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# Synthesis of Phenols and Aryl Silyl Ethers via Arylation of Complementary Hydroxide Surrogates

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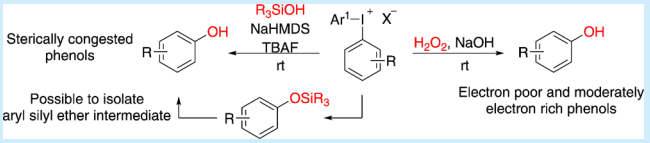
Supporting Information

**ABSTRACT:** Two transition-metal-free methods to access substituted phenols via the arylation of silanols or hydrogen peroxide with diaryliodonium salts are presented. The complementary reactivity of the two nucleophiles allows synthesis of a broad range of phenols without competing aryne formation, as illustrated by the synthesis of the anesthetic Propofol. Furthermore, silyl-protected phenols can easily be obtained, which are suitable for further transformations.

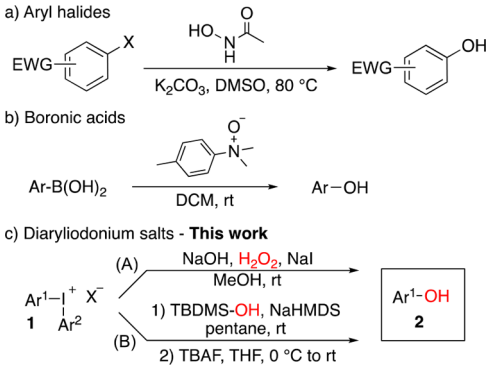



Phenols and their derivatives are highly prevalent in Nature, as well as in pharmaceutical applications and material science. They are also useful building blocks for further transformations.[1] Phenols have hence been targeted for decades and several efficient transition-metal-catalyzed methods for their synthesis exist.[2] However, metal-catalyzed procedures come with the use of potentially toxic reagents, high cost, elevated reaction temperatures, the need for complicated ligands, and the risk of trace metal impurities in the end product.[3] The development of transition-metal-free synthetic methodology toward phenols is therefore of high importance, and several advances have recently been made in this area.[4]

Maloney and co-workers developed an efficient synthesis of phenols using acetohydroxamic acid as a hydroxide surrogate in reactions with electron-deficient haloarenes and heteroarenes (Scheme 1a). The intermediary *O*-arylated product underwent a rearrangement to generate phenols in excellent yields, albeit with a limited substrate scope due to the $S_NAr$ nature of the reaction.[5]

In 2012, Falck and co-workers presented a mild and rapid hydroxylation of boronic acids using *N*-oxides (Scheme 1b).[6] While the transformation had a wide substrate scope and tolerated a broad range of functional groups, only one *ortho*-disubstituted phenol was presented. Furthermore, boronic acids are often expensive and prepared by metal-catalyzed routes.[7]

**Scheme 1. Metal-Free Synthesis of Phenols Using Hydroxide Surrogates**




Diaryliodonium salts are bench-stable electrophilic arylating reagents that can be acquired via facile and high-yielding one-pot syntheses from arenes or iodoarenes.[8,9] They have efficiently been used in many transition-metal-free arylations of different nucleophiles in recent years.[10] We have reported several protocols for the arylation of *O*-nucleophiles, including phenols and aliphatic alcohols.[11] Hydroxide was shown to be a useful base in the arylation of aliphatic alcohols,[11c] but could be arylated itself under certain conditions. Our efforts to synthesize phenols in this way were, however, in vain, as regioisomeric mixtures of diaryl ethers were obtained as the main products.[12] In an extensive mechanistic study on *O*-arylation with diaryliodonium salts, the side products were shown to originate from substrate oxidation or aryne intermediates, generated in the presence of hydroxide ions and other bases.[13]

While aryne problems are avoided using *ortho*-disubstituted diaryliodonium salts, this approach severely limits the substrate scope of the reaction. Furthermore, *O*-nucleophiles that are not prone to diarylation were needed in our quest for a phenol synthesis. Herein, we present two complementary routes to phenols from diaryliodonium salts, using easily available hydrogen peroxide or silanols as hydroxide surrogates to obtain a large scope of phenols at room temperature (Scheme 1c).

