

HETEROCYCLES, Vol. 98, No. 11, 2019, pp. 1489 - 1511. © 2019 The Japan Institute of Heterocyclic Chemistry
Received, 8th October, 2019, Accepted, 28th October, 2019, Published online, 1st November, 2019
DOI: 10.3987/REV-19-916

ASYMMETRIC CONSTRUCTION OF HETEROCYCLES VIA DEAROMATIVE COUPLING AND ADDITION REACTIONS OF PHENOL AND ANILINE DERIVATIVES

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Abstract – Efficient methods for the formation of chiral heterocycles are considerably important in the synthesis of naturally-occurring compounds and pharmaceutical products. This review highlights the formation of chiral heterocycles through dearomative bond-formations as the key reactions, wherein the phenol or aniline derivatives serve as the nucleophiles. Transition-metal-catalyzed intramolecular coupling reactions in the presence of chiral ligands afford the enantioenriched multicyclic compounds bearing heterocycles. Chiral bifunctional organocatalysts induce the formation of dearomative coupling products, which could be converted to heterocycles through further transformations.

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1. INTRODUCTION

The dearomatization reactions are attractive synthetic strategies for the constructions of alicyclic skeletons from readily available aromatic precursors.¹ For example, phenol derivatives are industrially economical feedstocks for the production of various functionalized polymers and materials, while dearomatization of phenol derivatives economically affords the corresponding 2,4- or 2,5-cyclohexadienones, which could be synthetic intermediates for further transformations (Figure 1).² Phenol derivatives and their dearomatized forms are ubiquitous structures in natural products and bioactive compounds. The dearomatization reaction occurs through biosynthetic oxidation, which can also form the highly functionalized six-membered-ring-bearing chiral carbon center. Thus, the development of catalytic dearomative bond formation reactions, especially for constructing asymmetric heterocycles, would provide a facile strategy for the synthesis of complex organic molecules.

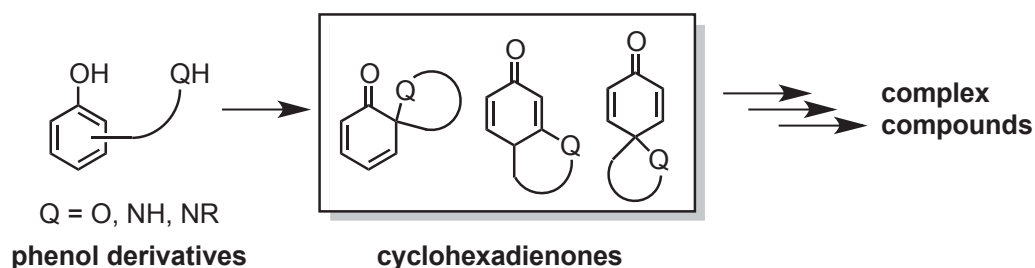


Figure 1. Dearomative bond formation of phenol derivatives for construction of cyclohexadienones

2. BACKGROUND

2.1 OXIDATIVE DEAROMATIZATION CATALYZED BY CHIRAL ARYL IODIDE

Over the past decades, various oxidative dearomatization reactions of phenol or naphthol derivatives to form spirocycles have been developed by using hypervalent iodine compounds, which are recognized as

mild and environmentally benign oxidants compared to toxic metal reagents.³⁻⁶ The combination of an oxidant and co-oxidant, such as *m*-chloroperbenzoic acid (*m*CPBA), facilitates the catalytic reactions for the dearomatization processes.^{7,8}

The first example of hypervalent-iodine(III)-catalyzed asymmetric dearomatization of 1-naphthol derivatives to form spirolactones bearing a chiral carbon center was achieved by the Kita and Dohi group in 2008 (Figure 2).⁹ In the presence of a chiral iodine(III) compound based on a rigid 1,1'-spirobiindane backbone, a 1-naphthol derivative with a carboxylic acid side chain underwent dearomative cyclization to afford the corresponding enantioenriched spirolactone. The combination of diiodide with *m*CPBA provides the efficient catalytic system. Furthermore, they optimized the catalyst structure to develop a functionalized spirobiindane bearing ethyl groups at the *ortho* positions of iodides.^{10,11} Since their pioneering works, various types of chiral iodoarenes have been reported for the catalytic dearomative spirocyclization.¹²⁻²²

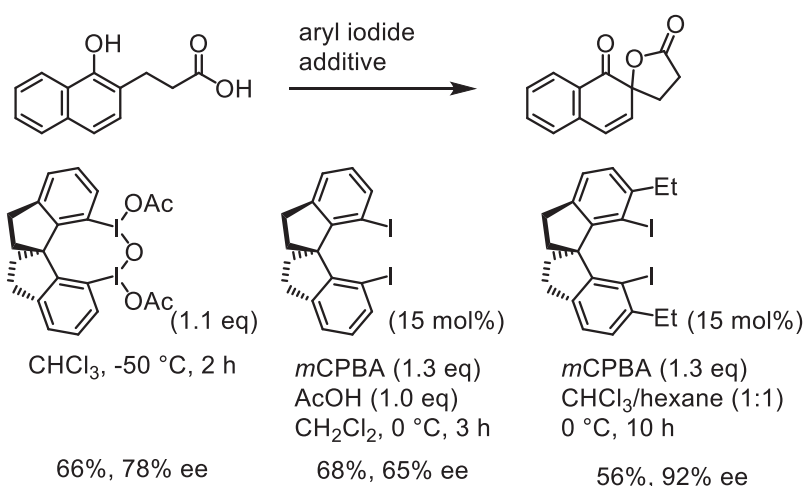


Figure 2. Chiral iodoarene-catalyzed dearomative heterocyclization developed by Kita and Dohi

2.2 OXIDATIVE DEAROMATIZATION VIA SET MECHANISM BY IRON COMPLEX

Owing to the resonance effect imparted by the hydroxy group, phenol derivatives can be also oxidized by metal oxidants to generate reactive intermediates. For example, several dearomatizing enzymes contain iron-active species that use dioxygen as a terminal oxidant. Moreover, metal oxidants including an iron center have been employed for the oxidative dearomative carbon-carbon bond formations.^{23,24}

The Katsuki group developed the iron-salan complexes for the oxidative coupling reactions of 2-naphthols, wherein a radical cation species generated from 2-naphthols through the one-electron oxidation is a key intermediate.^{23a} Without the appropriate nucleophile, the hydrogen atom abstraction of radical cation species occurs to generate an *ortho*-quinone methide (*o*-QM), which is a strong Michael

acceptor. Further investigation revealed the asymmetric synthesis of spirocyclic (*2H*)-dihydrobenzofuran through the *o*-QM formation/Michael addition/asymmetric oxidative dearomatization tandem reactions (Figure 3).^{23b,c} The reaction of 1,3-dimethyl-2-naphthol with phenol in the presence of the Fe(salan) catalyst afforded spirocyclic (*2H*)-dihydrobenzofuran in 86% yield with 91% ee.

