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Sulfone-quinone derivatives: a review on their synthetic methods, properties and applications

Fares Ghali *[a] and Mohammad Keshe *[b]

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This review presents seven synthetic approaches for sulfone compounds and two for quinone compounds, along with a discussion on their physical and chemical properties and reactivities with various organic compounds. It also highlights several notable applications of these derivatives, particularly in the biological and pharmaceutical fields, demonstrating their potential in the medical and industrial domains.

1. Introduction

Sulfur (Fig. 1) is a nonmetallic element that belongs to group 16 and period 3 of the periodic table. It has an atomic number of 16, and its symbol is "S" based on the word sulfur. In its elemental form, sulfur appears as a yellow crystalline solid and is used in both industrial and medical applications. The most stable allotrope of sulfur is the S8 ring, which is composed of eight sulfur atoms arranged in a crown-like structure, each with an oxidation state of zero.[1]

Sulfur is commonly found in organic compounds in various oxidation states. Fig. 2 illustrates some representative structures of sulfur-containing organic compounds.[2,3]

In sulfones, the sulfur atom exhibits an oxidation state of (+II) within the organic framework. The sulfone functional group consists of a sulfur atom that is doubly bonded to two oxygen atoms and singly bonded to two carbon atoms within an organic molecule.

Some examples of sulfone-containing organic compounds are shown in Fig. 3.[1–4]

In addition, the sulfonylurea derivatives of hydroquinones are essential components in the molecular structures of numerous industrially and biologically relevant compounds. They have a wide range of properties, including antitumor activity and HIV reverse transcriptase inhibition,[5] making them an attractive focus of research, both in terms of their synthesis methods and their various applications across diverse fields. This review covers both quinone and sulfone synthesis methods, providing a comprehensive explanation of the properties and applications of these compounds.

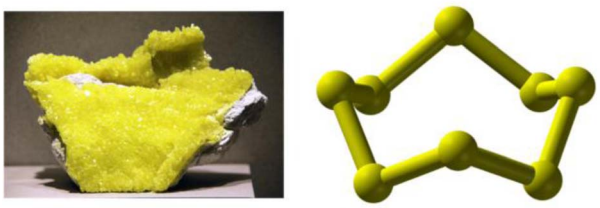


Fig. 1 Elemental sulfur.

2. Synthesis methods

The most common methods for synthesizing sulfone groups involve sulfide oxidation and electrosynthesis. However, these methods often require the use of strong acids or oxidizing agents, prompting the development of alternative synthetic approaches,[6] most of which are reviewed in this section.

(1) Surya Prakash and his colleagues reported a sulfone synthesis method *via* the mild oxidation of sulfides using a mixture of nitrate salts and chlorotrimethylsilane, achieving yields of up to 90%, as demonstrated in the synthesis of diphenyl sulfones (Scheme 1).[7]

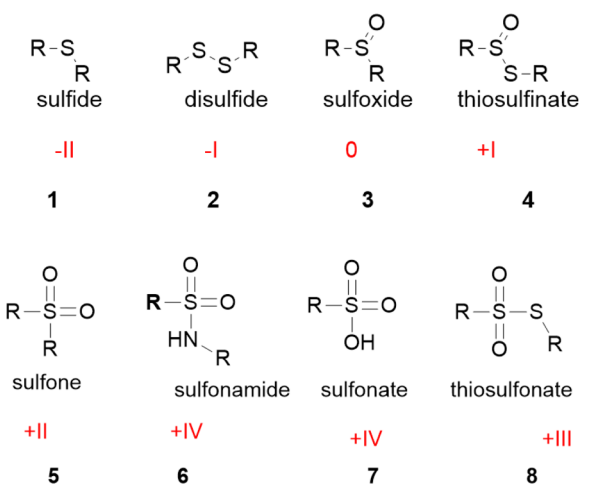
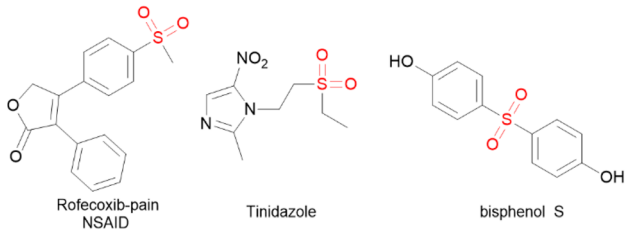


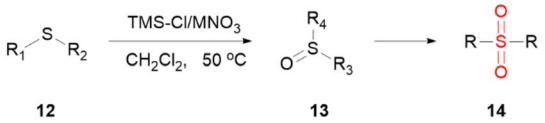
Fig. 2 Various oxidation states of sulfur in organic compounds.

[a]*Ms Student in Organic Chemistry, Department of Chemistry, Faculty of Science, University of Homs, Homs, Syria*
[b]*PhD in Organic Chemistry, Department of Chemistry, Faculty of Science, University of Homs, Homs, Syria. E-mail: mohammad.keshe@gmail.com*



9 10 11

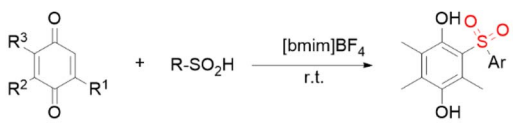
Fig. 3 Organic compounds containing the sulfone group.



12 13 14

	MNO_3	Time (h)	Yiled(%)
R1,2 =	KNO_3	3.5	90
R1=	NH_4NO_3	2	Mixture
R2= $-CH_3$			
R3,4=	KNO_3	1,5	85

Scheme 1 Synthesis of sulfones *via* oxidation processes.

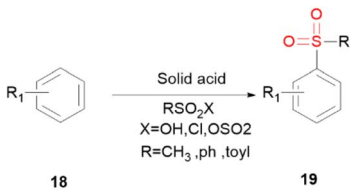


15 16 17

		Time(min)	Yield(%)
R1,R2,R3=H	R= Ph	25	92
R1,R2=H R3=Me	R=4-MeC_6H_4	30	95
	R=Ph	35	85
R1,R2=H R3=OMe	R=4-MeC_6H_4	30	87
	R=Ph	40	83

Scheme 2 Synthesis of sulfones using ionic liquids.

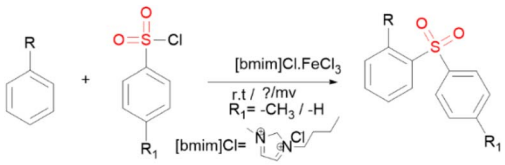
(2) In 2004, Yadav and his team published a study on the addition of aryl sulfonic acids to para-quinone derivatives. This study focused on the dual role of ionic liquids as both solvents and catalysts, achieving yields above 90% for some quinone derivatives (Scheme 2).[8]



18 19

	Sulfonylating agent	Catalyst	Time (t/h)	Product yielda (%)
m-Xylene	TsCl	Fe3+-mont	6	85
	Ts2O	Fe3+-mont	6	92
	TsOH	Fe3+-mont	24	52
	Ts2O	Al3+-mont	6	63
	Ts2O	Zn2+-mont	6	54
	Ts2O	Zn2+-mont	6	80

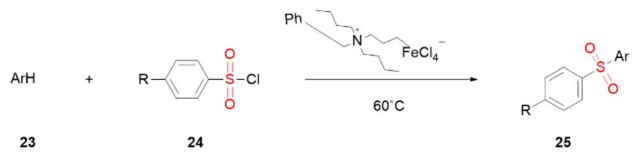
Scheme 3 Synthesis of sulfones *via* the Friedel–Crafts mechanism using solid acid catalysts.



20 21 22

		Time (h)	Yield (%)
R_1= CH_3	R=H	3	82
	R=Cl	8	76
	R=Br	5	68
	R=OMe	3	84

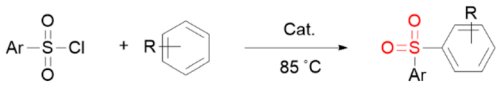
Scheme 4 Synthesis of sulfones *via* the Friedel–Crafts mechanism using ionic liquids.



23 24 25

Substrate	R	Time (min)	Yield (%)
	Me	1	96
	H	<1	94
	Me	1	97
	H	1	95

Scheme 5 Synthesis of sulfone using the Friedel–Crafts mechanism by using ionic liquids.



26 27 28

Cat.:Ps-$AlCl_3$ or SiO_2-$AlCl_3$ R=H,OMe,Me,ph Cl,Br / Ar=Cl,Br

Ar	Arene	Time (h)	Yield (%)
Ph	Benzene	1	92
Ph tolyl	Benzene	1,3	91
Ph tolyl	Toluene	1.1	95
Ph tolyl	Toluene	1	92

Scheme 6 Synthesis of sulfones *via* the Friedel–Crafts mechanism using polystyrene-$AlCl_3$ (ps-$AlCl_3$) and SiO_2–$AlCl_3$.

(3) Friedel–Crafts mechanisms, such as alkylation and acetylation, are well known and widely applied in organic synthesis. Many researchers have modified the Friedel–Crafts mechanism to synthesize sulfones using various catalysts and solvents in optimized yields.

In 2000, Boyapati M. Choudary and his team published a study on the use of solid acid catalysts, such as montmorillonite and zeolites, and their influence on product yield under optimized conditions; the yield reached 94% in some reactions using sulfone anhydride, as illustrated in Scheme 3.[9]

In the last reaction, sulfone was used in the form of sulfonyl chloride and sulfone anhydride in the presence of a hydroxide group.

The conditions for preparing the anhydride have been described by Lamafri Eld,[10] and the preparation of sulfonyl chloride has been detailed in various studies.[11,12] The application of basic ionic liquids in Friedel–Crafts sulfonation has become a well-established study using Lewis acidic $FeCl_3$ 1-butyl-3-methylimidazolium chloride ([bmim]Cl) as a catalytic system. They investigated the effects of temperature and time on various aromatic substrates, achieving yields of up to 95% within one hour (Scheme 4).[13]

In 2008, Kiumars Bahrami and colleagues expanded on this approach using a different basic ionic liquid, benzyl tributylammonium chloride. This method yielded over 90% for most compounds within 1 to 5 hours (Scheme 5).[14]

Kaveh Parvanak Borujeni and his colleague investigated the use of heterogeneous catalysts in Friedel–Crafts sulfonation to improve yields and facilitate catalyst recovery. The employed polystyrene-supported $AlCl_3$ (ps-$AlCl_3$) and silica-supported $AlCl_3$ (SiO_2–$AlCl_3$) as catalysts resulted in high yields, as shown in Scheme 6 and Table 1.[15]

2.1 Critical analysis for Friedel–Crafts sulfonation

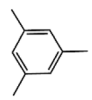
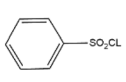
This synthetic route represents a classical approach for the preparation of sulfone groups (–SO_2–) due to its broad substrate compatibility and characteristically direct reaction pathway.

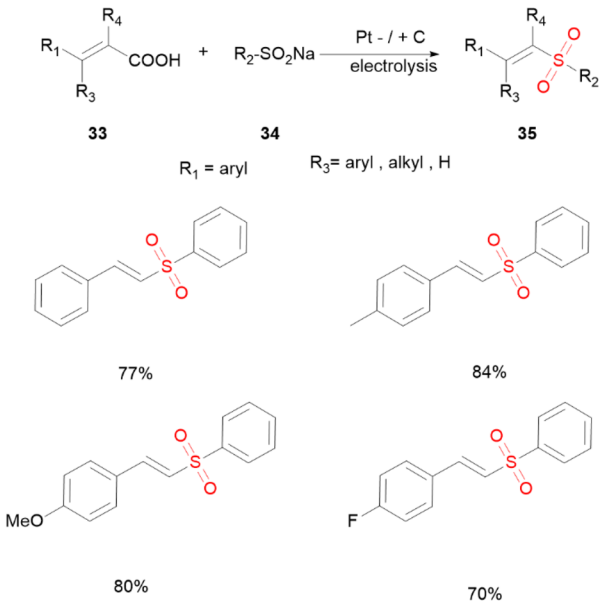
Nevertheless, this approach has several significant limitations.

These reactions often require Lewis acid catalysts that are highly sensitive to moisture, corrosive, and environmentally hazardous, such as anhydrous aluminum chloride. Moreover, such catalysts typically need to be supported on solid materials to enhance their catalytic efficiency, thereby introducing an additional step into the overall process.

