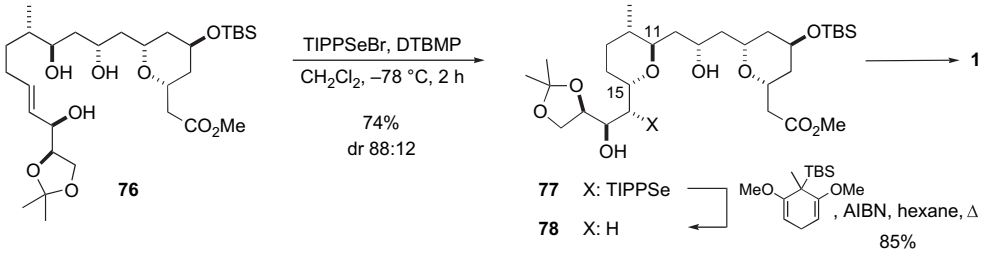
Palladium(0) catalysts also offer the opportunity for enantioselective cyclizations. Trost et al. have proved that

[‡] TIPPSeBr is prepared in situ from $(TIPPSe)_2$ and bromine.

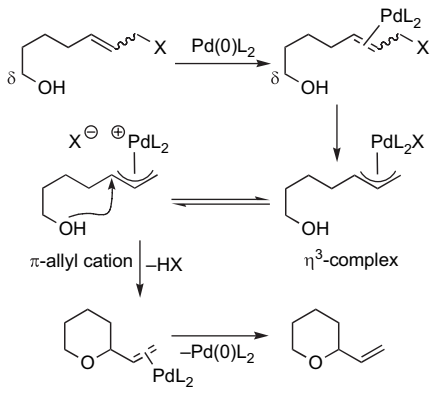


Conditions	*cis-trans*	Yield (%)
$Hg(OAc)_2$, Br_2, THF, rt	100:0	71
NBS, DMF, rt	100:0	77
NIS, CH_2Cl_2, rt	2.3:1	
NPSP, CSA, CH_2Cl_2, rt	1:1.8	87

Scheme 28.



Scheme 29.

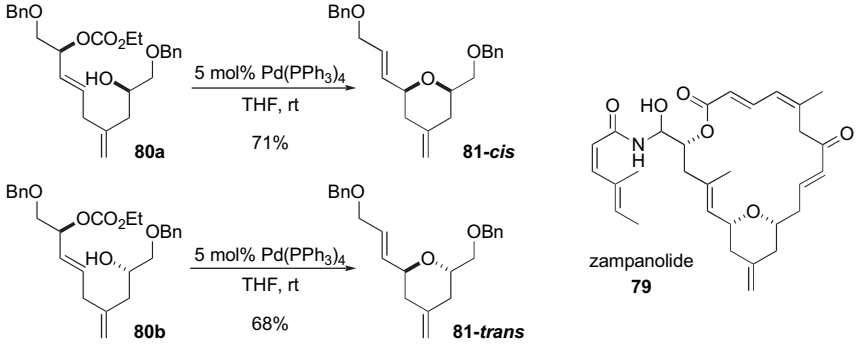


Scheme 30.

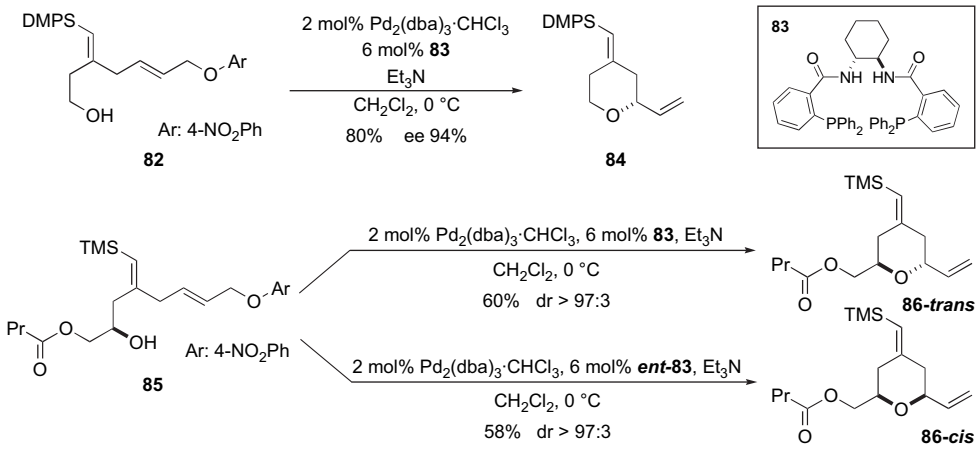
intramolecular asymmetric allylic alkylations[59] of hydroxy alkenes can be highly enantioselective, with the nucleophilic addition of the alcohol to the π-allylic cation being the enantio-determining step of the process.[60] As a case study, treatment of the hydroxy alkene **82** with a palladium catalyst generated by mixing $Pd_2(dba)_3 \cdot CHCl_3$, chiral diphosphine **83**, and Et_3N in CH_2Cl_2 at 0 °C provides the tetrahydropyran **84** in 80% yield and 94% ee (Scheme 32). Furthermore, the stereocontrol imparted by the catalyst is absolute on the more elaborated chiral substrate **85**, and the tetrahydropyran **86-*trans*** or the isomer **86-*cis*** is exclusively formed by switching the configuration of **83**.[61]

High stereochemical control has also been observed in δ-hydroxy alkenes containing other allylic leaving groups (Scheme 33). For instance, Pd(0)-catalyzed cyclization of carbonate **87** affords the tetrahydropyran **88** in high diastereomeric ratio, whereas **90** is obtained with complete stereocontrol from ester **89** in 96% yield.[62,63]

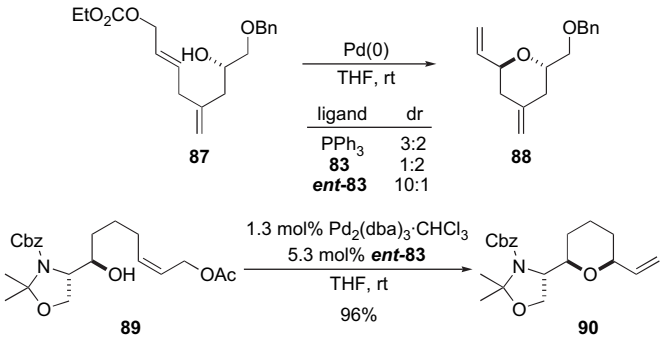
5.2.1.2. Catalysis by Pd(II). As previously mentioned, palladium(II) catalysts exhibit an electrophilic character that accounts for the formation of π-complexes with carbon–carbon double bonds, which easily undergo the addition of nucleophiles. In this manner, the Pd(II)-mediated intramolecular cyclization of hydroxy alkenes provides a straightforward



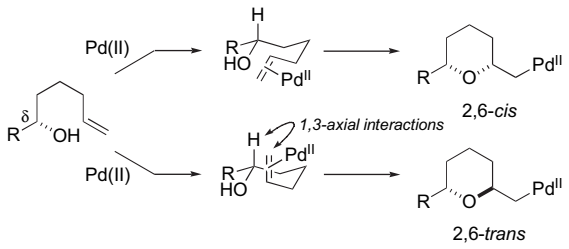
Scheme 31.



Scheme 32.



Scheme 33.



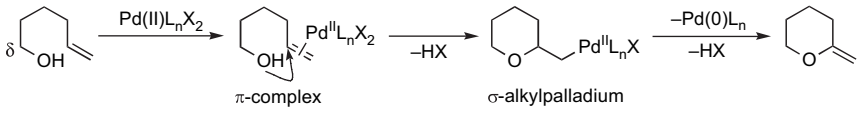
Scheme 35.

entry to oxygenated heterocycles. The regioselectivity of such cyclizations is commonly determined by the ring size, which facilitates the acquisition of pyrans from δ-hydroxy alkenes through a 6-*exo* ring closure (Scheme 34).[64–66] The nucleophilic attack of the hydroxyl on the corresponding π-complex usually occurs *anti* to the metal to produce a σ-alkylpalladium(II) intermediate, which next undertakes a β-hydride elimination. Importantly, Pd(0) is produced in the final step and, consequently, a mild re-oxidant to transform Pd(0) back into Pd(II) without affecting the substrates or products is required to obtain a process catalytic in palladium; otherwise, the process must be carried out using stoichiometric amounts of the Pd(II) complex.[67]

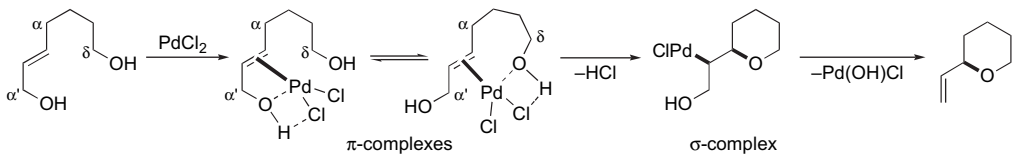
The rationale for the stereochemical outcome of these cyclizations usually hinges on the relative steric demands of the reversibly formed palladium intermediates.[65] Attention is then focused on the steric interactions engaged in the alternative approaches outlined in Scheme 35. Hence, 2,6-*cis* arrangements are often preferred, especially in the case where all the substituents are placed in equatorial positions or clearly unfavorable axial interactions are developed on the way to 2,6-*trans* isomers.

The success of such a strategy is intimately related to the regioselectivity of the β-hydride elimination step. Studies on this issue have proved that it is highly solvent dependent, DMSO being the best choice,[68] but, in spite of these accomplishments, these cyclizations have been scarcely applied to the synthesis of natural products.[69] This limitation has been overcome through the introduction of a hydroxy group at the allylic position.[70] As represented in Scheme 36, the key feature of this process entails the coordination of the allylic alcohol, α′-OH, to the metal. Then, the initial Pd–π-complex is selectively formed on the same face of the double bond as the α′-OH. This complex determines the approach of the δ-OH to the reacting center (*syn* attack) and, consequently, the stereochemical outcome of the cyclization. Eventually, the resultant σ-complex undergoes a selective Pd(II) elimination leading to a new olefinic bond. Hence, the overall sequence may be considered as a Pd-mediated S_N2' process that can proceed without any oxidant.

In this context, a chiral starting material can give access to disubstituted tetrahydropyrans stereoselectively (Scheme 37).



Scheme 34.



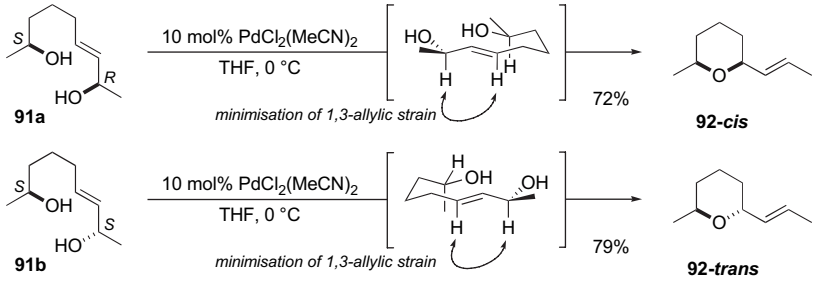
Scheme 36.

Indeed, chiral diols **91a**,**b** afford 2,6-*cis*- or 2,6-*trans*-tetrahydropyrans **92** as a single isomer in excellent yields, depending upon the configuration of the allylic stereocenter, α′, with perfect 1,3-chirality transfer. According to the mechanistic guidelines presented in Scheme 37, the π-face selectivity observed in these cyclizations can be rationalized by considering conformations on the α′-stereocenter, so that the most favored approaches avoid 1,3-allylic strain.[71]

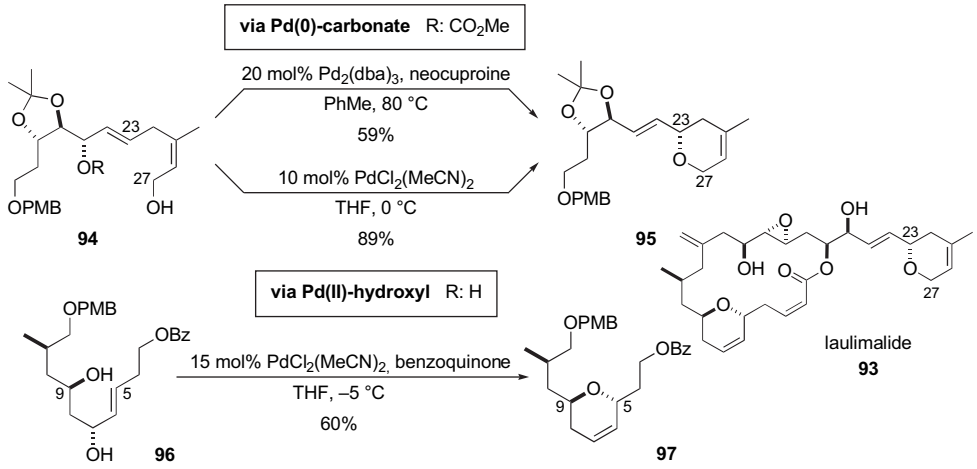
This strategy has been successfully applied to the construction of pyran rings embedded in the structure of laulimalide (**93** in Scheme 38). Moreover, it has been subjected to the Pd(0)-mediated methodology described in Section 5.2.1 for the synthesis of the C23–C27 dihydropyran **95**. Both the Pd complexes catalyze the 6-*exo*-like cyclization of **94** to **95** as a sole isomer in good-to-excellent yields. Furthermore, the 6-*endo*-*trig* cyclization of **96** occurs through a *syn*-S_N2' process to give exclusively the desired 2,6-*trans*-dihydropyran **97** in 60% yield.[70a]

As shown in Scheme 34, the Pd-mediated intramolecular addition of a hydroxyl group to an alkene leads to a σ-alkylpalladium(II) intermediate. This intermediate can then be trapped by CO and the resultant acylpalladium species is easily converted into the corresponding methyl ester (Scheme 39). Thus, the overall process is a 1,2-alkoxycarbonylation that avoids any β-elimination. In the case of chiral centers, the insertion of CO into the carbon–palladium bond usually retains the configuration that arises from the cyclization step, and so pyran-containing ester groups can be stereoselectively obtained as a result of these transformations.[72,73]

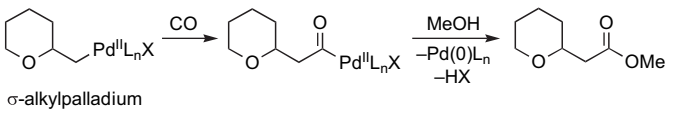
This methodology has been applied to the synthesis of leucascandrolide A (**1**)[1a] and phorboxazole A (**2a**).[2g] As shown in Scheme 40, the intramolecular alkoxycarbonylation of diol **98** in 1:1 MeOH–PhCN (the use of benzonitrile facilitates a cleaner and more efficient process) provides the desired 2,6-*cis*-tetrahydropyran **99** in 75% yield and dr >10:1. Noteworthy is the fact that the cyclization is highly selective and the two alcohols and two alkenes in **98** are completely differentiated, which simplifies the protecting-group strategy. Furthermore, the C22–C26 tetrahydropyran (**101**) of **2a** is prepared in high yield through the $Pd(OAc)_2$-mediated



Scheme 37. *Note*: Pd atoms have been omitted for clarity.



