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Natural products as inspiration for the development of new synthetic methods

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Abstract

Natural products have played an important role in shaping modern synthetic organic chemistry. In particular, their complex molecular skeletons have stimulated the development of many new synthetic methods. We highlight in this article some recent examples of synthetic design inspired by the biosynthesis of natural products.

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Natural products have played an important role in the evolution of synthetic organic chemistry. In particular, their complex molecular skeletons have stimulated the development of many new synthetic methods. We highlight in this article some recent examples of new synthetic design inspired by the biosynthesis of natural products.

Keywords

organic; synthesis

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INTRODUCTION

Natural products and their structural analogs constitute an essential part of current therapeutic agents.¹ The ability to chemically synthesize these small molecules is important to sustaining their supply for medicinal uses and functional studies. Despite the rapid advancement of synthetic chemistry, natural product biosynthesis constantly provides inspiration for the design of efficient synthetic strategies and stimulates the development of new chemical methods.² Performing bioinspired synthesis can in turn inform biosynthesis.

We highlight in this article some recent examples of natural product synthesis influenced by biosynthetic logics. Many of these syntheses do not directly mimic the biosynthetic pathways. Instead, they involve the development of a key transformation to form the molecular framework or functional group of interest by following the presumed biosynthetic pathways. Due to the diverse chemistry described in this article, we group the selected work into four sections: halogenation, oxygenation, dimerization, and cycloaddition. Oxidation, in particular single-electron oxidation chemistry, frequently used by biological systems serves as the common theme throughout these sections.

HALOGENATION CHEMISTRY

Halogenated natural products are an important class of secondary metabolites that frequently display useful biological properties.³ For example, nakiterpiosin (**1**) is a potent antiproliferative marine natural product that contains two types of halogen atoms on a rearranged steroid backbone (**2**) (Fig. 1).⁴ Although the biosynthetic pathway of this rearranged steroid remains to be characterized, its chlorine and bromine atoms are most likely introduced by radical C–H chlorination and ionic olefin bromoetherification, respectively.⁵ Catalysts that promote these halogenation reactions are highly valuable as incorporation of halogen atoms is a common strategy to enhance the potency or alter the physical properties of small molecule drugs.

Biological C–H chlorination is typically catalyzed by α -ketoglutarate (α KG)-dependent non-heme iron (Fe_{NH}) halogenases.⁶ The initial step of the catalytic cycle is activation of the enzyme by oxygen to give complex **3** (Fig. 2). Subsequent oxidative decarboxylation of α KG through **4** gives high-spin complex **5** that abstracts a hydrogen atom from the substrate. Rebound of the radical and the chloride of **6** yields **7** and the chlorinated product. Finally, ligand substitution regenerates catalyst **8**. A good example of this process is the sequential chlorination of L-leucine by BarB2 and BarB1 in the barbamide biosynthesis.⁷

Biological olefin halogenation, in contrast, typically operates through a two-electron instead of single-electron oxidation manifold. One well-recognized olefin halogenation enzyme is vanadium-dependent haloperoxidase (V-HPO) that exists in its resting state as **9** (Fig. 3).⁸ Activation of **9** by hydrogen peroxide provides the end-on intermediate **10** that eliminates a hydroxyl ligand to yield a side-on η^2 -peroxo species **11**. Next, halide reacts with the peroxo ligand of **11** to give hypohalite **12**. This halide oxidation reaction is likely assisted by a protonated basic residue and the resulting hypohalite dissociates before reacting with olefin.

The V-HPO-catalyzed olefin halogenation reactions in the biosynthesis of napyradiomycin antibiotics have been studied in detail by the Moore group.⁹ They found that incubation of SF2415B1 (**13**) with V-HPO NapH1 in the presence of hydrogen peroxide and chloride promoted an oxidative chlorination reaction to give chloriranium ion **14** that cyclized to yield napyradiomycin A1 (**15**). The second intramolecular chloroetherification of **15** is possibly catalyzed by NapH4 with the intermediacy of **16** to give meroterpenoid napyradiomycin B4 (**17**).

