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# Catalytic dehydrogenative aromatization of cyclohexanones and cyclohexenones

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Phenols and phenol derivatives serve as synthetic building blocks for the construction of compounds ranging from polymers to pharmaceuticals. Despite numerous methods for phenol synthesis, the catalytic dehydrogenation of carbocyclic compounds such as cyclohexanones and cyclohexenones to generate substituted phenol derivatives has received much attention. This review describes recent research progress concerning catalytic dehydrogenative aromatization and $I_2$ promoted oxidative aromatization reactions in view of the types of cyclohexanone and cyclohexenone substrates and reactions, including the associated mechanisms and developments.

## 1 Introduction

Aromatic compounds are a ubiquitous class of molecules. Besides their tremendous use as organic solvents, dyes, polymers and precursors for the food industry, aromatic moieties represent the core skeleton involved in countless essential biological processes. Consequently, modern medicinal and pharmaceutical chemists have actively pursued the synthesis of novel aromatic molecules.

Phenols are an important class of aromatic compounds with many uses; these include, but are not limited to, pharmaceuticals, herbicides, electronic materials, and polymeric materials.[1] Among them, chiral phenols are one of the most important class of natural products and bioactive substances with a wide range of biological activities such as Pteroside,[2] Catechin,[3] Tolterodine,[4] Myristinin A,[5] etc.[6] From a synthetic viewpoint, the development of methods to construct phenols is a topic of growing interest.[7] Accordingly, methods to prepare phenolic compounds have been developed throughout the history of organic chemistry. Most of the methods for the preparation of substituted phenols involve various kinds of modifications of aromatic precursors (Scheme 1).

Among the many processes utilized in practice, the so-called Cumene process (Scheme 1a) that involves the partial oxidation of cumene followed by rearrangement chemistry (Hock process) is widely utilized as the most practical industrial process to replace the classical sulfonation or chlorobenzene (Scheme 1b) followed by alkali fusion (Dow process).[8] Electrophilic aromatic substitutions (Scheme 1c) promoted by the strong electron directing effect of the hydroxyl group are classical chemical reactions that remain among the most versatile methods for the synthesis of substituted phenols; however, the strong electron directing effects associated with these reactions limit their utility in the preparation of *ortho*- and *para*-substituted derivatives.[9] The selective synthesis of substituted phenols typically relies on the introduction of chemical functional groups to the aromatic ring with patterns of metal-catalyzed hydroxylation of aryl halides (Scheme 1d),[10] and C–H activation and hydroxylation of arenes (Scheme 1e).[11] Many complementary approaches leading to substituted phenols make use of Sandmeyer hydroxylation reactions (Scheme 1f)[12] and anodic oxidation[13] (Scheme 1g). The main restriction of this approach lies in the activating or deactivating and orienting effects of the substituents that limit the application of the synthetic methods, and the introduction of chemical functional groups with specific patterns around the aromatic ring is a key challenge in the preparation of these molecules.

Although there are a large number of classical and modern methods for the synthesis and structural modification of the phenol scaffold, the development of alternative approaches for the straightforward preparation of structurally diverse phenols is a field of constant interest.[14]

Dehydrogenative aromatization is one of the most important oxidative transformations in organic synthesis and cyclohexanones and cyclohexenones are cheap and stable and are widely used as raw materials to prepare many important bulk chemicals including aromatic phenols and phenolic derivatives.[15] It has been known for many years that cyclohexanones can be dehydrogenated into phenol. Indeed, the transformation of cyclohexanones into phenols dates back to the early

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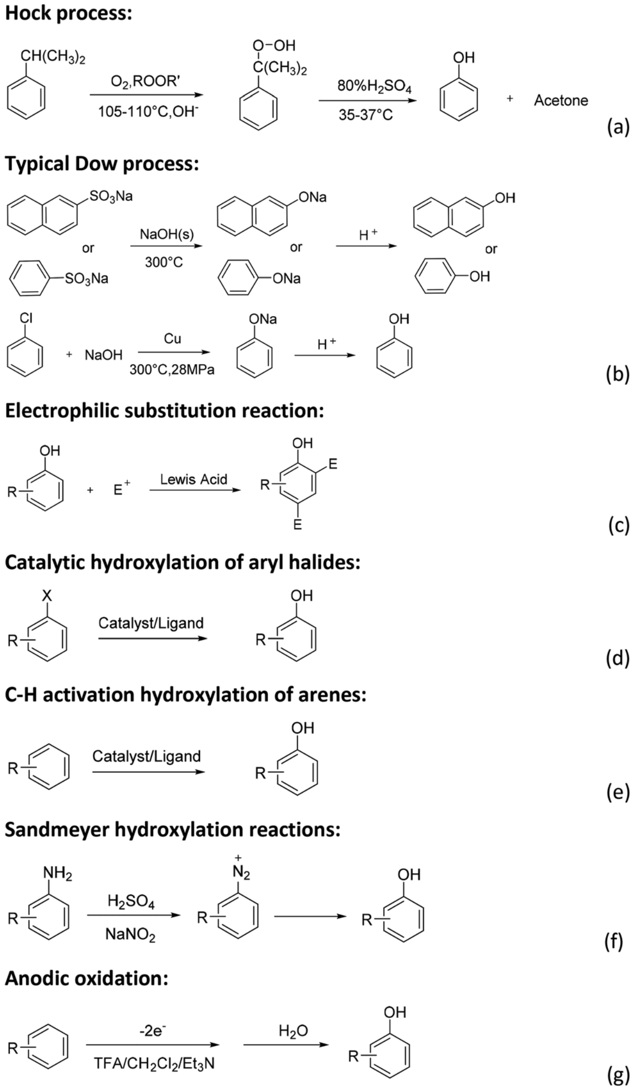


**Scheme 1** Access to phenol and phenol derivatives; R = H or alkyl group, X = halogen.

twentieth century,[16] with chloranil and DDQ being the classic and useful stoichiometric dehydrogenation reagents.[17] Substitution reactions of the α-position of ketones with halogens,[18] sulfur,[19] and selenium[20] groups, with subsequent elimination of these groups, are stoichiometric and cumbersome procedures for the preparation of α,β-unsaturated ketones which undergo a second dehydrogenation followed by tautomerization to yield the desired phenol product. However, most of reported methods for the synthesis of phenols *via* oxidative dehydrogenation of cyclohexanones have met with a limited degree of success in regard to atom economy. The low yields, the use of a stoichiometric reagent as a hydrogen acceptor, harsh reaction conditions and long reaction time are undesirable, especially for synthesis on a technical scale.

Along with the rapid development of catalytic chemistry in the last few decades, a wide range of aromatization strategies have been explored and successfully employed, including the transition-metal-catalyzed[21] and non-metal catalytic[22] aromatization of cyclic compounds, such as cyclohexanones and cyclohexenones.

