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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[1] 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

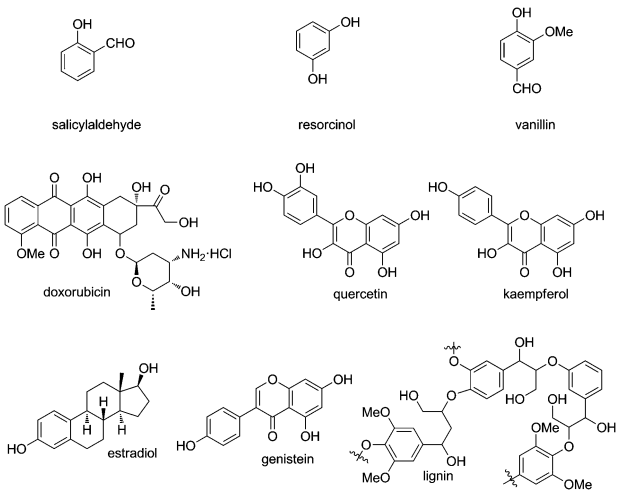

Fig. 1 Natural products and bioactive molecules containing phenol motifs.

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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.[2] 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.

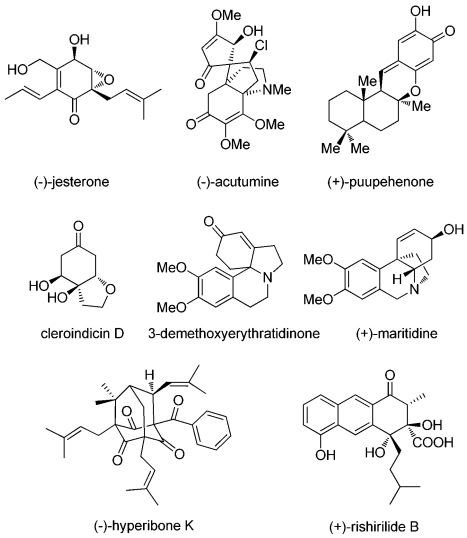
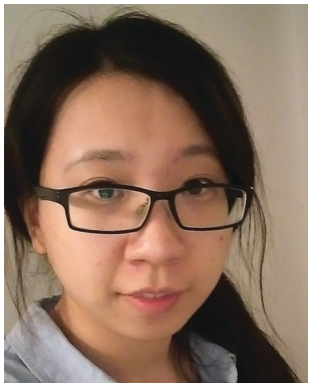


Fig. 2 Natural products and bioactive molecules containing cyclohexadienone backbones.

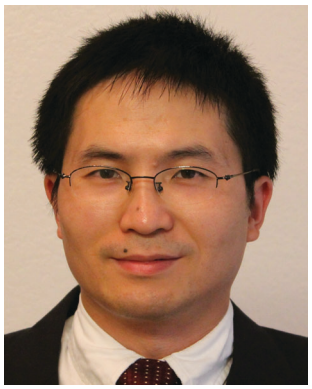


Wen-Ting Wu

Wen-Ting Wu was born in 1989 in Suzhou, Jiangsu province, China, and received her BS degree from Soochow University in 2012. She then joined Shanghai Institute of Organic Chemistry (SIOC) for her PhD degree under the supervision of Prof. Shu-Li You and Prof. Liming Zhang. Her research focused on the gold-catalyzed dearomatization reactions.

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



Liming Zhang

Liming Zhang was born in Pingxiang, China, in 1972. He received his B.S. degree in chemistry from Nanchang University in 1993, his first Master's degree in organometallic chemistry with Professor Zhengzhi Zhang from Nankai University in 1996, and his second Master's degree in organic chemistry with Professor Michael P. Cava from the University of Alabama in 1998. He obtained his Ph.D. degree with Professor Masato Koreeda from the medicinal chemistry program at the University of Michigan in 2003 and then carried out a post-doctoral study with Professor Sergey A. Kozmin at the University of Chicago. He started his independent academic career as Assistant Professor at the Department of Chemistry, University of Nevada, Reno, in July of 2005 and continued at the University of California Santa Barbara in July of 2009. He is currently a Professor of Organic Chemistry. His research interests include late transition metal-catalyzed reactions, natural product synthesis and medicinal chemistry.

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Dr Shu-Li You received his BSc in chemistry from Nankai University in 1996. He obtained his PhD from 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. From 2004, he worked at the Genomics Institute of the Novartis Research Foundation as a Principal Investigator before returning to SIOC in 2006. His research interests include asymmetric catalysis, synthetic methodology, natural product synthesis, as well as medicinal chemistry.