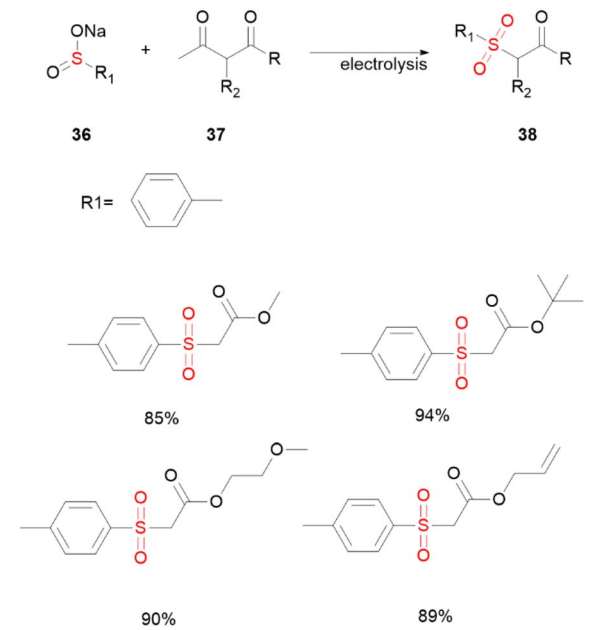
In many instances, the reaction conditions are relatively harsh, involving elevated temperatures and extended reaction times. These factors can lead to undesirable side reactions or degradation of sensitive functional groups, particularly when alkyl sulfonyl chlorides are involved.

Table 1 Reaction conditions for the synthesis of sulfone derivatives *via* the Friedel–Crafts mechanism

Entry	Sulfonylation agent	Catalyst	Time	Temp.°C	Yields (%)	Ref
 29	TsCL	Fe^{3+}-mont	6	120	85	
	Ts_2O	Fe^{3+}-mont	6	120	92	8
	TsOH	Fe^{3+}-mont	24	138	63	
 29	R^1-C_6H_4–SO_2CL	[bmim]Cl·$FeCl_3$	2	30	89	12
 29	 31	[BTBA]Cl·$FeCL_3$	1 h	60	96	13
 30	 32	Ps-$ALCL_3$ and SiO_2-$ALCl_3$	1.3 h	85	92	14



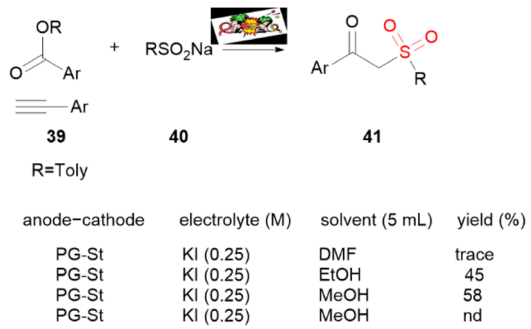
Scheme 7 Electrochemical synthesis of the sulfone group using sulfate salts.



Scheme 8 Electrochemical synthesis of the sulfone group using a sulfate salt.

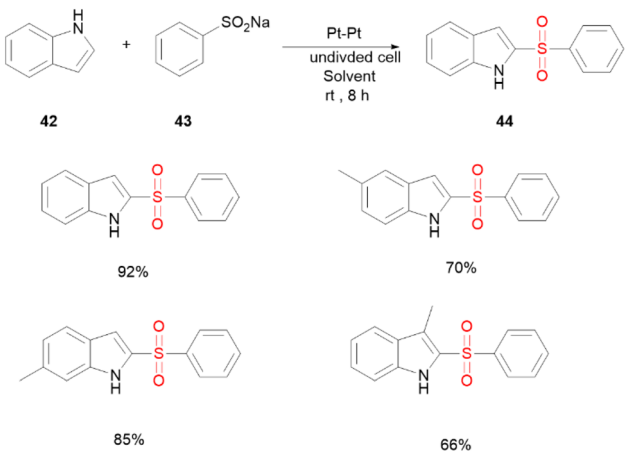
This process frequently requires the use of highly reactive and moisture-sensitive starting materials, such as sulfonic acid anhydrides or sulfonyl chlorides. When the starting substrate contains a sulfonic acid group, it must first be transformed into these derivatives, which requires the use of hazardous reagents, such as thionyl chloride.

Reaction selectivity is often low, which complicates downstream separation and purification procedures.



anode–cathode	electrolyte (M)	solvent (5 mL)	yield (%)
PG-St	KI (0.25)	DMF	trace
PG-St	KI (0.25)	EtOH	45
PG-St	KI (0.25)	MeOH	58
PG-St	KI (0.25)	MeOH	nd

Scheme 9 Electrochemical synthesis of the sulfone group using a sulfate salt in various solvents.



Scheme 10 Electrochemical sulfonation of indole using sodium benzene sulfate.

Due to the high temperatures employed, solvents with high boiling points must be used, making solvent removal more challenging and potentially energy-intensive.

To address these issues, future strategies should focus on developing green catalysts and selecting solvents that reduce ecological impact while enhancing reaction performance. Additionally, alternative activation techniques, such as microwave or photochemical catalysis, may help mitigate the need for harsh conditions and improve reaction selectivity. Computational modeling can also be employed to predict reaction behavior, guide selectivity, and optimize regioselectivity.

There is no doubt that sulfate salts play a vital role in the sulfonate synthesis.

2.4 This subsection reviews several studies that have investigated sulfate salts, either as intermediates or as starting materials.[16–18] In 2016, Peng Qian and his colleagues published a study on the synthesis of sulfones from sodium sulfate salts; they examined the effect of various electrodes (such as gold and carbon) and different electrolytes on the reaction, particularly focusing on the interaction between cinnamic acid and sodium sulfate under various conditions, as illustrated in Scheme 7.[19]

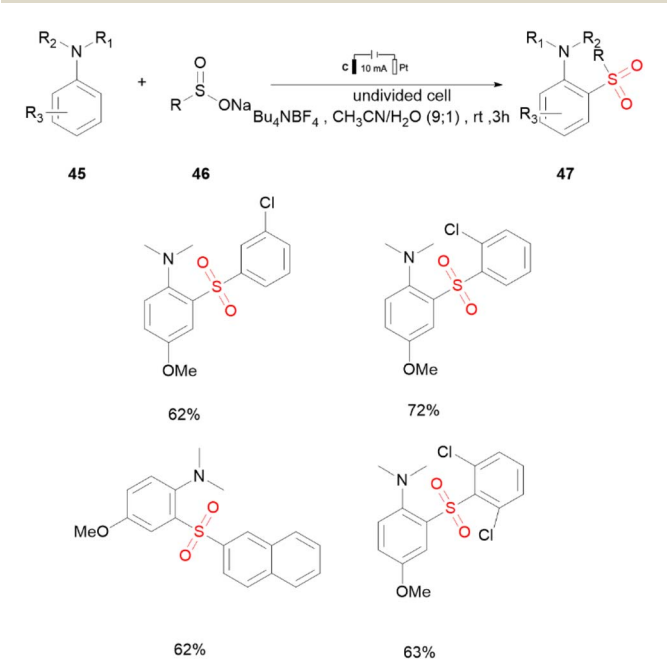
In 2015, a β-keto ester was synthesized using organic sulfate salt and carbonyl compounds in DMSO as the solvent. Nickel

and carbon electrodes were used, and ammonium acetate served as the supporting electrolyte. The reaction gave good yields, reaching up to 90%, as shown in Scheme 8.[20]

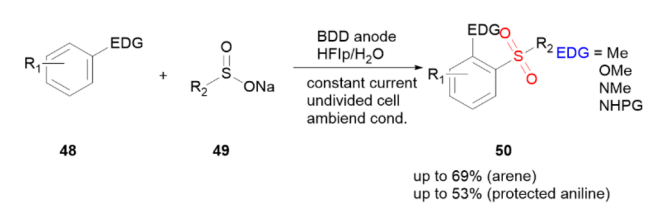
β-Ketosulfone was synthesized from methylaryl ketone sulfate and aryl acetylene with sodium sulfate under mild electrochemical conditions. In 2019, Issa Yavari and Sina Shaabanzadeh reported a reaction using various electrolytes, such as methanol and ethanol, and the reaction gave a moderately acceptable yield, as shown in Scheme 9.[21]

In 2017, Mei-Lin Feng and colleagues investigated the electrochemical sulfonation of indole using sodium benzene sulfate in an undivided cell under mild, metal-free conditions. The reaction gave excellent yields, and further studies on these conditions have enabled the synthesis of various products from suitable sulfone derivatives and indole or its analogues, as shown in Scheme 10.[22]

In 2019, Yan-Chen Wu and his colleagues from Nanchang Hangkong University and Hunan University investigated the sulfonation of *N*,*N*-disubstituted anilines. Their study examined the effect of various reaction conditions on the yield in an undivided electrochemical cell, with the reaction achieving up to 91% yield under optimal conditions, as illustrated in Scheme 11.[23]



Scheme 11 Electrochemical sulfonation of *N*,*N*-disubstituted anilines.



Scheme 12 Electrochemical synthesis of aryl sulfones and aniline sulfonate under metal-free conditions.

In 2019, the syntheses of aryl sulfones and aniline sulfones were investigated under metal-free conditions following the general reaction depicted in Scheme 12.[24]

2.2 Critical analysis for electrochemical synthesis

Electrochemical sulfonation is a promising alternative to traditional synthetic methods for introducing sulfone groups owing to its catalyst-free nature, operational simplicity, and alignment with the principles of green chemistry.

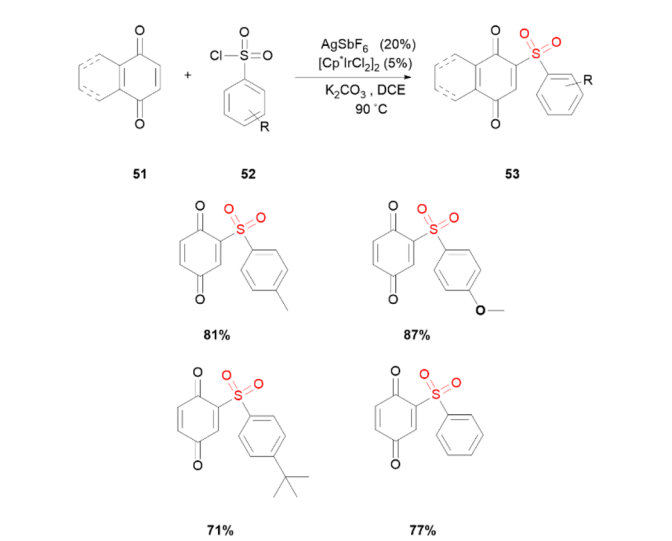
The application of electric current in electrochemical cells, whether divided or undivided, significantly reduces reliance on corrosive reagents and minimizes the formation of undesirable side products.

However, several challenges remain, including the need for precise control over the cell design and applied potential to prevent overoxidation or unwanted side reactions. Additionally, this technique may not be suitable for substrates bearing multiple reactive functional groups or heterocyclic systems.

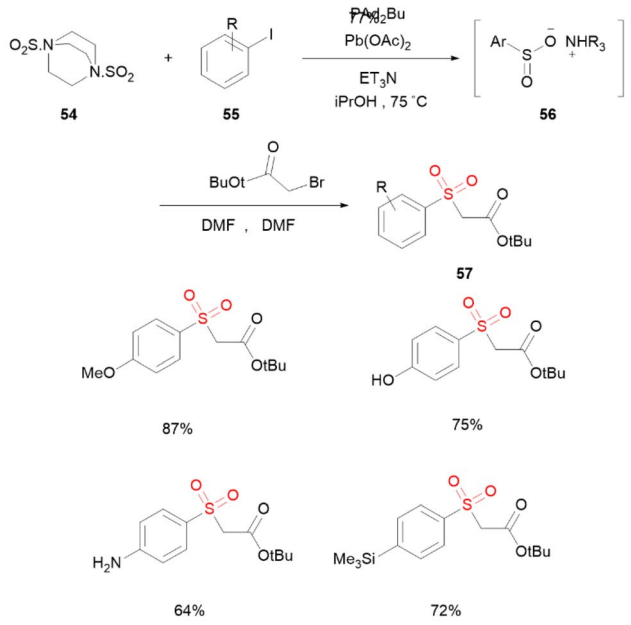
Therefore, expanding the substrate scope and employing computational electrochemical modeling to predict the oxidation potential and reaction kinetics are recommended to improve the overall efficiency of the process.

(5) With the advancement of organic synthesis, several new methodologies have emerged for constructing organic molecules, including the electrical methods previously mentioned. Over the past two decades, metal–organic catalysis has significantly developed in this field. This progress is exemplified by the construction of organic molecules *via* cross-conjugation of C–X bonds or direct C–H activation reactions.[25,26] In 2015, Long Wang and his colleagues employed organoiridium complexes to synthesize sulfone groups on benzoquinone and naphthoquinone substrates, achieving yields exceeding 80% in some cases, as illustrated in Scheme 13.[27]

In 2014, a research article was published that included a study of the use of organic palladium catalyst where



Scheme 13 Synthesis of the sulfone group using metal–organic catalysts.



