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Rh-Catalyzed Reactions of 1,4-Benzoquinones with Electrophiles: C−H Iodination, Bromination, and Phenylselenation

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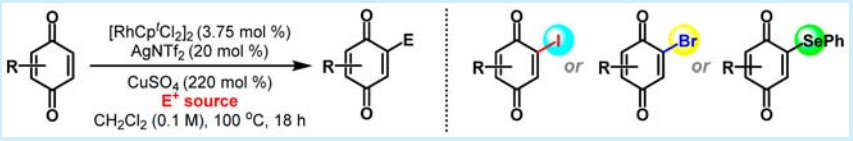
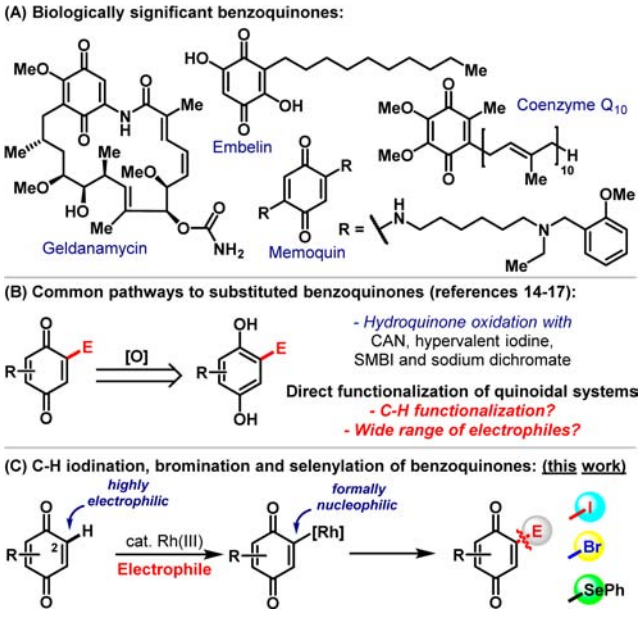
Supporting Information



ABSTRACT: Under Rh-catalyzed conditions, typically electrophilic 1,4-benzoquinones exhibit nucleophilic reactivity, such that exposure to appropriate electrophiles generates products of C−H iodination, bromination, and phenylselenation. This provides a mild and general method for direct halofunctionalization, and the first method that can achieve direct C−H phenylselenation of this compound class. The scope and limitations of the new protocols are outlined, and representative derivatizations are highlighted.

Substituted benzoquinones play key roles in diverse biological processes (Scheme 1A). For example, coenzyme Q_{10} functions as an electron carrier in the electron transport chain, a process that drives production of ATP.[1,2] Benzoquinones are also cytotoxic by virtue of their ability to stimulate oxidative stress or effect alkylation of cellular nucleophiles.[3] As such, benzoquinones are considered privileged structures, often possessing antitumor,[4] antimalarial,[5] or leishmanicidal activity.[6] Recently, embelin, a naturally occurring quinone isolated from *Embelia ribes*, has been described as an effective photodynamic therapeutic candidate for the treatment of tumors.[7,8] Memoquin is of interest as a multitarget-directed ligand for the development of Alzheimer's therapeutics.[9] Finally, geldanamycin, a benzoquinone-based member of the ansamycin family, is a potent inhibitor of Hsp90 and has provided inspiration for the development of new antitumor compounds.[10,11]

Scheme 1



Unsurprisingly, there has been significant recent interest in the development of methodologies for the C−H functionalization of benzoquinones, especially as such approaches might allow analogue synthesis by late stage derivatization.[12] Predominant efforts have focused on C−C bond forming strategies that exploit the high electrophilicity of the quinone core. Additionally, aryl diazonium salts have been employed to effect radical-based C−C bond formations.[12f] By contrast, catalytic halo- and hetero-functionalizations are less well developed, despite the established synthetic versatility of the products. Direct C−H halogenation of benzoquinones is difficult, usually requiring forcing conditions or activated substrates.[13] Consequently, iodo- or bromo-benzoquinones are often obtained by oxidation of hydroquinone precursors, an approach that has obvious limitations (Scheme 1B).[14−17]

Recently, we described Rh-catalyzed C-5 selective C−H iodinations of naphthoquinones using electrophilic iodine sources.[18] Under appropriate conditions we also found that C-2 selective processes were possible. The lack of general methods to promote reaction of benzoquinone C−H bonds with electrophiles prompted us to explore the possibility of effecting related Rh-catalyzed processes on this substrate class (Scheme 1C). *If successful, this would enable the highly electrophilic benzoquinone C-2 position to function as a nucleophile.* At the outset, this was considered challenging because benzoquinones possess multiple

