We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

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

*Andivelu Ilangovan and
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 β -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, β -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-PPh₃-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, cumarin, 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.

Acknowledgements

AKTP would like to thank UGC-RFSMS (F.No.25-1/2014-2015 (BSR)/7-22/2007-(BSR) Dated: 13.03.2015), New Delhi, for the award of the fellowship for Ph.D.

Conflict of interest

The authors declare no conflict of interest.

Author details

Andivelu Ilangoan* and Thumadath Palayullaparambil Adarsh Krishna
School of Chemistry, Bharathidasan University, Tiruchirappalli, Tamilnadu, India

*Address all correspondence to: ilangoanbdu@yahoo.com

IntechOpen

© 2020 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

References

- [1] Judy LB, Tareisha D. Formation and biological targets of quinones: Cytotoxic versus cytoprotective effects. *Chemical Research in Toxicology*. 2017;**30**(1): 13-37. DOI: 10.1021/acs.chemrestox.6b00256
- [2] Thomson RH. Naturally Occurring Quinones IV. London: Blackie Academic; 1997
- [3] Marcin S, Artur O. Electronic connection between the quinone and cytochrome redox pools and its role in regulation of mitochondrial electron transport and redox signaling. *Physiological Reviews*. 2015;**95**:219-224. DOI: 10.1152/physrev.00006.2014
- [4] Judy LB, Michael AT, Trevor MP, Glenn D, Terrence JM. Role of quinones in toxicology. *Chemical Research in Toxicology*. 2000;**13**(3):135-160. DOI: 10.1021/tx9902082
- [5] Azadeh G, Jayne G, Jennifer RB, Cecilia CR, Jennette AS, Adam MC. A focused library synthesis and cytotoxicity of quinones derived from the natural product bolinaquinone. *Royal Society Open Science*. 2018;**5**(4): 1-23. DOI: 10.1098/rsos.171189
- [6] Eun JS, Jae HK, Kayoung K, Chan BP. Quinone and its derivatives for energy harvesting and storage materials. *Journal of Materials Chemistry A*. 2016; **4**:11179-11202. DOI: 10.1039/C6TA03123D
- [7] Bolton JL, Dunlap TL, Dietz BM. Formation and biological targets of botanical o-quinones. *Food and Chemical Toxicology*. 2018;**120**: 700-707. DOI: 10.1016/j.fct.2018.07.050
- [8] Almeida WP, Correia CR. A total synthesis of the sesquiterpene quinone metachromin-A. *Tetrahedron Letters*. 1994;**35**(9):1367-1370. DOI: 10.1016/S0040-4039(00)76220-4
- [9] Crooke ST, Bradner WT. Mitomycin C: A review. *Cancer Treatment Reviews*. 1976;**3**(3):121-139. DOI: 10.1016/S0305-7372(76)80019-9
- [10] Norman AR, Norcott P, McErlean CS. Overview of the synthesis of carbazoloquinone natural products. *Tetrahedron Letters*. 2016;**57**(36): 4001-4008. DOI: 10.1016/j.tetlet.2016.07.092
- [11] Sharna-kay AD, Downer-Riley NK. An improved synthesis of balsaminone A. *Synlett*. 2019;**30**(03):325-328. DOI: 10.1055/s-0037-1611975
- [12] Hussain H, Krohn K, Ahmad VU, Miana GA, Green IR. Lapachol: An overview. *ARKIVOC Journal*. 2007;**2**: 145-171
- [13] Ojha S, Al Tae H, Goyal S, Mahajan UB, Patil CR, Arya DS, et al. Cardioprotective potentials of plant-derived small molecules against doxorubicin associated cardiotoxicity. *Oxidative Medicine and Cellular Longevity*. 2016;**2016**:1-19. DOI: 10.1155/2016/5724973. Article ID 5724973
- [14] Yusuf MA, Singh BN, Sudheer S, Kharwar RN, Siddiqui S, Abdel-Azeem AM, et al. Chrysophanol: A natural anthraquinone with multifaceted biotherapeutic potential. *Biomolecules*. 2019;**9**(2):68. DOI: 10.3390/biom9020068
- [15] Zhou YX, Xia W, Yue W, Peng C, Rahman K, Zhang H. Rhein: A review of pharmacological activities. *Evidence-Based Complementary and Alternative Medicine*. 2015;**2015**:1-10. DOI: 10.1155/2015/578107
- [16] Gu JQ, Graf TN, Lee D, Chai HB, Mi Q, Kardono LB, et al. Cytotoxic and antimicrobial constituents of the bark of *Diospyros maritima* collected in two

