Catalytic asymmetric dearomatization (CADA) reactions of phenol and aniline derivatives

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Phenols are widely used as starting materials in both industrial and academic society. Dearomatization reactions of phenols provide an efficient way to construct highly functionalized cyclohexadienones. The main challenge to make them asymmetric by catalytic methods is to control the selectivity while overcoming the loss of aromaticity. In this tutorial review, an up to date summary of recent progress in CADA reactions of phenol and aniline derivatives is presented.

Key learning points
(1) Overview of current developments in the catalytic asymmetric dearomatization reactions of phenol and aniline derivatives.
(2) Main challenges confronted in this field: control of chemo-, regio- and enantioselectivities while overcoming the high energy barrier during the dearomatization process.
(3) General strategies employed in this area: oxidative and non-oxidative dearomatization reactions of phenol and aniline derivatives.

1. Introduction

Phenol and its derivatives are widespread in nature such as natural products, bioactive molecules and lignin, the latter of which is a significant component in the support tissue of plants (Fig. 1). They often serve as a class of readily available chemical feedstocks and are mainly obtained via the Hock process starting from cumene. On the other hand, the intriguing chemical properties of phenol and its derivatives have captured enormous attention of chemists from both industry and academia for centuries. As a class of electron-rich arenes containing a hydroxyl group bound directly to the aromatic ring, phenols are sensitive towards oxidation, which is also the reason why phenols are suitable radical scavengers and often employed as oxidation inhibitors. Meanwhile, there exists an intrinsic tautomeric keto–enol equilibrium in phenol and its derivatives, and the enol form is more stable than its keto tautomer due to the formation of the aromatic system.

In addition, dearomatization reactions of phenol and its derivatives have been studied intensively for a long time since they provide an efficient way to construct highly functionalized cyclohexadienones, which often appear in diverse biologically active natural products and pharmaceuticals (Fig. 2). However, how to make them asymmetric by catalytic methods has been daunting chemists for dozens of decades. In the past decade, considerable progress has been achieved in catalytic asymmetric...
dearomatization (CADA) reactions, which are attractive synthetic strategies to transform aromatic compounds to three-dimensional molecules containing quaternary carbon centers, and spiro or bridged backbones in many cases. The main challenge in the CADA reactions of phenol and aniline derivatives is to control the reaction selectivity including chemo-, regio-, and enantioselectivities while overcoming the loss of aromaticity.

Thanks to the development of asymmetric catalysis in general, breakthroughs have recently been achieved in CADA reactions with excellent selectivities. In this tutorial review, these breakthroughs will be discussed under two categories, i.e., oxidative and non-oxidative CADA reactions of phenol and aniline derivatives.

Fig. 2 Natural products and bioactive molecules containing cyclohexadienone backbones.

2. CADA reactions of phenol and its derivatives under oxidative conditions

Phenols are electron-rich aromatic rings and are readily oxidized through the loss of one or two electrons. Historically, oxidative dearomatization reactions of phenol and its derivatives have been investigated intensely. Due to the commercial availability of oxidants, such as PhI(OAc)_2 and 2,3-dichloro-5,6-dicyano-p-quinone (DDQ), and the development of efficient catalytic systems, oxidative dearomatization reactions of phenols have become a

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conventional methodology in organic synthesis and particularly in natural product synthesis.

2.1 Chiral hypervalent iodine involved reactions

Since the first organic hypervalent iodine was prepared by Willgerodt in 1886, hypervalent iodine reagents have evolved into commonly used oxidants in organic synthesis and regarded as of low toxicity, in contrast to many metal oxidants. Generally, it was postulated that there exist two types of key intermediates in the hypervalent iodine mediated oxidative dearomatization reactions of phenols: one is phenoxy-iodoarene catalysts by ortho-functionalization in 2013 and discovered (R)-C1c as the optimal catalyst, which has ethyl groups ortho to the iodine atoms and hence provides extensive equatorial surroundings around them (Scheme 2, eqn (3)). Thus, an excellent level of asymmetric induction is realized in the catalytic oxidation of naphthol 1a. A plausible transition-state model was established based on the ortho-substituent effect and the results of X-ray analysis, where the tethered carboxylic acid moiety attacks the re-face of the enol moiety of 1a to afford 2a with the R configuration.

