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Asymmetric Catalysis

Catalytic Asymmetric Dearomatization Reactions

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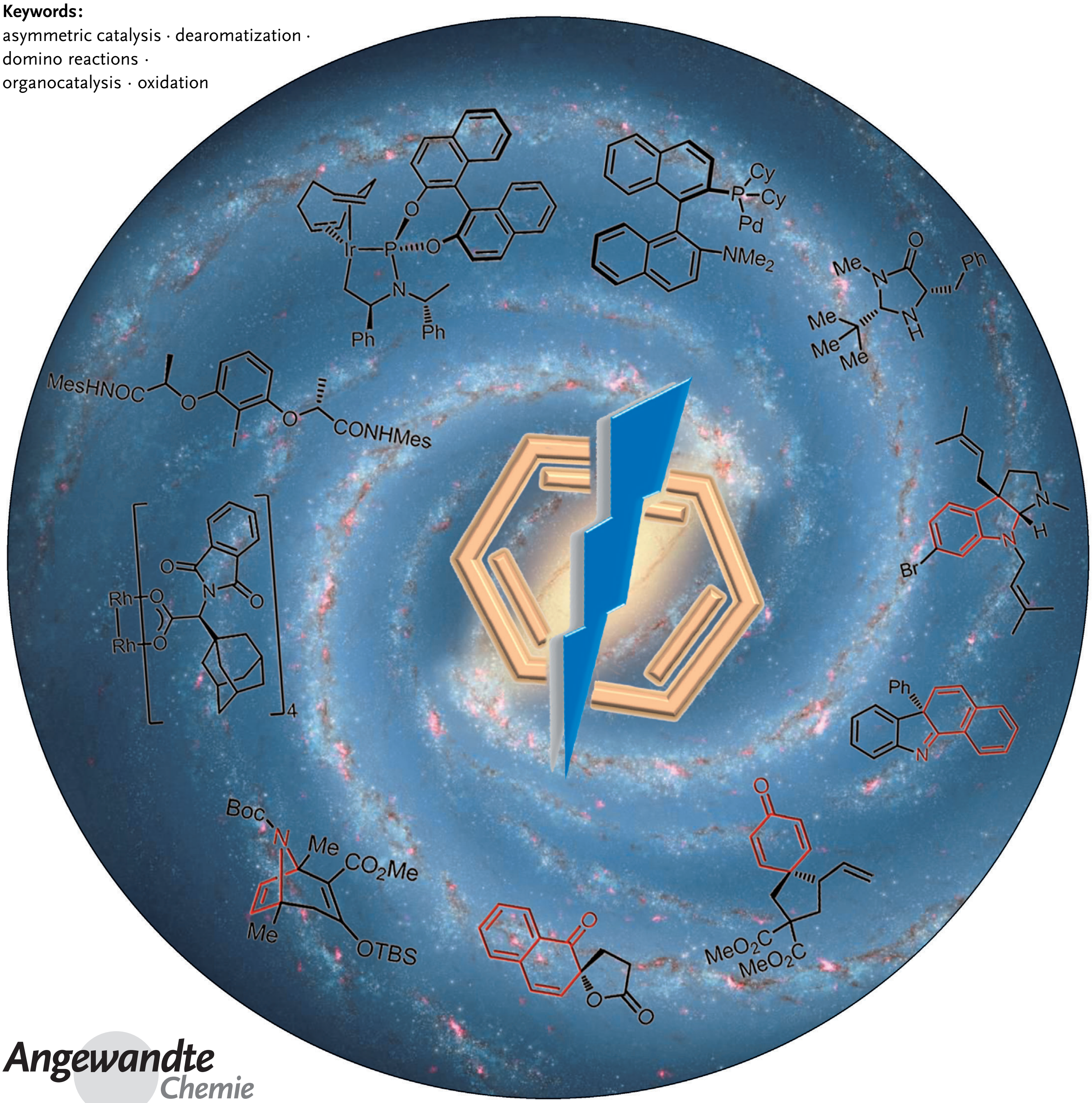
asymmetric catalysis · dearomatization · domino reactions · organocatalysis · oxidation



This Review summarizes the development of catalytic asymmetric dearomatization (CADA) reactions. The CADA reactions discussed herein include oxidative dearomatization reactions, dearomatization by Diels–Alder and related reactions, the alkylative dearomatization of electron-rich arenes, transition-metal-catalyzed dearomatization reactions, cascade sequences involving asymmetric dearomatization as the key step, and nucleophilic dearomatization reactions of pyridinium derivatives. Asymmetric dearomatization reactions with chiral auxiliaries and catalytic asymmetric reactions of dearomatized substrates are also briefly introduced. This Review intends to provide a concept for catalytic asymmetric dearomatization.

From the Contents

1. Introduction

Aromatic compounds are widely distributed in nature and serve as very important synthetic materials in both academia and industry. Significant progress has been made towards the development of highly efficient methods to introduce substituents onto a variety of aromatic rings. Dearomatization reactions are also important transformations of aromatic compounds as they lead directly to a variety of ring systems, including heterocyclic skeletons. Heterocycles are frequently occurring key moieties of natural products and pharmaceuticals. The possibility of forming quaternary carbon centers through intramolecular dearomatization reactions enables the construction of spiro or bridged compounds in an extremely straightforward manner. In fact, owing to their high efficiency in converting relatively simple molecules into much more complicated structures, dearomatization reactions have been applied extensively in the total synthesis of natural products. Moreover, the fully developed methodologies for aromatic substitution have provided versatile arenes that are compatible with dearomatization reactions.

Although many dearomatization protocols have been developed, either as new methods or during the synthesis of functional molecules, known reactions are mainly limited to racemic compounds. Enantioselective processes are rather rare, especially those based on catalytic methods. Furthermore, the majority of enantioselective reactions rely on a strategy of chiral-substrate control. Undoubtedly, the sparsity of enantioselective processes is mainly due to the high energy barrier encountered during the process of dearomatization, which generally requires harsh reaction conditions that make the control of regioselectivity and stereoselectivity very challenging. However, recent progress in both asymmetric dearomatization reactions with chiral reagents and catalytic asymmetric dearomatization reactions has shown the great potential of this area.

Recently, a comprehensive review by Roche and Porco described the application of dearomatization strategies in the total synthesis of natural products.[1] A previous review by Quideau and co-workers summarized the oxidative dearomatization of phenols in natural product synthesis.[2] Several other elegant reviews have also appeared and in most cases focused on a relatively specific topic, such as nucleophilic dearomatization[3] or transition-metal-mediated dearomatization reactions.[4] However, to our knowledge, there has not been a review on the use of catalytic methods for asymmetric dearomatization reactions. Thus, this Review concentrates on the development of various catalytic asymmetric dearomatization processes for the construction of chiral molecules. Some closely related approaches, including chiral-reagent-mediated and diastereoselective dearomatization reactions, are also covered.

Notably, this Review does not discuss the asymmetric hydrogenation of aromatic compounds,[5] a strategy which can also be regarded as a very important branch of dearomatization reactions. Furthermore, the dearomatization of 2-silyloxy-substituted furans, pyrroles, indoles, and thiophenes[6] will not be covered, since compounds of this type are generally synthesized from the corresponding lactones or lactams and are highly reactive. Finally, we have not included enzymatic asymmetric dearomatization reactions, which are particularly effective for simple benzene derivatives.[7,8]

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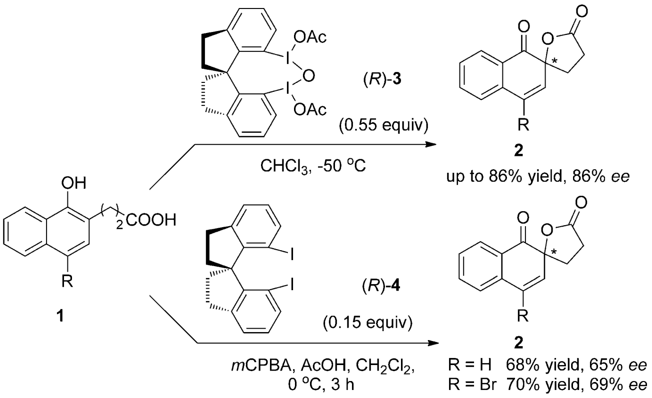
2. Oxidative Dearomatization Reactions

The oxidation of electron-rich arenes or heteroarenes to break their aromatic systems has been known for a long time as an extremely useful concept in organic synthesis. Particularly in the realm of phenol and indole chemistry, many elegant total syntheses of natural products have made use of this powerful method as a key step.[2,9,10]

In the field of oxidative dearomatization reactions, hypervalent iodine compounds have frequently served as oxidants because of their ready availability and straightforward handling. The development of chiral iodanes paved the way for the elaboration of enantiomerically enriched molecules directly from achiral substrates during the oxidative dearomatization process. However, since these chiral hypervalent iodine reagents are typically expensive and potentially explosive, their use in catalytic amounts in conjunction with cheaper and safer co-oxidants has become a practical solution and attracted much attention from chemists.[11] Transition-metal-catalyzed asymmetric oxidative dearomatization reactions with stoichiometric achiral iodanes are definitely another efficient solution. Recently, progress has also been made in the development of oxidants other than iodanes for these transformations. This section is devoted to the enantioselective oxidative dearomatization of electron-rich aromatic compounds.

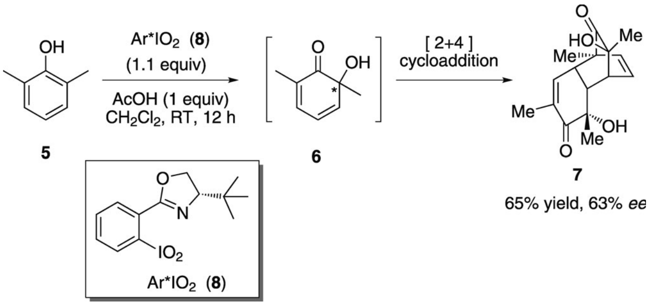
The elaboration of chiral molecules on the basis of oxidative dearomatization reactions of phenols with a chiral auxiliary has been widely applied in the total synthesis of natural products, although this strategy for the construction of complicated chiral compounds is relatively old. More desirable than chiral-substrate control in the asymmetric oxidative dearomatization of phenols and related aromatic compounds is the use of chiral hypervalent iodine compounds as reagents or even catalysts. However, this strategy is very challenging, and significant breakthroughs have been made only recently. In 2008, Kita and co-workers reported the first enantioselective dearomatization reaction of phenols with a chiral hypervalent iodine compound.[12,13] A quantitative amount of the chiral oxidant (*R*)-**3** with a rigid spirobiindane backbone was used to transform 1-naphthols **1** into *ortho*-spirolactones **2** in satisfactory yields and enantioselectivity. When a catalytic amount of (*R*)-**4**, the precursor of (*R*)-**3**, was used with *m*CPBA as the co-oxidant, moderate yields and enantioselectivity could be attained with selected substrates (Scheme 1).



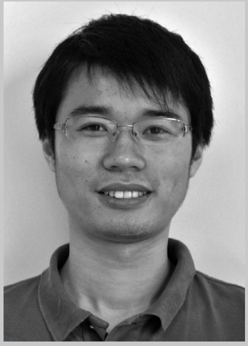
Scheme 1. Enantioselective oxidative dearomatization and spirocyclization of 1-naphthols with a chiral iodoarene and *m*CPBA.[13]

Soon afterwards, Boppisetti and Birman reported the first chiral organoiodine(V) reagent **8** for an asymmetric transformation of *ortho*-alkyl phenols into *ortho*-quinol Diels–Alder dimers.[14] Although the enantioselectivity was only moderate (for example, **7** was obtained in 65 % yield with 63 % *ee*), this newly designed iodine(V) reagent with a chiral oxazoline group still has great potential and the ability to inspire further developments in this area (Scheme 2).

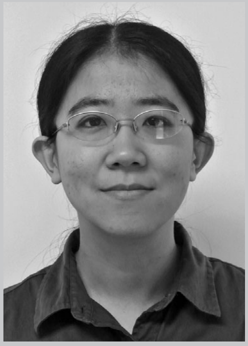
In 2009, Quideau et al. reported an asymmetric oxidative dearomatization reaction of phenols by iodanes generated in situ from chiral iodoarenes and *m*CPBA.[15] The use of



Scheme 2. Enantioselective oxidative dearomatization and dimerization of a phenol with a chiral hypervalent iodine reagent.[14]

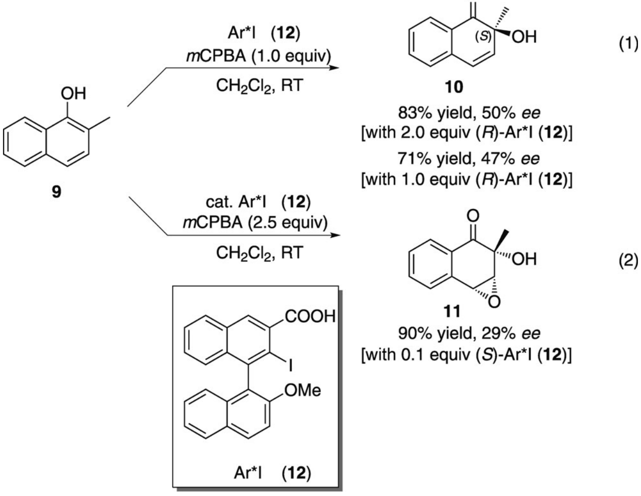


Chun-Xiang Zhuo was born in Fujian (China) in 1986. He received his BSc in chemistry from Hunan University in 2009 and then joined the research group of Professor Shu-Li You at the Shanghai Institute of Organic Chemistry as a PhD student. His current studies focus on transition-metal-catalyzed dearomatization reactions.



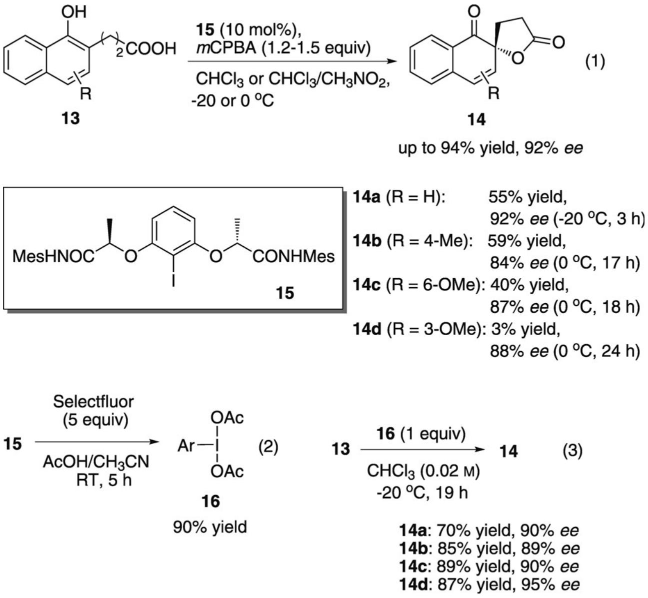
Wei Zhang was born in Tianjin (China) in 1978. She received her BSc in chemistry from the University of Science and Technology of China in 2000 and completed her PhD in 2007 at the University of Chicago under the direction of Prof. Hisashi Yamamoto. She then spent three years doing postdoctoral studies at Northwestern University in medicinal chemistry with Prof. Richard B. Silverman. In 2010, she joined the You research group as an associate professor. Her research is focused on asymmetric catalysis.

a stoichiometric amount of the chiral iodoarene and *m*CPBA as the co-oxidant enabled the *ortho*-hydroxylative phenol dearomatization with a moderate level of enantioselectivity [Scheme 3, Eq. (1)]. When a catalytic amount of the chiral iodoarene **12** was used with excess *m*CPBA, subsequent epoxidation occurred with only modest enantioselectivity [Scheme 3, Eq. (2)]. The authors also discussed plausible mechanistic pathways for this reaction. Experimental observations strongly supported the generation of a chiral iodine(V) species.



Scheme 3. Enantioselective oxidative dearomatization of a 1-naphthol with a chiral iodoarene and *m*CPBA.[15]

Later, Ishihara and co-workers designed a series of C_2-symmetric chiral iodoarenes, which were used as catalysts for the asymmetric oxidative spirolactonization of naphthol derivatives.[16] With 10 mol% of the optimal iodoarene **15** and 1.2–1.5 equivalents of *m*CPBA as the oxidant, a broad range of substrates **13** were converted into the corresponding spirolactones **14** with high levels of enantioselectivity [Scheme 4, Eq. (1)]. Interestingly, the authors believed that the actual catalyst was an iodine(III) species generated in situ through the oxidation of **15** by *m*CPBA. To support their hypothesis, they synthesized and isolated the chiral iodosylarene diacetate **16** [Scheme 4, Eq. (2)]. Selected substrates were tested with a stoichiometric amount of **16**, and parallel levels of enantioselectivity were observed, as experimental evidence for their hypothesis [Scheme 4, Eq. (3)].

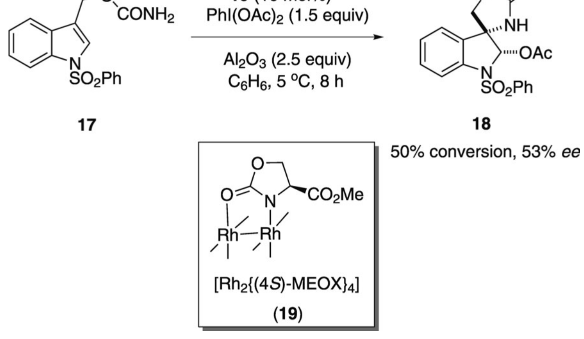


Scheme 4. Enantioselective oxidative dearomatization and spirocyclization of 1-naphthols with a chiral iodoarene and *m*CPBA.[16]

Shu-Li You received his BSc in chemistry from Nankai University in 1996. He completed his PhD at the Shanghai Institute of Organic Chemistry (SIOC) in 2001 under the supervision of Prof. Li-Xin Dai before doing postdoctoral studies with Prof. Jeffery W. Kelly at The Scripps Research Institute. He worked at the Genomics Institute of the Novartis Research Foundation as a Principal Investigator from 2004 until his return to SIOC in 2006. His research interests include asymmetric catalysis, synthetic methodology, natural product synthesis, and medicinal chemistry.

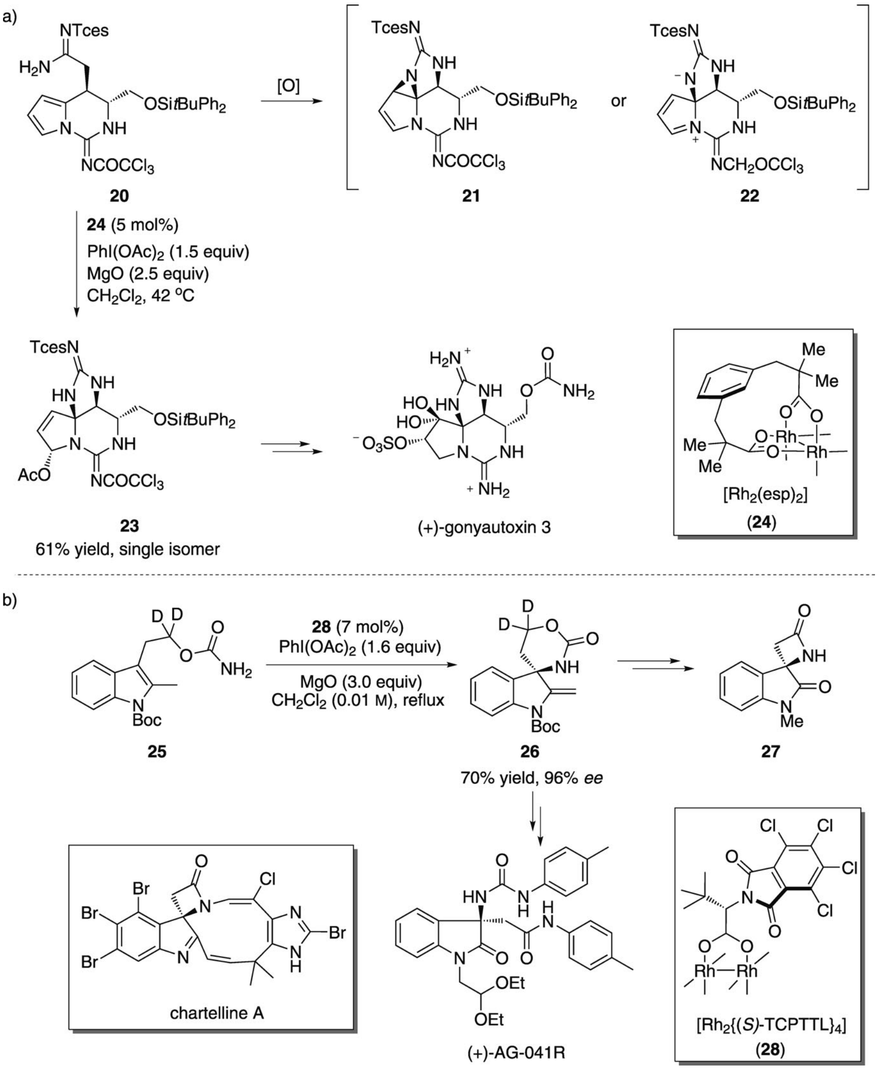
In 2003, Che and co-workers reported an enantioselective aziridination of sulfonamides and carbamates under the catalysis of a chiral $Rh^{II,II}$ dimer.[17] In the first asymmetric oxidative dearomatization reaction of an indole through the intramolecular aziridination of an indole carbamate, spiroindoline **18** was formed with moderate conversion and enantioselectivity (50% conversion, 53% *ee*; Scheme 5).