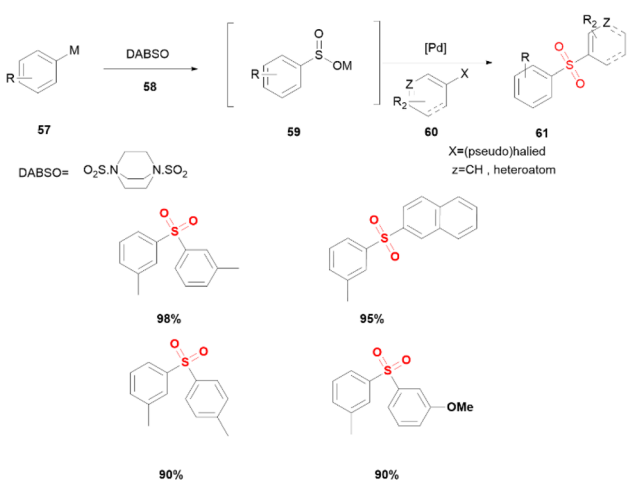
Pd(OAc)2 (10 mol%), ligand (20 mol%), DABSO (1.1 equiv), Et3N (3.0 equiv), iPrOH [0.2m], 75 °C

Scheme 14 Synthesis of the sulfone group using metal–organic catalysts.

halobenzene derivatives were used with DABSO compound in the presence of palladium catalyst where an intermediate stage of sulfate is formed ammonium aryl followed by the formation of the expected sulfonic compound as shown in Scheme 14.[28]

Pd(OAc)2 (10 mol%), ligand (20 mol%), DABSO (1.1 equiv.), Et3N (3.0 equiv.), iPrOH [0.2 m], 75 °C.

In 2013, Edward J. Emmett and colleagues employed palladium catalysts using DABSO as the sulfone group source. Their study focused on evaluating various organopalladium catalysts to identify the most efficient. Numerous sulfonic derivatives were synthesized *via* this reaction, as illustrated in Scheme 15.[29]



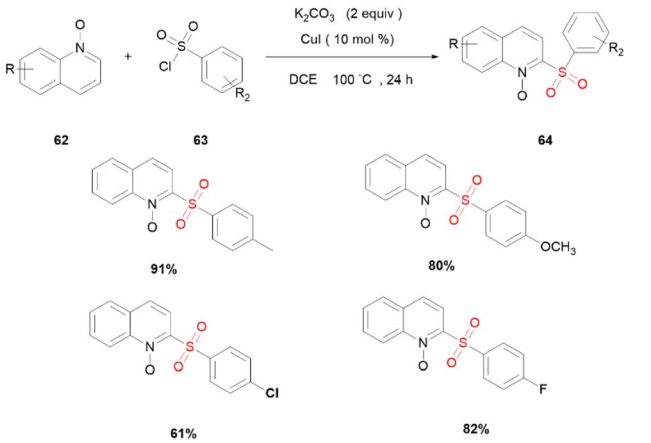
Scheme 15 Synthesis of the sulfone group *via* metal–organic catalysis.

In 2013, the application of copper catalysts in sulfone synthesis was investigated due to their cost-effectiveness compared to other metal catalysts. The primary reaction involved quinoline *N*-oxides and aryl sulfonyl chlorides, as illustrated in Scheme 16.[30]

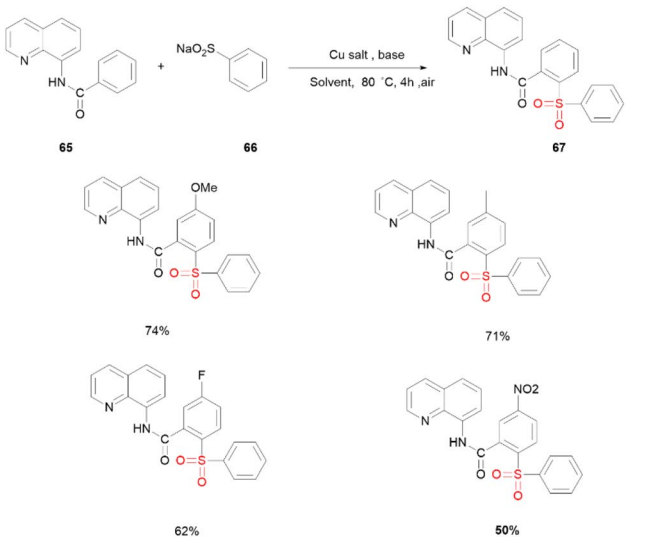
In 2015, Jidan Liu revisited the use of copper catalysts for the direct C–H bond sulfonation of benzoic acid derivatives. This method utilized a sodium sulfate salt and employed an 8-aminoquinoline moiety as a bidentate directing group, as illustrated in Scheme 17.[31]

2.3 Critical analysis of metal–organic catalysts

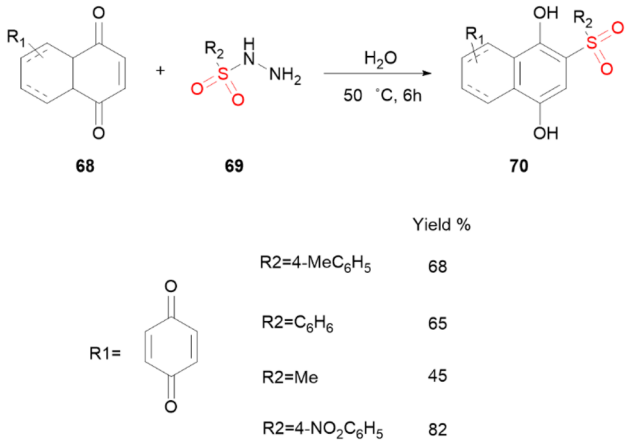
According to previous studies, organometallic catalysts—such as those based on palladium and copper—have demonstrated good efficiency in the formation of carbon–sulfur bonds under relatively mild conditions, achieving high yields and excellent selectivity. This has rendered them valuable tools for the synthesis of sulfone derivatives.



Scheme 16 Synthesis of the sulfone group using copper catalysts.



Scheme 17 Direct C–H bond sulfonation of benzoic acid derivatives using copper catalysts.

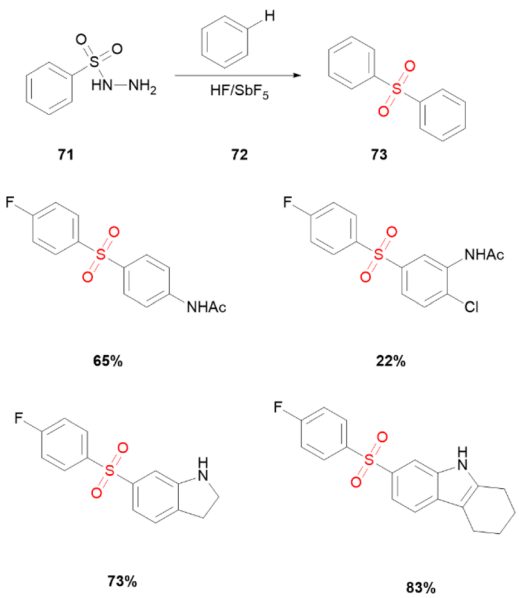


Scheme 18 Synthesis of the sulfone group using sulfonyl aryl hydrazides.

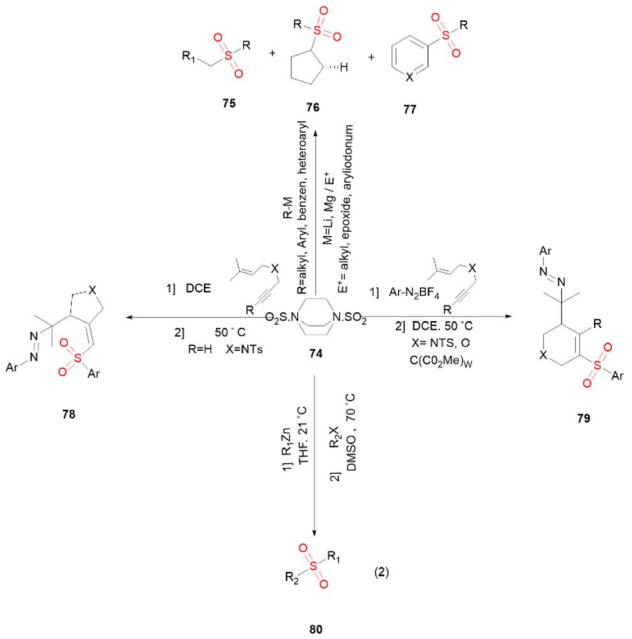
However, these catalysts have several drawbacks; they are often expensive and sensitive to moisture and air and sometimes require an inert atmosphere. Furthermore, residual metal contamination may conflict with the principles of green chemistry and limit catalyst recyclability.

Therefore, future research should focus on the development of less toxic, earth-abundant alternatives, such as iron and manganese catalysts or fully organic catalytic systems. Additionally, the inherent complexity in understanding the catalytic behavior and predicting the plausible mechanisms remain challenging.

(6) From the above, it can be concluded that sulfone synthesis typically requires either oxidation processes or the use of non-green or costly reagents. To circumvent these limitations, Bin Li and his colleagues employed sulfonylaryl hydrazides in an aqueous medium and achieved good yields, as illustrated in Scheme 18.[5]



Scheme 19 Synthesis of the sulfone group using sulfonyl aryl hydrazides.



Scheme 20 Synthesis of the sulfone group using DABSO.

In 2021, Paul Bourbon and colleagues utilized these compounds to synthesize various sulfonic organic compounds, as illustrated in Scheme 19.[32]

2.7 The significance of the DABSO compound in the synthesis of organic sulfone groups is considerable, as evidenced by recent studies.[29,30] Therefore, we review some general reaction schemes by employing DABSO for sulfone synthesis, as illustrated in Scheme 20.

(**75–77**)…[33] (**78, 79**)…[34]

(**80**)…[35]

2.4 Final comparative assessment of synthetic approaches

Among the reviewed synthetic strategies for the preparation of sulfone derivatives, each method demonstrates distinct advantages and limitations based on reaction conditions, environmental impact, and substrate scope. However, from a critical standpoint, electrochemical synthesis appears to offer the most promising path forward, particularly due to its alignment with green chemistry principles, absence of metal catalysts, and operational simplicity.

Although Friedel–Crafts sulfonation and metal-catalyzed methods remain effective for specific substrates and yield optimization, they suffer from environmental drawbacks and limited scalability in eco-conscious settings.

Therefore, although no single method can be universally superior, electrochemical approaches represent the best compromise between efficiency, sustainability, and practicality, especially in academic and exploratory research settings. Future advancements in electrode design and substrate compatibility could further enhance their industrial relevance.

3. Chemical properties

Following the development of the electronic octet theory, the structure of sulfones was reevaluated. The initially proposed structure (I) was revised to the accepted structure (II), as illustrated in Fig. 5.[36]

Over time, the correlation between structures I, II, and III and their physical and chemical properties was investigated. This was examined using infrared spectroscopy in a study by Amstutz ED and colleagues.[37] The above structural formulas are directly related to resonance situations involving adjacent electronic systems.

Harry Szmant elucidated the electronic effects and clarified the previously proposed structures. It was explained that in the presence of electron-withdrawing substituents, structure I is favored in vinyl sulfate. Conversely, with electron-donating substituents, sulfone structure II is preferred. Additionally, structure III is relevant in acidic media, where hydrogen bonding plays a significant role,[38] as illustrated in Fig. 6.

The influence of the organic sulfone group on the acidity or basicity of the associated organic compound is linked to the electron distribution around the sulfone moiety. This, in turn, depends on the nature of the substituent attached to the sulfone group. If the substituent is electron-withdrawing, as in *p*-(4-nitrophenylsulfonyl) benzoic acid, it increases the pK_a value, resulting in lower acidity. Conversely, if the substituent is electron-donating, as in *p*-(4-aminophenylsulfonyl) benzoic acid, it decreases the pK_a value, leading to higher acidity.[39] Organic compounds containing the sulfone group can undergo a wide range of typical organic reactions, whether these reactions involve the sulfone group directly or the rest of the molecule bearing this functional group. These include addition, rearrangement, and other transformation reactions.[40,41] Rearrangement reactions, in particular, are an important class of transformations for sulfonic organic compounds. They are considered efficient synthetic strategies that align with the principles of green chemistry.[42] In such reactions, the atomic arrangement of the compound changes without the loss of any atoms, resulting in a new molecular structure. The subsequent section highlights selected rearrangement reactions involving sulfone-containing compounds.