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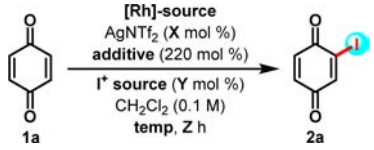
Table 1. Selected Optimization Results



entry	Rh source	X	additive	I^+ source	Y	temp (°C)	Z	**2a**
1	$[RhCp^tCl_2]_2$ (2%)	10	$CuSO_4$	DIH	100	100	18	30
2	$[RhCp^*Cl_2]_2$ (2%)	10	$CuSO_4$	DIH	100	100	18	24
3	$[RhCp^{CF3}Cl_2]_2$ (2%)	10	$CuSO_4$	DIH	100	100	18	2
4	$[RhCp^{i\text{-}Pr}Cl_2]_2$ (2%)	10	$CuSO_4$	DIH	100	100	18	7
5	$[RhCp^tCl_2]_2$ (2%)	10	none	DIH	100	100	18	20
6	$[RhCp^tCl_2]_2$ (3.75%)	20	$CuSO_4$	DIH	100	100	18	83
7	$[RhCp^tCl_2]_2$ (3.75%)	20	$CuSO_4$	NIS	150	100	18	42
8	$[RhCp^tCl_2]_2$ (3.75%)	20	$MgSO_4$	DIH	150	100	18	32
9	$[RhCp^tCl_2]_2$ (3.75%)	20	$CuSO_4$	DIH	150	80	18	46
10	$[RhCp^tCl_2]_2$ (3.75%)	20	$CuSO_4$	DIH	150	100	18	95

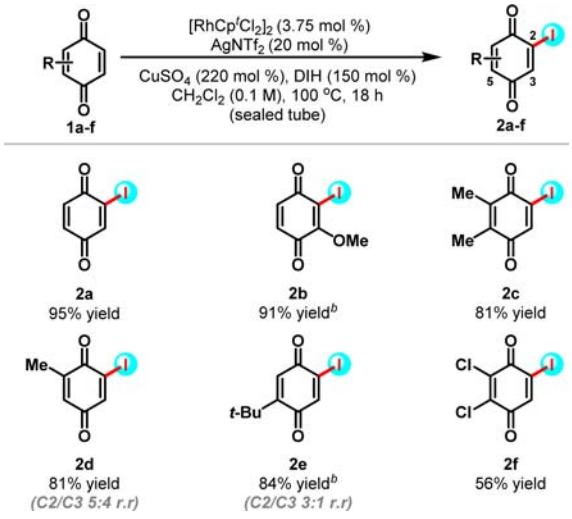
competing sites for C−H functionalization and are considerably more electrophilic than naphthoquinones, thereby rendering the prospect of the proposed umpoled processes uncertain. Nevertheless, as outlined below, we have found that this approach is feasible, enabling mild and general methods for C−H iodination, bromination, and phenylselenation.

Preliminary studies sought to develop a protocol for C−H iodination of benzoquinones. To this end, CH_2Cl_2 solutions of benzoquinone **1a** and 1,3-diiodo-5,5-dimethylhydantoin (DIH) were exposed to a range of in situ generated cationic Rh(III)-systems at 100 °C (Table 1). Initially, rhodium precatalysts modified with different Cp-based ligands were screened (entries 1−4),[19] which revealed that $[RhCp^tCl_2]_2$/$AgNTf_2$ (2/10 mol %) in combination with $CuSO_4$ could deliver target **2a** in 30% yield (entry 1). Interestingly, bis-iodination of **1a** was not observed under these conditions, and only a 20% yield of **2a** was obtained when $CuSO_4$ was omitted (entry 5). To improve the process further, the loading of $[RhCp^tCl_2]_2$ was increased to 3.75 mol %, and this enabled the generation of **2a** in 83% yield (entry 6). Other iodine sources, such as *N*-iodosuccinimide, were less effective under these conditions (entry 7). Further refinement involved increasing the loading of DIH to 150 mol %, and this provided **2a** in 95% yield (entry 10). Alternate metal sulfate additives, such as $MgSO_4$ (entry 8), were less effective, and lower reaction temperatures also led to diminished yields of the target (entry 9).

The scope of the C−H iodination protocol is outlined in Scheme 2. Compounds **1a−f** underwent iodination to furnish targets **2a−f** in good to excellent yield. Iodination of methoxy-substituted system **1b** provided **2b** in 91% yield, with exclusive selectivity for the electronically more activated position. Conversely, iodination for methyl-substituted system **1d** occurred on the side opposite the C6-methyl group, such that **2d** was formed as a 5:4 mixture of C2:C3 regioisomers. For **1e**, which possesses a bulkier *tert*-butyl substituent, regioselectivity was higher (3:1 C2:C3), favoring the C−H bond distal to the C5-substituent; the regioisomers of **2e** were readily separable by column chromatography. As expected, the process is less efficient for systems possessing electron-withdrawing substituents. For example, iodination of 2,3-dichloro system **1f** provided adduct **2f** in 56% yield.

