Development of Hypervalent Iodine(V) Catalysis for Selective Oxidation of Phenols

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Chapter 1

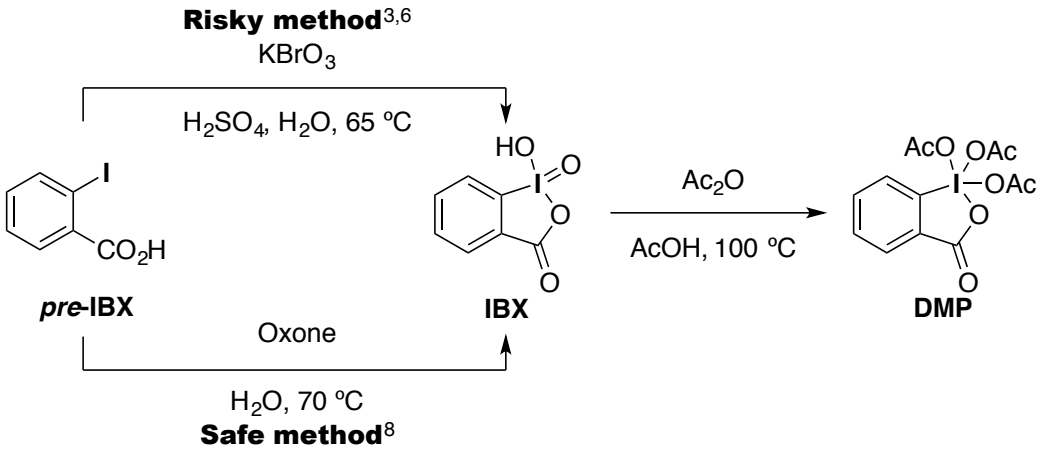
Introduction and General Summary

1-1. Introduction

The oxidation reaction is one of the most widely used transformations in synthetic organic chemistry. Traditionally, toxic heavy metal oxidants or precious transition metal-based catalysts have been used for oxidation reactions. Recently, because of their environmentally benign characteristics, hypervalent iodines have been the focus of great attention as alternatives to toxic metal oxidants such as Pb(IV), Tl(III), Cr(VI), and Os(VIII).[1] However, due to their potentially shock-sensitive explosiveness and/or poor solubility in common organic solvents, the stoichiometric use of hypervalent iodines has been limited.[1] Therefore, the catalytic use of these compounds would be desirable from both economical and environmental perspectives.

To date, several hypervalent organoiodine(V) reagents have been developed for oxidation reactions.[1] Representative examples include 2-iodoxybenzoic acid (IBX) and Dess–Martin periodinane (DMP). IBX was first synthesized by Meyer's group in 1893.[2] However, the practical application of IBX has been restricted due to its low solubility in common organic solvents, except for DMSO. Almost a century later, in 1983, Dess and Martin used IBX as a precursor for the synthesis of DMP, which was recognized as a selective and mild oxidant (*Scheme 1*).[3,4] In 1994, Frigerio and Santagostino first used IBX in DMSO as a stoichiometric oxidant for the oxidation of alcohols to the corresponding carbonyl compounds.[5] Previously, IBX was synthesized from 2-iodobenzoic acid (*pre*-IBX) with the use of potassium bromate as an oxidant under strong acidic conditions (*Scheme 1*).[3,6] However, some bromate or other impurity in the samples was later found to be explosive.[7]

Scheme 1. IBX and DMP as Representative Hypervalent Iodine(V) Compounds[3,6,8]



In 1999, Santagostino's group developed an alternative method for the preparation of IBX by using Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) as an environmentally safe oxidant (*Scheme 1*).[8] This

simple and secure preparation of IBX from *pre*-IBX has made it one of the most popular oxidants. IBX is now recognized as a powerful oxidant for a variety of oxidative transformations (*Figure 1*).[9]

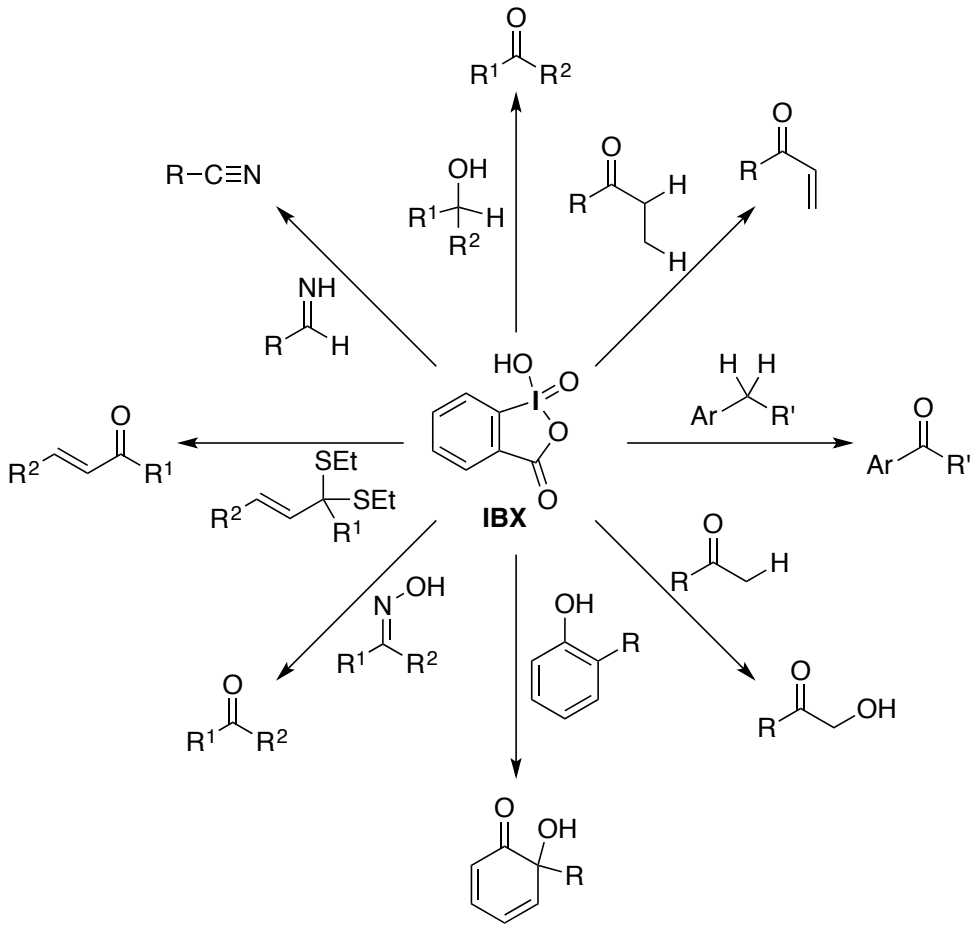
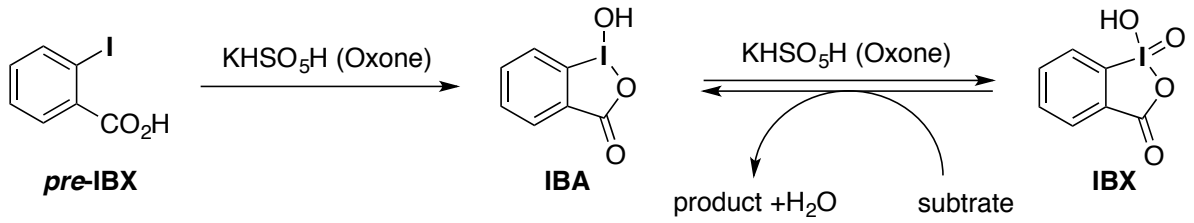


Figure 1. IBX as a powerful yet selective oxidant for a variety of oxidative transformations.[9]

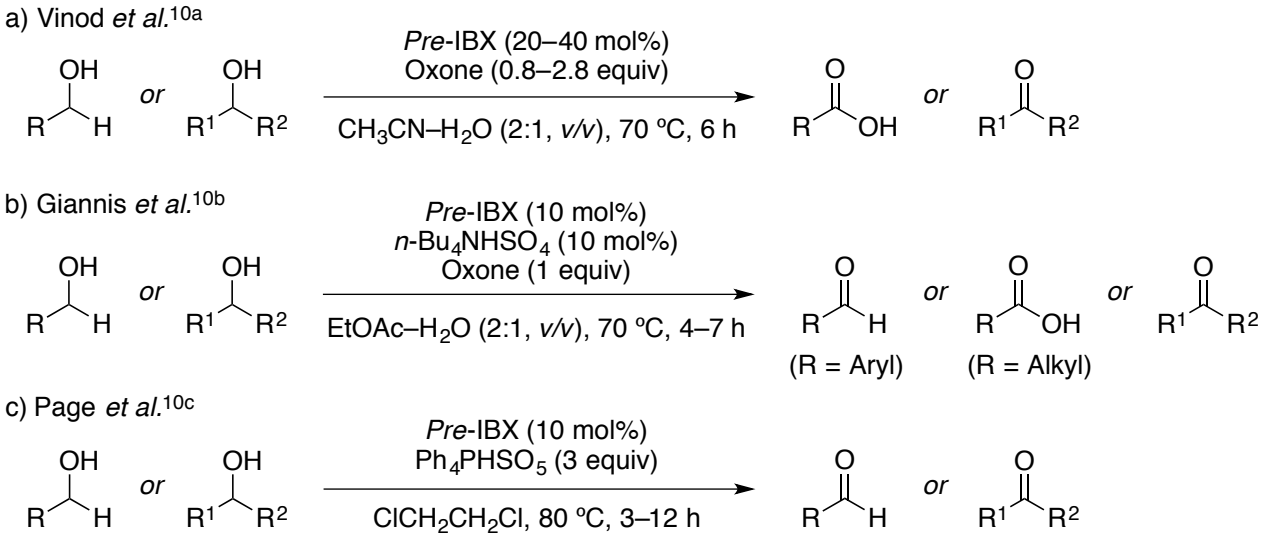
However, the stoichiometric use of IBX results in the generation of equimolar amounts of organoiodine waste such as 2-iodobenzoic acid. In 2005, inspired by Santagostino's method,[8] Vinod and colleagues reported the first catalytic use of IBX for the oxidation of alcohols by using Oxone as a co-oxidant (*Scheme 2*).[10a] Importantly, catalytically active organoiodine(V) species could be generated *in situ* from a catalytic amount of *pre*-IBX with Oxone under aqueous conditions. Primary and secondary alcohols were oxidized to the corresponding carboxylic acids and ketones, respectively, in aqueous acetonitrile (*Scheme 3a*).[10a] However, a large amount of precatalyst (20 to 40 mol%) was required, and the aldehydes could not be obtained selectively from the oxidation of primary alcohols under these conditions. In 2006, Giannis and colleagues reported the IBX-catalyzed oxidation of alcohols with Oxone in an ethyl acetate/water biphasic solvent system. (*Scheme 3b*).[10b] Importantly, tetrabutylammonium sulfate was used as a phase

transfer catalyst to generate tetrabutylammonium peroxymonosulfate *in situ* under biphasic conditions that included Oxone. The catalyst loading of *pre*-IBX could be reduced to 10 mol%, and primary benzylic alcohols could be selectively oxidized to the corresponding aldehydes. However, the oxidation of primary aliphatic alcohols afforded the corresponding carboxylic acids. In 2007, Page and colleagues reported the IBX-catalyzed selective oxidation of primary and secondary alcohols to the respective aldehydes and ketones in dichloroethane in the presence of tetraphenylphosphonium peroxymonosulfate (TPPP, $Ph_4P^+HSO_5^-$) as a soluble oxidant in organic solvents (*Scheme 3c*).[10c] TPPP was prepared from Oxone and tetraphenylphosphonium chloride by counterion exchange.

Scheme 2. *In Situ* Generation and Catalytic Use of IBX



Scheme 3. IBX-catalyzed Oxidation of Alcohols[10]

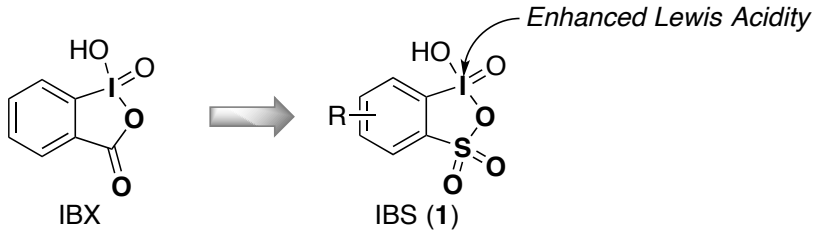


To develop a more active organoiodine(V) catalyst, our group focused on 2-iodoxybenzenesulfonic acids (IBSes, **1**), which are thia-analogues of IBX. The oxidation potential as well as the Lewis acidity of iodine(V) on **1** was envisioned to be higher than that of IBX due to its strong electron-withdrawing sulfo group (*Scheme 4a*).[11] In 2006, Zhdankin and colleagues first reported the preparation and spectroscopic characterization of **1a** (R = H) (*Scheme*

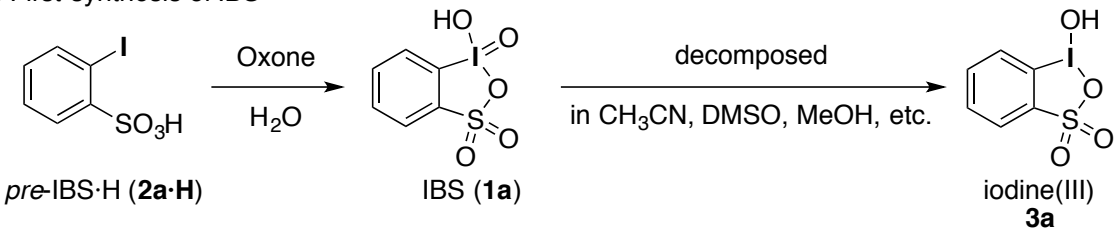
4b).[12] **1a** could be prepared from the oxidation of 2-iodobenzenesulfonic acid (*pre*-IBS, **2a**·H) with Oxone. However, **1a** was found to be unstable due to self-decomposition, and was highly reactive toward organic solvents such as dimethyl sulfoxide, methanol, and acetonitrile. Thus, it was not possible to investigate its oxidation ability.[12] In contrast, our group found that IBSes **1** could be prepared *in situ* from *pre*-IBSes (**2**·H, **2**·Na or **2**·K) and Oxone under nonaqueous conditions, and showed greater catalytic activity than IBX for alcohol oxidation reactions (*Scheme 4c*).[11]

Scheme 4. Development of IBS Catalysis

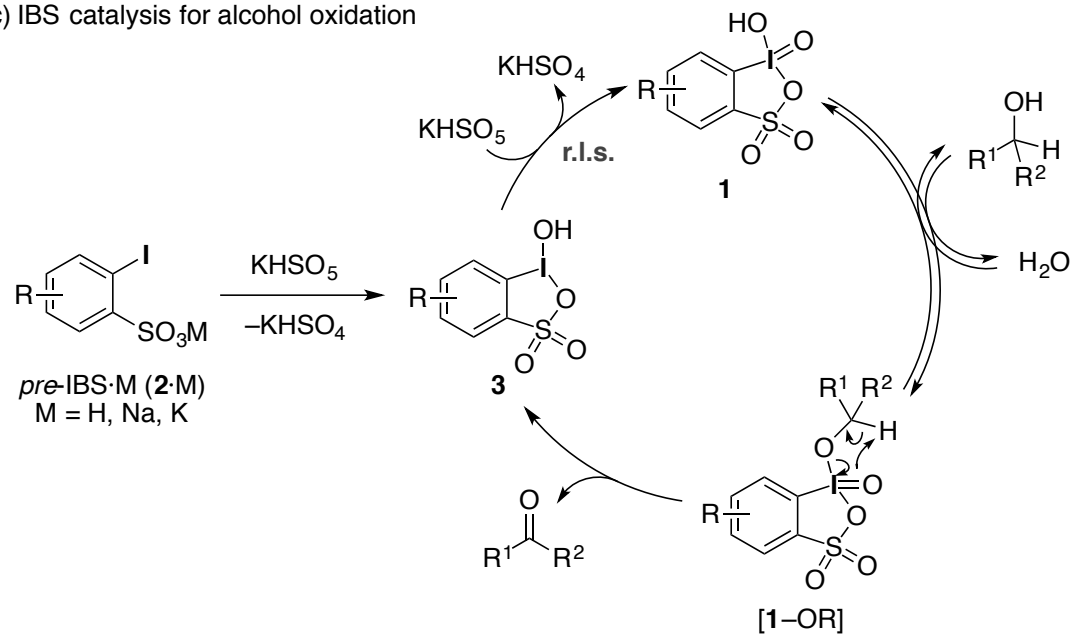
a) 2-Iodoxybenzenesulfonic acid (IBS, a thia-analogue of IBX)



b) First synthesis of IBS[12]

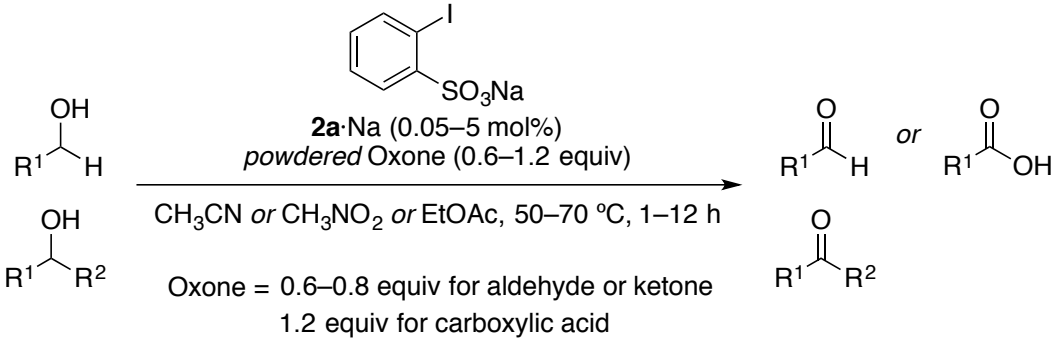


c) IBS catalysis for alcohol oxidation



With the use of IBX/Oxone catalysis, a variety of primary and secondary alcohols could be oxidized efficiently under optimized nonaqueous conditions (*Scheme 5*).[11] Importantly, both primary benzylic and aliphatic alcohols could be oxidized selectively to the corresponding aldehydes and carboxylic acids by controlling the amount of Oxone used in the presence of *pre*-IBS **2a**·Na (0.05–5 mol%). Theoretical calculations revealed that Goddard's *hypervalent twisting*[13] would be the rate-determining step for the *stoichiometric* oxidation of alcohols with not only IBX but also IBSes. The relatively ionic character of the intramolecular hypervalent iodine(V)–OSO_2 bond of IBS might lower the twisting barrier of the alkoxyperiodinane intermediate [**1**–OR] (*Scheme 4c*).[11] However, the rate-limiting step (r.l.s.) of *catalytic* alcohol oxidations might be the regeneration of iodine(V) species from iodine(III) **3**, because the reaction rate under catalytic conditions was increased with the use of powdered Oxone due to its increased surface area (*Scheme 4c*).[11] Therefore, the generation of iodine(V) species **1** from **3** as well as **2** should be faster than with IBX (*Scheme 4c*).

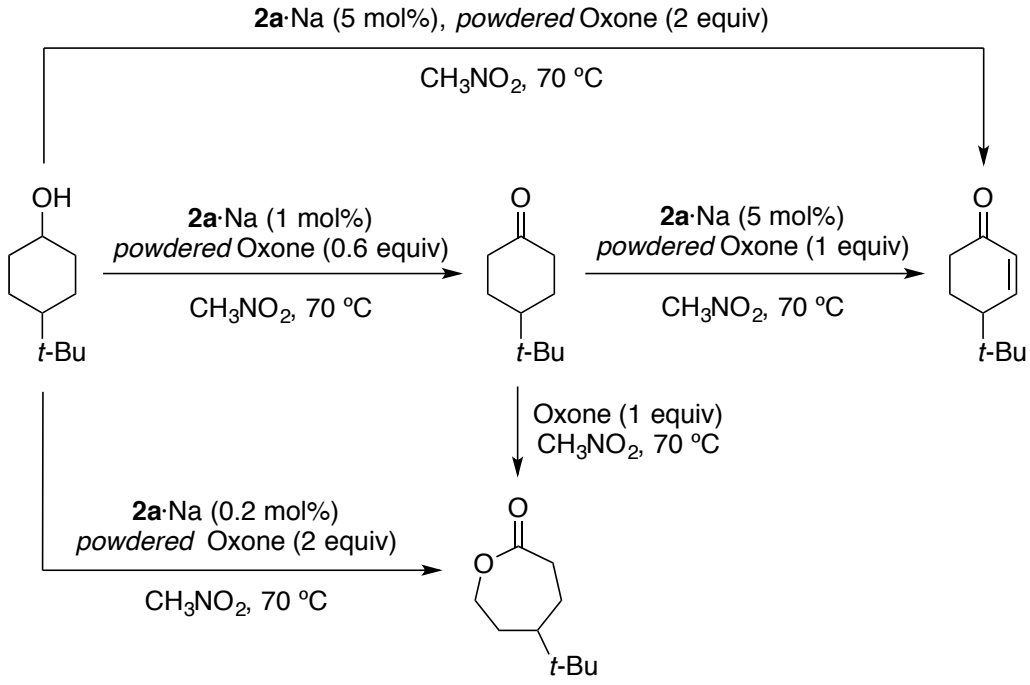
Scheme 5. IBS-Catalyzed Highly Efficient and Selective Oxidation of Alcohols with Oxone[11]



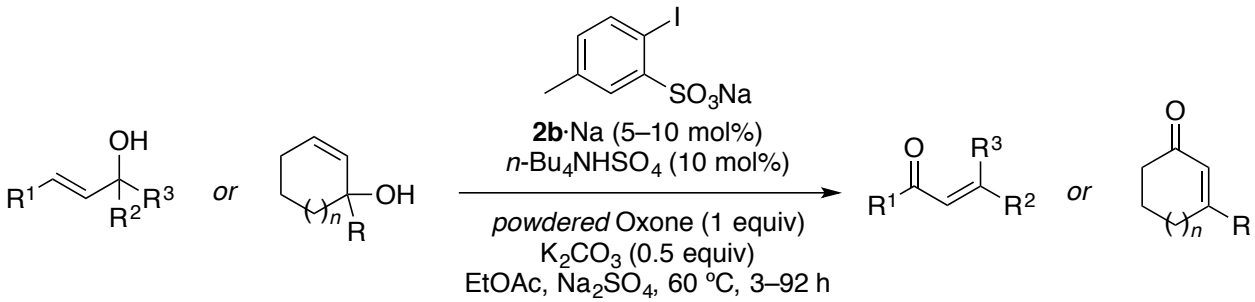
This catalytic system could be applied to the selective cascade oxidation of cyclohexanols to cyclohexanones, cyclohex-2-enones and oxepan-2-ones in excellent yields by controlling the amounts of both **2a**·Na and Oxone used (*Scheme 6*).[11] Notably, IBX could not catalyze these cascade reactions.

The first catalytic oxidative rearrangement of tertiary allylic alcohols has also been developed through the use of IBS/Oxone catalysis (*Scheme 7*).[14] The reaction proceeded with high chemoselectivity, and the corresponding cyclic or acyclic enones were obtained in good to high yields. Notably, IBS (**1a**) was found to be less effective as a catalyst than 5-Me-IBS (**1b**), which was generated *in situ* from *pre*-5-Me-IBS (**2b**·Na). Moreover, when potassium carbonate was used to buffer Oxone, and when tetrabutylammonium hydrogen sulfate was used as a solid–liquid phase transfer catalyst to generate soluble ammonium Oxone, a wide substrate scope was achieved.

Scheme 6. IBS-Catalyzed Selective Cascade Oxidations of Cycloalkanols[11]



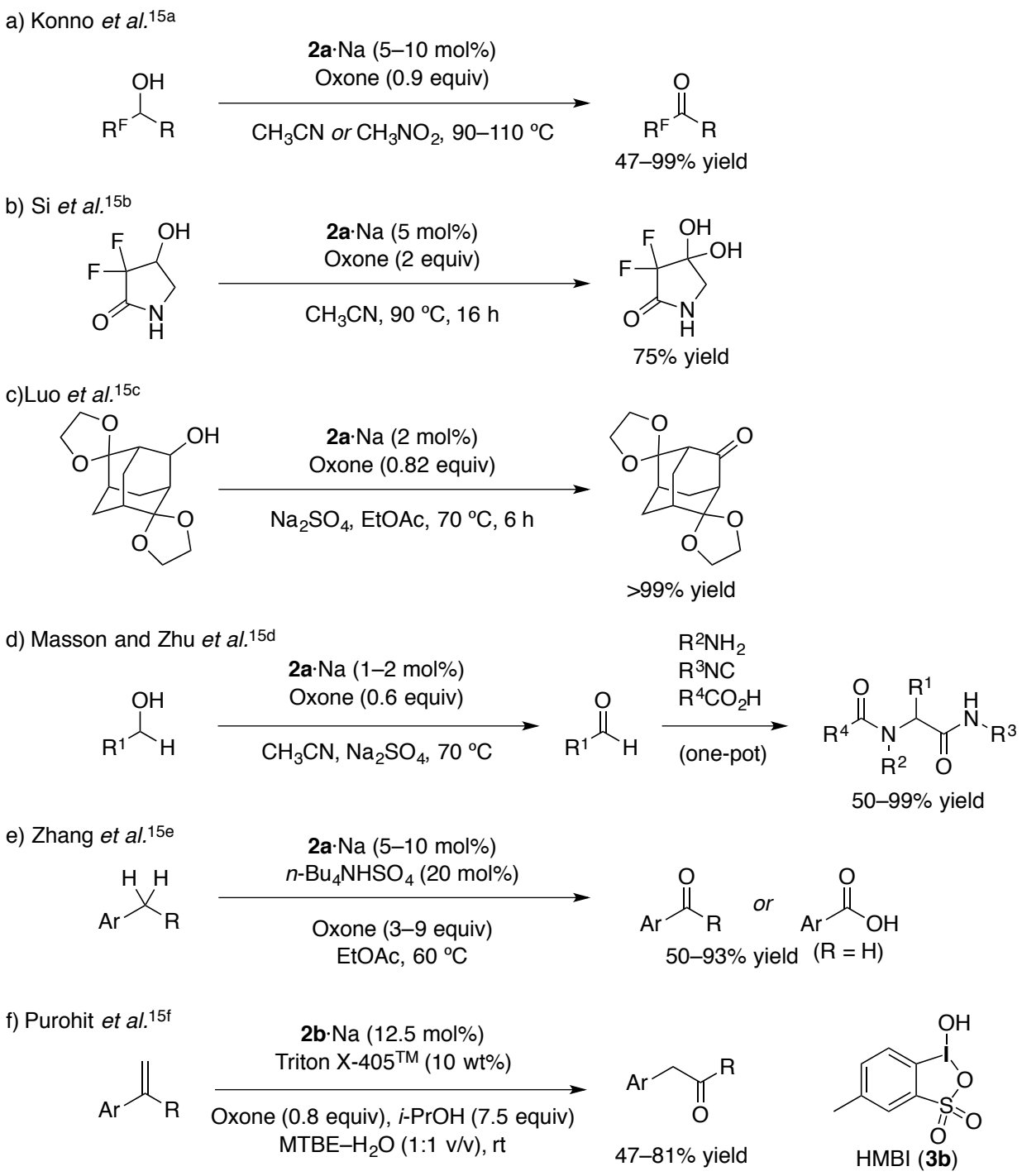
Scheme 7. 5-Me-IBS-Catalyzed Oxidative Rearrangement of *tert*-Allylic Alcohols[14]



Other research groups have applied IBS/Oxone catalysis to various oxidative transformations .[15] Konno and colleagues reported the highly efficient oxidation of fluoroalkyl alcohols to the corresponding ketones by using a catalytic amount (5–10 mol%) of **2a**·Na with Oxone under reflux conditions (*Scheme 8a*).[15a] Notably, this IBS-catalyzed method was found to be comparable to Dess–Martin stoichiometric oxidation with respect to efficiency and chemoselectivity, while other representative oxidation protocols such as Swern and PDC oxidations could not be used, especially for the oxidation of allylic or propargylic trifluoromethyl carbinols. Later, Lilly Research Laboratories applied IBS/Oxone catalysis to the oxidation of 3,3-difluoropyrrolidin-4-ol (*Scheme 8b*).[15b] The corresponding α,α-difluoroketone was obtained in high yield as a dehydrated form. This ketone was then transformed to (*R*)-3,3-difluoropyrrolidin-4-ol, which is a valuable building block in medicinal chemistry. Luo

and colleagues achieved a high-yield oxidation of adamantanol bearing two ketal groups by using 2 mol% of **2a**·Na with Oxone under mild conditions (*Scheme 8c*).[15c] The resulting ketone was used as a key synthetic intermediate for high energy-density polynitroadamantanes. Masson, Zhu and colleagues developed an Ugi four-component reaction of alcohols instead of aldehyde by using an IBS/Oxone system (*Scheme 8d*).[15d] On the other hand, Zhang and colleagues reported the

Scheme 8. IBS (or HMBI)/Oxone Catalysis for Various Oxidative Transformations[15]



IBS-catalyzed oxidation of benzylic C–H bonds to carbonyl compounds with Oxone (*Scheme 8e*).[15e] Purohit and colleagues reported the first example of an oxidative 1,2-shift of 1,1'-disubstituted olefins by using a catalytic amount of sodium 2-iodo-5-methyl-benzenesulfonate (**2b**·Na) with Oxone (*Scheme 8f*).[15f] The authors suggested that the catalytically active species is not 5-Me-IBS, but rather 1*H*-1-hydroxy-5-methyl-1,2,3-benziodoxanthiole-3,3-dioxide (HMBI, **3b**).

We have been interested in the extension of IBS catalysis to challenging reactions such as the catalytic, regio- and site-selective oxidation of phenols. This thesis focuses on the development of a highly efficient and selective oxidation of phenols to the corresponding 1,2-quinones and 1,2-quinols through the use of IBS/Oxone catalysis.

1-3. 5-Me-IBS-Catalyzed Regioselective Oxidation of Phenols to 1,2-Quinones (Chapter 2)

1,2-Quinones are highly useful synthons for the synthesis of natural products and biologically active compounds (*Figure 2*).[16,17] *ortho*-Selective oxidation of phenols is a powerful method for the preparation of these compounds. In Nature, *L*-dopaquinone, a precursor of melanin, is biosynthesized through a hydroxylase-mediated *ortho*-selective oxidation of *L*-tyrosine as a key process (*Scheme 9*).[17]

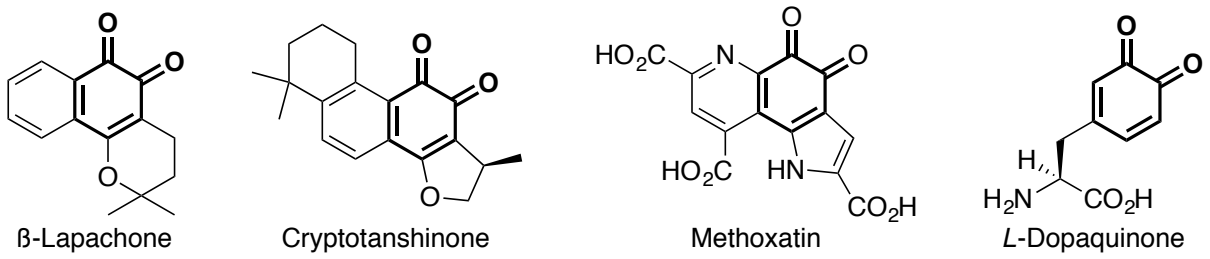
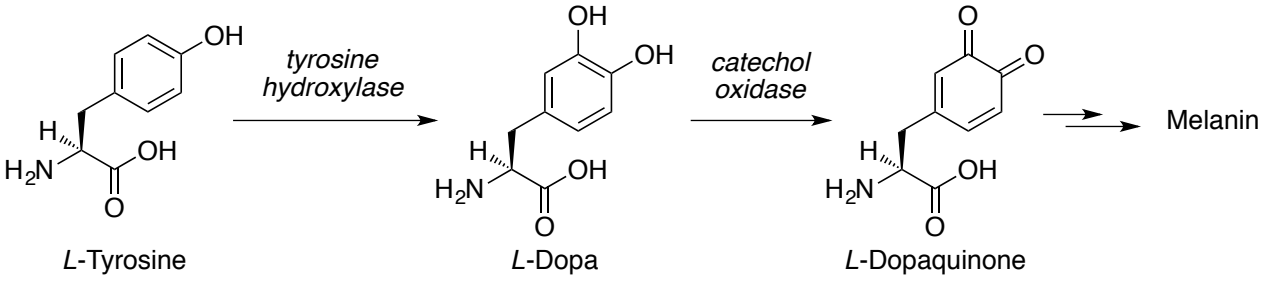


Figure 2. Biologically active compounds including 1,2-quinones.[16,17]

Scheme 9. Biosynthesis of Melanin *via ortho*-Selective Oxidation of *L*-Tyrosine[17]

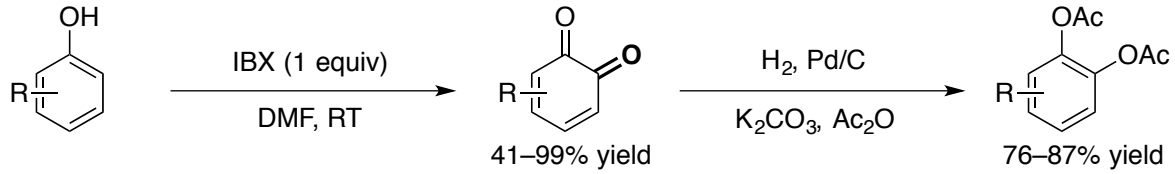


On the other hand, several chemical synthetic methods have been developed for the oxidation of phenols to, especially, *para*-quinones. In general, the oxidation of phenols with conventional

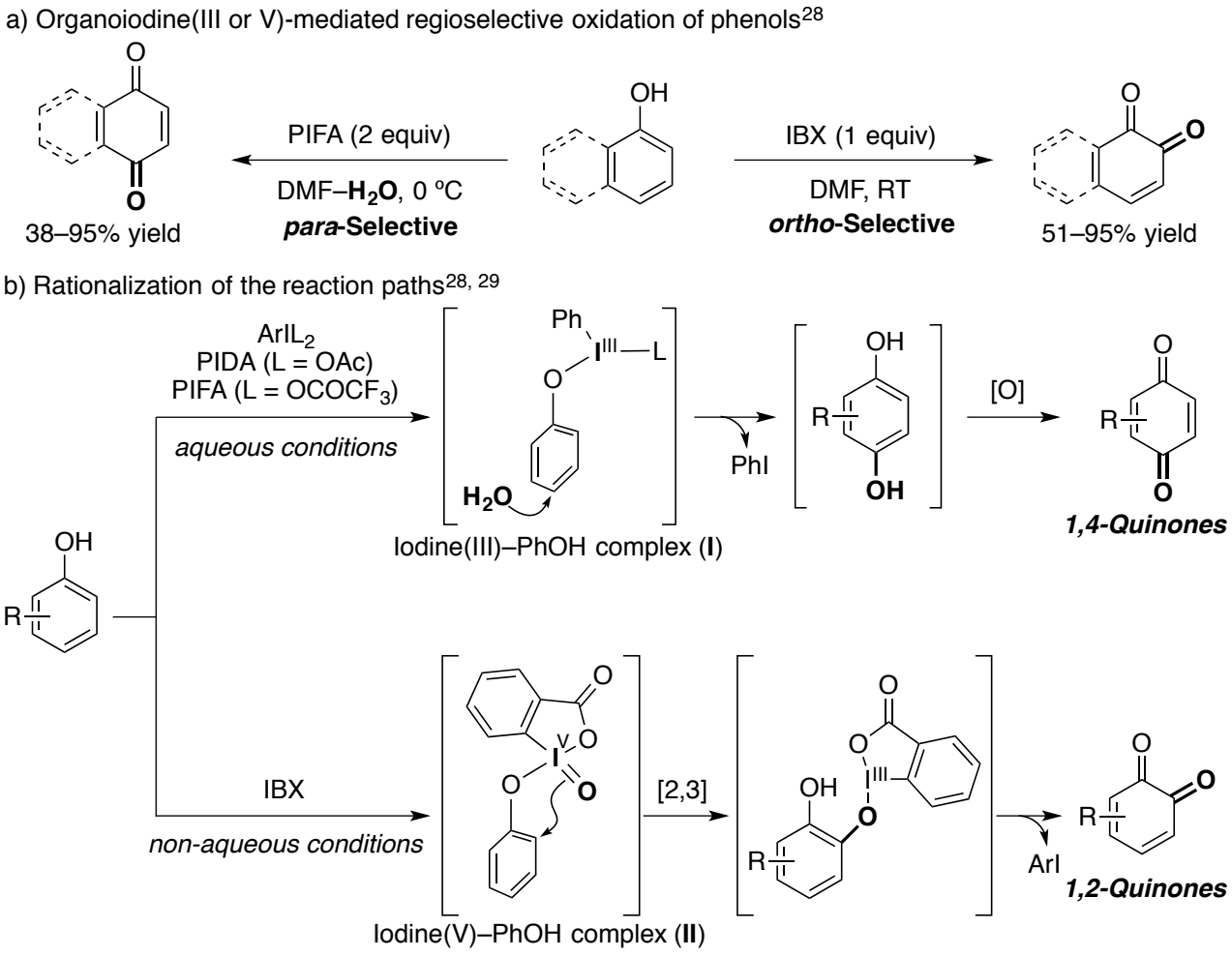
oxidants such as Fremy's radical,[18] $MeReO_3$,[19] dimethyldioxirane[20] and bisbenzeneselenic acid anhydrate[21] afforded *para*-quinones unless this was blocked by a substituent. However, less is known about the *ortho*-selective oxidation of phenols to *ortho*-quinone.[22]

In 2002, Pettus's group reported the first *ortho*-selective oxidation of phenols to 1,2-quinones using a stoichiometric amount of IBX as an oxidant (*Scheme 10*).[23] The corresponding 1,2-quinones or their catechol derivatives could be obtained in high yield. After Pettus' findings, IBX oxidation has been applied to the synthesis of various biologically important compounds such as catecholestrogen,[24] catecholamine,[25] hydroxytyrosol,[26] flavonoid[27] derivatives, and so on.