- geographical locations in Indonesia. *Journal of Natural Products*. 2004;**67**(7): 1156-1161. DOI: 10.1021/np040027m
- [17] Akhter S, Rony SR, Al-Mansur MA, Hasan CM, Rahman KM, Sohrab MH. Lawsonol, a new bioactive naphthoquinone dimer from the leaves of *Lawsonia alba*. *Chemistry of Natural Compounds*. 2018;**54**(1):26-29. DOI: 10.1007/s10600-018-2251-0
- [18] Quinone Chemistry, Web of Science-Search for peer-reviewed journals, articles, book chapters and open access content. 2019
- [19] Zhengkai C, Binjie W, Jitan Z, Wenlong Y, Zhanxiang L, Yuhong Z. Transition metal-catalyzed C–H bond functionalizations by the use of diverse directing groups. *Organic Chemistry Frontiers*. 2015;**2**:1107-1295. DOI: 10.1039/C5QO00004A
- [20] Alison EW, Shannon S. Quinone-catalyzed selective oxidation of organic molecules. *Angewandte Chemie International Edition*. 2015;**54**(49): 14587-14977. DOI: 10.1002/anie.201505017
- [21] Ruipu Z, Sanzhong L. Bio-inspired quinone catalysis. *Chinese Chemical Letters*. 2018;**29**(8):1193-1200. DOI: 10.1016/j.ccllet.2018.02.009
- [22] Huaisu G, Weilin G, Yang L, Xiaohua R. Quinone-modified metal-organic frameworks MIL-101(Fe) as heterogeneous catalysts of persulfate activation for degradation of aqueous organic pollutants. *Water Science and Technology*. 2019;**79**(12):2357-2365. DOI: 10.2166/wst.2019.239
- [23] Lysons TW, Sanford MS. Palladium catalyzed ligand directed C–H functionalization reactions. *Chemical Reviews*. 2010;**110**:1147-1169. DOI: 10.1021/cr900184e
- [24] Liu C, Zhang H, Shi W, Lei A. Bond formations between two nucleophiles: Transition metal catalyzed oxidative cross-coupling reactions. *Chemical Reviews*. 2011;**111**:1780-1842. DOI: 10.1021/cr100379j
- [25] Yuta F, Victoriano D, Ian BS, Ryan G, Matthew DB, Baran PS. Practical C–H functionalization of quinones with boronic acids. *Journal of American Chemical Society*. 2011; **133**(10):3292-3295. DOI: 10.1021/ja111152z
- [26] Yu W, Hjerrild P, Jacobsen KM, Tobiesen HN, Clemmensen L, Poulsen TB. A catalytic oxidative quinone heterofunctionalization method: Synthesis of stronglylophorine-26. *Angewandte Chemie International Edition*. 2018;**57**(31):9805-9809. DOI: 10.1002/anie.201805580
- [27] Engler TA, Reddy JP. An unusual gamma-silyl effect in titanium tetrachloride catalyzed arylation of 1,4-benzoquinones. *Journal of Organic Chemistry*. 1991;**56**:6491. DOI: 10.1021/jo00023a005
- [28] Pirrung MC, Liu Y, Deng D, Halstead DK, Li Z, May JF, et al. Methyl scanning: Total synthesis of demethylasterriquinone B1 and derivatives for identification of sites of interaction with and isolation of its receptors. *Journal of American Chemical Society*. 2005;**127**:4609-4626. DOI: 10.1021/ja044325h
- [29] Zhang HB, Liu L, Chen YJ, Wang D, Li CJ. Synthesis of aryl-substituted 1,4-benzoquinone via water-promoted and In(OTf)₃-catalyzed in situ conjugate addition-dehydrogenation of aromatic compounds to 1,4-benzoquinone in water *Advance Synthesis and Catalysis*. 2006;**348**:229-235. DOI: 10.1002/adsc.200505248
- [30] Katarzyna K, Oleg MD, Marta W, Pietrusiewicz KM. Brønsted acid catalyzed direct oxidative arylation of 1,4-naphthoquinone. *Current*

Chemistry Letters. 2014;**3**:23-36. DOI: 10.5267/j.ccl.2013.10.001

[31] Li BJ, Yang SD, Shi ZJ. Recent advances in direct arylation via palladium-catalyzed aromatic CH activation. *Synlett*. 2008;**07**:949-957. DOI: 10.1055/s-2008-1042907

[32] Yijun W, Shuai Z, Liang HZ. Recent advances in direct functionalization of quinones. *European Journal of Organic Chemistry*. 2019;**12**(31):2179-2201. DOI: 10.1002/ejoc.201900028

[33] Nuria T, Echavarren AM, Paredes MC. Palladium catalyzed coupling of 2-bromonaphthoquinones with stannanes: A concise synthesis of antibiotics WS 5995 A and C and related compounds. *Journal of Organic Chemistry*. 1991;**56**:6490-6494

[34] Gan X, Jiang W, Wang W, Hu L. An approach to 3,6-disubstituted 2,5-dioxybenzoquinones via two sequential suzuki couplings: Three-step synthesis of Leucomelone. *Organic Letters*. 2009;**11**(3):589-592. DOI: 10.1021/ol802645f

[35] Hadden MK, Hill SA, Davenport I, Matts RL, Blagg BS. Synthesis and evaluation of Hsp90 inhibitors that contain the 1,4-naphthoquinone scaffold. *Bioorganic and Medicinal Chemistry*. 2009;**17**:634-640. DOI: 10.1016/j.bmc.2008.11.064

[36] Hassan Z, Ullah I, Ali I, Khera RA, Knepper I, Ali A, et al. Synthesis of tetra aryl-p-benzoquinones and 2,3-diaryl-1,4-naphthoquinones via Suzuki-Miyaura cross-coupling reactions. *Tetrahedron*. 2013;**69**:460-469. DOI: 10.1016/j.tet.2012.11.040