Our first approach involved the use of 50% aqueous hydrogen peroxide as a hydroxide surrogate. The lower basicity and higher nucleophilicity of the peroxide anion, compared to hydroxide,[14] might be exploited to avoid aryne formation. Our envisioned reaction pathway involved ligand exchange of the formed peroxide anion with diaryliodonium salt **1a** to provide the T-shaped intermediate **A**, followed by ligand coupling to

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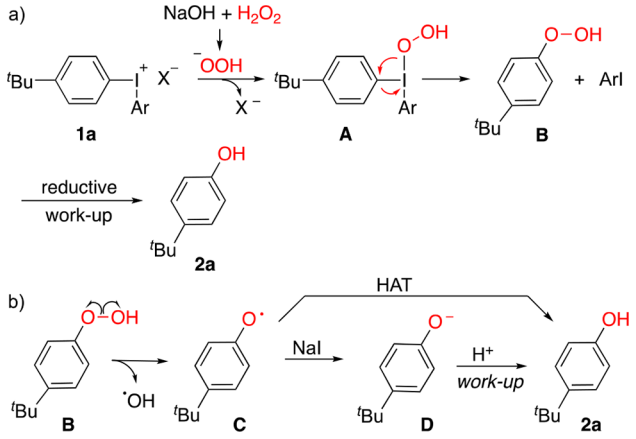
aryl peroxide **B** (Scheme 2a), according to the common arylation mechanism under metal-free conditions.[10] A reductive workup would then deliver phenol **2a**, thus avoiding further arylation to the diaryl ether.[11d]

**Scheme 2. Envisioned Reaction and Proposed Mechanism**




Furthermore, this approach was interesting from a fundamental point of view, as the unusual combination of iodine(III) reagents with an oxidative reagent might lead to formation of iodine(V) rather than the desired nucleophilic reactivity.

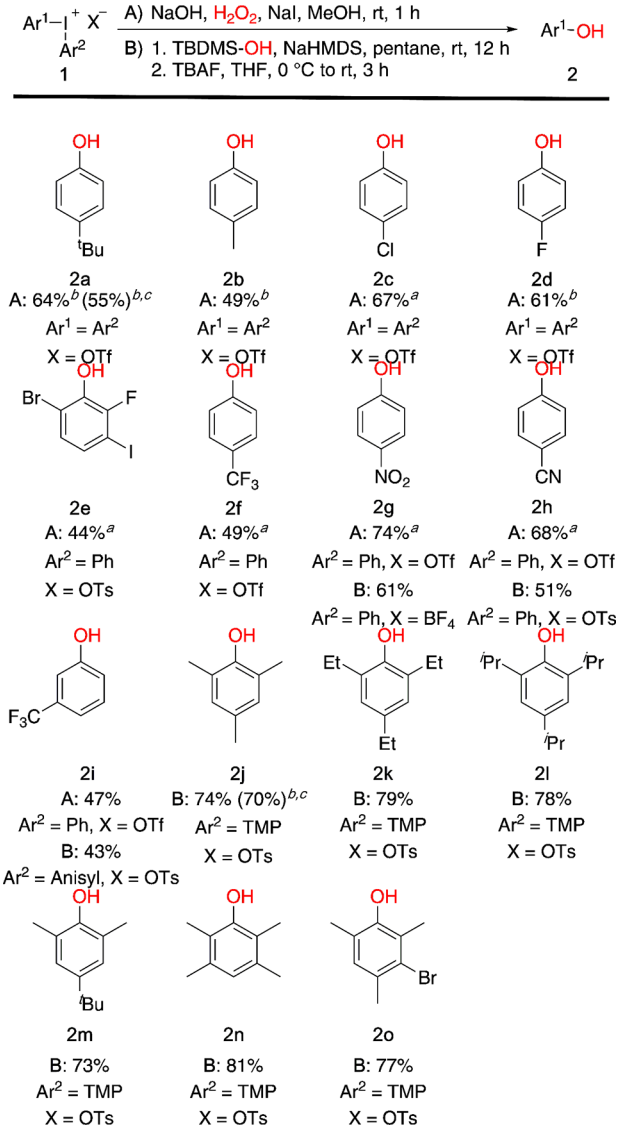
A thorough optimization study using 50% aqueous hydrogen peroxide with di(*tert*-butylphenyl)iodonium triflate (**1a**) under basic, open flask conditions revealed that the reaction was finished within 1 h in methanol.[9] Quantitative recovery of the formed iodoarene was possible, and addition of NaI resulted in improved yield of **2a** and formation of elemental iodine.[15] The reductive workup employed in preliminary experiments proved to be unnecessary.