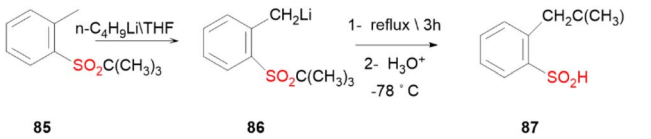
In 1966, W. E. Truce and colleagues investigated the rearrangement reactions of mesityl 1-naphthyl sulfone and mesityl 2-naphthyl sulfone using potassium *tert*-butoxide as a base in dimethyl sulfoxide (DMSO). The reactions were followed by acidic work-up and resulted in the formation of two isomeric sulfinic acid derivatives: 2-(2′-naphthylmethyl)-4,6-dimethylbenzenesulfinic acid and 2-(1′-naphthylmethyl)-4,6-dimethylbenzenesulfinic acid, as illustrated in Scheme 21.[43]

In 1985, Edmund J. Madaj revisited the rearrangement reactions of sulfones in the presence of a strong base. This time, the base used was *n*-butyllithium in tetrahydrofuran (THF). The reaction involved *o*-tolyl *tert*-butyl sulfone, resulting in the formation of *o*-neopentylbenzenesulfinic acid, as illustrated in Scheme 22.[44]

Before the previously mentioned study, in 1958, William E. Truce and William J. Ray Jr. conducted a rearrangement reaction using *n*-butyllithium on *ortho*-methyldiaryl sulfones. The results of their study are illustrated in Scheme 23.[45]

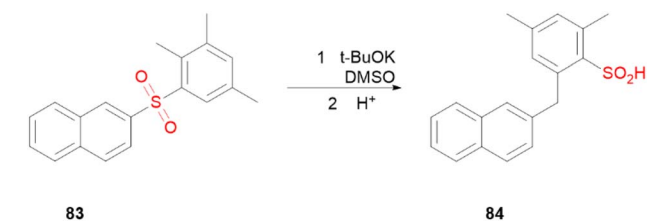
The electron-withdrawing nature of the sulfonyl group exerts a significant acidifying effect on adjacent α-hydrogen atoms, similar to the behavior of carbonyl groups. This enhanced acidity facilitates a wide range of chemical transformations,[46,47] including nucleophilic addition,[48] alkylation,[49] cross-coupling,[50] and acylation[51] aldol. In 2014, Lucie Rehová and her colleagues investigated alkylation reactions involving the synthesis of phenyl sulfone derivatives using *n*-butyllithium *n*-BuLi., as illustrated in Scheme 24.[52]

In 2020, Manjula D. Rathnayake employed the alkylation reaction as a key step in the synthesis of alkylated phenyl sulfone derivatives, achieving a yield of 85%, as shown in Scheme 25.[53]

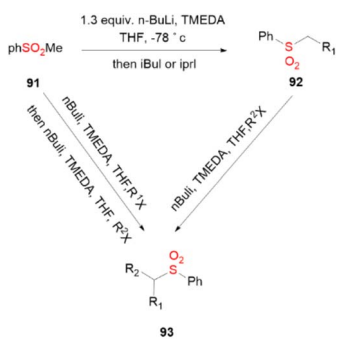


Scheme 22 Rearrangement reaction of sulfones in the presence of a strong base.

Scheme 23 Rearrangement reaction using *n*-butyllithium on *ortho*-methyldiaryl sulfones.



Scheme 21 Rearrangement reactions of the sulfone group.



Scheme 24 Alkylation reaction on the α-sulfone site.

In 2023, Lijun Lu and his colleagues conducted an α-alkylation reaction using organomanganese catalysts in a basic medium at a rate of 0.5 mol%, employing the corresponding alcohol derivative as the alkylating agent, as illustrated in Scheme 26.[54]

However, the sulfone group is also involved in acylation reactions. In 1988, Marcus W. Thomsen utilized an acylation reaction in the presence of a lithium base (28 mmol) with (13 mmol) methyl phenyl sulfone to synthesize β-keto sulfones, as illustrated in Scheme 27.[55]

In 2003, Alan R. Katritzky and his colleagues performed various acylation reactions using *n*-butyllithium *n*-BuLi., starting from sulfonic organic compounds and *N*-acylbenzotriazoles. The study focused on the synthesis of multiple derivatives, which differed in their alkyl substituents, as depicted in Scheme 28.[56]

In 2011, Jirí Pospísil carried out various synthesis reactions on sulfone compounds to obtain β-acyl and β-alkoxycarbonyl heterocyclic sulfone derivatives. The acylation reactions employed $LiN(TMS)_3$ (2.2 eq.) as a catalyst and tetrahydrofuran (THF) as the solvent, achieving high yields of up to 97%, as illustrated in Scheme 29.[57]

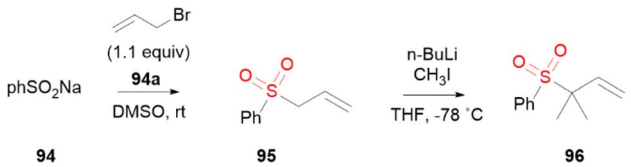
Moving on to aldol-type reactions, in 1981, Masahiro Hirama utilized the addition of sulfonylallyl carbanions to α, β-unsaturated ketones. This transformation served as an intermediate step, followed by a rearrangement reaction, as illustrated in Scheme 30.[58]

Two years later, in 1983, T. Curving investigated the same reaction using 1,1-disulfone compounds with aldehydes under alkaline conditions, as depicted in Scheme 31.[59]

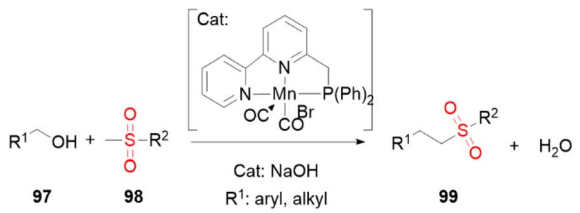
In 1994, Carmen Nájera and his colleagues investigated the delithiation reaction of 2-(chloromethyl)-3-tosypropene with *n*-butyllithium at −90 °C. One of the resulting products was formed through aldol condensation with an alkyl aldehyde, as illustrated in Scheme 32.[60]

The previously discussed interactions are summarized in the diagram presented in Fig. 7 and Table 2.

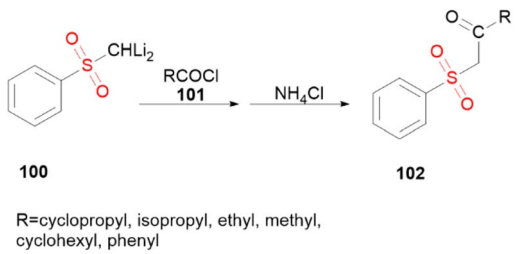
The reactivity of sulfone compounds is not limited to the aforementioned reactions (Fig. 8). They also participate in



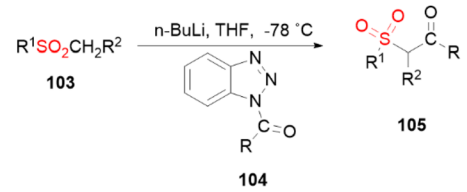
Scheme 25 Alkylation reaction as a key step in the synthesis of alkylated phenyl sulfone derivatives.



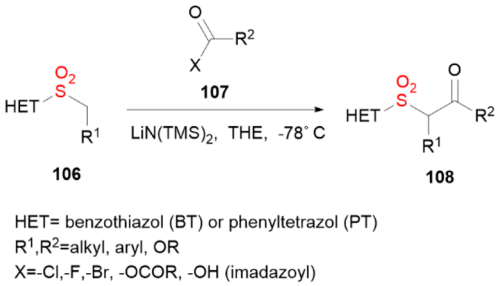
Scheme 26 α-Alkylation reaction using organomanganese catalysts in a basic medium.



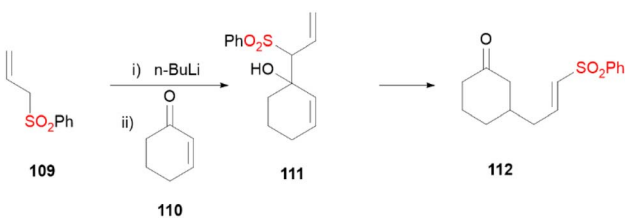
Scheme 27 Acylation reaction on the α-sulfone site.



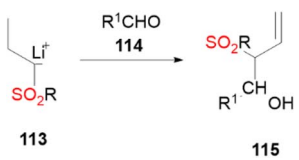
Scheme 28 Acylation reaction on the α-sulfone site.



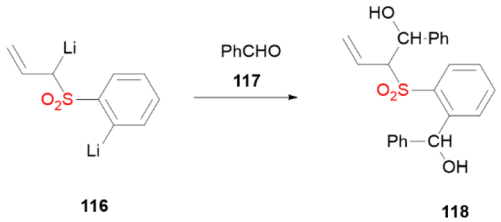
Scheme 29 Acylation reaction to obtain β-acyl and β-alkoxycarbonyl heterocyclic sulfone derivatives.



Scheme 30 Aldol reaction on the α-sulfone site.



Scheme 31 Aldol reaction on the α-sulfone site.



116 118

Scheme 32 Delithiation reaction of 2-(chloromethyl)-3-tosypropene with *n*-butyllithium at −90 °C.

a wide range of additional transformations, such as halogenation reactions[61] and reactions with epoxides.[62,63]

4. Physical properties

Following the discussion of the chemical properties, it is important to examine the physical properties of compounds containing the sulfone group. First, we consider the intermolecular interactions formed by this functional group, most notably hydrogen bonding, as previously discussed and illustrated in Fig. 4.[38]

As a consequence of the aforementioned characteristics, the sulfone group has been utilized to modify polymer structures, aiming to tailor their physical properties.

For example, in 2015, Farideh Abbasi and his colleagues modified the structure of polyimides by introducing the sulfone group to the structure of the polymer to change some of its properties, especially solubility in different solvents, where the sulfone group was introduced to this polymer to create a balance between the properties of sulfone polymers and

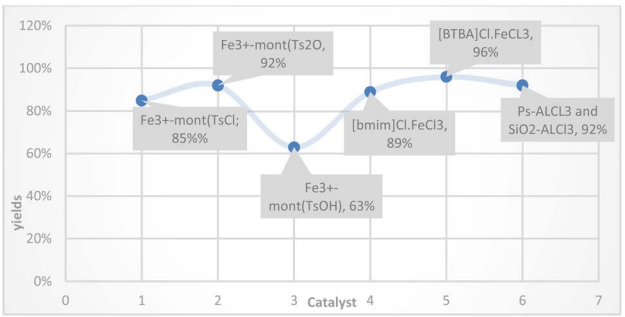


Fig. 4 Change in yields upon the use of different catalysts and reagents.

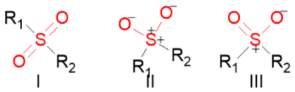
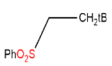
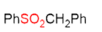
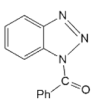
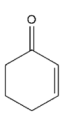
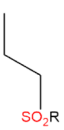


Fig. 5 Structures of sulfones.

polyimide polymers, as sulfone polymers have a low degree of glass transition and solubility, thus obtaining a polymer with good mechanical and physical properties.[64] The incorporation of sulfone groups into polymeric structures contributes to the development of high-performance polymers characterized by excellent chemical and thermal stability, high mechanical strength and flexibility, optical transparency, elevated glass transition temperatures, and favorable film-forming properties.[65,66]

Table 2 Summary of the reactions of organic compounds bearing the sulfone group

Reaction type	Entry	Reagent	Catalyst	Time	Temp. °C	Yields (%)	Ref.
		EtI	*n*-BuLi	20 m	−78	95	52
Alkylation reaction		CH_3I	*n*-BuLi	—	−78	85	53
			[Mn] NaOH	24H	150	98	54
Acylation reaction	$C_6H_5SO_2CH_2Li$	Cyclopropanecarboxylic chloride	*n*-BuLi	30 m	−30	74	55
			*n*-BuLi	—	−78	95	56
	PhCOCl	PhCOCl	$LiN(TMS)_2$	—	−78	97	57
			*n*-BuLi	2.5 m	−78	69	58
Aldol reactions		C_2H_5CHO	*n*-BuLi			79	59

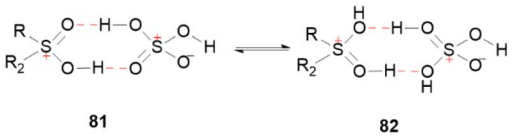


Fig. 6 Hydrogen bonds formed by the sulfone group.

5. Uses of sulfones

Organic compounds containing the sulfone group exhibit diverse bioactivities across multiple domains. In the pharmaceutical field, they have demonstrated significant non-steroidal anti-inflammatory activity (**119**),[67] antibacterial properties, and several other pharmacological effects.[68] However, their medical relevance is also substantial. For instance, certain sulfone-containing compounds, such as 2-anilino-3-phenylsulfonyl-6-methylpyridine derivatives, act as corticotropin-releasing factor (CRF) modulators (**120**).[69] The sulfone group also plays a significant role in food additives, being a core structural component of well-known compounds, such as saccharin and acesulfame-K (**121**).[70] Furthermore, sulfones are utilized in the agricultural sector, particularly in the development of agrochemicals, such as the herbicide mesotrione (**122**).[71] In addition to the aforementioned roles, the sulfone group is also widely involved in organic synthesis. For instance, it has been utilized in the synthesis of the natural product lycopodine *via* the Michael addition reaction (**123**).[72] Moreover, sulfones commonly serve as key intermediates in numerous synthetic pathways,[73,74] including the development of various polymeric materials (**124**),[75–77] as illustrated in Fig. 9.