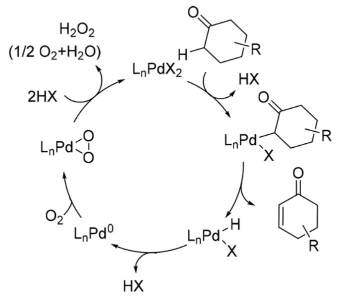
Despite the rather extensive literature on dehydrogenation, almost no comprehensive review of this topic is available in recent years. An earlier comprehensive review by Harvey in 1978[21a] was directed toward dehydrogenation of polycyclic hydroaromatic compounds. Numerous examples of the use of palladium-catalysed cycloaddition and coupling, anodic oxidation monohydroxylation and other methods for the synthesis of phenols were summarized by George in 2000.[14e] Molecular iodine, as an expedient reagent for oxidative aromatization reactions of all types of α,β-unsaturated ketones and cyclic compounds, was reviewed by Banerjee[22c] and Mphahlele.[22d] More recently, different direct stoichiometric and catalytic palladium procedures leading to α,β-unsaturated carbonyl compounds from the corresponding ketones, aldehydes, esters, lactones and amides were summarized by Muzart in 2010,[21c] and mini-reviews of Pd-catalysed aerobic dehydrogenation of C–H bonds in cyclohexanones were surveyed by Keβler and Prechtl in 2012.[7k] A review and summary of the Li and Deng group's efforts at the formation of substituted arenes through tandem nucleophilic addition and oxidative aromatization was reported by Girard and Huang in 2015.[15e] Newer methods of dehydrogenation have not, to our knowledge, been reviewed.

Prompted by the scant attention paid by the published literature reviews to the comprehensive catalytic dehydrogenative aromatization of cyclohexanones/cyclohexenones, we decided to review the methods developed to date involving transition-metal-catalyzed oxidative aromatization such as palladium and copper catalysts and metal-free strategies for the transformation of cyclohexenones and cyclohexanones into substituted phenols.

### 1.1 Palladium-catalyzed dehydrogenation

Catalytic dehydrogenation of saturated C–C bonds in carbocyclic structures represents a compelling alternative strategy for the preparation of substituted arenes.[23] The most generally satisfactory catalysts are platinum metal and palladium supported on activated charcoal with heterogeneous dehydrogenation. Those heterogeneous catalytic dehydrogenation methods often suffer from poor product selectivity and incompatibility with functionalized substrates. Certain palladium complexes catalyze the dehydrogenation reactions of saturated ketones to α,β-unsaturated ketones.[24] Among these are the $Pd(OAc)_2$/Cu(II)/$O_2$ dehydrogenation system, Pd-phosphine complexes, $Pd(OAc)_2/NaCO_3$/ADP (allyl diethyl phosphate) *etc.*, acting directly or indirectly on ketones, aldehydes or their silyl enolates into their α,β-unsaturated derivatives.

Very recently, based on the research on dehydrogenation of cyclohexanones *via* sequential Pd-mediated C–H activation/β-hydride elimination steps and the oxidation of the $Pd^{II}$-hydride intermediate, which proceeds *via* reductive elimination of HX followed by aerobic oxidation of $Pd^0$ to regenerate the $Pd^{II}$ catalyst (Scheme 2),[25] Stahl and his co-workers made significant progress in the conversion of substituted cyclohexanones to the corresponding phenols with a palladium-catalyzed homogeneous aerobic dehydrogenation process.[26]

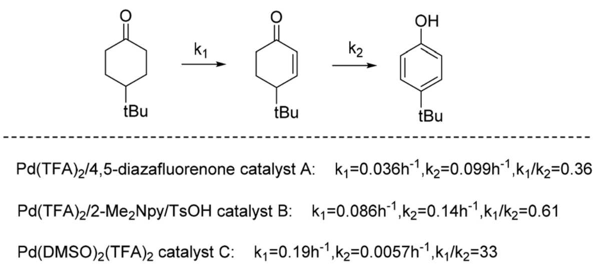


**Scheme 2** Proposed mechanism for the $Pd^{II}$-catalyzed dehydrogenation of cyclic ketones.

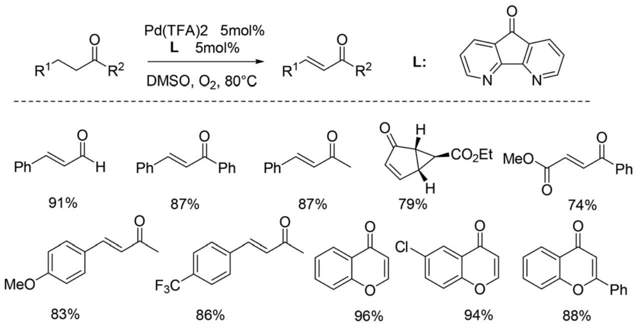
The catalytic approach proceeded very efficiently by using 3–5 mol% palladium trifluoroacetate [$Pd(TFA)_2$], *p*-toluenesulfonic acid (TsOH), 2-(N,N-dimethylamino)pyridine and 1 atm of molecular oxygen, a highly desirable oxidant from chemical, environmental, and economic perspectives, at 80 and generated water as an easily removable by-product. The optimized catalytic conditions proved to be effective in the preparation of a number of substituted phenol derivatives including those bearing alkyl, aryl, and/or ester substituents. Another attraction of this catalytic condition is that it extends utility to the numerous substituted arenes or phenols including meta-substituted derivatives by introducing an appropriate nucleophile into the catalytic system, through the selective control of nucleophilic addition[27] or conjugate addition to cyclohexenones.[28]

$Pd^{II}$-Catalyzed direct dehydrogenation of carbonyl compounds with $O_2$ as the oxidant represents an appealing atom-economical alternative to dehydrogenation of ketones, aldehydes and other carbonyl compounds. Shortly afterwards, according to different substrates, Stahl and co-workers reported the corresponding Pd catalyst systems that enable selective aerobic dehydrogenation to afford enones successively. In order to compare the reactivity of the catalyst system, they evaluated the rate constants by kinetic simulation of the reaction time courses to a simple 4-*tert*-butylcyclohexanone to 4-*tert*-butylcyclohexenone to 4-*tert*-butylphenol sequential kinetic model (Scheme 3). Preliminary analysis of the reaction time courses for each of these reactions shows that the $Pd(TFA)_2$/4,5-diazafluorenone catalyst (A)[29] behaves similarly to the $Pd(TFA)_2$/2-$Me_2$Npy/TsOH catalyst (B).[26] Both of these catalysts show a preference for the formation of the phenol product, owing to faster dehydrogenation of the cyclohexenone to the phenol relative to the initial dehydrogenation step that affords the enone. In contrast, the first dehydrogenation step ($k_1$) is much faster than the second ($k_2$) when the $Pd(DMSO)_2(TFA)_2$ catalyst (C) is used as the catalyst,[30] resulting in high selectivity for the enone product.

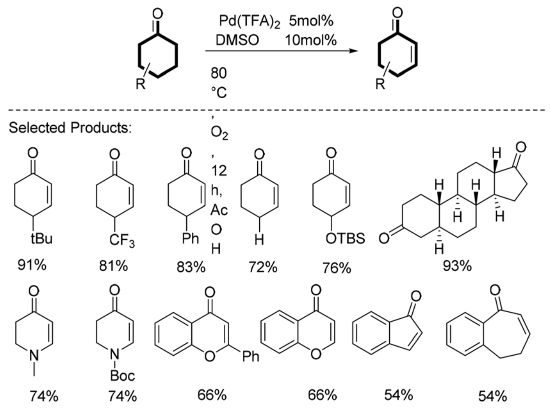
In summary, the three $Pd^{II}$-catalytic dehydrogenation systems have different tendencies; the $Pd(TFA)_2$/4,5-diazafluorenone catalyst (A) significantly expands the utility of direct aerobic α,β-dehydrogenation of carbonyl compounds including aldehydes, acyclic ketones, chromones, and flavones derivatives (Scheme 4), while the application of the $Pd(DMSO)_2(TFA)_2$ catalyst (C) is in the direct dehydrogenation of cyclic ketones, heterocyclic ketones and several steroid derivatives to the corresponding enones (Scheme 5). At the same time, Huang and Zhao's group worked together to report a general dehydrogenation procedure to form α,β-unsaturated aldehydes, ketones, esters and azobenzenes in two kinds of catalytic systems including $Pd(OAc)_2/K_2CO_3$ and $Pd(OAc)_2$/4,5-diazafluorenone catalysts,[31] both of which require a catalytically weak inorganic base and air as the sole oxidant (Scheme 6). More excitingly, even esters, azobenzenes and specific alcohols were successfully dehydrogenated as well. The catalytic potassium carbonate may ensure a subtle balance between Lewis acidity and basicity for a successful catalytic cycle.