Scheme 38.

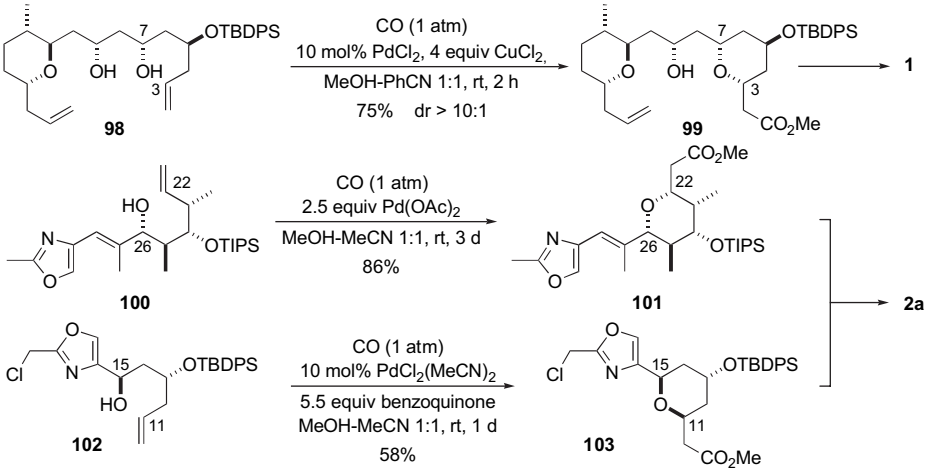


Scheme 39.

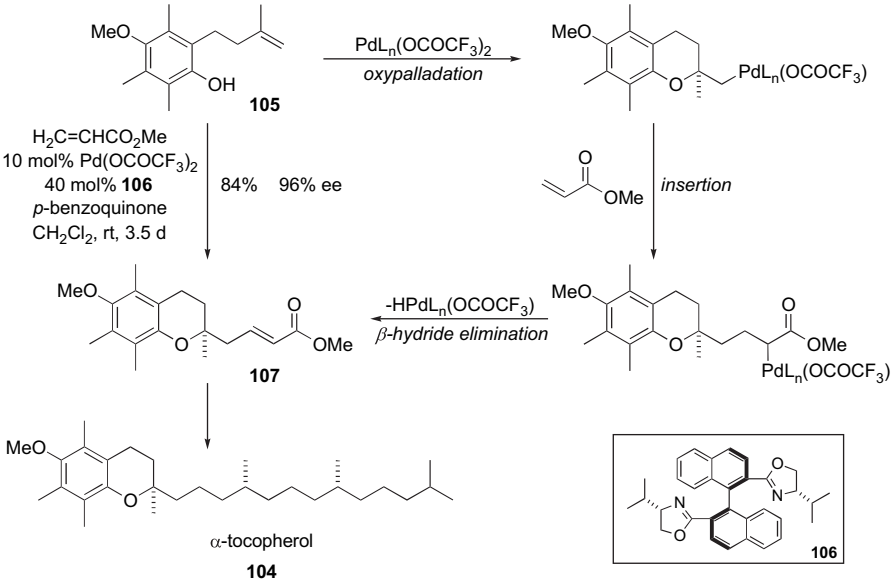
cyclization of hydroxy alkene **100**, although 2.5 equiv of the Pd(II) reagent is needed for complete conversion because of its reduction by CO during the course of the reaction (acetonitrile is used to minimize such deactivation).[74] In turn, the parallel ring closure of **102** has been carried out in the presence of a large excess of *p*-benzoquinone to afford 2,6-*cis*-tetrahydropyran **103** in 58% isolated yield.

The σ-alkylpalladium(II) intermediates can also be trapped through a Heck reaction. This possibility is nicely illustrated by a palladium-catalyzed sequence along the synthesis of α-tocopherol (**104** in Scheme 41).[75] Indeed, the reaction of **105** with methyl acrylate in the presence of catalytic amounts of $Pd(OCOCF_3)_2$, the chiral ligand **106**, and *p*-benzoquinone affords chroman **107** with 96% ee in 84% yield. This two-step sequence is assumed to proceed via the enantioselective oxypalladation of **105**. The resultant σ-alkylpalladium complex then undergoes a Heck reaction with methyl acrylate and, finally, a β-hydride elimination delivers the desired product.

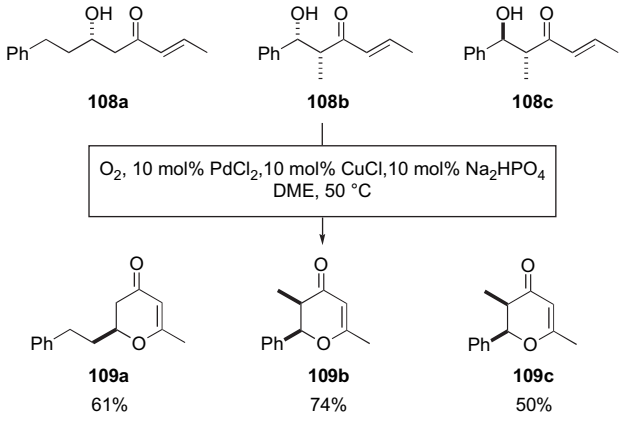
A conceptually different strategy to the synthesis of 2,3-dihydro-4*H*-pyranones such as **109a–c** takes advantage of the reactivity of enones. As represented in Scheme 42, it relies on the oxidative cyclization of β-hydroxy enones **108a–c** with $PdCl_2$. Thus, this methodology represents a new approach to the enantioselective assemblage of these useful intermediates, based on a 6-*endo* ring closure of a Pd(II)–π-complex followed by a completely regioselective β-hydride elimination, without affecting the integrity of the existing stereocenters.[76]



Scheme 40.



Scheme 41.



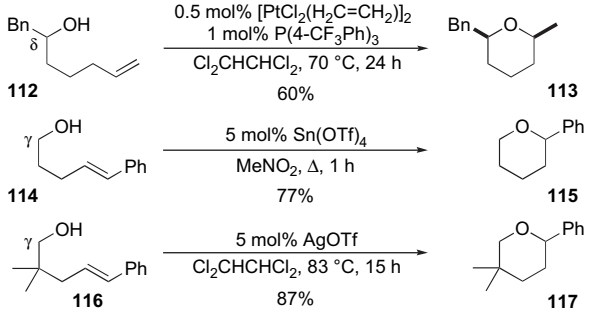
Scheme 42.

A related cyclization involving a 6-*endo* ring closure of an α,β-unsaturated ketone has been used to build the dihydropyranyl enone unit of several *Alstonia* alkaloids, such as alstophylline (**110** in Scheme 43).[77] Although the detailed mechanism is not clear, the process is believed to involve the formation of a Pd–π-complex on **111**, removal of the silyl group, and nucleophilic attack of the deprotected alcohol on the palladium complex. Finally, β-hydride elimination provides **110**, while the Pd(0) is re-oxidized to Pd(II) by *t*-BuOOH.

5.2.2. Other metal-mediated cyclizations

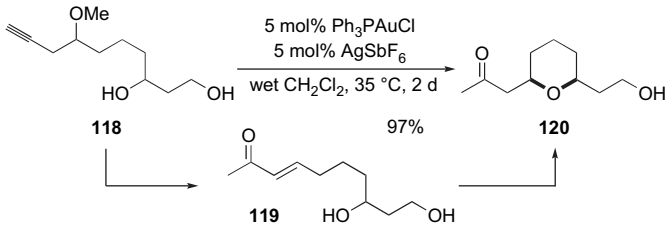
Besides palladium chemistry, there is a handful of emerging catalytic methodologies for the cyclization of δ- and γ-hydroxy alkenes, based on the activation of the olefin by other metals, e.g., platinum,[78] tin,[79] silver,[80] or cerium[81] (Scheme 44). The mechanism that accounts for such processes involves the electrophilic activation of olefin according to the guidelines illustrated in Scheme 19. The regioselectivity is well defined for δ-hydroxy alkenes, whereas ring closure of γ-hydroxy alkenes **114** and **116** is apparently ruled by the Markovnikov tenet, in which the stabilization provided by substituents of the olefin seems to support the formation of tetrahydropyrans over their tetrahydrofuran counterparts. Synthetically, the scope of these approaches is still limited and they cannot compete with the performance of palladium catalysts, but they offer new avenues to the construction of tetrahydropyrans and constitute a promising area of research.

Remarkably, gold catalysts can participate in a cascade sequence that presumably involves a 6-*exo* ring closure of a hydroxy enone intermediate through a metal activation of the carbon–carbon double bond.[82] Indeed, treatment of homopropargylic ether



Scheme 44.

118 with $Ph_3PAuCl–AgSbF_6$ in wet CH_2Cl_2 gives the enone intermediate **119** that cyclizes to 2,6-*cis*-tetrahydropyran **120** in excellent yield (Scheme 45).

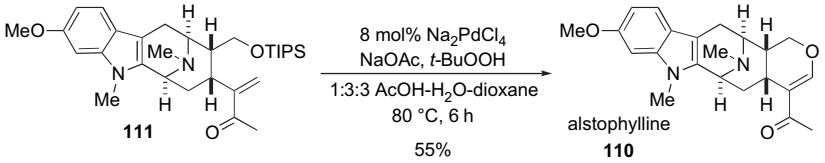


Scheme 45.

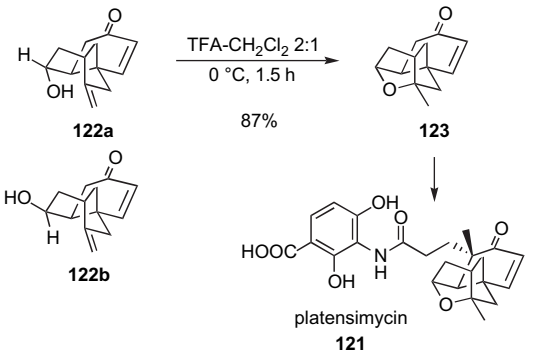
5.3. Acid-mediated cyclizations

Acid-mediated cyclizations of hydroxy alkenes represent a particular class of processes, as they are promoted by stoichiometric or catalytic amounts of Brønsted acids. Although the mechanistic issues of these cyclizations are rather speculative, their regioselectivity is usually controlled by the Markovnikov tenet and most of them involve strong Brønsted acids. Actually, they are commonly carried out in the presence of large quantities of these reagents. This is the situation observed during the synthesis of platensimycin (**121** in Scheme 46),[83] in which treatment of a 2:1 mixture of diastereomers **122a** and **122b** with TFA (TFA–CH_2Cl_2 2:1) gives the cage-like structure **123** in 87% yield, based on the isomer **122a** present in the mixture. Interestingly, the undesired diastereomer **122b** is recovered unchanged.[84]

It also occurs that these cyclizations can be carried out under catalytic conditions.[79,85] For instance, the ring closure of hydroxy vinylsilanes such as **124** to **125** using a catalytic amount of Brønsted acids has been thoroughly studied

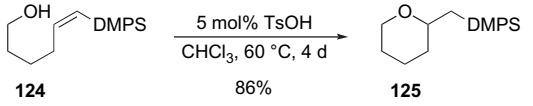


Scheme 43.



Scheme 46.

(Scheme 47). A plausible mechanism for this cyclization involves the formation of a β-silylcarbenium ion intermediate by protonation of the sp^2-carbon α to the silyl group and the subsequent intramolecular attack of the hydroxy oxygen on the cationic center.[86]



Scheme 47.

