Transition metal-promoted biomimetic steps in total syntheses

Xu-Wen Li and Bastien Nay*

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.

1 Introduction

The d-block transition metals occupy a special place in biological processes, being involved in catalysis, structure, transport, signaling and sometimes sensing. 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, 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, eight belong to transition metals, mainly from the fourth row and...
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.6

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 Mn₄CaO₅ photosynthetic clusters8), sulphur (sometimes as sulphides, for example in Fe/Mo/S clusters,7,8 or as hemes9) and/or nitrogen ligands (for example, histidine ligands of zinc in phosphotriesterase10), 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 nature),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

Xu-Wen Li received his bachelor degree in pharmaceutical engineering at Tianjin University (China) in 2007. He then joined the group of Prof. Jin-Feng Hu to study natural product chemistry at East China Normal University, and received his master degree in 2010. Xu-Wen undertook his doctoral research in the group of Dr. Bastien Nay at the National Museum of Natural History, Paris, for which he was awarded his PhD from the University Pierre and Marie Curie in December 2013, after working on the bio-inspired synthesis of hirsutellones. His research interests focus on the chemical synthesis of biologically active natural products and synthetic methodologies.

Bastien Nay is a CNRS researcher at the National Museum of Natural History in Paris, where he is conducting research in natural product chemistry, with a particular interest for synthetic strategies and the biosynthesis and ecology of fungal natural products. He first received a diploma of pharmacy from Bordeaux University, and then a PhD of Organic Chemistry from Toulouse University (2000), under the guidance of Prof. Joseph Vercauteren. He then worked as a research associate at Nottingham University in the group of Prof. J. Stephen Clark, and at the ICSN, Gif-sur-Yvette, France, in the group of Dr. Christiane Poupat, before joining the CNRS in 2004.
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.

Scheme 1 \(\alpha\)-Hydroxylation dependence of dimanganese-thioesterase products in a fungal PKS \((X = H\) or \(O, H)\). 16 ACP: acyl carrier protein.

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 methylyrthritol 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 methylyrthritol 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).

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\(\beta\)-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 peroxo 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-deacetyl-baccatin 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 trichothecone mycotoxin. 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 polypetides 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 aminopyrrolinitrin 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 3 Oxidation steps involving P450s in taxol biosynthesis.
Dioxygenases are important enzymes in the oxidative metabolism of natural products, many of them incorporating a non-heme iron co-factor and occasionally an α-oxoacid (e.g. 2-oxoglutarate) as a co-substrate, which is oxidatively cleaved. The biosynthesis of vindoline involves such an oxidation at the late stage by desacetoxyvindoline 4-hydroxylase, while complex ring rearrangements have been described in the terpenoid series.

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). 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. The electrophilic X⁺ reactive 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 or polyketides like 13 (Scheme 4).

### 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 biosynthetic hypotheses. The older one, the Cane–Celmer–Westley hypothesis, was proposed in 1983 to explain the formation of the tetrahydrofuran-rich monensin A (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). 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 (Scheme 5b).

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

#### 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 (KMnO₄) in the 1960s, the range of useful transition metal oxides (MO₄) 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 MO₄-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.
The stereospecificity of the oxidative cycloaddition was found to be complete during the conversion of 1,5-hexadiene into bis(hydroxymethyl)tetrahydrofuran by KMnO₄, with all new bonds formed by suprafacial processes leading to cis-THF rings. 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. Asymmetric induction was provided by Evans' norephedrine-derived chiral oxazolidinone during the oxidative cyclization of 1,5-dienes for the synthesis of THF-based ionophores. 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). The same conditions were used by McDonald and Towne for the synthesis of compounds 16, Scheme 6a) into bis(THF) (17,18). They were the first to claim the strategy as biomimetic, in reference to Townsend and Basak, although the conditions were limited to secondary hydroxydienes, especially in the presence of a co-oxidant and a pyridine. High stereoinduction was observed in favour of the cis-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 oxorchromium reagents, which were able to perform the oxidative cyclization of alkenes and tertiary hydroxyalkenes into cis-cycloethers, Re(vi) oxides (e.g. Re₂O₇) 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, especially in the presence of a co-oxidant and a pyridine. The method was used by Keinan, Sinha and co-workers and by McDonald and Towne 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 acylperrenephens as less acidic reagents, for example [Cl₂CHCO₂]ReO₂ in the presence of 2,6-lutidine. 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 alkoxorhenium intermediate, decreasing the stereoselectivity in the formation of tris(THF) compounds made in one steps from hydroxytrienes. Rules were then proposed by Sinha et al. to predict the stereoselectivity in tandem oxidative polycyclizations with rhenium(vi) 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.