Different from Kita’s rigid chiral iodoarene (R)-C1b, Ishihara and coworkers designed and developed a series of conformationally flexible C2-symmetric chiral iodoarenes, represented by C2, which turned out to be an effective type of precatalysts for the enantioselective Kita oxidative spirolactonization reaction. Three units contained in the C2-symmetric chiral iodoarenes – an iodoaryl moiety, chiral linkers, and subfunctional groups – work cooperatively based on hydrogen-bonding. Under analogous conditions, the desired dearomatized products 2 could be obtained in up to 94% yield and 92% ee (Scheme 3).

In 2013, with the further modified C2-symmetric chiral iodoarene C3, Ishihara and coworkers expanded the substrate scope, previously limited to 1-naphthol derivatives, to phenols, and realized their highly enantioselective oxidative dearomatization reactions. Under optimized conditions, both electron-rich and electron-deficient phenols 3 were oxidized into various cyclohexadienones 4 in excellent enantiomeric excess. For the reactive cyclohexadienone products, Diels–Alder reactions were carried out in one-pot with different dienophiles to deliver the
corresponding bridged products 5 as single diastereomers in up to 99% ee. Control experiments implied that the addition of protic polar MeOH or HFIP is essential for achieving satisfactory yields and enantioselectivity and it was proposed by the authors that the alcohol additives play the role of ligands of iodine(III) species (Scheme 4).

Recently, Ibrahim and coworkers 9 reported another chiral iodoarene C4 based on a totally different backbone. Bearing a rigid and congested all-carbon anti-dimethanoanthracene framework, the C2-symmetric C4, in the presence of m-CPBA, can catalyze the Kita oxidative spirolactonization reaction in moderate yields and enantioselectivity (Scheme 5).

Previously, intramolecular nucleophiles were limited to carboxylic acids. As a result, the oxidative dearomatization reactions could only deliver spirolactone products. In 2015, Gong and coworkers10 expanded the nucleophiles to include appropriately tethered electron-rich arenes in the form of anilides. Hence, with C2 as precatalyst and m-CPBA as the stoichiometric oxidant, various chiral spirooxindoles 7 possessing all-carbon spiro-stereogenic centers can be obtained in satisfactory yields and enantioselectivity (42–80% yields and 80–92% ee). They also investigated the effect of alcohol and water as additives and discovered that the addition of both TFE (2,2,2-trifluoroethanol) and H2O is beneficial for both yield and enantioselectivity due to the facilitation of the associative pathway (Scheme 6).

Besides intramolecular oxidative dearomatization reactions, asymmetric intermolecular dearomatization reactions have also been realized with chiral iodoarenes. In 2009, Quideau and coworkers11 reported asymmetric dearomatization reactions of 2-methyl-1-naphthol (Scheme 7). When excess chiral iodoarene C5 (2 equiv.) and m-CPBA (1 equiv.) are used, the ortho-hydroxylative phenol dearomatization reaction is achieved with a moderate level of asymmetric induction (50% ee). On the other hand, the use of a catalytic amount of C5 (0.1 equiv.) and excess m-CPBA (2.5 equiv.) led to the double oxidized product 9 with decreased enantioselectivity (29% ee). Experimental observations support that a chiral iodine(V) species was generated in situ from the iodoarene and m-CPBA. With further modified chiral bis(\(\lambda^5\)-iodane) C5', dearomatized product 8 can be obtained in 73% ee.12

Despite the difficulty, intermolecular oxidative dearomatization reactions of phenols were achieved by Harned and coworkers in 2013.13 On the basis of computational molecular modeling of the transient associative intermediate of type A (Scheme 1), a new chiral aryl iodide catalyst C6 derived from 8-iodotetralone and tartaric acid was designed and applied in an intermolecular oxidative dearomatization reaction of phenols. The para-quinols 11 were formed with low to moderate enantioselectivity. In comparison, the intramolecular dearomatization reaction of para-substituted phenol 12 afforded the spirocycle 13 without notable improvement in asymmetric induction (Scheme 8).

2.2 SET oxidation reactions

In the previous section, phenol derivatives are oxidized by chiral hypervalent iodoses in two-electron processes via the attack of either the associative intermediate A or the dissociative intermediate B by nucleophiles. In addition, these electron-rich arenes can also undergo oxidations in single electron transfer processes (SET) involving radical intermediates.

