

Advances in Catalytic Asymmetric Dearomatization

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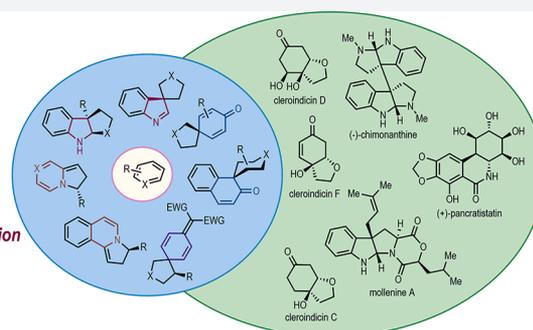
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ABSTRACT: Asymmetric catalysis has been recognized as the most enabling strategy for accessing chiral molecules in enantioenriched forms. Catalytic asymmetric dearomatization is an emerging and dynamic research subject in asymmetric catalysis, which has received considerable attention in recent years. The direct transformations from readily available aromatic feedstocks to structurally diverse three-dimensional polycyclic molecules make catalytic asymmetric dearomatization reactions of broad interest for both organic synthesis and medicinal chemistry. However, the inherent difficulty for the disruption of aromaticity demands a large energy input during the dearomatization process, which might be incompatible with the conditions generally required by asymmetric catalysis. In this Outlook, we will discuss representative strategies and examples of catalytic asymmetric dearomatization reactions of various aromatic compounds and try to convince readers that by overcoming the above obstacles, catalytic asymmetric dearomatization reactions could advance chemical sciences in many respects.

Advances in
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■ INTRODUCTION

Since the discovery of benzene by Michael Faraday in 1825,¹ the research and application of aromatic compounds in both the academic and industrial levels have been contributing to the development of humankind for almost two centuries. As bulk and fundamental chemical feedstocks, aromatic compounds play a prominent role in organic synthesis. However, as a result of “aromaticity”, the extraordinary stability caused by the delocalization of the π -electrons,² aromatic compounds mainly participate in substitution reactions, where a hydrogen atom on the aromatic ring is replaced by a functional group; yet, its aromaticity is not disrupted (Scheme 1a).³ On the other hand, dearomatization is another general but relatively underdeveloped type of transformation of aromatic compounds where a functional group is added to the aromatic ring, leading to the permanent loss or significant decrease of its aromaticity (Scheme 1b). Historically, Birch reduction,⁴ Buchner ring-expansion,⁵ and the Reimer–Tiemann reaction⁶ of para-substituted phenols were among the rare examples of named reactions for dearomatization (Scheme 1c), which were usually operated under harsh conditions or with narrow substrate scopes. Notably, the nucleophilic addition⁷ and hydrogenation reactions⁸ of aromatic compounds can be promoted by chiral catalysts. Besides, enzyme-catalyzed transformations are well-known for dearomatization reactions, which are exemplified by the arene cis-dihydroxylation promoted by arene dioxygenase enzymes.⁹

The preparation of chiral molecules in enantioenriched forms is of great importance in synthetic chemistry,¹⁰

pharmaceutical industry,¹¹ and materials science.¹² Among various available methods to this end, homogeneous asymmetric catalysis is probably the most efficient and diverse one.¹³ The great achievements in this area were acknowledged by the Nobel Prize in Chemistry in 2001 to Knowles, Noyori, and Sharpless in honor of their contributions for the development of asymmetric hydrogenation and oxidation reactions, respectively.¹⁴ One of the most active directions in asymmetric catalysis in recent years is to push the limit of functional groups compatible with diverse transformations to those traditionally regarded as “inert” ones. In this regard, catalytic asymmetric dearomatization (CADA) reactions¹⁵ have emerged as a powerful synthetic strategy in the past decade, which makes various aromatic units reactive functionalities for asymmetric synthesis.

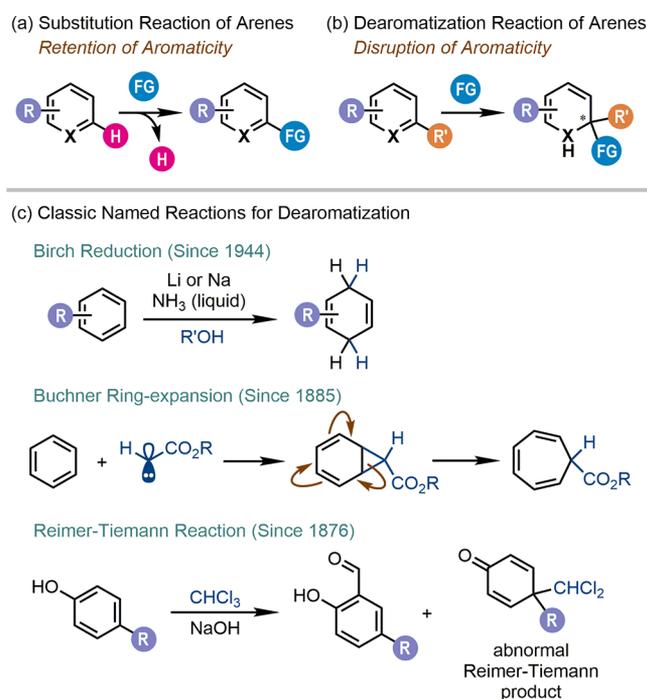
The most distinctive feature of catalytic asymmetric dearomatization reactions is the potential for exploring previously untouched chemical spaces.¹⁶ They not only provide alternative retrosynthetic strategies to access known polycyclic molecules but also serve as indispensable tools to forge novel molecular scaffolds with diverse and unprecedented topologies. Particularly, the increased levels of

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Scheme 1. (a, b) General Reaction Types of Arenes and (c) Classic Named Reactions for Dearomatization



saturation resulting from dearomatization, and of stereoisomerism led by the incorporation of new stereogenic centers, make the libraries of products of catalytic asymmetric dearomatization reactions appealing in the drug-discovery process.

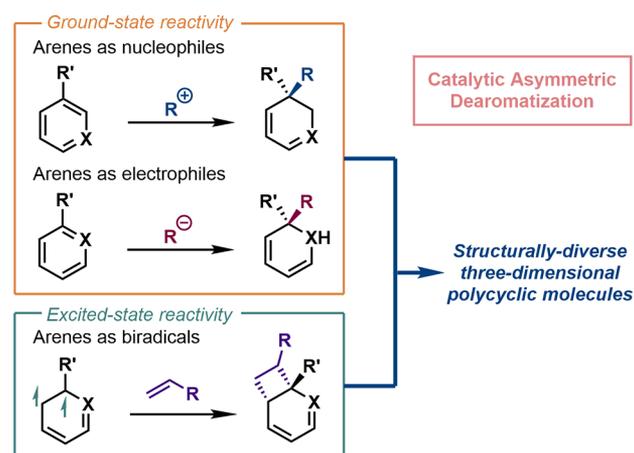
However, multiple challenges associated with catalytic asymmetric dearomatization reactions need to be addressed. In general, the extraordinary stability of aromatic compounds makes the dearomatization process thermodynamically unfavorable. Therefore, many successful dearomatization reactions are usually coupled with the irreversible formation of a strong carbon–carbon, carbon–hydrogen, or carbon–heteroatom bond to compensate the energetic uphill required by the disruption of aromaticity. Meanwhile, achieving high stereochemical control during the dearomatization process is another challenging task. The design and development of enabling chiral catalytic systems is a key solution to reduce the energetic barriers of dearomatization and at the same time to distinguish between the subtle diastereomeric transition states.

