



HAL
open science

Recent Advances in Direct C-H Radical Alkylation of 1,4-Quinones

Maxime Donzel, Deniz Karabiyikli, Leandro Cotos Munoz, Mourad Elhabiri,
Elisabeth Davioud-Charvet

► **To cite this version:**

Maxime Donzel, Deniz Karabiyikli, Leandro Cotos Munoz, Mourad Elhabiri, Elisabeth Davioud-Charvet. Recent Advances in Direct C-H Radical Alkylation of 1,4-Quinones. *European Journal of Organic Chemistry*, 2021, 2021 (25), pp.3622-3633. 10.1002/ejoc.202100452 . hal-03249134

HAL Id: hal-03249134

<https://hal.science/hal-03249134>

Submitted on 7 Oct 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Recent Advances in Direct C-H Radical Alkylation of 1,4-Quinones

Maxime Donzel^[a], Deniz Karabiyikli^[a], Leandro Cotos^[a], Mourad Elhabiri^[a], Elisabeth Davioud-Charvet^{*[a]}

[a] M. Donzel, Deniz Karabiyikli, Dr. Leandro Cotos, Dr. Mourad Elhabiri, Dr. Elisabeth Davioud-Charvet
UMR7042 Université de Strasbourg–CNRS–UHA, Laboratoire d'Innovation Moléculaire et Applications (LIMA) Team Bio(IN)organic and Medicinal Chemistry, European School of Chemistry, Polymers and Materials (ECPM), 25 Rue Becquerel, Strasbourg 67087, France
http://lima.unistra.fr/cbm/
E-mail: elisabeth.davioud@unistra.fr

Abstract: 1,4-Quinones display unique redox and biological properties and have multiple applications in a wide array of fields, including health. Synthesis of diversely-substituted quinone-based compounds remains difficult and usually consists of multiple step sequences. Interest in direct C-H radical alkylation of 1,4-quinones has thus continuously grown over this last decade. These reactions involve addition of carbon-centered radicals generated from radical precursors through decarboxylative alkylation, hydrogen-atom

abstraction, or by carbon-halogen bond reduction. Recent progresses in radical chemistry, including photoredox catalysis, have provided useful tools for quinone functionalization. This review describes the recent progress with these methodologies, including the new promising three-component cascade reactions involving quinones and alkenes, allowing the preparation of complex substituted 1,4-quinones in a single step.

1. Introduction

1,4-Quinones represent an important class of ubiquitous compounds in nature, especially in plants, bacteria or fungi. This scaffold exhibits remarkable redox properties due to its alternating Csp² and Csp bonds and electron-deficient nature acting as a 1- or 2-electron reversible and efficient redox-cycler. It is responsible for a wide range of biological activities in different key pathways. Among the numerous examples is the vital role of the isoprenoid quinone coenzyme Q₁₀ (also also called ubiquinone)^[1] in cellular bioenergetics, serving as a main cofactor in the mitochondrial electron transport chain of eukaryotic cells through aerobic respiration and ATP production. Another example is the role of vitamin K (Figure 1)^[2] involved in the carboxylation of glutamate residues for the regulation of prominent physiological mechanisms such as blood coagulation, bone metabolism or neuroprotection.^[3]

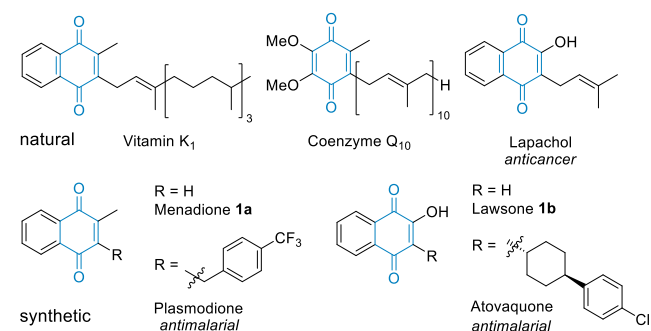


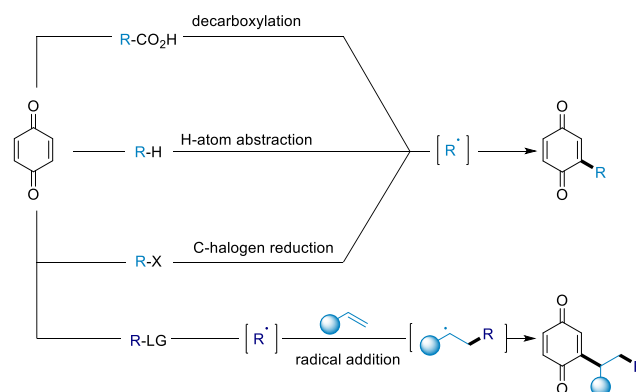
Figure 1. Natural and synthetic alkylated 1,4-quinones.

Compounds containing a quinone core also serve as important building blocks in synthetic chemistry, in various fields,^[4] most notably in medicinal chemistry. For instance, some 1,4-quinones such as menadione **1a** and lawsone **1b** derivatives (Figure 1), display potent antimalarial,^[5] antibiotic or anticancer^[6] activities. Their unique redox properties were shown essential for the design

of quinoidal systems as activable fluorescent probes for biological imaging.^[7]

Radical chemistry has existed since the origins of organic chemistry, when it appeared in the early 19th century. It was historically considered uncontrollable and chaotic. However, it has slowly emerged as a major component of organic synthesis (frequently referred to the renaissance of radical chemistry)^[8] thanks to both the development of new methodologies and the elucidation of radical mechanisms. Due to the remarkable capacity of quinones to act as efficient radical acceptors,^[9] radical chemistry has become an essential field in its own right for molecular functionalization, and many synthetic processes have been described in literature in the last ten years.

In this review article, we will mainly focus on the very recent advances in quinone alkylation, since this field has been evolving very rapidly over the last few years. Arylations and other functionalization of quinones, partly based on intramolecular photoredox reactions, have been thoroughly discussed in two recent reviews, and no significant breakthroughs have been described since.^[10]



Scheme 1. Different methods of radical alkylation reviewed in this article.

For this reason, except for a few cases, previously reviewed alkylation processes will not be expanded in further detail in this

MINIREVIEW

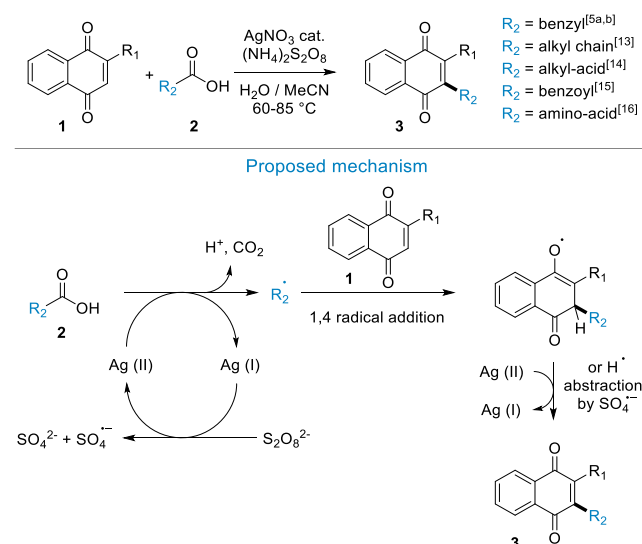
report. reviewed alkylation processes will not be expanded in further detail in this report.

Radical alkylation of quinones generally involves the addition of a carbon-centered radical generated from a radical precursor. The latter is often activated by an external agent such as a transition metal, an oxidant or a reductant. Here, we will review the the addition of carbon-centered alkyl radicals generated from decarboxylation, hydrogen-atom abstraction and reduction of carbon-halogen bonds, which are currently the main three processes used for direct functionalization of quinone with carbon-centered radicals. We will also explore the broad diversity of three-component cascade reactions involving quinones and alkenes, which have been extensively developed very recently, opening the field to the preparation of complex substituted 1,4-quinones in a single step (Scheme 1).

2. Radical generation by decarboxylation

The most popular and convenient method used to functionalize quinones is the Kochi-Anderson reaction,^[11] which is a one-step decarboxylation reaction from carboxylic acids under radical conditions. It was first described by Anderson and Kochi, who demonstrated that the oxidative decarboxylation of acids by peroxydisulfate ion (i.e., persulfate) is markedly accelerated by the *in situ* generated Ag(II), making the AgNO₃/(NH₄)₂S₂O₈ oxidant system a prerequisite for this reaction.

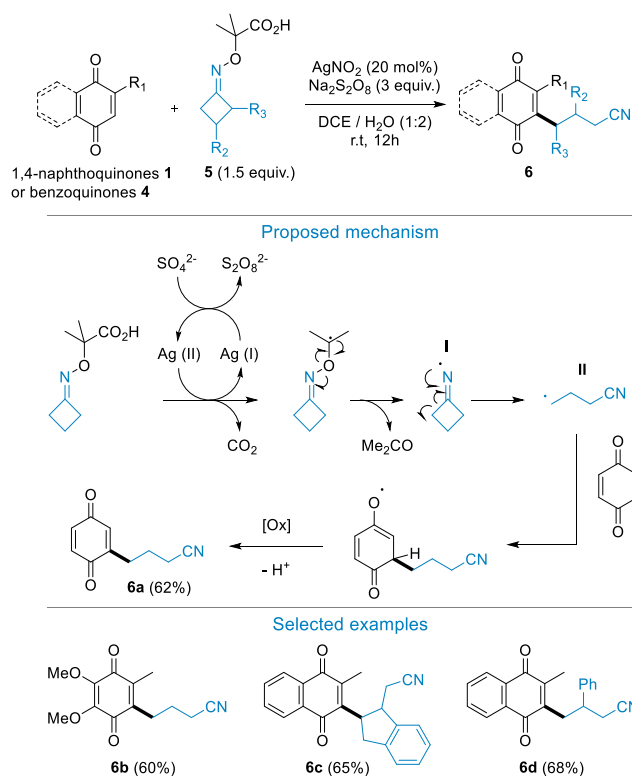
This procedure was applied for the first time to the alkylation of 1,4-quinones by Jacobsen and Torsell in the early 1970's^[12] and has since been particularly well exploited in radical alkylation of 1,4-naphthoquinones **1** (Scheme 2).



