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REVIEW

Transition metal-promoted biomimetic steps in total syntheses

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Covering: 1960 to present

This review summarizes the state-of-the-art on the use of transition metals in synthetic steps inspired by biosynthesis. After an introduction showing the importance of metals in life processes, with special emphasis on biosynthetic processes, their place in biomimetic synthesis will be described. Topics include oxidative cyclizations for polyether synthesis, electrophilic and radical cyclizations of polyprenoids, the role of palladium in electrocyclizations, oxidative biaryl couplings and other rearrangement steps.

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1 Introduction

The d-block transition metals occupy a special place in biological processes, being involved in catalysis, structure, transport, signalling and sometime sensing.[1,2] Some of them are essential to life despite low concentrations, while others are present in gram amounts in living organisms, like iron, which carries molecular oxygen, catalyses oxidation or transfers electrons. In biosynthetic steps, transition metals are crucial in the oxidation of the C–H bond or alkene oxidation during the decoration of secondary metabolites. For the synthetic chemist, biomimetic strategies utilizing transition metals can take two directions. First, such catalysis can be used to perform the biosynthetic connection steps, but not necessarily using metals operating in the life processes. Transition metal cations are susceptible to interaction with substrates through their σ and π orbitals, polarizing bonds and activating functional group transformations and compound rearrangements. This will be the main part of this review, which will be classified according to the reaction type. Second, the transition metal catalyst can be used in biomimetic methodologies, mimicking enzymatic processes of metalloproteins. This domain can have many applications, somewhat dealing with green chemistry,[3,4] but will not be covered here. Before starting this discussion, it is important to define the place of transition metals in biological processes, especially in the biosynthetic context.

2 A short survey of transition metals in biological processes and biosynthesis

2.1 Overview of the biological functions of transition metals

Among the twenty elements that are essential to life,[1] eight belong to transition metals, mainly from the fourth row and

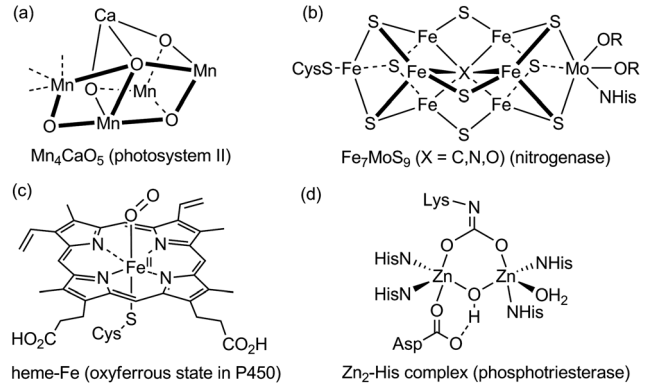

Fig. 1 Examples of biological transition metal complexes performing water oxidation to dioxygen (a), nitrogen reduction to ammonia (b), substrate oxidation (c) or hydrolysis (d).

usually in their cationic form. These are iron, copper, manganese, molybdenum, cobalt, nickel and vanadium, which can all be involved, but not exclusively, in redox processes, plus zinc which has an important role as a Lewis acid and a structural template. Additional transition metals, such as tungsten, chromium, titanium and cadmium, are non-essential but potentially important to some organisms. These metals are part of the total metallome, which includes bound (to proteins, polysaccharides, membranes or nucleotides) and free elements. The metal content of an organism is directly related to the surrounding environment and external nutrients.[5]

Under life conditions, all reactions involving these metals occur in an aqueous medium or an enzyme active site and under ambient or physiological temperatures. Thanks to their increased covalent chemistry and their strong Lewis acid properties, compared to other metals, transition metals are mostly bound to biomolecules, through oxygen (sometimes as oxides, for example in the cubane-like Mn_4CaO_5 photosynthetic clusters[6]), sulphur (sometimes as sulphides, for example in Fe/Mo/S clusters,[7,8] or as hemes[9]) and/or nitrogen ligands (for example, histidine ligands of zinc in phosphotriesterase[10]), with various coordination geometries (Fig. 1).

Thus when they are involved in a biological reaction, the activated transition metals have a high electron affinity for their substrate while being strongly retained by the biological "matrix", even though changes in the coordination number of the metal occur. The coordination of the metal by the biological matrix favours an entatic (under tension) state which activates the metal centre, since the coordination geometry is usually distorted.[11] Many biological systems have provided a fruitful source of inspiration for the bioinorganic and organometallic chemists seeking to reproduce life reactions using biomimetic catalysts and methodologies.[3,12]

2.2 The place of transition metals in biosynthetic steps

The role of transition metals in the secondary metabolism, as for primary metabolism, is important from the gene regulation level to the enzymatic level. Indeed, the biosynthetic lines can be regulated at the genetic level by transcription factors such as zinc finger proteins, as exemplified by fumonisin biosynthesis regulation in *Fusarium verticillioides*.[13] Metals are also involved at all biosynthetic stages, from construction of the carbon skeleton (usually involving electrophilic reactions catalyzed by Lewis acids) to functional decoration (most often through oxidations by heme and non-heme proteins).

Owing to their electronic properties (ionic radii, charges and hardness natures),[14] the divalent zinc and manganese ions are characterized by divergent preferences for protein ligands. They behave as electrophilic catalysts, stabilizing hydroxide ions, which become excellent nucleophiles in the active site of hydrolytic metalloenzymes,[10,15] or any negative charge developing in a transition state. The studies of fungal polyketide synthases (PKS) involved in the biosynthesis of anthracenones and naphthacenones revealed the bifunctional nature of a dimanganese thioesterase in which the metals interact with the

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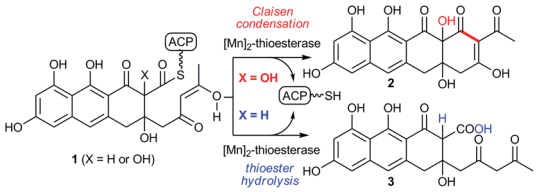
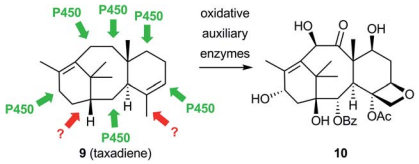


Scheme 1 α-Hydroxylation dependence of dimanganese-thioesterase products in a fungal PKS (X = H or OH).[16] ACP: acyl carrier protein.

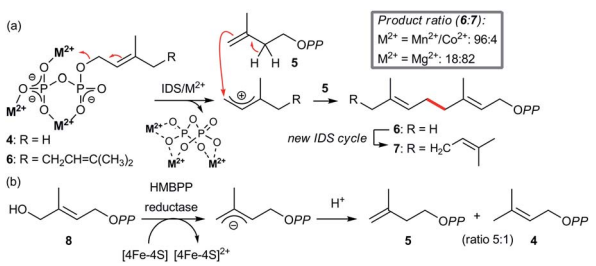


Scheme 3 Oxidation steps involving P450s in taxol biosynthesis.

substrate.[16] This enzyme performs either a Claisen condensation into naphthacenone **2** or the hydrolytic release of the anthracenone product **3**, depending on whether the thioester substrate **1** is α-hydroxylated (X = OH) or not (X = H), respectively (Scheme 1). In the polyketide cyclase RemF, which produces resistomycin in *Streptomyces resistomycificus*, the Claisen condensation may be catalysed by an unusual octahedral zinc binding site.[17] The metal ion would serve as a Lewis acid in this reaction, as in class II aldolases.[18]

Electrophilic activation is common in terpenoid construction. Class I terpenoid synthases (*e.g.* farnesyl diphosphate synthase) use a trinuclear metal cluster to catalyze the formation of a carbocation from dimethylallyl diphosphate (DMAPP, **4**) and the addition of isopentenyl diphosphate (IPP, **5**) to deliver the C_{10} adduct geranyl diphosphate (GPP, **6**) (Scheme 2), which can be elongated in its turn to farnesyl diphosphate (FPP, **7**).[19,20] The metal cluster usually contains three Mg^{2+} cations but divalent transition metals such as Mn^{2+} can be involved instead. Recently, insect isoprenyl diphosphate synthases (IDS) have been shown to follow divergent terpenoid pathways, leading to variable product length, depending on the available divalent metal cofactor.[21] The chain length depends on the size of the hydrophobic pocket in the active site, which is affected by the van der Waals radii of the metal ions (1.73, 1.90 and 0.96 Å for Co^{2+}, Mn^{2+} and Mg^{2+}, respectively). Therefore the IDS of the juvenile horseradish leaf beetles yielded 96% of the C_{10}-GPP and 4% of the C_{15}-FPP in the presence of Co^{2+} or Mn^{2+}, whereas this ratio was inverted in the presence of Mg^{2+} with 18% of GPP and 82% of FPP.