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). These authors never claimed their syntheses were biomimetic, on the contrary defending the Cane–Celm–Westley hypothesis. 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 and the total synthesis of asimicin 19,17–19 17,18-bisepi-trilocellins C and D (23,24),19 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 alken oxidative cyclizations, especially the oxidation of dienes by OsO₄,70–72 or RuO₄.73–78 The same stereoselectivity as with KMnO₄ 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 RuO₄ or OsO₄, leading in one step to complex penta-THF systems with all-threo stereochemistry.

Rules for the synthesis of acetogenins synthesized by Keinan and Sinha. The red THF rings were made in the presence of an oxorhenium(vi) oxidant while the others were constructed by conventional methods. The adjacent THF rings in 22–24 were obtained in one oxidizing step.

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

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

---

**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).

> 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).

---

**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),

Gagné imagined a gold(i)-phosphite-catalyzed cascade cyclization of allenyl epoxides (26, Scheme 7). 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 Martin during the Nicholas reaction of Co₂(CO)₆-propargylic alcohols bearing remote epoxy esters, leading to cyclic ethers (Scheme 8). This strategy was used in an elegant total synthesis of teurilene into the tris(THF) intermediate 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. The formation of the tetrahydrofuran 34 was realized in 87% yield in the presence of Pd₂dba, and the chiral diphosphine (S)-C₅₂₆TunePhos.

Sc(O Tf)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 dienediene moiety followed by a transannular epoxide opening (Scheme 10).

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(O Tf)₂-mediated prenylation–cyclization of tryptamine ethylcarbamate (39) in the presence of prenyl bromide, Bu₄NI and the Hüning’s base (Scheme 11). 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 S₅₋₄ mechanism.

5 Biomimetic cyclizations of polypropenoids

Bioinspired polypropenoid cyclizations inspired natural product chemists since the structure of polycyclic terpenoids were first elucidated. Stork and Eschenmoser were the first to formulate geometrical and stereoelectronic rules for these polycyclizations in the 1950s and the first biomimetic syntheses of polypropenoids through cationic processes were reported by Johnson in 1968 and van Tamelen in 1975. Furthermore, an oxidative radical pathway was imagined by Breslow in 1962 for these transformations and was supported by synthetic studies from the same author and from Julia. Since then, extensive work has been carried out on these biomimetic cascade cyclizations, which can be initiated by electrophilic Brønsted or Lewis (mainly SnCl₄ and BF₃·OEt₂) 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 Hg²⁺) either with a nucleophilic heteroatom of the polyene substrate, like in squalene oxide 42 (Scheme 12), or directly with an olefin of the
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(CF₃CO₂)₂, as
initiators. The cyclized organomercury intermediates (45, 
Scheme 13a) could be further functionalized by reduction
(NaBH₄), bromination (Br₂, leading to 46) or internal nucleo-
philic termination. This methodology was used by Hoye for
the total synthesis of aplysistatin (47, Scheme 13b), a bromi-
nated marine natural product with antileukemic properties.

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 isopelargonin (51, Scheme 13c). A mercury–
selenium exchange (PhSeSePh, hν) was applied by McMurry in
the total synthesis of the complement inhibitor K-76, a fungal
meroterpenoid. Furthermore in the polyketide series, the
electrophilic mercury salt strategy was also applied by Sato
et al. to the biomimetic synthesis of prostaglandin E₁. It allowed the
construction of the five-membered ring, releasing an alcohol
after oxidation of the BrHgR intermediate (O₂, NaBH₄). More
recently Gagné reported the use of Pt(n) catalysts for the
oxidative cyclization of 1,5-dienes and trienes leading to bi- and
dicercaclcyclen (57) (Scheme 15). It is obvious in this case that the
polyene substrate is analogous to the enzyme substrate oxido-
squalene. 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 and an alternative
biomimetic strategy was designed.