Aryl peroxides are known to be unstable and rapidly decompose into radicals via homolytic cleavage of the O–O bond to form phenols via hydrogen atom transfer (HAT) or aryloxides via a reductive mechanism.[16] Based on that, and the experimental results described above,[9] we suggest that the ligand coupling product **B** undergoes spontaneous homolytic cleavage of the O–O bond to deliver the aryloxy radical **C** and a hydroxy radical (Scheme 2b). **C** is transformed to phenol **2a**, either via HAT from solvent molecules or by trapping with iodide to furnish the aryloxide **D** and an iodine radical. Alternatively, the iodide could trap the hydroxy radical and thus limit side reactions. A control experiment showed that aryloxide **D** was unreactive toward further arylation under these conditions. Likewise, arylation of **B** to form ArO–OAr proved unfeasible.[9] Alternative mechanistic pathways, e.g. a Baeyer–Villiger type reaction of intermediate **A**, are are less likely but cannot be ruled out at present.[9]

The peroxide methodology proved suitable for iodonium salts decorated with highly electron-withdrawing to moderately electron-donating substituents. To reach phenols from strongly electron-donating and *ortho*-dialkylated iodonium salts, we envisioned silanols to be suitable hydroxide surrogates, as demonstrated in the Ir-catalyzed synthesis of allylic alcohols.[17] To our delight, *tert*-butyl-dimethylsilanol (TBDMS–OH) could be arylated with *ortho*-dialkylated diaryliodonium salts **1** under conditions similar to those developed for the synthesis of sterically congested alkyl aryl ethers.[11d] *In situ* desilylation with TBAF to cleave the Si–O bond allowed isolation of phenols **2**.[18] This method was also applicable when using electron-deficient diaryliodonium salts lacking *ortho*-substituents.

The combined scope of these two complementary routes is depicted in Scheme 3 (Methods A and B, respectively). The

**Scheme 3. Phenol Scope**[a]




[a]Conditions A: Salt **1** (0.5 mmol), NaOH (2 equiv), $H_2O_2$ (aq. 50%, 2.1 equiv), NaI (1 equiv), and MeOH (5 mL). Conditions B: (1) Salt **1** (0.5 mmol), TBDMS–OH (1.1 equiv), NaHMDS (1.1 equiv) and anhydrous pentane (3 mL); (2) concentrated in vacuo followed by addition of THF (3 mL) and TBAF (1.2 equiv) at 0 °C. [b]Purified by acid–base extraction. [c]2.0 mmol scale.

peroxide method (A) furnished *p*-alkyl-substituted phenols **2a** and **2b**, as well as *p*-chloro, *p*-fluoro, and multihalogenated phenols **2c–2e** in moderate to good yields. Electron-withdrawing phenols could be obtained using both methods, yielding *p*-$CF_3$, *p*-$NO_2$, *p*-CN, and *m*-$CF_3$ substituted phenols **2f–2i**.

The silanol method (B) also furnished sterically congested, *ortho*-dialkylated phenols **2j–2o** in high yields. Aryl groups with highly electron-donating substituents, such as 4-OMe, could not be transferred due to decomposition of **1** in Method A,



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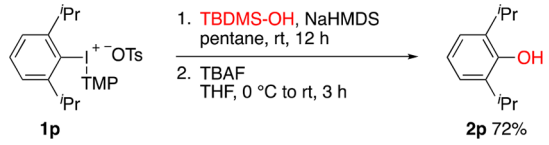
whereas Method B gave rise to a complicated reaction mixture originating from aryne formation,[9] as shown by trapping experiments with furan.[19] Good to excellent recovery of the iodoarene was possible in both methods, which improves the sustainability in large-scale reactions.[9]

The chemoselectivity of the two protocols was investigated with phenyl, anisyl, and 2,4,6-trimethoxyphenyl (TMP) dummy groups ($Ar^2$).[20] Both methods showed clear electronic preferences, and the phenyl dummy could be used in the transfer of EWG-substituted aryl groups (products **2e**–**2i**). More electron-rich dummy groups were unsuitable in method A, which is highly unusual in *O*-arylations under metal-free conditions. This might be due to the formation of hydroxide radicals during the reaction. The silanol method tolerated phenyl, anisyl, and TMP as dummy groups, which is practical as such iodonium salts are easily prepared and alleviate the waste of more expensive aryl moieties.