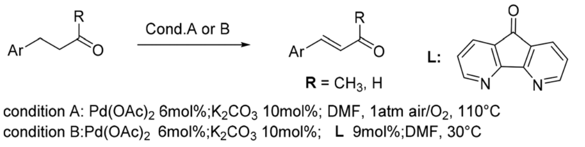
**Scheme 3** Comparison of Pd catalysts in the dehydrogenation of 4-*tert*-butylcyclohexanone. $Pd(TFA)_2$/4,5-diazafluorene catalyst A: $k_1$ = 0.036 $h^{-1}$, $k_2$ = 0.099 $h^{-1}$, $k_1/k_2$ = 0.36. $Pd(TFA)_2$/2-$Me_2$Npy/TsOH catalyst B: $k_1$ = 0.086 $h^{-1}$, $k_2$ = 0.14 $h^{-1}$, $k_1/k_2$ = 0.61. $Pd(DMSO)_2(TFA)_2$ catalyst C: $k_1$ = 0.19 $h^{-1}$, $k_2$ = 0.0057 $h^{-1}$, $k_1/k_2$ = 33.



**Scheme 4** Pd-Catalyzed aerobic dehydrogenation of aldehydes and ketones.



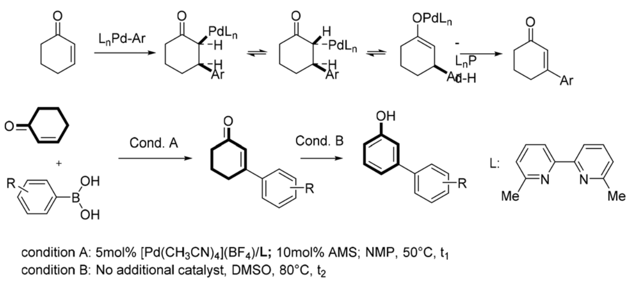
**Scheme 5** Cyclic enones from ketone derivatives.



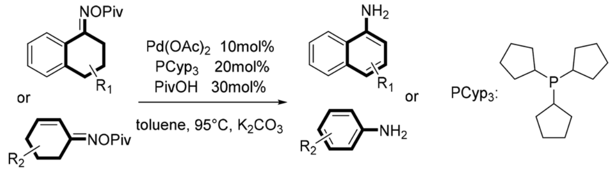
**Scheme 6** Aerobic dehydrogenation of aldehydes and ketones. Condition A: Pd(OAC)$_2$ 6 mol%; K$_2$CO$_3$ 10 mol%; 1 atm air/O$_2$, 110 °C. Condition B: Pd(OAC)$_2$ 6 mol%; K$_2$CO$_3$ 10 mol%; **L** 9 mol%; DMF, 30 °C.

The classical electrophilic and nucleophilic aromatic substitution could hardly afford *meta*-substituted phenols because of the strong *ortho*/*para*-directing effect of the hydroxy group. In 2013, Stahl's group described a new palladium catalyst and reaction so that *meta*-substituted phenols could be accessed efficiently by an aerobic oxidative Heck/dehydrogenation sequence with cyclohexenone.[32] Upon screening diverse PdX$_2$ sources, ligands, additives, and solvents, they found the optimized reaction conditions for aerobic dehydrogenation incuding the dicationic palladium(II) complex [Pd(CH$_3$CN)$_4$](BF$_4$)$_2$ as a catalyst, 6,6′-dimethyl-2,2′-bipyridine (L) as the ancillary ligand, and 9 mol% AMS (anthraquinone-2-sulfonic acid sodium salt) as the additive. Then, the catalyst [Pd(CH$_3$CN)$_4$](BF$_4$)$_2$/L proved to be very effective at the oxidative Heck reactions with cyclohexenone and arylboronic acids as well. Finally, the one-pot fashion of oxidative Heck/dehydrogenation of cyclohexenones and arylboronic acids to afford 3-substituted phenol derivatives was realized under the reaction conditions (Scheme 7). The synthesis of URB597 from cyclohexenone and the commercially available benzamide-derived boronic acid indicated that the reaction has potential utility and functional-group compatibility.

At the same time, Stahl *et al.* reported a new reaction condition for the convenient synthesis of aromatic primary anilines from tetralones and cyclohexenones on the basis of their Pd-catalyzed aerobic dehydrogenation to substituted phenols.[33] The Semmler–Wolff reaction is a classic but rarely used method for the synthesis of aromatic primary amines involving dehydration of cyclohexenone- and tetralone-derived oximes. A major advantage of this complementary route is that their efforts were focused on the *in situ* condensation of an amine with the ketone, followed by dehydrogenation of the imine or enamine intermediate. Upon the identification of suitable reaction conditions, the catalytic system proved to be successful in the aromatization of substituted tetralone- and cyclohexenone-derived pivaloyl oximes (Scheme 8). These Pd-catalyzed Semmler–Wolff-type reactions for the conversion of substituted cyclohexenone oximes to primary anilines provide an important demonstration of the complementarity of dehydrogenation and cross-coupling methods to access valuable substituted aromatic molecules.



**Scheme 7** One-pot oxidative Heck/dehydrogenation reactions to prepare substituted phenols. Condition A: 5 mol% [Pd(CH$_3$CN)$_4$](BF$_4$)/L; 10 mol% AMS; NMP, 50 °C, $t_1$. Condition B: No additional catalyst, DMSO 80 °C, $t_2$.

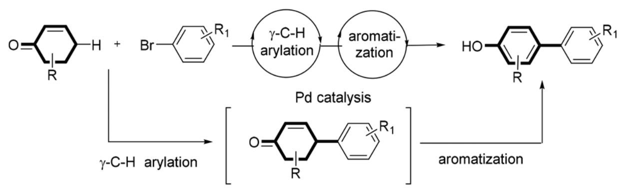


**Scheme 8** Aromatization of substituted tetralone pivaloyl or cyclohexenone pivaloyl oximes.

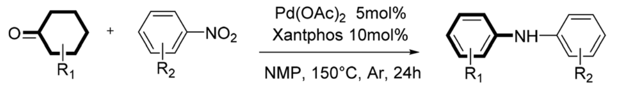
In 2012, the metal palladium catalytic dehydrogenation showed the development trend of the breakthrough. On the basis of the predecessors' work, cyclohexanones or cyclohexenones were used as arylation sources, and the transformation process commonly involves a sequential, nucleophilic addition with nucleophilic reagents such as amine compounds, dehydration and catalytic oxidative dehydrogenation aromatization, providing convenient routes to the preparation of the final aromatic compounds.

