Trends in Applying C–H Oxidation to Total Synthesis of Natural Products

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Trends in Applying C–H Oxidation to Total Synthesis of Natural Products

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Yuanyou Qiu,[a] and Shuanhu Gao[a*]

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C-H functionalization remains one of the frontier challenges in organic chemistry and drives quite an active area of research. It has recently been applied in various novel strategies for the synthesis of natural products. It can dramatically increase synthetic efficiency when incorporated into retrosynthetic analyses of complex natural products, making it an essential part of current trends in organic synthesis. In this Review, we focus on selected case studies of recent applications of C-H oxidation methodologies in which the C-H bond has been exploited effectively to construct C-O and C-N bonds in natural product syntheses. Examples of syntheses representing different types of C-H oxidation are discussed to illustrate the potential of this approach and inspire future applications.

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1 Introduction

Total synthesis remains the ultimate test of strategies and methodologies developed, it also serves as the foundation of studies of medicinal chemistry and chemical biology of natural products. Increasing demand for efficient and scalable syntheses have put pressure on organic chemists to develop rigorous synthetic approaches in which the carbon skeleton and oxidation state can be precisely controlled. Every so often, a new strategy or methodology comes along that dramatically improves on classical approaches. The traditional synthetic approach to constructing C-C or C-X bonds is via transformations of reactive functional groups. In this approach, C-H and C-C single bonds are always considered inert. However, the field of C-H functionalization has been gaining rapidly in importance, with many review articles[1] already written about

[a] *Shanghai Key Laboratory of Green Chemistry and Chemical Processes, School of Chemistry and Molecular Engineering, East China Normal University, 3663N Zhongshan Road, Shanghai 200062 (P. R. China)* Email: shgao@chem.ecnu.edu.cn

method development, mechanisms, reaction scopes, and applications to total syntheses.[2]

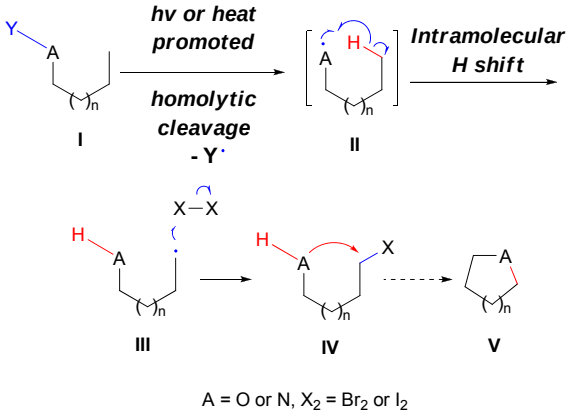
For example, C-H oxidation has been studied extensively over the past decade and has found a growing number of applications in total synthesis of natural products.[2] C-H oxidation is most often defined as direct transformation of a C-H bond to a C-X bond at a higher oxidation state. Obviously, functionalization of the C-H bond to C-O, C-halogen, C-N, C-S or C-C raises the possibility of integrating a diverse range of functional groups, which can lead to transformations more effective than those obtained through traditional approaches. We believe that this methodology will be used frequently to achieve late-stage modifications in medicinal chemistry and drug discovery projects. C-O and C-N bonds are the most frequent carbon-hetero bonds in naturally occurring molecules and contribute to the diversity and complexity of natural products. Traditionally these bonds are formed via functional group interconversion, olefin oxidation and fragmentation. A much simpler approach is direct oxidation of C(sp^3/sp^2)-H to C-O or C-N. We expect that this and other C-H oxidations will become increasingly important to organic chemists during retrosynthetic analysis and planning of late-stage modifications.

This review article will describe recent applications of C-H oxidation methodologies to form C-O and C-N bonds in natural product syntheses and give readers information invaluable for designing new retrosynthetic routes to complex natural products. The selected examples were chosen from studies published from 2006 to 2015. We regret that for reasons of space, we could not include every published example of C–H oxidation in natural product synthesis.

2 Intramolecular Radical-Promoted Remote C-H Oxidation

2.1 Introduction to the Reactions

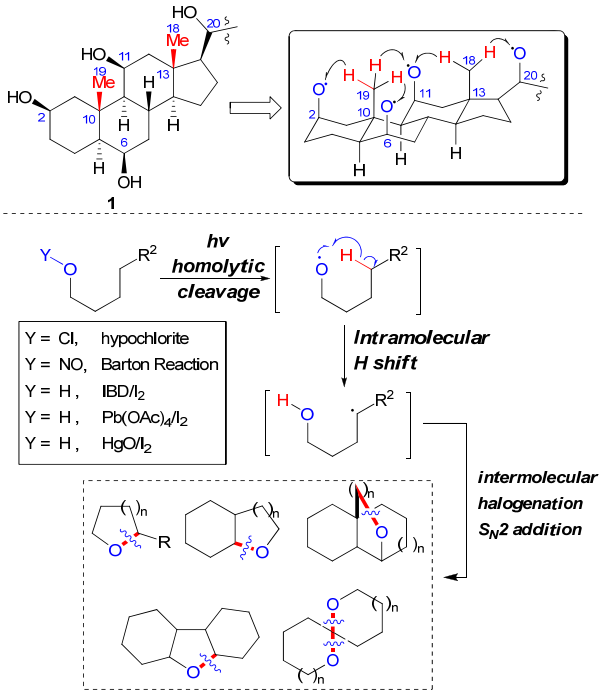
Key to oxidizing C-H bonds in synthetic processes is selective activation of the appropriate bond, since C-H bonds are ubiquitous in organic molecules. The selectivity of C-H oxidation depends largely on bond stereochemistry and reactivity. A well-established method for activating C (sp^3)-H bonds involves an intramolecular hydrogen shift, initiated by reactive species such as heteroatom radicals.[3] This method was first described by Hofmann, Löffler and Freytag more than 130 years ago, when they transformed *N*-haloamines into cyclic amines by causing an intramolecular hydrogen shift from an aliphatic C-H bond to a nitrogen radical.[4] This so-called Hofmann-Löffler-Freytag (HLF) reaction has since been developed into a useful C-H bond activation strategy, and its reaction mechanism has been well studied (Scheme 1). Thermolysis or photolysis initiates homolytic cleavage of the labile bond between two heteroatoms (Y-A bond) in **I**, leading to formation of oxygen- or nitrogen-centered radicals **II**. Regioselective hydrogen abstraction, usually via a 6-membered transition state, then generates a new carbon-centered radical **III**, which is trapped intermolecularly by halogen radicals. Under basic conditions, the heteroatom displaces the halogen to give the hetero-ring **V** via an intramolecular S_N2 reaction.



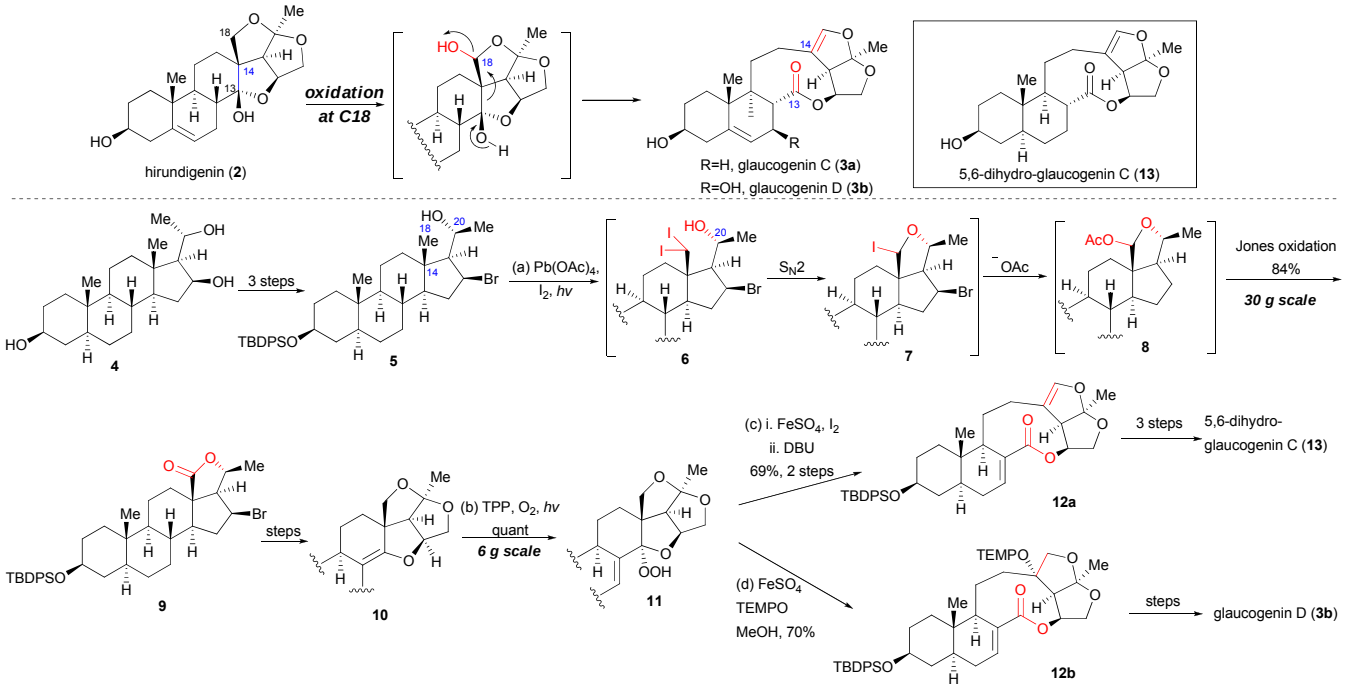
Scheme 1. Hofmann-Löffler-Freytag (HLF) reaction.

2.2 Total Synthesis of Glaucogenin D and 5,6-dihydro-glaucogenin C

Intramolecular oxygen-centered, radical-induced C-H oxidation has proven effective with rigid substrates, especially for the synthesis and late-stage modification of steroids. For instance, such intramolecular remote activation can be used to selectively oxidize two axial methyl groups at C-10 and C-13 of steroid **1** (Scheme 2). The hydrogen abstraction at C-19 can



Scheme 2. Intramolecular Oxygen-centered, Radical-induced C-H Oxidation of Steroid.

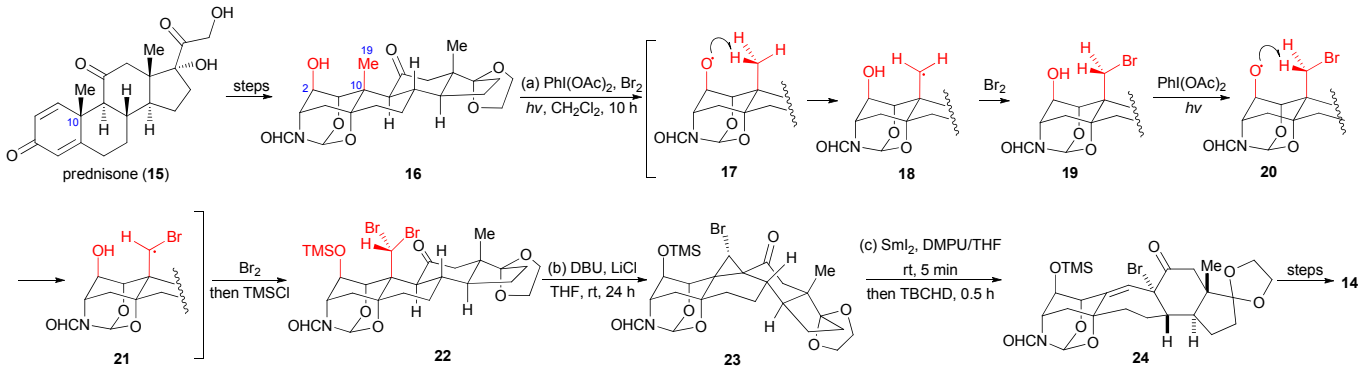


Scheme 3. Synthesis of 5,6-dihydro-glaucogenin C and glaucogenin D. *Reagents and conditions:* (a) $Pb(OAc)_4$ (5.0 equiv), I_2 (1.5 equiv), $CaCO_3$ (3.0 equiv), cyclohexane, *hv*, 2 h, then Jones oxidation, 84%; (b) TPP (cat.), O_2, CH_2Cl_2, *hv*, 0 °C, 1 h, quant.; (c) i. $FeSO_4$ (2.0 equiv), I_2 (2.0 equiv), MeOH, rt, 1 h, ii. DBU (10.0 equiv), toluene, 80 °C, 1 h, 69%, 2 steps; (d) $FeSO_4$ (2.0 equiv), TEMPO (2.0 equiv), MeOH, rt, 1 h, 70%. (TPP = 5,10,15,20-tetraphenyl-21H,23H-porphine, DBU = 1,8-Diazabicyclo(5.4.0)undec-7-ene, TEMPO = 2,2,6,6-tetramethylpiperidin-1-yloxyl.)

originate selectively at the axial oxygen-centered radicals attached at C-2, -6 or -11. The rigid tetracyclic ring features 1,3-disubstituted axial bonds containing both methyl and hydroxyl groups, and this geometry favors a 6-membered transition state, thereby facilitating hydrogen transfer. The same strategy can be adapted to selectively functionalize the methyl group on C-13 via the heteroatom-centered radicals on C-11 or -20. Indeed, such intramolecular remote oxidation has proven to be reliable and scalable for the preparation of steroid-related natural molecules, such as glaucogenin C and D as well as cortistatin A.