Oguma and Katsuki disclosed that the Fe(salan) complex C7 can catalyze the aerobic intermolecular oxidative dearomatization
reaction of 1,3-disubstituted 2-naphthols 14 with nitroalkanes14 or phenols 1615 as external nucleophiles, affording cyclic enones 15 and 17 in excellent yields and enantioselectivity, respectively. It was proposed that once 2-naphthols 14 were coordinated by C7, radical cation species C would be generated from SET oxidation by O2 in the air. The radical cation species C could be trapped by nitroalkane to deliver the corresponding dearomatized products 15 bearing an all-carbon quaternary stereocenter. On the other hand, the radical cation species C could be further transformed into a strong Michael acceptor by γ-H abstraction and the subsequent Michael addition with phenols 16 took place to yield useful spirocyclic (2H)-dihydrobenzofurans 17 (Scheme 9).

3. CADA reactions of phenol and aniline derivatives under non-oxidative conditions

Phenols are electron-rich aromatic compounds and hence display considerable nucleophilicity (Fig. 3). There are several nucleophilic sites on the phenol ring, O, C2 and C4, and only the reactions involving the carbon nucleophilic sites can be employed in dearomatization reactions. Moreover, the selectivity over these nucleophilic sites can be challenging. As such, substrates are often delicately designed to achieve desired chemo-, regio- and enantioselectivities.

Due to the aromaticity, the enol form of phenol is much more stable than its keto tautomers, which are dearomatized. If some substrate intrinsically prefers the keto tautomers, its dearomatization reaction can be relatively facile. The most common factors that contribute to the keto forms are (1) additional hydroxy groups on the benzene ring; (2) additional arenes annulated to the phenolic benzene ring; (3) the formation of phenolate; (4) bulky groups in the ortho-positions of phenol; and (5) electron-withdrawing substituents in the ortho- and para-positions of phenol.

Besides phenols, naphthols have frequently been utilized as model substrates due to their relatively weak aromaticity. In addition, anilines and aminonaphthalenes are also electron-rich aromatic compounds and can undergo similar dearomatization reactions.

In general, dearomatization reactions of phenols can be regarded as functionalization of enols, and selected examples below are classified according to the types of functionalization.

3.1 Alkylative dearomatization reactions

ortho-Substituted phenols easily undergo alkylation with carbon-based electrophiles, and racemic protocols have been extensively documented and broadly applied in the synthesis. However, only a few catalytic asymmetric cases have been reported.

In 2007, Porco and coworkers16 succeeded in the construction of the bicyclo[3.3.1]nonane framework via alkylative dearomatization annulation during the synthesis of polyprenylated phloroglucinol natural products. In 2010, they realized the asymmetric
variant\textsuperscript{17} by utilizing a chiral phase-transfer catalyst derived from cinchona alkaloids. Hence, with C8 as the chiral phase-transfer catalyst and 5 equivalents of CsOH-H\textsubscript{2}O as the base, the previously reported cascade, i.e., Michael addition–elimination–Michael addition–aldol reaction sequence, occurs smoothly with clusiaphenone B as substrate in a nonracemic manner, affording adamantane 18 in 71\% yield and 90\% ee. The product was further transformed into (-)-hyperibone K, which permits the assignment of its absolute configuration (Scheme 10).

Using aziridines 19 as alkylative reagents and the catalyst generated from \textsuperscript{8}Bu\textsubscript{2}Mg and a newly designed Box–OH ligand L1, Wang and coworkers realized in 2015 asymmetric dearomatization reactions of \(\beta\)-naphthol derivatives 14 in excellent yields and enantioselectivity.\textsuperscript{18} Their investigations on the possible activation mode indicate that the \textit{in situ} generated magnesium catalyst interacts with both \(\beta\)-naphthol 14\textit{a} and \(N\)-(2-picolinoyl)-meso-aziridine 19\textit{a} to form a relatively rigid chiral environment. Interestingly, a positive nonlinear effect was also observed in the reaction (Scheme 11).

In the same year, You and coworkers\textsuperscript{19} employed chiral thiourea C9 as catalyst to achieve intermolecular asymmetric dearomatative Michael additions of \(\beta\)-naphthols 14\textit{a} to nitroethylene. Functionalized \(\beta\)-naphthalenones 21 bearing an all-carbon quaternary stereogenic center are formed in good yields with excellent enantio control. To demonstrate the synthetic utility of this chemistry, enantioenriched 21\textit{a} is transformed into aminotetralin 21\textit{aa} and carbamate 21\textit{bb}, the latter of which serves as a key intermediate in the synthesis of the common propellane core structure of the hasubanan alkaloids. A plausible working model was also postulated, where the hydrogen bonds between thiourea C9 and nitroethylene and the hydroxy group of \(\beta\)-naphthol provide a highly ordered transition state, which enables the high level of enantioselective induction (Scheme 12).

