Product Class 1: Benzo-1,4-quinones

Product Subclass 1: Metal-Substituted Benzo-1,4-quinones

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General Introduction

This section deals with the synthesis and applications of metal-substituted benzo-1,4-quinones. The chemistry of such compounds remains largely unexplored, despite significant advances by the groups of Liebeskind and Moore. From the examples reported, most of the compounds in this product subclass appear to be air stable. Standard safety precautions should be observed during the synthesis and handling of these compounds.

Although there are many examples of metal coordination with benzo-1,4-quinones,[1,2] there are few reports dealing with direct metal substitution on the quinone moiety. The synthesis of iron-substituted benzo-1,4-quinone 1 has been reported, and the structure has been confirmed by a combination of crystallographic, analytical, and spectroscopic techniques (Scheme 1).[3] However, to date benzo-1,4-quinone 1 represents the only example of such an iron-substituted quinone.

\[ \text{Scheme 1} \quad \text{Synthesis of an iron-Substituted Benzo-1,4-quinone}^{[3]} \]

![Chemical Structure]

The best explored and most synthetically useful metal-substituted benzo-1,4-quinones are the stannyquinones, which are the focus of Sections 28.1.1.1.1, 28.1.1.1.2, and 28.1.1.2.1. Silicon- and boron-substituted benzo-1,4-quinones (see Sections 28.1.1.1.3–28.1.1.1.7 and 28.1.1.2.2–28.1.1.2.3) have received rather less attention than the tin-substituted benzo-1,4-quinones. They can be formed by elaboration of substituted aromatic systems, by electrocyclic ring opening of cyclobutenones, or by benzannulation protocols. These compounds have also found application as coupling reagents in palladium-catalyzed reactions. There is one report of the synthesis of a germanium-substituted benzo-1,4-quinone, but the reactivity of this compound has not been studied.[4]

for references see p 29
28.1.1.1 Synthesis of Product Subclass 1

28.1.1.1.1 Method 1:
Tin-Substituted Benzo-1,4-quinones by Cyclobutone Ring Expansion

The first reported synthesis of a stannyquinone proceeds via ring expansion of an alkynyldihydroxycyclobutone and this class of quinones has since evolved into a versatile family of synthons. In fact, stannyquinones have been shown to undergo a variety of reactions, including palladium-catalyzed allylation, oxidative dimerization, and cross-coupling reactions (see Section 28.1.1.2.1).

The general strategy for the synthesis of stannyquinones relies on the alkynylation of squaric acid derivatives 2, followed by the thermal rearrangement of the resulting cyclobutenones 3, in the presence of tributyl(methoxy)stannane, to give benzo-1,4-quinones 4 (Scheme 2). The overall sequence proceeds with good yields (32–90%), and tolerates several functional groups. Furthermore, the brightly colored tin-substituted benzo-1,4-quinones are air-stable, can be purified by chromatography, and can be stored over a prolonged period of time in a refrigerator.

Scheme 2 Synthesis of Tin-Substituted Benzo-1,4-quinones

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Yield (%)</th>
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<tr>
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<tr>
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<td>Bu</td>
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<td>32</td>
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The proposed mechanism of this reaction is shown in Scheme 3. Upon heating, the alkynyldihydroxycyclobutone 3, or its stannylated derivative 5, can undergo electrocyclic ring opening to generate the reactive vinyl ketene 6. This ketene may then undergo a 6π-electrocyclization reaction to give diradical hydroquinone derivatives 7. Intramolecular transfer of the tributylstannyl group from oxygen to the proximal carbon gives tin-substituted benzo-1,4-quinones 4.
Ferrocenyl-substituted benzo-1,4-quinones can be constructed in a similar manner. Vinylolation of ferrocenylcyclobutenedione 8 with a vinyl lithium species produces the corresponding cyclobutene 9 that, upon thermolysis, undergoes ring expansion to form hydroquinone 10 (Scheme 4). Oxidation of 10 with lead(IV) oxide gives the ferrocenylbenz o-1,4-quinone 11. The overall sequence is regioselective, with the ferrocenyl group occupying the C2 position, and the substituents (R₁ and R₂) occupying the C3 and C5 positions, respectively. Several examples have been reported, which proceed in good yield (56–85%) over two steps from 9.

\[ \text{Scheme 3} \quad \text{Proposed Mechanism for Formation of Tin-Substituted Benzo-1,4-quinones by Ring Expansion}^{[6]} \]

\[ \text{Scheme 4} \quad \text{Regioselective Synthesis of Ferrocenylbenz o-1,4-quinones}^{[8]} \]

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
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<td>[6]</td>
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<td>Me</td>
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<td>[6]</td>
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<td>Me</td>
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<td>Ph</td>
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<td>Ph</td>
<td>75</td>
<td>[6]</td>
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</table>

* From 9.