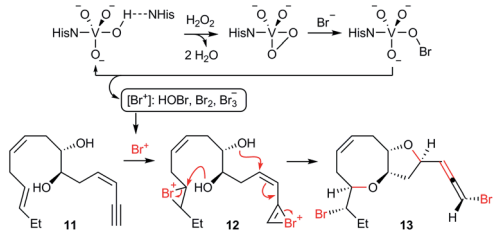
Redox processes are complementary to this electrophilic activation as they can change the oxidation level of metabolites and tune their reactivity. The last two key enzymes in the methylerythritol phosphate (MEP) pathway of the isoprenoid biosynthesis are (*E*)-4-hydroxy-3-methylbut-2-enyl diphosphate (HMBPP: **8**) synthase[22] and HMBPP reductase[23,24] in *Escherichia coli*, which both contain a reducing [4Fe-4S] cluster. HMBPP synthase is able to convert methylerythritol cyclodiphosphate into HMBPP thanks to a radical mechanism involving two electron transfers, while HMBPP reductase converts HMBPP (**8**) into IPP (**5**) and DMAPP (**4**) in a 5 : 1 ratio *via* two successive electron transfers from the Fe/S cluster (Scheme 2b).



Scheme 2 Transition metals in terpene biosynthesis: (a) metal-dependence of the product ratio of an insect isoprenyl diphosphate synthase (IDS) and (b) reduction of HMBPP by a reductase associated to Fe/S cluster.

Once a carbocyclic skeleton has been formed, the chemical diversity can be expanded by further transformations, for instance by oxidations involving activation of molecular oxygen and performed by oxidases, dioxygenases, or mono-oxygenases. Among mono-oxygenases, the iron-dependent cytochrome P450 enzymes play an extremely important role in the biosynthesis of natural products. A plethora of examples are available, including the hydroxylation of non-activated aliphatic or aromatic CH bonds.[25] The first structurally characterized one in 1995 was the protein P450EryF responsible for the 6*S*-hydroxylation of 6-deoxyerythronolide B during erythromycin biosynthesis.[26] The P450 co-factor is a heme linked to a cysteine group by an axial thiolate bond and which, in the high spin state of iron, is able to fix molecular oxygen. Depending on the enzyme, dioxygen is converted into a peroxy or hydroperoxy radical or a ferryl-oxo intermediate, leading to nucleophilic, electrophilic or radical oxidations.[25] Among typical examples in terpene biosynthesis, taxadiene (**9**) oxidation leads to 10-deacetylbaccatin III (**10**), the precursor of taxol, after at least six oxidation steps performed by P450s (Scheme 3).[27] The conversion of trichodiene into isotrichotriol is performed by P450Tir4 from *Fusarium graminearum*, which alone catalyzes four successive oxidations, three hydroxylations and one epoxidation, during the biosynthesis of the trichothecene mycotoxins.[28] It is also possible that oxidation steps trigger substrate rearrangements, as found in the conversion of flavanones into isoflavones,[29] in the polycyclization of polyketides like hirsutellones,[30,31] the rearrangement of alkaloids like littorine into hyoscyamine aldehyde after benzylic oxidation,[32] or the oxidative coupling of aromatic substrates.[33]

Nitrogen oxidations of aminoarenes into nitroarenes have been described,[34] either by Rieske oxygenases consisting of the Rieske [2Fe-2S] cluster and a non-heme iron-histidine binding site, or by di-iron monooxygenases, as illustrated by aminopyrrolnitrin oxygenase[35] or *p*-aminobenzoate oxygenase.[36] The reaction involves the sequential oxidation of the amine through hydroxylamine and nitroso compounds towards the nitro group.



Scheme 4 Bromination–cyclization mechanism of a vanadium bromoperoxidase (V-BrHP) leading to *Laurencia* bromopolyketides.

Dioxygenases are important enzymes in the oxidative metabolism of natural products, many of them incorporating a non-heme iron co-factor[37] and occasionally an α-oxoacid (*e.g.* 2-oxoglutarate) as a co-substrate, which is oxidatively cleaved.[38,39] The biosynthesis of vindoline involves such an oxidation at the late stage by desacetoxyvindoline 4-hydroxylase,[40] while complex ring rearrangements have been described in the terpenoid series.[41]

The last important oxidation enzymes involving a transition metal in the secondary metabolism are vanadium haloperoxidases (V-HPO), which catalyze the halogenation of various substrates, in particular marine natural products (Scheme 4).[42,43] On the contrary to iron in heme haloperoxidases, the vanadium atom of V-HPO maintains its vanadate V(v) oxidation state throughout the catalytic cycle.[44,45] The electrophilic X^+ reactive species would be generated and reacting inside the enzyme active site as indicated by the high regio- and stereospecificity of the reaction. The halonium would be formed by the two-electron oxidation of halide anions involving a peroxovanadium intermediate formed from the coordination of hydrogen peroxide. The activation of double bonds by activated halogen species was shown to be important in the halogenation–cyclization of terpenoids[43,46,47] or polyketides like **13** (Scheme 4).[48]

3 Bio-inspired oxidative cyclizations involving oxometals in polyether syntheses

3.1 The biosynthetic model of Townsend and Basak for polycycloethers

The biosynthesis of polyether natural products has been the object of important research and speculations, leading to two

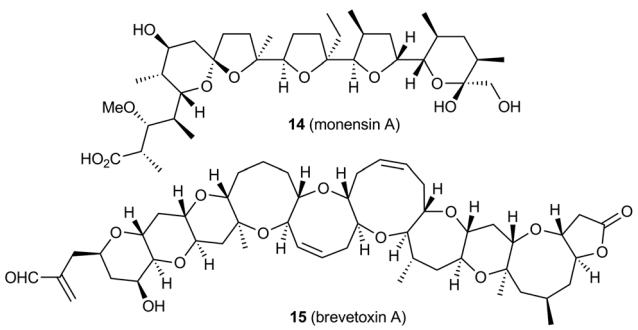
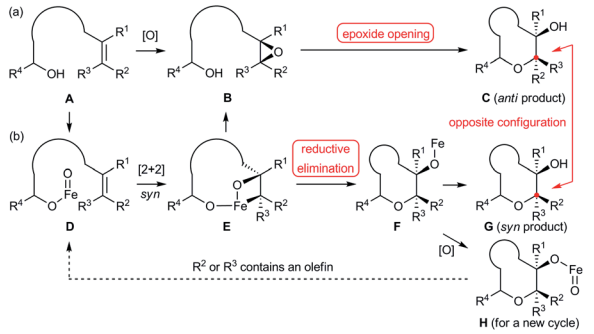


Fig. 2 Structures of monensin A (**14**) and brevetoxin A (**15**).



Scheme 5 Two hypotheses for ladder polyether biosynthesis: (a) Cane–Celmer–Westley model; (b) Townsend–Basak model.

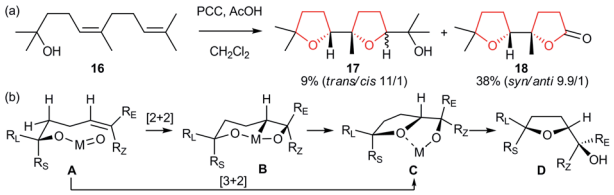
biosynthetic hypotheses. The older one, the Cane–Celmer–Westley hypothesis, was proposed in 1983 to explain the formation of the tetrahydrofuran-rich monensin A **14** (Fig. 2). It describes a two-step process involving the epoxidation of a hydroxylated (poly)olefin precursor (**A**) into a (poly)epoxide (**B**), followed by a cascade cyclization of the polyether framework (**C**) by intramolecular epoxide opening (Scheme 5a).[49] In 1991, based on experimental works suggesting that the biochemical machinery is able to carry out *oxidative cyclizations*, Townsend and Basak proposed an alternative biosynthetic model involving a *syn*-oxidative polycyclization (Scheme 5b) and generalized it to fused polycycloethers like brevetoxin A **15**.[50,51]

Basically, Townsend and Basak postulated that an alkoxy oxometal **D** derived from the hydroxy polyolefin **A** would undergo [2 + 2] cycloaddition (*syn*-addition) to afford an alkoxy metallaoxetane **E**. Reductive elimination of the metal would release a cycloether **F** bearing an alkoxymetal whose oxidation into a new alkoxy oxometal **H** would allow a new oxidative cyclization.