Scheme 10. IBX-Mediated *ortho*-Selective Oxidation of Phenols to 1,2-Quinones[23]



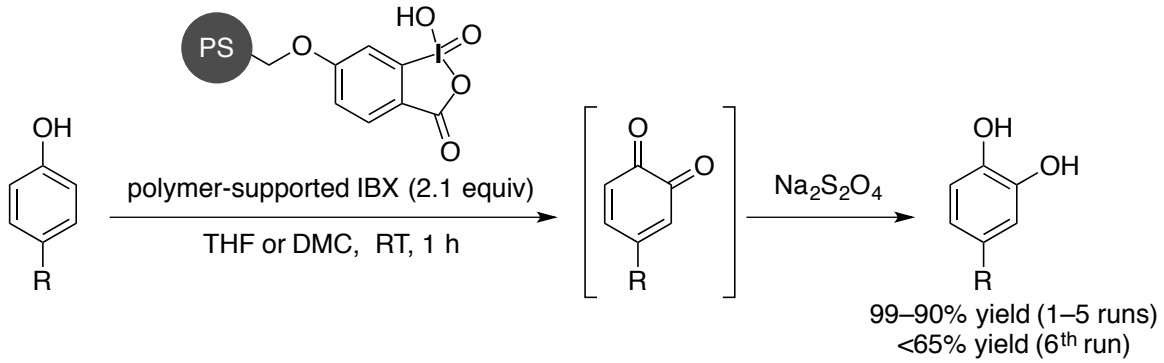
Scheme 11. Hypervalent Iodine(III or V)-Mediated Oxidation of Phenols[30]



Harvey and colleagues reported the hypervalent organoiodine(III or V)-mediated regioselective oxidation of polycyclic aromatic phenols to the corresponding *ortho*- or *para*-quinones (*Scheme 11a*).[28] Oxidation with an iodine(III) such as PIDA or PIFA under aqueous conditions afforded the corresponding 1,4-quinones through the nucleophilic addition of water to the iodine(III)–phenol intermediate **I** (*Scheme 11b*).[28,29] In contrast, oxidation with IBX as an iodine(V) oxidant under non-aqueous conditions afforded the corresponding 1,2-quinones *via* [2,3]-sigmatropic rearrangement from an iodine(V)–phenol intermediate **II** (*Scheme 11b*).[28,29] However, in general, both oxidation methods required a stoichiometric amount of hypervalent iodine compound as an oxidant.

In 2009, Bernini's group reported the *ortho*-selective oxidation of phenols by using polystyrene (PS)-supported IBX (*Scheme 12*).[30] The corresponding catechols were obtained in high yields *via* 1,2-quinones followed by reduction with $Na_2S_2O_4$. Although PS-supported IBX was reusable, re-oxidization to iodine(V) was still required, and the reactivity of the reagent gradually degraded.

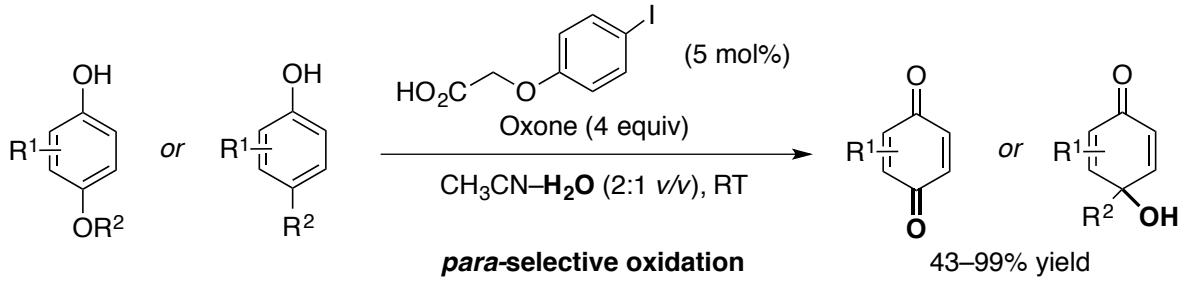
Scheme 12. Polymer-Supported IBX-Mediated *ortho*-Selective Oxidation of Phenols[30]



After Ochiai's,[31a] Kita's,[31b] and Vinod's[10] independent seminal contributions to hypervalent iodine(III and V) catalysis, the organoiodine-catalyzed oxidation of phenols to quinones was developed. In 2010, Yakura and colleagues reported the *para*-selective oxidation of 1,4-hydroquinones or 4-substituted phenols to the corresponding 1,4-quinones or 1,4-quinols, respectively, by using a catalytic amount of 4-iodophenoxyacetic acid with Oxone under aqueous acetonitrile conditions (*Scheme 13*).[32] *In situ*-generated iodine(III) species might be the actual catalytic species. However, before our studies, the hypervalent organoiodine(V)-catalyzed *ortho*-selective oxidation of phenols to 1,2-quinones had not yet been reported. This might be attributed to the fact that, while the previously developed organoiodine(V)/Oxone catalysis required aqueous conditions to dissolve Oxone, *ortho*- and *para*-oxidations might be competing reactions in

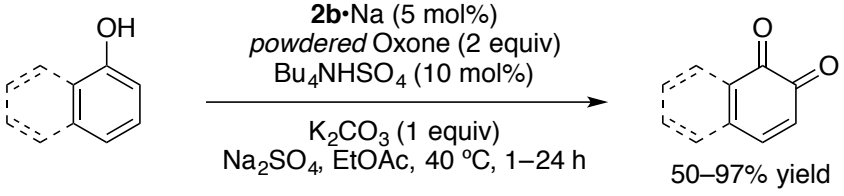
the presence of water (*Scheme 11b*). In contrast, we previously found that an IBS/Oxone system provided efficient catalytic activity under nonaqueous conditions.[12] Therefore, we envisioned that the catalytic *ortho*-selective oxidation of phenols could be achieved with the use of IBS catalysis.

Scheme 13. Hypervalent Iodine(III)-Catalyzed *para*-Selective Oxidation of Phenols[32]



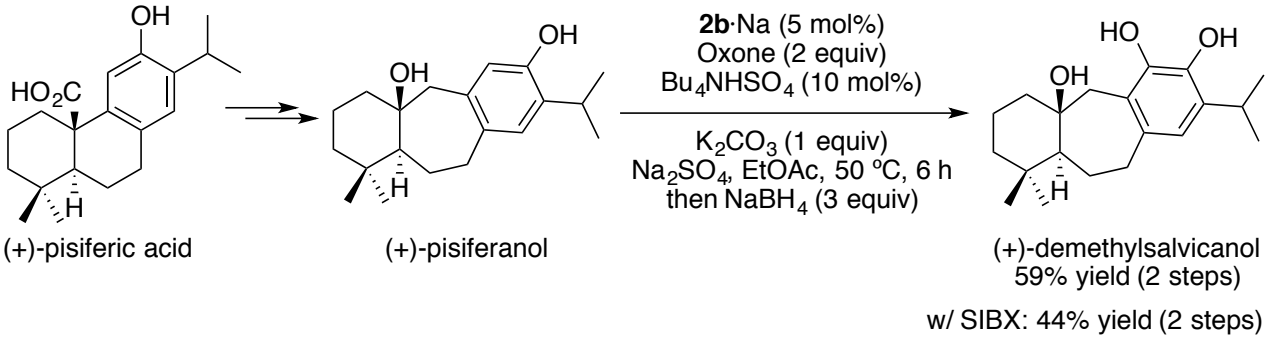
Chapter 2 describes the first example of the hypervalent organoiodine(V)-catalyzed *ortho*-selective oxidation of phenols (*Scheme 14*).[33] Various *ortho*-unsubstituted phenols, naphthols and phenanthrols could be oxidized to the corresponding 1,2-quinones in good to excellent yields using catalytic amounts of sodium 2-iodo-5-methylbenzenesulfonate (*pre*-5-Me-IBS, **2b**·Na) and stoichiometric amounts of Oxone as an oxidant under mild reaction conditions. In the oxidations of aliphatic alcohols, high temperatures (60–70 °C) were used.[12] In contrast, lower temperatures (40 °C) were required for the oxidation of phenols to suppress over-oxidation and other side-reactions. Importantly, the reaction rate of the oxidation under these mild and nonaqueous conditions was further accelerated in the presence of a phase transfer catalyst such as tetrabutylammonium hydrogen sulfate, an inorganic base such as potassium carbonate, and a dehydrating agent such as sodium sulfate. Notably, the use of 2-iodobenzoic acid (*pre*-IBX) as a precatalyst instead of *pre*-IBSes was unsuccessful under these nonaqueous mild conditions. Moreover, 1,4-quinones were obtained as major products under aqueous conditions, which indicated that nonaqueous conditions were essential for the preparation of 1,2-quinones in high yields.

Scheme 14. 5-Me-IBS-catalyzed *ortho*-selective oxidation of phenols to 1,2-quinones



Our *ortho*-selective catalytic oxidation protocol has been applied to ~~the~~ natural product synthesis. Matsushita and colleagues reported the efficient synthesis of a diterpenoid *ortho*-hydroquinone, (+)-demethylsalvicanol, from (+)-pisiferic acid via the 5-Me-IBS-catalyzed *ortho*-oxidation of (+)-pisiferanol (*Scheme 15*).[34] Notably, a lower chemical yield was observed with the use of stabilized IBX (SIBX)[29] as a stoichiometric oxidant.

Scheme 15. IBS-catalyzed *ortho*-Selective Phenol Oxidation to Natural Product Synthesis[34]



1-4. 4,5-Me$_2$-IBS-Catalyzed Highly Site-Selective Oxidation of 2-Substituted Phenols to 1,2-Quinols (Chapter 3)

As 1,2-quinones, 1,2-quinols and their [4+2]-cyclodimers are highly important synthons for the synthesis of natural products and biologically active compounds.[35] These compounds also constitute the main structural elements of many natural products such as wasabidienones, humulone, microstegiol, danshenol A, lacinilenes, biscarvacrol, grandifloracin, aquaticol, bacchopetiolone, chamaecypanone C, and so on (*Figure 3*).[35,36] Recently, the *in situ*-generated organoiodine(III or V)-catalyzed regioselective oxidations of phenols to 1,4-benzoquinols,[32] 1,4-benzoquinones,[32] and 1,2-benzoquinones[33] have been developed (*vide supra*). However, the catalytic *ortho*-selective hydroxylative dearomatization of 2-substituted phenols to 1,2-benzoquinols has not yet been achieved. *Chapter 3* describes the first organoiodine(V)-catalyzed oxidation to 1,2-benzoquinols with high site-selectivity.

Conventionally, IBX has been used as a stoichiometric oxidant for the *ortho*-selective hydroxylative dearomatization of 2-substituted phenols to 1,2-benzoquinols.[37,38] In 2002, Pettus and colleagues reported the first example of the IBX-mediated oxidation of 2-susbtituted phenols (*Scheme 16a*).[23] They examined only the oxidation of 2,6-xylenol, and a reductive process was required to release 2-iodobenzoic acid from the IBA diester of cyclodimer. Later, Quideau and colleagues developed a general procedure for the *ortho*-selective oxidation of 2-substituted phenols and naphthols using a stoichiometric amount of SIBX (*Scheme 16b*).[37a] The oxidation of phenols

followed by the acid-mediated release of iodine(III) species from the initially formed IBA diester of cyclodimer afforded the corresponding cyclodimers, whereas the oxidation of naphthols afforded the corresponding *ortho*-naphthoquinols directly *via* the *in situ* hydrolysis of iodine(III) species. This oxidation procedure was then applied to the synthesis of several natural products.[37] However, due to its low reactivity, the substrate scope was limited to electron-donating group-substituted highly reactive phenols and long reaction times were required (1–7 days). Additionally, no site-selectivity was observed for the oxidation of unsymmetrically 2-substituted phenols: the maximum possible yield of the 1,2-benzoquinol-derived cyclodimers is reported to be 50%.[37,38]

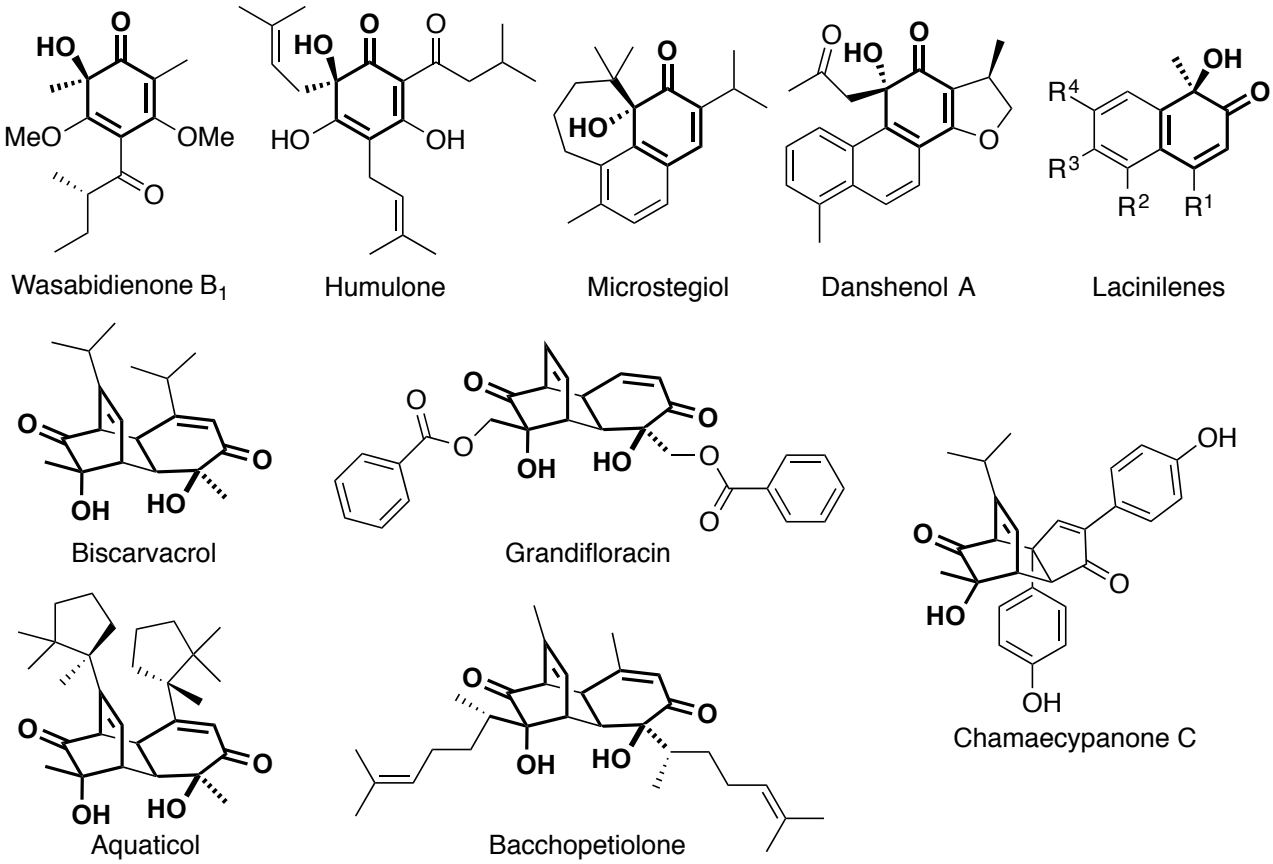
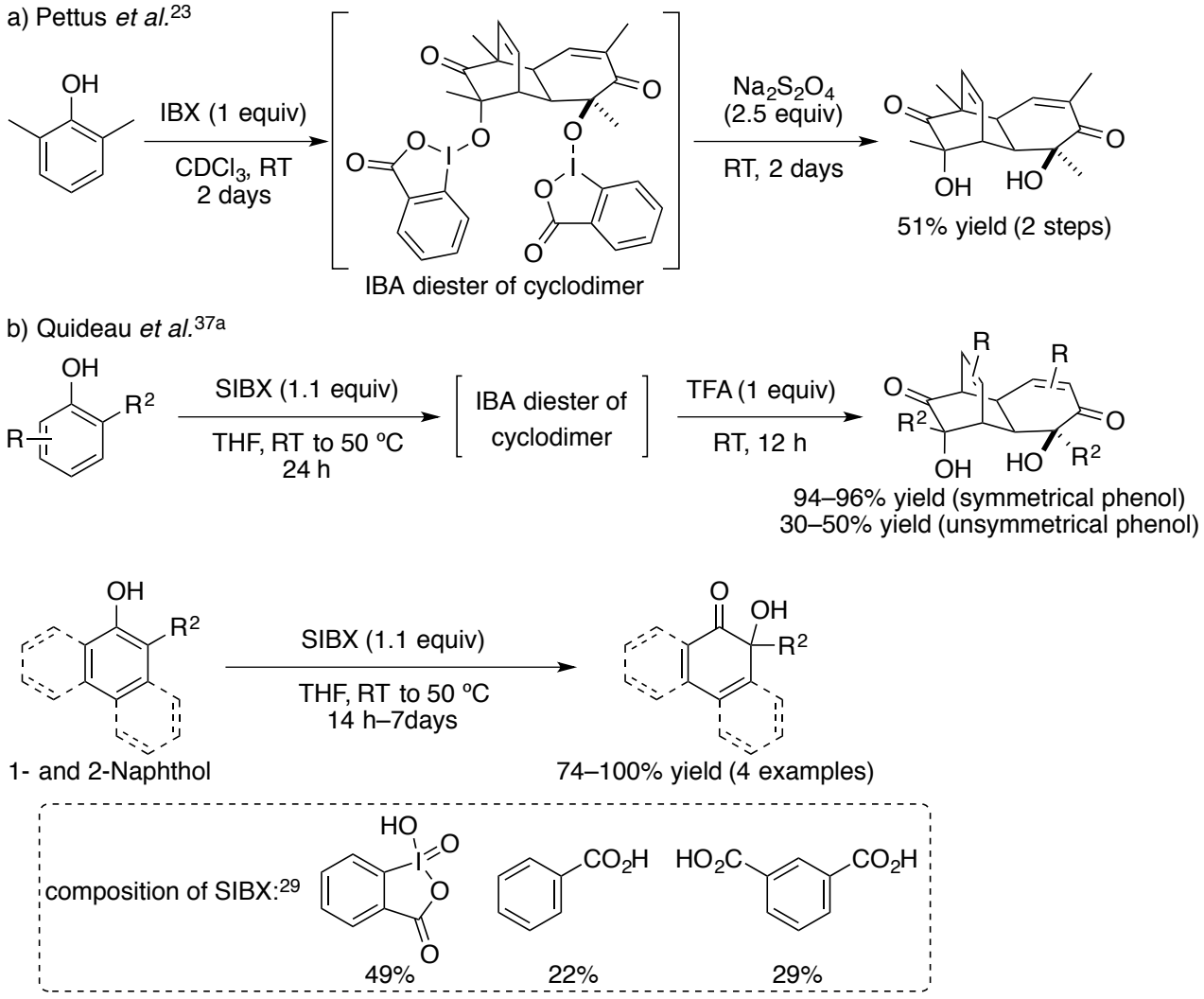


Figure 3. Natural products including 1,2-quinols, their cyclodimers and derivatives.[36]

The proposed reaction mechanism for the organoiodine(V)-mediated oxidation of phenols is summarized in *Figure 4*. IBX reversibly combines with phenols to give iodine(V)-phenol complex **4a**, which serves to transfer oxygen from an iodoxy (I^V=O) to either the 2- or 6-position *via* concerted intramolecular [2,3]-sigmatropic rearrangement.[29] During this process, the competition between electronic and steric factors might lead to nonselective oxidation. Oxygen transfer at the substituted 2-position affords the 1,2-benzoquinol–iodine(III) ester **5a**, which then readily undergoes cyclodimerization to give **6a**. 1,2-Benzoquinols **8** or cyclodimers **9** are then

obtained after hydrolysis. On the other hand, a reaction at the nonsubstituted 6-position affords catechol–iodine(III) monoester **7a**, after rapid aromatizing keto/enol tautomerization. Undesired 1,2-benzoquinones **10** are then obtained *via* the *in situ* reduction of iodine(III) to iodine(I). Importantly, reductive or strong-acidic work-up is required to release iodine(III), 2-iodosobenzoic acid, from **5a** or **6a** (*Scheme 16*).[23,37a] Due to this necessity, the catalytic use of IBX for 1,2-benzoquinols would be difficult. To overcome these issues, we introduced IBS catalysis for the site-selective hydroxylative dearomatization of phenols. Since the iodine(V) atom of IBS is more Lewis-acidic than that of IBX, we envisioned that a larger partial positive charge (δ^+) would be generated for the IBS–phenol complex **4b**. This might lead to a high reactivity and preferential oxygen transfer at a substituted 2-position of unsymmetrical phenols. Moreover, due to its strong electron-withdrawing sulfo group, iodine(III) species would be readily released *in situ* from quinol (**5b**) or cyclodimer (**6b**), which would make the catalytic use of IBS possible.

Scheme 16. IBX-Mediated *ortho*-Selective Oxidation of 2-Substituted Phenols to 1,2-Quinols[23,37a]



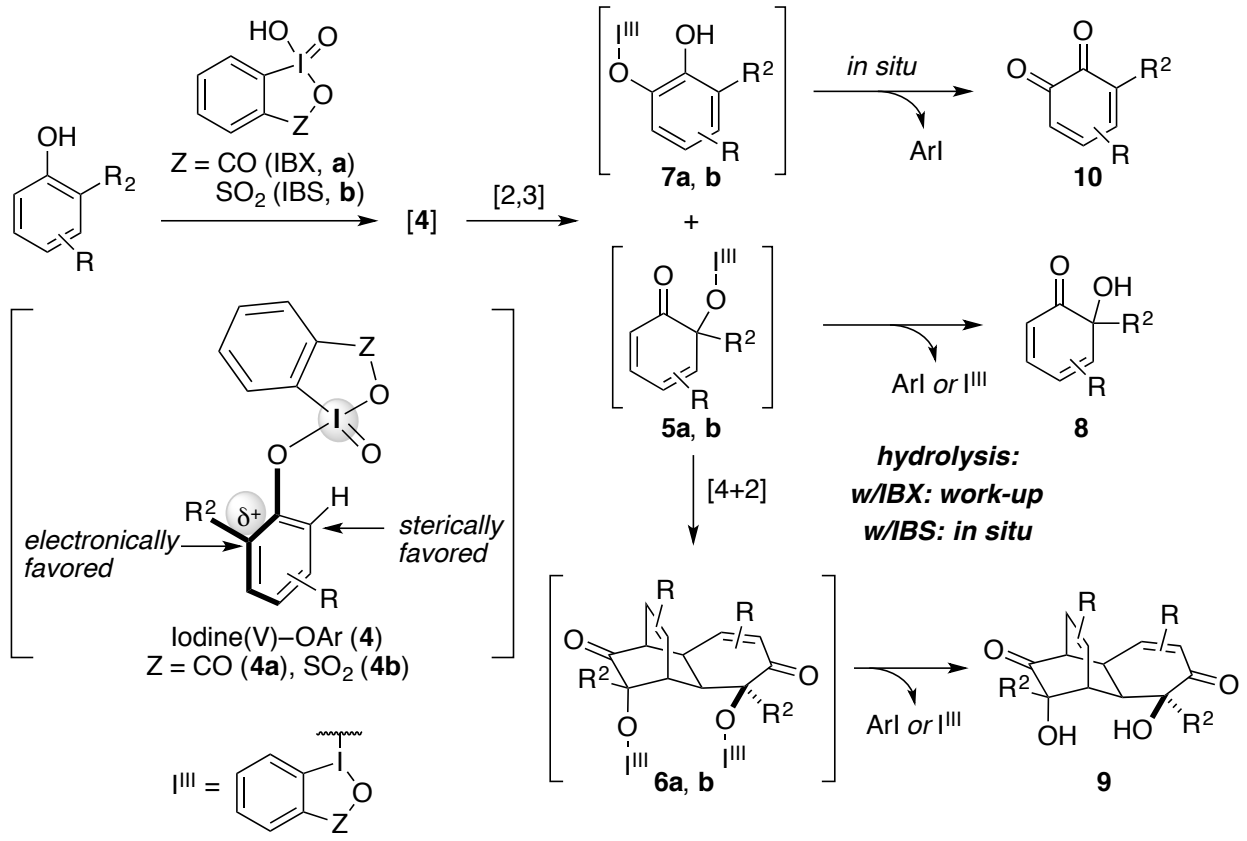
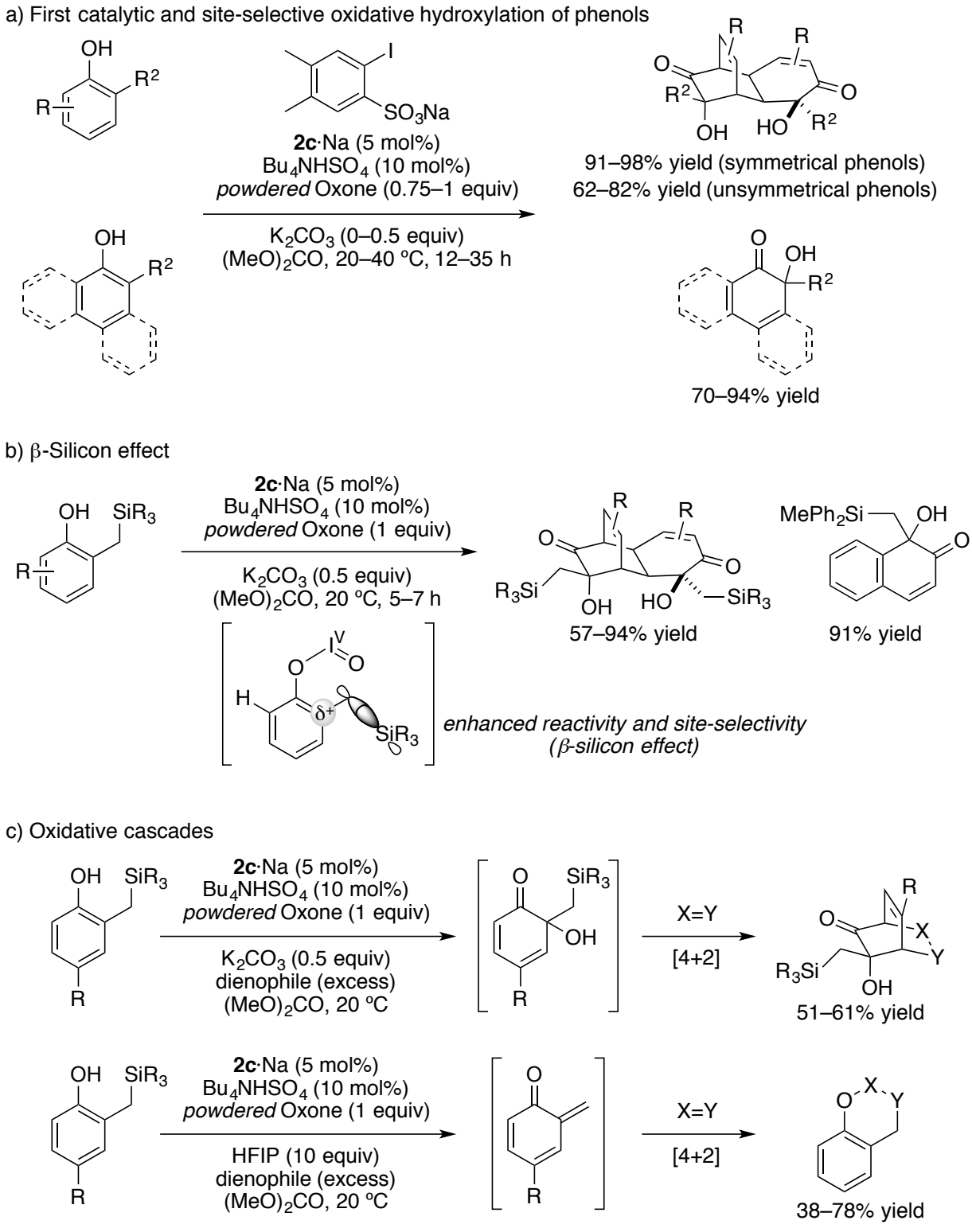


Figure 4. Proposed reaction mechanism for the organoiodine(V)-mediated oxidation of phenols.

Chapter 3 describes the first example of the catalytic and site-selective hydroxylative dearomatization of 2-substituted phenols to the corresponding 1,2-quinols or their cyclodimers.[39] We achieved the site-selective oxidation of 2-substituted unsymmetrical phenols to 1,2-quinols in the presence of a catalytic amount of *pre*-4,5-Me_2-IBS (**2c**·Na) with Oxone as an oxidant (*Scheme 17a*).[39] The corresponding 1,2-quinols or their [4+2]-cyclodimers including natural products such as biscarvacrol and lacinilene C methyl ether (LCME) could be obtained in high yields. Importantly, the reaction rate and chemoselectivity were significantly improved with the use of 4,5-Me_2IBS (**1c**) and potassium carbonate to buffer Oxone under milder conditions. Compared to even stoichiometric oxidations with IBX,[23,37,38] the present IBS-catalyzed oxidation with Oxone extended the substrate scope. To further stabilize the partial positive charge that developed at an alkylated 2-position, we introduced a trialkylsilylmethyl substituent at the 2-position of phenols. As a result, the reaction rate and both the site-selectivity and chemoselectivity were significantly improved by a β-silicon effect (*Scheme 17b*).[40] The corresponding silyl-substituted 1,2-quinols or their [4+2]-cyclodimers could be transformed to various useful structural motifs *via* cascade [4+2]-cycloaddition reactions (*Scheme 17c*).[39]

Scheme 17. 4,5-Me_2-IBS-Catalyzed Highly Site-Selective Oxidation to 1,2-Quinols[39]



1.5. Conclusion

In summary, we have developed the first hypervalent organoiodine(V)-catalyzed regio- and site-selective oxidation of phenols. 2-Iodoxybenzenesulfonic acids (IBSes), which were generated

in situ from 2-iodobenzenesulfonic acids with Oxone, successfully catalyzed these reactions under mild nonaqueous conditions. 2-Unsubstituted phenols could be converted to the corresponding 1,2-quinones with high regioselectivity. Symmetrical or unsymmetrical 2-substituted phenols could be converted to the corresponding 1,2-quinols or their cyclodimers with excellent regio- and/or site-selectivities. Several natural compounds such as biscarvacrol and lacinilene C methyl ether could be synthesized in high yield under mild reaction conditions. Compared to even stoichiometric oxidations with IBX, the present IBS-catalyzed oxidation with Oxone extended the substrate scope for the synthesis of both 1,2-quinone and 1,2-quinols. Importantly, the oxidation reaction rate could be improved with the use of "*buffered* Oxone", which was prepared by *pre*-mixing Oxone with potassium carbonate. Moreover, both the reaction rate and site-selectivity to 1,2-quinols could be improved by the introduction of a trialkylsilylmethyl substituent at the *ortho*-position of phenols. By taking advantage of the silicon effect, we achieved unprecedented oxidative [4+2]-cycloaddition cascade reactions to give various useful structural motifs.