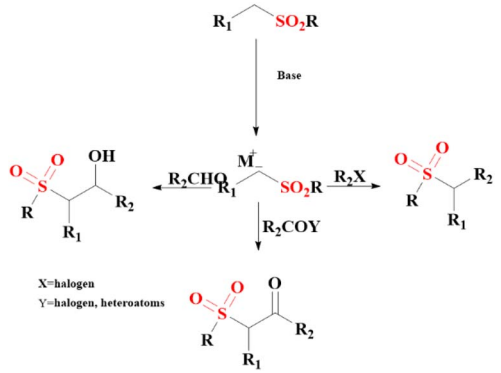


Fig. 7 Summary of previous interactions.

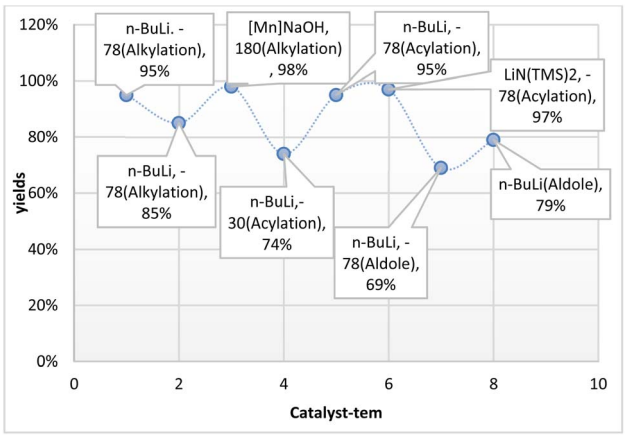


Fig. 8 Yields of different reactions upon varying the catalysts and temperatures.

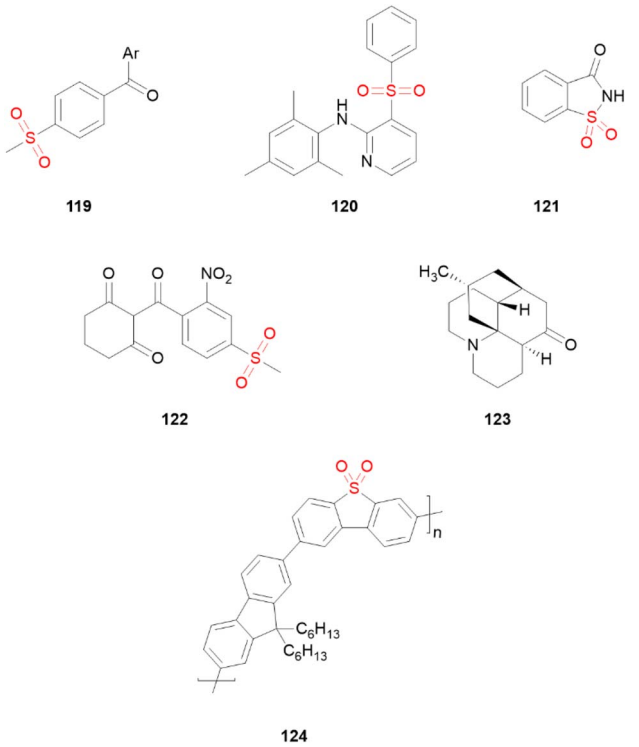


Fig. 9 Structures of sulfones with various applications.

5.1 Critical analysis of sulfone derivatives in biological and industrial applications

Sulfone-containing compounds are widely recognized for their applications in various fields, including medicinal chemistry, materials science, and catalysis. In the biological domain, aryl and heteroaryl sulfones have shown antimicrobial, anti-inflammatory, and anticancer activities, with several sulfone-based drugs (*e.g.*, dapsone) already in clinical use. However, most newly reported sulfone derivatives are evaluated only through preliminary bioassays, often lacking comprehensive toxicity, selectivity, or pharmacokinetic profiling.

Structurally, the presence of the sulfone group enhances molecular polarity and metabolic stability, yet its influence on biological targets is not always predictable due to variable positioning and conjugation. Furthermore, in industrial settings, sulfone polymers such as polysulfones and polyethersulfones are valued for their thermal and chemical resistance, yet their synthesis remains energy-intensive and dependent on non-renewable starting materials.

Thus, although sulfone scaffolds offer valuable functionality, future efforts should aim to deepen the structure–activity

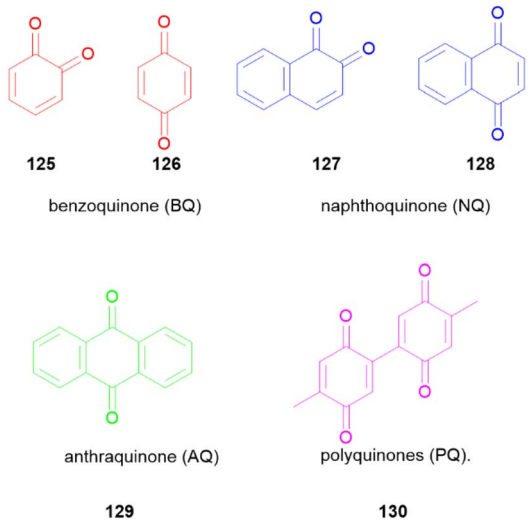


Fig. 10 Structures of quinones.

understanding, expand green synthetic access, and improve scalability without compromising performance or safety.

6. Quinones

Quinones are a class of cyclic conjugated diketones in which the carbon atoms of the carbonyl groups are incorporated into the ring structure. The term "quinone" is etymologically derived from the Quechua word "kina–kina," meaning "holy bark".[78–80] Quinones are widely distributed in plants, fungi, bacteria, arthropods, and echinoderms.[79] Organic compounds containing the quinone moiety are known to exhibit a wide range of biological activities, including antitumor, antibacterial, and antimalarial activities, which are discussed later.[81]

Quinones are generally classified into four major categories: benzoquinones (BQ), naphthoquinones (NQ), anthraquinones (AQ), and polyquinones (PQ), as illustrated in Fig. 10.[82,83]

There are many derivatives of quinone compounds, including amino (**131**),[84,85] thiol (**132**),[86] ether (**133**),[87] chlorine (**134**),[88] sulfone (**135**),[89] alcohol (**136**),[90] sulfonamide (**137**)[91] and sulfonate (**138**)[92] derivatives, as shown in Fig. 11.

Quinones can also incorporate heterocyclic ring systems. As reported in ref. 79, the synthesis of some heterocyclic quinone derivatives has been achieved, as illustrated in Fig. 12.

Fig. 13 illustrates the number of research articles published in recent years, highlighting the growing interest in and significance of studying these compounds.[82]

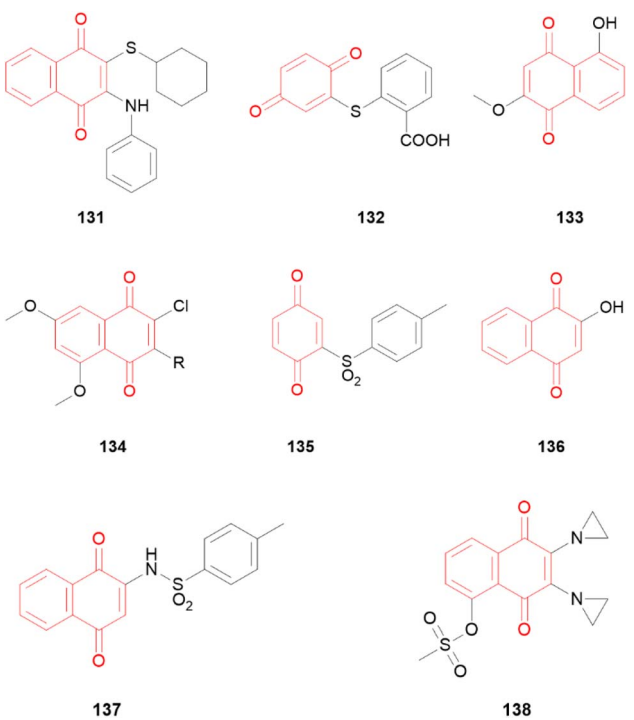


Fig. 11 Structures of some quinone derivatives.

7. Synthetic methods

Numerous methods exist for the synthesis of quinones, varying in both reaction mechanisms and starting materials. In the following sections, we will discuss these methods.

7.1 By oxidation

Oxidation using suitable oxidizing agents is the most common method for the synthesis of quinones.[93] Typical examples include the oxidation of hydroquinones, *p*-aminophenol, or *p*-phenylenediamine, as illustrated in Scheme 33.

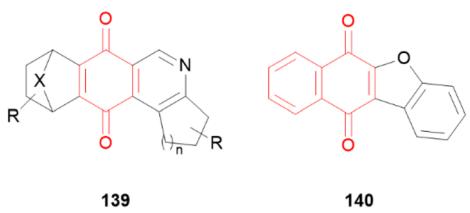


Fig. 12 Heterocyclic quinone derivatives.

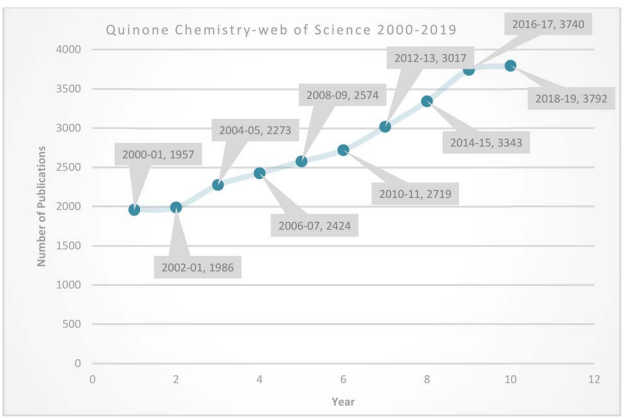
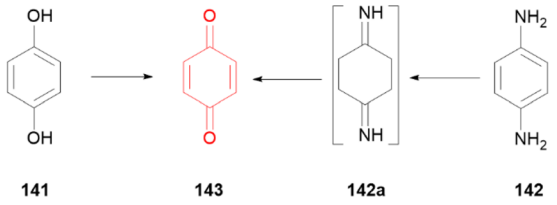
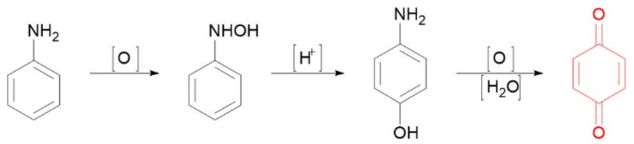


Fig. 13 Number of scientific articles published from 2000 to 2019 on quinones.



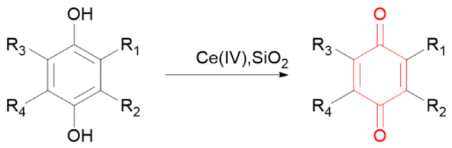
141 143 142a 142

Scheme 33 Quinone synthesis from *p*-aminophenol or *p*-phenylindinamine.



144 144a 145 146

Scheme 34 Quinone synthesis from aniline.



147 148

R1	R2	R3	R4	Yiled %
H	H	H	H	98
CH3	H	H	H	97
C6H5	H	H	H	97
Cl	H	HH	H	95

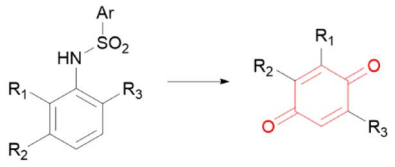
Scheme 35 Quinone synthesis *via* oxidation using cerium and silica (SiO_2) as the catalytic system.