### 3.2 Allylative dearomatization reactions

Asymmetric allylic alkylation (AAA) reactions have become one of the most reliable and versatile methods for the formation of C–C bonds with desirable enantioselectivity, and a wide range of nucleophiles including phenol and its derivatives can be employed. However, \(O\)-allylation of phenol substrates dominates over \(C\)-allylation, which has only been realized in a handful of cases and rarely displays good chemo-, stereo- and enantioselectivities.

In 2010, Hamada and coworkers\textsuperscript{20} reported one successful study on Pd-catalyzed enantioselective intramolecular allylic dearomatization reaction of \textit{para}-substituted phenol 22\textit{a}. With L2 as the chiral ligand, the spirocyclohexadienone 23\textit{a} was formed in 80% yield, 9.2 : 1 dr and 89\% ee (Scheme 13).

In 2011, You and coworkers\textsuperscript{21} accomplished an Ir-catalyzed intramolecular asymmetric allylic dearomatization reaction of phenols. In the presence of a catalytic amount of [Ir(cod)Cl]\textsubscript{2}, the chiral phosphoramidite ligand L3 and 2 equivalents of Li\textsubscript{2}CO\textsubscript{3}, a series of \textit{para}-substituted phenols 22 were converted into various 5- or 6-membered spirocyclohexadienone derivatives 23 in excellent yields and enantioselectivity (up to 97\% ee) (Scheme 14).

The two cases above both have the nucleophilic moiety substituted on the phenol \textit{para}-position to avoid the potential

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**Scheme 10** Enantioselective allylative dearomatization reaction of clusiaphenone B reported by Porco.

**Scheme 11** Enantioselective allylative dearomatization reaction of \(\beta\)-naphthol derivatives reported by Wang.

**Scheme 12** Enantioselective allylative dearomatization reaction of \(\beta\)-naphthol derivatives reported by You.
competition of alkylations at the phenolic oxygen and/or at the ortho position. When it comes to the intermolecular scenario, it can be a great challenge to address all three issues: chemo-, regio-, and enantioselectivities. In 2013, You and coworkers realized a palladium-catalyzed intermolecular asymmetric allylic dearomatization reaction of naphthol derivatives. Hence, with various substituted allylic carbonates as the allylating reagents, an array of b-naphthalenones with an all-carbon quaternary chiral center could be constructed in good to excellent yields, and with excellent chemo- and enantioselectivities. This intermolecular example establishes a promising precedent for future development in this area (Scheme 15).

3.3 Arylative dearomatization reactions

Cross-coupling reactions are powerful tools in organic synthesis. Especially, Pd-catalyzed asymmetric cross-coupling reactions have been investigated intensively, and ground-breaking discoveries have been realized quite recently owing to the development of various chiral ligands. In general, phenols are employed as intramolecular nucleophiles to attack electrophilic Pd intermediates en route to multi-functionalized dearomatized products.

An early study in this area was reported by Buchwald in 2009, where anilines instead of phenols undergo asymmetric dearomatization reaction. In the reaction, LiO\textsubscript{t}Bu was used to promote deprotonation of the aniline NH, which in turn increases the nucleophilicity of the naphthalene C2-position and hence facilitates its attack at the Pd(II) center. With KenPhos L\textsubscript{5} as the chiral ligand, various benzocarbazole derivatives were obtained in good to excellent yields and with mostly outstanding enantioselectivity (Scheme 16).

In 2011, Buchwald and coworkers broadened the substrate scope to include phenols. On the basis of racemic Pd-catalyzed arylative dearomatization reaction of phenols, the asymmetric version was carried out with (S,S)-L\textsubscript{6} as ligand, and the spirocyclohexadienone products were isolated in good to excellent yields and enantioselectivity (up to 91% ee) (Scheme 17). The above two studies demonstrated that Pd-catalyzed cross-coupling reactions can offer versatile strategies for the CADA reaction of phenol derivatives. In 2014, You and coworkers reported another application of this strategy. With a broad range of 5-hydroxyl indolines as substrate, Pd-catalyzed intramolecular arylative dearomatization reactions delivered various sterically congested tetracyclic spiroamines in excellent yields. One of the products was converted to 3-demethoxyerythratidinone upon selective hydrogenation, thereby offering an efficient and straightforward synthetic route to this natural product.
product (Scheme 18, eqn (1)). Their preliminary studies suggested that asymmetric catalysis is also feasible (Scheme 18, eqn (2)).