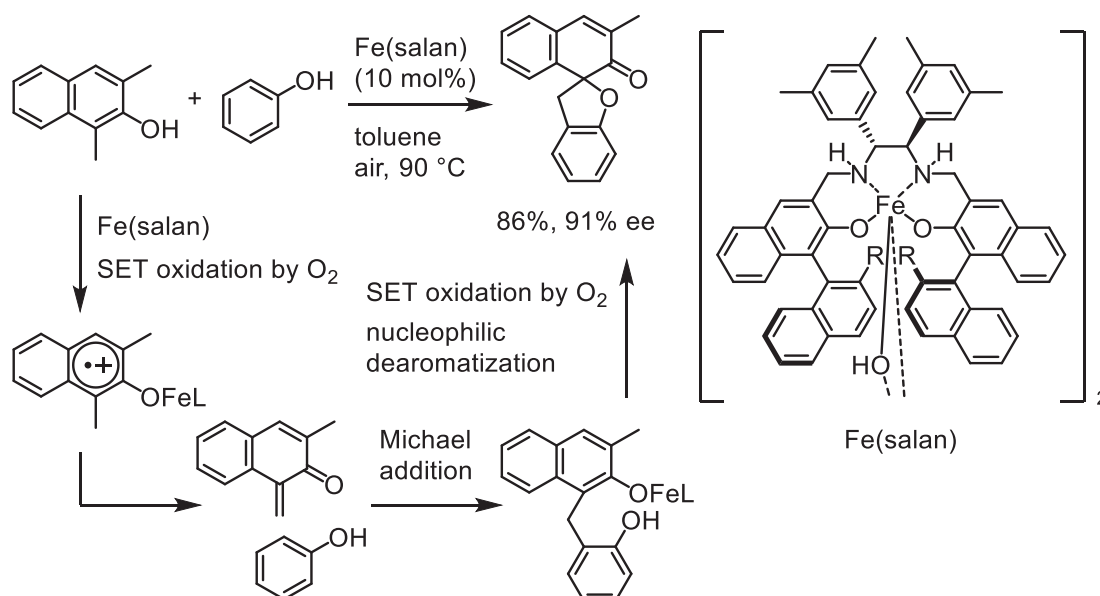


Figure 3. Iron-catalyzed oxidative dearomatization via SET reaction reported by Katsuki

2.3 TWO APPROACHES FOR DEAROMATIVE BOND FORMATIONS

As mentioned above, the oxidative dearomative bond formation of phenols has been achieved by a hypervalent iodine(III) or iron complex. In these reactions, phenol derivatives are activated by the electrophilic intermediate, such as phenoxy- λ^3 -iodine or iron phenoxide. The nucleophilic attack of carboxylic or hydroxy groups on these intermediates affords the corresponding products, spirolactones or spirocyclic ethers, respectively (Figure 4a). In general, however, phenol and aniline derivatives potentially serve as nucleophiles owing to the electron donation from oxygen or nitrogen atoms. The Friedel–Crafts reaction of these compounds with no substituent group at the *ortho*- or *para*-positions results in the aromatic substitution reaction through the nucleophilic attack followed by rearomatization. When the reaction position has a substituent group or the rearomatization step is slow, the dearomatization product could be generated (Figure 4b). The utilization of this reaction for cyclization by using an asymmetric catalyst could form chiral heterocycles. This review highlights the progress in the asymmetric construction of heterocycles through dearomatization reactions, in which phenol and aniline derivatives act as a nucleophile. Although considerable catalytic dearomative bond formations employing various aromatics have been developed, we focused on the reaction of phenol and aniline derivatives affording chiral heterocycles in single or a few steps. The details of each reaction are described in the

following sections, which are classified on the basis of the reaction types.

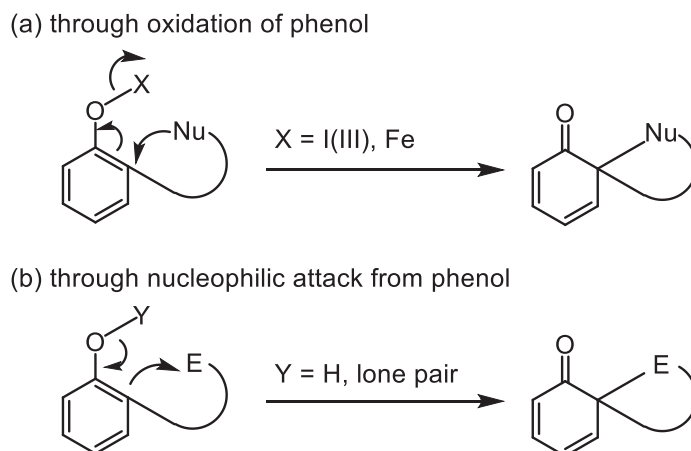


Figure 4. Two approaches for dearomative bond formations (Nu = nucleophile, E = electrophile)

3. CARBON-CARBON BOND FORMATION CATALYZED BY TRANSITION METAL

The transition-metal-catalyzed coupling reaction forming carbon-carbon and carbon-heteroatom bonds is an effective tool for the synthesis of natural products, pharmaceuticals, and functional materials.²⁵ Various combinations of transition-metal catalysts and chiral ligands have been developed to achieve the enantioselective bond formation, including the formation of chiral all-carbon quaternary centers. For example, the palladium-catalyzed cross-coupling reaction typically starts from the generation of organopalladium intermediates (R-Pd-X) (Figure 5a).²⁶ In the presence of nucleophiles (Nu-H), ligand exchange occurs in the presence of a base to give the intermediate (R-Pd-Nu), which undergoes reductive elimination to form the corresponding cross-coupling products (R-Nu). Alternatively, the direct substitution reaction of nucleophiles with an organometallic intermediate leads to the formation of products.

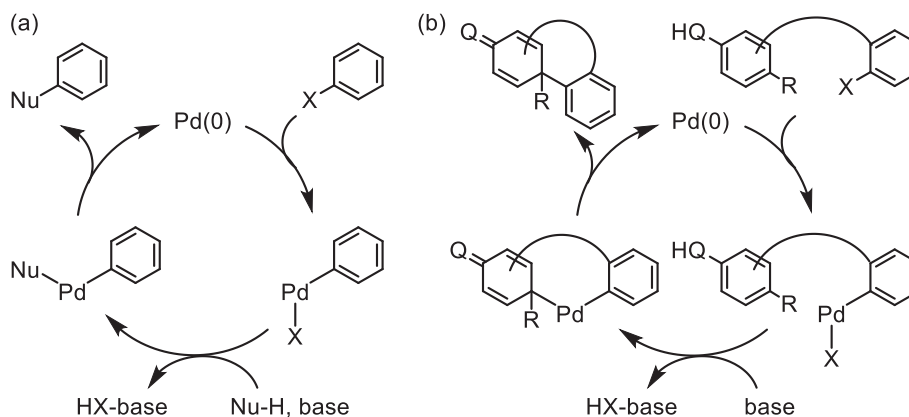


Figure 5. Palladium-catalyzed cross-coupling of Ar-X with nucleophile (X = halogen)
 (a) General catalytic cycle (b) Intramolecular dearomative coupling (Q = O or NR')

Employing phenol or aniline derivatives as a nucleophile for the enantioselective intramolecular coupling reaction can facilitate the asymmetric dearomative construction of the cyclization product (Figure 5b). In the following section, dearomative carbon-carbon bond formations through the transition-metal-catalyzed coupling reaction generating asymmetric heterocycles are introduced.

