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Recent advances in chemical dearomatization of nonactivated arenes

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Abstract:

Dearomatization reactions provide a synthetic connection between readily available, simple aromatic starting materials and more saturated intermediates of greater molecular complexity and synthetic utility. The last decade has witnessed a steady increase in the development of dearomative methods, providing new synthetic approaches to high-value building blocks and natural products. This review highlights advances both in the area of dearomatization methodologies for the most chemically inert arenes and in synthetic applications of such strategies.

1. Introduction

Aromatic molecules belong to one of the most fundamental and abundant classes of organic compounds and are widely used across all areas of molecular sciences. Not surprisingly, the chemistry of these molecules is an exceptionally rich field and is distinctive due to their unique reactivity patterns and inherent stability. One area of particular interest for synthetic organic chemists is that of dearomatizations, transformations capable of disturbing the aromatic π–system and providing unsaturated, and often functionalized, products (Scheme 1). By utilizing arenes as starting materials, dearomative strategies offer rapid access to more complex, value-added, and synthetically versatile intermediates from readily available sources of hydrocarbons.[1] This direct, simplicity-to-complexity synthetic logic is becoming increasingly popular in the fields of natural product synthesis and small-molecule medicinal chemistry, where a high degree of functionality and structural diversity (sp^3-content) is often desired.[2] Consequently, the number of reports on the development and application of dearomatization processes has steadily increased in recent decades (Scheme 1), and will likely continue to grow, especially with recent advances in transition metal catalysis,[3] asymmetric catalysis,[4] and biocatalysis.[5]

In principle, every aromatic compound can undergo dearomatization. However, due to their reduced resonance stabilization energy, heteroaromatics, such as furan, pyrrole, or pyridine, are more prone to dearomative transformations compared to arenes, such as benzene (Scheme 2).[4] In the case of arenes, dearomatization reactions can be classified into several categories, including reductive, oxidative, transition-metal-mediated, and cycloaddition-based processes. Several excellent reviews on the

dearomatization of arenes have appeared during the last decade, covering enantioselective,[4] transition-metal-mediated,[6-8] photochemical,[9,10] and nucleophilic dearomatizing reactions and their synthetic application.[11] Dearomative elaborations of electronically activated arenes (phenols and anilines), as well as their applications in synthesis, have also been covered.[4,12-14] Thus, the aim of this review is to provide a complementary overview of recent developments, specifically involving dearomatizations of more resistant, nonactivated arenes and their synthetic applications.

2. Dearomative hydrogenations

The area of dearomative reduction has seen major developments in recent years, both in terms of heterogeneous and homogeneous catalysis.[15-17] However, partial reduction has been achieved only with heterogeneous catalysis, as exemplified with the Asahi's Chemical Co. process for the production of cyclohexene from benzene (Scheme 3).[18] Thus, using a specifically engineered bilayered Ru-particle catalyst, containing $ZnSO_4$ as a co-catalyst and ZrO_2 as the optimal dispersing agent, hydrogenation of benzene (**1**) to cyclohexene (**2**) was achieved with 60% selectivity. Moreover, in order to obtain high selectivity, the reaction has to be properly agitated to generate a four phase system in which reactants and products transfer through dissolution, diffusion, and extraction. Interestingly, the acidic zinc salt has been shown to play a key role for suppressing over-reduction by stabilizing the reduced intermediate and inhibiting resorption of cyclohexene.

The vast majority of commonly used catalytic dearomative hydrogenations of more elaborated arenes employ heterogeneous catalysts. A hallmark example of dearomative reduction in the preparation of complex small molecules is Hoffmann-La Roche's synthesis of the antiviral agent oseltamivir phosphate (**6**, Tamiflu™, Scheme 4).[19] The synthetic sequence commenced with readily available pyrogallol derivative **3**, which was converted in several steps to the corresponding diethyl isophthalate **4**, a key precursor for dearomative hydrogenation. Upon exposure of **4** to hydrogen and a catalytic amount of ruthenium immobilized on alumina, a fully saturated *bis*-ester **5** was obtained in 82% yield. Interestingly, the application of rhodium on alumina, another commonly used dearomative hydrogenation catalyst, resulted in a complex mixture containing only 10% of **5**. Five additional steps, including an enzymatic resolution, delivered oseltamivir phosphate (**6**).

With chiral precursors, the diastereoselectivity of dearomative heterogeneous hydrogenation was highly substrate dependent. The interaction of the aromatic moiety with the catalyst, and consequently the adsorption onto the catalytic surface during the course of the reaction, was affected by the steric repulsion and electronic attraction between the lateral arene substituents and the catalyst (Scheme 5).[20,21] For example, dearomative reduction of several 1-substituted indanes **7** under Rh/Al_2O_3 catalysis revealed that substrates containing alkyl (Entry 1), hydroxy, alkoxy, and carboxylate groups (Entries 3–8) favored diastereoisomer **8** based on steric repulsion. It is of note that substrates possessing hydroxyl and

carboxylic acid motifs (Entries 3, 6, and 7) did not exhibit a strong anchoring interaction with the surface of the catalyst (haptophilicity); such an effect is often observable in the hydrogenation of alkenes. In contrast, an amino group (Entry 2) showed strong haptophilicity, delivering complementary diastereoisomer **9** with high selectivity.

Chiral auxiliaries can also be used to achieve diastereoselective hydrogenation of arenes with heterogeneous catalysis (Scheme 6a).[22,23] For instance, the *o*-toluic acid derivative **10**, which contains pyroglutamic acid methyl ester as a steering element, underwent highly selective hydrogenation to give *cis*-2-methylcyclohexanecarboxylic acid derivative **11** in 97.5:2.5 dr. Key factors for high selectivity in this reaction included the use of several equivalents of EDCA (ethyldicyclohexylamine) with respect to Rh, alumina as the support for the rhodium catalyst, and a pyroglutamic acid auxiliary instead of the analogous proline ester. The addition of EDCA drastically improved selectivity, supposedly by adsorbing onto the metal surface and enhancing selectivity for a favorable orientation of the substrate.

An elegant diastereoselective hydrogenation of quinolines was accomplished utilizing a hydrogen bond-enforced conformational lock between the auxiliary and substrate (Scheme 6b).[24] To this end, exposure of 2-oxazolidinone-substituted quinoline **12** to Adam's catalyst in trifluoroacetic acid delivered reduced product **13** in 95% yield and 89:11 dr. The strong acid proved crucial for high selectivity, as the protonated quinoline core engaged in hydrogen bonding with the oxazolidinone. Such an interaction rigidified the structure such that the top face was shielded by the substituent of the auxiliary and adsorption of the substrate through the bottom face was preferred. The influence of auxiliary substituent size on selectivity of hydrogenation was rather unexpected, as the corresponding benzyl and *tert*-butyl auxiliaries were less effective than the isopropyl variant. Further hydrogenation of **13** with Rh/C with increased hydrogen pressure, resulted in complete reduction as well as removal of the oxazolidinone, furnishing decahydroquinoline **14** in 99% yield and 97:3 dr.

Recently, alternative hydrogenation catalysts have been developed which combine characteristics of both homogeneous and heterogeneous catalysis (Scheme 7).[25-27] This unique approach employed nonexchangeable binding to a single face of the catalyst throughout the reduction cycle, which accounted for the high levels of *cis*-selectivity observed. The electrophilic zirconium precatalyst Cp^*ZrBz_3 was chemisorbed to Brønsted acidic sulfated oxide through non-directional ion-pairing between Zr-centers and the charge-delocalized oxide surface. With this catalyst scaffold, a variety of hydrocarbon arenes underwent exclusive all-*cis* hydrogenation. In addition, more challenging arenes, such as disubstituted benzene derivatives, naphthalene, and trisubstituted benzene derivatives, were good substrates, delivering products **15**–**18**. Unfortunately, due to the highly electrophilic nature of the catalyst, substrates possessing polar functionality were found to be incompatible with this reduction process.

Though the first examples of dearomative hydrogenations under homogeneous catalysis are nearly fifty years old, this field has recently experienced a renaissance. This rather long induction period perhaps

originates from the initial use of air sensitive Co-, Ru-, and Rh-based catalysts, limited substrate scope, and low turnovers. Such challenges rendered these approaches less practical when compared to the more robust and versatile heterogeneous catalysts. Recent advances in this area have greatly improved the scope of these transformations and provided the first reports of highly enantioselective reductions.[16] For example, chemoselective hydrogenation of arenes in the presence of ketones is now possible through the use of Rh-NHC catalyst **19** (Scheme 8).[28-30] A range of ketones delivered cyclohexane derivatives in high yields as well as *cis*-selectivity for bicyclic substrates. The cyclic (alkyl)(amino)carbene ligand, one of the most nucleophilic (σ-donating) stable carbenes, was shown to be crucial for this reaction; likely because σ-donation to the Rh metal results in stronger binding with an arene substrate alongside decreased oxophilicity at the metal center. Finally, this catalyst was also compatible with phenols, delivering cyclohexanones without over-reduction to alcohols.

Enantioselective catalytic hydrogenation of non-activated arenes is still an unmet challenge in organic synthesis. The current state-of-the-art is the Ru-catalyzed reduction of substituted naphthalenes (Scheme 9).[31] In this reaction, the combination of a Ru-PhTrap catalyst and either DBU or TMG as the base led to enantioselective partial hydrogenation of naphthalene derivatives. The observed enantioinduction of this process proved to be substrate dependent, as exemplified by the different results for the products **24** and **25,** derived from constitutional isomers. Moreover, in naphthalene derivatives containing alkyl and alkoxy substituents, the more electron rich ring reacted preferentially (e.g. **26**). Unfortunately, greater structural deviation from aryl esters (**24** – **25**) or aromatic ethers (**26** – **27**) to a substrate containing a benzylic ether (**28**), resulted in poorer selectivity, and no reaction was observed with dialkyl substituted naphthalenes. Nevertheless, this report embodied the first enantioselective reduction of hydrocarbon arenes, and it represents an important foundation for future exploration in this area.

In addition to achieving higher stereoselectivity, further development of homogenous catalysis could also improve the chemoselectivity of these processes and greatly expand their substrate scope. A key example of such an enabling transformation is a recently reported Rh-catalyzed hydrogenation of fluoroarenes (Scheme 10).[32] By using Rh-NHC catalyst **19** with the cyclic (alkyl)(amino)carbene ligand, a range of fluoroarenes were transformed into the corresponding fluorinated saturated products. In addition to fluorobenzene (**29**), a number of mono- and polyfluorinated benzene analogues underwent reduction, delivering products **30** – **39**. Even hexafluorobenzene provided all-*cis* hexaflourocyclohexane (**39**) in >20:1 dr, albeit with slightly reduced yield (34%); this approach represented a major synthetic advance, as a previous route to this product from glucose required 12 steps. Moreover, heteroatom-based functional groups, such as boronate (**30**), alkoxide (**32**) and Boc-protected amine moieties (**31** and **34**) were all well tolerated, either on the ring or on a side chain. Finally, higher-order arenes, such as 1-fluoronaphthalene, could be dearomatized using this method, furnishing product **40** in 74% yield and 6:1

dr. Overall, this approach greatly simplified the preparation of specific types of fluorinated products and demonstrates the advantage of homogenous catalysis.

3. Nucleophilic dearomatizing reactions

In the past few decades, there have been numerous reports of dearomatization reactions intitated by nucleophilic attack of reactive species into aromatic rings. While this chemistry has been reviewed extensively elsewhere, more recent developments are highlighted below.[11] For instance, *tert*-butyllithium-mediated intramolecular dearomative addition of vinyl iodides into aromatic rings has been developed (Scheme 11).[33,34] After formation of the vinyl lithium species from the corresponding butadienyl iodides, the dearomatized products **41** – **46** were isolated after quenching the reaction with a variety of electrophiles at –78 °C. When an aqueous workup is employed, product **41** is isolated in 69% yield, along with 21% yield of the 1,4-dearomatized isomer. In the case of carbon dioxide (**42**), allyl (**43**), trimethylsilyl (**44**), ketone (**45**), or acid chloride (**46**) electrophile products, only the 1,2-dearomatized products were isolated.

Interestingly, when phenyl butadiene substrates were employed in the reaction, both the 1,2- and 1,4-dearomatized products were obtained with some electrophiles (Scheme 12).[34] While the reactions with naphthalene-derived starting materials underwent dearomatization and could be trapped with an electrophile at –78 °C, reactions with the corresponding phenyl substrates had to be warmed from –78 °C to 0 °C after formation of the vinyllithium species in order for the dearomative cyclization to occur. The ratio of isomeric products was determined by the aromatic substrate and electrophile used. For the product **47**, formed via quenching with benzaldehyde, the 1,4-dearomatized compound was isolated as the major product in 56% yield, with 26% yield of the 1,2-product. However, when substituted benzaldehydes were used as electrophiles, the 1,2-dearomatized product was the major product in many cases, including for the brominated and methoxylated products **48** and **49**. When the reaction was quenched with a ketone, such as for **50**, or an imine to generate **51**, the 1,4-dearomatized compound was the sole product. This was also true for substituted phenyl substrates, as shown with **52** and **53**. Based on these results, the authors suggest that the selectivity of the reaction is more dependent on the sterics of the starting aromatic substrate and electrophile, rather than on an electronic effect.

Intermolecular alkyllithum addition has also been developed for a variety of arene starting materials. Dearomatization of chiral phenyl oxazoline compounds via organolithium addition and trapping with electrophiles has been shown for naphthalene derivatives.[35] Recently, the scope of this transformation has been extended to substituted benzene derivatives through the key addition of *N,N'*-dimethylpropyleneurea (DMPU) to disrupt lithium aggregates (Scheme 13).[36] Thus, a series of phenyl oxazolines were exposed to alkyllithium reagents in the presence of DMPU, then quenched with either methyl iodide or ammonium chloride to afford the corresponding dearomatized products **54** – **61** as

single diastereomers.[36a] Isopropyl (**56**, **57**, **59**, and **61**), *sec*-butyl (**54**, **58**, and **60**), and *tert*-butyl lithium (**55**) all acted as the nucleophile in this reaction, albeit with reduced yield in the case of the *tert*-butyl nucleophile. Substituted phenyl oxazolines could be used, with methoxy (**56 – 58**), phenyl (**59**), or fluoride (**61**) substituents; however, in the case of the phenyl substituted starting material, a significant amount (30%) of the product formed via deprotonation and quenching was observed alongside the product of nucleophilic addition. Moreover, the product **56** was carried forward through a series of steps to generate the mannose analogue **62** and altrose analogue **63**, and the dr was determined to be greater than 99:1 in both cases, suggesting that the chiral backbone of the oxazoline provides significant stereoinduction.