Further studies of O-radical formation have expanded the scope of this intramolecular remote oxidation extraordinarily. Most nitrite esters (Barton reaction)[5] and hypochlorites[6] need to be isolated prior to homolytic cleavage, while alkyl hypoiodites and lead (IV) alkoxide are generated *in situ* from the corresponding alcohols using reagents such as iodobenzene diacetate $[PhI(OAc)_2]$[7] and lead tetraacetate.[8] This approach has been used to efficiently construct cyclic ethers with different ring sizes and skeletons, including fused, bridged and spiro structures (Scheme 2).

It was in 1965 that Meystre and co-workers developed a scalable methodology to selectively oxidize the angular methyl group on C-13 of steroids to prepare lactones.[9] In 2011, Tian and co-workers applied this strategy in the synthesis of glaucogenin C (**3a**) and D (**3b**),[10] which are rearranged steroids that potently inhibit alphavirus-like positive-strand RNA viruses.[11] The biogenetic hypothesis suggested that the unusual 9-membered lactone of glaucogenin C (**3a**) and D (**3b**) may be formed from hirundigenin (**2**) through hydroxylation at C-18 and subsequent Grob-type fragmentation of the C13-C14 bond (Scheme 3). The synthesis commenced from the readily available C-21 steroid **4**, which could be transformed to bromide **5** in 3 steps. The methyl group on C-14 was then selectively oxidized through oxygen-centered, radical-promoted C-H oxidation. Photolysis of **5** in the presence of lead tetraacetate (LTA) and iodine followed by the Jones oxidation gave lactone **9** in 84% yield (30 g scale). This reliable reaction adheres to the general principle of a 6-membered transition state. The ligands exchange of hydroxyl group on C-20 with lead tetraacetate generated a lead alkoxide, which was easily homolyzed to reveal the high energy O-centered radical. This O-radical was capable of regioselectively abstracting the accessible hydrogen atom at C-18 to give the carbon-centered radical. The recombination of the carbon radical with iodine gave the desired iodide product. Further oxidation through the same process lead the formation of *gem*-diiodide **6**. Cyclization of **6** via intra- and intermolecular S_N2 attack resulted acetate **8**, which was immediately oxidized to lactone **9**. Compound **9** was then converted to **10**, a derivative of hirundigenin (**2**). The Schenck ene reaction of **10** with singlet oxygen afforded the alkoxy hydroperoxide **11** in quantitative yield with high regio- and



Scheme 4. Total Synthesis of Cortistatin A. *Reagents and conditions*: (a) $PhI(OAc)_2$ (5.0 equiv), Br_2 (8.0 equiv), CH_2Cl_2, -30 °C, 10 h, then TMSCl (5.0 equiv), imidazole (5.0 equiv), 0 °C, 15 min, 57%; (b) DBU (2.0 equiv), LiCl (5.0 equiv), THF, rt, 85%; (c) SmI_2 (2.2 equiv), 1:9 DMPU:THF, rt, 5 min, then TBCHD (1.1 equiv), -72 °C, 0.5 h. (TMSCl = trimethylsilyl chloride, DBU = 1,8-Diazabicyclo(5.4.0)undec-7-ene, THF = tetrahydrofuran, DMPU = N,N-dimethyl propylene urea, TBCHD = 2,4,4,6-tetrabromo-2,5-cyclohexadienone.)

stereoselectivity. Treatment of **11** with $FeSO_4$ and I_2 followed by highly regioselective elimination afforded **12a** in 69% yield over two steps through alkoxy radical-induced β-fragmentation. **12a** could be readily transformed to 5,6-dihydro-glaucogenin C (**13**) via reduction and deprotection. This radical intermediate could also be trapped by adding 2,2,6,6-tetramethylpiperidin-1-yloxyl (TMPO) to give **12b** in 70% yield. Later, the same group accomplished the total synthesis of glaucogenin D (**3b**) using **12b** as the advanced substrate.[10b]

2.3 Total Synthesis of Cortistatin A

Cortistatins were isolated from the Indonesian marine sponge by Kobayashi and co-workers in 2006.[12] These marine steroidal alkaloids have attracted considerable attention from synthetic chemists[13] because of their unique structures and potential as anti-angiogenic agents. Cortistatin A (**14**) shows the strongest ability to selectively inhibit proliferation of HUVEC cells.[12] Structurally, cortistatins contain a common rearranged steroidal core, which could be biogenetically considered as an expansion of the B ring of normal steroids through incorporation of a C-19 angular methyl group into the rare oxabicyclo[3.2.1] octane B ring (Figure 1).

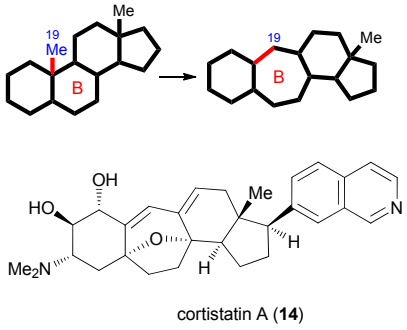


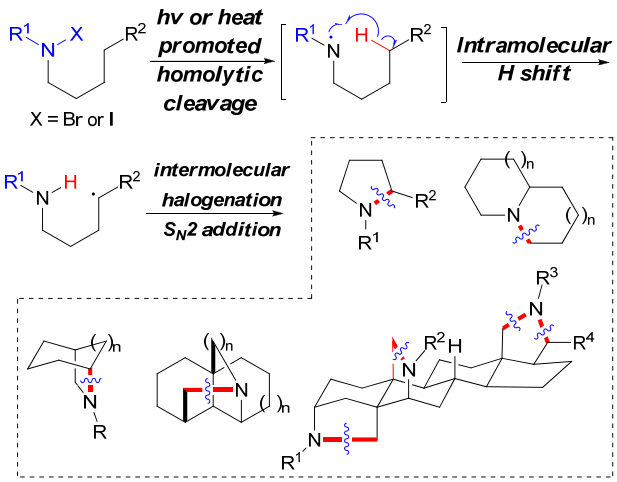
Figure 1. Structure of Cortistatin A.

In 2008, Baran and co-workers reported an elegant semisynthetic route to cortistatin A (**14**) from prednisone (**15**).[14] The biggest challenge of this synthetic design was how to achieve regiospecific functionalization of the angular C-19 methyl group in **15**, as well as the subsequent B ring expansion. The group first converted **15** to **16,** leaving the axial hydroxyl group at C-2 exposed as an initiator of selective C-H oxidation (Scheme 4). Irradiation of the mixture of **16** with $PhI(OAc)_2$ and Br_2 yielded an unstable dibromo alcohol, which was directly silylated with TMSCl to give **22** in 57% overall yield. This selective *gem*-dibromination proceeded through double oxygen-centered, radical-promoted C-H functionalization. The oxygen radical **17** formed readily from homolytic cleavage of alkyl hypoiodite, which promoted intramolecular hydrogen transfer from the C-19 angular methyl group. Treating **22** with DBU and LiCl gave the bromocyclopropane **23**, the precursor for the key ring expansion step. Regioselective fragmentation of the bromocyclopropane motif in **23** occurred via samarium diiodide-induced radical reaction, and the resulting enolate was trapped with 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCHD) to afford the α-bromo ketone **24**, the core skeleton of cortistatins.

2.4 Total Synthesis of Isoatisine

Nitrogen-centered, radical-promoted intramolecular C-H oxidation has also been studied extensively, and it has proven useful in the synthesis of alkaloids. These reactions normally proceed under acidic conditions in order to facilitate homolytic cleavage of the preformed N-halogen bond. The hydrogen shift is guided by the newly generated nitrogen-centered radical in the same way as described above for O-radicals. Suárez and co-workers simplified the HLF reaction and made it suitable for more labile molecules when they discovered that photolysis of phosphoramidate with iodosylbenzene and iodine under neutral conditions efficiently generates an N-radical rather than the preformed N-halogen amine.[15] This modification not only simplified the HLF reaction

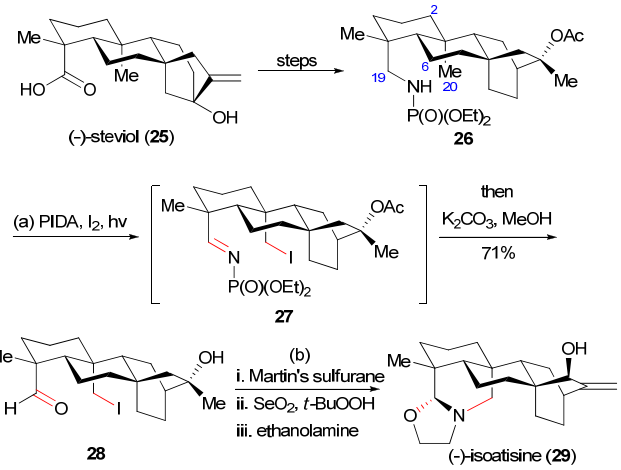
but also allowed its use with more sensitive molecules. The N-radical is then suitable for subsequent H-abstraction and oxidation, even in the case of substrates containing rigid skeletons and/or acyclic structures. This method has been used to efficiently construct various substituted pyrrolidines, fused bicyclic aza-rings, bridged aza-rings and steroidal alkaloids (Scheme 5).



Scheme 5. Nitrogen-centered, Radical-promoted Intramolecular C-H Oxidation.

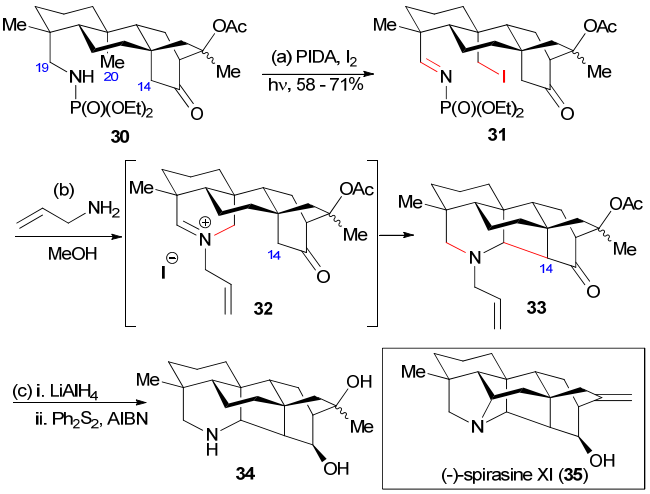
One example that shows the power of the HLF reaction was reported by Baran and co-workers in the synthesis of (−)-isoatisine and the core skeleton of hetidines.[16] Their synthetic analysis was based on the biogenetic relationships between the diterpenoids *ent*-atisane and related diterpenoid-alkaloids. The biggest challenge of this design was how to efficiently introduce nitrogen and selectively activate the C-20 angular methyl group in order to build bridged or caged hetero-rings. The group therefore selected *ent*-kaurane (-)-steviol (**25**) as the precursor of C-H oxidation, which they had already synthesized earlier.[17] As shown in Scheme 6, **25** was first converted to **26** with a directing group phosphoramidate at C-19, allowing subsequent C − H activation at C-20. Under Suárez conditions,[15] photolysis of **26** with PIDA and I_2 in DCE provided the iodo-imine intermediate **27**. In this process, the N-radical was generated through homolytic fragmentation of a hypothetical iodoamide intermediate, which selectively induced 1,7-hydrogen abstraction from C-20 instead of the typically more favorable 1,6-hydrogen abstraction from C-2 or C-6. Treating **27** directly with potassium carbonate and methanol without purification yielded iodo-aldehyde **28**, which was effectively transformed to (−)-isoatisine (**29**) through a three-step sequence of selective dehydration, allylic oxidation and condensation with ethanolamine.