Scheme 2. Alkylation of quinones via silver-catalyzed decarboxylation of acids.

In 1991, Zhang's group explored this reaction to synthesize a large array of vitamin K derivatives by direct radical alkylation of vitamin K₃, also known as menadione **1a** (Figure 1).^[13] Then, Davioud-Charvet's group applied this methodology for the introduction of various alkyl-acids and alkyl-amines into 2-substituted naphthoquinone scaffolds **1** for the preparation of potential inhibitors of trypanothione reductase of *Trypanosoma cruzi*.^[14] This approach is still used by the team for the benzylation

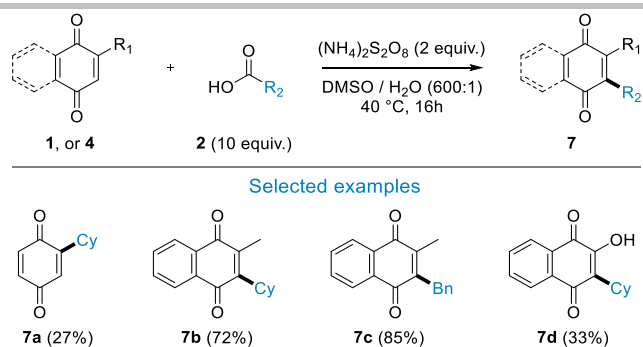
of menadione through decarboxylation of acids, leading to the potent antimalarial 3-benzylmenadiones, e.g. plasmodione (Figure 1)^[5a,b], or for the benzoylation of menadione **1a** to prepare the 3-benzoylmenadiones.^[15] In a similar approach, Dessolin and co-workers also described the direct alkylation of naphthoquinones with amino acids (Scheme 2).^[16] This method is still actively used and has even been revisited for the functionalization of quinones, as demonstrated by Wang's team in the gram-scale synthesis of various coenzyme Q derivatives.^[17] Also in the same context, Xu and co-workers developed a decarboxylative cyanoalkylation of heteroarenes and quinones **4** via iminyl radical and cyclobutyl opening at room temperature (Scheme 3).^[18] The authors suggested a mechanism whereby, after an Ag(II)-catalyzed decarboxylation of the coupling partner, a cyclic α-imino-oxy acid derivative **5**, acetone is released while liberating an iminyl radical **I**, thus triggering cycle opening to form a carbon-centered radical **II** (Scheme 3). This cyanoalkyl radical **II** then undergoes free radical addition to the quinone, followed by oxidation, resulting in the formation of the cyanoalkylated quinone **6**. These conditions allowed the efficient functionalization of coenzyme Q₁₀ or menadione **1a** in good yields, leading to **6b** and **6c-d** derivatives, respectively (Scheme 3).



Scheme 3. Cyano-alkylation of quinones via cyclobutyl intermediate opening.

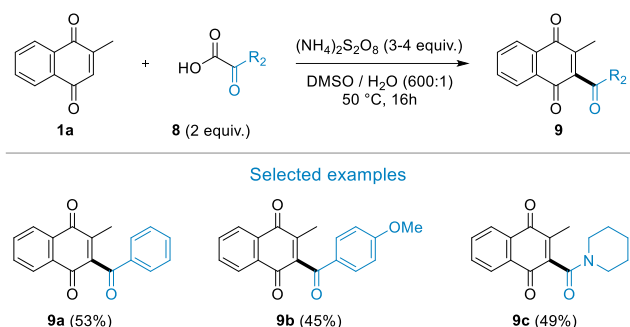
Over the last decade, radical generation by decarboxylation has been continuously revisited,^[19] including *inter alia* for the functionalization of quinones. For example, Lee and co-workers developed a silver-free Kochi-Anderson-type C-H alkylation of heteroarenes and quinones using ammonium persulfate in a mixture of water and DMSO as the sole reagent under mild temperature conditions. This process allowed the alkylation of various naphthoquinones including menadione **1a** and lawsone **1b**, leading to **7b-d** derivatives (Scheme 4).^[20]

MINIREVIEW



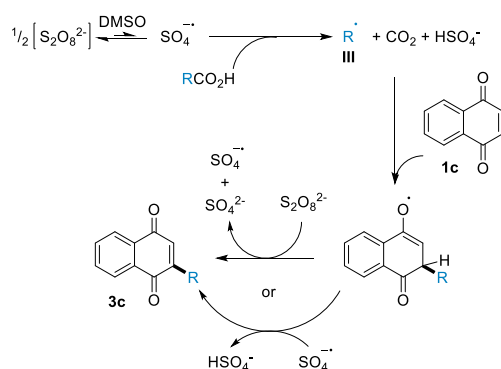
Scheme 4. Silver-free radical decarboxylation.

Subsequently, they described an acylation and carbamoylation version of this procedure.^[21] Although this reaction was shown to be efficient with heteroaromatic substrates as radical acceptors, only a few examples of quinone functionalization with moderate yields have been described (Scheme 5).



Scheme 5. Silver-free radical acylation and carbamoylation of quinones.

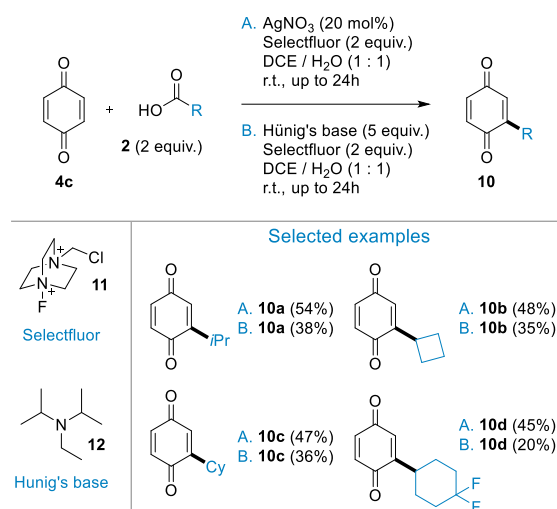
The authors demonstrated that under these specific conditions, $\text{SO}_4^{\cdot-}$ radicals can be generated gently in DMSO in the absence of any metal catalyst and play a crucial role in the decarboxylation process (Scheme 6).



Scheme 6. Proposed mechanism of the silver-free decarboxylation.

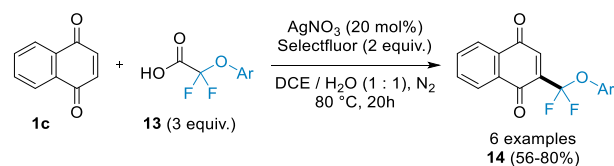
DMSO was shown to be essential for the reaction, as the decomposition of the persulfate ion is described as occurring much more evenly in this solvent. After decarboxylation, the radical intermediate III reacts with the quinone, which is regenerated by single-electron transfer from $\text{S}_2\text{O}_8^{2-}$ or hydrogen abstraction from $\text{SO}_4^{\cdot-}$.

Recently, Baxter *et al.* showed that selectfluor **11** could be used as a mild alternative to the strong oxidant ammonium persulfate.^[22] These conditions allowed the reaction to occur at room temperature and to lead to selective mono-alkylation of the highly reactive 1,4-benzoquinone **4c** with moderate to satisfactory yields (Scheme 7.A.). In comparison, the standard $\text{AgNO}_3/(\text{NH}_4)_2\text{S}_2\text{O}_8$ system applied to the same 1,4-quinone invariably leads to lower yield with a majority of polysubstituted compounds.^[23] The same research team also found that the Hünig's base **12**, used as an additive under similar experimental conditions, significantly improved the reactivity. When carried out without any metal additive, the radical process led to slightly lower yields (Scheme 7.B.).^[24]



Scheme 7. Selectfluor-mediated alkylation of 1,4-benzoquinones.

In 2020, the AgNO_3 /selectfluor system was used by Qing's group to introduce the CF_2OAr motif from the corresponding difluoroacetic acids **14** in various heteroaromatic compounds and the 1,4-naphthoquinone **1c** (Scheme 8).^[25] Noteworthy, the conventional use of persulfate as an oxidant did not yield any target product, making selectfluor an useful alternative.



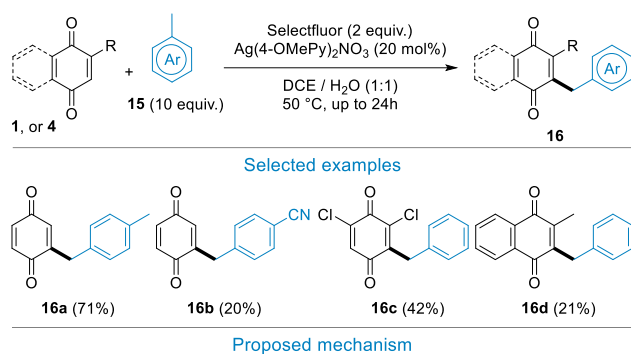
Scheme 8. Selectfluor-mediated introduction of difluoroalkylethers on 1,4-naphthoquinone.

Although decarboxylation is the mainly used method for radical generation by C-C bond cleavage, it is worthy to note the development of 1,4-dihydropyridines as radical precursors by Molander and his coworkers.^[26] These precursors, synthesized in one-step from readily available benzaldehydes, were proven to be highly efficient alkylating agents of quinones.