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Chapter 2

5-Me-IBS-Catalyzed Regioselective Oxidation of Phenols to 1,2-Quinones

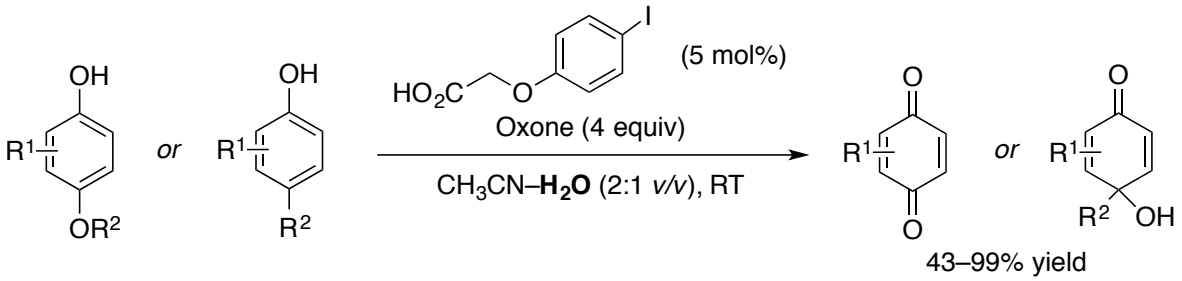
Abstract: We have developed the first example of hypervalent iodine(V)-catalyzed regioselective oxidation of phenols to 1,2-quinones. The reaction rate of IBS-catalyzed oxidation under nonaqueous conditions was further accelerated in the presence of an inorganic base such as potassium carbonate, a phase transfer catalyst such as tetrabutylammonium hydrogen sulfate, and a dehydrating agent such as anhydrous sodium sulfate.

Introduction

1,2-Quinones are useful synthetic intermediates for the synthesis of medicinally and biologically important compounds.[1] To date, numerous methods have been developed for the preparation of quinones by the oxidation of phenols or their derivatives.[2] For example, the oxidation of phenols with Fremy's radical,[3] $MeReO_3$,[4] dimethyldioxirane,[5] or benzeneseleninic anhydride[6] mostly gives 1,4-quinones, unless blocked by a substituent. However, there have been only a few studies on the direct conversion of a phenol into 1,2-quinones. In 2002, Pettus and colleagues reported the regioselective oxidation of phenols with stoichiometric amounts of 2-iodoxybenzoic acid (IBX) to the 1,2-quinones.[7] After Pettus' pioneering findings, this method was applied to the synthesis of biologically active compounds such as acatecholestrogen,[8] catecholamine,[9] hydroxytyrosol,[10] and flavonoid[11] derivatives. In 2010, Harvey and colleagues reported the regiospecific oxidation of polycyclic aromatic phenols to quinones using hypervalent iodine(III and V) reagents.[12] Accordingly, oxidation with IBX in non-aqueous DMF gives 1,2-quinones, while oxidation with bis(trifluoro-acetoxy)iodobenzene (PIFA) in aqueous DMF gives 1,4-quinones selectively.

Recently, the hypervalent organoiodine(III or V)-catalyzed oxidation reactions by using a suitable co-oxidant have also been extensively investigated.[13] From 2007 to 2009, Yakura and colleagues reported the *para*-selective oxidation of 4-alkoxyphenols or 4-arylphenols to the corresponding 1,4-quinones or 1,4-quinols, respectively, in excellent yields by using catalytic amounts of 4-iodophenoxyacetic acid with Oxone ($KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) as a co-oxidant in aqueous acetonitrile (*Scheme 1*).[14] To the best our knowledge, however, there are no successful examples of a catalytic hypervalent iodine system for the *ortho*-selective oxidation of phenols to 1,2-quinones.

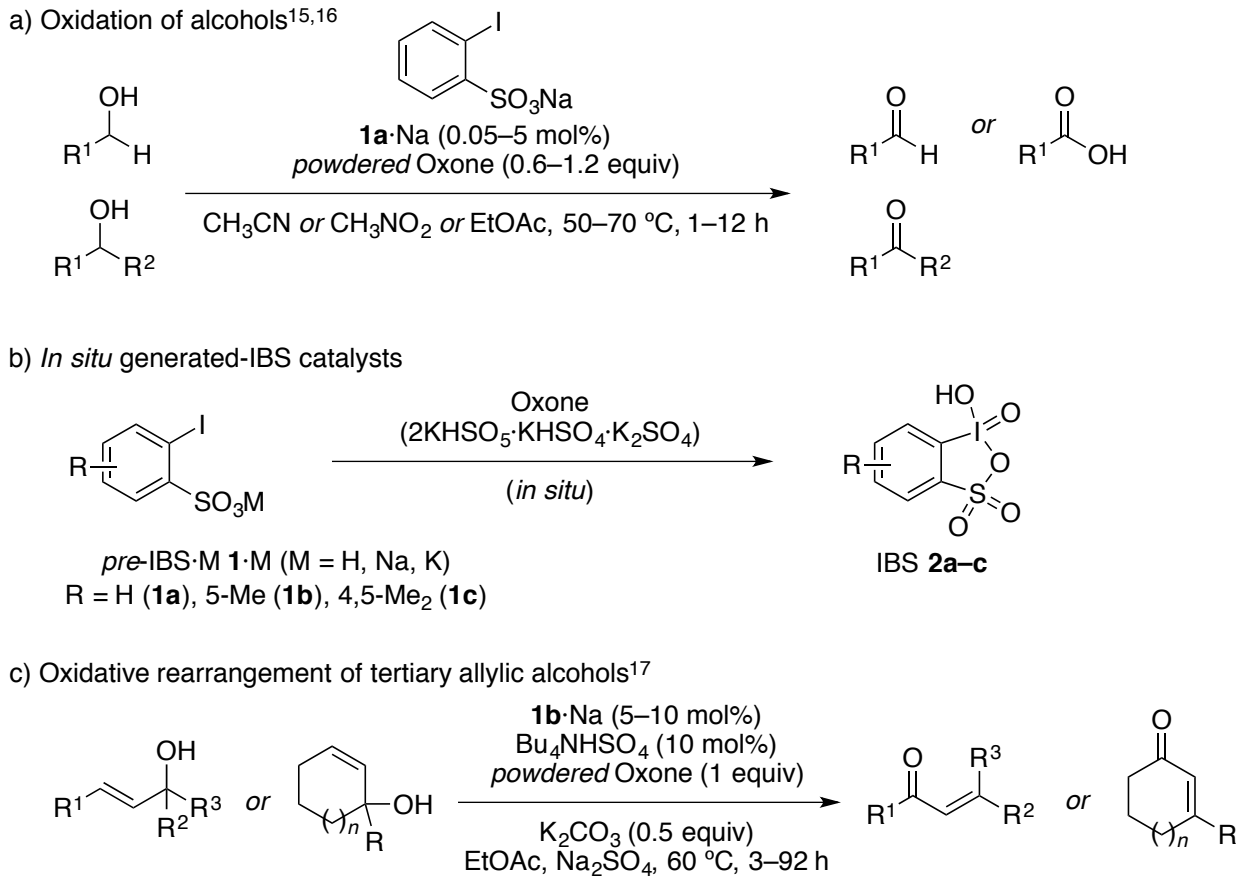
Scheme 1. Hypervalent Iodine-Catalyzed *para*-Selective Oxidation of Phenols[14]



We recently reported a highly efficient and chemoselective oxidation of various alcohols to carbonyl compounds such as aldehydes, carboxylic acids, and ketones with *powdered* Oxone in the

presence of catalytic amounts (1–5 mol%) of 2-iodobenzenesulfonic acids (*pre*-IBSes, **1**) or their sodium salts (**1**·Na) under nonaqueous conditions (*Scheme 2a*).[15,16] 2-Iodoxybenzenesulfonic acids (IBSes) **2** as organoiodine(V), which are generated *in situ* from **1** and Oxone, serve as the actual catalysts for the oxidations (*Scheme 2b*).[15,16]

Scheme 2. 2-Iodobenezenesulfonic Acid (IBS) Catalysis[15–17]



According to theoretical calculations,[15] the relatively ionic character of the intramolecular hypervalent I(V)-OSO_2 bond of IBS **2a** lowers the twisting barrier of the alkoxyperiodinane intermediate. In fact, **2** shows much more catalytic activity than IBX.[15] The oxidation rate in **2a**-catalyzed oxidation under nonaqueous conditions is further accelerated by the use of *powdered* Oxone due to its increased surface area. When Oxone is used under nonaqueous conditions, wastes derived from Oxone can be removed by simple filtration. Furthermore, we developed the oxidative rearrangement of tertiary allylic alcohols to β-disubstituted α,β-unsaturated ketones with Oxone catalyzed by *in situ*-generated 5-Me-IBS (**2b**) (*Scheme 2c*).[17] The addition of inorganic bases such as potassium carbonate, and a phase transfer catalyst such as tetrabutylammonium hydrogen sulfate (Bu_4NHSO_4), extended the substrate scope for oxidative rearrangement reactions.

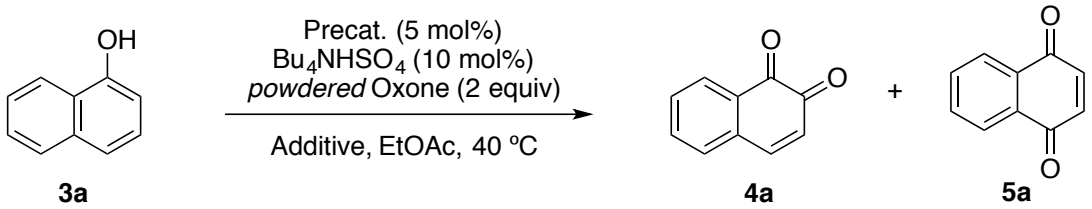
Recently, the IBS/Oxone catalytic oxidation system was applied to benzylic oxidation[18] and oxidation of fluorinated alcohols.[19] As part of our continuing interest in the IBS-catalyzed oxidation system, we report here the *in situ*-generated IBS-catalyzed regioselective oxidation of phenols to 1,2-quinones with Oxone.[20]

Results and Discussion

Initially, we investigated the reactivity and regioselectivity of the oxidation of 1-naphthol (**3a**) using conventional hypervalent catalysts under non-aqueous conditions (*Table 1*). A mixture of **3a**, *powdered* Oxone (2 equiv) and Bu_4NHSO_4 (10 mol%), as a solid-liquid phase transfer catalyst, was heated in ethyl acetate at 40 ºC in the presence of 5 mol% of iodobenzene or Yakura's *pre*-catalyst (4-iodophenoxyacetic acid, **6**) (entries 2 and 3).[14] However only trace amounts of desired product was detected, and more than 80% of **3a** was recovered with small amount of unidentified side-products. Additionally, the use of *pre*-IBX (**7**) gave both 1,2-naphthoquinone (**4a**) and 1,4-naphthoquinone (**5a**) each in 5% yield, and 80% of **3a** was recovered (entry 4). Although **3a** was completely consumed fully and chemical yields of both **4a** and **5a** were increased under harsh reaction conditions (CH_3CN, 70 °C) that was used for the oxidation of alcohols,[15] various unidentified side-product were also obtained. (entry 5). In sharp contrast, and to our delight, when *pre*-IBS (**1a**·Na) was used under mild conditions, **3a** was completely consumed in 11 h, and quinones **4a** and **5a** were obtained in respective yields of 64% and 5% together with highly polar compounds (entry 6). As expected from our previous work,[15,17] the use of *pre*-5-Me-IBS (**1b**·Na) or *pre*-4,5-Me_2-IBS (**1c**·Na) gave slightly better results, and the former gave the best results (entries 7 and 8). Interestingly, when the oxidation was conducted in aqueous acetonitrile, **5a** was obtained selectively as a major product in 51% yield (entry 9). We found that the carbon(1)-carbon(2) bond of 1,2-quinone (**4a**) was oxidatively cleaved under identical aqueous conditions to highly polar compounds including *trans*-2-carboxycinnamic acid (**8**)[21] and other minor unidentified compounds (*Scheme 3*). These results indicated that non-aqueous conditions were essential for the preparation of 1,2-quinones in high yields. According to our previous works, the selective oxidation of acid-sensitive alcohols could be achieved in the presence of anhydrous sodium sulfate as a dehydrating agent.[15,17] Additionally the oxidation rate and selectivity could be further accelerated with the use of additional base to buffer the acidity of the reaction mixture.[17] Based on these previous findings, the reaction of **3a** was carried out in the presence of 1 equivalent of potassium carbonate and anhydrous sodium sulfate under the modified conditions in entry 6. Thus, **4a** was obtained in 78% yield after 1 h, when Oxone and K_2CO_3 were sufficiently premixed in the presence of anhydrous Na_2SO_4 in ethyl acetate at room temperature for 24 h before the

addition of **2b**, **3a**, and Bu_4NHSO_4 (entry 10). Notably, the use of Bu_4NHSO_4 was essential for the present oxidation, since almost no reaction occurred in its absence (entry 11).

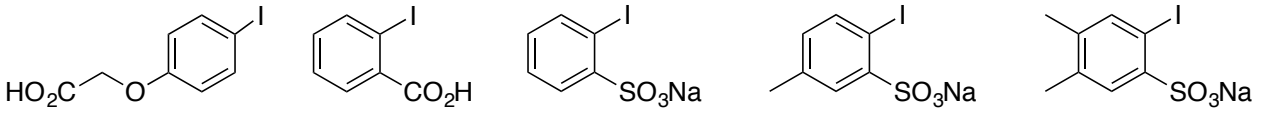
Table 1. Optimization of Reaction Conditions



3a **4a** **5a**

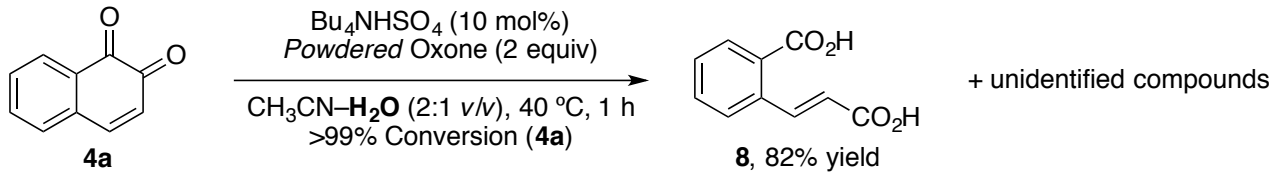
Entry	Precat.	Additive (equiv)	Time (h)	**4a**, Yield (%)[a]	**5a**, Yield (%)[a]
1	–	–	24	<1	<1
2	PhI	–	24	<1	<1
3	**6**	–	24	<1	<1
4	**7**	–	24	5	5
5[b]	**7**	–	24	16	10
6	**1a**·Na	–	11	64[c]	5[c]
7	**1b**·Na	–	8	69[c]	6
8	**1c**·Na	–	9	67[c]	6
9[d]	**1b**·Na	–	3.5	<1	51
10[e]	**1b**·Na	K_2CO_3 (1)	1	78[c]	*6*[c]
11[f]	**1b**·Na	K_2CO_3 (1)	24	<1	<1

[a] ^{1}H NMR analysis. [b] The reaction was performed in CH_3CN at 70 °C. [c] Isolated yield. [d] The reaction was performed in CH_3CN–H_2O (2:1, *v*/*v*) instead of EtOAc. [e] After a mixture of Oxone and K_2CO_3 in ethyl acetate was vigorously stirred in the presence of Na_2SO_4 for 24 h at room temperature, **1a**·Na, **3a** and Bu_4NHSO_4 were added. [f] In the absence of Bu_4NHSO_4.



Yakura's Precat. (**6**) *pre*-IBX (**7**) *pre*-IBS (**1a**•Na) *pre*-Me-IBS (**1b**•Na) *pre*-Me$_2$-IBS (**1c**•Na)

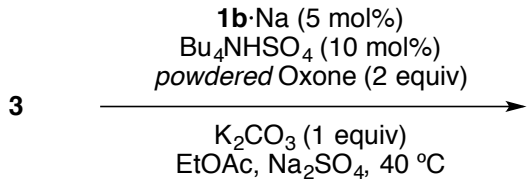
Scheme 3. Oxidative Carbon-Carbon Bond Cleavage of **4a** to **8** under Aqueous Conditions

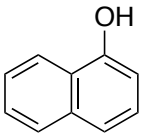
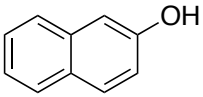
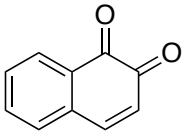
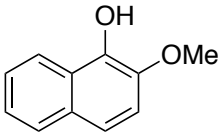
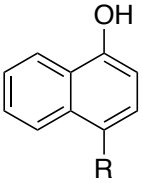
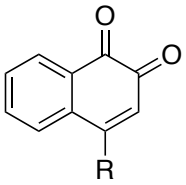
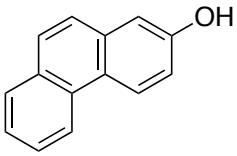
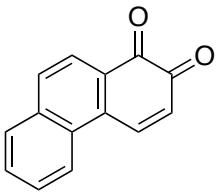
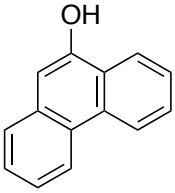
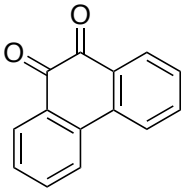
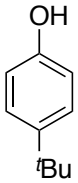
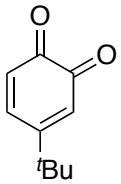
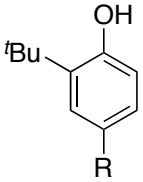
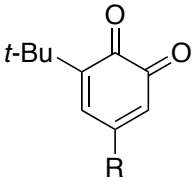


4a **8**, 82% yield

To explore the generality of the *in situ*-generated 5-Me-IBS-catalzed oxidation of phenols with Oxone, various naphthols, phenanthrols, and phenols (**3b–l**) were examined as substrates under the optimized conditions: *powdered* Oxone (2 equiv) and potassium carbonate (1 equiv) in ethyl acetate were vigorously stirred at room temperature for 24 h in the presence of anhydrous sodium sulfate,

Table 2. 5-Me-IBS-Catalyzed Oxidation of Naphthols, Phenanthrols and Phenols **3**[a]

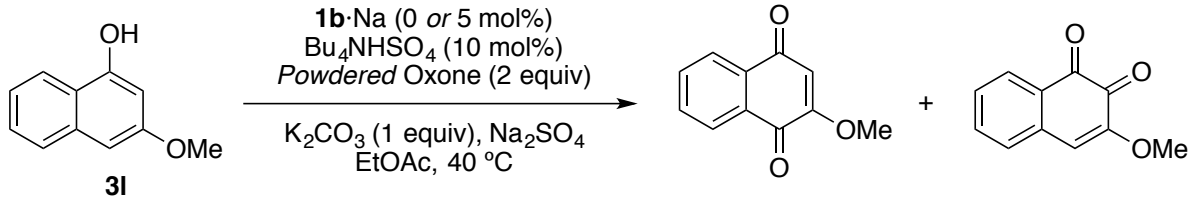


Entry	Substrate	**3**	Product	**4**	Time (h)	Yield (%)[b]
1		**3a**		**4a**	1	78
2		**3b**		**4a**	4	84
3		**3f**		**4a**	2	72
4		**3c** (R = Cl)		**4c**	5	80
5		**3d** (R = Br)		**4d**	3	75
6		**3e** (R = OMe)		**4e**	2	50[c]
7		**3g**		**4g**	2	90
8		**3h**		**4h**	2	97
9		**3i**		**4i**	5	63
10		**3j** (R = OMe)		**4j**	5	66[d]
11		**3k** (R = *t*-Bu)		**4k**	24	73

[a] Reaction conditions: **3** (1 mmol), *powdered* Oxone (2 mmol), K_2CO_3 (1 mmol), **1b**·Na (0.05 mmol), Bu_4NHSO_4 (0.1 mmol), Na_2SO_4 (1 g), EtOAc (10 mL), 40 °C. Oxone and K_2CO_3 were premixed in EtOAc for 24 h at room temperature in the presence of anhydrous Na_2SO_4. [b] Isolated yield. [c] 1,4-Naphthoquinone (**5a**) was obtained in 15% yield. [d] 2-*tert*-Butyl 1,4-quinone (**5j**) obtained in 16% yield.

and then **1b** (5 mol%), **3a** and Bu_4NHSO_4 (10 mol%) were added and the resulting mixture was heated to 40 ºC (*Table 2*). As expected, **4a** was obtained in slightly better yield by the oxidation of 2-naphthol **3b** than by the oxidation of **3a** (entries 1 and 2). 4-Bromo- or chloro-substituted 1-naphthols **3c** and **3d** gave the corresponding 1,2-quinones in high yields (entries 4 and 5). Notably, the desired 1,2-quinones were obtained as a major product under our catalytic conditions even with the oxidation of 4-methoxy-1-naphthol (**3e**) and 4-methoxyphenol (**3j**) (entries 6 and 10). In contrast, the previous iodine(III)-mediated oxidation of *para*-alkoxy phenols gave 1,4-quinones exclusively.[14] Additionally, the oxidation of phenanthrols (**3g**) and (**3h**) gave the desired 1,2-quinones in excellent yields (entries 7 and 8). These polycyclic aromatic quinones were obtained in only moderate yields by stoichiometric oxidations with IBX.[12] The oxidation of 2,4-di-*tert*-butylphenol (**3k**) gave desired 1,2-quinone (**4k**) in 73% yield after 24 h (entry 11). In contrast, the oxidation of 3-methoxy-1-naphthol (**3l**) gave 1,4-quinone (**5l**) rather than 1,2-quinone (**4l**) as a major product (*Scheme 4*). Additionally, the oxidation of **3l** with Oxone even in the absence of **1b** also gave **5l** selectively, but in lower yield after longer reaction time.

Scheme 4. Oxidation of 3-Methoxy-1-Naphthol **3l**



1b·Na (5 mol%), 3 h:	81% yield	<5%
1b·Na (0 mol%), 6 h:	63% yield	<5%

Based on previous studies[12,15–17] and present results, a proposed reaction mechanism is depicted in Figure 1. *In situ*-generated IBS (**2**) reversibly combines with **3** to give IBS-phenol complex **A**, which serves to transfer oxygen from an iodoxy group (I^V = O) to the *ortho*-site of the phenol through concerted intramolecular [2,3]-rearrangement. During this process, the iodine(V) atom is concurrently reduced to the iodine(III)-catechol complex **C**, which gives 1,2-quinones **4** and *pre*-IBS **1**. The catalytic cycle of IBS **2** can be accomplished by the regeneration of **2** through the successive oxidations **1** and **9** with tetrabutylammonium peroxymonosulfate, Bu_4NHSO_5, which can be generated *in situ* from $KHSO_5$ and Bu_4NHSO_4.

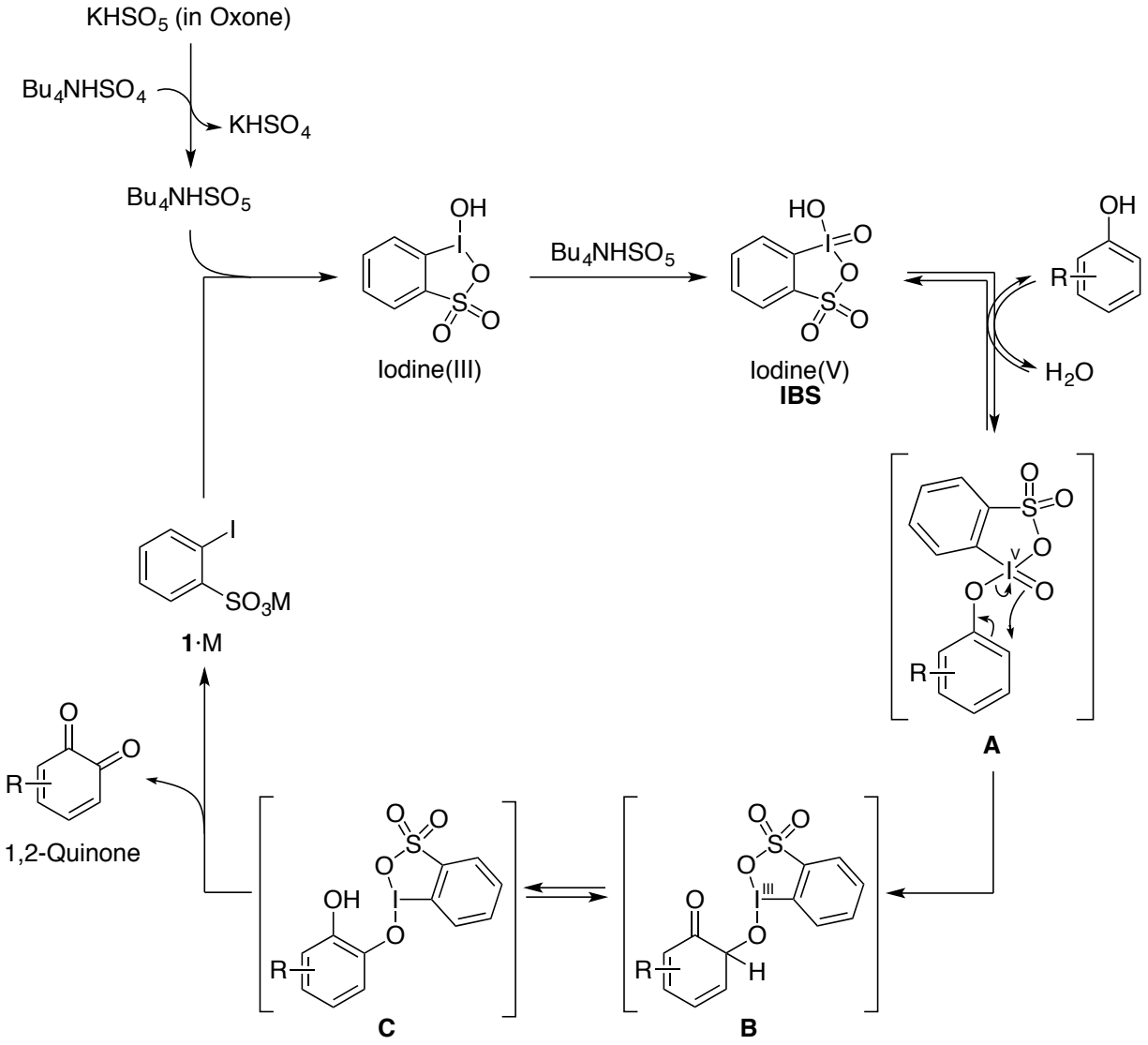


Figure 1. Possible mechanism for the IBS-catalyzed *ortho*-selective oxidation of phenols.

While, the reason for the *para*-selective oxidation of **3l** is not yet clear, a plausible mechanism is depicted in Figure 2. The peroxy-IBS complex **D** might be generated reversibly *in situ* from IBS and ammonium Oxone. Electrophilic aromatic oxidation at the highly nucleophilic carbon(4) position of **3l** with **D** gives **E**, which easily tatutomerizes to IBS-hydroquinone complex **F**. Finally, the oxidation of hydroquinone gives 1,4-quinone **5l** and iodine(III) **9**. Notably, **5l** was also obtained by the oxidation of **3l** with only Oxone (*Scheme 4*).[22] The reactivity of Oxone should be accelerated by complexation with IBS.[23] Thus, the oxidation was faster and the chemical yield of **5l** was higher in the presence of IBS (*Scheme 4*).

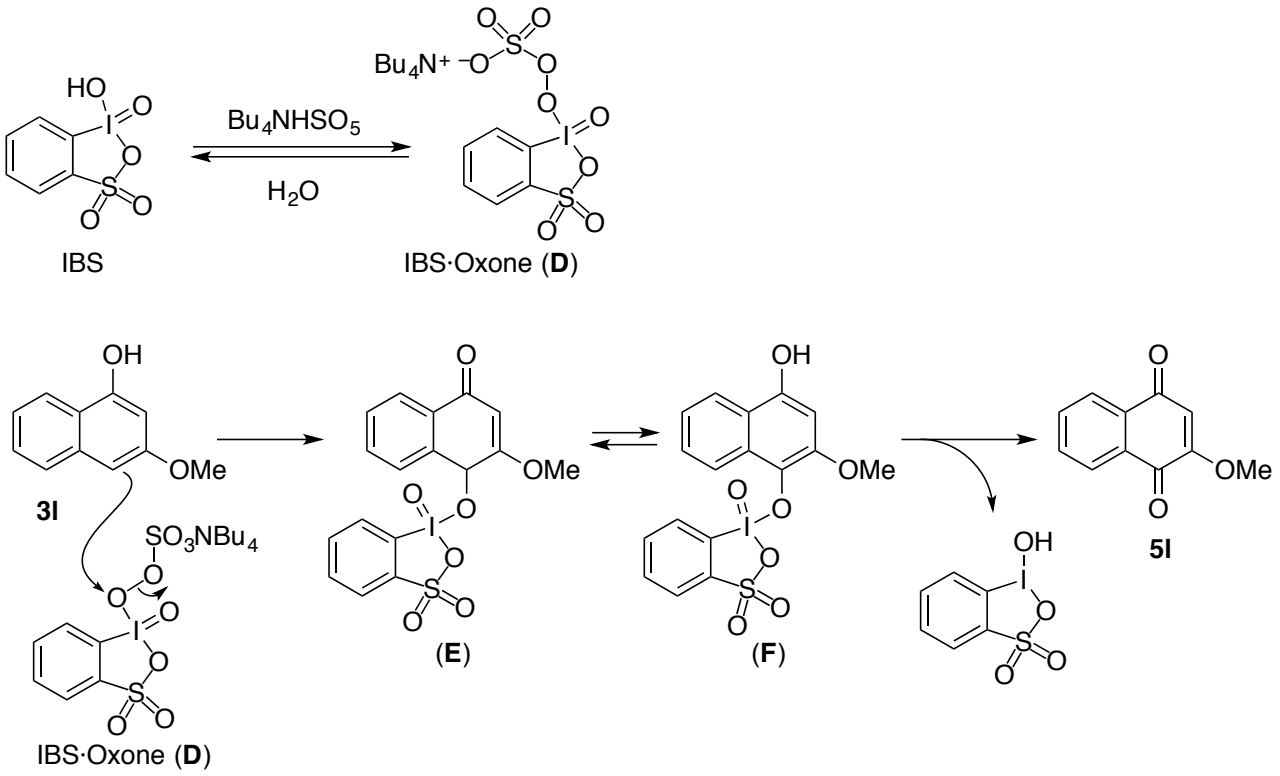


Figure 2. Possible mechanism for the *para*-selective oxidation of **3l**.

Conclusion

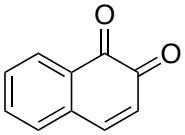
We have developed the first example of hypervalent iodine(V)-catalyzed *ortho*-selective oxidation of phenols to 1,2-quinones. Various phenols could be oxidized to the corresponding 1,2-quinones in good to excellent yields using catalytic amounts of sodium salts of 2-iodobenzenesulfonic acids (*pre*-IBSes) and stoichiometric amounts of Oxone as a co-oxidant under mild conditions. The reaction rate of IBS-catalyzed oxidation under nonaqueous conditions was further accelerated in the presence of an inorganic base such as potassium carbonate, a phase transfer catalyst such as tetrabutylammonium hydrogen sulfate, and a dehydrating agent such as anhydrous sodium sulfate.

Experimental Section

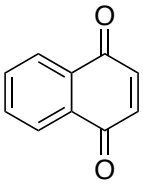
General methods: Infrared (IR) spectra were recorded on a JASCO FT/IR 460 plus spectrometer. ^{1}H NMR spectra were measured on a JEOL ECS-400 (400M MHz) spectrometer at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on a JEOL ECS-400 (100 MHz) spectrometers. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.00 ppm). For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254} 0.25 mm) were used. The products were purified by column chromatography on silica gel (E. Merck Art. 9385). High-resolution mass spectral analysis (HRMS) was performed at Chemical Instrument Center, Nagoya University. Pre-catalysts were prepared according to known procedures. Additionally, 1a and 1b (as potassium salts) are also commercially available from Junsei Chemical Japan, TCI and Sigma-Aldrich. Starting materials **3c**,[25] **3e**,[24] **3g**,[12] and **3l**[26] were prepared according to known procedures. In experiments that required solvents, ethyl acetate, acetonitrile and nitromethane were purchased from Wako Pure Chemical Industries, Ltd. in "anhydrous" form and used without any purification. Other simple chemicals were analytical-grade and obtained commercially.

General procedure for the oxidation phenol to quinone:

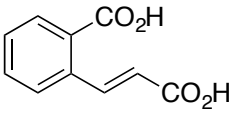
A mixture of *powdered* Oxone (1.2 g, 2.0 mmol), potassium carbonate (0.14 g, 1.0 mmol) and anhydrous sodium sulfate (1.0 g, dried by a heat-gun under *vacuum* before use), in ethyl acetate (4.0 mL) was vigorously stirred at room temperature for 24 h. To the resulting mixture were added **3** (1.0 mmol), *n*-Bu_4NHSO_4 (34 mg, 0.10 mmol), **1b** (17 mg, 0.050 mmol), and EtOAc (6.0 mL), and the resulting mixture was stirred vigorously at 40 ºC. The reaction was monitored by TLC analysis. After the reaction was completed, the reaction mixture was cooled to room temperature and the solids were filtered-off and washed with EtOAc. The filtrate was washed with water, and the aqueous layers were extracted with EtOAc. The combined organic layers were washed by water and brine, and dried over anhydrous Na_2SO_4. The solvents were removed under *vacuo*, and the residue was purified by column chromatography on silica gel (hexane–EtOAc as eluent) to give the corresponding quinones **4** or **5**.



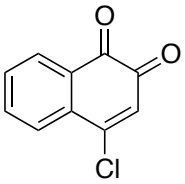
1,2-Naphthoquinone (4a):[27] Brown solid; **TLC**, R_f = 0.21 (hexane–EtOAc = 4:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 6.45 (d, *J* = 10 Hz, 1H), 7.25 (d, *J* = 8.2 Hz, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.53 (dd, *J* = 6.4, 7.8 Hz, 1H), 7.66 (ddd, *J* = 1.4, 5.9, 6.4 Hz, 1H), 8.13 (d, *J* = 7.3 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 128.0, 130.0, 130.3, 131.0, 131.7, 134.9, 136.0, 145.6, 179.0, 181.0.



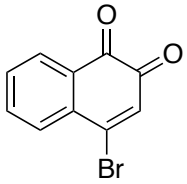
1,4-Naphthoquinone (5a):[28] Yellow solid; **TLC**, R_f = 0.41 (hexane–EtOAc = 4:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 6.99 (s, 1H), 7.77 (m, 2H), 8.10 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 128.6, 132.0, 134.1, 138.8, 185.2.