This Outlook focuses on how the advances in catalytic asymmetric dearomatization reactions impact the research of organic chemistry with innovative mechanistic understanding, expanded chemical space, and transformative synthetic routes toward complex target molecules.

In this Outlook, we would like to give a personal perspective on this dynamic research field with a few representative examples in which aromatic compounds participate in

asymmetric dearomatization reactions as nucleophiles, electrophiles, and excited state biradicals (Scheme 2). Selective

Scheme 2. General Strategies for Catalytic Asymmetric Dearomatization Reactions



applications of asymmetric dearomatization reactions in total synthesis will also be covered. Rather than being a comprehensive review, this Outlook will focus on how advances in catalytic asymmetric dearomatization reactions impact the research of organic chemistry with innovative mechanistic understanding, expanded chemical space, and transformative synthetic routes toward complex target molecules.

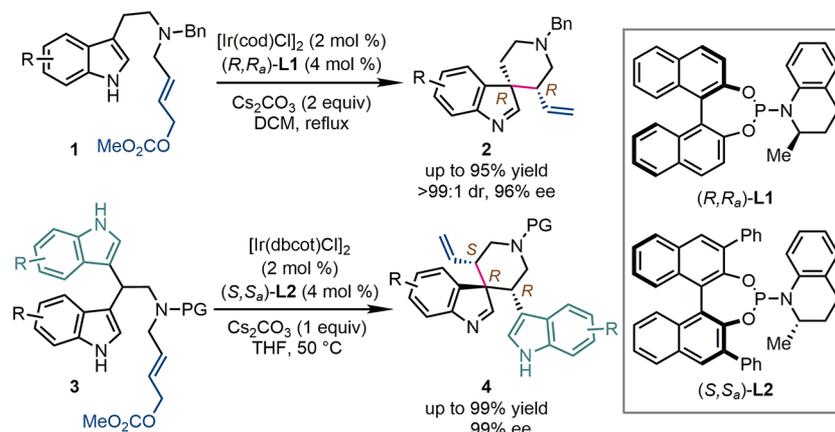
■ ARENES AS NUCLEOPHILES

In the most-studied type of catalytic asymmetric dearomatization reaction, electron-rich arenes react with an appropriately tethered electrophile, leading to various spirocyclic molecules. Particularly, the reactions involving the electrophilic π -allyliridium species catalyzed by a chiral Ir-complex have exhibited general synthetic potential and a broad scope.¹⁷

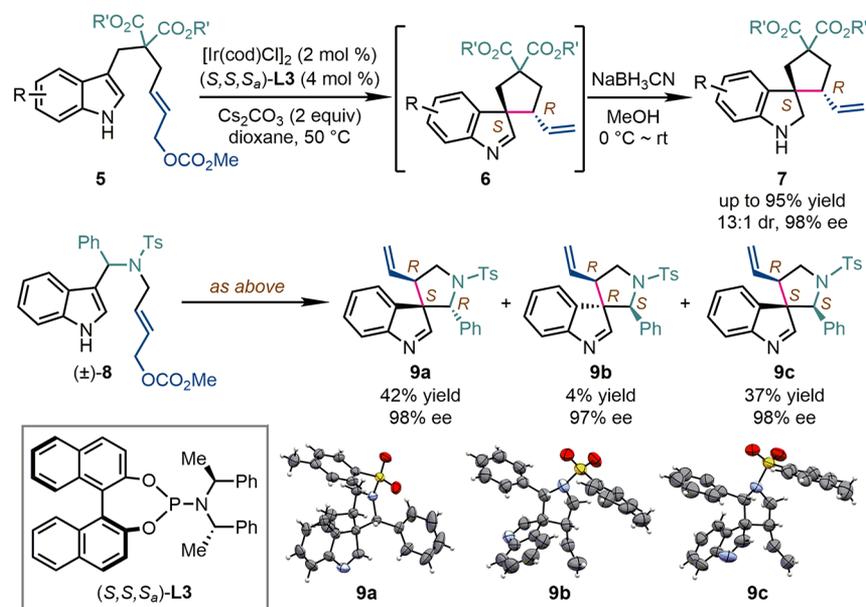
In 2010, our group reported the first Ir-catalyzed intramolecular asymmetric allylic dearomatization reaction (Scheme 3).¹⁸ In the presence of a catalyst consisting of $[\text{Ir}(\text{cod})\text{Cl}]_2$ and Me-THQphos (R,R_d)-L1, tryptamine-derived allylic carbonates **1** were converted smoothly to chiral six-membered-ring spiroindolenines **2** in up to 95% yield. Two contiguous stereogenic centers including a quaternary one were established with excellent stereochemical control (up to >99:1 dr and 96% ee). This reaction mode was recently extended to bis(indol-3-yl) substituted allylic carbonates **3**.¹⁹ The enantioselective desymmetrization of **3** was realized under slightly modified conditions, allowing the exclusive formation of chiral six-membered-ring spiroindolenines decorated with an additional indole ring (**4**) in up to 99% yield and 99% ee. Notably, the core structure of **2** is related to the orally active growth hormone secretagogue MK-677 (ibutamoren) and other bioactive molecules.²⁰

When the linkage between the indole core and the allylic carbonate in the substrates was shortened by one methylene group, the synthesis of chiral five-membered-ring spiroindolenines was also achieved (Scheme 4). The asymmetric allylic dearomatization of indol-3-yl allylic carbonates **5** by an Ir-catalyst derived from the Feringa phosphoramidite (S,S,S_a)-L3 led to spiroindolenines **6**, whose imine moiety was reduced *in situ* by NaBH_3CN to afford the corresponding spiroindolenines **7**

Scheme 3. Synthesis of Six-Membered-Ring Spiroindolenines via Ir-Catalyzed Asymmetric Allylic Dearomatization Reactions



Scheme 4. Synthesis of Five-Membered-Ring Spiroindolenines via Ir-Catalyzed Asymmetric Allylic Dearomatization Reactions