Addition of lithiated nucleophiles into benzene derivatives has also found use in the total synthesis of shellfish toxins, including isodomic acid B (**66**) (Scheme 14).[37] Thus, deprotonation of aryl amide **64** in the presence of a chiral lithium amide gave intramolecular nucleophilic attack into the anisole ring to afford, after column chromatography and enol ether deprotection, the α,β–unsaturated ketone **65** in 67% yield and 93:7 er, which could be improved to 99:1 er (51% yield) after recrystallization. This material served as the key building block for the pyrrolidine motif in this class of natural products.

4. Radical dearomatizations

Addition of carbon-centered radicals to unsaturated systems is a widely used and powerful strategy for achieving carbofunctionalization of π-systems. Aside from alkenes and alkynes, the two most explored unsaturated manifolds, multiple reports document addition of ketyl radicals to arenes. A large portion of developed systems have consisted of intramolecular samarium(II) iodide-mediated cyclizations, including the example shown in Scheme 15.[38] A variety of substituents were tolerated on the arene, at either the *para* (**67**) or *ortho* (**68**) positions relative to the alkyl chain containing the ketone. In contrast, *meta*-substituted substrates were found to be challenging, as they either did not proceed to the desired product at all or furnished rearomatized products. For this class of substrate, the corresponding dearomatized, alkylated products **69** and **70** were observed when the reaction was quenched with an electrophile other than a proton source. The yield of the reaction was highly dependent on the reaction conditions and the substituents on the arene. A combination of THF and hexamethylphosphoramide (HMPA) was generally needed to form a samarium species that was sufficiently reducing to form ketyl radicals and induce cyclization.[38,39] Mechanistically, the persistence of ketyl radicals and the ability of samarium(II) to reduce ketones and other carbonyls to these species in low equilibrium concentrations allowed for addition into aromatic rings. Upon reduction of ketone **71** to ketyl radical **72**, the samarium-bound radical cyclized into the aromatic ring to form cyclohexadienyl radical **73**. This underwent further reduction to carbanion **74**, which was protonated to form 1,4-cyclohexadiene **75**.

In an interesting example, ketones of type **76** underwent dearomative single-electron-transfer reduction to spirocyclic products **77** (Scheme 16).[40,41] The reaction generated a mixture of diastereomeric products **77a** and **77b** in a 1:1.3 ratio at 0 °C and a 1.7:1 ratio at –78 °C, with the stereochemistry likely being dictated by the protonation of a Sm-enolate ion. In this reaction, intramolecular attack of the ketyl radical **78** occurred onto the more polarized position, *para* to the ester group, to deliver cyclohexadienyl radical intermediate **79**. A second reduction by SmI_2 occurred from the same face as the oxygen atom, and protonation of the resulting anion **80** followed by SmI_2-mediated 1,4-reduction of **81** and enolate protonation gave the diastereomeric mixture **82**. Importantly, an analogous secondary alkyl iodide radical coupling parter did not afford the desired product under the reaction conditions, implying that the samarium(II) species was either not capable of reducing a secondary alkyl iodide to a secondary radical, or more likely, that the resulting radical was incapable of cyclizing onto the electron-deficient aromatic ring.

Samarium-mediated cyclization of polynuclear arenes resulted in formation of a single constitutional and diastereoisomer (Scheme 17), as the cyclization step was highly dependent on the steric interactions between the alkoxysamarium and arene motifs.[42-44] Specifically, linear methyl ketones **83** and **86** tethered to a naphthalene core delivered tricycles **85** and **87** as single diastereoisomers. The diastereoselectivity of this transformation resulted from a chair-like transition state, as exemplified by **84**. Likewise, a variety of cyclic ketones **88** – **91** performed well, delivering steroidal tetracycles **92** – **95**. These types of products were amenable to further manipulations, as demonstrated by the hydrogenation of **92** using palladium on carbon to produce **96** and epoxidation with *m*CPBA to form the corresponding epoxide **97**. Alternatively, deoxygenation of alcohol **92** to **98** could be achieved using ionic reduction. Interestingly, during the course of the reduction, the dihydronaphthalene core was oxidized to the aromatic compound.

Related free radical addition-based dearomatization reactions of arenes are known, but are more rare. In most cases, the products generated in radical additions to arenes are rearomatized.[45] However, there are a few reports of intermolecular additions of aryl radicals to arenes to generate 1,4-cyclohexadienes (Scheme 18).[46,47] The key enabling additive in this process was phenyl selenium hydride, which is approximately a 500-fold faster hydrogen donor than Bu_3SnH. This substoichiometric reagent shuffled hydrogen atoms between Bu_3SnH and the relatively stable cyclohexadienyl radical intermediate. Iodobenzoic acid could be utilized in this reaction, giving product **99**, and iodophenols were also competent substrates (**100** – **101**). In all cases, solvent quantities of benzene were used as an aryl radical acceptor. The resulting cyclohexadienes could be converted into aryl cyclitols; for example, **101** could be dihydroxylated under Upjohn conditions to form cyclitol **102**.

5. Transition-metal-mediated dearomatizations

In recent years, stoichiometric η^2–aryl metal complexes have been employed in dearomatization reactions, and this work has been reviewed extensively elsewhere.[8] The salient feature of this dearomatization is an induced polarization of an arene substrate after η^2-complexation with the metal, generating a partial negative charge at the position distal to the metal binding site. This facilitates reaction of the aryl ring with electrophiles, generating intermediates with stabilized cationic character. Subsequent attack by a nucleophilic species regenerates the neutral complex; after decomplexation from the metal, a number of different 1,2- and 1,4-substituted dearomatized products can be accessed in a stereo- and regioselective manner. Though stoichiometric metal complexes have to be used, a recyclable molybdenum-based complex **103** for the dearomatization of naphthalene and anthracene scaffolds has been described recently (Scheme 19a).[48] In this process, anthracene complex **103** was exposed to triflic acid, followed by *N*-methylpyrrole and triethylamine, to afford **104** in 27% yield. In the presence of iodine, the dearomatized product **105** was oxidatively cleaved from the molybdenum complex in 39% yield. The starting complex **103** can be regenerated in 96% yield through reduction by sodium metal and recomplexation with anthracene.

While many complexes with electron-rich and -neutral arene substrates had been utilized in Row 6 metal-based dearomatization, the scope of electron-deficient substrates had been limited, due to the frequency with which electron-poor substrates have π–systems that can competitively bind to the metal center.[49] Recent advances showcased the dearomatization of an η^2–(α,α,α-trifluorotoluene)-tungsten complex, which also revealed the effect of an electron-withdrawing group on the regioselectivity of the reaction (Scheme 19b).[50] To this end, exposure of tungsten complex **106** to triflic acid, followed by lithium dimethyl malonate (LiDMM), afforded cyclohexadiene product **107** in 80% yield, with addition of the malonate to the *meta* position relative to the trifluoromethyl substituent. Interestingly, upon a second exposure to acid, followed by addition of a hydride, the overall reduction occurs in a 1,4-fashion across the diene to afford the cyclohexene complex **108** in 72% yield. This product can be oxidatively decomplexed from tungsten in 69% yield using nitrosonium hexafluorophosphate to form cyclohexene **109**.

These dearomatization processes can also occur in an enantioselective fashion; initially accomplished using chiral rhenium[51] and tungsten-based[52] metal complexes, molybdenum-based systems have been explored more recently (Scheme 19c).[53] Thus, α–pinene-derived molybdenum complex has been applied for the enantioselective dearomatization of trifluorotoluene and naphthalene. Pinene complex **110** was synthesized as a single stereoisomer and could be converted to enantioenriched trifluorotoluene complex **111** with high levels of stereoretention. Protonation and nucleophilic attack with 1-methoxy-2-methyl-1-(trimethylsiloxy)-propene (MMTP) afforded diene complex **112** in 63% yield. Iodine-mediated decomplexation gave the cyclohexadiene product **113** in 71% yield, and 97:3 er. Therefore, the

stereochemical information was transferred from pinene complex **110** to **113** with high levels of enantiospecificity.

In contrast to rhenium-, tungsten- and molybdenum-arene complexes, chromium[6,7] and ruthenium[54-56] can form η^6–complexes with arenes (Scheme 20). These complexes react with nucleophiles to generate resonance- and metal-stabilized cyclohexyldienyl anions, which subsequently react with a variety of electrophiles to generate *trans*-1,2-difunctionalized dearomatized products after oxidative or acidic decomplexation of the metal. In an illustration of the utility of this method, it was shown that disilyl-substituted anisole derivative **114** could be combined with $Cr(CO)_6$ to generate chromium-arene adduct **115**.[57,58] This complex reacted *meta* to the methoxy group with *in situ* generated vinyl lithium. The resulting anion was subsequently reacted with propargyl bromide in DMPU. Upon workup, the enol ether and TMS groups were hydrolyzed and enyne **116** was generated in 55% yield. An additional five steps, including a Sonagashira coupling and a Nicholas reaction, resulted in bicyclic enediyne **117**.

Over the past fifteen years, research in this field has mostly focused on understanding and improving the enantioselectivity of these processes, and there have been a number of methods to induce stereoselectivity during the addition of the nucleophile. More recently, it was shown that using chiral auxiliaries derived from isoborneol resulted in very high levels of diastereoselectivity (Scheme 21).[59] Thus, exposure of phenylisoborneol phenyl ether **118** to a lithium ester enolate and subsequent acidic decomplexation gave dienol ether **119** in 72% yield and 96:4 dr. The origin of this remarkable 1,5-asymmetric induction, from the aryl ether stereogenic center to the *meta*-position of the arene, was studied using NMR and x-ray crystallography. These investigations suggested that the phenyl group on the auxiliary orients the $Cr(CO)_3$ tripod of **118**, activating the arene at the *meta*-position through stereoelectronic effects.

Prochiral chromium-arene complexes could also undergo desymmetrization, as showcased in the total synthesis of (+)-ptilocaulin (**124**, Scheme 22).[60] Optically pure **121** was prepared through enantioselective deprotonation/silylation of **120** in 87% yield and 93.5:6.5 er, which was further enriched to >99:1 er *via* a single recrystallization. This intermediate was deprotonated a second time, and a crotyl side chain was appended via formation of an arylcuprate to give product **122**. The key dearomatization step involved an addition of a lithiated dithiane; the anionic product was trapped with TMSCl to avoid an undesired aromatic side product. Finally, acidic hydrolysis delivered the desired enone **123** in 45% yield and >99:1 er, highlighting the efficacy of the planar to point chirality transfer. Five additional steps were needed to achieve the synthesis of (+)-ptilocaulin (**124**).

Although chromium- and manganese-based arene complexes have been the most extensively explored, recent reports showcase that ruthenium can also be used for dearomative transformations (Scheme 23). For example, deprotonation of a β–keto phosphonate with sodium hydride resulted in intramolecular addition of the resulting stabilized anion into the arene, and subsequent one pot Horner–

Wadsworth–Emmons olefination delivered spirolactam products **125** – **127**.[54-56] Alternatively, similar cyclohexadienyl complexes were formed through Morita–Baylis–Hillman cyclizations, using stoichiometric PBu_3 with NaH to form **129** – **131**.[55] These products could be demetalated, as exemplified by the oxidation of **125** with $CuBr_2$ in methanol and under a CO atmosphere to afford methoxy diene **128**, likely by addition of methanol to one of the termini of an intermediate cyclohexadienyl cation. Moreover, the *para*-methoxy substituted **131** generated from the trialkylphosphine-mediated cyclization could be oxidized to dienone **132** upon treatment with $CuCl_2$.

6. Transition-metal-catalyzed dearomatizations

Palladium catalysis has been utilized for the dearomative allylation of a variety of halomethyl substituted arene substrates. In one example, benzyl chlorides could be effectively coupled with tributyl allyl stannane in the presence of $Pd_2(dba)_3$ and triphenyl phosphine (Scheme 24), affording dearomatized products **133** – **136**.[61] Alkyl substituents were tolerated at multiple positions relative to the starting chloride (**134** and **135**). In addition to benzene derivatives, a naphthalene core could be dearomatized using this method (e.g. **136**). The proposed mechanism involved oxidative addition of a palladium(0) catalyst into the benzylic halide to form the benzylic palladium(II) intermediate **137**, which would be in equilibrium with the corresponding π–benzyl complex **138**. Transmetalation of the allyl stannane afforded diallyl complex **139**, which then underwent reductive elimination to regenerate the palladium(0) catalyst and produce the dearomatized product **133**.

The scope of this reaction was expanded to include naphthalene substituted allyl chloride starting materials (Scheme 25).[62] While cinnamyl chlorides could not be dearomatized using this approach, giving instead the products coupled at the terminal position of the allyl fragment, the naphthyl compounds afforded the corresponding 1,2-dearomatized products **140** – **143**, including compounds with alkyl (**141**), bromide (**142**), and *O*-benzoyl (**143**) substituents. Additionally, this approach could be extended to allyl phenanthrene derivatives. In the case of the benzoyl substituted product **143**, deprotection of the enol benzoate under basic conditions with sodium hydroxide in ethanol provided access to the corresponding ketone without isomerization of the remaining olefins.

Aside from benzyl and allyl chlorides, this methodology was also used for the dearomatization of diarylmethyl chlorides (Scheme 26).[63] Thus, the application of this allylation strategy to these substrates provided dearomatized products **144** – **147**. When both aryl groups were benzene derivatives, the dearomatization occurred on the ring bearing the more electron-donating substituent, as seen in product **144**. If one of the aryl rings in the starting material had a naphthalene core, the naphthalene motif was selectively dearomatized, as shown in products **145** and **146**, unless the naphthyl ring was connected at the 2-position, as in **147**. A second allylation occurred in the case of **146**, which bore a bromide at the 4-position in the starting material.