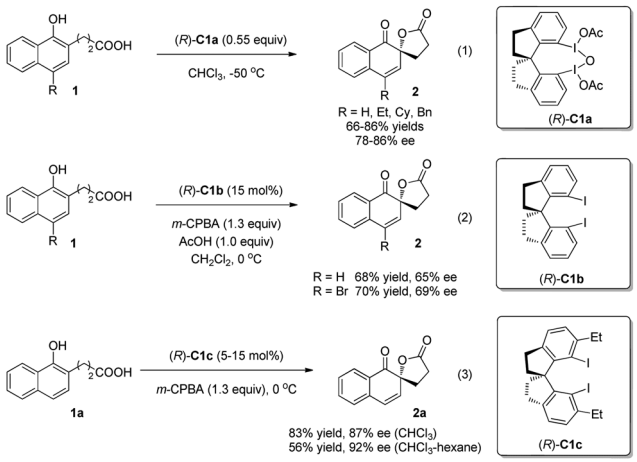
conventional methodology in organic synthesis and particularly in natural product synthesis.

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.[3] 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-λ^3-iodane species **A** and another is discrete phenoxenium ion **B** (Scheme 1).[4] With the utilization of chiral hypervalent iodine reagents, the asymmetric reactions could be achieved *via* the associative intermediate **A**.

However, the development of chiral hypervalent iodines as reagents or even catalysts with high efficiency and satisfactory enantioselectivity has been a challenging task for many years. Breakthroughs were achieved in the past decade attributed to the considerable efforts from the groups of Kita, Ishihara, Quideau, Ibrahim and Gong, respectively. The commonly used strategy to realize the enantioselective oxidative reactions of phenol and its derivatives is the combination of catalytic chiral iodides as pre-catalysts and *m*-CPBA as the stoichiometric co-oxidant.

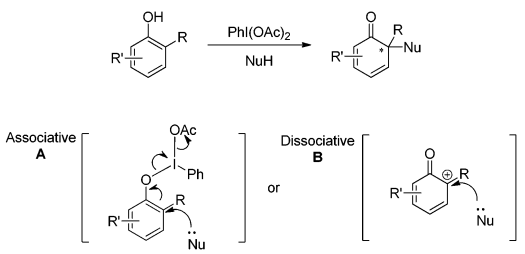
In 2008, Kita and coworkers[5] reported a new chiral hypervalent iodine(III) reagent (*R*)-**C1a** bearing a rigid spirobiindane backbone to achieve the first enantioselective oxidative dearomatization reaction of 1-naphthol derivatives **1** to construct a chiral *ortho*-spirolactone structure **2** in 66–86% yields and 78–86% ee (enantiomeric excess) (Scheme 2, eqn (1)). They also found that the combination of *m*-chloroperoxybenzoic acid (*m*-CPBA) and 15 mol% of the corresponding chiral iodoarene (*R*)-**C1b** could generate (*R*)-**C1a** *in situ* and achieve comparative results (Scheme 2, eqn (2)). Moreover, the chiral iodoarene (*R*)-**C1b** can be easily recovered by column chromatography, which renders this new asymmetric oxidative dearomatization method practical. Later on, Kita and coworkers[6] modified the rigid chiral spirobiindane 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.



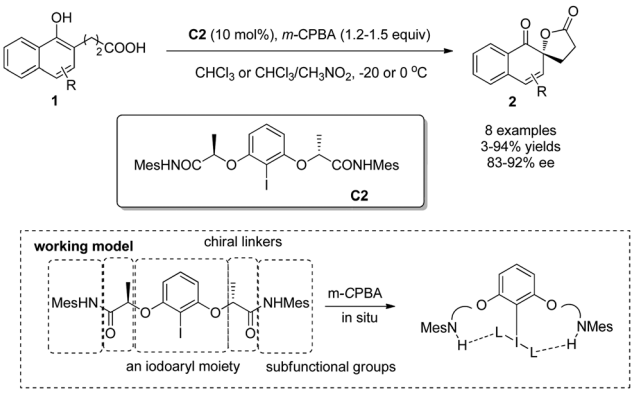
Scheme 2 Enantioselective intramolecular oxidative dearomatization reaction of naphthols reported by Kita.

Different from Kita's rigid chiral iodoarene (*R*)-**C1b**, Ishihara and coworkers[7] designed and developed a series of conformationally flexible C_2-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 C_2-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).

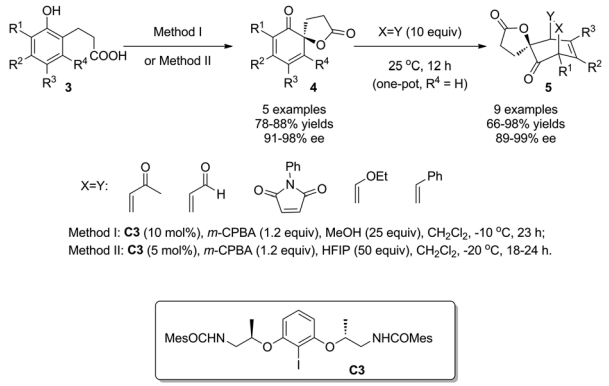
In 2013, with the further modified C_2-symmetric chiral iodoarene **C3**, Ishihara and coworkers[8] expanded the substrate scope, previously limited to 1-naphthol derivatives,[5–7] to phenols, and realized their highly enantioselective oxidative dearomatization reactions. Under optimized conditions, 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



Scheme 1 Two postulated intermediates of hypervalent iodine mediated oxidative dearomatization reactions of phenols.