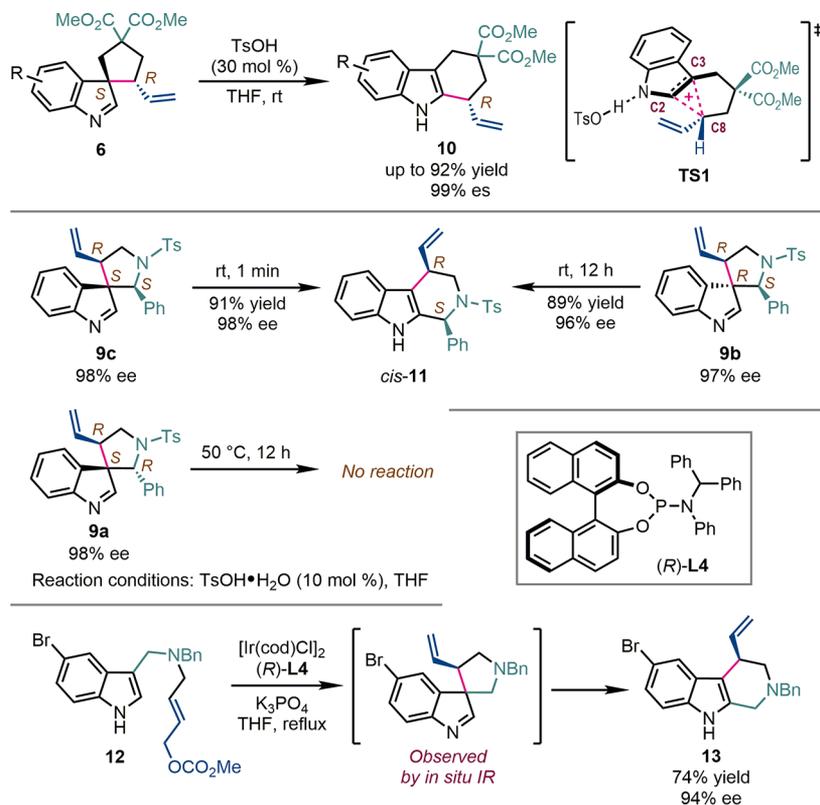


in up to 95% yield, 13:1 dr, and 98% ee.²¹ Alternatively, when racemic indol-3-yl methanamine-derived allylic carbonates (\pm)-**8** were subjected to the same reaction conditions, three diastereoisomers of five-membered-ring aza-spiroindolenines **9a–c** were delivered in high enantiopurity (up to 98% ee).²² To be noted, in all the above syntheses of chiral spiroindolenines, the absolute configuration of the allylic stereogenic center was dominated by the chiral Ir-catalyst, while the usually high facial selectivity for the prochiral nucleophiles should be attributed to the structurally well-defined intramolecular cyclization transition states.

The most intriguing reactivity of the chiral spiroindolenines is their stereoselective ring-expansive migration (Scheme 5). When treated with a catalytic amount of tosylic acid (30 mol %), five-membered-ring spiroindolenines **6** underwent allyl migration, affording tetrahydrocarbazoles **7** in up to 92% yield. Interestingly, this allyl migration was highly stereoretentive, with *es* values of up to 99% [*es* = (*ee*_{product}/*ee*_{substrate}) × 100%], and the absolute configuration at the allylic position remained unchanged during the migration.²¹ Comprehensive mechanistic studies revealed that the allyl migration proceeded through a “three-center–two-electron (3c–2e)”-type transition

state (TS1). The attractive interaction between the positively charged allyl moiety and the electron-rich indole ring guaranteed the stereoretentive nature of the migration process.²³ It was also found that if two potential migratory groups were available for a spiroindolenine, the one with the stronger ability to stabilize positive charge was more reactive. In addition, the activity of spiroindolenines toward ring-expansive migration was also influenced by other stereogenic centers in the molecule. Therefore, the treatment of the three diastereoisomers of five-membered-ring aza-spiroindolenines **9a–c** with tosylic acid provided significantly varied outcomes. The iminium migration of **9c** was finished within 1 min at room temperature, while the similar reaction of **9b** required 12 h. Both reactions delivered tetrahydro- β -carboline *cis*-**11** in high yields and *es* values. In contrast, **9a** remained intact in the presence of tosylic acid even at 50 °C for 12 h. However, with stronger acid (saturated HCl in THF), **9a** underwent ring-expansive migration with the configuration of the iminium carbon partially reversed.²² Guided by these mechanistic insights, a one-pot asymmetric allylic dearomatization/ring-expansive iminium migration sequence of allylic carbonate **12** was realized with the Ir-catalyst derived from BHPphos (*R*-

Scheme 5. Stereoselective Ring-Expansive Migration of Spiroindolenines



L4, which furnished tetrahydro- β -carboline **13** in 74% yield and 94% ee. The N-Bn methanamine tether that was originally attached to the C3 position of the indole ring finally moved to the C2 position. The proposed spiroindolenine intermediate was observed by *in situ* IR spectroscopy experiments.²⁴

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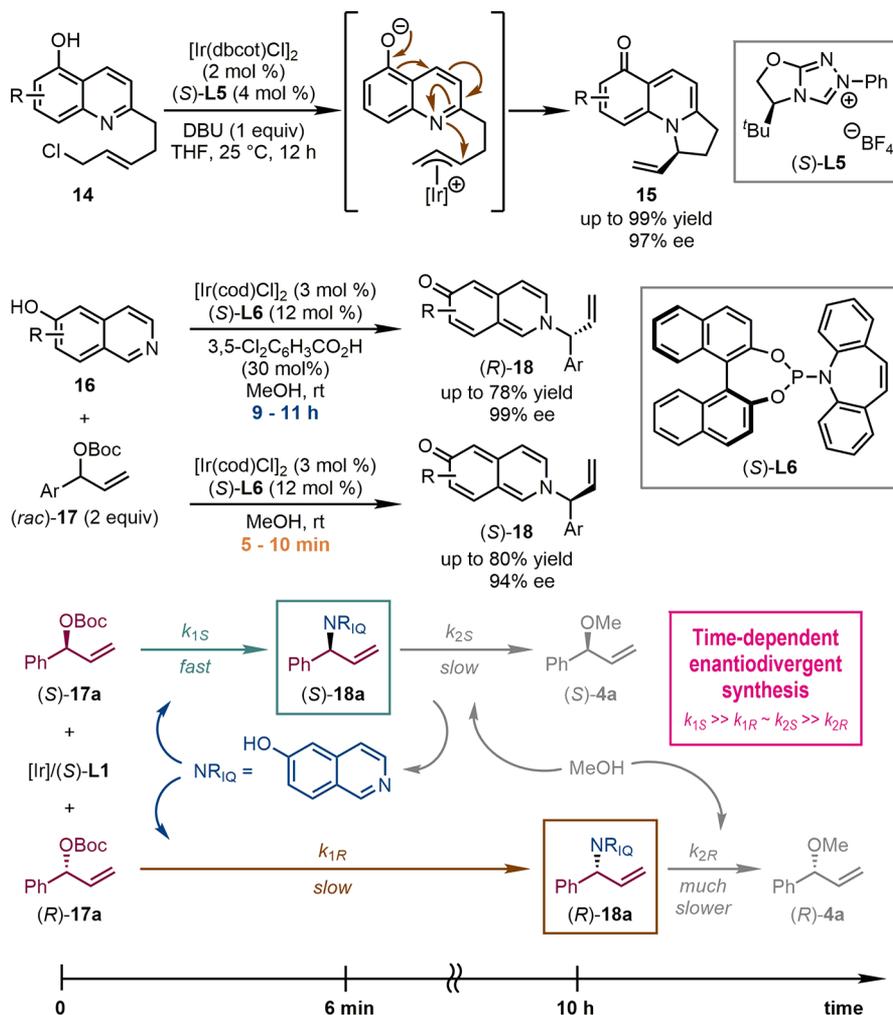
Mechanistically, the enantioselective formation and ring-expansive migration of five-membered-ring spiroindolenines are closely related to asymmetric Pictet–Spengler reactions.²⁵ On the basis of the systematic studies on the chemistry of spiroindolenines, we demonstrated the relationship of the electronic properties of the substrates, reaction pathways, and stereochemistry of asymmetric Pictet–Spengler reactions by density functional theory (DFT) calculations and Born–Oppenheimer molecular dynamics (BOMD) simulations.²⁶ A unified two-dimensional mechanistic spectrum with two limiting conditions was proposed and successfully applied in the rational designs of a series of asymmetric transformations of spiroindolenines beyond classic Pictet–Spengler reactions.²⁷