While allyl stannanes initially proved to be an ideal allyl nucleophile due to their pronounced reactivity, the toxicity associated with these reagents was undesirable. Therefore, a recent modification using allyl boronic esters as nucleophiles for this reaction was reported (Scheme 27).[64] For a series of *para*-substituted benzyl chlorides, the dearomatized products **135**, **148** – **151** were achieved. This reaction tolerated aryl halides (**149**) pendant phenyl rings (**150**), benzothiophene (**151**) and alkyl groups (**135**, **148**, and **149**); however, when substrates lacking substituents in the *para* position were exposed to the reaction conditions, pure dearomatized products could not be isolated, as these products underwent rearomatization under acidic conditions. As another alternative, malonate derivatives have also been reported to act as nucleophiles for the dearomatization of benzylic chlorides.[65]

Allenyl stannanes also acted as nucleophiles in reactions with benzyl and diarylmethyl chlorides, as depicted in Scheme 28.[66] With $Pd(PPh_3)_4$ as the catalyst and TBAF as an additive to activate the stannane, both propargyl and allenyl dearomatized products **152** – **155** were observed. In the case of *para*-substituted chloromethyl benzene derivatives, only the propargyl products **152** – **154** were identified. Alkyl substituents were tolerated (**152** and **154**); however, the substrate bearing a *tert*-butyl **154** generated only 25% yield of the desired product. In addition, an aldehyde motif could be tolerated under the reactions as its protected dioxolane form, affording product **153** in 92% yield. When diaryl methyl chlorides were utilized as starting materials, a mixture of propargyl and allenyl products were observed, as exemplified in product **155**, with the propargyl compound as the major product. Alternatively, chloromethyl and chloroallyl naphthalenes could be dearomatized using this approach. Using the same catalyst source, and in the absence of TBAF, these substrates were reacted with tributyl allenyl stannane to form the products **156** – **159**. The formation of the propargyl or allenyl product was dependent upon the nature of the starting material. When the naphthalene starting material contained a methyl ester at the 4-position, only the allenyl product **157** was isolated, whereas in the phenyl-containing product **156**, only the propargyl isomer was formed. In addition to chloromethyl naphthalene-derived starting materials, chloromethyl anthracene (**158**) and naphthalene possessing a trifluoroacetate leaving group (**159**) could be used to form the allenyl and propargyl dearomatized products, respectively.

Chromium catalysis has also been used for asymmetric dearomatization of halomethyl naphthalenes (Scheme 29).[67] For example, using chromium(II) chloride and the chiral ligand **160**, a series of bromomethyl naphthalene substrates combined with aliphatic aldehydes underwent enantioselective dearomative elaboration to provide *bis*-homoallylic alcohols **161** – **165**. This reaction tolerated primary chlorides (**162**) and protected alcohols (**161**), as well as alkoxy (**164**) and alkyl (**165**) substituents on the bromomethyl naphthalene. In addition to 1-bromomethyl naphthalenes, 2-bromomethyl substrates were also compatible with the reaction (e.g., **163**). The stereochemical outcome of this reaction was rationalized through a closed transition state. After formation of an organochromium species, the

aldehyde was alkylated through a Zimmerman–Traxler transition state, with the facial selectivity determined by the chiral substituents on the ligand.

In addition to benzylic halides, palladium-catalyzed decarboxylative alkylation of biaryl enol carbonates gave dearomatized products (Scheme 30).[68] The formation of dearomatized products **166** – **169** was dependent on the use of tri(2-furyl)phosphine as the ligand; when triphenylphosphine was employed, only the aromatic benzylation product was observed. Electron-donating and -withdrawing substituents on the phenyl portion were tolerated, apart from a nitro substituent, which resulted in sole formation of the analogous fully aromatized product. In the case of a substituent at the 4-position of the naphthyl core (**169**), the dearomatization occurred in a 1,4-fashion, rather than the 1,2-selective transformation. This switch in selectivity was likely due to the increased favorability of the internal π–benzyl palladium species for the 4-methyl substrate (**170** vs **171**). A number of different substituted enol carbonate fragments proved compatible with these conditions, and a diastereomeric mixture was obtained when a branched ketone was generated (e.g. **168**).

7. Dearomative cycloadditions

While addition reactions enable direct introduction of variety of functionality, cycloaddition processes between aromatic hydrocarbons and alkenes are known to increase structural complexity through the formation of bridged or fused bicyclic dearomatized products (Scheme 31).[9,10] Formally, [2+2], [3+2], and [4+2] cycloadditions have all been documented in the literature, with most examples utilizing photochemical activation of one of the cycloaddition partners. Under a photochemical regime, the inherent electronic nature of either cycloaddition partner, as well as the resulting exciplex, determines the major course of the addition, leading to *ortho*, *meta*, or *para* selectivity.

Although *ortho*- and *para*-cycloadditions of alkenes and arenes are still relatively underdeveloped, photomediated *meta*-cycloadditions have been widely studied, both mechanistically and synthetically. Specifically, alkene-arene *meta*-cycloadditions have been used as a key tactic to synthesize a range of polycyclic natural products, with this critical step often occurring early in the synthetic route. Examples of two such impressive syntheses are shown in Scheme 31: penifulvin C (**174**)[69] and ceratopicanol (**177**).[70] Alkenes **172** and **175** underwent intramolecular 1,3-, or *meta*-additions to form cyclopropane intermediates **173** and **176**, which were both taken on to their respective natural products in a few additional steps. Such *meta* alkene-arene cycloadditions enable rapid access to complex intermediates; this topic has been extensively reviewed elsewhere.[9,10] Nevertheless, considerable work is still needed to increase the synthetic utility of the corresponding *ortho* and *para* selective transformations.

In addition to cycloaddition reactions between alkenes and arenes, the intramolecular Diels–Alder reaction between allenes and arenes was established as early as 1982 in the case of anilines (the Himbert allene/arene cycloaddition).[71] This surprising reactivity was attributed to several factors, including both

the partial activation of the benzene ring with a nitrogen-based substituent and the high energy content of the allene. More recently, an important modification was developed where the amide nitrogen linker was replaced with a methylene tether (Scheme 32).[72] Since these cycloadditions are nearly thermoneutral, a computation-guided approach was used to predict thermodynamically favorable reactions. Thus, a variety of allene substrates could be converted to the products **178** – **181**. However, when R was a TMS group, no product formation was observed and there was decomposition of the starting material.

Building upon stoichiometric studies by Kochi and Wallis, the use of catalytic osmium tetroxide with benzene (**1**) under UV irradiation resulted in the formation of cyclitol derivatives **182** and **183** (Scheme 33).[73,74] The proposed mechanism of this transformation was based upon the development of a charge-transfer interaction between benzene and osmium tetroxide. Thus, upon formation of this ground-state complex, excitation with UV light led to electron transfer and formation of the osmate ester, which was converted to the inositol or conduritol equivalent in the presence of an oxygen-transfer reagent/oxidant like barium perchlorate or sodium bromate. The crude reaction mixture was treated with sodium disulfite and acetylated to form the tetra- (**183**) or hexaacetate (**182**).[73] Substituted arenes, including toluene and halogenated arenes also proceeded to the corresponding polyhydroxylated products, but with lower reactivity. Using sodium bromate as the oxygen transfer reagent, alkyl bromide **184** could be produced in 8% yield under osmium catalysis.[74] This intermediate was converted to pinitol (**185**) after epoxide formation, nucleophilic opening of the epoxide, and acid-catalyzed deprotection of the acetonide.

While the 1,3-dipolar cycloaddition between azomethine ylides and polynuclear arenes was first reported in 1971 by Huisgen,[75] these dearomative processes have seen further exploration and development only recently.[76,77] For example, intermolecular reaction between electron-withdrawing nitroarenes and electron-rich, nonstabilized azomethine ylides, generated *in situ* from a silylated hemiaminal and trifluoroacetic acid, gave *mono*- or *bis*-cycloadducts **186** – **191** (Scheme 34). The dipole addition across a nitroarene occurred with carbon-carbon bond formation at the *ipso* position. For the arene substrates that underwent *bis*-cycloaddition, the second dipole component added from the opposite face with respect to the first. The regioselectivity for this transformation was highly substrate dependent as seen for products **186** – **188**. For naphthalene nitroarenes **189** and **190,** significant yields of the *mono*-cycloadducts were obtained, likely due to the extra stabilization of the styrene product. Additionally, heteroarenes, such as quinoline derivative **191**, reacted under these conditions. A concerted mechanism was proposed for this transformation, although charge-transfer or stepwise radical mechanisms could not be ruled out.

Similar selectivities were observed using palladium-catalyzed dearomative [3+2] cycloaddition of trimethylenemethane with electron-deficient arenes (Scheme 35).[78] In the presence of $Pd(dba)_2$ and phosphoramidite ligand **192**, a number of different nitroarenes successfully underwent dearomatization

to form the racemic products **194** – **197**. Interestingly, 1-nitronaphthalene gave rise to a 1:1 mixture of the [3+2] and [4+3] cycloadducts (not shown); however, placing a methyl group at the 2- or 4- position led to exclusive formation of complementary cycloadducts **196** and **197**. Moreover, when the reaction was conducted using chiral *bis*-diamidophosphite ligand **193**, the alkynyl fused ring systems **198** and **199** were produced in 77% and 63% yield and 97.5:2.5 and 92.5:7.5 er, respectively.

Lewis acid activation of aryl-substituted α,β–epoxy or aziridinyl enolsilanes could induce a formal intramolecular dearomative [4+3] cycloaddition (Scheme 36).[79] This reaction was proposed to proceed in a stepwise manner, with the attack of the arene ring onto the epoxide forming an intermediate cyclohexadienyl cation that was then trapped by the silyl enol ether to give the product. Several aromatic substrates delivered tricyclic products, with yields depending on the length of the tether. Thus, the yield of the desired 7,6,5-ring fusion product **200** was 22%, while homologated 7,6,6-analogue **201** was produced in 43% yield. A more electron-rich dimethyl-substituted substrate delivered **202** in 89% yield. For a substrate containing an aziridine, the product **203** was produced in 67% yield. Polynuclear arenes also worked well, as exemplified with 1-naphthalene derived **204**. In this case, a stereochemical outcome for the observed selectivity could be rationalized by minimization of the developing 1,2-torsional strain compared to 1,3-diaxial strain (**205** vs. **206**).

Phenoxonium-based electrophiles were employed to dearomatize unactivated arenes (Scheme 37).[80] The use of tailored sulfone-appended phenol derivatives with hypervalent iodine reagents produced dearomatized products **210** – **212**. The sulfone group was required to stabilize the positive charge in phenoxonium intermediate **207**, which was generated from the phenol and *bis*(pivalate)iodobenzene (PIB) and trapped with an aromatic dipolarophile (**207**→ **208**→ **209**). Several arenes participated in this reaction, including benzene (**210**), naphthalene (**211**), and iodobenzene derivatives (**212**). The phenol moiety could be replaced with an aryl sulfonamide, which resulted in generation of the corresponding dihydropyrrole derivatives (not shown).

The Buchner reaction is an important reaction that expands aromatic rings into cycloheptatrienes, and many developments and applications of this transformation to the synthesis of natural products have been documented.[81] Recently, a rhodium-catalyzed intramolecular cyclopropanation of simple arenes was reported, securing norcaradiene products with a highly decorated cyclopropane core (Scheme 38).[81] In particular, acceptor-acceptor diazo compounds proved optimal and gave products **213** – **218**. It is of note that the *para*-substituted substrates gave more stable norcaradiene products, as the analogous *meta*-substituted compounds readily underwent C–C bond scission/rearomatization to benzo-fuzed cycloheptanones. Moreover, the substituent on the *N*-atom of the amide-linked substrates (**216** – **218**) played an important role in decreasing competitive carbene dimerization, likely through sterically-induced amide conformations.

8. Arenophile-mediated dearomatizations

A conceptually new dearomative platform was recently reported based on photochemical dearomative *para*-cycloaddition between arenes and small molecules termed arenophiles (e.g. *N*-methyl-1,2,4-triazoline-3,5-dione, MTAD, **219**),[82] followed by subsequent transformations of the resulting cycloadducts (Scheme 39). The underlying principle of this approach is that cycloaddition with arenophiles can be seen as an isolation of two π–bonds in the aromatic starting material *via* formation of the bicyclic intermediate **220**. This renders them amenable to further olefin-type reactions, affording functionalized compounds **221**. Afterwards, a retrocycloaddition of the arenophile moiety provides diene **222**; alternatively, fragmentation leads to 1,4-*syn*-diaminocyclohexene derivative **223**.

This arenophile-based strategy was used for dearomative *syn*-dihydroxylation (Scheme 40).[82] Thus, MTAD cycloaddition and subsequent *in situ* modified Upjohn dihydroxylation delivered functionalized bicycle **224**. Tosyl amide proved to be crucial, as it facilitated osmate ester hydrolysis at lower temperatures. After acetonide protection to form **225**, cycloreversion was accomplished via urazole hydrolysis to the bicyclic hydrazine and subsequent oxidation to the diazene. This could be achieved in one pot using hydrazine or KOH for hydrolysis and Cu(II) chloride as the oxidant. Using this sequence, a range of benzene derivatives was converted to the corresponding dihydrodiols **228** – **231**. In contrast to reactions requiring UV irradiation, halogen-containing substrates, such as bromobenzene (**231**), as well as heteroatom-based functional groups at the benzylic position (e.g. **229**) were tolerated. Moreover, this method enabled direct preparation of small and functionally-dense hydroxylated biologically active compounds, such as MK7607 (**232**) and a desmethylated phomentrioloxin analogue (**233**) from feedstock materials such as benzyl acetate and bromobenzene. It is of note that this dearomative protocol provided dihydrodiols that are orthogonal to the enzymatic process known as microbial arene oxidation.