\[ \text{for references see p 29} \]
2-Ferrocenyl-3-isopropoxy-5-methylbenzene-1,4-diol (10, R¹ = OiPr; R² = Me) and
2-Ferrocenyl-3-isopropoxy-5-methylbenzo-1,4-quinone (11, R¹ = OiPr; R² = Me);
Typical Procedure:⁶⁶
A soln of 9 (R¹ = OiPr; R² = Me; 275.0 mg, 0.75 mmol) in dioxane (15 mL) was refluxed under
argon for 5 h. The mixture was allowed to cool to rt, and the solvent was removed under
reduced pressure. Final purification was achieved by flash chromatography (silica gel,
hexane/EtOAc 19:1). Two fractions were isolated; the first fraction, a green solid (hexane/EtOAc
9:1, R₂ = 0.56), was identified as 11 (R¹ = OiPr; R² = Me); yield: 46.5 mg (17%). The
second fraction (hexane/EtOAc 9:1, R₂ = 0.44) was identified as 10 (R¹ = OiPr; R² = Me),
and isolated as bright yellow crystals; yield: 198.0 mg (72%). Hydroquinone 10 (R¹ = OiPr;
R² = Me; 80.0 mg, 0.22 mmol) and PbO₂ (525.8 mg, 2.20 mmol) in CH₂Cl₂ (5 mL) were stirred
at rt for 30 min. After filtration, the solvent was removed under reduced pressure. Purifica-
tion was achieved by flash chromatography (silica gel, hexane/EtOAc 9:1); yield:
74.8 mg (94%).

28.1.1.2

Method 2:
Tin-Substituted Benzo-1,4-quinones by Stannylation of Benzo-1,4-quinones

An alternative approach for the synthesis of stannyquinones is based on the reaction of
benzo-1,4-quinone with tribenzylchlorostannane.⁷⁷ The addition of the tin reagent may
be accelerated by microwave irradiation, and by using basic alumina as an additive, as
shown in the synthesis of stannyquinone 12 (Scheme 5).⁷⁷

Scheme 5  Synthesis of a Stannylated Benzo-1,4-quinone via
the Reaction of Tribenzylchlorostannane with Benzo-1,4-quinone⁷⁷

\[
\begin{align*}
\text{O} & + \text{Bn₃SnCl} \rightarrow \begin{array}{c}
\text{O} \\
\text{O}
\end{array} \\
& \text{basic alumina, MeOH, microwave, 1 min} \\
& 12
\end{align*}
\]

The reaction has been applied to both benzo-1,4-quinone and naphtho-1,4-quinone, and
proceeds in excellent yield (94–96%).

2-(Tribenzylstanny)benzo-1,4-quinone (12); Typical Procedure:⁷⁷
Bn₃SnCl (0.01 mol) and benzo-1,4-quinone (0.01 mol) were dissolved in MeOH (10 mL) and
basic alumina was added to the mixture. The reaction was then made homogeneous,
dried in air, placed in an alumina bath, and irradiated in a microwave oven for 30–60 s.
On completion of the reaction, as followed by TLC every 10 s, the mixture was eluted
from the alumina using acetone. Removal of the solvent yielded the stannylated benzo-
1,4-quinone 12; yield: 94%.

28.1.1.3

Method 3:
Silicon-Substituted Benzo-1,4-quinones by Reaction of
Organolithium Species

Silicon-substituted benzo-1,4-quinones can be readily synthesized via a sequence of reac-
tions that is summarized in Scheme 6. Lithiation of silylated bromohydro-1,4-quinone 13
at −78°C produces adduct 14 which, upon warming to −20°C, undergoes spontaneous re-
arrangement to form the O-lithiated compound 15. Without isolation, compound 15 can
be oxidized with 2,3-dichloro-5,6-dicyanobenzo-1,4-quinone to the corresponding silyl-
ated benzo-1,4-quinone 16.⁸⁸⁹
Scheme 6  Synthesis of Silylbenzo-1,4-quinones by Lithiation of Hydro-1,4-quinones

The ortho-directed metation of methoxybenzenes, followed by quenching of the resulting anion with chlorotrimethylsilane, can also produce silylated hydroquinones which, upon oxidation with ammonium cerium(IV) nitrate, give rise to the corresponding benzo-1,4-quinones. This strategy has led to the synthesis and spectroscopic evaluation of a variety of silylated benzo-1,4-quinones. However, these strategies suffer disadvantages due to the availability of the brominated aryl precursors and the regioselectivity of the lithiation process.

2-Chloro-5-(pentamethyldisilanyl)benzo-1,4-quinone (16, R¹ = Cl); Typical Procedure:

To a soln of 13 (R¹ = Cl; 1.54 g, 3.19 mmol) in Et₂O (50 mL) was added a hexane soln of BuLi (6.51 mmol) at 0 °C. The mixture was stirred at 0 °C for 25 min and then warmed to rt at which it was stirred for 40 min. To the mixture was added an Et₂O soln of DDQ (0.934 g, 4.12 mmol) at 0 °C, and this mixture was stirred for 30 min at 0 °C and for another 110 min at rt. The mixture was then hydrolyzed with H₂O. The organic layer was separated, and the aqueous layer was extracted with hexane. The organic layer and the extracts were combined, washed with H₂O and brine, dried (Na₂SO₄), and filtered. The filtrate was concentrated under reduced pressure, and the residue was chromatographed (silica gel, hexane/toluene) to give 16 (R¹ = Cl) as orange crystals; yield: 0.462 g (53%); mp 73.8–74.3 °C.