[37] Louvis AR, Silva NAA, Semaan FS, Da-Silva FC, Saramago G, Souza LC, et al. Synthesis, characterization and biological activities of 3-aryl 1,4-naphthoquinones green palladium-catalysed Suzuki cross coupling. *New*

Journal of Chemistry. 2016;**40**:7643-7656. DOI: 10.1039/C6NJ00872K

[38] Redondo MC, Veguillas M, Ribagorda M, Carreno MC. Control of the regio- and stereoselectivity in Diels Alder reactions with quinone boronic acids. *Angewandte Chemie International Edition*. 2009;**48**(2):370-374. DOI: 10.1002/anie.200803428

[39] Liebeskind LS, Foster BS. Stannylquinones synthesis and utilization as quinone carbanion synthetic equivalents. *Journal of the American Chemical Society*. 1990;**112**(23):8612-8613. DOI: 10.1021/ja00179a072

[40] Lanny SL, Steven WR. Substituted quinone synthesis by palladium-copper cocatalyzed cross-coupling of stannylquinones with aryl and heteroaryl iodides. *Journal of Organic Chemistry*. 1993;**58**:408-413. DOI: 10.1021/jo00054a025

[41] Liu RH, He YH, Yu W, Zhou B, Bing H. Silver catalyzed site-selective ring-opening and C–C bond functionalization of cyclic amines: Access to distal aminoalkyl-substituted quinones. *Organic Letters*. 2019;**21**:4590-4594. DOI: 10.1021/acs.orglett.9b01496

[42] Jardim GA, Silva TL, Goulart MO, de Simone CA, Barbosa JM, Salomão K, et al. Rhodium-catalyzed CH bond activation for the synthesis of quinonoid compounds: Significant anti-trypanosoma cruzi activities and electrochemical studies of functionalized quinones. *European Journal of Medicinal Chemistry*. 2017;**136**:406-419. DOI: 10.1016/j.ejmech.2017.05.011

[43] Dias GG, Rogge T, Kuniyil R, Jacob C, Menna-Barreto RF, da Silva Júnior EN, et al. Ruthenium-catalyzed C–H oxygenation of quinones by weak O-coordination for potent trypanocidal

- agents. Chemical Communications. 2018;**54**(91):12840-12843. DOI: 10.1039/C8CC07572G
- [44] Jardim GA, Bozzi ÍA, Oliveira WX, Mesquita-Rodrigues C, Menna-Barreto RF, Kumar RA, et al. Copper complexes and carbon nanotube–copper ferrite-catalyzed benzenoid A-ring selenation of quinones: An efficient method for the synthesis of trypanocidal agents. New Journal of Chemistry. 2019;**43**(35): 13751-13763. DOI: 10.1039/C9NJ02026H
- [45] Yakkala PA, Giri D, Chaudhary B, Auti P, Sharma S. Regioselective C–H alkylation and alkenylation at the C5 position of 2-amino-1, 4-naphthoquinones with maleimides under Rh (III) catalysis. Organic Chemistry Frontiers. 2019;**6**(14): 2441-2446. DOI: 10.1039/C9QO00538B
- [46] Dias GG, Nascimento TA, de Almeida AK, Bombaça AC, Menna-Barreto RF, Jacob C, et al. Ruthenium (II)-catalyzed C–H Alkenylation of quinones: Diversity-oriented strategy for trypanocidal compounds. European Journal of Organic Chemistry. 2019; **9**(13):2344-2353. DOI: 10.1002/ejoc.201900004
- [47] Yu D, Chen XL, Ai BR, Zhang XM, Wang JY. Tetrabutylammonium iodide catalyzed hydroxylation of naphthoquinone derivatives with tert-butyl hydroperoxide as an oxidant. Tetrahedron Letters. 2018;**59**(40): 3620-3623. DOI: 10.1016/j.tetlet.2018.08.052
- [48] Castellano S, Bertamino A, Gomez-Monterrey I, Santoriello M, Grieco P, Campiglia P, et al. A practical, green, and selective approach toward the synthesis of pharmacologically important quinone-containing heterocyclic systems using alumina-catalyzed Michael addition reaction. Tetrahedron Letters. 2008;**49**(4): 583-585. DOI: 10.1016/j.tetlet.2007.11.148
- [49] Satish G, Polu A, Ramar T, Ilangovan A. Iodine-mediated C–H functionalization of sp, sp², and sp³ carbon: A unified multisubstrate domino approach for isatin synthesis. The Journal of Organic Chemistry. 2015; **80**(10):5167-5175. DOI: 10.1021/acs.joc.5b00581
- [50] Ilangovan A, Satish G. Copper-mediated selective C–H activation and cross-dehydrogenative C–N coupling of 2'-aminoacetophenones. Organic Letters. 2013;**15**(22):5726-5729. DOI: 10.1021/ol402750r
- [51] Ilangovan A, Polu A, Satish G. K₂S₂O₈-mediated metal-free direct C–H functionalization of quinones using arylboronic acids. Organic Chemistry Frontiers. 2015;**2**(12):1616-1620. DOI: 10.1039/C5QO00246J
- [52] Ashok P, Ilangovan A. Transition metal mediated selective C vs N arylation of 2-aminonaphthoquinone and its application toward the synthesis of benzocarbazoledione. Tetrahedron Letters. 2018;**59**(5):438-441. DOI: 10.1016/j.tetlet.2017.10.075
- [53] Ilangovan A, Saravanakumar S, Malayappasamy S. γ-Carbonyl quinones: Radical strategy for the synthesis of evelynin and its analogues by C–H activation of quinones using cyclopropanols. Organic Letters. 2013; **15**(19):4968-4971. DOI: 10.1021/ol402229m
- [54] Rajasekar S, Krishna TA, Tharmalingam N, Andivelu I, Mylonakis E. Metal-free C–H thiomethylation of quinones using iodine and DMSO and study of antibacterial activity. ChemistrySelect. 2019;**4**(8):2281-2287. DOI: 10.1002/slct.201803816
- [55] Krishna TPA, Sakthivel P, Ilangovan A. Iron-mediated site-selective oxidative C–H/C–H cross-coupling of aryl radicals with quinones:

Synthesis of β -secretase-1 inhibitor B and related arylated quinones. *Organic Chemistry Frontiers*. 2019;**6**:3244-3251. DOI: 10.1039/c9qo00623k

[56] Ramos-Peralta L, López-López LI, Silva-Belmares SY, Zugasti-Cruz A, Rodríguez-Herrera R, Aguilar-González CN. Naphthoquinone: Bioactivity and green synthesis. *The Battle Against Microbial Pathogens: Basic Science, Technological Advances and Educational Programs*. 2015:542-550

[57] Lavergne O, Fernandes AC, Bréhu L, Sidhu A, Brézak MC, Prévost G, et al. Synthesis and biological evaluation of novel heterocyclic quinones as inhibitors of the dual specificity protein phosphatase CDC25C. *Bioorganic and Medicinal Chemistry Letters*. 2006;**16**(1):171-175. DOI: 10.1016/j.bmcl.2005.09.030

[58] Arnone A, Merlini L, Nasini G, de Pava OV. Direct amination of naphthazarin, juglone, and some derivatives. *Synthetic Communications*. 2007;**37**(15):2569-2577. DOI: 10.1080/00397910701462864

[59] Bukhtoyarova AD, Rybalova TV, Ektova LV. Amination of 5-hydroxy-1,4-naphthoquinone in the presence of copper acetate. *Russian Journal of Organic Chemistry*. 2010;**46**(6): 855-859. DOI: 10.1134/S107042801006012

[60] Tuyun AF, Bayrak N, Yıldırım H, Onul N, Mataraci Kara E, Ozbek CB. Synthesis and in vitro biological evaluation of aminonaphthoquinones and benzo[b]phenazine-6,11-dione derivatives as potential antibacterial and antifungal compounds. *Journal of Chemistry*. 2015;**2015**:1-8. DOI: 10.1155/2015/645902

[61] Janeczko M, Demchuk OM, Strzelecka D, Kubiński K, Masłyk M. New family of antimicrobial agents

derived from 1,4-naphthoquinone. *European Journal of Medicinal Chemistry*. 2016;**29**(124):1019-1025. DOI: 10.1016/j.ejmech.2016.10.034

[62] Suryavanshi PA, Sridharan V, Menéndez JC. Expedient, one-pot preparation of fused indoles via CAN-catalyzed three-component domino sequences and their transformation into polyheterocyclic compounds containing pyrrolo [1,2-a] azepine fragments. *Organic and Biomolecular Chemistry*. 2010;**8**(15):3426-3436. DOI: 10.1039/C004703A

[63] Tapia RA, Cantuarias L, Cuéllar M, Villena J. Microwave-assisted reaction of 2,3-dichloronaphthoquinone with aminopyridines. *Journal of the Brazilian Chemical Society*. 2009;**20**(5):999-1002. DOI: 10.1590/S0103-50532009000500027

[64] Gouda MA, Eldien HF, Girges MM, Berghot MA. Synthesis and antioxidant activity of novel series of naphthoquinone derivatives attached to benzothiophene moiety. *Medicinal Chemistry*. 2013;**3**(2):2228-2232. DOI: 10.4172/2161-0444.1000143

[65] Brandy Y, Brandy N, Akinboye E, Lewis M, Mouamba C, Mack S, et al. Synthesis and characterization of novel unsymmetrical and symmetrical 3-halo- or 3-methoxy-substituted 2-dibenzoylamino-1, 4-naphthoquinone derivatives. *Molecules*. 2013;**18**(2): 1973-1984. DOI: 10.3390/molecules18021973

[66] Mital A, Sonawane M, Bindal S, Mahlavat S, Negi V. Substituted 1,4-naphthoquinones as a new class of antimycobacterial agents. *Der Pharma Chemica*. 2010;**2**(3):63-73

[67] Tran NC, Le MT, Nguyen DN, Tran TD. Synthesis and biological evaluation of halogen substituted 1,4-naphthoquinones as potent

antifungal agents. *Molecular Diversity Preservation International*. 2009;1-7

[68] Liu R, Li H, Ma WY. A new method for the biomimetic synthesis of 2-hydroxy-3-amino-1,4-naphthoquinone. *Advanced Materials Research*. 2013;781: 287-290. DOI: 10.4028/www.scientific.net/AMR.781-784.287