Eventually, Lewis acids can also be involved in the intramolecular hydroxyalkoxylation of unactivated olefins, leading to tetrahydropyrans. These processes presumably proceed through the formation of a Lewis acid–OH complex that enhances the acidity of the hydroxyl proton.[86,87] Furthermore, polycyclic compounds such as (−)-caparrapi oxide and (+)-8-epicaparrapi oxide (**126** and **127**, respectively, in Scheme 48) have been obtained from hydroxy alkene **128** in the presence of stoichiometric amounts of chiral LBA (*L*ewis acid-assisted chiral *B*rønsted *A*cid) complexes **129** and ***ent*-129**. Indeed, the asymmetric ring closure of **128** induced by **129** gives an 81:19 mixture of **130** (>99% ee) and **131** (21% ee), whereas the parallel cyclization induced by ***ent*-129** provides a 14:86 mixture of **130** (27% ee) and **131** (98% ee). Eventually, optically pure **130** and **131** are isolated in 74 and 73% yield by column chromatography.[88]

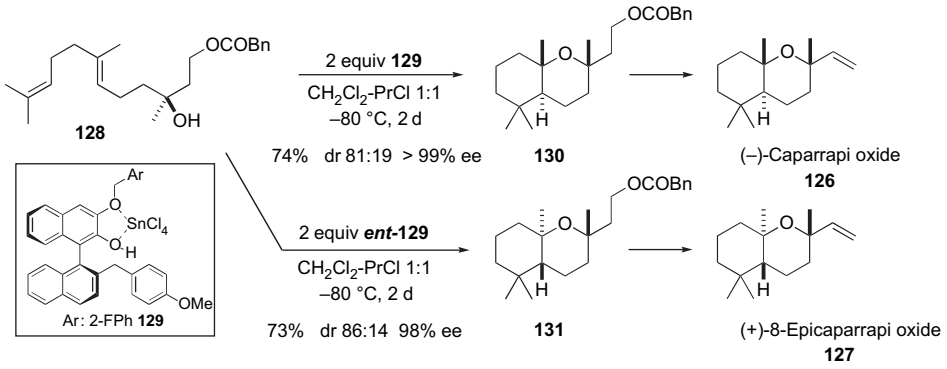
6. Allene-mediated cyclizations

Allenes containing a nucleophile can undergo intramolecular cyclizations on treatment with transition metal catalysts.[89] In particular, gold-catalyzed cycloisomerization of β- or δ-hydroxyallene gives access to six-membered oxygenated heterocycles in a straightforward manner. As occurs for alkenes (see Scheme 19), the initial coordination of the gold catalyst to one of the terminal double bonds of a β-hydroxyallene such as **132** gives rise to the formation of an intermediate, which, upon nucleophilic attack of the oxygen, is converted into a σ-gold complex through a 6-*endo-trig* ring closure (Scheme 49). Subsequent protodemetallation of this complex furnishes the corresponding dihydropyran **133**.[90] Likewise, δ-hydroxyallene **134** undergoes a 6-*exo-trig* hydroalkoxylation to form the corresponding 2-alkenyl tetrahydropyran derivative **135** in excellent yield.[91] Remarkably, gold-mediated hydroalkoxylation of **134** in the presence of the chiral diphosphine **136** affords **135** in 96% yield and 88% ee.[92]

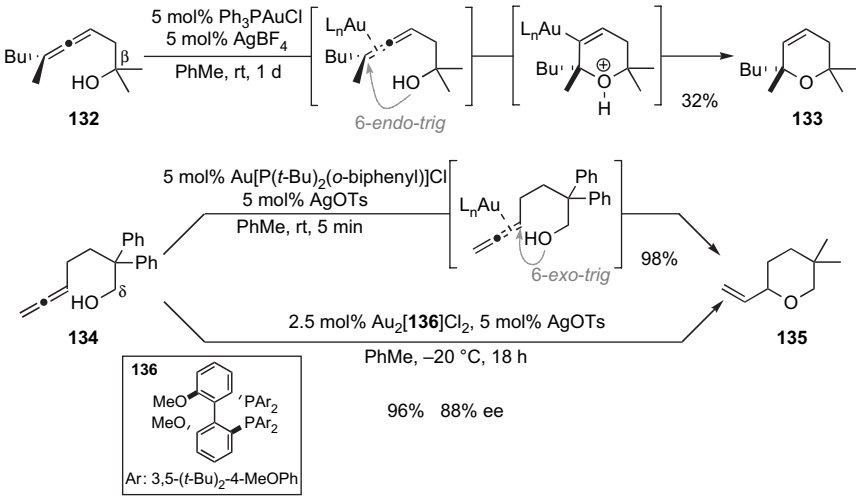
7. Alkyne-mediated cyclizations

A conceptually related set of approaches based on the electrophilic activation of carbon–carbon triple bonds have also proved to be a highly efficient entry into the synthesis of six-membered oxygenated heterocycles.[93] Indeed, the catalytic metal-mediated intramolecular cyclizations of precursors containing alkynes and different oxygenated nucleophiles can be exploited for the construction of a wide array of oxygen-containing heterocycles.

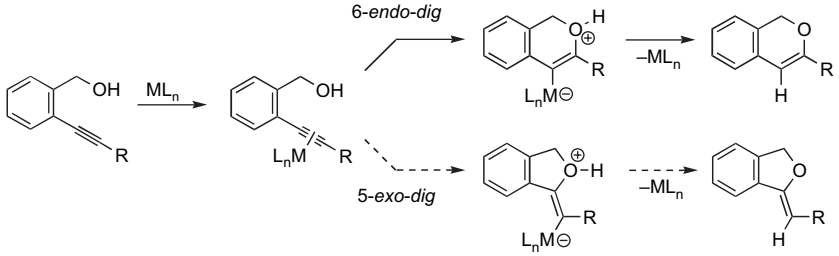
Surprisingly, the simplest strategy based on the use of hydroxy alkynes had been scarcely applied to date, but recent reports on the cyclization of 4- and 5-alkynol have established the synthetic potential of such an approach. In this context, palladium[94,95] and iridium[96] complexes catalyze the 6-*endo-dig* ring closure of 2-alkynylbenzyl alcohols with internal triple bonds to the corresponding isochromenes in good yields. The mechanism for this transformation is outlined in Scheme 50. As for alkenes or allenes, initial coordination of the metal to the carbon–carbon triple bond enhances its electrophilicity and facilitates the attack of the hydroxyl. Then, a protodemetallation step renders the cyclic enol ether and regenerates the catalytic species.



Scheme 48.



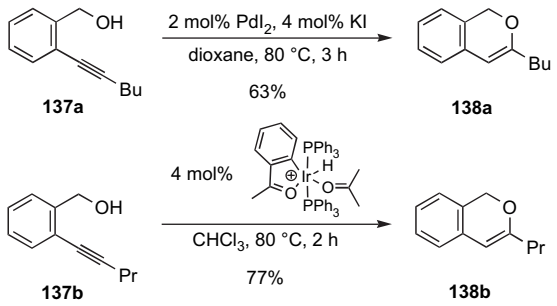
Scheme 49.



Scheme 50.

As shown in Scheme 50, an alternative pathway involving a 5-*exo-dig* ring closure threatens the success of such methodology. A comprehensive analysis of the regioselectivity of this cyclization for palladium catalysts has revealed that the 6-*endo-dig* is favored over the 5-*exo-dig* mode by alkyl, rather than aryl, substitution on the triple bond, low solvent polarity (dioxane), high temperatures (80–100 °C), and dilute conditions.[94,97] Keeping these limitations in mind, both palladium(II) and iridium(III) catalysts provide a good entry into isochromenes **138a**,**b** from 2-alkynylbenzyl alcohols **137a**,**b** (Scheme 51).

Working in the 4-alkynol arena, a tandem palladium(II)-catalyzed reaction offers an appealing entry into the synthesis of dihydropyrans.[98] As represented in Scheme 52, the palladium-catalyzed addition of a terminal alkyne to a hydroxy



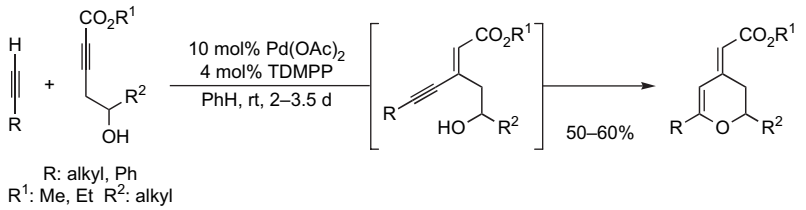
Scheme 51.

ynoate initially affords a conjugated adduct, which undergoes a 6-*endo-dig* cyclization. Remarkably, the resultant dihydropyran contains an exocyclic carbon–carbon double bond with a well-defined geometry (for an outstanding application of this palladium-based tandem synthesis and a related ruthenium process, see Scheme 89).

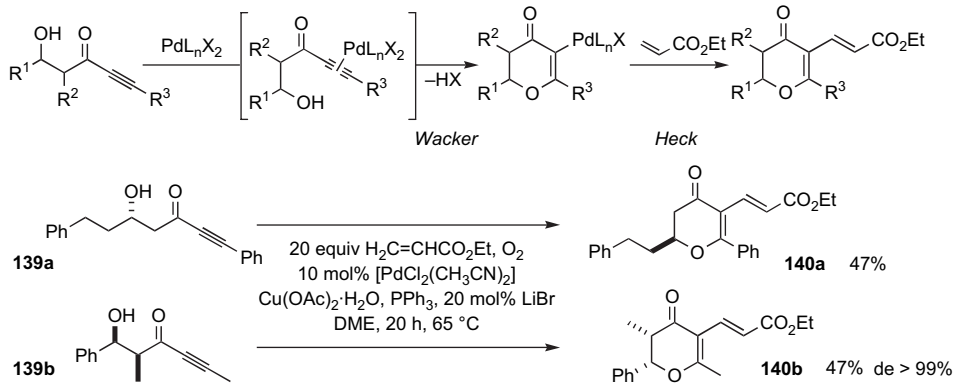
Furthermore, a palladium(II)-catalyzed 6-*endo-dig* cyclization of β-hydroxy ynones, similar to that outlined in Scheme 42, has recently been disclosed.[99] Differently, the σ-alkenylpalladium intermediate obtained in this reaction undergoes insertion of ethyl acrylate to form trisubstituted dihydropyranones featuring an alkenyl substituent α to the carbonyl (Scheme 53). Thus, the overall process entails a cascade Wacker–Heck reaction that involves the chemoselective coupling of two electron-deficient reactants. This Wacker–Heck sequence does not affect the stereochemical integrity of the starting β-hydroxy ynones **139a**,**b** and affords the corresponding dihydropyranones **140a**,**b** in good yields.

Otherwise, 5-alkynols with a terminal triple bond undergo completely regioselective 6-*exo-dig* ring closures to exocyclic enol ethers in the presence of palladium,[100] iridium,[101] platinum,[102] or gold[102,103] catalysts (Scheme 54). Their mechanism is also based on the electrophilic activation of the alkyne according to the guidelines previously described, but, differently, the competitive 7-*endo-dig* pathway is never observed.

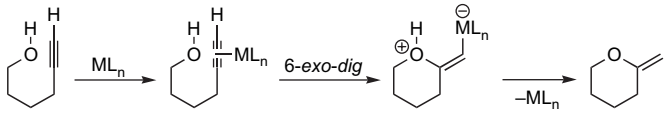
Interestingly, the resultant cyclic enol ethers can be the starting point for further transformations. For instance, treatment of



Scheme 52.



Scheme 53.

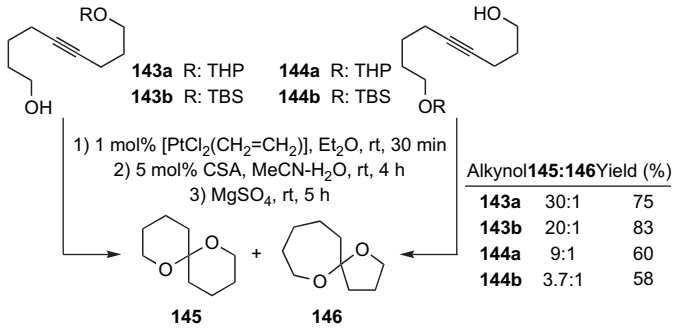


Scheme 54.

alkynols **141** (Scheme 55) with platinum or gold catalysts leads to the enol ethers, which undergo a Prins-type cyclization through an oxocarbenium intermediate that eventually affords the eight-membered carbocycles **142** as a sole diastereomer in excellent yields, irrespective of the catalyst.[102]

Internal alkynols can also participate in highly regioselective cycloisomerizations, provided that the resultant enol ethers are satisfactorily trapped by other nucleophiles. For instance, platinum(II)-catalyzed hydroxyalkoxylation of alkynols **143a**,**b** and **144a**,**b** deliver selectively spiroketal **145** through initial 6-*exo-dig* or 6-*endo-dig* ring-closure modes, respectively (Scheme 56).[104–106]

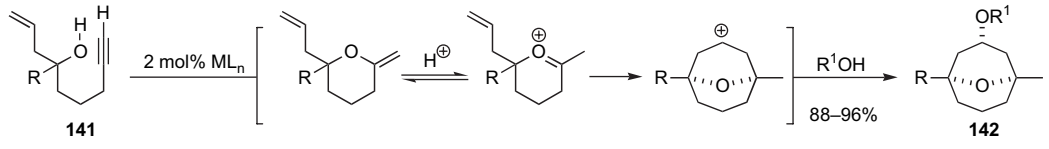
A similar gold-catalyzed 6-*exo-dig* cyclization plays a crucial role in the synthesis of the trioxadispiroketal of azaspiracids (**62** in Scheme 24). As represented in Scheme 57 (see also



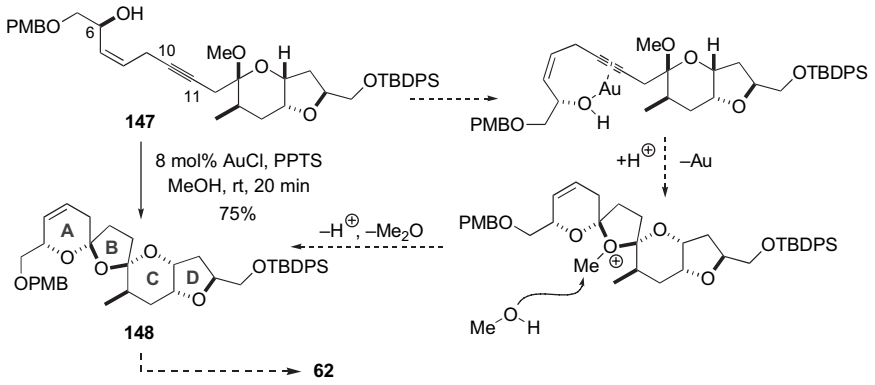
Scheme 56.

Scheme 91), the assemblage of the A–D rings starting from alkynol **147** relies on the addition of the C6 hydroxy group across the C10–C11 alkyne followed by the engagement of the C13 ketal exocyclic oxygen atom to form the desired spiroketal.[107] Remarkably, treatment of **147** with catalytic amounts of AuCl and PPTS furnishes **148** in 75% yield.

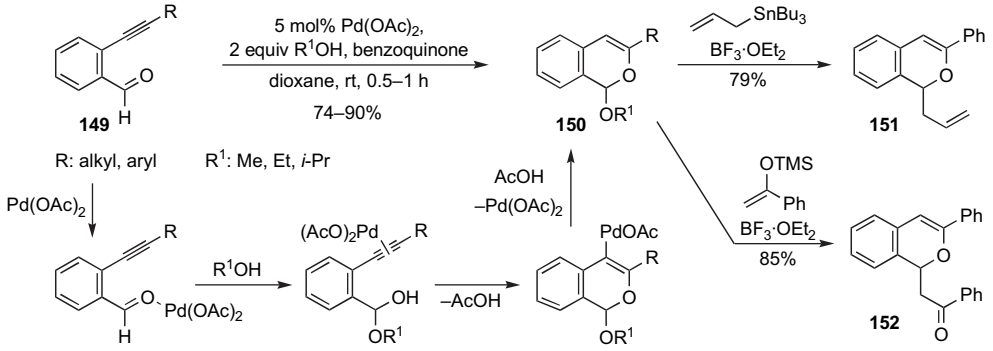
A closely related methodology takes advantage of the hydroxyl-like character of hemiacetals. Yamamoto et al. have reported that the simultaneous activation of a carbonyl and



Scheme 55.