3.1 DEAROMATIVE ARYLATION WITH PALLADIUM CATALYST

In 2009, the Buchwald group reported the first asymmetric transition-metal-catalyzed dearomatization for the formation of an all-carbon quaternary stereocenter through an intramolecular electrophilic aromatic substitution-type reaction.^{27a} 1-Aminonaphthalene was converted to 6a-phenyl-6a*H*-benzo[*a*]carbazole in 96% yield with 93% ee in the presence of Pd(dba)₂ (3 mol%), 2-*N,N*-dimethylamino-2'-dicyclohexylphosphino-1,1'-binaphthyl (KenPhos) (6 mol%), and LiO*t*Bu (1.2 eq) in THF at 70 °C (Figure 6). Other chiral binaphthylphosphine and cyclohexylphosphine ligands also produced the desired product, whereas the Phox ligand or phosphoramidite derivative resulted in the recovery of the substrate. The deprotonation of amine increased the electron density of the naphthyl group, which reacts with the palladium(II) center generated through oxidative addition to afford the cyclization product. In 2011, the same group developed a palladium-catalyzed dearomative cyclization employing phenol derivatives that forms chiral spirocyclohexadienones, although construction of heterocycles was not demonstrated.^{27b} Since the pioneering works by the Buchwald group, catalytic dearomative intramolecular coupling reactions forming various chiral heterocycles have been examined. You and co-workers employed *para*-aminophenol derivatives to construct chiral spiroheterocycles including an erythrinan skeleton.²⁸ The reaction of the 5-hydroxyindoline derivative with the combination of the [Pd(C₃H₅)Cl]₂ catalyst and 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (RuPhos) produced the corresponding tetracyclic compound in 90% yield (Figure 7). Moreover, chiral ligands were found to induce asymmetric cyclization, although optimization is required for achieving satisfactory reactivity and enantioselectivity. The authors applied the dearomatization reaction to the synthesis of 3-demethoxyerythratidinone (Figure 8).

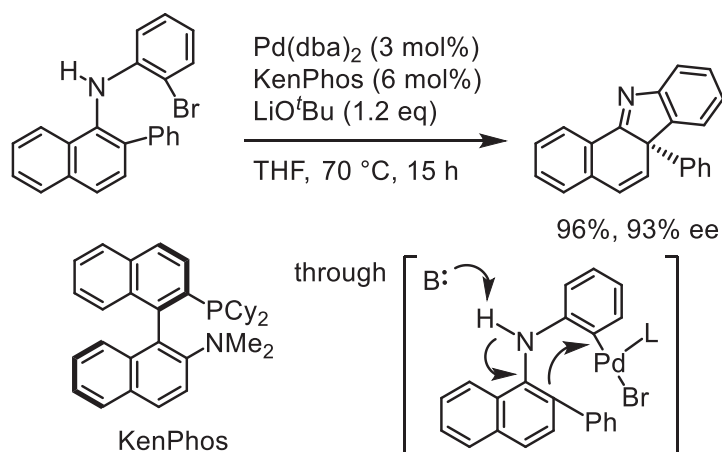


Figure 6. Palladium-catalyzed dearomative arylation reported by Buchwald group

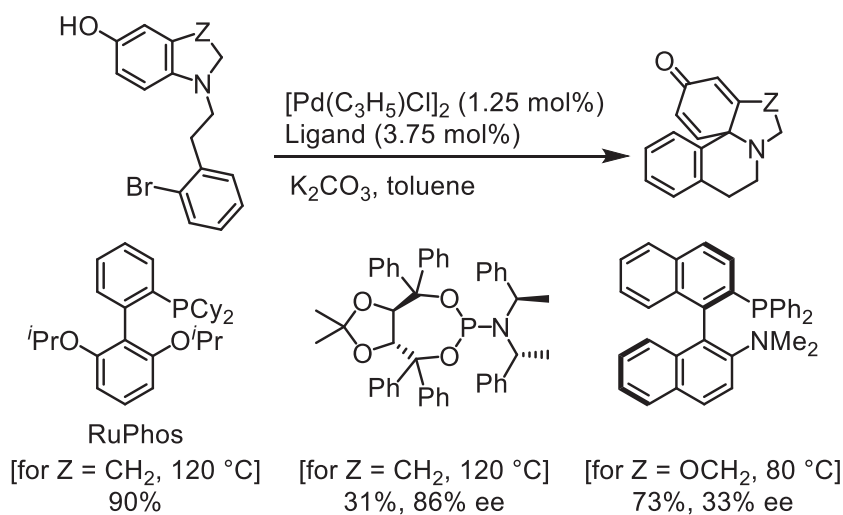


Figure 7. Palladium-catalyzed dearomative arylation reported by You group

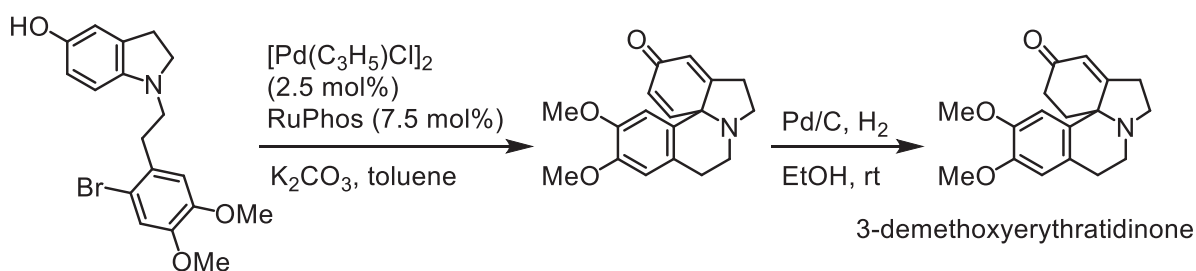


Figure 8. Asymmetric synthesis of 3-demethoxyerythratidinone

The Tang group employed benzylaminophenols as a starting material to synthesize a chiral 6,10b-dihydrophenanthridin-3(5H)-one skeleton.^{29,30} A phosphoramidite-protected benzylamine underwent enantioselective dearomative cyclization to give the desired product bearing all-carbon quaternary center

in 96% yield with 96% ee in the presence of the $[\text{Pd}(\text{cinnamyl})\text{Cl}]_2$ catalyst, 4-(anthracen-9-yl)-3-(*tert*-butyl-2,3-dihydrobenzo[*d*][1,3]oxaphosphole) (AntPhos), and K_2CO_3 (Figure 9). On the other hand, other protecting groups, such as sulfonyl groups, gave the mixture with the undesired biaryl product. Furthermore, the same group achieved the total synthesis of (–)-crinine and (–)-aspidospermidine by using the chiral dearomative cyclization products prepared by their reaction systems (Figure 10).

