Hypervalent Compounds

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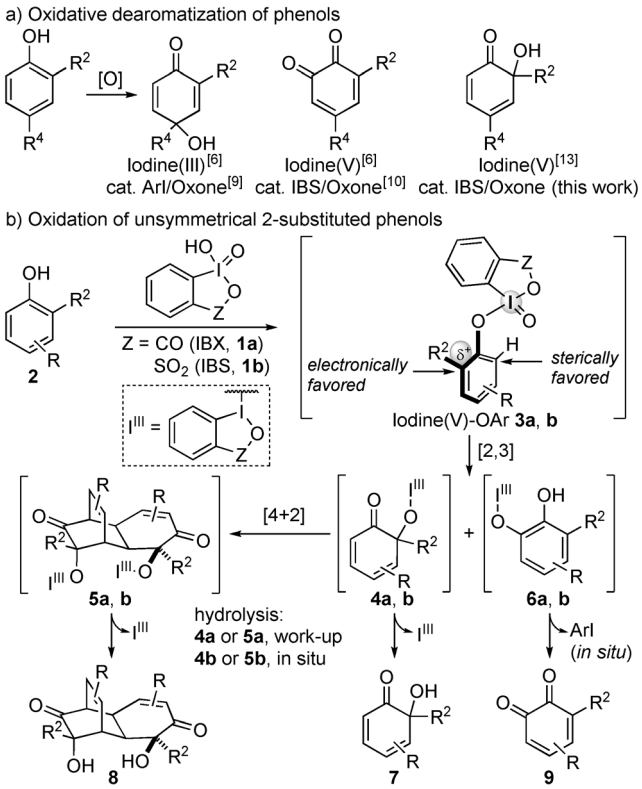
4,5-Dimethyl-2-Iodoxybenzenesulfonic Acid Catalyzed Site-Selective Oxidation of 2-Substituted Phenols to 1,2-Quinols

*Muhammet Uyanik, Tatsuya Mutsuga, and Kazuaki Ishihara**

Abstract: *A site-selective hydroxylative dearomatization of 2-substituted phenols to either 1,2-benzoquinols or their cyclodimers, catalyzed by 4,5-dimethyl-2-iodoxybenzenesulfonic acid with Oxone, has been developed. Natural products such as biscarvacrol and lacinilene C methyl ether could be synthesized efficiently under mild reaction conditions. Furthermore, both the reaction rate and site selectivity could be further improved by the introduction of a trialkylsilylmethyl substituent at the 2-position of phenols. The corresponding 1,2-quinols could be transformed into various useful structural motifs by [4+2] cycloaddition cascade reactions.*

1,2-Quinols and their [4+2] cyclodimers are highly attractive synthons for the synthesis of biologically active compounds.[1] These compounds also constitute the main structural elements of many natural products such as biscarvacrol,[2] chamaecypanone C,[3] grandifloracin,[4] lacinilenes,[5] etc.[1] Numerous synthetic methods have been developed for these compounds through the hydroxylative dearomatization of phenols using either hypervalent iodine(III) or iodine (V) reagents.[6,7] In general, iodine(III) and iodine(V) reagents have been used for *para*- and *ortho*-selective oxidations, respectively (Scheme 1 a).[6] Recently, in situ generated organoiodine(III)- and organoidodine(V)-catalyzed[8] regioselective oxidation to 1,4-benzoquinols,[9] 1,4-benzoquinones,[9] and 1,2-benzoquinones[10] has also been developed. However, the catalytic site-selective hydroxylative dearomatization of 2-substituted phenols to 1,2-benzoquinols has not yet been reported. Herein we report the first organoiodine-(V)-catalyzed site-selective oxidation to 1,2-benzoquinols.