The stereochemical outcome of this model is interesting since in order to get a natural product like monensin A (**14**),[52] the polyolefin substrate should have an inverted geometry of double bonds (*Z versus E*) compared to the Cane–Celmer–Westley model. That is critical as we know that biological *E* and *Z* olefins do not have the same enzymatic origin.[53,54]

3.2 Oxometals for the synthesis of tetrahydrofurans: mechanism, stereocontrol and natural product synthesis

The literature concerning the use of oxometals for the synthesis of polyethers through oxidative cyclizations, tetrahydrofurans (THF) in particular, provides a textbook case for the topic of this review if we consider the large number of metals described for this purpose. Indeed, starting with manganese ($KMnO_4$) in the 1960s,[55] the range of useful transition metal oxides (MO_x) for such transformations has extensively grown, with many examples based on Cr, Fe, Mn, Os, Re, Ru or V for most biosynthetic related cases. Although the general mechanism for the MO_x-promoted cyclization can be related to the one described in Scheme 5b, the [2 + 2] *syn*-addition of oxometals on the olefin has been a matter of debate, with [3 + 2] cycloaddition of O–M═O and the olefin being suggested as an alternative mechanism.[56,57]



Scheme 6 Regio- and stereospecificity in the PCC-mediated oxidative cyclization of the hydroxydiene **16** (a); general mechanism of the oxometal mediated synthesis of THF rings (b).

The stereospecificity of the oxidative cycloaddition was found to be complete during the conversion of 1,5-hexadiene into bis(hydroxymethyl)tetrahydrofuran by $KMnO_4$, with all new bonds formed by suprafacial processes leading to *cis*-THF rings.[58] Although the reaction was not linked at this time to any biosynthetic mechanism, it was used to stereoselectively synthesize the terminal THF unit of ionomycin.[59] Asymmetric induction was provided by Evans' norephedrine-derived chiral oxazolidinone during the permanganate-promoted oxidative cyclization of 1,5-dienes for the synthesis of THF-based ionophores.[60] More relevant to the Townsend–Basak model and the discussion below was the observation of a substituent effect during the transannular *syn* oxidative cyclization of 5-hydroxycyclooctenes by pyridinium chlorochromate (PCC).[61] The same conditions were used by McDonald and Towne for the *syn*-stereospecific oxidative bicyclization of nerol-derived compounds (**16**, Scheme 6a) into bis(THF) (**17**,**18**).[62] They were the first to claim the strategy as biomimetic, in reference to Townsend and Basak, although the conditions were limited to tertiary alcohols. High stereoinduction was observed in favour of *trans*-THF rings consistent with the cyclization of a chair-like conformer of the alkoxy-tethered chromate ester **A** (M = Cr(O)OH) in which the alkene adopts a pseudoequatorial position during the oxidative [2 + 2] addition (Scheme 6b). Accordingly, stereoinduction was higher with *Z*- than with *E*-alkenes.

Apart from permanganate and oxochromium reagents, which were able to perform the oxidative cyclization of alkenes and tertiary hydroxyalkenes into *cis*-cycloethers, Re(VII) oxides (*e.g.* Re_2O_7) rapidly showed their complementary utility in the transformation of 5-hydroxyalkenes, including primary and secondary ones, into 2-hydroxymethyl-*trans*-tetrahydrofurans under the conditions developed by Kennedy and co-workers,[63] especially in the presence of a co-oxidant and a pyridine.[63c] The method was used by Keinan, Sinha and co-workers[64,65] and by McDonald and Towne[66,67] for the biomimetic synthesis of bis(THF) derivatives from secondary hydroxydienes, especially for the synthesis of annonaceous acetogenins. The conditions were improved by McDonald who used acylperrhenates as less acidic reagents, for example $(Cl_2CHCO_2)ReO_3$ in the presence of 2,6-lutidine.[66] The mechanism of this reaction parallels the one depicted in Scheme 6b, with a preference for the [3 + 2] addition. However, it was observed that the growing poly(THF) can have chelation effects on the alkoxyrhenium intermediate, decreasing the stereoselectivity in the formation of tris(THF) compounds made in one steps from hydroxytrienes.[68] Rules

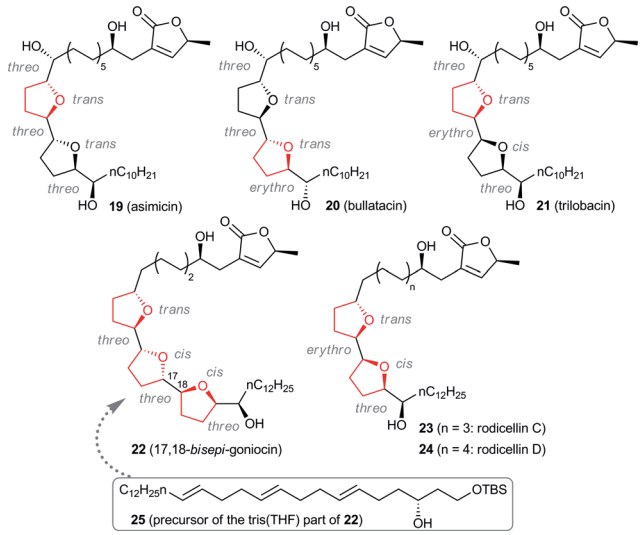
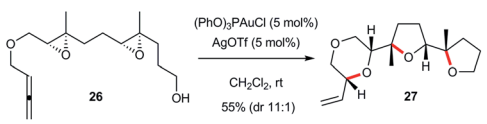


Fig. 3 Structures of acetogenins synthesized by Keinan and Sinha. The red THF rings were made in the presence of an oxorhenium(VII) oxidant while the others were constructed by conventional methods. The adjacent THF rings in **22**–**24** were obtained in one oxidizing step.

were then proposed by Sinha *et al.* to predict the stereoselectivity in tandem oxidative polycyclizations with rhenium(VII) oxides: the first THF ring is always produced with a *trans* selectivity but the outcome of the next cyclization depends on the *threo*/*erythro* relationship between the two vicinal oxygen functions resulting from the first cyclization.[69]

Thanks to the combined use of various oxidative conditions and benefiting from specific stereocontrol of the reactions, Keinan, Sinha and co-workers performed a prolific work on the total synthesis of acetogenins (Fig. 3).[65] These authors never claimed their syntheses were biomimetic, on the contrary defending the Cane–Celmer–Westley hypothesis.[70] However, the analogy of their approach with the Townsend–Basak hypothesis makes them well suited for this discussion. They developed a modular approach for the synthesis of chemical libraries of acetogenins[65a,71] and the total synthesis of asimicin (**19**),[71a] bullatacin (**20**),[71a] trilobacin (**21**),[71b] 17,18-*bisepi*-goniocin (**22**),[72] rodicellins C and D (**23**,**24**).[70] The tris(THF) part of compound **22** in particular was made in one step from an all-*E* 13-hydroxy-1,5,9-triene (**25**).

Many other oxidizing reagents were used for similar alkene oxidative cyclizations, especially the oxidation of dienes by OsO_4[73,74] or RuO_4.[75,76] The same stereoselectivity as with $KMnO_4$[55,58] was observed, leading to *cis*-THF rings. Beautiful examples of tandem oxidative polycyclizations of squalene have been reported by Piccialli and co-workers, either in the presence of RuO_4 or OsO_4, leading in one step to complex penta-THF systems with an all-*threo* stereochemistry.[77]



Scheme 7 [Au^+]-catalyzed synthesis of polycycloether **27** by Gagné.

4 Electrophilic cyclizations for the synthesis of natural cycloethers

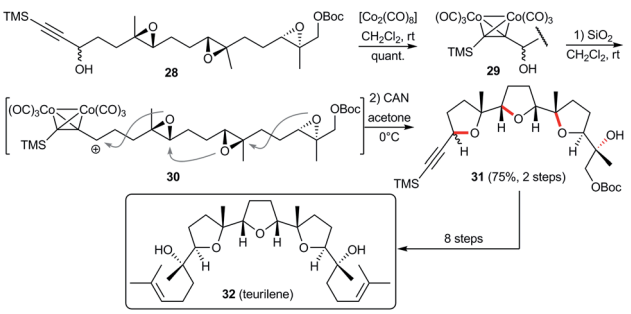
In reference to the Cane–Celmer–Westley hypothesis for ladder polyether biosynthesis (Scheme 5a),[49a] Gagné imagined a gold(I) phosphite-catalyzed cascade cyclization of allenyl epoxides (**26**, Scheme 7).[78] Fused and chained oxacycle structures (**27**) commonly found in natural products (see Fig. 2 and 3) were constructed with a regioselectivity depending on the substitution and functional pattern of the substrate.