Imahori *et al.* developed a Pd-catalyzed tandem γ-arylation/aromatization of 2-cyclohexen-1-one derivatives with aryl bromides, which is an alternative approach to the *p*-C–H arylation of phenol with a phenol surrogate (Scheme 9).[34] In this catalytic system, a broad range of *p*-aryl phenols could be efficiently synthesized in a single reaction step on the basis of C–H arylation.

Deng's group[35] presented a complementary palladium catalytic system for the synthesis of diarylamine from nitroarenes and cyclohexanone derivatives using the dehydrogenation and borrowing the hydrogen methodology for the first time (Scheme 10). The reaction tolerated a wide range of functionalities. Various diarylamines were selectively obtained in good to excellent yields.



**Scheme 9** Pd-Catalyzed tandem γ-arylation/aromatization of 2-cyclohexen-1-one derivatives.



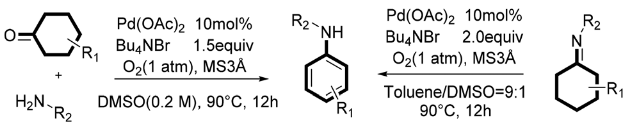
**Scheme 10** Palladium-catalyzed one-pot diarylamine formation from nitro-arenes and cyclohexanones.

Based on the observations of Stahl *et al.* and their own, the authors proposed a plausible mechanism for this transformation. First, the reaction starts with a primary dehydrogenation to derivatives of 2-cyclohexenone and transfers dihydrogen to the palladium catalyst. Meanwhile, nitrobenzene can be reduced into aniline by the hydride. Then, the condensation of 2-cyclohexenone with aniline generates an imine intermediate which undergoes dehydrogenation and reduction to yield the final diphenylamine.

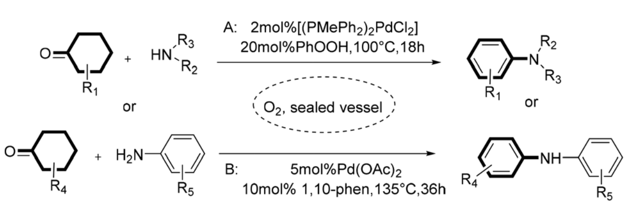
Yoshikai *et al.* developed a palladium-catalyzed aerobic dehydrogenation reaction for the synthesis of arylamines.[36] The catalytic system consisting of $Pd(OAc)_2$ (10 mol%), $Bu_4NBr$ (2 equiv.), $O_2$ (1 atm), and toluene/DMSO (9 : 1) promoted the dehydrogenative aromatization reaction of six-membered cyclic imines at 90 °C to afford the diarylamine (Scheme 11). Then they attempted the direct synthesis of arylamines from cyclohexanones and amines *via* condensation/dehydrogenative aromatization in one pot under slightly varied reaction conditions and attained success. A plausible reaction mechanism for the dehydrogenative aromatization reaction was proposed which is analogous to the dehydrogenation reaction of cyclohexanone to phenol.

At the same time, the Li and Deng group described two aerobic $[(PMePh_2)_2PdCl_2]/PhCO_2H$ and $Pd(OAc)_2$/1,10-phenanthroline catalyst systems for the preparation of aromatic amines;[37] the former was suitable for the arylation of secondary amines with 2-cyclohexen-1-ones, and the latter was appropriate for the conversion of anilines into the corresponding diaryl amines with cyclohexanones (Scheme 12). In this reaction, palladium was used as the metal catalyst and $O_2$ as the sole terminal oxidant, generating water as the only by-product. Both alkyl amines such as piperidine, morpholine, dibenzylamine, indoline, diallylamine and aromatic amines proved to be efficient coupling partners for this transformation.

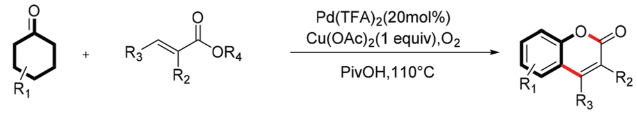
In 2013, the Hong group reported an efficient method for the preparation of coumarins *via* a Pd(II)-catalyzed dehydrogenation–oxidative Heck–cyclization process.[38] In this reaction, $Pd(TFA)_2$ was used as the metal catalyst and $Cu(OAc)_2$ and molecular oxygen as the oxidizing agents in PivOH (Scheme 13). Under optimized conditions, the substrate scope is broad and permits the construction of a variety of substituted coumarins starting from the readily available cyclohexanones in a single synthetic operation.



**Scheme 11** Palladium-catalyzed dehydrogenative aromatization to aryl-amines.



**Scheme 12** Palladium-catalyzed dehydrogenative aromatization to aryl-amines.



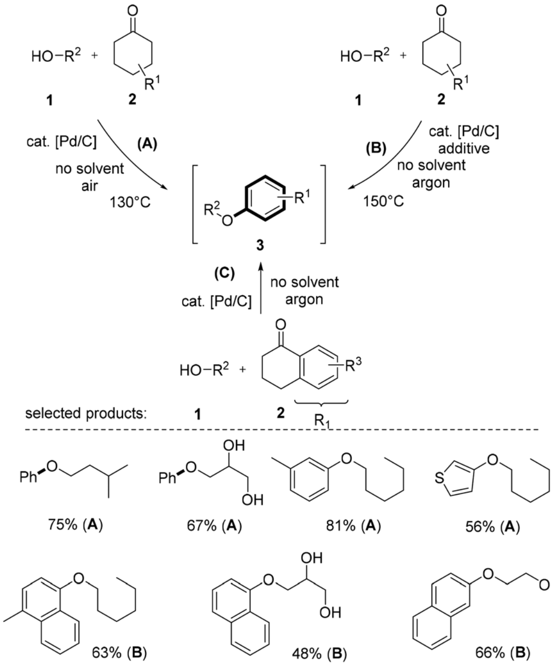
**Scheme 13** One-pot synthesis of coumarins from cyclohexanones and butyl acrylates.

Having achieved dehydrogenative aromatization of various cyclohexanones, cyclohexenones and preformed imines, it is conceivable that by introducing another appropriate nucleophilic reagent such as alcohol into the catalytic system, through the selective control of nucleophilic addition followed by dehydrogenation, it would afford substituted aryl ethers. Lemaire's group has always focused on establishing new and eco-efficient processes for the preparation of glycerol ethers.[39] In 2012, they reported a solvent-free dehydrogenative arylation of readily available cyclohexanone or tetralones with alcohols and glycerol in air under heterogeneous Pd/C catalysis.[40] The route gave straightforward, green and safe access to aryl ethers without the use of any additive, and could be applied for the preparation of aryl amines by optimizing the experimental parameters. However, it has its own limitations at the moment, for example, low boiling point alcohol and less reactive substrates.

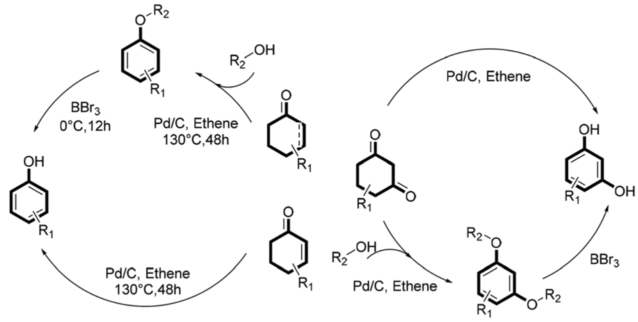
To overcome the observed limitations, the authors developed alternative and safe non-aerobic conditions which had three different pathways for the preparation of aryl ethers later (Scheme 14).[41] Not only did they explore the scope of the dehydrogenative arylation in route A, but also they overcome the above limitations in most cases when the reaction was performed in route B with an alkene as additive, though the reaction rate was often lower. Route C was also applicable to the reactions of tetralone derivatives. The key to the reaction mechanism seems to be the formation of an enol ether which is dehydrogenated to afford the final product.