In 2008, Mulcahy and Du Bois proposed the synthesis of (+)-gonyautoxin 3[18] with a rhodium-catalyzed oxidative C–H amination as a key step.[19] When **20** was used as the substrate, the rhodium-catalyzed oxidative dearomatization reaction based on the amination of the pyrrole nucleus by the guanidine nitrenoid could occur through either an aziridine **21** or a dipolar species **22**, both of which underwent subsequent nucleophilic attack to yield the desired compound (Scheme 6a). This pathway was very efficient, and the key intermediate **23** for the synthesis of (+)-gonyautoxin 3 was obtained as



Scheme 5. Rhodium-catalyzed asymmetric oxidative dearomatization of an indole through intramolecular aziridination.[17]

a single isomer in 61 % yield. Subsequently, in 2009, Iwabuchi and co-workers described a highly enantioselective oxidative dearomatization reaction of 2-(*N*-Boc-2-alkylindol-3-yl)ethylcarbamates on the basis of rhodium-catalyzed nitrenoid chemistry.[20a] The efficient conversion of **25** into **26** with excellent enantioselectivity thus provided a reliable platform for the enantiocontrolled synthesis of the spiro-β-lactam core **27** of the chartellines (Scheme 6 b). The same strategy was later applied to the enantioselective synthesis of (+)-AG-041R, a potent gastrin/CCK-B receptor antagonist.[20b]

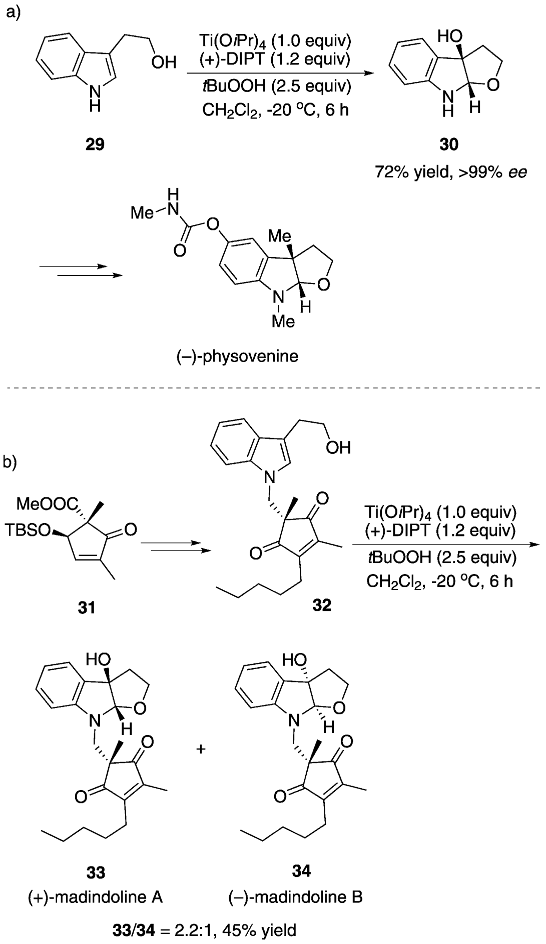


Scheme 6. Rhodium-catalyzed stereoselective synthesis of (+)-gonyautoxin 3[18] and (+)-AG-041R[20] through the intermolecular oxidative dearomatization of a pyrrole and an indole, respectively.

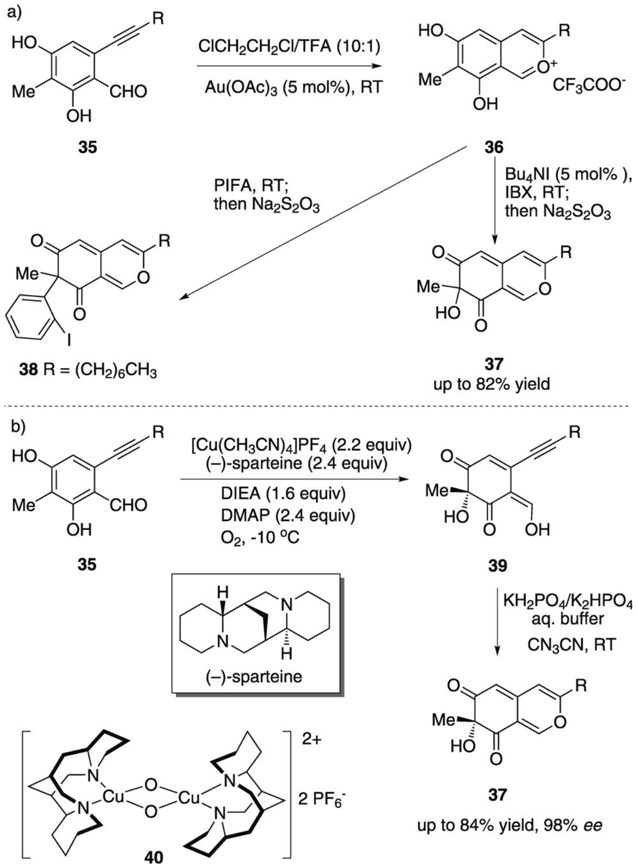
In 2000, Ōmura and co-workers established an asymmetric epoxidation–ring-closure reaction of tryptophol (**29**).[21] The highly enantiomerically enriched 3a-hydroxyfuroindoline **30** was obtained in good yield under the conditions of the Sharpless asymmetric epoxidation (Scheme 7). This enantioselective synthetic method was employed in the total synthesis of (+)-madindoline A, (−)-madindoline B, and (−)-physovenine as either the starting step or at a late stage.

For the total synthesis of azaphilones, Porco and co-workers developed an approach involving the cycloisomerization of *o*-alkynyl benzaldehydes **35** to 2-benzopyrylium salts **36** and subsequent oxidation to 6*H*-isochromene ring systems **37** (Scheme 8 a).[22a] First, the oxidative dearomatization step was successfully carried out in a racemic manner by the use of IBX as the oxidant. Several azophilones **37** were obtained in good yields from this oxidation reaction and the subsequent reductive workup. Interestingly, another frequently used hypervalent iodine reagent, PIFA, promoted the formation of **38**. Unfortunately, attempts to develop an enantioselective version of this oxidative dearomatization sequence failed. However, with the chiral complex derived from $[Cu(CH_3CN)_4]PF_6$ and (−)-sparteine, an asymmetric oxidative dearomatization reaction of **35** led to enantiomerically enriched enols **39**, the KH_2PO_4/K_2HPO_4-mediated cycloisomerization of which afforded azaphilones **37** in good yields with excellent enantioselectivity (Scheme 8 b).[22b] The copper complex **40** was believed to be the real chiral oxidant. This methodology was used as the key step for a series of syntheses of (−)-mitorubrin and related chiral azaphilone natural products, such as (−)-mitorubrinol, (−)-mitorubrinal, and (−)-mitorubrinic acid.[22c]

The same strategy was further applied to the synthesis of (+)-sclerotiorin and (+)-8-*O*-methylsclerotiorinamine by Porco, O'Brien, and co-workers.[23] Only (−)-sparteine exists in nature, and azaphilone products with an *R* quaternary carbon center were formed when **40** was used in the oxidative dearomatization step. Thus, only the enantiomers of naturally occurring (+)-sclerotiorin and (+)-8-*O*-methylsclerotiorinamine could be synthesized with this complex. O'Brien and co-workers have devoted much effort to the development of (+)-sparteine surrogates,[24] which were employed by Porco et al. for the enantioselective construction of (+)-sclerotiorin and (+)-8-*O*-methylsclerotiorinamine. Various (+)-sparteine surrogates were screened for the reaction of **35 a** as the model substrate, and **41** was found to be the optimal ligand for the oxidative dearomatization, which proceeded with similar enantioselectivity to that observed with (−)-sparteine [Scheme 9, Eq. (1)]. Thus, enantiomerically pure (*S*)-**37 b** was obtained under the optimized conditions with the chiral Cu^{II} oxidant derived from (+)-sparteine surrogate **41**. Compound (*S*)-**37 b** was further converted



Scheme 7. Oxidative dearomatization of tryptophols through a cascade reaction involving Sharpless asymmetric epoxidation and ring closure.[21]



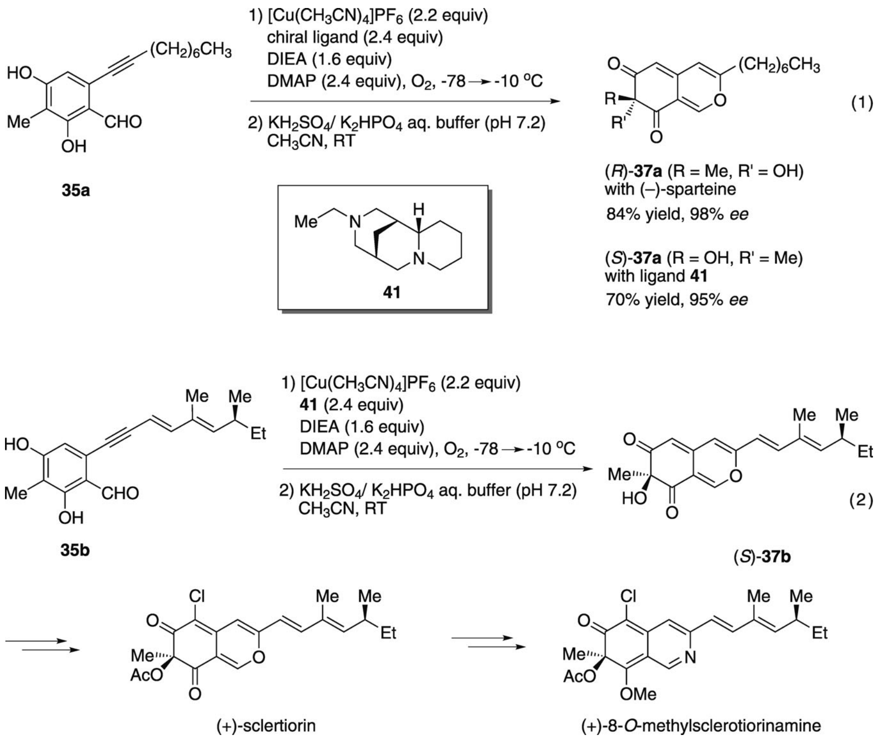
Scheme 8. Copper-mediated oxidative dearomatization of phenols with (−)-sparteine as the chiral ligand.[22]

into (+)-sclerotiorin and (+)-8-*O*-methylsclerotiorinamine through subsequent manipulations (Scheme 9).

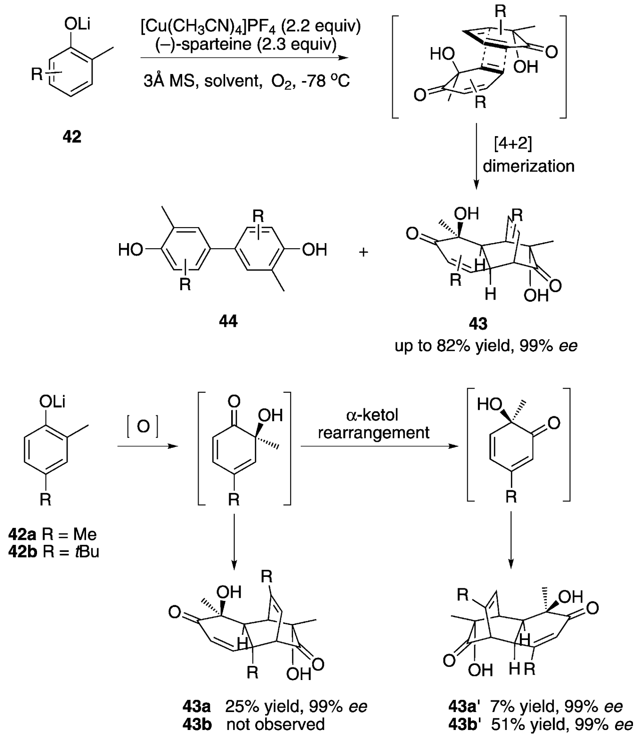
Porco and co-workers also demonstrated that complex **40** derived from [Cu(CH$_3$CN)$_4$]PF$_6$ and (−)-sparteine was an efficient chiral oxidant in an enantioselective oxidative dearomatization of phenols and subsequent [4+2] dimerization.[14,25] A number of preformed *ortho*-methyl lithium phenolates **42** underwent the oxidative hydroxylation and homodimerization cascade to afford bicyclo[2.2.2]octenones **43** with high levels of enantioselectivity (Scheme 10). The formation of biaryl by-products **44** was possible, and a stereoselective ketol rearrangement was observed for 2,4-disubstituted phenols.

In 2008, Movassaghi et al. reported an oxidative dearomatization reaction of 2-aryl tryptamines with a subsequent rearrangement to afford oxindoles with a quaternary C3 atom and a C3 aryl group.[26] 2-Aryl 3-hydroxyindolenines **46** were accessed conveniently through the oxidation of **45** with Oxone, and the following Lewis acid catalyzed rearrangement proceeded efficiently to yield the corresponding 3-aryl oxindoles **47**, which share a common substructure with various natural alkaloids (Scheme 11 a). In a preliminary study towards a stereoselective transformation by this method, the oxidation of the chiral substrate **49** afforded diastereomers **50a** and **50b** in a 2:1 ratio. The oxidative dearomatization of **45** with *t*BuOCl generated 3-chloroindolenines **48**, which were hydrolyzed to give a mixture of **46** and **47**. An enantioselective protocol based on the use of aspartyl peptide catalysts has since been developed by Movassaghi, Miller, and co-workers.[27] Structurally diverse 2-aryl 3-hydroxyindolenines **52** were afforded with moderate to good enantioselectivity under the oxidative conditions with chiral peptide **54**. Sc(OTf)$_3$ promoted the transformation of indolenines **52** into the corresponding 3-aryl oxindoles **53** with complete retention of the enantiomeric purity.[26,27]

Han and Movassaghi successfully applied the strategy of the enantioselective oxidative dearomatization of tryptamines to the total synthesis of (−)-trigonoliimines A, B, and C.[28] Exposure of the bistryptamine **55** to the Davis oxaziridine **57** afforded a mixture of **56a** and **56b** with moderate regioselectivity and excellent enantioselectivity (Scheme 12). The liberation of two amino groups in the mixture of **56a** and **56b** spontaneously afforded a mixture of **58a** and **58b** in excellent yield with retention of the enantiomeric purity. Compounds **58a** and **58b** served as precursors to (−)-trigonoliimine A and (−)-trigonoliimine B, respectively. Additionally, heating of the mixture of **56a** and **56b** in trifluoroethanol efficiently yielded a mixture of **59a** and **59b**, and further manipulations of **59a** finally provided (−)-trigonoliimine C.



Scheme 9. Copper-mediated oxidative dearomatization of phenols with a (+)-sparteine surrogate as the chiral ligand for the total synthesis of azaphilones.[23]



Scheme 10. Copper-mediated enantioselective oxidative dearomatization of phenols with complex **40** derived from $[Cu(CH_3CN)_4]PF_6$ and (−)-sparteine and subsequent [4+2] dimerization.[25]

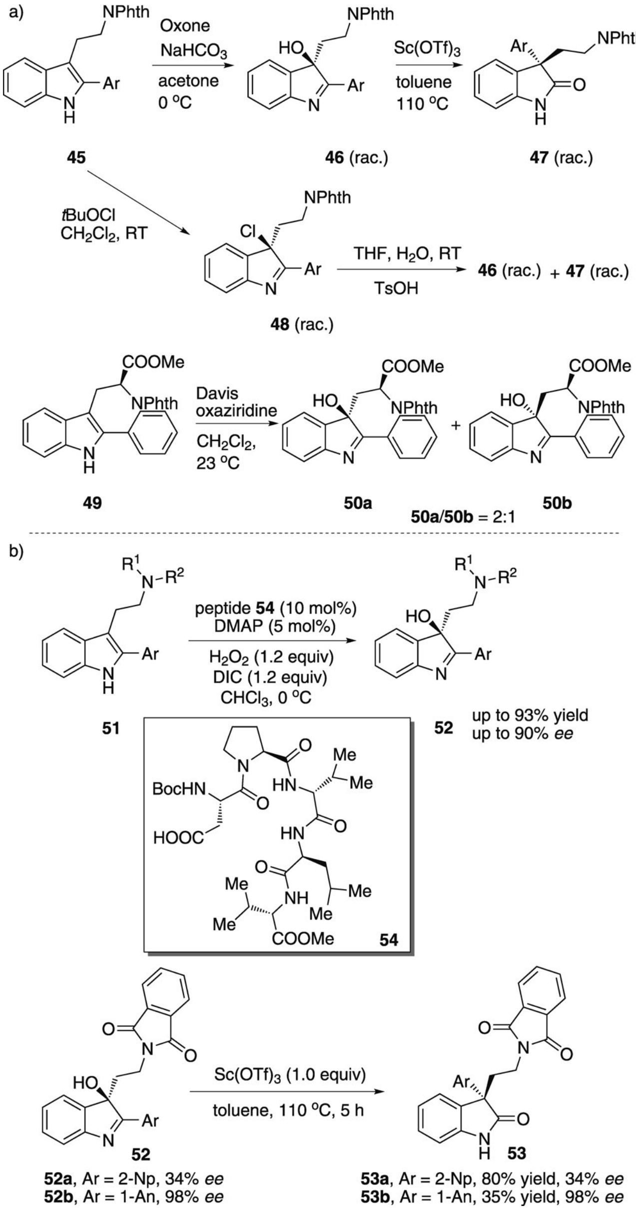
3. Dearomatization by Diels–Alder and Related Reactions

Diels–Alder reactions of vinyl indoles were first described by Noland and co-workers in 1959.[29a] Such transformations form the basis of a very useful strategy for the dearomatization of indoles to construct carbazole frameworks. For a long time, progress in this area was limited to non-enantioselective reactions.[29,30] In 2008, Bernardi, Ricci, and co-workers developed the first catalytic asymmetric Diels–Alder reaction of 3-vinyl indoles.[31a] Use of the bifunctional organocatalyst **64** enabled the dearomatization of 3-vinyl indoles **60** through a Diels–Alder pathway with various dienophiles, such as **61** and **62**, to provide enantiomerically enriched carbazole derivatives **63** (Scheme 13 a). Recently, Barbas and co-workers reported a highly efficient bisthiourea-catalyzed asymmetric Diels–Alder reaction of 3-vinyl indoles **60** with methyleneindolinones **65**.[31b] Carbazolespirooxindole derivatives **66** containing multiple contiguous stereogenic centers were afforded in almost quantitative yield with excellent stereoselectivity through dearomatization of the vinyl indoles (Scheme 13 b).

Diels–Alder reactions involving furans are also an important pathway for the construction of various oxygen-containing heterocyclic compounds by taking advantage of the dearomatization strategy. Very recently, Shibatomi et al. reported a highly enantioselective Diels–Alder reaction of β-fluoromethylacrylates **68** with furans **69** (Scheme 14).[32] This dearomatization process of furans was carried out in the presence of a Lewis acid activated chiral oxazaborolidine catalyst **71**, which was developed by Futatsugi and Yamamoto and demonstrated high efficiency in asymmetric Diels–Alder reactions.[33] The resulting tri-, di-, and monofluoromethylated cyclohexenes **70** were obtained as nearly pure enantiomers.