Scheme 57.



Scheme 58.

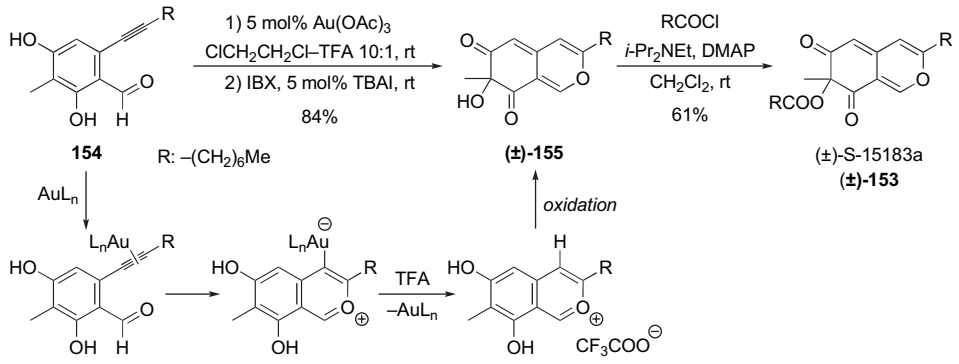
a carbon–carbon triple bond by palladium(II) catalysts allows the construction of cyclic alkenyl ethers from acetylenic aldehydes. Indeed, cyclization of 2-alkynylbenzaldehydes **149** proceeds smoothly in the presence of $Pd(OAc)_2$ to provide acetals **150** in high yields (Scheme 58).[108] The authors propose a mechanism in which the palladium catalyst initially acts as a Lewis acid, promoting the formation of the corresponding hemiacetal. Then, coordination of the metal to the alkyne facilitates the *anti* attack of the hydroxyl from the side opposite to the metal via a 6-*endo-dig* pathway.[§] The resultant vinylpalladium intermediate is subsequently protonated to afford the final alkenyl acetal with complete regioselectivity. Noteworthy is the fact that the high reactivity of the benzylic acetal in **150** (R: Ph, R^1: Me) makes possible the introduction of carbon nucleophiles via Hosomi–Sakurai allylation and Mukaiyama aldol reactions to afford **151** and **152** in high yields.[109]

Other oxygenated nucleophiles such as carboxylic acid derivatives and carbonyls have also been utilized in this type of cyclization.[93a,110] A step forward in this area relies on the electrophilic activation of the carbon–carbon triple bond of 2-alkynylbenzaldehydes and related systems. Now, the nucleophilic attack of the carbonyl oxygen on the electronically deficient alkyne produces a 2-benzopyrylium-like intermediate, which can undergo further transformations that ultimately offer a rich assortment of structures.[111–114]

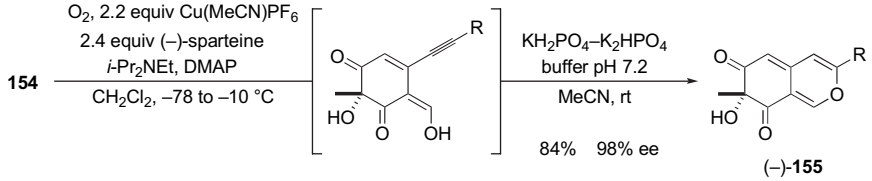
This methodology has been applied to the synthesis of (±)-*S*-15183a (**153** in Scheme 59), a member of the azaphilones, a family of natural products containing a highly oxygenated bicyclic core and a quaternary stereocenter.[115] The reported synthesis takes advantage of a gold-mediated cycloisomerization of 2-alkynylbenzaldehyde **154** followed by oxidation of the resultant 2-benzopyrylium salt. As outlined in Scheme 59, a plausible mechanism for this transformation entails the coordination of the gold catalyst to the triple bond followed by cyclization and protodemetallation to furnish the 2-benzopyrylium salt. Eventually, oxidation of this salt affords in 84% overall yield the desired oxygenated heterocycle **155** as a racemic mixture.

Having developed a straightforward route to the bicyclic core, attention was focused on the asymmetric oxidation of the benzopyrylium salt. However, all attempts were unsuccessful and a new strategy, based on the initial oxidation of the aromatic ring, was disclosed. Remarkably, the Cu_2[(−)-sparteine]$_2O_2$-mediated enantioselective oxidative dearomatization of **154** provides a hydroxy derivative, which undergoes the desired cycloisomerization under very mild conditions to afford (−)-**155** in 98% ee and 84% overall yield (Scheme 60). It is

[§] It is worth pointing out that the aromatic ring is crucial to the observed regioselectivity. The reaction of the equivalent carbon-tethered acetylenic aldehydes, 4-alkynals, mainly yields the corresponding five-membered acetals through 5-*exo-dig* cyclizations.



Scheme 59.

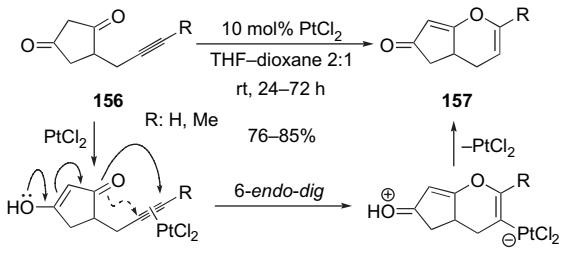


Scheme 60.

worth emphasizing that the 6-*endo-dig* ring closure is carried out without any metal at pH 7.2.[116,117]

Other systems available for this chemistry are 4-propargyl-1,3-cyclopentanediones **156** represented in Scheme 61. Metal-mediated cyclization of these 1,3-diketones admits catalysts based on palladium,[118] platinum, tungsten, and mercury.[119] Noteworthy is the fact that the platinum-mediated catalysis of terminal and substituted alkynes affords exclusively the bicycles **157** in high yields at room temperature. These 6-*endo-dig* cyclizations are supposed to proceed under kinetic control by coordination of the catalyst to the triple bond. Then, the alkyne–metal complex undergoes *anti* attack of the carbonyl oxygen and the resultant vinylplatinum intermediate is protonated to afford the oxabicycle **157**. Since related 1,3-cyclohexadienones are prone to 5-*exo-dig* ring closures, the excellent regioselectivity observed for **156** is presumably due to subtle intrinsic strain on the way to the *exo*- or *endo*-bicyclic systems.

As well as these catalytic processes, there are some stoichiometric metal-free methodologies based on the iodine-mediated electrophilic activation of the substituted carbon–carbon triple bond of 2-alkynylbenzaldehydes that allow for the highly efficient construction of six-membered oxygenated



Scheme 61.

heterocycles[120,121] and other carbocycles.[122] For instance, addition of the iodonium ion generated from $Ipyr_2BF_4/HBF_4$ to the triple bond of 2-alkynylbenzaldehydes **149** leads to an iodobenzopyrylium salt, which, in turn, reacts with nucleophiles and offers a straight and useful access to highly elaborated oxygenated heterocycles **158–161** (Scheme 62).[120] Importantly, most of these transformations can be carried out following a procedure based on the use of iodine.[121]

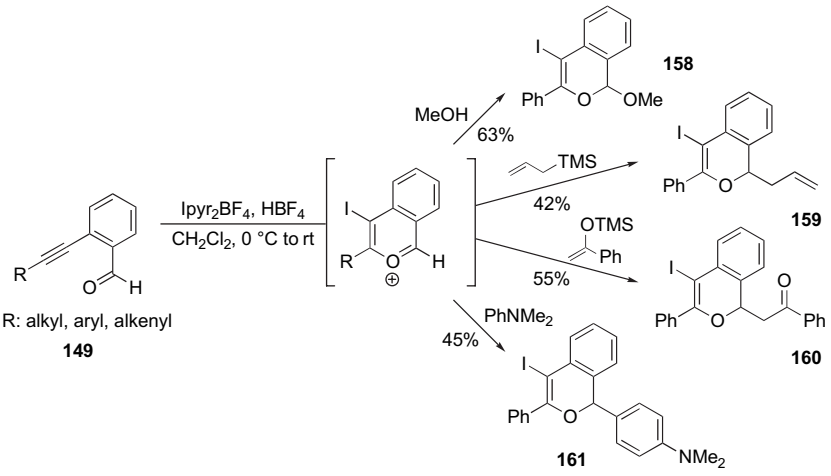
8. Other metal-promoted cyclizations

In addition to the methodologies just described, metals can also catalyze other cyclizations that require the in situ generation of transition metal–carbenoid species. Such transformations encompass the cycloisomerization of 4-alkynols via metal vinylidene complexes and the intramolecular addition of oxygenated nucleophiles to metal carbenes obtained from diazo precursors.

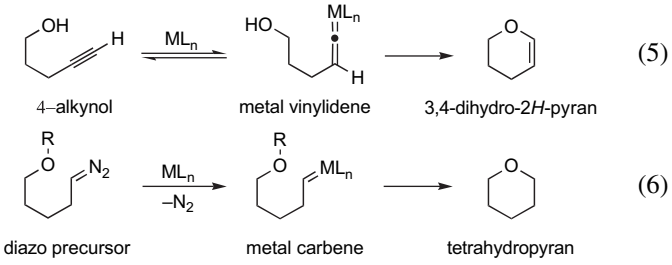
This chapter also takes into account a less studied transformation: the intramolecular etherification of aryl and vinyl halides catalyzed by palladium and copper.

8.1. Cyclizations of 4-alkynols

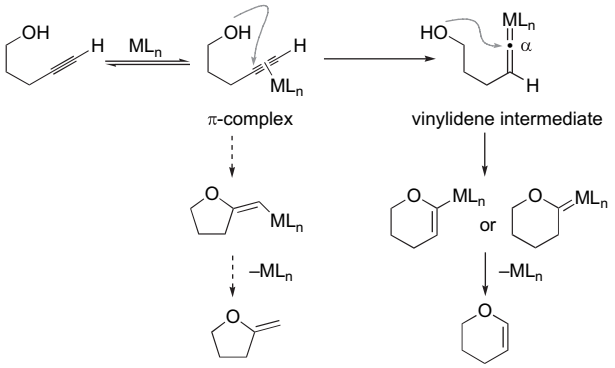
The transition metal-mediated isomerization of hydroxy alkynes containing a terminal carbon–carbon triple bond represents a highly valuable route for preparing 3,4-dihydro-2*H*-pyrans (see Eq. 5 in Scheme 63).[123] Unlike the methodologies previously discussed, these processes proceed through a metal vinylidene intermediate that undergoes intramolecular attack by an alcohol. Thus, the key element of such cyclizations relies on providing metal vinylidene intermediates reactive enough to sustain a catalytic process. These species arise from the initial



Scheme 62.



Scheme 63.



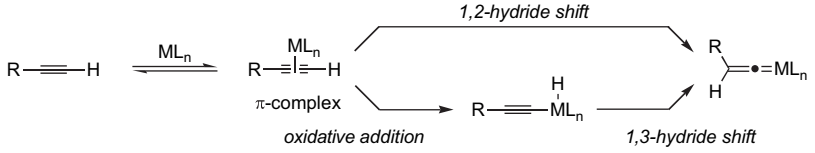
Scheme 65.

coordination of a metal to a terminal alkyne (Scheme 64). Then, the resultant π-complex undergoes either a 1,2-hydrogen migration over the triple bond or an oxidative addition of the C(sp)–H bond to the metal center and subsequent 1,3-shift of the hydride to the alkyne ligand.[124,125]

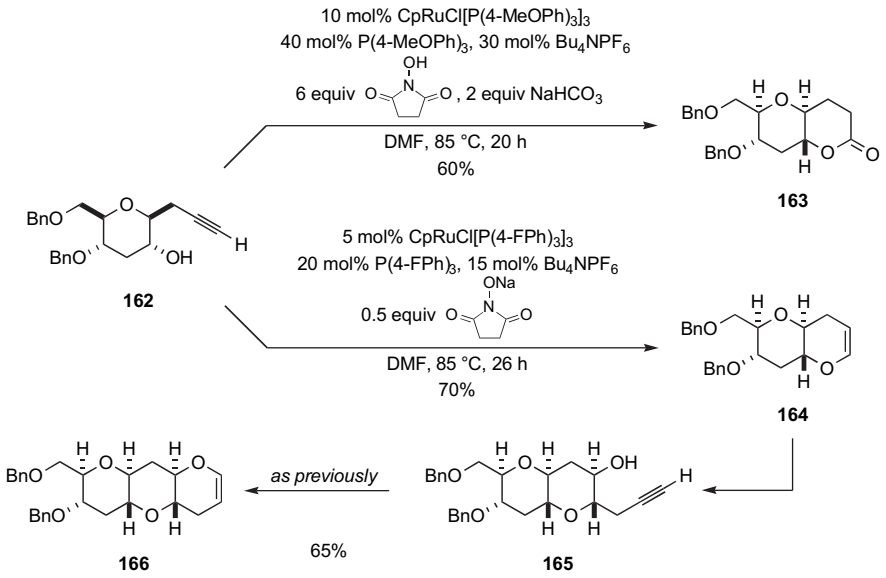
The α-carbon in the Cβ=Cα=ML_n moiety exhibits electrophilic properties and undertakes additions of nucleophiles that eventually lead to formal anti-Markovnikov products. Importantly, the intramolecular attack of the hydroxyl on the Cα-center of the vinylidene intermediate derived from 4-alkynols must override a competitive pathway arising from the simple addition to the activated π-complex (Scheme 65). Thus, the structural elements on the substrate, the catalyst, and the reaction conditions have to be carefully chosen to avoid such a 5-*exo-dig* ring closure. These conditions are rather stringent and few metals form vinylidene intermediates that are able to take part in catalytic sequences. To date, this limited group includes rhodium,[126] ruthenium,[127] and mostly, tungsten complexes.[123,128]

Ruthenium(II) complexes [$CpRuCl(PR_3)_3$] catalyze the highly selective synthesis of lactones and cyclic enol ethers, depending on the phosphine and the amount of *N*-hydroxysuccinimide employed (Scheme 66).[127a] Indeed, electron-rich arylphosphines such as $P(4\text{-}MeOPh)_3$ and a large excess of *N*-hydroxysuccinimide produce six-membered lactones, whereas electron-poor arylphosphines such as $P(4\text{-}FPh)_3$ and small amounts of the sodium salt of *N*-hydroxysuccinimide provide the corresponding dihydropyrans. Unfortunately, none of these conditions can be applied to substrates bearing oxygenated substituents at the propargylic position. Despite this limitation, the efficiency of ruthenium(II) catalysts has been proved for the assemblage of structurally complex fused polyethers such as **163**–**166** from **162**.[127b]

Tungsten-like chemistry has attracted much attention.[123] The most common tungsten complex used for the cycloisomerization of 4-alkynols is $W(CO)_6$, which is photochemically activated in situ to generate the true catalytic species, presumably $W(CO)_5$.[129,130] The cyclization is routinely carried out



Scheme 64.



