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C–H Activation Strategies for Heterofunctionalization and Heterocyclization on Quinones: Application in the Synthesis of Bioactive Compounds

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Thumadath Palayullaparambil Adarsh Krishna*

Abstract

Quinone moieties in general and heterofunctionalized or heterofused quinones in particular find application in several fields such as medicinal chemistry, natural products, and functional materials. Due to its striking applications, scientists developed useful methods for the synthesis of quinone derivatives. C–H activation strategy is a fast-developing and straightforward concept, used in the construction of a diverse variety of bonds such as carbon–carbon (C–C) and carbon–hetero (C–O/N/S/P) bonds and also used is the heterofunctionalization/heterocyclization of quinones. Such approaches are useful in making use of unfunctionalized quinones for the synthesis of heterofunctionalized or heterocycle-fused quinones. The redox active nature and ligand-like properties make it difficult to carryout C–H activation on quinones. In this chapter we summarized recent developments on strategies used for C–hetero atom bond formation on quinones via C–H activation, leading to heterofunctionalization and synthesis of heterofused quinones.

Keywords: quinone moiety, C–H activation strategy, heterofunctionalization approaches, biomolecules

1. Introduction

Inspired by quinone's reactive electrophilic character, easily accessible oxidation states [1], ubiquitous natural presence [2], and important roles played in living systems (phosphorylation to electron transfer process) [3], chemists tried to mimic its acts through synthetic equivalents consisting of biologically active compounds [4], natural product analogs [5], and functional materials [6]. Consequently, several methods were developed for the synthesis of quinone derivatives. Depending upon the basic subunits (**Figure 1**), quinones are classified as benzoquinone (BQ), naphthoquinone (NQ), anthraquinone (AQ), and polyquinones (PQ).

Current, statistics on number of publications (**Figure 2**) appeared during the past two decades, ever growing research highlights, interests, importance, and applications of quinone chemistry [18].

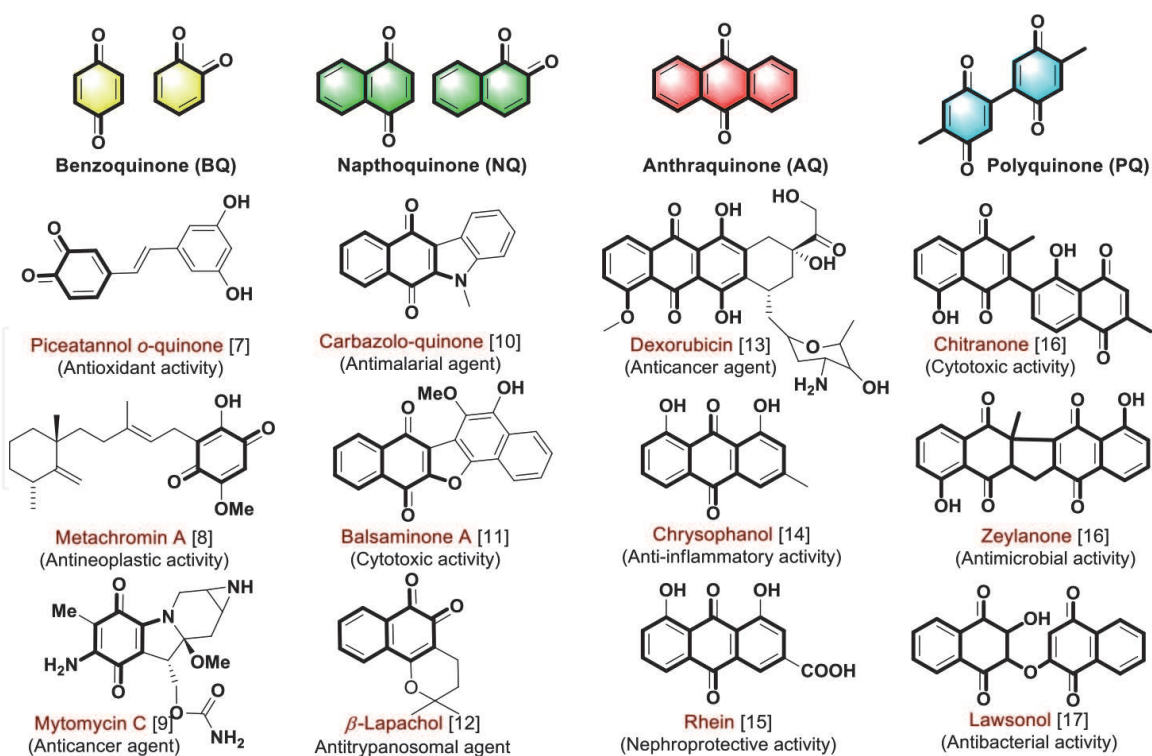


Figure 1.
Selected biologically important quinone molecules [7–17].

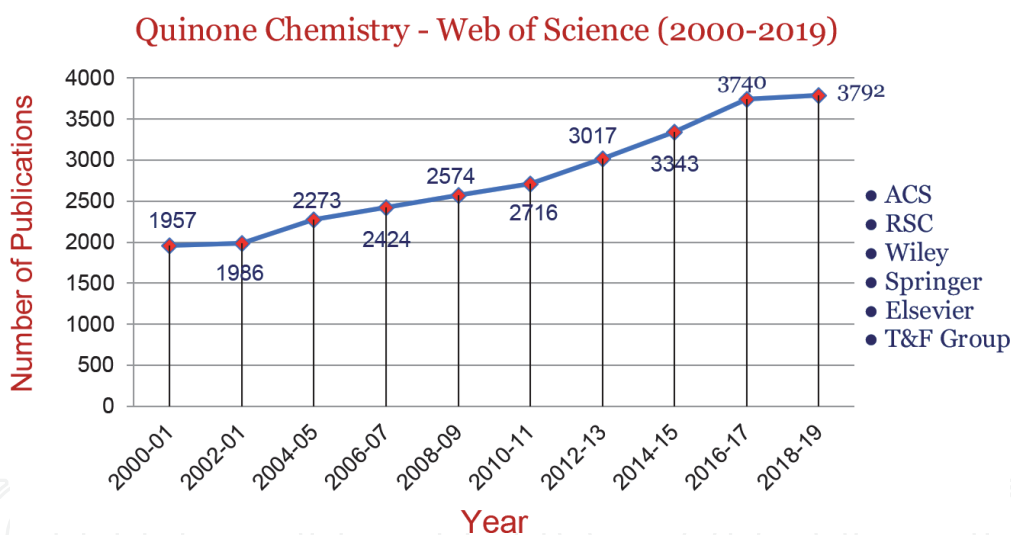


Figure 2.
Trends in the number of publications on quinones in the last 20 years based on the web of science data.

2. C–H activation and heterofunctionalization of quinones

The construction of carbon–carbon (C–C) bond or carbon–hetero atom (C–X) bond on quinone has been reported either using pre-functionalized starting materials or direct functionalization of C–H bonds [19–24]. The first step in C–H functionalization is activation, followed by the formation of an intermediate carbon–metal (C–M) bond, and final replacement with a functional group (FG). C–H activation reaction is advantageous as it is straightforward and atom economic and does not require pre-functionalization [31]. Some typical steps involved in C–H activation reaction mechanisms are oxidative addition, σ -bond metathesis, electrophilic activation, 1,2-addition, and metalloradical. C–H activation is a difficult

process as it involves breaking of C–H bond having high energy (CH_4 , 100 kcal/mol; benzene, 110 kcal/mol) and high pK_a value (>40). In case of quinones, it is further more difficult, [32–34] as it interacts with transition metal reagents, such as Pd (Heck-type reaction), through redox reaction and ligand [35, 36] formation. The report made by Baran et al., in 2011, on coupling of quinones with boronic acids [25] for the formation of C–C bond, and by Poulsen et al., in 2018, for heterofunctionalization on quinone [26], is a notable example on C–H activation reactions on quinones. Approaches for functionalization of quinone can be broadly classified as Lewis acid (MX_3)-promoted nucleophilic addition of electron-rich arenes [27–30], transition metal-catalyzed addition of aryl radicals generated from pre-functionalized starting material [31, 32], and transition metal-catalyzed cross-coupling of halo-quinones [33–37].

Conventional methods for the heterofunctionalization (HF) of quinones involves pre-functionalization of C–H bond to form organo-halide [33–37] (Cl, Br, and I) or organo-boronic acid ($-\text{B}(\text{OH})_2$) [38] or organo-metallic (SnBu_3) [39, 40] starting materials and finally to heterofunctionalization (**Figure 3**). Pre-functionalization combined with separation and purification leads to additional steps, generates waste, and lowers the efficiency drastically.

The arylation (C–C bond formation) of quinone is one of the thoroughly studied reactions using several aryl coupling partners with and without a directing group [32]. Poulsen and coworker's [26] demonstration of the synthesis of natural product stronglylophorine-26, an inhibitor of cancer cell invasion, via C–H heterofunctionalization of quinone (**Figure 4**) sets a good example on the importance of direct C–H heterofunctionalization reaction of quinones.

The undirected C–H functionalizations are much common in quinone chemistry. The presence of a directing group (DG) is helpful in achieving site-specific C–H functionalization of quinone. However, the development of efficient synthetic approaches for site-specific C–H functionalization of quinones is challenging [41–47]. This could be achieved either by manipulation of the reagent used or the presence of a directing group. For example, Junior and coworkers [41] demonstrated Rh-catalyzed C5 and C2 site-selective C–H halogenation of naphthoquinone (**Figure 5**). Similarly, by changing the type of reagent TBAI-TBHP [43] or $\text{RuCl}_2(p\text{-cymene})\text{-PIFA}$ [47], hydroxyl group was introduced on quinone at C-2 or C-5 position (**Figure 5**) site specifically.

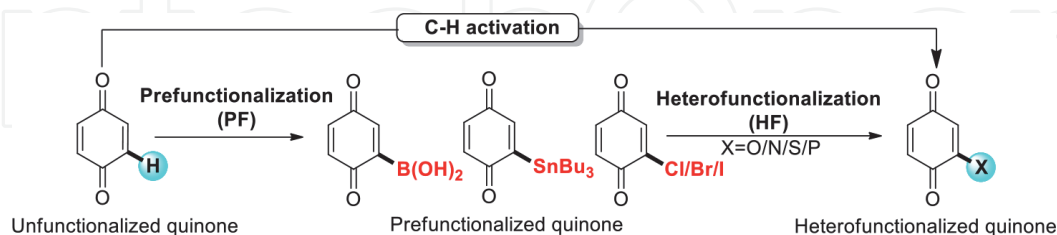


Figure 3.
 Conventional heterofunctionalization vs. C–H activation approach.

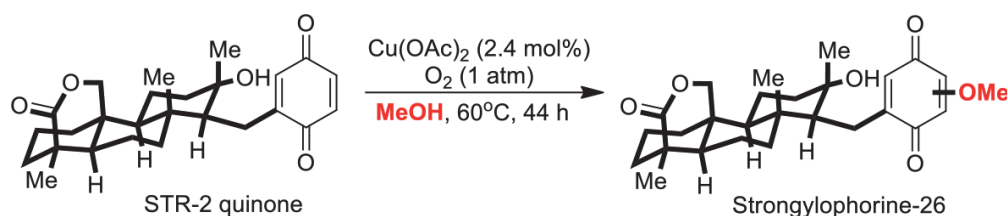


Figure 4.
 Example on direct C–H heterofunctionalization of quinone.