Scheme 3 Enantioselective intramolecular oxidative dearomatization reaction of naphthols reported by Ishihara.



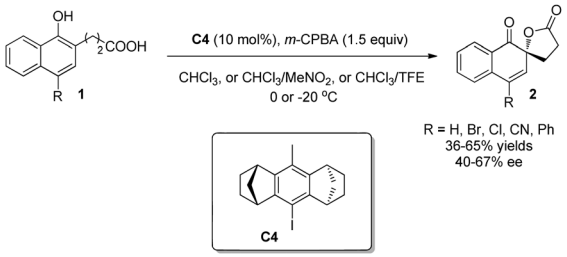
Scheme 4 Enantioselective intramolecular oxidative dearomatization reaction of phenols reported by Ishihara.

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).

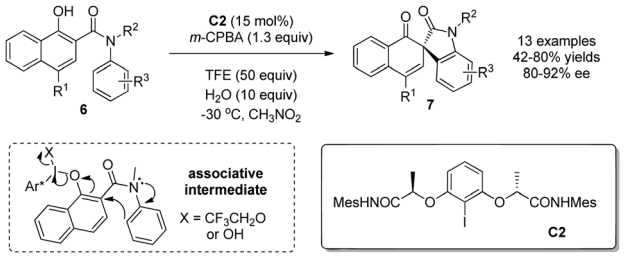
Recently, Ibrahim and coworkers[9] reported another chiral iodoarene **C4** based on a totally different backbone. Bearing a rigid and congested all-carbon anti-dimethanoanthracene framework, the C_2-symmetric **C4**, in the presence of *m*-CPBA, can catalyze the Kita oxidative spirolactonization reaction 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 coworkers[10] 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 H_2O is beneficial for both yield and enantioselectivity due to the facilitation of the associative pathway (Scheme 6).

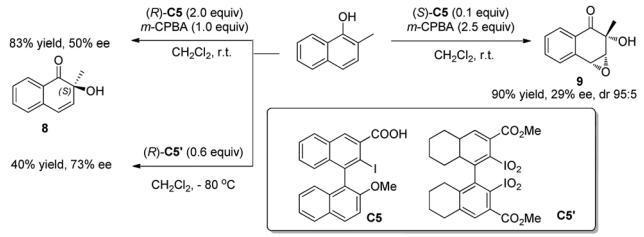
Besides intramolecular oxidative dearomatization reactions, asymmetric intermolecular dearomatization reactions have also been realized with chiral iodoarenes. In 2009, Quideau



Scheme 5 Enantioselective intramolecular oxidative dearomatization reaction of naphthols reported by Ibrahim.



Scheme 6 Enantioselective synthesis of spirooxindoles reported by Gong.



Scheme 7 Enantioselective intermolecular oxidative dearomatization reaction of naphthols reported by Quideau.

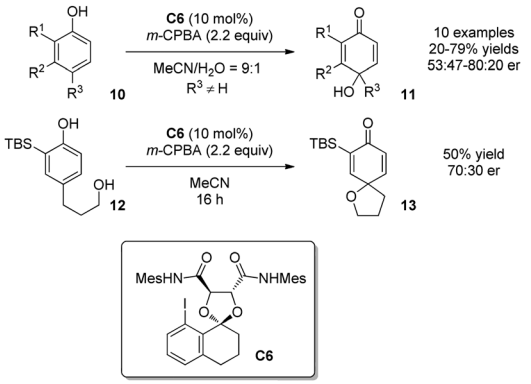
and coworkers[11] reported asymmetric dearomatization reactions of 2-methyl-1-naphthol (Scheme 7). When excess chiral iodoarene **C5** (2 equiv.) and *m*-CPBA (1 equiv.) are used, the *ortho*-hydroxylative phenol dearomatization reaction is achieved with a moderate level of asymmetric induction (50% 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(λ^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 **10**. 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

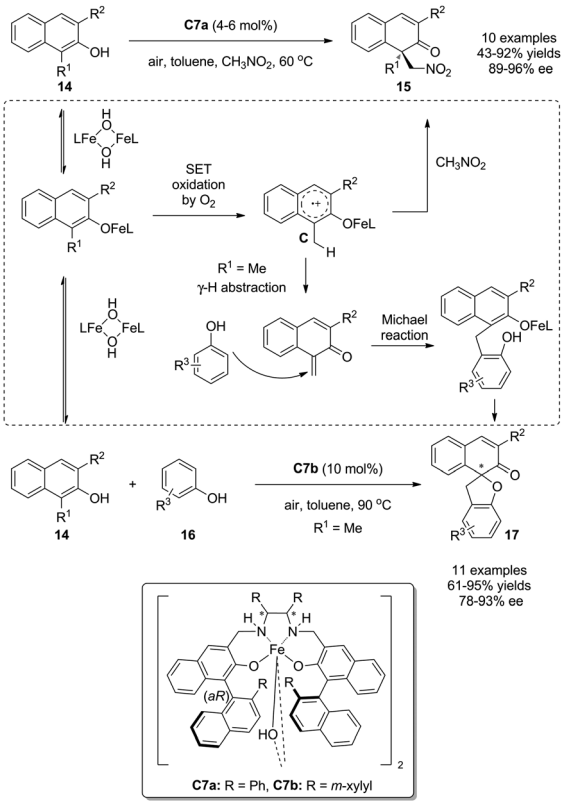
In the previous section, phenol derivatives are oxidized by chiral hypervalent iodines in two-electron processes *via* the attack of either the associative intermediate **A** or the dissociative intermediate **B** by nucleophiles. In addition, these electron-rich arenes can also undergo oxidations in 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