Great progress has also been made in other dearomatization reactions by cycloaddition processes. In 2003, Harmata et al. reported an asymmetric organocatalytic [4+3] cycloaddition reaction involving the dearomatization of furans.[34] In the presence of the MacMillan catalyst **75**, silyloxypentadienals **72** reacted with furans **73** to provide compounds **74** with excellent enantioselectivity (Scheme 15 a). Recently, this highly efficient dearomatization protocol was applied by Sun, Lin, and co-workers to build the core of englerin A (Scheme 15 b).[35]

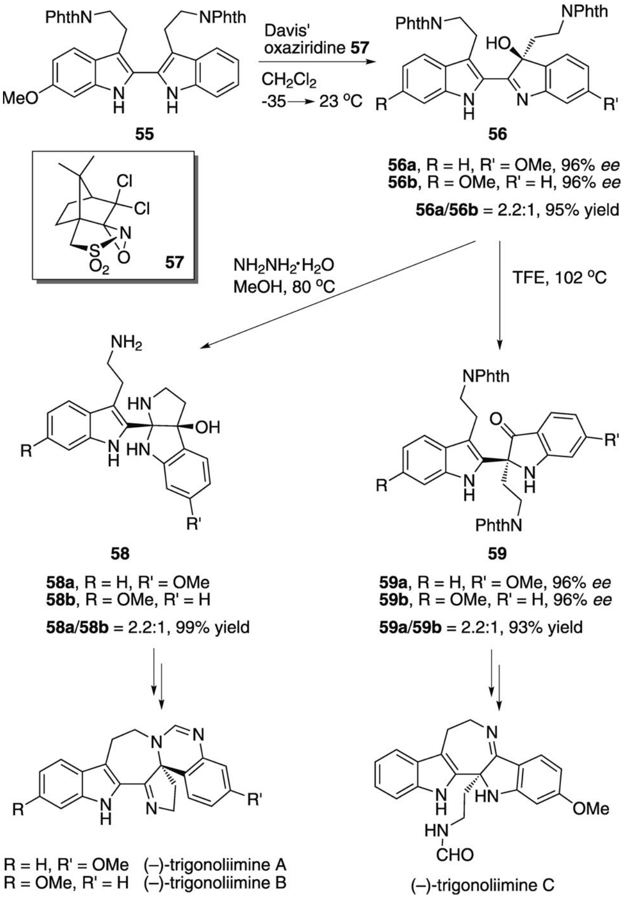
Hsung and co-workers have developed a range of stereoselective [4+3] cycloaddition reactions of nitrogen-stabilized oxyallyl cations; various ring systems, such as furans and pyrroles, can serve as the diene.[36] These typically Lewis acid promoted dearomatization reactions have great synthetic potential. In 2005, Huang and Hsung reported a highly enantioselective [4+3] cycloaddition of nitrogen-stabilized oxyallyl cations derived from allenamides. The reaction was catalyzed by a chiral Cu^{II} complex.[37] As outlined in



Scheme 11. Enantioselective oxidative dearomatization of aryl-substituted tryptamines.[26,27]

Scheme 16, the asymmetric dearomatization of substituted furans **69** proceeded smoothly to give exclusively the corresponding *endo* products in satisfactory yield and enantioselectivity.

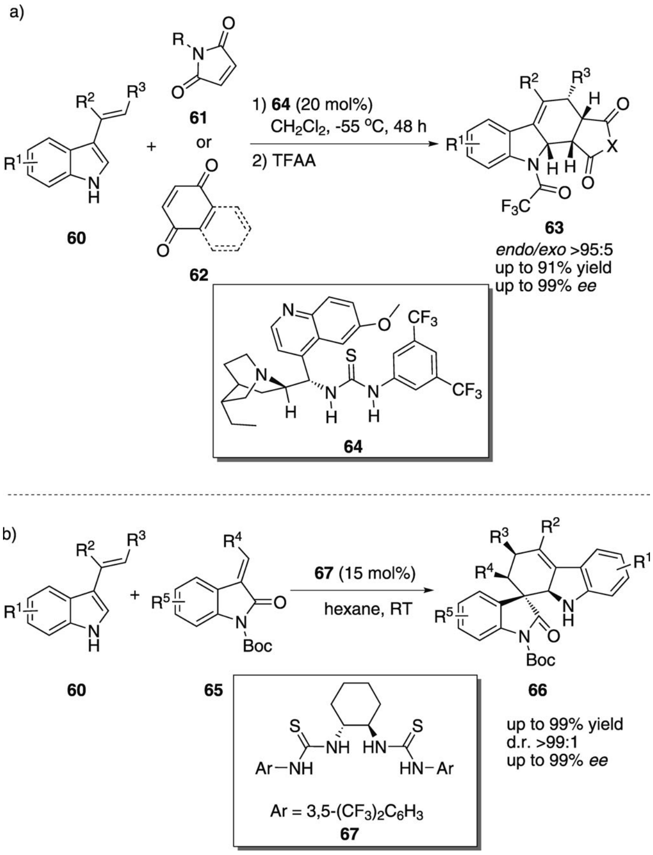
In 2007, Reddy and Davies reported a rhodium-catalyzed asymmetric dearomatization of pyrroles through a [4+3] cycloaddition reaction to construct enantiomerically enriched tropane derivatives.[38a] In an earlier study, an asymmetric variant of this transformation was developed by using a chiral auxiliary on the vinyl carbenoid **84**, and the desired product **85** was formed with good diastereoselectivity (Scheme 17a).[38b] However, with a chiral Rh^{II} prolinate catalyst, **85** could be obtained with only moderate enantioselectivity (up to 51% *ee*). Later, with $[Rh_2(S\text{-PTAD})_4]$ as the catalyst, tropane derivatives **88** were formed with excellent enantioselectivity and in good yields through the asymmetric dearomatization of protected pyrroles **86** (Scheme 17b).



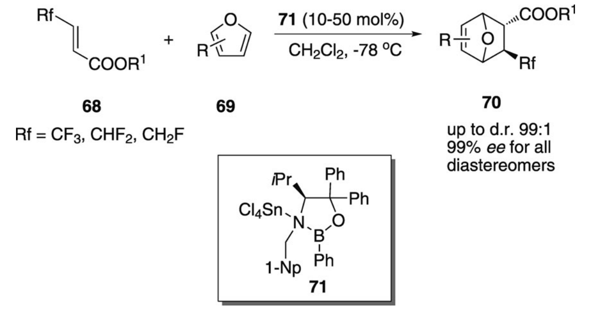
Scheme 12. Oxidative dearomatization of tryptamines for the total synthesis of (−)-trigonoliimines A, B, and C.[28]

Recently, Hashimoto and co-workers reported an enantioselective dearomatization reaction of indoles through an intermolecular cycloaddition with diazodiketoester-derived carbonyl ylides.[39] With the chiral dirhodium carboxylate catalyst **28**, fused indolines **92** with either a six-membered or a seven-membered ring were obtained with excellent enantioselectivity and diastereoselectivity (Scheme 18).

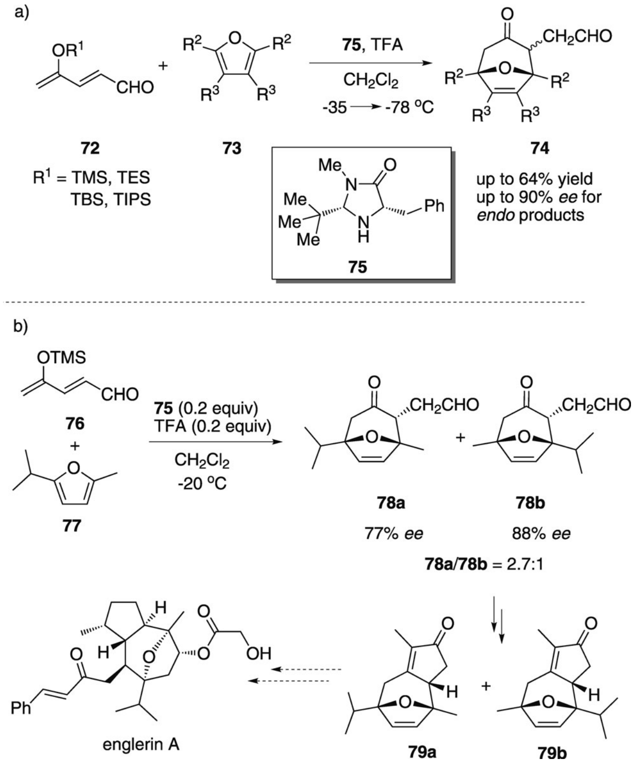
In 2010, Reisman and co-workers developed an enantioselective dearomatization of 3-substituted indoles to construct pyrroloindolines through a formal [3+2] cycloaddition reaction.[40] An earlier study by Piersanti and co-workers demonstrated that Lewis acids were highly efficient in promoting the conjugate addition of 3-nonsubstituted indoles **93** ($R^3 = H$) with 2-amidoacrylates **94**, which were believed previously to be poor electrophiles (Scheme 19, pathway a).[41] On the basis of this finding, Reisman and co-workers proposed that 3-substituted indoles **93** ($R^3 \neq H$) could participate in the conjugation reaction with **94** to generate iminium ions **96**, which could be trapped by the intramolecular amide moiety to form pyrroloindolines **95**. Under the optimal conditions for this dearomatization sequence, with (*R*)-binol as the chiral catalyst in the presence of a stoichiometric amount of $SnCl_4$, functionalized pyrro-



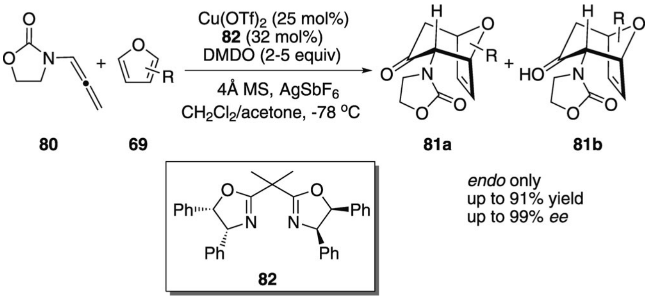
Scheme 13. Organocatalytic enantioselective dearomatization of 3-vinyl indoles by Diels–Alder reactions.[31]



Scheme 14. Enantioselective dearomatization of furans through a Diels–Alder reaction in the presence of a Lewis acid activated chiral oxazaborolidine catalyst.[32]



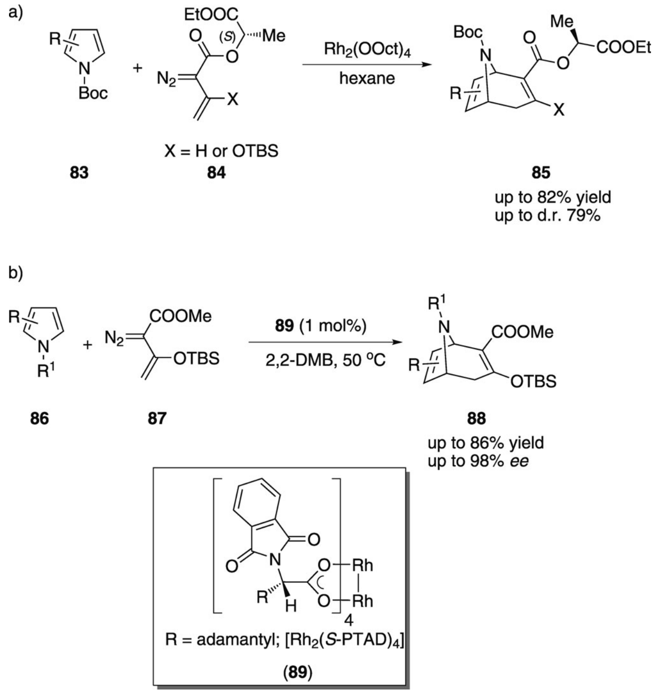
Scheme 15. Organocatalytic enantioselective dearomatization of furans through a [4+3] cycloaddition reaction.[34,35]



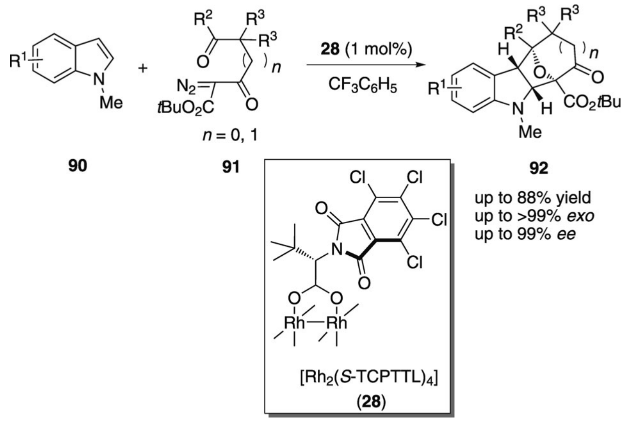
Scheme 16. Asymmetric dearomatization of furans by [4+3] cycloaddition reactions involving nitrogen-stabilized oxyallyl cations.[37]

loindolines **95** were generated with excellent enantioselectivity.

In 2008, Linton and Kozlowski reported an interesting dearomatization pathway of indoles through a catalytic enantioselective Meerwein–Eschenmoser Claisen rearrangement.[42a] Indole-containing 2-amino allyl vinyl ethers **100** were designed, and various hydrogen-bonding catalysts as well as Lewis acids were demonstrated to be effective in promoting the desired [3,3′] sigmatropic rearrangement. The chiral complexes derived from $Pd(SbF_6)_2$ and a bisphosphane ligand (binap or difluorophos) or a phosphanyloxazoline ligand (*t*Buphox) were revealed to be optimal Lewis acid catalysts for the highly enantioselective construction of synthetically useful oxindoles **101** with a quaternary stereogenic center (Scheme 20a). In a deuterium labeling experiment, the absence of **103** as a product excluded the possibility of a mechanism involving the formation and addition of Pd^{II}–π-allyl cation species. Recently, Kozlowski and co-workers extended this dearomatization approach to a catalytic enantioselective Saucy–Marbet Claisen rearrangement.[42b] Thus, propargyl-substituted indoles **105** were converted into allenyl products **106** in high yield with high enantioselectivity (Scheme 20b).



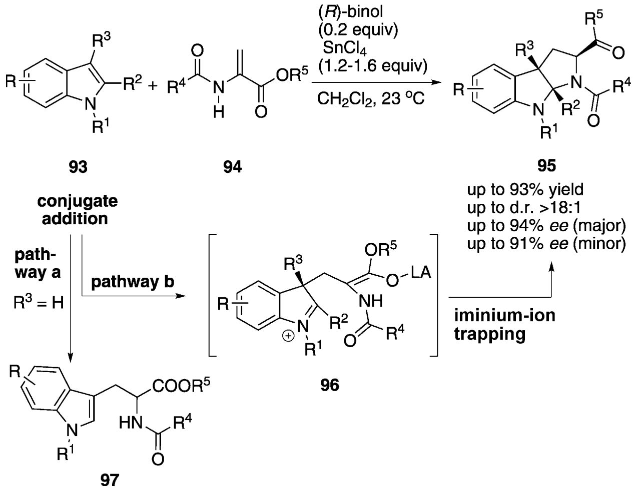
Scheme 17. Asymmetric dearomatization of pyrroles by a rhodium-catalyzed [4+3] cycloaddition.[38]



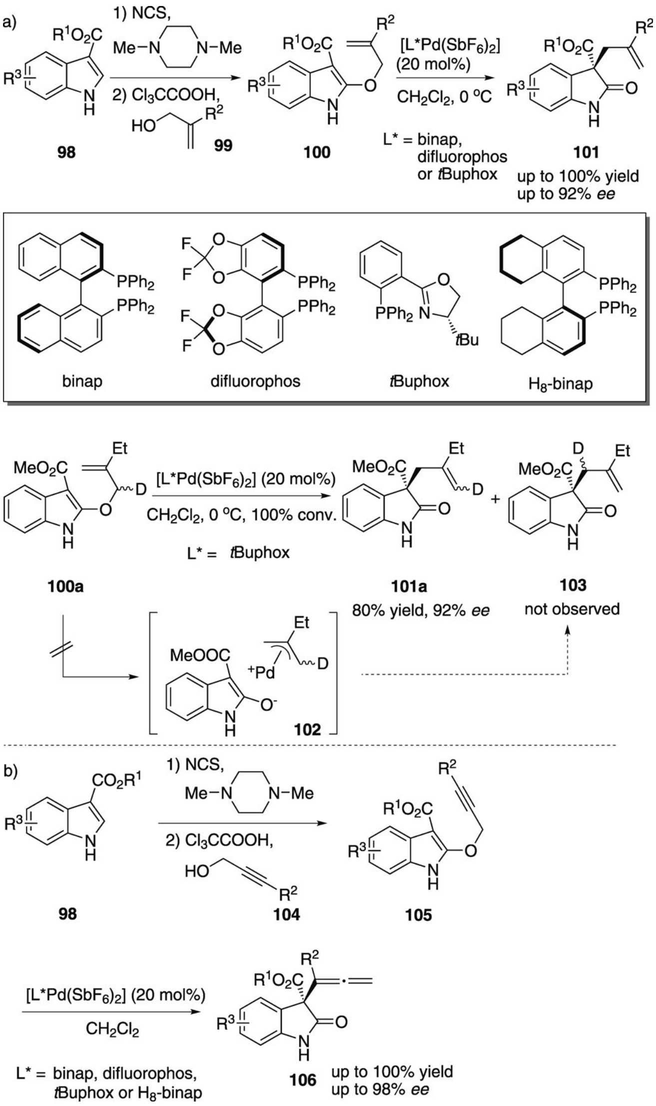
Scheme 18. Enantioselective dearomatization of indoles with a chiral dirhodium carboxylate catalyst.[39]

4. Alkylative Dearomatization Reactions

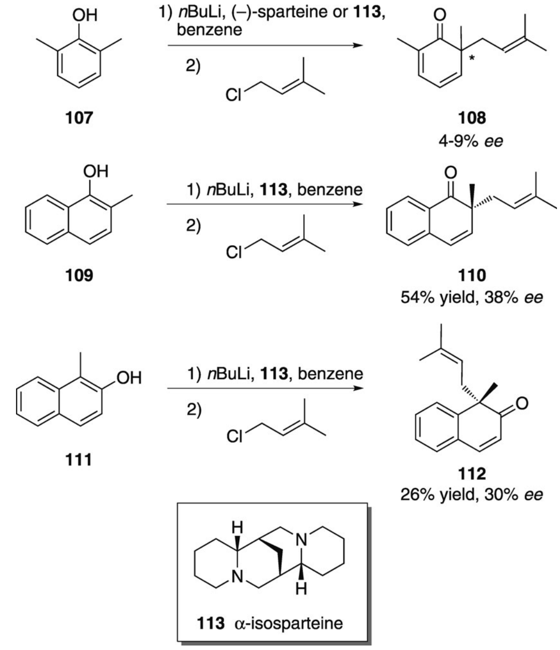
As electron-rich aromatic rings, *ortho*-substituted phenols and naphthols readily undergo alkylation reactions with electrophiles to provide synthetically useful substituted cyclohexadienones and naphthalenones, respectively. This dearomatization process has been fully developed and broadly applied in synthesis with racemic substrates. In 2006, Fráter and co-workers reported a stereoselective alkylative dearomatization of phenols and naphthols in the presence of a chiral base.[43] Phenol **107** as well as naphthols **109** and **111** underwent C-alkylation in the presence of *n*BuLi and a chiral ligand (Scheme 21). Although the chiral reagents derived from (−)-sparteine (or α-isosparteine (**113**)) and *n*BuLi only



Scheme 19. Enantioselective dearomatization of indoles by a formal [3+2] cycloaddition in the presence of a chiral Lewis acid.[40,41]



Scheme 20. Palladium-catalyzed enantioselective dearomatization of indoles through a Meerwein–Eschenmoser Claisen rearrangement.[42]



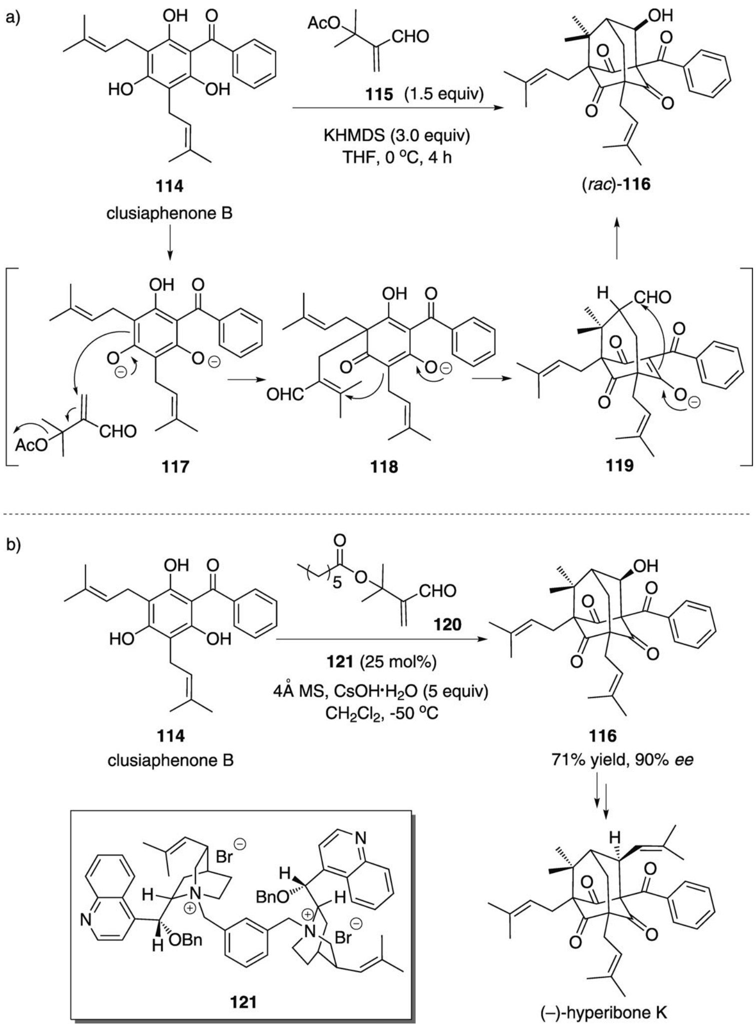
Scheme 21. Stereoselective alkylative dearomatization of phenols and naphthols in the presence of a chiral base.[43]

promoted the reaction with low to medium enantioselectivity, this strategy undoubtedly inspired further developments.