The observation that iron complexes catalyze both C–H and olefin oxidation whereas vanadium complexes only catalyze halogenation of olefin in nature inspired the Chen group to initiate a program to expand the synthetic utility of vanadium complexes (Fig. 5).¹⁰ Focusing on the development of vanadium-catalyzed C–H halogenation reactions, they first found that high-valent vanadium complexes catalyze C–H oxygenation effectively whereas low-valent vanadium complexes are efficient C–H halogenation catalysts. For C–H oxygenation, vanadocene dichloride catalyzes benzylic C(sp³)–H oxidation of 3-ethylbenzoic acid (**18**) to give ketone **19** with no aromatic C(sp²)–H oxidation.^{10a} The regioselectivity of this vanadium catalyst system is complementary to that of other vanadium catalysts¹¹ and the popular iron catalysts.¹² They also found that vanadium-Schiff base complexes catalyze oxidative Strecker reaction¹³ of *para*-methoxyphenyl (PMP)-protected primary amines effectively.^{10b} For C–H halogenation, vanadium(III) oxide catalyzes selective C(sp³)–H fluorination of L-menthone (**20**) with Selectfluor to give fluoride **21**.^{10c}

During the study of vanadium-catalyzed C–H fluorination, the Chen group made a serendipitous observation that irradiation of 4-ethylacetophenone (**22**), a colorless monoarylketone, with light generated from a household compact fluorescent lamp (CFL) in the presence of Selectfluor gave benzylic fluoride **23** directly (Fig. 6). Recognizing that this photochemical reaction is mechanistically related to Norrish–Yang reaction¹⁴ and Breslow's directed C–H oxidation,¹⁵ they hypothesized that photoexcited carbon-oxo (carbonyl) groups are functionally equivalent to high-spin metal-oxo species and the reactivity of photoexcited ketones toward C–H abstraction¹⁶ can be tuned by changing the n/π^* energy gap. They first probed the feasibility of catalytic, intermolecular C–H functionalization and successfully found that irradiation of ethylbenzene (**24**) in the presence of 5 mol % of acetophenone yielded **25**. C–H chlorination could also be achieved by replacing Selectfluor with *N*-chlorosuccinimide (NCS).¹⁷

The Chen group subsequently showed that diarylketones could catalyze benzylic C–H fluorination and the selective formation of mono- or difluorination products could be achieved by catalyst-control.¹⁸ For example, 9-fluorenone catalyzed benzylic C–H monofluorination of **26** to give **27** whereas xanthone catalyzed difluorination to give **28** (Fig. 7). The de Frutos and Kappe groups further found that the efficiency of this photoreaction could be improved by flow chemistry and black-light irradiation.¹⁹

Selective fluorination of unactivated C(sp³)–H groups could also be achieved by using acetophenone as the catalyst.²⁰ With a larger n/π^* gap, acetophenone is a colorless oil and has only a trace amount of absorption in the visible light region (λ_{max} 325 nm). Nonetheless, its photoexcitation could be achieved by off-band CFL-irradiation due to

residual absorption. This off-band absorption phenomenon has also been observed by the Melchiorre group.²¹ CFL-irradiation of **29**, Selectfluor, and a catalytic amount of acetophenone gave **30** with good regioselectivity. The Chen group has further used off-band CFL-irradiation to promote the coupling of cyclopentenone (**31**) (λ_{max} 320 nm) and 2-propanol (**32**) to generate the Fraser-Reid ethereal C–H functionalization²² product **33**.

Recently, the MacMillan group has demonstrated that photoredox chemistry could also promote ethereal C–H abstraction–conjugate addition.²³ For example, a photoexcited iridium(III) complex could oxidize quinuclidine to an aminium radical cation that abstracted a hydrogen atom from **32** (Fig. 8). Conjugate addition of the resulting carbon-center radical to **34** followed by cyclization then yielded **35**. Additionally, thiyl radical could also mediate ethereal C–H abstraction.²⁴ For example, irradiation of a mixture of isoquinoline (**36**) and methanol (**37**) in the presence of a photoredox catalyst and a thiol led to the formation of **38** through an ethereal C–H abstraction followed by a Minisci-type addition of the resulting α -radical of **37** to **36**. Loss of a proton from **38** provided **39** that underwent a spin-center shift (SCS)²⁵ and a hydrogen-atom transfer to give the dehydrated alkylation product **40**. SCS is also an important step in the DNA biosynthesis wherein ribonucleotide reductase (RNR) catalyzes the transformation of **41**, the C–H abstraction product of RNA, into **42**.²⁶

Regarding olefin halogenation, the Snyder group has recently developed an enantioselective olefin chlorination reaction to achieve the asymmetric synthesis of napyradiomycin A1 (7-demethyl-**15**).²⁷ Treatment of **43** with a chiral Lewis acid derived from borane and 1,1'-biphenanthrene-2,2'-diol (BIPHNOL) gave complex **44** (Fig. 9). Reaction of **44** with chlorine gas afforded anti-dichloride **45** that was converted into chlorohydrin **46**. Subsequent Johnson–Claisen rearrangement provided **47**. Finally, introduction of the geranyl side chain by Julia–Kocienski olefination furnished ent-napyradiomycin A1.

