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Published in:
Israel Journal of Chemistry

DOI:
[10.1002/ijch.202100014](https://doi.org/10.1002/ijch.202100014)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

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Citation for published version (APA):

Alachouzos, G., & Frontier, A. J. (2021). Cyclization Strategies for the Concurrent Installation of Multiple Quaternary Stereogenic Centers. *Israel Journal of Chemistry*, 61(7-8), 469-485.
<https://doi.org/10.1002/ijch.202100014>

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Cyclization Strategies for the Concurrent Installation of Multiple Quaternary Stereogenic Centers

Georgios Alachouzos^[a] and Alison J. Frontier^{*[b]}

Dedicated to Prof. Barry Trost in celebration of his 80th birthday.

Abstract: In this review we highlight the general cyclization strategies currently available to organic chemists for the concurrent and stereoselective installation of multiple *Quaternary Stereogenic Centers* (QSC) atoms in cyclic or polycyclic architectures. QSCs embedded in rigid cyclic architectures are motifs found in many blockbuster drugs and important bioactive natural product classes, and yet, direct access to these structures stereoselectively from simple precursors remains a significant challenge. Underscoring the difficulty associated with their synthesis, such topologically three-dimensional molecules are underrepresented in existing small molecule compound libraries, which are instead

dominated by linear or flat molecules. This review focuses on methods disclosed in both natural product synthesis and methodology studies since the turn of the 21st century. The cases to be examined successfully achieve these challenging transformations: (1) *one-step assembly of the cyclized architecture*; and (2) *concurrent stereoselective installation of multiple (≥ 2) new QSCs*. These cyclization strategies, which address the aforementioned fundamental challenges in complex molecule synthesis, have been categorized into five broad groups: i) Biomimetic Polyene Cyclization Cascades; ii) Cyclization Cascades of Prochiral Alkenes; iii) Cycloadditions; iv) Dearomatizations; v) Electrocyclizations.

Keywords: synthetic methods · natural products · total synthesis · stereoselectivity · cyclization reactions

1. Introduction

Pharmaceutical chemists aim to design drugs to selectively interact with biological targets in order to bring about therapeutic effects. The biological environments and biochemical processes that are targeted by pharmaceutical drugs are three-dimensional.^[1] Small molecule natural products exhibit highly selective activities towards their natural biological target, which can be attributed to their structural complexity and rigid three-dimensional architecture.^[2]

Scheme 1 shows a selection of both naturally occurring and synthetic bioactive small molecules from the WHO List of Essential Medicines containing one or multiple *Quaternary Stereogenic Centers* (QSCs) embedded in commonly occurring (5-, 6- or 7-membered) carbocyclic or heterocyclic rings. The three-dimensional rigidity imposed by (1) substituents branching off from one or more QSCs and (2) the presence of a single or polycyclic ring system minimizes the molecular degrees of freedom of a molecule and has been understood to translate to selectivity towards a given biological target.^[2–4] Hence, novel small molecule drug candidates, which often seek to mimic the biological action of natural products, must also be fit for this three-dimensional lock-and-key game.

Paradoxically, synthetic small molecule libraries from the last few decades which exist to drive 21st century pharmaceutical innovation, have primarily consisted of low-complexity, non-chiral, two-dimensional molecular scaffolds.^[5–7] The low success rates of the flatter molecules from these libraries to

result in successfully approved drugs suggest that they are less suited to engage three-dimensional biological targets.^[8]

Although a variety of factors determine the progression or failure of a drug candidate,^[9] the synthetic methods to access suitable molecular scaffolds play a crucial capacity in the process. Therefore, there is a need to increase structural, chiral, and topological complexity of molecules in such libraries to improve their success rate as drug candidates.

Access to previously unattainable carbon-based structural backbones of both synthetic or natural drug candidates relies primarily on the development of new synthetic organic methods.^[7] To this end, an important research direction for 21st century organic synthesis is to expand the arsenal of methods capable of forming not only carbon-carbon (C–C) bonds in polycyclic systems, but also capable of introducing three-dimensional complexity through concurrent, stereoselective installation of multiple QSCs.^[10–12]

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Scheme 1. WHO Model List of Essential Medicines Containing QSCs in a Cyclic Architecture.

Methodologies that install a single or isolated QSC in either acyclic and cyclic systems have been disclosed by many synthetic organic research groups in the last decades.^[11] On the other hand, reactions that immediately furnish multiple QSCs are much less common, as new practical and design challenges arise during these reactions. One such challenge, particularly in the case of vicinal QSC installation (see Scheme 2), is that the steric hindrance in the reaction transition state and product often renders a C–C bond-forming reaction to be very slow or even kinetically prohibitive. Furthermore, contrary to simply installing a single QSC, methodologies that install multiple QSCs must ideally be fully diastereoselective. This requires that stereocontrol be extended to both newly formed QSCs, as four configurational combinations are potentially generated. This fundamental challenge in complex organic molecule synthesis has captured the attention of the synthetic community for decades.^[10,12–14]

Despite these challenges, innovative methodologies that allow for the installation of two vicinal QSCs in acyclic or linear systems in a single step have been disclosed.^[15,16] Though these transformations yield valuable stereochemical building blocks, they still do not *directly furnish (poly)cyclic*

Scheme 2. An Overview of the Cyclization Strategies Covered in this Review.

products with multiple QSCs, whose rigid three-dimensional topology is demanded by nature's biological targets.^[3]

Ideally, for this ultimate challenge, pharmaceutical chemists would have transformations at their fingertips which both (1) *cyclize* topologically simple, linear, and easily accessible substrates via ring closing C–C bond formation and (2) stereoselectively *install the multiple desired QSCs*, to directly yield complex three-dimensional topologies in a single synthetic operation. In this review, we outline the general strategies that have emerged since the turn of the century that can be brought to bear upon this challenging endeavor.

In an effort to provide a general overview, we have selected a single or seminal example of a given general strategy. Many reactions that are shown are asymmetric transformations, though there are notable diastereocontrolled cyclizations that have also been included to convey the range

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Dr. Georgios Alachouzos obtained his BS in Life Science and Technology and his MS in Chemistry summa cum laude from Universiteit Leiden. George then pursued PhD studies in the group of Professor Frontier (University of Rochester) enabled by a Fulbright PhD Fellowship. George is currently conducting his post-doctoral research in the lab of Prof. Ben Feringa at Rijksuniversiteit Groningen, supported by an EMBO Fellowship.

of strategies.. Lastly, we have made an effort to still mention or reference similar cases or applications of cyclization cascades that generate two or more QSCs that we are not able to show, to stimulate further literature study by the reader.

2. Cyclization Strategies

2.1 Biomimetic Polyene Cyclization Cascades

In this first section we will highlight synthetic transformation disclosures from roughly the last two decades in which synthetic chemists have borrowed inspiration from nature herself. Nature has cultivated an expertise in the concurrent installation of multiple QSCs during enzymatic small molecule cyclization reactions. No single example underscores this expertise more than the enzymatic cyclization of squalene or its oxide,^[17,18] a polycyclization which is ubiquitous in virtually all living species. Scheme 3 illustrates the diverse regiochemical and stereochemical outcomes that are observed from polycyclization variants of this single triterpene.