3. Radical generation by hydrogen-atom abstraction

MINIREVIEW

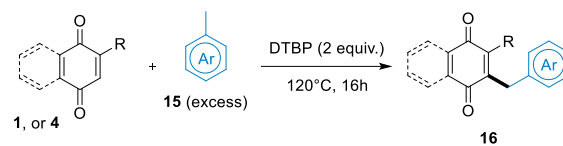
Based on previous work on decarboxylation with the Ag(I)/selectfluor couple and on formation of a diazabicyclo radical dication **IV** (TEDA²⁺) after 1-electron reduction or photolysis, selectfluor was shown to act as an effective hydrogen transfer agent for the generation of carbon-centered radicals to enable new bond formation.^[27] Hence, Baxter's team developed an original radical benzylation of 1,4-quinones **4** by Csp³-H abstraction starting from toluene derivatives **15**.^[28] Using this process, 1,4-benzoquinones could be mono-benzylated with good yields. However, arene bearing electron-withdrawing groups in *para*-position were found to be poor coupling partners (**16b**) as illustrated in menadione alkylation, which resulted in 3-benzylmenadione **16d** with moderate yield (Scheme 9).



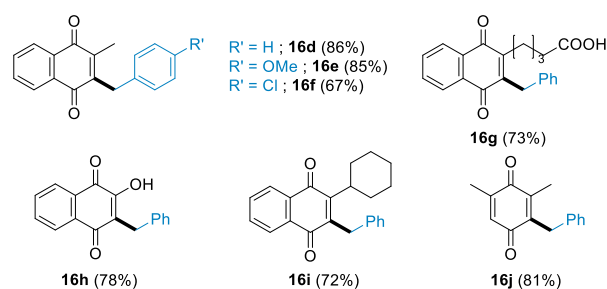
Scheme 9. Radical benzylation of quinones via selectfluor-mediated C-H abstraction.

Quinone benzylation via a Csp³-H abstraction has been well explored in recent years. The early work was developed in 2014 by Duan and coworkers when they reported a copper-catalyzed benzylation of various coumarins, which turned out to be compatible with menadione.^[29] Later, inspired by this method, Wang's group developed a copper-free oxidative cross-dehydrogenative coupling between various quinones **1,4** and toluene derivatives **15**.^[30] This reaction proceeds via di-*tert*-butyl peroxide (DTBP)-assisted hydrogen-abstraction on the benzylic Csp³ to generate highly reactive benzyl radicals, prone to react readily with electrophilic quinones. Various quinones, including 2-substituted-1,4-naphthoquinones **16e-i** and substituted 1,4-benzoquinones **16j** were successfully benzylated by diversely substituted toluene derivatives (Scheme 10). The main drawback of this process is likely the use of toluene derivatives **15** in large

excess used both as a reactant and as a solvent, limiting the scope of the reaction to cheap or easily available starting materials.

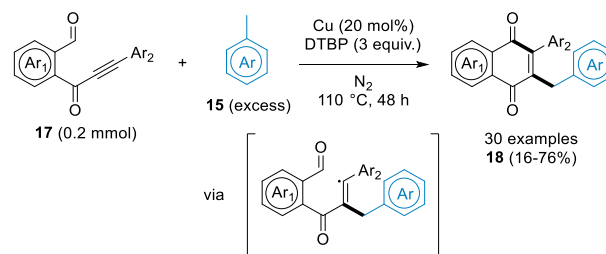


Selected examples



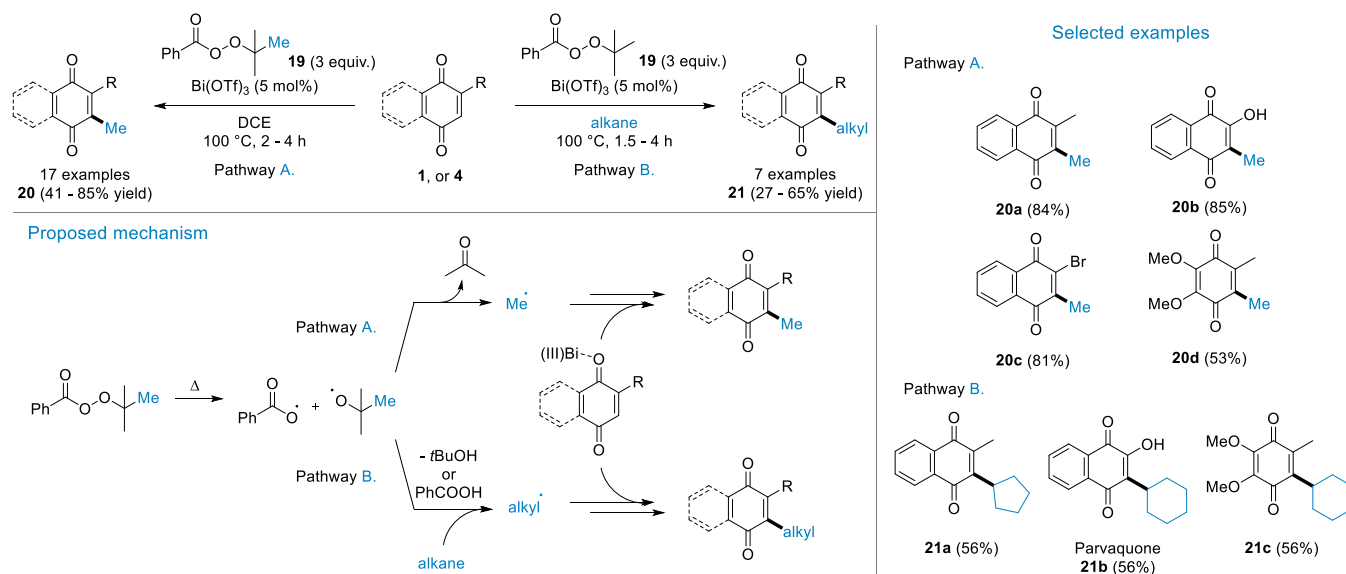
Scheme 10. Radical benzylation of quinones via DTBP-mediated C-H abstraction.

Noteworthy, a similar process was recently described for the cyclization of 2-(3-arylopropyl)benzaldehydes **17** in the presence of catalytic copper powder leading to 3-benzylated 2-aryl-1,4-naphthoquinones **18** (Scheme 11).^[31] Strictly speaking, this process is not a direct functionalization of quinones but allows for the formation of a very wide range of various 1,4-naphthoquinones in a single step.



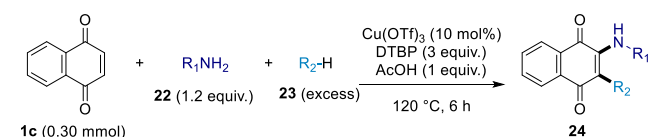
Scheme 11. Cascade radical formation of benzylated 1,4-naphthoquinones.

Obviously, radical generation by hydrogen-abstraction has not been applied to benzylation reactions only. At the end of the 20th century, Chuang's group studied a direct manganese-mediated alkylation of various 1,4-naphthoquinones with malonates.^[32] In 2016, Lee's group described a direct copper-catalyzed cycloalkylation using *tert*-butyl hydroperoxide (TBHP) as hydrogen-abstraction agent starting from cycloalkanes.^[33] Finally, Wang's team extended their benzylation method to the direct alkylation of quinones using *tert*-butyl peroxybenzoate (**19**) and bismuth(III) trifluoromethanesulfonate as catalyst.^[34] Remarkably, they showed that TBPB **19** could act as a radical methyl donor allowing the radical methylation of numerous

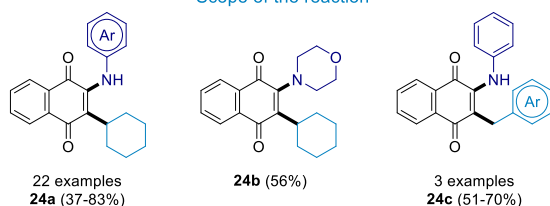


Scheme 12. Bismuth-catalyzed quinone alkylation.

bismuth-activated quinones in good yields (Scheme 12, Pathway A). On the other hand, the use of an alkane as a solvent promoted the corresponding alkylation via hydrogen-abstraction from the alkane by one of the resulting radicals of the homolytic cleavage of TBPB **19** (Scheme 12, Pathway B). This radical alkylation has been explored very recently by the same team to develop the first direct one-pot dual amination-alkylation of the 1,4-naphthoquinone **1c**.^[35] It is proposed that in the presence of a source of copper(II) as catalyst, 1,4-Michael addition of the amine **22** occurs first, followed by 1,4-radical addition of the alkyl radical generated by the DTBP-mediated hydrogen abstraction from the alkane **23** (Scheme 13).



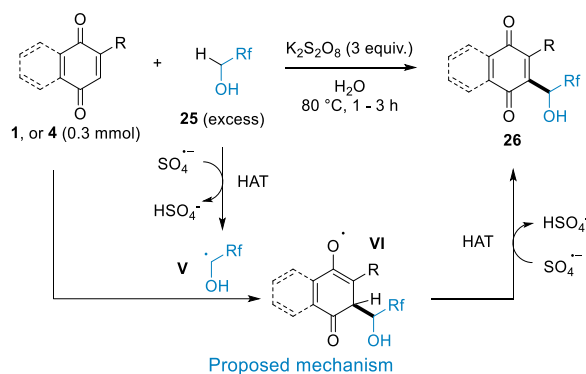
Scope of the reaction



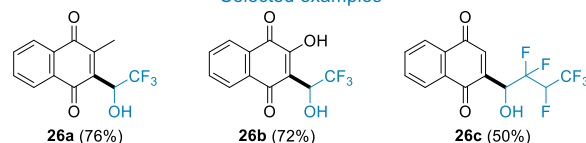
Scheme 13. Dual amination-alkylation of 1,4-naphthoquinone.