Subsequently, they made further investigations to extend this transformation to other nucleophiles like amines.[42] The products were prepared by dehydrogenative alkylation of cyclohexanone derivatives with various amines or nitro compounds under safe conditions, without the need for an atmosphere of molecular oxygen linked to flammability risks. Very recently, Hayashi and coworkers reported a similar type of dehydrogenation by using the Pd/C-ethylene system.[43] It should be noted that ethylene functions as a hydrogen acceptor with gaseous ethane as the only byproduct. In addition, the catalytic system would be appropriate for the synthesis of resveratrol from 1,3-cyclohexanediones (Scheme 15).[44]

In 2014, Deng's group reported a palladium-catalyzed greener approach for the synthesis of 3-arylindoles using cyclohexanones as the aryl source and free indoles, in which molecular oxygen was used as an efficient hydrogen acceptor in the

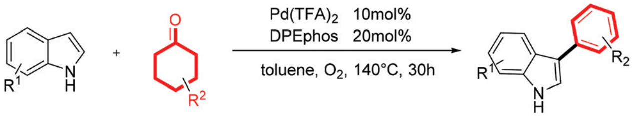


**Scheme 14** Strategies developed for the preparation of aromatic ethers.

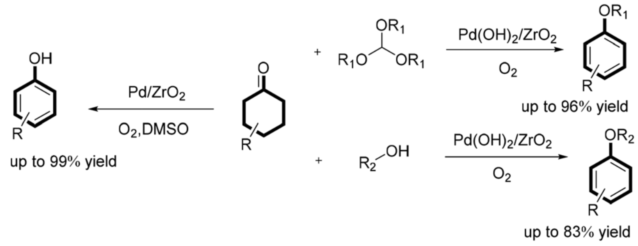


**Scheme 15** Oxidative aromatization of cyclohexanones, cyclohexenones and 1,3-cyclohexanediones.

transformation (Scheme 16).[45] The method was applicable to various cyclo-hexanones and indoles *via* an alkylation and dehydrogenation sequence in one pot and showed good regioselectivity. What is of great significance is designing an environmentally benign approach for the preparation of biaryls and arylated heteroarenes from the readily available starting materials cyclohexanones.



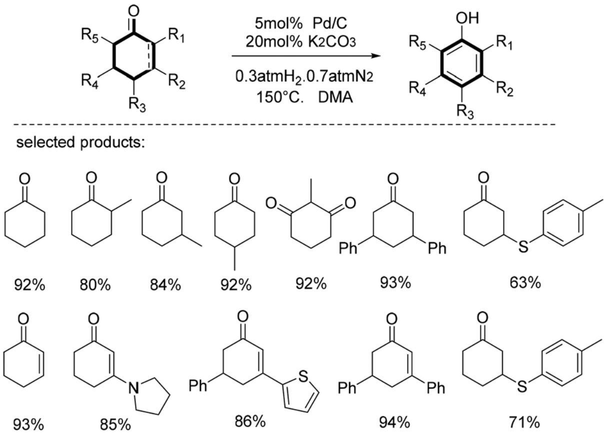
**Scheme 16** Reaction of various indoles with cyclohexanones.



**Scheme 17** Aerobic oxidation of cyclohexanones to phenols and aryl ethers over supported Pd catalysts.

Later on, a novel catalytic system containing supported Pd catalysts for the preparation of phenols and aryl ethers was described by Tokunaga and co-workers (Scheme 17).[46] Among several metal oxide supported Pd catalysts, using $ZrO_2$ supported $Pd(OH)_2$ was proposed for the synthesis of phenols in excellent yield and aryl ethers in moderate to excellent yields. The proposed mechanism involved the activation of cyclohexanone by $Pd(OH)_2$ on the metal oxide surface, to produce Pd-enolate intermediate, and a cyclic enone is formed followed by β-hydride elimination. Then the acetal was formed by cyclic enone and alcohols, and subsequent elimination and oxidation yielded aryl ether.

Almost at the same time, Liu's group described a palladium(0)/$H_2$ catalytic system for the formation of phenols through a palladium-catalyzed dehydrogenation of substituted cyclohexanones and 2-cyclohexenones with high isolated yields.[47] In view of the fact that the dehydrogenation of organic compounds is a thermodynamically unfavorable process, reactions are typically carried out with stoichiometric oxidants or sacrificial hydrogen acceptors (Scheme 18). The innovation lies in requiring no oxidants or hydrogen acceptors with $H_2$ as the only byproduct, which can be used as a cocatalyst to help power the reaction. This method for phenol synthesis manifests a high atom economy, and is inherently devoid of the



**Scheme 18** Palladium-catalyzed dehydrogenation of cyclic ketones and cyclo-hexenones to phenols and $H_2$.

complications normally associated with oxidative dehydrogenations.

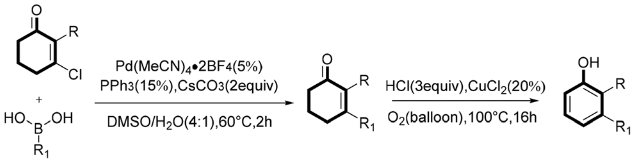
In a homogeneous catalyst system, the active molecular Pd(II) species generate soluble Pd nanoparticles that serve as the active catalyst during steady-state dehydrogenation of the substrate. Shah reported the conversion of cyclohexanone to the corresponding cyclohexenone and phenol catalyzed by Pd, Pd-1, Pd-cube, Cu, Ni, Ag@Pd and Ni–Sn nanocatalysts.[48] Among the different nanocatalysts, the Pd nanocatalyst showed the best performance. Jin and Mizuno described a heterogeneous acceptorless dehydrogenation aromatization of cyclohexanones in the presence of a Ni–Mg–Al layered triple hydroxide-supported Pd catalyst.[49] Both cyclohexanols and cyclohexylamines efficiently proceeded to give the corresponding phenols and anilines, respectively, in moderate to high yields with the release of molecular hydrogen.

Orellana's group reported a new approach to the synthesis of *meta*-substituted phenols in which a single palladium catalyst accomplishes a Suzuki–Miyaura cross-coupling between a β-chloro-cyclohexenone and an arylboronic acid, and oxidation of the resulting cyclohexenone to the corresponding phenol upon the introduction of a terminal oxidant of $O_2$ and an electron transfer mediator of $CuCl_2$ (Scheme 19).[50] This tandem reaction can also be used to prepare *ortho*,*meta*-disubstituted sterically congested phenols, as well as trisubstituted phenols.

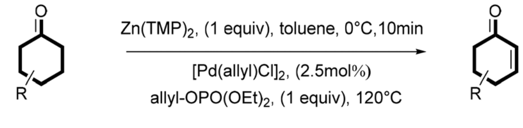
More recently, based on their previous work,[51] Newhouse presented a complementary allyl-palladium catalysis system for the one-step synthesis of α,β-unsaturated ketones *via* their zinc enolates (Scheme 20).[52] The use of a less basic zinc amide and a nonelectrophilic allyl phosphate oxidant was crucial for achieving a broad range of architecturally diverse ketone substrates.