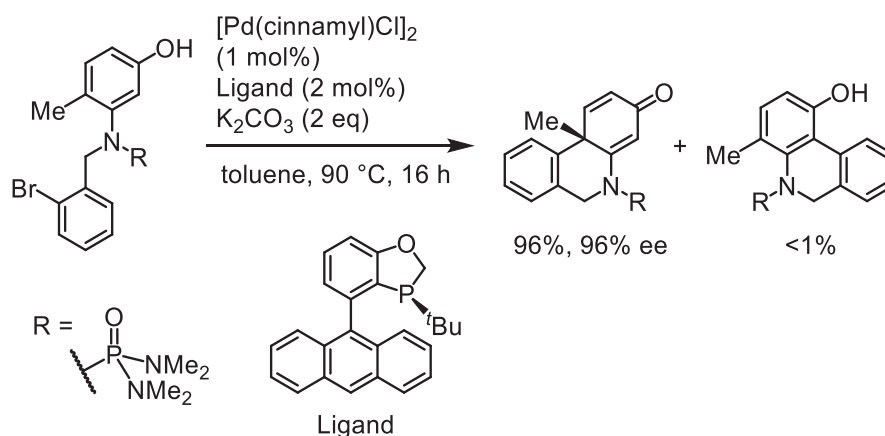


Figure 9. Palladium-catalyzed dearomative arylation reported by the Tang group

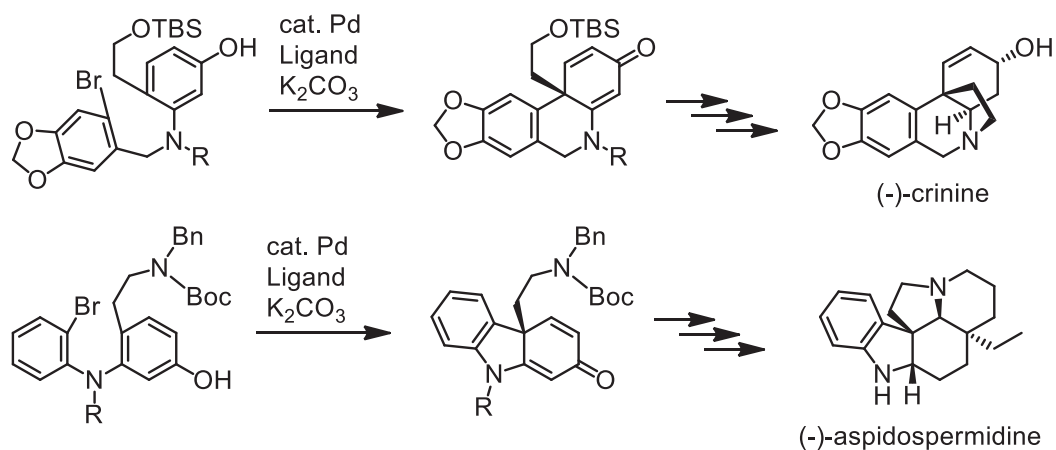


Figure 10. Preparation of synthetic intermediates for (–)-crinine and (–)-aspidospermidine

3.2 DEAROMATIVE ALLYLATION WITH IRIIDIUM CATALYST

Hamada reported the palladium-catalyzed intramolecular dearomative allylation of phenols bearing allyl carbonate for the formation of substituted spirocyclohexadienones.³¹ In this reaction, the allylpalladium complex served as an electrophile, which is generated through the decarboxylation of allyl carbonate. The You group developed an asymmetric version of this dearomative allylation by employing an iridium complex with a chiral ligand.³² In the presence of 4 mol% of $[\text{Ir}(\text{cod})\text{Cl}]_2$, 8 mol% of chiral

phosphoramidite ligand, and 2 equiv of Li_2CO_3 , the phenol derivative gave enantioenriched spirocyclohexadienones with NTs linked five-membered-ring in 92% yield with 95% ee (Figure 11). The chiral iridium complex was generated in situ, and then the dearomative allylation proceeds to construct the heterocyclic ring with the chiral carbon.

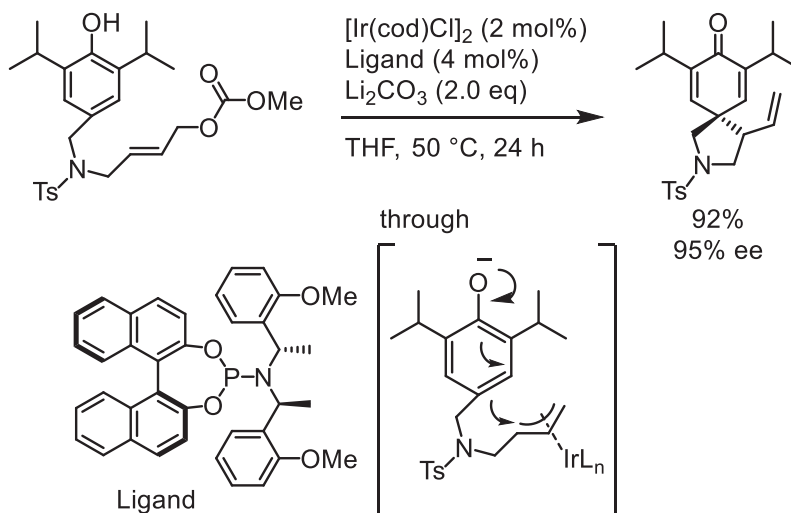


Figure 11. Iridium-catalyzed dearomative allylation reported by the You group

3.3 DEAROMATIVE ALKENYLATION/ARYLATION WITH GOLD CATALYST

The above mentioned catalytic asymmetric dearomatization reactions have focused on the oxidative single C–C bond formation. The Tanaka group demonstrated the first example of the dearomative intramolecular double C–C bond formation induced by a cationic platinum catalyst.³³ They applied this system to the asymmetric dearomatization reaction in the presence of a chiral gold catalyst.^{34a} The treatment of 3-benzyl-substituted propiolic acid 1-naphthylamide in the presence of a cationic gold(I) catalyst, $\text{AuCl}(\text{SMe}_2)$, combined with 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) and AgBF_4 afforded the corresponding pentacyclic compounds, wherein the double C–C bond formation proceeded at the *ipso/ortho* or *ipso/para* positions (Figure 12, top). On the other hand, the combination of PtCl_2 with BINAP failed to form the dearomative products. The use of (*R*)-xyl-BINAP and AgSbF_6 improved the yields and selectivities. The isolated chiral gold(I) catalyst, (*R*)-xyl-BINAP- $(\text{AuCl})_2$, was also effective to form the dearomatization products. Further investigation disclosed that various alkynyl 1-naphthylamides could be employed to afford the corresponding pentacyclic compounds (Figure 12, bottom).^{34b}