Method 4: Silicon-Substituted Benzo-1,4-quinones by Cyclobutenone Ring Expansion

An alternative approach toward the synthesis of silylated benzo-1,4-quinones is based on the thermal rearrangement of 4-alkynylcyclobut-2-enones. Conceptually, this sequence is similar to that employed for the formation of stannylated benzo-1,4-quinones (Section 28.1.1.1.1). Reaction of cyclobutenedione 17 with lithium acetylides, followed by quenching of the resulting alkoxide at –78 °C with chlorotrimethylsilane, produces 4-alkynylcyclobut-2-enones 18 (Scheme 7). Thermal ring expansion of 18 produces the silylated benzo-1,4-quinone 21, presumably through the intermediate vinylketene 19 and the zwitterionic quinone 20. The reaction yields vary (36–80%), and the main byproduct is cyclopentenedione 23, obtained via the zwitterionic species 22. The extent of this side reaction is influenced by the substitution on the alkyne moiety and by the nature of the silyl.

For references see p 29
group. Despite side reactions, this strategy allows the synthesis of polysubstituted benzo-1,4-quinones with direct silicon bond attachment on the C5 carbon.

**Scheme 7** Synthesis of Silyl-Substituted Benzo-1,4-quinones via Ring Expansion of Cyclobutenediones\[^{[13]}\]

<table>
<thead>
<tr>
<th>R(^1)</th>
<th>Yield(^a) (%) of 21</th>
<th>Ref</th>
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</thead>
<tbody>
<tr>
<td>Bu</td>
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<td>[^{[13]}]</td>
</tr>
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<td>CH(_2)OTMS</td>
<td>80</td>
<td>[^{[13]}]</td>
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<td>CH(_2)OTHP</td>
<td>41</td>
<td>[^{[13]}]</td>
</tr>
<tr>
<td>CH(Me)OTHP</td>
<td>36</td>
<td>[^{[13]}]</td>
</tr>
<tr>
<td>TMS</td>
<td>55</td>
<td>[^{[13]}]</td>
</tr>
<tr>
<td>(CH(_2))(_2)C(=)CH</td>
<td>42</td>
<td>[^{[13]}]</td>
</tr>
<tr>
<td>Bn</td>
<td>74</td>
<td>[^{[13]}]</td>
</tr>
<tr>
<td>H</td>
<td>75</td>
<td>[^{[13]}]</td>
</tr>
</tbody>
</table>

\(^a\) From 18.

Benzo-1,4-quinones substituted with silyl groups at the C6 position can be formed via the same strategy using silylated acetylides, such as lithium (trimethylsilyl)acetylide, as the nucleophile (Scheme 8).
In this case, the organolithium addition to the cyclobutenedione 24 should be quenched with ammonium chloride and not with chlorotrimethylsilane. Intermediate 25 is thermolysed to provide trimethylsilyl-substituted benzo-1,4-quinone 26 in 46% yield. A variation of this strategy includes partial hydrogenation of 25 using Lindlar's catalyst to form 27 which, upon thermolysis at 138 °C, gives rise to hydro-1,4-quinone 28. Oxidation of 28 to 26 can be achieved with ammonium cerium(IV) nitrate on silica gel, albeit in low yields (27%).

2-Butyl-5,6-dimethoxy-3-(trimethylsilyl)benzo-1,4-quinone (21, R¹ = Bu); Typical Procedure: A solution of freshly distilled hex-1-ynic (0.32 g, 3.87 mmol) and freshly distilled THF (50 mL) in a dry 100-mL, round-bottomed flask, was stirred at -78 °C under an atmosphere of N₂. A 2.29 M solution of BuLi (1.6 mL, 3.70 mmol) was introduced dropwise by syringe, and the resulting light yellow solution was stirred for 30 min. This mixture was then transferred via cannula to a solution of 17 (0.5 g, 3.52 mmol) in THF (50 mL) at -78 °C. The mixture was stirred for 45 min, quenched with TMSCl (2 mL), and was allowed to reach rt. The solvent was removed under reduced pressure, and flash chromatography (silica gel, hexanes/EtOAc 5:1) gave 18 (R¹ = Bu) as a light yellow oil; yield: 620 mg (79%).

Alkyne 18 was then thermolysed in refluxing xylene for 15 min. The solvent was removed under reduced pressure, and the resulting red oil was purified by column chromatography (hexanes/EtOAc 5:1) to give 21 (R¹ = Bu) as a yellow oil (hexanes/EtOAc 9:1, Rf = 0.39); yield: 465 mg (75%).