In the studies discussed so far, excellent asymmetric inductions were achieved only in limited cases. In 2015, Tang and coworkers\textsuperscript{26} developed a P-chiral biaryl monophosphine ligand \( \text{L8} \) and applied it in a novel enantioselective palladium-catalyzed dearomative cyclization reaction. A range of chiral phenanthrene derivatives \( \text{33} \) were obtained in excellent enantiomeric excess. This efficient method provides a facile way to synthesize terpenes and steroids, which is demonstrated in the syntheses of chiral kaurene intermediate \( \text{33a} \), boldenone skeleton \( \text{33b} \), and antimicrobial diterpene totaradiol \( \text{33cc} \) (Scheme 19).

### 3.4 Alkenylative dearomatization reactions

The electrophilic Pd(II) intermediates mentioned above can undergo insertion reactions with alkynes prior to dearomatization, which can be regarded as alkenylative dearomatization reactions of phenols. In 2015, Luan and coworkers\textsuperscript{27} realized a Pd-catalyzed enantioselective annulation of phenol derivatives \( \text{34} \) with alkynes \( \text{35} \), affording the spirocycle \( \text{36} \) with an all-carbon quaternary stereogenic center in superb yields and excellent enantioselectivity (up to 97% ee). Interestingly, the reaction achieves an axial-to-central chirality transfer, where the spirocyclic molecules \( \text{36} \) of central chirality are formed from dynamic kinetic resolutions of racemic axial chiral biaryls \( \text{34} \) (Scheme 20).

Besides Pd, Rh can also catalyze insertion reactions of alkynes. Almost at the same time, You and coworkers\textsuperscript{28} succeeded in a Rh-catalyzed asymmetric alkenylative dearomatization reaction of 1-aryl-2-naphthols \( \text{37} \) via \( \text{C(sp^2)}-\text{H} \) functionalization/alkyne insertion/annulation reaction. In the presence of a chiral Cp/Rh catalyst \( \text{C10} \) and \( \text{Cu(OAc)}_2 \), and air as the oxidants, the reaction was initiated by a hydroxyl group-directed \( \text{C(sp^2)}-\text{H} \) functionalization by a Rh complex, followed by alkyne insertion and dearamative reductive elimination to afford highly enantioenriched spirocyclic enones \( \text{38} \) bearing an all-carbon quaternary stereogenic center in mostly good yields (Scheme 21).

It is well-known that cationic gold(I) can activate alkynes toward attack by external nucleophiles, resulting eventually in the trans addition of \( \text{H–Nu} \) across the C–C triple bond. With phenols and anilines as nucleophiles, this fundamental gold catalysis can lead to alkenylative dearomatization reactions of these electron-rich arenes. In 2015, Tanaka and coworkers\textsuperscript{29} realized the conversion of 1-aminonaphthalene derivatives \( \text{39} \) to two different products \( \text{40 and 40'} \), the ratio of which depends on the \( \text{R} \) group, in good to excellent yields and ee (Scheme 22, eqn (1)). In addition, the substrates with electron-rich heteroarenes appended to the ynamide (Scheme 22, eqn (2)) or displaying altered arrangement of the functional groups (Scheme 22, eqn (3)) can also undergo similar dearomatization reaction.\textsuperscript{30}

In addition to the intramolecular enantioselective alkenylative dearomatization reactions of phenols, an intermolecular Mg-catalyzed conjugate addition of \( \beta \)-naphthols \( \text{14} \) to yrones \( \text{45} \)
was recently realized by Wang and coworkers. Like the reaction discussed in Scheme 11, the chiral magnesium catalyst generated in situ by reaction of $^{65}$Bu$_2$Mg with L10 is proposed to interact with both substrates in the transition state. Notably, good to excellent Z-selectivity and enantioselectivity were obtained for a wide range of substrates (Scheme 23).

### 3.5 Halogenative dearomatization reactions

The aforementioned allylative, allylative, arylative and alkenylative dearomatization reactions form C–C bonds and are generally promoted or catalyzed by metal complexes. When it comes to asymmetric C–X (X = F, Cl) bond formation in dearomatization reactions, organocatalysts have exhibited outstanding performance.