Shortly before, Liu's group found that these hydrogen abstraction methods can also be successfully applied to the coupling of fluorinated alcohols **25** to quinones **1**, or **4**.^[36] In a heated water/polyfluorinated alcohol mixture, potassium persulfate decomposes to the sulfate radical ($\text{SO}_4^{\cdot-}$), which allows the hydrogen atom abstraction (HAT) from the polyfluorinated alcohol **25** to generate a key radical **V**. This latter readily reacts with the electrophilic quinone, and the corresponding radical adduct **VI** is then converted to the target quinone **26** via a second HAT from the sulfate radical. This reaction is compatible with a large array

of polyfluorinated alcohols and quinones, including starting menadione **1a** or lawsone **1b** resulting in **26a** and **26b** derivatives (Scheme 14). The authors also showed that coumarin and chromone were also suitable radical acceptors.



Selected examples

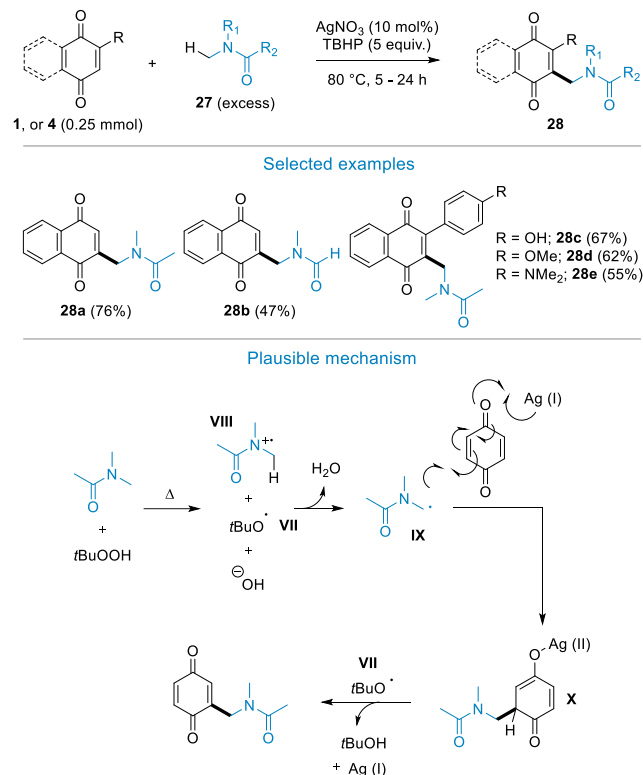


Scheme 14. Quinone functionalization with polyfluorinated alcohols. Rf = perfluoroalkyl.

Regarding other more diversified alkylations, Ilangovan's team, who previously published the radical opening of cyclopropanols to generate alkyl-ketone functionalized quinones,^[37] described in 2020 an original direct functionalization of quinones with dialkylamides using the $\text{AgNO}_3/\text{TBHP}$ couple (Scheme 15).^[38] In their report, the authors postulated that the thermally generated *tert*-butoxyl radical **VII** reacted with the alkylamide, first to generate the *N*-acyliminium alkyl radical **VIII** and subsequently the *N*-alkyl radical **IX**. This key radical intermediate firstly undergoes a silver-catalyzed conjugated addition to the quinone, and then the resulting radical adduct **X** reacts again with the *tert*-butoxyl radical **VII** to regenerate Ag(I) and the quinone moiety.

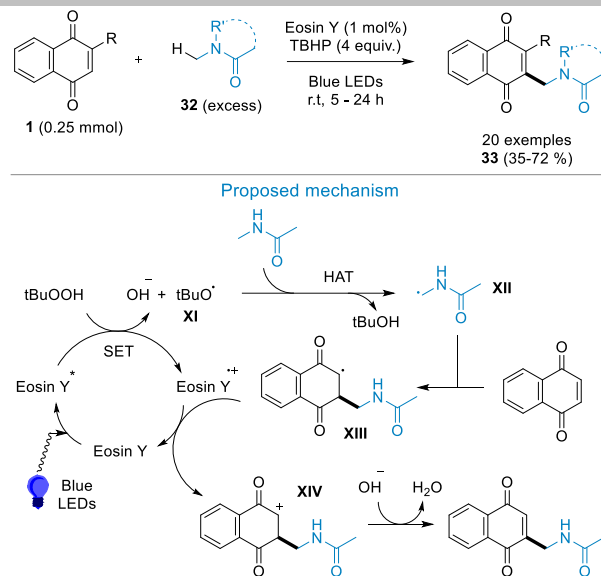
MINIREVIEW

Although a broad range of quinones **28** were directly functionalized by dimethylacetamide (DMA), access to various dialkylamides was however rather limited (Scheme 15).



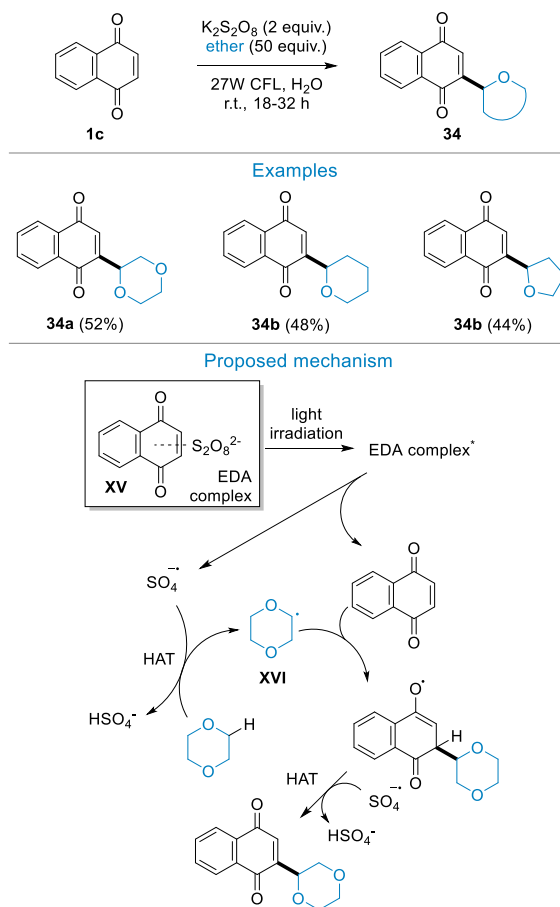
Scheme 15. Silver-catalyzed alkylamidation of quinones.

Shortly after, Ilangoan's group described a photocatalyzed version of this reaction, compatible with mono- and di-alkylamides **32** (Scheme 16).^[39] Eosin Y was used as a photosensitizer, generating upon blue LED photoexcitation $t\text{BuO}^\bullet$ **XI** and Eosin Y^{•+} via a single-electron transfer. Radical **XI** then undergoes HAT from the alkylamide. The resulting terminal radical **XII** reacts with the quinone to form a radical intermediate **XIII**. Radical **XIII** is then converted to the cationic species **XIV**, via SET with Eosin Y^{•+}, and afford after loss of water the alkylated quinone **33**. These conditions allowed alkylation of diversely substituted 1,4-naphthoquinones in much milder conditions with good yields (Scheme 16). Surprisingly, in the fast-evolving groundbreaking field of photochemistry over the past decade, this was so far the only example of functionalization of a quinone by a photosensitive catalyst.^[40]



Scheme 16. Photocatalyzed alkylamidation of 1,4-naphthoquinones.

Devari and Shah, however, reported in 2016 a photosensitizer-free alkylation of various electron-deficient arenes, including few examples of 1,4-naphthoquinones, with cyclic ethers in the presence of $\text{K}_2\text{S}_2\text{O}_8$ and under light-irradiation (Scheme 17).^[41]



Scheme 17. Photosensitizer-free light-induced alkylation of quinones with cyclic ethers.

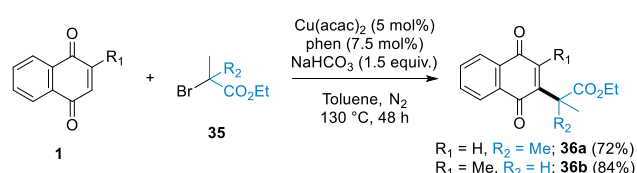
MINIREVIEW

The authors proposed the formation of an electron donor-acceptor (EDA) complex **XV** between $S_2O_8^{2-}$ and the electron-deficient arene. Upon light irradiation of this EDA complex, $S_2O_8^{2-}$ undergoes a homolytic cleavage to generate $SO_4^{\cdot-}$, which, following HAT with ethers, leads to the formation of α -oxyalkyl radicals **XVI**. The latter radical **XVI** reacts with the quinone and affords, likely after HAT from $SO_4^{\cdot-}$, the alkylated naphthoquinone **34** with moderate yield (Scheme 17).

Furthermore, as discussed earlier, most of the described radical alkylations proceeding by HAT suffer from the use of an excess of alkyl precursors, making it difficult to functionalize quinones starting from complex or expensive adducts.