2-tert-Butoxy-3-methyl-5-(trimethylsilyl)benzo-1,4-quinone (26); Typical Procedure: A 1.5 M solution of BuLi in hexane (2.2 mL, 2.6 mmol) was added to a solution of (trimethylsilyl)acetylene (3.4 mmol) in dry THF (35 mL) at -78 °C. The resulting mixture was added to a solution of 24 (528 mg, 3.14 mmol) in dry THF (25 mL) at -78 °C. The mixture was stirred at -78 °C for 10 min, quenched with 5% aq NH₄Cl (20 mL), and was allowed to warm to rt. The mixture was then extracted with Et₂O (2 × 30 mL), and the organic layers were com-

for references see p 29
bined, dried (MgSO₄), and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexanes/EtOAc 3:1) to give 25 as a white solid; yield: 560 mg (67%).

The heating of 25 in refluxing MeCN for 2 h gave, after purification by flash column chromatography, the benzo-1,4-quinone 26 (hexanes/EtOAc 9:1, Rf = 0.36), as a yellow oil which solidified upon cooling; yield: 380 mg (69%); mp 36–38 °C.

28.1.1.5 Method 5: 
Silicon-Substituted Benzo-1,4-quinones by Carbene Annulation

An alternative strategy for the synthesis of silicon-substituted benzo-1,4-quinones is based on the reaction of unsaturated Fischer chromium–carbene complexes with alkyne.¹⁷ A representative example of what is formally a [3+2+1]-cycloaddition reaction (also referred to as the Dötz benzannulation) is shown in Scheme 9.¹⁸

![Scheme 9](image)

Treatment of alkynyglycoside 29 with alkenyl-carbene complex 30 at 50–55 °C affords, after oxidative work up with ammonium cerium(IV) nitrate, silylbenzo-1,4-quinone 31 in 61% yield. Chromium–carbene complexes of indole²⁷ and dihydropyran have also been used in related benzannulation reactions (Scheme 10).¹⁹

![Scheme 10](image)

Dihydropyran–carbene complex 32 reacts smoothly with phenyl(trimethylsilyl)acetylene to give (trimethylsilyl)benzo-1,4-quinone 33 in 66% yield after 38 hours. Substantial protodesilylation is observed if the oxidative workup is performed with ammonium cerium(IV) nitrate in hydrochloric rather than nitric acid.

2-(4,6-Di-O-acetyl-2,3-deoxy-α-D-erythro-hex-2-enopyranosyl)-5-(trimethylsilyl)- 
benzo-1,4-quinone (31); Typical Procedure:²⁸

A Schlenk flask was charged with carbene complex 30 (331 mg, 0.991 mmol) and Calkynyglycoside 29 (260 mg, 1.09 mmol) and diluted with THF (20 mL). The mixture was degassed (3 × freeze–pump–thaw cycles), and then stirred under argon at 55 °C for 18 h. Upon completion of the reaction (TLC), a 0.5 M soln of CAN (7.0 mL, 3.5 mmol) in HNO₃
was added, and stirring was continued for 30 min at rt. The mixture was washed with brine and extracted with Et₂O (2 x 20 mL), and the combined organic layers were dried (MgSO₄). The solvents were removed under reduced pressure and the residue was purified by flash chromatography (EtOAc/hexane 1:3, Rf = 0.62) to give 31 as a deep orange oil; 228 mg (61%).

28.1.1.6 Method 6: Silicon-Substituted Benzo-1,4-quinones by Nucleophilic Substitution

Another strategy toward the synthesis of metal-substituted benzo-1,4-quinones is based on the nucleophilic substitution of halogenated quinones with silyl20,21 or germityl21 Grignard reagents. This reaction produces silylated hydro-1,4-quinones that, upon pyridinium chlorochromate oxidation, lead to the corresponding benzo-1,4-quinones (Scheme 11).

Scheme 11 Nucleophilic Substitution of Halogenated Quinones20

\[
\begin{array}{cccc}
\text{Cl} & \text{Cl} & \text{OTMS} & \text{TMS} \\
\text{Cl} & \text{Cl} & \text{TMS} & \text{OTMS} \\
\end{array}
\]

For example, p-chloranil (34, 2,3,5,6-tetrachlorobenzo-1,4-quinone) reacts with chlorotrimethylsilane and magnesium, using a mixture of tetrahydrofuran and hexamethyldiphosphoramide as solvent, to give the persilylated hydro-1,4-quinone 35. After pyridinium chlorochromate oxidation, the desired quinone 36 is obtained in 72% yield. This approach allows for the direct accessing of polymetal-substituted benzo-1,4-quinones.

2,3,5,6-Tetrakis(trimethylsilyl)benzo-1,4-quinone (36); Typical Procedure20

**CAUTION:** Hexamethyldiphosphoramide is a possible human carcinogen and an eye and skin irritant.

To a mixture of TMSCI (47.1 g, 434 mmol), Mg (10.6 g, 43.5 mmol), and HMPA (9.5 mL) in THF (100 mL) was added a soln of p-chloranil (34; 11.8 g, 48.1 mmol) in THF (150 mL) at rt. After stirring at rt overnight, the mixture was hydrolyzed with sat. aq NaHCO₃. The organic layer was separated, and the aqueous layer was extracted with hexane. The organic layer and the extracts were combined, washed with H₂O and brine, dried (Na₂SO₄), and filtered. The filtrate was concentrated under reduced pressure, and the residue was chromatographed (silica gel, hexane/benzene (CAUTION: carcinogen)) to give 35 as colorless crystals; yield: 13.2 g (51%); mp 240°C. A soln of 35 (1.01 g, 1.86 mmol) and PCC (0.825 g, 3.83 mmol) in CH₂Cl₂ (2 mL) was refluxed for 1.5 h. The mixture was concentrated and chromatographed (silica gel, hexane) to give 36 as deep red crystals; yield: 0.529 g (72%); mp 182°C.