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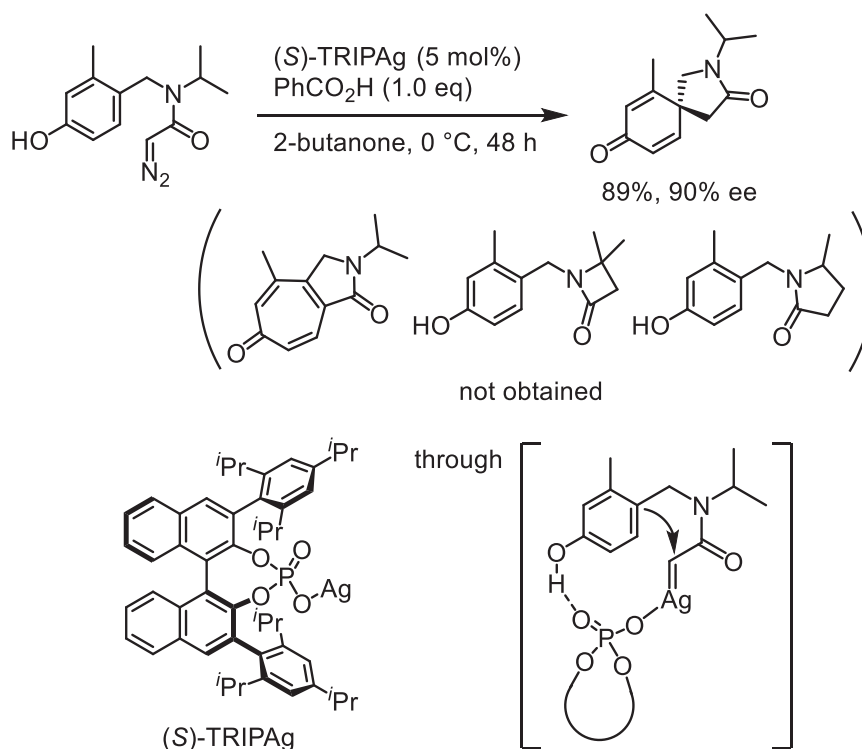


Figure 13. Silver-catalyzed dearomative C-H insertion reported by the Nemoto group

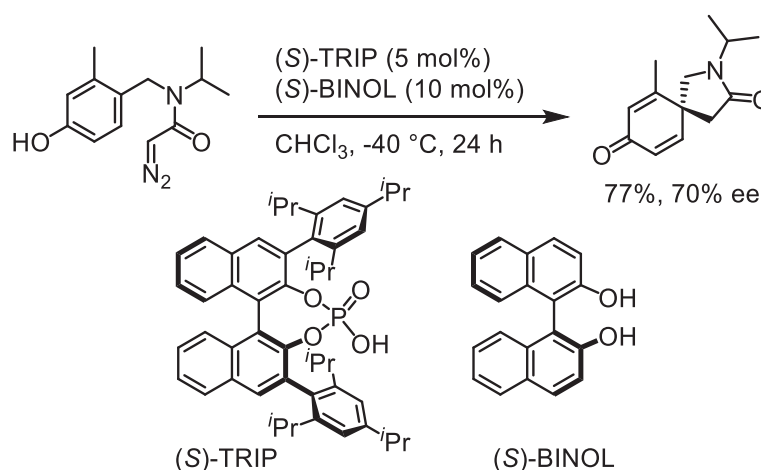


Figure 14. Dearomative C-H insertion catalyzed by Brønsted acid

4. DEAROMATIVE MICHAEL ADDITION WITH ORGANOCATALYST

Asymmetric bond formations through the reaction of nucleophiles with carbonyl compounds, such as aldol reaction, Mannich reaction, and Michael addition, have been achieved by using organocatalysts.³⁸ Chiral thiourea³⁹ and phosphoric acid⁴⁰ catalysts are examples of the bifunctional organocatalysts, which have base and acid moieties in the same molecules. The double activation of both nucleophiles and

electrophiles by the bifunctional base and acid moieties, through non-covalent hydrogen bonding, is an effective strategy for the asymmetric bond formations (Figure 15). By using phenol derivatives as a nucleophile, similar to an enole, with a bifunctional organocatalyst, enantioselective dearomative carbon-carbon bond formations can proceed. In the following section, the reactions of 2-naphthols with Michael acceptors in the presence of chiral thiourea or phosphoric acids are described. Although the intramolecular cyclization through the dearomative Michael addition has not yet been reported, heterocycles are readily constructed by the additional transformations.

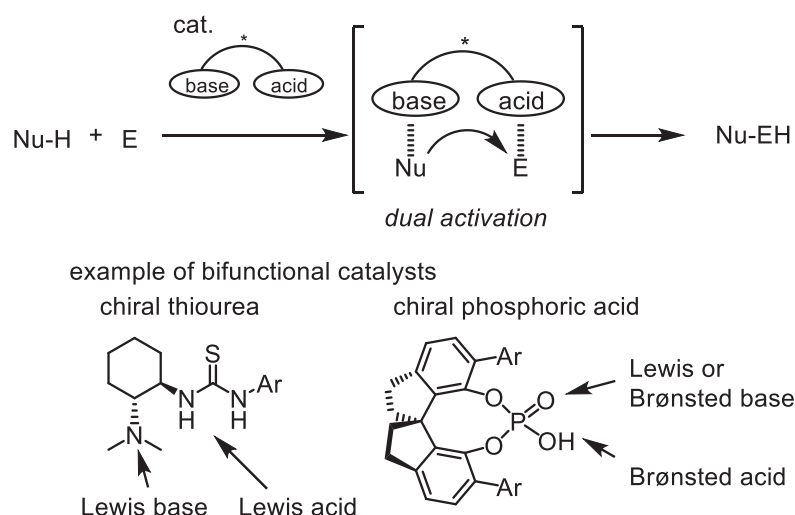


Figure 15. Asymmetric bond formation using chiral bifunctional organocatalysts

4.1 DEAROMATIVE MICHAEL ADDITION WITH CHIRAL THIOUREA CATALYST

The You group used chiral thiourea catalysts for the activation of nitroethylene to achieve the asymmetric dearomatization reaction of naphthol.⁴¹ In the presence of thiourea catalysts, the reaction of 2-naphthol with nitroethylene proceeded to afford the enantioenriched Michael addition product in 79% yield with 97% ee (Figure 16). The thiourea catalyst is considered to serve as a bifunctional catalyst, wherein the two N-H bonds of the thiourea moiety and the tertiary amine would interact with nitroethylene and the hydroxy group of 2-naphthol, respectively, through hydrogen bonding. Therefore, the two substrates are oriented in a highly ordered conformation, facilitating the *Re* face attack of 2-naphthol on the β -carbon atom of nitroethylene. The reduction of nitroethane-substituted β -naphthalenones produced a tricyclic compound, which was converted to the pyrrolidine-fused tetralin (Figure 17).