The core skeleton of hetidines **34** was built through a similar strategy from **30,** which contains the basic structural features and a directing group (Scheme 7). Intramolecular C-H oxidation of the C-20 methyl group was effective and yielded a mixture of iodo-imine **31** and its regio-isomer C-14

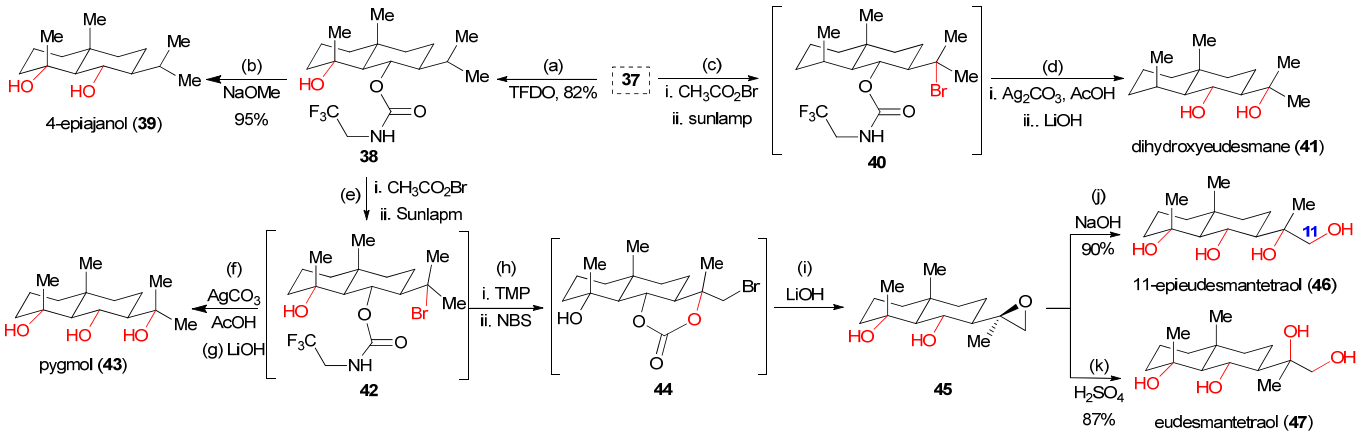


Scheme 6. Total Synthesis of Isoatisine. *Reagents and conditions*: (a) PIDA (4.0 equiv), I_2 (5.0 equiv), DCE, 90-W sunlamp, 40 °C, 40 min, then K_2CO_3 (25.0 equiv), MeOH, 65 °C, 36 h, 71%; (b) i. Martin's sulfurane (2.0 equiv), CH_2Cl_2, −78 to 23 °C, ii. SeO_2 (4.0 equiv), *t*-BuOOH (30.0 equiv), CH_2Cl_2, 0 °C, 1 h, 63%, 2 steps, iii. ethanolamine (3.0 equiv), MeOH, 23 °C,89%. (PIDA = phenyliodine diacetate, DCE = 1,2-dichloroethane.)

iodination product in moderate yield. Condensing **31** with allylamine in methanol at 60 °C generated the iminium **32**, which underwent deprotonation and isomerization to form the C-20 iminium species and induced the key transannular Mannich cyclization, ultimately giving **33** in 78% yield. Reduction of the ketone and deprotection of the allyl group afforded the cage-shaped product **34,** which has the basic structure of hetidines.



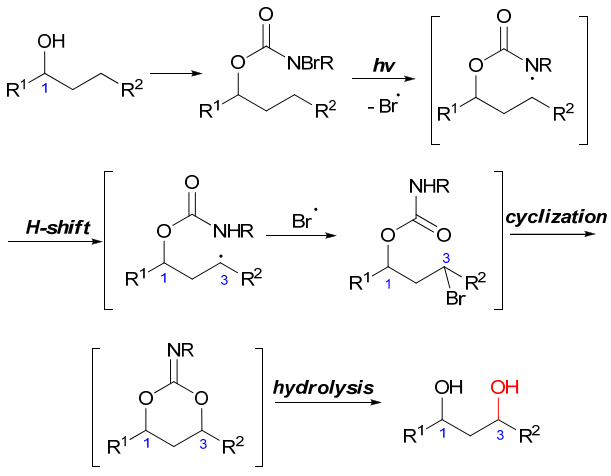
Scheme 7. Synthetic Studies of Spirasine XI. *Reagents and conditions*: (a) PIDA (4.0 equiv), I_2 (5.0 equiv), DCE, 90-W sunlamp, 35 °C, 1 h, 58−71%; (b) allylamine (5.0 equiv), MeOH, 60 °C, 12 h, 78%; (c) i. $LiAlH_4$ (4.0 equiv), ether, 0 °C, 1 h, 62%, ii. Ph_2S_2 (1.5 equiv), AIBN (0.2 equiv), benzene, 80 °C, 2 h, 78%. (PIDA = phenyliodine diacetate, DCE = 1,2-dichloroethane, AIBN = azobis(isobutyronitrile).)



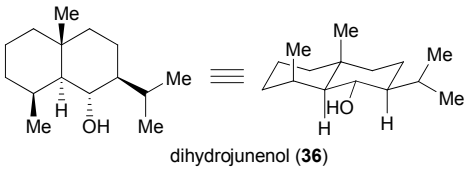
Scheme 10. Synthesis of the Eudesmane Family of Terpenes. *Reagents and conditions*: (a) TFDO (1.0 equiv), CH_2Cl_2, -20 °C, portion-wise addition of TFDO over 30 min, then additional 30 min, 82%; (b) NaOMe (5.0 equiv), MeOH, 70 °C, 2 h, 95%; (c) i. CH_3CO_2Br (1.0 equiv), CH_2Cl_2, 0 °C, 5 min; $PhCF_3$, 100-W sunlamp, rt, 10 min; (d) i. Ag_2CO_3 (1.2 equiv), CH_2Cl_2, rt, 30 min, then aqueous acetic acid, rt, 30 min, ii. LiOH (10.0 equiv), THF/H_2O, rt, 10 min, 43% (39% yield recovered 37); (e) CH_3CO_2Br (1.0 equiv), CH_2Cl_2, 0 °C, 5 min; $PhCF_3$, 100-W sunlamp, 20 min; (f) Ag_2CO_3 (1.2 equiv), CH_2Cl_2, rt, 30 min, then aqueous acetic acid, rt, 30 min; (g) LiOH (10.0 equiv), THF/H_2O, rt, 10 min, 52% (30% recovered 38); (h) i. TMP (2.0 equiv), toluene, 80 °C, 12 h, ii. NBS (2.0 equiv), CH_2Cl_2, rt, 6 h, then aqueous acetic acid, rt, 30 min; (i) LiOH (10.0 equiv), THF/H_2O, rt, 10 min, 27% (37% yield recovered 38); (j) 3 M NaOH, DMSO, 80 °C, 2 h, 90%; (k) 0.1 M H_2SO_4, DME, rt, 1 h, 87%. (TFDO = methyl(trifluoromethyl)dioxirane, THF = tetrahydrofuran, TMP = 2,2,6,6-tetramethylpiperidine, NBS = N-bromosuccinimide, DMSO = dimethylsulphoxide, DME = 1,2-dimethoxyethane.)

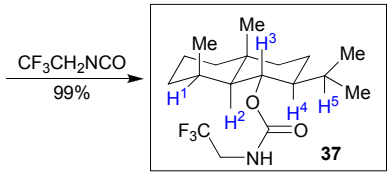
2.5 Synthesis of the Eudesmane Family of Terpenes

The mechanism of the HLF reaction served as the inspiration for Baran and co-workers to develop a method to convert alcohol to 1,3-diol via heteroatom-centered, radical-promoted intramolecular C-H functionalization (Scheme 8).[18] To realize the site-selective activation at C-3, a unique trifluoroethyl-substituted carbamate was introduced as a directing group to initiate the unfavorable 1,6-hydrogen atom transfer (via a seven-membered transition state). The mild reaction was performed in neutral solution under visible light and gave the desired bromide in good yield. Treating the bromide with Ag_2CO_3 generated the cyclized iminocarbonate, which was hydrolyzed using acetic acid and K_2CO_3 to provide 1,3-diol. This practical method allows preparation of 1,3-tertiary and benzylic diols with excellent chemo- and regioselectivity.



Scheme 8. Heteroatom-centered, Radical-promoted Intramolecular C-H functionalization to Prepare 1,3-diol.





Scheme 9. Preparation of 37. *Reagents and conditions*: CF_3CH_2NCO (1.0 equiv), Py (4.0 equiv), DMAP (cat.), CH_2Cl_2, rt, 1 h, 99%. (DMAP = 4-dimethylaminopyridine)

The synthetic potential of this methodology was demonstrated when it was applied to syntheses of the eudesmane family of terpenes.[19a] The gram-scale preparation of dihydrojunenol (**36**), with the basic carbon skeleton of eudesmane terpenes, was achieved through a nine-step sequence.[19b] The next challenge was how to induce the regio- and stereo-selective C-H (1, 4 and 5) oxidation with the only functional group in **36**. To achieve this selectivity, the hydroxyl group was transformed to carbamate

37 (Scheme 9). According to Curci's protocol, methyl-(trifluoromethyl)-dioxirane (TFDO) was selected as an oxidant to achieve site-specific intermolecular oxidation of the C-H_1 bond (Scheme 10).[20] Surprisingly, **38** bearing the hydroxyl group with the desired stereochemistry was obtained in 82% yield on a gram scale. Mechanistic studies to explain the selectivity between C-H_1 and C-H_5 of in this C-H oxidation suggest that it may be originated from strain release in going to the electrophilic transition state of the oxidation.[19c] Basic hydrolysis of **38** gave 4-epiajanol (**39**). A carbamate-directed intramolecular radical reaction was used to selectively oxidize the C-H_5 bond. Site-specific bromination of **37** to **40** was achieved under optimized conditions, and subsequent cyclization and hydrolysis efficiently converted **40** to dihydroxyeudesmane (**41**). Using the same procedure, **38** could be further oxidized to generate other terpenes in the eudesmane family, including pygmol (**43**), 11-epieudesmantetraol (**46**) and eudesmantetraol (**47**) with higher oxidation states.

2.6 Conclusion

Long after its discovery, radical-promoted intramolecular remote C-H oxidation continues to develop as a powerful method to selectively oxidize C (sp^3)-H bonds for the synthesis of complex natural molecules. The advantages of this approach include relatively mild conditions, tolerance of diverse functional groups and elegant regioselectivity. The stereochemistry of the reaction is controlled mainly by the chemical microenvironment of the reacting groups, which to some extent limits the reaction scope. These issues should be addressed in future studies that explore selective intermolecular reaction models and the feasibility of enantioselective catalytic processes.

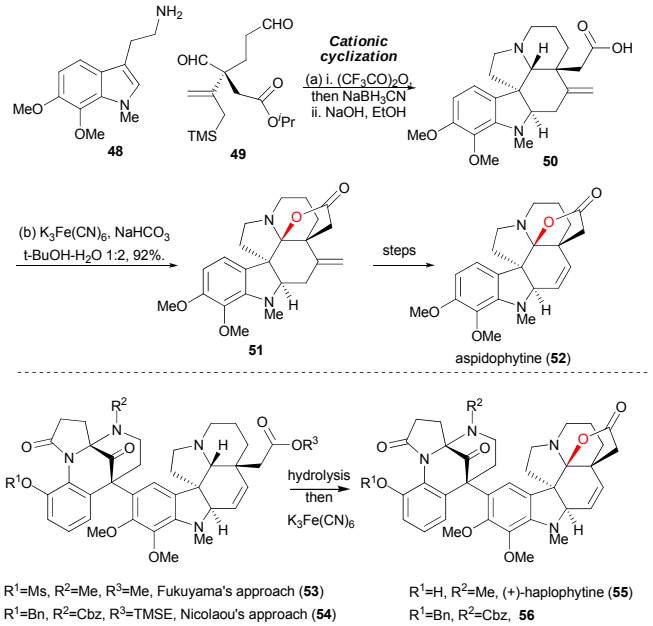
3 Selective Oxidation of a C-H bond Adjacent to an Amino Group

3.1 Introduction

Nitrogen-containing natural products form a large family and are produced by different natural sources, including plants, animals, bacteria and fungus. They play an important role in the lives of these organisms, and they also account for most small-molecule therapeutic agents. Since nitrogen can adopt oxidation states ranging from -3 to +5, functional groups and heterocycles containing this atom can adopt more diverse and complex structures than molecules containing other heteroatoms. As a result, total synthesis of this family of natural products is challenging. Different oxidants are required to achieve higher oxidation states; oxidations are always accompanied by hydrogen shift, dehydrogenation and C-H oxidation. For instance, hemiaminal moieties can be formed using site-selective C-H oxidation adjacent to an amino group. This strategy has been used in the synthesis of the indole alkaloids aspidophytine and haplophytine, as well as in the synthesis of the pyrrole-imidazole alkaloids axinellamine A, B, massadine and massadine chloride.