[69] Bayen S, Barooah N, Sarma RJ, Sen TK, Karmakar A, Baruah JB. Synthesis, structure and electrochemical properties of 2, 5-bis (alkyl/arylamino) 1,4-benzoquinones and 2-arylamino-1, 4-naphthoquinones. *Dyes and Pigments*. 2007;75(3):770-775. DOI: 10.1016/j.dyepig.2006.07.033

[70] Yadav JS, Reddy BV, Swamy T, Shankar KS. Green protocol for conjugate addition of amines to p-quinones accelerated by water. *Monatshefte für Chemie-Chemical Monthly*. 2008;139(11):1317. DOI: 10.1007/s00706-008-0917-1

[71] Liu B, Ji SJ. Facile synthesis of 2-amino-1,4-naphthoquinones catalyzed by molecular iodine under ultrasonic irradiation. *Synthetic Communications*. 2008;38(8):1201-1211. DOI: 10.1080/00397910701866254

[72] Lisboa CD, Santos VG, Vaz BG, de Lucas NC, Eberlin MN, Garden SJ. C–H functionalization of 1,4-naphthoquinone by oxidative coupling with anilines in the presence of a catalytic quantity of copper (II) acetate. *The Journal of Organic Chemistry*. 2011; 76(13):5264-5273. DOI: 10.1021/jo200354u

[73] Sharma U, Katoch D, Sood S, Kumar N, Singh B, Thakur A, et al. Synthesis, antibacterial and antifungal activity of 2-amino-1,4-naphthoquinones using silica-supported perchloric acid ($\text{HClO}_4\text{-SiO}_2$) as a mild, recyclable and highly efficient heterogeneous catalyst. *Indian Journal of Chemistry*. 2013;54:1431-1440

[74] Devenderan R, Kasi P. Metal-free, base promoted sp^2 C–H functionalization in the sulfonamidation of 1, 4-naphthoquinones. *Organic and Biomolecular Chemistry*. 2018;16(29): 5294-5300. DOI: 10.1039/C8OB00818C

[75] Chen XL, Dong Y, He S, Zhang R, Zhang H, Tang L, et al. A one-pot approach to 2-(N-substituted amino)-1,4-naphthoquinones with use of nitro compounds and 1,4-naphthoquinones in water. *Synlett*. 2019;30(05):615-619. DOI: 10.1055/s-0037-1610689

[76] Feng M, Tang B, Liang SH, Jiang X. Sulfur containing scaffolds in drugs: Synthesis and application in medicinal chemistry. *Current Topics in Medicinal Chemistry*. 2016;16(11): 1200-1216

[77] Ge B, Wang D, Dong W, Ma P, Li Y, Ding Y. Synthesis of arylsulfonyl-quinones and arylsulfonyl-1,4-diols as FabH inhibitors: Pd-catalyzed direct C–sulfone formation by C–S coupling of quinones with arylsulfonyl chloride. *Tetrahedron Letters*. 2014;55(40): 5443-5446. DOI: 10.1016/j.tetlet.2014.08.023

[78] Wang L, Xie YB, Yang QL, Liu MG, Zheng KB, Hu YL, et al. Ir-catalyzed C–S coupling of quinones with sulfonyl chloride. *Journal of the Iranian Chemical Society*. 2016;13(10):1797-1803. DOI: 10.1007/s13738-016-0897-8

[79] Yu X, Wu Q, Wan H, Xu Z, Xu X, Wang D. Copper and triphenylphosphine-promoted sulfenylation of quinones with arylsulfonyl chlorides. *RSC Advances*. 2016;6(67):62298-62301. DOI: 10.1039/C6RA11301J

[80] Zhang C, McClure J, Chou CJ. Silver-catalyzed direct thiolation of quinones by activation of aryl disulfides to synthesize quinonyl aryl thioethers. *The Journal of Organic Chemistry*. 2015; 80(10):4919-4927. DOI: 10.1021/acs.joc.5b00247