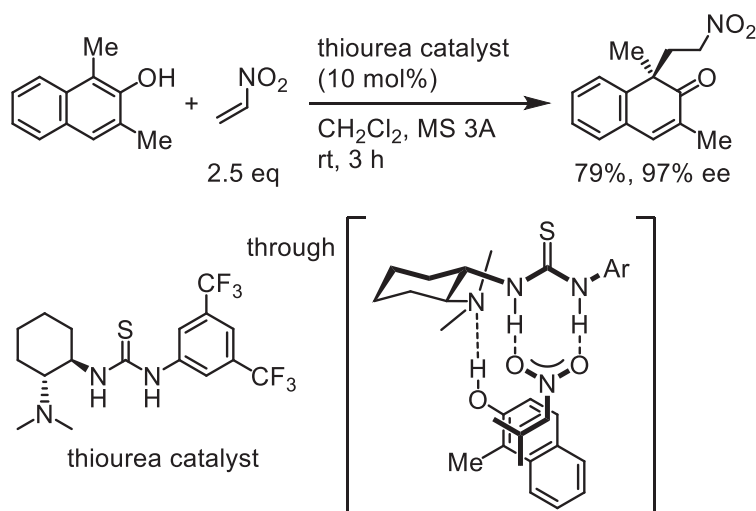


Figure 16. Dearomative Michael addition with thiourea catalyst reported by the You group

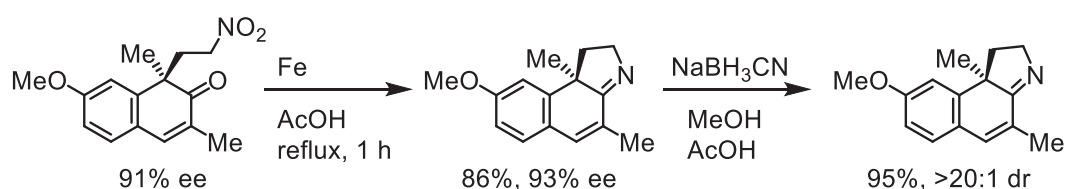


Figure 17. Construction of chiral pyrrolidine-fused tetralin

4.2 DEAROMATIVE MICHAEL ADDITIONS WITH CHIRAL PHOSPHORIC ACIDS

Quinone derivatives were also used as the Michael acceptor for the dearomative bond formations in the presence of chiral phosphoric acid.⁴² The reaction of 1,3-dimethyl-2-naphthol with quinone in CH₂Cl₂ at room temperature for 36 h produced the dearomatization product bearing quinone in 95% yield with 98% ee, which was induced by spirocyclic phosphoric acid (Figure 18). In this reaction, the chiral phosphoric acid serves as a bifunctional catalyst activating both substrates, and the Michael addition proceeds to give the enol product, which is transformed to the quinone derivative through tautomerization followed by oxidation. The resulting product was converted to dihydrobenzofuran derivatives by the treatment with sodium borohydride and dehydration.

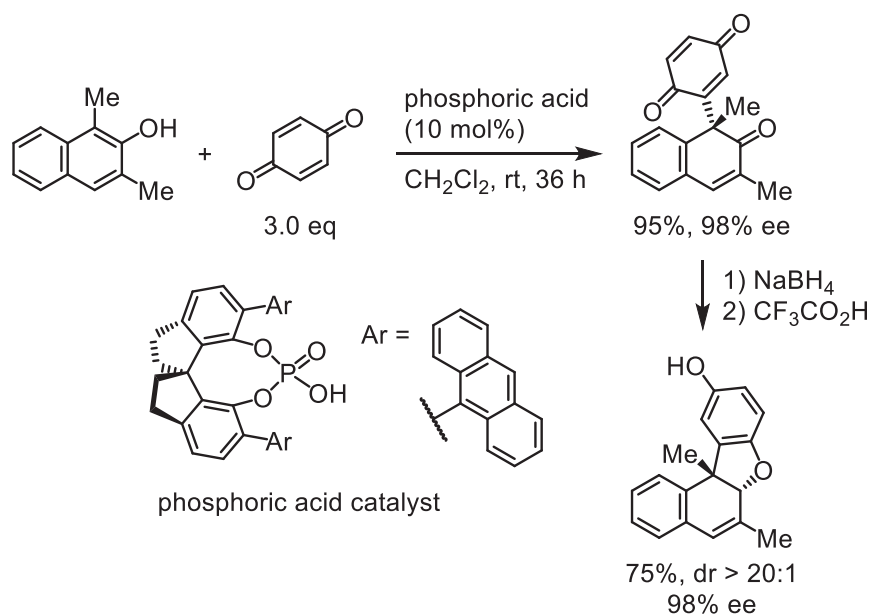


Figure 18. Dearomative Michael addition with quinone catalyzed by phosphoric acid

The Chen and Zhou group employed quinone monoimides, which can transform to aryl groups through aromatization without further oxidation as the Michael acceptor.⁴³ The enantioselective dearomative bond formation proceeded with the chiral phosphoric acid rather than a thiourea catalyst. Treatment of 1-methyl-2-naphthol with 1.5 equiv of quinone monoimide in the presence of 10 mol% of chiral phosphoric acid in CH_2Cl_2 at $-78\text{ }^\circ\text{C}$ for 41 h afforded the desired dearomative arylation product in 99% yield with 97% ee (Figure 19). The desired enantioenriched cyclohexadienones with an all-carbon quaternary stereocenter were prepared with excellent yields and enantioselectivities. Hydrogenation of the resulting product produced hemiketal (Figure 20). Dihydrobenzofuran derivative was obtained through reduction followed by intramolecular etherification.