The intramolecular attack of a cation by epoxide nucleophiles was achieved by Martín during the Nicholas reaction of $Co_2(CO)_6$-propargylic alcohols bearing remote epoxy esters, leading to cyclic ethers (Scheme 8).[79] This strategy was used in an elegant total synthesis of teurilene **32**.[79b] The key step involved the SiO_2-mediated formation of a cation (**30**) from the cobalt complex **29** and the stereoselective cascade cyclization into the tris(THF) intermediate **31** in 75% yield.

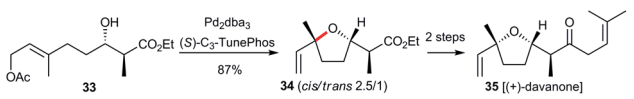
Intramolecular palladium-catalyzed stereoselective allylic *O*-alkylation at the tertiary centre of allylic acetate **33** (Scheme 9) is a rare example of a Tsuji–Trost reaction with biomimetic significance, which was applied by Vosburg to the synthesis of the terpene (+)-davanone **35**.[80] The formation of the tetrahydrofuran **34** was realized in 87% yield in the presence of Pd_2dba_3 and the chiral diphosphine (*S*)-C_3-TunePhos.

$Sc(OTf)_3$ hydrate was used by Trauner to promote the biomimetic conversion of the furanocembranoid coralloidolide E (**37**), obtained by the epoxidation of coralloidolide A (**36**), to coralloidolide B (**38**) in 63% yield, through hydration of the dienedione moiety followed by a transannular epoxide opening (Scheme 10).[81]

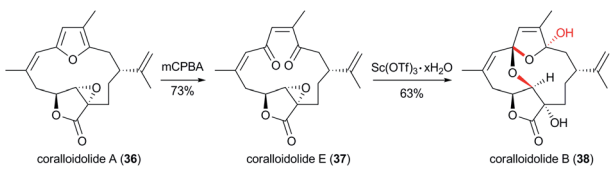
Lastly, we want to expand this section to the formation of azacycles, although examples are rare in this category. Debromoflustramine B (**41**), a prenylated hexahydropyrrolo[2,3-*b*]indoline, was synthesized by Ganesan in three steps from tryptamine, through the biomimetic $Zn(OTf)_2$-mediated prenylation–cyclization of tryptamine ethylcarbamate (**39**) in the presence of prenyl bromide, Bu_4NI and the Hünig's base (Scheme 11).[82] The natural product **41** was obtained after a rather nontrivial reduction of the carbamate. The first biomimetic prenylation step was thought to proceed through an S_N1 mechanism.[83]



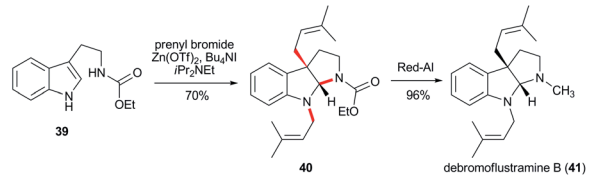
Scheme 8 Key steps in the synthesis of teurilene **32** by Martín.



Scheme 9 Vosburg's synthesis of (+)-davanone (**35**).



Scheme 10 Trauner's synthesis of coralloidolide B (**38**).



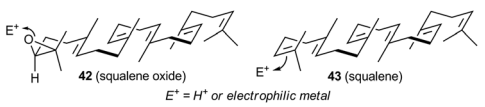
Scheme 11 Ganesan's synthesis of debromoflustramine B (**41**).

5 Biomimetic cyclizations of polyprenoids

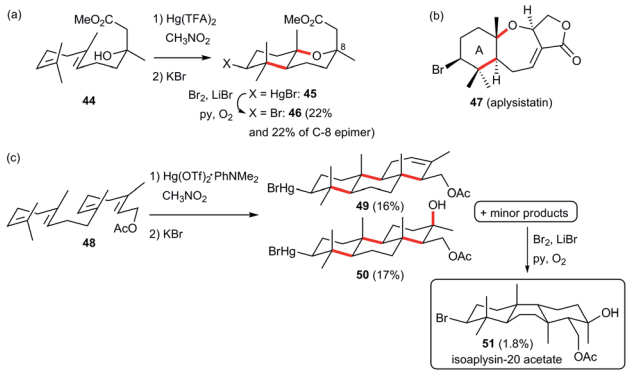
Biosynthetic polyprenoid cyclizations inspired natural product chemists since the structure of polycyclic terpenoids were first elucidated.[84] Stork[85] and Eschenmoser[86] were the first to formulate geometrical and stereoelectronic rules for these polycyclizations in the 1950s and the first biomimetic syntheses of polyprenoids through cationic processes were reported by Johnson in 1968,[87] and van Tamelen in 1975.[88] Furthermore, an oxidative free radical pathway was imagined by Breslow in 1962[89] for these transformations and was supported by synthetic studies from the same author[89b] and from Julia.[90] Since then, extensive work has been carried out on these biomimetic cascade cyclizations, which can be initiated by electrophilic Brønsted or Lewis (mainly $SnCl_4$ and $BF_3{\cdot}OEt_2$) acids or by radical promoters. However, the use of transition metal-based catalysts, discussed in the following section, has been frequently encountered.

5.1 Electrophilic polycyclizations in terpenoid synthesis

An electrophilic cyclization can be initiated by the interaction of an electrophilic reagent (H^+ or a metal like Hg^{2+}) either with a nucleophilic heteroatom of the polyene substrate, like in squalene oxide **42** (Scheme 12), or directly with an olefin of the



Scheme 12 Modes of activation for polyene cyclization.



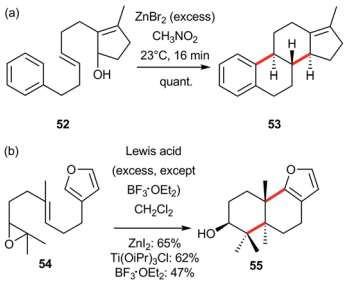
Scheme 13 (a) Hoye's Hg^{2+}-mediated 1,5-diene cyclization; (b) structure of aplysistatin (**47**) whose A-ring was constructed by this method; (c) Nishizawa's biomimetic cyclization of diterpenes.

substrate, like in squalene **43**. In both cases a cationic centre is generated which triggers the cyclization.

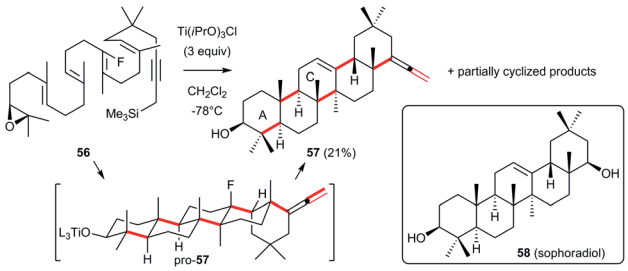
5.1.1 Polyene cyclization through olefin activation by an electrophilic metal. Early works on electrophilic cyclization of polyenes employed mercury salts, usually $Hg(CF_3CO_2)_2$, as initiators.[91] The cyclized organomercury intermediates (**45**, Scheme 13a) could be further functionalized by reduction ($NaBH_4$), bromination (Br_2, leading to **46**) or internal nucleophilic termination.[92] This methodology was used by Hoye for the total synthesis of aplysistatin **47** (Scheme 13b), a brominated marine natural product with antileukemic properties.[92c] It is possible that the biosynthesis of **47** proceeds through direct activation of a polyene by a Br^+ species (see the analogy with Scheme 4).

A similar strategy applied by Nishizawa to geranylgeranyl esters (**48**) was effective to construct tricyclic terpenoids (**49**,**50**), among them a minor product which was brominated into the diterpene isoaplysin-20 acetate **51** (Scheme 13c).[93] A mercury–selenium exchange (PhSeSePh, *hν*) was applied by McMurry in the total synthesis of the complement inhibitor K-76, a fungal meroterpenoid.[94] Furthermore in the polyketide series, the electrophilic mercury salt strategy was also applied by Sato *et al.* to the biomimetic synthesis of prostaglandin E_1. It allowed the construction of the five-membered ring, releasing an alcohol after oxidation of the BrHgR intermediate (O_2, $NaBH_4$).[95] More recently Gagné reported the use of Pt(II) catalysts for the oxidative cyclization of 1,5-dienes and trienes leading to bi- and tricyclic systems, with a mechanism related to model **43**.[96]

5.1.2 Polyene cyclization through epoxide of allylic alcohol activation in the presence of a transition-metal Lewis acid. Tertiary carbocations and allylic cations are common intermediates in terpene biosynthesis and synthesis. They are generated, for example, from polyprenyl diphosphates or oxides in the active site of terpene synthases or cyclases in which metal cofactors are involved as illustrated in Scheme 2. Johnson used $ZnBr_2$ to promote the biogenetic-like one-step cyclization of the cyclopentenol **52** into the corresponding tetracyclic compound **53** in quantitative yield (Scheme 14a).[97] The effect of arene functionalization on the *ortho–para* selectivity of the last cyclization was also studied. Furans were used by Tanis and Herrington as terminators



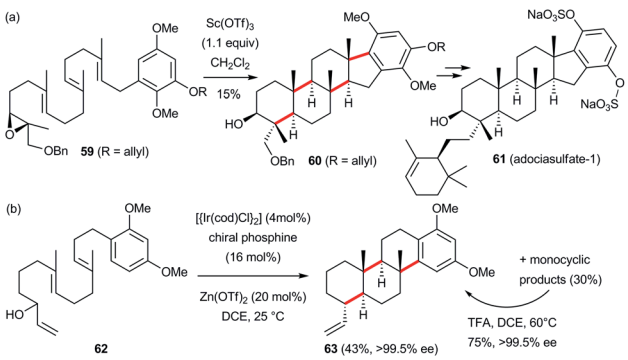
Scheme 14 Zn^{2+}- and Ti^{4+}-catalyzed cationic cyclizations of an allylic alcohol (a) and an epoxide (b).