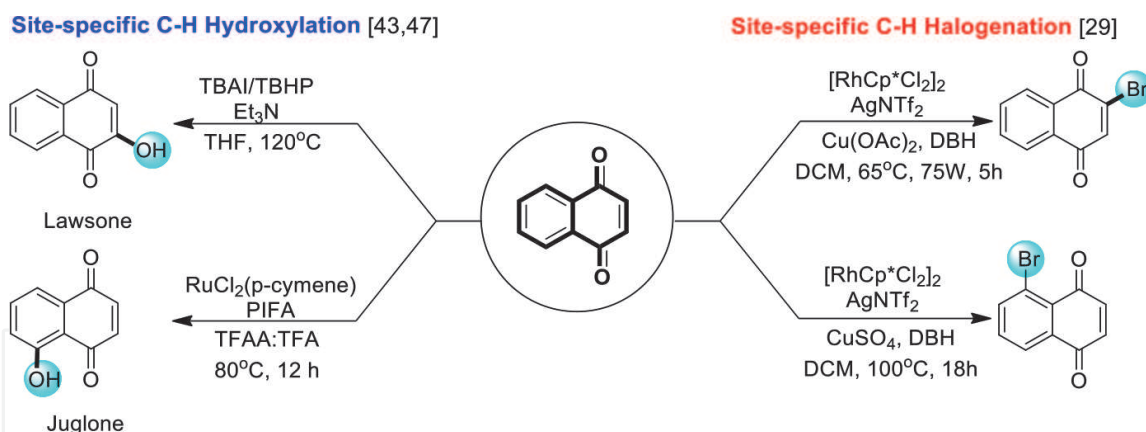


Figure 5.
Site-selective C–H functionalization on quinone or aryl ring.

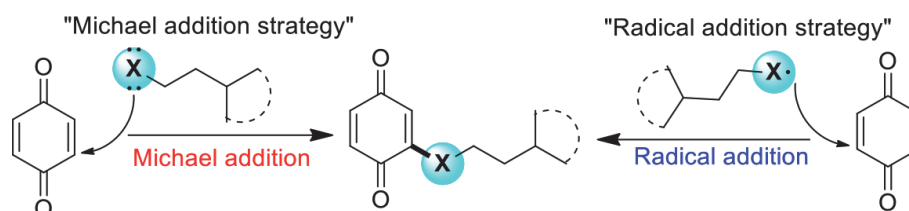


Figure 6.
Heterofunctionalization strategies.

The electrophilic character of quinone enables it to undergo facile nucleophilic attack using electron-rich nucleophilic species such as amino (R-NH_2), hydroxyl (R-OH), and thiol (R-SH) groups, as in the case of classical Michael addition [48]. Using *p*-benzoquinone most of the nucleophilic reaction leads to the forms mono-, di-, tri-, and tetra-substituted benzoquinone and most of the times hydroquinones.

In continuation of our interest on the development of C–H activation methodologies [49–55], we have developed methods for C–H functionalization of quinones [51–55]. A review article covering C–H activation of quinone with main emphasis on C–C bond-forming reactions has been reported [32]. C–H heterofunctionalization of quinone has been carried out using various catalytic systems, consisting of metal/nonmetal catalysts, organocatalyst, photocatalyst, etc. By choosing appropriate catalysts/reagents/additives, we can change the reaction pathway like radical/electrophilic/nucleophilic, etc. (**Figure 6**). For example, recently we developed an I_2 -DMSO system [54] for C–H/S–H and FeCl_3 - $\text{K}_2\text{S}_2\text{O}_8$ system [55] for C–H/C–H radical cross-coupling reactions, which normally occurs via Michael and Friedel-Crafts pathway.

Under this chapter we summarized C–H activation strategies used in heterofunctionalization and heterocyclization of quinones and its application in the synthesis of bioactive heterocycles during the past decade.

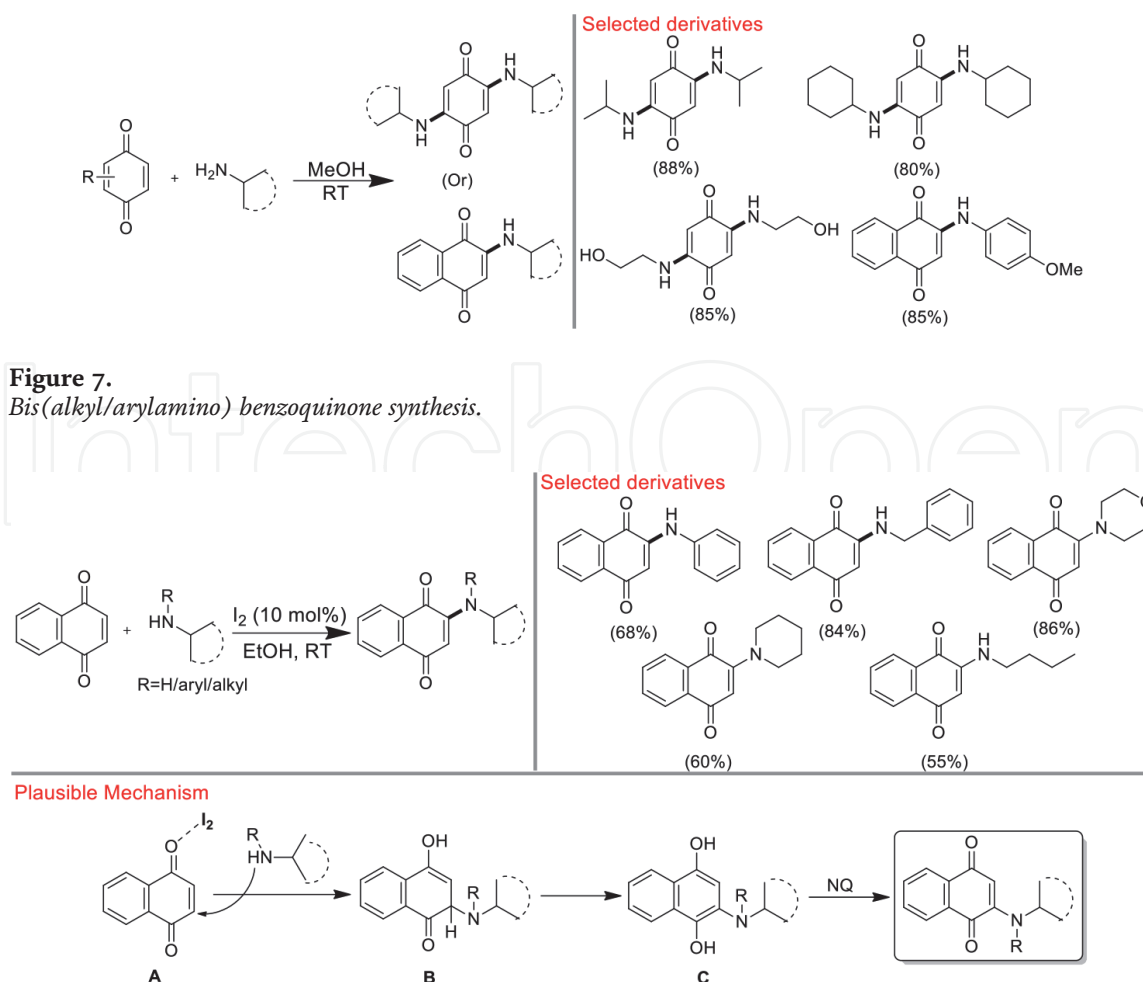
2.1 C–H activation and C–N bond formation on quinones

Aminoquinone derivatives find prominent application in medicinal chemistry and are good building blocks for many heterocyclic compounds [56]. C–N bond-forming reactions are of great importance in quinone chemistry, and in general, oxidative coupling and nucleophilic substitution reactions are involved [57–61]. It has been intensively studied using pre-functionalized quinones [62–68]. Hence, we covered some of the important C–N bond formation methodologies through C–H activation strategies which are given below.

Amines undergo smooth conjugate addition to *p*-quinones in polar solvents at ambient temperature in the absence of a catalyst and additives. Baruah et al., in 2007, synthesized a series of 2,5-bis(alkyl/arylamino)1,4-quinones from the reaction of 1,4-benzoquinone (BQ) with different amines under aerobic condition [69]. The reaction was found to be exceptionally selective and leads to only 2,5-bis(alkyl/arylamino)1,4-benzoquinones of the corresponding amine (**Figure 7**). 2,5-Isomer is formed exclusively due to electrostatic reasons. This is further evident from the fact that 1,4-naphthoquinone (NQ) on reaction with amines gives monosubstituted derivatives. In another study, Yadav et al. [70] studied H₂O-accelerated C–H amination to form highly substituted benzoquinone. In this reaction, water played a dual role of simultaneously activating the *p*-quinone and amine.

Molecular iodine-promoted direct C–H amination of NQ under ultrasonic irradiation was developed by Liu and Ji [71]. The method employs cheap, nontoxic molecular iodine as the catalyst; the desired products were obtained in moderate to excellent yield (**Figure 8**). In mechanism, molecular iodine activates the carbonyl group of the NQ to give intermediate (**A**) and is followed by amine attack at unsaturated position to give the initial addition product (**B**) which tautomerizes to form hydroquinone (**C**), which subsequently undergoes rapid oxidation finally to form quinone system [71].

Garden et al., in 2011, developed Cu(II)-catalyzed amination of NQ by oxidative coupling with derivatives of aniline (**Figure 9**). The best isolated yield was obtained in the presence of catalytic amount of copper, and the hydrated Cu(II) acetate shortens reaction time and reduces side-product formation. The study on the mechanism shows that Michael addition of anilines to NQ is facilitated by Cu(II)



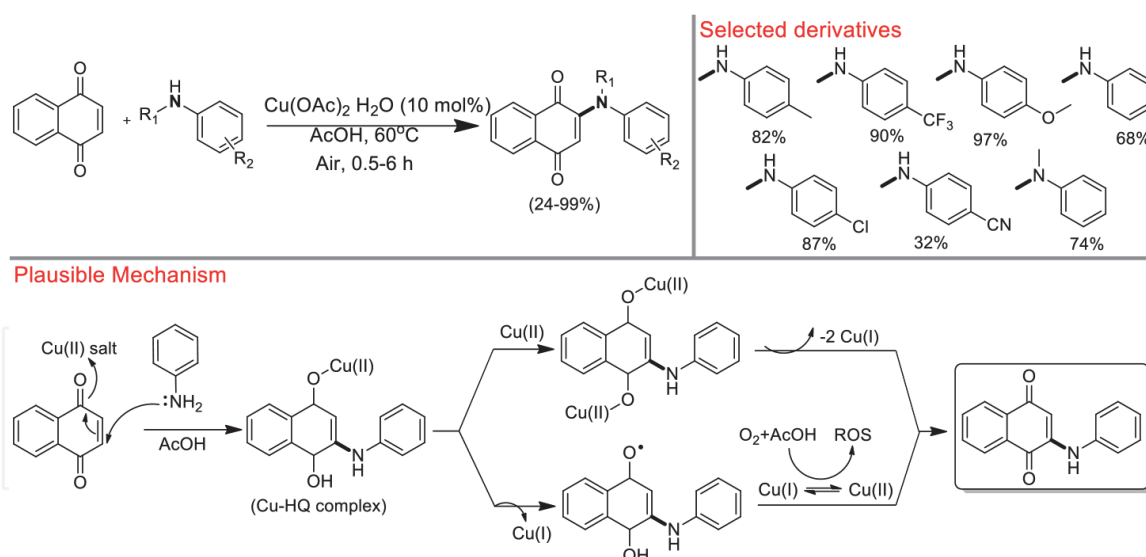


Figure 9.
Cu(II)-catalyzed oxidative coupling with anilines.

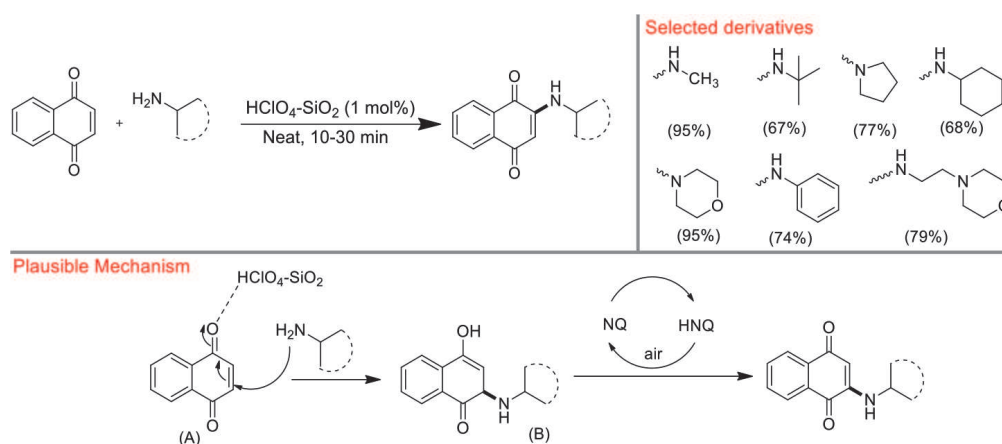


Figure 10.
HClO₄-SiO₂-supported C–N bond on naphthoquinone.

salt. The copper–hydroquinone (Cu–HQ) complex interacts directly with oxygen to give the quinone product or could pass through sequential one electron oxidation steps where the resulting Cu(I) species would then be reoxidized to Cu(II) by oxygen. The mechanistic proposal was supported by ESI-MS experiment, to find that the only copper species reliably observed was the copper cation as the isotopologues Cu(I)(ACN)₂ + (*m/z* 145) and Cu(I)(ACN)₂ + (*m/z* 147) in an approximately 2:1 ratio [72].