The scope of Ir-catalyzed asymmetric allylic dearomatization reactions could be extended to a variety of fused bicyclic (hetero)aromatic compounds, including naphthols,²⁸ (iso)-quinolines,²⁹ benzoxazoles, benzothiazoles, and benzimidazoles,³⁰ etc. However, in most cases, the aromaticity of only

one aromatic ring was perturbed, while the other, usually a phenyl ring, remained intact. It was believed that the restoration of the aromaticity of this phenyl ring might be a key compensating factor to the unfavorable dearomatization process. In this regard, the simultaneous weakening of the aromaticity of two consecutive aromatic rings was an ambitious challenge in the area of catalytic asymmetric dearomatization reactions. In 2018, we disclosed an Ir-catalyzed intramolecular asymmetric allylic amination of hydroxyquinoline-derived allylic chlorides **14** (Scheme 6).³¹ The deprotonation of the hydroxyl group promoted the nucleophilicity of the nitrogen atom of **14**, which facilitated the desired asymmetric allylic amination reactions. The utilization of an *N*-heterocyclic carbene ligand derived from a chiral triazolium salt (*S*)-L5 permitted the high yields (up to 99%) and excellent enantiopurity (up to 97% ee) of cyclic conjugated enone products **15**. Theoretical analyses including NICS(1)_{ZZ} (the ZZ tensor component of the nuclear independent chemical shift values at the points 1 Å above the ring centers) and multicenter bond indices confirmed that the aromaticity of both rings of the quinoline substrates decreased significantly in this reaction.

The simultaneous weakening of the aromaticity of two consecutive aromatic rings was an ambitious challenge in the area of catalytic asymmetric dearomatization reactions.

Scheme 6. Ir-Catalyzed Asymmetric Allylic Amination with 5-Hydroxyquinoline and 6-Hydroxyisoquinoline Derivatives



Very recently, we realized the intermolecular version of this reaction and uncovered an unprecedented phenomenon in asymmetric catalysis, namely, time-dependent enantiodivergent synthesis (Scheme 6).³² The asymmetric allylic amination reactions between hydroxyisoquinolines **16** and racemic *tert*-butyl allylic carbonates [(*rac*)-**17**, 2 equiv] were promoted by a chiral Ir-complex derived from Carreira-type (phosphoramidite, olefin) ligand (*S*)-**L6**. Interestingly, each enantiomer of the desired products **18** could be obtained in high yields and enantiopurity when the reactions were quenched at different reaction times [(*R*)-**18**, up to 78% yield, 99% ee for 9–11 h; (*S*)-**18**, up to 80% yield, 94% ee for 5–10 min]. Systematic mechanistic investigations revealed that four independent transformations, allylic amination of (*S/R*)-**17** with hydroxyisoquinolines **16** and allylic etherification of (*S/R*)-**18** with methanol, proceeded in the presence of the same chiral Ir-catalyst. The appropriate permutation of individual reaction rates was crucial for achieving enantiodivergent synthesis of **18** with the reaction time as a key parameter.

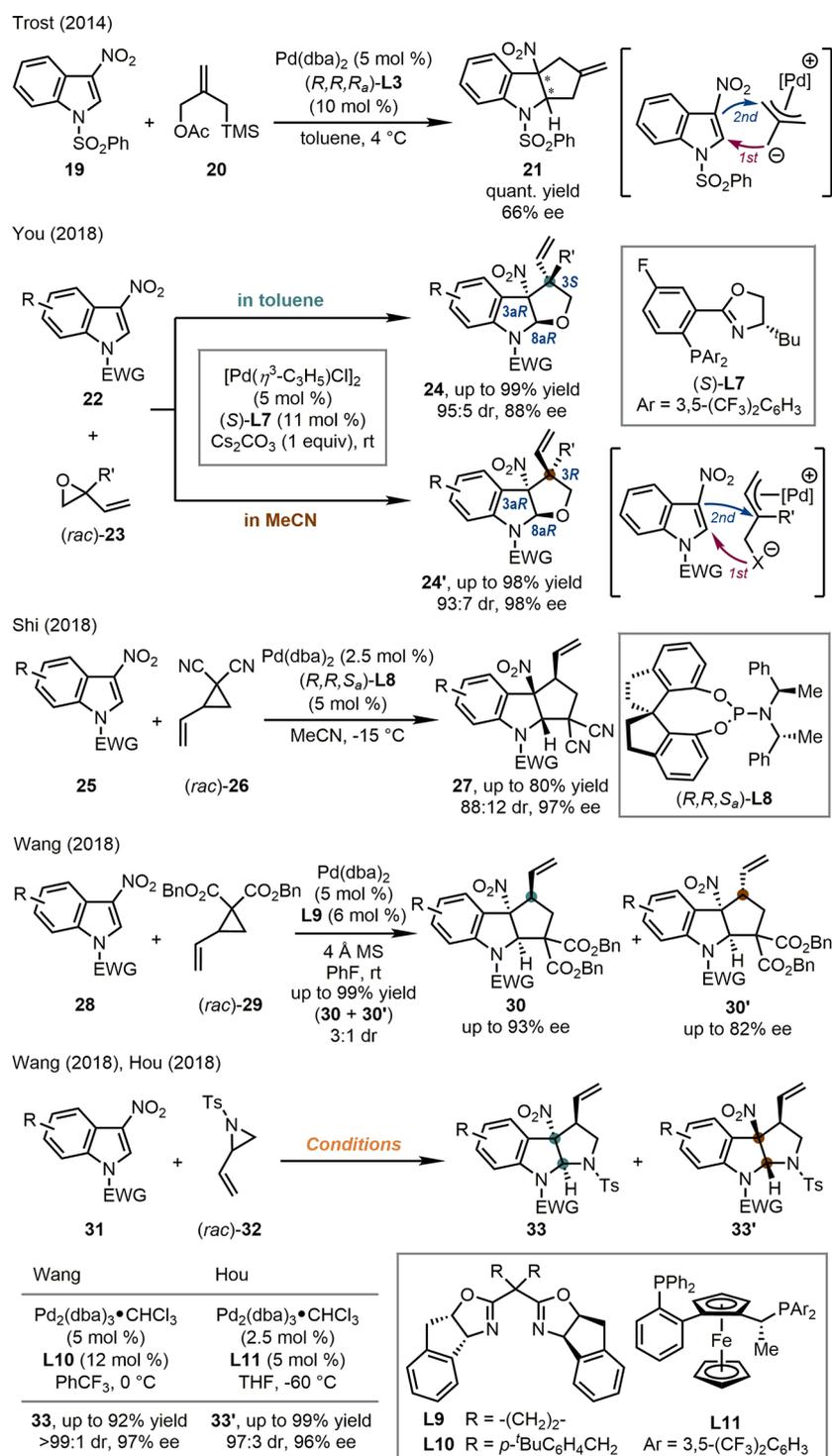
■ ARENES AS ELECTROPHILES

The asymmetric nucleophilic addition to electron-deficient (hetero)aromatic compounds constitutes another important category of dearomatization reactions, with the Reissert reaction being the most famous example.⁷ In this section, we highlight some recent contributions on the catalytic asym-