Scheme 8 Enantioselective oxidative dearomatization reaction of phenols reported by Harned.

reaction of 1,3-disubstituted 2-naphthols **14** with nitroalkanes[14] or phenols **16**[15] 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 O_2 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 (2*H*)-dihydrobenzofurans **17** (Scheme 9).



Scheme 9 Fe(salan) complex-catalyzed aerobic asymmetric dearomatization reactions of naphthols reported by Katsuki.

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

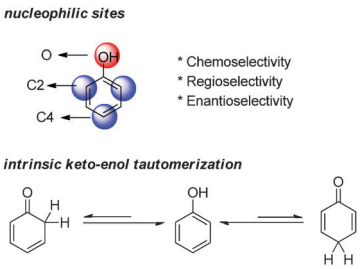


Fig. 3 Nucleophilic sites on the phenol ring and the intrinsic keto–enol tautomerization of phenol.

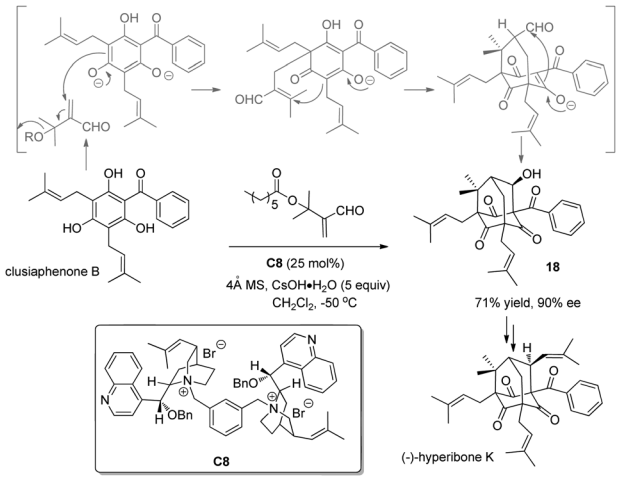
aromatic compounds and can undergo similar dearomatization reactions.

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 coworkers[16] 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



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

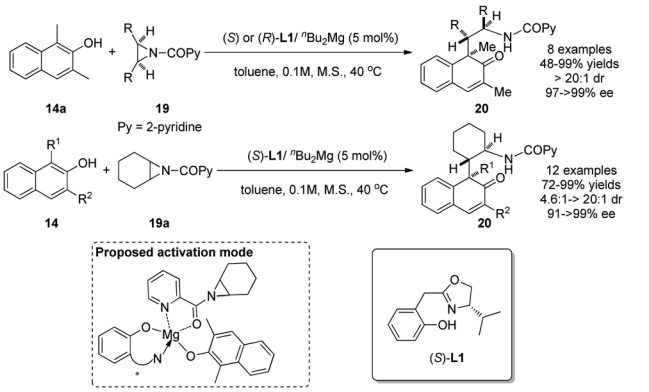
variant[17] by utilizing a chiral phase-transfer catalyst derived from cinchona alkaloids. Hence, with **C8** as the chiral phase-transfer catalyst and 5 equivalents of $CsOH{\cdot}H_2O$ as the base, the previously reported cascade, *i.e.*, Michael addition–elimination–Michael addition–aldol reaction 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 $^{n}Bu_2Mg$ and a newly designed Box–OH ligand **L1**, Wang and coworkers realized in 2015 asymmetric dearomatization reactions of β-naphthol derivatives **14** in excellent yields and enantioselectivity.[18] Their investigations on the possible activation mode indicate that the *in situ* generated magnesium catalyst interacts with both β-naphthol **14a** and *N*-(2-picolinoyl)-*meso*-aziridine **19a** 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[19] employed chiral thiourea **C9** as catalyst to achieve intermolecular asymmetric dearomative Michael additions of β-naphthols **14′** to nitroethylene. Functionalized β-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** is transformed into aminotetralin **21aa** and carbamate **21bb**, 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 β-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