The processes in Scheme 2 are enabling in the sense that C−H iodination of benzoquinones is challenging, with limited reports of high yielding processes.[20] To expand the scope of our approach further, we sought functionalizations using other highly reactive

Scheme 2. Scope of the C−H Iodination of Benzoquinones[a]



[a]<5% *bis*-iodination was observed in all cases. [b]120 mol % of DIH.

electrophiles. Processes involving electrophilic bromine sources were particularly appealing because of the flexibility that the resulting C−Br bond would provide. Although C−H bromination of benzoquinones has been achieved, existing approaches usually require highly activated substrates, such that selective monobromination is often difficult.[13] Using DBH in place of DIH, we found that bromination of benzoquinone **1a** proceeded smoothly to afford **3a** in 82% yield (Scheme 3). Brominations of **1b**, **1e**, and **1f** exhibited similar trends in reactivity to the iodination protocol. Surprisingly, however, bromination of **1d** occurred with high selectivity at the more hindered (but also more activated) site to afford benzoquinone **3d** in 68% yield; this result contrasts the regioselectivity observed for the conversion of **1d** to **2d**. The structural assignments of **2d** and **3d** were made using 2D NMR experiments (HSQC, HMBC). Bromination of **1c** to generate **3c** appeared to proceed efficiently, but the target was highly unstable such that degradation was observed immediately upon isolation; the reasons for this instability are unclear.

As described by the Jacob group[21] and more recently by the da Silva Júnior and Braga groups,[22] selenium-containing quinones possess significant antitumor activity. This may be due to their ability to act as multifunctional redox agents capable of generating

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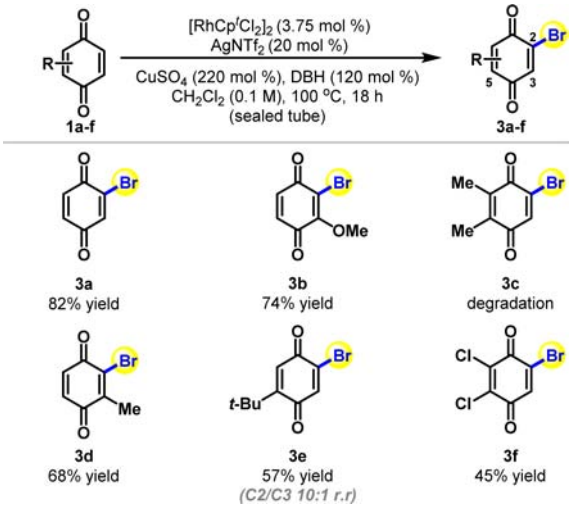
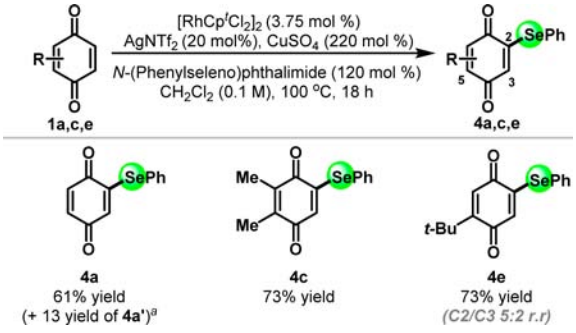
Scheme 3. Scope of the C−H Bromination of Benzoquinones[a]



[a]<5% *bis*-bromination was observed in all cases.

and using intracellular reactive oxygen species (ROS). These features are intrinsically related to ROS balance in cancer cells resulting in induction of cell death.[21,22] Accordingly, efforts were undertaken to effect Rh-catalyzed C−H phenylselenation reactions (Scheme 4).[23] Using 100 mol % of *N*-(phenylseleno)-

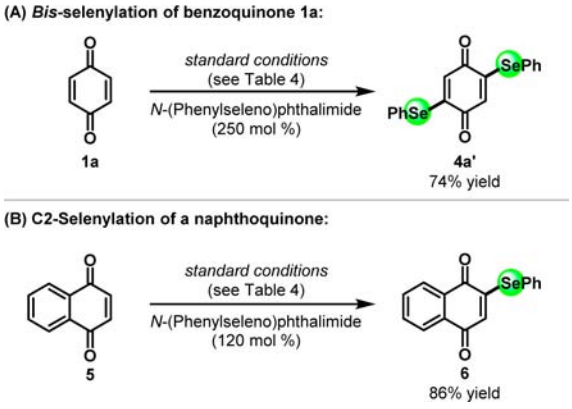
Scheme 4. Scope of the C−H Phenylselenation of Benzoquinones



[a]100 mol % of *N*-(phenylseleno)phthalimide was used.