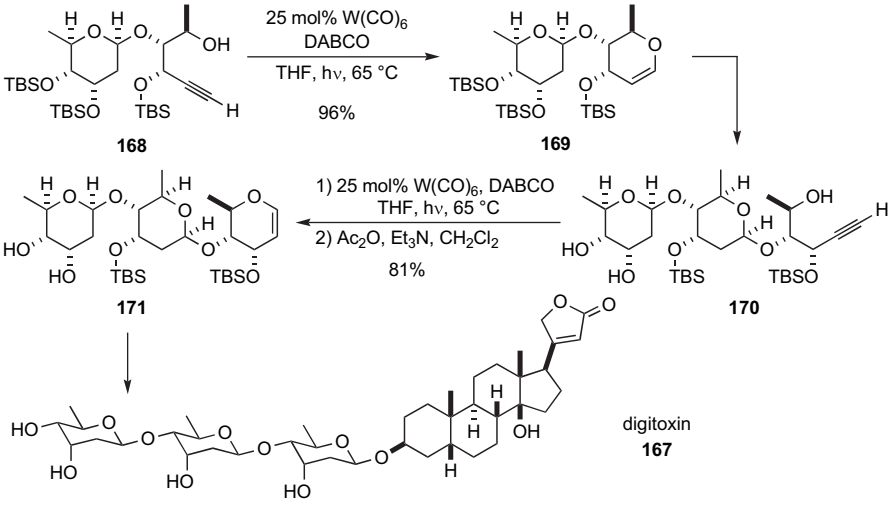
Scheme 66.

with 5–25 mol % $W(CO)_6$ and an excess of a tertiary amine (DABCO often gives better results than Et_3N) in THF or toluene under constant irradiation at 350 nm. Remarkably, these tungsten-based catalysts tolerate substituents at the propargylic position and are compatible with a wide variety of functional groups such as alcohols, ethers, amides, and carbamates.[131] This methodology has been successfully applied to the construction of the trisaccharide component of digitoxin (**167** in Scheme 67). Thereby, iterative alkynol cycloisomerization based on $W(CO)_6$ constitutes the most important feature of the synthetic sequence that provides glycal **171** and eventually allows for the total synthesis of digitoxin.[132]

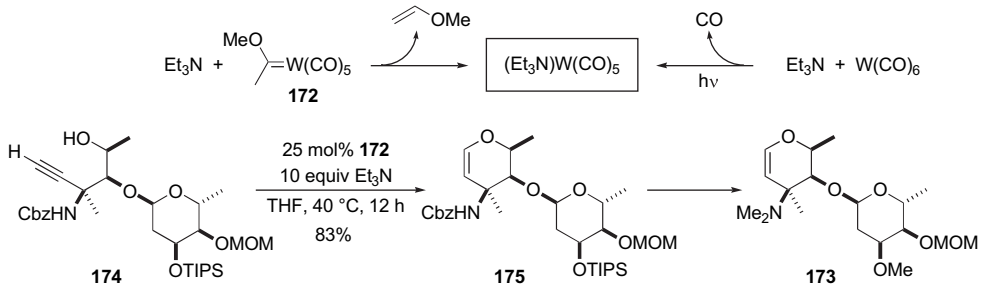
In addition to $W(CO)_6$, a preformed $THF \cdot W(CO)_5$ complex has been employed.[133,134] Moreover, a recent communication has disclosed a new catalytic system that does not require photochemical activation, based on (methoxymethylcarbene)pentacarbonyl tungsten (**172** in Scheme 68).[135] The optimal results are obtained with 25 mol % of oxacarbene **172** in the presence of 10 equiv of Et_3N by simple warming to 40 °C in THF. This experimental procedure has been successfully applied to the synthesis of the altromycin disaccharide **173** via **174** and **175**.

8.2. Cyclizations of diazo compounds

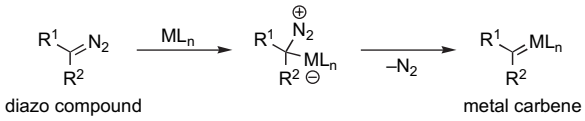
Metal carbenes are easily obtained from diazo compounds in the presence of copper and rhodium complexes. The accepted mechanism for this transformation combines the Lewis acid character of the metal complex and the basic properties of the carbon center of the diazo precursor. Hence, formation of an acid–base adduct is followed by back donation of electron density from the metal with concomitant loss of nitrogen, thus producing the metal carbene (Scheme 69).[136,137]



Scheme 67.



Scheme 68.

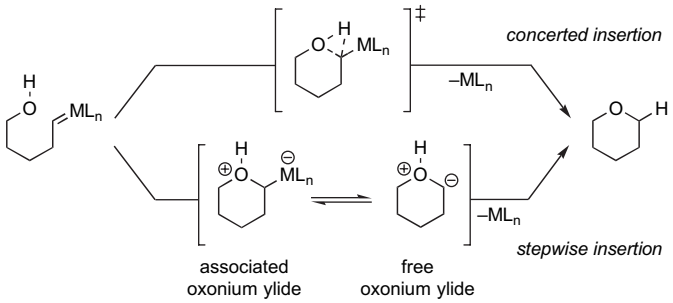


Scheme 69.

Stabilized diazo compounds, particularly α-diazo ketones or esters, are suitable precursors for metal carbenes that exhibit electrophilic properties at the carbon center, which allow them to undergo attack of nucleophiles with the eventual release of the metal. In particular, catalytic conversion of the diazo groups into the corresponding metal carbenes followed by intramolecular reaction with alcohols, ethers, or carbonyls affords a wide variety of oxygenated heterocycles (see Eq. 6 in Scheme 63). As the reacting roles are clearly defined, the regioselectivity of such cyclization is not at all troublesome and the only concern lies in the configuration of the resultant stereocenters.

The use of alcohols as the nucleophilic source for these cyclizations has been seldom exploited for the synthesis of pyran-like structures. Probably, more synthetic applications are lacking because the mechanism of the process is not fully understood. Studies on the insertion of metal carbenes into a polar O–H bond suggest that this transformation proceeds through a concerted pathway, as for parallel reactions with nonpolar C–H or Si–H bonds (Scheme 70).[136,138] However, evidence supporting a stepwise mechanism has also been reported.[139] The latter model entails the formation of an oxonium ylide, either free or associated to the metal, followed by a rapid [1,2]-hydrogen shift.

This methodology has been applied to the synthesis of 2-deoxy-β-KDO (**176** in Scheme 71). Metal–carbene ring



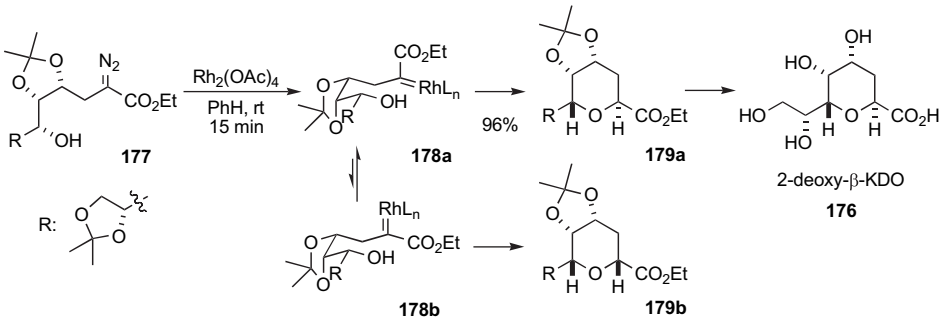
Scheme 70.

closure of the polyoxygenated α-diazo ester **177** produces 2,6-*trans* tetrahydropyran **179a** as the sole diastereomer in almost quantitative yield when the reaction is carried out with $Rh_2(OAc)_4$ in benzene at room temperature.[140] Otherwise, a 4:1 mixture of epimers **179a** and **179b** is obtained when benzene is replaced by chloroform or wet benzene. The rationale for this behavior assumes that the intramolecular attack proceeds on two alternative chair-like conformations **178a** and **178b**, the population of which is strongly solvent dependent.[141]

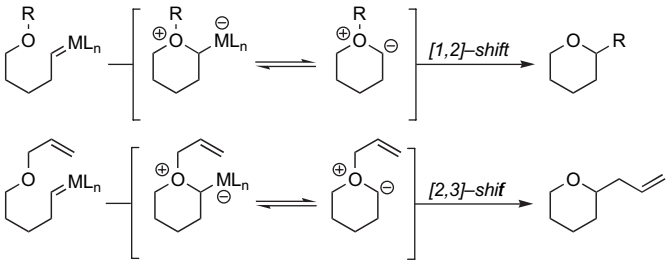
Ethers can also react with metal carbenes via an oxonium ylide intermediate to give six-membered oxygenated heterocycles. Although it is still unclear whether an associated or free oxonium ylide is the true intermediate for such transformation, it is generally accepted that these species can evolve through a [1,2]- or [2,3]-shift for allyl ethers (Scheme 72). Irrespective of the pathway, copper catalysts usually provide better results than their rhodium counterparts, presumably because they favor ylide formation over competitive C–H bond insertion.

In this context, copper-catalyzed cyclizations of α-diazo ketones containing an allyl ether have already been applied to the synthesis of natural products.[142,143] As an example, stereoselective oxonium ylide [2,3]-rearrangements have been used in an iterative approach for the construction of fused polyethers.[142] As shown in Scheme 73, treatment of allyl α-diazo ketone **180** with $Cu(tfacac)_2$ provides the bicyclic compound **181** in 80% yield and excellent diastereomeric ratio. Epimerization of **181** to the more stable equatorial isomer needed for eventual iteration and reduction of the resulting mixture delivers the alcohol **182** in 86% yield. Then, further functional-group manipulations afford the α-diazo ketone **183**, ready for a new cyclization–epimerization–reduction sequence leading via **184** to polyether **185**.

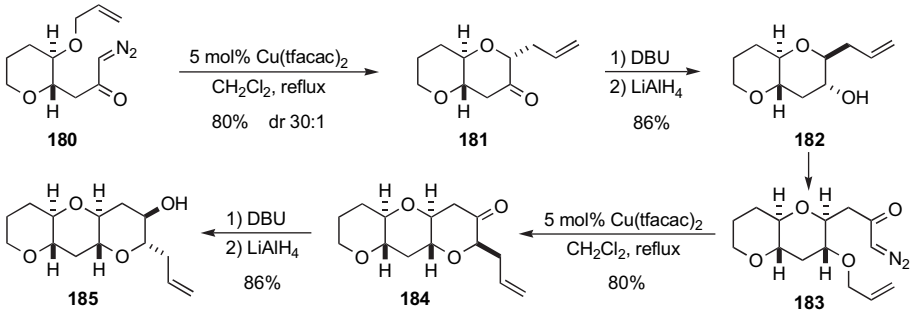
The use of carbonyls as oxygenated nucleophiles for the intramolecular addition to metal carbenes has received much attention. Attack of the oxygen atom of the C=O bond on a metal carbene produces a transient carbonyl ylide that can participate in 1,3-dipolar cycloadditions (Scheme 74). Thus, ring closure based on the nucleophilic addition of a carbonyl to a metal carbene represents the first step in a cascade sequence that gives access to structurally complex bicyclic systems. In this context, rhodium complexes afford higher yields than the copper adducts, because they enable diazo decomposition under milder conditions. Thus, cyclization



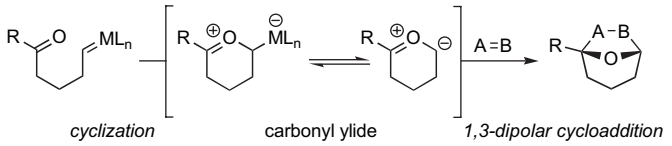
Scheme 71.



Scheme 72.



Scheme 73.



Scheme 74.

methodologies that take advantage of the carbonyl ylide reactivity currently employ rhodium(II) catalysts.[144–146]

The power of the carbonyl ylide cycloaddition methodology for the rapid assemblage of bicyclic systems has been proved in the stereoselective synthesis of structurally complex natural products such as zaragozic acid C[147] and polygalolide A[148] (**186** and **187**, respectively, in Fig. 4).[149]

The first example entails the intermolecular trapping of the carbonyl ylide intermediate from α-diazo ester **188** with 3-butyn-2-one to construct the cycloadduct **189** as a single diastereomer in 72% yield (Scheme 75).[147] The second example deals with an intramolecular version of such a cascade sequence from α-diazo ketone **190**, in which a simple olefin acts as dipolarophile to obtain diastereoselectively the tricyclic adduct **191** in 73% yield.[148] Surprisingly, the synthetic material shows a higher specific rotation than the samples obtained from natural sources, which suggests that polygalolide A might be biosynthesized through a poorly stereoselective pathway.[150]

Since the cycloaddition step can be faster than metal decomplexation from the carbonyl ylide, enantioselective tandem sequences can also be achieved by positioning chiral ligands on the rhodium catalyst.[151] This approach has been applied to the synthesis of pseudolaric acid A (**192** in Scheme 76).[152] Indeed, a substrate-controlled cascade from the α-diazo ketone **193** in the presence of achiral rhodium catalysts is found to favor the formation of the oxatricycle **194a**, whereas a chiral Rh_2[(*S*)-bptv]$_4$ catalyst smoothly delivers a mixture containing the desired diastereomer **194b** as the major component in 82% overall yield.