Scheme 15 Johnson's pentacyclization towards sophoradiol (**58**).

of cationic cyclizations, especially for the synthesis of 3β-hydroxy pallescensin-A (**55**) from epoxydendrolasin **54** (Scheme 14b).[98] ZnI_2 and $Ti(OiPr)_3Cl$ were used to promote the cyclization in 65% and 62% yields, respectively, giving better results than $BF_3 \cdot OEt_2$ (47%).

The catalyst $Ti(OiPr)_3Cl$ (3–7 equiv.) was used by Johnson for epoxide opening-initiated polyene cyclizations, a work culminating with the first example of biomimetic pentacarbocyclization of **57** (Scheme 15).[99] It is obvious in this case that the polyene substrate **56** is analogous to the enzyme substrate oxidosqualene **42**. In this work, the fluorine atom in **56** was expected to control the regiochemistry of the cyclization to provide the six-membered C-ring. Unfortunately, compound **57** could not be converted to sophoradiol **58** and an alternative biomimetic strategy was designed.



Scheme 16 (a) Overman's biomimetic key step in the total synthesis of adociasulfate-1 (**61**); (b) Carreira's iridium-based catalytic system for terpenoid tricyclization.

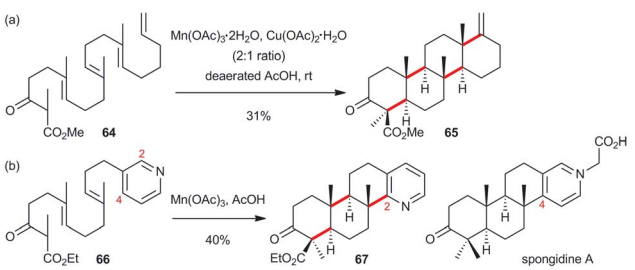
Other transition metal salts were used by some authors for cationic polyene cyclizations, such as $FeCl_3$ and $Sc(OTf)_3$.[100,101] In particular, Overman described the enantioselective synthesis of the kinesin motor protein inhibitor adociasulfate-1 (**61**, Scheme 16a), using an epoxide opening-initiated polyene tetracyclization terminated by an arene (**59**), with a 15% yield leading to **60** (meaning 62% yield per ring) in the presence of $Sc(OTf)_3$.[101] In this case, $FeCl_3$ gave also 10% yield of **60**.

Very recently, another catalytic system for the enantioselective cyclization of polyenes was reported by Carreira (Scheme 16b), with a secondary allylic alcohol (**62**) used as an internal activating group.[102] The reaction was based on the combination of $[\{Ir(cod)Cl\}_2]$ and $Zn(OTf)_2$ in the presence of a chiral phosphine ligand leading to polycyclic compounds (**63**) with good to excellent yields and enantiomeric excess.

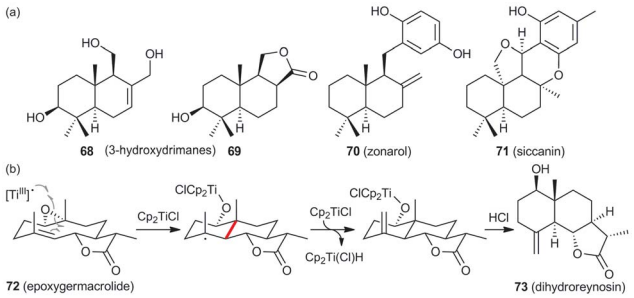
5.2 Radical polycyclizations in terpenoid synthesis mediated by single-electron metal donors

The initiation of radical polycyclization can be realized through single-electron transfer by the action of metals such as $[Mn^{III}]$ and $[Ti^{III}]$ on functional groups, such as β-ketoesters, epoxides or alkyl halides.[103] Zoretic reported in 1990 a concerted intramolecular radical cyclization of β-ketoester tetraene **64** by the combined action of $Mn(OAc)_3$ and $Cu(OAc)_3$ (2 : 1 ratio, in degassed AcOH), forming all four cycles of D-homo-5α-androstane-3-one **65** in 31% yield (Scheme 17).[104] Steroid skeletons in the 5α-pregnane series were obtained in similar conditions.[105] González and Molina-Navarro attempted a synthesis of spongidines by a $Mn(OAc)_3$-mediated radical cascade terminating onto a pyridine ring.[106] Interestingly the pyridine ring cyclized through its position 2 rather than position 4 which was required to get the natural product, leading to an isomeric spongidine.

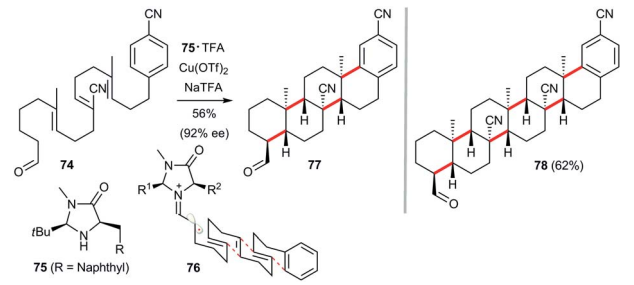
Starting from acyclic epoxy-polyenes, the homolytic opening of the epoxide in the presence of stoichiometric quantities of Cp_2TiCl (generated from a mixture of Cp_2TiCl_2 and Mn) led to 6-*endo*-selective radical cyclizations terminated by an oxidative step.[107] Barrero thus synthesized the drimane skeleton from 10,11-epoxyfarnesyl acetate, through two consecutive 6-*endo*-cyclizations leading to the *trans* decalin. Cárdenas and Cuerva developed a catalytic version of this reaction based on the combination of TMSCl and 2,4,6-collidine to regenerate Cp_2TiCl_2 from the end-



Scheme 17 Zoretic's synthesis of D-homo-5α-androstane-3-one **65**; (b) González and Molina-Navarro's attempts of cyclization towards spongistatins from the pyridine **66**.



Scheme 18 (a) Some sesquiterpenes and meroterpenoids synthesized by the titanocene-catalyzed epoxypolyene radical cyclization; (b) the mechanism of the transannular cyclization of dihydroreynosin **73**.



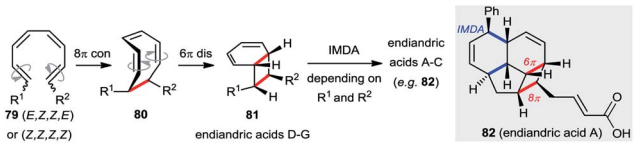
Scheme 19 McMillan polyene cyclization *via* organo-SOMO catalysis.

product $Cp_2Ti(Cl)H$, and showed that the cyclization takes place in a nonconcerted fashion.[108] The ring size, from five- to seven-membered, could be controlled by varying the substitution pattern of the polyprenoid substrate.[108b,109] Several naturally occurring 3-hydroxydrimane sesquiterpenes (**66**, **67**, Scheme 18a),[110] meroterpenoids (**68**,**69**),[111,112] sclareol oxides,[113] the triterpenes achilleol B[114] and (+)-*seco*-C-oleanane,[115] the lanostane-type DNA-polymerase inhibitor fomitellic acid,[116] onocerane triterpenes[117] and the anti-inflammatory (+)-myrrhanol A[118] were synthesized by Ti^{III}-mediated cyclizations. The transannular cyclization onto epoxides of costunolide and germacranolide (**70**), ten-membered carbocyclic sesquiterpenes, was used by Barrero and Oltra for the total synthesis of eudesmanolides like dihydroreynosin **73** (Scheme 18b).[119]

Finally, McMillan and Rendler recently reported impressive enantioselective polyene cyclizations *via* an organocatalytic SOMO (Singly Occupied Molecular Orbital) activation strategy performed on polyunsaturated aldehydes (Scheme 19).[120] The cyclization proceeds after activation of the aldehyde **74** as an iminium by the imidazolidinone catalyst **75**, followed by the single-electron oxidation by $Cu(OTf)_2$ giving an α-imino radical intermediate (**76**) leading to product **77**. Up to six new cycles (**78**) could be formed during the reaction with excellent yields and enantiomeric excess.