Halonium ion is a versatile intermediate that can react with a carbon- or nitrogen-nucleophile in addition to an oxygen-nucleophile.²⁸ For example, polyene cyclization²⁹ can be initiated by olefin halogenation. The Faulkner group has found that addition of a Lewis acid facilitates halogenative *C*-cyclization.³⁰ Whereas treating geranyl acetate (**48**) with *N*-bromosuccinimide (NBS) only gave bromohydrin **49**, performing this reaction in the presence of silver fluoroborate under otherwise identical conditions provided the *C*-cyclization product **50** (Fig. 10).

The poor efficiency and low stereoselectivity associated with halogenative *C*-cyclization was the major limitation of this reaction. However, the Ishihara group has recently found that chiral phosphoramidites effectively promote asymmetric halogenative *C*-cyclization of polyprenoids.³¹ For example, reaction of 4-(homogeranyl)toluene (**51**) with *N*-iodosuccinimide (NIS) in the presence of a chiral phosphoramidite gave a mixture mono- and biscyclization products that converged into the cyclic product **52** upon treatment with chlorosulfonic acid (Fig. 11). Notably, *rac*-**52** was formed quantitatively when tri-*n*-butylphosphine was used as the promoter.

Recently, the Snyder group has developed a series of novel halogenating reagents that effectively promote halogenative cyclization.³² Using **48** as the substrate to examine the

ability of a series of bromosulfonium ions to induce brominative *C*-cyclization, they found that bromodiethylsulfonium bromopentachloroantimonate (BDSB) induced the formation of **50** smoothly.³³ BDSB is an air-stable crystalline solid prepared from bromine, diethyl sulfide, and antimony pentachloride. The sulfur Lewis base modulates the reactivity of the bromonium ion and the antimony Lewis acid sequesters the bromide to prevent dibromination. Treatment of α -farnesyltoluene (**53**) with BDSB provided the tandem cyclization product **54** (Fig. 12). The Snyder group has also used BDSB-promoted brominative cyclization to accomplish the syntheses of a series of natural products including laurefucin (**55**) and peyssonol A (**56**).³⁴

Chlorodiethylsulfonium hexachloroantimonate (CDSC), the corresponding chlorinating reagent, can also promote halogenative polyene cyclization despite lower efficiency than BDSB.^{34a} Additionally, reaction of iodine with diethyl sulfide and antimony pentachloride provided the iodinating reagent IDSI. Although IDSI is not stable at room temperature and forms a dimer through a chlorine atom bridge, the Snyder group has successfully used IDSI-mediated iodinative polyene cyclization to achieve the synthesis of fungal metabolite K-76 (**57**).

OXYGENATION CHEMISTRY

Biological systems use controlled C–H oxidation to generate a diverse array of secondary metabolites from simple starting materials. For example, oxidative modification of carbon skeletons assembled from oligomerization and cyclization of isoprene units provides a large variety of terpene family of natural products.³⁵ Enzymes responsible for C–H oxidation typically contain an iron or copper cluster such as **58–60** (Fig. 13).³⁶ Mechanistically, biological C–H hydroxylation is similar to C–H chlorination, comprising a C–H abstraction followed by a rebound with the oxygen ligand. For example, the iron-dependent epoxidase HppE binds to and abstracts the α -hydrogen atom of (*S*)-2-hydroxypropyl-1-phosphonate (S-HPP) (**59**) in producing fosfomicin.³⁷ Efforts to reconstitute the C–H oxidation metal complexes have led to the development of a series of powerful C–H hydroxylation catalysts that are useful to small-molecule synthesis.³⁸

The Baran group has recently developed a series of bioinspired C–H oxidation strategies for general terpenoid synthesis.³⁹ They first found that site-specific hydroxylation of **61** could be achieved by trifluoroethyl carbamate-mediated Hofmann–Löffler–Freitag reaction to give **62** after cyclization and hydrolysis (Fig. 14).^{39a} They then demonstrated that oxidation of **61** with methyl(trifluoromethyl)dioxirane (TFDO)⁴⁰ proceeded with the alternative “strain-relieving” selectivity⁴¹ to give **63** after removal of the carbamate group.^{39b}

The Baran group has also used a series of redox and stereochemical relay chemistries to achieve the synthesis of ouabagenin.^{39i,39j} The synthesis started with protection of adrenosterone to give **64** (Fig. 15). Selective functionalization of a C–H group at the C19 position of **64** was achieved by UV-irradiation of the C11-ketone⁴² to promote a Norrish–Yang cyclization.¹⁴ Oxidation of the resulting cyclobutanol **65** with NIS induced C11–C19 cleavage presumably through the intermediacy of a hypoiodite. Subsequent hydrolysis of the C3-ketal protecting group and the C19-iodide occurred with olefin migration to yield the

conjugated ketone **66**. The C5-oxygen atom was then introduced with the desired stereochemistry through nucleophilic epoxidation of enone **66** from its less hindered convex face. Oxidation of the resulting epoxyketone provided epoxyenone **67**. The C1-oxygen atom was introduced by subjecting **67** to another nucleophilic epoxidation. Reduction of the resulting bisepoxide **68** with aluminum amalgam delivered triol **69**. Further reduction of the C3 and C11-ketone groups, protection of the hydroxyl groups, and hydrolysis of the ketal group provided boronate **70**.