As an alternative, cycloadduct **225** could be converted to the corresponding diamine derivative **227** by a two-step protocol involving urazole hydrolysis/hydrazine benzoylation and SmI_2-mediated cleavage of N–N bond. Again, a series of benzene-derived cycloadducts were successfully converted to the corresponding diaminodiols **234** – **237**. Importantly, since cycloaddition/dihydroxylation proceeded in a highly regio- and diastereoselective fashion, single constitutional and diastereoisomers were obtained. Finally, polynuclear arenes also proved to be good substrates for this process and could be diaminodihydroxylated in two steps. After cycloaddition and *in situ* dihydroxylation, the resulting oxidized cycloadducts underwent urazole fragmentation with hydrazine and Raney nickel-mediated hydrogenolysis to furnish products **238** – **240**. Halogens, such as bromo-substituted naphthalene (**238**), and heterocycles, attached as pyridine (**239**), or embedded as in case of acridine (**240**) were well tolerated in this two-step sequence.

This methodology was also applied to the total synthesis of the Amaryllidaceae alkaloids lycoricidine (**243**) and narciclasine (**244**).[83] Using a Narasaka-Sharpless variant of the dearomative dihydroxylation

strategy, bromobenzene (**241**) was converted into functionalized boronic ester **242**.[84] This compound was transformed into lycoricidine in a few additional steps, including a key transpositive Suzuki coupling and nitroso Diels–Alder reaction. Narciclasine (**244**) was achieved through late-stage hydroxylation of a lycoricidine intermediate.[85]

Similarly, an arenophile-based dearomative platform was also applied to chemoselective reduction of arenes (Scheme 41).[86] Thus, after cycloaddition with MTAD, the resulting cycloadducts were exposed to diimide, generated *in situ* from potassium azodicarboxylate and acetic acid, resulting in the reduced bicycles **245**. Several benzene derivatives were dearomatized using this process, with the reduction occurring exclusively at the least substituted olefin within the cycloadduct. Subsequent cycloreversion, using base and $CuCl_2$ as an oxidant, provided cyclohexa-1,3-dienes **246**. Alkyl (**248**), silyl (**249**), alcohol (**250** and **252**) and amine (**251**) containing substrates worked well, and benzylic heteroatom-incorporating substituents (**252** and **253**) were tolerated under these conditions. In addition to providing complementary products to Birch reduction, as well as extending the arene substrate scope to allow reduction of benzylic heteroatom-containing starting materials, this process also provided different site selectivity in the reduction for 2-phenylbenzoic acid (**254**), reducing the more electron rich phenyl group. Moreover, reduced cycloadducts of type **245** were converted to the corresponding *syn*-1,4-diaminocyclohexene derivatives **255** – **259** using the SmI_2-mediated fragmentation conditions described above. Polynuclear arenes underwent site-selective dearomative *bis*-1,4-hydroamination in two steps; after cycloaddition/reduction the intermediate cycloadducts were fragmented using hydrazine for urazole cleavage and hydrogenation. In addition to naphthalenes (**260**, **261**), more elaborated heteroarenes (**262**, **263**) also gave products as single constitutional and diastereoisomers. Importantly, the arenophile motif could be formally substituted through retrocycloaddition/cycloaddition sequence, as exemplified in the naphthalene-derived saturated cycloadduct **265**. After hydrolysis of the urazole to the cyclic hydrazine, a simple oxygen oxidation expelled nitrogen and formed endoperoxide which underwent Kornblum– DeLaMare rearrangement to γ-hydroxy ketone **266**. Similarly, hetero-Diels–Alder reaction using nitrosobenzene, followed $CuCl_2$-mediated N–O cleavage, afforded *syn*-1,4-aminoalcohol **267**.

In addition to olefin functionalization chemistry, arene-arenophile cycloadducts are also competent substrates for transition metal catalyzed reactions. Specifically, low-valent metals could undergo oxidative addition, expelling one of the *bis*-allylic bridgehead nitrogens and forming unsaturated complexes amenable to nucleophilic addition. For example, the application of nickel catalysis in combination with Grignard reagents gave 1,2-*trans*-carboaminated products **268** (Scheme 42).[87] This transformation likely proceeds through oxidative addition to form the Ni-bound substrate (**269** → **270** → **271**) and subsequent transmetalation to deliver cationic cyclohexadienyl species **272**. Such intermediates are known to react with nucleophiles exclusively at the termini, due to the localization of positive

charge.[88] Thus, reductive elimination (**272** → **273**) and diene decomplexation reveals the carboaminated product **274**. In case of benzene, the corresponding cyclohexadienyl intermediate **271** is symmetric; therefore, using a chiral Phosferrox *P,N*-ligand resulted in an efficient desymmetrization. A range of aryl (**275** – **277, 280**) and alkenyl (**278** and **279**) magnesium reagents gave products in good yields, high enantioselectivity, and exclusive 1,2-*trans* selectivity. Using this dearomative protocol, naphthalene also underwent desymmetrization, delivering product **280**.

Moreover, this method could be used for dearomatization of substituted arenes, albeit in a racemic fashion with dppf as the ligand. Alkyl-, benzyl alcohol, or trifluoromethyl-substituted benzene derivatives (**281** – **283**), as well as naphthalene-based substrates possessing a variety of functional groups (e.g. **284** and **285**) reacted successfully with phenylmagnesium bromide. Importantly, heterocycles could also be used, as demonstrated with quinoline derivative **286**. Although only 1,2-*trans* selectivity was observed, these substrates also led to formation of constitutional isomers, resulting from complementary ring opening of nonsymmetrical arene-arenophile cycloadducts. Finally, this dearomatization strategy provides intermediates that can be elaborated further. Accordingly, naphthalene (**264**) could be readily converted to optically pure amine **287**, ketone **288**, or tetraline derivative **289** in just a few steps. Furthermore, benzene underwent dearomative 1,2-carboamination reaction to deliver diene **290** in 75% yield and 98:2 er, which was a key intermediate in the total synthesis of pancratistatin (**291**).[89]

Different transition metals have exceptionally rich repertoires of nucleophilic additions to their complexes containing unsaturated ligands, as well as unique metal-dependent mechanisms that can deliver complementary products. In fact, this was the case for palladium-catalyzed ring-opening of arene-arenophile cycloadducts (Scheme 43).[90] As this metal cannot support an η^5–coordination mode, carboamination gave the complementary 1,4-*syn* products **292**. Thus, exposing an arene to MTAD and visible light and forming bicyclic intermediate **220**, followed by subsequent addition of a Pd catalyst and the lithium enolates of esters or ketones, provided dearomatized products in a 1,4-*syn* fashion. Mechanistically, this reaction proceeds through oxidative addition (**220** → **293**) and outer-sphere attack of the enolate (**293** → **292**), causing double inversion and net retention. The regioselectivity of this process was the result of attack at the allylic or benzylic position in the polarized Pd-allyl system. A variety of ketones, including aryl (**294**, **297**, **298**, **308**, and **309**) and both linear and cyclic aliphatic (**295**, **299**, and **300**) nucleophiles were successfully incorporated into an aromatic core. Esters (**296**, **301**, **306**, and **307**) also proved to be good nucleophiles for this dearomatization. Unsymmetrically substituted enolates gave diastereoisomeric products (**294**, **298**, **299**, and **307**) with 2.1:1 – 20:1 dr. In addition to benzene and naphthalene, substituted arenes yielded dearomatized compounds **308** and **309**, albeit as a mixture of constitutional isomers, with ratios depending on the size and position of substituents in the substrate. The unsaturated products offered numerous possibilities for downstream manipulations, including complete reduction (**302**) or conversion to diketone **303**, dioldiketone **304**, and amine **305** in

just a few steps. Finally, the enantioselectivity of this transformation was established for naphthalene. Thus, *t*Bu-Phosferrox proved to be a good ligand for reactions with ketones, as exemplified with formation of **310** in 68% yield and 97:3 er. As a second example, DTBM-SEGPHOS provided optimal results for esters, forming **311** in 72% yield and 95:5 er.

Conclusion

While Birch reduction, dearomative hydrogenation, and the limited collection of addition and cycloaddition reactions represented the only viable options for the dearomatization of nonactivated arenes just a few decades ago, this field has seen significant expansion and refinement in recent years. Specifically, dearomative hydrogenations now permit the incorporation of traditionally incompatible substituents and pendant functional groups, such as fluorine atoms or ketones, without undesired further reduction. Moreover, the first example of catalytic, enantioselective dearomative reduction represents a recent milestone for this class of transformation and suggests that there will likely be more development in this area in the future. Radical-based processes have also seen a renaissance, especially with respect to dearomative ketyl addition into mono- and polynuclear arenes.

Perhaps the most extensively developed class of reactions, at present, is the transition-metal-mediated dearomative functionalizations. Though the numerous opportunities that reactions of η^2– and η^6–metal bound arenes offer are awe-inspiring, the stoichiometric nature of these processes has prevented their widespread use. Perhaps recent reports, which showcase the ease of recycling the metal complex, will further pave the way for this chemistry. On the other hand, catalytic transition-metal-based dearomatizations of nonactivated arenes are still relatively underdeveloped and are limited mainly to benzyl halides as substrates.

Historically, the focus of dearomative cycloadditions has been confined to the area of alkene-arene cycloadditions; however, recent methods have provided more general access to products with [2+1], [3+2], and [4+3] connectivity. The use of arenophiles, through which dearomatization occurs via [4+2] cycloaddition, enables olefin-like functionalization to occur at a single double bond of starting arene. In combination with transition-metal catalysis, this chemistry further permits powerful dearomative aminofunctionalizations of nonactivated arenes, providing a unique pathway to highly functionalized small molecules.

Despite the above-mentioned advances, there is still potential for significant growth in this field. In contrast to olefin chemistry, dearomative functionalizations are heavily underdeveloped. The synthetic options available for the introduction of functionality into aromatic frameworks are very limited, compared to the arsenal of reactions that exist for alkenes and dienes. Moreover, functional group compatibility and site-selectivity in dearomative transformations are still very limited, precluding the late-stage application of dearomatizations in more complex

molecular settings. Nevertheless, given the abundance and frequent use of arenes across all molecular sciences, the development and application of dearomatization reactions will likely see steady and continuous growth.

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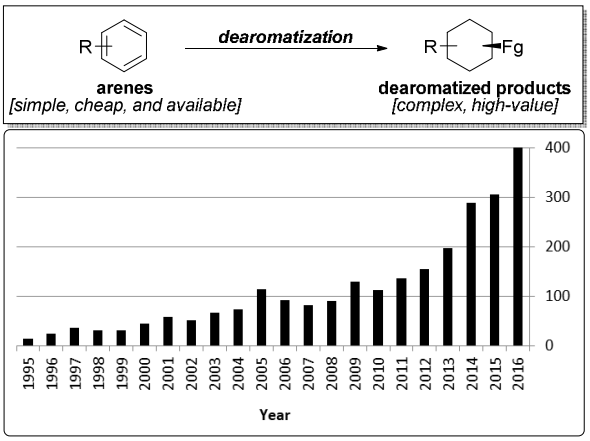
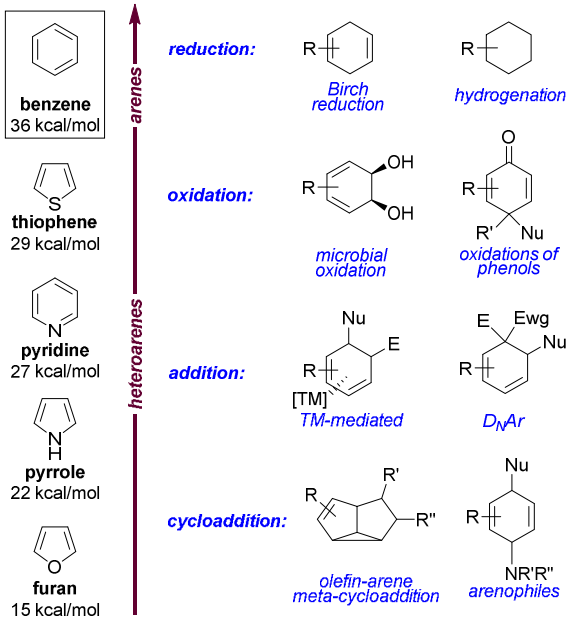
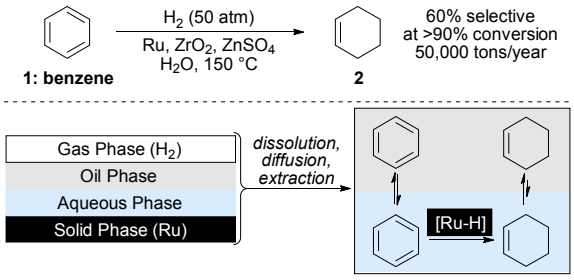


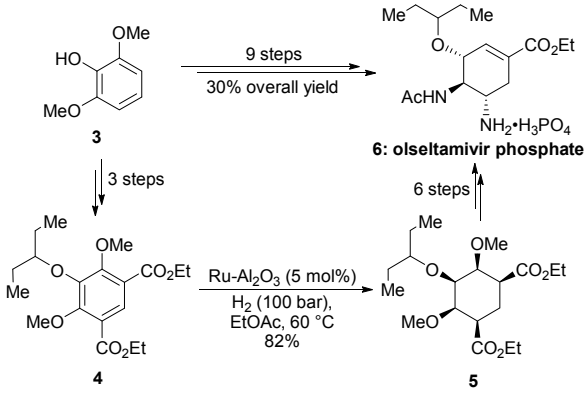
Scheme 1 Dearomatization and number of publications using the term "dearomatization" in the title or abstract since the year 1995.



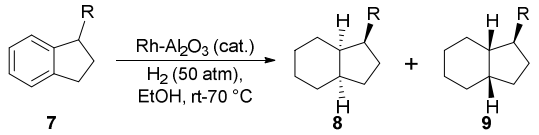
Scheme 2 Resonance stabilization of simple aromatic compounds and general classification of dearomatization reactions.



Scheme 3 Asahi's Chemical Co. chemoselective hydrogenation of benzene (**1**).