6 The role of palladium catalysts in biomimetic electrocyclizations

Electrocyclizations are pericyclic reactions involving 4π, 6π or 8π systems leading to four- six- and eight-membered cycles,



Scheme 20 Biosynthetic origin of endiandric acids (*e.g.* **82**).

during which one π bond is converted into one σ bond.[121] The reverse reaction (with ring-opening) is possible and involves the conversion of σ bonds to π bonds. These reactions can be spontaneous, *i.e.* without the involvement of a catalytic system and can occur in living cells.[122] They obey the well-defined stereochemical Woodward–Hoffmann rules,[123] depending on the ground and excited states related to thermal and photochemical activation, respectively. In fact, since these reactions involve high-order conjugated polyene substrates, the use of transition metals is of primary importance, either for the construction of substrates (*e.g.* palladium-catalyzed olefin couplings) or for substrate activation, for example by olefin isomerization.

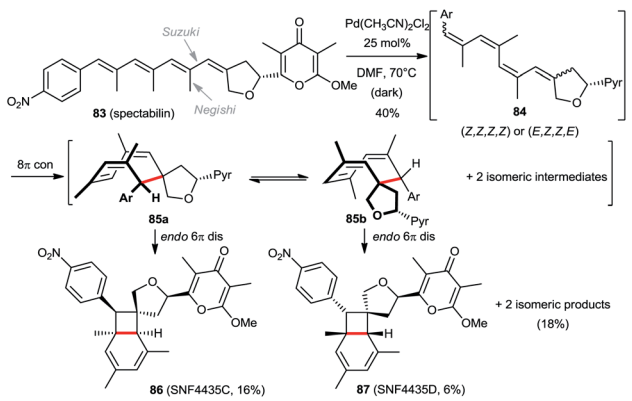
Three decades ago, Black hypothesized that the biosynthesis of endiandric acids (*e.g.* **82**, Scheme 20) follows two consecutive electrocyclizations.[124] Nicolaou first used a pericyclic cascade for the total synthesis of these natural products, showcasing the power of this approach, and thus supported Black's biosynthetic mechanism.[125] The tetraene substrate of the electrocyclization was obtained by the catalytic hydrogenation of a 1,7-diene-3,5-diyne in the presence of the Lindlar Pd-catalyst and quinoline at 25 °C. The tetraene product (**79**) was not isolated, spontaneously leading to the bicyclo[4.2.0] octadiene natural products (**81**), through an octatriene intermediate (**80**). Very recently, an all-*Z* tetraene reactive precursor was obtained by Sherburn by the reduction of a tetrayne in the presence of Rieke zinc for the synthesis of the monomeric units of kingianins.[126]

Trauner[127] and Baldwin[128] independently undertook synthetic studies on the compounds SNF4435 C and D (**86**, **87**). The compounds are structurally related to spectabilin 77 (Scheme 21), a natural product with (all-*E*)-tetraene which was thus preserved from electrocyclization. While Trauner used a Stille coupling to reach a spontaneously cyclizing (*E*,*Z*,*Z*,*E*)-substrate (speculating whether palladium catalyzes the electrocyclization),[129] Baldwin synthesized the all-*E* natural product **83** through Suzuki and Negishi couplings and finally employed $Pd(CH_3CN)_2Cl_2$ to isomerize it into the reactive (*E*,*Z*,*Z*,*E*)-precursor **84** which underwent 8π electrocyclization to **85a** and **85b**, accompanied by two isomeric products.[130] These two intermediates led respectively to the natural products **86** and **87** through spontaneous 6π cyclization. Prior to these biomimetic studies, Parker had accomplished an enantioselective total synthesis of (−)-SNF4435 C and (+)-SNF4435 D (**86**,**87**), using a Stille coupling to build a reactive (*E*,*Z*,*Z*,*Z*)-tetraene precursor which underwent *endo* selective closure.[131] Furthermore, when performing the synthesis of a (*E*,*E*,*Z*,*Z*)-intermediate isomeric to spectabilin, again through Stille coupling in the presence of $Pd(PPh_3)_4$ and copper(I) thiophene-2-carboxylate, Parker observed a biomimetic [1,7]-hydrogen shift from the THF ring, leading to (−)-arabilin.[132]

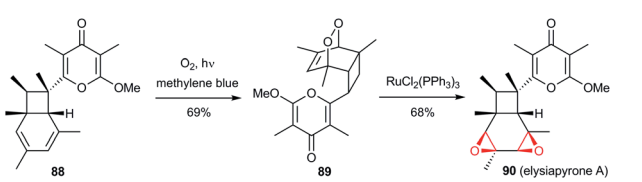
In the same compound series, the biomimetic synthesis of elysiapyrones was reported by Trauner and co-workers who used transition metal catalysis in the key steps.[133] The authors used their Stille coupling strategy to assemble a reactive (*E*,*Z*,*Z*,*E*)-tetraene which spontaneously underwent electrocyclization into two *endo* and *exo* bicyclo[4.2.0]octadienes. Among them, the major *endo* product **88** was converted into the endoperoxide **89** by photochemical oxygenation (Scheme 22). Finally, applying Noyori's conditions for the biomimetic isomerization of the endoperoxides, in the presence of $RuCl_2(PPh_3)_3$,[134] cleanly afforded the diepoxide natural product **90** in 68% yield.

Before closing this part, total syntheses in other natural product series have to be mentioned, using the oxa 6-π electrocyclization of a substrate constructed by the use of transition metal reagents. Epoxyquinols A and B (**94**,**95**) and epoxytwinol A (**96**) were thus independently synthesized by Hayashi[135] and Porco (Scheme 23).[136]

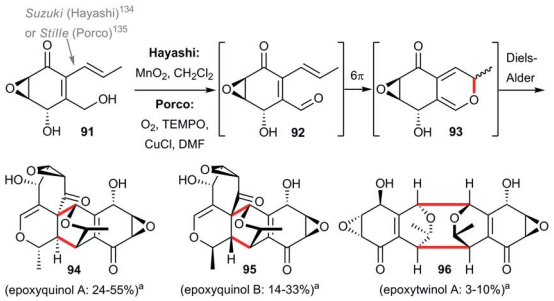
Both authors used different palladium couplings to get intermediate **91**[137] and different conditions to oxidize the alcohol, MnO_2 for Hayashi or O_2 in the presence of TEMPO and CuCl for Porco. The oxidation provided the aldehyde **92** which underwent 6π electrocyclization to get the reactive diene **93**, direct precursor of the natural products through Diels–Alder reactions. Lastly, the synthesis of the alkaloids exiguamine by Trauner also employed an oxa electrocyclization arising from the AgO-mediated oxidation and tautomerization of a catechol precursor.[138]



Scheme 21 Baldwin's biomimetic conversion of spectabilin **83** into SNF4435 C (**86**) and D (**87**) through Pd-catalysis.



Scheme 22 Trauner's synthesis of elysiapyrone A (**90**).



Scheme 23 Synthesis of epoxyquinols. [a] Yields depending on the conditions (solvent in particular). Hayashi also isolated 1% of epoxyquinol C.[135b]

7 Metal oxidants in biaryl couplings

Biaryl couplings, especially those involving phenolic radicals, are extremely important reactions in natural product chemistry.[139] They have been used not only in the biomimetic synthesis of polyphenolics (flavonoids, gallates, lignans) but also in that of alkaloids as diverse as morphinanes and vancomycines. The most employed transition metal oxidants are based on oxidized states of iron, copper, manganese and vanadium.