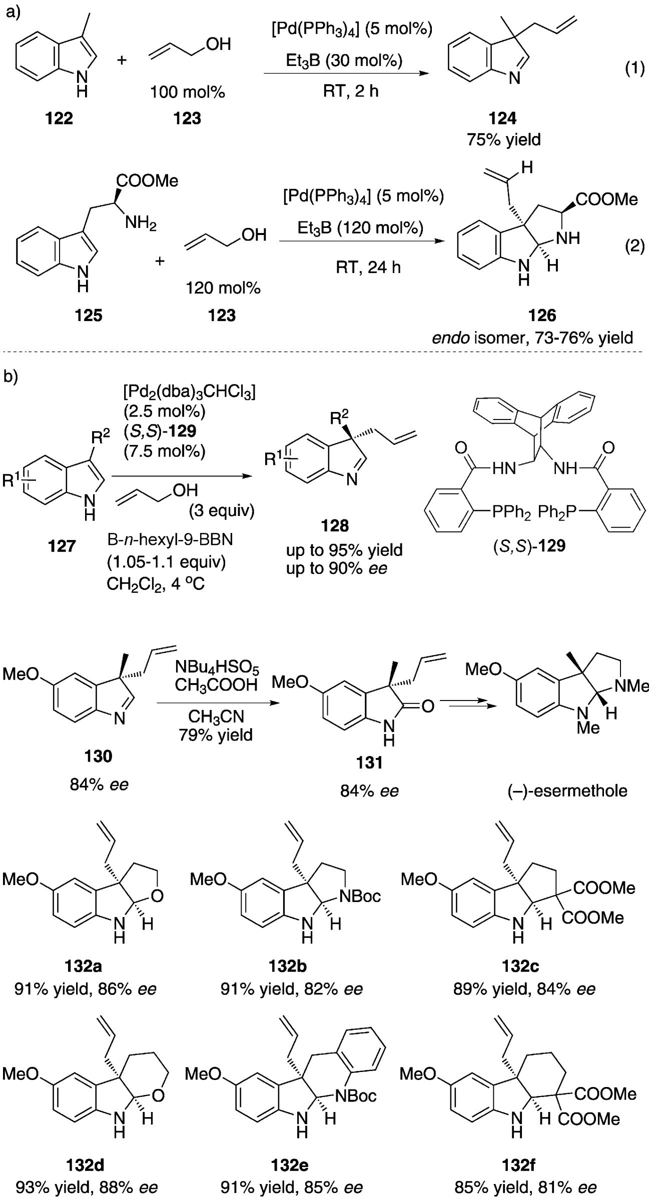
During the course of their studies towards the total synthesis of polyprenylated acyl phloroglucinols, Porco and co-workers developed elegant alkylative dearomatization–annulation processes to construct these polycyclic natural products.[44] This research group recently used a chiral phase-transfer catalyst derived from the cinchona alkaloids to carry out their previously reported domino Michael addition–elimination–Michael addition–aldol reaction sequence (Scheme 22 a)[44a] in an enantioselective manner (Scheme 22 b).[45] With the chiral phase-transfer catalyst **121** and 5 equivalents of the base, the alkylative dearomatization reaction and subsequent intramolecular transformations occurred smoothly. In this way, the adamantane **116** was synthesized in a very concise and efficient manner (71% yield, 90% *ee*). Adamantane **116** was further manipulated to complete the total synthesis of (−)-hyperibone K.

5. Transition-Metal-Catalyzed Dearomatization Reactions

In 2005, Tamaru and co-workers reported the highly selective C3-allylation of indoles with various allylic alcohols in the presence of Et_3B under palladium catalysis.[46,47] When 3-methylindole (**122**) was treated with allyl alcohol in the presence of Et_3B, C3-allylation occurred to give the corresponding dearomatization product **124** with a quaternary carbon center [Scheme 23 a, Eq. (1)]. An efficient asymmetric synthesis based on the use of a chiral auxiliary was developed for the allylation of L-tryptophan methyl ester (**125**). The product **126** was obtained as a single *endo* diastereomer in 73–76% yield through a cascade reaction involving dearomative allylation and alkylative amination [Scheme 23 a, Eq. (2)]. Shortly afterwards, a catalytic enantioselective version of this dearomative C3-allylation of 3-substituted indoles was investigated by Trost and Quancard.[48] Since this palladium-catalyzed transformation was believed to proceed via a π-allyl palladium intermediate, the authors used the chiral anthracene-derived ligand **129**[49] with *B*-*n*-hexyl-9-BBN for the enantioselective construction of a quaternary center at the 3-position of indoles. Chiral 3,3-disubstituted indolenines **128** were synthesized with up to 90% *ee* from typical electron-rich indoles **127**. A protocol for the oxidation of indolenine **130** to the oxindole **131** was also developed and led to a formal synthesis of (−)-esermethole (Scheme 23 b). Furthermore, indole substrates bearing a pendant nucleophile underwent cyclization by addition to the



Scheme 22. Organocatalytic enantioselective dearomatization of phenols through an alkylative dearomatization–annulation sequence (b) based on a previously reported racemic process (a).[44a,45]



Scheme 23. Dearomative C3-allylation of 3-substituted indoles.[47,48]

imine to yield the corresponding indolines **132a–f** in excellent yields. The resulting *cis*-5,5- and *cis*-5,6-fused heterocyclic rings are frequently found in natural products.

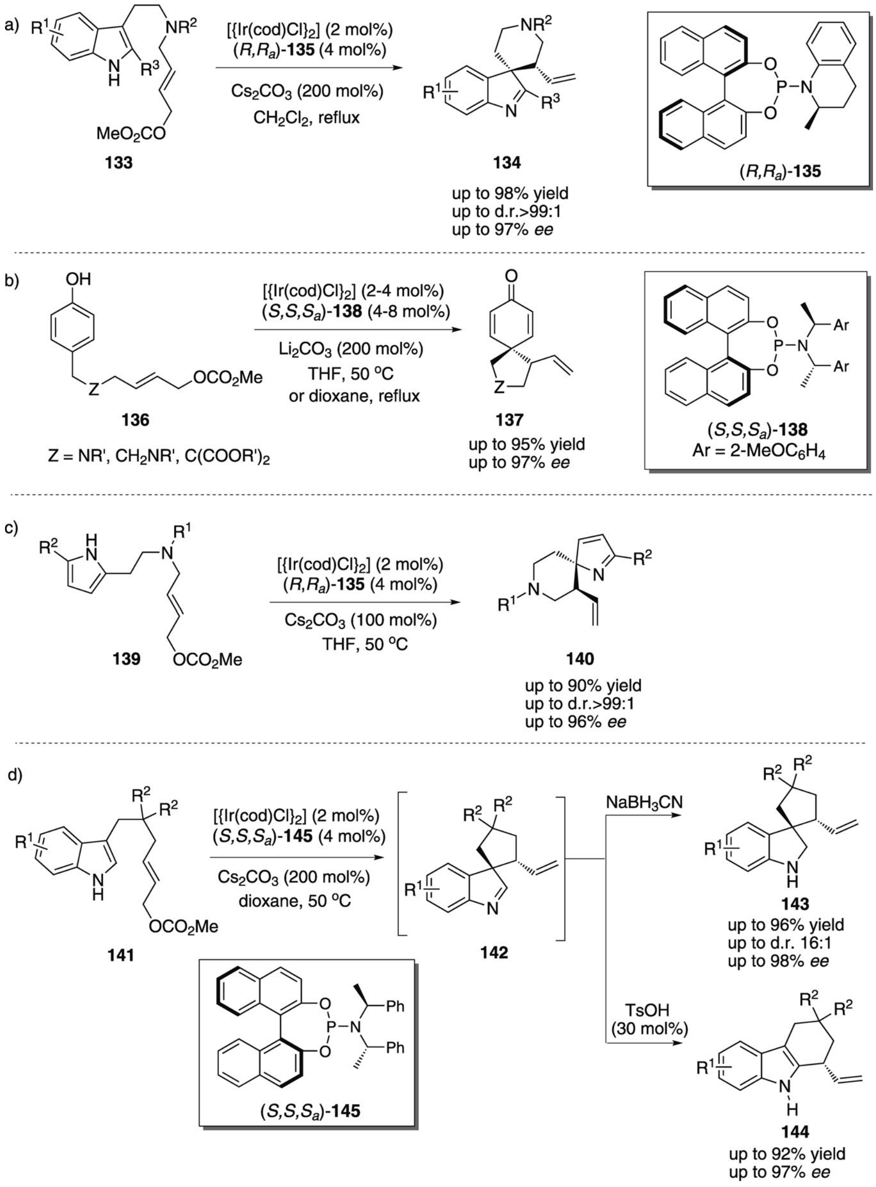
Inspired by these pioneering studies,[47,48,50] You and co-workers reported an intramolecular asymmetric dearomatization reaction of indoles through iridium-catalyzed allylic alkylation in 2010.[51a,52] With the phosphoramidite ligand **135**, the iridium-catalyzed intramolecular allylic C3-alkylation of indoles **133** afforded highly enantiomerically enriched spiroindolenine derivatives **134**. This reaction features facile access to chiral spiro compounds from readily available substrates and the construction of two contiguous stereogenic centers (Scheme 24a). Later, an iridium-catalyzed intramolecular asymmetric allylic dearomatization reaction of phenols was developed.[51b] Thus, *para*-substituted phenols **136** were converted into various five- or six-membered spirocyclohexadienone derivatives **137** in excellent yields and enantioselectivity (Scheme 24b). Very recently, You and co-workers found that the iridium-catalyzed allylic dearomatization protocol was also applicable to pyrroles.[51c] Although the allylic alkylation of pyrroles was more challenging than the equivalent reaction of indoles in terms of regioselectivity and enantioselectivity, the allylic dearomatization of pyrroles **139** with the catalyst derived from [{Ir(cod)Cl}$_2$] and ligand **135** provided bicyclic spiro-2*H*-pyrroles **140** in excellent yields, diastereoselectivity, and enantioselectivity (Scheme 24c). They also developed an enantioselective synthesis of spirocyclopentane-1,3′-indoles **143** through an iridium-catalyzed allylic dearomatization reaction and in situ reduction with NaBH$_3$CN. They found that intermediates **142** underwent a stereospecific migration upon the addition of TsOH to yield the corresponding 2,3,4,9-tetrahydro-1*H*-carbazoles **144** and proposed a nonclassical carbocation transition state for this process (Scheme 24d).[51d]

In 2010, Hamada and co-workers reported an intramolecular dearomatization of phenols through a palladium-catalyzed allylic alkylation reaction.[53a] This study successfully applied the well-developed palladium-catalyzed allylic substitution reaction to a dearomatization event in a phenol system, and the process provided spirocyclohexadienones in good yields and diastereoselectivity. The authors also presented one successful asymmetric example in the presence of the chiral ligand (*R*,*R*)-**129** (Scheme 25). Recently, the authors also applied this protocol to the enantioselective dearomatization of naphthol derivatives.[53b]

In 2009, Buchwald and co-workers reported an intramolecular enantioselective palladium-catalyzed dearomatization reaction of naphthalene derivatives.[54a,55] The authors expected that the deprotonation of anilines **148** would increase the electron density in the naphthalene moiety, which would then participate in an intramolecular nucleophilic attack on the aromatic Pd^{II} species **151** to generate compounds **149** (Scheme 26a). This approach was very successful with the chiral phosphine ligand (*R*)-**150**: the benzocarbazole products **149** were formed in excellent yields and enantioselectivity. Recently, Buchwald and co-workers developed a palladium-catalyzed arylative dearomatization of phenols to yield spirocyclohexadienone products in good to excellent yields.[54b] Preliminary studies on the control of enantioselectivity in this transformation demonstrated that the products **153** with a spirocyclic all-carbon quaternary center could be formed with high enantioselectivity (up to 91% *ee*; Scheme 26b).

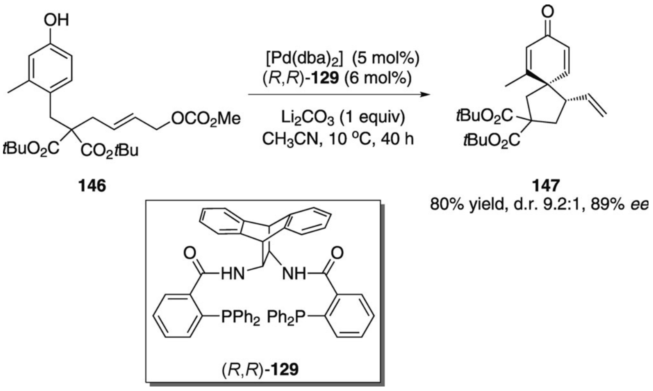
6. Cascade Asymmetric Dearomatization Sequences

In this section, we discuss cascade sequences involving asymmetric dearomatization as the key step. In their elegant total synthesis of (−)-flustramine B, MacMillan and co-workers successfully established a strategy involving the dearomatization of tryptamine and trapping of the resulting indolenine intermediate with an amine.[56,57] As outlined in Scheme 27, a cascade dearomatization–cyclization sequence was initiated by Michael addition of the protected tryptamine **156** to acrolein activated by the chiral imidazolidinone **75**. The proposed iminium intermediate **158** spontaneously underwent cyclization through the intramolecular addition of an amine, and reduction of the aldehyde then provided pyrroloindoline **157** with 90% *ee*. (−)-Flustramine B was then synthesized from **157** with high efficiency. MacMillan and co-workers also demonstrated that this enantioselective transformation catalyzed by a chiral secondary amine was compatible with a wide range of tryptamines and α,β-unsaturated aldehydes.



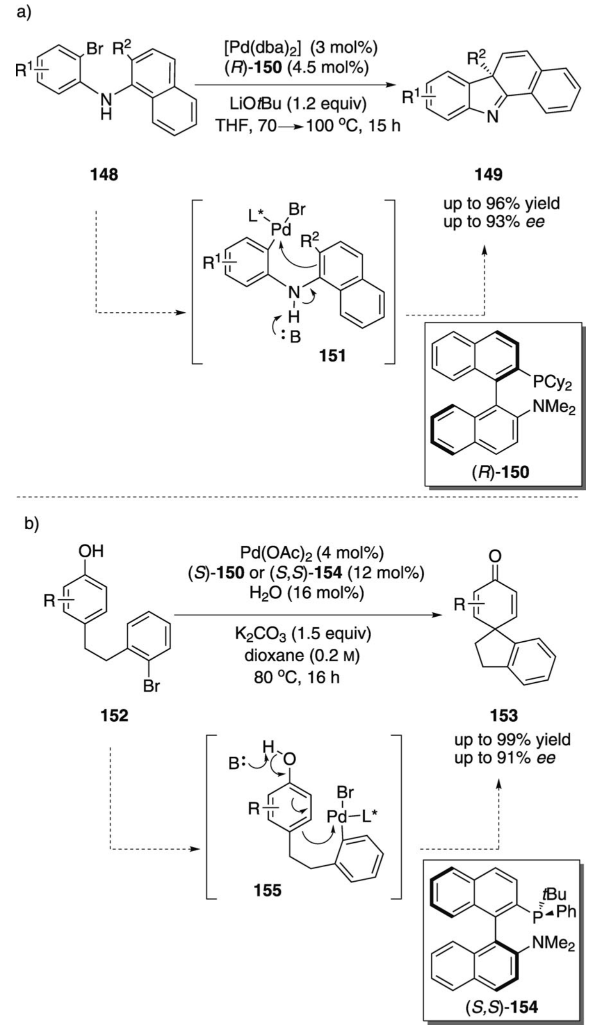
Scheme 24. Iridium-catalyzed asymmetric allylic dearomatization of indoles, phenols, and pyrroles.[51]

In 2009, in their total synthesis of (+)-minfiensine, MacMillan and co-workers developed an enantioselective cascade Diels–Alder/amine-cyclization sequence catalyzed by a chiral secondary amine to construct a tetracyclic carbazole framework from propynal and a tryptamine derivative (Scheme 28a).[58a,59] Dearomatization of the 2-vinyl tryptamine **159** occurred by an asymmetric *endo*-selective [4+2] reaction with propynal to afford the tricyclic enamine **161**, which underwent spontaneous isomerization to the corresponding iminium ion **162** in preparation for a further cyclization reaction through attack of the pendant amine. Amazingly, the whole sequence was catalyzed by the single chiral secondary amine **163** in association with TBA, and the designed tetracyclic pyrroloindoline **160** was obtained with excellent enantioselectivity and in good yield (87% yield, 96% *ee*). This elegant transformation served as the efficient key step in an enantioselective total synthesis of (+)-minfiensine. Recently, in the collective synthesis of six well-known alkaloid natural products, the organocatalytic dearomatization cascade sequence again showed its great potential as a key step.[58b] As shown in Scheme 28b, the 2-(vinyl-1-selenomethyl)tryptamines **164** were converted into **165** and **166** in good yields and enantioselectivity through a cascade sequence involving a Diels–Alder cycloaddition, β-elimination of methyl selenide, and conjugate addition of the amine with the corresponding enantiomer of catalyst **163**. Further manipulations of **165** and **166** furnished a series of alkaloid natural products.