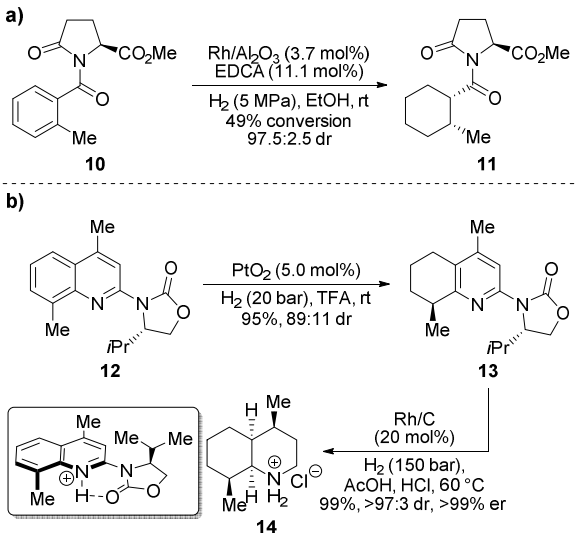


Scheme 4 Synthesis of olseltamvir.

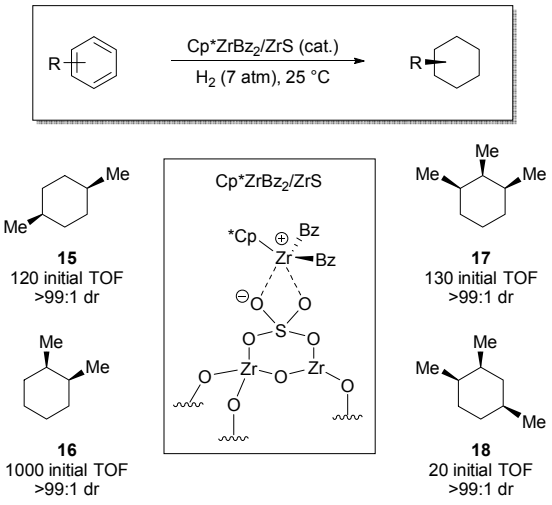


Entry	Substituent R	Yield	Selectivity (8:9)
1	-Me	92%	64:36
2	-NH_2	100%	1.5:98.5
3	-OH	88%	65:35
4	-OMe	91%	88:12
5	-OPr	88%	92:8
6	-CH_2OH	92%	52:48
7	-CO_2H	>92%	84:16
8	-CO_2Me	>92%	85:15

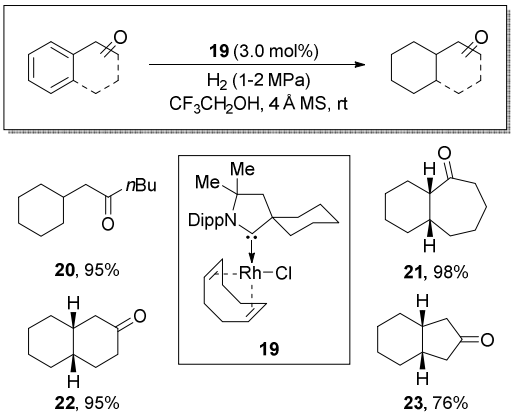
Scheme 5 Directed dearomative hydrogenations.



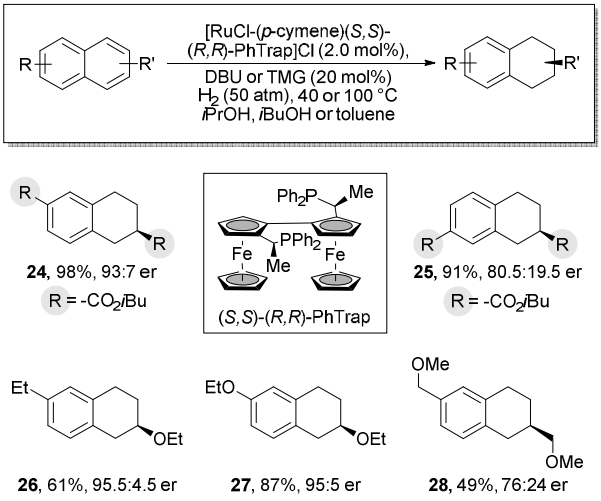
Scheme 6 Diastereoselective dearomative hydrogenation using pyroglutamic acid (a) and oxazolidinone (b) as a chiral auxiliary.



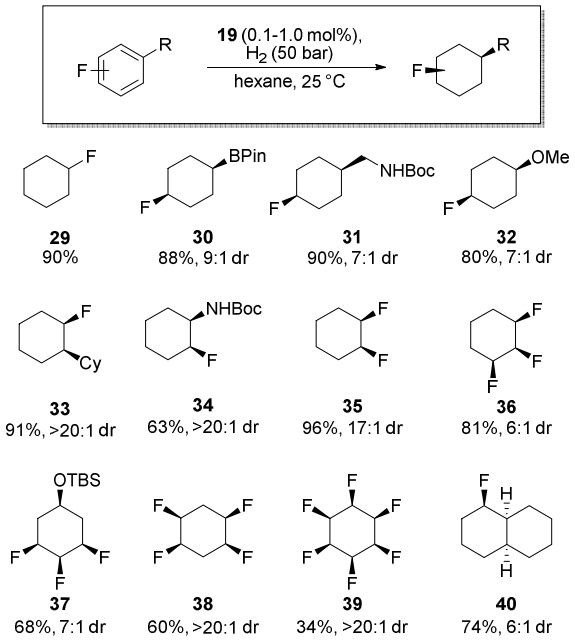
Scheme 7 Dearomative hydrogenation using single site supported catalyst.



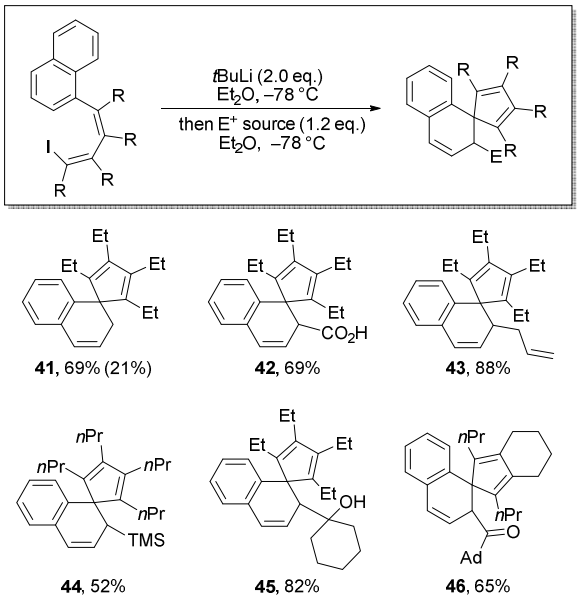
Scheme 8 Dearomative hydrogenation of aromatic ketones (Dipp = 2,6-diisopropylphenyl).



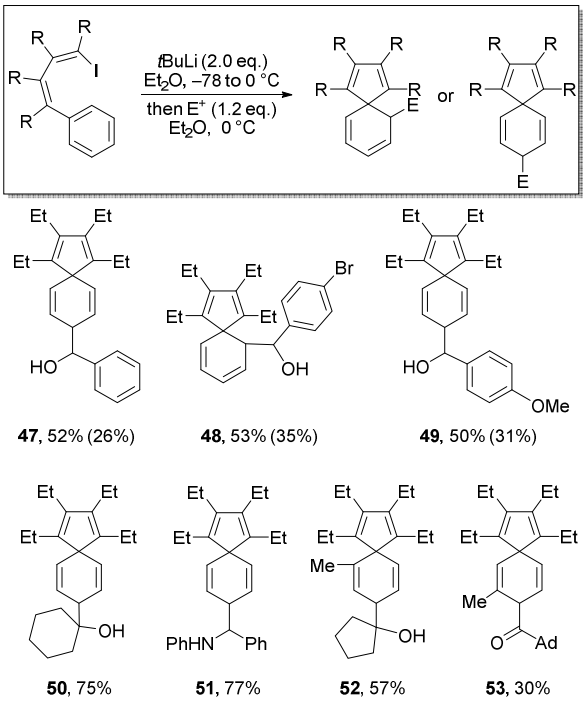
Scheme 9 Ru-catalyzed enantioselective dearomative hydrogenation of naphthalene derivatives.



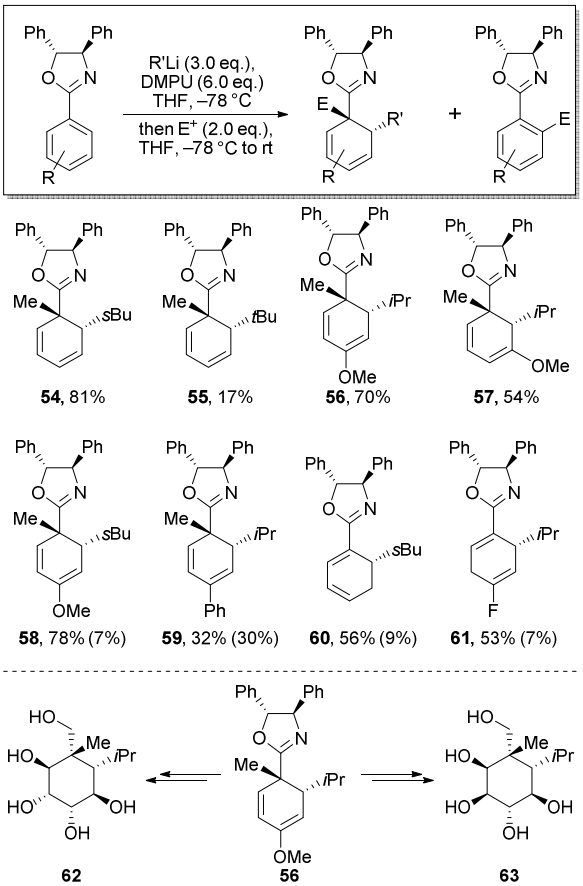
Scheme 10 Hydrogenation of aromatic fluorides.



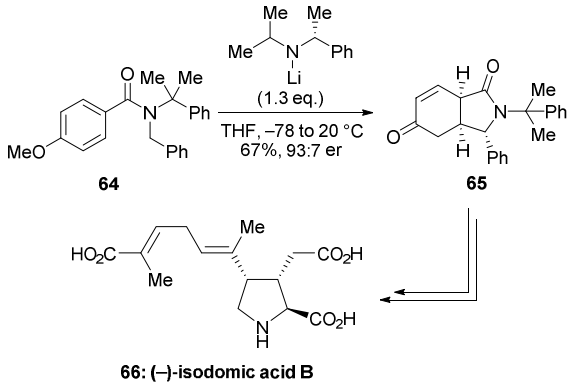
Scheme 11 Intramolecular nucleophilic dearomatization of butadienylithium naphthalene and derivatives.



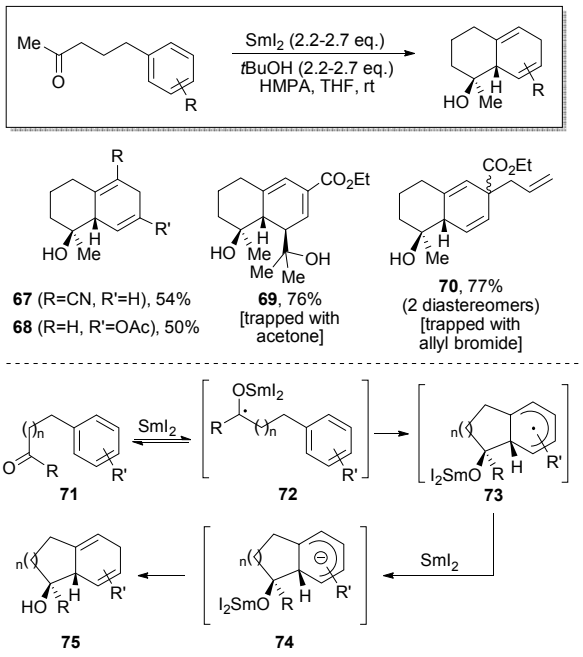
Scheme 12 Intramolecular nucleophilic dearomatization of butadienylithium benzene and derivatives.



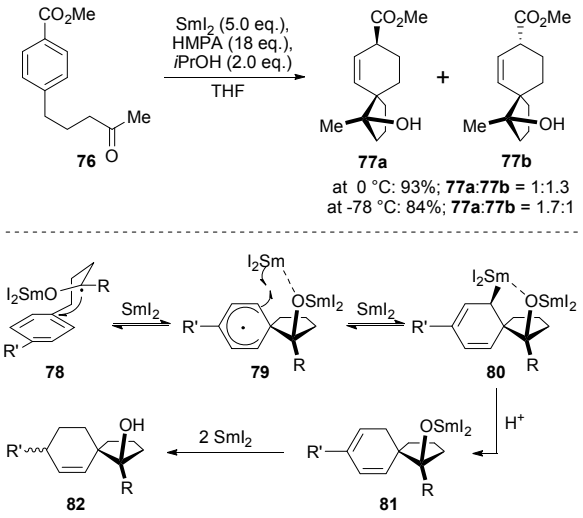
Scheme 13 Dearomatization of mononuclear aryl oxazolines via organolithium addition.



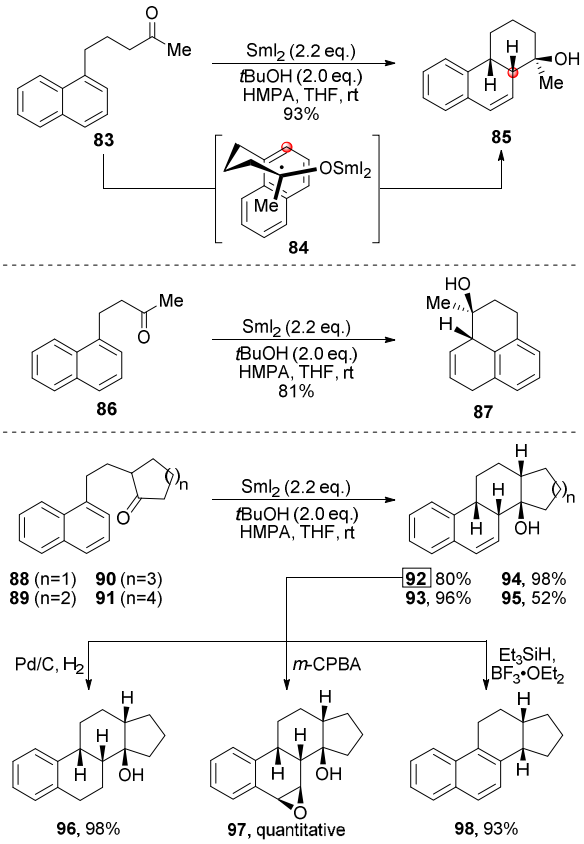
Scheme 14 Enantioselective synthesis of isodomic acid B (**66**).