3.2 Synthesis of Haplophytine

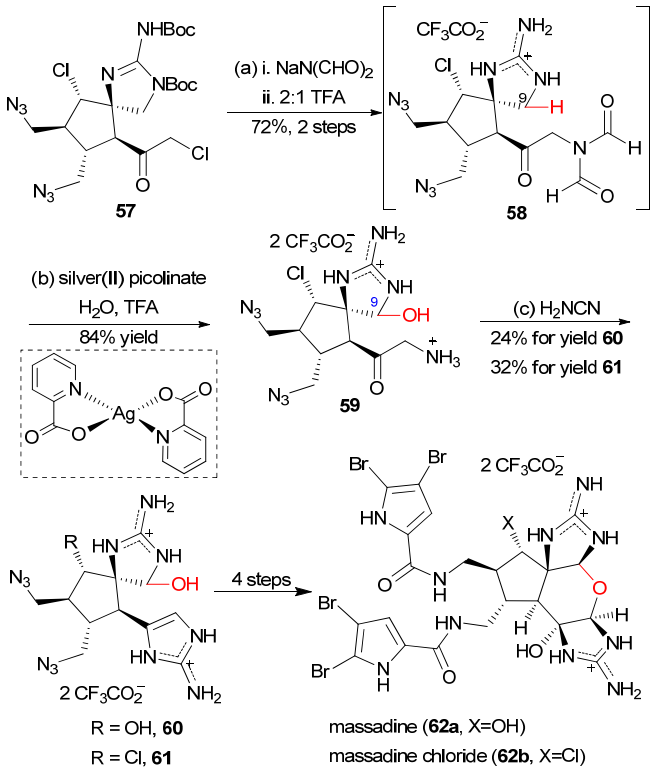
Haplophytine (**55**) was isolated from the dried leaves of the Mexican plant *Haplophyton cimicidum* by Snyder and co-workers in 1952.[21] Using x-ray analysis, Yates, Cava, and co-workers confirmed the dimeric structure of **55** as two segments connected by one C-C bond.[22] The monomeric indole alkaloid aspidophytine (**52**) was obtained by acidic degradation of (+)-haplophytine (**55**). The first breakthrough in synthesizing this family of alkaloids came when Corey and co-workers generated aspidophytine (**52**) in 1999.[23] The pentacyclic skeleton **50** was constructed using a convergent approach from **48** and **49** via an immonium cation-promoted cascade process (Scheme 11). Site-selective C-H oxidation of the tertiary amine **50** was used to form the lactone moiety. Treating **50** with potassium ferricyanide led to smooth intramolecular lactonization, affording **51** in 92% yield. Mechanistic studies by Burrows and co-workers[24] suggest that the reaction of ferricyanide with electron-rich trialkylamines involves one-electron abstraction that generates a radical cation intermediate. This intermediate selectively activates the adjacent C-H bond and promotes hydrogen abstraction, generating an iminium species that is trapped by the neighboring carboxylic acid, ultimately yielding **51**. This strategy has also been used in the total synthesis of haplophytine (**55**), reported independently in 2009 by Fukuyama and Tokuyama[25] and by Nicolaou[26] (Scheme 11).



Scheme 11. Synthesis of Haplophytine. *Reagents and conditions*: (a) i. CH_3CN, 23 °C, then $(CF_3CO)_2O$ (2.0 equiv), 0 °C, then $NaBH_3CN$ (5.0 equiv), 23 °C, 66%, ii. NaOH (60.0 equiv), EtOH, 75 °C, 20 h, 88%; (b) $K_3Fe(CN)_6$ (7.5 equiv), $NaHCO_3$ (15.0 equiv), *t*-BuOH-H_2O 1:2, 92%.

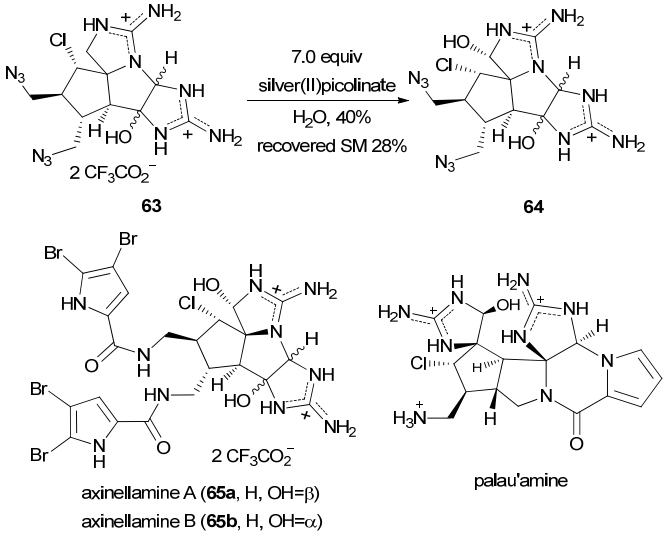
3.3 Synthesis of Axinellamine A, B, Massadine and Massadine Chloride

Axinellamine A and B (**65a**, **65b**),[27] massadine (**62a**) and massadine chloride (**62b**)[28, 29] are representatives of the family of pyrrole-imidazole alkaloids, which are among the most complex marine natural products isolated to date. Synthesizing these molecules is a major challenge because of their complex structure, which involves a tetracyclic bisguanidine core with eight contiguous stereocenters, and because of their highly polar nature. Baran and co-workers reported the elegant synthesis of **65a**-**b** and **62a**-**b** using a selective C-H oxidation strategy.[30, 31] The precursor **58** of C-H oxidation was prepared from **57** through a two-step sequence involving introduction of diformylamide and Boc-removal (Scheme 12). Extensive screening of reaction conditions identified silver (II) picolinate as the optimal oxidant for this C-H oxidation. Treating **58** with silver(II) picolinate in 10% TFA/H_2O gave the desired hemiaminal **59** in 84% isolated yield after deformylation. The reaction mechanism remains unclear, though TFA is known to accelerate the process significantly and increase conversion. Similar conditions for selective C-H oxidation of **63** were used



Scheme 12. Synthesis of Massadine and Massadine Chloride. *Reagents and conditions*: (a) i. sodium diformylamide (1.2 equiv), TBAI (0.1 equiv), THF, 23 °C, 2 h, 72%, ii. 2:1 CF_3CO_2H/CH_2Cl_2, 23 °C, 2 h, quant; (b) silver(II) picolinate (2.5 equiv), 9:1 H_2O/CF_3CO_2H, 23 °C, 35 min, then CF_3CO_2H (to 1:1 v:v), 38 °C, 18 h, 84%; (c) cyanamide (excess), 0.2 M NaOH (to pH 5.0), 78 °C, 2 h, 32% for **61**, 24% for **60**. (TBAI = tetrabutylammonium iodide, THF = tetrahydrofuran.)

in the synthesis of axinellamine A (**65a**) (Scheme 13).[31] Without TFA, the reaction of **63** with silver(II) picolinate had to be heated to 50 °C in H_2O, which gave two diastereomers of tetracycle **64** in 40% yield. Hemiaminal **59** was then converted to **61** with its hydroxy analogue **60** via formation of the second aminoimidazole ring. These advanced intermediates could be transformed, respectively, into massadine (**62a**) and massadine chloride (**62b**) in four more steps.[30a] This silver(II)-mediated selective oxidation of a C-H bond adjacent to an amino group is a reliable method for constructing hemiaminal groups in complex molecules with remarkable chemoselectivity.[30b] Using this protocol, Baran's group was able to achieve the total synthesis of palau'amine, the most challenging member of pyrrole-imidazole alkaloids.[31e] Baran and co-workers detailed the journey towards synthesis of this family of natural products in 2011.[31f]



Scheme 13. Synthesis of Axinellamine A and B. *Reagents and conditions*: silver(II) picolinate (7.0 equiv), H_2O, 50 °C, 19 h, 30% one diastereomer, 10% other diastereomer (28% recovery of starting material for minor diastereomer).

3.4 Conclusion

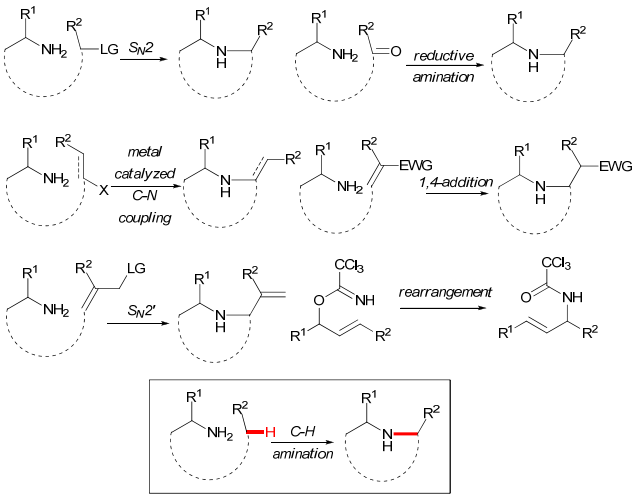
These two examples reveal the challenges of achieving the desired oxidation state during total synthesis of alkaloids. Unfortunately a general technique for oxidizing a C-H bond next to an amino group has yet to be developed. Since this bond cannot be strictly defined as inert, reaction conditions and oxidants must be screened in each particular case. Future studies are needed to discover more reactions that expand the toolbox of this C-H oxidation.

4 Metal-Catalyzed, Nitrenoid-Directed C-H Amination

4.1 Introduction to the Reactions

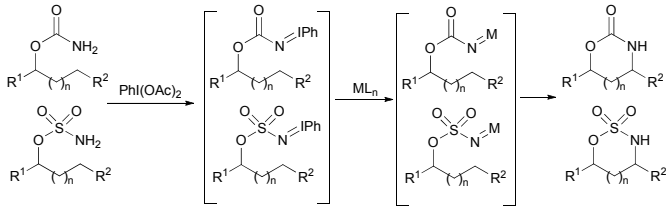
Key to the synthesis of nitrogen-containing natural products is C-N bond formation. This has traditionally been achieved

via reactions of nitrogen-based reactive groups with other functional groups; these reactions involve inter- or intramolecular S_N2 displacement, reductive amination, metal-catalyzed C-N bond coupling, 1,4-addition and S_N2' displacement (Scheme 14). In addition, some rearrangements of derivatives of allylic alcohols, carbonyls or esters via Curtius, Beckmann, Overmann and Schmidt reactions generate amines or amides. A disadvantage of these traditional approaches is that they sometimes add excessive steps to the overall synthesis in order to introduce desired functionalities.[32] An atom-economical[33] alternative that improves overall synthetic efficiency is direct installation of nitrogen into the hydrocarbon framework via selective C–H amination.



Scheme 14. Strategies of C-N bond formation.

Since its first discovery by Breslow and Gellman in the 1980s,[34] metal-catalyzed, nitrenoid-directed C-H amination has been studied extensively.[35] Originally, the necessary aryliodinane intermediates had to be preformed. Later, the groups of Che[36] and Du Bios[37] developed a one-pot operation in which aryliodinanes and metallonitrenoids form in situ, followed by direct C-H insertion. Currently, intramolecular C-H amination is used mainly in organic syntheses in which the starting substrates are readily available sulfamate esters or carbamates (Scheme 15). Treating these substrates with phenyliodine diacetate [$PhI(OAc)_2$] generates an iodoimine intermediate, which is decomposed by a metal catalyst to form the metallonitrene. Then direct C-H insertion occurs to form the C-N bond and afford the desired cyclic product. Studies of catalysts, regioselectivity, reaction conditions, substrate scope and synthetic applications of C-H amination have been explored by Du Bios and co-workers.[38]



Scheme 15. Metal-catalyzed, Nitrenoid-directed C-H Amination.