Conventionally, 2-iodoxybenzoic acid (IBX; **1a**)[11] or its stabilized form, SIBX,[12] has been used as a stoichiometric oxidant for the *ortho*-selective oxidation of 2-substituted phenols to 1,2-benzoquinols.[13] However, because of its low reactivity, the substrate scope was limited to phenols substituted with electron-releasing groups. Additionally, no site selectivity was observed for the oxidation of unsymmetrical 2-substituted phenols: the maximum possible yield of the 1,2-benzoquinol-derived cyclodimers is reported to be 50 %.[6a,13,14] IBX reversibly combines with phenols (**2**) to give the iodine(V)-phenol complex **3a** which serves to transfer oxygen from an iodoxy (I^V=O) to either the 2- or 6-position by a concerted intramolecular [2,3] sigmatropic rearrangement (Scheme 1 b).[6] During this process, the competition between electronic and steric factors might lead to non-selective oxidation. Oxygen transfer at the substituted 2-position affords the 1,2-benzoquinol-iodine(III) ester **4a**, which then readily undergoes cyclodimerization to give **5a**. Either 1,2-benzoquinols (**7**) or cyclodimers (**8**) are then obtained after hydrolysis. In contrast, a reaction at the nonsubstituted 6-position affords the catechol-iodine(III) monoester **6a**, after rapid aromatization by keto–enol tautomerization. Undesired 1,2-benzoquinones (**9**) are then



Scheme 1. Hypervalent iodine-mediated oxidation of 2-substituted phenols. IBS = 2-iodoxybenzenesulfonic acid.

obtained by the in situ reduction of iodine(III) to iodine(I). Importantly, either a reductive or strongly acidic work-up is required to release iodine(III) and 2-iodosobenzoic acid, from either **4a** or **5a**.[13] Because of this necessity, it would be difficult to use IBX catalytically for 1,2-benzoquinols. To overcome these issues, we introduced IBS (**1b**) catalysis[15] for the *ortho*-selective hydroxylative dearomatization of phenols.

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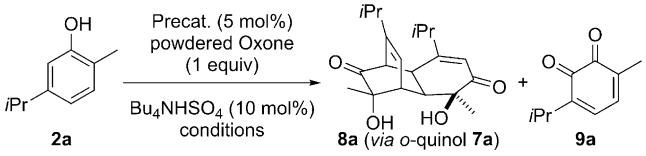
Since the iodine(V) atom of **1b** is more Lewis-acidic than that of **1a**,[15a] we envisioned that a larger partial positive charge (δ^+) would be generated for the IBS-phenol complex **3b**. This complex might lead to a high reactivity and preferential oxygen transfer at a substituted 2-position of unsymmetrical phenols (Scheme 1b). Moreover, because of its strong electron-withdrawing sulfo group, the iodine(III) species would be readily released in situ from either **4b** or **5b**, and would make the catalytic use of IBS possible.

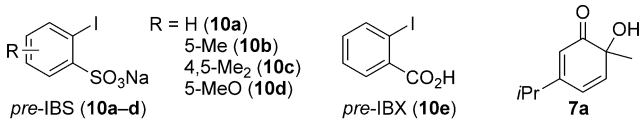
First, we investigated the oxidation of carvacrol (**2a**) as a 2-substituted phenol using IBS catalysts, which were generated in situ from the *pre*-IBS **10** and Oxone (Table 1).

Table 1: Investigation of the IBS-catalyzed oxidation of carvacrol (**2a**).