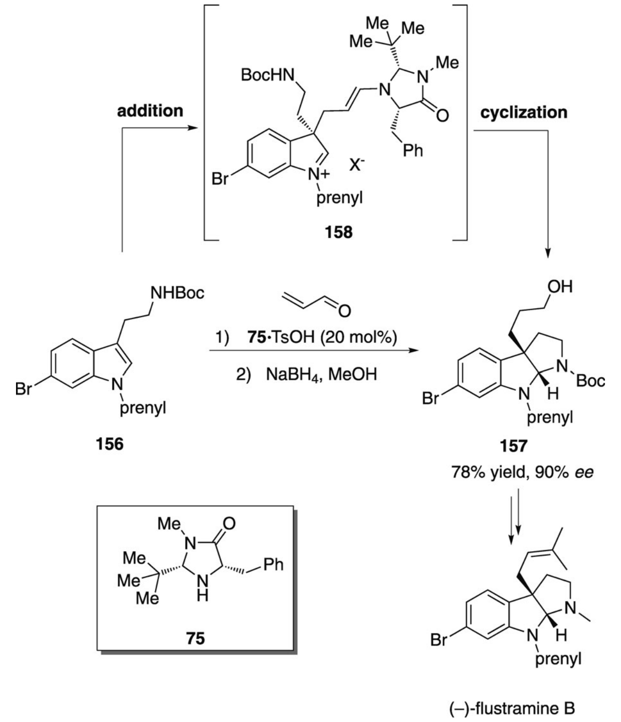


Scheme 25. Palladium-catalyzed enantioselective dearomatization of a phenol by an *ipso*-Friedel–Crafts allylic alkylation.[53]

Recently, You and co-workers reported an organocatalytic enantioselective dearomatization of indoles through a Michael/Mannich cyclization cascade.[60a] With the quinine-derived primary amine **170** as the catalyst, a series of enantiomerically enriched tetracyclic compounds **168** containing three contiguous stereogenic centers were obtained in satisfactory yields and diastereoselectivity (Scheme 29a). This protocol demonstrates the efficiency of the cascade strategy for enantioselective dearomatization reactions as well as the potential for building complex molecules. For example, **169**, the core structure of (+)-kreysiginine, was synthesized in a short sequence from one of the products **168**. Later, they established a formal [4+2] cycloaddition of 2,3-



Scheme 26. Palladium-catalyzed enantioselective arylative dearomatization of naphthalenes and phenols.[54]



Scheme 27. Organocatalytic enantioselective dearomatization of a tryptamine through a cascade dearomatization–cyclization sequence.[56]

disubstituted indoles **171** with methyl vinyl ketone in the presence of a catalytic amount of the quinine-derived primary amine **170** and pentafluorobenzoic acid (PFBA; Scheme 29 b).[60b] This intermolecular Michael/Mannich cyclization cascade takes advantage of the dearomatization of indoles to provide bridged indoline scaffolds **172** containing two quaternary carbon centers in excellent yields and enantioselectivity.

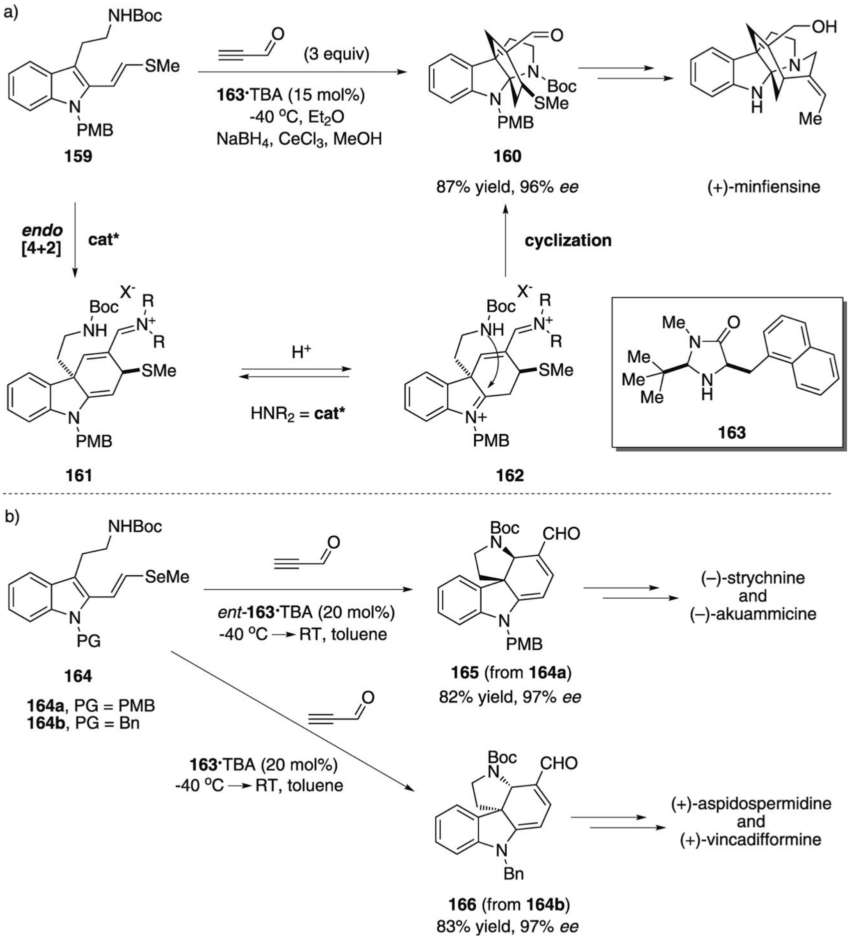
An organocatalytic enantioselective dearomatization reaction of indoles through a fluorocyclization cascade was recently developed by Gouverneur and co-workers.[61a] With $(DHQ)_2PHAL$ as the catalyst, indoles **173a** and **173b** with a pendant heteronucleophile tethered at the C3 or N1 position were smoothly converted into the corresponding dearomatized polycyclic products with moderate to good enantioselectivity (Scheme 30). As the first asymmetric organocatalytic fluorocyclization, this protocol paved the way for the synthesis of highly enantiomerically enriched fluorosubstituted polycyclic compounds through a dearomative approach. It should be noted that very recently, the enantioselective organocatalytic dearomatization reaction of thiophene by either a fluorocyclization or a bromocyclization cascade was realized by Toste and co-workers.[61b,c]

In 2012, Bandini and co-workers reported a unique enantioselective dearomatization cascade of indoles with chiral gold catalysts that has great potential for the construction of stereodefined polycyclic indoline alkaloids.[62] Either tetracyclic fused furoindolines **176** or dihydropyranylindolines **177** could be formed with satisfactory stereoselectivity through the gold-catalyzed cascade sequence involving intramolecular hydroindolination of the propargylic alcohol moiety of **175** and subsequent trapping of the iminium intermediate (Scheme 31).

Very recently, Zhu and MacMillan described an enantioselective arylation–cyclization process based on copper bisoxazoline catalysis and the use of diaryl iodonium salts.[63] Various pyrroloindolines **179** bearing a C3 aryl group could be prepared in excellent yields and enantioselectivity through the copper(I)-catalyzed cascade involving arylative dearomatization and amine–iminium cyclization (Scheme 32). This mild and highly efficient catalytic protocol provides a new strategy for the construction of enantiomerically enriched pyrroloindolines, which are important structural motifs of many biologically active alkaloids.

7. Nucleophilic Dearomatization Reactions of Electron-Deficient Aromatic Rings

The activation of pyridines (or other nitrogen-containing aromatic rings) by acylation or alkylation, followed by



Scheme 28. Enantioselective dearomatization of tryptamines through a Diels–Alder/amine-cyclization sequence.[58]

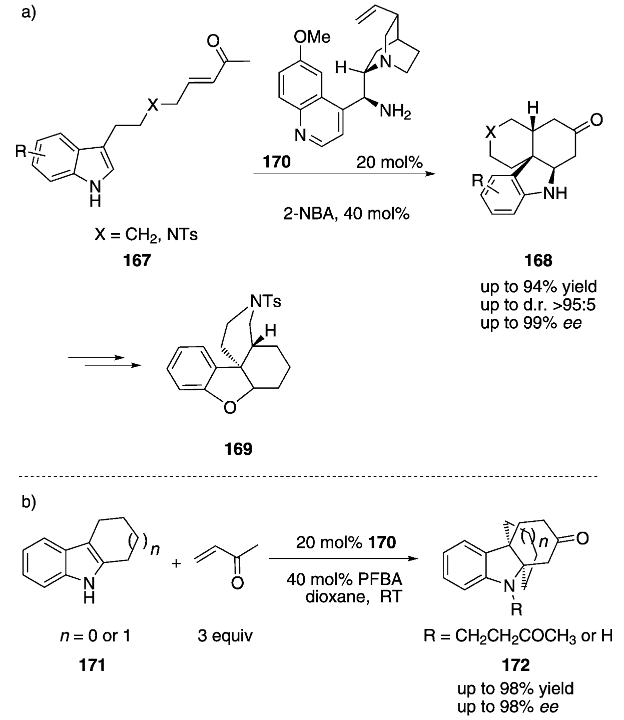
cleavage of the pyridine ring through the attack of a nucleophile, is a very useful dearomatization strategy.[64]

The Reissert reaction is a dearomatization approach involving the activation of nitrogen-containing aromatic rings by the formation of a covalent bond between the nitrogen atom and an acyl group. This reaction, first reported as the addition of KCN to quinoline in the presence of benzoyl chloride,[65] has been developed further with other nucleophiles, such as Grignard reagents and TMSCN.[64,66] In early enantioselective Reissert-type reactions, either chiral nucleophiles or chiral acylating reagents were used. In 2001, a highly regio- and stereoselective process for the dearomatization of pyridines was reported by Comins et al.[67] With the aid of the chiral acylating reagent **181**, the dearomatization product **182** was formed with excellent diastereoselectivity. Further manipulations of **182** led to the total synthesis of (+)-allopumiliotoxin 267A (Scheme 33).[67]

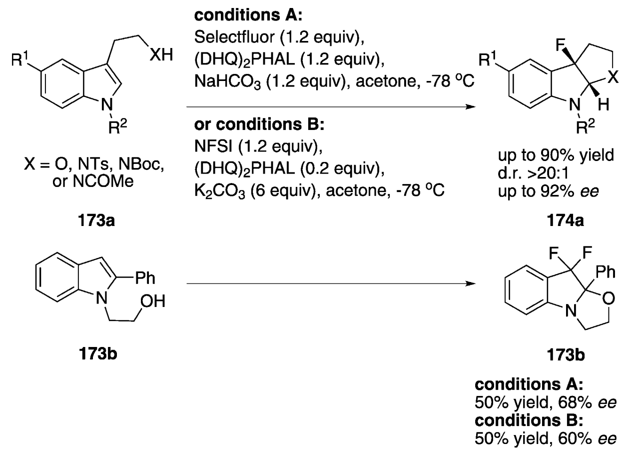
Reissert-type reactions are promoted by Lewis acids.[68] Enantioselective Reissert reactions catalyzed by chiral Lewis acids are more attractive strategies for asymmetric dearomatization than asymmetric Reissert reactions in which a stoichiometric amount of a chiral reagent is used. In 2000, Shibasaki and co-workers documented the first catalytic asymmetric Reissert-type reactions of quinoline and isoquinoline derivatives.[69a,b] Good to excellent yields and enantioselectivity were observed for the formation of dearomatization products **185** and **186** in the presence of the Lewis acid–Lewis base bifunctional catalyst **187** (Scheme 34 a). Shortly afterwards, the same research group reported the use of the bifunctional catalyst **190** for the unprecedented catalytic enantioselective construction of a quaternary stereocenter in a Reissert-type reaction (Scheme 34 b).[69c] In 2004, Shibasaki and co-workers successfully applied their chiral bifunctional catalyst **193** to the Reissert reaction of more challenging pyridine derivatives (Scheme 34 c).[69d]

Enantioselective Reissert reactions catalyzed by chiral organocatalysts have also been well developed.[70] In 2005, Jacobsen and co-workers described an asymmetric dearomatization of isoquinolines by an acyl-Mannich process catalyzed by chiral thiourea derivatives.[71] With 10 mol % of the optimal organocatalyst **195**, isoquinolines **183** were activated by acylating reagents and then subjected to nucleophilic attack by the silyl ketene acetal **196**. This reaction provided access to the useful enantiomerically enriched dihydroisoquinoline building blocks **194** (Scheme 35).

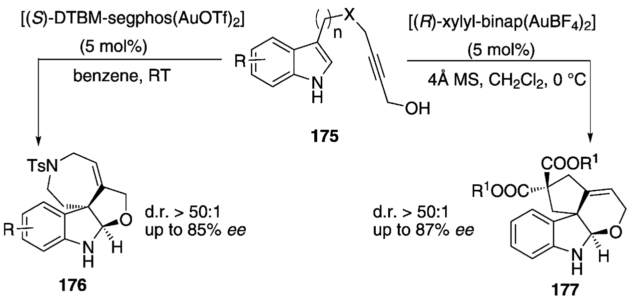
At the same time, Jørgensen and co-workers reported an organocatalytic enantioselective dearomatization reaction of alkylated isoquinolines.[72] With the chiral pyrrolidine derivative **200** as the catalyst, activated isoquinolinium ions **197** were



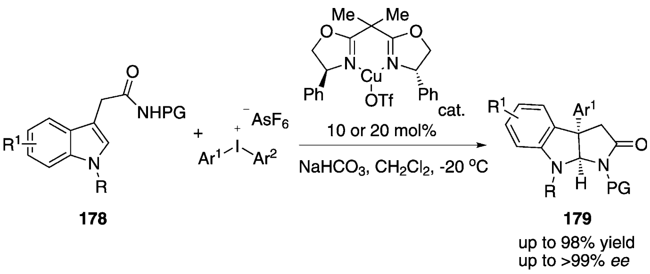
Scheme 29. Organocatalytic enantioselective dearomatization of indoles through a Michael/Mannich cyclization cascade.[60]



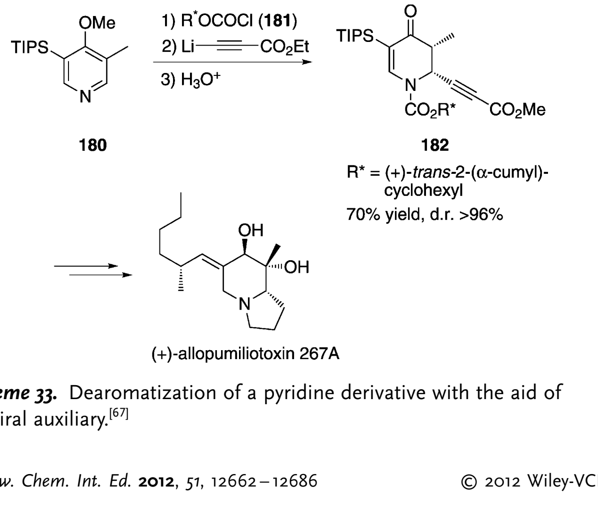
Scheme 30. Organocatalytic enantioselective dearomatization of indoles through a fluorocyclization cascade.[61a]



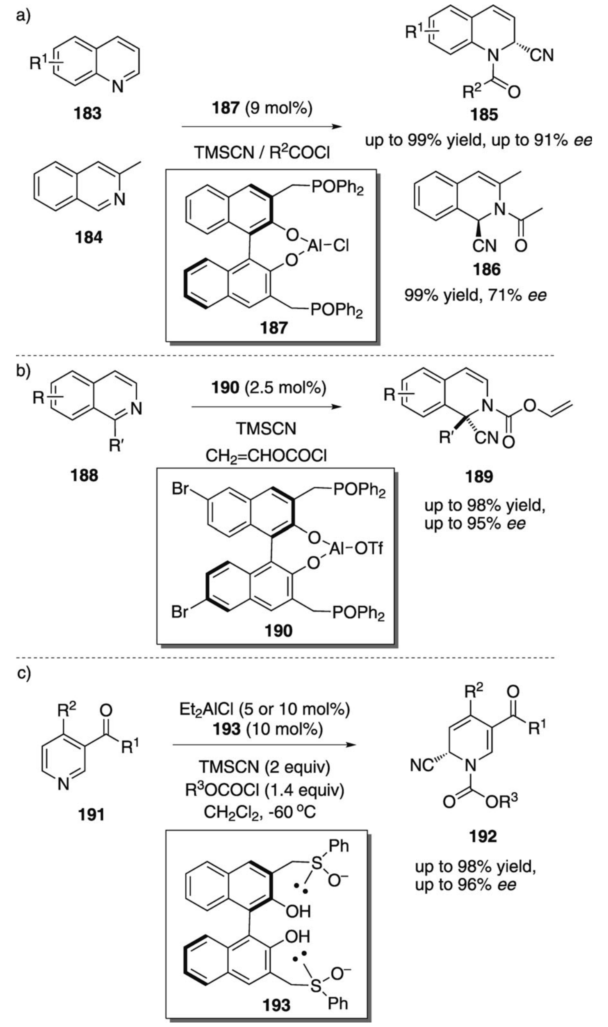
Scheme 31. Enantioselective dearomatization cascade of indoles in the presence of chiral gold catalysts.[62]



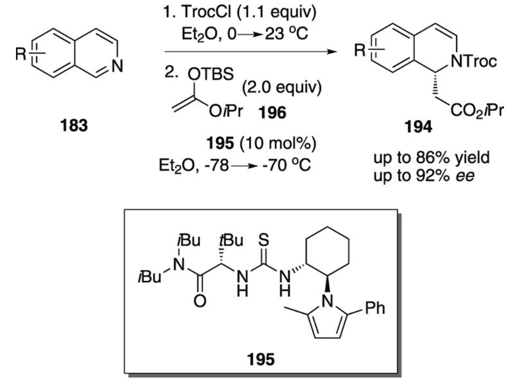
Scheme 32. Enantioselective dearomatization cascade of tryptamines in the presence of a chiral copper catalyst.[63]



Scheme 33. Dearomatization of a pyridine derivative with the aid of a chiral auxiliary.[67]



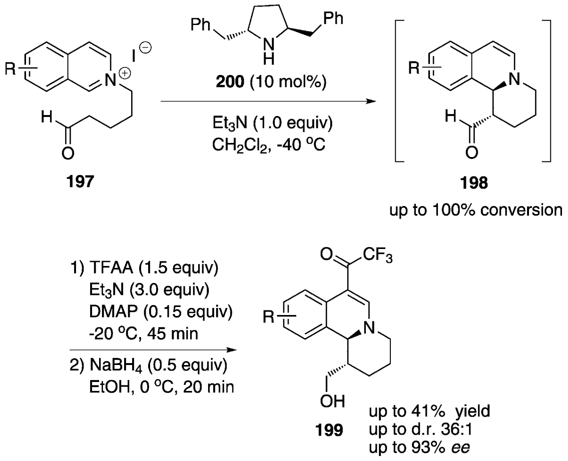
Scheme 34. Enantioselective dearomatization of quinolines, isoquinolines, and pyridines by Reissert reactions catalyzed by chiral Lewis acids.[69]



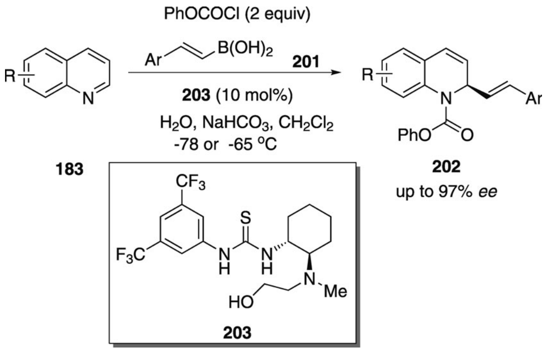
Scheme 35. Organocatalytic enantioselective dearomatization of isoquinolines by an acyl-Mannich reaction.[71]

converted into **198** through an intramolecular annulation (Scheme 36). Further manipulations of **198** provided stable 1,2-dihydroisoquinolines **199** with good to excellent enantioselectivity and diastereoselectivity. Chiral 1,2-dihydrophalazine derivatives can also be synthesized by this approach.

In 2007, Takemoto and co-workers ingeniously designed a new thiourea catalyst **203**, which activated organoboronic acids sufficiently to facilitate the enantioselective dearomatization of quinolines even at low temperature.[73] Excellent enantioselectivity was observed in the reaction of various quinolines **183** and organoboronic acids **201** in the presence of a combination of H_2O and $NaHCO_3$ as additives (Scheme 37).

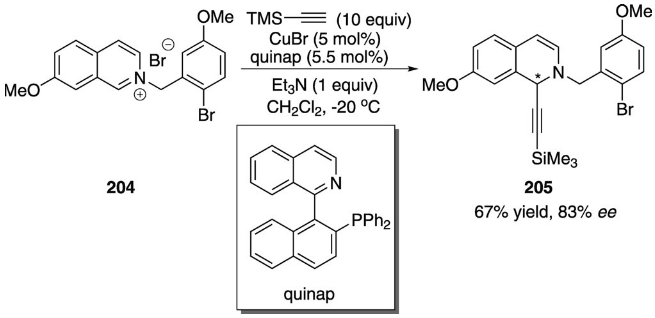


Scheme 36. Organocatalytic enantioselective dearomatization of alkylated isoquinolines.[72]



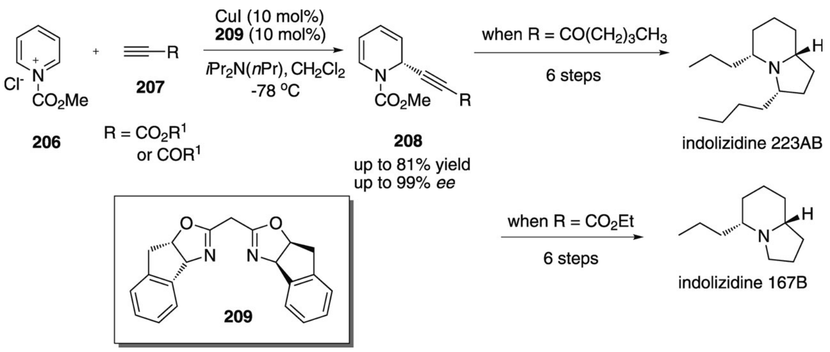
Scheme 37. Enantioselective dearomatization of quinolines by a thiourea-catalyzed Petasis-type reaction.[73]

In 2006, Taylor and Schreiber reported the copper(I)-catalyzed enantioselective addition of a terminal alkyne to the isoquinolinium ion **204** to give the dearomatization product **205** (Scheme 38).[74] Although only one substrate for the reaction was described, this study inspired further developments.