metric dearomative cyclization reactions of 3-nitroindoles initiated by nucleophilic additions at the C2 position of the indole ring.

In 2014, the Trost group reported one example of Pd-catalyzed asymmetric dearomative cyclization of *N*-phenylsulfonyl 3-nitroindole **19** with trimethylenemethane (TMM)-donor **20** (Scheme 7).³³ The Pd-TMM complex formed *in situ* from Pd(*dba*)₂, chiral phosphoramidite (*R,R,R*)-**L3**, and **20** underwent a formal [3 + 2] cyclization with **19**, leading to **21** in quantitative yield with 66% ee. Inspired by this pioneering work, our group achieved stereodivergent dearomative [3 + 2] cyclization of a series of 3-nitroindoles **22** with racemic 2-vinylloxiranes (*rac*)-**23** catalyzed by a Pd-complex derived from [Pd(η^3 -C₃H₅)Cl]₂ and a novel PHOX ligand (*S*)-**L7** (Scheme 7).³⁴ The reaction started with the oxidative addition of (*rac*)-**23** with the Pd-catalyst, which resulted in a zwitterionic species that underwent the dearomative cyclization with **22**. Interestingly, the diastereoselectivity of the reactions was significantly influenced by the solvent. The two stereogenic centers on the indoline ring of the target products always adopted the *cis* configuration (3aR and 8aR when R' \neq H) due to the ring strain, while the absolute configuration at the allylic position was the opposite in toluene [**24** (3*S*), up to 99% yield, 95:5 dr, 88% ee] or acetonitrile [**24'** (3*R*), up to 98% yield, 93:7 dr, 98% ee]. Finally, Hammett analyses and ESI-MS experiments suggested varied rate-determining steps in the two

Scheme 7. Pd-Catalyzed Asymmetric Dearomatization of 3-Nitroindoles

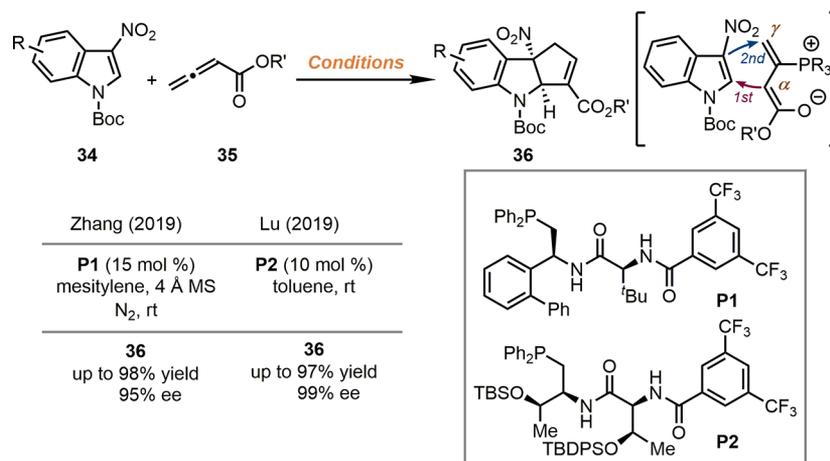


reaction systems, namely, the first addition to 3-nitroindole in toluene and the second addition to π -allylpalladium moiety in acetonitrile, respectively.

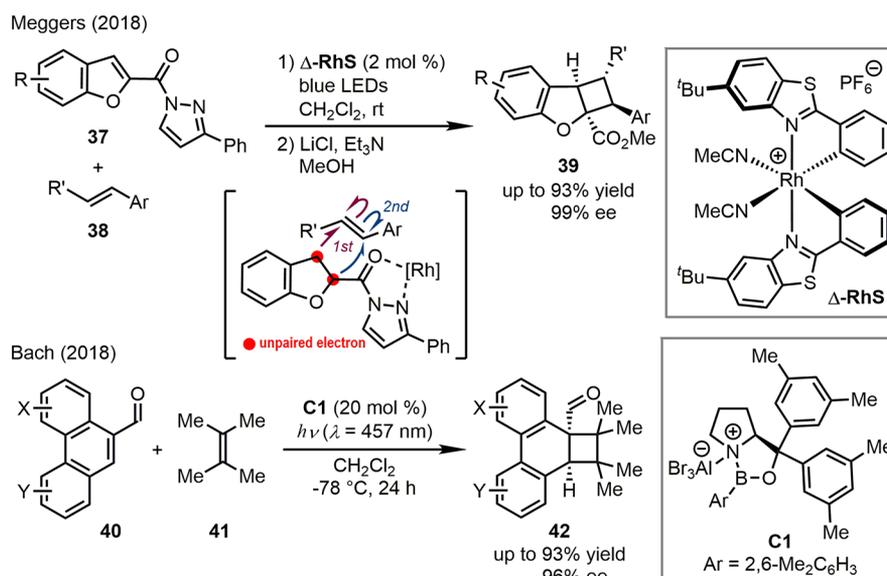
Almost at the same time, the groups of Shi,³⁵ Wang,³⁶ and Ding and Hou³⁷ independently reported the Pd-catalyzed asymmetric dearomative cyclization [3 + 2] reactions of 3-nitroindoles with vinyl cyclopropanes [(*rac*)-26 and (*rac*)-29] and vinyl aziridines [(*rac*)-32], respectively (Scheme 7). Although different chiral Pd-complexes, derived from chiral phosphoramidite ligand [(*R,R,S_a*)-L8], BOX ligands (L9, and

L10), or bisphosphine ligand (L11), were identified as the optimal catalysts in each case, these reactions all proceeded in similar sequences, accessing densely substituted chiral cyclopenta[*b*]indolines (27, 30, and 30') or pyrroloindolines (33 and 33') with high yields and good stereochemical controls. It should be noted that in the reactions of vinyl aziridines, the relative configurations of the major products were different in the two reaction systems. Therefore, the stereodivergent syntheses of these pyrroloindolines could be achieved when each enantiomer of L10 and L11 was applied.