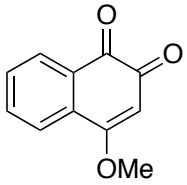
***trans*-2-Carboxycinnamic acid (8):**[21] Pale yellow solid; **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 6.43 (d, *J* = 16 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1h), 7.60 (t, *J* = 6.8 Hz, 1H), 7.82 (d, *J* = 7.3 Hz, 1H), 7.88 (dd, *J* = 0.9, 7.8 Hz, 1H), 8.31 (d, *J* = 16 Hz, 1H); **^{13}C NMR** (DMSO-d_6, 100 MHz) δ 121.4, 127.8, 129.8, 130.4, 131.1, 132.2, 134.9, 142.6, 167.5, 168.2.



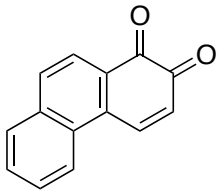
4-Chloro-1,2-Naphthoquinone (4d): Brown solid; **TLC**, R_f = 0.58 (hexane–EtOAc = 1:1); **IR** (KBr) 1658, 1582, 1322, 1287, 1242, 936, 769 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 6.76 (s, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.77 (t, *J* = 7.8 Hz, 1H), 7.90 (d, *J* = 7.8 Hz, 1H), 8.17 (d, *J* = 7.8 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 127.7, 128.0, 130.2, 130.6, 132.2, 132.7, 135.9, 152.8, 178.1, 178.4; **HRMS** (FAB+) *m/z* calcd for $C_{11}H_{14}O_3Cl$ (M+H) 193.0056, found 193.0054.



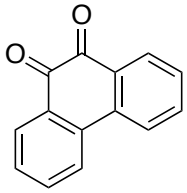
4-Bromo-1,2-Naphthoquinone (4e):[29] Brown solid; **TLC**, R_f = 0.62 (hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.05 (s, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.77 (t, *J* = 7.3 Hz, 1H), 7.90 (d, *J* = 7.8 Hz, 1H), 8.15 (d, *J* = 7.3 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 130.1, 130.6, 130.9, 132.1, 133.6, 136.0, 145.9, 178.2.



4-Methoxy-1,2-Naphthoquinone (4f):[30] Yellow solid; **TLC**, R_f = 0.29 (hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 4.08 (s, 3H), 5.99 (s, 1H), 7.59 (dd, *J* = 7.3, 7.8 Hz,1H), 7.71 (t, *J* = 7.8 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 8.13 (d, *J* = 7.3 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 57.0, 103.2, 124.9, 129.2, 130.4, 131.7, 132.1, 135.1, 168.8, 179.5, 179.6.

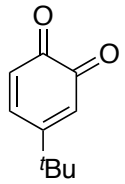


1,2-Phenanthraquinone (4g):[12] Red solid; **TLC**, R_f = 0.54 (hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 6.59 (d, *J* = 10 Hz, 2H), 7.70 (m, 2H), 7.91 (m, 1H), 7.98 (d, *J* = 8.2 Hz, 1H), 8.17 (d, *J* = 8.2 Hz, 1H), 8.31 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 123.6, 124.4, 127.7, 128.6, 129.4, 129.7, 129.8, 131.4, 132.0, 137.3, 139.6, 179.5, 180.8.

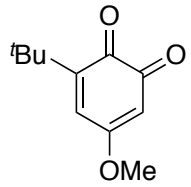


9,10-Phenanthraquinone (4h):[31] Yellow solid; **TLC**, R_f = 0.50 (hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.47 (dd, *J* = 7.3, 7.8 Hz, 2H), 7.72 (ddd, *J* = 1.4, 6.9, 7.3 Hz, 2H), 8.03 (d, *J* = 8.3 Hz, 2H), 8.20 (dd, *J* = 1.4, 6.4 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 124.1, 129.7, 130.5,

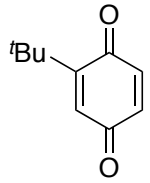
131.0, 135.9, 136.2, 180.3.



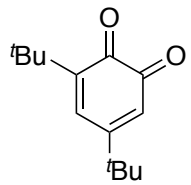
4-*tert*-Butyl-1,2-benzoquinone (4i):[32] Brown solid; **TLC**, R_f = 0.38 (hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.24 (s, 9H), 6.29 (d, *J* = 2.2 Hz, 1H), 6.40 (d, *J* = 10 Hz, 1H), 7.19 (dd, *J* = 2.5, 10 Hz, 1H); **^{13}C NMR** (DMSO-d_6, 100 MHz) δ 27.4, 35.3, 123.2, 129.4, 140.2, 161.5, 180.0.



3-*tert*-Butyl-5-methoxy-1,2-benzoquinone (4j): Red solid; **TLC**, R_f = 0.42 (hexane–EtOAc = 1:1); **IR** (KBr) 1649, 630, 1589, 1440, 1367, 1228, 1007, 900, 783 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.26 (s, 9H), 3.84 (s, 3H), 5.73 (d, *J* = 2.7 Hz, 1H), 6.62 (d, *J* = 3.2 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 28.9, 35.2 56.7, 101.0, 133.0, 151.5, 170.0, 178.6, 179.9; **HRMS** (FAB+) *m/z* calcd for $C_{11}H_{14}O_3$ (M+H) 195.1021, found 195.1013.

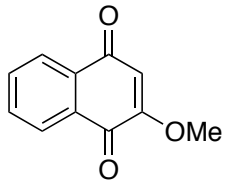


2-*tert*-Butyl-1,4-benzoquinone (5j):[33] Brown solid; **TLC**, R_f = 0.71 (hexane–EtOAc = 4:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.30 (s, 9H), 6.61 (d, *J* = 1.4 Hz, 1H), 6.69 (d, *J* = 1.4 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 29.2, 35.3, 131.6, 135.0, 138.7, 156.1, 188.5.



3,5-Di-*tert*-butyl-1,2-benzoquinone (4k):[33] Brown solid; **TLC**, R_f = 0.71 (hexane–EtOAc = 1:1);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (s, 9H), 1.27 (s, 9H), 6.22 (d, J = 2.3 Hz, 1H), 6.93 (d, J = 2.3 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 28.0, 29.3, 35.6, 36.1, 122.2, 133.6, 150.0, 163.4, 180.2, 181.2.



3-Methoxy-1,4-naphthoquinone (5l):[34] Yellow solid; **TLC**, R_f = 0.46 (hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 3.90 (s, 3H), 6.17 (s, 1H), 7.73 (m, 2H), 8.10 (d, J = 8.0 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 56.6, 110.0, 126.3, 126.8, 131.1, 132.1, 133.4, 134.5, 160.5, 180.2, 185.0.

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Chapter 3

4,5-Me_2-IBS-Catalyzed Highly Site-selective Oxidation of 2-Substituted Phenols to 1,2-Quinols

Abstract: We have developed a site-selective hydroxylative dearomatization of phenols to 1,2-quinols or their cyclodimers catalyzed by 4,5-dimethyl-2-iodoxybenzenesulfonic acid (4,5-Me_2IBS) with Oxone. Importantly, both the reaction rate and site-selectivity were further improved by the introduction of a trialkylsilylmethyl substituent at the 2-position of phenols. The corresponding 1,2-benzoquinols could be transformed to various useful structural motifs *via* cascade [4+2]-cycloaddition reactions.

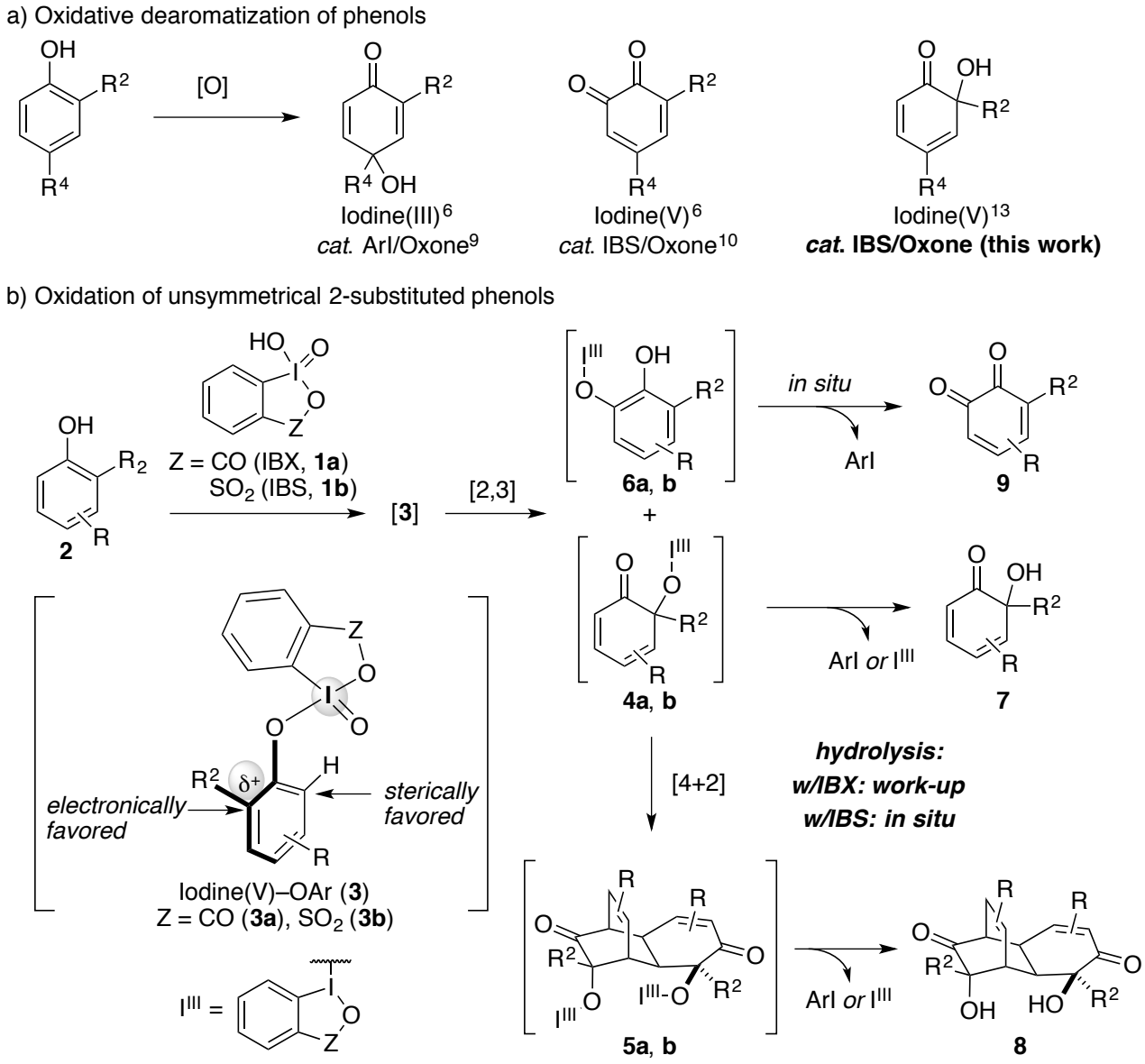
Introduction

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 biscarvacol,[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 hypervalent iodine reagents.[6,7] In general, iodine(III) and iodine(V) reagents have been used for *para*- and *ortho*-selective oxidations, respectively (*Scheme 1a*).[6] Recently, *in situ* generated organoiodine(III or V)-catalyzed[8] regioselective oxidation to 1,4-benzoquinols,[9] 1,4-benzoquinones[9] and 1,2-benzoquinones[10] have also been developed. However, the catalytic site-selective hydroxylative dearomatization of 2-substituted phenols to 1,2-benzoquinols has not been reported. Here, we report the first organoiodine(V)-catalyzed site-selective oxidation to 1,2-quinols.

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, due to its low reactivity, the substrate scope was limited to electron-releasing group-substituted high reactive phenols. Additionally, no site-selectivity was observed for the oxidation of unsymmetrical 2-substituted phenols: maximum possible yield of the 1,2-benzoquinol-derived cyclodimers is reported to be 50%.[6a,13] IBX reversibly combines with phenols **2** to give iodine(V)–phenol complex **3a**, which serves to transfer oxygen from an iodoxy (IV = O) to either the 2- or 6-position *via* concerted intramolecular [2,3]-sigmatropic rearrangement (*Scheme 1b*).[6] During this process, the competition between electronic and steric factors might lead to nonselective 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**. 1,2-Benzoquinols **7** or cyclodimers **8** are then obtained after hydrolysis. On the other hand, a reaction at the nonsubstituted 6-position affords catechol–iodine(III) monoester **6a**, after rapid aromatizing keto-enol tautomerization. Undesired 1,2-benzoquinones **9** are then obtained *via* the *in situ* reduction of iodine(III) to iodine(I). Importantly, reductive or strong-acidic work-up is required to release iodine(III), 2-iodosobenzoic acid, from **4a** or **5a**.[13] Due to this necessity, it would be difficult to use IBX catalytically for 1,2-benzoquinols. To overcome these issues, we introduced 2-iodoxybenzenesulfonic acid (IBS, **1b**) catalysis[14] for the *ortho*-selective hydroxylative dearomatization of phenols. Since iodine(V) atom of **1b** is more Lewis-acidic than that of **1a**,[14a] we envisioned that a larger partial positive charge (δ^+) would be generated for the IBS–phenol complex **3b**. This might lead to a high reactivity and prefential oxygen transfer at a substituted

2-position of unsymmetrical phenols (*Scheme 1b*). Moreover, due to its strong electron-withdrawing sulfo group, iodine(III) species would be readily released *in situ* from quinol (**4b**) or cyclodimer (**5b**), which would make the catalytic use of IBS possible.

Scheme 1. Hypervalent Iodine-Mediated Oxidation of Phenols

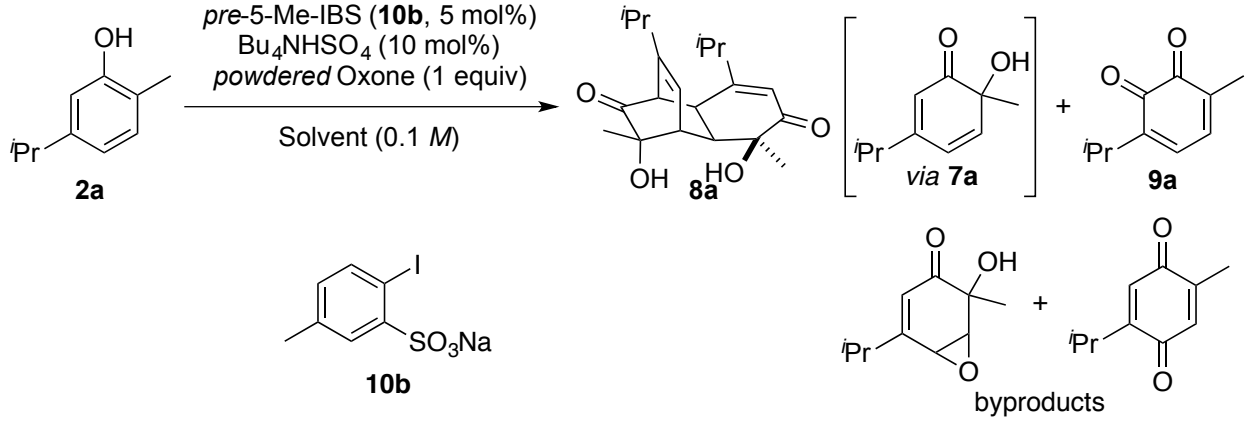


Results and Discussion

First, we investigated the oxidation of carvacrol **2a** as a 2-substituted phenol using IBS catalysts, which were generated *in situ* from *pre*-IBS and Oxone (*Table 1*). A mixture of **2a**, *powdered* Oxone and Bu_4NHSO_4 (10 mol%), as a solid-liquid phase transfer catalyst, was heated in ethyl acetate at 40 ºC in the presence of 5-mol% of *pre*-5-Me-IBS (**10b**). To our delight, the reaction proceeded smoothly and natural product biscarvacrol (**8a**) was obtained in 60% yield *via*

the *in situ* dimerization of 1,2-benzoquinol **7a** (entry 1). However, undesired 1,2-benzoquinone **9a** was also obtained in 25% yield along with epoxyquinol[7b] and 1,4-benzoquinone[7b] in a combined yield of 5%. 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 (entries 3–10). Additionally, the site- and chemoselectivity were further increased by the lowering the reaction temperature to 20 ºC, and **8a** could be obtained in 80% yield (entry 12). However, a long reaction time was required to complete the reaction.

Table 1. Initial Investigation of the IBS-Catalyzed Oxidation of Carvacrol

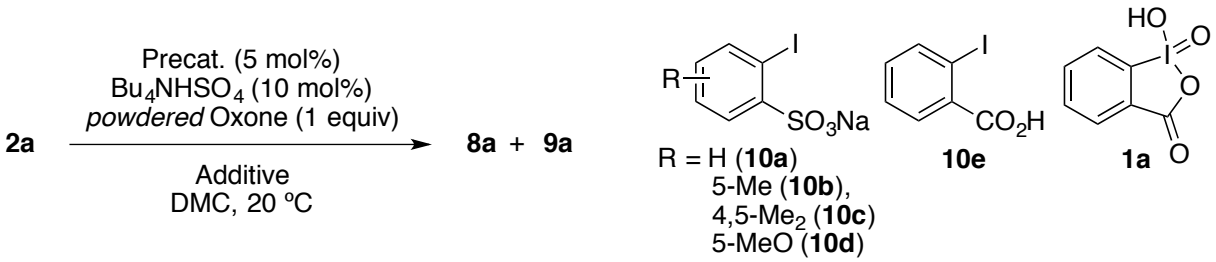


Entry	Solvent	*T* (°C)	Time (h)	**2a**, Conv. (%)[b]	Yield (%)[b]		
					8a[b]	**9a**[b]	Byproducts[c]
1	EtOAc	40	16	>99	60	25	5
2[d]	EtOAc	40	24	0	0	0	0
3	DMC	40	16	>99	73	17	5
4	EC	40	12	>99	70	19	5
5	CH_3NO_2	40	16	>99	66	0	<5
6	CH_3CN	40	16	>99	59	0	<5
7	HFIP	40	16	>99	*messy*		
8	Toluene	40	20	>99	58	0	5
9	CH_2Cl_2	40	16	36	20	1	10
10	DMC[e]	40	16	>99	72	15	<5
11	DMC	60	6	>99	68	19	10
12	DMC	20	80	>99	80	15	<5

[b] Determined by NMR analysis. [c] These byproducts could not be isolated. The formation of these compounds was confirmed by comparing *in situ* NMR chemical shifts with literature values.[7b] The combined yields of these byproducts are determined by *in situ* NMR analysis of reaction mixture just before quench. [d] In the absence of Bu_4NHSO_4. [e] DMC (0.2 *M*). DMC, dimethyl carbonate; EC, ethylene carbonate; HFIP, 1,1,1,3,3,3-Hexafluoro-2-propanol.

Next, we investigated the substituent effect of IBS catalysts (*Table 2*). As in our previous studies,[14a] the regeneration iodine(V) species might be rate-limiting for the present phenol oxidation. Indeed, the reaction rate at 20 ºC was accelerated by 1.5- to 3-fold with the use of electron-donating group-substituted[14a] *pre*-catalysts (*entries 2–4 versus entry 1*). Although the highest reactivity was observed with *pre*-5-MeO-IBS (**10d**) (entry 4), it was unstable under these conditions (entry 5). Additionally, the reaction rate could be further accelerated with the use of "*buffered*" Oxone,[10] which was prepared by premixing of Oxone and potassium carbonate in DMC at room temperature and **8a** was obtained in 82% yield after a shorter reaction time (entry 6). A brief screening of the stoichiometric amount of potassium carbonate used and the premixing time of these solid reagents (entries 7–11) revealed that the premixing of 1 equivalent of Oxone with 0.5 equivalent of potassium carbonate for more than 12 hours was optimal (entries 6 and 7). On the other hand, as

Table 2. Investigation of Precatalysts and Buffered Oxone for the Oxidation of Carvacrol



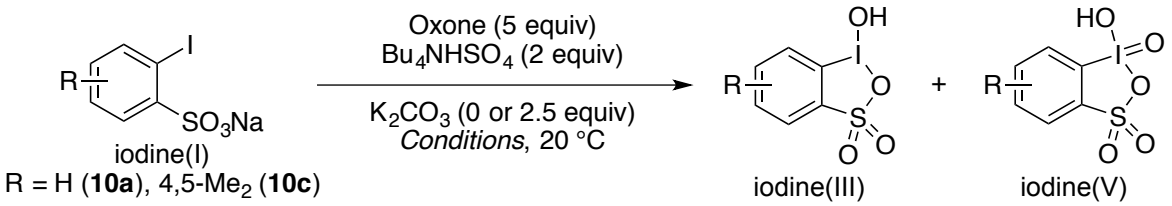
Entry	Precat.	Additive (equiv)	Time (h)	**8a**, Yield (%)[a]	**9a**, Yield (%)[a]
1	**10b**	–	120	80	15
2	**10a**	–	80	80	15
3	**10c**	–	48	82[b]	15
4	**10d**	–	36	80	15
5[c]	**10d**	–	16	28	24
6	**10c**	K_2CO_3 (0.5)[d,e]	24	82[b]	15
7	**10c**	K_2CO_3 (0.5)[d,e]	24	80	15
8	**10c**	K_2CO_3 (0.5)[d,e]	24	50	<5
9	**10c**	K_2CO_3 (0.5)[d,e]	24	30	<5
10	**10c**	K_2CO_3 (0.6)[d,e]	24	20	<5
11	**10c**	K_2CO_3 (0.3)[d,e]	24	55	<5
12[f]	**10e**	–	40	3	<1
13[g]	**1a**[f]	–	24	55	40

[a] Determined by NMR analysis. [b] Isolated yield. [c] at 40 ºC in EtOAc. **10d** was decomposed under these conditions. [d] "*Buffered*" Oxone was prepared *via* vigorous stirring of Oxone in the presence K_2CO_3 in dimethyl carbonate at room temperature. [f] Premixing time of Oxone and K_2CO_3 = 24 h (entries 6, 10, 11), 12 h (entry 7), 6 h (entry 8), 0 h (entry 9). [f] at 40 °C. **2a** (90%) was recovered. [g] Stoichiometric oxidation: Reaction was performed with IBX (**1a**, 1.1 equiv) in DMC (0.1 *M*) at 20 °C in the absence of Oxone and Bu_4NHSO_4.

expected, almost no reaction proceeded with the use of *pre*-IBX (**10e**) (entry 12). Additionally, the stoichiometric oxidation of **2a** with IBX (1.1 equiv), even under our optimized conditions, afforded **8a** in 55% yield along with **9a** in 40% yield (entry 13).

However, the beneficial roles of buffered Oxone for the present oxidation is not clear yet. The use of buffered Oxone is almost ineffective for the oxidation of iodine(I) to iodine(III and V) under both aqueous and non-aqueous conditions (*Table 3*). Moreover, it was confirmed that **10c** was much more easily oxidized to hypervalent iodine species than that of **10a**. Since IBSes are not stable enough to isolate in pure form, we could not investigate the stoichiometric oxidation with the use of IBS.

Table 3. Effect of Buffered Oxone for the Oxidation of Iodine(I) to Iodine(III and V)



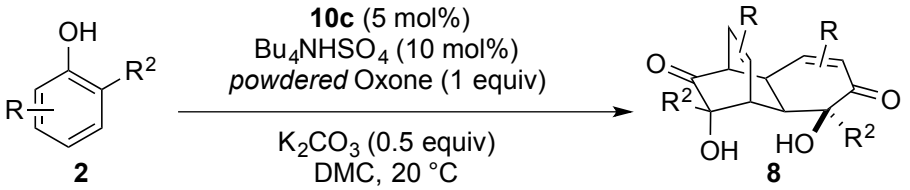
Time (h)	Ratio of Iodine(I:III:V) in CD_3CN–D_2O (1:1, *v*/*v*)				Ratio of Iodine(I:III:V) in CD_3CN		
	10a w/o K_2CO_3	**10a** w/ K_2CO_3	**10c** w/o K_2CO_3	**10c** w/ K_2CO_3	**10c** w/o K_2CO_3	**10c**, w/ K_2CO_3	**10c** w/ K_2CO_3[a]
1	49:51:0	47:43:0	0:80:20	0:80:20	99:0:0	90:0:10	90:0:10
5	21:59:20	22:57:21	0:45:55	0:45:55	90:0:10	85:0:15	85:0:15
24					41:0:59	43:0:57	45:0:55

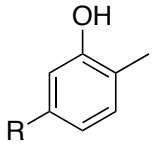
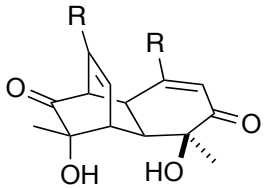
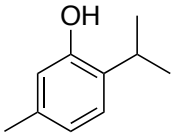
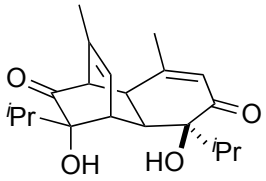
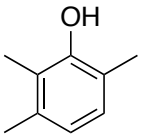
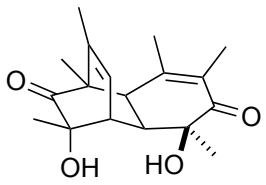
[a] A solution of Oxone and K_2CO_3 was premixed for 24 h before the addition of **10c** and PTC.

Various 2-substituted phenols were examined under the optimized reaction conditions (*Tables 4 and 5*). The oxidation of unsymmetrical phenols **2b**–**g** was conducted at 20 ºC by using *pre*-catalyst **10c** and buffered Oxone to induce high site-selectivity (*Table 4*). The corresponding cyclodimers **8b**–**g** were obtained in good to high yields (62–80%) regardless electronic nature of the substituents. Oxidation of 5-methoxy-2-methylphenol (**2c**) proceeded smoothly, however, cyclodimerization process required high temperatures for the reaction to complete. The benzoquinone side products **9** or their reductive catechol forms could not be isolated with these reactions, except for the oxidation of **2f**. Notably, oxidation of 2,3,6-trimethylphenol (**2g**) proceeded selectively at the less hindered 6-position to give the corresponding cyclodimer **8g** in 70% yield. On the other hand, the *ortho*-selective oxidation of symmetrical 2,6-disubstituted phenols **2h**–**l** proceeded smoothly at 40 ºC, and the corresponding cyclodimers **8h**–**l** were obtained

in excellent yields (*Table 5*). In contrast to low temperature conditions (20 ºC) that are required for the site-selective oxidation of unsymmetrical phenols, almost same results were obtained with both *pre*-catalysts **10a** and **10c** at 40 ºC. Notably, in contrast to IBX-mediated oxidations,[13] electron-withdrawing group-substituted phenols such as **2d**, **2e**, **2i**, **2k** and **2l** could be oxidized smoothly with the use of our IBS/Oxone catalysis. For example, oxidation of **2i** bearing two ester groups at both *ortho*-positions using a stoichiometric amount of IBX did not proceed even at elevated temperatures.

Table 4. Regio- and Site-selective Oxidation of Unsymmetrical 2-Substituted Phenols[a]



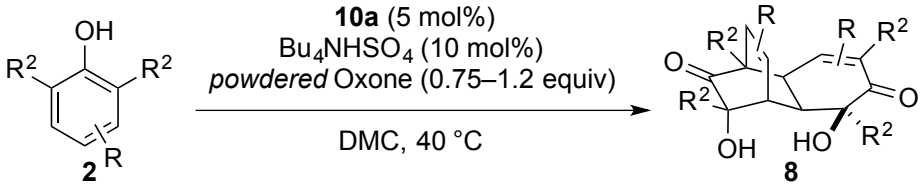
Entry	Substrate	2	Product	8	Time (h)	Yield (%)[b]
1		**2b** (R = Me)		**8b**	24	65
2[c]		**2c** (R = OMe)		**8c**	48	70
3		**2d** (R = F)		**8d**	24	62
4		**2e** (R = Br)		**8e**	24	80
5		**2f**		**8f**	24	66[d]
6		**2g**		**8g**	24	70[e]

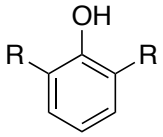
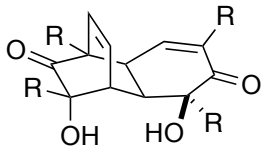
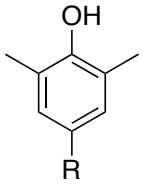
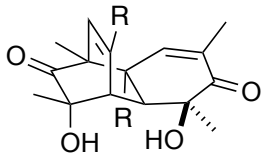
[a] Reaction conditions: **2** (0.5 mmol), *powdered* Oxone (0.5 mmol), K_2CO_3 (0.25 mmol), **10c** (0.025 mmol), Bu_4NHSO_4 (0.05 mmol), DMC (5 mL), 20 ºC. Oxone and K_2CO_3 were premixed in DMC for 24 h at room temperature. [b] Isolated yield. [c] at 80 ºC. [d] **9a** was obtained in 17% yield. *e* The isomeric *ortho*-benzoquinol, oxidation product at the 2-position, was isolated in 22% yield.

The selective oxidation of *ortho*-substituted 1- or 2-naphthols **2m–s** under optimized conditions gave the corresponding *ortho*-naphthoquinols **7m–s** (*Scheme 3*). Notably, the catalytic oxidation of naphtholic ester **2o** completed within 35 h; for comparison, the IBX-mediated stoichiometric oxidation required 7 days.[13c] Furthermore, the antibacterial natural product lacinilene C methyl ether (**7s**)[5] could be synthesized by the clean oxidation of another natural

product, 2-hydroxy-7-methoxycadalene (**2s**),[5a] in 91% yield. In contrast highly toxic diphenylseleninic anhydride[5c] or Zr(IV)/TBHP[5d] had been required previously for the oxidation of **2s** to **7s**.

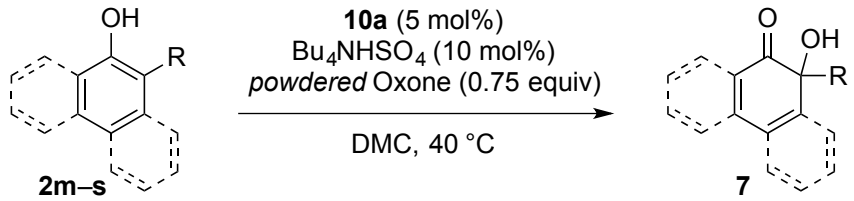
Table 5. Regioselective Oxidation of Symmetrical 2,6-Disubstituted Phenols[a]

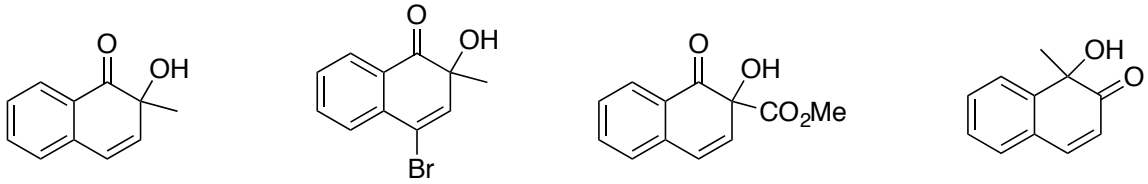


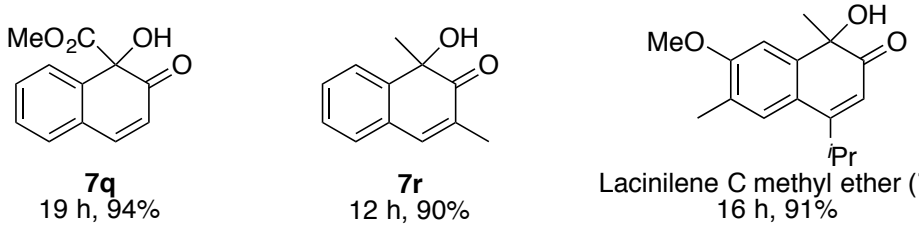
Entry	Substrate	**2**	Product	**8**	Time (h)	Yield (%)[b]
1		**2h** (R = Me)		**8h**	16	98
2[c]		**2i** (R = CO_2Me)		**8i**	16	98
3		**2j** (R = Me)		**8j**	16	94
4		**2k** (R = Ac)		**8k**	12	91
5		**2l** (R = CO_2Me)		**8l**	12	91

[a] Reaction conditions: **2** (0.5 mmol), *powdered* Oxone (0.375 mmol), **10a** (0.025 mmol), Bu_4NHSO_4 (0.05 mmol), DMC (5 mL), 40 ºC. [b] Isolated yield. [c] Oxone (1.2 equiv).

Scheme 2. Oxidation of Naphthols to *ortho*-Naphthoquinols



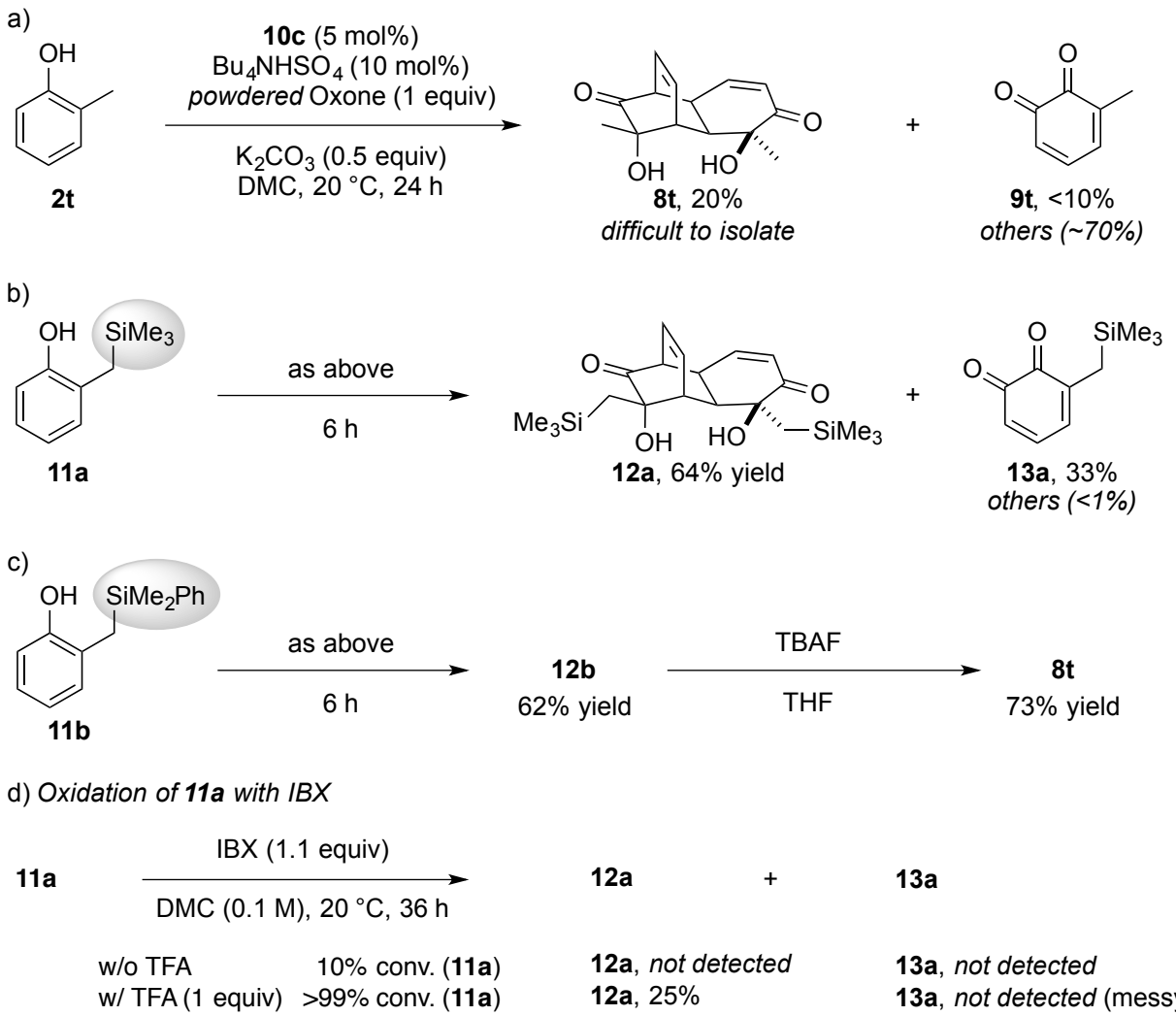




Reaction time and isolated yields are shown. [a] EtOAc instead of DMC. [b] Oxone (1 equiv).