## 1.2 Copper-catalyzed dehydrogenation

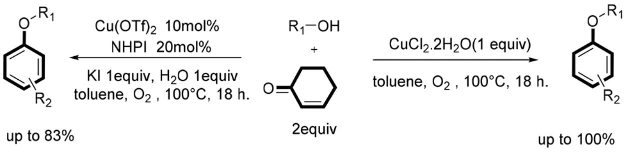
In the past few decades, transition-metal-catalyzed dehydrogenation of carbocyclic compounds such as cyclohexanones and cyclohexenones to generate substituted phenol derivatives has received much attention.[53] Compared to other transition-metal catalysts, copper salts are relatively inexpensive and easy to handle, exhibit low toxicity, and also exhibit good functional tolerance and havefound widespread application in homogeneous catalysis.



**Scheme 19** Synthesis of *meta*-substituted phenols by Suzuki–Miyaura cross-coupling and oxidation.



**Scheme 20** Palladium-catalyzed α,β-dehydrogenation of ketones.



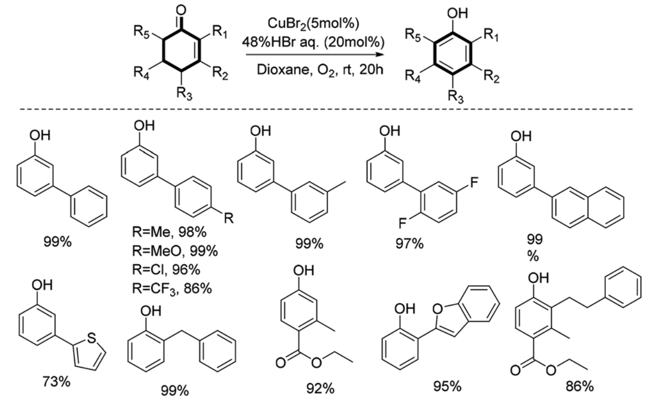
**Scheme 21** Copper-catalyzed reaction of various alcohols with 2-cyclohexenones.

The different oxidation states of copper ($Cu^0$, $Cu^I$, $Cu^{II}$, and $Cu^{III}$) can be easily accessed by both radical pathways and powerful two-electron bond-forming pathways *via* organometallic intermediates, similar to those of palladium. And it can associate well with a large number of different functional groups *via* Lewis acid interactions or π-coordination that allows copper to catalyze the oxidation and oxidative union of many substrates.[54]

In 2012, Li's group described a copper-catalyzed aerobic synthesis of aromatic ethers (Scheme 21).[55] At first, they found that the use of only one equivalent of $CuCl_2 \cdot 2H_2O$ in toluene under an $O_2$ atmosphere at 100 °C afforded dehydrogenative coupling. Then they went on to attempt at further improving this reaction by reducing the amount of copper catalyst required and using $O_2$ as the sole terminal oxidant. With the use of the co-catalyst *N*-hydroxy-phthalimide (NHPI, 20 mol%) in the presence of potassium iodide (KI, 1 equiv.) and water (1 equiv.), a catalytic amount of copper triflate ($Cu(OTf)_2$, 10 mol%) provided aryl-ethers in high yields. The two approaches tolerated a wide range of substrates, including primary and secondary alcohols with several functional groups and various 2-cyclohexenone derivatives. Even natural alcohols such as β-citronellol, (−)-borneol, (−)-menthol, cholesterol, *etc.* and natural ketones such as (*R*)-carvone were successfully transformed. Diols and diketones were also suitable reactants, and afforded the corresponding diethers in good yields.

The methods advantageously enrich and complement the existing synthetic methods for the preparation of aromatic ethers, and allow access to a wide variety of related functionalized products. In addition, the catalytic reaction with $O_2$ as the terminal oxidant generates water as the only by-product and makes this approach green and practical.

In 2013, Kikushima and Nishina developed a catalytic oxidative aromatization reaction of 2-cyclohexenones to afford phenol derivatives in the presence of a catalytic amount of $CuBr_2$ and aqueous HBr under molecular oxygen (Scheme 22).[56] The highlight of the approach is that instead of a high reaction temperature and a stoichiometric additive, a cheap and ligand-free copper catalyst is combined with catalytic HBr under mild conditions. Based on the previous literature,[57] they illustrated a plausible reaction pathway followed by several verified experiments. Bromination of cyclohexenone



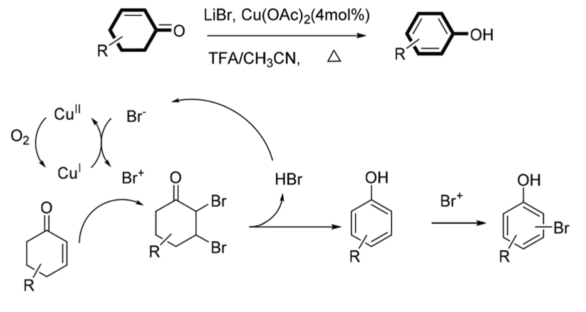
Scheme 22 Synthesis of mono-, di- or tri-substituted phenols.

occurs to give α-bromination product along with reduced copper(I) species and hydrogen bromide in the first step; then the dehydrobromination of the bromide leads to an intermediate which undergoes dehydrobromination followed by tautomerization to yield the phenol product; meanwhile, the reduced copper(I) would be oxidized by molecular oxygen and HBr to regenerate the copper(II) species. An oxidative aromatization/bromination sequence was also demonstrated to obtain bromophenols with excess HBr.

Later, Reddy, Liu and co-workers described a catalytic method to convert substituted cyclohexenones into the corresponding phenols and bromophenols *via* a bromination/dehydrobromination reaction using copper acetate as the catalyst in the presence of LiBr and $CF_3COOH$ under oxygen (Scheme 23).[58] A significant feature of this chemistry is that bromination of phenol can be controlled by manipulation of the reaction conditions with the use of excess LiBr. But this aromatization methodology was found to not be applicable to cyclohexanone. Finally, the phenomenon was explained from such viewpoints as the reaction conditions, controlled experiments and transformation mechanism.

The conversion of substituted cyclohexenones into the corresponding phenols can be achieved using copper salts. However, few examples of Cu-catalyzed aromatization involved cyclohexanones.

As mentioned above, chiral phenols are one of the most important class of natural products and bioactive substances; for example, *ortho* functionalized phenols, especially the simple 4-alkyl-2-(1-phenylalkyl) phenols, are highly attractive architectures that exist in a number of drugs and natural products.[1f,g,6,59]



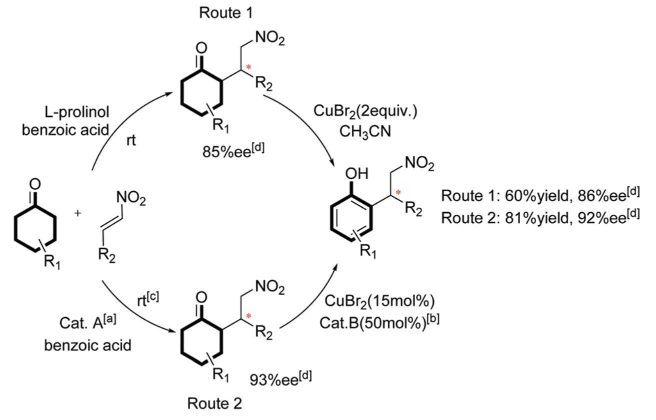
Scheme 23 Aromatization of substituted 2-cyclohexenones.