_for references see p 29_
28.1 Method 7:  
Boron-Substituted Benzo-1,4-quinones by Carbene Benzannulation

Benzo-1,4-quinone boronic esters can be prepared through the Dötz annulation of Fischer carbene complexes.\textsuperscript{[22,23]} These reactions proceed with a high degree of regiochemical control and good overall yield.

**Scheme 12** Synthesis of Benzo-1,4-quinone Boronic Esters\textsuperscript{[22]}

For example, boronic ester 38 is reacted with chromium–carbene complex 37 via a cycloaddition process to form, after oxidation with ammonium cerium(IV) nitrate, the corresponding benzo-1,4-quinone boronic ester 39 (Scheme 12). The desired product 39 is isolated together with the protodeboronated adduct 40. This reaction selectively produces the C5 boronic esters.

2-Phenyl-3-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-5,6,7,8-tetrahydronaphtho-1,4-quinone (39) and 2-Phenyl-5,6,7,8-tetrahydronaphtho-1,4-quinone (40);  
**Typical Procedure:**\textsuperscript{[22]}

To a soln of 37 (100 mg, 0.327 mmol) in THF (6.4 mL) was added alkyne 38 (195 mg, 0.980 mmol) via syringe under N\textsubscript{2}. The reaction was stirred at 45 °C for 14 h and then concentrated under reduced pressure. The residue was dissolved in Et\textsubscript{2}O (5 mL) and treated with 0.5 M CAN (8 equiv) in 0.1 M aq HNO\textsubscript{3}. The reaction was stirred at rt for 30 min and quenched with H\textsubscript{2}O. The product was extracted with Et\textsubscript{2}O and purified by chromatography (silica gel) to afford quinone boronate ester 39 as a yellow oil; yield: 83%. The protodeboronated quinone 40 was also obtained; yield: 14%.

28.1.2 Applications of Product Subclass 1 in Organic Synthesis

28.1.2.1 Method 1:  
Palladium-Catalyzed Cross-Coupling Reactions of Tin-Substituted Benzo-1,4-quinones

Direct attachment of a tributylstannyl group to a benzo-1,4-quinone provides the option to synthesize substituted benzo-1,4-quinones by palladium-catalyzed cross-coupling reactions. In these reactions, the stannylated carbon functions as a formal quinone carbanion equivalent. This strategy is versatile and applicable to a variety of substitution patterns that are difficult to access through traditional methodology, such as the elaboration of preexisting aromatic or heteroaromatic precursors.
**Variation 1:**
**Allylation**

Stannylated benzo-1,4-quinones 41 can undergo cross-coupling reactions with allylic halides to produce allylated quinones 42 in good to excellent yields (Scheme 13).

![Scheme 13](image)

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<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
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<td></td>
</tr>
</tbody>
</table>

Due to the mild and neutral conditions of the palladium-catalyzed couplings, a variety of functional groups are tolerated, both on the organostannane reagent and also upon the electrophile. This allows for the preparation of a wide range of highly substituted benzo-1,4-quinones.

**Variation 2:**
**Coupling with Aromatic and Heteroaromatic Iodides**

A general and high-yielding route to a variety of aryl- and hetaryl-substituted quinones 44, via a palladium-copper cocatalyzed cross coupling of stannyquinones 43 with aryl and heteroaryl iodides has been developed.[24] In most cases, "ligand-free" conditions using tris(dibenzylideneacetone)dipalladium(0) (2.5%) and copper(I) iodide (50%) give the fastest reactions and highest yields (Scheme 14).

---

*for references see p 29*
Scheme 14  Cross Coupling of Aryl and Hetaryl Iodides with Stannyquinones in a Palladium-Copper Cocatalyst System\textsuperscript{[24]}