The early work of Barton and Kirby on the biogenetic origin of Amaryllidaceae alkaloids led them to report the biomimetic synthesis of galanthamine **99**, thus confirming its structure (Fig. 4).[140] The key step was an intramolecular phenol coupling of *N*,*O*-dimethylnorbelladine **97** into Pummerer's ketone narwedine **98**, in the presence of MnO_2 (0.5% yield) or K_3FeCN_6 (1.4% yield). Narwedine was then reduced into galanthamine and its epimer by $LiAlH_4$. Davidson and Scott had previously

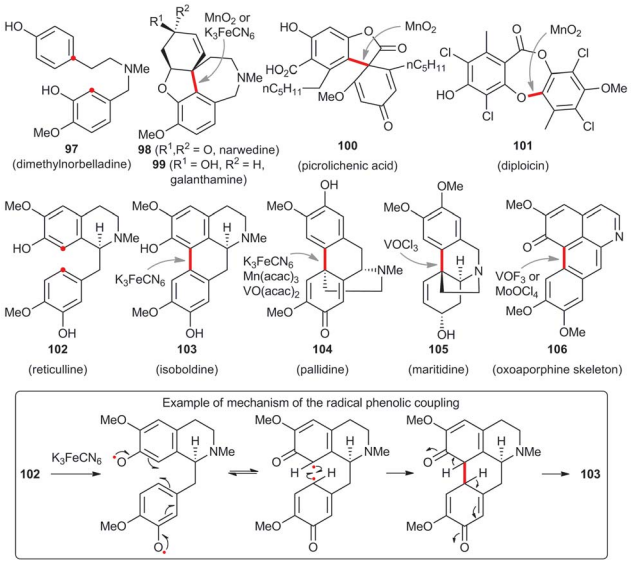


Fig. 4 Natural products synthesized by phenol couplings: the red bold bond is formed through phenolic coupling during the synthesis (oxidative reagent shown); an example of radical phenolic coupling is given between reticuline (**102**) and isoboldine (**103**).

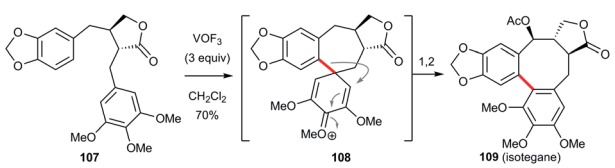
reported the biomimetic synthesis of picrolichenic acid **100** by the radical coupling using MnO_2,[141] while Brown *et al.* used the same reagent to make the diphenyl ether linkage of diploicin **101**, another lichenic depside.[142] Kametani reported the oxidative cyclization of the benzylisoquinoline reticuline (**102**) into the aporphine isoboldine (**103**) and the morphinane pallidine (= isosalutaridine, **104**) in the presence of K_3FeCN_6, respectively, in 0.4 and 0.9% yields, resulting from divergent regioselectivities.[143] Silver carbonate on Celite[144] and vanadium oxychloride[145] proved to be alternative oxidizing reagents for this transformation.[143b] Manganese and vanadyl acetylacetonate were used by Szántay for the synthesis of pallidine (**104**) by the oxidative cyclization of *N*-ethoxycarbonylnorreticuline performed in 32% yield.[146]

Schwartz and Holton utilized their reagent $VOCl_3$[145] in diethyl ether to oxidize *N*-trifluoroacetyl-*O*-methylnorbelladine into a tricyclic intermediate toward maritidine (**105**) in 24% yield.[147] Several oxidants were compared by Kupchan and Liepa to oxidize a benzylisoquinoline into the oxoaporphine skeleton **106**.[148] The best reagents were VOF_3 (59% yield) and $MoOCl_4$ (62%). A phenylethylisoquinoline was similarly oxidized into an homoaporphine toward homoerythrina alkaloids.[149]

Vanadium oxyfluoride was also used by Damon and Schlessinger during their biogenetically inspired synthesis of the lignan-lactones isostegane (**109**) from the biaryl lignan compound **107** (Scheme 24), through a spirodiene **108**.[150] The analogous compounds steganacin and deoxyschizandrin were respectively synthesized by Kende[151] and by Stevenson[152] using a similar approach. Neoisostegane and steganolide A were biomimetically synthesized by Landais and Robin, using $Ru(CF_3CO_2)_4$ as the oxidant, generated by the acylation of RuO_2 in dichloromethane. Excellent yields (>96%) were reported for this reaction.[153]

The VOF_3-mediated oxidative coupling reaction (performed in trifluoroacetic acid) was used by Evans in his total synthesis of vancomycin antibiotics through intermediate **110** (Fig. 5).[154] The particular conditions used (VOF_3, $BF_3{\cdot}OEt_2$, $AgBF_4$) were needed to avoid side reactions while reductive quenching (Zn or $NaBH(OAc)_3$) was related to the radical cation mechanism. Yang and co-workers also used VOF_3 in their total synthesis of the alkaloid decinine **111**.[155] The dimerization of *N*-methyltryptamine into *rac*-chimonanthine **112** was realized by Ishikawa thanks to $Mn(OAc)_3$, VOF_3 and V_2O_5.[156] The reaction was also used for the asymmetric synthesis of more complex alkaloids from L-tryptophan methyl ester.

Ellagitanins are excellent targets for biomimetic radical couplings,[157] as exemplified by Feldman's total synthesis of tellimagrandin I.[158] VOF_3 was presented as an attractive



Scheme 24 Schlessinger's synthesis of isostegane **109**.

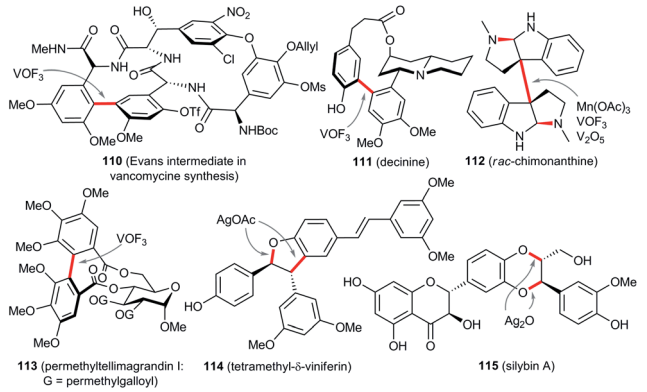
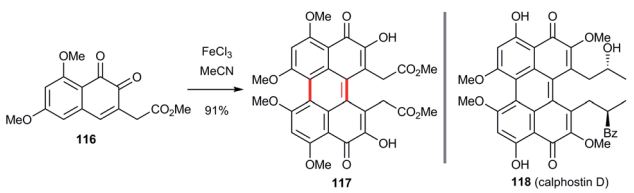


Fig. 5 Biomimetic oxidative C–C, C–O and C–N couplings; mechanisms are related to the one shown in Fig. 4.

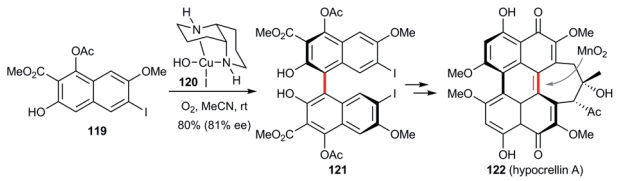
alternative to $Pb(OAc)_4$, allowing the synthesis of permethylated tellimagrandin I (**113**, Fig. 5). Silver salts and other manganese, copper or iron oxidants were tested to promote the radical oligomerization of resveratrol.[159,160] A methylated analogue of δ-viniferin (**114**) was obtained in the presence of AgOAc in 36% yield by Velu.[161] Depending on the oxidant, the authors observed variable selectivity during the coupling, leading to several oligostilbene series. The outcome of the reaction was explained by hard and soft acid and base properties of the reagents. Radical couplings in milk-thistle flavonolignans may proceed through single electron oxidation of coniferyl alcohol and its reaction with the taxifolin catechol. That was demonstrated by Croatt and co-workers[162] who used Ag_2O as an oxidant to react coniferyl alcohol and taxifolin into four silybins in a combined 52% yield (*e.g.* **115**).

Lastly, the binaphthyl couplings and perylenequinone syntheses are interesting as several chiral catalysts based on Cu, V, Fe and also Ru were developed to make these syntheses asymmetric.[139c] A high-yielding approach to the natural perylenequinone **117** was described by Diwu and Lown who used catalytic $FeCl_3$ (10 mol% in acetonitrile) to oxidize the *o*-naphthoquinone **116**, giving the natural product in 91% yield (Scheme 25).[163] This biomimetic reaction implies two binaphthyl couplings involving both Fe^{3+} and Fe^{2+} species present in the solution. Using the same method, Merlic performed the total synthesis of calphostins (*e.g.* **118**).[164]

Kozlowski developed a chiral 1,5-diaza-*cis*-decalin copper complex for aerobic binaphthyl couplings toward perylenequinone and bisanthraquinone syntheses, providing excellent yields and enantiomeric excess.[165] This allowed the



Scheme 25 Lown's biomimetic synthesis of perylenequinone **117**.



Scheme 26 Kozlowski biomimetic synthesis of hypocrellin A (**122**).