Scheme 8. Phosphine-Catalyzed Asymmetric Dearomatization of 3-Nitroindoles



Scheme 9. Visible-Light-Promoted Asymmetric Dearomatization Reactions



Besides, the groups of Arai,³⁸ and Stanley³⁹ realized the Cu-catalyzed asymmetric dearomative [3 + 2] cyclization reactions of 3-nitroindoles with azomethine ylides. Yuan and co-workers⁴⁰ reported the corresponding [3 + 2] and [4 + 2] reactions of 3-nitroindoles with 3-isothiocyanato oxindoles or Nazarov reagents by quinine-based chiral bifunctional thiourea/thiocarbamate catalyst, or chiral Zn-complex. Notably, the asymmetric dearomative cyclization reactions could also be extended to 2-nitrobenzofurans.⁴¹

Recently, chiral phosphine-catalyzed dearomative [3 + 2] cyclization reactions between 3-nitroindoles **34** and allenolates **35** were reported by the groups of Zhang⁴² and Lu⁴³ independently (Scheme 8). In this reaction design, the addition of chiral phosphines **P1** or **P2** to allenolates generated the key zwitterionic species, which subsequently attacked 3-nitroindoles with its α -terminus. After the second C–C bond-formation between the C3-position of the indole ring and the γ -terminus, and the extrusion of the phosphine catalyst, the desired cyclopenta[*b*]indoline products **36** were delivered in good yields with high enantioselectivity in both cases. Besides, Wang, Guo and co-workers realized asymmetric dearomative

[3 + 2] cyclization reactions of 2-nitrobenzofurans by applying similar strategies.⁴⁴

■ ARENES AS EXCITED STATE BIRADICALS

Visible-light-promoted [2 + 2] reactions via an energy transfer mechanism have recently witnessed considerable attention from the synthetic chemistry community.⁴⁵ Particularly, mediated by a suitable photosensitizer, aromatic compounds in excited states can be generated and display distinctive reactivity compared with the original ground-state molecules. It has been proven that, if appropriately decorated, the arenes in excited states can be further activated by chiral Lewis acid catalysts, which allows the asymmetric dearomatization reactions with external unsaturated functionalities via [2 + 2] cycloaddition.

In 2018, Meggers, Baik, and co-workers reported the first visible-light-promoted asymmetric dearomatization reactions (Scheme 9).⁴⁶ 2-*N*-Acylpyrazole benzofurans **37** were identified as the suitable substrate for the coordination to the chiral Lewis acid Δ -RhS. The resulting complex reached its first singlet excited state (S_1) under the irradiation of blue LEDs. The subsequent intersystem crossing led to the

corresponding triplet excited state (T_1), which reacted with external olefins **38**, furnishing asymmetric dearomative [2 + 2] cycloaddition reactions. After the hydrolysis of the *N*-acylpyrazole moiety and the methyl esterification, the desired dearomatized products **39** were obtained in high yields (up to 93%) and good regio- and enantioselectivities (up to 99% ee). DFT calculations revealed a stepwise cyclization between the 1,2-biradical of the T_1 state arenes and the olefins. The origin of regioselectivity was well-explained based on the resonance stabilization for the unpaired electron by the neighboring aryl or carbonyl groups. A working model was also proposed, accounting for the experimentally observed absolute configuration of the major products.

If appropriately decorated, the arenes in excited states can be further activated by chiral Lewis acid catalysts, which allows the asymmetric dearomatization reactions with external unsaturated functionalities

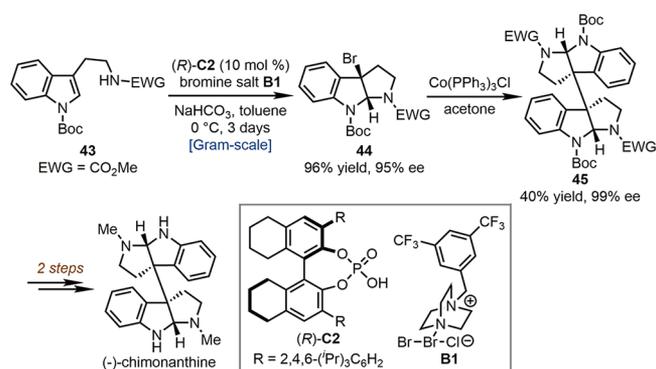
The Bach group achieved significant progress on visible-light-promoted asymmetric cycloaddition reactions (Scheme 9).⁴⁷ Guided by the UV/vis spectra of phenanthrene-9-carboxaldehyde in the presence of variable amounts of EtAlCl₂, it was confirmed that the coordination to a Lewis acid would induce a bathochromic shift of the π - π^* transition of **40** (from 316 to 387 nm). Therefore, the utilization of a chiral Lewis acid catalyst would promote the asymmetric photocycloaddition of **40** under long wavelength irradiation by inhibiting the racemic background reactions of uncoordinated substrates. This reaction design was successfully executed using various alkenes including **41** as the partners in the presence of chiral oxazaborolidine **C1** and visible light ($\lambda = 457$ nm). The desired products **42** were delivered smoothly in up to 93% yield with 96% ee.

■ APPLICATIONS IN TOTAL SYNTHESSES

Catalytic asymmetric dearomatization reactions have been applied in the total syntheses of complex molecules and provided unprecedented retrosynthetic disconnection strategies. The asymmetric dearomative cyclizations of tryptamine derivatives are probably the most widely studied methods for the construction of the key pyrroloindoline skeletons in diverse indole-based natural products.⁴⁸ In this regard, MacMillan and co-workers have made pioneering contributions and completed the total syntheses of (–)-(debro)flustramine B, (–)-diazonamide A, hodgkinsine, and a series of related natural products using iminium catalysis or Cu-catalyzed asymmetric arylation with iodonium salts as the key steps.⁴⁹

In 2013, Xie, Lai, Ma, and co-workers developed a highly enantioselective dearomative bromocyclization reaction and applied this reaction in the total synthesis of (–)-chimonanthine (Scheme 10).⁵⁰ The reaction of tryptamine derivative **43** with electrophilic brominating reagent **B1** in the presence of a chiral phosphoric acid (*R*)-**C2** afforded bromo-substituted pyrroloindoline **44** on a gram scale (96% yield, 95% ee). Subsequently, **44** underwent Co-catalyzed dimerization leading to the pyrroloindoline dimer **45**. The enantiopurity of **45** was improved to 99% ee probably due to the resolution during the

Scheme 10. Total Synthesis of (–)-Chimonanthine by the Asymmetric Dearomative Bromocyclization Reaction