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
terpenoid 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 ZnBr₂ to
promote the biogenetic-like one-step cyclization of the cyclo-
pentenol 52 into the corresponding tetracyclic compound 53 in
quantitative yield (Scheme 14a). The effect of arene functionali-
zation on the ortho–para selectivity of the last cyclization was also
studied. Furanans were used by Tanis and Herrington as terminators
of cationic cyclizations, especially for the synthesis of 3β-hydroxy
pallescensin-A (55) from epoxydendrolasin 54 (Scheme 14b). ZnI₂
and Ti(OiPr)₃Cl were used to promote the cyclization in 65% and
62% yields, respectively, giving better results than BF₃·OEt₂ (47%).

The catalyst Ti(OiPr)₃Cl (3–7 equiv.) was used by Johnson for
epoxide opening-initiated polyene cyclizations, a work culmi-
nating with the first example of biomimetic pentacarbocycliza-
tion of 57 (Scheme 15). It is obvious in this case that the
polyene substrate is analogous to the enzyme substrate oxido-
squalene. 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 13 (a) Hoye’s Hg²⁺-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.

Scheme 14 Zn²⁺- and Ti⁴⁺-catalyzed cationic cyclizations of an allylic
alcohol (a) and an epoxide (b).

Scheme 15 Johnson’s pentacyclization towards sophoradiol (58).

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 polycyclic cyclizations, such as FeCl₃ and Sc(OTf)₃. In particular, Overman described the enantioselective synthesis of the kinesin motor protein inhibitor adociasulfate-1 (Scheme 16a), using an epoxide opening-initiated polycylene tetrayculation terminated by an arenne (59), with a 15% yield leading to 60 (meaning 62% yield per ring) in the presence of Sc(OTf)₃. In this case, FeCl₃ 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. 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] and [Ti] on functional groups, such as β-ketoesters, epoxides or alkyl halides. 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)₂ (2 : 1 ratio, in degassed AcOH), forming all four cycles of ν-homo-5α-androstan-3-one 65 in 31% yield (Scheme 17). Steroid skeletons in the 5α-pregnane series were obtained in similar conditions. González and Molina-Navarro attempted a synthesis of spongiones by a Mn(OAc)₃-mediated radical cascade terminating onto a pyridine ring. 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 spongione.

Starting from acyclic epoxy-polyenes, the homolytic opening of the epoxide in the presence of stoichiometric quantities of Cp₂TiCl (generated from a mixture of Cp₂TiCl₂ and Mn) led to 6-endo-selective radical cyclizations terminated by an oxidative step. 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 Cp₂TiCl₂ from the end-product Cp₂Ti(Cl)H, and showed that the cyclization takes place in a nonconcerted fashion. The ring size, from five- to seven-membered, could be controlled by varying the substitution pattern of the polypropenyl substrate. Several naturally occurring 3-hydroxydrimane sesquiterpenes (66, 67, Scheme 18a), meroterpenoids (68, 69), 110,112 scolare oxides, 111 the tri-terpenes achilleol B 114 and (+)-seco-C-oleanane, 112 the lanostane-type DNA-polymerase inhibitor formetillic acid, 116 oncoreane tri-terpenes 117 and the anti-inflammatory (+)-myrhanol A 118 were synthesized by Ti(IV)-mediated cyclizations. The transannular cyclization onto epoxides of costunolide and germacrangenolide (70), ten-membered carboxycyclic sesquiterpenes, was used by Barrero and Oltra for the total synthesis of eudesmanolides like dihydroreynosin 73 (Scheme 18b).

Finally, McMillan and Rendler recently reported impressive enantioselective polycyclic cyclizations via an organocatalytic SOMO (Singly Occupied Molecular Orbital) activation strategy performed on polysaturated aldehydes (Scheme 19). 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,
during which one π bond is converted into one σ bond. 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. They obey the well-defined stereoechemical Woodward–Hoffmann rules, 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. 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. 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]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 RuCl₃(PPh₃)₃, 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 ox a 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 Hayashi135 and Porco (Scheme 23).136