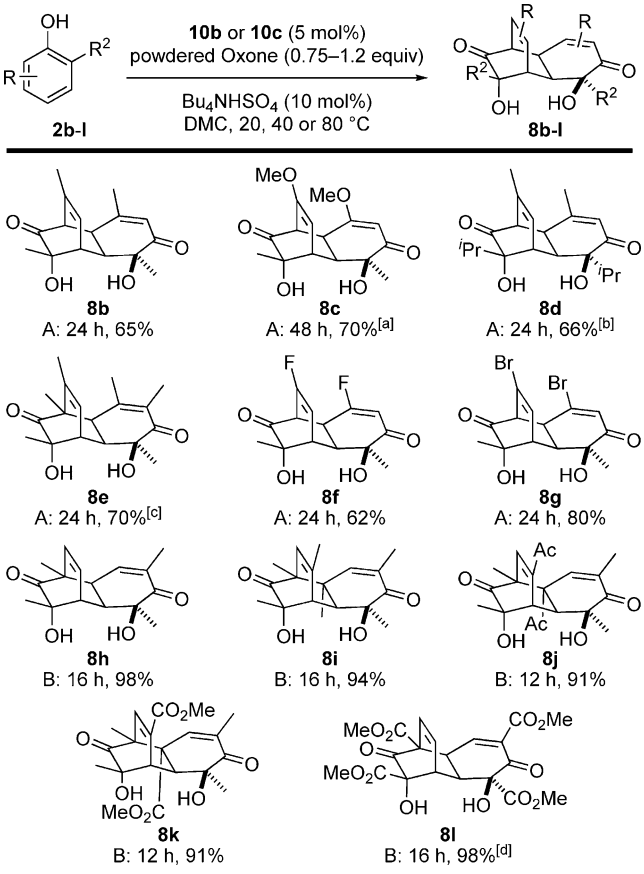
Entry	Precat.	Solvent	T [°C]	t [h]	**8a** Yield [%][a]	**9a** Yield [%][a]
1	**10a**	EtOAc	40	16	65	23
2[b]	**10a**	EtOAc	40	24	0	0
3	**10a**	DMC	40	16	73	17
4	**10a**	DMC	20	120	80	15
5	**10b**	DMC	20	80	80	15
6	**10c**	DMC	20	48	82[c]	15
7	**10d**	DMC	20	36	80	15
8[d]	**10c**	DMC	20	24	82[c]	15
9[e]	**10e**	DMC	40	24	3	–

[a] Determined by NMR analysis of the crude reaction mixture. [b] In the absence of Bu_4NHSO_4. **2a** (>99%) was recovered. [c] Yield of isolated product. [d] Buffered Oxone, which was prepared by vigorous stirring of Oxone in the presence of K_2CO_3 (0.5 equiv) in DMC at room temperature for 24 h, was used. [e] **2a** (90%) was recovered.



A mixture of **2a**, powdered Oxone (1 equiv), and Bu_4NHSO_4 (10 mol%), as a solid–liquid phase-transfer catalyst, was heated in ethyl acetate at 40°C in the presence of 5 mol% of **10a**. To our delight, the reaction proceeded smoothly and the natural product biscarvacrol (**8a**) was obtained in 65% yield by the in situ dimerization of the 1,2-benzoquinol **7a**, and the yield is higher yield than that for stoichiometric IBX oxidation[13c,14] (entry 1). However, undesired the 1,2-benzoquinone **9a** was also obtained in 23% yield along with epoxyquinol and 1,4-benzoquinone in a combined yield of 10%. Notably, no reaction occurred in the absence of a phase-transfer catalyst (entry 2). A brief solvent screening revealed that dimethyl carbonate (DMC), as a more polar solvent than ethyl acetate, improved the site selectivity (entry 3).[16] Additionally, the site- and chemoselectivity were further increased by lowering the reaction temperature to 20°C (entry 4). However, a long reaction time was required to complete the reaction. As in our previous studies,[15a] the regeneration of the iodine(V) species might be rate-limiting for the present phenol oxidation. Indeed, the reaction rate at 20°C was accelerated by 1.5- to 3-fold with the use of precatalysts substituted with electron-donating groups[15a] (**10b–d**; entries 5–7). Although the highest reactivity was observed with 5-MeO-*pre*-IBS (**10d**), it was unstable under these reaction conditions. Additionally, the oxidation rate could be further accelerated with the use of buffered Oxone,[10] which was prepared by premixing of Oxone and potassium carbonate (0.5 equiv) in DMC at room temperature, and **8a** was obtained in 82% yield after a shorter reaction time (entry 8). As expected, almost no reaction proceeded with the use of the **10e** (entry 9).