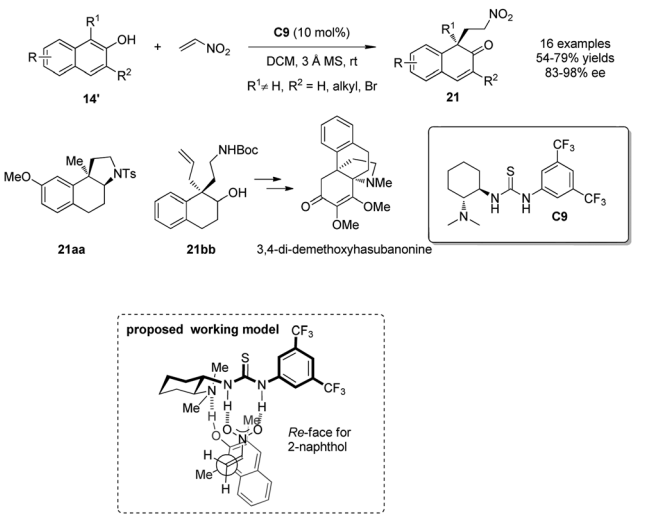
Scheme 11 Enantioselective alkylative dearomatization reaction of β-naphthol derivatives reported by Wang.

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.

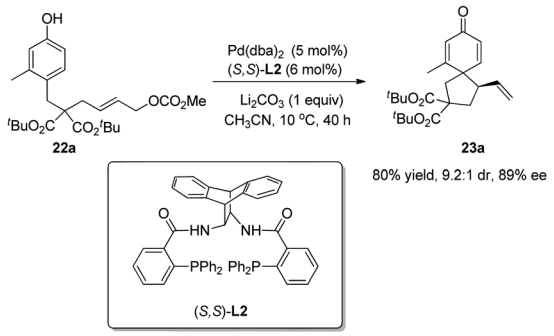
In 2010, Hamada and coworkers[20] reported one successful study on Pd-catalyzed enantioselective intramolecular allylic dearomatization reaction of *para*-substituted phenol **22a**. With **L2** as the chiral ligand, the spirocyclohexadienone **23a** was formed in 80% yield, 9.2 : 1 dr and 89% ee (Scheme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

In 2011, You and coworkers[21] accomplished an Ir-catalyzed intramolecular asymmetric allylic dearomatization reaction of phenols. In the presence of a catalytic amount of $[Ir(cod)Cl]_2$, the chiral phosphoramidite ligand **L3** and 2 equivalents of Li_2CO_3, a series of *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 *para*-position to avoid the potential



Scheme 12 Enantioselective alkylative dearomatization reaction of β-naphthol derivatives reported by You.



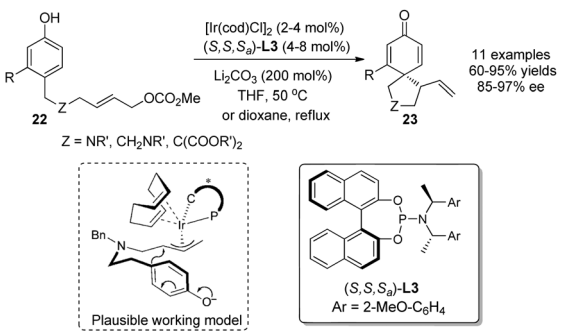
Scheme 13 Pd-catalyzed asymmetric intramolecular allylic dearomatization reaction of phenols reported by Hamada.

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[22] realized a palladium-catalyzed intermolecular asymmetric allylic dearomatization reaction of naphthol derivatives **14**. Hence, with various substituted allylic carbonates **24** as the allylating reagents, an array of β-naphthalenones **25** 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).

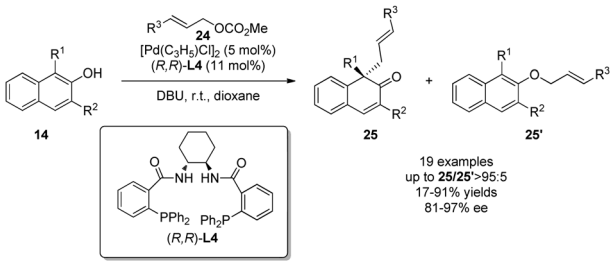
3.3 Arylative dearomatization reactions

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.[23] In the reaction, LiO^{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 **L5** as the chiral ligand, various benzocarbazole derivatives **27** were obtained



Scheme 14 Ir-catalyzed asymmetric intramolecular allylic alkylation dearomatization reaction of phenols reported by You.

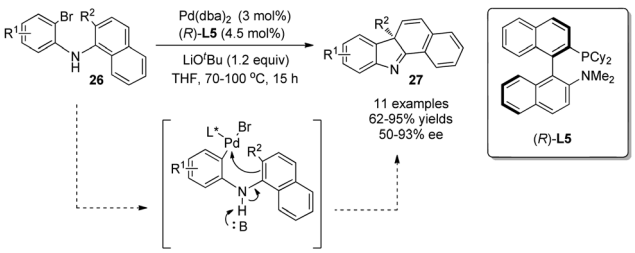


Scheme 15 Pd-catalyzed asymmetric intermolecular allylic dearomatization reaction of naphthols reported by You.