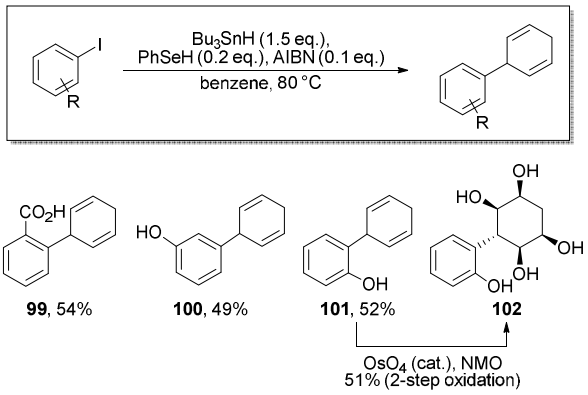
Scheme 15 Intramolecular SmI_2-mediated radical-based dearomatization of mononuclear arenes.



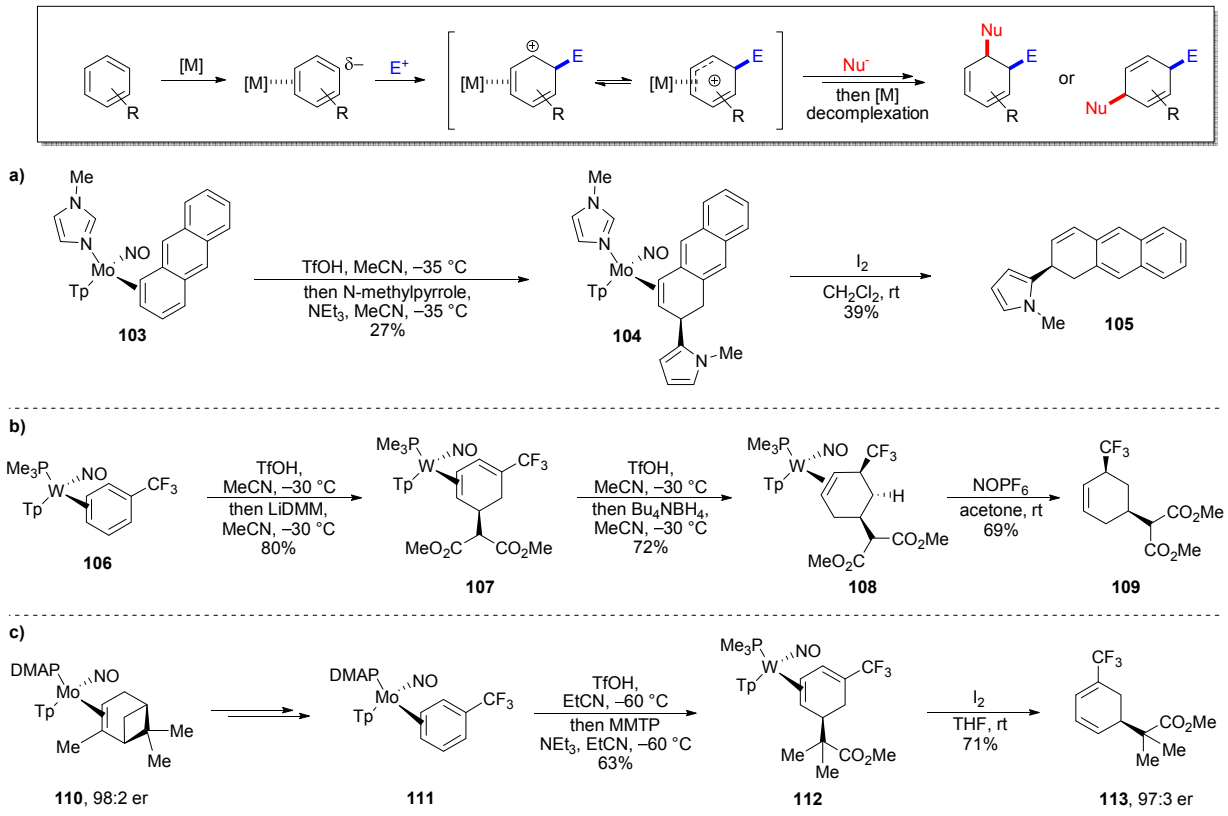
Scheme 16 Intramolecular SmI_2-mediated radical-based dearomatization of a benzoic ester.



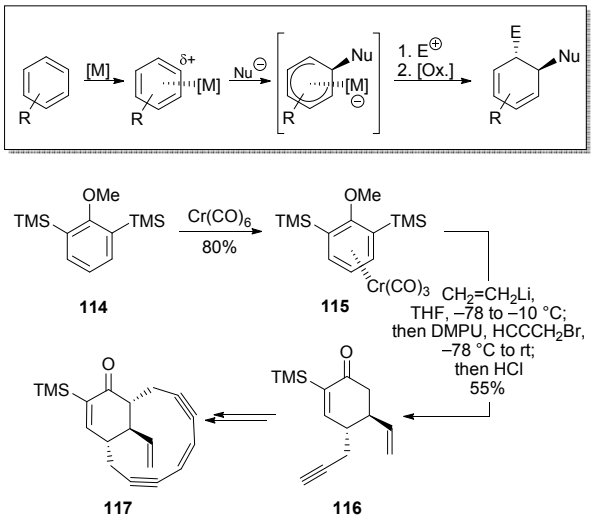
Scheme 17 Intramolecular SmI_2-mediated radical-based dearomatization of polynuclear arenes.



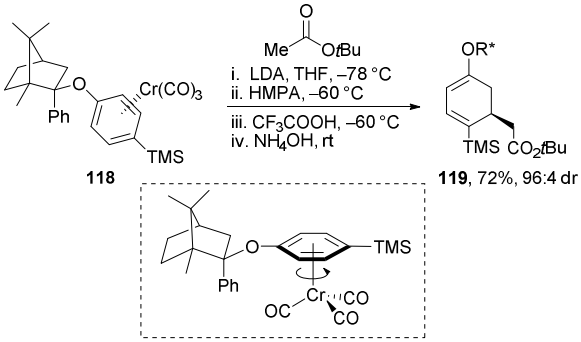
Scheme 18 Dearomative addition of aryl radicals into benzene.



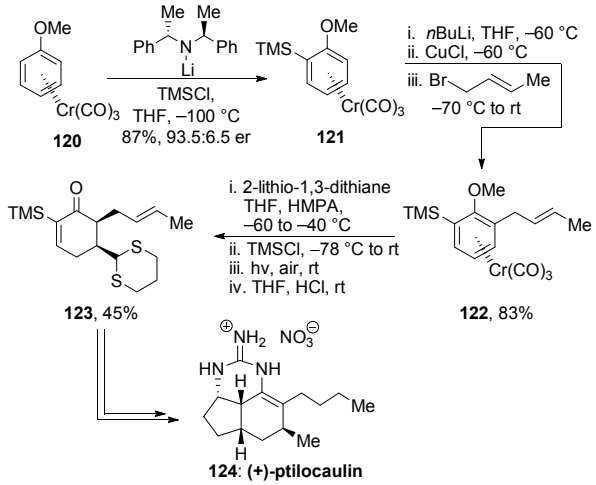
Scheme 19 Transition-metal-mediated dearomative functionalization via η^2–complexation and recent developments.



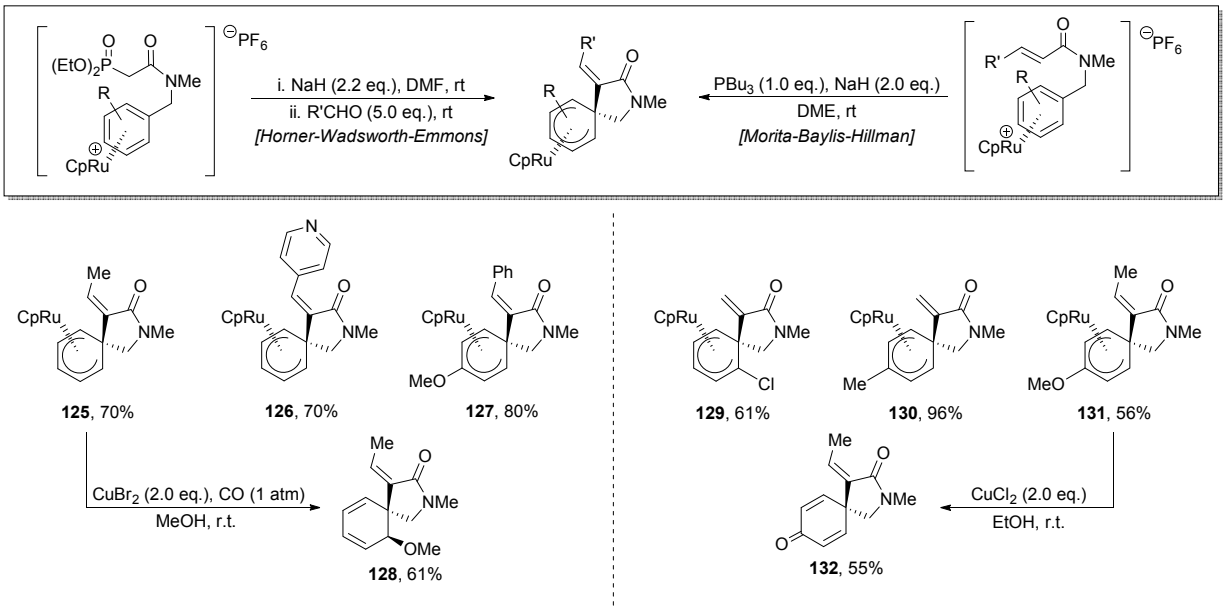
Scheme 20 Transition-metal-mediated dearomative functionalization via η^6–complexation and recent application.



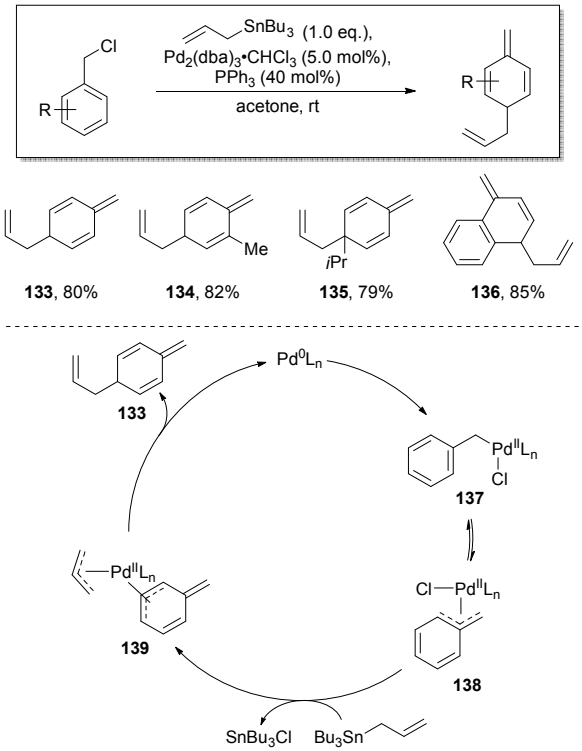
Scheme 21 Diastereoselective chromium-mediated dearomatization using isoborneol-based auxiliary.



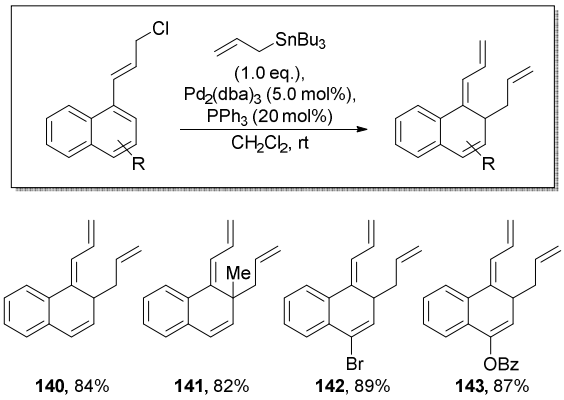
Scheme 22 Total synthesis of (+)-ptilocaulin (**124**).



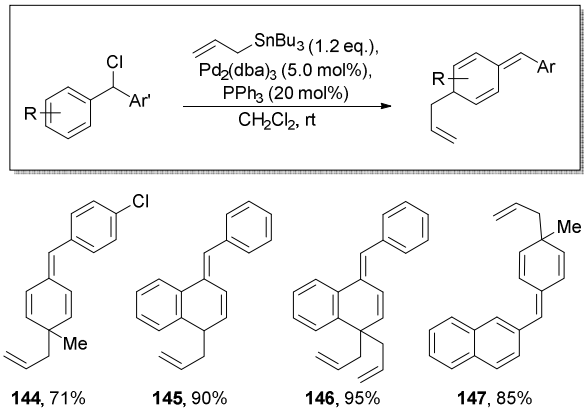
Scheme 23 Ru-mediated dearomatization.



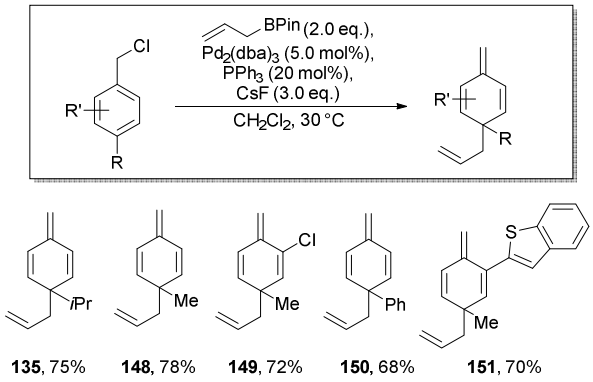
Scheme 24 Pd-catalyzed dearomative allylation of benzyl chlorides.