Scheme 3. Naturally Occurring Polyene Cyclizations and Resulting Biomimetic Strategy.

Scheme 4. The Corey Biomimetic Polyene Cyclization towards **2** Promoted by Chiral Brønsted Acid.

Synthetic chemists have unsurprisingly sought to mimic this polyene cyclization strategy in the laboratory.^[17] One faithful example, mimicking how nature triggers the polycyclization by the opening of an epoxide “warhead” by an acid, comes from the key step of the 1996 total synthesis of natural product phytosterol dammaranediol II by Corey and co-workers.^[19] However, cases have since followed where synthetic chemists have successfully demonstrated that functional groups other than epoxides can also initiate similar cascades by serving as precursors to cationic intermediates.

The polycyclization shown in Scheme 4 highlights a 2014 methodology study also helmed by Corey and coworkers.^[20] Here, simple polyenes **1** with an electron-rich arene at one terminus and a trisubstituted alkene “warhead” at the other can be activated to reveal cationic intermediates in the presence of a chiral Brønsted acid. The acid is formed *in situ* from the combination of a BINOL derivative and Lewis acid SbCl_5 and was developed in the Corey lab around that time. When the terminal alkene in **1** is protonated at the least substituted position by the chiral catalyst an efficient polycyclization of intermediate **3** occurs with all double-bonds and the terminal arene participating in the cyclization, ultimately generating product polycycle **2** containing two QSCs (plus one additional non-stereogenic quaternary carbon) efficiently and enantioselectively. The method was also successfully applied towards the synthesis of natural products (+)-dysideapalaunic acid and dehydroabietic acid in the same year.^[21]

Similar methods to induce biomimetic polycyclization with non-metal electrophilic atoms were recently developed by the Denmark lab and others.^[22] These studies prove that one can induce cation formation from a terminal alkene “warhead” in comparable polyene systems with other electrophilic non-metal reagents. Although these will not be shown here in detail, they do demonstrate that many non-biological electrophilic initiators can be employed in these biomimetic polycyclizations.^[17]

Naturally, methods to induce cation formation from non-naturally occurring functional groups have recently emerged as well. Polyenes containing terminal alkynes (such as **4** in Scheme 5) have been illustrated as suitable “warheads” towards cationic intermediates for polyene cyclizations that install multiple QSCs in this seminal 2010 study by the Toste

Scheme 5. The Toste Biomimetic Polyene Cyclization towards **5** Triggered by a Cationic Au Lewis Acid Catalyst.

group.^[23] For this method, a cationic Au catalyst activates the alkyne in **4** via intermediate **6**, thus rendering it susceptible to the biomimetic polycyclization, ultimately furnishing polycyclic **5** after rearomatization of the arene terminus. The polycyclic product **5** contains two QSCs, is formed in good yield, with very high enantioselectivities.

Since this trailblazing study, a similar study was reported in the next year by the Corey group employing indium as the Lewis acid promoter in polycyclizations of polyenes with alkyne termini to efficiently and stereoselectively generate polycyclic products with multiple QSCs.^[24] Likewise, just another year later Carreira showed that iridium can promote similar polycyclization induced by the action of an iridium catalyst, with an allyl alcohol as the cationic precursor.^[25] This final method was also applied towards the first synthesis of natural product mycoleptodiscin A by the Li group, in 2015.^[26]

The ability of these robust, multiple QSC-forming transformations to engage in complex cascades is illustrated successfully in the following 2008 study from the Loh group towards the total synthesis of natural product antiochic acid (**11**) (Scheme 6).^[27] Here, the biomimetic cyclization a simple polyene **8** with an arene terminus and alkene “warhead” is combined with an intermolecular Prins reaction with enantioenriched acetal **9**. The Lewis acid SnCl_4 promotes oxocarbenium **12** formation, which is then susceptible to attack by the alkene terminus of polyene **8**, also subsequently inducing the biomimetic polyene cyclization towards key synthetic intermediate **10**, containing two QSCs and a total of five new stereogenic centers.

This example is particularly interesting, since reactant **9** is incorporated as a type of rudimentary auxiliary to control the excellent diastereoselectivity observed in the product **10**, before being cleaved *en route* to natural product **11** later in the synthesis.

Exotic variants of biomimetic polycyclizations that proceed via radical intermediates have been known for decades.^[28–30] Very recently, innovative new methods to generate such radicals have also garnered attention.^[31] One such example, applied to this problem of multiple QSC installation during the polycyclization, was illustrated in the 2010 study by MacMillan and coworkers.^[32] In this study the exothermicity of radical C–C bond formation is elegantly

harnessed towards the polycyclization of highly congested systems. In these reactions, asymmetric SOMO catalysis enables the construction of fused polycycles **14** containing up to five QSCs (Scheme 7)! Polyenes **13** with a saturated aldehyde functionality on one terminus and an arene on the other, undergo enamine **15** formation in the presence of the imidazolidinone organocatalyst, before becoming oxidized by the Cu(I). Radical iminium **16** then undergoes a cascade cyclization with the polyene chain to form up to six new rings and forging multiple QSCs along the way. Newly formed radical **17** is then oxidized by another equivalent of Cu(I) before furnishing the polycyclic product **14** after hydrolysis and regeneration of the catalyst. The reaction proceeds in good yield and excellent diastereo- and enantioselectivities were observed.

In sum, these *complex polycyclizations* enable *concurrent stereoselective installation of multiple QSCs* and represent notable synthetic achievements. Moreover, the cases discussed in this section (and more not shown) illustrate how some of the giants in complex molecule synthesis have been able to successfully mirror methods employed by the one omnipresent expert at synthesizing topologically complex molecules: *nature*.

The natural propensity of linear polyenes to preorganize in chairlike conformations undoubtedly contributes to the regio- and diastereoselectivity observed in these cyclizations. In the examples summarized above, chemical ingenuity is illustrated in the novel mechanisms of initiation. Furthermore, advancements in this field of biomimetic polyene cyclizations have enabled these transformations to take place in the reaction flask and in organic solvent. Free of the tightly controlled chemical environment of the enzymatic pocket, these synthetic methods can engage structural variants of naturally occurring polyenes, in order to deliver novel, non-natural polycyclic adducts with QSC content beyond what nature typically provides.

Scheme 6. The Loh Prins/Biomimetic Polyene Cyclization Cascade towards **10** Triggered by a Sn Lewis Acid.

Scheme 7. The MacMillan Radical Polyene Cyclization towards Fused Polycycles **14** Enabled by SOMO-Catalysis.