Heterogeneous SiO₂-supported HClO₄ catalyst promoting highly efficient and clean conjugate addition of primary and secondary amines with NQ was described by Upendra et al. [73]. Under the catalytic-ultrasonication condition, corresponding 2-amino-1,4-naphthoquinone derivatives were obtained in moderate to high yields without using any solvent (**Figure 10**). The proposed mechanism of this reaction includes two steps such as addition and oxidation. Nucleophilic addition of amines to HClO₄-SiO₂-activated naphthoquinone (A) leads to adduct (B). Further, the adduct (B) oxidized to afford NQ as final product. The authors also described a possibility of aerobic oxidation of hydroquinone (HNQ).

A base-promoted C(sp²)-H sulfonamidation of 1,4-naphthoquinones via [3 + 2] cycloaddition reaction using sulfonyl azides was reported by Ramanathan and Pitchumani [74]. The straightforward, atom, and step-economic protocol provided desired product in moderate to good yield (**Figure 11**). The active alkene moiety of

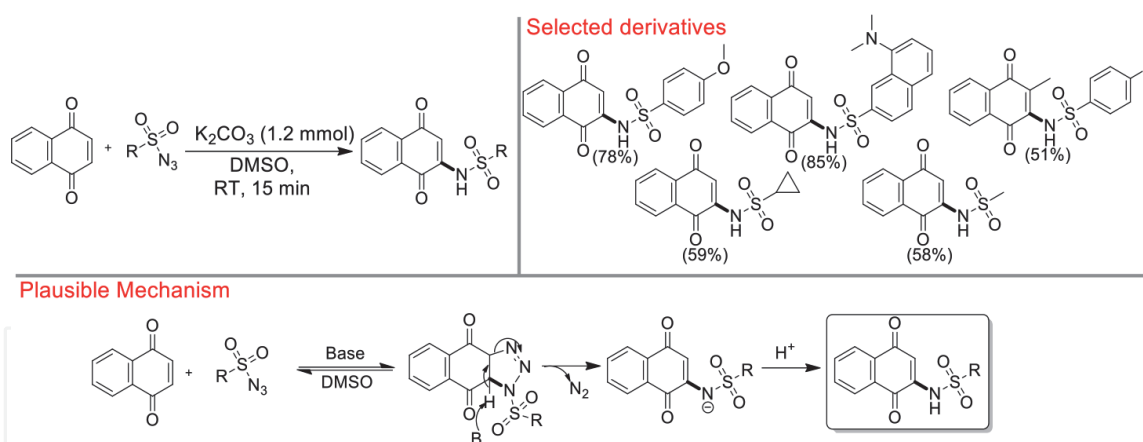


Figure 11.
*K₂CO₃ promoted 1,4-quinone *sp*² C–H sulfonamidation.*

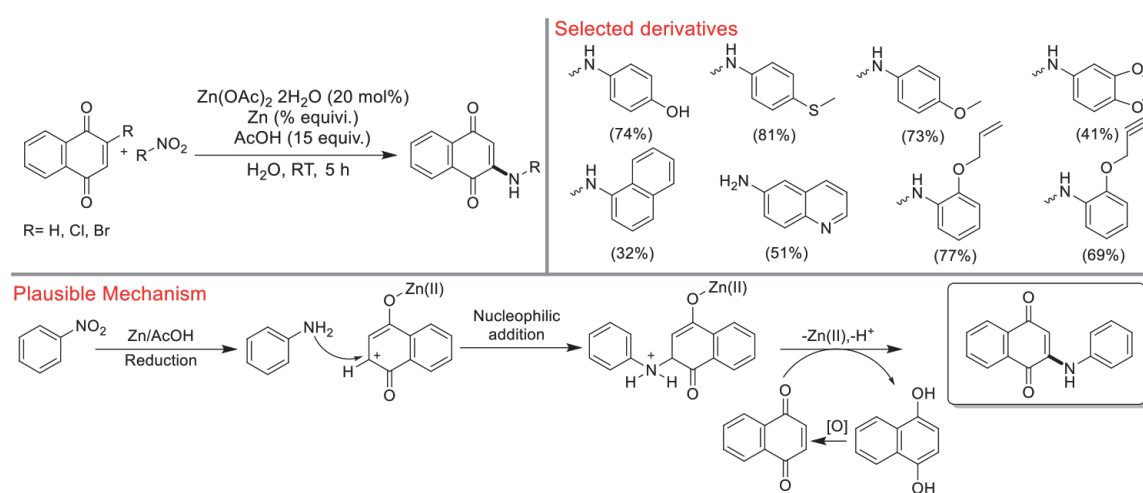


Figure 12.
Zn(II) catalyzed amination using nitro compounds.

quinone undergoes a thermal azide-alkene [3 + 2] cycloaddition followed by proton abstraction, ring opening, and elimination of a nitrogen molecule to form sulfonamidation products. Moreover, they successfully used phosphoryl azide for –NH₂ transfer on NQ and Menadione under optimal condition.

Recently, Chen et al. [75] developed an efficient protocol for the preparation of aminated naphthoquinone starting from NQ and nitro compounds. In the presence of Zn/AcOH system, the nitro compounds were reduced to the corresponding amines (**Figure 12**). Lewis acid Zn(OAc)₂·2H₂O, 1,4-naphthoquinone is activated to generate the complex, and the intermediate reacts with aniline through 1,4-nucleophilic addition to give the adduct (**A**). Then, compound (**A**) can be oxidized to afford product in the presence of molecular oxygen along with losing a proton and the Lewis acid.

Some of the amination reactions, including multicomponent reactions, which lead to the formation of quinone-fused nitrogen heterocycles are described under the Section 3.1.

2.2 C–H activation and C–S bond formation on quinones

Thioethers are common building blocks, found in numerous biologically active compounds and in medicinally useful natural products [76]. The C–S bond construction via direct functionalization of C–H bond with sulfenylating reagents is an

important reaction. Several metal and metal-free catalysts are developed for coupling of quinones with various sulfenylating reagents.

Coupling of arylsulfonyl salts with quinones in the presence of $\text{Pd}(\text{OAc})_2\text{-K}_2\text{CO}_3$ system was developed by Ge et al. [77]. Pd directed C–sulfone to form quinone by C–S coupling (**Figure 13**). Mechanistic study shows that initially oxidative addition of Pd with sulfonyl chloride affords intermediate species **A** which is followed by carbopalladation to form intermediate **B**. After $\beta\text{-H}$ elimination, intermediate **B** released the coupling product to complete the catalytic cycle.

In another study, Huang et al., in 2016, developed reaction with $[\text{Cp}^*\text{IrCl}_2]_2\text{-AgSbF}_6$ [78] system. Like palladium-catalyzed carbopalladation on sulfonyl chloride, here Ir(I) to form carboiridation (**Figure 14**). Further similar way, $\beta\text{-H}$ elimination leads to the final product.

CuI-PPh_3 catalytic system was used for the synthesis of quinonyl thioethers [79]. It was reported to produce sulfonyl-quinones when palladium catalyst was used [77]. In this reaction arylsulfonyl chloride (PhSOCl) was formed on reaction with PPh_3 (**Figure 15**) which on reaction with intermediate **B** (which might have been

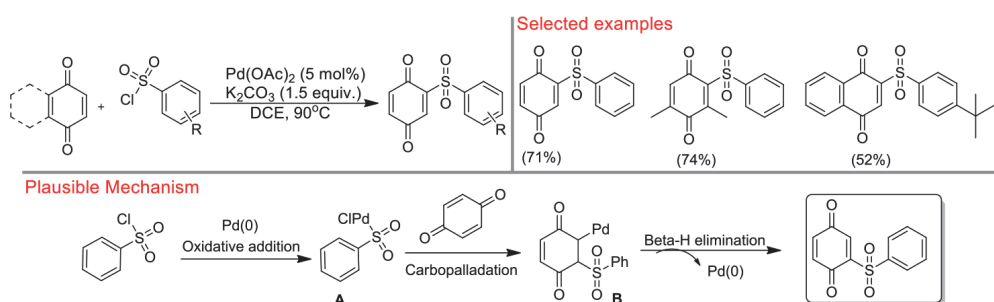


Figure 13.
Pd-catalyzed direct C–sulfone formation on quinone.

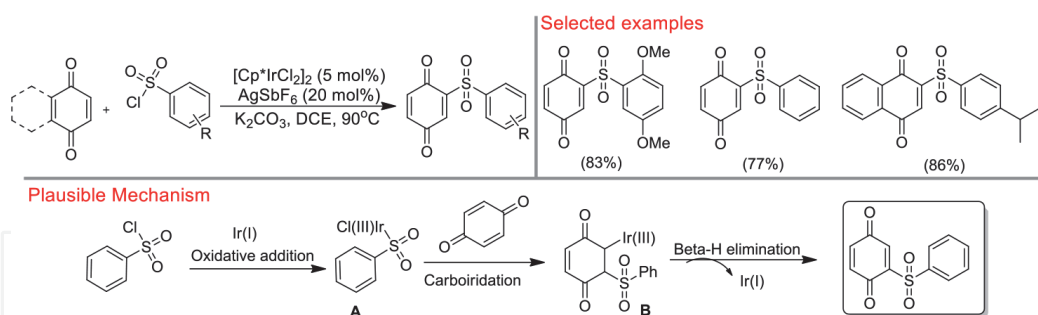


Figure 14.
Ir-catalyzed C–S coupling of quinones with sulfonyl chloride.

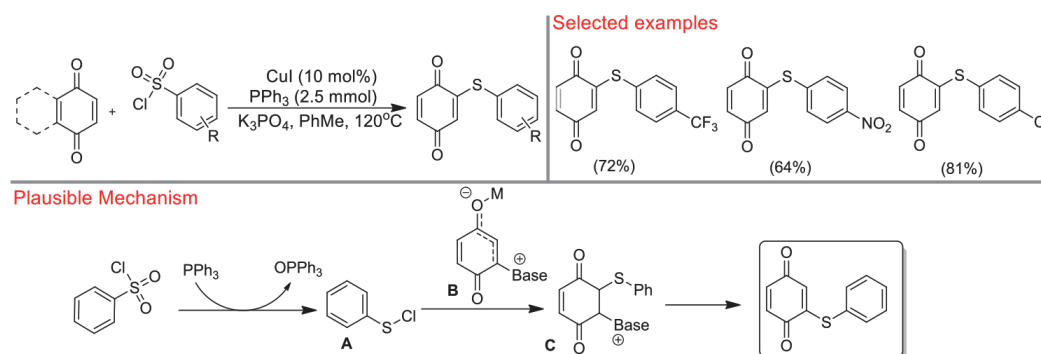


Figure 15.
Cu- PPh_3 -promoted sulfenylation of quinones.

formed with the help of base through Baylis-Hillman process) produced arylthioquinone derivatives.

In 2015 Chou et al. [80] used silver catalyst system for the reaction of various aryl disulfides to synthesize a variety of quinonyl aryl thioether moderate to high yields. The authors carried out some control experiments to predict the plausible mechanism. Studies indicate that the reaction is initiated by active disulfide-silver intermediates formed through interactions of the silver with aryl disulfides in DMSO (**Figure 16**).

Furthermore, under metal-free conditions, various sulfonylating reagents such as [bmim]BF₄-arylsulfinic acids [81], NH₄I-sodium arylsulfonates [82], and H₂O-arylsulfonyl hydrazides [83] systems gave sulfonyl hydroquinones.