4.2 Total Synthesis of Tetrodotoxin

Tetrodotoxin (**66**) was isolated in 1909 from the ovaries of the puffer fish (*Spheroides rubripes*),[39] and it shows significant potential as a selective blocker of voltage-gated Na^+ ion channels. The highly complex structure features a densely functionalized skeleton including an oxygenated cyclohexane, a unique ortho-acid and cyclic guanidine aminal moiety. The total synthesis poses substantial structural challenges: installation of a highly oxidized skeleton, and installation of a bridgehead nitrogen-containing quaternary center at C-8a. The first total synthesis of **66** was achieved in 1972 by Kishi and co-workers, who introduced the C-N bond at an early stage via Beckmann rearrangement (Figure 2).[40] Thirty years later, Isobe and co-workers developed the first asymmetric approach to synthesizing **66,** in which they used intramolecular conjugate addition between the carbamate and unsaturated ester group to install the bridgehead C-N bond.[41] In 2003, Du Bios and co-workers reported another approach involving stereospecific metal-mediated nitrene and carbene C-H insertion reactions.[42]

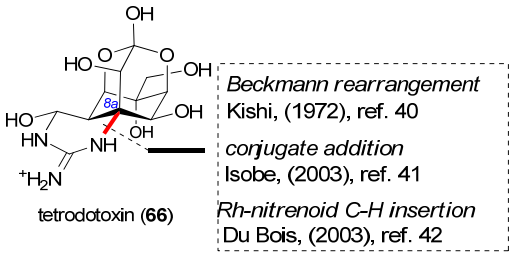
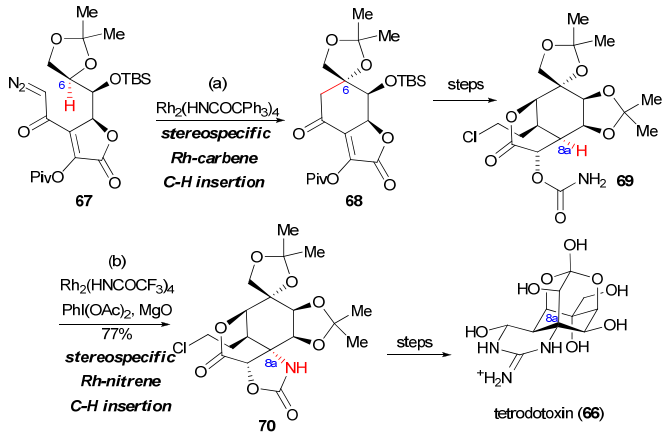


Figure 2. Synthetic Studies of Tetrodotoxin.

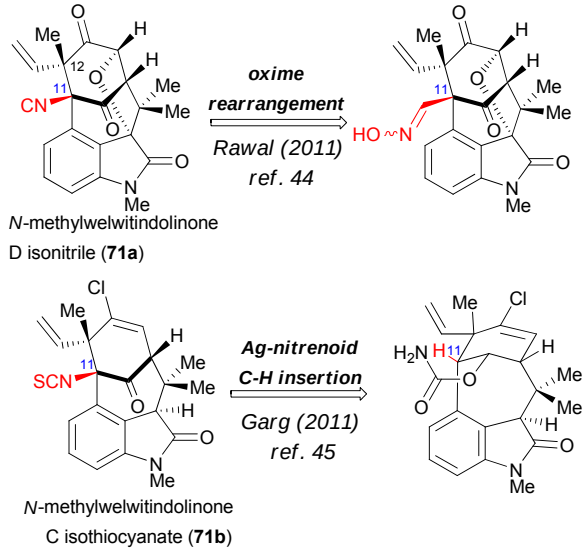
In their synthesis, Rh-catalyzed C-H insertion at C-6 was applied to regioselectively close the six-membered ring and furnish the functionalized cyclohexanone (Scheme 16). Treating diazoketone **67** with 1.5 mol % Rhacetamide catalyst $Rh_2(HNCOCPh_3)_4$ afforded the desired cyclic product **68**. Stereospecific C-H amination then installed the nitrogen-containing quaternary center at C-8a. After oxidizing carbamate **69** with $PhI(OAc)_2$, the newly formed aryliodinane intermediate reacted efficiently with $Rh_2(HNCOCPh_3)_4$ to give Rh-nitrenoids, which underwent stereoselective C-H amination to give the desired adduct **70** in 77% yield.



Scheme 16. Total Synthesis of Tetrodotoxin. *Reagents and conditions*: (a) $Rh_2(HNCOCPh_3)_4$ (1.5 mol%), CCl_4; (b) $Rh_2(HNCOCF_3)_4$ (10 mol%), $PhI(OAc)_2$, MgO, C_6H_6, 65 °C, 77%.

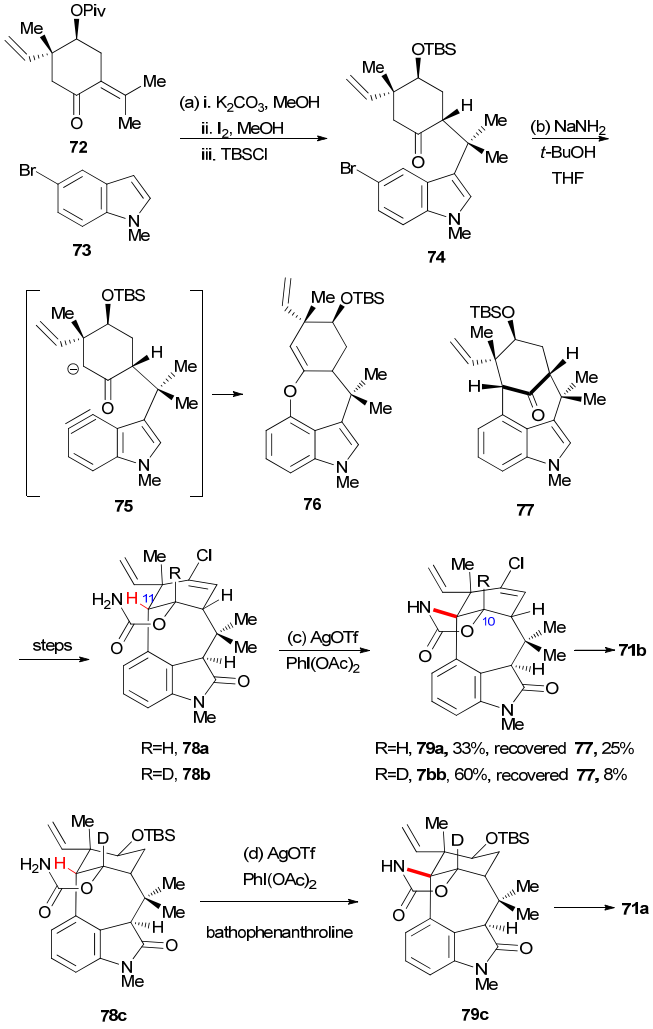
4.3 Total Synthesis of *N*–Methylwelwitindolinone C isothiocyanate

The welwitindolinones belong to a family of polycyclic oxindole-containing alkaloids isolated from the blue-green algae *Hapalosiphon welwitschii* and *Westiella intricate*.[43] This alkaloid family shares a bicyclo[4.3.1]decane ring fixed within a densely functionalized tetracyclic skeleton. A challenge to the synthesis was constructing the bridgehead isothiocyanate or isonitrile groups on C-11 adjacent to the quaternary stereocenter at C-12. A breakthrough towards the total synthesis of *N*-methylwelwitindolinone D isonitrile (**71a**) came in 2011 when Rawal and co-workers derived the isonitrile moiety from the neopentyl aldehyde via an oxime rearrangement (Scheme 17).[44] In the same year, Garg and co-workers reported the synthesis of *N*-methylwelwitindolinone C isothiocyanate (**71b**) using a late-stage intramolecular nitrene insertion to furnish the C-N bond at the C-11 bridgehead.[45]



Scheme 17. Synthetic Studies of Welwitindolinones.

The synthesis started from an I_2-promoted addition of bromoindole **73** to enone **72** to couple two fragments and yield the adduct **74** in 54% yield over two steps (Scheme 18). After TBS-protection of the hydroxyl group, **75** was used in the key indolyne cyclization. Treating **75** with $NaNH_2$ and *t*-BuOH in THF afforded the desired indolyne adducts **77** and O-arylated product **76** (2.5:1 ratio) in 46% yield via an intramolecular addition of an enolate onto an *in situ*-generated "indolyne" intermediate **75**. The major product **77** was then transformed into carbamate **78a** through 9 steps, including introduction of the vinyl chloride and oxindole moieties. To form the C-N bond, C-H insertion promoted by



Scheme 18. Total Synthesis of *N*–Methylwelwitindolinone C isothiocyanate**.** *Reagents and conditions*: (a) i. K_2CO_3 (2.5 equiv), MeOH, 60 °C, ii. I_2 (0.2 equiv), MeOH, 23 °C, 54%, 2 steps, iii. TBSCl (3.0 equiv), imidazole (5.0 equiv), DMAP (1.0 equiv), TBAI (1.0 equiv), DMF, 100 °C, 90%; (b) $NaNH_2$ (10.5 equiv), *t*-BuOH (3.5 equiv), THF, 23 °C, 46%; (c) AgOTf (0.5 equiv), $PhI(OAc)_2$ (2.0 equiv), bathophenanthroline (0.5 equiv), CH_3CN, 82 °C, 33%, (**79a** from **78a** 25% recovered **77**), (60%, 79b from 78b, 8% recovered **77**); (d) AgOTf, $PhI(OAc)_2$, bathophenanthroline, CH_3CN, 82 °C, 70%. (TBSCl=t-butyldimethylchlorosilane, DMAP=4-dimethylaminopyridine, TBAI = tetrabutylammonium iodide, DMF = N,N-dimethylformamide, THF = tetrahydrofuran.)

crucial metallonitrenoids was investigated. Rh catalysis proved ineffective for this transformation, leading only to recovery of substrates. In contrast, using AgOTf in the presence of ligand bathophenanthroline and $PhI(OAc)_2$ converted **78a** to the desired oxazolidinone **79a** in 33% yield; ketone **77** was recovered in 25% yield as the major byproduct. The recovered **77** presumably formed via undesired insertion of the intermediate nitrene species into the C–H bond at C-10. Remarkably, introducing a deuterium at C-10 dramatically improved the efficiency of this cyclization. Exposing **78b** to the same reaction conditions as for nitrene insertion yielded the desired **79b** in 60% yield, and ketone **77** was recovered in 8% yield. These results indicated that a deuterium kinetic isotope effect may improve the selectivity of C-H functionalization. Further transformations from **79a** led to the total syntheses of **71b** and *N*-methylwelwitindolinone C isonitrile.[45d] The same strategy for transforming **78c** into **79c** allowed the successful total synthesis of *N*-methylwelwitindolinone D isonitrile (**71a**) in 2012.[45b]

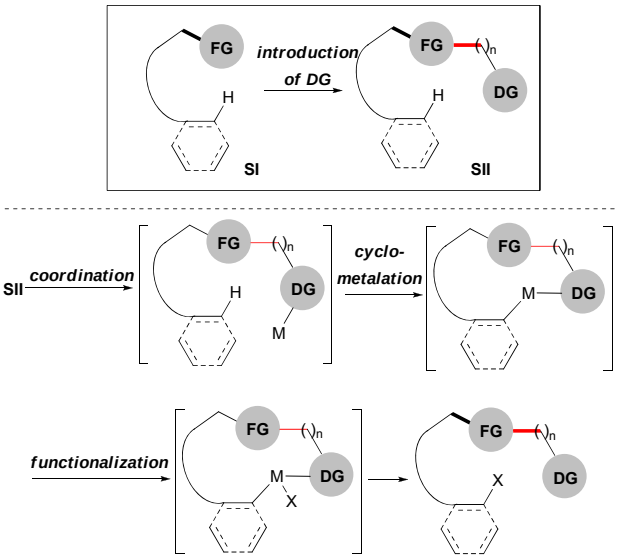
4.4 Conclusion

Metal-catalyzed, nitrenoid-directed C-H amination provides a new approach for forming nitrogen-containing quaternary stereocenters. The syntheses of tetrodotoxin and welwitindolinones demonstrated well the power of C-H functionalization in the synthesis of complex natural products. This operation allows a greater range of reactive functional groups to be masked as inert C–H bonds than can be done using traditional transformations. In this way, C-H functionalization avoids unnecessary side reactions and simplifies the structures of reaction components.

5 Metal-Catalyzed C–H Oxidation

5.1 Introduction to the Reactions

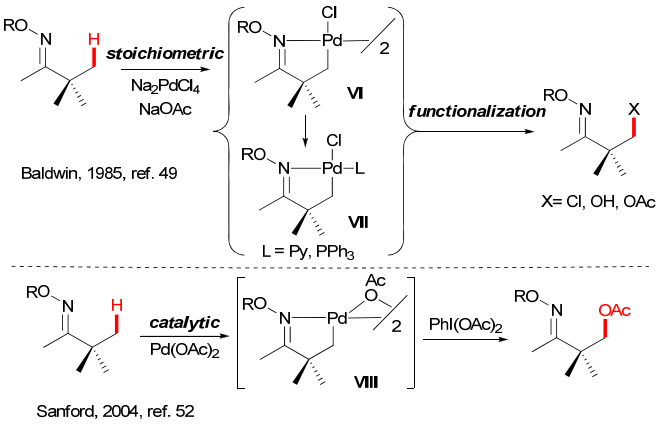
One challenge in metal-catalyzed C-H functionalization is selectively activating the inert C-H bond in order to generate a reactive C-M bond. This selective activation is always achieved using a directing group (DG), which coordinates the metal and delivers the catalyst selectively to a proximal C-H bond. Numerous directing groups have been developed for C-H activation; most are nitrogen- or oxygen-centered heterocycles or functional groups (FG).[46] Synthetic utility is greatest when the directing group lies within an existing functional group on a substrate. Otherwise, directing groups must first be installed in the substrate and then removed after C-H activation, necessitating two additional steps. Some directing groups may be transformed into other functionalities necessary for subsequent transformations or cleared away by traceless removal. As shown in Scheme 19, metal-catalyzed C-H activation normally involves a sequence of coordination, C-M bond formation via cyclometalation and C-M bond functionalization to yield a C-X bond. This general strategy has been used extensively in studies of C-H functionalization, and methodologies for metal-catalyzed direct transformation of C-H bonds to C-O, C-N, C-X (halogen), C-S, and C-C bonds have now become reality. This strategy has begun to influence the design of natural product total synthesis.