2.2 Cyclization Cascades of Prochiral Alkenes

In this section we will continue to examine cyclization cascades but will shift the focus to cases that do not mimic nature. Similar to the cascades in the previous section, these cyclizations feature the combination of multiple prochiral alkenes in an iterative process. While biomimetic cyclizations are limited to variations on the classical polyene reactant, the strategic methods presented in this section engage a wide range of prochiral alkene reactants, including dienes, alkene Michael acceptors, and enols/enolates/enamines. Furthermore, these non-natural cascades can leverage both inter- and intramolecular reactions, thus enabling bi- or even trimolecular cyclizations.

To illustrate the conceptual difference of these strategies from the biomimetic strategies previously discussed, we have elected to show the reader an example from a 2019 methodology study by Chen and coworkers.^[33] Here, a cationic cascade is triggered by a simple protonation, not unlike the protonation of a “warhead” from the biomimetic examples seen in the previous section.

In their methodology study, the authors achieved a Brønsted acid-catalyzed double cyclization of twisted dienes **18** to form perpendicularly-helical architectures **19** containing two vicinal QSCs (Scheme 8).^[33] Both alkene moieties in **18** are sequentially protonated at the least substituted carbon, revealing cationic prochiral electrophiles **20** and **22** which undergo nucleophilic attacks by the electron-rich arenes. The products **19** obtained after rearomatization are highly congested, and the yields are generally high. In sum, with a simple design principle in mind, the authors demonstrated that sequential hydroarylation events on both tertiary alkenes can lead to the installation of two QSCs in the cyclized product.

2.2.1 Michael Addition/Alkylation Cyclization Cascades

The electrophilic nature of Michael-acceptors paired with the nucleophilic nature of the resulting enols/enolates/enamines make these types of cascades an ideal strategic platform for the assembly of cyclic products with concurrent multiple QSC installation. Scheme 9 shows a general overview of the

Scheme 8. The Chen Acid-catalyzed Synthesis of Helically Twisted Architectures **19**.

Scheme 9. A General Michael Addition/Alkylation Cyclization Strategy.

cyclization design. Stereoselective addition of a carbon nucleophile to the fully substituted β -carbon of a Michael acceptor will result in the stereoselective formation of a QSC at that carbon. Subsequent stereoselective capture of the resulting enol (or enolate, or enamine) by an electrophilic carbon functionality (ketones, alkyl halides, etc.) will result in a second QSC being installed in the product. It should be noted that if the Nu and E functionalities themselves are an enol/enolate/enamine or a Michael acceptor, respectively, then these could also potentially serve as QSC precursor atoms.

Typically, cyclization cascades that proceed via these two distinct mechanistic steps will form both QSCs with a high degree of diastereoselectivity as the second QSC is usually formed on the same face that the first QSC was formed. Finally, if external chiral information (e.g. from a chiral catalyst) can effect the stereoselective installation of the first QSC, then the entire cascade can be rendered enantioselective.

Cyclization cascades that achieve all these design philosophies will be shown next, from a study reported by the Barbas group in 2011 (Scheme 10).^[34] In this study, racemic chiral indolinones **23a** are combined with prochiral indolinones **24a** in the presence of thiourea organocatalyst **25** under very mild conditions to generate enantioenriched bispirooxindoles **26a**. Spirooxindoles such as the drug Cipargamin are an important molecular class of antimalarial and antiparasitic agents.^[35]

The products **26a** contain two QSCs and a total of four stereogenic centers and were formed in excellent yields, diastereoselectivities and enantioselectivities (Scheme 10). In the cascade mechanism that Barbas and coauthors proposed,^[34] the enolate generated from the deprotonation of indolinone **23a** engages electrophile **24a** in a Michael addition, installing a QSC and a tertiary stereogenic center, and generating new enolate **27a**. This new nucleophile can engage the pendent ketone moiety from **27a**, thus forming a second congested C–C bond containing the second QSC.

Two very comparable studies were reported in 2012 and 2014 by the Wang group.^[36,37] In these variations, similar substrates **23b/23c** and **24b/24c** are reacted in the presence of a squaramide organocatalyst under mild basic conditions (Scheme 10). The mechanism proceeds like the previous example, where enolates from **23b/23c** engage electrophiles **24b/24c** to form an initial C–C bond and a QSC, with the newly generated enolate undergoing intramolecular alkylation with the pendent primary alkyl bromide or Michael acceptor. Enantioselectivities are high but the diastereoselectivity in the alkyl bromide case is low when compared to the examples

Scheme 10. Three Studies on the Organocatalyzed Synthesis of Congested Spirooxindoles **26a–c**.

shown from the previously shown Barbas study,^[34] suggesting that these organocatalysts exert diminished stereocontrol during such alkylation events.

A more complex cascade will be discussed next, from the 2014 methodology study from the Enders group.^[38] In this synthetic study, highly congested spiropyrazolones **33** containing one or two QSCs and a total of 6 stereogenic centers are assembled in an asymmetric multicomponent reaction (Scheme 11). Various pharmaceutical drugs such as metamizole,^[39] edaravone,^[40] and various HIV-integrase inhibitor leads contain the pyrazolone subunit.^[41] The authors of the

Scheme 11. The Enders Organocatalyzed Synthesis of Congested Spiropyrazolones **33**.

methodology study propose that an enolate generated from the deprotonation of reactant **30** by the squaramide organocatalyst **32** engages the β -nitrostyrene thus generating a stable persistent anion **34**, which then undergoes Michael addition with the second electrophile pyrazolone **31**. Finally, the newly formed enolate **35** can cyclize by engaging the ketone moiety, forming the spirocycle product. Sadly, the example shown is the only example from the scope of this study in which two QSCs are formed, and the yield is poor, highlighting the kinetic challenges of installing multiple QSCs in congested polycycles.

These last four studies thus highlight how the fully substituted sp^2 -carbon atoms in enol/enolate/enamine and Michael acceptor reactants or resulting intermediates can serve as prochiral precursor atoms to QSCs in complex cyclization cascades.

2.2.2 Transition Metal-Enabled Cyclization Cascades

Next, we will examine the transition metal-mediated cyclization of polyenes containing prochiral alkenes (or even alkynes) into cyclic products containing multiple QSCs. Transition metals offer an excellent platform for these strategies as they often proceed under mild reaction conditions and tolerate many sensitive functionalities.^[42,43] Moreover, literature cases to be examined will establish that transition metals even enable the emergence of the prochiral alkene/alkyne functionality from different functional groups, ultimately enabling new types of reactivities.

A conceptually simple double-Heck cyclization to generate two vicinal QSCs from a tetrasubstituted prochiral alkene was demonstrated by Overman and coworkers in 1999 (Scheme 12).^[44] In this total synthesis of hexahydropyrroloindole alkaloids **39** and **40**,^[45] a common synthetic intermediate **39** with a central, tetrasubstituted alkene was divergently converted to either **38a** or **38b**, both containing the requisite vicinal QSCs in natural products **39** and **40**, respectively. The stereodivergent outcome seemingly depends on the nature of the diol protecting group in **37**. Thus, in this cyclization, two

Scheme 12. A Cascade Double-Heck Cyclization From the Overman Total Synthesis of Various Natural Products from the Hexahydropyrroloindole Class.