Notably, I₂-DMSO system [54] for the thiomethylation of quinone was recently developed by us (**Figure 17**). Based on the verification experiments, we proposed plausible radical pathway. At 120°C, DMSO decomposes to CH₃SH and CH₂O. Meanwhile, iodine releases two iodine radicals at high temperature that reacts with CH₃SH to yield methylthiyl radical (**A**). The addition of methylthiyl radical (**A**) to naphthoquinone results in the formation of radical intermediate (**B**) which should lose H• to another iodine radical leading to the formation of the product.

Moreover, very recently, CuI-O₂ [84] and Co(OAc)₂-O₂ [26] systems were utilized for direct thiol addition to quinone to form ether. In addition, there are limited reports available for the conversion of hydroquinone to quinone followed by in situ C–S bond formation. Notably, under metal-free condition Runtao et al. [85] utilized S-alkylisothiuronium salts on hydroquinone for the synthesis of quinonyl

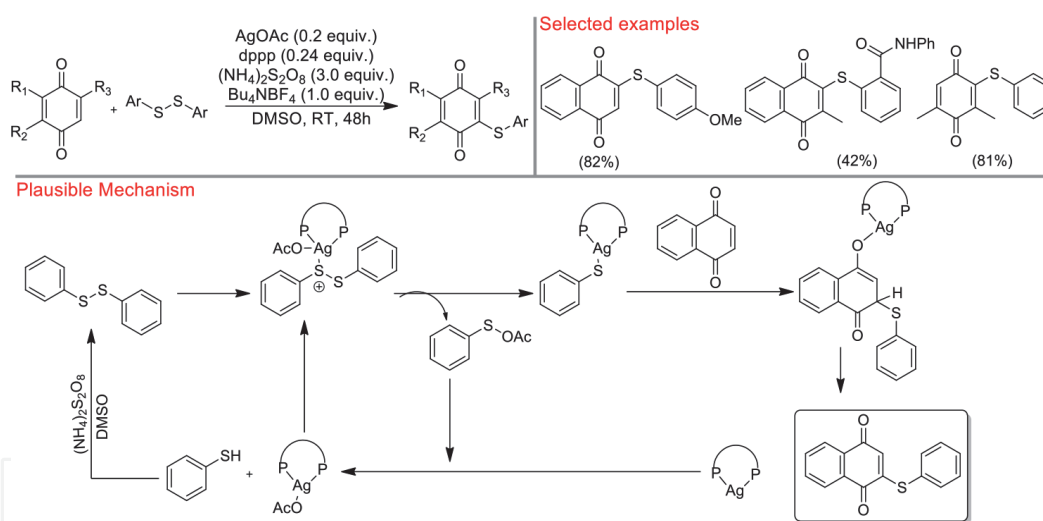


Figure 16.
Silver-catalyzed direct thiolation of quinones.

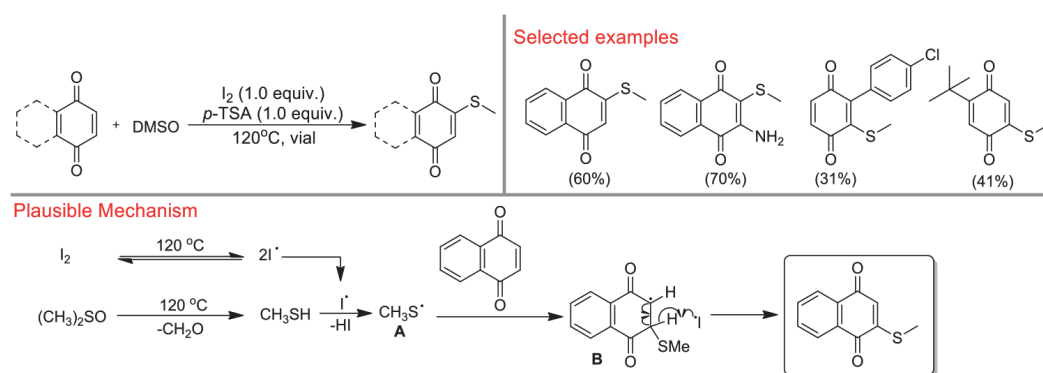


Figure 17.
I₂-DMSO-promoted thiomethylation on quinone.

thioether. In another study, laccase-catalyzed thiol Michael addition on naphthohydroquinone [86] and hydroquinone [87, 88] was observed. Less selectivity and poor yield are the main drawbacks of these enzymatic reactions.

2.3 C–H activation and C–O bond formation on quinones

Naturally occurring quinone molecules, containing C–O link, such as byrsonimaquinone, balsaminone A, maturone and lambertelinare, are biologically important. Several methods for the construction of C–O bond through the activation of C–H bonds on quinone have developed rapidly. However, this research area is less explored than C–N and C–S bond formation as oxygen has lower nucleophilicity than nitrogen and sulfur. In this section, we discuss the formation of the C–O bond through C–H functionalization.

In 2007, Tamura et al. [89] developed a simple method for the synthesis of dibenzofuranquinones, which is the core structure of the natural products balsaminone A, utilizing a novel oxidative cyclization of the quinone-arenols under the special condition (**Figure 18**). As an application of this method to natural product synthesis, a facile synthesis of violet-quinone was demonstrated.

Coupling of propargyl carbonate with quinone through Claisen rearrangement to furanonaphthoquinones (FNQ) was recently established by Zhiyu et al. [90] (**Figure 19**). Though two groups have reported the synthesis of FNQ, both of these methods had several disadvantages. The first method reported by Perez et al. [91] needs use of Cs_2CO_3 , CsI, and CuI as mediator. The second method reported by da Silva Emery et al. [92] employs CuI as catalyst, which still required rigorous condition of refluxing for 24 h.

Weitz reported a useful method for the introduction of hydroxy group through a sequence of in situ Weitz-Scheffer-type epoxidation/epoxide cleavage reaction with $\text{H}_2\text{O}_2/\text{Na}_2\text{CO}_3/\text{H}_2\text{SO}_4$ [93]. In 2013, Schwalbe showed that brominated naphthoquinones could be hydroxylated with nucleophilic substitution under KOH/MeOH [94]. In 2016, Martins has accomplished the Suzuki coupling reactions between 2-hydroxy-3-iodo-1,4-naphthoquinone and boronic acids to prepare several 2-hydroxy-3-aryl-1,4-naphthoquinones by palladium catalyst [37]. In general

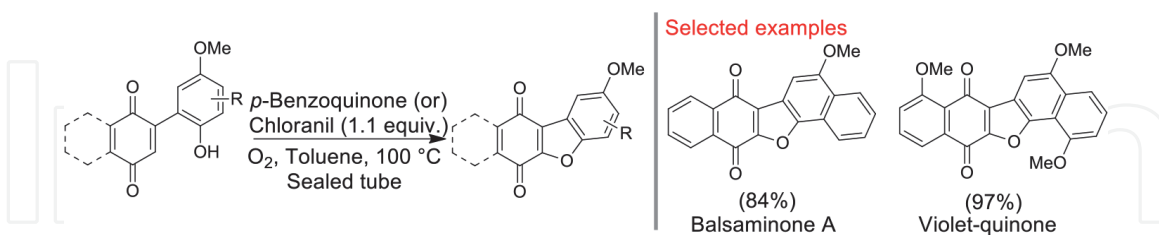


Figure 18.
Oxidative cyclization of quinone-arenols.

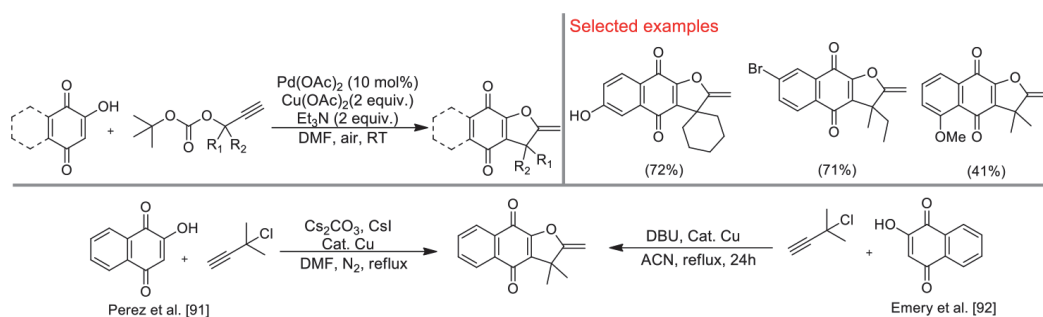


Figure 19.
Synthesis of Furano-naphthoquinone.

most of the existing methods suffer from the requirement for strong alkaline or acidic conditions, metal catalysts, pre-halogenation, and fairly limited substrate scope.

Recently, hydroxylation of naphthoquinone derivatives using tetrabutylammonium iodide (TBAI) as a catalyst and *tert*-butyl hydroperoxide (TBHP) as an oxidant was disclosed by Wang and coworkers [35]. This methodology allowed direct installation of hydroxyl groups on the quinone ring which was used for the synthesis of the corresponding substituted lawsone derivatives (**Figure 20**). Interestingly, parvaquone and lapachol were synthesized by this methodology.

Poulsen et al. [26] disclosed powerful methods for oxidative *p*-quinone functionalization using $\text{Co}(\text{OAc})_2$ and $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ with a collection of O, N, and S-nucleophiles, wherein oxygen was used as the terminal oxidant (**Figure 21**). Preliminary mechanistic observations and synthesis of the cytotoxic natural product stronglylophorine-26 for the first time were presented.

2.4 C–H activation for multiple heterofunctionalization of quinones

Multicomponent reactions (MCRs) constitute one of the most efficient tools in modern synthetic organic chemistry, since they have all features that contribute to an ideal synthesis. Features of this type of reaction are (i) high atom efficiency, (ii) quick and simple implementation, (iii) time and energy saving, (iv) environment friendly, and (v) offer a target and diversity-oriented synthesis. Under this section we have classified some of the multicomponent reaction which let the formation of multiple heterofunctionalization of quinones but not heterocyclization.

Hong et al., in 2017, reported Ag(I)-mediated one-pot multicomponent reaction in which BQ, diarylphosphine oxides, and imines underwent regioselective CDC reaction to undergo dual C–H/P–H (phosphination) and C–H/N–H (amination) on 1,4-benzoquinone (BQ), and the desired products were obtained in moderate yield (**Figure 22**). Under the optimized condition when 1,4-naphthoquinone (NQ) instead of BQ, and aniline instead of corresponding imine was used, lowering of yield of the desired product was observed. Moreover, interestingly a competitive side reaction, namely, hydrophosphinylation reaction was observed in the absence of Ag(I). In this strategy Ag(I) plays versatile role such as a mediator and oxidant. The authors characterized the X-ray crystal structures of several new functionalized quinone derivatives [95].

Based on the control experiments, Ag(I)-mediated mechanism was proposed. Firstly, Ag(I) ions coordinate with BQ oxygen atom, rendering BQ to act as a better

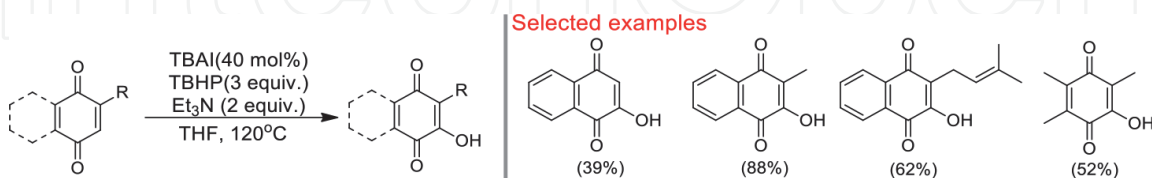


Figure 20.
Hydroxylation of naphthoquinone derivatives.

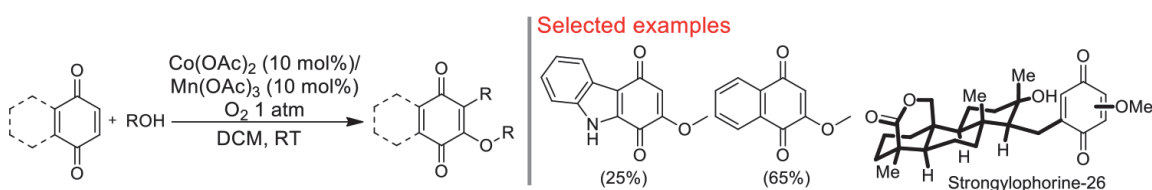


Figure 21.
Oxidative C–H functionalization of *p*-quinone with alcohols.