\[
\begin{array}{cccc}
\text{R}^1 & \text{R}^2 & \text{Ar}^1 & \text{Conditions} & \text{Yield (\%)} & \text{Ref} \\
\hline
\text{Me} & \text{Me} & 4-\text{O}_2\text{N}_2\text{C}_6\text{H}_4 & \text{Pd}_2(\text{dba})_2\text{, Cul, DMF, air, 60°C} & 85 & [24] \\
\text{Me} & \text{Me} & 2-\text{O}_2\text{N}_2\text{C}_6\text{H}_4 & \text{Pd}_2(\text{dba})_2\text{, Cul, DMF, Ph}_3\text{As, N}_2\text{, 60°C} & 82 & [24] \\
\text{Me} & \text{Me} & 3-\text{O}_2\text{N}_2\text{C}_6\text{H}_4 & \text{Pd}_2(\text{dba})_2\text{, Cul, DMF, Ph}_3\text{As, N}_2\text{, 60°C} & 80 & [24] \\
\text{Me} & \text{Me} & 4-\text{MeOC}_6\text{H}_4 & \text{Pd}_2(\text{dba})_2\text{, Cul, DMF, Ph}_3\text{As, N}_2\text{, 60°C} & 91 & [24] \\
\text{Me} & \text{Me} & \text{Ph} & \text{Pd}_2(\text{dba})_2\text{, Cul, DMF, air, 60°C} & 84 & [24] \\
\text{Me} & \text{OMe} & \text{Bu} & \text{Pd}_2(\text{dba})_2\text{, Cul, DMF, air, 60°C} & 88 & [24] \\
(CH=\text{CH})_2 & \text{TMS} & 4-\text{O}_2\text{N}_2\text{C}_6\text{H}_4 & \text{Pd}_2(\text{dba})_2\text{, Cul, DMF, air, 60°C} & 76 & [24] \\
\text{Me} & \text{Me} & \text{Me} & \text{Pd}_2(\text{dba})_2\text{, Cul, DMF, Ph}_3\text{As, N}_2\text{, 60°C} & 61 & [24] \\
\text{Me} & \text{Me} & \text{Me} & \text{Pd}_2(\text{dba})_2\text{, Cul, DMF, air, 60°C} & 76 & [24] \\
\text{Me} & \text{OMe} & \text{Bu} & \text{Pd}_2(\text{dba})_2\text{, Cul, DMF, air, 60°C} & 69 & [24] \\
(CH=\text{CH})_2 & \text{TMS} & \text{Pd}_2(\text{dba})_2\text{, Cul, DMF, air, 60°C} & 49 & [24]
\end{array}
\]

For slow reactions, the addition of triphenylarsine (20\%) as a supporting ligand is found to be beneficial, since it inhibits the precipitation of palladium black and prolongs the catalyst lifetime. In certain slow reactions, a symmetrical quinone dimer forms, via oxidative homocoupling of the starting stannyquinone,\textsuperscript{[25]} but the use of an inert atmosphere and rigorously degassed solvents usually eliminates this problem. This reaction is also applicable to other quinones such as naphtho- and anthraquinones.\textsuperscript{[26]}

2,3,5-Trimethyl-6-(4-nitrophenyl)benzo-1,4-quinone (44, R\textsuperscript{1} = R\textsuperscript{2} = R\textsuperscript{3} = Me; Ar\textsuperscript{1} = 4-\text{O}_2\text{N}_2\text{C}_6\text{H}_4); Typical Procedure\textsuperscript{[24]}

In a 10-mL round-bottomed flask was dissolved Pd\textsubscript{2}(dba)\textsubscript{2} (10 mg, 0.011 mmol, 2.5 mol\%) in DMF (1 mL), and the mixture was stirred for 1 min. 1-Iodo-4-nitrobenzene (0.23 g, 0.92 mmol) in DMF (2 mL) was added, and the soln was warmed to 60°C for 2 min. 2,3,5-Trimethyl-6-(tributylstanny)benzo-1,4-quinone (43, R\textsuperscript{1} = R\textsuperscript{2} = R\textsuperscript{3} = Me; 0.20 g, 0.45 mmol) in DMF (2 mL) was added followed immediately by Cul (43 mg, 0.23 mmol). When the starting material was consumed (30 min to 1 h) as judged by TLC (Et\textsubscript{2}O/hexanes 1:9), the
mixture was cooled to rt, diluted with Et₂O (30 ml), and washed with 10% aq KF (2 x 20 ml). The mixture was then dried (MgSO₄), passed through a silica gel plug, and concentrated under reduced pressure. The resulting yellow solid was purified by gravity chromatography. Two sequential columns (silica gel, Et₂O/hexanes 1:4; then silica gel, hexanes/CH₂Cl₂ 1:9) gave a yellow solid; yield: 0.10 g (85%). Recrystallization (acetone/MeOH/H₂O) gave 44 as large bright yellow crystals; mp 138.8–139.4 °C.

28.1.1.2.3 Variation 3: Oxidative Dimerization

Stannylquinones 45 can also undergo homocoupling reactions under palladium(II) catalysis to give 2,2'-bisquinones 46, a common motif found in many naturally occurring quinones (Scheme 15). In fact, in the absence of any electrophilic cross-coupling partners, the oxidative dimerization proceeds in respectable yields under mild conditions.