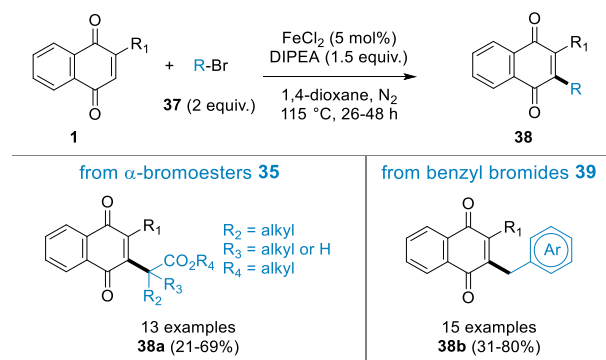
3. Radical generation by C-halogen reduction

Rare examples of alkylation of quinones by dehalogenation of a radical precursor have been reported. Particularly, Li's group described the copper-catalyzed alkylation of diverse heteroarenes, including 1,4-naphthoquinones and coumarins, with various alkyl halides.^[42] $Cu(acac)_2$ and 1,10-phenanthroline (phen) were combined to form a catalytic system for the reduction of the C-Br bond and formation of the corresponding alkyl radical (Scheme 18).

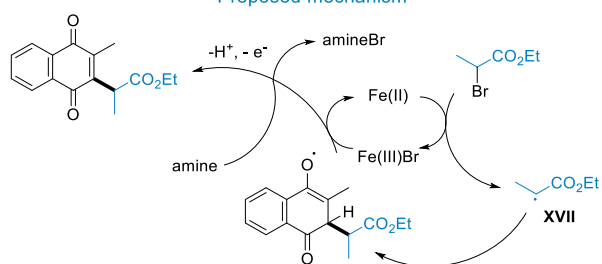


Scheme 18. Copper-catalyzed alkylation of 1,4-naphthoquinones.

Under inert atmosphere and intense heating, menadione **1a** and 1,4-naphthoquinone **1c** were alkylated with α -bromo-esters **35** in the presence of a base, but only these two examples of alkylated naphthoquinones **36a** and **36b** have been described so far.



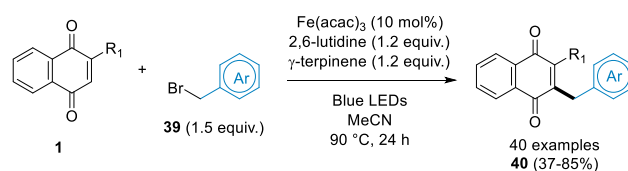
Proposed mechanism



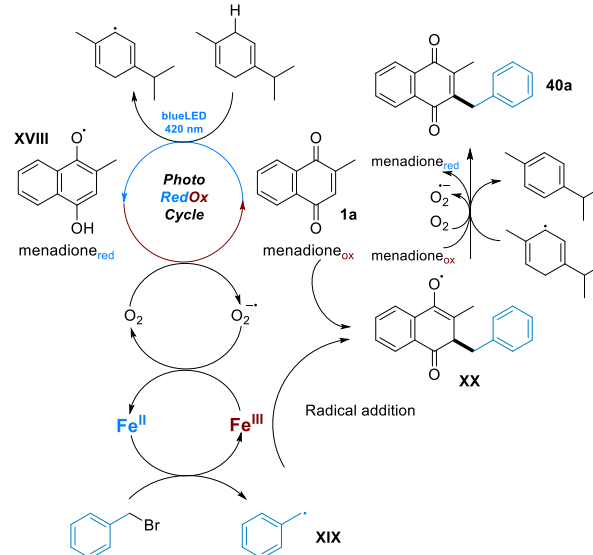
Scheme 19. Iron(II)-catalyzed alkylation of quinones.

Later, the same group described an iron-catalyzed version of this alkylation process with a greater scope (Scheme 19).^[43] A $Fe(II)$ catalyst was added to reduce the C-Br bond to form the corresponding radical species **XVII**, in the presence of a base under heating, allowing the functionalization of diversely 2-substituted naphthoquinones from various α -bromoesters **38a** and benzyl bromides **39**, leading to **38a** and **38b** derivatives.

In parallel, we have developed the first photoredox $Fe(III)$ -catalyzed benzylation of 1,4-naphthoquinones (Scheme 20).^[44] Based on previous reports about quinone photoreactivity, we proposed a mechanism where the photoreduction of the starting menadione **1a** is assisted by γ -terpinene under blue light irradiation. The resulting semiquinone radical **XVIII** is then re-oxidized by ambient oxygen generating superoxide anion radical continuously. This radical is known to reduce $Fe(III)$ to $Fe(II)$, which can then reduce the C-Br bond of benzyl bromide to generate the corresponding radical **XIX**. After benzyl radical addition to menadione, the resulting benzylated semiquinone **XX** is re-oxidized by oxygen or the starting menadione **1a** to continue the redox cycle resulting in the formation of the benzylated menadione **40a** (Scheme 19). More than 40 examples of diversely substituted 1,4-naphthoquinones **40** were synthesized with good yields.



Proposed mechanism



Scheme 20. Iron-catalyzed photoredox benzylation of quinones.

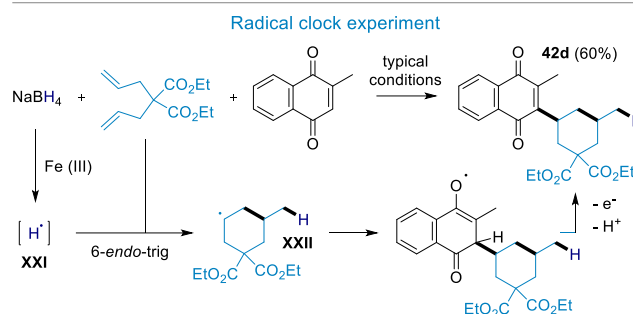
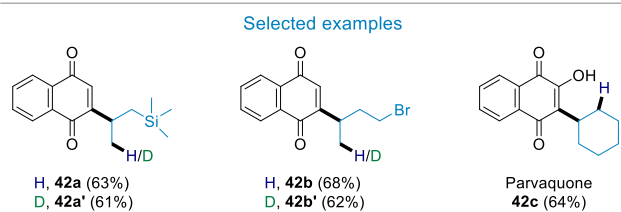
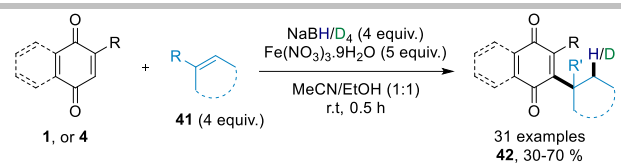
To date, these are the only examples of direct quinone alkylation by dehalogenative radical generation. However, as discussed just below, this method is beginning to be applied in three-component-reaction with quinones. It is highly likely that this field will continue to grow exponentially in the coming years, as halogenated starting materials are common building blocks and represent an important starting material in organic synthesis. However, carbon-halogen bond reduction remains difficult, especially for inactivated alkyl halides, and most of the described

MINIREVIEW

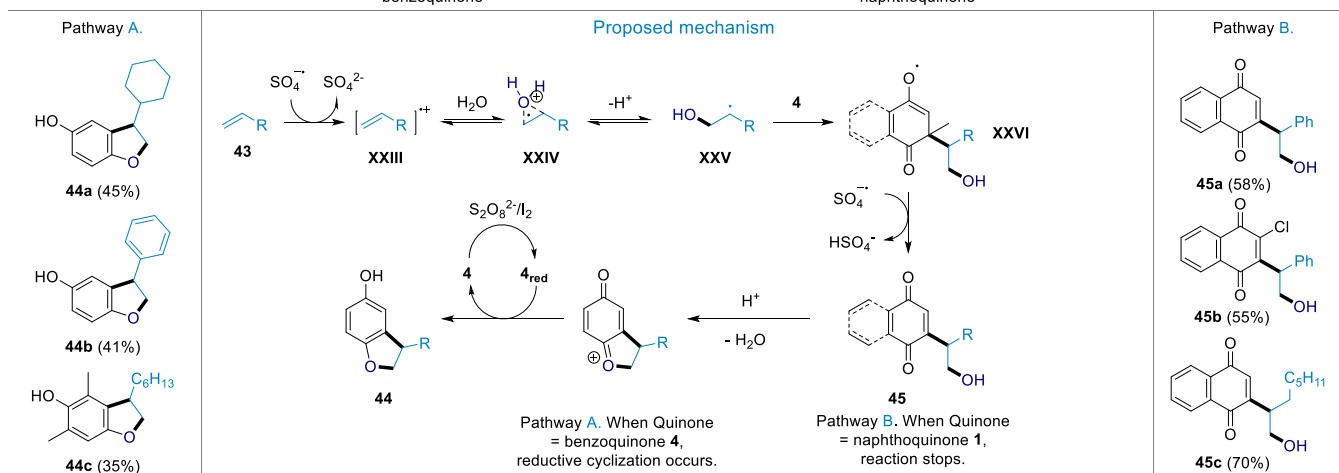
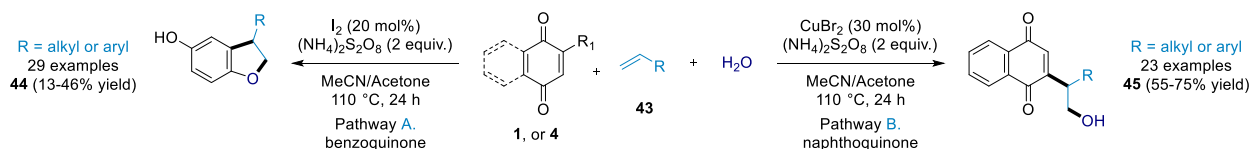
methods are rarely compatible with quinone redox properties (i.e., as an oxidant). Nevertheless, recent advances in the abstraction of halogen atoms (XAT) constitute very promising prospects for future development.^[45]

4. Cascade three-component alkylation

During the last decade, C-C bond construction via radical generation from starting olefins has been extensively studied. A common system used for this purpose is the couple Fe(III)/reductant.^[46] In 2019, Liu's group developed, using the Fe(NO₃)₃·9H₂O/NaBH₄ couple, an efficient free radical alkylation of quinones **4** with olefins **41** compatible with a large array of starting materials, including allylsilanes (Scheme 21).^[47] The authors demonstrated that a hydrogen radical **XXI** is formed by 1-electron oxidation of NaBH₄. This newly formed radical can then react with an olefin to form a new C-H bond and a carbon-centered radical **XXII**, which in turn can then alkylate a quinone. The mechanism was suggested from a radical clock experiment where radical cyclization of a diene via a 6-endo-trig cyclization was observed (Scheme 21). Furthermore, using NaBD₄ instead of NaBH₄ led to the insertion of deuterium atom into the olefin, confirming that the reductant is indeed the H/D donor in this reaction.