phthalimide as an electrophile, compound **4a** was prepared in 61% yield, accompanied by a 13% yield of bis-selenated product **4a′**. The protocol was extended to selective monophenylselenation of **1c** and **1e**, which provided benzoquinones **4c** and **4e** in high yield. Increasing the loading of *N*-(phenylseleno)-phthalimide to 250 mol % enabled the selective generation of bis-functionalization adduct **4a′** in 74% yield (Scheme 5A). The protocol can also be employed on naphthoquinones, and to exemplify this **6** was generated as the sole product in 86% yield by phenylselenation of 1,4-naphthoquinone **5** (Scheme 5B); the structure of **6** was confirmed by single crystal X-ray diffraction. Previous approaches to the phenylselenation of quinones exploit the nucleophilicity of the phenyl selenide anion. However, this approach often leads to competing bis-phenylselenation. Indeed, Ueno has described the preparation of **6** in 73% yield as a mixture with 2,3-bis(phenylseleno)-1,4-naphthoquinone.[24] In the present study, high or exclusive monophenylselenation can be achieved by exploiting an electrophilic selenium source.

Scheme 5



We have investigated derivatizations of 2-iodo-1,4-benzoquinone **2a** to demonstrate the utility of the halogenated benzoquinones prepared here (Figure 1). Reaction of **2a** with

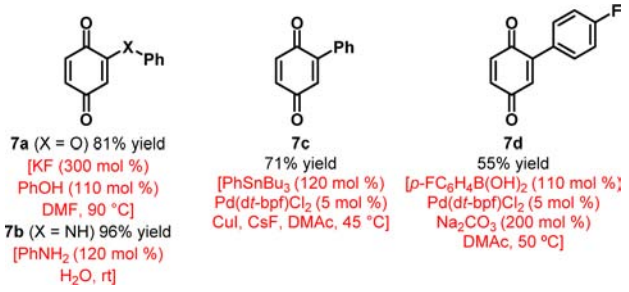


Figure 1. Derivatizations of **2a**.

phenol and aniline afforded products **7a** and **7b** in 81% and 96% yield, respectively. Palladium-catalyzed coupling reactions can also be performed, as demonstrated by Stille coupling of **2a** with $PhSnBu_3$, which afforded **7c** in 71% yield.[25] Suzuki couplings are also viable, as demonstrated by the synthesis of *p*-fluorophenyl analogue **7d**.

Finally, it is pertinent to comment on possible mechanisms for the processes described here. Glorius and co-workers have already delineated potential pathways for the reaction of catalytically generated C(sp^2)−RhCp intermediates with NBS or NIS;[26] at the present stage we consider similar mechanisms to be feasible for the processes described here. The role of $CuSO_4$ may be to act as a Lewis acid, either enhancing the reactivity of the electrophile and/or sequestering the leaving group derived byproduct ((halo)-5,5-dimethylhydantoin, phenylselenol).[27] We have not yet determined the rate-determining step of the processes described here, which is likely either the C−H cleavage step or reaction of the metalated intermediate with the electrophile.[28]

In conclusion, we have reported efficient and reliable methodologies for C−H iodination, bromination, and phenylselenation of benzoquinones. This provides a mild and general method for direct halofunctionalization and the first method that can achieve C−H phenylselenation of this compound class. The halogenated products are useful for a range of redox neutral C−C and C−X bond forming derivatizations, whereas the selenated products are of high medicinal value in their own right. The chemistry opens up new avenues for preparing complex quinone systems and is likely to find wide use. The ability to render the highly electrophilic C-2 position of benzoquinones nucleophilic is

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of particular interest, as it demonstrates the power of catalytic C−H metalation in the design of umpoled strategies.[29]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01586.

Experimental procedures; characterization data and copies of NMR spectra for all the new compounds; structural assignments of all compounds were based on detailed NMR analysis (DEPT, COSY, HSQC, HMBC) (PDF)
X-ray data for **2a** (CIF)
X-ray data for **2e** (CIF)
X-ray data for **6** (CIF)

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Notes

The authors declare no competing financial interest.

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(27) Under the conditions shown in Table 1, entry 10, replacement of $CuSO_4$ with other Cu(II) salts, such as $Cu(OAc)_2$ or $Cu(OTf)_2$, provided inferior results ($Cu(OAc)_2$: 10% yield of **2a**, $Cu(OTf)_2$: complex mixture of products).
(28) Because the reactions described here are conducted in sealed tubes we have been unable to undertake accurate side-by-side rate measurements for the iodination of **1a** and *deuterio*-**1a**. An intramolecular competition experiment between **1a** and *deuterio*-**1a** is given in the Supporting Information. For a discussion on the interpretation of KIE measurements, see: Hartwig, J. F.; Simmons, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066.
(29) Attempts to promote reactions with other electrophiles, such as selectfluor, NCS, and *N*-(phenylthio)phthalimide, have so far been unsuccessful. A full study will be reported in due course.

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