However, the oxidation of 2-cresol (**2t**) as the simplest substrate gave a complex mixture, and desired cyclodimer **8t** was obtained in only 20% yield (*Scheme 3a*). To stabilize the 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 α-trimethylsilyl-*o*-cresol (**11a**) proceeded smoothly and the corresponding cyclodimer **12a** was obtained in 64% yield along with quinone **13a** in 33% yield (*Scheme 3b*). Both the site-selectivity and the reaction rate were enhanced by the β-silicon effect.[15] Notably, oxidative desilylation was not observed under our oxidative conditions. A variety of trialkylsilyl groups could be easily installed at the benzylic position, and easily removed after the oxidation. For instance, **8t** could be isolated in good yield from the oxidation of phenol **11b** followed by TBAF-mediated desilylation (*Scheme 3c*). On the other hand, as expected, almost no reaction proceeded with the use the

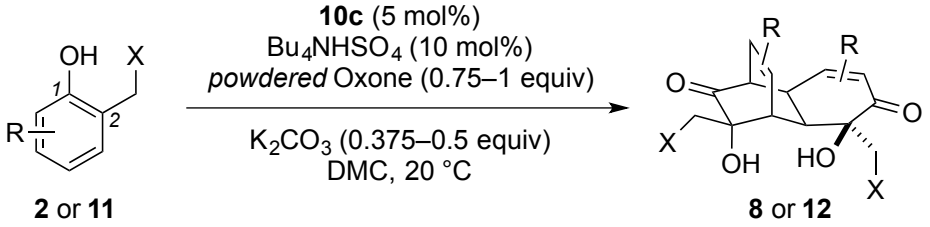
Scheme 3. Oxidation of 2-Cresol (**2t**) and Its Silylated Analogues

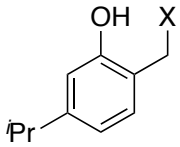
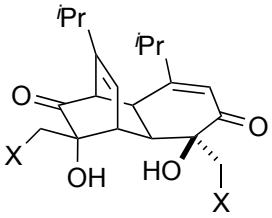
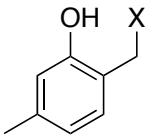
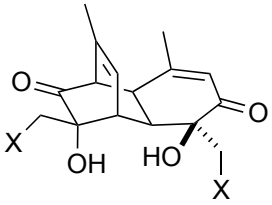
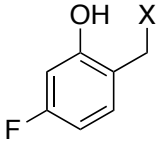
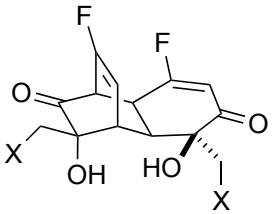
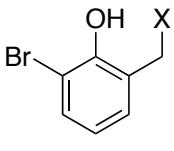
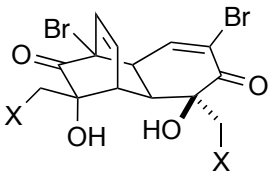


stoichiometric amount of IBX instead of IBS/Oxone catalysis (*Scheme 3d*). Additionally, although **11a** was completely consumed fully under harsh reaction conditions with trifluoroacetic acid (TFA), various unidentified side-product were also obtained (*Scheme 3d*).

The oxidation of various 2-(silylmethyl)phenols **11** was examined under optimized conditions (*Table 6*). The reaction of the silylated analogue of carvacrol **11c** gave cyclodimer **12c** exclusively. Moreover, compared to their non-silyl counterparts **2b**, **2d** and **2u**, phenols **11d-f** bearing electron-donating or -withdrawing substituents at *meta*- or *ortho*-positions gave their corresponding cyclodimers in higher yields after shorter reaction times. Additionally, the oxidation of 1-silylmethyl-2-naphthol **11g** also proceeded smoothly and desired *ortho*-naphthoquinol **14g** was isolated in high yield (*Scheme 4*).

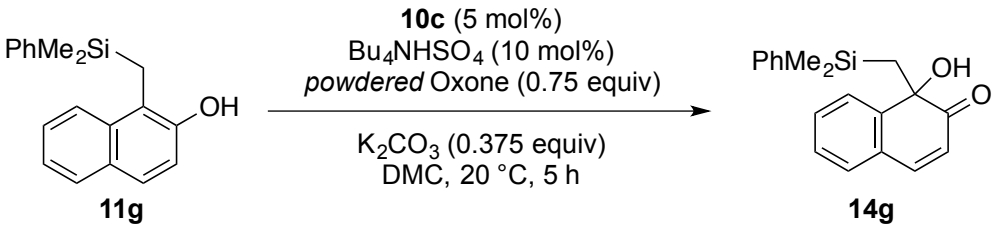
Table 6. Oxidation of Various 2-(Silylmethyl)phenols **11**



Entry	Substrate	**2**	Product	**8**	Time (h)	Yield (%)[a]
1[b]		**11c** (X = $SiMe_3$)		**12c**	5	94
2		**2a** (X = H)		**8a**	24	82[c]
3		**11d** (X = $SiMe_3$)		**12d**	5	72
4		**2b** (X = H)		**8b**	24	65
5		**11e** (X = $SiMe_3$)		**12e**	7	83
6		**2d** (X = H)		**8d**	24	62
7		**11f** (X = $SiMe_3$)		**12f**	5	57
8		**2u** (X = H)		**8u**	44	27

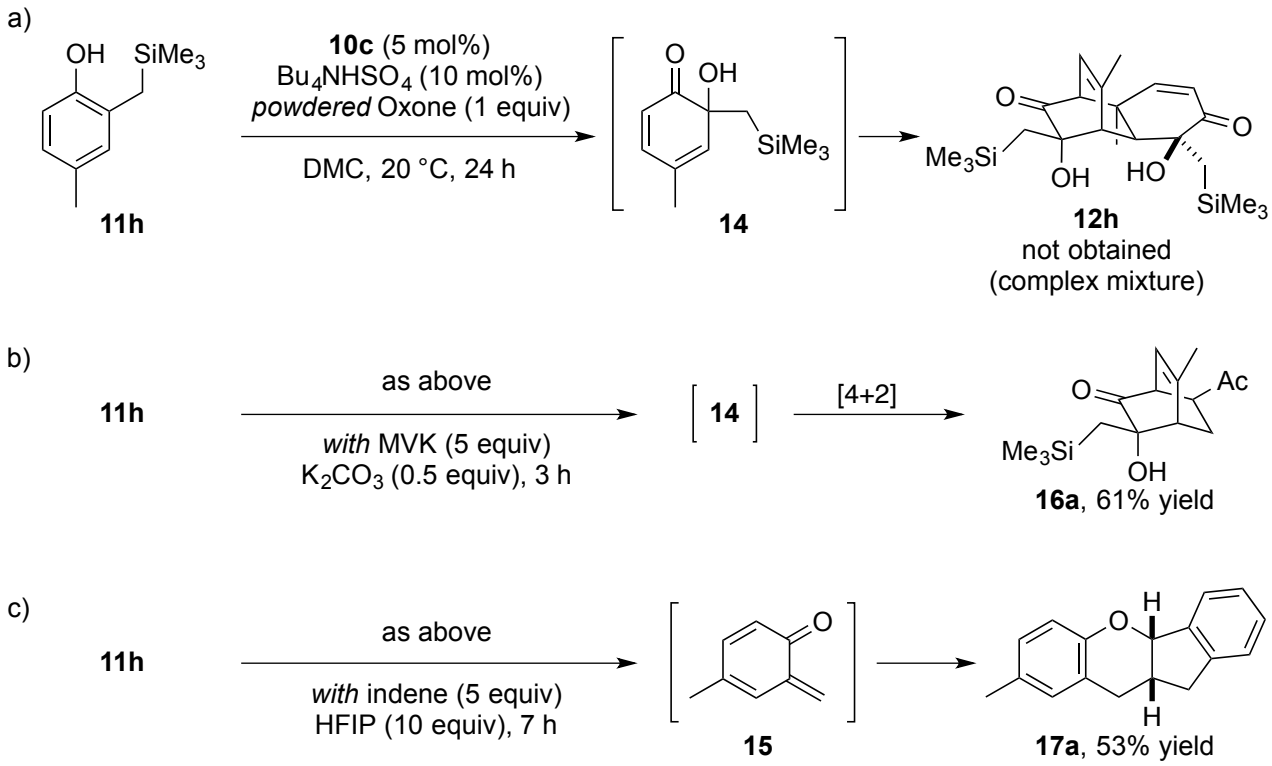
[a] Isolated yield. [b] Oxone (0.75 equiv), K_2CO_3 (0.375 equiv). [c] **9a** was obtained in 15%.

Scheme 4. Oxidation of 1-Silylmethyl-2-Naphthol **14g**



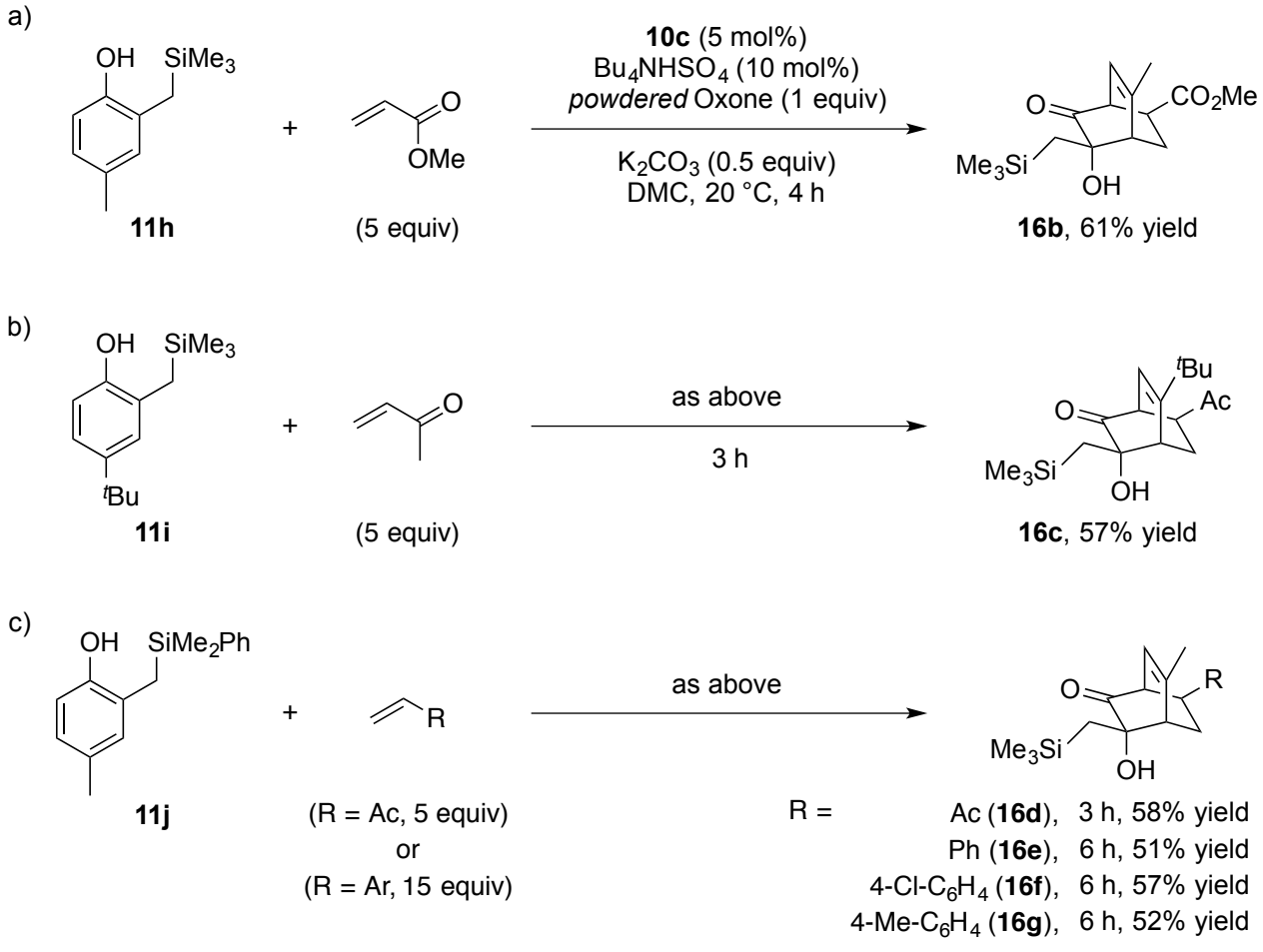
On the other hand, the oxidation of 4-methylphenol **11h** gave a complex mixture of products, and neither the desired 1,2-benzoquinol nor its cyclodimer could be isolated (*Scheme 5a*). We speculated that, due to the acidity of Oxone, Peterson olefination[16] of unstable **14** might proceed preferentially to gibe 1,2-benzoquinone 2-methide **15**, which readily undergoes decomposition.[17] This failure provided us an opportunity to achieve unprecedented cascade reaction. In deed, 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 [4+2]-cycloadduct **16a** in good yield as a single diastereomer (*Scheme 5b*).[18] On the other hand, **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 5c*).[17]

Scheme 5. Oxidative Cascade Reactions

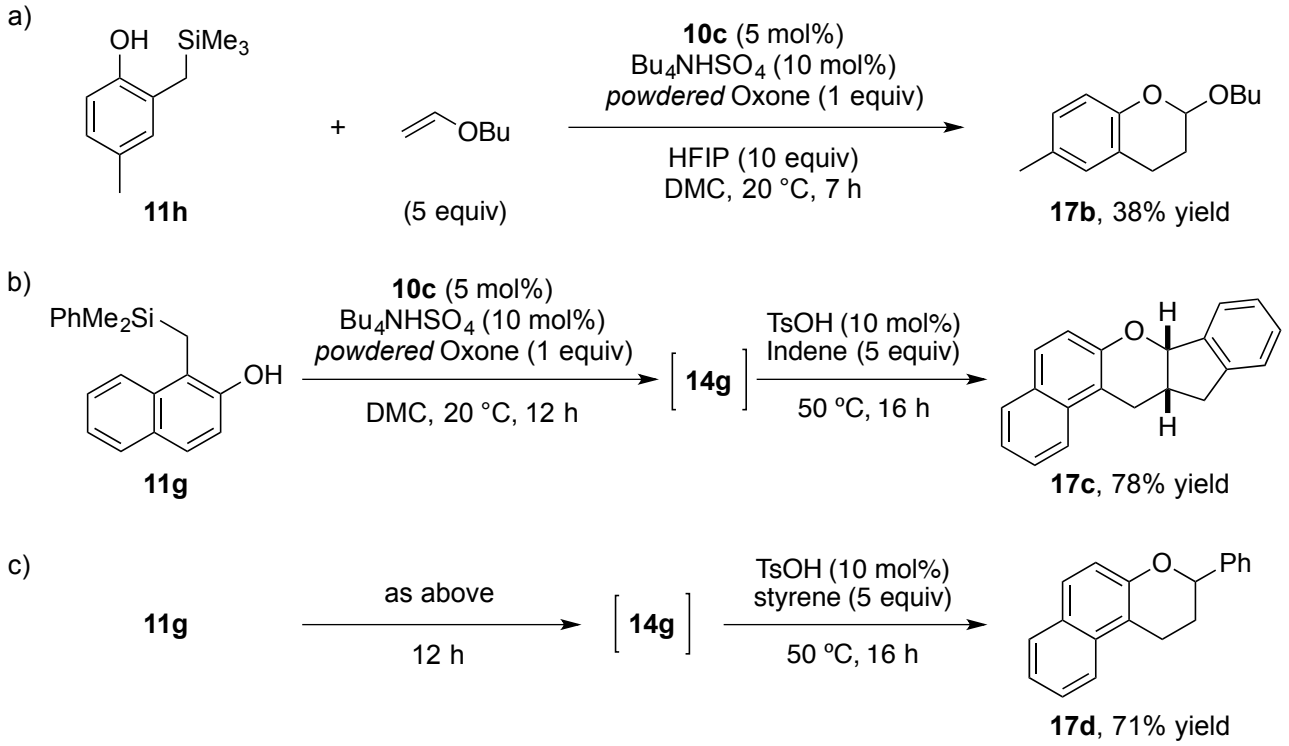


Other examples are shown in *Schemes 6 and 7* for the cascade [4+2]-cycloaddition of both 1,2-benzoquinols and 1,2-benzoquinone 2-methides with several dienophiles, such as MVK, methyl acrylate, aryl alkenes, and alkyl vinyl ether. Notably to accelerate the generation of *ortho*-quinone methide from stable *ortho*-naphthoquinol **14g** derived from 2-naphthol **11g**, a catalytic amount of *para*-toluene sulfonic acid was used instead of HFIP and the cycloadducts **17c** and **17d** were obtained in high yield. Importantly, the IBS-catalyzed chemoselective oxidation of phenols proceeded efficiently under these mild conditions even in the presence of an excess amount of alkenes. *ortho*-Naphthoquinol **14g** derived from 2-naphthol **11g**, a catalytic amount of *para*-toluene sulfonic acid (TsOH) was used instead of HFIP and the cycloadducts **17c** and **17d** were obtained in high yield. Importantly, the IBS-catalyzed chemoselective oxidation of phenols proceeded efficiently under these mild 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., acetylenedicarboxylates, aryl or alkyl acetylenes) gave complex reaction mixtures (Scheme 8).

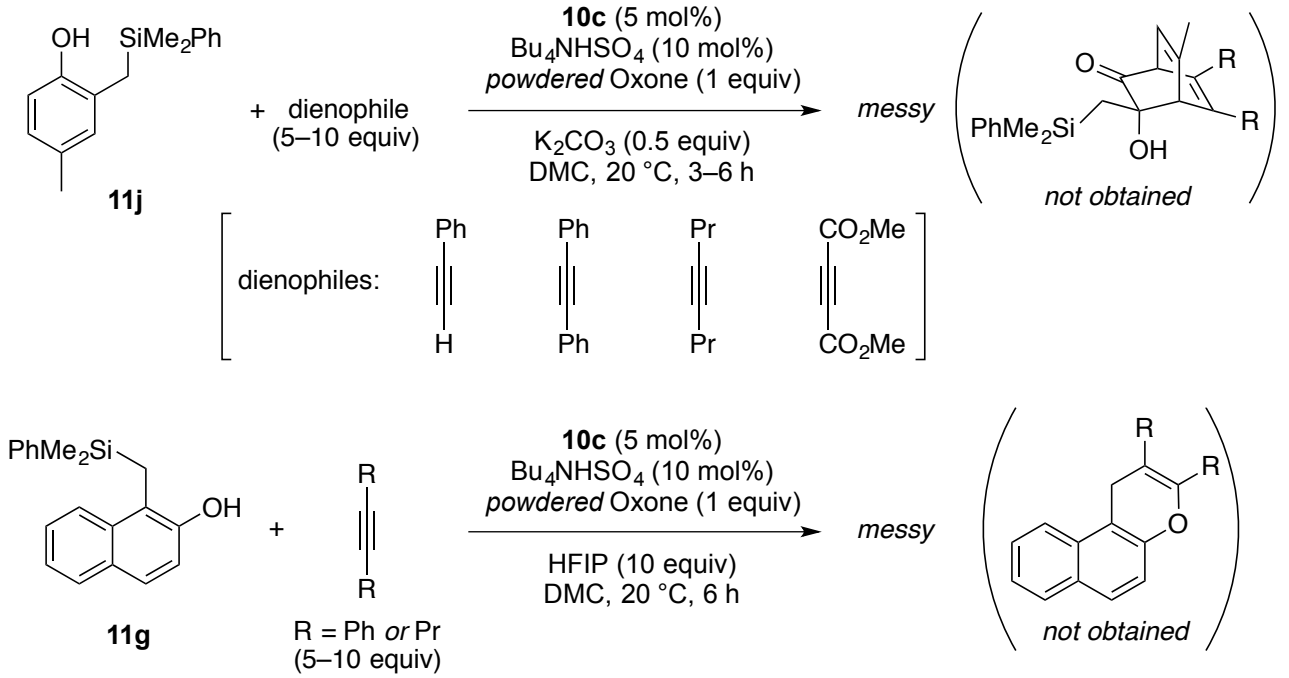
Scheme 6. Oxidative Cascade Reaction to [4+2]-Cycloadducts **16** *via* 1,2-Quinols



Scheme 7. Oxidative Cascade Reaction to Chromanes **17** *via ortho*-Quinone Methide



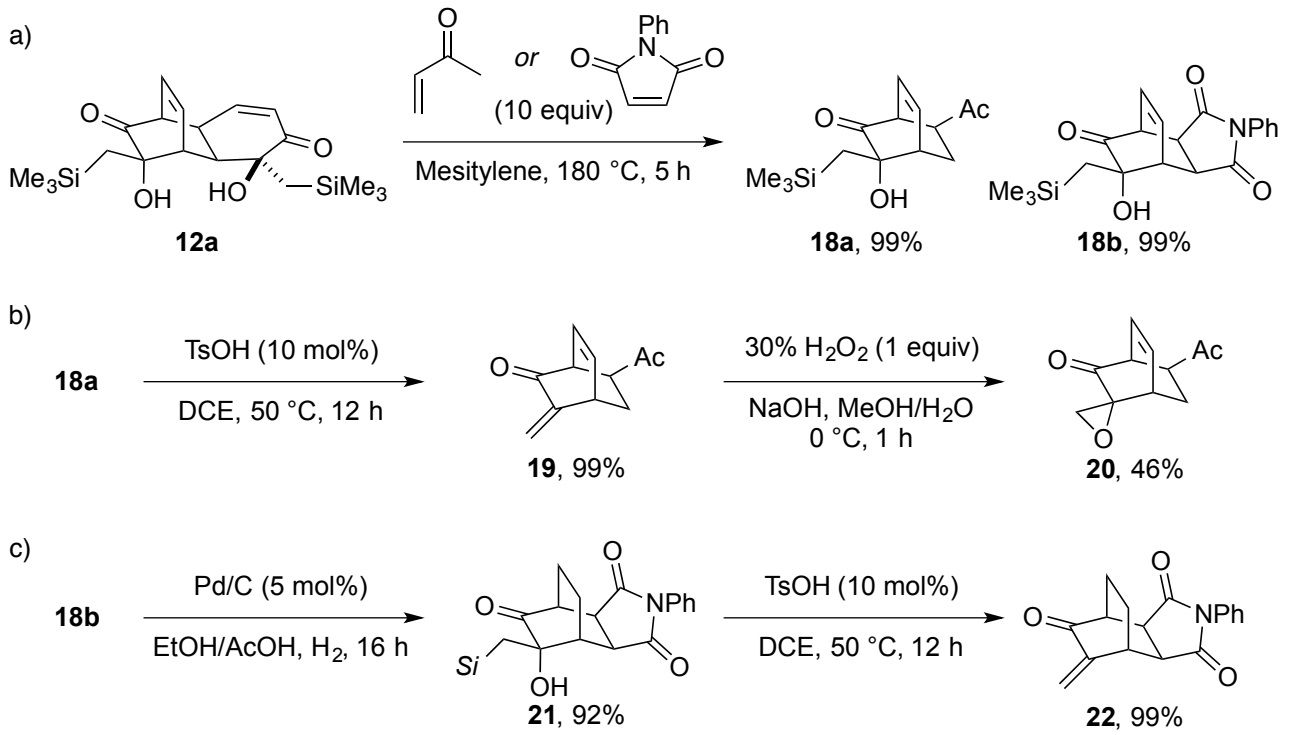
Scheme 8. Unsuccessful Examples for the Oxidative Cascade Reactions



A tandem *retro*-[4+2]/[4+2] cycloaddition of cyclodimer **12a** with MVK or maleimide afforded the corresponding adducts **18** quantitatively (*Scheme 9a*). **18a** could be easily transformed to spiroepoxide **20** through acid-catalyzed Peterson olefination followed by

nucleophilic epoxidation of the resulting enone **19** (*Scheme 9b*). On the other hand, we succeeded in the efficient synthesis of the unique α-methylenebicyclo[2.2.2]octanone core (**22**) of natural products or biologically active compounds such as crotogoudin,[19] 15-oxospiramilactone,[20] etc., from **18b** through the chemoselective hydrogenation of alkene to **21** followed by olefination (*Scheme 9c*).

Scheme 9. Additional Synthetic Utility of Silylated Benzoquinols



Conclusion

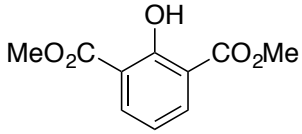
In conclusion, we have succeeded in the first site-selective hydroxylative dearomatization of phenols by using IBS/Oxone catalysis. The corresponding 1,2-quinols or their [4+2]-cyclodimers including natural products such as biscarvacrol and lacinilene C methyl ether could be obtained in high yield. The reaction rate and chemoselectivity were improved significantly with the use of 4,5-Me$_2$IBS **10c** and buffered Oxone under milder conditions. Furthermore, both the reaction rate and site-selectivity were further improved by the introduction of a trialkylsilylmethyl substituent at the *orhto*-position of phenols. The corresponding 1,2-quinols could be transformed to various useful structural motifs *via* cascade [4+2]-cycloaddition reactions.

Experimental Section

Infrared (IR) spectra were recorded on a JASCO FT/IR 460 plus spectrometer. ^{1}H NMR spectra were measured on a JEOL ECS-400 (400 MHz) spectrometer at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; quin = quintet; m = multiplet; brs = broad singlet), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on a JEOL ECS-400 (100 MHz) and Bruker AVANCE III HD (125 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.00 ppm). For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254} 0.25 mm) were used. The products were purified by column chromatography on silica gel (E. Merck Art. 9385 or Fuji Silysia NH-DM 1020). High-resolution mass spectral analysis (HRMS) was performed at Chemical Instrument Center, Nagoya University (JEOL JMS-700).

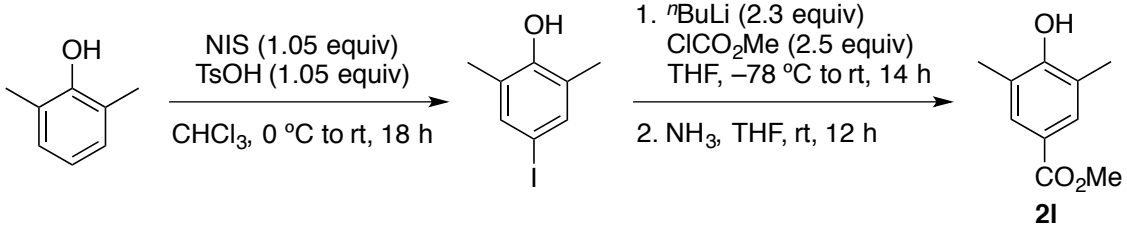
In experiments that required solvents, dimethyl carbonate (DMC), ethyl acetate (EtOAc), acetonitrile and nitromethane were purchased from Wako Pure Chemical Industries, Ltd. as the "anhydrous" and used without further purification. *pre*-4,5-Me$_2$-IBS (**10c·Na**) and *pre*-5-MeO-IBS (**10d·Na**) were prepared according to known procedures.[14a] *pre*-IBS (**10a·K**) and *pre*-5-Me-IBS (**10b·K**) are commercially available from Wako Pure Chemical Industries, Ltd., Junsei Chemical Japan, or Aldrich Chemical Co., Inc. Powdered Oxone was prepared according to known procedure.[14a] Other simple chemicals were analytical-grade and obtained commercially and used without further purification.

Synthesis and Characterization of Substrates



Dimethyl 2-hydroxyisophthalate (2i):[21] **2i** was prepared from 2,6-dimethylphenol according to the literature.[3] White solid; **TLC**, R_f = 0.33 (hexane–EtOAc = 4:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 3.96 (s, 6H), 6.93 (t, *J* = 8.0 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 11.8 (brs, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 52.5, 116.5, 118.4, 136.3, 161.5, 168.1.

Synthesis of 2l:

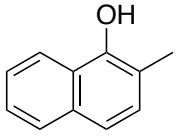


2l

To a stirring mixture of 2,6-dimethylphenol (0.610 g, 5.00 mmol) and *p*-toluenesulfonic acid monohydrate (1.00 g, 5.30 mmol) in $CHCl_3$ (40.0 mL) was added NIS (1.20 g, 5.30 mmol) at 0 °C. The resulting mixture was allowed to room temperature. After stirring for 18 h, to the resulting mixture was added aqueous $NaHCO_3$, and aqueous layers were extracted with $CHCl_3$ (twice). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo*. The residue was purified by column chromatography on silica gel (hexane–EtOAc as eluent) to give 4-iodo-2,6-dimethylphenol (1.20 g, 4.83 mmol, 97% yield).

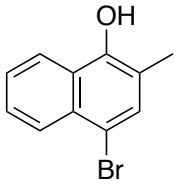
To a solution of this compound (1.20 g, 4.83 mmol) in dry THF (20.0 mL) was added *n*-BuLi (6.90 mL, 11.0 mmol, 1.6 *M* in hexane) at –78 °C. After stirring for 1 h at –78 °C, methyl chloroformate (0.920 mL, 12.0 mmol) was added dropwise at –78 °C. The reaction mixture was allowed to room temperature gradually. After stirring for 14 h at room temperature, the resulting mixture was quenched by aqueous NH_4Cl at 0 °C, and aqueous layers were extracted with Et_2O (twice). The combined organic layers were washed with brine with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo*. To a stirring mixture of this crude mixture in THF (10.0 mL) was added aqueous NH_3 (25%, 1.50 mL) at room temperature. After stirring for 12 h, the reaction was neutralized with aqueous NH_4Cl, and aqueous layers were extracted with EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo*. The residue was purified by column chromatography on silica gel (hexane–EtOAc as eluent) to give **2l** (0.339 g, 1.88 mmol, 39% yield).

Methyl 4-hydroxy-3,5-dimethylbenzoate (2l):[22] White solid; **TLC**, R_f = 0.24 (hexane–EtOAc = 4:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.28 (s, 6H), 3.87 (s, 3H), 5.01 (brs, 1H), 7.71 (s, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 15.8, 51.8, 121.9, 122.8, 130.5, 156.3, 167.1.

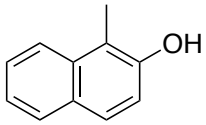


2-Methyl-1-naphthol (2m):[23] **2m** was prepared from 1-hydroxy-2-naphthoic acid according to

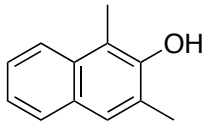
the literature.[4] White solid; **TLC**, R_f = 0.52 (hexane–EtOAc = 4:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.41 (s, 3H), 5.07 (brs, 1H), 7.24 (d, *J* = 8.2 Hz, 1H), 7.37–7.48 (m, 3H), 7.77 (d, *J* = 7.2 Hz, 1H), 8.12 (d, *J* = 8.2 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 15.6, 116.1, 120.1, 120.8, 124.1, 125.3, 125.4, 127.6, 128.9, 133.4, 148.4.



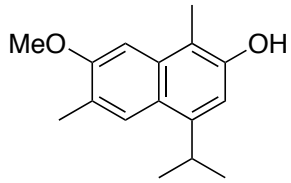
4-Bromo-2-methyl-1-naphthol (2n): **2n** was prepared from 4-bromo-1-hydroxy-2-naphthoic acid as **2o**.[4] 77% yield. Pale yellow solid; **TLC**, R_f = 0.50 (hexane–EtOAc = 4:1); **IR** ($CHCl_3$) 3455, 2877, 1654, 1377, 1177 845 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.40 (s, 3H), 5.06 (brs, 1H), 7.51–7.57 (m, 3H), 8.13 (d, *J* = 7.2 Hz, 1H), 8.15 (d, *J* = 7.2 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz), δ 15.3, 112.9, 117.3, 121.4, 125.4, 125.9, 126.7, 126.9, 131.3, 132.2, 148.4; **HRMS** (FAB+) *m/z* calcd for [$C_{11}H_9{}^{79}BrO$]/[$C_{11}H_9{}^{81}BrO$] ([M]/[M+2]) 235.9837/237.9816, found 235.9833/237.9827.



1-Methyl-2-naphthol (2o):[24] **2o** was prepared from 2-hydroxy-1-naphthoic acid as **2o**.[4] White solid; **TLC**, R_f = 0.56 (hexane–EtOAc = 4:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.54 (s, 3H), 4.81 (brs, 1H), 7.07 (d, *J* = 8.8 Hz, 1H), 7.34 (dd, *J* = 6.8, 8.8 Hz, 1H), 7.50 (dd, *J* = 6.8, 8.2 Hz, 1H), 7.63 (d, *J* = 8.8 Hz, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.92 (d, *J* = 8.8 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 10.4, 115.2, 117.5, 123.1(2C), 126.3, 127.3, 128.4, 129.2, 133.8, 150.4.