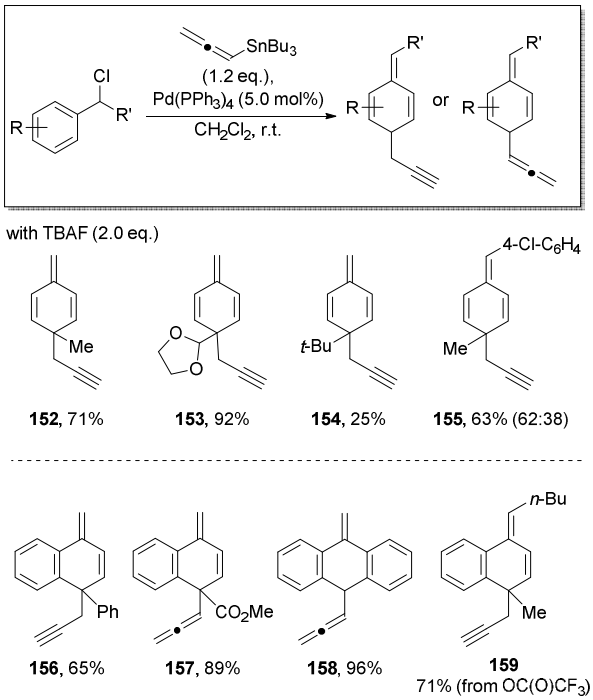
Scheme 25 Pd-catalyzed dearomative allylation of cinnamyl chlorides.



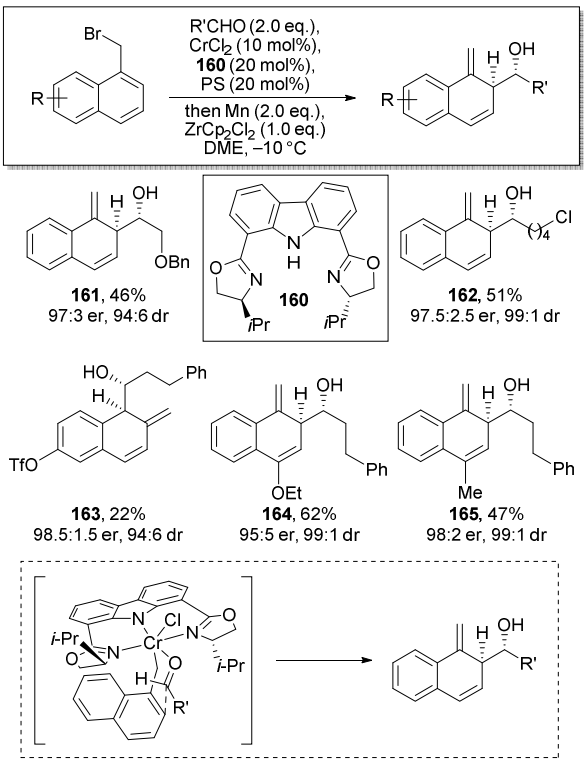
Scheme 26 Pd-catalyzed dearomative allylation of diaryl chlorides.



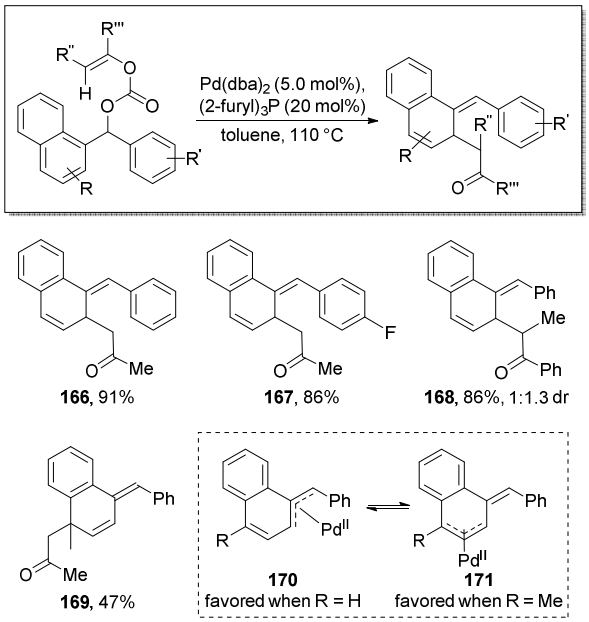
Scheme 27 Pd-catalyzed dearomative allylation of benzyl chlorides with allylboronate.



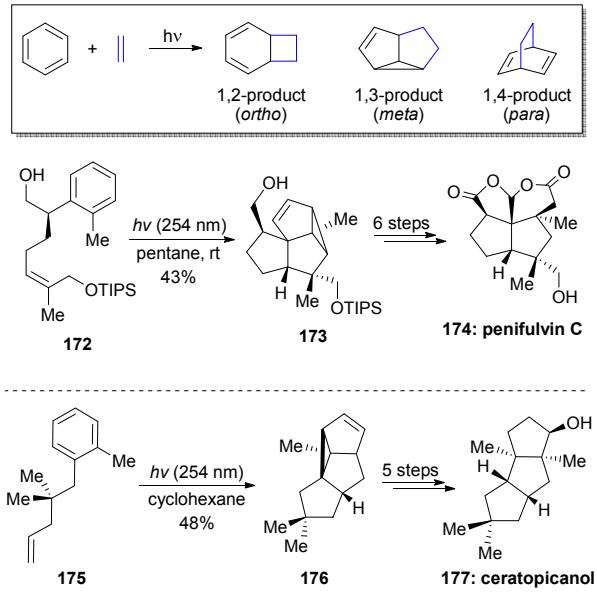
Scheme 28 Pd-catalyzed dearomative allylation using allenylstannanes.



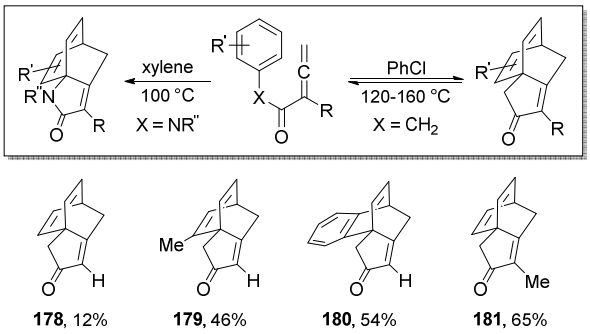
Scheme 29 Cr-catalyzed dearomative allylation of aldehydes using benzyl bromides.



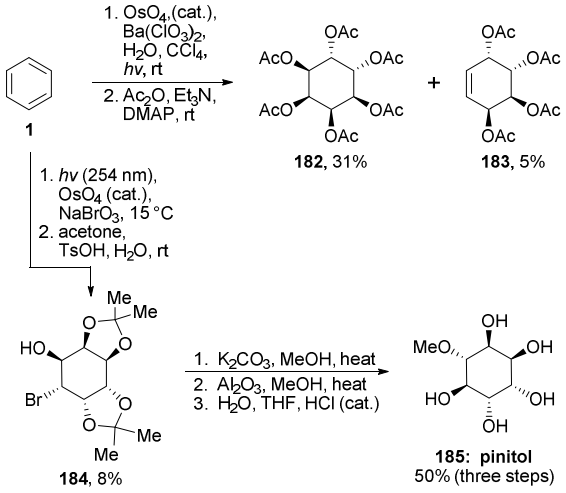
Scheme 30. Dearomative Pd-catalyzed decarboxylative benzoylation.



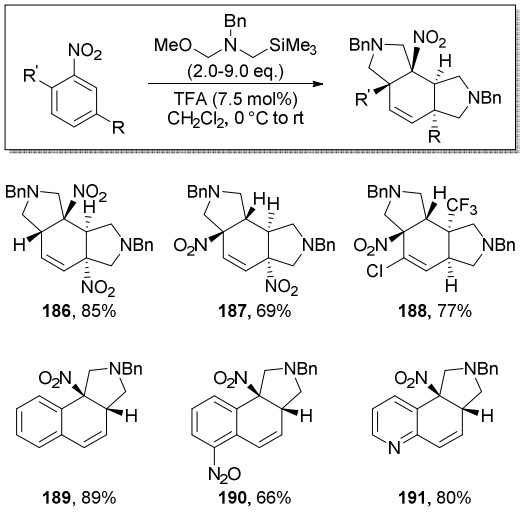
Scheme 31. Alkene-arene dearomative cycloaddition and applications of *meta*-alkene arene cycloaddition in total synthesis.



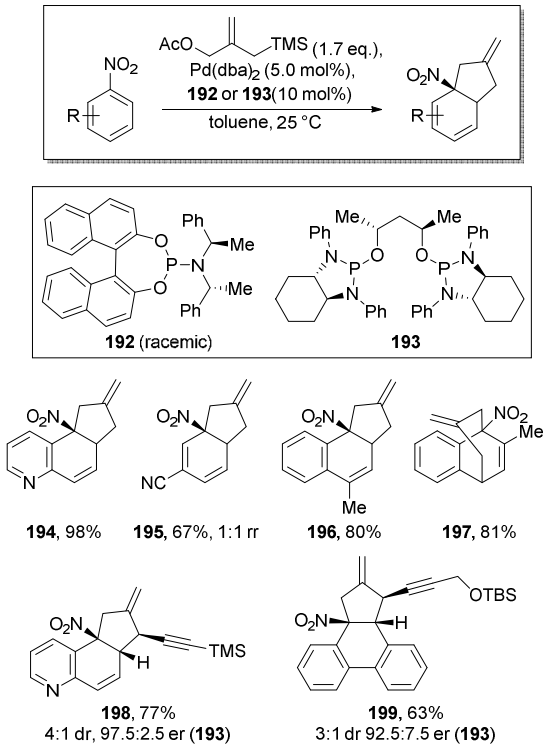
Scheme 32 Arene-allene cycloaddition.



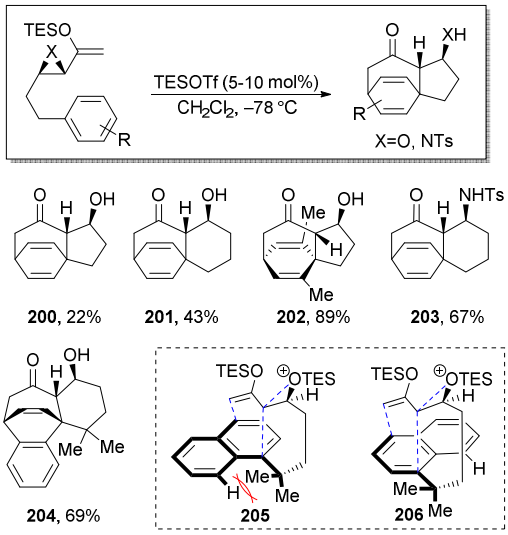
Scheme 33 Os-catalyzed dearomative polyhydroxylation.



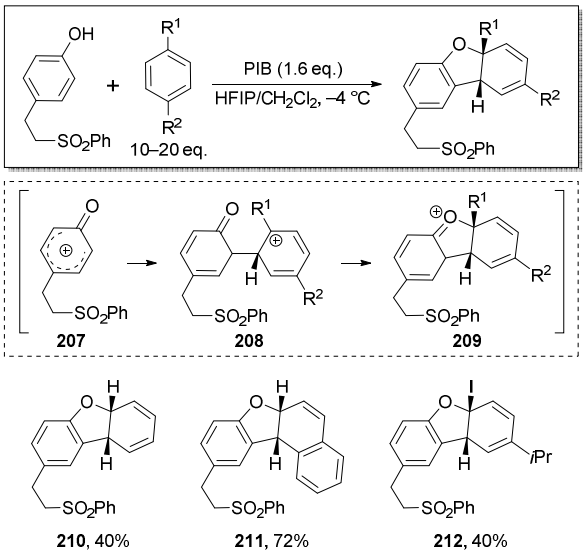
Scheme 34 [3+2] cycloaddition between azomethane ylide and nitroarenes.



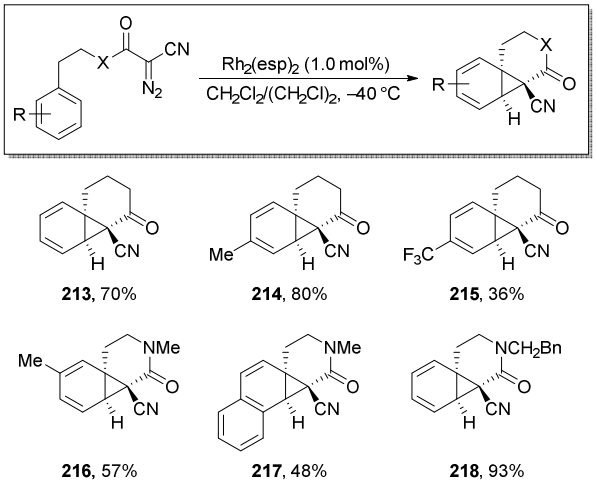
Scheme 35 Pd-catalyzed trimethylenemethane [3+2] cycloaddition with nitroarenes.



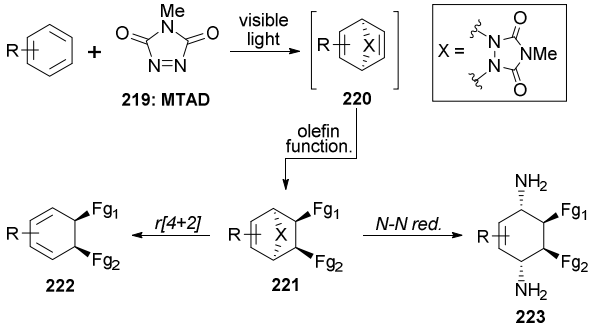
Scheme 36 Intramolecular [4+3] dearomative cycloaddition.