“carbopalladation” steps effectively convert a prochiral tetra-substituted alkene into a pair of vicinal QSCs.

It should be mentioned that in the 1990s the Overman group has also applied similar reaction conditions to effect the Heck-type biomimetic polycyclization cascades (of polyene reactants inspired by nature) similar to those discussed in Section 2.1, but these will not be discussed at further length.^[46,47]

In the next 2014 study from the Ooi, transition metal catalysis enables the emergence of reactive intermediates enabling formal [3 + 2] cyclizations, stereoselectively forging two QSCs in densely functionalized pyrrolidines.^[48] Two possible mechanisms for the cascade are shown (Scheme 13). Chiral racemic oxazolidinone **41** undergoes activation with the chiral palladium catalyst, generating π -allyl complex **45** after decarboxylation. The authors propose that complex **46** undergoes a direct concerted [3 + 2] cyclization with $\alpha\beta$ -unsaturated ester **42** to yield product **44** containing two QSCs. Alternatively, a stepwise Michael addition of the anionic nitrogen nucleophile onto **42a** as an electrophile and subsequent capture of the allyl cation by the generated enolate species **47** is also a viable mechanism. Notably, the high diastereoselectivity of the cyclization, particularly the relative 1,2-*syn* relationship between the phenyl and nitrile groups which is unchanged from the reactant **42**, suggest that this reaction may indeed be concerted as the authors suggest. However, no further mechanistic evidence is provided to support or dispute either mechanism.

The authors then proceeded to demonstrate the utility of the product **44** in two functionalization pathways. In the first instance, **44** is converted to alcohol **48** via reduction of the ester group, followed by removal of the nitrogen protecting group. The second functionalization pathway involves a five-step sequence, including the ozonolytic cleavage of the vinyl group, followed by Mitsunobu reaction and lactamization, to fuse a γ -lactam in **49** containing a two QSCs at the ring juncture to the previously constructed pyrrolidine. These derivatized products share certain scaffold similarities with key non-peptidic thrombin inhibitors.^[49] A conceptually similar asymmetric palladium-catalyzed decarboxylative annula-

Scheme 13. The Ooi Palladium-catalyzed Synthesis of Congested Pyrrolidines **44** via Formal [3 + 2] Cyclization.

tion of carbonates (in lieu of carbamates **41**) that was reported by Zhang and coauthors in the same year.^[50]

Thus, these studies demonstrate that by understanding the reactivity of π -allyl complex **45**, one can engage it with a carbon nucleophile at the most substituted position to generate a single QSC, or in the case where the carbon nucleophile is a fully substituted enolate (derived from **42**, Scheme 13) to generate a pair of vicinal QSCs.

The following 2008 case by the Shibata group harnesses the action of sequential carbometallation events, to form unique cyclized architectures **52** containing two new QSCs.^[51] In this method, reactants **51** containing isolated alkene and alkyne moieties are cyclized towards intermediate **53** in the presence of a chiral Rh catalyst, thus involving the alkyne and most proximal bisubstituted alkene. Intermediate **53** then undergoes “carborrhodination” with the distal alkene, before reductive elimination, regeneration of the catalyst and generation of products **52**, in modest to excellent yield and in excellent enantioselectivity.

Though mechanistically complex, the design principles behind this transformation are simple; each fully substituted prochiral carbon at both 1,1-bisubstituted alkene moieties is ultimately converted into a QSC via discrete Rh-mediated C–C bond-forming events, for a total of two QSCs.

Another mechanistically complex, yet effective transition metal-mediated cascade cyclization was demonstrated by Trost and coworkers in 2014.^[52] Here, the unique action of Ru on unsaturated bonds is demonstrated as racemic reactants **55**, containing a propargyl alcohol and 1,1-bisubstituted alkene are converted to bicyclic products **57**. The authors propose that catalyst **56** coordinates to the properly alcohol in complex **55**, thus inducing the 1,2-hydrogen shift towards organoruthenium species **58**. In turn, **58** undergoes intramolecular “carborrhuthenation” with the previously uninvolved alkene, producing the first QSC in intermediate **60**. A second “carborrhuthenation” then occurs to form the congested cyclopropane and installing the second QSC in the isolated product **57**. Yields and enantioselectivities form the observed products are modest to high.

As with the case in Scheme 14, this case in Scheme 15 shows how the QSCs in the products are derived from the fully substituted carbon from isolated alkenes moieties in the reactants or in the intermediates.

Scheme 14. The Shibata Carborrhodination Cascade towards Highly Cyclized Architectures **52**.

Scheme 15. The Trost Carboruthenation Cascade towards Strained Fused Bicyclic Pyrrolidines **57**.

A final example to be examined is the key step of the first total synthesis of (–)-lingzhiol (**63**) by Yang, Yu, Gong and coworkers from 2014.^[53] The natural product contains a carbobicyclo[4.3.0]nonane core with two vicinal QSCs at the ring fusion interface. During the key step of this synthesis, homopropargyl alcohol **61** (a single diastereoisomer and enantiomer) undergoes a rhodium-catalyzed formal ring contraction to generate aldehyde **62** (also a single diastereoisomer and enantiomer) containing two new QSCs and key structural features to access the [4.3.0]-bicyclic ring moiety in the natural product (Scheme 16). The authors describe an intriguing mechanism which is supported by density functional theory (DFT) calculations. Starting with coordination of the rhodium catalyst to the terminal alkyne moiety in **61**, fragmentation of the carbocycle is induced via retropropargylation leading to allenyl rhodium intermediate **65**. The organorhodium species **65** then nucleophilically adds to the αβ-unsaturated aldehyde in a 1,4-addition, yielding conformationally twisted enolate species **66**, which finally undergoes C–C bond formation forging both QSCs, before “protoderhodination” to yield product **62**. Notably, the authors claim that though point chirality from reactant **61** is lost during the fragmentation, the subsequent axially chiral intermediates are captured with full fidelity, resulting in full chirality transfer from reactant to product **61**. Product **62** was then subjected to six more synthetic operations, including a reductive lactonization and oxidation state manipulations to finally yield the natural product **63**.

Scheme 16. The Key Step from the Yang/Yu/Gong Synthesis of (–)-lingzhiol (**63**).

This demonstration cleverly harnesses the reactive intermediates that were predicted to be generated from the action of Rh on homopropargyl alcohols. The mechanism is undoubtedly complex and the production of the two vicinal QSCs in **38** showcase an extremely elegant strategic approach towards cyclization cascades with concurrent multiple QSC installation.

To summarize, the cascade cyclizations of prochiral π -systems described here reveal a disparate group of strategies for the *concurrent stereoselective installation of multiple QSCs*. These transformations all feature C–C bond forming pathways with excellent kinetics and capitalize upon (1) organocatalysis as a means to control cyclizations using aldol, Mannich or Michael addition chemistry, or (2) transition metal catalysis using complexes that can orchestrate reactions stereoselectively in 3D space.