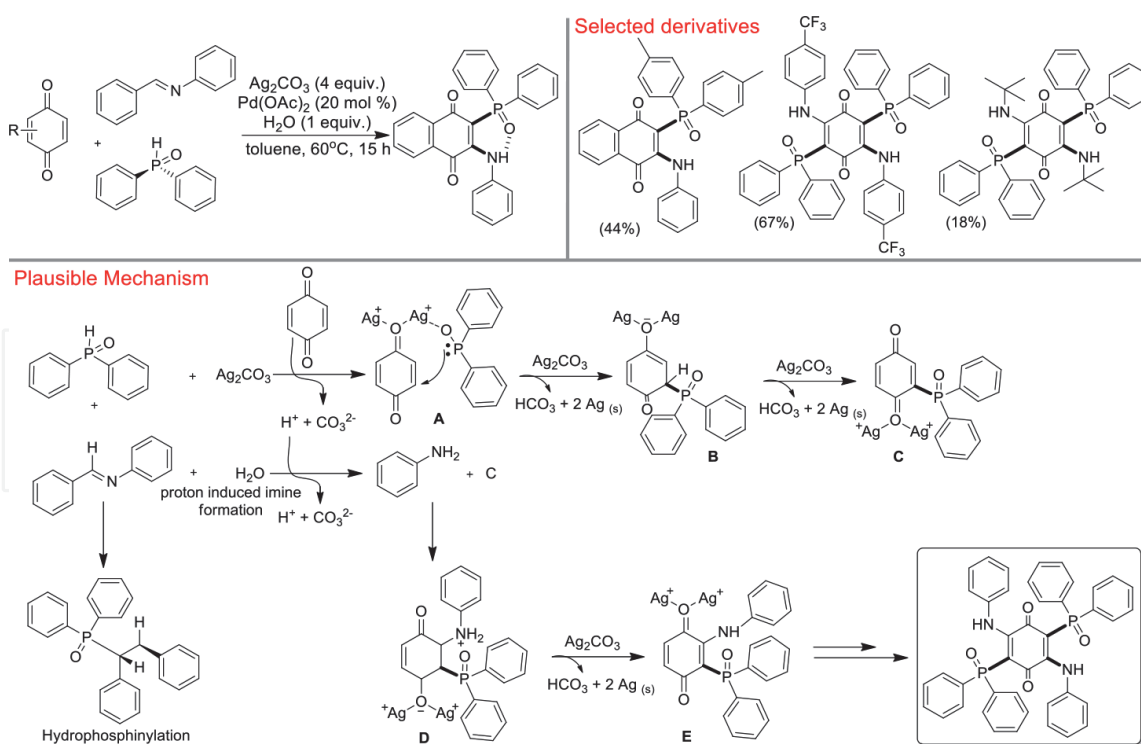


Figure 22.
Ag-mediated regioselective phosphination and amination.

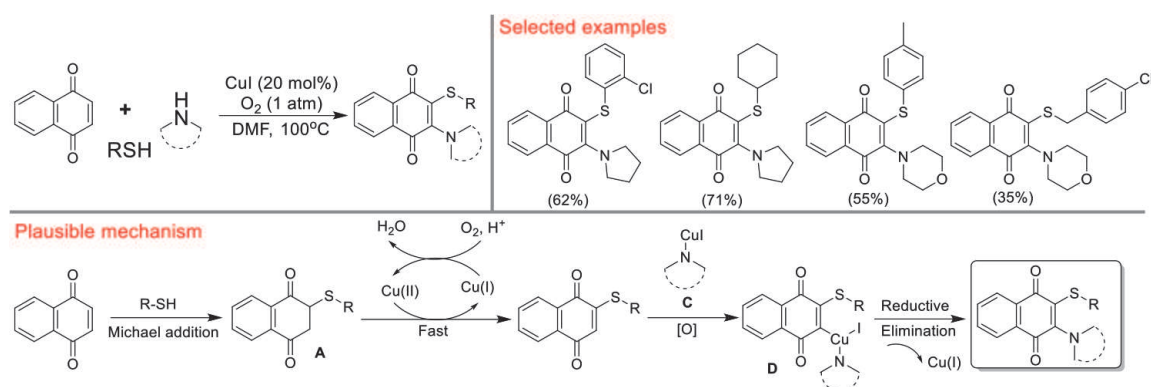


Figure 23.
Cu-catalyzed thioamination on quinone.

electrophile for diarylphosphine oxides, which is presumably released from the adduct (**A**). After the formation of intermediate (**B**), deprotonation takes place with the assistance of CO_3^{2-} , and then two electrons transfer from the intermediate to two AgI ions to give monosubstituted product (**C**) along with two equivalents of AgO species. Further, nucleophilic attack of aniline at the three positions of (**C**) forms intermediate (**D**) which subsequently forms 2,3-disubstituted intermediate (**E**) by deprotonation with the assistance of CO_3^{2-} . Yuan et al. [96] also reported C–P and C–N bond formation on quinone under the same conditions.

One-pot three-component strategy for the direct thioamination of 1,4-naphthoquinone with thiols and amines was recently disclosed by Bing et al. [84]. This approach employed a catalytic amount of CuI as a catalyst and molecular oxygen as a green oxidant. Various 2-amino-3-thio-1,4-naphthoquinones products could be synthesized in moderate to good yields. This catalytic method represents a step-economic and convenient method for the difunctionalization of 1,4-naphthoquinone. Based on the systematic control experiment, the authors proposed the plausible mechanism shown in **Figure 23**. First, the Michael addition of 1,4-naphthoquinone and thiol gave intermediate (**A**), which was immediately oxidized

to intermediate (**B**) by Cu(I)/O₂. Further, the oxidative addition of amine and CuI afforded the Cu(II) species (**C**), which then reacted with intermediate (**B**) giving Cu(III) species (**D**). Finally, intermediate (**D**) underwent reductive elimination producing the desired product.

3. C–H activation for the synthesis of quinone-heterocycle-fused hybrids

Heterocyclic compounds having oxygen (O), nitrogen (N), or sulfur (S) atoms are of tremendous importance [97, 98]. C–X bond formation on quinone gives heterofunctionalized quinones which are very important in organic chemistry and medicinal chemistry, especially due to their striking biological activities [1]. Mitomycin C is an approved quinone-based anticancer drug having pyrrolidine ring [99]. Several other heterofused/linked quinone molecules show good pharmacological properties [100–102]. Structure activity relationship studies from quinonoid compounds showed that the position and increasing the number of heteroatoms are important factors to achieve biological activities [103]. In general, heterocyclization strategies on quinone is mainly classified into three, namely, C–X bond formation, C–C bond formation, and cascade C–C and C–X bonds formations (**Figure 24**).

Selections of suitable intermediates for the synthesis of heterocyclic compounds are very important. Quinones are important intermediate for the assembly of heterocycles. There are several C–H activation methods which are disclosed for the synthesis of valuable heterocyclic compounds such as phenazine, carbazole, indole, phenothiazine, benzothiophene, benzofuran, coumarin, chromene, etc.

Hybrid molecules are based on the principle of combining partial or whole structures in order to create new and possibly more active molecular entities [104–106]. Hybrid molecules can incorporate two or more pharmacophore which lead to the generation of new bioactive compound which show both the activities or altogether a new kind of bioactivity. This is useful to achieve activity on “multiple targets” of a biological system, and this is called multicomponent therapeutic strategy [107].

To achieve synthesis of hybrid organic molecules, different strategies have been adopted time to time [105]. Quinones display wide variety of biological activity, hence combining quinone skeleton with another bioactive heterocycle should basically provide a hybrid organic molecules which may show some valuable biological activity profiles. Some of the interesting quinone-heterocycle-fused hybrid molecules found in the literature are shown in **Figure 25**. There were several strategies developed for the synthesis of quinone-based hybrid molecules [108–111].

Recently, Mancini et al. [112] selected different compounds acting as inhibitors of the cancer protein targets tubulin, human topoisomerase II, and ROCK1 (**Figure 26**).

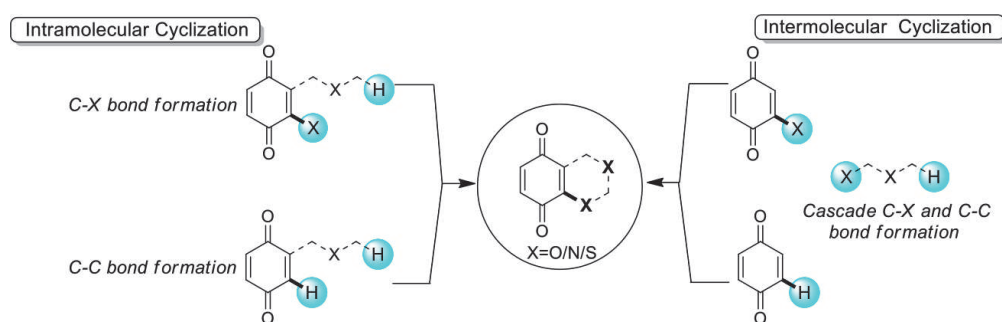


Figure 24.
Heterocyclization approaches on quinone.

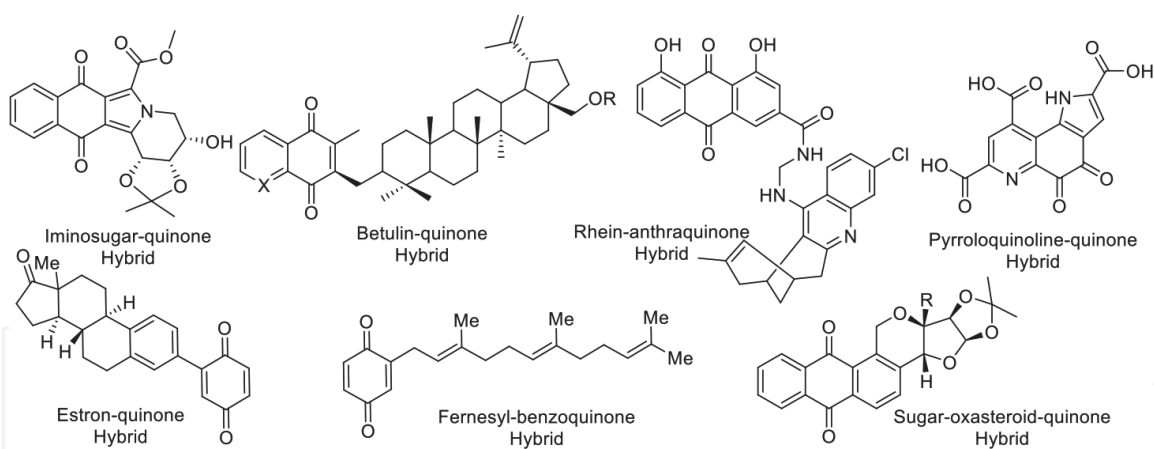


Figure 25.
Selected quinone-heterocycle hybrid molecules.

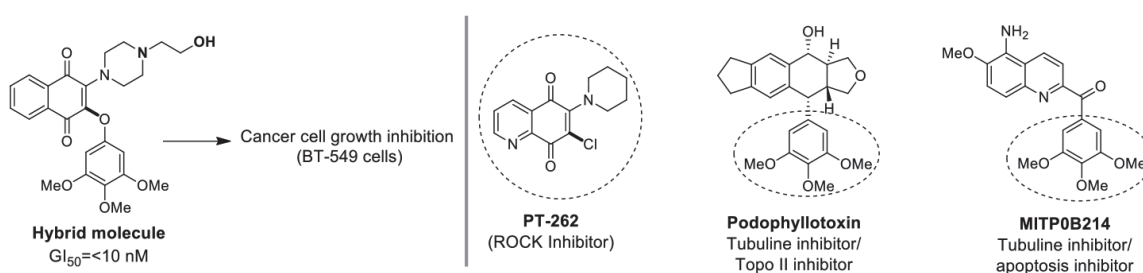


Figure 26.
Quinone-heterocycle hybrids showing anticancer activity.