Scheme 38. Enantioselective addition of a terminal alkyne to an isoquinolinium ion in the presence of a copper catalyst.[74]

In 2007, Ma and co-workers reported a Cu^I/bisoxazoline-catalyzed addition of propiolates and terminal alkynes **207** to the 1-acyl pyridinium salt **206** to afford highly functionalized dihydropyridines **208** in good yields and excellent enantioselectivity.[75] It was found that the carbonyl group adjacent to the alkyne moiety in **207** was essential for the enantioselective addition. This method was used for the concise synthesis of indolizidines 167B and 223AB (Scheme 39).

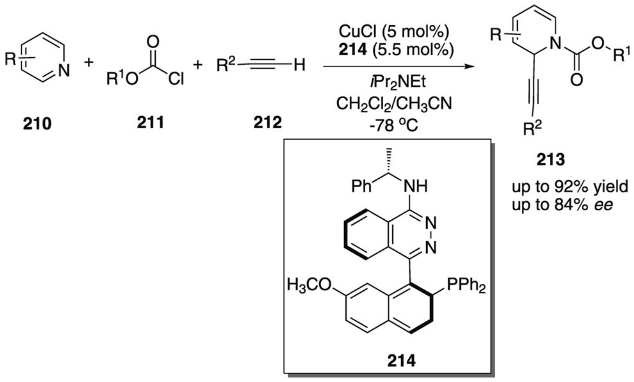


Scheme 39. Cu^I/bisoxazoline-catalyzed addition of propiolates and terminal alkynes to a 1-acyl pyridinium salt.[75]

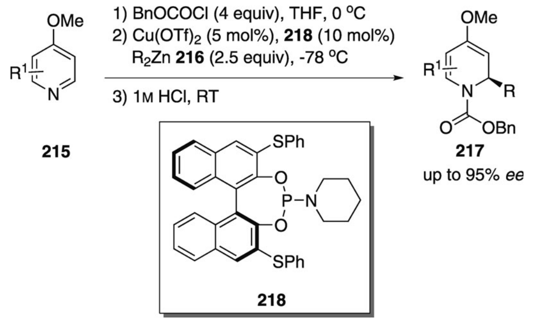
Soon afterwards, Arndtsen and co-workers reported a similar copper(I)-catalyzed asymmetric dearomatization of pyridines, quinolines, and isoquinolines with terminal alkynes as the nucleophiles to yield propargyl carbamates **213**.[76] With ligand **214**, a broader range of alkynes **212** could be used than in the reaction reported by Ma and co-workers[75] (Scheme 40).

In 2009, Feringa and co-workers reported a successful copper(II)-catalyzed asymmetric dearomatization of pyridines in a direct alkylative Reissert-type process.[77] With a catalyst derived from $Cu(OTf)_2$ and the chiral phosphoramidite ligand **218**, the corresponding products **217** were formed with excellent enantioselectivity (Scheme 41). Although excess amounts of BnOCOCl and the zinc reagent were needed, this synthetically useful dearomatization protocol has great potential owing to the good tolerance of a wide range of alkyl groups on the organozinc reagent.

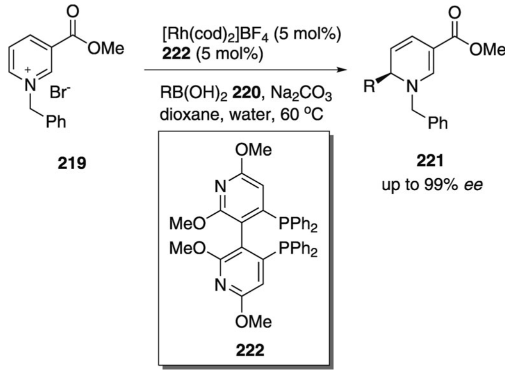
Recently, Nadeau et al. developed a catalytic enantioselective addition of boronic acids to *N*-benzylnicotinate salts.[78] With a catalyst generated from $[Rh(cod)_2]BF_4$ and ligand **222**, a variety of 6-substituted dihydropyridines **221** were formed from **219** in good yields with excellent enantioselectivity (Scheme 42). These products can be readily transformed into synthetically useful piperidines.



Scheme 40. Copper(I)-catalyzed enantioselective dearomatization of pyridines with terminal alkynes.[76]



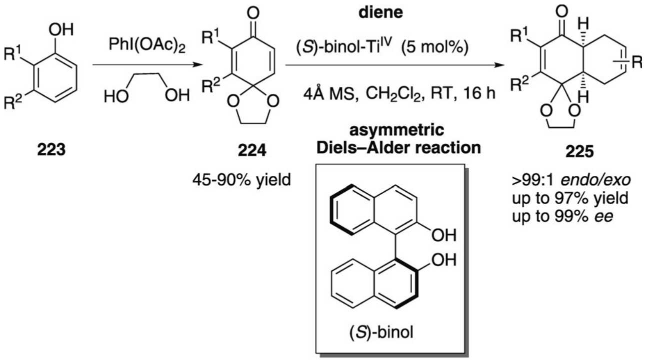
Scheme 41. Copper(II)-catalyzed asymmetric dearomatization of pyridines through a direct alkylative Reissert reaction.[77]



Scheme 42. Rhodium-catalyzed asymmetric dearomatization of *N*-benzylnicotinate salts through the addition of boronic acids.[78]

8. Stepwise Strategy: Dearomatization/Asymmetric Catalysis

Many stereoselective oxidative dearomatization processes still rely on a diastereoselective strategy controlled by chiral substrates. The direct oxidative dearomatization of phenols, indoles, and pyrroles for the construction of optically pure molecules is undoubtedly desirable; however, highly efficient enantioselective catalytic protocols are still limited in this regard. Therefore, an alternative stepwise strategy has been developed that combines dearomatization and asymmetric catalysis. For example, the *para*-oxidative dearomatization product of phenol is a *meso* molecule with an α,β-unsaturated ketone moiety. This unsaturated ketone can be subjected to various catalytic asymmetric transformations. Several research groups have used this strategy involving oxidative dearomatization followed by catalytic enantioselective desymmetrization to develop elegant methods for the construction of highly enantiomerically enriched molecules. An early study was reported in 2001 by Breuning and Corey, who were aiming to develop an efficient enantioselective Diels–Alder reaction of quinones.[79] In using 1,4-quinone monoketals **224** instead of the corresponding quinines, they not only took advantage of the stronger Lewis basicity of **224** in this chiral Lewis acid catalyzed process, but also applied the oxidative dearomatization of phenols as a convenient way to synthesize **224**. This highly efficient two-step sequence was used with a chiral Ti^{IV} catalyst to convert various substituted phenols **223** into the synthetically useful compounds **225** in satisfactory yields with excellent enantioselectivity (Scheme 43).

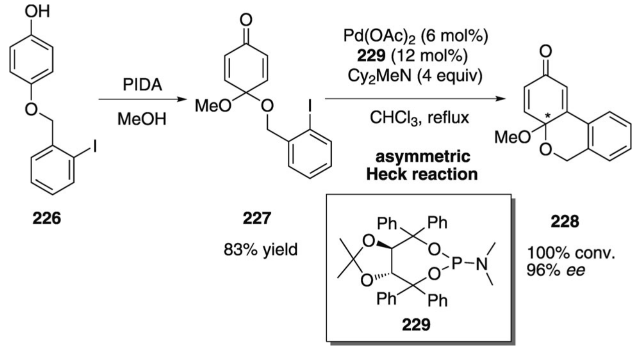


Scheme 43. Dearomatization of phenols and further desymmetrization through an asymmetric Diels–Alder reaction.[79]

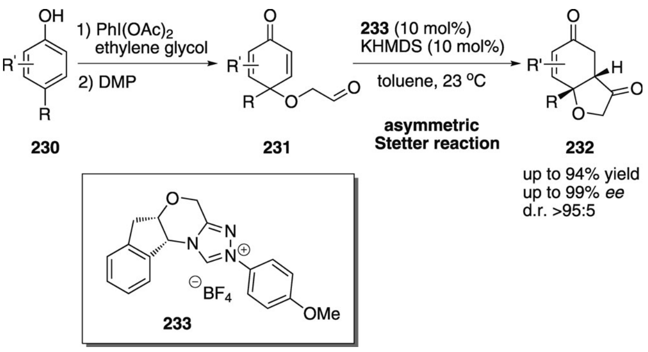
In 2002, Feringa and co-workers reported an enantioselective intramolecular Heck reaction of cyclohexadienone **227** in the presence of $Pd(OAc)_2$ and the taddol-derived ligand **229** (Scheme 44).[80] The oxidative dearomatization of phenol **226** provided the symmetrical compound **227** in 83 % yield. Desymmetrization of **227** then yielded **228** with full conversion and excellent enantioselectivity.

Liu and Rovis coupled the oxidative dearomatization of phenols with an asymmetric intramolecular Stetter reaction catalyzed by an N-heterocyclic carbene (NHC; Scheme 45).[81] Symmetrical cyclohexadienones **231** bearing an aldehyde moiety were conveniently obtained from their phenol precursors, and the subsequent enantioselective Stetter reaction in the presence of the chiral triazolium salt **233** afforded products **232** in excellent yields, enantioselectivity, and diastereoselectivity.

In 2008, Gaunt and co-workers reported a one-pot protocol combining an oxidative dearomatization process with a subsequent asymmetric intramolecular Michael reaction catalyzed by pyrrolidine **237**.[82] This elegant process directly converted various *para*-substituted phenols **234** into the polycyclic molecules **236** with three contiguous stereo-

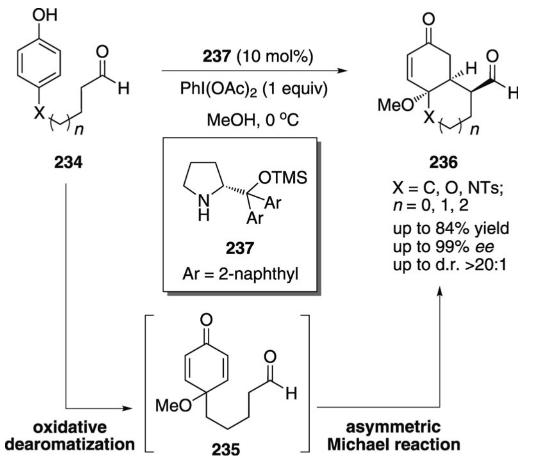


Scheme 44. Dearomatization of a phenol and enantioselective intramolecular Heck reaction of the resulting cyclohexadienone.[80]



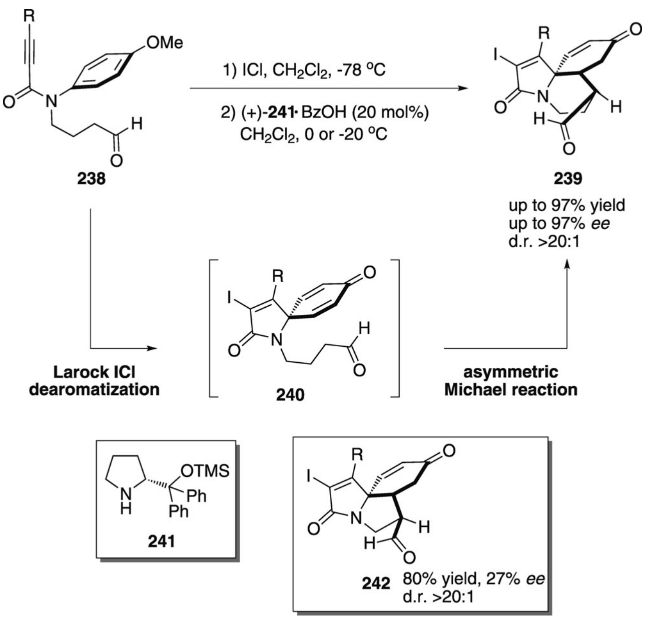
Scheme 45. NHC-catalyzed asymmetric intramolecular Stetter reaction of cyclohexadienones resulting from the oxidative dearomatization of phenols with ethylene glycol.[81]

genic centers (Scheme 46). The intermediate **235** resulting from oxidative dearomatization of the corresponding phenol could be isolated, and the highly efficient one-pot procedure provided products **236** without any decrease in enantioselectivity or diastereoselectivity with respect to the stepwise procedure.



Scheme 46. Oxidative dearomatization and subsequent asymmetric intramolecular Michael addition of the pendant aldehyde to the cyclohexadienone ring.[82]

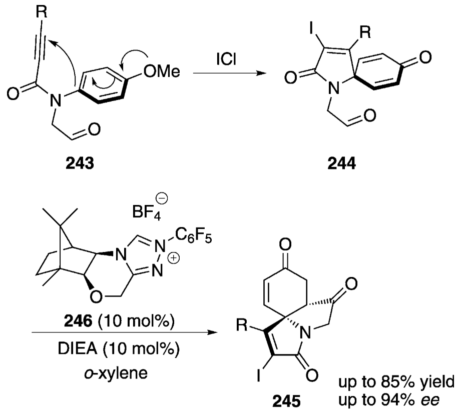
Owing to the success of this one-pot strategy, Gaunt and co-workers continued to explore this approach with different intramolecular dearomatization processes.[83] Thus, a Larock *ipso* iodocylization of alkynyl arenes **238** in the presence of ICl to give iodine-substituted spirocyclic cyclohexadienones **240** was followed by an asymmetric Michael addition catalyzed by pyrrolidine **241**. The resulting highly functionalized tricyclic molecules **239** with a quaternary stereogenic center were formed in good yields with satisfactory enantioselectivity and excellent diastereoselectivity (Scheme 47). However, the enantioselectivity of this process was poor for the generation of a five-membered ring in the asymmetric Michael addition step; thus, compound **242** was afforded in good yield but with just 27 % *ee*.



Scheme 47. Dearomatization of *N*-(4-methoxyphenyl)amides and further desymmetrization through an asymmetric Michael reaction.[83]

Inspired by the studies of Liu and Rovis as well as Gaunt and co-workers,[81,83] Jia and You examined an enantioselective desymmetrization of cyclohexadienones by an NHC-catalyzed intramolecular Stetter reaction.[84] With 10 mol % of the D-camphor-derived triazolium salt **246** as the precatalyst, the dearomatized products **244** (synthesized from **243** by the Larock *ipso*-iodocylization reaction) were converted into tricyclic products **245** in moderate to good yields with excellent enantioselectivity (Scheme 48).

Recently, You and co-workers reported a series of oxidative dearomatization reactions of phenols followed by asymmetric Michael reactions catalyzed by chiral organocatalysts (Scheme 49).[85] An intramolecular oxo-Michael reaction catalyzed by the chiral phosphoric acid **250** afforded enantiomerically enriched 1,4-dioxanes **249** from the products **248** of oxidative dearomatization. A concise synthetic sequence, which started with the oxidative dearomatization of a phenol **247** (R = CH_2CH_2OH) and a subsequent highly enantioselective oxo-Michael reaction, was then applied as



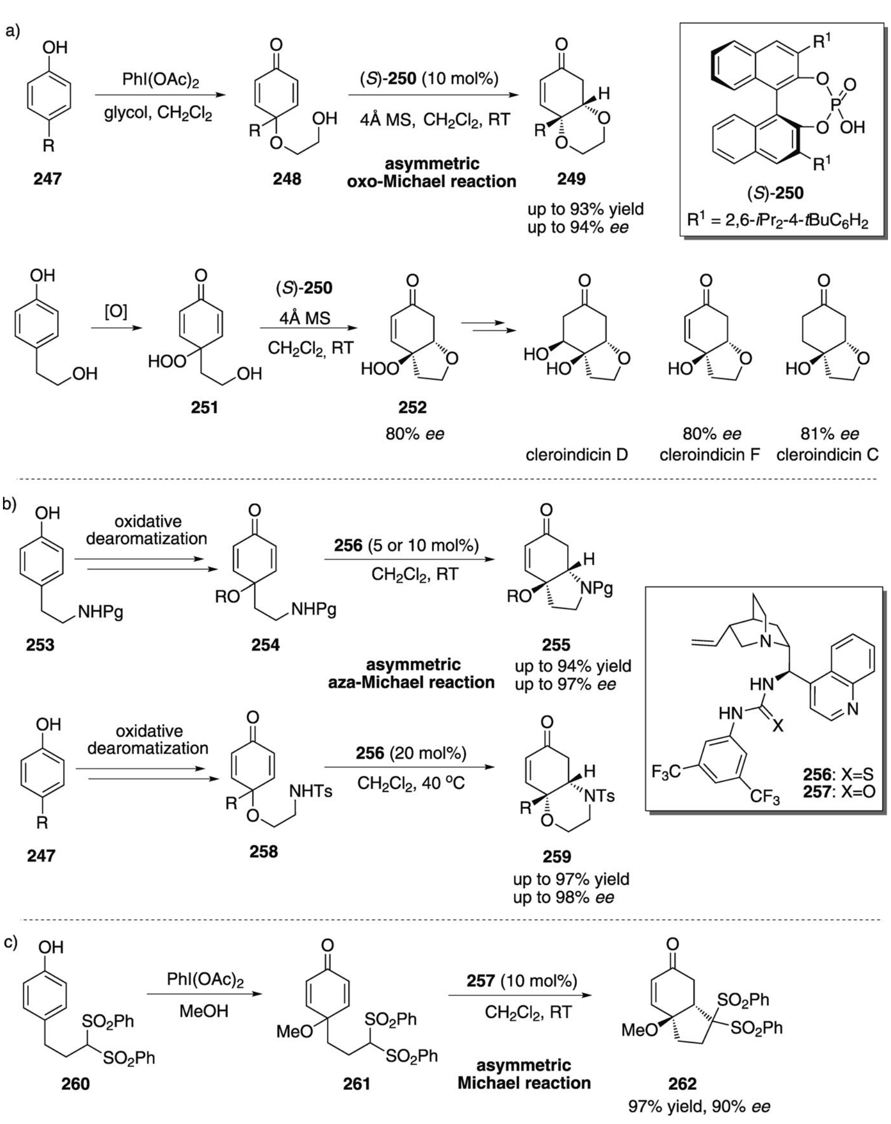
Scheme 48. Dearomatization of N-(4-methoxyphenyl)amides by the Larock *ipso*-iodocylization reaction and enantioselective desymmetrization of the resulting cyclohexadienones through an NHC-catalyzed intramolecular Stetter reaction.[84]

the key step to the asymmetric total synthesis of cleroindicins D, F, and C (Scheme 49a). These concise total syntheses highlight the potential of the oxidative dearomatization–catalytic enantioselective desymmetrization strategy for the construction of complex chiral molecules from relatively simple phenols. Later, They extended this strategy to a thiourea-catalyzed asymmetric aza-Michael reaction for the synthesis of pyrrolidine derivatives **255** and morpholine derivatives **259** in excellent yield and enantioselectivity (Scheme 49b). Very recently, You and co-workers also developed a urea-catalyzed Michael addition. In this case, strong electron-withdrawing groups, such as bisphenyl sulfones, were needed in the substrate for the reaction to proceed efficiently with good enantioselectivity (Scheme 49c).