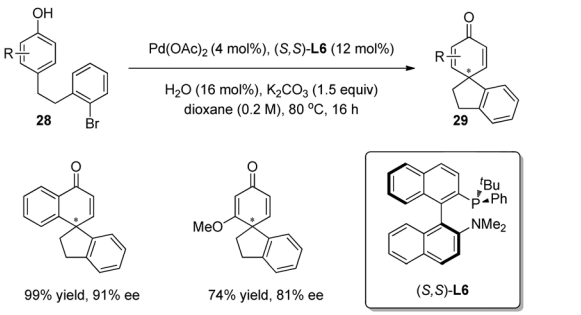
in good to excellent yields and with mostly outstanding enantioselectivity (Scheme 16).

In 2011, Buchwald and coworkers[24] broadened the substrate scope to include phenols. On the basis of racemic Pd-catalyzed arylative dearomatization reaction of phenols **28**, the asymmetric version was carried out with (*S*,*S*)-**L6** as ligand, and the spirocyclohexadienone products **29** were isolated in good to excellent yields and enantioselectivity (up to 91% ee) (Scheme 17).

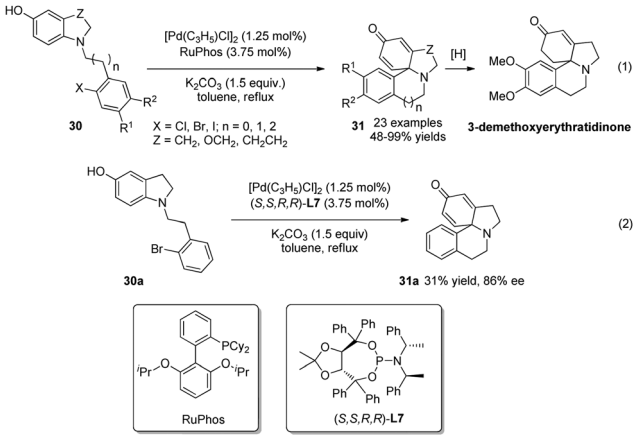
The above two studies demonstrated that Pd-catalyzed cross-coupling reactions can offer versatile strategies for the CADA reaction of phenol derivatives. In 2014, You and coworkers[25] reported another application of this strategy. With a broad range of 5-hydroxyl indolines **30** as substrate, Pd-catalyzed intramolecular arylative dearomatization reactions delivered various sterically congested tetracyclic spiroamines **31** 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



Scheme 16 Pd-catalyzed asymmetric intramolecular arylative dearomatization reaction of aminonaphthalenes reported by Buchwald.



Scheme 17 Pd-catalyzed asymmetric intramolecular arylative dearomatization reaction of phenols reported by Buchwald.



Scheme 18 Pd-catalyzed asymmetric intramolecular arylative dearomatization reaction of 5-hydroxyl indolines reported by You.

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[26] developed a P-chiral biaryl monophosphine ligand **L8** and applied it in a novel enantioselective palladium-catalyzed dearomative cyclization reaction. A range of chiral phenanthrenone derivatives **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 **33a**, boldenone skeleton **33b**, and antimicrobial diterpene totaradiol **33cc** (Scheme 19).

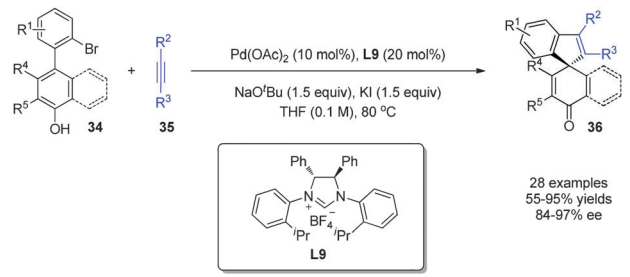
3.4 Alkenylative dearomatization reactions

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[27] realized a Pd-catalyzed enantioselective annulation of phenol derivatives **34** with alkynes **35**, affording the spirocycle **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 **36** of central chirality are formed from dynamic kinetic resolutions of racemic axial chiral biaryls **34** (Scheme 20).

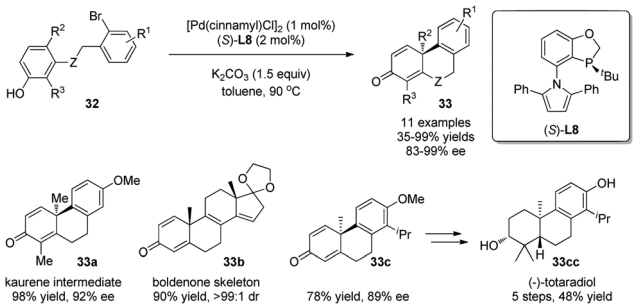
Besides Pd, Rh can also catalyze insertion reactions of alkynes. Almost at the same time, You and coworkers[28] succeeded in a Rh-catalyzed asymmetric alkenylative dearomatization reaction of 1-aryl-2-naphthols **37** *via* C(sp^2)–H functionalization/alkyne insertion/annulation reaction. In the presence of a chiral Cp/Rh catalyst **C10** and $Cu(OAc)_2$ and air as the oxidants, the reaction was initiated by a hydroxyl group-directed C(sp^2)–H functionalization by a Rh complex, followed by alkyne insertion and dearomative reductive elimination to afford highly enantioenriched spirocyclic enones **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 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[29] realized the conversion of 1-aminonaphthalene derivatives **39** to two different products **40** and **40′**, the ratio of which depends on the 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.[30]