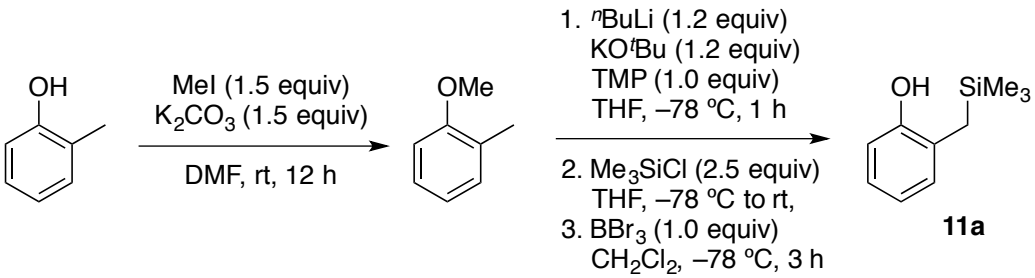


1,3-Dimethyl-2-naphthol (2r):[24] **2r** was prepared from 1-bromo-2-naphthol according to the literature.[5] White solid; **TLC**, R_f = 0.57 (hexane–EtOAc = 10:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.42 (s, 1H), 2.52 (s, 1H), 4.88 (brs, 1H), 7.31 (dd, *J* = 7.6, 8.0 Hz, 1H), 7.43 (dd, *J* = 7.6, 8.8 Hz, 1H), 7.48 (s, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ .10.6, 17.0, 114.4, 122.9, 123.1, 125.3, 125.4, 127.0, 127.7, 129.0, 132.5, 150.0.



4-Isopropyl-7-methoxy-1,6-dimethyl-2-naphthol (2s):[5d] **2s** was prepared from 2-methoxytoluene and succinic anhydride according to literature.[5d] White solid; **TLC**, R_f = 0.39 (hexane–EtOAc = 10:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.35 (d, *J* = 6.8 Hz, 1H), 2.37 (s, 3H), 2.46 (s, 3H), 3.65 (sep, *J* = 6.8 Hz, 1H), 3.96 (s, 3H), 4.72 (brs, 1H), 6.83 (s, 1H), 7.09 (s, 1H), 7.77 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 10.7, 17.0, 23.6, 28.3, 55.1, 101.2, 111.2, 111.7, 122.0, 124.7, 124.9, 134.4, 143.6, 150.0, 157.0.

Synthesis of 11a:[25]



To a stirring mixture of *ortho*-cresol (1.08 g, 10.0 mmol) and potassium carbonate (2.10 g, 15.0 mmol) in DMF (30.0 mL) was added methyl iodide (0. 930 mL, 15.0 mmol) at room temperature. After stirring for 12 h, the solids were filtered-off and washed with Et_2O. The filtrate was neutralized with 1*M* HCl, and the aqueous layers were extracted Et_2O (twice). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo*. The residue was purified by column chromatography on silica gel (hexane–Et_2O as eluent) to give *ortho*-cresol methyl ether (1.22 g, 9.99 mmol, 99% yield).

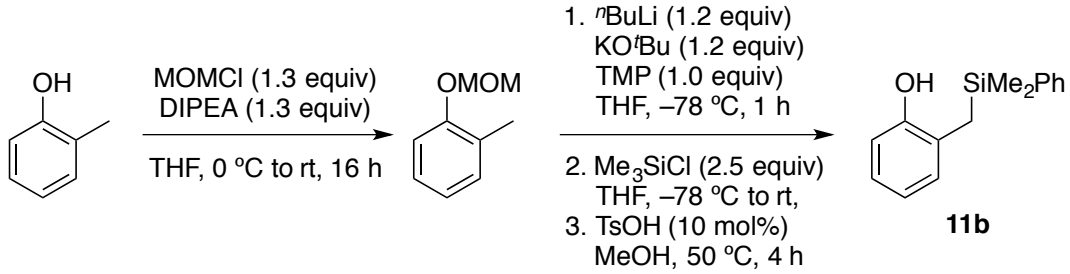
To a solution of *ortho*-cresol methyl ether (1.22 g, 9.99 mmol) in dry THF (50.0 mL) was added *n*-BuLi (7.50 mL, 12.0 mmol, 1.6 *M* in hexane) at –78 °C. After stirring for 15 min at –78 °C, to the resulting mixture was added dropwise potassium *tert*-butoxide (12.0 mL, 12.0 mmol, 1.0 *M* in THF), and then 2,2,6,6-tetramethylpiperidine (1.70 mL, 9.99 mmol). After stirring for 1 h at –78 °C, to the resulting mixture was added dropwise chlorotrimethylsilane (3.20 mL, 25.0 mmol) was added at –78 °C. The reaction mixture was allowed to room temperature gradually. After stirring for 5 h at room temperature, the resulting mixture was quenched with aqueous NH_4Cl, and the aqueous layers were extracted Et_2O (twice). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo*. The residue was

purified by column chromatography on silica gel (hexane–Et_2O as eluent) to give (2-methoxybenzyl)trimethylsilane (1.93 g, 9.95 mmol, 99% yield).

To a stirring solution of this methyl ether (1.93 g, 9.95 mmol) in dry CH_2Cl_2 (30.0 mL) was added dropwise BBr_3 (9.95 mL, 9.95 mmol, 1.0 *M* in CH_2Cl_2) at –78 ºC. The resulting mixture was allowed to room temperature. After stirring for 3 h, the resulting mixture was poured into a water/ice mixture (20 mL). The aqueous layers were separated and extracted with CH_2Cl_2 (twice). The combined organic layers were washed with brine, and dried over anhydrous $MgSO_4$. The solvents were removed under *vacuo*, and the residue was purified by column chromatography on silica gel (hexane–EtOAc as eluent) to give **11a** (1.28 g, 7.92 mmol, 80% yield).

2-((Trimethylsilyl)methyl)phenol (11a):[26] Yellow oil; **TLC**, R_f = 0.30 (hexane–EtOAc = 10:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.03 (s, 9H), 2.06 (s, 2H), 4.47 (brs, 1H), 6.73 (d, *J* = 7.2 Hz, 1H), 6.83 (dd, *J* = 1.6, 8.0 Hz, 1H), 6.95–6.99 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ –1.6, 20.2, 115.0, 120.7, 125.2, 126.8, 130.0, 152.4.

Synthesis of 11b:[25]



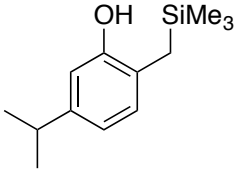
To a stirring mixture of *ortho*-cresol (1.08. g, 10.0 mmol) and *N*,*N*-diisopropylethylamine (2.30 mL, 13.0 mmol) in THF (30.0 mL) was added chloromethyl methyl ether (0.990 mL, 13.0 mmol) at 0 ºC. The reaction mixture was allowed to room temperature. After stirring for 16 h, the resulting mixture was quenched with aqueous NH_4Cl, and the aqueous layers were extracted Et_2O (twice). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo*. The residue was purified by column chromatography on silica gel (hexane–Et_2O as eluent) to give 1-(methoxymethoxy)-2-methylbenzene (1.52 g, 9.99 mmol, 99% yield).

To a solution of MOM ether (1.52 g, 9.99 mmol) in dry THF (50.0 mL) was added *n*-BuLi (7.50 mL, 12.0 mmol, 1.6 *M* in hexane) at –78 ºC. After stirring for 15 min at –78 ºC, to the resulting mixture was added dropwise potassium *tert*-butoxide (11.0 mL, 11.0 mmol, 1.0 *M* in THF), and then 2,2,6,6-tetramethylpiperidine (1.70 mL, 9.99 mmol). After stirring for 1 h at –78 ºC, to the resulting mixture was added dropwise chloro(dimethyl)phenylsilane (4.20 mL, 25.0

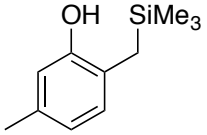
mmol) was added at –78 °C. The reaction mixture was allowed to room temperature gradually. After stirring for 5 h at room temperature, the resulting mixture was quenched with aqueous NH_4Cl, and the aqueous layers were extracted Et_2O (twice). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo*. The residue was purified by column chromatography on silica gel (hexane–Et_2O as eluent) to give (2-(methoxymethoxy)benzyl)dimethyl(phenyl)silane (2.84 g, 9.92 mmol, 99% yield).

A solution of this ether (2.84 g, 9.92 mmol) in MeOH (30.0 mL) was stirred at 50 ºC in the presence of *para*-toluenesulfonic acid monohydrate (0.189 g, 0.992 mmol). After stirring for 4 h, the resulting mixture was cooled to room temperature, and then poured into H_2O. The aqueous layers were extracted EtOAc (twice). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed under *vacuo*, and the residue was purified by column chromatography on silica gel (hexane–Et_2O as eluent) to give **11b** (1.68 g, 6.92 mmol, 70% yield).

2-((Dimethyl(phenyl)silyl)methyl)phenol (11b):[27] Yellow oil; **TLC**, R_f = 0.32 (hexane–EtOAc = 10:1); **^{1}H NMR** ($CDCl_3$ 400 MHz) δ 0.30 (s, 9H), 2.31 (s, 2H) 4.33 (brs, 1H), 6.98 (d, *J* = 7.2 Hz, 1H), 6.80 (t, *J* = 7.2 Hz, 1H), 6.90 (d, *J* = 7.2 Hz, 1H), 6.98 (t, *J* = 7.2 Hz, 1H), 7.34–7.37 (m, 3H), 7.50 (d, *J* = 6.8 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ –3.2, 19.7, 115.2, 121.0, 125.6, 126.0, 127.7, 128.0, 129.0, 130.0, 133.5, 133.7, 138.6, 152.5.

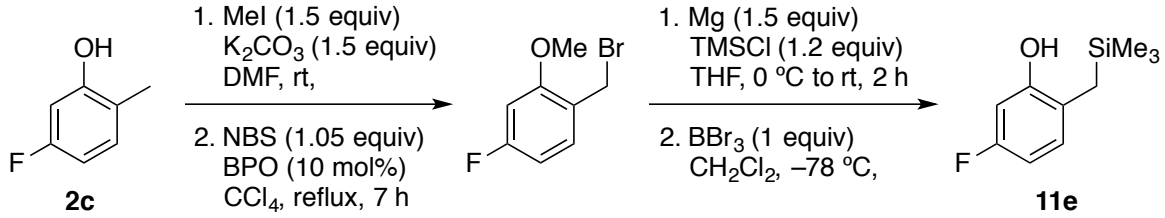


5-Isopropyl-2-((trimethylsilyl)methyl)phenol (11c): **11c** was prepared from carvacrol (**2a**) as described above for **11b**. 58% yield (for 3 steps). Yellow oil; **TLC**, R_f = 0.31 (hexane–EtOAc = 10:1); **IR** (neat) 3462, 2988, 1504, 1251, 876 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.02 (s, 9H), 1.22 (d, *J* = 6.8 Hz, 6H), 2.01 (s, 2H), 2.81 (sep, *J* = 6.8 Hz, 1H), 4.39 (brs, 1H), 6.61 (s, 1H), 6.68 (dd, *J* = 1.2, 8.0 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ –1.6, 19.7, 24.0, 33.5, 113.1, 118.7, 123.4, 129.8, 146.4, 152.2; **HRMS** (FAB+) *m/z* calcd for [$C_{13}H_{22}OSi$] (M) 222.1440, found 222.1445.



5-Methyl-2-((trimethylsilyl)methyl)phenol (11d): **11d** was prepared from *p*-xylenol (**2b**) as described above for **11b**. 57% yield (for 3 steps). Yellow oil; **TLC**, R_f = 0.30 (hexane–EtOAc = 10:1); **IR** (neat) 3435, 2954, 2896, 1419, 1237, 845 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.02 (s, 9H), 2.01 (s, 2H), 2.26 (s, 3H), 4.43 (brs, 1H), 6.56 (s, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ –1.5, 19.7, 20.8, 115.7, 121.4, 123.2, 129.9, 135.0, 152.2; **HRMS** (FAB+) *m/z* calcd for [$C_{11}H_{18}OSi$] (M) 194.1127, found 194.1136.

Synthesis of 11e:



To a stirring mixture of 5-fluoro-2-methylphenol (**2c**, 0.540 mL, 5.00 mmol) and potassium carbonate (1.00 g, 7.50 mmol) in DMF (15.0 mL) was added methyl iodide (0.470 ml, 7.50 mmol) at room temperature. After stirring for 16 h, the solids were filtered-off and washed with Et_2O. The filtrate was neutralized with 1*M* HCl, and the aqueous layers were extracted Et_2O (twice). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo*. The residue was purified by column chromatography on silica gel (hexane–Et_2O as eluent) to give 4-fluoro-2-methoxy-1-methylbenzene (0.698 g, 4.98 mmol, 99% yield).

To a mixture of this methyl ether (0.698 g, 4.98 mmol) and benzoyl peroxide (0.120 g, 0.498 mmol) in CCl_4 (30.0 mL) was added *N*-bromosuccinimide (0.931 g, 5.23 mmol). The resulting mixture was refluxed with stirring for 7 h. The reaction mixture was cooled to room temperature, the solids were then filtered-off and washed with CH_2Cl_2. The filtrate was poured into H_2O, and the aqueous layers were extracted with CH_2Cl_2 (twice). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed under *vacuo*, and the residue was purified by column chromatography on silica gel (hexane–Et_2O as eluent) to give 1-(bromomethyl)-4-fluoro-2-methoxybenzene (0.872 g, 3.98 mmol, 80% yield).

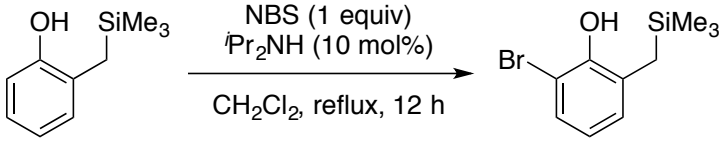
To a mixture of magnesium turnings (0.150 g, 5.97 mmol) and a crystal of iodine under N_2 was added dry THF (10.0 mL), and the resulting mixture was stirred for 10 min at room temperature.

To this mixture was added dropwise chlorotrimethylsilane (0.606 mL, 4.78 mmol) followed by a solution of aryl bromide (0.872 g, 3.98 mmol) in dry THF (10.0 mL) at 0 ºC. The resulting mixture was allowed to room temperature. After stirring for 2 h at room temperature, the reaction was quenched with brine, and the aqueous layers were extracted with EtOAc (twice). The combined organic layers were washed with brine, and dried over anhydrous $MgSO_4$. The solvents were removed under *vacuo*, and the residue was purified by column chromatography on silica gel (hexane–Et_2O as eluent) to give (4-fluoro-2-methoxybenzyl)trimethylsilane (0.499 g, 2.35 mmol, 59% yield).

To a solution of this compound (0.499 g, 2.35 mmol) in dry CH_2Cl_2 (10.0 mL) was added dropwise BBr_3 (2.35 mL, 2.35 mmol, 1.0 *M* in CH_2Cl_2) at –78 ºC. The resulting mixture was allowed to room temperature. After stirring for 3 h, the resulting mixture was poured into a water/ice mixture (5.00 mL). The aqueous layers were separated and extracted with CH_2Cl_2 (twice). The combined organic layers were washed with brine, and dried over anhydrous $MgSO_4$. The solvents were removed under *vacuo*, and the residue was purified by column chromatography on silica gel (hexane–Et_2O as eluent) to give**11e** (0.238 g, 1.20 mmol, 51% yield).

5-Fluoro-2-((trimethylsilyl)methyl)methyl)phenol (11e): Yellow oil; **TLC**, R_f = 0.32 (hexane–EtOAc = 10:1); **IR** ($CHCl_3$) 3452, 3085, 2990, 1734, 1683, 1362, 1147, 884 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.01 (s, 9H), 1.98 (s, 2H), 4.56 (brs, 1H) 6.48–6.56 (m, 2H), 6.85 (m, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 0.3, 15.9, 106.3, 106.5, 107.6, 107.8, 130.9, 131.0; **^{19}F NMR** ($CDCl_3$, 376 MHz), δ –115; **HRMS** (FAB+) *m/z* calcd for [$C_{10}H_{15}FOSi$] (M) 198.0876, found 198.0877.

Synthesis of 11f:[28]

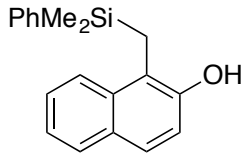


11a **11f**

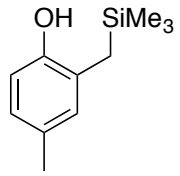
To a flame-dried flask equipped with a Soxhlet apparatus were added **11a** (0.360 g, 2.00 mmol), diisopropylamine (0.028 mL, 0.200 mmol) and CH_2Cl_2 (15.0 mL). The thimble was filled with *N*-bromosuccinimide (0.356 g, 2.00 mmol). The resulting mixture was stirred under reflux conditions. After consumption of *N*-bromosuccinimide in the thimble, the reaction mixture was cooled to room temperature, and then treated with 2 *M* aqueous sulfuric acid. The aqueous layers were extracted with CH_2Cl_2 (twice). The combined organic layers were washed with brine, and dried over anhydrous $MgSO_4$. The solvents were removed under *vacuo*, and the residue was purified by column chromatography on silica gel (hexane–Et_2O as eluent) to give **11f** (0.394 g, 1.52

mmol, 76% yield).

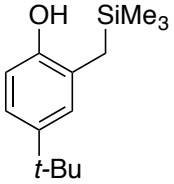
2-Bromo-6-((trimethylsilyl)methyl)phenol (11f): Yellow oil; **TLC**, R_f = 0.32 (hexane–EtOAc = 10:1); **IR** (neat) 3520, 2954, 2898, 1595, 1450, 1235, 1134, 857 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.01 (s, 9H), 2.13 (s, 2H), 5.43 (brs, 1H), 6.65 (dt, *J* = 1.2, 7.8 Hz, 1H), 6.88 (d, 7.8 Hz, 1H), 7.16 (dd, *J* = 1.2, 7.8 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ –1.6, 21.2, 110.3, 121.1, 127.6, 128.8, 129.2, 149.0; **HRMS** (FAB+) *m/z* calcd for [$C_{10}H_{15}{}^{79}$BrOSi]/ [$C_{10}H_{15}{}^{81}$BrOSi] ([M]/[M+2]) 258.0076/260.0055, found 258.0088/260.0057.



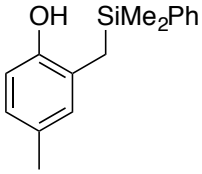
1-((Dimethyl(phenyl)silyl)methyl)-2-naphthol (11g): **11g** was prepared from 1-methylnaphthalen-2-ol (**2r**) as described above for **11b**. 44% yield (for 3 steps). White solid; **TLC**, R_f = 0.52 (hexane–EtOAc = 4:1); **IR** (KBr) 3303, 2920, 1923, 1664, 1624, 1363, 911, 739 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.26 (s, 6H), 2.71 (s, 2H), 4.41 (brs, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 7.29–7.39 (m, 5H), 7.52–7.55 (m, 3H), 7.74–7.77 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ –2.6, 15.2, 117.7, 118.5, 122.9, 123.8, 125.6, 125.8, 128.0, 128.4, 129.3, 129.5, 132.9, 133.6, 139.0, 149.3; **HRMS** (FAB+) *m/z* calcd for [$C_{19}H_{20}$OSi] (M) 292.1283, found 292.1288.



4-Methyl-2-(trimethylsilyl)methyl)phenol (11h): **11h** was prepared from 2,4-dimethylphenol as described above for **11a**. 74% yield (for 3 steps). Yellow oil; **TLC**, R_f = 0.63 (hexane–EtOAc = 4:1); **IR** (neat) 3466, 2954, 1606, 1507, 1249, 855 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.01 (s, 9H), 2.02 (s, 2H), 2.23 (s, 3H), 4.32 (brs, 1H), 6.62 (t, *J* = 4.4 Hz, 1H), 6.76 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ –1.6, 20.2, 20.6, 114.8, 125.6, 126.3, 129.7, 130.6, 150.2; **HRMS** (FAB+) *m/z* calcd for [$C_{11}H_{18}$OSi] (M) 194.1127, found 194.1128.



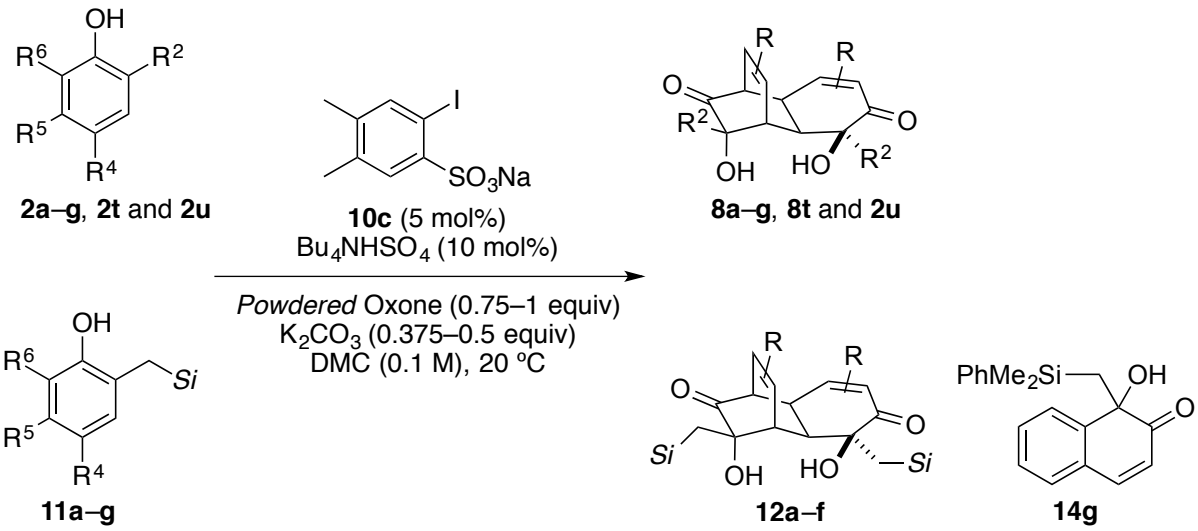
4-(*tert*-Butyl)-2-((trimethylsilyl)methyl)phenol (11i): **11i** was prepared from 4-*tert*-butyl-2-methylphenol as described above for **11b**. 65% yield (for 3 steps). Yellow oil; **TLC**, R_f = 0.30 (hexane–EtOAc = 10:1); **IR** (neat) 3435, 2957, 1506, 1247, 856 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.02 (s, 9H), 1.27 (s, 9H), 2.05 (s, 2H), 4.35 (brs, 1H), 6.65 (d, J = 8.8 Hz, 1H), 6.96–6.98 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ –1.6, 20.4, 31.5, 33.9, 114.4, 121.8, 125.7, 127.3, 143.2, 150.0; **HRMS** (FAB+) *m/z* calcd for [$C_{11}H_{18}OSi$] (M) 236.1596, found 236.1594.



2-((Dimethyl(phenyl)silyl)methyl)-4-methylphenol (11j): **11j** was prepared from 2,4-dimethylphenol as described above for **11b**. 61% yield (for 3 step). White solid; **TLC**, R_f = 0.34 (hexane–EtOAc = 10:1); **IR** (KBr) 3455, 2986, 1735, 1688, 1362, 1147, 877 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.32 (s, 6H), 2.23 (s, 3H), 2.27 (s, 2H), 4.22 (brs, 1H), 6.60 (d, J = 8.0 Hz, 1H), 6.72 (s, 1H), 6.79 (d, J = 8.0 Hz, 1H), 7.38–7.40 (m, 3H), 7.53–7.54 (m, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ –3.35, 19.7, 20.5, 115.2, 125.8 (2C), 127.4, 127.8, 129.2, 129.8, 130.8, 133.6, 133.9, 138.7, 150.3; **HRMS** (FAB+) *m/z* calcd for [$C_{16}H_{20}OSi$] (M) 256.1283, found 256.1288.

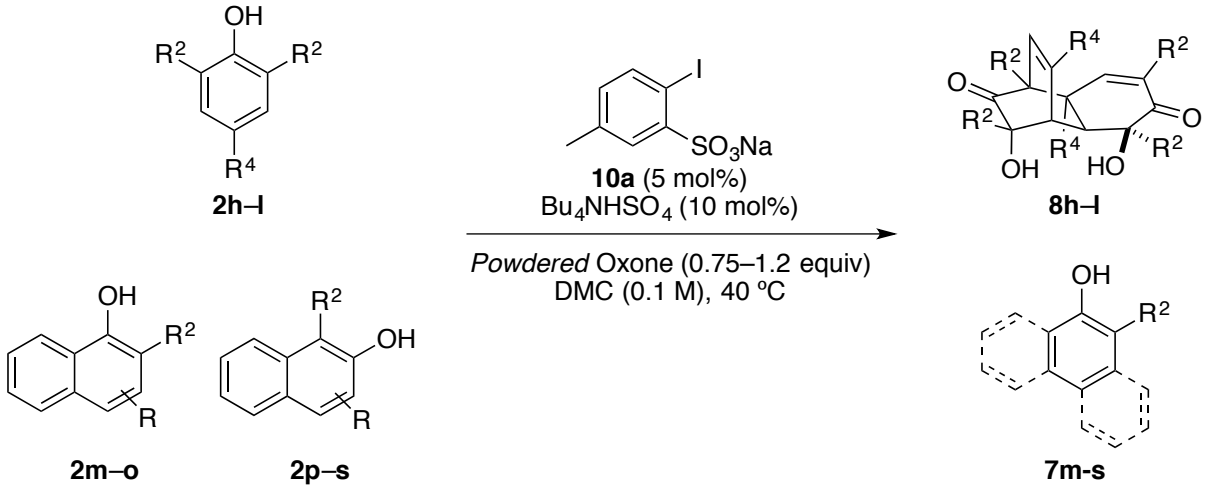
Representative Procedures for the Hydroxylative Dearomatization Reactions

Oxidation of Nonsymmetrically Substituted 2-Alklyphenols and 2-Naphthol 11g (Method A):



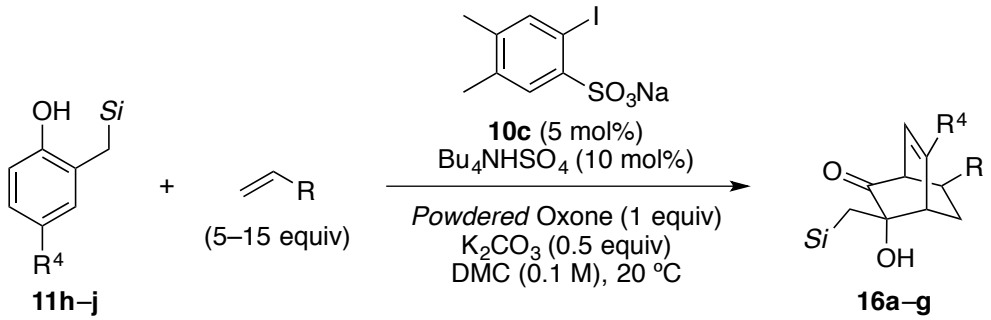
A mixture of *powdered* Oxone (0.310 g, 0.500 mmol) and potassium carbonate (0.0346 g, 0.250 mmol) in dimethyl carbonate (3.00 mL) was vigorously stirred at room temperature for 24 h. To the resulting mixture were added **2a** (0.0750 g, 0.500 mmol), **10c** (9.00 mg, 0.0250 mmol), Bu_4NHSO_4 (17.0 mg, 0.0500 mmol) and dimethyl carbonate (2.00 mL) at 20 ºC. The resulting mixture was stirred vigorously at 20 ºC. The reaction was monitored by TLC analysis. After 24 h, the solids were filtered-off and washed with EtOAc. The filtrate was washed with aqueous $NaHSO_3$ and water, and the aqueous layers were extracted with EtOAc (twice). The combined organic layers were washed with brine, and dried over anhydrous $MgSO_4$. The solvents were removed under *vacuo*, and the residue was purified by column chromatography on silica gel (hexane-EtOAc as eluent) to give **8a** (0.0683 g, 0.205 mmol, 82% yield).

Oxidation of Symmetrically Substituted Phenols and Naphthols (Method B):



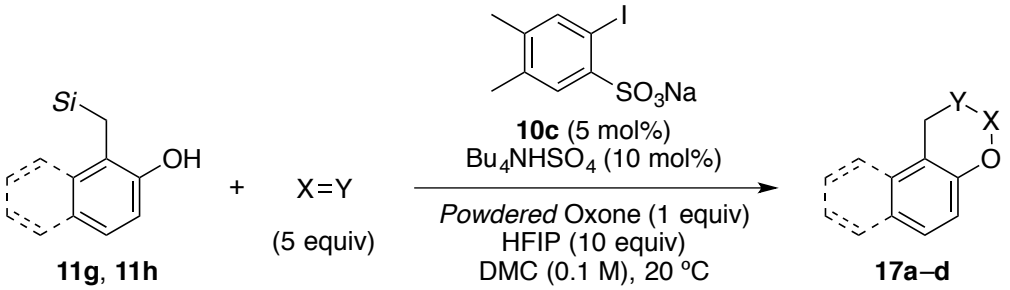
A mixture of **2h** (0.0611 g, 0.500 mmol), *powdered* Oxone (0.231 g, 0.375 mmol) and Bu_4NHSO_4 (17.0 mg, 0.0500 mmol) in dimethyl carbonate (5.00 mL) was vigorously stirred at 40 ºC in the presence of **10a** (8.40 mg, 0.0250 mmol). The reaction was monitored by TLC analysis. After 16 h, the reaction mixture was cooled to room temperature and the solids were filtered-off and washed with EtOAc. The filtrate was washed with aqueous $NaHSO_3$ and water, and the aqueous layers were extracted with EtOAc (twice). The combined organic layers were washed with brine, and dried over anhydrous $MgSO_4$. The solvents were removed under *vacuo*, and the residue was purified by column chromatography on silica gel (hexane-EtOAc as eluent) to give **8h** (0.0676 g, 0.245 mmol, 98% yield).

Oxidative Cascade Reactions to 16 (Method C):



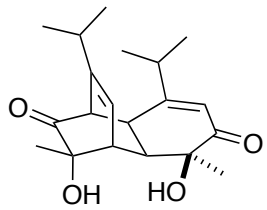
A mixture of *powdered* Oxone (0.310 g, 0.500 mmol) and potassium carbonate (0.0346 g, 0.250 mmol) in dimethyl carbonate (3.00 mL) was vigorously stirred at room temperature for 24 h. To the resulting mixture were added methyl vinyl ketone (0.208 mL, 2.50 mmol), **10c** (9.00 mg, 0.0250 mmol) and Bu_4NHSO_4 (17.0 mg, 0.0500 mmol) at 20 ºC. To the resulting mixture was added dropwise **11h** (0.0972 g, 0.500 mmol) in dimethyl carbonate (2.00 mL) over 3 minutes. The resulting mixture was stirred vigorously at 20 ºC. The reaction was monitored by TLC analysis. After 3 h, the solids were filtered-off and washed with EtOAc. The filtrate was washed with aqueous $NaHSO_3$ and water, and the aqueous layers were extracted with EtOAc (twice). The combined organic layers were washed with brine, and dried over anhydrous $MgSO_4$. The solvents were removed under *vacuo*, and the residue was purified by column chromatography on silica gel (hexane-EtOAc as eluent) to give **16a** (0.0849 g, 0.305 mmol, 61% yield).

Oxidative Cascade Reactions to 17 (Method D):

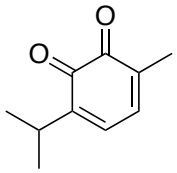


A mixture of **11h** (0.0972 g, 0.500 mmol), indene (0.290 g, 2.50 mmol), *powdered* Oxone (0.310 g, 0.500 mmol), 1,1,1,3,3,3-hexafluoro-2-propanol (0. 520 mL, 5.00 mmol) and Bu_4NHSO_4 (17.0 mg, 0.0500 mmol) in dimethyl carbonate (5.00 mL) was vigorously stirred at 20 ºC in the presence of **10c** (9.00 mg, 0.0250 mmol). The reaction was monitored by TLC analysis. After 7 h, the solids were filtered-off and washed with EtOAc. The filtrate was washed with aqueous $NaHSO_3$ and water, and the aqueous layers were extracted with EtOAc (twice). The combined organic layers were washed with brine, and dried over anhydrous $MgSO_4$. The solvents were removed under *vacuo*, and the residue was purified by column chromatography on silica gel (hexane-EtOAc as eluent) to give **17a** (0.0628 g, 0.264 mmol, 53% yield).

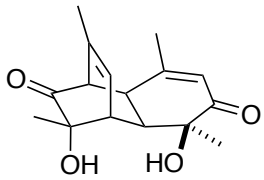
Characterization of Products:



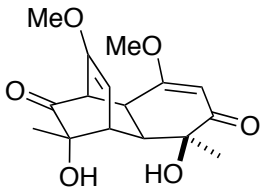
3,10-Dihydroxy-6,12-di-isopropyl-3,10-dimethyltricyclo[6.2.2.0^{2,7}]dodeca-5,11-diene-4,9-dione ((±)-Biscarvacrol, 8a):[13c] **Method A**: Oxone (1 equiv), K_2CO_3 (0.5 equiv), 24 h, 0.0683 g, 82% yield. White solid; **TLC**, R_f = 0.43 (hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.86 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 1.12 (t, *J* = 6.8 Hz, 6H), 1.23 (d, *J* = 6.8 Hz, 6H), 1.83 (sep, *J* = 6.8 Hz, 1H), 2.48 (sep, *J* = 6.8 Hz, 1H), 2.61 (brs, 1H), 3.08–3.15 (m, 2H), 3.23 (d, *J* = 8.8 Hz, 1H), 3.36 (dd, *J* = 2.4, 6.8 Hz, 1H), 4.09 (brs, 1H), 5.84 (dt, *J* = 1.2, 6.8 Hz, 1H), 5.96 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 19.2, 20.0, 20.7, 22.9, 25.7, 32.2, 32.8, 33.2, 40.8, 41.8, 44.6, 55.8, 72.7, 73.5, 119.8, 126.1, 145.5, 166.5, 201.9, 212.3.



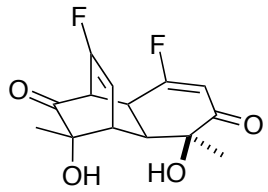
3-Isopropyl-6-methyl-1,2-quinone (9a): **Method A**: Oxone (1 equiv), K_2CO_3 (0.5 equiv), 24 h, 8.19 mg, 10% yield. Red solid; **TLC**, R_f = 0.64 (hexane–EtOAc = 1:1); **IR** ($CHCl_3$) 2897, 1761, 1753, 1451, 1221, 877 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.07 (d, *J* = 6.8 Hz, 6H), 1.94 (s, 3H), 2.92 (sep, *J* = 6.8 Hz, 1H), 6.64 (d, *J* = 6.8 Hz, 1H), 6.76 (dd, *J* = 1.6, 6.8 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 15.2, 21.4, 27.0, 133.0, 136.2, 137.1, 147.5, 180.6, 181.5; **HRMS** (FAB+) *m/z* calcd for [$C_{10}H_{13}O_2$] (M+H) 165.0916, found 165.0917.