Scheme 21. Cascade three-component alkylation of 1,4-naphthoquinones using the Fe(NO₃)₃·9H₂O/NaBH₄ couple, with diverse olefins.



Scheme 22. Oxidative alkylation of 1,4-quinones with alkenes.

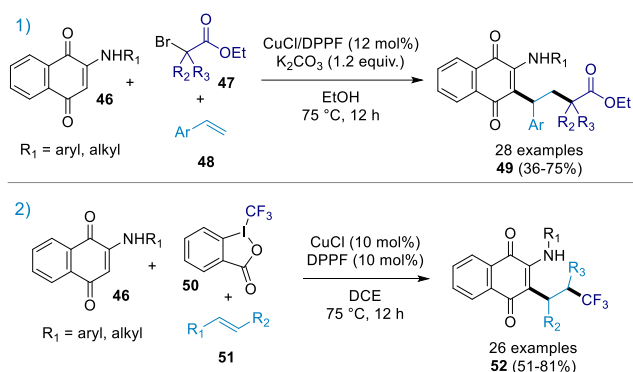
Simultaneously, Liu's team developed a synthesis of dihydrobenzofuranes by a three-component oxyarylation of alkenes using 1,4-benzoquinones **4** and water.^[48] This reaction proceeded in two steps. A first radical alkylation of a carbon-centered alcohol radical on a quinone generates the corresponding alcohol-bearing alkylated quinone, followed by reductive cyclization to form the dihydrobenzofuran core **44** (Scheme 22, Pathway A). Liu and co-workers were able to avoid reductive cyclization by changing the experimental conditions, i.e.,

switching from a (NH₄)₂S₂O₈/I₂ system with benzoquinones **4** to a (NH₄)₂S₂O₈/CuBr₂ system with naphthoquinones **1** (Scheme 22, Pathway B).^[49] They proposed a mechanism whereby the olefin is oxidized by SO₄^{•-} giving the alkenyl radical cation **XXIII**, which reacts with water to form a bridged radical cation complex **XXIV**. After regioselective opening of intermediate **XXIV** and loss of a proton, the new carbon centered radical **XXV** undergoes radical addition to the quinone. The resulting radical adduct **XXVI** is then oxidized by SO₄^{•-} to form the newly alkylated quinone **45**. In the

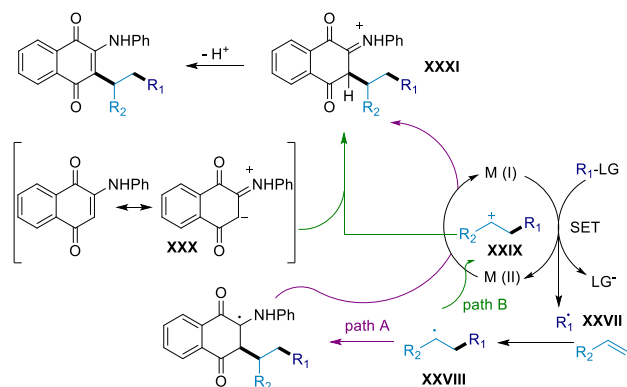
MINIREVIEW

case of a naphthoquinone **1** (NQ), the reaction stops there, but for a benzoquinone **4** (oxidized form)), the reaction continues and cyclization occurs. The authors also noted that the $(\text{NH}_4)_2\text{S}_2\text{O}_8/\text{I}_2$ mixture reduced benzoquinone **4** into the corresponding dihydroxyquinone **4_{red}** (reduced form), which allowed the reduction of the cyclic cationic intermediate to lead to the final dihydrobenzofurane **44**.

In recent years, three-component reactions have also been shown to be effective for the functionalization of 2-amino-1,4-naphthoquinones **46**. In 2019, Zhang's group successively reported two three-component reactions allowing access to complex substituted 1,4-naphthoquinones (Scheme, 23).^[50]



3) Proposed mechanism

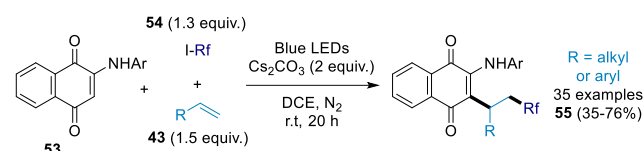


Scheme 23. Three-component alkylation of 2-amino-1,4-naphthoquinones.

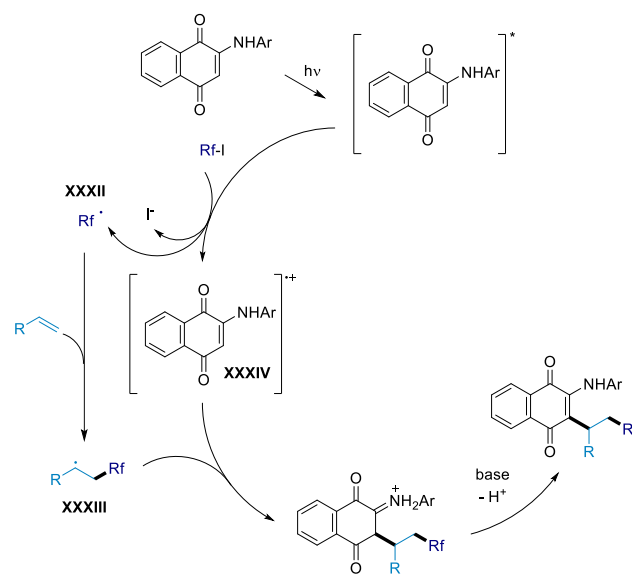
On one hand, α -bromocarboxylates **47**, styrenes **48** and 2-aminonaphthoquinones **46** reacted in the presence of a catalytic amount of CuCl and 1,1'-bis(diphenylphosphino)ferrocene (DPPF) added as a ligand (Scheme 23.1) and, on the other hand, Togni I reagent **50**, substituted alkenes **51** and 2-amino-1,4-naphthoquinones **46** were involved in a reaction with AgOAc and DPPF as catalytic system (Scheme 23.2). These two reactions are proposed to proceed through the same mechanism. A first radical intermediate **XXVII** is generated by single-electron transfer (SET) between the metallic complex and the radical precursor, and then participates in a radical addition on the alkene to form the second carbon-centered radical intermediate **XXVIII**. Two routes are then plausible; either this intermediate adds directly to the quinone (path A), or it undergoes a second SET with the metallic complex to form the corresponding carbocation **XXIX** (path B), which can be trapped by the rearrangement product **XXX** from the starting quinone. In both case, an iminium intermediate **XXXI** is formed and the quinone core is regenerated by

deprotonation (Scheme 23.3.). The fact that the reaction does not proceed if the amino group is replaced by an alkyl group led authors to prioritize path B, since enamine isomerization plays an important role in this path, even if, path A and direct radical alkylation cannot however be excluded.

Furthermore, under blue-light irradiation, the cascade reaction between perfluoroalkyl iodides **54**, alkenes **43** and 2-aryl-amino-1,4-naphthoquinones **53** was made possible without photocatalyst as demonstrated by Rao and co-workers (Scheme 24).^[51] Since 2-amino-naphthoquinones **53** absorb the blue light wavelengths and no coupling is observed between the perfluoroalkyl halide **54** and alkenes **43** in the absence of the quinone, the authors proposed a mechanism where the quinone itself acts as a photosensitizer. Indeed, when excited with a blue LED irradiation, 2-aminonaphthoquinone **53** is proposed to activate *in situ* the perfluoroalkyl iodide **54** into its perfluoroalkyl radical **XXXII** through a SET process. Subsequent addition of the radical to the alkene leads to a carbon-centered radical **XXXIII**, which then undergoes radical-radical coupling with the quinone radical-cation **XXXIV** affording the targeted compound after deprotonation (Scheme 24).



Proposed mechanism



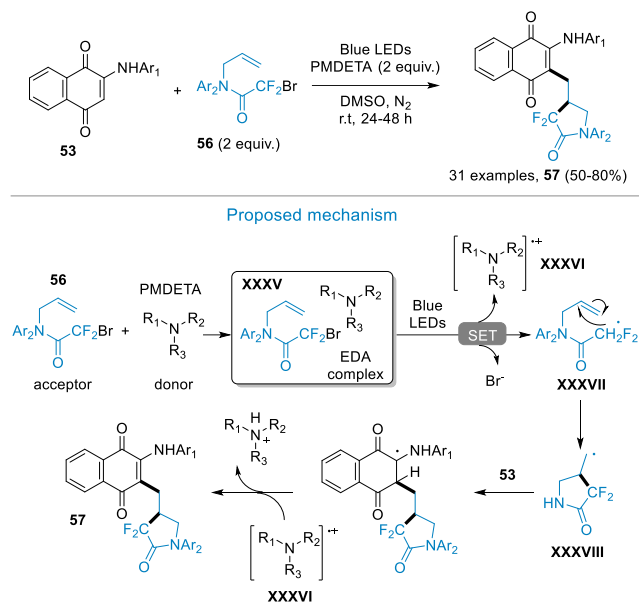
Scheme 24. Photocatalyzed three-component alkylation of 2-aminonaphthoquinones. Rf = perfluoroalkyl.