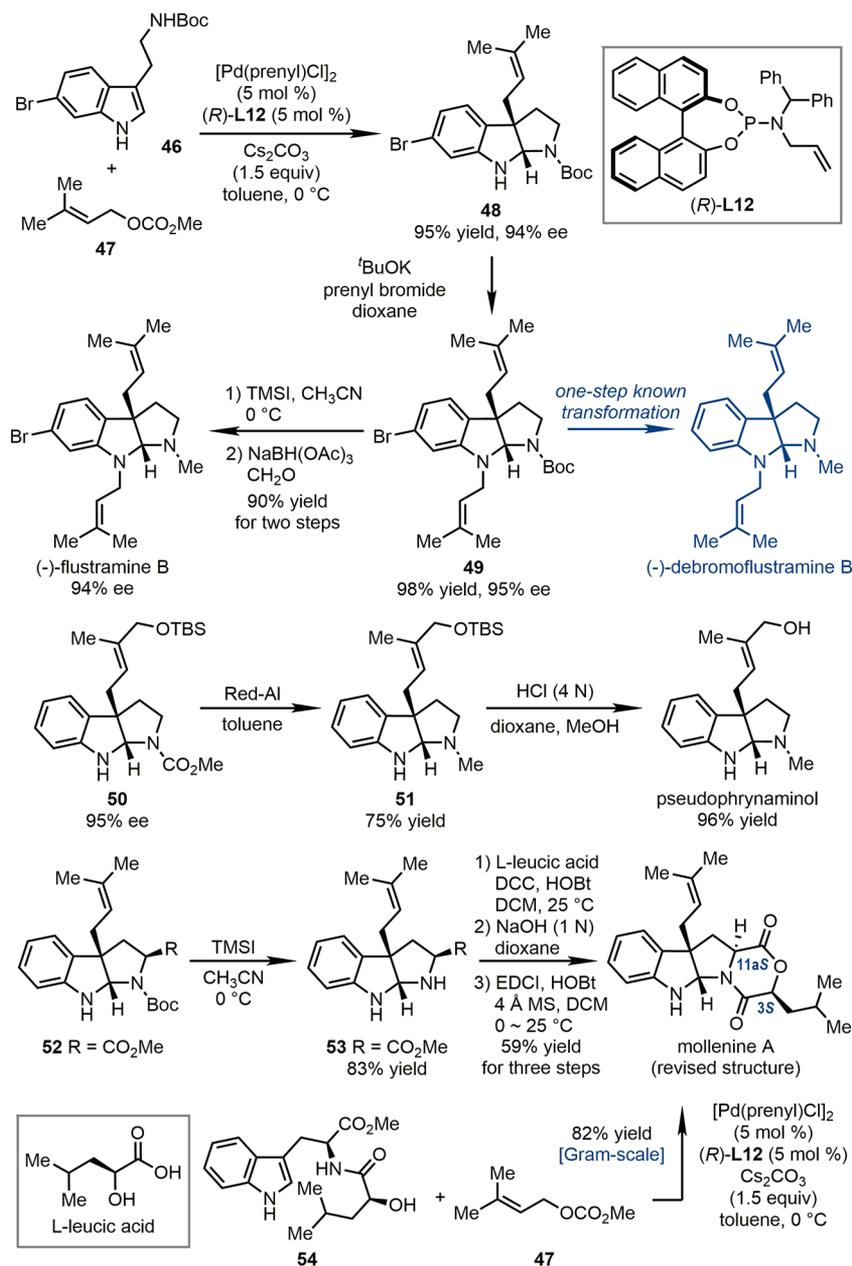


dimerization process. Finally, the total synthesis of (–)-chimonanthine was completed after two steps of functional group manipulations.

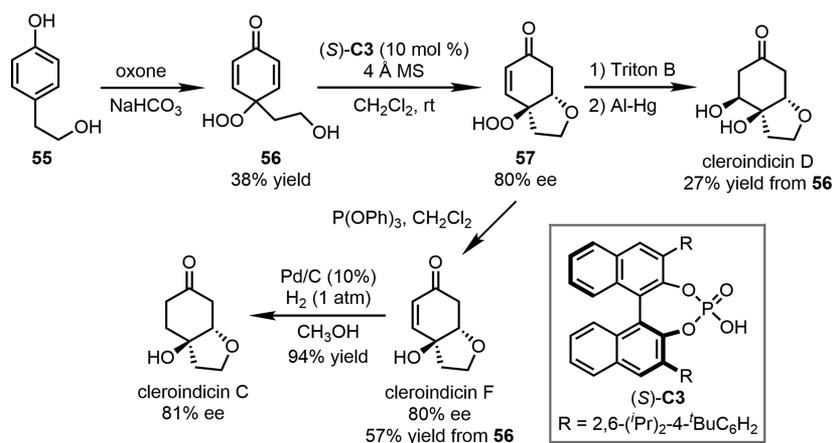
In 2018, our group developed Pd-catalyzed asymmetric dearomative prenylation reactions.⁵¹ With various C3-substituted indole derivatives as the substrates, this reaction enantioselectively installed a prenyl group or related isoprenoids at the C3 position of the indole ring with the concomitant cyclization of the side chain, leading to prenylated pyrroloindolines and related molecules. The synthetic potential of this reaction was exemplified by the expedient syntheses of a series of natural products containing the prenylated pyrroloindoline structural core (Scheme 11). For example, the reaction of 6-bromo-substituted tryptamine derivative **46** and prenyl carbonate **47** proceeded in the presence of Pd-catalyst derived from chiral phosphoramidite ligand Allylphos (*R*)-**L12**. The corresponding product **48** was obtained in 95% yield with 94% ee. The *N*-prenylation of **48** generated **49**, which was a known precursor for (–)-debromoflustramine B. Besides, simple two-step functional-group manipulations of **49** delivered (–)-flustramine B efficiently (90% yield). Starting from another chiral functionalized pyrroloindoline product **50**, the total synthesis of (–)-pseudophrynaminol was achieved by reducing the *N*-CO₂Me group and removing the silyl protecting group of a primary alcohol. Notably, this asymmetric dearomative prenylation reaction permitted the structure revision and facile synthesis of mollenine A. The treatment of prenylated pyrroloindoline **52**, which was generated from Boc-L-Trp-OMe, with TMSI led to the release of free secondary amine in **53** (83% yield). The subsequent condensation with L-leucic acid furnished the corrected structure of mollenine A (59% yield). In addition, mollenine A could also be obtained in gram scale (82% yield) from L-Trp-L-leucic acid **54** and prenyl carbonate **47** under the standard conditions of the asymmetric dearomative prenylation reaction. In this protocol, three chemical bonds were formed in a highly ordered manner.

Enantioselective transformations of the molecules obtained from dearomatization are another important strategy that has been employed in natural product syntheses. In 2010, our group reported chiral phosphoric acid-catalyzed intramolecular oxo-Michael addition reactions for the desymmetrization of cyclohexadienones.⁵² Using this reaction as a key step, the asymmetric synthesis of cleroidicins was realized (Scheme 12). The oxidative dearomatization of commercially available 4-(2-hydroxyethyl)phenol **55** by oxone delivered cyclohexadienone **56**. Subsequently, the desymmetrization of this

Scheme 11. Application of Pd-Catalyzed Asymmetric Dearomative Prenylation Reactions in Total Syntheses



Scheme 12. Asymmetric Syntheses of Cleroindicins based on Desymmetrization of Cyclohexadienones



molecule by intramolecular oxo-Michael addition in the presence of chiral phosphoric acid (*S*)-C3 was achieved, leading to bicyclic enone **57** in 80% ee. The treatment of **57** with Triton B and aluminum amalgam promoted intramolecular epoxidation and reduction, yielding cleroidicin D (27% yield from **56**). Besides, the reduction of the hydroperoxyl group in **57** by P(OPh)₃ generated cleroidicin F (80% ee, 57% yield from **56**). Further hydrogenation of the enone moiety of cleroidicin F with Pd/C furnished cleroidicin C in 94% yield with 81% ee.