The final stage of the synthesis involves a C17→C14 redox relay to introduce the C14 oxygen atom. To accomplish this challenging task, they first used Saegusa–Ito oxidation to generate an enone from **70** and then deconjugated the olefin to yield **71**. Fluorinated solvents, in particular perfluorotoluene (PFT), facilitated isomerization and suppressed the undesired C14-epimerization. Subsequently, they used cobalt-catalyzed Mukaiyama hydration⁴³ to produce the C14-oxygenated product **72**. The *syn*-stereochemistry at the 5,6-ring junction can be rationalized by addition of a cobalt hydride complex to the olefin from the convex face of **71**. Finally, introduction of a butenolide unit followed by deprotection furnished ouabagenin.

As part of a program that aims to recapitulate the biosynthetic pathway of Taxol using synthetic chemistry,^{39c–f} the Baran group has thoroughly examined the selectivity of various C–H oxidation reactions on the Taxol backbone.^{39f} Despite the presence of two olefins in taxadiene (**73**), conformational analysis suggested that the C5 position could be oxidized selectively for steric reasons (Fig. 16). This prediction is in line with Taxol biosynthesis wherein C5 oxidation occurs first in the oxidase phase.⁴⁴ Palladium(II)-catalyzed allylic acetoxylation of **73** provided the C5-functionalization product **74** with good regioselectivity and diastereoselectivity. They found that addition of anisole helped stabilize the palladium intermediate and improved the turnover numbers.

Analysis of the radical stability of the C–H abstraction product of **74** indicated that the C13 position would be the next oxidation site. An extensive exploration of allylic oxidation methods led to the identification of high-valent chromium-oxo complexes as the suitable catalysts. Oxidative cleavage and epoxidation of olefins could be suppressed with sodium bis(2-hydroxy-2-methylbutyrate)oxochromate, an oxidant initially developed by Roček for studying metal-catalyzed oxidative damage of DNA.⁴⁵ The bidentate tertiary α -hydroxy acid ligand stabilizes the Cr(V) metal and prevents it from disproportionating into Cr(VI) and Cr(III) species. The Baran group found that addition of manganese(IV) oxide as a co-oxidant helped reduce the amount of the Roček complex required for the C13-oxidation of **74** to give **75**. Selective C10 oxidation of **75** was next realized with radical bromination. The resulting bromide was then converted into triethylsilyl ether **76**. Subsequent reduction of the enone group and protection of the allylic alcohol yielded acetate **77**. Notably, bromination of 13-acetoxy-**74** occurred at the C18 position instead. This result is consistent with the site-selectivity predicted by comparing the radical stability of the corresponding C–H abstraction products. Finally, treatment of **77** with iodoxybenzoic acid (IBX) promoted silyl deprotection and allylic oxidation to afford taxadiene **78**. The first three biosynthetic oxidative modifications of the Taxol backbone could thus be carried out by chemical means.

DIMERIZATION CHEMISTRY

Single-electron redox is a common strategy for generating reactive species in nature. It has long been postulated that many complex natural products are produced through this mechanism. For example, Robinson and Woodward have proposed that cyclotryptamine alkaloids are produced by oxidative dimerization of *N*₆-methyl tryptamine (**79**) (Fig. 17).⁴⁶ Single-electron transfer (SET) oxidation of **79** would generate radical cation **79**^{•+} that dimerized to **80**.⁴⁷ Cyclization of **80** would then provide chimonanthe (**81**) that existed in equilibrium with **82**, the hydrolysis product of **80/81**.⁴⁸ Amino formation by engaging functional groups across the two subunits of **82** would provide calycanthine (**83**) and CPC-2 (**84**). Both the *C*₂-symmetric and meso forms of **81** have been found in nature.

The first bioinspired synthesis of **81** was reported by the Hendrickson group who used two-electron oxidation of 3-(2-methylaminoethyl)oxindole to form the C3–C3' linkage.⁴⁹ Later, the Scott group found that dimerization of **79** via SET oxidation could be achieved by treating the magnesium salt of **79** with iron(III) chloride to give **81** directly.⁵⁰ They further demonstrated that **81** isomerized in hot hydrochloric acid to give a 1:4 mixture of **81** and **83**. This oxidative dimerization reaction has been revisited by the Rodrigo,⁵¹ Verotta,⁵² and Takayama⁵³ groups more recently.