The facile reaction setup was further improved by investigating alternative product purifications to omit flash chromatography. An acid–base extraction proved sufficient to provide pure products, as demonstrated with a range of phenols (**2a**, **2b**, **2d**, **2j**), including a 2 mmol scale synthesis of phenol **2j** in 70% yield.

To illustrate the utility of the presented methodology, we targeted the synthesis of the commonly used anesthetic drug Propofol (**2p**).[21] The unsymmetric iodonium salt **1p** was thus prepared from the corresponding iodoarene and TMP-H.[9] Pleasingly, phenol **2p** was obtained with complete chemoselectivity and in good yield using the standard conditions in Method B (Scheme 4).

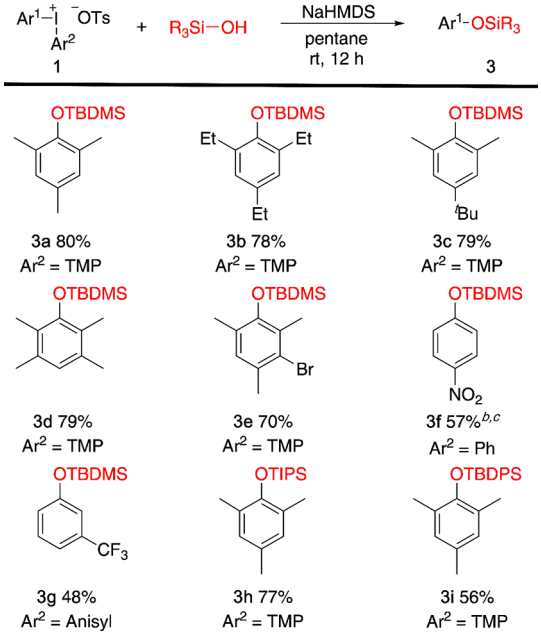
**Scheme 4. Synthesis of Propofol**




During the writing of this manuscript, it was reported that the known *O*-arylation of oximes with diaryliodonium salts[22] could be utilized to obtain phenols after cleavage of the surrogate.[23] While high-yielding, the scope does not include sterically hindered phenols and involves the formation of benzonitrile as waste from the used surrogate.

Aryl silyl ethers are important compounds in transformations where the phenol oxygen must be protected, and they were recently demonstrated as excellent precursors to fluorosulfate reagents.[24] While commonly synthesized by silylation of phenols, their formation can also be envisioned by C–O rather than Si–O bond formation.[25] As aryl silyl ethers are formed as intermediates in Method B, we investigated the isolation of these compounds. Indeed, a range of *ortho*-alkylated aryl silyl ethers (**3a**–**3e**) could be obtained in comparable yields to those achieved in the phenol synthesis using TBDMS-OH (Scheme 5). Also, aryl silyl ethers with electron-withdrawing substituents (**3f**, **3g**) could be isolated, although partial formation of phenol **2g** was unavoidable. Arylation of other silanols was investigated next, and we were pleased to see that tri-isopropylsilanol (TIPS-OH) and *tert*-butyl-diphenylsilanol (TBDPS-OH) were also compatible with the reaction conditions, delivering products **3h** and **3i**.

**Scheme 5. Aryl Silyl Ether Scope**[a]




[a]Conditions: Salt **1** (0.5 mmol), $R_3SiOH$ (1.1 equiv), and NaHMDS (1.1 equiv) in anhydrous pentane (3 mL). [b]$BF_4$ used as counterion. [c]Phenol **2g** formed in 15% yield.

To conclude, two transition-metal-free methods with complementary reactivity have been developed for the synthesis of substituted phenols. The combined scope includes the synthesis of highly sterically congested, electron-rich phenols in good yields, as well as phenols with electron-withdrawing substituents. The benefits of the methodology include the use of stable, easily available, and inexpensive reagents, the ease of reaction setup, the room temperature reactions in non-halogenated solvents, and the avoidance of transition metal catalysts. The utility of the protocol has been demonstrated by the synthesis of the anesthetic drug Propofol. The methodology was extended to the isolation of aryl silyl ethers in good yields, which allows for further transformations where a protected phenol is required.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00287.

Experimental details and spectral data for novel compounds, as well as NMR spectra of all products (PDF)

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### Notes

The authors declare no competing financial interest.



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