In 2013, Toste and coworkers realized a fluorinative dearomatization reaction of phenols 47 by using a BINOL-derived phosphate [e.g., (S)-C11] as the chiral anion phase-transfer catalyst (PTC). Selectfluor acts as the electrophilic fluorine source and reacts with 47 to yield various cyclohexadienones 48 bearing a chiral quaternary F-containing stereocenter in generally satisfactory yields and with excellent asymmetric induction. In addition, para-fluorination is achieved with the substrate 49 lacking ortho-substituents in good ee. Interestingly, products of type 52 readily undergo [4+2] dimerization, leading to single diastereomers 52'. A working model, as shown in Scheme 24, is proposed to rationalize the asymmetric induction.

Subsequently, a homogeneous organocatalytic asymmetric chlorinative dearomatization reaction of naphthalenes 54 was realized by You and coworkers in 2015. Using (DHQD)$_2$PHAL derived from cinchonine as catalyst and 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) as the electrophilic chlorine source, the operationally simple reaction provides facile access to chiral chlorinated naphthalenones 55 in excellent yields and ee under mild conditions. In addition, it tolerates a broad range of functional groups. The postulated mechanism entails that the phthalazine nitrogen in the catalyst interacts with the hydroxyl group of naphthol via a hydrogen bond and the tertiary amine nitrogen in quinuclidine acts as a Lewis base to deliver Cl$^-$. Notably, intermolecular deamorative chlorination of 1-naphthol derivative 56 was also realized with high enantioselectivity (Scheme 26).

### 3.6 Aminative dearomatization reactions

CADA reactions of phenol derivatives can also be achieved via electrophilic amination reactions. Recently, both Bronsted and Lewis acids have been employed as catalysts to activate azodicarboxylates toward nucleophilic attack by naphthols 14. This deamorative reaction can furnish aminated-naphthalenones 59 featuring a tertiary amine moiety in mostly excellent yields and ee (Scheme 26).

In 2015, You and coworkers realized this type of reactions by using chiral phosphoric acid (CPA) as catalyst. Notably, the catalyst loading can be as low as 0.1 mol% without affecting the yields and enantioselectivity. Intriguingly, C13 was found to be the optimal catalyst when the substituent on the naphthol 3-position is H.

Besides chiral Bronsted acids, the chiral Sc(III)/pybox complexes derived from L10 and L11 were employed by Luan and coworkers in the same year as effective catalysts for the same aminative deamorative reactions, affording 59 in excellent yields and ee.

Moreover, the combination of Sc(OTf)$_3$ and the $N,N'$-di-oxide L12, developed by Feng’s group, is also highly effective in achieving the aminative deamorative reaction in good to superb yields and with excellent enantioselectivity.

### 3.7 Rearrangement deamorative reactions

Inspired by the deamoratizing [3,3]-sigmatropic diaza-Cope rearrangement in the Fischer indole synthesis, List and coworkers recently developed an asymmetric version of this...
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**Scheme 25** Organocatalytic asymmetric chlorinative dearomatization reaction of naphthols reported by You.

**Scheme 26** Asymmetric dearomatization reaction of naphthols via amination reactions reported by You, Luan and Feng.

**Scheme 27** Asymmetric dearomatization reaction of naphthols via aryl hydrazine rearrangement reaction reported by List.

4. Conclusions

In conclusion, two types of CADA reactions of phenol and aniline derivatives are described in this tutorial review. In the oxidative dearomatization reactions, the phenol moiety is oxidized, and the thus-generated intermediate reacts with nucleophiles; on the other hand, phenol itself is electron-rich and can react with electrophiles in the non-oxidative dearomatization reactions. The recent progress discussed in this tutorial reveals that a variety of strategies can be employed to achieve CADA reactions of phenol and its derivatives. In general, naphthols are more susceptible to dearomatization reactions than phenols, and the addition of base or additional interaction between chiral catalysts and the hydroxyl group of phenols is beneficial to both yield and enantioselectivity.

This progress also illustrates that the CADA reactions of readily available phenol derivatives provide unconventional strategies for streamlining synthesis of complex molecules and natural products of high value. It is expected that the strategies successfully employed in these CADA reactions would soon be applied to other aromatic systems, thereby enabling CADA reaction as a general approach to the manipulation of aromatic compounds.

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Notes and references