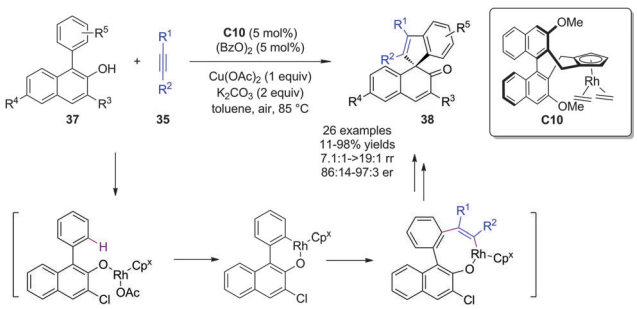
In addition to the intramolecular enantioselective alkenylative dearomatization reactions of phenols, an intermolecular Mg-catalyzed conjugate addition of β-naphthols **14** to ynones **45**



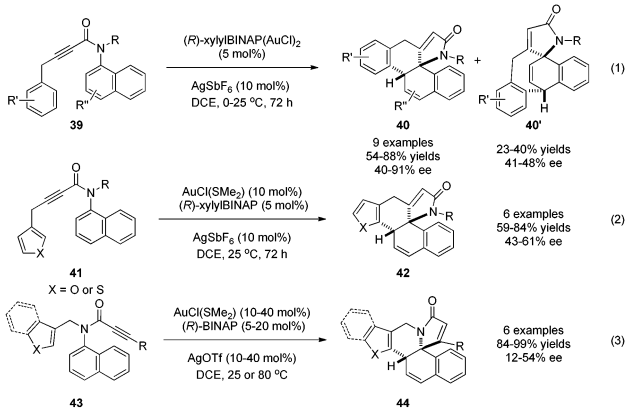
Scheme 20 Pd-catalyzed asymmetric intramolecular dearomatization reaction of phenols reported by Luan.



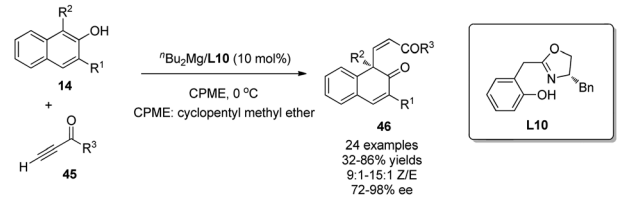
Scheme 19 Pd-catalyzed asymmetric intramolecular arylative dearomatization reaction of phenols reported by Tang.



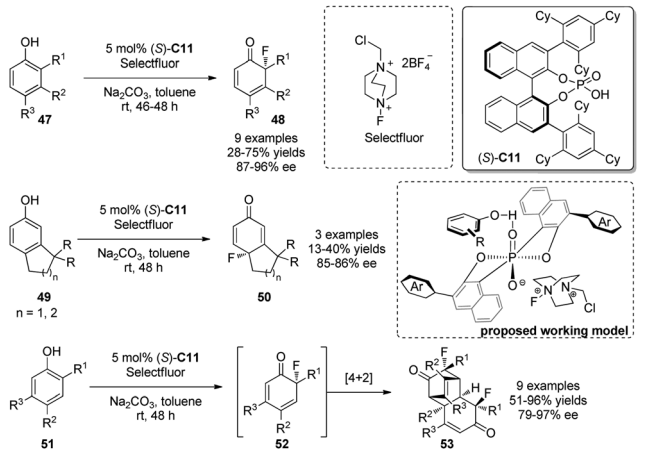
Scheme 21 Rh-catalyzed asymmetric alkenylative dearomatization reaction of naphthols reported by You.



Scheme 22 Gold-catalyzed asymmetric alkenylation dearomatization reaction of aminonaphthalenes reported by Tanaka.



Scheme 23 Mg-catalyzed asymmetric alkenylative dearomatization reaction of naphthols reported by Wang.



Scheme 24 PTC-catalyzed asymmetric flourinative dearomatization reaction of phenols reported by Toste.

was recently realized by Wang and coworkers.[31] Like the reaction discussed in Scheme 11,[15] the chiral magnesium catalyst generated *in situ* by reaction of $^{n}Bu_2Mg$ 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 alkylative, 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[32] 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 naphthols **54** was realized by You and coworkers in 2015.[33] Using $(DHQD)_2PHAL$ 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 dearomative chlorination of 1-naphthol derivative **56** was also realized with high enantioselectivity (Scheme 25).