The synthesized quinone-hybrid molecules displayed good and sometimes better growth inhibition GI_{50} than the ROCK inhibitor Y-27632, the Topo II inhibitor podophyllotoxin, and the tubulin inhibitor combretastatin A-4.

In this direction in the forthcoming sections, we have listed out methods known for the synthesis of quinone-heterocycle hybrid molecules and some of its importance.

3.1 C–H activation for the synthesis of quinone-fused heterocycle hybrids through two component reaction

The oxidative coupling reactions of NH isoquinolones with 1,4-benzoquinone proceeded efficiently to form spiro compounds through C–C and C–N bond in the presence of an Ir(III) catalyst (**Figure 27**) [113]. $Cu(OAc)_2 \cdot H_2O$ was used as external oxidant for substrates such as NQ and other substituted 1,4-benzoquinone. The authors performed preliminary mechanistic experiments and a catalytically competent five-membered iridacycle was isolated and structurally characterized, thus revealing a key intermediate in the catalytic cycle. The first step of mechanism is likely to be a $C(sp^2)$ -H activation process affording a five-membered iridacycle intermediate **A**. The coordination of BQ to **A** delivers intermediate **B**. The migratory insertion of the coordinated BQ into the Ir–C bond leads to intermediate **C** which on protonation by HOAc forms intermediate **D**. Subsequent iridation occurs at the α -position to afford iridacycle **I**, which undergoes a C–N reductive elimination to afford the final product and $Cp^*Ir(I)$. $Cp^*Ir(I)$ is oxidized by BQ in the presence of HOAc to $Cp^*Ir(Oac)_2$ for the next catalytic cycle.

In another study, an Rh-catalyzed substrate-tunable oxidative annulation and spiroannulation reaction of 2-arylindoles with benzoquinone was reported by

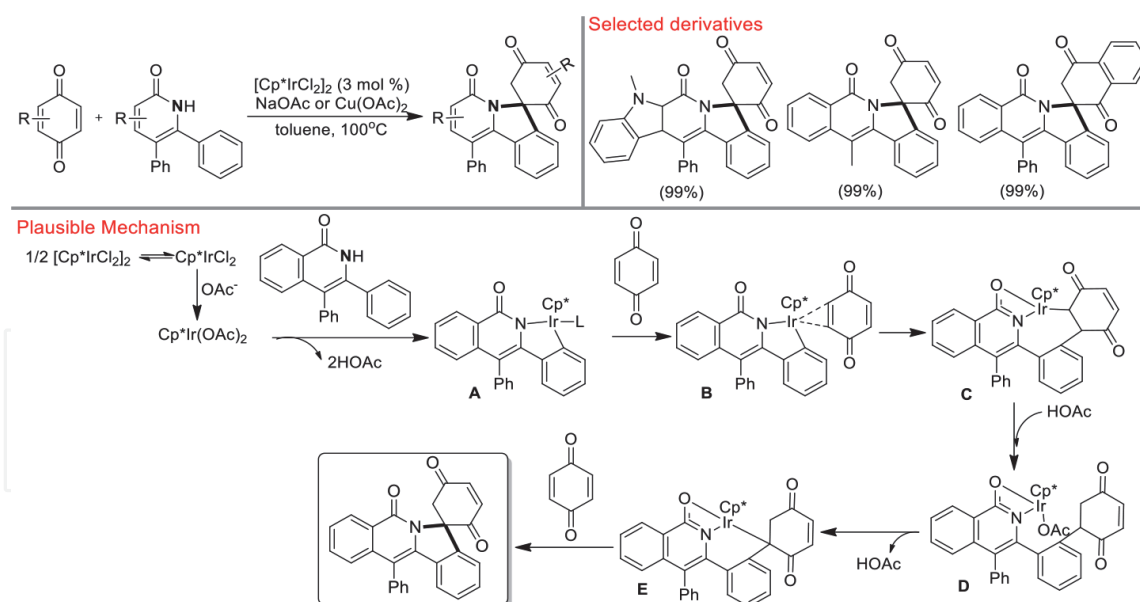


Figure 27.
Ir(III)-catalyzed oxidative coupling of NH isoquinolones.

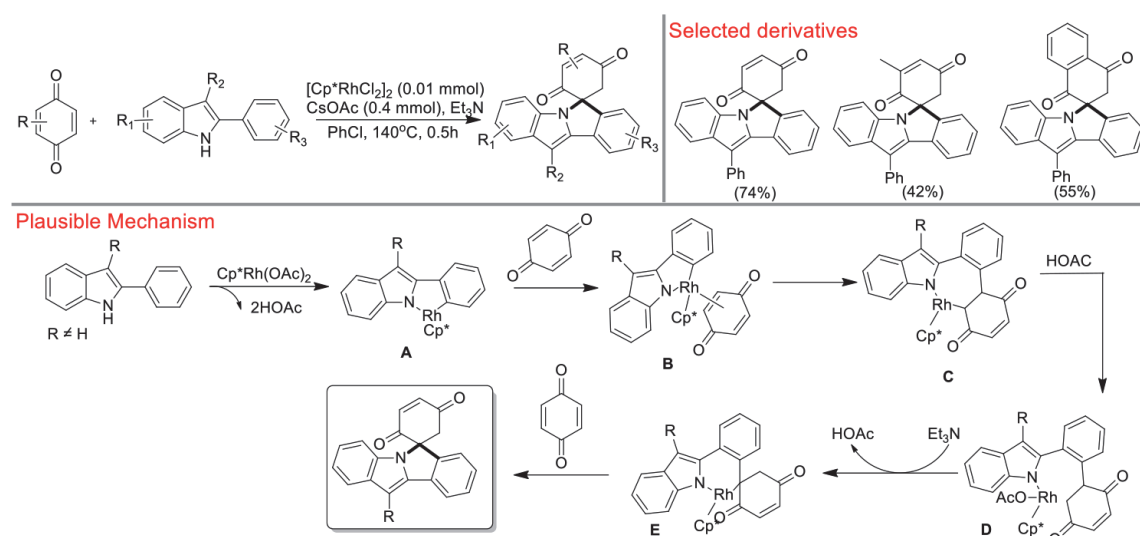


Figure 28.
Rh(III)-catalyzed oxidative coupling of NH indoles.

Shenghai et al. [114]. Mechanistic study revealed that Rh(III)-catalyzed dual N–H/C–H bond cleavage of indole occurs to afford a rhodacycle (A). Further, the coordination of BQ to A yields (B), which undergoes a migratory insertion of the coordinated BQ into the Rh–C bond to furnish (C). Further (C) undergoes a selective Rh–C protonolysis with one equivalent of HOAc to afford the key intermediate (D).

Subsequently, the promotion of nucleophilic attack by Et₃N, the tertiary α-C atom on the Rh center, generates I, which undergoes a C–N reductive elimination to give the desired product and a Rh(I) species. The Rh(I) species is oxidized to the active Rh(III) catalyst by BQ in the presence of HOAc (**Figure 28**).

Cu(II)-catalyzed sequential C,N-difunctionalization reaction between naphthoquinone and β-enaminones [115] which leads to the formation of indaloquinone. New C–C and C–N bonds are easily formed in the reaction course. Cu(II) salt plays a dual role as Lewis acid and oxidative catalyst, and O₂ acts as the terminal oxidant. Based on the experimental results, a plausible reaction pathway was suggested by the authors as shown in **Figure 29**.

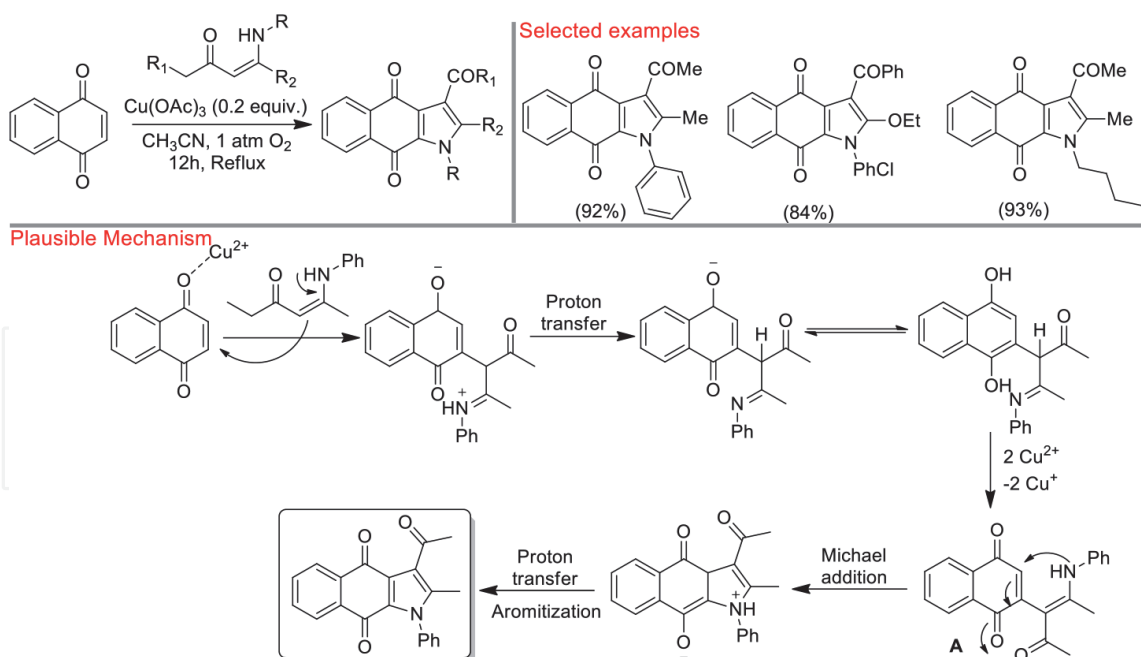


Figure 29.
Cu(II)-catalyzed NQ sequential C,N-difunctionalization.

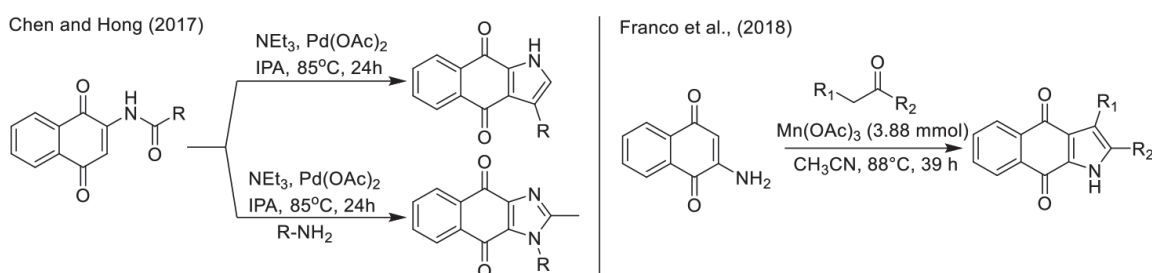


Figure 30.
Pd/Mn-catalyzed C–H functionalization of amino NQ derivatives.

First, nucleophilic attack of α -carbon atom of β -enaminone to Cu^{2+} complexed NQ followed by tautomerization and oxidation by Cu^{2+} results in the formation of intermediate (A). Further, intramolecular Michael addition takes place. Finally, oxidative aromatization affords cyclic product. To complete the catalytic cycle, molecular oxygen was involved for the oxidation of Cu(I) and regeneration of Cu(II).

Chen and Hong [116] reported Pd(II)-catalyzed *ortho*-CH functionalization of amido-substituted 1,4-naphthoquinone with primary and tertiary amines (**Figure 30**). The reaction occurred through an intramolecular rearrangement followed by oxidation process, which lead to the formation of imidazole and pyrrole ring-fused quinone derivatives. In another study, Franco and coworkers [117] performed oxidative free-radical reaction of quinone with either aldehydes or simple ketones in the presence of $\text{Mn}(\text{OAc})_3$ to afford a series of indole-naphthoquinone-fused heterocycles [117].

Mito et al., in 2016, developed a method for benzo[f]indole-4,9-diones from inactivated naphthoquinone with α -aminoacetals [118]. This reaction underwent via intramolecular nucleophilic attack of aminoquinones to aldehydes. Based on the detailed mechanistic studies, the authors proposed the plausible mechanism represented in **Figure 31**.