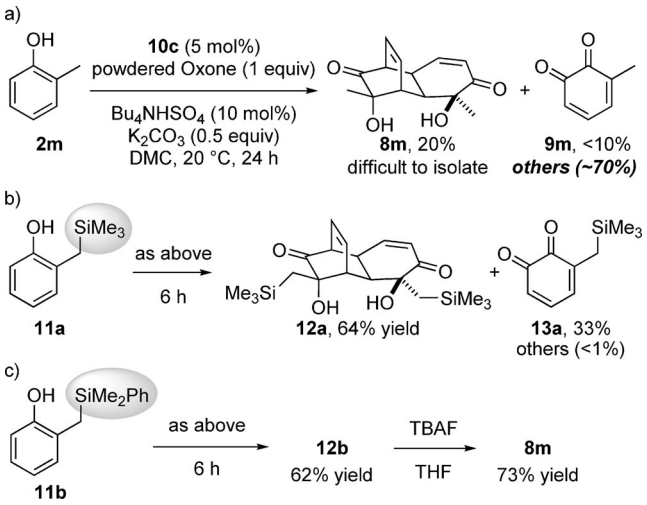
Various 2-substituted phenols were examined under the optimized reaction conditions (Scheme 2).[16] The oxidation of unsymmetrical phenols (**2b–g**) was conducted at 20°C by using **10c** and buffered Oxone (method A) to induce high site selectivity. The corresponding cyclodimers **8b–g** were obtained in good to high yields (62–80%) regardless of the electronic nature of the substituents. Oxidation of 5-methoxy-2-methylphenol (**2c**) proceeded smoothly, however, the



Scheme 2. Regio- and site-selective oxidation of phenols (**2**) to the corresponding cyclodimers (**8**). Methods, reaction time, and yields of isolated products are shown. Method A: **10c**, Oxone (1 equiv), K_2CO_3 (0.5 equiv), 20°C; Method B: **10b**, Oxone (0.75 equiv), 40°C. [a] at 80°C. [b] The benzoquinone **9a** was isolated in 17% yield. [c] The *ortho*-benzoquinol, oxidation product at the 2-position, was isolated in 22% yield. [d] Oxone (1.2 equiv).

cyclodimerization process required high temperatures for the reaction to go to completion. The benzoquinone side products **9** or their reductive catechol forms could not be isolated from these reactions, except for the oxidation of **2d**. Notably, oxidation of 2,3,6-trimethylphenol (**2e**) proceeded selectively at the less hindered 6-position to give the corresponding cyclodimer **8e** in 70% yield. In contrast, the *ortho*-selective oxidation of the symmetrical 2,6-disubstituted phenols **2h–l** proceeded smoothly at 40°C (method B), and the corresponding cyclodimers **8h–l** were obtained in excellent yields. In contrast to the low-temperature conditions (20°C) required for the site-selective oxidation of unsymmetrical phenols, almost the same results were obtained with both **10b** and **10c** at 40°C.[16] Notably, in contrast to IBX-mediated oxidations,[13] phenols substituted with electron-withdrawing groups (**2f**, **2g**, and **2j–l**) were oxidized smoothly with the use of our IBS/Oxone catalysis. For example, the oxidation of **2l**, bearing two ester groups at both *ortho*-positions, using a stoichiometric amount of IBX did not proceed even at elevated temperatures.