Inspired by this radical dimerization hypothesis, the Movassaghi group developed a net single-electron oxidation strategy⁵⁴ and used it to complete the syntheses of a series of cyclotryptamine dimers.^{2f,47,55} They first prepared **85** from *N*_α-methoxycarbonyl-L-tryptophan methyl ester and introduced a bromine atom to its C3a position (Fig. 18).⁵⁶ Next, they photolyzed dimanganese decacarbonyl [Mn₂(CO)₁₀] to generate Mn(CO)₅ that abstracted the bromine atom⁵⁷ from **86**. Homodimerization of the resulting C3a-radical gave the *C*₂-symmetric product **87** with excellent optical purity. They later found tris(triphenylphosphine)cobalt(I) chloride [CoCl(PPh₃)₃] to be a more effective reductive radical coupling promoter.⁵⁸ Fewer byproducts were formed with this highly reactive single-electron reducing agent and the reaction could be performed on a gram-scale. Finally, decarboxylation and deprotection of **87** provided **81**. Using this radical coupling strategy, the Movassaghi group has further achieved the syntheses of WIN 64821 and ditryptophenamine,⁵⁹ and the Sodeoka group the synthesis of chaetocin A.⁶⁰

In addition to the debrominative coupling strategy, the Movassaghi group has also developed a diazene fragmentation strategy to enable heterodimerization.⁶¹ Here, they used the Du Bois C–H amination method⁶² to functionalize **88** into arylsulfamate ester **89** (Fig. 19).⁶³ Coupling of **89** with cyclotryptamine **90** yielded sulfamide **91**. Oxidation of **91** with 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) afforded diazene **92**. Photolysis of diazene **92** in the solid state as a thin film released the two cyclotryptamine radical fragments that coupled smoothly to yield the desired heterodimer **93** with minimal radical disproportionation and no cross-over products. Finally, deprotection and methylation furnished calycanthidine (**94**). The diazene fragmentation could also be carried out in viscous solvent such as *tert*-butanol that facilitated solvent-caged radical coupling.

The Movassaghi group has further developed a Friedel-Craft approach for the synthesis of sp^2 - sp^3 -linked dimeric cyclotryptamine alkaloids.⁶⁴ To establish the C-C linkage, they treated **95** with silver(I) hexafluoroantimonate to sequester its bromine atom (Fig. 20).^{64a} The resulting C3a cation was then trapped with trifluoroborate **96** to form the heterodimer. 18-Crown-6 was used to increase the solubility of the potassium trifluoroborate salt, enhance the nucleophilicity of **96** via ion pairing with **95**, and facilitate the elimination of trifluoroborate by dissociating the potassium ion. Without a trifluoroborate group on **96**, the dimerization gave a mixture of C6' and C7'-coupling products. Finally, removal of the protecting groups yielded naseaezine B (**97**).

The molecular skeleton of naseaezine has also inspired the MacMillan group to develop an asymmetric copper(I)-catalyzed arylation cyclization reaction.⁶⁵ Coupling of indole **98** with diaryliodonium salt **99** in the presence of a chiral copper(I) catalyst provided **100** with high enantioselectivity (Fig. 21). Mechanistically, insertion of Cu(I) into **99** gave a highly electrophilic Cu(III) species. Oxidation of **98** by this chiral Cu(III) salt followed by reductive elimination and cyclization yielded **100** and regenerated the Cu(I) catalyst. The Reisman group has also used a copper(I)-catalyzed arylation cyclization reaction to achieve the synthesis of **97**.⁶⁶ Using a α -diimine instead of bis(oxazoline) ligand significantly improved the diastereoselectivity and the C3:C2 arylation ratio. Coupling of cyclo-(Trp-Phe) (**101**) and diaryliodonium salt **102** gave **103** that could be transformed into **97** in just two steps (Fig. 21).

The Movassaghi group has also coupled reductive radical dimerization with diketopiperazine oxidation to accomplish the syntheses of epipolythiodiketopiperazine (EPT) alkaloids 11,11'-dideoxyverticillin A,⁶⁷ chaetocins, and 12,12'-dideoxytetracin A.⁶⁸ These EPT alkaloids contain a rare polysulfide motif critical to their anti-proliferative activities.^{64c} Notably, calicheamicin γ 1 is another highly cytotoxic polysulfide-containing natural product⁶⁹ that cleaves DNA with a diradical species generated from Bergman cyclization⁷⁰ upon glutathione activation.⁷¹