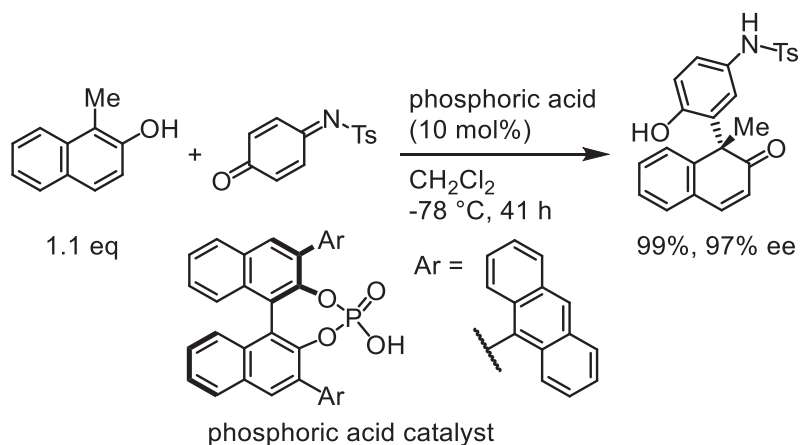


Figure 19. Dearomative Michael addition with quinone monoimide catalyzed by phosphoric acid

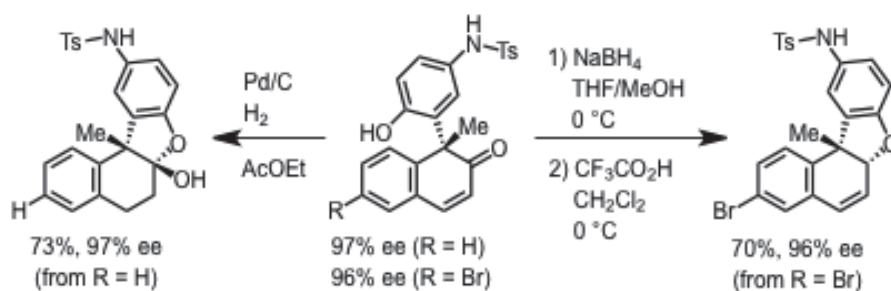


Figure 20. Transformations to chiral dihydrobenzofurans

5. DEAROMATIVE CARBON-HETEROATOM BOND FORMATIONS

The above mentioned dearomatization reactions would generate not only carbon-carbon bond, but also carbon-heteroatom bond by employing the corresponding heteroatom electrophiles. Asymmetric cyclizations through dearomative carbon-heteroatom bond formation has not been reported, whereas the dearomatization reactions employing chiral hypervalent iodine(III) or iron complex catalysts provide spiroheterocycles^{3–23} In the following section, the formation of heterocycles through the asymmetric introduction of heteroatom followed by cyclization is described.

5.1 DEAROMATIVE AMINATION

Chiral α -amino carbonyl compounds are valuable building blocks for biologically active compounds and natural products. Enantioselective amination of carbonyl compounds has been achieved by using azodicarboxylates as an electrophile. In 2015, three research groups independently demonstrated the asymmetric dearomative carbon-nitrogen bond forming reaction with azodicarboxylates.^{44–46}

The You group employed the chiral phosphoric acid as an activation catalyst.⁴⁴ The reaction of 1,3-dimethyl-2-naphthol with diethyl azodicarboxylate (DEAD) in the presence of a spirobiindane-type phosphoric acid afforded the α -amino carbonyl compounds quantitatively with 96% ee (Figure 21). On the other hand, the Luan group and the Feng group independently reported that scandium salt can induce the same reaction in the presence of appropriate ligands. The former group employed commercially available bis(oxazolonyl)pyridine (PyBOX) as the ligands.⁴⁵ The reaction of 1,3-dimethyl-2-naphthol with DEAD proceeded to form the corresponding product in 92% with 94% ee in the presence of a catalytic amount of $\text{Sc}(\text{OTf})_3$ and PyBOX bearing benzyl groups (Figure 22). The latter group demonstrated the combination of chiral N,N' -dioxide ligand and $\text{Sc}(\text{OTf})_3$ for the asymmetric dearomative amination.⁴⁶ When the chiral N,N' -dioxide bearing an adamantyl group was used with molecular sieves 5A and water, the asymmetric dearomative amination proceeded quantitatively with 95% ee (Figure 23).

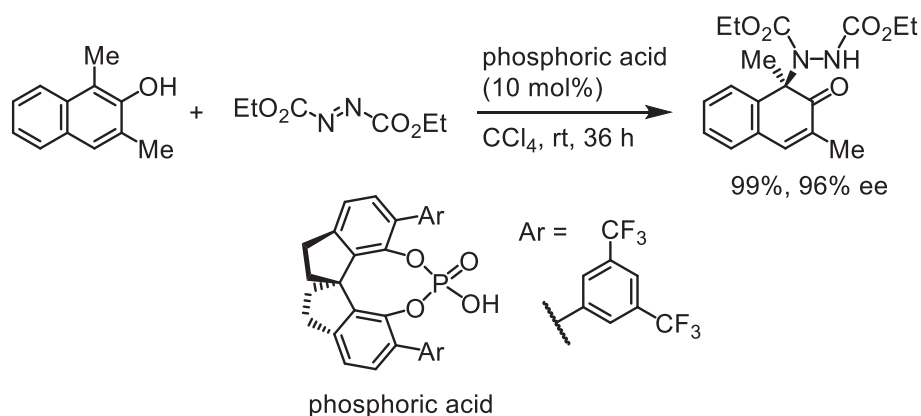


Figure 21. Dearomative coupling with azodicarboxylate catalyzed by phosphoric acid reported by You

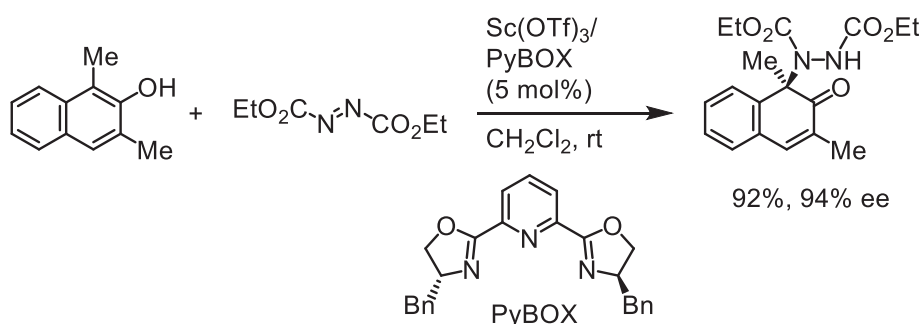


Figure 22. Scandium-catalyzed dearomative coupling with azodicarboxylate reported by Luan

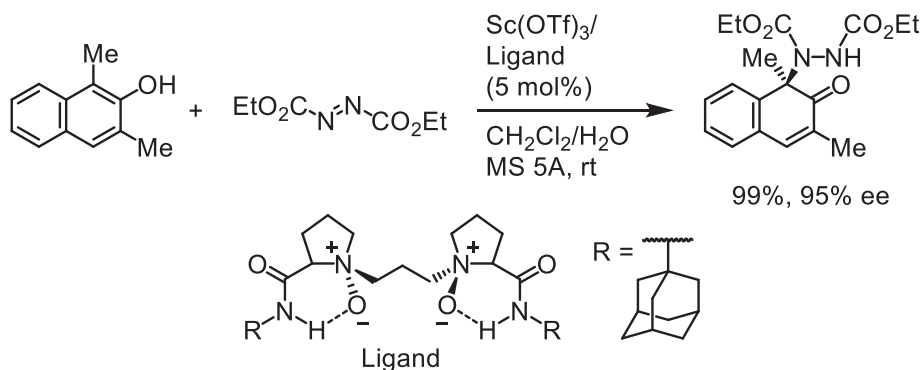


Figure 23. Scandium-catalyzed dearomative coupling with azodicarboxylate reported by Feng

The amination product from 1-allylated 2-naphthol was further transformed to spiroheterocyclic compounds through bromoamination or cross-metathesis/aza-Michael addition sequence (Figure 24). Furthermore, the reduction of the enone group produced cyclic carbamate in a high diastereoselective manner.