Haiming and coworkers [119] developed a simple protocol for the synthesis of highly functionalized 3-hydroxycarbazoles by acetic acid-promoted annulation of electron-rich anilines and quinones (**Figure 32**). This chemistry, although tolerant

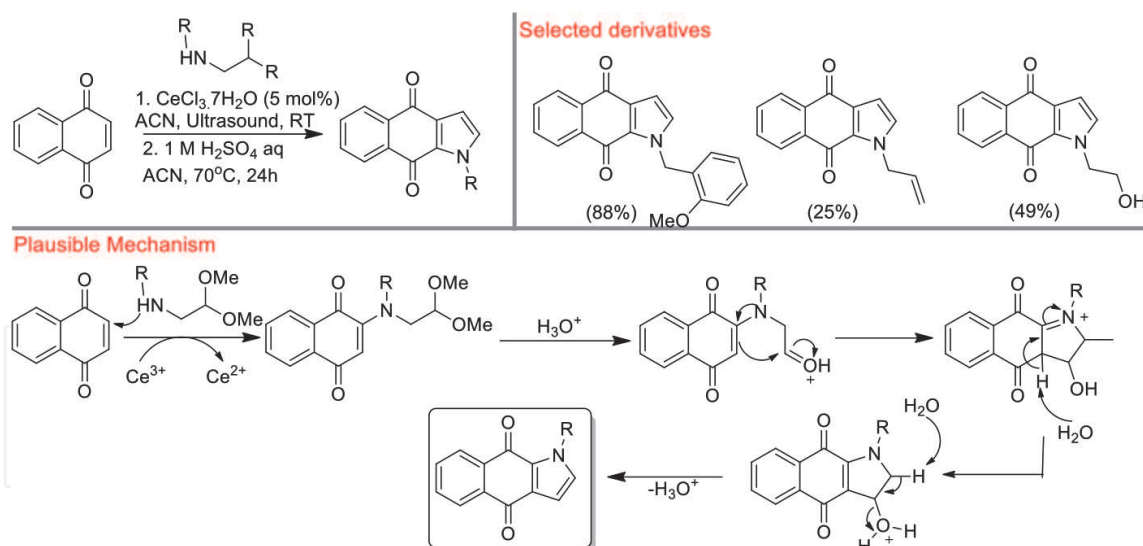


Figure 31.
Ultrasound-assisted one-pot synthesis.

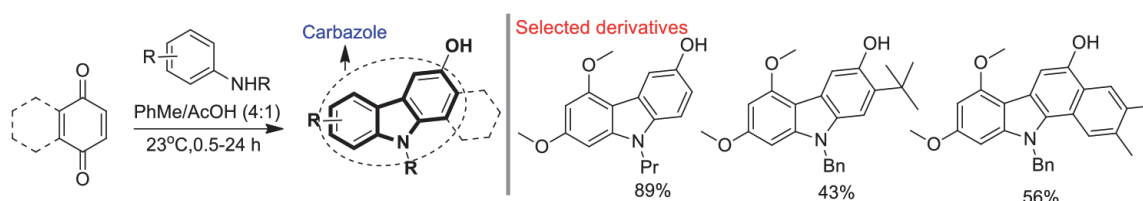


Figure 32.
Annulation of electron-rich anilines and quinones.

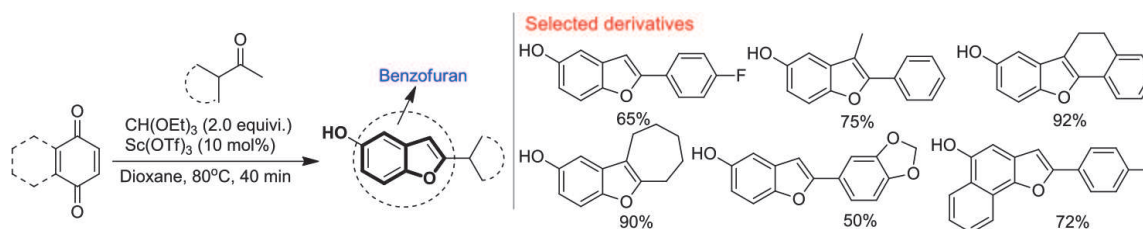


Figure 33.
Synthesis of benzofurans from ketones and 1,4-benzoquinones.

of various quinones, is sensitive to both steric and electronic elements on the anilines, as well as the steric hindrance introduced to the quinones. Although the yields are generally moderate, this reaction nevertheless provides a single-step alternative to prepare various otherwise difficult to make densely substituted 3-hydroxycarbazoles under mild conditions. Similarly to Nenitzescu indole synthesis, the mechanism of this carbazole formation is believed to involve a C–C bond formation by a Michael-type nucleophilic addition of aniline to quinone, followed by intramolecular cyclization and dehydration.

In another study, a sequential Michael addition and intramolecular cyclization reaction of ketones and 1,4-benzoquinones by using triethyl orthoformate as an additive (**Figure 33**). In the presence of $\text{Sc}(\text{OTf})_3$ as catalyst, triethyl orthoformate may be utilized to convert enolizable ketone into ethyl vinyl ether. As a result, nucleophilicity increases. This reaction is a simple way to obtain 5-hydroxybenzofurans. The authors used this methodology to synthesize some important 2-phenylbenzofuran derivatives [120].

Wang et al. [121] developed $\text{Pd}(\text{OAc})_2/\text{BQ}$ catalytic system for ring contraction reactions which allow 2-hydroxyl-1,4-naphthoquinones to convert into various

phthalides. The significance of phthalide and fulvene scaffolds as structural units should render this method attractive for both medicinal chemistry and synthetic ring contraction reactions chemistry, paving the way for efficient synthesis of other complex cyclic systems (**Figure 34**). Moreover, they utilized phthalides as versatile synthetic intermediates toward many other useful synthetic building blocks.

Peddinti et al., in 2014, reported [122] Michael addition of the 1,4-benzoxazinone derivatives, a novel class of vinylogous carbamates to the Michael acceptors. 1,4-Benzoxazinone derivative undergoes Michael addition with *p*-quinone in the presence of trifluoroacetic acid, and subsequent cyclization affords corresponding products (**Figure 35**).

A nucleophilic addition of terminal alkynes to 2-methoxy-1,4-benzoquinone afforded the corresponding quinols containing an alkyne unit [123], which were converted to phenols via mild Zn-mediated reduction. After proper protection of the free phenolic OH group, under metal-free system, 5-endo-dig iodocyclization allowed facile access to a number of 3-iodobenzofurans (**Figure 36**).

After successful establishment of kinetic controlled, Rh(III)-catalyzed annulation of C–H bonds with quinones for chemo-selective synthesis of dibenzo[*b,d*]pyran-6-ones [124] and phenanthridinones [125], Yang and coworkers [126] demonstrated a three-component cascade reaction for 6H-benzo[*c*]chromenes. Similarly, this reaction involved Rh(III)-catalyzed annulation of aryl ketone O-acyloximes, quinones, and acetone (**Figure 37**).

In another report [127], the synthesis of diverse dihydronaphtho[1,2-*b*]furans starting from 1,4-naphthoquinones and olefins in the presence of ceric ammonium nitrate (CAN) was reported. The reaction was based on the CAN-catalyzed [3 + 2] cycloaddition of 1,4-naphthoquinones. This methodology was also used to synthesize the biologically important natural product furomollugin in only two steps (**Figure 38**).

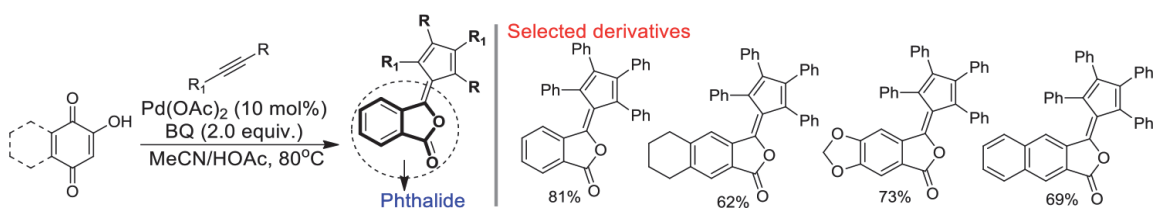


Figure 34.
Synthesis of phthalides via ring contraction reactions.

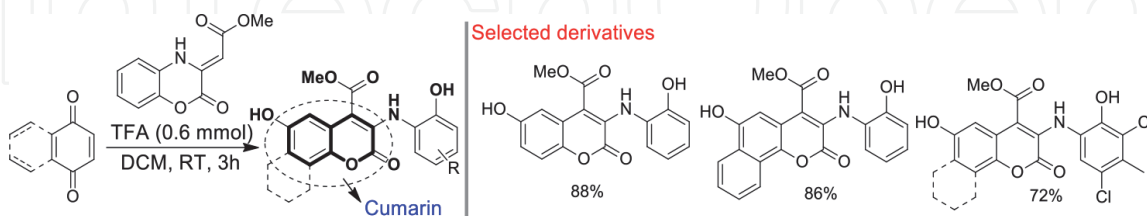


Figure 35.
TFA-catalyzed Michael addition reaction for coumarin.

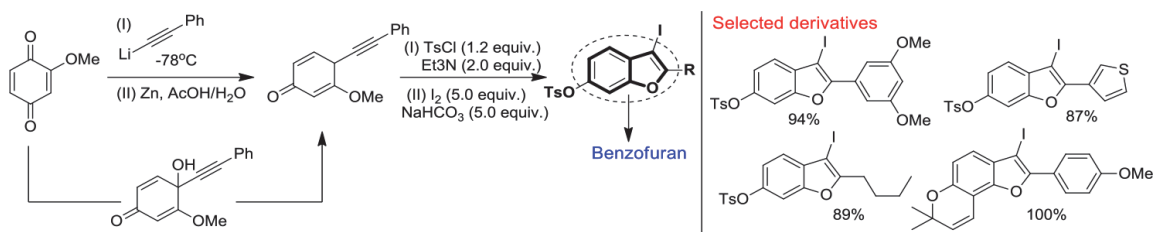


Figure 36.
5-Endo-dig iodocyclization reaction for 3-iodobenzofurans.

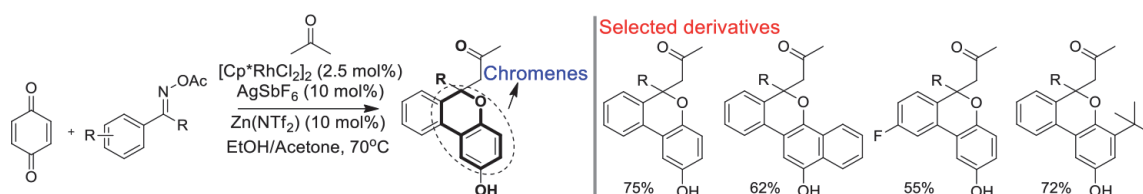


Figure 37.
Rh(III)-catalyzed annulation for benzochromenes.

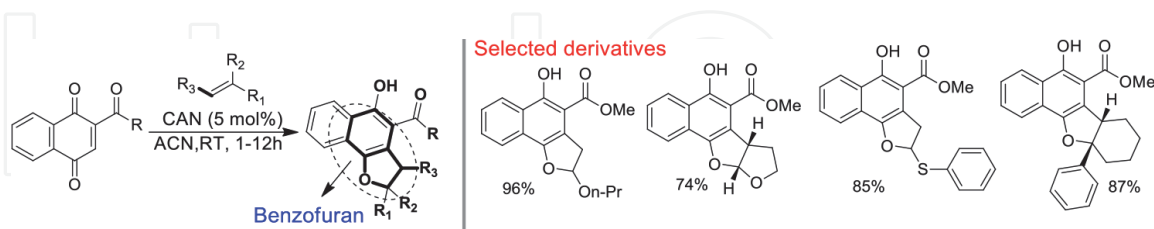


Figure 38.
CAN-catalyzed [3 + 2] cycloaddition of 1,4-naphthoquinones.