The synthesis of chaetocins by the Movassaghi group started with brominative cyclization of diketopiperazine **104** (Fig. 22).⁶⁸ Subsequent methylation of the amide and change of the hydroxyl protecting group afforded the coupling fragment **105**. Treatment of bromide **105** with $\text{CoCl}(\text{PPh}_3)_3$ induced the reductive radical coupling to give dimer **106**. Next, oxidation of the diketopiperazine with bis(pyridine)silver(I) permanganate ($\text{Py}_2\text{AgMnO}_4$) provided tetraol **107**. This C-H oxidation reaction proceeded with high stereoselectivity because of fast radical rebound after C-H abstraction. Thiolation of **107** at the C11 and C11' positions followed by global acylation with isobutyryl chloride and removal of the benzenesulfonate group afforded bithioester **108**. Selective hydrazinolysis of the thioesters followed by introduction of the trisulfide groups provided **109**. The indoline groups were then protected as trifluoroacetates. Ionization of the C15 and C15' aminals with concomitant loss of the trityl group led to the formation of the trisulfide bridges. Finally, cleavage of the acetates furnished chaetocin C (**110**).

A related diketopiperazine oxidation was developed by the Reisman group during the synthesis of a dihydrooxepine-containing ETP. They found that exposure of **111** to air in the

presence of tetrabutylammonium fluoride (TBAF) promoted a C–H oxidation of diketopiperazine to give diol **112** (Fig. 23).⁷² Treatment of the bisenolate of **112** with elemental sulfur under Nicolaou's sulfenylation conditions⁷³ afforded tetrasulfide **113**. Subsequently, acetylation of the hydroxyl groups and reductive cleavage of the tetrasulfide yielded a bisthiol intermediate. Finally, aerobic oxidation of this bisthiol established the disulfide linkage and furnished acetylaranotin (**114**).

The Shenvi group has recently developed a two-electron oxidative dimerization reaction to achieve the bioinspired synthesis of nuphar dimers, another interesting class of sulfur-containing natural products.⁷⁴ Following LaLonde's biosynthetic hypothesis,⁷⁵ they oxidized quinolizidine **115** to generate *N*-oxide **116** and set the stage for the dimerization (Fig. 24). Treatment of **116** with trifluoroacetic anhydride (TFAA) induced a Polonovski elimination and yielded α,β -unsaturated iminium ion **117**. Without isolation, **117** was reacted with sodium tetrasulfide to give enamine **118** that underwent a Mannich-type reaction with another molecule of **117** to afford enamine-iminium ion **119**. Subsequent cyclization of **119** provided **120** and established the molecular framework of the nuphar dimers. Finally, reduction of the hemiaminal groups afforded neothiobinupharidine (**121**). Because the diastereomeric thiobinupharidine is by far the most abundant component of the nuphar alkaloids, they proposed that biogenic dimerization of nuphar alkaloids is an enzyme-mediated event.

Very recently, the Wu group has developed a chiral ion pair strategy to change the stereoselectivity of the sulfide-mediated dimerization of **117**.⁷⁶ α -Aminonitrile **122** was used as a stable precursor of **117** (Fig. 25). Treatment of **122** with indium(III) triflate and 2,6-bis[(3a*R*,8a*S*)-(+)–8*H*-indeno[1,2-*d*]oxazolin-2-yl)pyridine (In-PyBOX) led to the formation of iminium ion **117** with a chiral counterion. This tight ion-pair reacted with sodium tetrasulfide and another molecule of **117** to give **123** bearing the thiobinupharidine stereochemistry. The neothiobinupharidine (**121**) core could be obtained as the major product when copper(II) triflate was used as the promoter. Conversion of the α -aminonitrile groups into hemiaminals and selective monoreduction yielded 6-hydroxythiobinupharidine (**124**). The Wu group further found that, unlike (–)-neothiobinupharidine (**121**) showing no apoptotic activity, **124** induced rapid apoptosis as judged by the cleavage of poly(ADP-ribose) polymerase 1 (PARP-1) by caspase 3. Moreover, all mono- and dihydroxylated dimeric nuphar alkaloids, including **120** that has not been isolated from a natural source, are equally potent. Meanwhile, the Zakarian group has also developed a Stevens-type ring expansion strategy to establish all four possible diastereomeric core skeletons of the nuphar dimers.⁷⁷