2.3 Cycloadditions

The next type of cyclization strategy to be discussed are cycloadditions, which offer excellent avenues for multiple QSC installation in common-sized rings. Cycloaddition reactions are often stereospecific due to orbital symmetry conservation. As a result, cycloadditions are ideal options when the concurrent stereoselective installation of multiple QSCs is desired.

The Diels-Alder [4 + 2] cycloaddition is a cyclization that forms 6-membered rings and has been employed to simultaneously install two or more QSCs.^[54,55] These cycloaddition strategies can be both involving reactants that cyclize in an intramolecular fashion, or even intermolecular, as examples Scheme 17 illustrates. Moreover, the prochiral precursor sp^2 -carbon atoms that eventually furnish the QSCs can be on either or both the diene or dienophile reactive group.

A first literature example that showcases this cyclization design philosophy is from the 2003 Rychnovsky total synthesis of natural products (–)-colombiasin A (**69**) and (–)-elisapterosin B (**71**) (Scheme 18).^[56] In this study, a serrulatane-like diene **67** serves as the common key precursor for a divergent cycloaddition strategy. In one leg of the synthesis, **67** undergoes a classical intramolecular Diels Alder [4 + 2] cycloaddition promoted by high temperature, to yield **68** in excellent yield. **68** is then demethylated to natural product **69**.

Scheme 17. General Cycloaddition Strategies.

Scheme 18. The Key steps from the Rychnovsky Synthesis of (–)-colombiasin A (**69**) and (–)-elisapterosin B (**71**) via Diverging [4+2] or [5+2] Cycloadditions.

Indeed, a similar strategy was used in the first total synthesis of natural product **69** by Nicolaou,^[57] and in subsequent syntheses of **69** by Jacobsen and Harrowven.^[58,59]

However, in the second leg of the Rychnovsky synthesis, **67** is subjected to a large excess of the Lewis acid BF₃, thus inducing a [5+2] cycloaddition towards natural product **71**, likely mediated via the demethylated intermediate **70**.

These cases illustrate how both carbons in a tetrasubstituted, electron-poor dienophile (in the case of the [4+2]) can be thought of as the strategic synthon towards cyclic products with vicinal QSCs. The next couple of examples illustrate how innovations in organocatalytic methods enabled the installation of multiple QSCs via (formal) [4+2] cycloaddition under very mild conditions.

One illustrative methodology study from the Melchiorre group involved the convergent asymmetric synthesis of highly congested bicyclo[2.2.2]octanes **75**.^[60] In one example of their scope, achiral indanone reactant **72** is gently heated in the presence of enone **73** and chiral organocatalyst **74** (Scheme 19).

The authors proposed that the dienamine **76** formed from the amine moiety of the catalyst and enone nucleophilically attacks the indolinone reactant **72** in an intermolecular Michael addition, generating a pair of tertiary stereogenic centers in enolate **77**. Enolate **77** then engages in an intramolecular Michael cyclization with the transient eniminium ion, forming

Scheme 19. The Melchiorre Organocatalyzed Synthesis of Congested Bicyclo[2.2.2]octanes **75**.

the final C–C bond and installing two QSCs, yielding **75** after hydrolysis and regeneration of the catalyst **74**. Though the mechanism claimed by the authors is a stepwise one, the outcome can be consolidated via a concerted [4+2] cycloaddition with the dienamine **76** performing the role of diene, and **72** performing the role of the dienophile. Though the yield of this single example from the scope is low, the focus of the study was not on the installation of vicinal QSCs.

A similar 2012 study by the Jørgensen group illustrates the similar strategic ease with which new ring systems containing vicinal QSCs can be forged via an asymmetric Diels–Alder [4+2] cycloaddition (Scheme 20).^[61] In this study, olefinic oxindoles **79** are employed as the dienophile, along with “cross trienamines” **84** derived from dienals **80** and organo-catalyst **81** as the diene component of the cycloaddition. The bicyclo[2.2.2]octane products **82** were functionalized via Horner–Wadsworth–Emmons olefination to characterized products **83** containing a total of five new stereogenic centers, including two vicinal QSCs.

These last two studies illustrate that installation of two vicinal QSCs during a [4+2] cycloaddition needn't be derived from prochiral carbons existing on the same reactant (as was the case in Scheme 20), overall providing the synthetic chemist with ample strategic options for where the QSCs are installed in the product hexacycle.

A 2012 methodology study by Chen and coworkers nicely illustrates the utility of a [4+2] strategy by combining the cycloaddition step with a subsequent aldol cyclization in their asymmetric cascade synthesis towards various caged tetrahydroxanthenes **89**.^[62] In this study prochiral reactants **86** and **87** are reacted under mild conditions in the presence of organocatalyst **88** (Scheme 21).

The enamine formed **90** from enal **87** undergoes an inverse electron demand Diels–Alder cycloaddition, generating tricyclic enol intermediate **91** after hydrolysis of the catalyst. Enolate **91** then undergoes a final intramolecular aldol cyclization to form the bridgehead cycle in the product **89** containing a total of six new stereogenic centers, including two QSCs. The examples generally proceed in high yields, with excellent diastereocontrol and high enantioselectivities.

Scheme 20. The Jørgensen Organocatalyzed Synthesis of Congested Bicyclo[2.2.2]octanes **83**.

Scheme 21. The Chen Organocatalyzed Synthesis of Congested Tetrahydroxanthenes **89**.

Similar cycloadditions can be effected where a heteroatom participates in the pericyclic reaction. The hetero-Diels-Alder employed during the key step from the 2010 Qin asymmetric synthesis of natural product (–)-perophoramidine (**97**) is an illustrative example (Scheme 22).^[63]

In this synthesis, Qin and coworkers accomplished the key step starting from reactants **92** and **93**. α -chlorolactam **92** first undergoes a AgClO_4 -promoted halide abstraction, giving rise to enamine intermediate **96** which undergoes diastereoselective hetero-Diels-Alder with tryptamine **93**, forging key synthetic intermediate **94** containing three new stereogenic centers, including two vicinal QSCs. Intermediate **94** is converted to the target molecule **97** in eight subsequent synthetic steps.

The next case, this time involving a $[4+2]/[3+2]$ cycloaddition cascade towards products with two QSCs, is derived

Scheme 22. The Key Step from the Qin Synthesis of (–)-perophoramidine (**97**).

Scheme 23. The Key Step $[4+2]$ /dipolar $[3+2]$ Cycloaddition Cascade from the Boger Synthesis of (+)-fendleridine (**100**).

from the 2010 Boger synthesis of natural product (+)-fendleridine (**100**) (Scheme 23).^[64] In this cascade reactant **98** undergoes an intramolecular thermal $[4+2]$ cycloaddition involving the 1,3,4-oxadiazole as the “diene” and the proximal 1,1-bisubstituted alkene to form intermediate **101** and installing the first of the two QSCs. However, under the high temperature conditions **101** extrudes a molecule of nitrogen via retro- $[4+2]$, revealing a new intermediate dipolar **102** which undergoes an intramolecular $[3+2]$ with the dipolarophile indole, forging the final QSC in **99** efficiently and diastereoselectively. Overall, this example shows deep and thoughtful strategic planning with regards to the choice of reactant and the understanding of the reactive intermediates generated.