Both authors used different palladium couplings to get intermediate 91137 and different conditions to oxidize the alcohol, MnO₂ for Hayashi or O₂ 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 ox a electrocyclization arising from the AgO-mediated oxidation and tautomeration of a catechol precursor.
reported the biomimetic synthesis of picrolonic acid \textbf{100} by the radical coupling using MnO$_2$,\textsuperscript{144} while Brown \textit{et al.} used the same reagent to make the diphenyl ether linkage of diplocicin \textbf{101}, another lichenic depside.\textsuperscript{145} Kametani reported the oxidative cyclization of the benzylisoquinoline reticuline (\textbf{102}) into the aporphine isoboldine (\textbf{103}) and the morphinan pallidine (= isosalutaridine, \textbf{104}) in the presence of K$_2$FeCN$_6$, respectively, in 0.4 and 0.9% yields, resulting from divergent regioselectivities.\textsuperscript{146} Silver carbonate on Celite\textsuperscript{147} and vanadium oxychloride\textsuperscript{148} proved to be alternative oxidizing reagents for this transformation.\textsuperscript{149} Manganese and vanadyl acetylacetonate were used by Szántay for the synthesis of pallidine (\textbf{104}) by the oxidative cyclization of 1-ethoxycarbonylnorreticuline performed in 32% yield.\textsuperscript{145}

Schwartz and Holton utilized their reagent VOCl$_3$\textsuperscript{145} in diethyl ether to oxidize 1-trifluoroacetyl-6-methylnorbelladine into a tricyclic intermediate toward maritidine (\textbf{105}) in 24% yield.\textsuperscript{146} Several oxidants were compared by Kupchan and Liepa to oxidize a benzylisoquinoline into the oxoaporphine skeleton \textbf{106}.\textsuperscript{147} The best reagents were VOCl$_3$ (59% yield) and MoOCl$_4$ (62%). A phenylethylisoquinoline was similarly oxidized into an homoaporphine toward homoeothyrlina alkaloids.\textsuperscript{149}

Vanadium oxyfluoride was also used by Damon and Schlessinger during their biogenetically inspired synthesis of the ligan-lactones isostegane (\textbf{109}) from the biaryl lignan compound \textbf{107} (Scheme 24), through a spirodiene.\textsuperscript{148} The analogous compounds stegecan and deoxyschizandrin were respectively synthesized by Kende\textsuperscript{150} and by Stevenson\textsuperscript{151} using a similar approach. Neoisostegane and steganolide A were biomimetically synthesized by Landais and Robin, using Ru(CF$_3$CO$_2$)$_3$ as the oxidant, generated by the alylation of RuO$_3$ in dichloromethane. Excellent yields (>96%) were reported for this reaction.\textsuperscript{152}

The VOF$_3$-mediated oxidative coupling reaction (performed in trifluoroacetic acid) was used by Evans in his total synthesis of vancomycin antibiotics through intermediate \textbf{110} (Fig. 5).\textsuperscript{153} The particular conditions used (VOF$_3$, BF$_3$-OEt$_2$, AgBF$_4$) were needed to avoid side reactions while reductive quenching (Zn or NaBH(OAc)$_2$) was related to the radical cation mechanism. Yang and co-workers also used VOF$_3$ in their total synthesis of the alkaloid decineline \textbf{111}.\textsuperscript{154} The dimerization of N-methyltryptamine into rac-chimonanthine \textbf{112} was realized by Ishikawa thanks to Mn(OAc)$_3$, VOF$_3$ and V$_2$O$_5$.\textsuperscript{155} The reaction was also used for the asymmetric synthesis of more complex alkaloids from L-tryptophan methyl ester.

Ellagitannins are excellent targets for biomimetic radical couplings,\textsuperscript{156} as exemplified by Feldman’s total synthesis of tellimagrandin I.\textsuperscript{157} VOF$_3$ was presented as an attractive

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{Scheme}
\caption{Scheme 23 Synthesis of epoxynorquinolines. a Yields depending on the conditions (solvent in particular). Hayashi also isolated 1% of epoxynorquinol C.\textsuperscript{\textsuperscript{158}}}
\end{scheme}