Scheme 15 Oxidative Dimerization of Stannylbenzoquinones

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Yield (%) of 46</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>80</td>
<td>[25]</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>Bu</td>
<td>73</td>
<td>[25]</td>
</tr>
<tr>
<td>OMe</td>
<td>Me</td>
<td>Bu</td>
<td>65</td>
<td>[25]</td>
</tr>
<tr>
<td>OMe</td>
<td>Me</td>
<td>TMS</td>
<td>68</td>
<td>[25]</td>
</tr>
<tr>
<td>(CH=CH)₂</td>
<td>Bu</td>
<td>78</td>
<td>[25]</td>
<td></td>
</tr>
<tr>
<td>(CH=CH)₂</td>
<td>TMS</td>
<td>65</td>
<td>[25]</td>
<td></td>
</tr>
<tr>
<td>(CH=CH)₂</td>
<td>OEt</td>
<td>66</td>
<td>[25]</td>
<td></td>
</tr>
</tbody>
</table>

These reactions are conducted in polar aprotic solvents, such as N-methylpyrrolidin-2-one, using a stoichiometric amount of benzo-1,4-quinone as the reoxidant, and 20% copper(I) iodide/10% dichlorobis(triphenylphosphine)palladium(II) as the cocatalyst system. The homocoupling reaction proceeds at room temperature under an air atmosphere to produce 2,2'-bisquinones 46 with yields of 65–80%.

_for references see p 29_
2,2′-Dibutyl-4,4′-dimethoxy-5,5′-dimethyl-1,1′-bis(cyclohexa-1,4-dienyl)3,3′,6,6′-tetrone (46, R¹ = OMe; R² = Me; R³ = Bu); Typical Procedure:∥

2-Butyl-6-methoxy-5-methyl-3-(tributylstannylo)benzo-1,4-quinone (45, R¹ = OMe; R² = Me; R³ = Bu; 500 mg, 0.92 mmol), benzo-1,4-quinone (100 mg, 0.92 mmol), PdCl₂(PPh₃)₂ (64 mg, 0.092 mmol), and freshly purified CuI (35 mg, 0.18 mmol) in anhyd NMP (4 mL) in a dry, 25-mL round-bottomed flask was stirred open to the air and monitored by TLC (silica, Et₂O/hexanes 1:9). After 40 min, the mixture was diluted with Et₂O (30 mL), and washed successively with H₂O (40 mL), 10% aq KF (2 × 30 mL), and 5% aq NaHCO₃ (40 mL). The resulting dark orange-brown soln was dried (Na₂SO₄), concentrated under reduced pressure, and the product was purified by flash chromatography (silica gel, Et₂O/hexanes 1:9) to afford a yellow-orange solid; yield: 152 mg (65%); mp 93.1–93.7 °C (MeOH).

28.1.2.1.4 Variation 4: Benzannulation

An extension of the palladium-mediated cross coupling of stannyquinones is the regio-controlled benzannulation approach to forming substituted naphtho- and anthraquinones (Scheme 16).∥ Coupling of stannybenzo-1,4-quinones 47 with 4-chlorocyclobut-2-enones 48, catalyzed using a palladium(0) species and tri-2-furylphosphine, produces intermediates 49, which undergo a thermal ring expansion to form the aromatic quinones 50.

![Scheme 16 Palladium-Catalyzed Benzannulation of Stannyquinones](image)

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>R¹</th>
<th>R³</th>
<th>X</th>
<th>Yield (%) of 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>OiPr</td>
<td>TMS</td>
<td>81</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>Ph</td>
<td>TMS</td>
<td>74</td>
</tr>
<tr>
<td>OiPr</td>
<td>Me</td>
<td>Me</td>
<td>OiPr</td>
<td>H</td>
<td>77</td>
</tr>
<tr>
<td>OiPr</td>
<td>Me</td>
<td>Me</td>
<td>Ph</td>
<td>H</td>
<td>81</td>
</tr>
<tr>
<td>(CH=CH₂)</td>
<td>Me</td>
<td>OiPr</td>
<td>TMS</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>(CH=CH₂)</td>
<td>t-Bu</td>
<td>OiPr</td>
<td>TMS</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>(CH=CH₂)</td>
<td>Ph</td>
<td>OiPr</td>
<td>TMS</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>(CH=CH₂)</td>
<td>Me</td>
<td>Ph</td>
<td>TMS</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>(CH=CH₂)</td>
<td>Ph</td>
<td>Me</td>
<td>TMS</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>(CH=CH₂)</td>
<td>Et</td>
<td>Et</td>
<td>TMS</td>
<td>95</td>
<td></td>
</tr>
</tbody>
</table>

∥ Ref to literature.
Several variably substituted naphtho- and anthraquinones have been synthesized using this method. The strategy is general and tolerates a variety of substituents on the 4-chlorocyclobut-2-enone 48. However, the reaction time for the thermolysis is highly dependent on the steric encumbrance of the C2 substituent (R²) on 48, ranging from 1–2 hours at 100°C for a methyl group to 16 hours at 100°C for a bulky tert-butyl substituent.