CYCLOADDITION CHEMISTRY

Cycloadditions, concerted or stepwise, are powerful tools in chemical synthesis. However, only a few enzymes have been identified with catalytic activities toward cycloaddition.⁷⁸ One good example is the recent discovery by the H.-w. Liu group that bacterial cyclase SpnF accelerates the transannular cycloaddition of **125** by 500 times to give **126** in the biosynthesis of spinosyn A (Fig. 26).⁷⁹ Results from computational studies support a concerted, asynchronous mechanism,⁸⁰ although the protein–substrate interactions that

stabilize the transition state are yet to be determined. Another example is the very recent discovery from the W. Liu group that bacteria use two sequential [4+2] cycloaddition reactions to produce pyrroindomycin.⁸¹ PyrE3 catalyzes the intramolecular Diels–Alder reaction of **127** to give **128**, and PyrI4 converts **128** into **129** with another intramolecular Diels–Alder reaction. Specifically, PyrI4 catalyzes the exo Diels–Alder reaction of **128** through activation of the tetramate dienophile of **128** with Q115 and formation of a lid-like structure of the N-terminal tail to impose conformational constraints on the β barrel catalytic core.⁸² Enzymes that catalyze 1,3-dipolar cycloaddition reactions have also been found recently during the study of a decarboxylation reaction in the bacterial biosynthesis of ubiquinone.⁸³

Marine sponges are also known to use various types of (formal) cycloaddition to create a diverse set of dimeric pyrrole–imidazole alkaloids from oroidin (**130**) or its debromonated congeners (Fig. 27).⁸⁴ For example, scep trin (**131**) is a [2+2] dimer, massadine (**132**) a [3+2] dimer, and ageliferin (**133**) a [4+2] dimer. Recently, the Molinski and Romo groups have provided metabiosynthetic evidence that these cycloadditions are promoted by a SET oxidation.⁸⁵ They showed that cell-free enzyme extracts collected from pyrrole–imidazole alkaloid-producing sponges promoted the dimerization of **130** through oxidoreductase-mediated SET oxidation to give **130**^{•+}. This radical cation would undergo a [2+2] cycloaddition⁸⁶ with another molecule of **130** to form dibromoscep trin radical cation (**134**). Subsequent oxidation and cyclization would then provide the observed product benzoscep trin C (**135**). The Molinski and Romo groups have further suggested that the high-energy radical species generated from SET-oxidation is responsible for the formation of various highly strained monomeric and dimeric pyrrole–imidazole alkaloids. The Chen group later found that **131**–**133** have inconsistent absolute stereochemistry. They proposed that scep trin (**131**), massadine (**132**), and ageliferin (**133**) are produced by enantiodivergent pathways through redox-neutral, reversible SET-promoted [2+2], [3+2], and [4+2] cycloadditions, respectively.

The Chen group has used a single-electron oxidation strategy to achieve the syntheses of a series of dimeric pyrrole–imidazole alkaloids.⁸⁷ For the synthesis of the [2+2] dimer scep trin (**131**), they applied Yoon's photoredox-promoted cycloaddition method⁸⁸ to construct its cyclobutyl core skeleton.^{87e–g} Starting from azidoimidazole **136**, reduction of the azido group followed by irradiation with visible light in the presence of a catalytic amount of tris[2-phenylpyridinato- C^2,N]iridium(III) [Ir(ppy)₃] provided the formal [2+2] cycloadduct **137** (Fig. 28). Consistent with Bauld's observation,⁸⁶ olefin isomerization readily occurred upon SET oxidation, leading to the formation of a mixture of C10 diastereomers. Transthio ketalization of **137** revealed the cyclobutyl core of scep trin and gave **138**.

For the synthesis of the [4+2] dimer ageliferin (**133**), the Chen group used an oxidative radical cyclization reaction to construct its cyclohexenyl core skeleton.^{87c–e} Treatment of **139** with manganese(III) acetate promoted a SET oxidation to give radical cation **140** (Fig. 29). Loss of a proton from **140** provided a β -dicarbonyl- α -radical that underwent tandem 5-exo/6-endo cyclizations followed by another SET oxidation to afford **141**. Subsequent decarboxylation provided the ageliferin core **142**.

Inspired by the observation that ageliferin (**133**) is a formal Diels–Alder reaction product of two molecules of hymenidin, the Romo⁸⁹ and the Lovely groups⁹⁰ have each developed an intramolecular [4+2] cycloaddition approach to construct the core skeleton of **133**. The Ohta group has further demonstrated that homodimerization of **143** gave the exo [4+2] cycloadduct **144** that could be transformed into 12,12'-dimethylageliferin (**145**) (Fig. 30).⁹¹