\section{Metal oxidants in biaryl couplings}

Biaryl couplings, especially those involving phenolic radicals, are extremely important reactions in natural product chemistry.\textsuperscript{159} They have been used not only in the biomimetic synthesis of polyphenolics (flavonoids, gallates, lignans) but also in that of alkaloids as diverse as morphinan 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 \textbf{99}, thus confirming its structure (Fig. 4).\textsuperscript{160} The key step was an intramolecular phenol coupling of N$_2$O-dimethylnorbelladine \textbf{97} into Pummerer’s ketone narwedine \textbf{98}, in the presence of MnO$_2$ (0.5% yield) or K$_2$FeCN$_6$ (1.4% yield). Narwedine was then reduced into galanthamine and its epimer by LiAlH$_4$. Davidson and Scott had previously

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Fig4}
\caption{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 (\textbf{102}) and isoboldine (\textbf{103}).}
\end{figure}

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{Scheme}
\caption{Scheme 24 Schlessinger’s synthesis of isostegane \textbf{109}.}
\end{scheme}

\begin{table}
\centering
\begin{tabular}{|c|c|}
\hline
\textbf{Table 1} & \textbf{Table 2} \\
\hline
\textbf{Column 1} & \textbf{Column 2} \\
\hline
\textbf{Row 1} & \textbf{Row 2} \\
\hline
\end{tabular}
\end{table}
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.¹⁶² 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-workers¹⁶³ who used Ag₂O 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.¹³⁹e A high-yielding approach to the natural perylenequinone 117 was described by Diwu and Lown who used catalytic FeCl₃ (10 mol% in acetonitrile) to oxidize the α-naphthoquinone 116, giving the natural product in 91% yield (Scheme 25).¹⁶⁴ This biomimetic reaction implies two binaphthyl couplings involving both Fe³⁺ and Fe²⁺ 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 bisanthaquinone syntheses, providing excellent yields and enantiomeric excess.¹⁶⁵ This allowed the asymmetric synthesis of nigerone,¹⁶⁶e hypocrellin A 122 (Scheme 26)¹⁶⁶e,d,e or the bisanthaquinone (S)-bisoranjidiol.¹⁶⁶f 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.¹⁶⁶g

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 monoterpene as α-pinene into camphene and limonene (Wagner–Meerwein shifts) performed by heterogenous catalysis (e.g. TiO₂).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 FeCl₃-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 SiO₂-supported silver nanoparticles, followed by an intermolecular cyclodaddition 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-acetosypryranone whose basic treatment led to an oxidopyrylium which underwent transannular [5 + 2] cycloaddition.¹⁷¹
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(PPh3)3Cl (27% yield). 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). Recently, equisetin was postulated by Gao as a biosynthetic precursor of fusarisetin A (131) through radical cyclization. The conversion was realized under an atmosphere of oxygen in the presence of Mn(OAc)3 and Cu(OAc)2, c and a 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. Analogous radical cyclizations were performed by Simpkins for the synthesis of ilalbinones A and B, two phloroglucinol-derived compounds. The cyclization was realized in 80% yield. The synthesis of 5,6-dihydroglaucogenin C (133) from (165,20S)-5x-pregnane-3β,16,20-triol was realized by Tian through the Fe(SO4)2-mediated fragmentation, in 69% yield, of a hydroperoxide installed by Schenck ene reaction.

The cytoskyrin cascade was described by Nicolaou who provided a full insight in the reactivity and mechanism associated to this biosynthetic sequence. Impressive transformations were reported, featuring a series of Michael additions and oxidations and making use of MnO2 as the oxidant. The conversion of anthraquinone 135 into the cytoskyrin model 136 was performed in 75% yield by an acidic treatment followed by MnO2-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 retro 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 FeCl3, furnishing the vinblastine precursor 139 in 77% (Scheme 29) and questioning the biomimetic relevance of this work. Ten years later, Sottomayor characterized the 3’,4’-
anhydrovinblastine synthase as a class III peroxidase possessing a high spin ferric heme, thus demonstrating the biomimetic nature of Kutney’s early synthetic work.

10 Acknowledgements

We acknowledge receipt of a scholarship for XWL by the China Scholarship Council. We thank the CNRS and the MNHN for daily financial support.

11 References and notes


2 The study of metals in chemical biology occupies an important place at the edge of inorganic chemistry and biology, as emphasized in the editorial of Nature Chem. Biol., 2008, 8, 143 (special issue on metals in chemical biology).