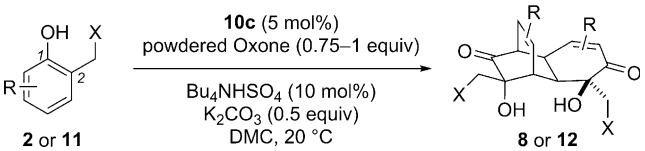
The oxidation of 2-cresol (**2m**), as the simplest substrate, gave a complex mixture, and the desired cyclodimer **8m** was obtained in only 20% yield (Scheme 3a). To stabilize the



Scheme 3. Oxidation of 2-cresol (**2m**) and its silylated analogues **11**. TBAF = tetra-*n*-butylammonium fluoride, THF = tetrahydrofuran.

partial positive charge developing at an alkylated 2-position, we introduced a trialkylsilylmethyl substituent at the 2-position of phenols. To our delight, the clean oxidation of the α-trimethylsilyl-*o*-cresol **11a** proceeded smoothly and the corresponding cyclodimer **12a** was obtained in 64% yield along with the quinone **13a** in 33% yield (Scheme 3b). Both the site selectivity and the reaction rate were enhanced by the β-silicon effect.[17] Notably, oxidative desilylation was not observed under our oxidative conditions. A variety of trialkylsilyl groups could be easily installed at the benzylic position,[16] and easily removed after the oxidation. For instance, **8m** could be isolated in good yield from the oxidation of the phenol **11b** followed by TBAF-mediated desilylation (Scheme 3c).

Table 2: Oxidation of various 2-(silylmethyl)phenols **11**.

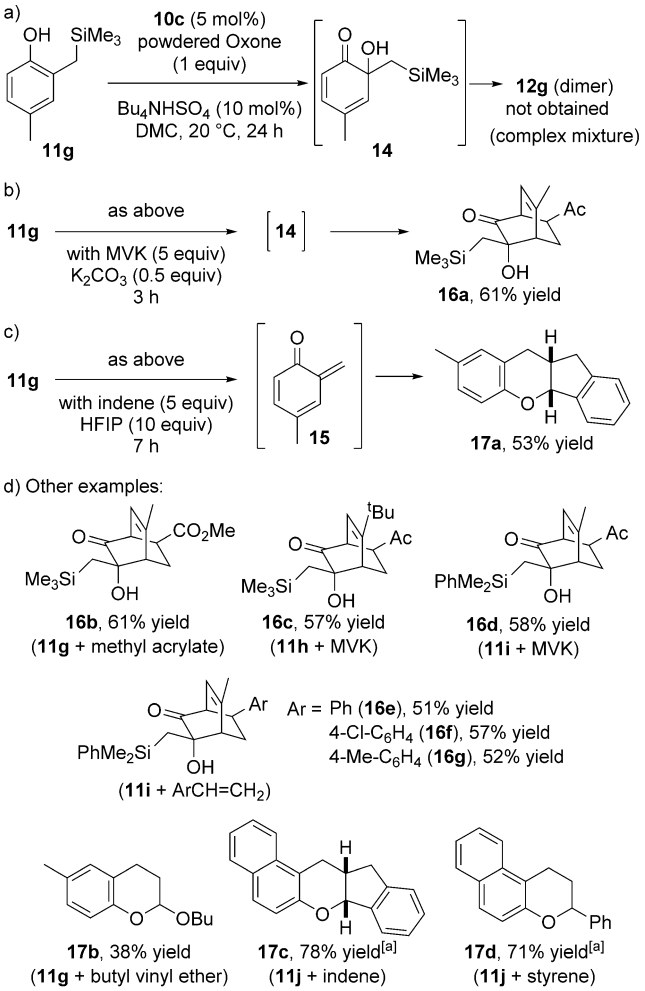


Entry	Substrate	X	R	*t* [h]	**8** or **12** Yield [%][a]
1	**11c**	$SiMe_3$	5-*i*Pr	5	94 (<5)[b]
2	**2a**	H	5-*i*Pr	24	82 (15)[b]
3	**11d**	$SiMe_3$	5-Me	5	72
4	**2d**	H	5-Me	24	65
5	**11e**	$SiMe_3$	5-F	7	83
6	**2f**	H	5-F	24	62
7	**11f**	$SiMe_3$	6-Br	5	57
8	**2n**	H	6-Br	44	27

[a] Yield of isolated product. [b] 1,2-Benzoquinone.