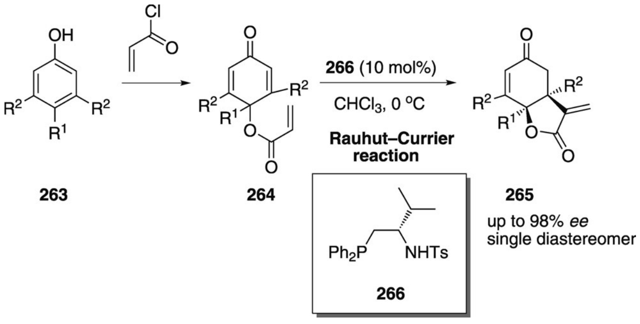
On the basis of a dearomatization reaction of symmetrical phenols **263** and a subsequent organocatalytic Rauhut–Currier reaction, Enders, Sasai, and co-workers recently developed an efficient approach to α-alkylidene-γ-butyrolactone core structures **265** as single diastereomers with high levels of enantioselectivity.[86] The chiral organocatalyst **266**, which contains both Lewis base and Brønsted acid moieties, was used for the desymmetrization of **264** (Scheme 50).

In 2011, Harned and co-workers developed an efficient sequential asymmetric approach to the construction of bicyclic (and even tricyclic) compounds by taking advantage of the oxidative dearomatization of phenols and an enantioselective Michael reaction catalyzed by a phase-transfer catalyst.[87] With 10 mol% of the cinchona-alkaloid-based phase-transfer catalyst **272**, prochiral cyclohexadienones **269** containing a tethered activated methylene group were desymmetrized to the corresponding products **270** with good regioselectivity and enantioselectivity (Scheme 51). Tricyclic cyclopropanes **271** were obtained when brominated substrates **269** ($R^4 = Br$) were used.

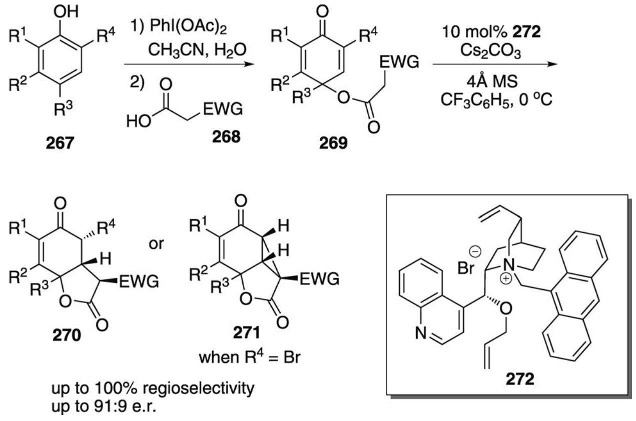
A Lewis acid promoted intramolecular ene reaction of indoles reported by Chen and co-workers proved to be a unique stepwise procedure for the dearomatization of indoles.[88] As shown in Scheme 52, chiral indole derivatives **275** were synthesized with good diastereoselectivity and with excellent enantioselectivity with respect to the major diastereomer. Upon exposure to a stoichiometric amount of $AlCl_3$,



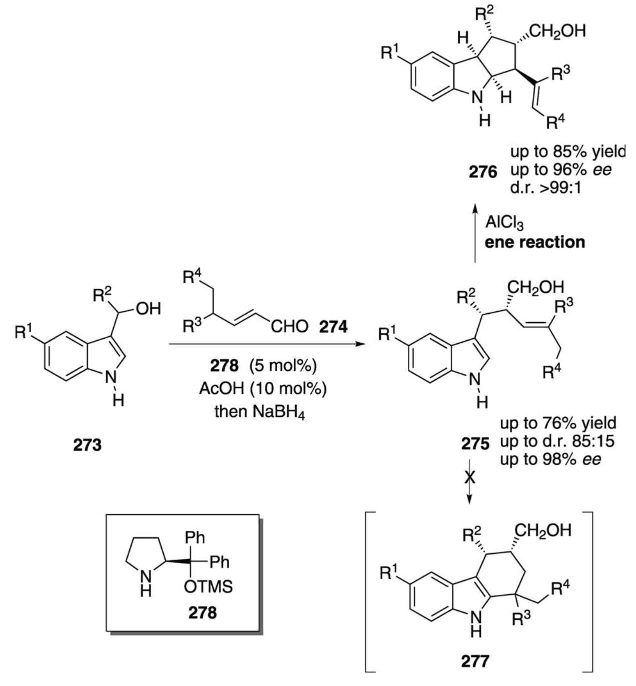
Scheme 49. Dearomatization of phenols and further desymmetrization through organocatalytic intramolecular asymmetric Michael reactions involving oxygen, nitrogen, and carbon nucleophiles.[85]



Scheme 50. Oxidative dearomatization of phenols with propenoyl chloride and subsequent organocatalytic Rauhut–Currier reaction.[86]



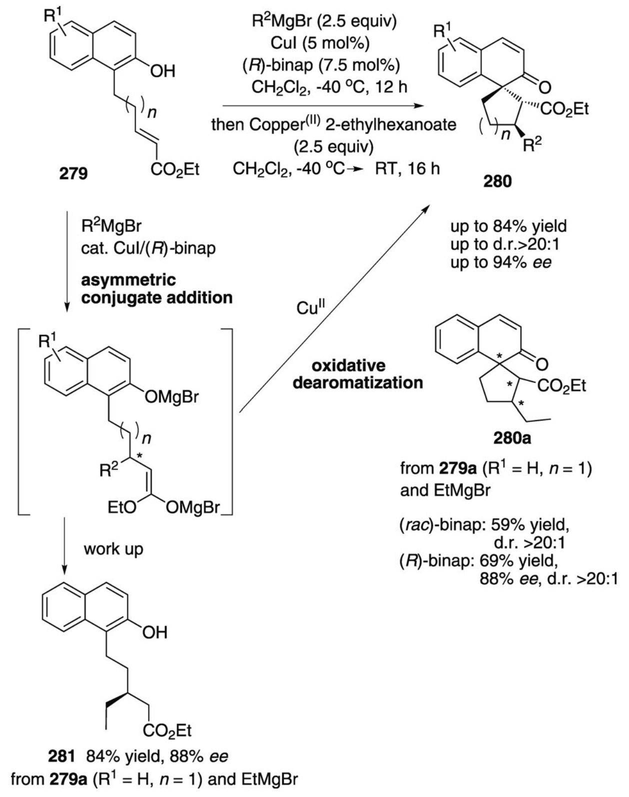
Scheme 51. Dearomatization of phenols with carboxylic acids and further desymmetrization through an intramolecular asymmetric Michael reaction.[87]



Scheme 52. Dearomatization of indoles through an ene reaction.[88]

compounds **275** underwent deromatization with complete diastereocontrol to give the ene products **276** without loss of enantiomeric purity. Interestingly, the originally proposed Friedel–Crafts products **277** could not be obtained from **275** under these conditions with a Lewis acid. Although chiral substrates were responsible for the high enantioselectivity of the dearomatization, the overall reaction was highly concise and has great potential for synthetic applications.

Recently, Feringa and co-workers developed a highly efficient sequential asymmetric approach to the construction of spirocyclic compounds that takes advantage of a copper(II)-mediated oxidative dearomatization process.[89,90] Naphthols **279** with a pendant α,β-unsaturated ester could undergo a copper(I)-catalyzed asymmetric conjugate addition followed by a copper(II)-mediated intramolecular oxidative dearomatization to afford benzofused spirocyclic cyclohexenones **280** with excellent diastereoselectivity and good enantioselectivity (Scheme 53). This one-pot strategy results in two new carbon–carbon bonds and three contiguous stereogenic centers, and the products are characterized by a high degree of functionality as well as molecular complexity. Investigation of the first step led to the isolation of **281** with 88% *ee*, which matched the enantiomeric purity of **280a** obtained under the one-pot conditions.[91]



Scheme 53. Dearomatization of naphthols through a sequence involving a copper(I)-catalyzed asymmetric conjugate addition and subsequent copper(II)-mediated oxidative dearomatization.[89]

9. Summary

As seen from this Review, catalytic asymmetric dearomatization (CADA) reactions are the most efficient methods for the conversion of electron-rich aromatic compounds from a “two-dimensional world” into enantiomerically pure diverse ring systems belonging to a “three-dimensional kingdom”. Significant progress has been made in this field, and CADA reactions have been shown to have great potential as a practical synthetic strategy. Pioneering studies with chiral hypervalent iodine catalysts have provided the basis for the catalytic asymmetric dearomatization of phenols and related electron-rich arenes. However, the practicality of these catalysts and the catalytic efficiency of these reactions still need further improvement. Diels–Alder and related reactions as well as alkylation reactions provide an efficient approach to the dearomatization of electron-rich arenes, in general without oxidants. The introduction of transition-metal-catalyzed reactions for asymmetric dearomatization has already been fruitful and will remain highly promising owing to the many transformation possibilities offered by organometallic chemistry. The availability of versatile chiral ligands will also ensure the success of this approach. Not only can cascade processes involving dearomatization reactions provide the driving force for the dearomative transformation but they can also lead to complex molecular structures in an enantiomerically pure form. In the case of electron-deficient aromatic compounds, such as pyridine derivatives, nucleophilic reactions following activation by carbonylation or alkylation of the nitrogen atom could proceed well in the presence of either chiral metal complexes or organocatalysts.

Despite the great potential of catalytic asymmetric dearomatization reactions, the development of this field is still in its infancy. There remain enormous challenges:

1) Owing to the diverse properties of arenes, it is impossible to have a general activation mode for all substrates.
2) The reactions are so far mainly limited to electron-rich arene substrates. There is great demand for the improvement of catalytic efficiency, intermolecular reactions, and chemoselectivity when multiple reactive sites exist in the arene, and for versatile reaction types suitable for dearomatization.
3) In general, the activation of pyridine derivatives by carbonylation or alkylation is necessary, and an undesired protecting group remains on the nitrogen atom of the products in many cases. CADA reactions without preactivation are highly desirable.
4) There are limited methods available for the enantioselective dearomatization of simple benzene derivatives.

Given these formidable challenges, diastereoselective dearomatization reactions or stepwise strategies involving dearomatization and asymmetric catalysis will serve as complementary methods in the foreseeable future. Overall, in light of the fast-paced development of organic chemistry, we have good reason to believe that catalytic asymmetric dearomatization reactions will receive much more attention in future and play a more important role in organic synthesis.

Abbreviations

Ac	acyl
An	anthracyl
9-BBN	9-borabicyclo[3.3.1]nonane
binol	1,1′-binaphthalene-2,2′-diol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bz	benzoyl
cod	cyclooctadiene
CSA	camphorsulfonic acid
Cy	cyclohexyl
dba	*trans,trans*-dibenzylideneacetone
$(DHQD)_2PHAL$	bis(dihydroquinidine)phthalazine
DIC	diisopropylcarbodiimide
DIEA	diisopropylethylamine
DIPT	diisopropyl tartrate
DMAP	4-dimethylaminopyridine
2,2-DMB	2,2-dimethylbutane
DMDO	dimethyldioxirane
DMP	Dess–Martin periodinane
DTBM-segphos	5,5′-bis(di(3,5-di-tert-butyl-4-methoxyphenyl)phosphanyl)-4,4′-bi-1,3-benzodioxole
EWG	electron-withdrawing group
HMDS	1,1,1,3,3,3-hexamethyldisilazane
IBX	2-iodoxybenzoic acid
*m*CPBA	*meta*-chloroperbenzoic acid
Mes	mesityl
MS	molecular sieves
2-NBA	2-nitrobenzoic acid
NCS	*N*-chlorosuccinimide
NFSI	*N*-fluorobenzenesulfonimide
Np	naphthyl
PFBA	pentafluorobenzoic acid
PG	protecting group
Phth	phthaloyl
PIDA	phenyliodonium diacetate
PIFA	phenyliodonium bis(trifluoroacetate)
PMB	*p*-methoxybenzyl
$Rh_2(OOct)_4$	rhodium(II) octanoate dimer
taddol	1,1,4,4-tetraphenyl-2,3-*O*-isopropylidene-L-threitol
TBA	tribromoacetic acid
TBS	*tert*-butyldimethylsilyl
Tces	2,2,2-trichloroethoxysulfonyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFE	2,2,2-trifluoroethanol
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TrocCl	2,2,2-trichloroethyl chloroformate
Ts	*p*-tosyl, *p*-toluenesulfonyl
xylyl-binap	2,2′-bis(di(3,5-xylyl)phosphanyl)-1,1′-binaphthyl

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[1] S. P. Roche, J. A. Porco, Jr., *Angew. Chem.* **2011**, *123*, 4154–4179; *Angew. Chem. Int. Ed.* **2011**, *50*, 4068–4093.

[2] L. Pouységu, D. Deffieux, S. Quideau, *Tetrahedron* **2010**, *66*, 2235–2261.

[3] F. López Ortiz, M. J. Iglesias, I. Fernández, C. M. Andújar Sánchez, G. R. Gómez, *Chem. Rev.* **2007**, *107*, 1580–1691.

[4] A. R. Pape, K. P. Kaliappan, E. P. Kündig, *Chem. Rev.* **2000**, *100*, 2917–2940.

[5] For reviews on the asymmetric hydrogenation of aromatic compounds, see: a) Y.-G. Zhou, *Acc. Chem. Res.* **2007**, *40*, 1357–1366; b) D.-S. Wang, Q.-A. Chen, S.-M. Lu, Y.-G. Zhou, *Chem. Rev.* **2012**, *112*, 2557–2590.

[6] For a review, see: G. Rassu, F. Zanardi, L. Battistini, G. Casiraghi, *Chem. Soc. Rev.* **2000**, *29*, 109–118.

[7] For reviews on enzymatic dearomatization, see: a) T. Hudlicky, J. W. Reed, *Synlett* **2009**, 685–703; b) D. R. Boyd, T. D. H. Bugg, *Org. Biomol. Chem.* **2006**, *4*, 181–192; c) R. A. Johnson, *Organic Reactions*, *Vol. 63*, Wiley, New York, **2004**, pp. 117–264; d) T. Hudlicky, D. Gonzalez, D. T. Gibson, *Aldrichimica Acta* **1999**, *32*, 35–62; e) M. Boll, *J. Mol. Microbiol. Biotechnol.* **2005**, *10*, 132–142.

[8] For selected recent asymmetric dearomatization reactions catalyzed by enzymes, see: a) M. A. Schätzle, S. Flemming, S. M. Husain, M. Richter, S. Günther, M. Müller, *Angew. Chem.* **2012**, *124*, 2697–2700; *Angew. Chem. Int. Ed.* **2012**, *51*, 2643–2646; b) D. R. Boyd, N. D. Sharma, B. McMurray, S. A. Haughey, C. C. R. Allen, J. T. G. Hamilton, W. C. McRoberts, R. A. More O'Ferrall, J. Nikodinovic-Runic, L. A. Coulombel, K. E. O'Connor, *Org. Biomol. Chem.* **2012**, *10*, 782–790.

[9] For selected examples of the oxidative dearomatization of phenols in natural product synthesis, see: a) S. Kodama, Y. Hamashima, K. Nishide, M. Node, *Angew. Chem.* **2004**, *116*, 2713–2715; *Angew. Chem. Int. Ed.* **2004**, *43*, 2659–2661; b) L. Liu, Y. Gao, C. Che, N. Wu, D. Z. Wang, C.-C. Li, Z. Yang, *Chem. Commun.* **2009**, 662–664; c) J. Liang, J. Chen, J. Liu, L. Li, H. Zhang, *Chem. Commun.* **2010**, *46*, 3666–3668; d) J. Y. Cha, Y. Huang, T. R. R. Pettus, *Angew. Chem.* **2009**, *121*, 9683–9685; *Angew. Chem. Int. Ed.* **2009**, *48*, 9519–9521; e) J. Y. Cha, G. L. Burnett IV, Y. Huang, J. B. Davidson, T. R. R. Pettus, *J. Org. Chem.* **2011**, *76*, 1361–1371; f) J. C. Green, T. R. R. Pettus, *J. Am. Chem. Soc.* **2011**, *133*, 1603–1608.

[10] For selected examples of the oxidative dearomatization of indoles in natural product synthesis, see: a) P. S. Baran, J. M. Richter, *J. Am. Chem. Soc.* **2005**, *127*, 15394–15396; b) K. A. Miller, S. Tsukamoto, R. M. Willams, *Nat. Chem.* **2009**, *1*, 63–68; c) H. Wu, F. Xue, X. Xiao, Y. Qin, *J. Am. Chem. Soc.* **2010**, *132*, 14052–14054; d) Z. Zuo, W. Xie, D. Ma, *J. Am. Chem. Soc.* **2010**, *132*, 13226–13228; e) Z. Zuo, D. Ma, *Angew. Chem.* **2011**, *123*, 12214–12217; *Angew. Chem. Int. Ed.* **2011**, *50*, 12008–12011; for the dearomatization of diketopiperazines by bromocyclization, see: f) M. Movassaghi, M. A. Schmidt, J. A. Ashenhurst, *Angew. Chem.* **2008**, *120*, 1507–1509; *Angew. Chem. Int. Ed.* **2008**, *47*, 1485–1487; g) J. Kim, J. A. Ashenhurst, M. Movassaghi, *Science* **2009**, *324*, 238–241; h) J. Kim, M. Movassaghi, *J. Am. Chem. Soc.* **2010**, *132*, 14376–14378; i) J. Kim, M. Movassaghi, *J. Am. Chem. Soc.* **2011**, *133*, 14940–14943; for the oxidative dearomatization of tryptophans through indole–aniline coupling, see: j) T. Newhouse, P. S. Baran, *J. Am. Chem. Soc.* **2008**, *130*, 10886–10887; k) T. Newhouse, C. A. Lewis, P. S. Baran, *J. Am. Chem. Soc.* **2009**, *131*, 6360–6361; l) T. Newhouse, C. A. Lewis, K. J. Eastman, P. S. Baran, *J. Am. Chem. Soc.* **2010**, *132*, 7119–7137; m) K. Foo, T. Newhouse, I. Mori, H. Takayama, P. S. Baran, *Angew. Chem.* **2011**, *123*, 2768–2771; *Angew. Chem. Int. Ed.* **2011**, *50*, 2716–2719.

[11] T. Yakura, M. Omoto, Y, Yamauchi, Y. Tian, A. Ozono, *Tetrahedron* **2010**, *66*, 5833–5840.

[12] For a review, see: S. Quideau, L. Pouységu, D. Deffieux, *Synlett* **2008**, 467–495.

[13] T. Dohi, A. Maruyama, N. Takenaga, K. Senami, Y. Minamitsuji, H. Fujioka, S. B. Caemmerer, Y. Kita, *Angew. Chem.* **2008**, *120*, 3847–3850; *Angew. Chem. Int. Ed.* **2008**, *47*, 3787–3790.

[14] J. K. Boppisetti, V. B. Birman, *Org. Lett.* **2009**, *11*, 1221–1223.

[15] a) S. Quideau, G. Lyvinec, M. Marguerit, K. Bathany, A. Ozanne-Beaudenon, T. Buffeteau, D. Cavagnat, A. Chénedé, *Angew. Chem.* **2009**, *121*, 4675–4679; *Angew. Chem. Int. Ed.* **2009**, *48*, 4605–4609; b) L. Pouységu, T. Sylla, T. Garnier, L. B. Rojas, J. Charris, D. Deffieux, S. Quideau, *Tetrahedron* **2010**, *66*, 5908–5917.

[16] a) M. Uyanik, T. Yasui, K. Ishihara, *Angew. Chem.* **2010**, *122*, 2221–2223; *Angew. Chem. Int. Ed.* **2010**, *49*, 2175–2177; b) M. Uyanik, T. Yasui, K. Ishihara, *Tetrahedron* **2010**, *66*, 5841–5851.

[17] J.-L. Liang, S.-X. Yuan, P. W. H. Chan, C.-M. Che, *Tetrahedron Lett.* **2003**, *44*, 5917–5920.

[18] J. V. Mulcahy, J. Du Bois, *J. Am. Chem. Soc.* **2008**, *130*, 12630–12631.

[19] a) M. Kim, J. V. Mulcahy, C. G. Espino, J. Du Bois, *Org. Lett.* **2006**, *8*, 1073–1076; b) P. M. Wehn, J. Lee, J. Du Bois, *Org. Lett.* **2003**, *5*, 4823–4826; c) K. Williams Fiori, J. J. Fleming, J. Du Bois, *Angew. Chem.* **2004**, *116*, 4449–4452; *Angew. Chem. Int. Ed.* **2004**, *43*, 4349–4352.

[20] a) S. Sato, M. Shibuya, N. Kanoh, Y. Iwabuchi, *Chem. Commun.* **2009**, 6264–6266; b) S. Sato, M. Shibuya, N. Kanoh, Y. Iwabuchi, *J. Org. Chem.* **2009**, *74*, 7522–7524.