Although limited to 2-amino-1,4-naphthoquinones **53**, these conditions are tolerant with various styrenes and alkyl-substituted alkenes **43** in one side and various sized polyfluorinated alkyl chains **54**.

Recently, Jin's group exploited the emerging field of electron donor-acceptor (EDA)^[52] complexes in visible-light-mediated reactions.^[53] The authors reported a tandem cyclization-arylation of unactivated alkenes with 2-amino-1,4-naphthoquinones **53**. *N*-allyl-2-bromo-2,2-difluoroacetamides **56** and *N,N,N',N'',N'''*-pentamethyl-diethylenetriamine (PMDETA) were demonstrated to form an EDA complex **XXXV**. Under blue light irradiation, a

MINIREVIEW

dehalogenation is observed leading to the formation of the difluoroalkyl radical **XXXVII** which in turn undergoes intramolecular cyclization to afford a cyclic radical **XXXVIII**. This intermediate is then immediately trapped by the quinone to generate, after hydrogen abstraction from the amino radical cation **XXXVI**, the targeted coupling product **57** (Scheme 25).



Scheme 25. Visible-light mediated tandem cyclization-arylation of alkenes with 2-amino-1,4-naphthoquinones.

To the best of our knowledge, this constitutes, with Shah's radical alkylation with cyclic ethers (see above),^[41] the only example of quinone functionalization with EDA complexes. These two reports undoubtedly open a new field of exploration for the functionalization of quinones.

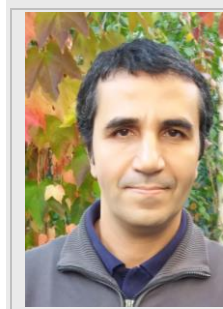
5. Conclusion

Herein, we have reviewed most of the recent advances in radical alkylation of quinones. As demonstrated by the overview described here, many advances have been made in recent years, opening up promising and interesting prospects despite the complexity of combining classical organic chemistry with quinones due to their unique electrochemical properties. We are convinced that this craze for the functionalization of quinones will intensify in the coming years, allowing even more breakthroughs in this field because, as we have shown, many of the methods described are still limited in diversity and efficiency but constitute a fertile ground for future discoveries.

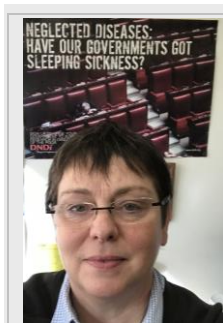
After obtaining his master degree in 2017 at Université Grenoble Alpes, Maxime DONZEL joined the group of Dr. Elisabeth Davioud-Charvet as a PhD student in the research unit UMR7042 CNRS-Unistra-UHA, named „Laboratoire d'Innovation Moléculaire et Applications“ (LIMA). His research interest is focused on finding new synthetic pathways to access functionalized quinones of therapeutic interest.



Mourad ELHABIRI obtained his Ph.D. at Strasbourg University in 1997 in Prof. R. Brouillard's group. During this period, he was interested in the chemistry of anthocyanins and their interactions with metal ions. In 1997, he joined the group of Prof. Jean-Claude Bünzli at EPFL in Lausanne (Switzerland) and worked on the synthesis and photophysical characterization of bimetallic lanthanides triple-stranded helicates. In 1999, he was recruited by the CNRS and focussed his interests on the physicochemical characterization of natural, biomimetic and bioinspired chelators as well as functional supramolecular edifices. During the last 10 years, he has been developing redox-active drugs against viral/parasitic pathogens and elucidating their mechanism of action. He is currently developing innovative functional Vis.-NIR fluorescent dyes for bioimaging.



Elisabeth DAVILOUD-CHARVET studied Pharmaceutical Sciences, prepared her PhD thesis in Prof. H.-P. Husson's group, at the Institute of Chemistry of Natural Substances, Gif-sur-Yvette, and earned her PhD degree in 1988, in Paris 11 University. In 2001, as visiting scientist, she joined the groups of Prof. G. Kenyon and Prof. C. Williams Jr. in Ann Arbor, at the University of Michigan, and was then invited by Prof. H. Schirmer and Prof. K. Becker as group leader in Biochemie-Zentrum Heidelberg (2002-2011) at Heidelberg University. In 2010, she established her independent group in the research unit UMR7042 CNRS-Unistra-UHA, named „Laboratoire d'Innovation Moléculaire et Applications“ (LIMA), located in the European School of Chemistry, Polymers and Materials (ECPM) from Strasbourg University. For more than 25 years she has been focusing on the medicinal chemistry of new redox-active drugs to cure (neglected) parasitic diseases targeting the redox equilibrium of human parasites.



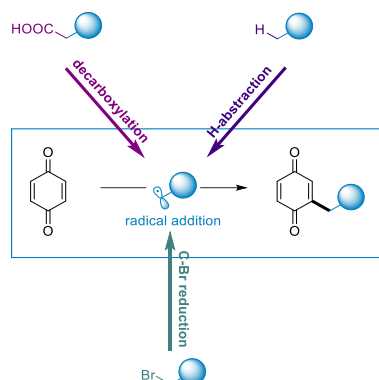
Acknowledgements

This work was supported by the French Centre National de la Recherche Scientifique (E.D.-C.), and the University of Strasbourg (E.D.-C., M.D.), the Laboratoire d'Excellence (LabEx) ParaFrap (grant LabEx ParaFrap ANR-11-LABX-0024 to E.D.-C.), and the ANR PRC2017 (grant PlasmPrim including the salary of the Ph.D. student M.D.).

Keywords: C-halogen reduction • C-H radical alkylation • 1,4-(naphtho)quinone • H-abstraction • (photo)redox