All the cases discussed thus far illustrate how prochiral carbons can be considered the ideal precursors for the transformation into QSCs via cycloaddition reaction (or cascade). One or both carbons in a trisubstituted or tetrasubstituted dienophile, and either or both of the fully substituted terminal carbons in the diene can be deployed as the strategic precursors of QSCs in the resulting hexacyclic products with two or more QSCs.

Modes of cycloaddition other than the classical $[4+2]$ will be shown in the following two examples. A 2007 Trost methodology study achieved the installation of a pair of vicinal QSCs in products **106** through the intermediacy of π -allyl Pd-complexes (Scheme 24).^[65] Here, reactant **103** containing an allyl acetate undergoes complexation with the Pd catalyst. The resulting π -allyl complex **107** undergoes $[3+2]$ cycloaddition with tetrasubstituted reactant **104**, with concurrent cleavage of the TMS group on **107**. The product **106** from this study is the only example in the synthetic scope where two QSCs are installed. However, the sole example illustrates the conceptual ease with which two QSCs can be installed by simply deploying a tetrasubstituted alkene **104** reactant instead of a trisubstituted one.

A final non-classical $[3+2]$ cycloaddition cascade where a pair of vicinal QSCs were installed concurrently comes from the key step of the 2014 total synthesis of (–)-crinipellin A (**110**) by Lee and coworkers.^[66]

Scheme 24. The Trost Synthesis of Spiroindole **106** via Palladium-catalyzed Formal $[3+2]$ Cycloaddition.

The authors of this total synthesis study were able to forge the final two QSCs in the natural product in a diastereoselective [3 + 2] cycloaddition cascade via a trimethylene methyl diyl (TMMD) intermediate (Scheme 25). In this key step, tosylhydrazone reactant **108** is deprotonated under strongly basic conditions inducing departure of a tosyl anion and generating primary alkyl diazo species **111**. The diazo species undergoes a dipolar [3 + 2] cycloaddition with the neighboring allene, to generate diazocycle **112**, which is a precursor to the TMMD intermediate. During heating, the loss of dinitrogen drives the formation of the TMMD biradical **113**, which the authors suggest undergoes a concerted [3 + 2] biradical cycloaddition to yield the product. However, it should be noted that the reaction outcome can be justified with a stepwise radical mechanism as well. The secondary and more reactive radical in TMMD intermediate **113** would be expected to undergo faster radical addition to the alkene and to regioselectively form the first C–C bond at the least hindered terminus of the alkene. The new biradical species **114** containing two tertiary radicals would then undergo very rapid intramolecular cyclization via radical-radical termination. Advanced intermediate **109** contains the entire carbocyclic core and all congested QSCs of the target molecule. With **109** in hand, the authors were able to complete the total synthesis of the target molecule in 12 synthetic operations.

2.4 Dearomatizations

Conceptually, one could imagine substituted sp^2 -carbon atoms from an arene to play the role of prochiral QSC precursors in cyclization strategies. Indeed, such strategies have attracted the attention of the synthetic community (Scheme 26).^[67] However, challenges include the need to defeat inherent uphill thermodynamics associated with the dearomatization of the arene reactant. Next, we will examine some successful general strategies towards this end.

A mechanistically straightforward but highly elegant first example to be shown is illustrated in the key step from the 2010 total synthesis of natural product (–)-hyperibone K (**119**) by the Porco group (Scheme 27).^[68] Porco and colleagues reported an extremely concise total synthesis in which all three

Scheme 25. The Key Step from the Lee Synthesis of (–)-crinipellin A (**110**).

Scheme 26. General Dearomatization Strategies

Scheme 27. The Key Step from the Porco Synthesis of (–)-hyperibone K (**119**).

QSCs in the adamantane of **119** are installed in a single synthetic step, and are strategically derived from the substituted 1-, 3- and 5-positions of an electron rich phenyl ring.

For this key step, the authors employed the much architecturally simpler natural product clusiaphenone B (**115**) as the reactant, as it contains the prerequisite prochiral carbons. The triphenolic reactant **115** is deprotonated under strongly basic conditions in the presence of enal **116** and chiral phase transfer catalyst **117**, inducing a symmetry-breaking stereoselective S_N2' attack of one face of the anionic arene on the enal, ultimately installing the first QSC in **120**. Deprotonation of a second phenolic hydroxyl group followed by intramolecular Michael addition of the arene nucleophile towards the enal forms the second QSC in **121**, and finally, a similar deprotonation and 1,2-addition into the aldehyde carbonyl generates adamantane **118** in great yield and excellent enantioselectivity. This advanced intermediate was converted to **119** in two steps and confirmed the absolute stereochemistry of **119**, enabling various studies towards its biological activity.

A conceptually opposite strategy of dearomatizing an aromatic ring to install two QSCs involves defeating inherent uphill dearomatization thermodynamics by deploying a reactive carbon nucleophile towards an electrophilic prochiral arene. This is demonstrated during the key step of the 2013 total synthesis of (±)-dehaloperophoramidine (**124**), the dehalogenated analogue of previously shown perophoramidine

(97), by Takemoto and colleagues (Scheme 28).^[69] Takemoto and colleagues illustrated how both vicinal QSCs present in the target molecule can be installed in a single synthetic operation, generating a highly congested chiral polycycle **123** from achiral reactants. This sequence involves lithium halogen exchange of aryl iodide **122**, allowing the generated aryl lithium species **125** to undergo a dearomatizing intramolecular nucleophilic arylation with the pyridyl ring to generate anion **126**. Subsequent addition of allyl iodide captures this anion to finally yield **123** as a single diastereoisomer. The product of this cascade cyclization was converted to the target **124** in just four more synthetic operations.

Defeating the uphill dearomatization thermodynamics has also been demonstrated with other reactive functional groups, such as carbenes. In 2011, the Reisman group disclosed the total synthesis of natural product (+)-salvileucalin B (**129**) via a key step Buchner dearomatization to simultaneously install all three necessary QSCs from the target molecule (Scheme 29).^[70]

The key step for this total synthesis involves the copper-catalyzed carbene generation from diazoketone reactant **127**. The carbene **130** undergoes dearomatizing cyclopropanation with the arene ring, forging three QSCs that are present in the target molecule. The cyclopropane product of the key step **128** was converted to the target molecule in five synthetic operations to complete the first total synthesis of this natural product.

Scheme 28. The Key Step from the Takemoto Synthesis of ($\pm$)-dehaloperophoramidine (**124**).

Scheme 29. The Key Step from the Reisman Synthesis of (+)-salvileucalin B (**129**).