[21] a) T. Sunazuka, T. Hirose, T. Shirahata, Y. Harigaya, M. Hayashi, K. Komiyama, S. Ōmura, A. B. Smith III, *J. Am. Chem. Soc.* **2000**, *122*, 2122–2123; b) T. Sunazuka, K. Yoshida, N. Kojima, T. Shirahata, T. Hirose, M. Handa, D. Yamamoto, Y. Harigaya, I. Kuwajima, S. Ōmura, *Tetrahedron Lett.* **2005**, *46*, 1459–1461.

[22] a) J. Zhu, A. R. Germain, J. A. Porco, Jr., *Angew. Chem.* **2004**, *116*, 1259–1263; *Angew. Chem. Int. Ed.* **2004**, *43*, 1239–1243; b) J. Zhu, N. P. Grigoriadis, J. P. Lee, J. A. Porco, Jr., *J. Am. Chem. Soc.* **2005**, *127*, 9342–9343; c) J. Zhu, J. A. Porco, Jr., *Org. Lett.* **2006**, *8*, 5169–5171.

[23] A. R. Germain, D. M. Bruggemeyer, J. Zhu, C. Genet, P. O'Brien, J. A. Porco, Jr., *J. Org. Chem.* **2011**, *76*, 2577–2584.

[24] a) M. J. Dearden, C. R. Firkin, J.-P. R. Hermet, P. O'Brien, *J. Am. Chem. Soc.* **2002**, *124*, 11870–11871; b) M. J. Dearden, M. J. McGrath, P. O'Brien, *J. Org. Chem.* **2004**, *69*, 5789–5792; c) P. O'Brien, *Chem. Commun.* **2008**, 655–667.

[25] S. Dong, J. Zhu, J. A. Porco, Jr., *J. Am. Chem. Soc.* **2008**, *130*, 2738–2739.

[26] M. Movassaghi, M. A. Schmidt, J. A. Ashenhurst, *Org. Lett.* **2008**, *10*, 4009–4012.

[27] F. Kolundzic, M. N. Noshi, M. Tjandra, M. Movassaghi, S. J. Miller, *J. Am. Chem. Soc.* **2011**, *133*, 9104–9111.

[28] S. Han, M. Movassaghi, *J. Am. Chem. Soc.* **2011**, *133*, 10768–10771.

[29] a) W. E. Noland, W. C. Kuryla, R. F. Lange, *J. Am. Chem. Soc.* **1959**, *81*, 6010–6017; b) W. E. Noland, R. J. Sundberg, *J. Org. Chem.* **1963**, *28*, 884–885; c) W. E. Noland, S. R. Wann, *J. Org. Chem.* **1979**, *44*, 4402–4410; for reviews of Diels–Alder reactions of vinyl indoles, see: d) U. Pindur, *Heterocycles* **1988**, *27*, 1253–1268; e) W. E. Noland, G.-M. Xia, K. R. Gee, M. J. Konkel, M. J. Wahlstrom, J. J. Condoluci, D. L. Rieger, *Tetrahedron* **1996**, *52*, 4555–4572; f) M. Bleile, T. Wagner, H.-H. Otto, *Helv. Chim. Acta* **2005**, *88*, 2879–2891.

[30] For the use of a chiral auxiliary in the Diels–Alder reaction of vinyl indoles with carbodienophiles, see: U. Pindur, G. Lutz, G.

Fischer, D. Schollmeyer, W. Massa, L. Schröder, *Tetrahedron* **1993**, *49*, 2863 – 2872.

[31] a) C. Gioia, A. Hauville, L. Bernardi, F. Fini, A. Ricci, *Angew. Chem.* **2008**, *120*, 9376 – 9379; *Angew. Chem. Int. Ed.* **2008**, *47*, 9236 – 9239; b) B. Tan, G. Hernández-Torres, C. F. Barbas III, *J. Am. Chem. Soc.* **2011**, *133*, 12354 – 12357.

[32] K. Shibatomi, F. Kobayashi, A. Narayama, I. Fujisawa, S. Iwasa, *Chem. Commun.* **2012**, *48*, 413 – 415.

[33] a) K. Futatsugi, H. Yamamoto, *Angew. Chem.* **2005**, *117*, 1508 – 1511; *Angew. Chem. Int. Ed.* **2005**, *44*, 1484 – 1487; b) K. Shibatomi, K. Futatsugi, F. Kobayashi, S. Iwasa, H. Yamamoto, *J. Am. Chem. Soc.* **2010**, *132*, 5625 – 5627.

[34] M. Harmata, S. K. Ghosh, X. Hong, S. Wacharasindhu, P. Kirchhoefer, *J. Am. Chem. Soc.* **2003**, *125*, 2058 – 2059.

[35] B.-F. Sun, C.-L. Wang, R. Ding, J.-Y. Xu, G.-Q. Lin, *Tetrahedron Lett.* **2011**, *52*, 2155 – 2158.

[36] For intermolecular [4+3] cycloaddition reactions of nitrogen-stabilized oxyallyl cations with furans, see: a) H. Xiong, R. P. Hsung, C. R. Berry, C. Rameshkumar, *J. Am. Chem. Soc.* **2001**, *123*, 7174 – 7175; for intramolecular [4+3] cycloaddition reactions of nitrogen-stabilized oxyallyl cations with furans, see: b) H. Xiong, J. Huang, S. K. Ghosh, R. P. Hsung, *J. Am. Chem. Soc.* **2003**, *125*, 12694 – 12695; c) C. Rameshkumar, R. P. Hsung, *Angew. Chem.* **2004**, *116*, 625 – 628; *Angew. Chem. Int. Ed.* **2004**, *43*, 615 – 618; for stereoselective [4+3] cycloaddition reactions of nitrogen-stabilized oxyallyl cations with pyrroles, see: d) J. E. Antoline, R. P. Hsung, J. Huang, Z. Song, G. Li, *Org. Lett.* **2007**, *9*, 1275 – 1278.

[37] J. Huang, R. P. Hsung, *J. Am. Chem. Soc.* **2005**, *127*, 50 – 51.

[38] a) R. P. Reddy, H. M. L. Davies, *J. Am. Chem. Soc.* **2007**, *129*, 10312 – 10313; b) H. M. L. Davies, J. J. Matasi, L. M. Hodges, N. J. S. Huby, C. Thornley, N. Kong, J. H. Houser, *J. Org. Chem.* **1997**, *62*, 1095 – 1105.

[39] N. Shimada, T. Oohara, J. Krishnamurthi, H. Nambu, S. Hashimoto, *Org. Lett.* **2011**, *13*, 6284 – 6287.

[40] a) L. M. Repka, J. Ni, S. E. Reisman, *J. Am. Chem. Soc.* **2010**, *132*, 14418 – 14420; b) M. E. Kieffer, L. M. Repka, S. E. Reisman, *J. Am. Chem. Soc.* **2012**, *134*, 5131 – 5137.

[41] E. Angelini, C. Balsamini, F. Bartoccini, S. Lucarini, G. Piersanti, *J. Org. Chem.* **2008**, *73*, 5654 – 5657.

[42] a) E. C. Linton, M. C. Kozlowski, *J. Am. Chem. Soc.* **2008**, *130*, 16162 – 16163; b) T. Cao, J. Deitch, E. C. Linton, M. C. Kozlowski, *Angew. Chem.* **2012**, *124*, 2498 – 2501; *Angew. Chem. Int. Ed.* **2012**, *51*, 2448 – 2451.

[43] M. A. Lovchik, A. Goeke, G. Fráter, *Tetrahedron: Asymmetry* **2006**, *17*, 1693 – 1699.

[44] a) J. Qi, J. A. Porco, Jr., *J. Am. Chem. Soc.* **2007**, *129*, 12682 – 12683; b) Q. Zhang, B. Mitasev, J. Qi, J. A. Porco, Jr., *J. Am. Chem. Soc.* **2010**, *132*, 14212 – 14215.

[45] J. Qi, A. B. Beeler, Q. Zhang, J. A. Porco, Jr., *J. Am. Chem. Soc.* **2010**, *132*, 13642 – 13644.

[46] For Et_3B-promoted palladium-catalyzed allylic substitution reactions with allylic alcohols, see: a) M. Kimura, M. Futamata, K. Shibata, Y. Tamura, *Chem. Commun.* **2003**, 234 – 235; b) R. Mukai, Y. Horino, S. Tanaka, Y. Tamura, M. Kimura, *J. Am. Chem. Soc.* **2004**, *126*, 11138 – 11139; c) M. Kimura, R. Mukai, N. Tanigawa, S. Tanaka, Y. Tamura, *Tetrahedron* **2003**, *59*, 7767 – 7777; d) Y. Horino, M. Naito, M. Kimura, S. Tanaka, Y. Tamura, *Tetrahedron Lett.* **2001**, *42*, 3113 – 3116; e) Y. Tamaru, H. Horino, M. Araki, S. Tanaka, M. Kimura, *Tetrahedron Lett.* **2000**, *41*, 5705 – 5709.

[47] M. Kimura, M. Futamata, R. Mukai, Y. Tamaru, *J. Am. Chem. Soc.* **2005**, *127*, 4592 – 4593.

[48] B. M. Trost, J. Quancard, *J. Am. Chem. Soc.* **2006**, *128*, 6314 – 6315.

[49] For reviews, see: a) B. M. Trost, *Chem. Pharm. Bull.* **2002**, *50*, 1 – 14; b) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921 – 2943.

[50] For a racemic intermolecular dearomatization of indoles through allylic alkylation, see: N. Kagawa, J. P. Malerich, V. H. Rawal, *Org. Lett.* **2008**, *10*, 2381 – 2384.

[51] a) Q.-F. Wu, H. He, W.-B. Liu, S.-L. You, *J. Am. Chem. Soc.* **2010**, *132*, 11418 – 11419; b) Q.-F. Wu, W.-B. Liu, C.-X. Zhuo, Z.-R. Rong, K.-Y. Ye, S.-L. You, *Angew. Chem.* **2011**, *123*, 4547 – 4550; *Angew. Chem. Int. Ed.* **2011**, *50*, 4455 – 4458; c) C.-X. Zhuo, W.-B. Liu, Q.-F. Wu, S.-L. You, *Chem. Sci.* **2012**, *3*, 205 – 208; d) Q.-F. Wu, C. Zheng, S.-L. You, *Angew. Chem.* **2012**, *124*, 1712 – 1715; *Angew. Chem. Int. Ed.* **2012**, *51*, 1680 – 1683.

[52] For the intramolecular asymmetric allylic alkylation of indoles, see: M. Bandini, A. Melloni, F. Piccinelli, R. Sinisi, S. Tommasi, A. Umani-Ronchi, *J. Am. Chem. Soc.* **2006**, *128*, 1424 – 1425.

[53] a) T. Nemoto, Y. Ishige, M. Yoshida, Y. Kohno, M. Kanematsu, Y. Hamada, *Org. Lett.* **2010**, *12*, 5020 – 5023; b) M. Yoshida, T. Nemoto, Z. Zhao, Y. Ishige, Y. Hamada, *Tetrahedron: Asymmetry* **2012**, *23*, 859 – 866.

[54] a) J. García-Fortanet, F. Kessler, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 6676 – 6677; b) S. Rousseaux, J. García-Fortanet, M. A. Del Aguila Sanchez, S. L. Buchwald, *J. Am. Chem. Soc.* **2011**, *133*, 9282 – 9285.

[55] For racemic versions of related Pd-catalyzed dearomatization processes, see: a) R. B. Bedford, C. P. Butts, M. F. Haddow, R. Osborne, R. F. Sankey, *Chem. Commun.* **2009**, 4832 – 4834; b) R. B. Bedford, N. Fey, M. F. Haddow, R. F. Sankey, *Chem. Commun.* **2011**, *47*, 3649 – 3651; for a recent example of the Pd-catalyzed enantioselective dearomative arylation of indoles, see: c) K.-J. Wu, L.-X. Dai, S.-L. You, *Org. Lett.* **2012**, *14*, 3772 – 3775.

[56] J. F. Austin, S.-G. Kim, C. J. Sinz, W.-J. Xiao, D. W. C. MacMillan, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5482 – 5487.

[57] For a diastereoselective dearomatization of indoles through an iminium-catalyzed alkylation – cyclization cascade, see: R. R. Knowles, J. Carpenter, S. B. Blakey, A. Kayano, I. K. Mangion, C. J. Sinz, D. W. C. MacMillan, *Chem. Sci.* **2011**, *2*, 308 – 311.

[58] a) S. B. Jones, B. Simmons, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 13606 – 13607; b) S. B. Jones, B. Simmons, A. Mastracchio, D. W. MacMillan, *Nature* **2011**, *475*, 183 – 188.

[59] For a racemic version of a dearomatization reaction of a 2-vinyltryptamine derivative through a Diels – Alder/amine-cyclization sequence, see: J. Lévy, J. Sapi, J.-Y. Laronze, D. Royer, L. Toupet, *Synlett* **1992**, 601 – 602.

[60] a) Q. Cai, C. Zheng, S.-L. You, *Angew. Chem.* **2011**, *123*, 8824 – 8828; *Angew. Chem. Int. Ed.* **2011**, *50*, 8665 – 8669; b) Q. Cai, S.-L. You, *Org. Lett.* **2012**, *14*, 3040 – 3043.

[61] a) O. Lozano, G. Blessley, T. M. del Campo, A. L. Thompson, G. T. Giuffredi, M. Bettati, M. Walker, R. Borman, V. Gouverneur, *Angew. Chem.* **2011**, *123*, 8255 – 8259; *Angew. Chem. Int. Ed.* **2011**, *50*, 8105 – 8109; for recent examples of the enantioselective dearomatization of thiophene by fluorocyclization or bromocyclization, see: b) V. Rauniyar, A. D. Lackner, G. L. Hamilton, F. D. Toste, *Science* **2011**, *334*, 1681 – 1684; c) Y.-M. Wang, J. Wu, C. Hoong, V. Rauniyar, F. D. Toste, *J. Am. Chem. Soc.* **2012**, *134*, 12928 – 12931.

[62] G. Cera, M. Chiarucci, A. Mazzanti, M. Mancinelli, M. Bandini, *Org. Lett.* **2012**, *14*, 1350 – 1353.

[63] S. Zhu, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2012**, *134*, 10815 – 10818.

[64] For a recent review, see: M. Ahamed, M. H. Todd, *Eur. J. Org. Chem.* **2010**, 5935 – 5942.

[65] A. Reissert, *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 1603 – 1614.

[66] For a review, see: W. E. McEwen, R. L. Cobb, *Chem. Rev.* **1955**, *55*, 511 – 549.

[67] D. L. Comins, S. Huang, C. L. McArdle, C. L. Ingalls, *Org. Lett.* **2001**, *3*, 469 – 471.

[68] S. Ruchirawat, N. Phadungkul, M. Chuankamnerdkarn, C. Thebtaranonth, *Heterocycles* **1977**, *6*, 43–46.

[69] a) M. Takamura, K. Funabashi, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 6327–6328; b) M. Takamura, K. Funabashi, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 6801–6808; c) K. Funabashi, H. Ratni, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 10784–10785; d) E. Ichikawa, M. Suzuki, K. Yabu, M. Albert, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 11808–11809.

[70] For an organocatalytic asymmetric dearomatization of azaaromatic compounds, see: T. Liang, J. Xiao, Z. Xiong, X. Li, *J. Org. Chem.* **2012**, *77*, 3583–3588.

[71] M. S. Taylor, N. Tokunaga, E. N. Jacobsen, *Angew. Chem.* **2005**, *117*, 6858–6862; *Angew. Chem. Int. Ed.* **2005**, *44*, 6700–6704.

[72] K. Frisch, A. Landa, S. Saaby, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 6212–6217; *Angew. Chem. Int. Ed.* **2005**, *44*, 6058–6063.

[73] Y. Yamaoka, H. Miyabe, Y. Takemoto, *J. Am. Chem. Soc.* **2007**, *129*, 6686–6687.

[74] A. M. Taylor, S. L. Schreiber, *Org. Lett.* **2006**, *8*, 143–146.

[75] Z. Sun, S. Yu, Z. Ding, D. Ma, *J. Am. Chem. Soc.* **2007**, *129*, 9300–9301.

[76] D. A. Black, R. E. Beveridge, B. A. Arndtsen, *J. Org. Chem.* **2008**, *73*, 1906–1910.

[77] M. Á. Fernández-Ibáñez, B. Maciá, M. G. Pizzuti, A. J. Minnaard, B. L. Feringa, *Angew. Chem.* **2009**, *121*, 9503–9505; *Angew. Chem. Int. Ed.* **2009**, *48*, 9339–9341.

[78] C. Nadeau, S. Aly, K. Belyk, *J. Am. Chem. Soc.* **2011**, *133*, 2878–2880.

[79] M. Breuning, E. J. Corey, *Org. Lett.* **2001**, *3*, 1559–1562.

[80] R. Imbos, A. J. Minnaard, B. L. Feringa, *J. Am. Chem. Soc.* **2002**, *124*, 184–185.

[81] a) Q. Liu, T. Rovis, *J. Am. Chem. Soc.* **2006**, *128*, 2552–2553; b) Q. Liu, T. Rovis, *Org. Process Res. Dev.* **2007**, *11*, 598–604.

[82] N. T. Vo, R. D. M. Pace, F. O'Hara, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 404–405.

[83] R. Leon, A. Jawalekar, T. Redert, M. J. Gaunt, *Chem. Sci.* **2011**, *2*, 1487–1490.

[84] M.-Q. Jia, S.-L. You, *Chem. Commun.* **2012**, *48*, 6363–6365.

[85] a) Q. Gu, Z.-Q. Rong, C. Zheng, S.-L. You, *J. Am. Chem. Soc.* **2010**, *132*, 4056–4057; b) Q. Gu, S.-L. You, *Chem. Sci.* **2011**, *2*, 1519–1522; c) Q. Gu, S.-L. You, *Org. Lett.* **2011**, *13*, 5192–5195.

[86] S. Takizawa, T. M.-N. Nguyen, A. Grossmann, D. Enders, H. Sasai, *Angew. Chem.* **2012**, *124*, 5519–5522; *Angew. Chem. Int. Ed.* **2012**, *51*, 5423–5426.

[87] R. Tello-Aburto, K. A. Kalstabakken, K. A. Volp, A. M. Harned, *Org. Biomol. Chem.* **2011**, *9*, 7849–7859.

[88] B. Han, Y.-C. Xiao, Y. Yao, Y.-C. Chen, *Angew. Chem.* **2010**, *122*, 10387–10389; *Angew. Chem. Int. Ed.* **2010**, *49*, 10189–10191.

[89] A. Rudolph, P. H. Bos, A. Meetsma, A. J. Minnaard, B. L. Feringa, *Angew. Chem.* **2011**, *123*, 5956–5960; *Angew. Chem. Int. Ed.* **2011**, *50*, 5834–5838.

[90] For a racemic Cu^{II}-catalyzed oxidative dearomatization of *N*-aryl amides, see: S. Chiba, L. Zhang, J.-Y. Lee, *J. Am. Chem. Soc.* **2010**, *132*, 7266–7267.

[91] During the galley-proof stage, several new relevant reports appeared: a) J. Zhang, Z. Chen, H.-H. Wu, J. Zhang, *Chem. Commun.* **2012**, *48*, 1817–1819; b) Q. Cai, C. Liu, X.-W. Liang, S.-L. You, *Org. Lett.* **2012**, *14*, 4588–4590; c) Z. Zhang, J. C. Antilla, *Angew. Chem.* **2012**, *124*, 11948–11952; *Angew. Chem. Int. Ed.* **2012**, *51*, 11778–11782; d) G. Özüduru, T. Schubach, M. M. K. Boysen, *Org. Lett.* **2012**, *14*, 4990–4993; e) D. M. Rubush, M. A. Morges, B. J. Rose, D. H. Thamm, T. Rovis, *J. Am. Chem. Soc.* **2012**, *134*, 13554–13557; f) H. Jiang, C. Rodríguez-Escrich, T. K. Johansen, R. L. Davis, K. A. Jørgensen, *Angew. Chem.* **2012**, *124*, 10417–10420; *Angew. Chem. Int. Ed.* **2012**, *51*, 10271–10274; g) Q.-L. Xu, L.-X. Dai, S.-L. You, *Chem. Sci.* **2012**, *3*, DOI: 10.1039/C2SC21085A; h) M.-Q. Jia, C. Liu, S.-L. You, *J. Org. Chem.* **2012**, *77*, DOI: 10.1021/jo3022555.