Scheme 19. General Process of Metal-Catalyzed C–H Oxidation.

5.2 Total Synthesis of Jiadifenolide

Jiadifenolide was isolated from the flowering plant *Illicium jiadifengpi* by Fukuyama and co-workers in 2009, and it shows potent neurotrophic properties.[47] It is a secoprezizaane-type sesquiterpene that has a caged architecture featuring two γ-lactones and seven contiguous stereocenters. The challenges of this synthesis were constructing the dense functionalities, high oxidation state structure and stereocenters. In 2014, Sorensen and co-workers reported an enantiospecific synthesis of jiadifenolide using oxime-directed C-H oxidation as a key transformation.[48] This methodology can be traced back to 1985, when Baldwin and co-workers used cyclopalladation reactions to study the functionalization of unactivated methyl groups (Scheme 20).[49] Treating pinacolone oxime with a stoichiometric amount of disodium tetrachloropalladate-sodium acetate in ethanol[50] gave the stable dimeric organopalladium species **VI**. Treating **VI** with other ligands, such as pyridine or triphenylphosphine, converted it to monomeric complexes (**VII**). The reactive C-Pd bond could be further functionalized to give the corresponding functional groups through chlorination or oxidation. This method has been used by Baldwin[49] to modify lupanone, and by Gribble and co-workers[51] to synthesize *β*-boswellic acid analogues. In 2004, Sanford and co-workers further studied this reaction. They developed a Pd-catalyzed C-H oxidation of unactivated sp^3 bonds using $PhI(OAc)_2$ as a stoichiometric oxidant to yield the acetoxylated product. Mechanistic studies suggest that the reaction proceeds through a two-electron oxidation process, involving a $Pd^{(II/IV)}$ transformation. [52]



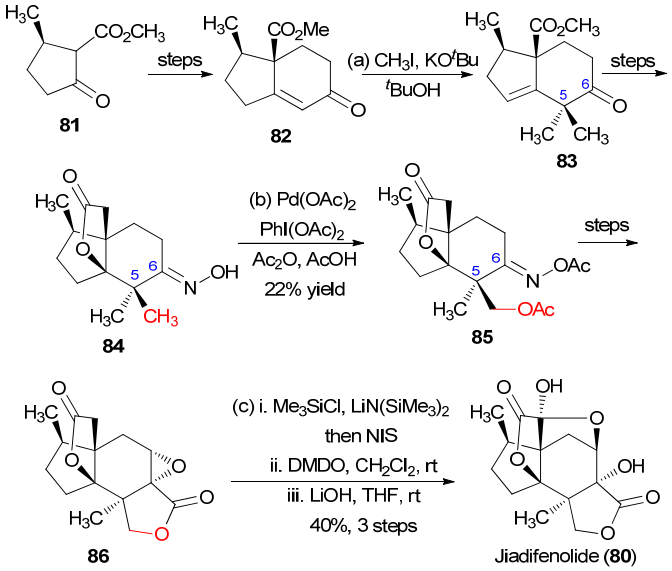
Scheme 20. Sp^3 C-H Oxidation via Cyclopalladation.

During Sorensen's synthesis of **80**, a selective C-H oxidation was planned to distinguish the dimethyl groups on C-5 and install the hydroxyl methyl group (Scheme 21). Bicyclic enone **82** was efficiently prepared from **80** through the Michael addition and ring-forming aldol condensation steps, which was subsequently converted to **83** via a base-mediated deconjugative dimethylation. Once the lactone was generated, the carbonyl group on C-6 was transformed into oxime as a directing group to afford **84**. Then selective oxidation of the methyl group at C-5 in **84** was attempted using stoichiometric or catalytic palladium. When Baldwin's conditions were applied, the major isomer was the undesired C-5 epimer. When Sanford's catalytic process was used, a mixture of two diastereomers along with overoxidized products were achieved, and the desired **85** was isolated in 22% yield. The newly formed hydroxylmethyl group was used to build another fused lactone **86**, which was further transformed into Jiadifenolide (**80**).

Synthetic studies of **80** and related natural products have also been carried out by the groups of Danishefsky,[53] Theodorakis,[54] Paterson and Dalby,[55] and more recently by Shenvi[56] and Zhang.[57] In contrast to other approaches, Sorensen's strategy uses selective C-H oxidation to furnish the hydroxyl methyl group needed for constructing the γ-lactone moiety. Though this strategy provides only moderate overall efficiency and yield, it is a bold innovation that provides new possibilities for C-H bond activation in the synthesis of complex molecules.

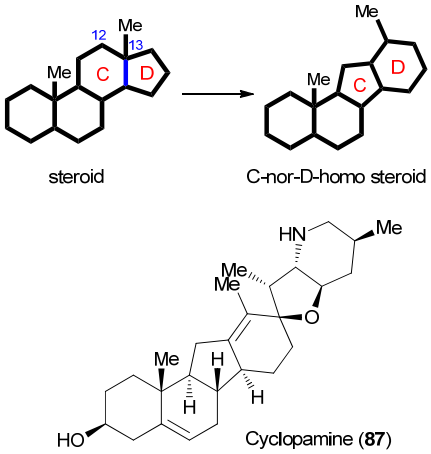
5.3 Total Synthesis of Cyclopamine

Cyclopamine (**87**) is a famous veratrum alkaloid, first isolated from corn lily (*Veratrum californicum*).[58] It was identified as the causative agent of the "malformed lamb disease" that gave rise to newborn lambs with a single eye in the middle of their foreheads in Idaho, USA, in the 1950s. The molecular target of cyclopamine is Smoothened (Smo), a seven-pass transmembrane protein that regulates the activity of the

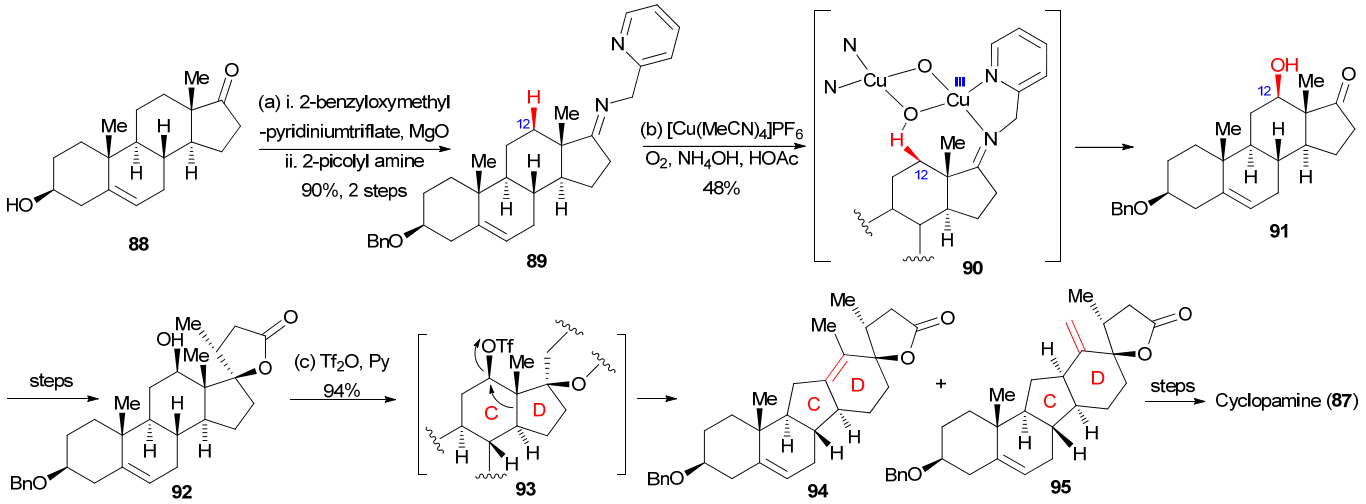


Scheme 21. Total Synthesis of Jiadifenolide. *Reagents and conditions*: (a) CH_3I (6.0 equiv), KO^tBu (3.1 equiv), ^{t}BuOH, r.t., 91%; (b) $Pd(OAc)_2$ (0.05 equiv), $PhI(OAc)_2$ (1.5 equiv), 1:1 Ac_2O/AcOH, 100 °C, 12 h, 22%; (c) i. Me_3SiCl (2.5 equiv), $LiN(SiMe_3)_2$ (2.1 equiv), THF, -78 °C, then NIS (1.1 equiv), ii. DMDO (0.05 M in acetone, 6.0 equiv), CH_2Cl_2, rt, iii. LiOH (2.0 equiv), THF, rt, 40%, 3 steps. (THF = tetrahydrofuran, NIS = N-iodosuccinimide, DMDO = dimethyl dioxirane.)

Hedgehog (Hh) signal transduction pathway.[59] Small-molecule inhibitors of Smo have attracted significant interest from chemists and biologists because of their drug potential. Cyclopamine contains unusual structural features, including C-nor-D-homo tetracyclic rings, a highly substituted furan ring and a piperidine unit. Biogenetically, C-nor-D-homo steroids may be derived from steroids via C ring contraction and D ring expansion by one carbon resulting from C-13→C-12 migration. A Merck research group first reported the biomimetic rearrangement of 12*β*-hydroxy steroids, generating the core skeleton of C-nor-D-homo steroid (Scheme 22).[60]

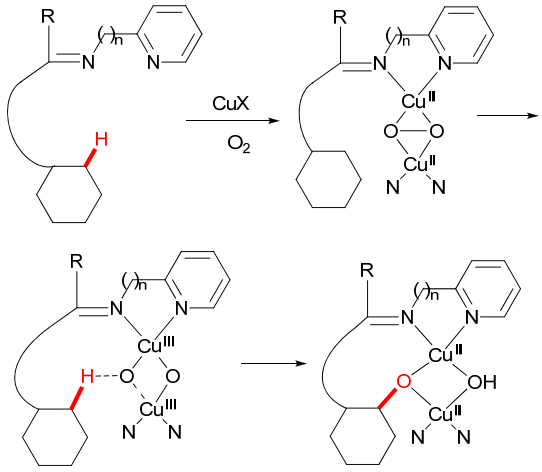


Scheme 22. Structure of Cyclopamine.



Scheme 24. Total Synthesis of Cyclopamine. *Reagents and conditions*: (a) i. 2-benzyloxymethylpyridinium triflate (2.0 equiv), MgO (2.0 equiv), $PhCF_3$, 85 °C, ii. 2-picolyl amine (5.0 equiv), *p*-TsOH (2.5 mol%), toluene, reflux, 90% (95% brsm), 2 steps; (b) $[Cu(MeCN)_4]PF_6$ (1.2 equiv), acetone, then O_2 (1 atm), then NH_4OH, then HOAc, MeOH, 48% (57% brsm); (c) Tf_2O (2.0 equiv), pyridine, 0 °C to 50 °C, 94% (3:7 ratio of **94** and **95**).

In 2009, Giannis and co-workers used this biogenetic approach to develop a synthesis of cyclopamine from a commercially available steroid dehydro-*epi*-androsterone (**88**).[61] Cu/O_2-promoted C-H hydroxylation was used to obtain the 12*β*-hydroxy derivative of **88.** This hydroxylation had previously been studied by Schönecker and co-workers using a bidentate pyridylethylamino as directing group.[62] Mechanistic studies by Réglier[63] and Schönecker[62] suggest that this selective C-H activation follows a different path than general metal-catalyzed C-H activation. Instead of C-Cu bond formation, this path may involve hydrogen abstraction induced by the Cu^{III}-O_2 species that forms *in situ* (Scheme 23). After protecting the hydroxyl group as benzyl ether, the carbonyl group at C-7 in **88** was condensed with 2-picolylamine to give **89** in 90% yield over 2 steps (Scheme 24).