For example, the synthesis of quinone from aniline is demonstrated in Scheme 34.[94]

In 1985, Alfred Fischer and his colleagues synthesized quinone *via* an oxidation reaction using cerium and silica (SiO_2) as the catalytic system. The reaction was completed within a short time (5 minutes), resulting in high yields, as illustrated in Scheme 35.[95]

In 1989, Alan T. Hewson and his colleagues synthesized quinones *via* the oxidation of *N*-arylsulfonamides using ceric ammonium nitrate (CAN) in an aqueous medium. The resulting products were extracted with ethyl acetate and subsequently purified by column chromatography on silica gel using a 1 : 4 mixture of ethyl acetate and petroleum ether as the eluent, as shown in Scheme 36 .[96]

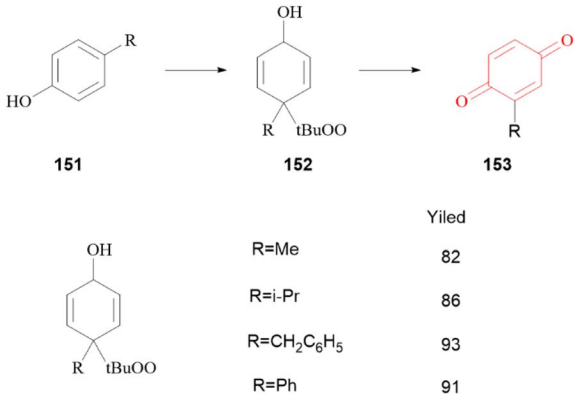
In 1995, Shun-Ichi Murahashi and his colleagues synthesized quinone derivatives from corresponding phenols using



149 150

	Yiled
a; R_1=CH_3, R_2=Br, R_3=H, Ar=Ph	26
b; R_1=CH_3, R_2=CO_2CH_3, R_3=H, Ar=p-To_1	29
c; R =R =CH_3, R_3=H, Ar=Ph	41
d ; R_2=C_1, R_2=R_3, Ar=p-To_1	18
e; R =R =R =H, Ar-p-To_1	49
f; R_1=R_3=C_1, R_2=H, Ar=Ph	34

Scheme 36 Quinone synthesis *via* the oxidation of *N*-arylsulphonamides using ceric ammonium nitrate.

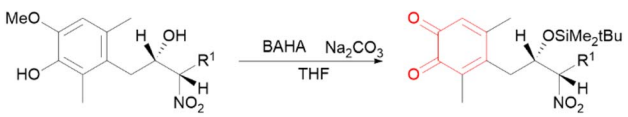


151 152 153

	Yiled
R=Me	82
R=i-Pr	86
R=$CH_2C_6H_5$	93
R=Ph	91

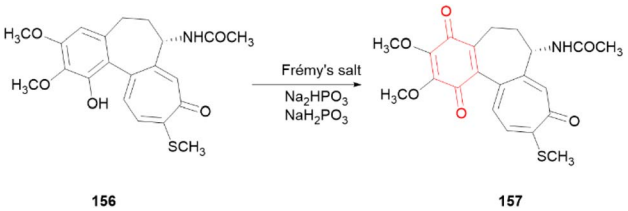
Scheme 37 Quinone synthesis from phenol using an oxidizing Ru catalyst with *tert*-butyl hydroperoxide in benzene or EtOAc as the solvent.

a ruthenium catalyst (0.18 mmol) and *tert*-butyl hydroperoxide. (24.0 mmol) as the oxidant in either benzene or ethyl acetate (EtOAc) as the solvent. Subsequent treatment with $TiCl_4$



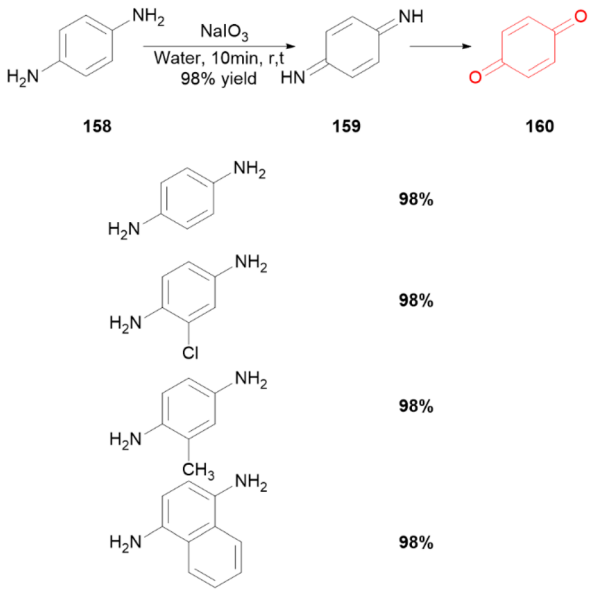
154 155

Scheme 38 Quinone synthesis using the oxidizing agent BAHA.



156 157

Scheme 39 Quinone synthesis using Frémy's salt in methanol at pH 6.

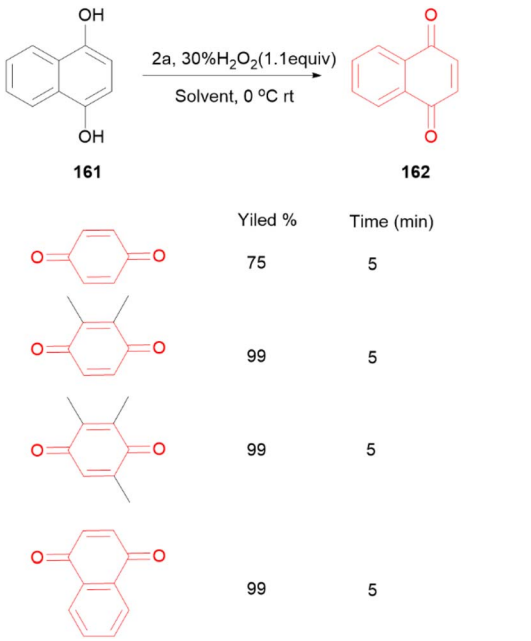


Scheme 40 Quinone synthesis from an aryl diamine using sodium periodate as the oxidizing agent.

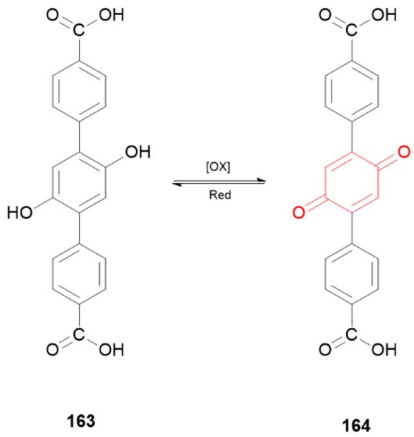
afforded high yields, ranging from 70% to 80%, as shown in Scheme 37.[97]

Tetsuya Takeya successfully synthesized a quinone derivative *via* an oxidation reaction using BAHA as the oxidizing agent and THF as the solvent. The reaction was carried out at −20 °C for five minutes, affording a product with 78.4% yield, as illustrated in Scheme 38.[98]

In 1998, Jian Gum and his colleagues successfully oxidized 1-demethylthiocolchicine to its corresponding 1,4-quinone using



Scheme 41 Synthesis of quinone *via* hydrogen peroxide oxidation.



Scheme 42 Synthesis of quinone from hydroquinone using various oxidation agents.

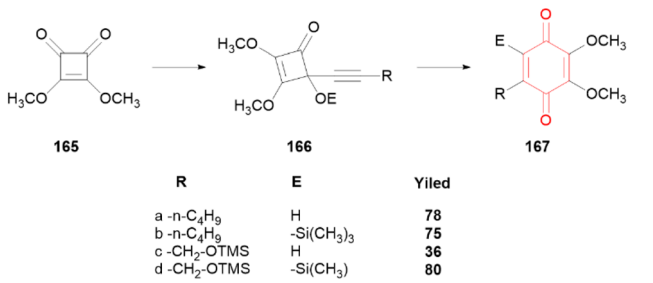
Frémy's salt in methanol at pH 6. The reaction afforded a 35% yield, as shown in Scheme 39 .[99]

In 2010, Vikas N. Telvekar and his colleagues successfully synthesized quinone from aryl diamine (4.62 mmol) using sodium periodate ($NaIO_3$) (2 equiv) as the oxidizing agent. The reaction afforded a high yield, as shown in Scheme 40 .[100]

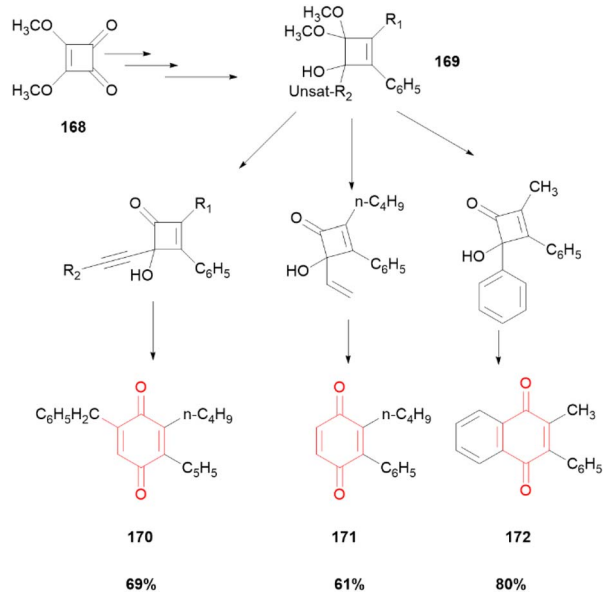
In 2013, Abdel-Moneim Abu-Elfotoh utilized the ruthenium(II)/dimethyl phenyloxazoline (Ru(II)/dm-Pheox) complex 2a and its macroporous polymer-supported catalyst to carry out an oxidation reaction. In this study, various reaction conditions, including solvent type and molar ratios, were investigated. The optimized reaction achieved an excellent yield of up to 99% within just 5 minutes, as shown in Scheme 41 .[101]

In 2015, Bo Gui and his colleagues investigated the oxidation of hydroquinone using various oxidizing agents. Their study focused on optimizing reaction conditions to improve yield and efficiency, as illustrated in Scheme 42.[102]

7.1.1 Critical insight. Most of the reported oxidation-based methods focus heavily on yield, which is understandable from a synthetic chemistry perspective. However, this often comes at the expense of other important factors such as substrate scope, operational simplicity, or environmental impact. In many cases, there is limited discussion of whether these high-yielding reactions are practical outside the lab. As the field moves



Scheme 43 Synthesis of quinone from a squaric acid derivative using lithium acetylide in THF at −78 °C, followed by treatment with trimethylsilyl chloride or ammonium chloride.



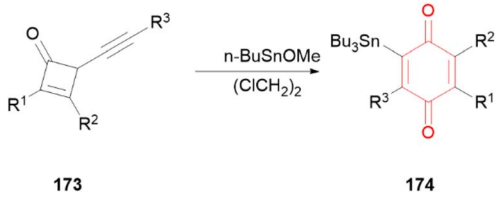
Scheme 44 Quinone synthesis from squaric acid derivatives.

forward, it may be more useful to consider not just how much product is obtained but also how cleanly, safely, and sustainably it can be made.

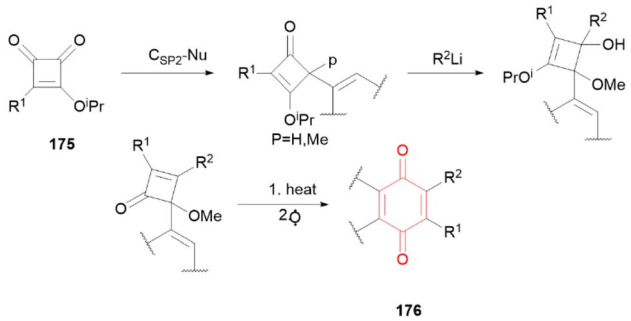
7.2 From squaric acid derivatives

Numerous quinone derivatives have been synthesized from squaric acid derivatives through multistep synthetic pathways, where the final stage typically involves cyclization under appropriate conditions to form the quinone ring. In 1988, Lafayette D. Foland and his colleagues developed a method for synthesizing quinone derivatives starting from dimethyl squarate. The compound was first converted to 4-alkynyl-2,3-dimethoxy-4-(trimethylsiloxy) or 4-(hydroxy) cyclobutenones, with yields ranging from 50% to 90%. These intermediates were then treated with the corresponding lithium acetylide in tetrahydrofuran (THF) at −78 °C, followed by quenching with either trimethylsilyl chloride or ammonium chloride. The resulting cyclobutenones were thermolyzed in p-xylene at 138 °C to afford the desired 1,4-benzoquinones, as illustrated in Scheme 43.[103]

In 1992, Leah M. Gayo developed a multi-step synthetic route for obtaining various quinone derivatives from squaric acid. The synthesis involved the preparation of specific ketal intermediates, followed by hydrolysis using hydrochloric acid in



Scheme 45 Quinone synthesis from squaric acid derivatives using *n*-Bu3SnOMe.



Scheme 46 Synthesis of quinones from the addition of alkynyl and CsP_2-based nucleophiles to cyclobutenedione 1.