Radical reactions also enable a facile reactivity mode towards dearomatizing arenes at their substituted sp^2 -carbons. The harnessing of the exothermic C–C radical coupling step towards the installation of two vicinal QSCs is nicely demonstrated in the 2008 Mulzer total synthesis of (–)-penifulvin A (**133**) (Scheme 30).^[71]

In the key step towards natural product **133**, a linear enantioenriched intermediate **131** is irradiated with UV light, inducing an intramolecular [3+2] radical cycloaddition between the ortho-substituted tolyl ring and the neighboring trisubstituted alkene on the reactant to dearomatize and install the first QSC in **134**. The resulting biradical **134** then undergoes radical-radical termination to furnish the second QSC in **132** in modest yield. It should be noted that the authors observed other radical-radical terminator side-products in addition to **132**. Nonetheless, **132** is formed as the single enantioenriched stereoisomer in a dearomatization that concludes at room temperature and was subsequently converted to the target molecule **133** in just four more steps.

Another case of dearomatizing a phenyl ring by radical coupling to effect simultaneous installation of two QSCs was demonstrated in the 2014 methodology study by Wang and coauthors.^[72] In this study a variety of trifluoromethylated 2-azaspiro[4.5]decanes **136** containing one or two QSCs are synthesized using via a copper-catalyzed trifluoromethyl radical transfer (Scheme 31). In this spirocyclization, Togni's reagent undergoes single electron oxidation by the Cu(I) catalyst, initiating a trifluoromethyl radical transfer to enamide reactant **135**. The radical intermediate **138** contains the radical

Scheme 30. The Photochemical [3+2] Cycloaddition Key Step from the Mulzer Synthesis of (–)-penifulvin A (**133**).

Scheme 31. The Wang Radical Cyclization to Trifluoromethylated 2-azaspiro[4.5]decanes **136**.

precursor to the first QSC, which is formed by intramolecular dearomatizing radical attack of the arene ring, but only forges a second spirocyclic QSC when an *ortho*- or *meta*-substituted phenol is employed as **135**. The spirocyclic radical intermediate **139** finally undergoes single electron oxidation to the product **136**, regenerating the Cu(I) catalyst. Though the relative stereochemistry of the two vicinal QSCs formed in this study is not controlled, this study still illustrates the utility of forming vicinal QSCs along a new C–C bond via congested radical cyclizations.

The cases examined illustrate how simple arenes, a structural moiety which is widely synthetically accessible, can serve as the synthetic precursor for *cyclization reactions or cascades that stereoselectively install multiple QSCs*. The commonality in methods towards dearomatizing a substituted sp^2 carbon from an aromatic ring into a QSC hinges on careful selection of a C–C bond forming step with sufficient exothermicity. The methods examined for reacting an arene range from conceptually simple, such as exposure to a highly reactive nucleophile or electrophile, to more complex or less obvious methods, such as exposure to carbenes or radicals.

2.5 Electrocyclizations

The Nazarov cyclization is an acid-promoted electrocyclic reaction that gives pentacyclic products containing new point chirality from linear, achiral reactants. The stereospecificity (owing to orbital symmetry constraints)^[73] of the Nazarov cyclization and its ability to engage in reaction cascades have enabled valuable strategies for installing multiple stereogenic centers during the assembly of carbocyclic target molecules.^[73–78]

Despite the uphill energetics surrounding the electrocyclic step of congested 3-oxypentadienyl cations, the Nazarov cyclization shows promise as a strategy towards concurrent multiple QSC installation. For instance, if either/both C1 and/or C5 in the pentadienyl cation **141** (see Scheme 32) is a fully carbon-substituted sp^2 carbon, then QSCs are installed at C1 and/or C5 of the resulting pentacyclic oxyallyl cation **142** and its isolable elimination product **143**.^[79] Additionally, the nucleophilic interruption by a carbon nucleophile (alkenes, enols/enolates, enamines, arenes, etc.) at

C2 or C4 of cation **142** also enables the formation of a QSC at either of these two carbons, as can be seen in products **144**.^[80–84]

The installation of a pair of vicinal QSCs at C1 and C5 is demonstrated nicely in an older literature example from the 1984 Harding total synthesis of ($\pm$)-trichodiene (**147**).^[85] The authors of this total synthesis study were able to effect a cascade Nazarov cyclization from divinylketone reactant **145** to ultimately install the necessary stereochemical features from the target molecule (Scheme 33). Since dienone **145** possesses two prochiral carbons at C1 and C5 that are fully substituted, they were both converted to QSCs in oxyallyl cation **149**. The authors also predicted that the usual elimination pathway seen in the classical Nazarov (see Scheme 33) would not transpire, and that instead a rearrangement involving concerted hydride shifts would occur to form a more stable tertiary cation **150**. This cation undergoes elimination and subsequent enolate protonation to give product **146** as an inconsequential mixture of epimers at the ketone α -tertiary center. This advanced intermediate **146** was then converted to the sesquiterpene target in six synthetic operations. However, it should be noted that the Nazarov cyclization of unactivated and C1/C5-congested pentadienyl cations (such as **148** used in this case) is extremely sluggish and requires stoichiometric amounts of (Lewis) acid to initiate the reaction.^[73]

A more recent methodology study disclosed by the Tius group in 2013 illustrates how uphill thermodynamics for the electrocyclic step with congested divinylketones can be overcome to effect vicinal QSC installation at C1 and C5.^[86] To this end, the authors describe the use of highly congested divinylketones **151** with “push-pull” functional groups at opposite sides of one of the alkene components in the reactant (a silyl ether at C4 and an ester at C5). The polarization enables the smooth Nazarov cyclization towards products **152** containing two new QSCs under catalytic Brønsted acidic conditions at room temperature (Scheme 34). The mechanism is that of the classical Nazarov cyclization, but the termination step involves the cleavage of the silyl group in oxyallyl cation **154** to yield the product **152**. One year after the disclosure of this study the same group disclosed an asymmetric variant of the same transformation, by employing chiral Brønsted acid catalysts.^[87]

Scheme 32. A Nazarov Cyclization Strategy.

Scheme 33. The Key Step from the Harding Synthesis of ($\pm$)-trichodiene (**147**).

Scheme 34. The Tius Brønsted Acid-catalyzed Synthesis of Congested Cyclopentanones **152**.

Aside from installation of vicinal QSCs at both C1 and C5 of the newly formed pentacycle, examples where QSCs have been installed from other prochiral carbons have been reported. A methodology study by West and coworkers from 1999 illustrates how a Nazarov cyclization can be combined with polyene cyclization similar to the biomimetic ones previously discussed in Section 2.1.^[78] In this example unactivated divinylketone reactant **155** underwent a Lewis acid-promoted electrocyclic cyclization, upon which the generated oxyallyl cation **158** undergoes polyene cyclization with the pendent alkene-arene system (Scheme 35). The tetracyclic ketone product **156** contains six new stereogenic centers, including two new QSCs. Moreover, the reaction is very rapid under the strongly Lewis acidic conditions employed, concluding in just five minutes at low temperature despite the unactivated nature of the reactant. The high reaction rate reflects the ease with which less congested pentadienyl cations electrocyclize (e.g. versus the Scheme 33 case), as the two QSCs formed in this example are not both formed along the new C1–C5 bond in the electrocyclizing pentadienyl cation but rather in the cyclizing polyene system.