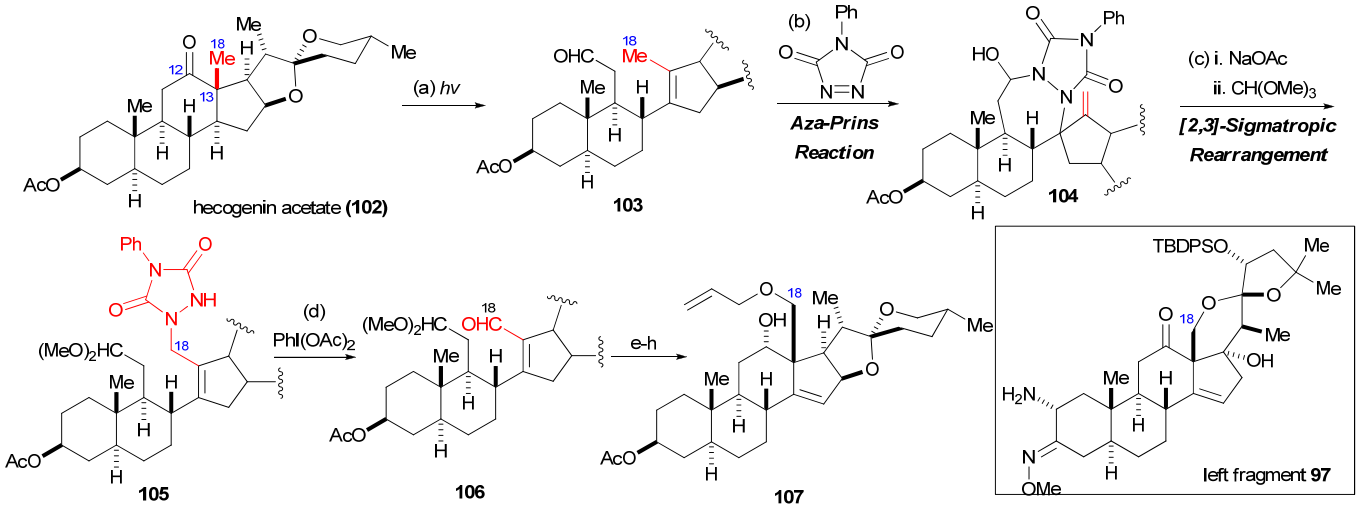


Scheme 23. Cu/O_2-promoted C-H Hydroxylation.

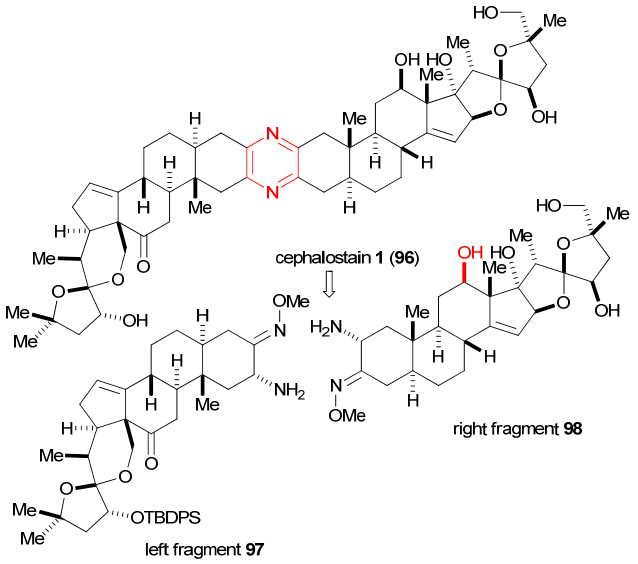
Treating **89** with tetrakis(acetonitrilo)copper(I) hexafluorophosphate in the presence of molecular oxygen afforded the hydroxylation product **91** in 48% yield. This reaction proceeded through a highly stereoselective pathway to deliver the desired 12*β*-hydroxy group with complete regio- and diastereoselectivity. Formation of the Cu^{III}-O_2 species **90** may promote selective functionalization of the 12*β*-C-H bond via hydrogen abstraction. **91** was then converted to lactone **92,** which served as the precursor of biomimetic rearrangement. Reacting **92** with trifluoromethanesulfonic anhydride (Tf_2O) in pyridine led to Wagner–Meerwein rearrangement, giving the desired C-nor-D-homo structure in 94% combined yield as a 3:7 mixture of regioisomers **94** and **95**.

5.4 Total Synthesis of (+)-Cephalostatin 1

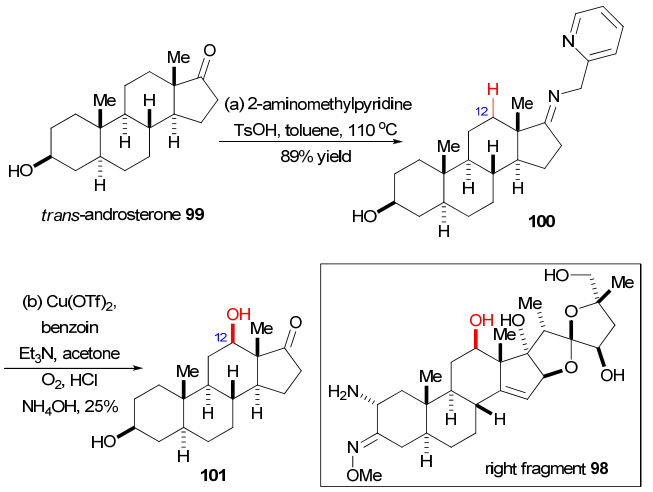
Cephalostatin 1 (**96**) was isolated from the hemichordate worm *Cephalodiscus gilchristi* in 1988,[64] and it exhibits subnanomolar-to-picomolar cytotoxicity against many of the 60 cell lines at the US National Cancer Institute (Scheme 25).[65] It belongs to a family of trisdecacyclic bis-steroidal pyrazines that possess two highly oxygenated steroidal skeletons and spiroketal units linked by a central pyrazine ring at C-2 and C-3.[66] In 2009, Shair and co-workers reported the total synthesis of this complex marine natural product through a convergent approach involving Cu/O_2-promoted C-H hydroxylation and a unique allylic oxidation selective for methyl groups.[67] The structural properties of **96** led the chemists to disconnect it into two steroidal units: the left fragment **97** and right fragment **98** (Scheme 25).



Scheme 27. Synthesis of Left Fragment **97**. *Reagents and conditions*: (a) *hv*, 1,4-dioxane, 25 °C; (b) 4-phenyl-1,2,4-triazoline-3,5-dione (1.0 equiv), dichloroethane, 25 °C, 61%, 2 steps; (c) i. NaOAc (0.1 equiv), DMF, 100 °C, 69%, ii. $CH(OMe)_3$ (1.5 equiv), *p*-TsOH·H_2O (0.1 equiv), MeOH, 25 °C; (d) $PhI(OAc)_2$ (1.5 equiv), MeCN/H_2O, 0 °C, 64%, 2 steps; (e) $NaBH_4$ (1.5 equiv), MeOH, 0 °C, 88%; (f) NaH (2.0 equiv), DMF, 0 °C; allyl bromide (5.0 equiv), 25 °C, 93%; (g) PPTS (0.43 equiv), acetone, 25 °C; (h) BF_3·OEt_2 (1.2 equiv), PhMe, 0 °C, 61%, 2 steps. (DMF = N,N-dimethylformamide, PPTS = pyridinium 4-toluenesulfonate.)



Scheme 25. Synthetic Analysis of Cephalostatin 1.



Scheme 26. Synthesis of Right Fragment **98.** *Reagents and conditions*: (a) 2-aminomethylpyridine (5.0 equiv), *p*-TsOH (2.5 mol%), toluene, 110 °C, 4 h, 89%; (b) $Cu(OTf)_2$ (1.2 equiv), benzoin (2.0 equiv), Et_3N (2.0 equiv), acetone, O_2 (1 atm), HCl, NH_4OH, rt, 30 h, 25%.

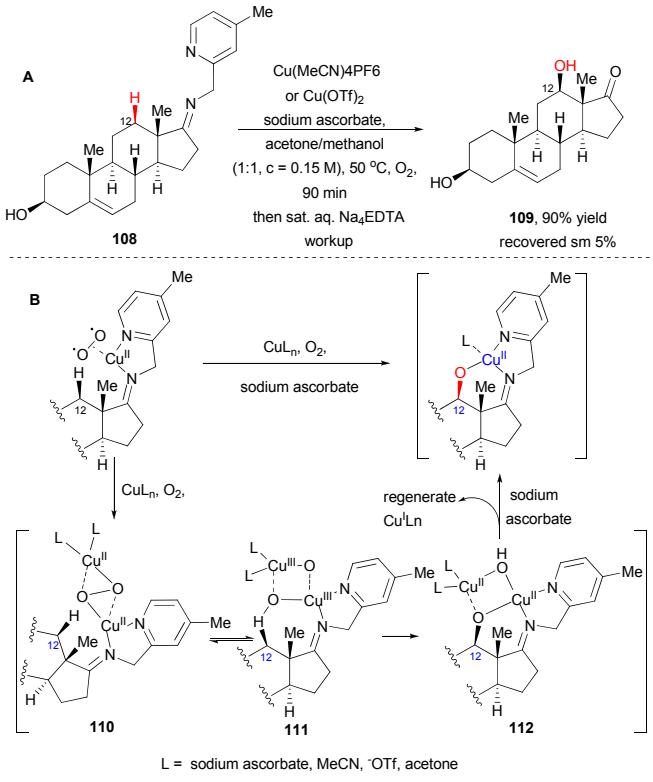
To prepare the right fragment **98**, the steroid trans-androsterone **99** was subjected to Cu/O_2-promoted C-H hydroxylation (Scheme 26). After installing the directing group 2-(aminomethyl) pyridine on the carbonyl group, **100** was achieved in 89% yield. Treating **100** with Cu(I) and oxygen prepared in situ [$Cu(OTf)_2$, benzoin, and Et_3N in acetone] led to selective hydroxylation at the unactivated C-12 position. Simple hydrolysis yielded diol **101** as a single diastereomer in 25% yield, and this was used as the basic skeleton to construct the spiroketal unit for the right fragment **98**.

Hecogenin acetate (**102**), a commercially available steroid, was used to prepare the left fragment **97** (Scheme 27). The most challenging step in this synthesis was the oxidation of the C-18 angular methyl group to a hydroxyl methyl group to allow rearrangement of the spiroketal. Photolysis of **102** led to cleavage of the C-12-C-13 bond to give **103** with aldehyde and allylic methyl groups. Various classical allylic oxidations of the C-18 methyl group failed due to poor regioselectivity and steric hindrance from the tetrasubstituted olefin. Then the researchers attempted an

unusual C-H activation of the C-18 methyl group. Treating **103** with 4-phenyl-1,2,4-triazoline-3,5-dione directly gave **104** with formation of a seven-membered aminal and terminal olefin. This transformation may proceed through hydrogen abstraction promoted by an intramolecular *aza*-Prins or ene reaction. The base sodium acetate promoted ring opening of the hemiaminal, followed by [2,3]-sigmatropic rearrangement to furnish **105** containing an allylic N-Ph urazole on C-18. After protecting the C-12 aldehyde as its dimethyl acetal, $PhI(OAc)_2$ oxidation of C-18 afforded aldehyde **106**. Ultimately, the C ring was resealed using acid-catalyzed acetal hydrolysis and Prins cyclization to give the C-18-oxygenated product **107**.

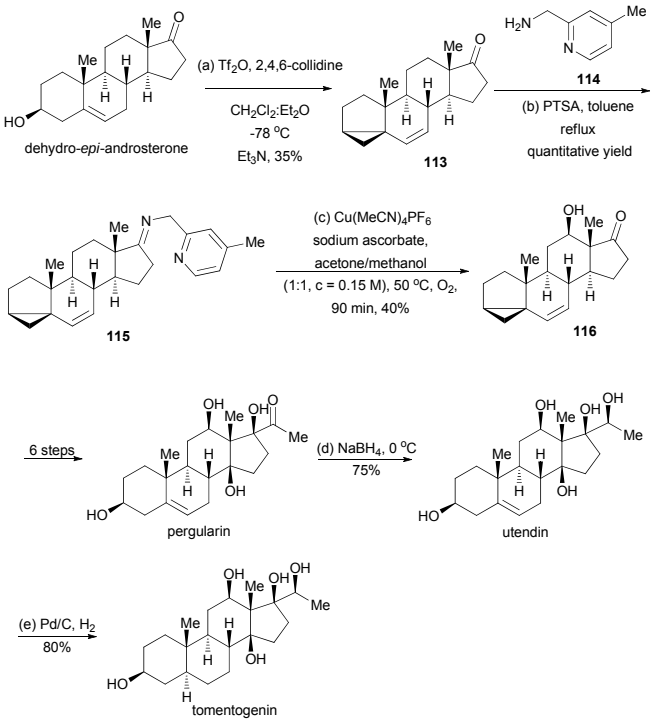
5.5 Synthesis of Polyoxypregnanes: Utendin, Pergularin and Tomentogenin

Recently, Baran and co-workers extended the studies of Cu/O_2 mediated C-H oxidation,[68] previously reported by Schönecker's group,[62] in an attempt to improve on the limitations of Schönecker's conditions, which included long reaction times, poor mass recovery, limited substrate scope and low yield. Starting from the same model substrate dehydro-*epi*-androsterone used by Schönecker's group (Scheme 28A), they extensively surveyed the reaction conditions, including directing group, copper source, reaction temperature and additives. Adding the reducing agent sodium ascorbate effectively improved the yields from Cu(I)- and Cu(II)-based systems. Of five directing groups tested, 4-methylpyridin-2-yl)methanamine proved to be the best. The desired C12-oxidized product **109** was obtained in 90% yield under the optimized conditions. This modified reaction occurs faster with higher yield and broader scope than the original one. Mechanistic studies suggest that C–H oxidation occurs via an oxygen-rebound mechanism involving the mixed active Cu-species **110** and **111** (Scheme 28B). Ascorbate appears to participate in the reaction as a weak copper ligand.