Although it is generally accepted that the [2+2] and [4+2]-type pyrrole–imidazole dimers are produced through enzymatic cycloadditions, it was long believed that the [3+2] pyrrole–imidazole dimers were derived from the [4+2] dimers through oxidative ring-contraction. This hypothesis was initially put forward by the Scheuer group to explain the biogenesis of palau'amine.⁹² They suggested that a [4+2] cycloaddition of 3-amino-1-(2-aminoimidazolyl)prop-1-ene (**146**) and 11,12-dehydrophakellin (**147**) would provide **148** (Fig. 31). Subsequently, a chloroperoxidase-mediated chlorination and ring contraction would give rise to **149**, the originally proposed palau'amine that possesses incorrect 11,12-relative stereochemistry.⁹³ Later, the structural revision of palau'amine called for a modification of the Scheuer hypothesis to involve an oxidative ring-contraction of **150** or **151** in order to reconcile the relative stereochemistry of the presumed biosynthetic intermediates with that of the revised palau'amine (**152**). This “Scheuer” rearrangement has since been studied by the Romo,^{89,94} Lovely,⁹⁵ and Baran⁹⁶ groups, and used by the Chen group^{87a,b,d,e,h} to complete the asymmetric syntheses of massadine (**132**)^{87e} and axinellamines.^{87h}

The use of Scheuer rearrangement to construct the cyclopentyl core of the [3+2]-type pyrrole–imidazole dimers was first reported by the Romo group.^{89a,94} They showed that oxidation of **153** with dimethyldioxirane (DMDO) gave the allylic oxidation product **154** that resembles the Scheuer Diels–Alder intermediate **148** (Fig. 32). Chlorination of **154** with Chloramine T induced a semipinacol-type ring-contraction to yield the Scheuer rearrangement product **155**. The Romo group has further inverted the C12 configuration of **155** to obtain 11,12-trans-**156**.^{94b} Comparing the ¹H NMR data of **156** with that of palau'amine (**152**) provided the first experimental support that palau'amine indeed contains a highly strained *trans*-fused 5,5-bicyclic molecular framework. The definitive proof of the revised structure of palau'amine was later provided by the Baran group⁹⁷ and the Namba–Tanino groups⁹⁸ through total synthesis.

The Chen group has also developed an asymmetric approach for the synthesis of the [3+2]-type pyrrole–imidazole dimers based on the Scheuer biosynthetic hypothesis.^{87a,b} They found that this key transformation could be carried out at a late stage. Treatment of **157** with titanium(IV) isopropoxide and *tert*-butyl hydroperoxide (TBHP) induced the ring-contraction reaction to yield **158** after C9-reduction (Fig. 33).^{87e,h} The hydroxyl group functioned as a directing group to help set up the desired spiro-configuration. Subsequent deprotection and oxidative cyclization provided massadine in its natural enantiomeric form (**132**). Interestingly, however, reduction and deprotection of **157** gave dibromoageliferin in its unnatural enantiomeric form (*ent*-Br₂-**133**). The mismatched absolute stereochemistries of massadine and (dibromo)ageliferin indicates that the Scheuer rearrangement is not operative in the biosyntheses of the [3+2]-type pyrrole–imidazole dimers.

On the basis of the above finding and their computational studies,^{87d} the Chen group proposed that sceptrin (**131**) and ageliferin (**133**) are derived from homodimerization of two hymenidin (**159**) molecules whereas massadine (**132**) is derived from heterodimerization of one oroidin (**130**) and one dispacamide A (**160**) molecule (Fig. 34).^{87e} SET oxidation of **159** would promote a [2+2] cycloaddition reaction of **159**^{•+}/**159** to give **131**^{•+} or a [4+2] cycloaddition reaction to give **161**^{•+}. Subsequent SET reduction would yield **131** and **161**. Tautomerization of **161** would then provide the aromatized product **133**. Similarly, SET oxidation of **160** would promote a [3+2] cycloaddition reaction of **160**^{•+}/**130** to give **162**^{•+}. Subsequent SET reduction, protonation, and trapping of the cation with water or chloride would provide “pre-massadines” (**163**). Oxidative cyclization of **163** would then give massadines (**132**). The homodimerization and heterodimerization are enantiomeric pathways, and the pathway selectivity of these SET-mediated cycloadditions is determined by the stability of the radical intermediates.

OUTLOOK

Oxidative modification is commonly used in natural product biosynthesis to introduce biological activities and increase structural complexity. In particular, single-electron oxidation is a versatile and powerful method to functionalize unreactive substrates. Although the resulting radical intermediates are remarkably compatible with many polar functional groups including nitrogen-containing heterocycles, due to the high reactivity of the energetic species generated by this process, chemists are yet to achieve the level of control that enzymes have. Recent bioinorganic studies have significantly improved our understanding of metalloenzymes that catalyze biological oxidation reactions. Attempts to reconstitute the catalytic metal clusters or mimic their activities have also been increasingly successful. We believe that continuous efforts in the development of artificial catalyst systems inspired by oxidative enzymes will help shape modern synthetic chemistry by providing currently unavailable synthetic tools.

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Biographies

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oxygenases/halogenases

C–H abstraction

reactivity tuned by the ligand

photoexcited organic ketones

C–H abstraction

reactivity tuned by the Ar and R groups

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