Moreover, the stereochemical outcome of these transformations can also rely on chiral Lewis acids affecting the cycloaddition step. Although the scope of these transformations is sometimes narrow, significant levels of enantioselectivity have been reported for the reaction of carbonyl ylides arising from α-diazo ketones **195** with substrates able to form chelates with chiral Pybox–lanthanide triflate catalysts (Scheme 77).[153]

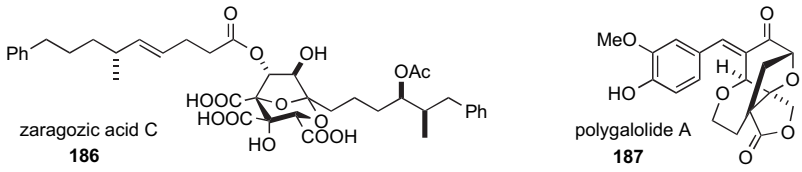
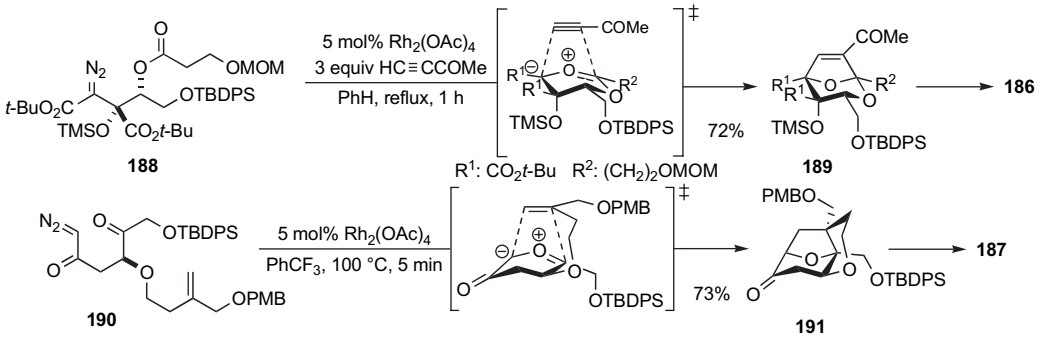
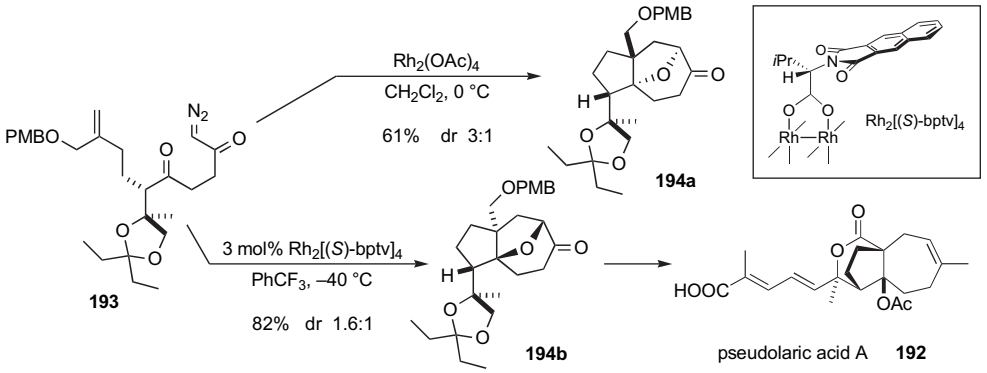


Figure 4.



Scheme 75.



Scheme 76.

8.3. Intramolecular etherification of aryl and vinyl halides

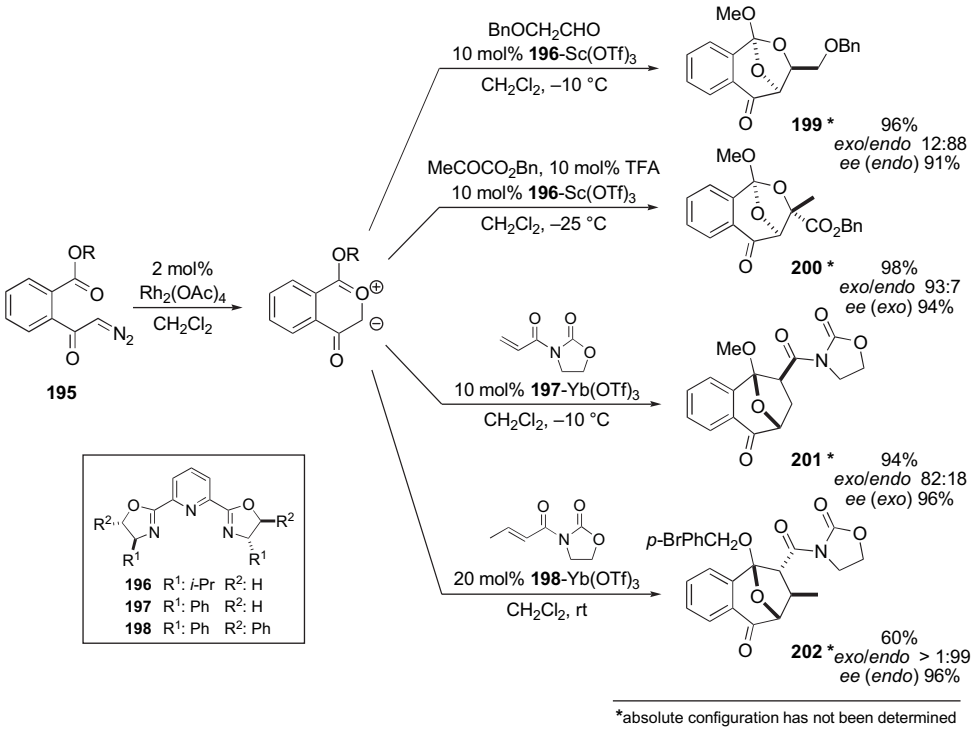
Although the coupling of oxygenated nucleophiles with aryl halides is a long-established method for the preparation of aryl ethers, the harsh reaction conditions commonly required to effect this transformation have restricted its synthetic scope. Indeed, there are relatively few examples for the construction of oxygen heterocycles through the intramolecular etherification of aryl halides.

This lack of synthetic methodologies was covered a few years ago by a procedure based on intramolecular palladium-catalyzed carbon–oxygen bond formation.[154] The reaction proceeds under mild conditions using bulky and electron-rich *o*-biarylphosphines in the presence of weak bases. Remarkably, the choice of the phosphine turns out to be crucial, since its steric bulk accelerates the reductive elimination step and minimizes the competitive β-hydride elimination pathway (Scheme 78).

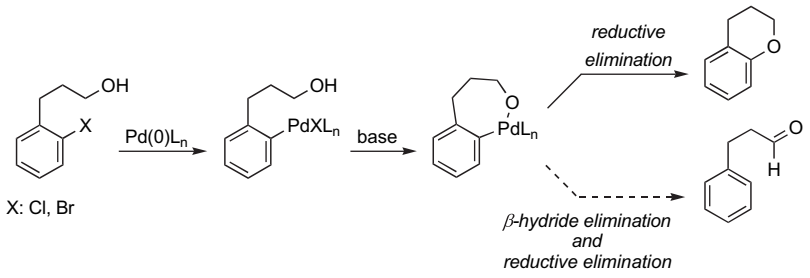
Aryl chlorides and bromides are suitable substrates for this transformation. Then, primary as well as secondary substrates can be cyclized in the presence of bulky dialkylphosphinobiaryl ligands such as **203a** and **203b** (Scheme 79). Moreover, aryl bromides in which the hydroxyl-bearing chain contains stereocenters and additional functional groups such as amines, amides, or esters also afford the corresponding heterocycles in high yields without erosion of the optical purity.

The potential of this transformation has been proved in the synthesis of several heterocyclic compounds with different biological activities.[154a,155] For instance, the intramolecular palladium-mediated etherification of the aryl bromide **204** generates the chroman ring **205**, which is easily transformed into (*S*)-equol (**206**), a metabolite with a high estrogenic activity (Scheme 80).[155d]

In spite of the success of this palladium-catalyzed cyclization, the pursuit of easy-to-handle reagents and easier procedures is fueling the development of new methodologies. A recent report on a copper-catalyzed intramolecular coupling of vinyl bromides is a good example of this emerging chemistry.[156] As illustrated in Scheme 81, the vinyl bromide **207** is



Scheme 77.



Scheme 78.

easily transformed into the tetrahydropyran **208** in the presence of a copper(I) salt and 1,10-phenanthroline.

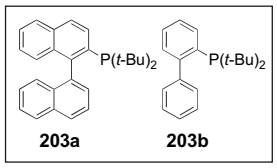
9. Intramolecular conjugate additions

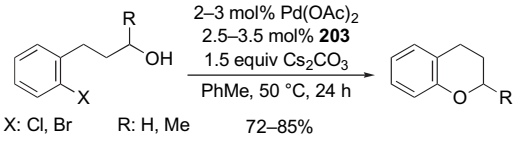
The venerable Michael reaction has found a fertile field of application in the synthesis of six-membered oxygenated heterocycles. As outlined in Scheme 82, intramolecular nucleophilic attack of an alcohol on the electronically deficient C(sp^2) or C(sp) center of α,β-unsaturated systems proceeds smoothly through *exo* and *endo* ring-closure modes to provide the corresponding pyrans.

9.1. 6-exo Ring closures

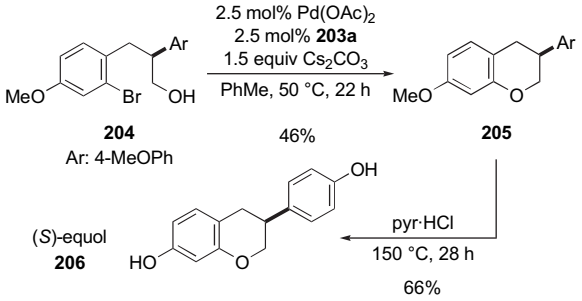
The most common procedure for the synthesis of tetrahydropyrans based on the Michael reaction involves 6-*exo-trig* cyclizations of α,β-unsaturated hydroxy ketones or esters (see Eq. 7 in Scheme 82). These transformations are usually carried out in the presence of stoichiometric, or even catalytic, amounts of base under thermodynamic control, which implies that the configuration of the new stereocenter can be predicted from conformational analysis of the resultant heterocycle. Therefore, considering that the most stable conformer of saturated six-membered heterocycles adopts the chair form as a rule, it is in general anticipated that these cyclizations mainly provide 2,6-*cis*-disubstituted tetrahydropyrans.[157] As represented in Scheme 83, this methodology has been largely applied to the synthesis of leucascandrolide A (**1**),[1d,g,j] phorboxazole A (**2a**),[2c] spongistatin 1 (**209**), and other natural products.[158,159]

However, careful optimization of the experimental conditions enables the acquisition of the kinetically favored 2,6-*trans* diastereomers.[160,161] Thereby, cyclization of hydroxy ester **210** affords either **211-*cis*** or **211-*trans*** tetrahydropyran under basic conditions (Scheme 84).[160b] The all-equatorial **211-*cis*** diastereomer is assumed to be the most stable isomer

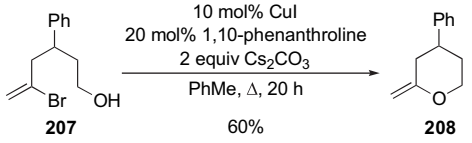




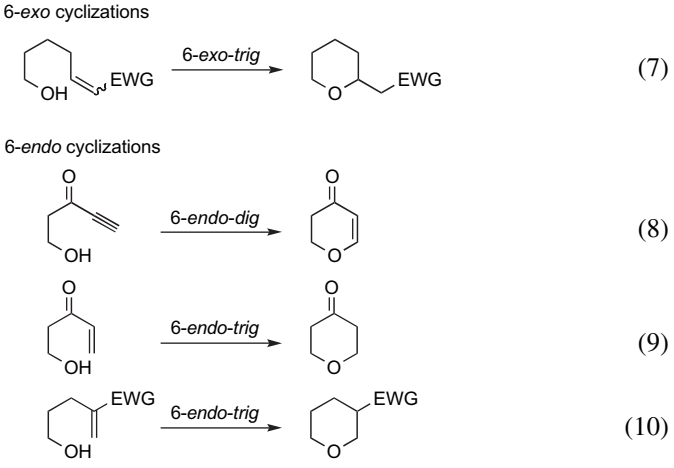
Scheme 79.



Scheme 80.



Scheme 81.



Scheme 82.

and is predominantly obtained at room temperature and long reaction times. Otherwise, low temperatures and shorter reaction times supply **211-*trans*** in good diastereomeric ratios.

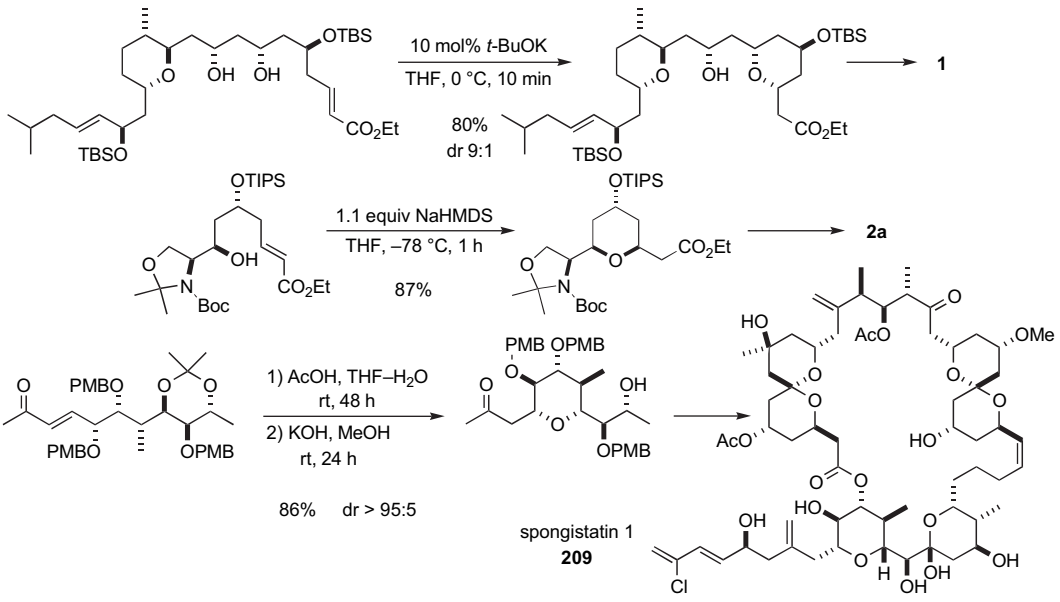
The synthesis of (+)-SCH-351448 (**212** in Scheme 85) takes advantage of analogous procedures.[162] Indeed, treatment of α,β-unsaturated ester **213** with a catalytic amount of base under equilibrating conditions (THF, 0 °C) provides the more stable 2,6-*cis*-disubstituted tetrahydropyran **214-*cis***, whereas low temperatures favor the cyclization to the 2,6-*trans* derivative **214-*trans***. Similarly, assemblage of the 2,6-*cis*-tetrahydropyran **216-*cis*** from α,β-unsaturated ester **215** is carried out at −35 °C, because the 2,6-*trans* isomer **216-*trans*** predominates when the reaction is conducted at −78 °C.