- [81] Yadav JS, Reddy BV, Swamy T, Ramireddy N. Ionic liquids-promoted addition of arylsulfinic acids to *p*-quinones: A green synthesis of diaryl sulfones. *Synthesis*. 2004;**2004**(11): 1849-1853. DOI: 10.1055/s-2004-829145
- [82] Yuan JW, Liu SN, Qu LB. Ammonium iodide-promoted unprecedented arylsulfonylation of quinone with sodium arylsulfonates. *Tetrahedron*. 2017;**73**(48):6763-6772. DOI: 10.1016/j.tet.2017.10.022
- [83] Tandon VK, Maurya HK. 'On water': Unprecedented nucleophilic substitution and addition reactions with 1,4-quinones in aqueous suspension. *Tetrahedron Letters*. 2009;**50**(43): 5896-5902. DOI: 10.1016/j.tetlet.2009.07.149
- [84] Zeng FL, Chen XL, He SQ, Sun K, Liu Y, Fu R, et al. Copper-catalyzed one-pot three-component thioamination of 1,4-naphthoquinone. *Organic Chemistry Frontiers*. 2019;**6**(9): 1476-1480. DOI: 10.1039/C9QO00091G
- [85] Lu Y, Zhao Y, Wang S, Wang X, Ge Z, Li R. An efficient synthesis of 2-thio-5-amino substituted benzoquinones via KI catalyzed cascade oxidation/michael addition/oxidation starting from hydroquinone. *RSC Advances*. 2016;**6**(14):11378-11381. DOI: 10.1039/C5RA26524J
- [86] Wellington KW, Gordon GE, Ndlovu LA, Steenkamp P. Laccase-catalyzed C–S and C–C coupling for a one-pot synthesis of 1,4-naphthoquinone sulfides and 1, 4-naphthoquinone sulfide dimers. *ChemCatChem*. 2013;**5**(6):1570-1577. DOI: 10.1002/cctc.201200606
- [87] Wellington KW, Bokako R, Raseroka N, Steenkamp P. A one-pot synthesis of 1,4-naphthoquinone-2, 3-bis-sulfides catalysed by a commercial laccase. *Green Chemistry*. 2012;**14**(9): 2567-2576. DOI: 10.1039/C2GC35926J
- [88] Schlippert M, Mikolasch A, Hahn V, Schauer F. Enzymatic thiol Michael addition using laccases: Multiple CS bond formation between *p*-hydroquinones and aromatic thiols. *Journal of Molecular Catalysis B: Enzymatic*. 2016;**126**:106-114. DOI: 10.1016/j.molcatb.2015.12.012
- [89] Takeya T, Kondo H, Otsuka T, Tomita K, Okamoto I, Tamura O. A novel construction of dibenzofuran-1,4-diones by oxidative cyclization of quinone-arenols. *Organic Letters*. 2007;**9**(15):2807-2810. DOI: 10.1021/ol070951i
- [90] Feng X, Qiu X, Huang H, Wang J, Xu X, Xu P, et al. Palladium (II)-catalyzed reaction of lawsones and propargyl carbonates: Construction of 2,3-furanonaphthoquinones and evaluation as potential indoleamine 2,3-dioxygenase inhibitors. *The Journal of Organic Chemistry*. 2018;**83**(15): 8003-8010. DOI: 10.1021/acs.joc.8b00872
- [91] Perez AL, Lamoureux G, Sánchez-Kopper A. Efficient syntheses of streptocarpone and (±)- α -dunnione. *Tetrahedron Letters*. 2007;**48**(21): 3735-3738. DOI: 10.1016/j.tetlet.2007.03.090
- [92] Da Silva Júnior PE, de Araujo NM, da Silva Emery F. Claisen rearrangement of hydroxynaphthoquinones: Selectivity toward naphthofuran or α -xiloidone using copper salts and iodine. *Journal of Heterocyclic Chemistry*. 2015;**52**(2): 518-521. DOI: 10.1002/jhet.2087
- [93] Weitz E, Scheffer A. Über die Einwirkung von alkalischem Wasserstoffsuperoxyd auf ungesättigte Verbindungen. *Berichte der Deutschen Chemischen Gesellschaft (A and B Series)*. 1921;**54**(9):2327-2344. DOI: 10.1002/cber.19210540922
- [94] Nasiri HR, Madej MG, Panisch R, Lafontaine M, Bats JW, Lancaster CR,

- et al. Design, synthesis, and biological testing of novel naphthoquinones as substrate-based inhibitors of the quinol/ fumarate reductase from *Wolinella succinogenes*. *Journal of Medicinal Chemistry*. 2013;**56**(23):9530-9541. DOI: 10.1021/jm400978u
- [95] Chang YC, Yuan PT, Hong FE. C–H bond functionalization of 1, 4-benzoquinone by silver-mediated regioselective phosphination and amination reactions. *European Journal of Organic Chemistry*. 2017;**2017**(17): 2441-2450. DOI: 10.1002/ejoc.201700109
- [96] Yuan PT, Pai CH, Huang SZ, Hong FE. Making CN and CP bonds on the quinone derivatives through the assistance of silver-mediated CH functionalization processes. *Tetrahedron*. 2017;**73**(48):6786-6794. DOI: 10.1016/j.tet.2017.10.037
- [97] Kalaria PN, Karad SC, Raval DK. A review on diverse heterocyclic compounds as the privileged scaffolds in antimalarial drug discovery. *European Journal of Medicinal Chemistry*. 2018; **158**:917-936. DOI: 10.1016/j.ejmech.2018.08.040
- [98] Buntrock RE. Review of heterocyclic chemistry. *Journal of Chemical Education*. 2012;**89**(11):1349-1350. DOI: 10.1021/ed300616t
- [99] Verweij J, Pinedo HM. Mitomycin C: Mechanism of action, usefulness and limitations. *Anti-Cancer Drugs*. 1990; **1**(1):5-13
- [100] Tisšler M. Heterocyclic quinones. In: *Advances in Heterocyclic Chemistry*. Vol. 45. Academic Press, Elsevier; 1989. pp. 37-150. DOI: 10.1016/S0065-2725(08)60329-3
- [101] Garuti L, Roberti M, Pizzirani D. Nitrogen-containing heterocyclic quinones: A class of potential selective antitumor agents. *Mini Reviews in Medicinal Chemistry*. 2007;**7**(5): 481-489. DOI: 10.2174/138955707780619626
- [102] Take Y, Oogose K, Kubo T, Inouye Y, Nakamura S, Kitahara Y, et al. Comparative study on biological activities of heterocyclic quinones and streptonigrin. *The Journal of Antibiotics*. 1987;**40**(5):679-684. DOI: 10.7164/antibiotics.40.679
- [103] Deniz NG, Ibis C, Gokmen Z, Stasevych M, Novikov V, Komarovska-Porokhnyavets O, et al. Design, synthesis, biological evaluation, and antioxidant and cytotoxic activity of heteroatom-substituted 1,4-naphtho- and benzoquinones. *Chemical and Pharmaceutical Bulletin*. 2015; **63**(12):1029-1039. DOI: 10.1248/cpb.c15-00607
- [104] Maier ME. Design and synthesis of analogues of natural products. *Organic and Biomolecular Chemistry*. 2015; **13**(19):5302-5343. DOI: 10.1039/C5OB00169B
- [105] Choudhary S, Singh PK, Verma H, Singh H, Silakari O. Success stories of natural product-based hybrid molecules for multi-factorial diseases. *European Journal of Medicinal Chemistry*. 2018; **151**:62-97. DOI: 10.1016/j.ejmech.2018.03.057
- [106] Ramsay RR, Popovic-Nikolic MR, Nikolic K, Uliassi E, Bolognesi ML. A perspective on multi-target drug discovery and design for complex diseases. *Clinical and Translational Medicine*. 2018;**7**(1):3. DOI: 10.1186/s40169-017-0181-2
- [107] Wink M. Evolutionary advantage and molecular modes of action of multi-component mixtures used in phytomedicine. *Current Drug Metabolism*. 2008;**9**(10):996-1009. DOI: 10.2174/138920008786927794
- [108] Kaliappan KP, Ravikumar V. Design and synthesis of novel sugar-oxasteroid-quinone hybrids.