- [1] A. Hidalgo-Gutiérrez, P. González-García, M. E. Díaz-Casado, E. Barriocanal-Casado, S. López-Herrador, C. M. Quinzii, L. C. López *Antioxidants* (Basel) **2021**, 10(4):520.
- [2] J. Stenflo, P. Fernlund, W. Egan, P. Roepstorff, *Proc. Natl. Acad. Sci. USA* **1974**, 71, 2730–2733.
- [3] a) G. L. Nelsestuen, T. H. Zytovicz, J. B. Howard, *J. Biol. Chem.* **1974**, 249, 6347–6350; b) C. Rodríguez-Olleros Rodríguez, M. Díaz Curiel, *J. Osteoporos.* **2019**, 2019:2069176 ; c) M. Vos, G. Esposito, J. N. Edirisinghe, S. Vilain, D. M. Haddad, J. R. Slabbaert, S. Van Meensel, O. Schaap, B. De Strooper, R. Meganathan, V. A. Morais, P. Verstreken. *Science* **2012**, 336, 1306-1310; d) B. J. Josey, E. S. Inks, X. Wen, C. J. Chou, *J. Med. Chem.* **2013**, 56, 1007-1022.
- [4] E. J. Son, J. H. Kim, K. Kim, C. B. Park, *J. Mater. Chem. A*, **2016**, 4, 11179–11202.
- [5] a) T. Müller, L. Johann, B. Jannack, M. Brückner, D. A. Lanfranchi, H. Bauer, C. Sanchez, V. Yardley, C. Deregnacourt, J. Schrével, M. Lanzer, R. H. Schirmer, E. Davioud-Charvet, *J. Am. Chem. Soc.* **2011**, 133, 11557–11571; b) E. C. Rodo, L. Feng, M. Jida, K. Ehrhardt, M. Bielitz, J. Boilevin, M. Lanzer, D. L. Williams, D. A. Lanfranchi, E. Davioud - Charvet, *Eur. J. Org. Chem.* **2016**, 1982–1993; c) O. P.S. Patel, R. M. Beteck, L. J. Legoabe, *Eur. J. Med. Chem.* **2021**, 210, 113084.
- [6] a) K. W. Wellington, *RSC Adv.* **2015**, 5, 20309–20338; b) F. Epifano, S. Genovese, S. Fiorito, V. Mathieu, R. Kiss, *Phytochem. Rev.* **2014**, 13, 37-49; c) R. Verma, *Anti-Cancer Agents Med. Chem.* **2006**, 6, 489-499; d) Y. Zhang, Y.-H. Luo, X.-J. Piao, G.-N. Shen, J.-R. Wang, Y.-C. Feng, J.-Q. Li, W.-T. Xu, Y. Zhang, T. Zhang, C.-Y. Wang, C.-H. Jin, *Bioorg. Med. Chem.* **2019**, 27, 1577–1587; e) S. N. Sunassee, C. G. L. Veale, N. Shunmoogam-Gounden, O. Osoniyi, D. T. Hendricks, M. R. Caira, J.-A. de la Mare, A. L. Edkins, A. V. Pinto, E. N. da Silva Júnior, M. T. Davies-Coleman, *Eur. J. Med. Chem.* **2013**, 62, 98–110; f) G. Viault, D. Grée, S. Das, J. S. Yadav, R. Grée, *Eur. J. Org. Chem.* **2011**, 1233-1241; g) V. Sanna, S. Nurra, N. Pala, S. Marceddu, D. Pathania, N. Neamati, M. Sechi, *J. Med. Chem.* **2016**, 59, 5209–5220; h) E. M. Hodnett, C. Wongwiechintana, W. J. Dunn, P. Marrs, *J. Med. Chem.* **1983**, 26, 570–574.
- [7] G. G. Dias, A. King, F. de Moliner, M. Vendrell, E. N. da Silva Júnior, *Chem. Soc. Rev.* **2018**, 47, 12-27.
- [8] M. Yan, J. C. Lo, J. T. Edwards, P. S. Baran, *J. Am. Chem. Soc.* **2016**, 138, 12692–12714.
- [9] E. T. Denisov, *Kinet. Catal.* **2006**, 47, 662–671.
- [10] a) Y. Wang, S. Zhu, L.-H. Zou, *Eur. J. Org. Chem.* **2019**, 2179–2201; b) Y. Ando, K. Suzuki, *Chem. Eur. J.* **2018**, 24, 15955–15964.
- [11] J. M. Anderson, J. K. Kochi, *J. Am. Chem. Soc.* **1970**, 92, 1651–1659.
- [12] a) N. Jacobsen, K. Torssell, *Acta Chem. Scand.* **1973**, 27, 3211-3216; b) J. Goldman, N. Jacobsen, K. Torssell, *Acta Chem. Scand.* **1974**, 28, 492-500.
- [13] B. Liu, L. Gu, J. Zhang, *Recl. Trav. Chim. Pays-Bas*, **1991**, 110, 99-103.
- [14] L. Salmon-Chemin, E. Buisine, V. Yardley, S. Kohler, M.-A. Debreu, V. Landry, C. Sergheraert, S. L. Croft, R. L. Krauth-Siegel, E. Davioud-Charvet, *J. Med. Chem.* **2001**, 44, 548-565.
- [15] L. Cotos, M. Donzel, M. Elhabiri, E. Davioud-Charvet, *Chem. Eur. J.* **2020**, 26, 3314-3325.
- [16] G. Naturale, M. Lamblin, C. Commandeur, F.-X. Felpin, J. Dessolin, *Eur. J. Org. Chem.* **2012**, 5774–5788.
- [17] W.-Y. Luo, B. Lu, Y.-F. Qiu, R.-Y. Zhou, Y.-J. Hea, J. Wang, *New J. Chem.* **2020**, 44, 8702–8704.
- [18] X. Li, X. Yan, Z. Wang, X. He, Y. Dai, X. Yan, D. Zhao, X. Xu, *J. Org. Chem.* **2020**, 85, 2504–2511.
- [19] R. S. J. Proctor, R. J. Phipps, *Angew. Chem. Int. Ed.* **2019**, 58, 13666-13699.
- [20] D. R. Sutherland, M. Veguillas, C. L. Oates, A.-L. Lee, *Org. Lett.* **2018**, 20, 6863–6867.
- [21] M. T. Westwood, C. J. C. Lamb, D. R. Sutherland, A.-L. Lee, *Org. Lett.* **2019**, 21, 7119–7123.
- [22] J. D. Galloway, D. N. Mai, R. D. Baxter, *Org. Lett.* **2017**, 19, 5772–5775.
- [23] A. Hamsath, J. D. Galloway, R. D. Baxter, *Synthesis*, **2018**, 50, 2915-2923.
- [24] J. D. Galloway, R. D. Baxter, *Tetrahedron*, **2019**, 75, 130665.
- [25] X.-L. Zhu, Y. Huang, X.-H. Xu, F.-L. Qing, *Org. Lett.* **2020**, 22, 5451–5455.
- [26] Á. Gutiérrez-Bonet, C. Remeur, J. K. Matsui, G. A. Molander, *J. Am. Chem. Soc.* **2017**, 139, 12251–12258.
- [27] a) C. R. Pitts, S. Bloom, R. Woltonist, D. J. Auvenshine, L. R. Ryzhkov, M. A. Siegler, T. Lectka, *J. Am. Chem. Soc.* **2014**, 136, 9780–9791; b) L. Niu, J. Liu, X.-A. Liang, S. Wang, A. Lei, *Nat. Commun.* **2019**, 10, 467; c) X.-A. Liang, L. Niu, S. Wang, J. Liu, A. Lei, *Org. Lett.* **2019**, 21, 2441–2444; d) For a review about TEDA²⁺: F. J. Aguilar Troyano, K. Merkens, A. Gómez - Suárez, *Asian J. Org. Chem.* **2020**, 9, 992–1007.
- [28] J. D. Galloway, D. N. Mai, R. D. Baxter, *J. Org. Chem.* **2019**, 84, 12131–12137.
- [29] S.-L. Zhou, L.-N. Guo, X.-H. Duan, *Eur. J. Org. Chem.* **2014**, 8094–8100.
- [30] Y. Dong, J. Yang, S. He, Z.-C. Shi, Y. Wang, X.-M. Zhang, J.-Y. Wang, *RSC Adv.* **2019**, 9, 27588–27592.
- [31] B. Zhu, H. Han, W.-K. Su, C. Yu, X. Jiang, *Adv. Synth. Catal.* **2021**, 363, 484–489.
- [32] a) C.-P. Chuang, S.-F. Wang, *Tetrahedron*, **1998**, 54, 10043–10052; b) M.-C. Jiang, C.-P. Chuang, *J. Org. Chem.* **2000**, 65, 5409–5412.
- [33] E. R. Baral, S. H. Kim, Y. R. Lee, *Asian J. Org. Chem.* **2016**, 5, 1134–1141.
- [34] J. Yang, Y. Dong, S. He, Z.-C. Shi, Y. Wang, J.-Y. Wang, *Tetrahedron*, **2019**, 75, 130729.
- [35] J. Yang, B. Wang, Y. Zhang, S. Zhang, S. He, Z.-C. Shi, J.-Y. Wang, *Org. Biomol. Chem.* **2021**, 19, 988–992.
- [36] J. Liu, D. Yu, Y. Yang, H. You, M. Sun, Y. Wang, X. Shen, Z.-Q. Liu, *Org. Lett.* **2020**, 22, 4844–4847.
- [37] A. Ilangovan, S. Saravanakumar, S. Malayappasamy, *Org. Lett.* **2013**, 15, 4968–4971.
- [38] S. Pandaram, A. Krishna T. P., A. Ilangovan, *Org. Biomol. Chem.* **2020**, 18, 3027–3031.
- [39] P. Sakthivel, T. P. A. Krishna, A. Ilangovan, *ChemistrySelect*, **2021**, 6, 2094–2100.
- [40] For reviews on visible light photocatalysis: a) C. K. Prier, D. A. Rankic, D. W. MacMillan, *Chem. Rev.* **2013**, 113, 5322–5363; b) N. A. Romero, D. A. Nicewicz, *Chem. Rev.* **2016**, 116, 10075–10166.
- [41] S. Devariab, B. A. Shah, *Chem. Commun.* **2016**, 52, 1490-1493.
- [42] D. Li, W.-C. Yang, *Tetrahedron Lett.* **2019**, 60, 1792-1795.
- [43] D. Li, X. Shen, *Org. Biomol. Chem.* **2020**, 18, 750-754.
- [44] M. Donzel, M. Elhabiri, E. Davioud-Charvet, *Manuscript accepted with minor revisions*, May 21, **2021**.
- [45] a) T. Constantin, M. Zanini, A. Regni, N. S. Sheikh, F. Juliá, D. Leonori, *Science*, **2020**, 367, 1021-1026; b) T. Constantin, F. Juliá, N. S. Sheikh, D. Leonori, *Chem. Sci.* **2020**, 11, 12822–12828.
- [46] J. C. Lo, D. Kim, C.-M. Pan, J. T. Edwards, Y. Yabe, J. Gui, T. Qin, S. Gutiérrez, J. Giacoboni, M. W. Smith, P. L. Holland, P. S. Baran, *J. Am. Chem. Soc.* **2017**, 139, 2484–2503.
- [47] S. Liu, T. Shen, Z. Luo, Z.-Q. Liu, *Chem. Commun.* **2019**, 55, 4027-4030.
- [48] G. Feng, S. Sun, G. Liu, H. Long, L. Liu, *Org. Lett.* **2018**, 20, 7522–7525.
- [49] L. Cao, H. Long, H. Guan, Y. Bi, G. Bi, H. Huang, L. Liu, *Tetrahedron Lett.* **2019**, 60, 1268-1271.
- [50] a) Y. Shangguan, F. Yang, H. Deng, H. Liu, Z. Liu, W. Zhuang, C. Qiao, A. Wang, Y. Xiao, C. Zhang, *J. Org. Chem.* **2019**, 84, 10649–10657; b) Q. Wang, B. Wang, H. Deng, Y. Shangguan, Y. Lin, Y. Zhang, Z. Zhang, Y. Xiao, H. Guo, C. Zhang, *J. Org. Chem.* **2019**, 84, 1006–1014.
- [51] L. Tang, F. Yang, Z. Yang, H. Chen, H. Cheng, S. Zhang, Q. Zhou, W. Rao, *Org. Lett.* **2021**, 23, 519–524.
- [52] For reviews and insights on EDA complexes: a) C. G. S. Lima, T. M. Lima, M. Duarte, I. D. Jurberg, M. W. Paixão, *ACS Catal.* **2016**, 6, 1389–1407; b) G. E. M. Crisenza, D. Mazzarella, P. Melchiorre, *J. Am. Chem. Soc.* **2020**, 142, 5461–5476; c) L. Zheng, L. Cai, K. Tao, Z. Xie, Y.-L. Lai, W. Guo, *Asian J. Org. Chem.* **2021**, 10, 711–748.
- [53] B. Sun, X. Shi, X. Zhuang, P. Huang, R. Shi, R. Zhu, C. Jin, *Org. Lett.* **2021**, 23, 1862–1867.

Entry for the Table of Contents



This review article describes the recent developments in direct C-H radical alkylation of 1,4-quinones through generation of radicals by decarboxylative alkylation, hydrogen-atom abstraction, or by carbon-halogen bond reduction, in the presence/absence of light-irradiation, along with the emerging three-component cascade reactions involving quinones and alkenes.

Institute and/or researcher Twitter usernames: [@redoxLCBM](#), [@ECPM_Unistra](#), [@LIMA_UMR7042](#), [@ParaFrap](#)