Furthermore, the stereochemical outcome of oxa-Michael cyclizations on α,β-unsaturated esters containing an additional hydroxy group at the allylic position is strongly influenced by the protecting group and the alkene geometry.[163–166] In this manner, kinetically controlled cyclization in aprotic basic conditions of α,β-unsaturated esters **217** affords 2,3-*cis*- or 2,3-*trans*-disubstituted tetrahydropyrans **218**, depending on the geometry of the carbon–carbon double bond. As shown in Scheme 86, tetrahydropyran **218-*trans*** is almost exclusively obtained from the (*Z*)-ester **217-*Z***, whereas the **218-*cis*** isomer is prepared in high diastereomeric ratios from (*E*)-ester **217-*E***. In both cases, NaH provides good results, but potassium bases such as KHMDS are the most convenient regarding both stereoselectivity and rate.[164a,b]

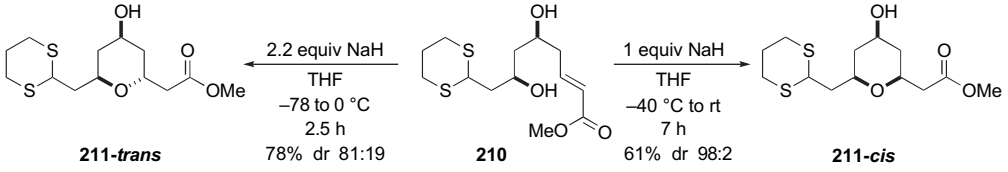
It has also been shown that (*E*)-α,β-unsaturated ester **219** cyclizes quantitatively to 2,3-*cis*-2,6-*cis*-tetrahydropyran **220** (Scheme 87), whereas (*Z*)-α,β-unsaturated ester **221** provides 2,3-*trans*-2,6-*trans*-tetrahydropyran **222a**, which can be equilibrated to the thermodynamically more stable 2,3-*cis*-2,6-*cis* **222b**.[167,168] Theoretical calculations on the intramolecular Michael addition on all these systems emphasize the important role of the cation, the conformational analysis of the α,β-unsaturated esters, and the reversibility of the process for the stereochemical outcome of such cyclizations.

One of the most appealing features of Michael-mediated cyclizations is that they can participate in cascade sequences.[169,170] This is the case for the double-cascade cyclization triggered by a 6-*exo*-*trig* oxa-Michael addition on the advanced intermediate **224** en route to tetronasin 1 (**223** in Scheme 88). Indeed, treatment of **224** with KHMDS in toluene at 0 °C gives exclusively the 2,6-*cis*-disubstituted tetrahydropyran **225** in an impressive 67% yield.[171]

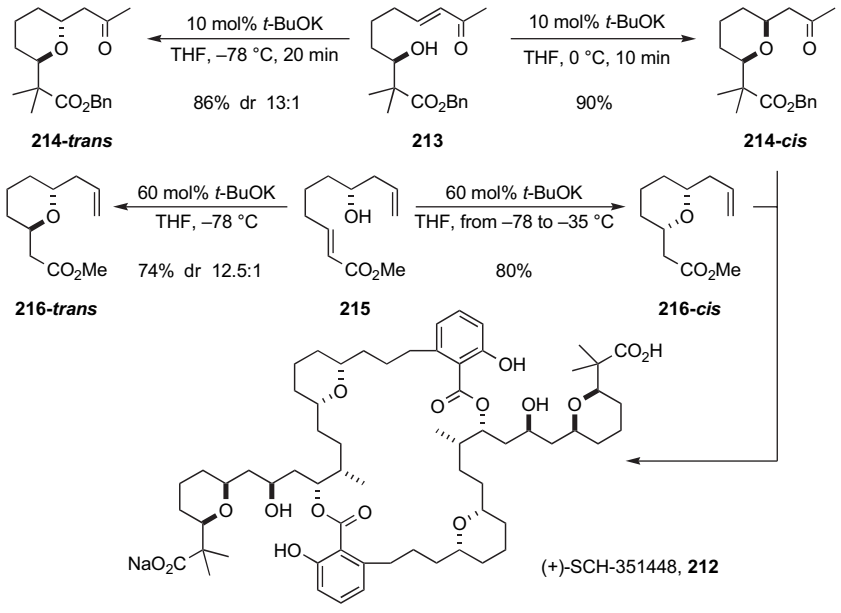
Moreover, a new route to 2,6-*cis*-tetrahydropyrans based on a tandem alkyne–enone coupling and a Michael addition has recently been disclosed.[172] As illustrated in Scheme 89, the ene–yne coupling of β,γ-unsaturated ketone **226** and TMS-protected homopropargylic alcohol **227** presumably provides a hydroxy enone, which undergoes a Michael-like cyclization to afford the C11–C15 2,6-*cis*-disubstituted tetrahydropyran **228** in good yield and diastereomeric ratio.[173] Mechanistically, the preference for the 2,6-*cis* diastereomer seems to arise from a late transition state, in which the relative stabilities would play a significant role. This ruthenium-based sequence is combined with a palladium-catalyzed dihydropyran synthesis previously reported (see Scheme 52). In this case, coupling of terminal alkyne **229** with hydroxy ynoate **230** in the presence of palladium(II) catalysts delivers the C19–C23 dihydropyran **231** in 55% yield. Both processes cover key transformations



Scheme 83.



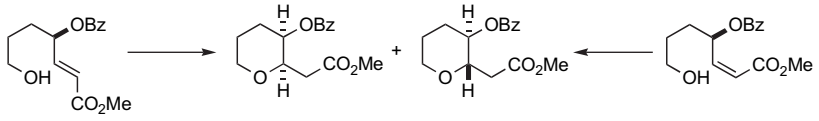
Scheme 84.



Scheme 85.

for the total synthesis of **232**, a ring-expanded analogue of bryostatin 1.

Ring closure of the putative intermediate represented in Scheme 89 is believed to be catalyzed by the ruthenium Lewis acid. Indeed, Michael-mediated cyclizations can also proceed under Brønsted acid conditions.[174] Although poorly exploited, this sort of reaction has been applied to 6-*exo*-*trig* cyclizations on α,β-unsaturated ketones for the synthesis of complex natural products. For instance, deprotection of 1,3-diol in **233** in acetic acid triggers the formation of 2,6-*trans*-tetrahydropyran **234** in excellent yield and moderate diastereoselectivity (Scheme 90);[175] reaction of lactol **235** with a stabilized

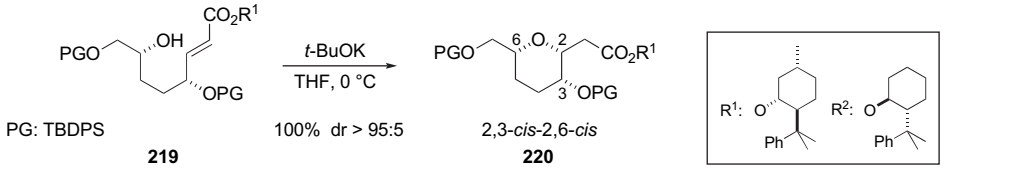


217-*E* **218-*cis*** **218-*trans*** **217-*Z***

2,3-*cis*-tetrahydropyran 2,3-*trans*-tetrahydropyran

Ester	Base	Solvent	T (°C)	dr (***cis-trans***)
217-*E*	KHMDS	PhMe	–78	9:1
217-*E*	NaH	THF	–78	9:1
217-*Z*	KHMDS	PhMe	0	1:20
217-*Z*	NaH	THF	0	1:11

Scheme 86.



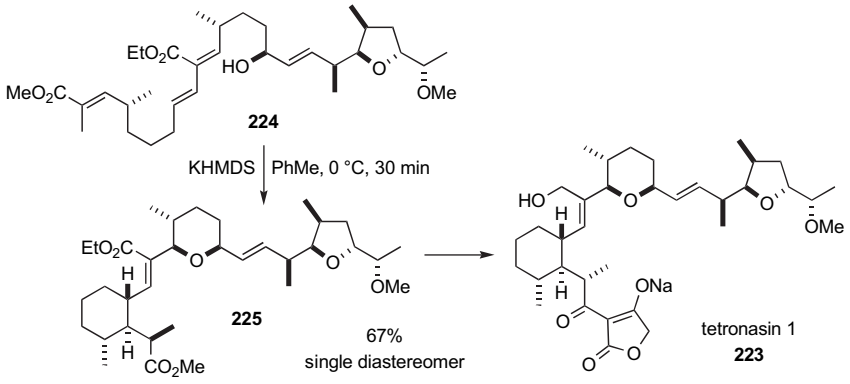
Scheme 87.

phosphorane provides enone **236**, which is cyclized by treatment with CSA to furnish 2,6-*cis*-tetrahydropyran **237** as the sole diastereomer in 73% yield over two steps[176] and, eventually, removal of isopropylidene acetal and silicon protecting groups in the advanced intermediate **238** en route to bryostatins with HF leads to the C1–C16 fragment **239** containing two 2,6-*cis*-tetrahydropyrans.[177,178]

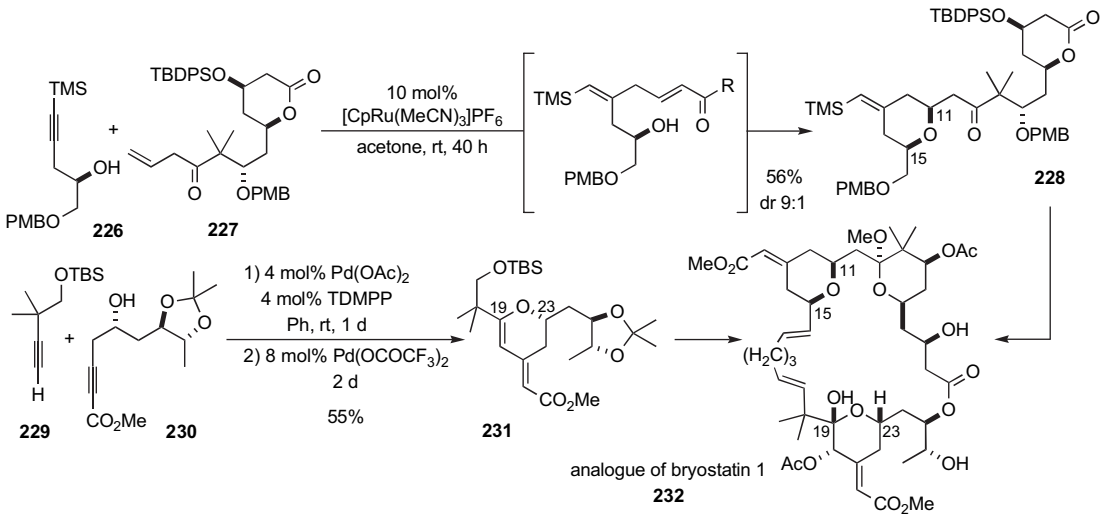
As well as all of these cyclizations, a 6-*exo-dig* ring-closure mode based on a Michael reaction is, in fact, possible. However, there is no clear example in the literature, because the enone generated in this cyclization process usually undergoes a second Michael addition, as can be appreciated in the synthesis of azaspiracids (**62** in Scheme 24, see also Scheme 57). In this case, the retrosynthetic analysis of the C27–C40 domain followed by Forsyth et al. relies on a formal *D*ouble *I*ntramolecular *H*etero *M*ichael *A*ddition (DIHMA) based on a 6-*exo-dig* cyclization followed by a stereoselective 6-*exo-trig* ring closure.[179] In this manner, the acid-mediated double intramolecular oxa-Michael addition on dihydroxy ynone **240** gives the bicyclic ketal **241** as a single diastereomer in excellent yield (Scheme 91).[180] Similarly, treatment of ynone **242** with TBAF promotes silyl ether cleavage and addition of the corresponding oxygen atoms upon C28 to provide in high yield the targeted FG-ring system **243** present in azaspiracids.[181]

9.2. 6-endo Ring closures

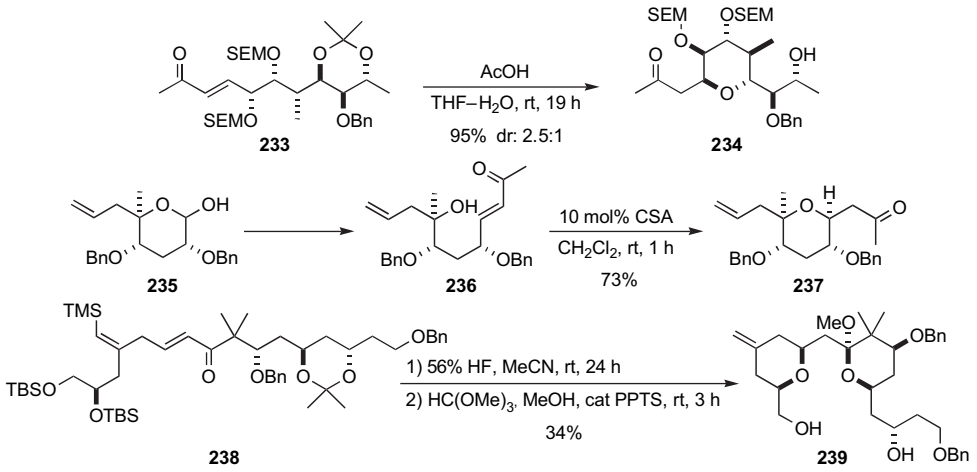
Contrary to the Michael-mediated 6-*exo-dig* cyclizations, parallel 6-*endo-dig* processes have been identified as a useful



Scheme 88.