The oxidation of various 2-(silylmethyl)phenols (**11**) was examined under optimized reaction conditions (Table 2). The reaction of the silylated analogue of carvacrol **11c** gave the cyclodimer **12c** exclusively (entry 1 versus entry 2). Moreover, compared to their nonsilyl counterparts **2d**, **2f**, and **2n**, the phenols **11d–f**, bearing electron-donating or electron-withdrawing substituents at either the *meta*- or *ortho*-positions, gave the corresponding cyclodimers in higher yields after shorter reaction times (entries 3, 5, and 7 versus entries 4, 6 and 8).

In contrast, the oxidation of the 4-methylphenol **11g** gave a complex mixture of products, and neither the desired 1,2-benzoquinol **14** nor its cyclodimer **12g** could be isolated (Scheme 4a). We speculated that, because of the acidity of Oxone, Peterson olefination[18] of the unstable **14** might proceed preferentially to give a 1,2-benzoquinone 2-methide **15**, which readily undergoes decomposition.[19] This failure provided us an opportunity to achieve unprecedented cascade reactions. Indeed, the elimination of silanol could be suppressed by the use of buffered Oxone, and a relatively clean reaction was achieved in the presence of excess methyl vinyl ketone (MVK) to give the [4+2] cycloadduct **16a** in good yield as a single diastereomer (Scheme 4b).[20] In contrast, **15** could also be trapped in the presence of electron-rich alkenes, such as indene, under acidic conditions to give the corresponding tetracyclic chroman **17a** (Scheme 4c).[19] Other examples are shown in Scheme 4d for the cascade [4+2] cycloaddition of both 1,2-benzoquinols and 1,2-benzoquinone 2-methides with several dienophiles, such as MVK, methyl acrylate, aryl alkenes, and alkyl vinyl ether.[16,21] Notably, to accelerate the generation of *ortho*-quinone methide from the stable *ortho*-naphthoquinol, derived from 2-naphthol **11j**, a catalytic amount of *para*-toluene sulfonic acid was used instead of HFIP and the cycloadducts **17c** and **17d** were obtained in high yield.[16] Importantly, the IBS-catalyzed chemoselective oxidation of phenols proceeded efficiently under these mild reaction conditions even in the presence of an excess amount of alkenes. However, the oxidative cascade cycloaddition of both *ortho*-quinols and *ortho*-quinone methides with acetylenes (e.g., acetylenedi-

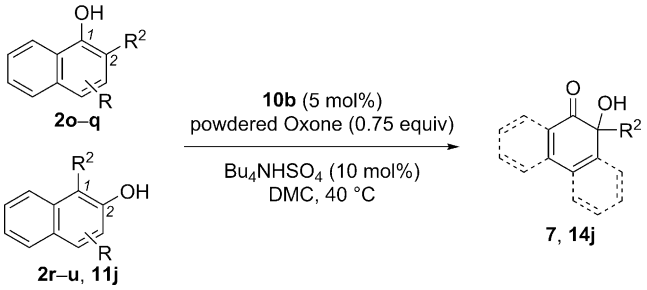


Scheme 4. Oxidative cascade reactions. [a] TsOH (10 mol%) was used instead of HFIP. TsOH and dienophile were added after the oxidation of **11j** was completed. For details, see the Supporting Information. HFIP = 1,1,1,3,3,3-Hexafluoro-2-propanol, MVK = methyl vinyl ketone, Ac = acyl.

carboxylates, aryl or alkyl acetylenes) gave complex reaction mixtures.