3.6 Aminative dearomatization reactions

CADA reactions of phenol derivatives can also be achieved *via* electrophilic amination reactions. Recently, both Brønsted and Lewis acids have been employed as catalysts to activate azodicarboxylates **58** toward nucleophilic attack by naphthols **14**. This dearomatization reaction can furnish aminated-naphthalenones **59** featuring a tertiary amine moiety in mostly excellent yields and ee (Scheme 26).

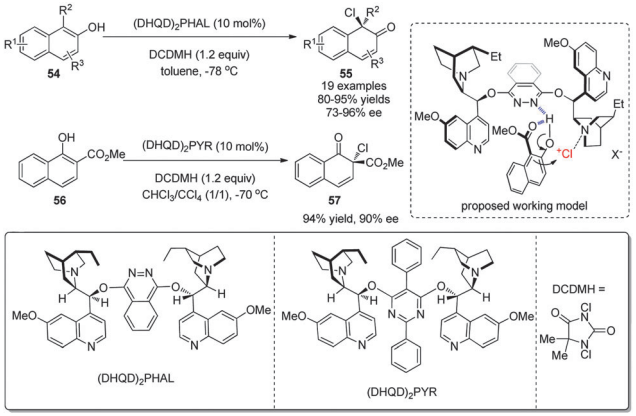
In 2015, You and coworkers[34] realized this type of reactions by using chiral phosphoric acid (CPA) as catalyst. Notably, the catalyst loading can be as low as 0.1 mol% without affecting the yields and enantioselectivity. Intriguingly, **C13** was found to be the optimal catalyst when the substituent on the naphthol 3-position is H.

Besides chiral Brønsted acids, the chiral Sc(III)/pybox complexes derived from **L10** and **L11** were employed by Luan and coworkers[35] in the same year as effective catalysts for the same aminative dearomatization reactions, affording **59** in excellent yields and ee.

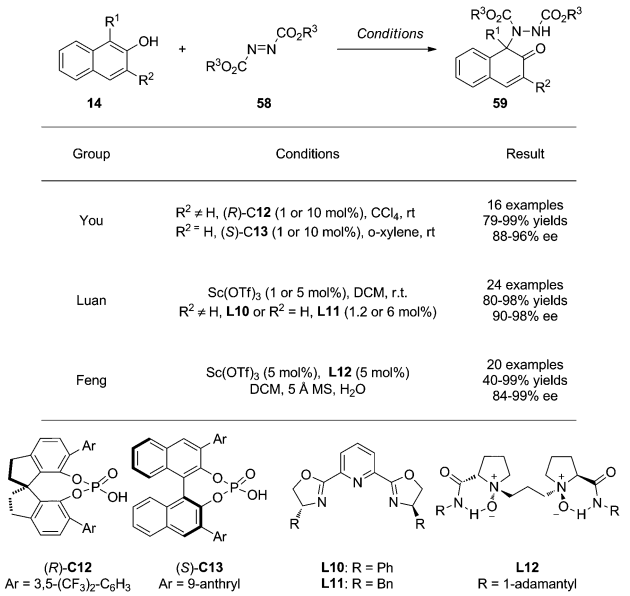
Moreover, the combination of $Sc(OTf)_3$ and the *N*,*N*′-di-oxide **L12**, developed by Feng's group, is also highly effective in achieving the aminative dearomatization reaction in good to superb yields and with excellent enantioselectivity.[36]

3.7 Rearrangement dearomatization reactions

Inspired by the dearomatizing [3,3]-sigmatropic diaza-Cope rearrangement in the Fischer indole synthesis, List and coworkers recently developed an asymmetric version of this



Scheme 25 Organocatalytic asymmetric chlorinative dearomatization reaction of naphthols reported by You.

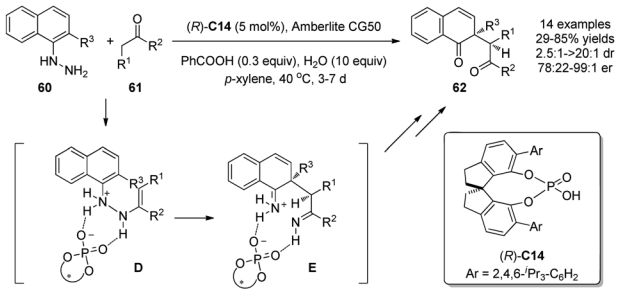


Scheme 26 Asymmetric dearomatization reaction of naphthols *via* amination reactions reported by You, Luan and Feng.

process by using chiral Brønsted acid (*R*)-**C14**.[37] This mild reaction converts aryl hydrazines **60** and ketones **61** to useful 1,4-diketones **62** possessing an all-carbon quaternary stereocenter with good to excellent enantioselectivity. It was proposed that the chiral Brønsted acid promotes the formation of the ene hydrazine intermediate **D** and facilitates its subsequent rearrangement to diimine **E**, which then undergoes hydrolysis instead of indole formation due to the nascent quaternary carbon center (Scheme 27).

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



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

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 be soon applied to other aromatic systems, thereby enabling CADA reaction as a general approach to the manipulation of aromatic compounds.

Acknowledgements

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