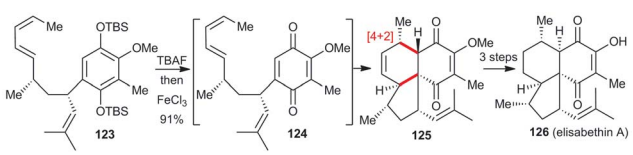
asymmetric synthesis of nigerone,[165c] hypocrellin A **122** (Scheme 26)[165d,e] or the bisanthraquinone (*S*)-bisoranjidiol.[165f] The mechanism of this reaction involving the asymmetric copper complex **120** was investigated, demonstrating prior oxygenation of the naphthol substrate which then serves as a cofactor combined to the Cu-catalyst to achieve highly selective oxidase reactivity.[165g]

8 Miscellaneous metal-promoted biomimetic reactions, rearrangements and cyclizations

Transition metals have played a crucial role in the catalysis of rearrangements of organic compounds. In some cases, the chemical transformation was biomimetic, as for example in the commercially important rearrangement of monoterpenes like α-pinene into camphene and limonene (Wagner–Meerwein shifts) performed by heterogenous catalysis (*e.g.* TiO_2).[166,167]

Cycloadditions can be catalyzed by Lewis acids. However, metals can also be used to form a reactive intermediate prior to cyclization. Mulzer employed the $FeCl_3$-oxidation of a dihydroquinone (**123**) into a quinone dienophile (**124**), which spontaneously underwent intramolecular Diels–Alder reaction to the tricyclic core **125** of elisabethin A (**126**), with a 91% yield over this sequence (Scheme 27).[168]

Two recent syntheses of brosimones A (**127**) and B by Porco (Fig. 6) featured a biomimetic dehydrogenation of the prenyl part of prenylchalcones by a mixture of Pt/C and SiO_2-supported silver nanoparticules, followed by an intermolecular cycloaddition between the resulting diene and the chalcone dienophile.[169] The biomimetic synthesis of pinnatal **128** was described by Trauner through $Sc(OTf)_3$-mediated intramolecular Diels–Alder reaction, after a 6π-electrocyclization providing the diene.[170] (+)-Intricarene **129** was synthesized by Pattenden through the $VO(acac)_2$-mediated oxidation of the furan ring of bipinnatin J. This released a 6-acetoxypyranone whose basic treatment led to an oxidopyrylium which underwent transannular [5 + 2] cycloaddition.[171]



Scheme 27 Mulzer's strategy toward elisabethin A (**126**).

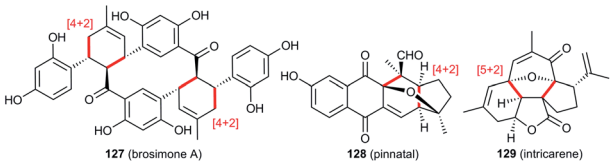


Fig. 6 Structures of brosimone A, pinnatal and intricarene arising from cycloadditions.

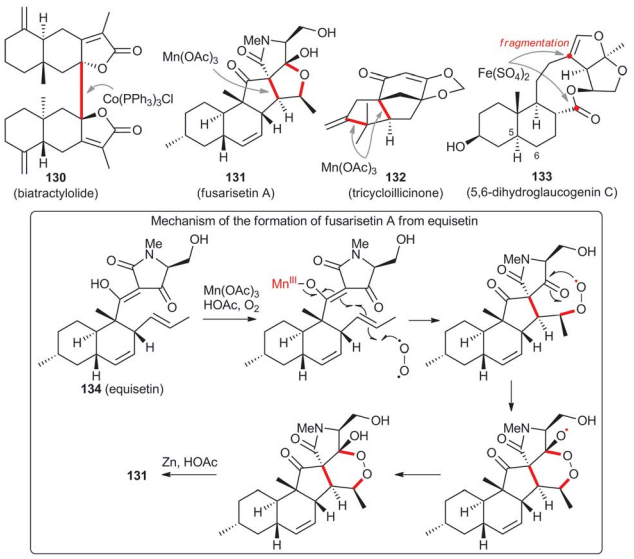


Fig. 7 Structures of biatractylolide, fusarisetin A, tricycloillicinone and 5,6-dihydroglaucogenin C; in the frame: mechanism of the oxidative cyclization of equisetin (**134**) into fusarisetin A (**131**).

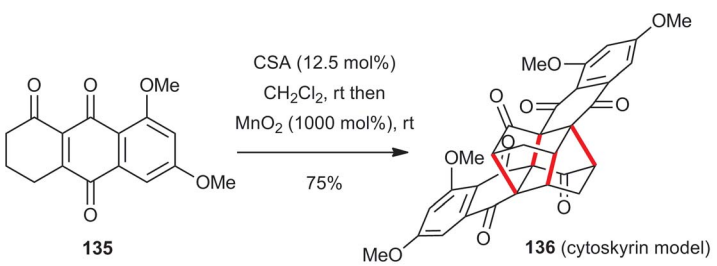
The biomimetic synthesis of biatractylolide (**130**, Fig. 7) and biepiasterolide was realized by Baldwin and co-workers, through the radical dimerization of the sesquiterpenoid chloroatractylolide in the presence of $Co(PPh_3)_3Cl$ (27% yield).[172] The same reagent was used by Nicolaou to get a bisanthraquinone precursor, intermediate toward a biomimetic model system for cytoskyrin and rugulosin syntheses (see below).[173] Recently, equisetin was postulated by Gao as a biosynthetic precursor of fusarisetin A (**131**) through radical cyclization.[174] The conversion was realized under an atmosphere of oxygen in the presence of $Mn(OAc)_3$ and $Cu(OAc)_2$,[103c] and after Zn-quenching, in 41% yield showing the viability of the hypothesis.

Illicinones are neurotrophic polycyclic compounds derived by the prenylation of safrole derivatives followed by radical cyclization. Tricycloillicinone **132** (Fig. 7) was synthesized by Danishefsky by the $Mn(OAc)_3$-mediated activation of a 1,3-diketo precursor.[175] Analogous radical cyclizations were performed by Simpkins for the synthesis of ialibinones A and B, two phloroglucinol-derived compounds.[176] The cyclization was realized in 80% yield. The synthesis of 5,6-dihydroglaucogenin C (**133**) from (16*S*,20*S*)-5α-pregnane-3β,16,20-triol was realized by Tian through the $Fe(SO_4)_2$ mediated fragmentation, in 69% yield, of a hydroperoxide installed by Schenck ene reaction.[177]

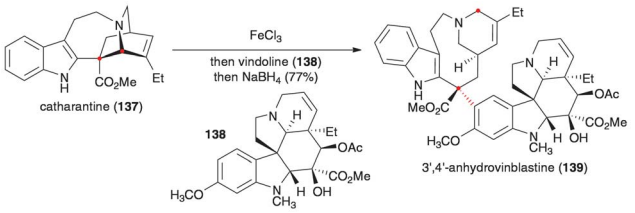
The cytoskyrin cascade was described by Nicolaou who provided a full insight in the reactivity and mechanism associated to this biosynthetic sequence.[173] Impressive transformations were reported, featuring a series of Michael additions and oxidations and making use of MnO_2 as the oxidant. The conversion of anthraquinone **135** into the cytoskyrin model **136** was performed in 75% yield by an acidic treatment followed by MnO_2-oxidation (Scheme 28).

9 Conclusion

The complexity and the diversity of natural products depend on the numerous biosynthetic pathways that life has developed to produce a chemical language. Our introduction showed the importance of transition metals in these biochemical processes which have been extensively studied and mimicked in the last decade in order to develop sustainable syntheses which strive to be as efficient as the biological ones. From the synthetic chemist's point of view, inspiration comes from the retron analysis of biosyntheses, providing insight on the reactivity of hypothetical biomimetic precursors. Metals can thus be envisaged to perform the key transformations as shown in the many examples above. In most cases, metal-promoted biomimetic steps may also be catalyzed by metallic species during biosynthetic processes, for example in oxidation steps. In that way, there should be no contradiction in claiming biomimicry while using transition metals in synthesis. To illustrate this purpose with a final example, we have to refer to the biomimetic synthesis and biosynthesis of 3′,4′-anhydrovinblastine (**139**). In 1988, Kutney and co-workers described the oxidative coupling of vindoline (**138**)to catharanthine (**137**) in the presence of $FeCl_3$, furnishing the vinblastine precursor **139** in 77% (Scheme 29) and questioning the biomimetic relevance of this work.[178] Ten years later, Sottomayor characterized the 3′,4′-



Scheme 28 Nicolaou's synthetic model for cytoskyrin (**136**).



Scheme 29 Kutney's biomimetic synthesis of anhydrovinblastine (**138**).

anhydrovinblastine synthase as a class III peroxidase possessing a high spin ferric heme,[179] thus demonstrating the biomimetic nature of Kutney's early synthetic work.

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