Scheme 28. Modification of Cu/O_2 Mediated C-H Oxidation and Mechanistic Studies.

The synthetic utility of this modified C-H oxidation was demonstrated in the total syntheses of the three polyoxypregnanes utendin, pergularin and tomentogenin. All syntheses proceeded from the key intermediate **116** (Scheme 29). Dehydro-*epi*-androsterone served again as the starting material, and it was transferred to **115** containing the directing group. Under the optimized conditions for Cu/O_2-mediated C-H oxidation, the desired **116** was obtained in 40% yield. Then **116** could be converted to pergularin in six more steps. Pergularin served as the precursor to prepare utendin and tomentogenin.



Scheme 29. Synthesis of Polyoxypregnanes: Utendin, Pergularin and Tomentogenin. *Reagents and conditions*: (a) Tf_2O (1.5 equiv), 2, 4, 6-collidine (1.6 equiv), CH_2Cl_2/Et_2O, -78 °C, Et_3N (15.0 equiv), 35%; (b) **114**, *p*-TsOH (cat.), toluene, reflux, quantitative yield; (c) $Cu(MeCN)_4PF_6$ (1.3 equiv), sodium ascorbate (2.0 equiv), acetone/methanol (1:1, c = 0.15 M), 50 °C, O_2, 90 min, 40%; (d) $NaBH_4$ (28.9 equiv), MeOH, 0 °C, 75% (d.r. = 5:1); (e) Pd/C (5 wt%), H_2, 23 °C, 24 h, 80% (d.r. = 5:1).

5.6 Conclusion

These examples of preparing natural products using metal-catalyzed C-H oxidation demonstrate its potential for even broader application in organic synthesis. Much work remains to be

done, despite considerable progress over the past two decades. Metal-catalyzed C-H functionalization remains an immature method sometimes requiring harsh conditions, expedient directing groups and complicated reaction systems. These disadvantages severely limit its reaction scope. We anticipate that these limitations will be overcome through further study of the reaction mechanism and discovery of new catalysts.

6 Metal-Catalyzed Remote Macrolactonization of Unactivated C(sp^3)-H bonds

6.1 Introduction to the Reactions

Natural macrocyclic lactones are a large family of natural products showing broad structural diversity, from 8-membered to 60-membered rings, as well as a diversity of promising biological activities. Several members of this family have been successfully used in therapeutics and biopesticides, such as erythromycin and epothilones. Therefore synthetic and medicinal chemistry studies of these natural molecules have attracted considerable attention from organic chemists. These lactones are most often synthesized using a convergent approach in which the target is disconnected into several fragments based on its structural features, functional groups and stereochemistry. The final macrocyclization is the most important step in total synthesis. The process most often used for this is secoacid macrolactonization, which remains a key step in total syntheses of most natural macrocyclic lactones.[69] In addition, other macrocyclizations have been used, including ring-closing metathesis (RCM), metal-catalyzed intramolecular coupling, Nozaki-Hiyama-Kishi (NHK) reaction, Julia coupling, Witting and Horner-Wadsworth-Emmons reactions (HWE) (Figure 3). More recently, C-H oxidation based on metal-catalyzed macrolactonization of allylic C-H bonds has allowed preparation of macrolide-containing natural products.[70]

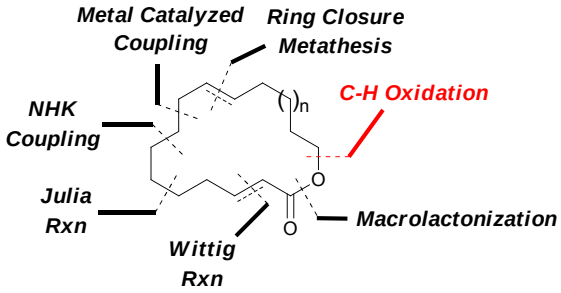
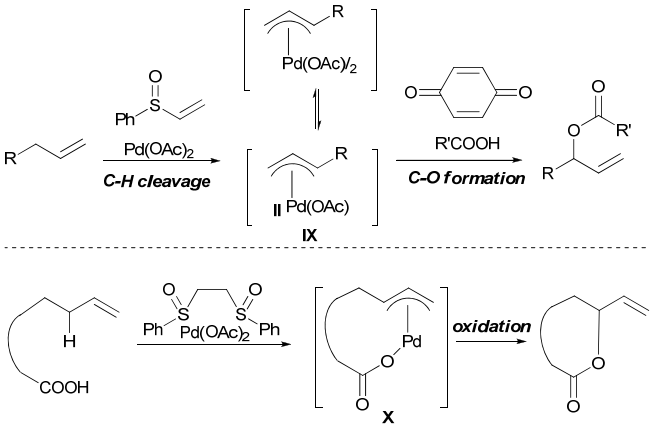


Figure 3. Strategies of Macrocyclization.

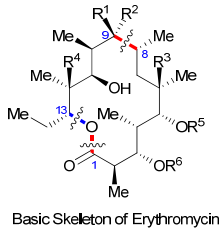
In 2005, White and co-workers reported a sulfoxide-promoted, catalytic $Pd(OAc)_2$/BQ allylic oxidation methodology, which afforded the branched allylic alkyl and aryl esters from terminal olefins and various carboxylic acids.[71] Mechanistic studies suggest serial ligand catalysis. It appears that sulfoxide serves as ligand to drive Pd-mediated allylic C-H cleavage, which generates the π-allylpalladium moiety **IX**. Subsequently, benzoquinone (BQ) promotes C-O bond-forming steps via inner-sphere reductive elimination (Scheme 30). Inspired by this selective allylic C-H oxidation, the same group developed an organometallic C-H oxidation macrolactonization.[70] Without the need to introduce additional directing groups, the carboxylic acid acts as both directing group and reactant in this macrolactonization. This mechanistic model is supported by the observed reaction pathway (Scheme 30). The reaction proceeded highly selectively to generate various 14- to 19-membered alkyl and aryl macrolides with diverse functional groups from linear alkenoic acids.



Scheme 30. Metal-catalyzed remote macrolactonization.

6.2 Total Synthesis of 6-deoxyerythronolide B

Erythromycin, a mixture of macrolide antibiotics with a 14-membered lactone ring, is produced through fermentation by the fungus *Streptomyces erythreus*. The major component in this mixture, erythromycin A, has been used successfully as an antibiotic for more than half a century.[72] Synthesis of this family of macrolides has been studied extensively over the past 30 years, and this work has provided a platform to evaluate new strategies.[73] The macrolactonization strategy is by far the approach most often used to close the 14-membered lactone ring (Figure 4).[73] Krische and co-workers reported an efficient approach to 6-deoxyerythronolide B (**117**) using enyne metathesis (formation of a C-8-C-9 bond) to construct the macrolides.[74] The compound **117** is regarded as the biogenic precursor of this macrolide family; it contains the basic 14-membered lactone and its oxidation state is lower than that of erythromycin A.[75] In 2009, White and co-workers reported the total synthesis of this natural macrolide using their own version of intramolecular C-H oxidation macrolactonization.[76]

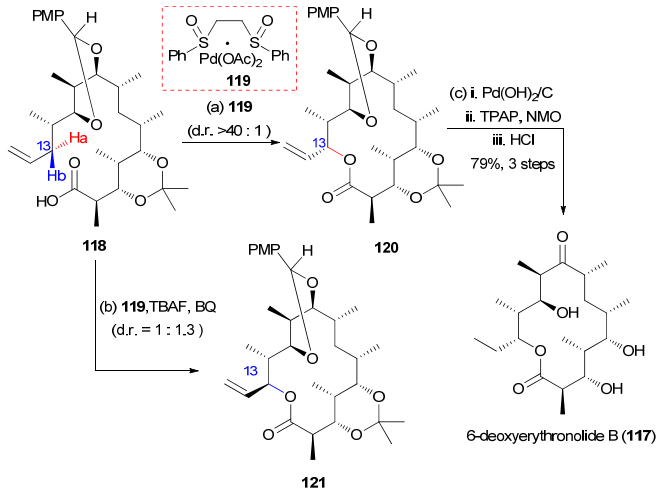


Methods for the macrocyclization:

Pathway a: ***Macrolactonization***
Woodward, 1981, ref. 73a; Corey, 1979, ref. 73b-c; Masamune, 1981, 73d; kochetkov, 1987, ref. 73e; Stork, 1987, ref. 73f; Yonemitsu, 1987, ref. 73g; Kinoshita, 1989, ref. 73h; Paterson, 1989, ref. 73i; Danishefsky, 1990, 73j; Mulzer, 1991, ref. 73k; Hoffmann, 1993, ref. 73l; Martin, 1997, ref. 73m, Evans, 1998, ref. 73n; Woerpel, 2003, ref. 73o; Carreira, 2005, ref. 73p.
Pathway b: ***Enyne Metathesis,*** Krische, 2013, ref. 74
Pathway c: ***C-H Oxidation***, White, 2009, ref. 76

Figure 4. Synthetic Studies of Erythromycin.

The linear alkenoic acid **118** was prepared through an 18-step sequence in 18% overall yield. The key late-stage C–H macrolactonization of **118** was then investigated (Scheme 31). Treatment of **118** with **119** (30 mol%) and BQ (0.02 M) afforded the 14-membered macrolide **120** with desired stereochemistry in 34% yield, with 45% recovery of starting material (r.s.m.). Diastereoselectivity of this macrolactonization appears to be determined by the chelate-controlled model, indicating that the selectivity can be adjusted by adding fluoride anion. Indeed, adding tetra-*n*-butylammonium fluoride (TBAF) to the reaction system led to C-13 diastereomer **121** in 20% yield (d.r.= 1.3:1, 75% r.s.m.). Hydrogenation, site-selective oxidation of the C-9 alcohol and acetonide removal converted **120** to 6-deoxyerythronolide B (**117**).



Scheme 31. Total Synthesis of 6-deoxyerythronolide B**.** *Reagents and conditions*: (a) 119 (0.3 equiv), BQ (2.0 equiv), 45 °C, 72 h, 34% +45% r.s.m. (56% + 8% r.s.m., recycled twice) (d.r. > 40 : 1); (b) 119 (0.3 equiv), BQ (2.0 equiv), TBAF (0.3 equiv), 45 °C, 72 h, 20% +75% r.s.m. (44% + 36% r.s.m., recycled twice) (d.r. = 1 : 1.3); (c) i. $Pd(OH)_2/C$ (20 wt%), H_2 (1 atm), ^{i}PrOH, 96%, ii. TPAP (0.3 equiv), NMO (5.0 equiv), 0 °C, 84%, iii. 1 M HCl_{aq} (10.8 equiv), 98%. (BQ = benzoquinone, TBAF = tetrabutylammonium fluoride, TPAP = tetra-n-propylammonium perruthenate, NMO = N-methylmorpholine oxide .)

6.3 Conclusion

Metal-catalyzed remote macrolactonization is a new approach for synthesizing natural macrolides. In contrast to traditional strategies, intramolecular allylic C-H oxidation can be used to furnish macro-lactones instead of the corresponding secoacids. This method will likely improve and find broader application through further study of its regio- and stereoselectivity as well as its scope, especially with respect to ring size.

7 Conclusions

The synthetic examples highlighted here illustrate the tremendous potential of C-H oxidation for constructing C-O and C-N bonds in natural product synthesis. This approach is likely to prove effective for generating various types of complex natural products, including steroids, terpenoids, alkaloids and macrolides. Even after two decades of study, however, much remains to be done to realize the full potential of C-H oxidation. Selective C-H functionalization remains an immature field and sometimes still requires harsh conditions. Directing groups do not always perform well, and the complexity of the reaction systems sometimes limits their scope dramatically. Further studies are needed to surmount these difficulties and lead to more efficient and versatile total and organic syntheses based on C-H bond activation.

8 Acknowledgements

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