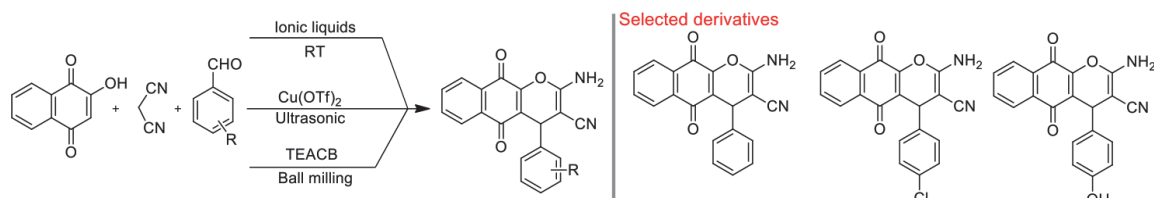


Figure 39.
Three-component synthesis of functionalized 4H-pyrans.

3.2 C–H activation for the synthesis of quinone-fused heterocycle hybrids through multicomponent reaction

The applications of MCRs have been sequenced with multiple ring-forming reactions that leads thereby to the synthesis of diverse heterocyclic scaffolds. MCRs on quinones were used for the generation of quinone-fused heterocycles.

Seven mild basic ionic liquids [128] made out of 1,8-diazabicyclo[5.4.0]-undec-7-en-8-ium acetate, pyrrolidinium acetate, pyrrolidinium formate, piperidinium acetate, piperidinium formate, *N*-methylimidazolium formate, and 3-hydroxypropylammonium acetate were used as catalyst for three-component coupling of aldehyde, malononitrile, and 2-hydroxynaphthoquinone for the formation of 2-amino-3-cyano-4-aryl-5,10-dioxo-5,10-dihydro-4H-benzo[*g*]chromene and hydroxyl naphthalene-1,4-dione derivatives under ambient and solvent-free conditions (**Figure 39**). The main advantages of this protocol are mild, solvent-free conditions, ecofriendly catalysts and easy to work-up procedure. Similar reaction was also reported by Javanshir et al. [129] and Manisankar et al. [130] using organocatalyst and copper catalyst, respectively.

Notably, Cao and coworkers [131] developed one-pot, pseudo-four-component reaction of 2-hydroxy-1,4-naphthoquinone, aromatic amine, and formaldehyde in aqueous media under ultrasound irradiation (**Figure 40**) naphthoquinone-fused oxazine derivatives under this operationally simple and efficient condition.

A proposed mechanism shows that amination reaction occurred first between the formaldehyde and amine, followed by H₂O elimination to furnish intermediate **A** which was then attacked by 2-hydroxy-1,4-naphthoquinone to furnish an intermediate **B**, which further reacted with formaldehyde and eliminated H₂O to produce intermediate **C**. At last the final product was formed through an intramolecular cyclization process.

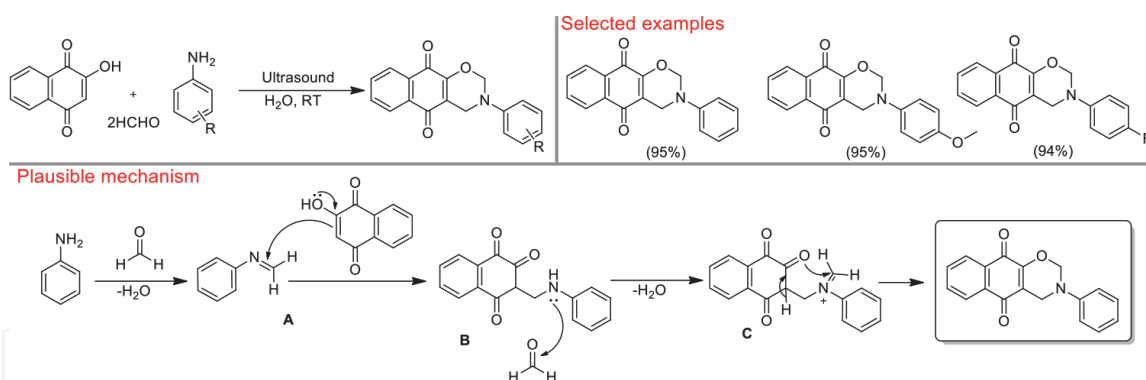


Figure 40.
Synthesis of naphthoquinone-fused oxazine derivatives.

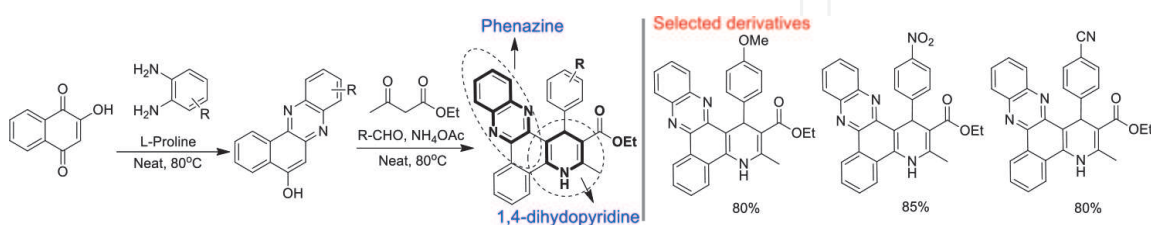


Figure 41.
Synthesis of phenazine-dihydropyridine molecules.

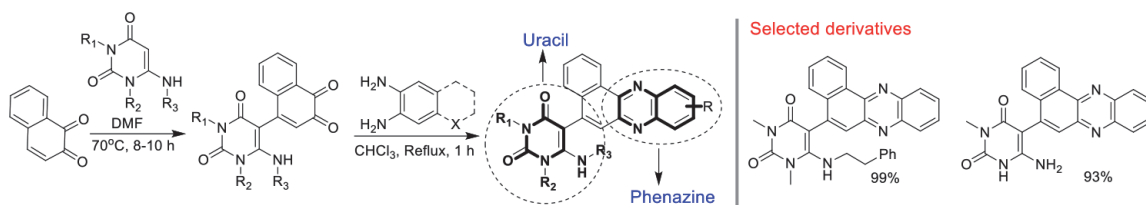


Figure 42.
Synthesis of uracil-phenazine molecules.

Afshin and coworkers [132] developed L-proline-catalyzed one-pot, two-step, five-component reaction for the synthesis of novel 1,4-dihydrobenzo[a]pyrido[2,3-c]phenazines by the condensation reaction of 2-hydroxynaphthoquinone, aromatic 1,2-diamines, aldehydes, ammonium acetate, and ethyl acetoacetate under conventional heating in solvent-free conditions. In this domino transformation, six bonds and two new rings such as phenazine and 1,4-dihydropyridine are efficiently formed (**Figure 41**). High yields, short reaction time, operational simplicity, easy work-up procedure, avoidance of hazardous or toxic catalysts, and organic solvents are the main advantages of this green methodology.

In another study [133], catalyst-free synthesis of aminouracils bearing naphthoquinone in DMF system was developed by Jamaledini et al. [133]. Further it was used as intermediate for the synthesis of uracil-phenazine linked heterocycles via condensation reaction with various vicinal diamines, in chloroform under reflux condition (**Figure 42**).

Copper-catalyzed, TEMPO-mediated straightforward synthesis of 2,3-disubstituted naphtho[2,1-b]thiophene-4,5-diones via cross-dehydrogenative thienannulation was reported [134]. The reaction proceeded via in situ generated naphthalene-1,2-diones by dearomatization of β -naphthols, followed by oxidative heteroannulation with α -enolic dithioesters chemoselectively (**Figure 43**).

Further, the naphtho[2,1-b]thiophene-4,5-diones undergo L-proline-catalyzed cross-dehydrogenative coupling (CDC) with *ortho*-phenylenediamine enabling

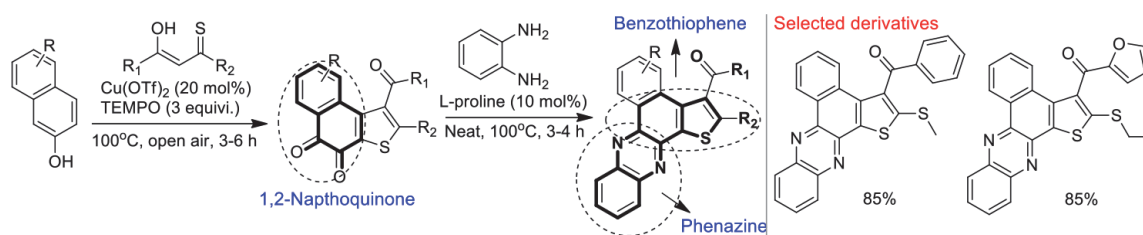


Figure 43.
Synthesis of benzothiophene-phenazine molecules.

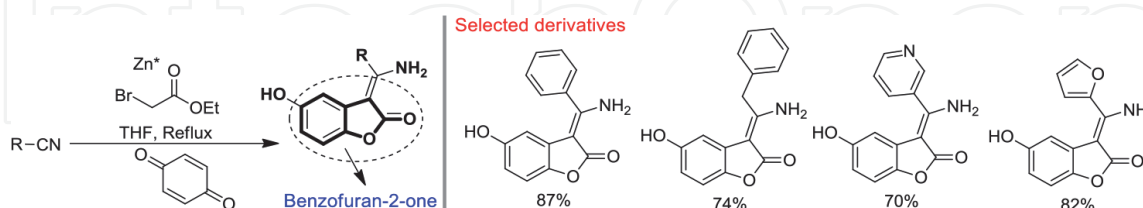


Figure 44.
Tandem Blaise-Nenitzescu reaction for benzofuran-2(3H)-ones.

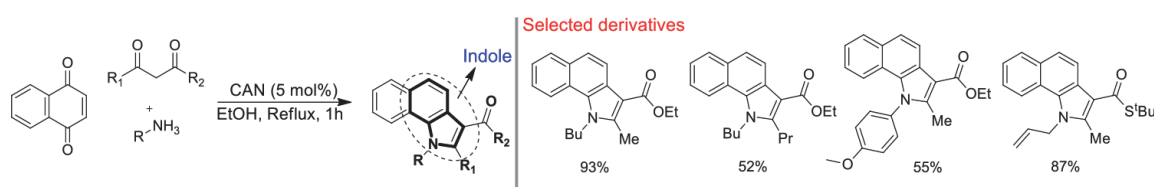


Figure 45.
CAN-catalyzed three-component domino sequences.

formation of pentacyclic benzo[a]thieno[3,2-c]phenazine derivatives in good yields under solvent-free conditions.

Interestingly, Lee and coworkers [134] reported one-pot synthesis of benzofuran-2(3H)-one derivatives from nitriles. This result underscore the high potential of the Blaise reaction intermediate as an amphiphilic organozinc complex for forming carbon–carbon bonds and provides a divergent synthetic platform toward heterocycles (**Figure 44**).

CAN-catalyzed three-component reaction between primary amines, β -dicarbonyl compounds, and functionalized or unfunctionalized naphthoquinones was reported by Menendez et al. [62]. The enamine formation Michael addition-intramolecular imine formation domino sequence starting from amines, β -dicarbonyl compounds, and quinones, in a three-component variation of the Nenitzescu indole synthesis (**Figure 45**). Further, protocol was extended to the synthesis of linear benzo[f]indolequinones by using pre-functionalized quinones as the starting materials. Moreover, the benzo[g]indole derivatives were transformed into 9,12-dihydro-8H-azepino[1,2-a]benzo[g]-indoles, a new class of fused indole derivatives, using a C-alkylation/ring-closing metathesis strategy.

4. Conclusion

Recent advances in the direct heterofunctionalization and heterocyclization of quinones were summarized in this chapter. Most of the C–hetero bond formation on quinone occurred via Michael addition in the presence/absence of a metal catalyst. Transition metal-catalyzed cross-coupling reactions were another important strategy for the direct functionalization of quinones. These reactions allowed for the

construction of not only simple coupling products but also many important biologically active compounds. Moreover, the formation of C–O bond on quinone was less explored than C–N and C–S bond formation; it may be due to the fact that oxygen has lower nucleophilicity than nitrogen and sulfur, and lack of suitable synthetic reagents that can tolerate the presence of oxygen functional groups. However, due to the unique electronic property of quinones, the types of direct functionalization remain limited, and great efforts are still needed in the future.

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Conflict of interest

The authors declare no conflict of interest.

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