Organic and Biomolecular Chemistry. 2005;3(5):848-851. DOI: 10.1039/B418659A

[109] Nepovimova E, Uliassi E, Korabecny J, Pena-Altamira LE, Samez S, Pesaresi A, et al. Multitarget drug design strategy: Quinone–tacrine hybrids designed to block amyloid- β aggregation and to exert anticholinesterase and antioxidant effects. *Journal of Medicinal Chemistry*. 2014;57(20):8576-8589. DOI: 10.1021/jm5010804

[110] Mallavadhani UV, Prasad CV, Shrivastava S, Naidu VG. Synthesis and anticancer activity of some novel 5,6-fused hybrids of juglone based 1,4-naphthoquinones. *European Journal Of Medicinal Chemistry*. 2014;83: 84-91. DOI: 10.1016/j.ejmech.2014.06.012

[111] Frenkel-Pinter M, Tal S, Scherzer-Attali R, Abu-Hussien M, Alyagor I, Eisenbaum T, et al. Naphthoquinone-tryptophan hybrid inhibits aggregation of the tau-derived peptide PHF6 and reduces neurotoxicity. *Journal of Alzheimer's Disease*. 2016;51(1):165-178. DOI: 10.3233/JAD-150927

[112] Defant A, Mancini I. Design, synthesis and cancer cell growth inhibition evaluation of new aminoquinone hybrid molecules. *Molecules*. 2019;24(12):2224. DOI: 10.3390/molecules24122224

[113] Zhou T, Li L, Li B, Song H, Wang B. Ir (III)-catalyzed oxidative coupling of NH isoquinolones with benzoquinone. *Organic Letters*. 2015; 17(17):4204-4207. DOI: 10.1021/acs.orglett.5b01974

[114] Guo S, Liu Y, Zhao L, Zhang X, Fan X. Rhodium-catalyzed selective oxidative (spiro) annulation of 2-arylindoles by using benzoquinone as a C2 or C1 synthon. *Organic Letters*. 2019; 21(16):6437-6441. DOI: 10.1021/acs.orglett.9b02336

[115] Sun JW, Wang XS, Liu Y. Copper (II)-catalyzed sequential C,N-difunctionalization of 1,4-naphthoquinone for the synthesis of benzo[f]indole-4,9-diones under base-free condition. *The Journal of Organic Chemistry*. 2013;78(20):10560-10566. DOI: 10.1021/jo401842d

[116] Chen SW, Hong FE. Palladium-catalyzed C–H functionalization of amido-substituted 1, 4-naphthoquinone in the presence of amines toward the formation of pyrroles and imidazoles. *ChemistrySelect*. 2017;2(31): 10232-10238. DOI: 10.1002/slct.201702173

[117] Acuña J, Piermattey J, Caro D, Bannwitz S, Barrios L, López J, et al. Synthesis, anti-proliferative activity evaluation and 3D-QSAR study of naphthoquinone derivatives as potential anti-colorectal cancer agents. *Molecules*. 2018;23(1):186. DOI: 10.3390/molecules23010186

[118] Luu QH, Guerra JD, Castaneda CM, Martinez MA, Saunders J, Garcia BA, et al. Ultrasound assisted one-pot synthesis of benzo-fused indole-4,9-dinones from 1,4-naphthoquinone and α -aminoacetals. *Tetrahedron Letters*. 2016; 57(21):2253-2256. DOI: 10.1016/j.tetlet.2016.04.031