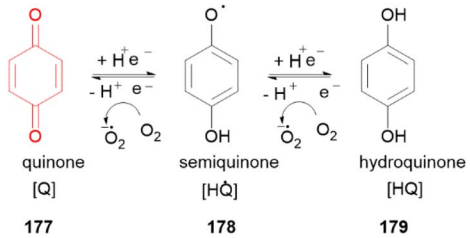


Fig. 14 Forms of quinone depending on the acidity of the medium.

chloroform to yield the desired quinone compounds, as shown in Scheme 44.[104]

In 1992, Lanny S. Liebeskind and colleagues investigated the mechanism of converting squaric acid into the target quinone. The process involves the formation of a diradical intermediate, followed by a rearrangement step facilitated by *n*-Bu_3SnOMe, as illustrated in Scheme 45.[105]

In 1992, Lanny S. Liebeskind and colleagues reported the addition of alkynyl and CsP_2-based nucleophiles to cyclobutenedione 1, yielding 1,2-adducts that undergo thermolysis to form quinones. The synthesis proceeds through multiple stages, as illustrated in Scheme 46.[106]

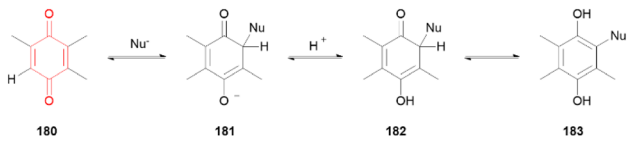


Fig. 15 Nucleophilic addition reaction mechanism of quinones.

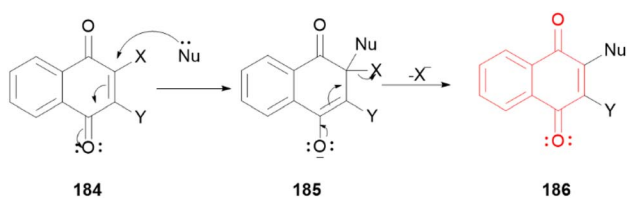


Fig. 16 Nucleophilic substitution reaction mechanism of quinones.

7.2.1 Critical insights. Although squaric acid derivatives offer a unique platform for the synthesis of quinones, the reported methods often involve multi-step sequences with strict temperature control, uncommon reagents, or harsh conditions, such as high-temperature thermolysis. Although some of these approaches yield structurally diverse quinones, their practical scalability and synthetic simplicity remain limited. Additionally, many of these pathways have not been widely adopted or further optimized in recent literature, suggesting that their broader applicability may be constrained by operational complexity or low atom economy.

8. Properties

8.1 Chemical properties

The chemical properties of quinones are primarily related to their various redox states. Quinones are characterized by their high oxidizability and reversible redox behavior[107] at higher solution pH values. Quinones in fully reduced and intermediate oxidation states undergo deprotonation, forming species such as QH^-, Q^{2-} (fully reduced state), and $Q^{\cdot-}$ (intermediate oxidation state), as shown in Fig. 14.[108]

In a reversible electron transfer reaction, quinones exhibit the ability to undergo oxidation and reduction in both directions, as depicted in the previous diagram.[109] This reversibility is attributed to the stability of the semiquinone radical intermediates, which is a result of resonance delocalization within the semiquinone structure.[110]

The presence of electron-donating substituents in hydroquinone (HQ_2) results in an increase in the pKa value and a decrease in the standard redox potential E_0 (Q/QH_2), while electron-withdrawing groups produce the opposite effect.[111] Additionally, enhanced resonance stabilization contributes to a further decrease in the E_0 (Q/QH_2) value.[108]

8.1.1 Reactions of quinones. Quinones participate in various chemical interactions primarily due to the presence of electrophilic centers in their structure. This electrophilicity enables quinones to effectively undergo nucleophilic addition reactions, as illustrated in Fig. 15.[112]

In addition to nucleophilic addition, quinones can also undergo nucleophilic substitution reactions, as demonstrated in Fig. 16.

Moreover, when benzoquinone is present in excess during addition reactions, it can act as an oxidizing agent, promoting the oxidation of hydroquinone to its corresponding quinone form, as illustrated in Fig. 17.[113]

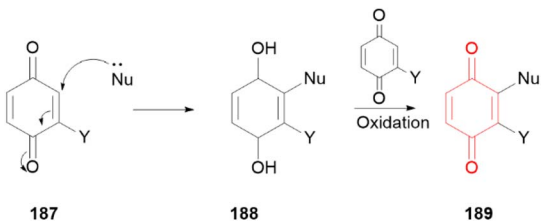
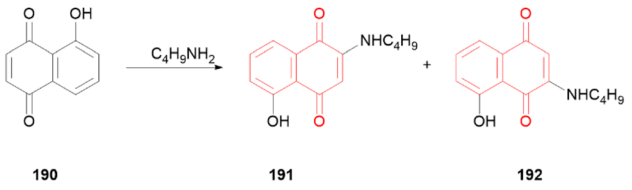
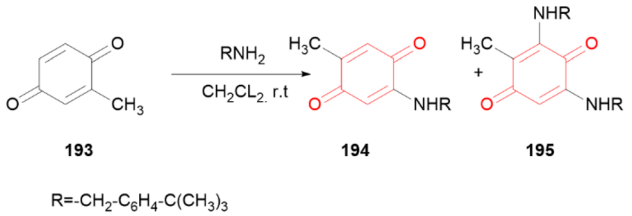


Fig. 17 Oxidation of hydroquinone in excess benzoquinone.



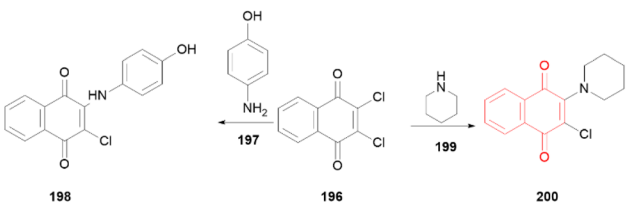
Scheme 47 Reaction of quinone with organic amines.



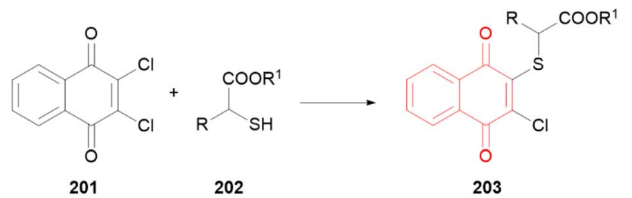
Scheme 48 The quinone reacted with 4-*tert*-butylbenzylamine in CH_2Cl_2.

8.1.2 C–NH–C synthesis. Aminoquinone derivatives have significant applications in medicinal chemistry and serve as valuable building blocks for the synthesis of various heterocyclic compounds.[114] In 2009, A. D. Bukhtoyarova and colleagues synthesized 2,6- and 2,8-bis(butylamino)-5-hydroxy-1,4-naphthoquinones under three different conditions: using butylamine alone, with copper, and with copper(II) acetate monohydrate, as illustrated in Scheme 47.[115]

In 2019, Aysecik Kacmaz synthesized several amino-substituted quinone derivatives, including 2-(4-*tert*-butylbenzylamino)-5-methylcyclohexa-2,5-diene-1,4-dione and 2,5-bis(4-*tert*-butylbenzylamino)-3-methylcyclohexa-2,5-diene-1,4-dione. The reaction was carried out between the corresponding quinone and 4-*tert*-butylbenzylamine in CH_2Cl_2 as the solvent. The products were extracted and purified using column



Scheme 49 Synthesis of various amino derivatives of quinone using water as the solvent.



Scheme 50 Reaction of quinone with organic thiols.

chromatography. However, the yields were relatively low, as shown in Scheme 48.[116]

In 2009, Vishnu K. Tandon and his colleagues synthesized various amino derivatives of quinone using water as a solvent, achieving high yields of up to 100%, as illustrated in Scheme 49.[113]

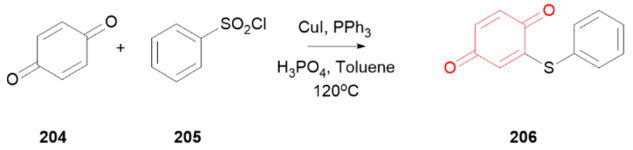
8.1.3 C–S–C synthesis. In 2005, Vishnu K. Tandon synthesized a series of 3-substituted-1,4-dioxo-1,4-dihydronaphthalen-2-yl-thioalkanoate derivatives (compounds **3–21**) and naphtho [2,3-b][1,4]-thiazine-5,10-diones. One of the key steps in the synthesis of these derivatives involves the preparation of a thioquinone intermediate, as illustrated in Scheme 50.[117]

In 2016, thioquinone was synthesized by reacting quinone with an appropriate sulfonyl chloride in the presence of copper(I) iodide and triphenylphosphine using toluene and other solvents. The reaction provided good yields, reaching up to 89%, as shown in Scheme 51.[118]

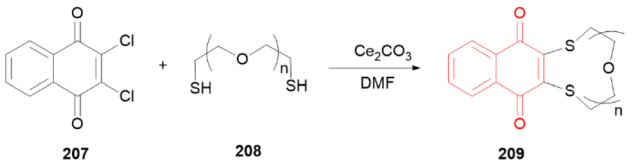
In 2001, Sheng-Tung Huang synthesized naphthoquinone derivatives using thiol-crown ethers in the presence of Ce_2CO_3 and DMF. The reaction proceeded for 24 hours, as shown in Scheme 52.[119]

8.1.4 C–O–C synthesis. In 2010, Vishnu K. Tandon and his colleagues were able to carry out nucleophilic substitution reactions of quinone compounds using a suitable alcohol and green solvents, such as water, with a detergent. Different types of detergent were studied, and the yields sometimes reached 94%, as shown in Scheme 53.[120]

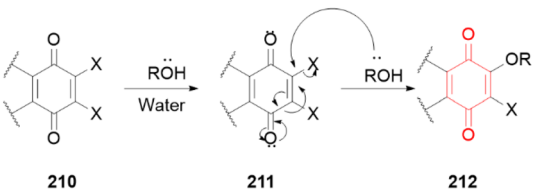
The previous approach was also used in 2011 by Vishnu K. Tandon. In addition to SDS, LD [Triton X-100 and TBAB] was used; the biological effectiveness of the products was studied,



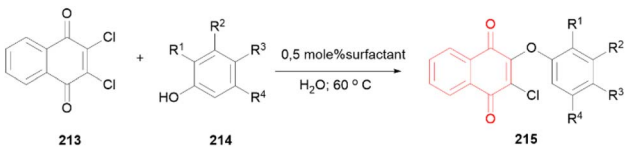
Scheme 51 Reaction of quinone with organic sulfonyl chloride.



Scheme 52 Reaction of quinone with thiol-crown.



Scheme 53 Reaction of quinones with using organic alcohols and water as the solvent.



Scheme 54 Reaction of quinone with organic alcohol in water.

and the resulting products had very high biological effectiveness, as shown in Scheme 54.[121]

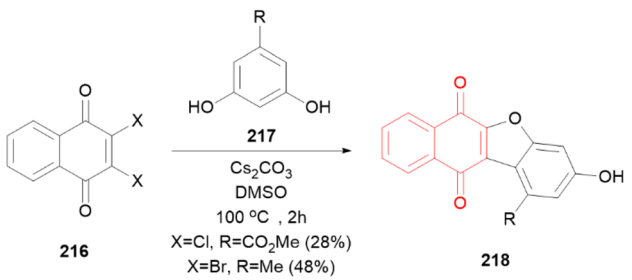
In 2019, a research paper was published by Nolan J. Blythe and her colleagues on the synthesis of heterocyclic derivatives containing an ether bond, in which the haloquinone and the appropriate phenolic compound were released using the solvent DMSO in the presence of Cs_2CO_3 for two hours at 100 ° C. The yield was 48%, as shown in Scheme 55.[122]

8.1.5 C–NH–SO_2–C synthesis. In 2018, Ramanathan Devenderan and her colleague reported the sulfonamidation reaction of 1,4-naphthoquinones *via* a [3 + 2] cycloaddition reaction using sulfonyl azides under mild reaction conditions, in which the appropriate conditions were studied for the reaction of a solvent and a base. The yield was approximately 72% using DMSO and K_2CO_3, as shown in Scheme 56.[123]

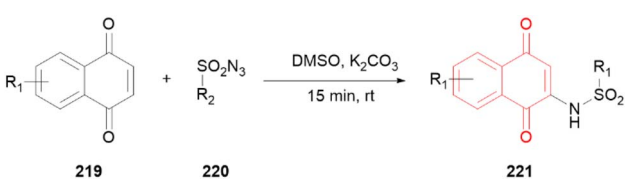
The Sulfonamidation reaction was conducted in 2017 by Medikonda V. Krishna Rao and her colleagues on 1,4-naphthoquinones in the presence of AgSbF6 and AgOAC with a DCE solvent at a temperature of 85 °C for 8 hours, and the yield reached 85%, as shown in Scheme 57.[124]

In 2023, Pallaba Ganjan Dalai and his colleagues were able to conduct the sulfamidation reaction of 1,4-naphthoquinone under metal-free conditions using 1,4-naphthoquinone derivatives and *N*-methoxy sulfonamides in a water solvent, as shown in Scheme 58.[125]

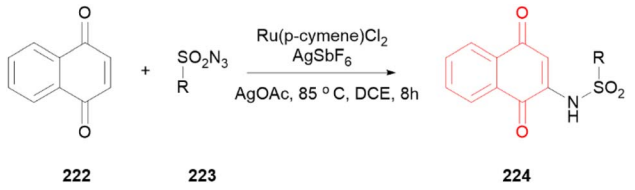
8.1.6 C–SO_2–C synthesis. The previous sections discussed various methods for synthesizing the sulfone group.[8–27]



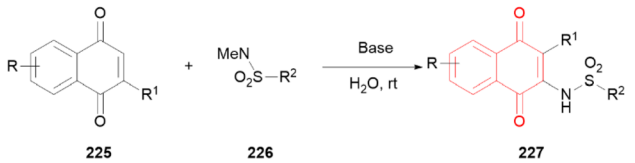
Scheme 55 Reaction of quinone with organic alcohol using the solvent DMSO in the presence of Cs_2CO_3.