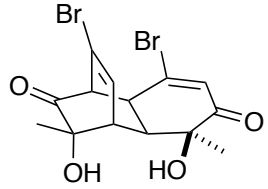
3,10-Dihydroxy-3,7,10,12-tetramethyltricyclo[6.2.2.0^{2,7}]dodeca-5,11-diene-4,9-dione (8b):[13c] **Method A**: Oxone (1 equiv), K_2CO_3 (0.5 equiv), 24 h, 0.0449 g, 65% yield. White solid; **TLC**, R_f = 0.24 (hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.25 (s, 3H), 1.30 (s, 3H), 1.61 (s, 3H), 2.00 (s, 3H), 2.37 (brs, 1H), 3.15–3.17 (m, 3H), 3.32 (dd, *J* = 1.2, 6.8 Hz, 1H), 4.01 (brs, 1H), 5.86 (d, *J* = 6.8 Hz, 1H), 6.02 (d, *J* = 8.4 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 21.5, 22.4, 25.9, 32.0, 41.1, 44.2, 44.7, 56.9, 73.0, 73.1, 124.8, 128.3, 136.5, 156.4, 201.4, 212.8.



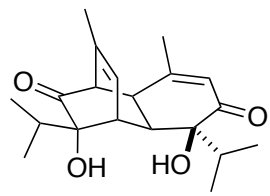
3,10-Dihydroxy-6,12-dimethoxy-3,10-dimethyltricyclo[6.2.2.0^{2,7}]dodeca-5,11-diene-4,9-dione (8c):[29] **Method A**: Oxone (1 equiv), K_2CO_3 (0.5 equiv), 80 °C, 48 h, 0.0540 g, 70% yield. White solid; **TLC**, R_f = 0.17 (hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.30 (s, 3H), 1.33 (s, 1H), 2.23 (brs, 1H), 3.17 (d, *J* = 8.8 Hz, 1H), 3.25 (dd, *J* = 1.6, 8.8 Hz, 1H), 3.32–3.37 (m, 2H), 3.43 (s, 3H), 3.68 (s, 3H), 4.13 (brs, 1H), 4.84 (dd, *J* = 1.6, 7.2 Hz, 1H), 5.43 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 25.5, 32.4, 40.1, 42.1, 43.3, 55.2, 56.1, 56.4, 72.5, 73.9, 96.2, 99.6, 154.4, 172.6, 201.0, 211.4.



6,12-Difluoro-3,10-Dihydroxy-3,10-dimethyltricyclo[6.2.2.0^{2,7}]dodeca-5,11-diene-4,9-dione (8d): **Method A**: Oxone (1 equiv), K_2CO_3 (0.5 equiv), 24 h, 0.0441 g, 62% yield. White solid; **TLC**, R_f = 0.25 (hexane–EtOAc = 1:1); **IR** (KBr) 3485, 3451, 2930, 2888, 2361, 1737, 1690, 1665 cm^{-1}; **^{1}H NMR** (CD_3CN, 400 MHz) δ 1.26 (s, 3H), 1.34 (s, 3H), 3.19 (dd, *J* = 2.4, 8.8 Hz, 1H), 3.26 (dd, *J* = 2.4, 8.8 Hz, 1H), 3.45 (d, *J* = 13 Hz, 1H), 3.61–3.62 (m, 1H), 3.83 (s, 1H), 3.98 (s, 1H), 5.49–5.51 (m, 1H), 5.93 (d, *J* = 13 Hz, 1H); **^{13}C NMR** (DMSO-d_6, 100 MHz) δ 25.1, 31.0, 43.7, 43.8, 52.4, 52.6, 56.3, 72.0, 73.1, 106.4, 108.8 (d, J_{C-F} = 11 Hz), 155.0 (d, J_{C-F} = 282 Hz), 171.7 (d, J_{C-F} = 284 Hz), 199.8 (d, J_{C-F} = 16 Hz), 207.1; **^{19}F NMR** (CD_3CN, 125 MHz) δ –104.3, –84.8; **HRMS** (FAB+) *m/z* calcd for [$C_{14}H_{15}F_2O_4$] (M+H) 285.0938, found 285.0937.

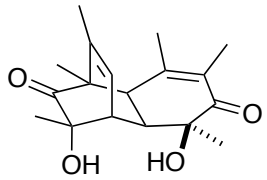


6,12-Dibromo-3,10-dihydroxy-3,10-dimethyltricyclo[6.2.2.0^{2,7}]dodeca-5,11-diene-4,9-dione (8e): **Method A**: Oxone (1 equiv), K_2CO_3 (0.5 equiv), 24 h, 0.0810 g, 80% yield. White solid; **TLC**, R_f = 0.40 (hexane–EtOAc = 1:1); **IR** (KBr) 3488, 3453, 2927, 2857, 2361, 1737, 1688, 1671 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.30 (s, 3H), 1.40 (s, 3H), 2.31 (brs, 1H), 3.20 (d, *J* = 8.8 Hz, 1H), 3.51 (dd, *J* = 1.6, 7.2 Hz, 1H), 3.62 (dd, *J* = 2.8, 8.8 Hz, 1H), 3.86 (brs, 1H), 3.91 (d, *J* = 2.8 Hz, 1H), 6.44 (dd, *J* = 1.6, 7.2 Hz, 1H), 6.67 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 25.7, 31.2, 42.1, 46.9, 49.5, 60.9, 72.6, 73.1, 117.4, 131.7, 134.4, 144.4, 198.1, 209.3; **HRMS** (FAB+) *m/z* calcd for [$C_{14}H_{15}{}^{79}Br_2O_4$]/[$C_{14}H_{15}{}^{79}Br^{81}BrO_4$]/[$C_{14}H_{15}{}^{81}Br_2O_4$] ([M+H]/[M+H+2]/[M+H+4]) 404.9332/406.9311/408.9291, found 404.9334/406.9318/408.9290.

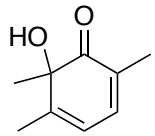


3,10-Dihydroxy-3,10-diisopropyl-6,12-dimethyltricyclo[6.2.2.0^{2,7}]dodeca-5,11-diene-4,9-dione

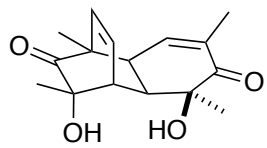
((±)-Bisthymol, 8f):[13c] **Method A**: Oxone (1 equiv), K_2CO_3 (0.5 equiv), 24 h, 0.0548 g, 66% yield. White solid; **TLC**, R_f = 0.55 (hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.59 (d, *J* = 6.4 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H), 0.85 (d, *J* = 6.4Hz, 3H), 0.98 (d, *J* = 6.4 Hz, 3H), 1.56–1.63 (m, 4H), 1.78 (sep, *J* = 6.4 Hz, 1H), 1.98 (s, 3H), 2.21 (brs, 1H), 3.10 (d, *J* = 7.8 Hz, 1H), 3.18 (s, 1H), 3.26–3.32 (m, 2H), 3.79 (brs, 1H), 5.84 (d, *J* = 6.8 Hz, 1H), 6.00 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 16.1, 16.3, 16.6, 16.7, 21.4, 22.1, 32.4, 37.2, 37.3, 41.9, 47.2, 57.2, 77.8, 78.2, 125.4, 126.5, 135.8, 155.9, 201.8, 214.9.



3,10-Dihydroxy-3,5,6,8,10,12-hexamethyltricyclo[6.2.2.0^{2,7}]dodeca-5,11-diene-4,9-dione (8g):[13c] **Method A**: Oxone (1 equiv), K_2CO_3 (0.5 equiv), 24 h, 0.0532 g, 70% yield. Pale yellow solid; **TLC**, R_f = 0.33 (hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.18 (s, 3H), 1.23 (s, 3H), 1.24 (d, *J* = 1.6 Hz, 3H), 1.45 (d, *J* = 1.6 Hz, 3H), 1.82 (s, 3H), 2.00 (s, 3H), 2.22 (brs, 1H), 2.88 (d, *J* = 8.8 Hz, 1H), 2.98 (dd, *J* = 2.4, 8.8 Hz, 1H), 3.34 (dd, *J* = 2.4, 6.8 Hz, 1H), 4.14 (brs, 1H), 5.97 (d, *J* = 6.8 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 13.5, 15.1, 18.7, 23.6, 26.2, 32.0, 41.1, 44.1, 48.8, 56.3, 71.9, 73.8, 76.7, 131.1, 132.2, 136.9, 148.4, 202.9, 213.8.

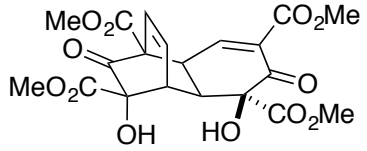


6-Hydroxy-2,5,6-trimethylcyclohexa-2,4-dienone:[13c] **Method A**: Oxone (1 equiv), K_2CO_3 (0.5 equiv), 24 h, 0.0167 g, 22% yield. Yellow oil; **TLC**, R_f = 0.60 (hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.36 (s, 3H), 1.91 (s, 3H), 1.99 (s, 3H), 3.42 (brs, 1H), 5.81 (d, *J* = 6.0 Hz, 1H), 6.73 (d, *J* = 6.0 Hz, 1H).

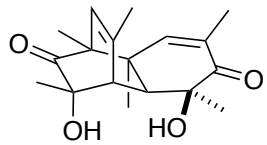


3,10-Dihydroxy-3,5,8,10-tetramethyltricyclo[6.2.2.0^{2,7}]dodeca-5,11-diene-4,9-dione (8h):[13c] **Method B**: Oxone (0.75 equiv), 16 h, 0.0677 g, 98% yield. White solid; **TLC**, R_f = 0.36 (hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.24 (s, 3H), 1.32 (s, 3H), 1.35 (s, 3H), 1.85 (s, 3H),

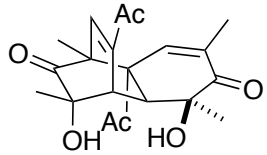
2.28 (brs, 1H), 2.86–2.89 (m, 1H), 3.25 (d, *J* = 8.4 Hz, 1H), 3.39 (d, *J* = 6.8 Hz, 1H), 4.01 (brs, 1H), 5.52 (d, *J* = 8.4 Hz, 1H), 6.24–6.30 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 15.6, 16.4, 26.2, 31.7, 42.6, 43.6, 44.2, 53.7, 72.9, 73.6, 133.2, 135.3, 135.7, 139.3, 203.0, 214.9.



Tetramethyl 6,9-dihydroxy-5,10-dioxotricyclo[6.2.2.0^{2,7}]dodeca-3,11-diene-1,4,6,9-tetracarboxylate (8i): **Method B**: Oxone (1.2 equiv), 72 h, 0.105 g, 93% yield. Pale red solid; **TLC**, R_f = 0.17 (hexane–EtOAc = 1:2); **IR** (KBr) 3422, 3357, 1748, 1720, 1701, 1691, 1679, 1173, 870 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 3.61 (dd, *J* = 1.6, 6.8 Hz, 1H), 3.70 (s, 3H), 3.71 (s, 3H), 3.78 (s, 3H), 3.92 (s, 3H), 3.78–3.95 (m, 2H), 4.08–4.17 (m, 1H), 4.55 (brs, 1H), 6.17 (dd, *J* = 1.2, 8.0, 1H), 6.42 (dd, *J* = 6.4, 8.4 Hz, 1H), 7.42 (d, *J* = 4.4 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 38.1, 40.6, 41.0, 52.7, 53.4, 53.7, 53.8, 63.6, 76.2, 79.2, 127.3, 131.7, 135.1, 153.8, 161.8, 167.3, 169.2, 169.5, 190.3, 198.4; **HRMS** (FAB+) *m/z* calcd for [$C_{20}H_{21}O_{12}$] (M+H) 453.1033, found 453.1029.

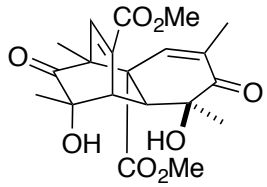


3,10-Dihydroxy-3,5,7,8,10,11-hexamethyltricyclo[6.2.2.0^{2,7}]dodeca-5,11-diene-4,9-dione (8j):[13c] **Method B**: Oxone (0.75 equiv), 16 h, 0.0714 g, 94% yield. White solid; **TLC**, R_f = 0.42 (hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.17 (s, 3H), 1.24 (s, 6H), 1.36 (s, 3H), 1.70 (s, 3H), 1.83 (s, 3H), 2.12 (brs, 1H), 2.80 (d, *J* = 2.0 Hz, 1H), 3.15 (s, 1H), 3.92 (brs, 1H), 5.04 (s, 1H), 6.03 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 12.4, 16.3, 21.4, 23.2, 25.2, 32.4, 45.3, 48.6 (2C), 57.7, 72.2, 73.7, 127.5, 133.0, 145.0, 145.2, 202.5, 214.2.

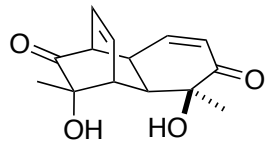


2,9-Diacyl-6,12-Dihydroxy-1,4,6,12-tetramethyltricyclo[6.2.2.0^{2,7}]dodeca-3,9-diene-5,11-dione (8k): **Method B**: Oxone (0.75 equiv), 12 h, 0.0820 g, 91% yield. White solid; **TLC**, R_f = 0.43 (hexane–EtOAc = 1:1); **IR** (KBr) 3490, 3464, 2930, 2856, 2361, 1737, 1688, 1671 cm^{-1}; **^{1}H NMR**

($CDCl_3$, 400 MHz) δ 1.19 (s, 3H), 1.29 (s, 3H), 1.36 (s, 3H), 1.92 (s, 3H), 2.19 (s, 3H), 2.39 (s, 3H), 3.36 (s, 1H), 3.47 (brs, 1H), 3.75 (brs, 1H), 4.07 (t, *J* = 2.0 Hz, 1H), 6.24 (d, *J* = 2.4 Hz, 1H,), 6.58 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 13.7, 16.7, 24.9, 25.6, 30.1, 30.6, 42.8, 49.4, 58.8, 63.8, 71.7, 73.1, 136.8, 137.1, 141.8, 146.6, 194.1, 201.4, 209.2, 210.5; **HRMS** (FAB+) *m/z* calcd for [$C_{20}H_{26}O_6$] (M+H) 361.1651, found 361.1652.

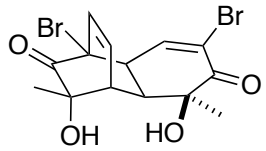


Dimethyl 6,12-dihydroxy-1,4,6,12-tetramethyl-5,11-dioxotricyclo[6.2.2.0^{2,7}]dodeca-3,9-diene-2,9-dicarboxylate (8l): **Method B**: Oxone (0.75 equiv), 12 h, 0.0892 g, 91% yield. White solid; **TLC**, R_f = 0.30 (hexane–EtOAc = 1:1); **IR** (KBr) 3445, 1743, 1709, 1685, 1444, 1253 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.25 (s, 3H), 1.33 (s, 6H), 1.87 (s, 3H), 3.41 (s, 1H), 3.51 (brs, 1H), 3.78 (s, 3H), 3.84 (s, 3H), 3.88 (s, 1H), 3.99 (brs, 1H), 6.40 (s, 1H), 6.45 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 13.6, 16.5, 25.7, 30.1, 44.2, 49.3, 52.4, 53.7, 58.0, 58.7, 71.7, 73.1, 135.8, 136.0, 138.9, 142.2, 163.7, 174.2, 201.5, 208.7; **HRMS** (FAB+) *m/z* calcd for [$C_{20}H_{25}O_8$] (M+H) 393.1544, found 393.1545.

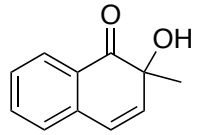


3,10-Dihydroxy-3,10-dimethyltricyclo[6.2.2.0^{2,7}]dodeca-5,11-diene-4,9-dione (8t):[30] **Method A**: Oxone (1 equiv), K_2CO_3 (0.5 equiv), 24 h, 0.0124 g, 20% yield. **8t** was also synthesized from **12b**: To a mixture of **12b** (0.0516 g, 0.100 mmol) in THF (2.00 mL) and phosphate buffer (pH 6.6, 1.00 mL, 1.0 *M* in water) was added tetrabutylammonium fluoride (0.800 mL, 0.800 mmol, 1.0 *M* in THF). The resulting mixture was stirred at 50 ºC. After 8 h, the reaction mixture was cooled to room temperature, and then the aqueous layers were extracted with EtOAc (twice). The organic layers were washed with brine, and dried over anhydrous $MgSO_4$. The solvents were removed under *vacuo*, and the residue was purified by column chromatography on silica gel (hexane-EtOAc as eluent) to give **8t** (0.0181 g, 0.0730 mmol, 73% yield). White solid; **TLC**, R_f = 0.40 (hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.26 (s, 3H), 1.37 (s, 3H), 2.23 (brs, 1H), 3.24–3.35 (m, 3H), 3.43 (d, *J* = 6.4 Hz, 1H), 3.95 (brs, 1H), 5.87 (m, 1H), 6.13 (dd, *J* = 1.2, 10 Hz, 1H), 6.33

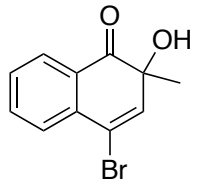
(t, *J* = 8.0 Hz, 1H), 6.49 (dd, *J* = 4.0, 10 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz), δ 26.0, 31.9, 39.8, 42.0, 45.1, 52.2, 73.0, 73.6, 76.7, 127.6, 127.9, 136.1, 146.7, 202.0, 212.7.



5,8-Dibromo-3,10-dihydroxy-3,10-dimethyltricyclo[6.2.2.0^{2,7}]dodeca-5,11-diene-4,9-dione (8u): Method B: Oxone (1 equiv), 44 h, 0.0274 g, 27% yield. Pale yellow solid; **TLC**, R_f = 0.40 (hexane–EtOAc = 1:1); **IR** (KBr) 3445, 1743, 1709, 1685, 1444, 1253 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.34 (s, 3H), 1.43 (s, 3H), 2.84 (brs, 2H), 3.45–3.50 (m, 4H), 6.00 (dd, *J* = 1.6, 8.2 Hz, 1H), 6.22–6.26 (m, 1H), 7.31 (d, *J* = 4.0 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz), δ 26.7, 31.4, 43.3, 43.5, 48.2, 70.3, 72.6, 74.7, 121.0, 133.8, 135.3, 145.4, 195.7, 203.8; **HRMS** (FAB+) *m/z* calcd for $[C_{14}H_{15}{}^{79}Br_2O_4]$/ $[C_{14}H_{15}{}^{79}Br^{81}BrO_4]$/$[C_{14}H_{15}{}^{81}Br_2O_4]$ ([M+H]/[M+H+2]/[M+H+4]) 404.9332/406.9311/408.9291, found 404.9340/406.9312/408.9301.

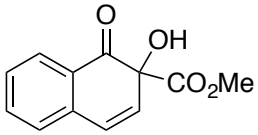


2-Hydroxy-2-methylnaphthalen-1(2*H*)-one (7m):[13c] **Method B**: Oxone (0.75 equiv), 16 h, 0.0706 g, 81% yield. Pale red solid; **TLC**, R_f = 0.27 (hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.46 (s, 3H), 3.40 (brs, 1H), 6.33 (d, *J* = 10 Hz, 1H), 6.49 (d, *J* = 10 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.37 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.59 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.98 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 28.2, 75.1, 124.0, 127.0, 127.3, 127.9, 135.0, 136.9, 137.6, 204.0.

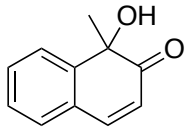


4-Bromo-2-hydroxy-2-methylnaphthalen-1(2*H*)-one (7n): Method B: Oxone (0.75 equiv), 12 h, 0.0886 g, 70% yield. Pale red solid; **TLC**, R_f = 0.37 (hexane–EtOAc = 4:1); **IR** (KBr) 3375, 1682, 1428, 1157. 876 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.48 (s, 3H), 3.42 (brs, 1H), 6.77 (s, 1H), 7.47 (dt, *J* = 4.4, 7.8 Hz, 1H), 7.71 (d, *J* = 4.4 Hz, 2H), 7.99 (d, *J* = 7.8 Hz, 1H); **^{13}C NMR**

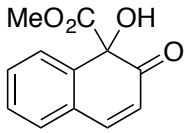
($CDCl_3$, 100 MHz) δ 27.9, 77.0, 118.4, 127.3, 128.1, 128.2, 129.3, 135.5, 135.9, 138.2, 202.1; **HRMS** (FAB+) *m/z* calcd for [$C_{11}H_{10}{}^{79}BrO_2$]/ [$C_{11}H_{10}{}^{81}BrO_2$] ([M+H]/[M+H+2]) 252.9859/254.9838, found 252.9869/252.9844.



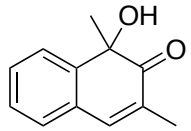
Methyl 2-hydroxy-1-oxo-1,2-dihydronaphthalene-2-carboxylate (7o):[13c] **Method B**: Oxone (0.75 equiv), 35 h, 0.0927 g, 85% yield. Pale yellow solid; **TLC**, R_f = 0.45 (hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 3.70 (s, 1H), 4.23 (brs, 1H), 6.13 (d, *J* = 9.6 Hz, 1H), 6.74 (d, *J* = 9.6 Hz, 1H), 7.28 (d, *J* = 7.8 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 1H), 7.62 (dt, *J* = 1.2, 7.8 Hz, 1H), 7.99 (d, *J* = 7.8 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 53.7, 77.8, 127.5, 127.8, 128.1, 128.8, 129.1, 129.7, 135.6, 137.5, 169.6, 196.6.



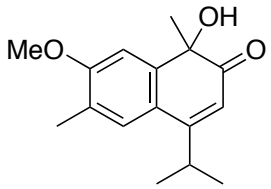
1-Hydroxy-1-methylnaphthalen-2(1*H*)-one (7p):[30] **Method B**: Oxone (0.75 equiv), 12 h, 0.0758 g, 87% yield. Pale yellow solid; **TLC**, R_f = 0.52 (hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.56 (s, 3H), 3.70 (brs, 1H), 6.21 (d, *J* = 10 Hz, 1H), 7.26–7.34 (m, 2H), 7.43–7.47 (m, 2H), 7.72 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 33.1, 77.1, 122.3, 125.4, 127.8, 128.2, 129.4, 130.6, 145.0, 145.9, 205.2.



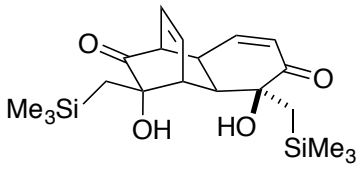
Methyl 1-hydroxy-2-oxo-1,2-dihydronaphthalene-1-carboxylate (7q): Method B: Oxone (0.75 equiv), 19 h, 0.103 g, 94% yield. White solid; **TLC**, R_f = 0.18 (hexane–EtOAc = 4:1); **IR** (KBr) 3420, 1738, 1692, 1268, 942, 866 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 3.66 (s, 3H), 4.50 (brs, 1H), 6.23 (d, *J* = 10 Hz, 1H), 7.36–7.45 (m, 3H), 7.51 (d, *J* = 10 Hz, 1H), 7.61 (d, *J* = 7.2 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 53.8, 79.0, 122.9, 127.0, 129.3, 129.7, 129.8, 130.7, 137.8, 147.3, 169.7, 197.2; **HRMS** (FAB+) *m/z* calcd for [$C_{12}H_{10}O_4$] (M+H) 219.0657, found 219.0666.



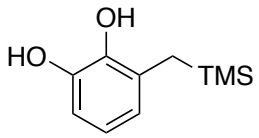
1-Hydroxy-1,3-dimethylnaphthalen-2(1*H*)-one (7r): Method B: Oxone (0.75 equiv), 12 h, 0.0846 g, 90% yield. Pale yellow solid; **TLC**, R_f = 0.64 (hexane–EtOAc = 1:1); **IR** (KBr) 3474, 2973, 2945, 2919, 1650 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.52 (s, 3H), 2.04 (s, 3H), 3.71 (brs, 1H), 7.20–7.30 (m, 3H), 7.36 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.65 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 15.4, 33.2, 76.9, 125.2, 127.7, 128.4, 128.5, 129.4, 130.2, 142.0, 144.0, 205.8; **HRMS** (FAB+) *m/z* calcd for [$C_{12}H_{12}O_2$] (M+H) 189.0916, found 189.0922.



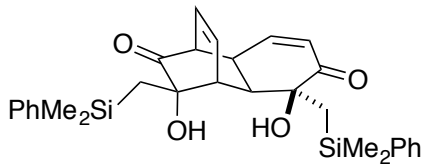
1-Hydroxy-4-isopropyl-7-methoxy-1,6-dimethylnaphthalen-2(1*H*)-one ((±)-Lacinilene C methyl ether, 7s):[5d] **Method B**: Oxone (0.75 equiv), 16 h, 0.118 g, 91% yield. Pale yellow solid; **TLC**, R_f = 0.44 (Hexane–EtOAc = 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.26 (d, *J* = 6.8 Hz, 3H), 1.28 (d, *J* = 6.8 Hz, 3H), 1.53 (s, 3H), 2.24 (s, 3H), 3.22 (sep, *J* = 6.8 Hz, 1H), 3.82 (brs, 1H), 3.93 (s, 3H), 6.03 (s, 1H), 7.21 (s, 1H), 7.36 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 16.2, 21.9, 22.2, 29.1, 34.0, 55.6, 76.8, 107.3, 114.7, 121.1, 125.3, 127.6, 145.5, 159.4, 164.2, 205.5.



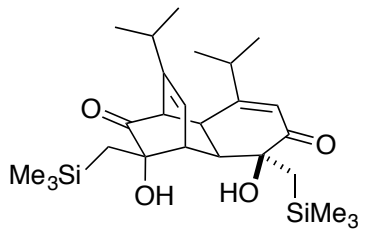
3,10-Dihydroxy-3,10-bis((trimethylsilyl)methyl)tricyclo[6.2.2.0^{2,7}]dodeca-5,11-diene-4,9-dione (12a): Method A: Oxone (1 equiv), K_2CO_3 (0.5 equiv), 6 h, 0.063 g, 64% yield. White solid; **TLC**, R_f = 0.31 (hexane–EtOAc = 4:1); **IR** (KBr) 3454, 3055, 2953, 1672, 1620, 1249 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.05 (s, 9H), 0.09 (s, 9H), 0.84 (d, *J* = 15 Hz, 1H), 0.97 (d, *J* = 15 Hz, 1H), 0.98 (d, *J* = 15 Hz, 1H), 1.10 (d, *J* = 15 Hz, 1H), 2.12 (brs, 1H), 3.20–3.27 (m, 2H), 3.37 (dd, *J* = 1.2, 8.0 Hz, 1H), 3.55 (d, *J* = 7.2 Hz, 1H), 3.89 (brs, 1H), 5.84 (dt, *J* = 1.6, 10 Hz, 1H), 6.10 (dd, *J* = 1.2, 10 Hz, 1H), 6.24 (dd, *J* = 1.2, 8.0 Hz, 1H), 6.42 (dd, *J* = 4.0, 10 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 0.1, 0.3, 27.6, 34.2, 40.5, 43.2, 44.4, 51.9, 75.3, 75.4, 128.0 (2C), 136.0, 146.3, 202.0, 214.6; **HRMS** (FAB+) *m/z* calcd for [$C_{20}H_{33}O_4Si_2$] (M+H) 393.1917, found 393.1921.



3-((Trimethylsilyl)methyl)catechol: Method C, 6 h, 0.0147 g, 15% isolated yield. The generation of the corresponding quinone **13a** was confirmed by i*n situ* NMR analysis with 33% yield. However, **13a** could not be isolated. This catechol was isolated after reductive work-up (aqueous $NaHSO_3$, 3 h at room temperature). Pale yellow oil; **TLC**, R_f = 0.22 (hexane–EtOAc = 4:1); **IR** ($CHCl_3$) 3460, 3407, 2875, 1622, 1430, 944 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.02 (s, 9H), 2.07 (s, 2H), 4.99–5.00 (brs, 2H), 6.54 (t, *J* = 7.2 Hz, 1H), 6.60 (d, *J* = 7.2 Hz, 1H), 6.65 (d, *J* = 7.2 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ –1.6, 20.2, 111.2, 119.9, 122.2, 127.5, 140.9, 143.0; **HRMS** (FAB) *m/z* calcd for [$C_{10}H_{16}O_2Si$] (M) 196.0920 found 196.0922.

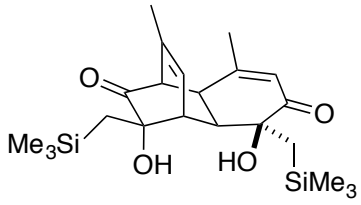


3,10-Dihydroxy-3,10-bis((dimethylphenylsilyl)methyl)tricyclo[6.2.2.0^{2,7}]dodeca-5,11-diene-4,9-dione (12b): Method A: Oxone (1 equiv), K_2CO_3 (0.5 equiv), 6 h, 0.0801 g, 62% yield. White solid; **TLC**, R_f = 0.34 (hexane–EtOAc = 4:1); **IR** (KBr) 3153, 3055, 2977, 1733, 1684, 1558, 1541, 1250, 1112, 907 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.37 (s, 3H), 0.39 (s, 3H), 0.40 (s, 3H), 0.42 (s, 3H), 1.05 (d, *J* = 15 Hz, 1H), 1.23–1.27 (m, 3H), 2.06 (brs, 1H), 3.12–3.13 (m, 2H), 3.28 (d, *J* = 7.6 Hz, 1H), 3.44 (d, *J* = 6.8 Hz, 1H), 3.80 (brs, 1H), 5.76 (t, *J* = 6.8 Hz, 1H), 5.92–5.99 (m, 2H), 6.30 (dd, *J* = 4.0, 10 Hz, 1H), 7.31–7.33(m, 3H), 7.37–7.40 (m, 3H), 7.46–7.47 (m, 2H), 7.54–7.55 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ –1.5 (2C), –1.4, –1.2, 27.2, 33.5, 40.2, 42.9, 44.5, 51.8, 75.0, 75.2, 127.7, 127.8, 127.9, 128.8, 129.1, 133.3, 133.6 (2C), 135.9, 138.9, 139.5, 146.1, 201.6, 213.9; **HRMS** (FAB+) *m/z* calcd for [$C_{30}H_{37}O_4Si_2$] (M+H) 517.2225, found 517.2223.

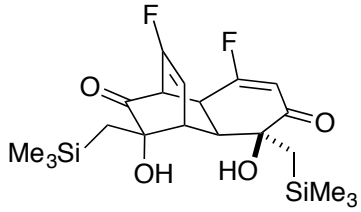


3,10-Dihydroxy-3,12-diisopropyl-3,10-bis((trimethylsilyl)methyl)tricyclo[6.2.2.0^{2,7}]dodeca-5,11-diene-4,9-dione (12c): Method A: Oxone (1 equiv), K_2CO_3 (0.5 equiv), 5 h, 0.112 g, 94% yield.

White solid; **TLC**, R_f = 0.33 (hexane–EtOAc = 4:1); **IR** (KBr) 3469, 2959, 1719, 1681, 1249, 843 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.02 (s, 9H), 0.09 (s, 9H), 0.75 (d, *J* = 16 Hz, 1H), 0.87–0.92 (m, 8H), 1.01 (d, *J* = 16 Hz, 1H), 1.11 (d, *J* = 6.8 Hz, 3H), 1.13 (d, *J* = 6.8 Hz, 3H), 1.82 (sep, *J* = 6.8 Hz, 1H), 2.04 (brs, 1H), 2.47 (sep, *J* = 6.8 Hz, 1H), 3.13–3.20 (m, 3H), 3.50 (d, *J* = 6.8 Hz, 1H), 3.97 (brs, 1H), 5.76 (d, *J* = 6.4 Hz, 1H), 5.93 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 0.1, 0.3, 19.2, 20.1, 20.8, 23.0, 27.6, 32.7, 33.2, 34.8, 42.2, 42.7, 43.9, 55.6, 75.1, 75.5, 120.3, 126.0, 145.6, 165.7, 202.1, 214.4; **HRMS** (FAB+) *m/z* calcd for [$C_{26}H_{46}O_4Si_2$] (M+H) 477.2851, found 477.2855.

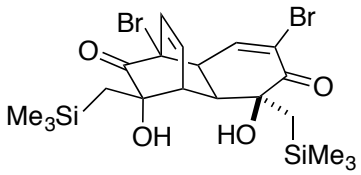


3,10-Dihydroxy-6,11-dimethyl-3,10-bis((trimethylsilyl)methyl)tricyclo[6.2.2.0^{2,7}]dodeca-5,11-diene-4,9-dione (12d): **Method A**: Oxone (1 equiv), K_2CO_3 (0.5 equiv), 5 h, 0.0757 g, 72% yield. White solid; **TLC**, R_f = 0.33 (hexane–EtOAc = 4:1); **IR** (KBr) 3493, 2950, 1721, 1667, 1244, 1178, 1009, 850 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.03 (s, 9H), 0.08 (s, 9H), 0.82–1.01 (m, 4H), 1.61 (s, 3H), 2.05 (s, 3H), 3.09 (d, *J* = 8.8 Hz, 1H), 3.14 (brs, 1H), 3.22 (d, *J* = 8.8 Hz, 1H), 3.46 (d, *J* = 6.8 Hz, 1H), 3.92 (brs, 1H), 5.78 (d, *J* = 6.8 Hz, 1H), 5.98 (d, *J* = 1.2 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 0.1, 0.3, 21.5, 22.3, 27.5, 34.3, 42.2, 43.9, 44.8, 56.6, 74.8, 75.4, 125.2, 128.3, 155.7, 201.5, 214.7; **HRMS** (FAB+) *m/z* calcd for [$C_{22}H_{37}O_4Si_2$] (M+H) 421.2225, found 421.2223.