[119] Pushkarskaya E, Wong B, Han C, Capomolla S, Gu C, Stoltz BM, et al. Single-step synthesis of 3-hydroxycarbazoles by annulation of electron-rich anilines and quinones. *Tetrahedron Letters*. 2016;57(50): 5653-5657. DOI: 10.1016/j.tetlet.2016.11.009

[120] Wu F, Bai R, Gu Y. Synthesis of benzofurans from ketones and 1,4-benzoquinones. *Advanced Synthesis and Catalysis*. 2016;358(14):2307-2316. DOI: 10.1002/adsc.201600048

[121] Wang L, Zhang J, Lang M, Wang J. Palladium-catalyzed ring contraction reaction of naphthoquinones upon

reaction with alkynes. *Organic Chemistry Frontiers*. 2016;**3**(5): 603-608. DOI: 10.1039/C6QO00045B

[122] Naganaboina RT, Nayak A, Peddinti RK. Trifluoroacetic acid-promoted Michael addition–cyclization reactions of vinylogous carbamates. *Organic and Biomolecular Chemistry*. 2014;**12**(21):3366-3370. DOI: 10.1039/c4ob00437j

[123] Jung Y, Kim I. Chemoselective reduction of quinols as an alternative to Sonogashira coupling: Synthesis of polysubstituted benzofurans. *Organic and Biomolecular Chemistry*. 2016; **14**(44):10454-10472. DOI: 10.1039/c6ob01941b

[124] Yang W, Wang S, Zhang Q, Liu Q, Xu X. Rh (iii)-catalyzed oxidative C–H bond arylation with hydroquinones: Sustainable synthesis of dibenzo[b,d]pyran-6-ones and benzo[d]naphtho[1,2-b]pyran-6-ones. *Chemical Communications*. 2015;**51**(4):661-664. DOI: 10.1039/C4CC08260E

[125] Yang W, Wang J, Wei Z, Zhang Q, Xu X. Kinetic control of Rh (III)-catalyzed annulation of C–H bonds with quinones: Chemoselective synthesis of hydrophenanthridinones and phenanthridinones. *The Journal of Organic Chemistry*. 2016;**81**(4): 1675-1680. DOI: 10.1021/acs.joc.5b02903

[126] Yang W, Wang J, Wang H, Li L, Guan Y, Xu X, et al. Rhodium (iii)-catalyzed three-component cascade synthesis of 6H-benzo[c]chromenes through C–H activation. *Organic and Biomolecular Chemistry*. 2018;**16**(38): 6865-6869. DOI: 10.1039/C8OB01938J

[127] Xia L, Lee YR. A novel and efficient synthesis of diverse dihydronaphtho [1,2-b] furans using the ceric ammonium nitrate-catalyzed formal [3 + 2] cycloaddition of 1,4-naphthoquinones to olefins and its application to

furomollugin. *Organic and Biomolecular Chemistry*. 2013;**11**(36):6097-6107. DOI: 10.1039/c3ob40977e

[128] Shaterian HR, Mohammadnia M. Effective preparation 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. *Journal of Molecular Liquids*. 2013;**177**:353-360. DOI: 10.1016/j.molliq.2012.10.012

[129] Dekamin MG, Alikhani M, Javanshir S. Organocatalytic clean synthesis of densely functionalized 4H-pyrans by bifunctional tetraethylammonium 2-(carbamoyl) benzoate using ball milling technique under mild conditions. *Green Chemistry Letters and Reviews*. 2016; **9**(2):96-105. DOI: 10.1080/17518253.2016.1139191

[130] Perumal M, Sengodu P, Venkatesan S, Srinivasan R, Paramsivam M. Environmentally benign copper triflate-mediated multicomponent one-pot synthesis of novel benzo[g]chromenes possess potent anticancer activity. *ChemistrySelect*. 2017;**2**(18):5068-5072. DOI: 10.1002/slct.201700170

[131] Cao YQ, Li XR, Wu W, Zhang D, Zhang ZH, Mo LP. A green approach for synthesis of naphthoquinone-fused oxazine derivatives in water under ultrasonic irradiation. *Research on Chemical Intermediates*. 2017;**43**(7): 3745-3755. DOI: 10.1007/s11164-016-2854-7

[132] Yazdani-Elah-Abadi A, Pour SA, Kangani M, Mohebat R. L-Proline catalyzed domino cyclization for the green synthesis of novel 1,4-dihydrobenzo[a]pyrido[2,3-c]phenazines. *Monatshefte für Chemie-Chemical Monthly*. 2017;**148**(12): 2135-2142. DOI: 10.1007/s00706-017-2008-7

[133] Jamaledini A,
Mohammadizadeh MR, Mousavi SH.
Catalyst-free, efficient, and green
procedure for the synthesis of 5-
heterocyclic substituted 6-aminouracils.
Monatshefte für Chemie-Chemical
Monthly. 2018;**149**(8):1421-1428. DOI:
10.1007/s00706-018-2164-4

[134] Shukla G, Srivastava A, Yadav D,
Singh MS. Copper-catalyzed one-pot
cross-dehydrogenative thienannulation:
Chemoselective access to naphtho[2,1-
b]thiophene-4,5-diones and subsequent
transformation to benzo[a]thieno[3,2-c]
phenazines. The Journal of Organic
Chemistry. 2018;**83**(4):2173-2181. DOI:
10.1021/acs.joc.7b03092