Scheme 56 Sulfonamidation reaction of quinones.



Scheme 57 Sulfonamidation reaction of 1,4-naphthoquinones in the presence of AgSbF6 and AgOAC.



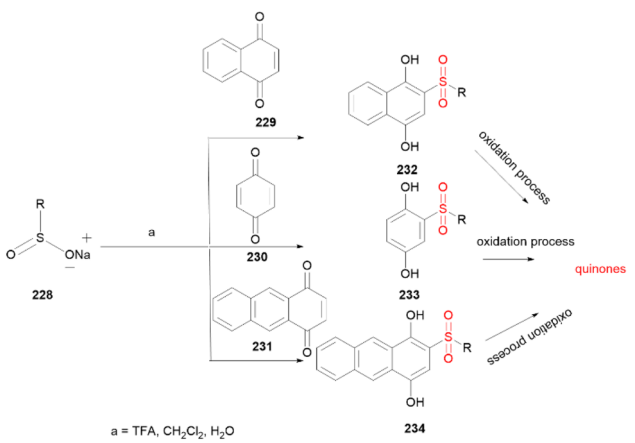
Scheme 58 Sulfonamidation reaction of 1,4-naphthoquinone under metal-free conditions.

However, in this section, we specifically focus on the synthesis of quinone-based sulfone compounds. In 2008, Mamoun M. Alhamadsheh and colleagues synthesized several 2-tosylnaphthalene-1,4-diol derivatives as reversible inhibitors of the *Escherichia coli* FabH enzyme. The synthesis involved the reaction of the sodium salt of sulfone with the appropriate quinone, followed by an oxidation step using MnO_2, as illustrated in Scheme 59.[126]

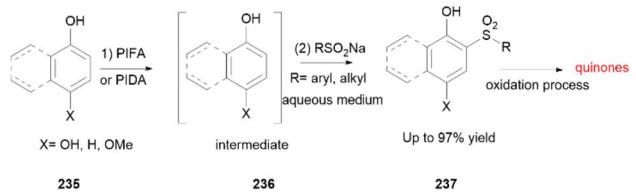
In 2020, Lingxin Meng and colleagues successfully synthesized various sulfone derivatives of naphthoquinone and hydroquinone with yields reaching up to 97%. The synthesis involved oxidation using PIFA and PIDA as oxidizing agents, followed by a reaction with the corresponding sulfonic reagent salt, as illustrated in Scheme 60.[127]

8.2 Physical properties

At the outset of discussing physical properties, it is important to address the general solubility of quinones. Solubility depends on several factors, including the nature of the solvent, temperature, concentration, stereochemistry, and the number of



Scheme 59 Reaction of quinone with an organic sodium salt.



Scheme 60 Oxidation using PIFA and PIDA and reaction of quinone with an organosulfonate salt.

Table 3 Melting points of quinones

Quinone	Melting point (°C)
1,4-Benzoquinone	115.7
1,2-Naphthoquinone	146
1,4-Naphthoquinone	128.5
9,10-Phenanthraquinone	208.5
9,10-Anthraquinone	286

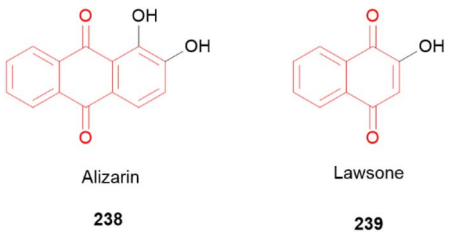


Fig. 18 Structures of alizarin and lawsone.

hydrogen bonds formed between the solute and solvent molecules. Given that quinones and their derivatives contain two carbonyl groups, they generally exhibit good solubility in most organic solvents.

The solubility of the quinone derivative, hydroquinone, was studied in 2006 by Xiaona Li and her colleagues using the laser-monitoring observation technique. Their study led to the discovery that the solubility of hydroquinone in any solvent was greater and was as follows: alcohol solvents > ester solvents > acetic acid > water.[128]

The melting point of these compounds depends on the number of carbon atoms in the quinone structure as well as the

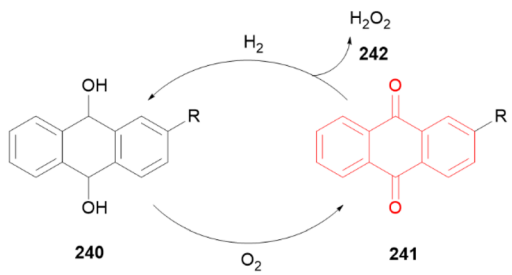


Fig. 19 Mechanism of the Riedl-Pfleiderer process.

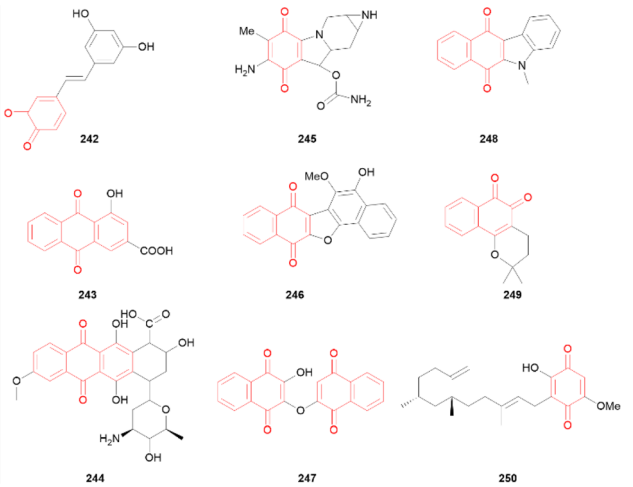


Fig. 20 Quinones that have industrial, pharmaceutical and biological importance.

position of the alternating carbonyl groups, as summarized in Table 3.[129]

8.2.1 Uses of quinone compounds. The first industrial use of quinone derivatives as pigments was in 1868, when the compound alizarin (238) (Fig. 17) was synthesized. This was the first time that a natural pigment was duplicated synthetically. This process replaced the expensive and labor-intensive extraction of Madder plant (*Rubia* sp.) roots, allowing subsequent production of Lawsone (Fig. 18) synthesis a compound that was used As a dye for the skin, fingernails, hair, cloth and leather, and it was extracting from the Henna plant.[130–132]

One of the most important uses of quinones is the synthesis of hydrogen peroxide. Hydrogen peroxide is manufactured almost exclusively by the Riedl-Pfleiderer process (Fig. 19), in which an anthraquinone is circulated between its reduced and oxidized forms by means of reduction with H_2, followed by oxidation with air and liberation of hydrogen peroxide.[133]

Due to the presence of phenolic OH groups in the quinone structure, it can be used as an antioxidant agent as well as catechol quinone derivatives.[134] Rhein(4,5-dihydroxyanthraquinone-2-carboxylic acid) is a quinone derivative of significant medical importance, as it is used in the treatment of hepatic diseases (**242**),[135] osteoarthritis (**243**),[136] diabetes,[137] atherosclerosis[138] and nephroprotective activity (**243**),[139] quinone derivatives have a role in fighting cancer cells, as does Doxorubicin (**244**)[140] and mitomycin (**245**),[141] It also has cytotoxic activity, such as Balsaminone A (**246**),[142] This compound also has antibacterial activity as does lawsonol [2-(1,4-dioxo-1,4-dihydronaphthalen-2-yloxy)-3-hydroxynaphthalene-1,4-dione] (**247**),[143] These compounds are also effective for treatment of some diseases, such as malaria and cancer, as we mentioned previously, as well as Carbazoloquinone alkaloids (**248**),[144] antitrypanosomal (**249**),[145] and antineoplastic activity (**250**)[146] as shown in Fig. 20.

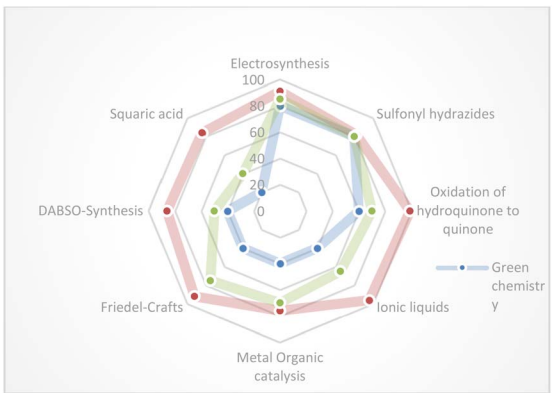


Fig. 21 Network diagram integrating product yield, green chemistry assessments and industrial uses.

8.2.2 Critical perspectives. The industrial and biomedical applications of quinone derivatives are undeniably significant, as exemplified by the historic synthesis of alizarin and the widespread use of anthraquinones in hydrogen peroxide production. Their antioxidant, antibacterial, and anticancer activities further underscore their pharmaceutical relevance. However, despite these successes, challenges remain in optimizing quinone derivatives for clinical use due to issues such as toxicity, bioavailability, and side effects. Additionally, although industrial processes like the Riedl-Pfleiderer method are well-established, ongoing efforts are required to improve their

Table 4 Summary of the comparative green metrics of the synthetic methods discussed in this review; methods based on electrochemical reactions and aqueous media stand out in terms of sustainability, while classical multi-step protocols rank the lowest

Synthetic method	Green chemistry rating out of 5	Notes
Electrosynthesis	●●●●○	Dose not require catalysts, is performed in an aqueous medium, and operates under mild conditions
Sulfonyl hydrazides	●●●●○	Aqueous medium, safe reagents, good yield
Oxidation of hydroquinone to quinone	●●●○○	High yields (99%) using green oxidizers, such as hydrogen peroxide
Ionic liquids	●●○○○	Sustainable liquid catalysts but not entirely environmentally friendly
Metal organic catalysis	●●○○○	Effective but relies on heavy metals
Friedel–Crafts	●●○○○	Use of strong acids and harsh reaction conditions
DABSO-synthesis	●●○○○	Special reagents are not practical for industrial applications
Squaric acid	●○○○○	Multiple steps, harsh solvent and reaction stages

sustainability and reduce environmental impact. Therefore, future studies should balance the promising biological activities of quinones with a critical assessment of their practical limitations and eco-friendly manufacturing.

8.2.2.1 Green chemistry perspective on sulfone and quinone synthesis. A network diagram integrating product yield, green chemistry assessments and industrial use is given below (Fig. 21 and Table 4).

9. Outlook

The synthetic chemistry of sulfone-quinone derivatives is clearly expanding, but major challenges remain. Future efforts should aim to develop fully sustainable, metal-free protocols that are scalable for industrial applications. Moreover, more attention must be paid to the biological profiling of these compounds, especially toxicity and pharmacokinetics, which are often overlooked. The integration of computational prediction tools and green energy sources (*e.g.*, photochemical or electrochemical activation) may lead to significant breakthroughs in selectivity and efficiency. Overall, the field is ripe for innovation, and interdisciplinary collaboration is essential to realize the full potential of these compounds.

10. Future directions

Development of metal-free catalytic systems for sulfone synthesis under green conditions.

Exploration of microwave and photochemical activation in quinone-sulfone coupling reactions.

Comprehensive *in vivo* evaluation of bioactive sulfone-quinone derivatives.

Application of computational chemistry to predict regioselectivity and reactivity.

Investigation of recyclable, solid-supported catalysts in Friedel–Crafts sulfonation.

11. Conclusions

This manuscript provides a comprehensive review of research on sulfone and quinone synthesis, integrating both topics for a focused review on sulfone-quinone synthesis. It also includes flowcharts, a critical analysis of key sections, and an assessment of the green chemistry value of each synthesis method from the perspective of the reviewers. It also includes a comprehensive review of the promising applications of these compounds, researchers' opinions on these applications, and methods for synthesizing them.

Conflicts of interest

There are no conflicts to declare.

Data availability

No new data were generated or analysed as part of this review.

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