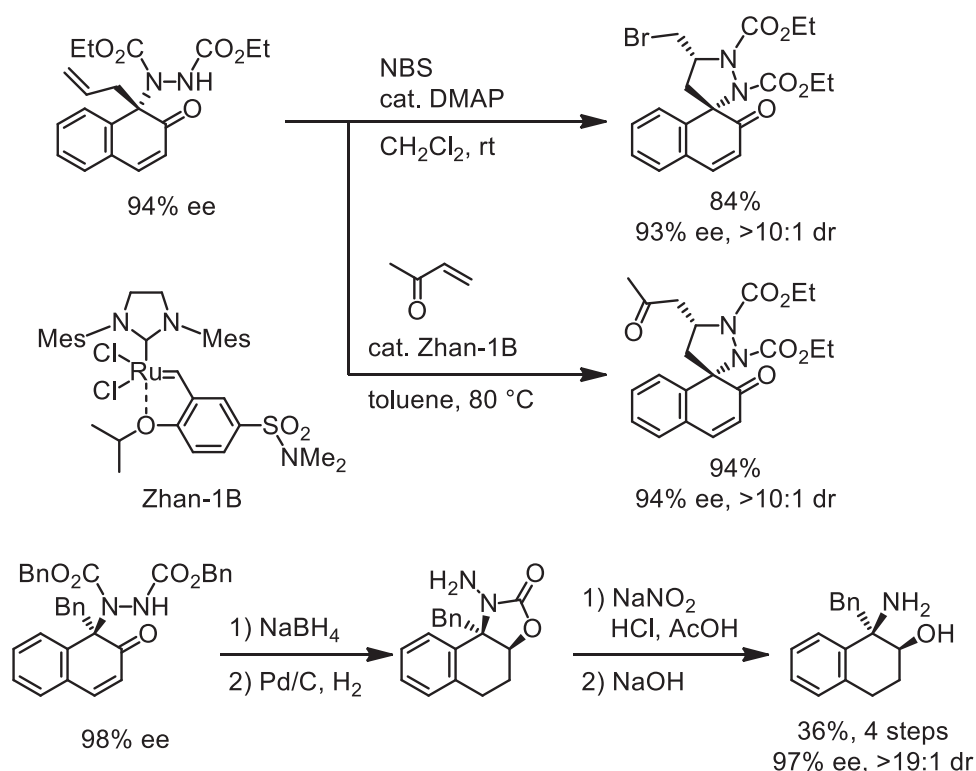


Figure 24. Transformations to heterocycles

5.2 DEAROMATIVE CHLORINATION

The Toste group demonstrated an enantioselective dearomative fluorination of phenols in the presence of chiral anion phase-transfer catalysis.⁴⁷ Inspired by the pioneering work, the You group developed the asymmetric dearomative chlorination of naphthols with homogeneous catalysis.⁴⁸ The reaction of 2-naphthol derivative with 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) as a chlorine source in the presence of 2 mol% hydroquinidine-1,4-phthalazinediyl diether ((DHQD)₂PHAL) afforded the chlorination product in 98% yield with 90% ee (Figure 25). Background reaction or undesired reactions such as electrophilic aromatic substitution at the *ortho*- or *para*-position did not proceed at all. 1-Naphthol derivative also gave the corresponding product in the presence of hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether ((DHQD)₂PYR). The chlorination product was converted to the asymmetric epoxide in 50% yield with high diastereoselectivity (>20:1) through the reduction of the carbonyl group followed by the treatment with NaOH aq.

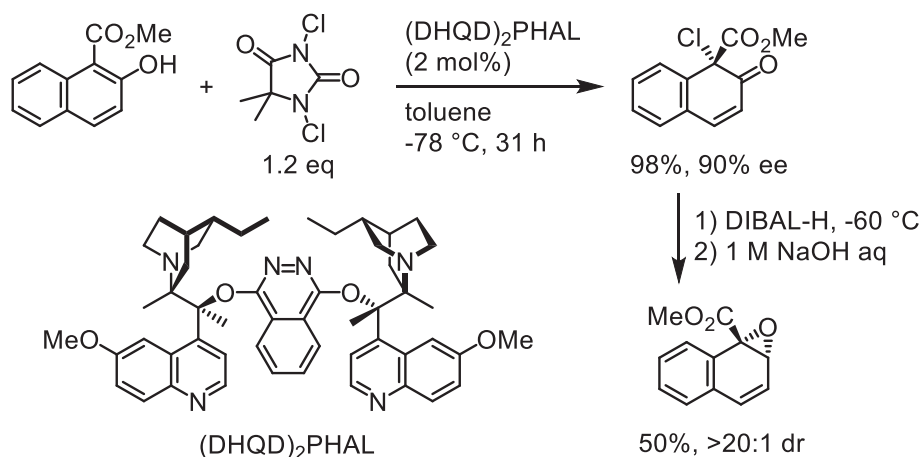


Figure 25. Dearomative chlorination with chiral organocatalyst followed by epoxidation

6. CONCLUSIONS

The catalytic asymmetric construction of heterocycles through the dearomative bond formation was achieved by the oxidation of phenol derivatives, intramolecular C–C coupling, and addition reactions. In the first cases, the reactions of phenol derivatives with oxidants, such as the hypervalent iodine(III) or iron complex, generated the electrophilic species, which react with the nucleophiles to form the dearomative products. On the other hand, the latter two cases involved the nucleophilic attack from phenol or aniline derivatives on the electrophiles activated by transition-metal catalysts or organocatalysts producing the dearomatized product, wherein the rearomatization reaction does not proceed due to the presence of the aromatic substituent groups.

The catalytic dearomative bond formations described in this review explained the formation of various attractive skeletons, such as cyclohexadienone, heterocycles, spirocycles, and chiral carbon including the all-carbon quaternary center. The strategies provided an effective tool for the synthesis of complex molecules bearing the chiral heterocycles, although some limitations exist, such as expansion of coupling partners and application for total synthesis. It is expected that further facile strategies for the construction of chiral heterocycles through dearomative bond formations will be designed and conducted for the development of asymmetric bond formations.

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