We previously developed a stereospecific copper(II)-mediated bromination/debromination aromatization sequence to functionalize nitrophenols from the corresponding γ-nitroketones.[60] In our continued efforts to develop more sustainable chemical reactions, we next attempted to further improve this reaction by reducing the amount of copper catalyst required (Scheme 24).[61] By merging organocatalysis with copper catalysis, we have developed a simple and efficient methodology for the synthesis of chiral phenols for the first time through tryptophan/$CuBr_2$ catalyzed bromination/debromination aromatization of chiral cyclohexanone derivatives. A variety of chiral phenol derivatives were obtained in good yields and high to excellent enantioselectivities.

### 1.3 Other metal-catalyzed dehydrogenations

From a synthetic viewpoint, the development of transition-metal-catalyzed aromatization of cyclohexanones and cyclohexenones is a topic of growing interest.[62] Except for metal palladium, precious metals, such as iridium,[62d,63] ruthenium,[64] gold,[65] and rhodium,[62b,66] could convert cyclohexanones or cyclohexenones into phenol derivatives. On the other hand, non-precious metals,[67] especially vanadium salts, could serve as effective catalysts to transform cyclohexenones into phenols.

Vanadium is a biologically essential element which exists in oxidation states ranging from −3 to +5 and generally converts between states *via* one-electron redox processes. Vanadium compounds in high oxidation states can induce oxidative transformations.[68] Hirao's group were dedicated to the research on metal vanadium and its application in organic



Scheme 24 Our approaches to chiral phenol derivatives. [a] Catalyst A: Prolinethiol ether (*S*)-2-((pyrrolidin-2-ylmethyl)thio)pyridine; [b] Catalyst B: L-Tryptophan; [c] rt means room temperature; [d] the ee values and yield are listed when $R_1$ = H and $R_2$ = Ph.

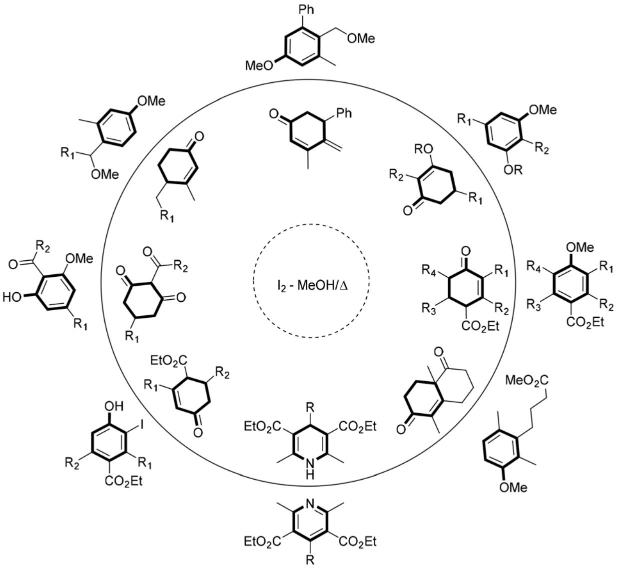
chemistry, and had been reported to induce the oxidative aromatization of α,β-unsaturated cyclohexenones to aryl ethers.[69] Based on the aerobic vanadium-catalyzed oxidative bromination reaction of arenes, alkenes, and alkynes,[70] they developed a vanadium-catalyzed oxidation system for the aromatization of 2-cyclohexenones to phenols under molecular oxygen (Scheme 25).[71] Instead of dehydrogenation, the reaction proceeds *via* bromination/dehydro-bromination induced by a system consisting of a vanadium salt and stoichiometric amounts of $Bu_4NBr$ or concentrated HBr as promoters.

### 1.4 Metal-free-catalyzed aromatization

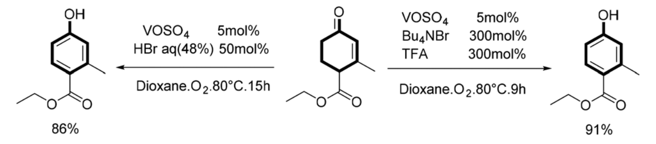
The catalytic dehydrogenation reaction is a highly desired functionalization method for unreactive $sp^3$ C–H bond activation. Catalytic dehydrogenation of saturated C–C bonds in carbocyclic structures represents a compelling alternative strategy for the preparation of substituted arenes. A number of materials can be used as hydrogen acceptors in metal-free strategies for the transformation of cyclohexenones and cyclohexanones into substituted phenols, such as molecular oxygen, halogens, sulfur-containing compounds and analogues, peroxide, *etc.*[19b,c,20b,e,i,72] Commercially available iodine has played an important role in organic synthesis. Because of its simple structure and stable performance, it has found widespread use both in conduction of selective transformation and showing interesting and varied reactions.[22c,d] This section mainly focuses on reviews on the application of molecular iodine and hypervalent iodine reagents in oxidative aromatization reactions.

Iodine in methanol was being used as a novel reagent for the conversion of 2-cyclohexen-1-ones into the corresponding anisole derivatives. In 1980, Tamura and Yoshimoto reported the aromatization of cyclohexenones using iodine in methanol under reflux.[73] Based on the observations of this work, both a series of aromatizations of applicable cyclohexenones and derivatives and catalytic methodologies of iodine were developed (Scheme 26).[74]

Iodine catalyzed aromatization is simple, mild, selective and new. The utility of iodine in the conversion of cyclohexanones to substituted catechols by the use of DMSO and a catalytic amount of iodine has recently been reported by Jiao's group in 2016.[75] Inspired by the recently developed DMSO oxidative reactions, among the halide-containing reagents, only iodine has the best catalytic effect on the oxygenation of the C–H bond. This metal-free and simple system proved to be a versatile protocol for the synthesis of highly valuable substituted catechols *via* selective oxygenation and dehydrogenation. In order to understand the mechanism of this transformation and the chemoselectivity between catechol and phenol, $^{18}O$-labeling control experiments and density functional theory (DFT) calculations were conducted. The additional oxygen atom in the catechol product originates from DMSO, and α-iodo cyclohexanone and cyclohexane-1,2-dione were possible intermediates for this reaction (Scheme 27). In addition, cyclohexenones and multisubstituted cyclohexanones were favored to deliver phenol products under the present conditions, which were the first example of a metal-free oxidative transformation of cyclohexanones to phenols.