2-Isoproxy-3,7-dimethyl-6-phenynaphtho-1,4-quinone (50, R¹ = OiPr; R² = R³ = Me; R⁴ = Ph); Typical Procedure[26]

In a 15-mL, two-necked flask fitted with a reflux condenser, a soln of 47 (R¹ = OiPr; R² = Me; X = H; 0.69 g, 1.5 mmol) and 48 (R³ = Me; R⁴ = Ph; 280 mg, 1.45 mmol) in dioxane (8 mL) was degassed (3× freeze–pump–thaw cycles). To this red soln was added Pd₂dba₃ (10 mg, 0.011 mmol, 1.2 mol%) and tri-2-furylphosphine (10 mg, 0.043 mmol, 4.8 mol%). The mixture was degassed one final time and stirred at rt for 15 min. The mixture was slowly warmed to 80°C (bath temperature), and maintained at that temperature for 6 h. The mixture was then refluxed for 2 h, cooled to rt, treated with sat. aq KF (4 mL), and stirred vigorously for 15 min. The resulting red suspension was poured into sat. aq KF (15 mL) and extracted with Et₂O (3×20 mL). The extracts were washed with sat. aq KF (15 mL), H₂O (15 mL), and brine (15 mL). The combined extracts were dried (Na₂SO₄), filtered through a pad of Celite, and concentrated to an orange solid. Purification by chromatography (silica gel, hexane/EtOAc 40:1) and recrystallization (hexane) afforded orange needles; yield: 392 mg (81%); mp 115–115.5°C (hexane).

28.1.1.2.2

**Method 2: Silicon/Halide-Exchange Reactions of Silicon-Substituted Benzo-1,4-quinones**

Silylquinones can be transformed into halogenated quinones, which are themselves versatile starting materials for palladium(0)-catalyzed coupling processes (Scheme 17).[19]

**Scheme 17** Application of Silylbenzo-1,4-quinones in Palladium Cross-Coupling Reactions[19]

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>Yield (%) of 52</th>
<th>Yield (%) of 53</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(CH₂)₃</td>
<td>C=CTMS</td>
<td>70</td>
<td>65</td>
<td>[19]</td>
</tr>
<tr>
<td>O(CH₂)₂</td>
<td>CH₂CH=CH₂</td>
<td>70</td>
<td>60</td>
<td>[19]</td>
</tr>
<tr>
<td>O(CH₂)₃</td>
<td>C=CPH</td>
<td>70</td>
<td>92</td>
<td>[19]</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>80</td>
<td>62</td>
<td>[19]</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>80</td>
<td>64</td>
<td>[19]</td>
</tr>
<tr>
<td>Ph</td>
<td>H</td>
<td>60</td>
<td>30</td>
<td>[19]</td>
</tr>
</tbody>
</table>

For example, silylquinones 51 can be converted into iodoquinones 52, via an ipso-iodination using iodine monochloride, which in turn allows the regioselective synthesis of quinones 53. In essence, silicon-substituted quinones can act as surrogates for palladium-catalyzed cross-coupling reactions, leading to highly functionalized benzo-1,4-quinones.

*For references see p 29*
6-Iodo-7-phenyl-3,4-dihydro-2H-1-benzopyran-5,8-dione [52, \(R^1, R^2 = O(CH_2)_3\)];
**Typical Procedure:**\(^{19}\)
A soln of 51 [\(R^1, R^2 = O(CH_2)_3\); 80 mg, 0.26 mmol] in CCl\(_4\) (10 mL) (CAUTION: toxic) was stirred in an ice bath while ICl (90 mg, 0.53 mmol) in CCl\(_4\) (10 mL) was added over a period of 10 min. After the mixture was stirred for an additional 5 min, the ice bath was removed. The mixture was stirred for 2 h at rt, and then poured into sat. aq NaHSO\(_4\). Normal aqueous workup followed by column chromatography (silica gel, hexane/\(EtOAc\) 4:1, \(R_f=0.21\)) gave the iodobenzo-1,4-quinone 52 as yellow needle-shaped crystals after recrystallization (MeOH/hexane); yield: 70 mg (70%); mp 148–149°C.

7-Phenyl-6-[(trimethylsilyl)ethynyl]-3,4-dihydro-2H-1-benzopyran-5,8-dione
[53, \(R^1, R^2 = O(CH_2)_3, R^3 = C(CH_3)\)];
**Typical Procedure:**\(^{10}\)
To a soln of 52 [\(R^1, R^2 = O(CH_2)_3\); 55 mg, 0.16 mmol] and tributyl[(trimethylsilyl)ethynyl]stannane (0.18 g, 0.47 mmol) in THF (8 mL) was added Pd[PPh\(_3\)]\(_4\) (10 mg, 5 mol %). The mixture was degassed (3 x freeze-pump-thaw cycles), heated to 80°C, and then allowed to stir under N\(_2\) for 2 d. The dark colored mixture was filtered, and the filtrate was concentrated and purified by flash chromatography (silica gel, hexane/\(EtOAc\) 3:1, \(R_f=0.46\)), to give the benzo-1,4-quinone 53 as orange prism-like crystals after recrystallization (MeOH/hexane); yield: 30 mg (65%); mp 114–115°C.

**Method 3:**
**Oxidation of the Boron Substituent in Boron-Substituted Benzo-1,4-quinones**
Benzo-1,4-quinone boronic ester 54 can be readily oxidized with basic hydrogen peroxide to form the corresponding hydroxybenzo-1,4-quinone 55 in good yield (Scheme 18).\(^{21}\)

**Scheme 18** Oxidation of Benzo-1,4-quinone Boronic Esters\(^{21}\)
References