On the other hand, the selective oxidation of *ortho*-substituted 1- or 2-naphthols (**2o**–**u**) under optimized reaction conditions gave the corresponding *ortho*-naphthoquinols **7o**–**u** (Table 3).[16] Notably, the catalytic oxidation of the naphtholic ester **2q** was complete within 35 hours (entry 3), whereas the IBX-mediated stoichiometric oxidation required 7 days.[13c] Furthermore, the antibacterial natural product lacinilene C methyl ether **7u**[5] could be synthesized by the clean oxidation of another natural product, 2-hydroxy-7-methoxycadalene (**2u**),[5a] in 91% yield (entry 7). In contrast, either highly toxic diphenylseleninic anhydride[5c] or Zr^{IV}/TBHP[5d] had been required previously for the oxidation of **2u** to **7u**. To avoid the Peterson elimination, the oxidation of **11j** was performed with buffered Oxone under milder reaction conditions, and the desired **14j** was isolated in high yield (entry 8). Overall, compared to IBX-mediated stoichiometric oxidations,[13] higher chemical yields were achieved with our

Table 3: Site-selective oxidation of naphthols to *ortho*-naphthoquinols.



Entry	2	R^2	R	t [h]	7 Yield [%][a]
1[b]	**2o**	Me	H	16	81
2[c]	**2p**	Me	4-Br	12	70
3	**2q**	CO_2Me	H	35	85
4	**2r**	Me	H	12	87
5	**2s**	CO_2Me	H	19	94
6	**2t**	Me	3-Me	12	90
7	**2u**	Me	4-*i*Pr-6-Me-7-MeO	16	91[d]
8[e]	**11j**	CH_2SiMe_2Ph	H	5	91

[a] Yield of isolated product. [b] EtOAc instead of DMC. [c] Oxone (1 equiv). [d] Lacinilene C methyl ether (**7u**). [e] The reaction was performed with precatalyst **10c** in the presence of K_2CO_3 (0.375 equiv) at 20 °C.

IBS/Oxone catalytic oxidation under milder reaction conditions for both the phenols and naphthols examined.

In conclusion, we have succeeded in the first site-selective hydroxylative dearomatization of phenols by using IBS/Oxone catalysis. The corresponding 1,2-quinols or their [4+2] cyclodimers, including natural products such as biscarvacrol and lacinilene C methyl ether, could be obtained in high yield. The reaction rate and chemoselectivity were improved significantly with the use of **10c** and buffered Oxone under milder reaction conditions. Furthermore, both the reaction rate and site selectivity were further improved by the introduction of a trialkylsilylmethyl substituent at the *ortho*-position of phenols. The corresponding 1,2-quinols could be transformed into various useful structural motifs by [4+2] cycloaddition cascade reactions. Studies directed towards either the diastereoselective or enantioselective synthesis of 1,2-quinols by using either chiral phenols bearing chiral trialkylsilylmethyl group at the 2-position or chiral hypervalent iodine(V) catalysts, respectively, is underway in our laboratories.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: hypervalent compounds · iodine · oxidation · phenol · silicon

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[21] Additional synthetic utility of silylated benzoquinols is demonstrated in the Supporting Information.

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Communications

Hypervalent Compounds

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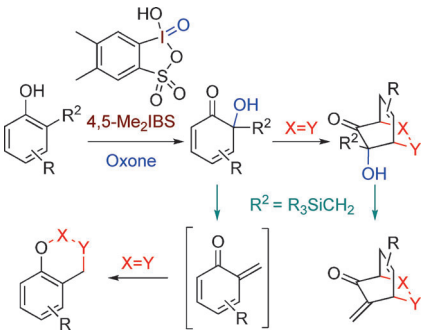
4,5-Dimethyl-2-Iodoxybenzenesulfonic Acid Catalyzed Site-Selective Oxidation of 2-Substituted Phenols to 1,2-Quinols



An oxidation cocktail: A site-selective hydroxylative dearomatization of phenols to deliver either 1,2-quinols or their cyclodimers, catalyzed by 4,5-Me_2IBS with Oxone, is described. Importantly, both the reaction rate and site-selectivity were improved by the introduction of a trialkylsilylmethyl substituent at the 2-position of the phenols. The corresponding 1,2-benzoquinols could be transformed into various useful structural motifs by [4+2] cycloaddition cascade reactions.