We saw potential in both the classical and the interrupted Nazarov cyclization as strategies for multiple QSC installation in pentacyclic products and have therefore continued pursuing the development of this electrocyclic cyclization in our lab. Our recent discoveries of the new *halo*-Nazarov reaction exhibit more favorable kinetics and thermodynamics,^[88] enabling milder reaction conditions without “push-pull” functional groups, all while tolerating a wider subset of non-participating functional groups. Furthermore, these studies have enabled

Scheme 35. The West Lewis Acid-promoted Synthesis of Congested Tetracyclic Ketones **156**.

access to the key reactive pentadienyl cation intermediate **141** (see **164**) from simpler, more stable, and more conveniently accessible substrates other than divinylketones **140** (see Scheme 32). These improvements have advanced Nazarov electrocyclization strategies as a strategy multiple QSC-containing complex polycycles.

Our penultimate demonstration of the utility of this method is shown in our recent study involving our multicomponent *halo*-Prins/arene-interrupted *halo*-Nazarov cascade.^[89] In this study, we took aldehydes or ketones bearing a pendent electron-rich arene **159**, enyne alcohols **160** and tetrabutylammonium halide salts TBAX and combined them under acidic conditions to effect a cascade reaction that ultimately furnishes polycycles **162** containing up to three potential QSCs (see Scheme 36).

Under the acidic conditions, and with concurrent removal of water, **159** and **160** are combined to form oxocarbenium **163**, which undergoes an alkynyl *halo*-Prins cyclization to **161**. In previous iterations of this method **161** was a stable and fully isolable intermediate.^[90] However, in this cascade the carefully timed addition of HFIP promotes the second phase of the cascade *in situ*. **161** is ionized by proton-mediated ether opening, giving rise to pentadienyl cation **164**, which in turn electrocyclizes to haloallyl cation **165**. Up to two QSCs could potentially be formed at C1 and C5 during this step. **165** is finally captured diastereoselectively by the pendent electron-rich arene, which after aromatization furnishes **162** and installs a final QSC with perfect stereocontrol.

Beyond forming congested polycycles such as **162**, the alkynyl *halo*-Prins/arene-interrupted *halo*-Nazarov cascade is also capable of transferring remote chirality from reactants to product, if a chiral enyne alcohol is used. Astoundingly, the cascade conducted with chiral racemic reactant **167** proceeds with full transfer of chirality from the single stereogenic center in the reactant to the three stereogenic centers (including two QSCs) in product **168** (see Scheme 37). A combination of experimental and DFT studies of this complex stereochemical phenomenon was published from our lab last year.^[91]

Scheme 36. The Frontier Alkynyl *halo*-Prins/Arene-interrupted *halo*-Nazarov Cascade.

Scheme 37. Chirality Transfer in the Frontier Alkynyl *halo*-Prins/Arene-interrupted *halo*-Nazarov Cascade.

In sum, electrocyclization manifolds constitute a powerful means for *assembling pentacyclic products with concurrent stereoselective installation of multiple QSCs*. Beyond the possibility of installing a pair of vicinal QSCs at C1 and C5, which are formed *stereospecifically*, the cyclization can be combined with other C–C bond forming reactions to enable installation of additional QSCs at other sites of the product pentacycle (e.g. at C2) through various cationic cascades.

3. Summary and Outlook

In this review we have identified five strategies *capable of installing two or more QSC during cyclization*: i) Biomimetic Polyene Cyclization Cascades; ii) Cyclization Cascades of Prochiral Alkenes; iii) Cycloadditions; iv) Dearomatizations; v) Electrocyclizations. Some of the examples we have presented leverage more than one of these strategic concepts. Many of the cases shown were employed in total synthesis campaigns and therefore emphasize the value of these protocols for the rapid assembly of complex molecules.

To achieve QSC installation during cyclization, a reaction must overcome a kinetic barrier that is intrinsically higher than cyclizations forming rings with less congestion. In addition to this, stereocontrol of a reaction that combines two or more prochiral tri- or tetrasubstituted prochiral alkenes is particularly challenging, for several reasons. In any strategy of general utility, the prochiral tri- or tetrasubstituted alkene reactants must be convenient to synthesize, and it is often required that they are prepared as single E/Z isomers. Moreover, these reactants must retain their E/Z stereochemical integrity under the reaction conditions, and in cascade strategies their E/Z configurations must be maintained throughout the entire process. This challenge is particularly present in alkene cascades, which often involve cationic or anionic intermediates with rotatable bonds or isomerizable configurations. These E/Z isomerization problems are avoided when the prochiral alkene resides within a ring, as is the case in many of the strategies reviewed.

In sum, the often-excellent diastereoselective outcomes observed in the examined strategies arise from capitalizing upon at least one of the following phenomena:

- i) Preorganization of the cyclizing prochiral reactant due to conformational, sterical and/or orbital factors.
- ii) Rigidity in the cyclizing reactant or intermediate by fixation of prochiral alkenes in preexisting ring systems or coordination by a transition metal.

To this end, an aromatic ring is a powerful starting point, as it is a convenient reservoir of the requisite tri- or tetrasubstituted prochiral alkene. In similar spirit, strategies involving multiple concerted C–C bond forming events such as cycloadditions and electrocyclizations also often avoid the dangers of isomerization in an intermediate and are therefore well represented among the success stories as well.

Analysis of the cases presented here allows us to appreciate the challenges chemists must overcome if they hope to develop efficient new methods for generating topologically complex (poly)cyclic scaffolds – especially when directly derived from acyclic alkene precursors. For the broadest reaction scope, access to configurationally pure tri- or tetrasubstituted alkene reactants is essential. To overcome steric demand during installation of QSC during cyclization, each C–C bond forming reaction must be kinetically accessible, be it a one-step or a three-step sequence. To control stereochemistry during C–C bond formation, it helps if the system is preorganized. With preorganization, orbital symmetry can be conserved in pericyclic processes, and existing stereogenic centers can exert the maximum impact in cyclizations that are substrate-controlled. For asymmetric cyclizations, the system needs to be susceptible to the influence of promoters and catalysts, a tall order when the unsaturations in a reactant is comprised of alkenes only. Finally, it is necessary to create a reaction environment that will preserve the stereochemical integrity of any long-lived charged intermediates formed from the reactant alkenes. If these design principles can be incorporated into synthetic planning, we are optimistic that efficient new cyclizations strategies can be developed for the construction of topologically complex polycyclic systems.

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Manuscript received: March 1, 2021

Revised manuscript received: April 20, 2021

Version of record online: May 16, 2021