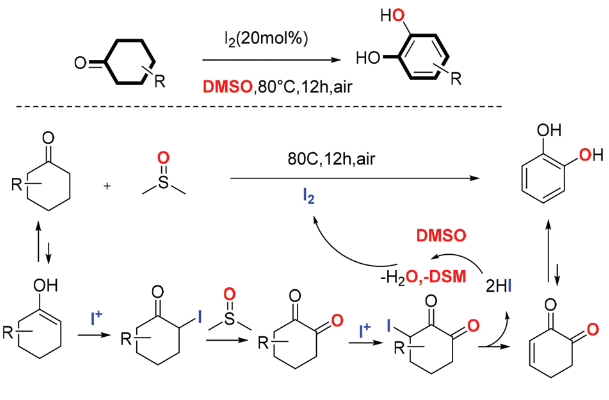


**Scheme 26** Oxidative aromatization of 2-cyclohexenone derivatives and analogues using iodine in methanol.

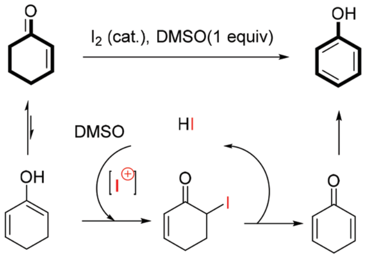


**Scheme 25** Oxidative aromatization catalyzed by $VOSO_4$.

The same year, as a continuous further study, they reported another very interesting research study on the metal-free route to substituted phenols from simple and readily available cyclohexenones and cyclohexenone equivalents (Scheme 28).[76] With the use of a cheap and common DMSO oxidant, a catalytic amount of $I_2$ (20 mol%) provided phenols in high yields. This reaction tolerated a broad range of substi-



**Scheme 27** Conversion of cyclohexanones to catechols.



**Scheme 28** Metal-free oxidative process for the preparation of diverse substituted phenols.

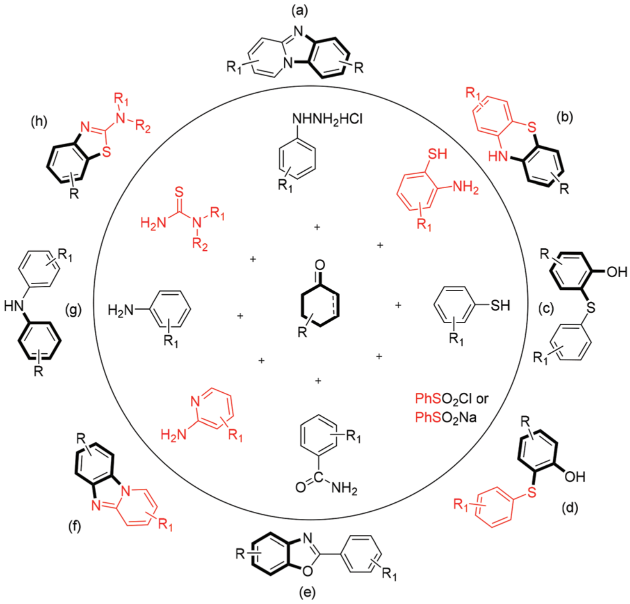
tuents including some easily oxidizable or reducible functionalities such as the sulfide, vinyl, or allyl group. Challenging *meta*- and multiple-substituent phenols could be well prepared by this method.

Beyond these, in recent years, using cyclohexanones as aryl sources for coupling reactions *via* a dehydrogenation–tautomerization sequence had provided new synthetic routes for C–C, C–N, C–O and C–S bond formation as well as heterocycles (Scheme 29).

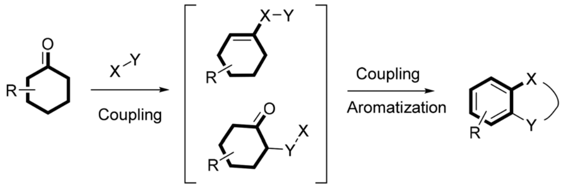
Deng and co-workers has carried on pioneering reports. In 2012, they developed a one-pot synthesis of carbazoles from arylhydrazine hydrochlorides and cyclohexanones in moderate to good yields (Scheme 30a).[77] One year later, they employed 2-aminobenzene-thiols as double-site coupling reagents and cyclohexanones as coupling partners for the first for the metal free synthesis of phenothiazines in good yields (Scheme 30b).[78] The same year, the formation of 2-arylsulfanylphenols from thiols and cyclohexanones was described (Scheme 30c).[79] In 2014, they have developed an iodine-promoted approach for the synthesis of 2-arylsulfanylphenols using cyclohexanones as a reliable phenol source and aromatic sodium sulfinates or sulfonyl chlorides as efficient coupling partners under transition-metal-free conditions (Scheme 30d).[80] Shortly after this, the synthesis of 2-arylbenzoxazoles from readily available cyclohexanones and benzamides was described. Under the optimal conditions (KI/$p$-TsOH/DMSO/O$_2$), a range of 2-arylbenzoxazole were obtained with a broad functional group tolerance (Scheme 30e).[81] In addition to nitrogen-containing pyrido[1,2-*a*]benzimidazole synthesis, 2-aminopyridines and cyclohexanones were smoothly promoted by iodine *via* a dehydrogenation–aromatization process using molecular oxygen as the green oxidant in good to high yields in 2015 (Scheme 30f).[82] Iodine mediated metal-free direct amination/aromatization of 2-cyclohexenones to iodo-*N*-aryl-anilines and *N*-arylanilines was reported by Barros in 2012 (Scheme 30g).[83] Jiang and co-workers had effectively utilized thioureas and cyclohexanones for the preparation of 2-aminobenzothiazoles through a sulfanylphenol intermediate *via* the generation of the α-C–S bond (Scheme 30h).[84]

Luo's group developed the first desymmetrizing dehydrogenation process catalyzed by a chiral primary amine (Scheme 31).[85] Both 4-mono- and 4,4-disubstituted cyclohexanones would be generated by chiral 4-substituted cyclohexenones containing a remote γ-stereocenter smoothly through ketone enamine oxidation by IBX in high yield with good enantioselectivity.

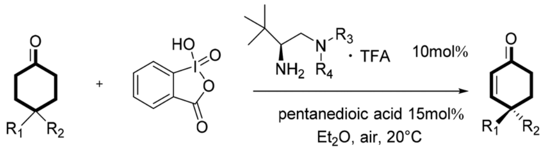
In summary, as an efficient, readily available and easy-to-handle oxidizing agent, molecular iodine shows good performances, and obvious superiority in the aromatization of cyclohexenone/anones derivatives and their analogues. The generality and brevity of iodine mediated oxidative aromatization reactions and the accompanying high yields make this methodology a suitable alternative to metal-catalyzed aromatization of related derivatives.



**Scheme 30** Synthesis of heterocycles from cyclohexanones/cyclohexenones.



**Scheme 29** Tandem C1 and C2 coupling of cyclohexanone.



**Scheme 31** Catalytic desymmetrizing dehydrogenation of 4-substituted cyclo-hexanones.

## 2 Conclusions

The transformation of cycloalkanes into aromatic compounds, such as phenols, is a fundamental reaction in organic chemistry. In this work an attempt has been made to summarize the progress in the catalytic dehydrogenative aromatization of cyclohexa(e)nones which are used as arylation sources. It was shown that catalytic dehydrogenative aromatization has evolved into a hot research topic. A major advantage of the catalytic conversion of cyclohexa(e)nones into phenols is the ready availability of the reactants. In addition, it's worth mentioning that molecular oxygen is the most attractive oxidant throughout all these catalytic oxidative processes, and the corresponding water is the main byproduct. Meanwhile, due to the low level of heavy metal content in some fine chemicals and pharmaceutically active ingredients, the metal-free strategy for the transformation of cyclohexa(e)nones into substituted phenols will be expected. As mentioned above, chiral phenols are among the representative structural motifs in numerous natural products, pharmaceuticals, and biologically active compounds. For further prospects in this field, the synthetic methods of such chiral phenol precursors are highly attractive. We expect that this review will serve as a valuable critical overview of the area, and it is hoped that this contribution will help encourage further research in this field.

## Conflicts of interest

We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

## Acknowledgements

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