Sarlah and workers systematically studied the dearomatization of plain aromatics (benzene, naphthalene, tetracene, etc.) with *N*-methyl-1,2,4-triazoline-3,5-dione (MTAD) as an arenophile under visible light. The reaction afforded the arene-arenophile adduct which could be trapped under low temperature by olefin-like transformation or transition-metal-catalyzed amino functionalization reactions.⁵³ This reaction found broad applications in the total syntheses of polycyclic natural products (Scheme 13).⁵⁴ For example, treating the arene-arenophile adduct with a chiral Ni-complex derived from PHOX ligand **L13** and the aryl Grignard reagent generated *trans*-1,2-carboamination products **58** with high enantiopurity (96% ee) on a >10 g scale. The two-step oxidation of the

resulting 1,4-diene moiety of **58** delivered **59**. The subsequent urazole reduction and Co-catalyzed carbonylative coupling furnished (+)-7-deoxypancratistatin, from which a formal C–H oxidation led to (+)-pancratistatin. Notably, the synthesis of *trans*-1,2-carboamination products **58** could be upgraded to >20 g scale without erosion of yield and enantioselectivity with reduced loading of Ni-precursor and **L13**. With this reaction as the first step, the total syntheses of (+)-lycoridine and (+)-narciclasine could be finished in six steps on a >8 g scale and seven steps on a gram scale, respectively.

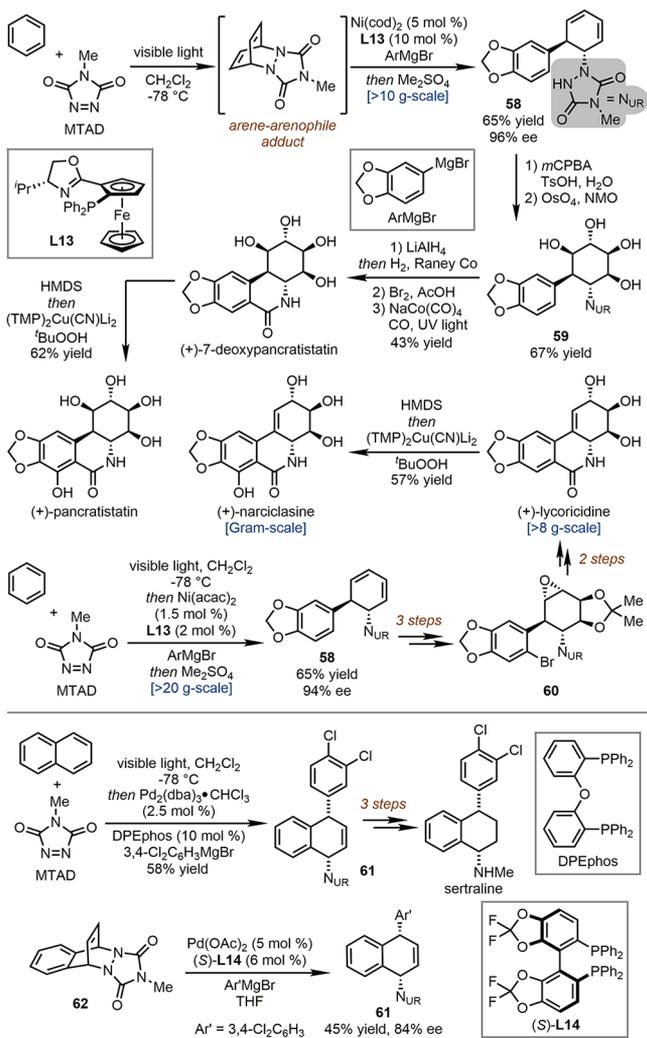
Sarlah and co-workers also developed Pd-catalyzed dearomative *syn*-1,4-carboamination of naphthalenes with the aryl Grignard reagent.⁵⁵ Product **61** could be readily transformed to sertraline in three steps (Scheme 13). It was confirmed that the isolated arene-arenophile adduct **62** underwent an enantioselective ring-opening reaction in the presence of a Pd-catalyst derived from chiral bisphosphine ligand DI-FLUORPHOS (*S*)-**L14**. Compound **61** could be obtained in 45% yield with 84% ee.

SUMMARY AND PERSPECTIVES

The progress in catalytic asymmetric dearomatization reactions in recent years has exerted great influence on organic chemistry. The dearomatization processes are now no longer the “forbidden zone” for versatile chemical synthesis. On the contrary, the exploration of previously untouched chemical spaces brings about numerous opportunities for advancing the chemical sciences in multiple respects. As showcased by the examples discussed in this Outlook, the energetically unfavorable disruption of aromaticity can be readily compensated by irreversible formation of carbon–carbon, carbon–hydrogen, or carbon–heteroatom bonds. In addition, asymmetric dearomatization processes deliver polycyclic skeletons with increased saturation and stereochemical complexity. The dearomatized products with structural diversity might serve as the novel candidates for drug discovery. Mechanistically, dearomatized intermediates have been proposed for many classic organic reactions. Overlooking such dearomatization pathways might lead to incorrect structure assignment for the products. In this regard, deep understanding of the dearomatized species and manipulating their reactivities would undoubtedly contribute to the development of novel synthetic methods. Finally, the asymmetric dearomatization reactions employ aromatic systems, traditionally regarded as “inert” structural units, as reactive functional groups, thus providing innovative retrosynthetic plans for complex molecules.

However, there are still significant challenges that should be overcome for further development in this area. Currently, some certain types of “activated” arenes such as indoles, phenols, pyridines, etc. are generally utilized. In contrast, the direct catalytic asymmetric dearomative transformations of “non-activated” arenes such as benzenes, naphthalenes, etc. are rather limited.⁵⁶ Notably, several examples of asymmetric hydrogenation of this kind of arenes have been reported.⁵⁷ To break through this predicament, one probably needs very reactive reaction partners that are generated under mild conditions and well embedded in a subtle chiral environment. To this end, we expect that the implementation of modern catalytic technologies, such as visible-light-catalysis,⁵⁸ electrocatalysis,⁵⁹ nanocatalysis, etc., can revolutionize the seminal dearomatization reactions discussed in the Introduction by bringing about their catalytic asymmetric variants. In addition,

Scheme 13. Synthetic Applications of Arenophile-Mediated Dearomative Functionalization



the known enzyme-promoted asymmetric dearomatization of nonactivated arenes might provide an alternative solution by stimulating de novo design of small molecule catalysts that mimic relevant enzymes or by improving the performance of such enzymes employing directed evolution technology. We are quite confident that the dynamic research on catalytic asymmetric dearomatization reactions will push the frontier and shape the future of synthetic chemistry.

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Notes

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