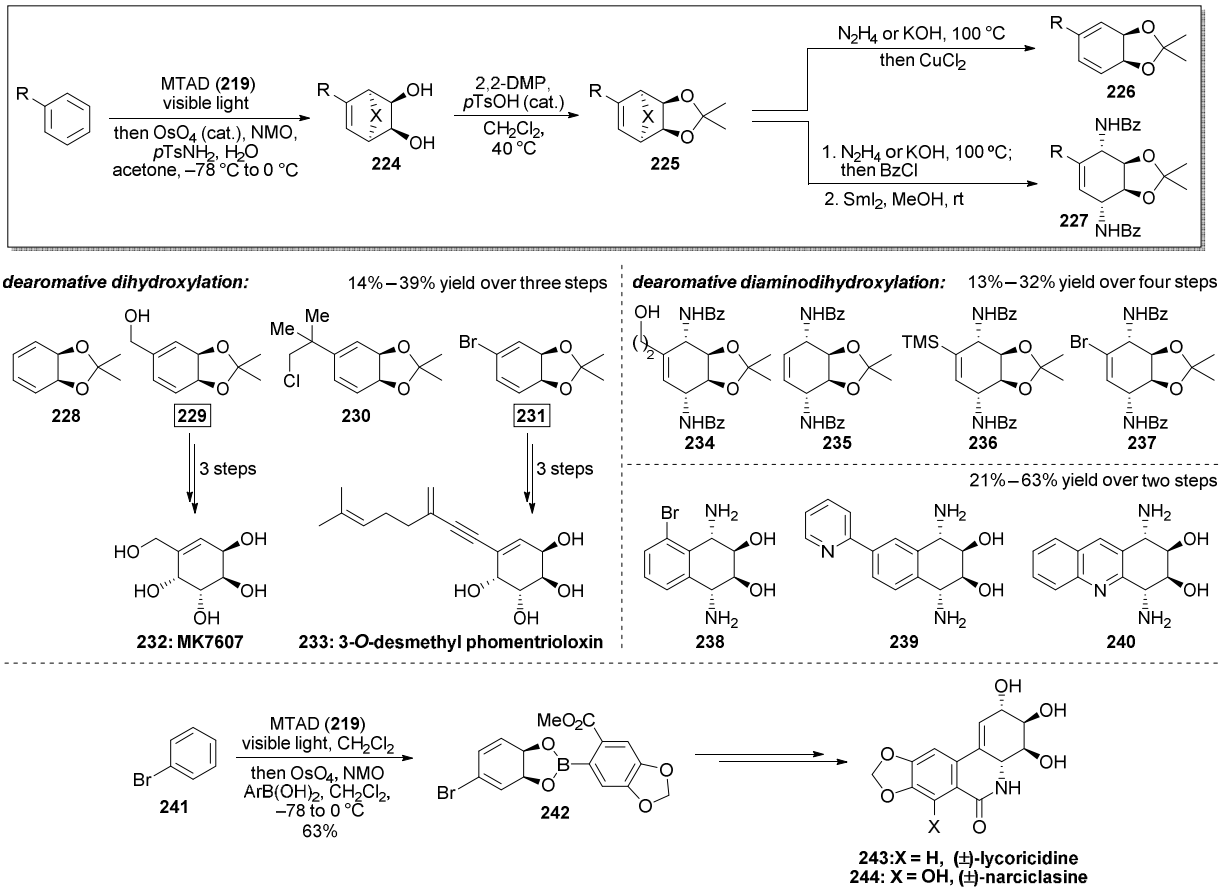
Scheme 37 Phenoxium-based dearomative intramolecular [3+2] cycloaddition.



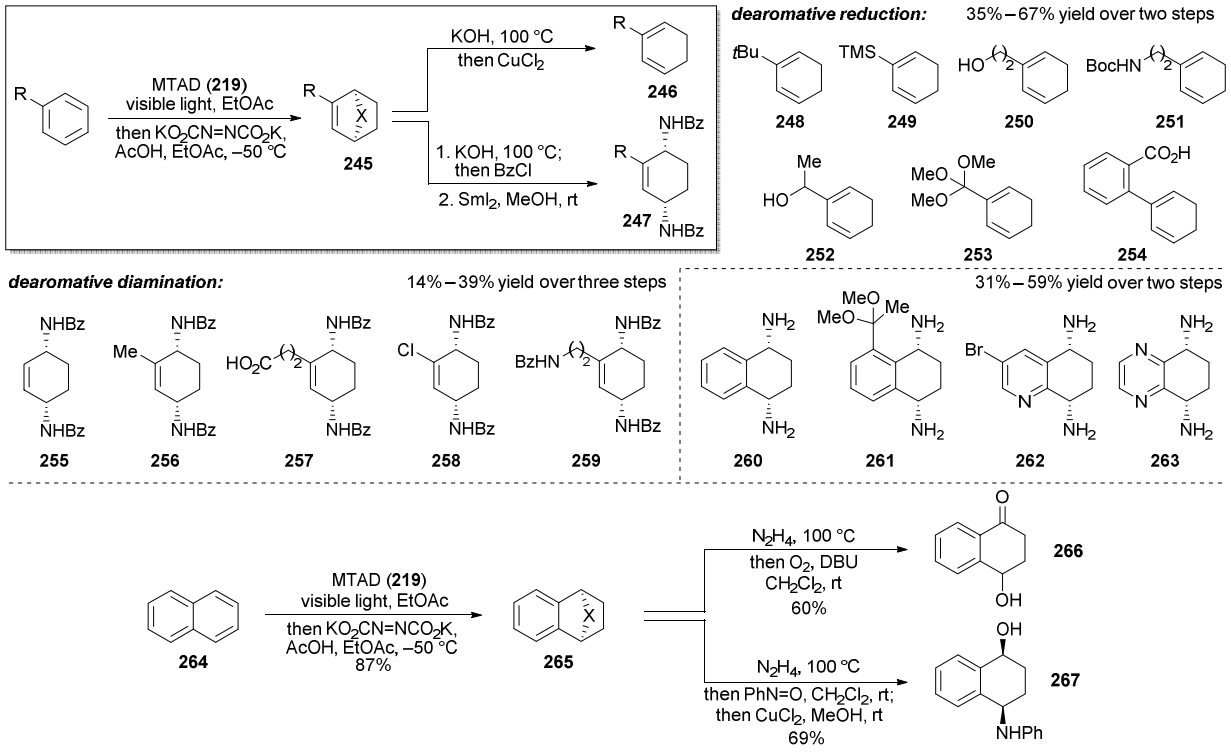
Scheme 38. Rh-catalyzed intramolecular dearomative [2+1] cycloaddition.



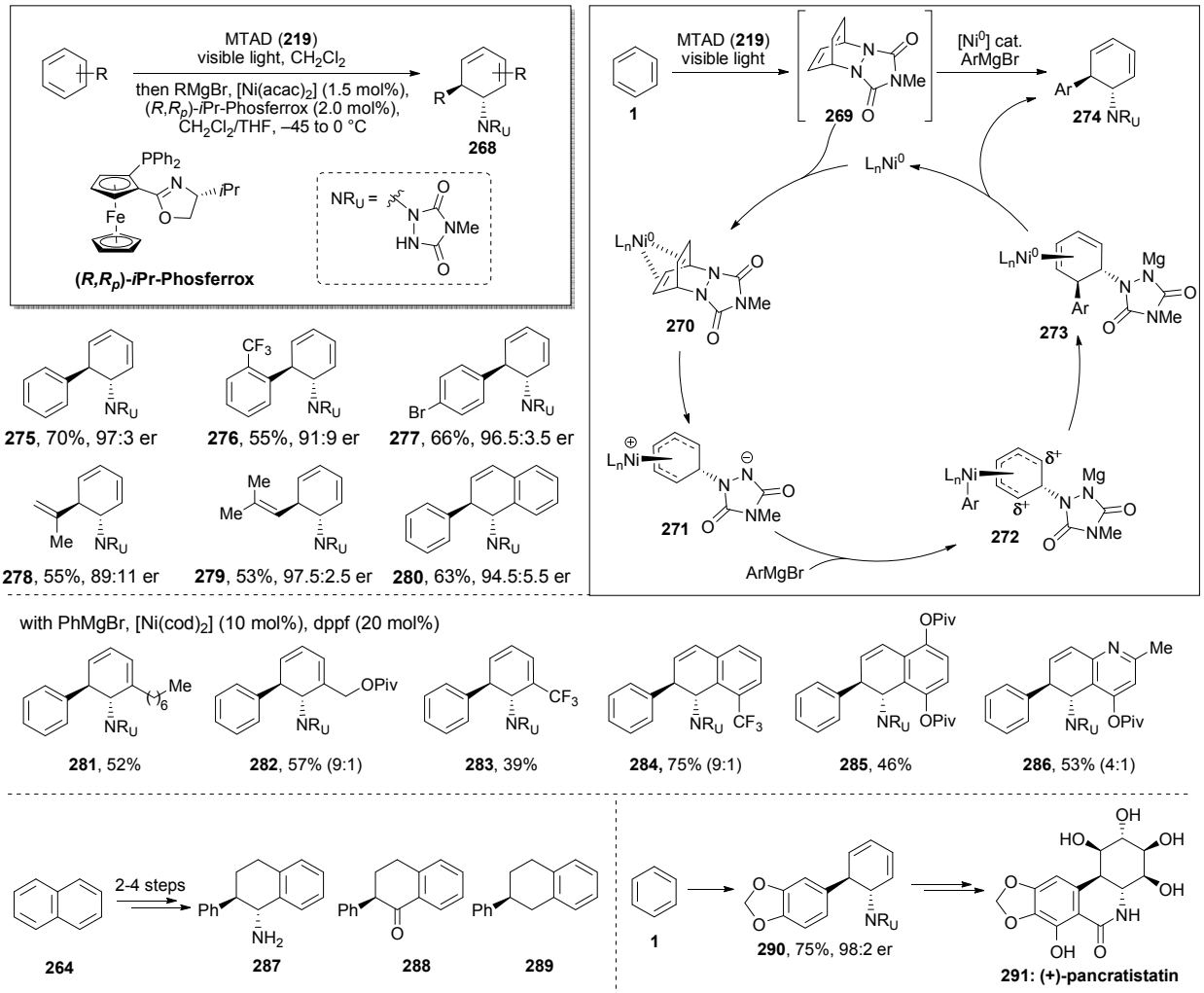
Scheme 39 Olefin-like dearomatization using arenophiles.



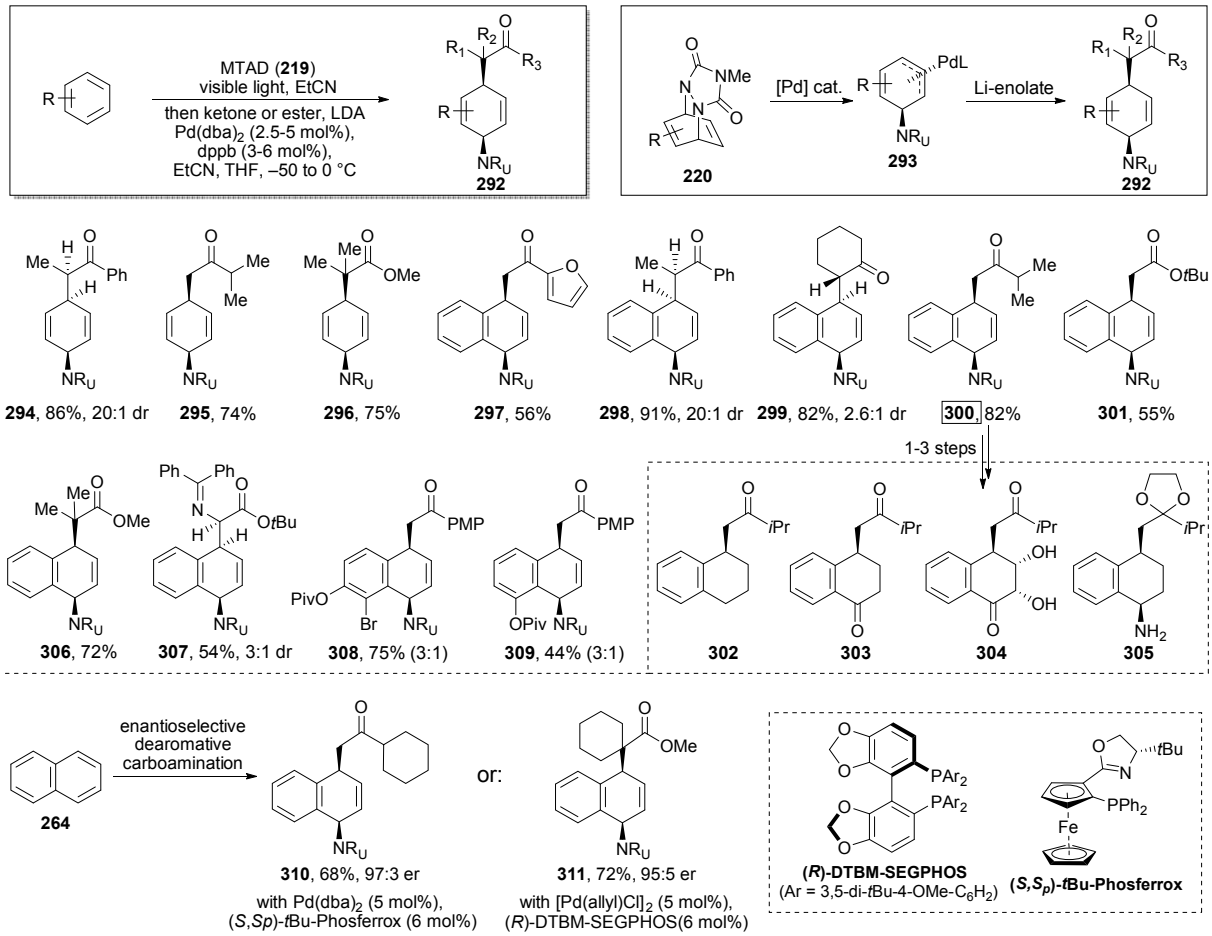
Scheme 40 Arenophile-based dearomative dihydroxylation.



Scheme 41 Arenophile-based dearomative reduction.



Scheme 42 Ni-catalyzed dearomative *trans*-1,2-carboamination.



Scheme 43 Pd-catalyzed dearomative *syn*-1,4-carboamination.

A comprehensive review of recent developments and applications of dearomatization of simple, nonactivated aromatic compounds.