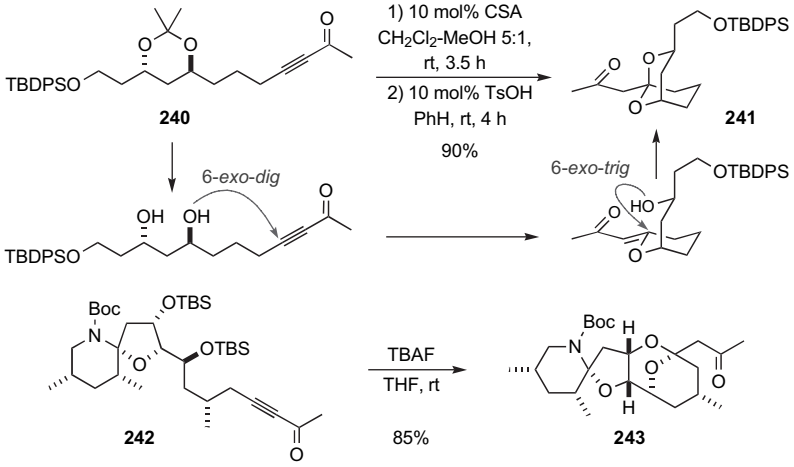


Scheme 89.



Scheme 90.

tool to gain access to pyranones (see Eq. 8 in Scheme 82). In particular, 6-*endo-dig* cyclizations of *o*-alkynoylphenols provide an appealing entry into the synthesis of the heterocyclic structures present in many natural products. The selectivity of these reactions turns out to be highly dependent upon the experimental conditions. Indeed, base-catalyzed cyclization of *o*-alkynoylphenols can proceed through a 5-*exo-dig* or 6-*endo-dig* pathway to afford, respectively,



Scheme 91.

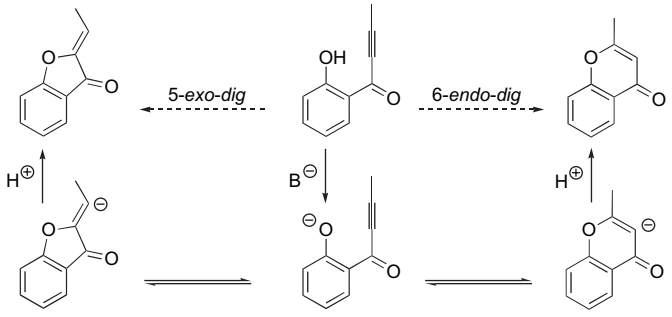
benzofuranones or benzopyranones. According to the experimental results, theoretical calculations on a model ketone shown in Scheme 92 have revealed that the transition states for both processes are very close in energy. Nevertheless, the 6-*endo-dig* product is thermodynamically favored and can be obtained under equilibrating conditions in the absence of proton donors.[182]

This approach has been successfully applied to the synthesis of several members of a family of antibiotics containing an anthrapyran core.[183,184] As represented in Scheme 93, basic treatment of ynone **244** under aprotic conditions promotes a highly selective 6-*endo-dig* cyclization to the tetracyclic compound **245** that is further elaborated into the antibiotic AH-1763 IIa (**246**).[184a] Alternatively, this type of cyclization can also be carried out under acidic conditions, but the mechanism is still unclear.[185]

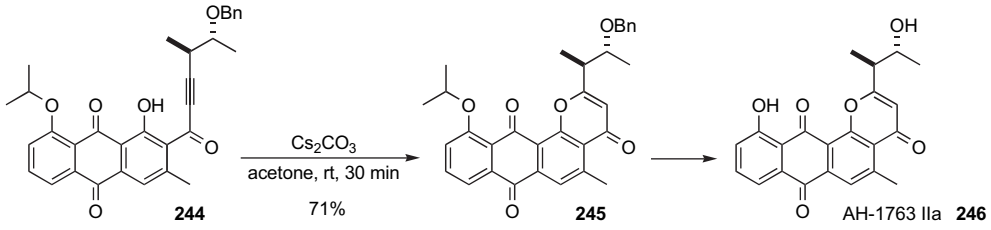
Overshadowed by 6-*exo-trig* cyclizations, the related 6-*endo-trig* ring-closure mode (see Eq. 9 in Scheme 82) had traditionally attracted not much attention. However, the increasing interest in the asymmetric synthesis of di- and tetrahydropyranones has modified this situation, since this type of cyclization emerges as an appealing alternative to the hetero-Diels–Alder reaction. Initial reports on 6-*endo-trig* cyclizations of α,β-unsaturated ketones are due to Paterson and Osborne.[186] In particular, the aldol adducts obtained through stereoselective reactions from β-chloro vinyl ketones undergo Lewis acid-mediated cyclizations that eventually give dihydropyranones.[187] Application of this methodology to methyl ketone **247** and 3-benzoyloxypropanal supplies aldol **248**, which is easily converted into the desired dihydropyranone **249** (Scheme 94). Further recrystallization provides an enantiomerically pure material that has been employed for the total synthesis of swinholide A,[188a] scytophycin C,[188b] and, more recently, laulimalide (**93** in Scheme 38).[188c]

Aldol adducts lacking the β-chlorine atom can also take part in these cyclizations to afford the tetrahydropyranones. A comprehensive survey of the ability of Brønsted and Lewis acids as well as palladium(II) complexes to enhance the electrophilicity of enones **250** has identified Amberlyst-15, Al$(ClO_4)_3\cdot 9H_2O$, and $[Pd(MeCN)_4](BF_4)_2$ as suitable catalysts to carry out the desired 6-*endo-trig* cyclization (**250a**,**b** to **251a**,**b**) under mild conditions (Scheme 95).[76b,189] As anticipated for a thermodynamically controlled reaction, Amberlyst-15 affords the all-equatorial products after extended reaction times. Interestingly, the palladium-mediated cyclizations are irreversible and give access to the other isomers in excellent diastereomeric ratios.

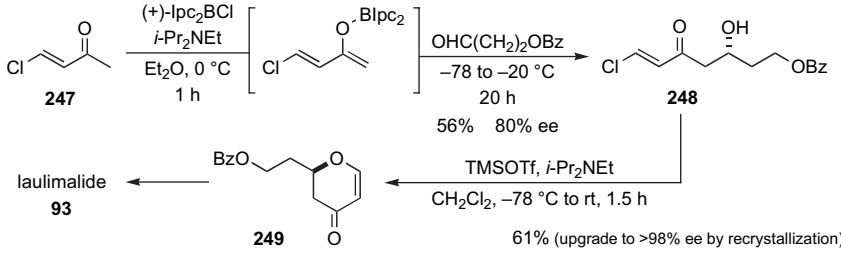
Another aldol reaction is at the center of a different methodology. Aldol compounds arising from β-keto esters can participate in an acid-mediated Knoevenagel condensation that generates a highly reactive α,β-unsaturated keto ester, which undergoes a 6-*endo-trig* cyclization based on a reversible oxa-Michael addition. Finally, decarboxylation of the resultant system provides the 2,6-*cis*-disubstituted tetrahydropyranones.[190,191] This methodology has been applied to the preparation of (±)-centrolobine (**252** in Scheme 96). The reported sequence takes advantage of a Mukaiyama aldol reaction to



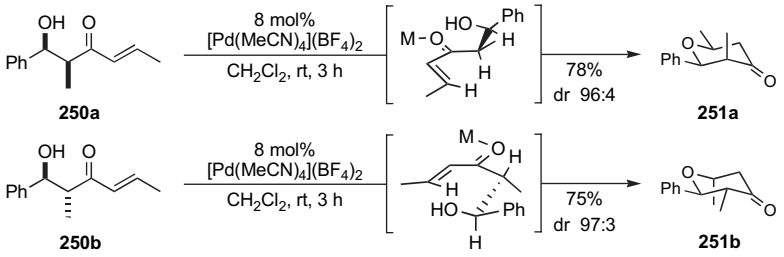
Scheme 92.



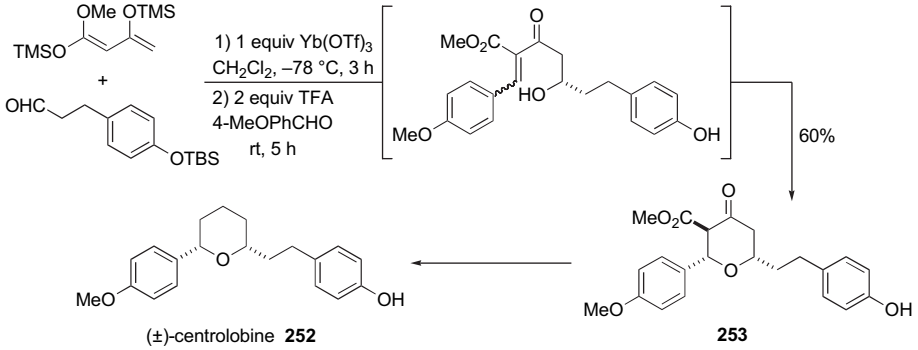
Scheme 93.



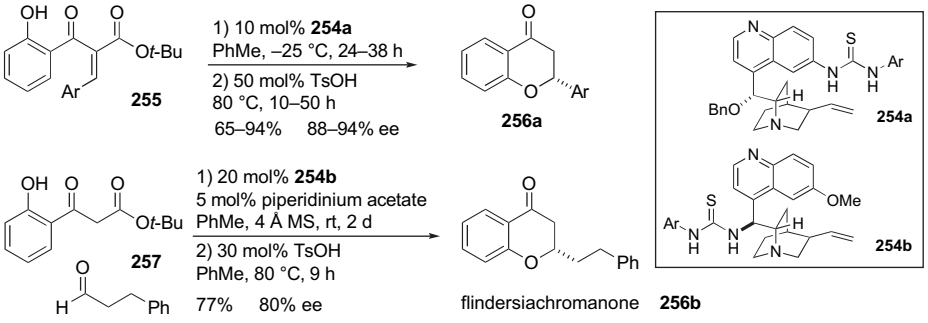
Scheme 94.



Scheme 95.



Scheme 96.



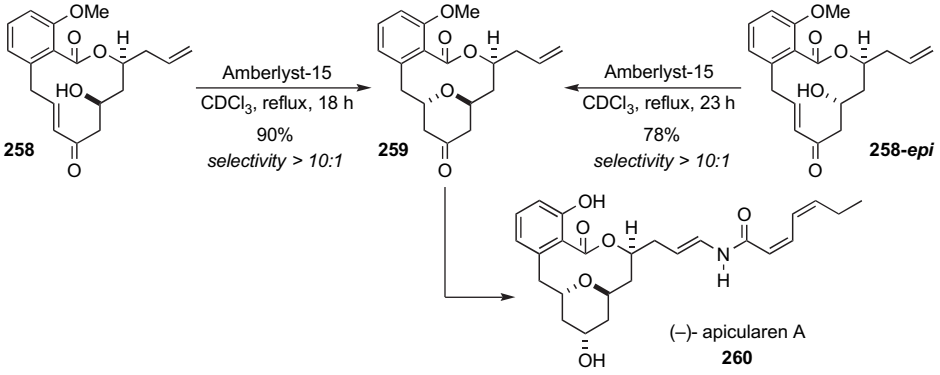
Scheme 97.

install the first appendage of the tetrahydropyran. Then, addition of anisaldehyde and TFA to the reaction mixture affords the tetrahydropyranone **253** and further functional-group manipulations deliver (±)-centrolobine.[192]

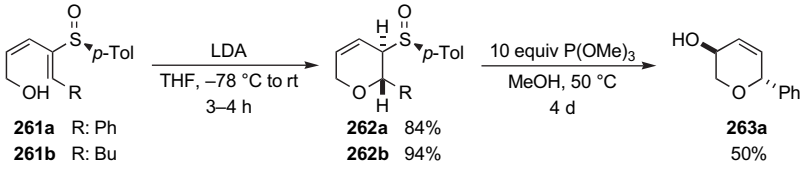
Closely connected to this methodology, it has recently been discovered that the chiral thiourea-based catalysts **254**, shown in Scheme 97, activate α-alkylidene-β-keto esters **255** and trigger intramolecular conjugate additions of phenol to the corresponding flavanones **256**. Remarkably, a one-pot reaction involving the simple β-keto ester **257**, hydrocinnamaldehyde, piperidinium acetate, and chiral thiourea **254b** in the presence of molecular sieves in toluene at room temperature followed by decarboxylation affords the natural product, flindersiachromanone **256b**, in 80% ee and 77% overall yield.[193,194]

Although 2,6-*cis*-disubstituted tetrahydropyranones are usually the most stable diastereomers, other elements in the structure can alter this situation. For instance, thermodynamically controlled transannular conjugate addition on α,β-unsaturated ketone **258** affords 2,6-*trans*-disubstituted tetrahydropyranone **259**, used as an advanced intermediate in a formal total synthesis of (−)-apicularen A (**260** in Scheme 98). Interestingly, exposure of epimer **258-*epi*** to identical conditions yields the same tetrahydropyranone **259**.[195]

In contrast to the above examples, some 6-*endo-trig* cyclizations match the model reaction represented by Eq. 10 in Scheme 82.[196] For instance, chiral dienyl sulfoxides **261** have been identified as suitable precursors of dihydropyrans. This process is based on a highly stereoselective conjugated addition (the examples shown in Scheme 99 afford a single diastereomer) followed by subsequent transformations of the resultant allylic sulfoxides **262**.[197] Interestingly, this methodology accepts additional stereocenters and other substituents on the double bond of the dienyl sulfoxide.



Scheme 98.



Scheme 99.

10. Conclusions

As this report proves, the apparently simple construction of pyrans through C–O bond formation is surprising, with an extremely varied array of methodologies ranging from the venerable S_N2- or Michael-based cyclizations to the more recent transition metal-catalyzed reactions. The scope and synthetic efficiency of such ring-forming methodologies have already been established along with the total synthesis of a large number of structurally complex natural products, but, in spite of these outstanding achievements, the increasing demand for more selective processes to gain access in a straightforward manner to six-membered oxygenated heterocycles is fueling the development of new concepts and methodologies. Remarkable examples are the recent developments in epoxide-mediated cyclizations that allow selective formation of the pyrans over the more favored furans or the spectacular simultaneous construction of up to three fused tetrahydropyran units in a cascade sequence. Moreover, emerging methodologies such as platinum- or gold-catalyzed cyclizations of hydroxy alkenes, allenes, and alkynes will undoubtedly play a major role in further developments in this field.

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