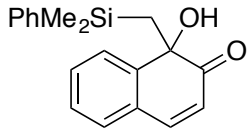


6,11-Difluoro-3,10-Dihydroxy-3,10-bis((trimethylsilyl)methyl)tricyclo[6.2.2.0^{2,7}]dodeca-5,11-diene-4,9-dione (12e): **Method A**: Oxone (1 equiv), K_2CO_3 (0.5 equiv), 7 h, 0.0889 g, 83% yield. White solid; **TLC**, R_f = 0.30 (hexane–EtOAc = 4:1); **IR** (KBr) 3473, 3104, 3073, 2952, 2909, 1732, 1689, 835 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.05 (s, 9H), 0.09 (s, 9H), 0.98–1.07 (m, 4H), 2.21 (brs, 1H), 3.36–3.40 (m, 2H), 3.49 (dt, *J* = 2.4, 12 Hz, 1H), 3.58 (dd, *J* = 1.6, 6.0 Hz, 1H), 3.89 (brs, 1H), 5.40 (sep, *J* = 2.4 Hz, 1H), 5.91 (d, *J* = 12 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 0.1, 0.3, 27.1, 34.1 (d, $J_{C–F}$ = 9.5 Hz), 41.0, 41.6, 42.6, 52.5, 74.8, 76.0, 105.8, 108.9 (m), 156.0 (d, $J_{C–F}$ = 321 Hz), 172.2 (d, $J_{C–F}$ = 323 Hz), 200.3, 210.0; **^{19}F NMR** ($CDCl_3$, 376 MHz) –101.3, –82.0;

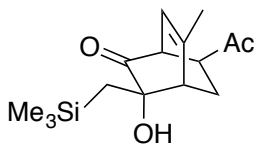
HRMS (FAB+) *m/z* calcd for [$C_{20}H_{32}F_2O_4Si_2$] (M+H) 429.1723, found 429.1725.



5,8-Dibromo-3,10-dihydroxy-3,10-bis((trimethylsilyl)methyl)tricyclo[6.2.2.0^{2,7}]dodeca-5,11-diene-4,9-dione (12f): **Method A**: Oxone (1 equiv), K_2CO_3 (0.5 equiv), 5 h, 0.0785 g, 57% yield. White solid; **TLC**, R_f = 0.29 (hexane–EtOAc = 4:1); **IR** (KBr) 3430, 3378, 1764, 1692, 1438, 1122, 855 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.35 (s, 9H), 0.75 (s, 9H), 0.91 (d, *J* = 15 Hz, 1H), 1.04–1.27 (m, 3H), 1.28 (d, *J* = 15 Hz, 1H), 2.35 (brs, 1H), 3.37–3.40 (m, 1H), 3.57 (d, *J* = 8.0 Hz, 1H), 3.62 (d, *J* = 6.8 Hz, 1H), 3.8 (brs, 1H), 6.02 (d, *J* = 8.0 Hz, 1H), 6.16 (t, *J* = 8.0 Hz, 1H), 7.27 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 0.2 (2C), 28.5, 33.7, 42.6, 44.6, 49.0, 70.4, 75.1, 76.4, 121.3, 133.9, 135.2, 145.3, 195.6, 205.6; **HRMS** (FAB+) *m/z* calcd for [$C_{20}H_{32}{}^{79}Br_2O_4Si_2$]/[$C_{20}H_{32}{}^{79}Br^{81}BrO_4Si_2$] ([M+H]/[M+2+H]/ [M+4+H]) 549.0122/551.0102/553.0081, found 549.0131/551.0106/553.0092.

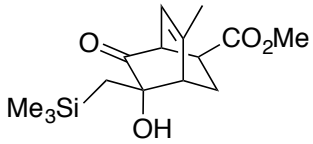


1-((Dimethyl(phenyl)silyl)methyl)-1-hydroxynaphthalen-2(1*H*)-one (14g): **Method A**: Oxone (0.75 equiv), K_2CO_3 (0.375 equiv), 5 h, 0.140 g, 91% yield. Pale yellow solid; **TLC**, R_f = 0.43 (hexane–EtOAc = 4:1); **IR** (KBr) 3154, 2253, 1676, 1471, 1391, 908, 733 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.18 (s, 3H), 0.21 (s, 3H), 1.55 (d, *J* = 15 Hz, 1H), 1.62 (d, *J* = 15 Hz, 1H), 3.66 (brs, 1H), 5.97 (d, *J* = 10 Hz, 1H), 7.18–7.35 (m, 4H), 7.62 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ –2.1 (2C), 35.4, 78.8, 122.6, 125.8, 127.6, 128.2, 128.9, 129.2, 130.2, 133.5, 138.3, 145.2, 145.8, 205.1; **HRMS** (FAB+) *m/z* calcd for [$C_{19}H_{21}O_2Si$] (M+H) 309.1305, found 309.1305.

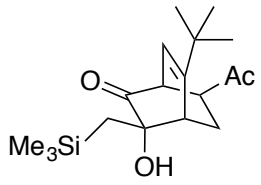


7-Acetyl-3-hydroxy-5-methyl-3-((trimethylsilyl)methyl)bicyclo[2.2.2]oct-5-en-2-one (16a): **Method C**: **11h**, methyl vinyl ketone (5 equiv), 3 h, 0.0855 g, 61% yield. White solid; **TLC**, R_f = 0.33 (hexane–EtOAc = 4:1); **IR** ($CHCl_3$) 3019, 1734, 1699, 1652, 1558, 1541, 1216 756 cm^{-1}; **^{1}H**

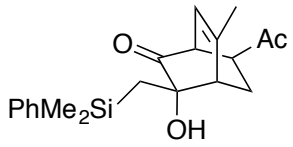
NMR ($CDCl_3$, 400 MHz) δ 0.11 (s, 9H), 0.73 (d, *J* = 15 Hz, 1H), 1.16 (d, *J* = 15 Hz, 1H), 1.62–1.65 (m, 2H), 1.88 (s, 3H), 2.14 (s, 3H), 2.36 (m, 1H), 2.85 (brs, 1H), 2.95–3.03 (m, 1H), 3.39 (dd, *J* = 2.0, 6.0 Hz, 1H), 5.65 (d, *J* = 6.0 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 0.55, 21.5, 21.9, 25.8, 28.4, 47.9, 48.5, 49.0, 76.7, 118.0, 145.8, 206.1, 213.3; **HRMS** (FAB+) *m/z* calcd for [$C_{15}H_{25}O_3Si$] (M+H) 281.1567, found 281.1570.



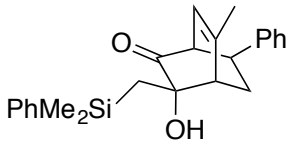
Methyl 8-hydroxy-5-methyl-7-oxo-8-((trimethylsilyl)methyl)bicyclo[2.2.2]oct-5-ene-2-carboxylate (16b): **Method C**: **11h**, methyl acrylate (5 equiv), 4 h, 0.0889 g, 61% yield. White solid; **TLC**, R_f = 0.30 (hexane–EtOAc = 4:1); **IR** (KBr) 2954, 2253, 1732, 1699, 1558, 1457, 1250, 903, 733 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.08 (s, 9H), 0.69 (d, *J* = 15 Hz, 1H), 1.16 (d, *J* = 15 Hz, 1H), 1.64–1.70 (m, 1H), 1.87 (s, 3H), 2.30 (brs, 1H), 2.40 (dt, *J* = 2.4, 10 Hz, 1H), 2.81 (t, *J* = 2.4 Hz, 1H), 2.92–2.97 (m, 1H), 3.40 (dd, *J* = 2.0, 6.4 Hz, 1H), 3.64 (s, 3H), 5.66 (dd, *J* = 2.0, 4.4 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 0.59, 21.7, 22.8, 25.9, 40.6, 40.9, 47.6, 47.9, 48.9, 52.2, 74.3, 76.7, 118.2, 146.4, 173.6, 213.0; **HRMS** (FAB+) *m/z* calcd for [$C_{15}H_{25}O_4Si$] (M+H) 297.1517, found 297.1520.



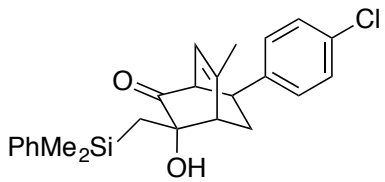
7-Acetyl-5-(*tert*-Butyl)-3-hydroxy-3-((trimethylsilyl)methyl)bicyclo[2.2.2]oct-5-en-2-one (16c): **Method C**: **11i**, methyl vinyl ketone (5 equiv), 3 h, 0.0919 g, 57% yield. White solid; **TLC**, R_f = 0.29 (hexane–EtOAc = 4:1); **IR** (KBr) 3465, 1724, 1705, 1444, 961, 844 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.13 (s, 9H), 0.79 (d, *J* = 15 Hz, 1H), 1.11 (s, 9H), 1.16 (d, *J* = 15 Hz, 1H), 1.54–1.58 (m, 1H), 2.14 (s, 3H), 2.38–2.43 (m, 1H), 2.98–3.02 (m, 1H), 3.17 (brs, 1H), 3.46 (dd, *J* = 2.0, 6.4 Hz, 1H), 5.67 (dd, *J* = 2.0, 6.4 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 0.45, 23.4, 26.5, 28.4, 28.7, 35.3, 44.7, 48.9, 49.3, 74.7, 115.1, 157.0, 205.9, 213.5; **HRMS** (FAB+) *m/z* calcd for [$C_{18}H_{32}O_3Si$] (M+H) 323.2037, found 323.2035.



7-Acetyl-3-((dimethyl(phenyl)silyl)methyl)-3-hydroxy-5-methylbicyclo[2.2.2]oct-5-en-2-one (16d): **Method C**: **11j**, methyl vinyl ketone (5 equiv), 3 h, 0.0993 g, 58% yield. White solid; **TLC**, R_f = 0.31 (hexane–EtOAc = 4:1); **IR** (KBr) 3458, 1711, 1691, 1392, 1231, 847 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.40 (s, 3H), 0.42 (s, 3H), 0.94 (d, *J* = 15 Hz, 1H), 1.41 (d, *J* = 15 Hz, 1H), 1.51–1.57 (m, 1H), 1.76 (s, 3H), 2.11 (s, 3H), 2.20 (brs, 1H), 2.31 (m, 1H), 2.70 (d, *J* = 2.0 Hz, 1H), 2.95 (dt, *J* = 2.0, 5.6 Hz, 1H), 3.35 (dd, *J* = 1.2, 6.4 Hz, 1H), 5.62 (dd, *J* = 1.2, 5.6 Hz, 1H), 7.36–7.38 (m, 3H), 7.58–7.59 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ –1.0, –0.9, 21.5, 22.1, 25.7, 28.4, 48.1, 48.5, 48.8, 74.5, 76.8, 118.1, 128.1, 129.3, 133.8, 139.2, 146.0, 206.3, 212.8; **HRMS** (FAB+) *m/z* calcd for [$C_{21}H_{30}O_3Si$] $(M+H)^+$ 357.1880, found 357.1880.

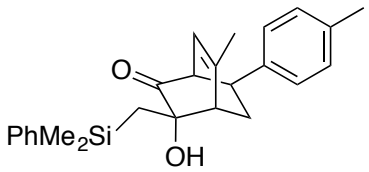


3-((Dimethyl(phenyl)silyl)methyl)-3-hydroxy-5-methyl-7-phenylbicyclo[2.2.2]oct-5-en-2-one (16e): **Method C**: **11j**, styrene (15 equiv), 6 h, 0.107 g, 51% yield. White solid; **TLC**, R_f = 0.57 (hexane–EtOAc = 4:1); **IR** ($CHCl_3$) 3464, 2926, 2359, 1725, 1249, 1113, 833cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.42 (s, 3H), 0.44 (s, 3H), 0.99 (d, *J* = 15 Hz, 1H), 1.40–1.47 (m, 2H), 1.90 (s, 3H), 2.11 (brs, 1H), 2.62 (dt, *J* = 2.8, 9.6 Hz, 1H), 2.79 (d *J* = 2.0 Hz, 1H), 3.11 (dd, *J* = 2.0, 6.0 Hz, 1H), 3.27–3.30 (t, *J* = 7.2 Hz, 1H), 5.65 (d, *J* = 6.0 Hz, 1H), 7.10 (d, *J* = 7.2 Hz, 1H), 7.16–7.26 (m, 3H), 7.37–7.38 (m, 3H), 7.58–7.60 (m, 2H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ –1.0, 0.0, 21.5, 25.8, 28.5, 41.7, 49.0, 54.0, 74.2, 118.4, 126.5, 127.6, 128.0, 128.4, 129.4, 133.8, 139.3, 144.5, 146.0, 213.2; **HRMS** (FAB+) *m/z* calcd for [$C_{24}H_{29}O_2Si$] $(M+H)^+$ 377.1931, found 377.1933.

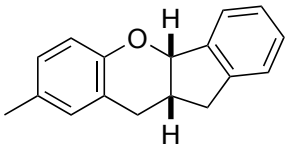


7-(4-Chlorophenyl)-3-((dimethyl(phenyl)silyl)methyl)-3-hydroxy-5-methylbicyclo[2.2.2]oct-5-en-2-one (16f): **Method C**: **11j**, 4-chlorostyrene (15 equiv), 6 h, 0.117 g, 57% yield. White solid; **TLC**, R_f = 0.51 (hexane–EtOAc = 4:1); **IR** ($CHCl_3$) 3440, 2954, 1716, 1490, 1247, 1113, 835 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.42 (s, 3H), 0.44 (s, 3H), 0.98 (d, *J* = 16 Hz, 1H), 1.33–1.39

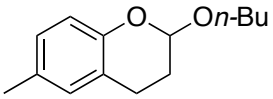
(m, 1H), 1.45 (d, *J* = 1.6 Hz), 1.89 (s, 3H), 2.10 (brs, 1H), 2.61 (dt, *J* = 2.8, 10 Hz, 1H), 2.78 (d *J* = 2.4 Hz, 1H), 3.07 (dd, *J* = 1.6, 6.4 Hz, 1H), 3.24–3.28 (m, 1H), 5.63 (d, *J* = 6.0 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.33–7.39 (m, 3H), 7.59–7.61 (m, 2H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ –1.0, 0.0, 21.5, 25.8, 28.6, 41.0, 48.9, 53.8, 74.1, 118.1, 127.9, 128.0, 128.5, 128.9, 129.2, 132.3, 133.8, 142.9, 146.3, 212.8; **HRMS** (FAB+) *m/z* calcd for [$C_{24}H_{28}{}^{35}ClO_2Si$]/[$C_{24}H_{28}{}^{37}ClO_2Si$] ([M+H]/[M+2+H]) 411.1542/413.1512, found 411.1536/413.1512.



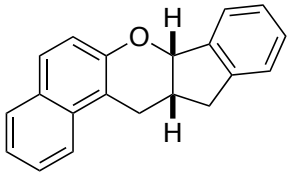
3-((Dimethyl(phenyl)silyl)methyl)-3-hydroxy-5-methyl-7-(*p*-tolyl)bicyclo[2.2.2]oct-5-en-2-one (16g): Method C: **11j**, 4-methylstyrene (15 equiv), 6 h, 0.102 g, 52% yield. White solid; **TLC**, R_f = 0.55 (hexane–EtOAc = 4:1); **IR** ($CHCl_3$) 3480, 2953, 1713, 1646, 1514, 1427, 1248, 1123, 831cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.42 (s, 3H), 0.44 (s, 3H), 1.38–1.47 (m, 2H), 1.89 (s, 3H), 2.11 (brs, 1H), 2.30 (s, 3H), 2.60 (dt, *J* = 2.8, 9.6 Hz, 1H), 2.79 (d, *J* = 2.4 Hz, 1H), 3.10 (dd, *J* = 1.2, 6.4 Hz, 1H), 3.26 (m, 1H), 5.64 (d, *J* = 6.0 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 7.37–7.39 (m, 3H), 7.59–7.61 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ –1.1, –1.0, 20.9, 21.5, 25.8, 28.5, 41.2, 48.9, 54.1, 71.8, 118.4, 127.5, 128.0, 129.0, 129.2, 133.8, 136.2, 139.2, 141.4, 145.9, 213.4; **HRMS** (FAB+) *m/z* calcd for [$C_{25}H_{31}O_2Si$] $(M+H)^+$ 391.2088, found 391.2090.



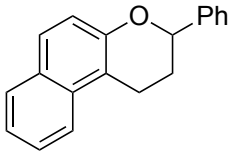
8-Methyl-4b,10,10a,11-tetrahydroindeno[1,2-*b*]chromene (17a):[15] **Method D**: **11h**, indene (5 equiv), 7 h, 0.0626 g, 53% yield. Pale yellow solid; **TLC**, R_f = 0.77 (hexane–EtOAc = 10:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.24 (s, 3H), 2.54–2.64 (m, 1H), 2.79 (dd, *J* = 4.8, 16 Hz, 1H), 2.91–2.97 (m, 2H), 3.09 (dd, *J* = 6.4, 16 Hz, 1H), 5.49 (d, *J* = 6.4 Hz, 1H), 6.75 (d, *J* = 7.8 Hz, 1H), 6.87–6.89 (m, 2H), 7.22–7.27 (m, 3H), 7.51 (dd, *J* = 2.8, 6.4 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 20.6, 28.2, 37.0, 37.8, 81.7, 116.7, 123.5, 125.1, 125.3, 126.8, 127.7, 128.6, 129.3, 129.9, 142.5, 142.6, 153.0.



2-Butoxy-6-methylchromane (17b): **Method D**: **11h**, *n*-butyl vinyl ether (5 equiv), 7 h, 0.0419 g, 38% yield. White solid; **TLC**, R_f = 0.78 (hexane–EtOAc = 10:1); **IR** ($CHCl_3$) 2986, 2954, 1663, 1571, 1486, 1221, 1217, 905 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.89 (t, *J* = 7.2 Hz, 3H), 1.32 (m, 4H), 1.47 (d, *J* = 5.6 Hz, 2H), 1.96 (d, *J* = 13 Hz, 1H), 2.14 (d, *J* = 13 Hz, 1H), 2.24 (s, 3H), 3.45 (dd, *J* = 2.8, 6.8 Hz, 1H), 3.65 (dd, *J* = 2.8, 6.8 Hz, 1H), 5.33 (q, *J* = 5.2, Hz, 1H), 6.76–6.81 (m, 2H), 6.87 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 13.9, 19.3, 20.2, 20.4, 20.6, 31.8, 65.0, 99.1, 114.4, 125.2, 130.0, 130.1, 130.3, 151.9; **HRMS** (FAB+) *m/z* calcd for [$C_{14}H_{21}O_2$] (M+H) 221.1536, found 221.1533.

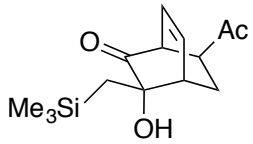


7a,12,12a,13-Tetrahydrobenzo[*f*]indeno[1,2-*b*]chromene (17c): **Method D** (modified): Reaction was performed in the absence of HFIP. After the oxidation of **11g** was completed (12 h), to the resulting mixture were added indene (5 equiv) and TsOH (10 mol%), and the resulting mixture was stirred at 50 °C for 16 h; 0.106 g, 78% yield. White solid; **TLC**, R_f = 0.75 (hexane–EtOAc = 10:1); **IR** (KBr) 2977, 2964, 1621, 1581, 1577, 1285, 991 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.94 (m, 2H), 3.04–3.16 (m, 2H), 3.36 (dd, *J* = 6.9, 16 Hz, 1H), 5.48 (d, *J* = 5.0 Hz, 1H), 7.09 (d, *J* = 8.7 Hz, 1H), 7.22–7.46 (m, 3H), 7.45–7.60 (m, 3H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 23.1, 37.0, 37.3, 79.9, 112.7, 119.1, 121.6, 123.1, 124.9, 125.3, 126.2, 126.8, 127.4, 128.5, 128.8, 129.1, 132.8, 142.9, 143.0, 152.2; **HRMS** (FAB+) *m/z* calcd for [$C_{20}H_{17}O$] (M+H) 273.1274, found 273.1277.

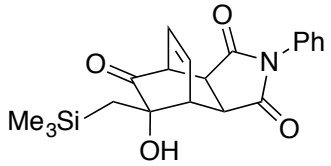


3-Phenyl-2,3-dihydro-1*H*-benzo[*f*]chromene (17d):[33] **Method D** (modified): Reaction was performed in the absence of HFIP. After the oxidation of **11g** was completed (12 h), to the resulting mixture were added styrene (5 equiv) and TsOH (10 mol%), and the resulting mixture was stirred at 50 °C for 16 h; 0.092 g, 71% yield. Note-1: with original method D [w/HFIP (10 equiv),

styrene was added at the beginning of the reaction, 20 °C, 6 h then 40 °C, 16 h]: **17d**, 35% yield; **14g**, 40% yield. Note-2: with modified method D [w/TsOH (10 mol%), TsOH and styrene were added at the beginning of the reaction, 40 °C, 16 h]: **17d**, <10% yield; **11g**, >70% recovered. White solid; **TLC**, R_f = 0.63 (hexane–EtOAc = 10:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.22–2.30 (m, 1H), 2.38–2.44 (m, 1H), 3.17–3.21 (m, 2H), 5.14 (dd, *J* = 2.4, 10 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 1H), 7.32–7.43 (m, 5H), 7.48–7.52 (m, 3H), 7.65 (d, *J* = 9.2 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 21.7, 29.7, 77.5, 113.6, 119.2, 121.9, 123.3, 126.1, 126.3, 127.8, 127.9, 128.4, 128.5, 128.6, 129.0, 133.0, 141.5, 152.6.

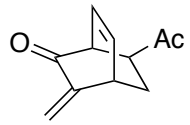


7-Acetyl-3-hydroxy-3-((trimethylsilyl)methyl)bicyclo[2.2.2]oct-5-en-2-one (18a): A mixture of **12a** (39 mg, 0.10 mmol) and methyl vinyl ketone (0.0830 mL, 1.00 mmol) in mesitylene (2.00 mL) was stirred at 150 ºC. After stirring for 3 h, the resulting mixture was cooled to room temperature. The solvents were removed under *vacuo*, and the residue was purified by column chromatography on silica gel (hexane-EtOAc as eluent) to give **18a** (0.0527 g, 0.198 mmol, 99% yield). White solid; **TLC**, R_f = 0.32 (hexane–EtOAc = 4:1); **IR** (KBr) 3480, 2954, 1734, 1715, 1388, 1186, 846 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.10 (s, 9H), 0.85 (d, *J* = 15 Hz, 1H), 1.10 (d, *J* = 15 Hz, 1H), 1.59–1.64 (m, 1H), 2.15 (s, 3H), 2.15 (brs, 1H), 2.46 (t, *J* = 12 Hz, 1H), 3.01–3.09 (m, 2H), 3.7 (dd, *J* = 0.8, 6.0 Hz, 1H), 6.10 (t, *J* = 7.2 Hz, 1H), 6.39 (t, *J* = 7.2 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 0.3, 22.6, 27.3, 28.4, 42.8, 48.6, 74.6, 126.1, 136.3, 206.0, 213.4; **HRMS** (FAB+) *m/z* calcd for [$C_{14}H_{24}O_3Si$] (M+H) 267.1411 found 267.1410.

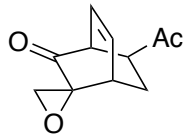


9-Hydroxy-4-phenyl-9-(trimethylsilyl)methyl-4-azatricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5,8-trione (18b): A mixture of **12a** (39 mg, 0.10 mmol) and *N*-phenylmaleimide (0.0170 g, 1.00 mmol) in mesitylene (2.00 mL) was stirred at 150 ºC. After stirring for 3 h, the resulting mixture was cooled to room temperature. The solvents were removed under *vacuo*, and the residue was purified by column chromatography on silica gel (hexane-EtOAc as eluent) to give **18b** (0.0732 g, 0.198 mmol, 99% yield). White solid; **TLC**, R_f = 0.16 (hexane–EtOAc = 4:1); **IR** ($CHCl_3$) 3441,

2945, 2879, 1752, 1677, 1291, 877, 756 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.15 (s, 9H), 0.87 (d, *J* = 16 Hz, 1H), 1.18 (d, *J* = 16 Hz, 1H), 2.35 (brs, 1H), 3.36 (dd, *J* = 3.2, 8.4 Hz, 1H), 3.67–3.72 (m, 1H), 3.77–3.84 (m, 2H), 6.29 (dd, *J* = *J* = 1.6, 7.8 Hz), 6.44 (dt, *J* = 1.6, 7.8 Hz, 1H), 7.20 (dd, *J* = 1.2, 7.8 Hz, 1H), 7.39–7.47 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 0.3, 27.3, 39.2, 42.0, 45.1, 47.8, 73.7, 126.3, 127.5, 128.8, 129.2, 131.6, 134.6, 175.1, 177.1, 210.2; **HRMS** (FAB+) *m/z* calcd for [$C_{20}H_{24}NO_4Si$] (M+H) 370.1469 found 370.1469.

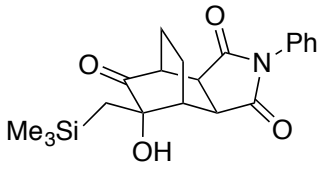


7-Acetyl-3-methylenebicyclo[2.2.2]oct-5-en-2-one (19): To a solution of **18a** (0.0530 g, 0.200 mmol) in 1,2-dichloroethane (5.00 mL) was added *p*-toluenesulfonic acid monohydrate (3.80 mg, 0.0200 mmol). The resulting mixture was stirred at 50 ºC for 12 h. The reaction mixture was poured into water and the aqueous layers were extracted with CH_2Cl_2 (twice). The organic layers were washed with brine, and dried over anhydrous $MgSO_4$. The solvents were removed under *vacuo*, and the residue was purified by column chromatography on silica gel (hexane-EtOAc as eluent) to give **19** (0.0350 g, 0.200 mmol, 99% yield). White solid; **TLC**, R_f = 0.17 (hexane–EtOAc = 4:1); **IR** ($CHCl_3$) 2910, 1772, 1752, 1392, 1193, 753 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.98–1.99 (m, 2H), 2.19 (s, 3H), 3.00 (dd, *J* = 1.6, 6.4 Hz, 1H), 3.57 (dd, *J* = 1.6, 8.0 Hz, 1H), 3.63 (d, *J* = 6.4 Hz, 1H), 5.23 (s, 1H), 5.82 (s, 1H), 6.11 (dt, *J* = 1.2, 8.0 Hz, 1H), 6.48 (dt, *J* = 1.2, 8.0 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 28.5, 28.6, 40.1, 46.9, 50.1, 116.1, 126.2, 136.3, 141.7, 197.4, 206.1; **HRMS** (FAB+) *m/z* calcd for [$C_{11}H_{13}O_2$] (M+H) 177.0910, found 177.09.

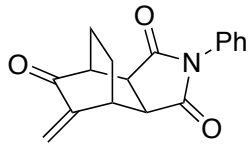


8-Acetylspiro[bicyclo[2.2.2]octane-2,2'-oxiran]-5-en-3-one (20):[34] To a solution of **19** (0.0350 mg, 0.200 mmol) and sodium hydroxide (0.0800mg, 2.00 mmol) in a mixture of methanol (5.00 mL) and H_2O (1.00 mL) was added 30% hydrogen peroxide (0.0210 mL, 0.200 mmol) at 0 ºC. After stirring for 1 h at 0 °C, the reaction mixture was diluted with brine and the aqueous layers were extracted with CH_2Cl_2 (twice). The organic layers were washed with brine, and dried over anhydrous Na_2SO_4. The solvents were removed under *vacuo*, and the residue was purified by column chromatography on silica gel (hexane-EtOAc as eluent) to give **20** (0.0180 mg, 0.0920 mmol, 46% yield). White solid; **TLC**, R_f = 0.19 (hexane–EtOAc = 1:1); **^{1}H NMR** ($CDCl_3$, 400

MHz) δ 1.91–2.07 (m, 1H), 2.21 (s, 3H), 2.32 (dt, *J* = 2.4, 8.0 Hz, 1H), 2.61–2.68 (m, 1H), 2.91 (d, *J* = 6.0 Hz, 1H), 3.17–3.19 (m, 2H), 3.69 (dd, *J* = 1.6, 8.0 Hz, 1H), 6.21 (t, *J* = 6.4 Hz, 1H), 6.52 (dt, *J* = 1.6, 6.4 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 24.2, 28.4, 38.2, 47.7, 49.5, 53.1, 57.5, 126.9, 135.0, 204.1, 205.2.



9-Hydroxy-4-phenyl-9-(trimethylsilyl)methyl-4-azatricyclo[5.2.2.0^{2,6}]undecan-3,5,8-trione (21): To a solution of **18b** (0.0740 mg, 0.200 mmol) in EtOH (2.00 mL) and acetic acid (2.00 mL) was added Pd/C (3.70 mg, 5 wt%) at room temperature. After stirring for 16 h at room temperature under H_2 (balloon), the resulting mixture was filtered through celite and washed with EtOAc. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane-EtOAc as eluent) to give **21** (0.068 mg, 0.180 mmol, 92% yield). White solid; **TLC**, R_f = 0.20 (hexane–EtOAc = 4:1); **IR** (KBr) 3452, 2945, 2879, 1752, 1392, 1193, 756 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.15 (s, 9H), 1.04 (d, *J* = 15 Hz, 1H), 1.19 (d, *J* = 15 Hz, 1H), 1.71–2.00 (m, 4H), 2.49 (brs, 1H), 2.75 (d, *J* = 3.2 Hz, 1H), 2.95 (d, *J* = 1.6 Hz, 1H), 3.24 (m, 1H), 3.69 (ddd, *J* = 1.6, 3.2, 8.4 Hz, 2H), 7.31 (dd, *J* = 2.0, 8.4 Hz, 2H), 7.43 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.51 (ddd, *J* = 1.2, 2.0, 8.4 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 0.57, 17.5, 17.6, 24.3, 38.9, 39.6, 41.3, 41.7, 126.3, 128.9, 129.3, 131.7, 175.8, 178.0, 215.6; **HRMS** (FAB+) *m/z* calcd for [$C_{20}H_{26}NO_4Si$] (M+H) 372.1626, found 372.1628.



4-phenyl-9-methylene-4-azatricyclo[5.2.2.0^{2,6}]undecan-3,5,8-trione (22): To a solution of **21** (0.068 mg, 0.180 mmol) in 1,2-dichloroethane (3.00 mL) was added *p*-toluenesulfonic acid monohydrate (3.40 mg, 0.0180 mmol). The resulting mixture was stirred at 50 ºC for 12 h. The reaction mixture was poured into water and the aqueous layers were extracted with CH_2Cl_2 (twice). The organic layers were washed with brine, and dried over anhydrous $MgSO_4$. The solvents were removed under *vacuo*, and the residue was purified by column chromatography on silica gel (hexane-EtOAc as eluent) to give (hexane-EtOAc as eluent) to give **22** (0.051 mg, 0.180 mmol, 99% yield). White solid; **TLC**, R_f = 0.13 (hexane–EtOAc = 4:1); **IR** (KBr) 2949, 2879, 1705,

1636, 1391, 1196, 750 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.78–1.97 (m, 4H), 3.08 (d, *J* = 2.8, Hz, 1H), 3.22 (dd, *J* = 3.6, 10 Hz, 1H), 3.30 (dd, *J* = 3.6, 10 Hz, 1H), 3.40 (d, *J* = 2.8 Hz, 1H), 5.48 (s, 1H), 6.18 (s, 1H), 7.31(d, *J* = 8.2 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.52 (dd, *J* = 7.8, 8.2 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 18.7, 21.0, 37.8, 40.5, 43.1, 43.5, 120.2, 126.2, 129.0, 129.4, 131.5, 144.4, 176.0, 176.5, 198.7; **HRMS** (FAB+) *m/z* calcd for [$C_{17}H_{16}NO_3$] (M+H) 282.1125, found 282.1130.

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Research Achievement

Publications

Chapter 2

1. "IBS-Catalyzed Regioselective Oxidation of Phenols to 1,2-Quinones with Oxone"
   Muhammet Uyanik, Tatsuya Mutsuga, Kazuaki Ishihara
   Molecules, **2012**, *17*, 8604–8616.
   Special Issue: Hypervalent Compounds.

2. "2-ヨードベンゼンスルホン酸(*pre*-IBS)と Oxone を用いる選択的酸化反応"
   ウヤヌク ムハメット, 六鹿 達矢, 石原 一彰
   和光純薬時報, **2013**, *81*, 4, 5–9.

Chapter 3

3. "4,5-Dimethyl-2-iodoxybenzenesulfonic Acid-catalyzed Highly Site-selective Oxidation of 2-Substituted Phenols to 1,2-Quinols"
   Muhammet Uyanik, Tatsuya Mutsuga, Kazuaki Ishihara
   Angew. Chem. Int. Ed. **2017**, *56*, in press.

International conferences

Poster Presentations

1. "IBS-Catalyzed *ortho*-Selective Oxidation of Phenols to 1,2-Quinols"
   ◯Tatsuya Mutsuga, Muhammet Uyanik, Kazuaki Ishihara
   4th International Conference on Hypervalent Iodine Chemistry, P-18, Hilton Narita, Chiba, Japan, July 2014.

Domestic conferences

Oral Presentations

1. "IBS 触媒と Oxone を用いる芳香族化合物の酸化反応"
   ◯六鹿 達矢, Uyanik Muhammet, 石原 一彰
   日本化学会第 92 春季年会, 3K5-56, 慶應大学, 神奈川, 2012 年 3 月

2. "超原子価ヨウ素触媒(V)と Oxone を用いるフェノール類の位置選択的酸化反応とその合成的応用"
   ◯六鹿 達矢, Uyanik Muhammet, 石原 一彰
   日本化学会第 93 春季年会, 3E6-42, 立命館大学, 滋賀, 2013 年 3 月

3. “超原子価ヨウ素触媒(V)と Oxone を用いるフェノール類のオルト位選択的酸化反応による 1,2-キノールの合成”
◯六鹿 達矢, Uyanik Muhammet, 石原 一彰
日本化学会第 94 春季年会, 3B7-04, 名古屋大学, 愛知, 2014 年 3 月

4. “IBS 触媒を用いるフェノール類の *ortho* 位選択的酸化反応による 1,2-キノールの合成”
◯六鹿 達矢, Uyanik Muhammet, 石原 一彰
日本化学会第 95 春季年会, 1E3-42, 日本大学, 千葉, 2015 年 3 月

5. “IBS 触媒を用いるフェノール類の *ortho* 位選択的酸化反応による 1,2-キノールの合成”
◯六鹿 達矢, Uyanik Muhammet, 石原 一彰
第 107 回有機合成シンポジウム, 2-5, 慶應義塾大学, 東京, 2015 年 6 月

6. “IBS-Catalyzed Regioselective Oxidation of Phenols and Its Synthetic Application”
◯Tatsuya Mutsuga, Muhammet Uyanik, Kazuaki Ishihara
日本化学会第 96 春季年会, 4H2-11, 同志社大学, 京都, 2016 年 3 月

7. “IBS-Catalyzed *site*-Selective Oxidation of Phenols”
◯Tatsuya Mutsuga
第二回野依フォーラム若手育成塾, 26, 名古屋大学, 愛知, 2016 年 7 月

8. “IBS-Catalyzed Site-Selective Oxidation of Phenols to 1,2-Quinols”
◯Tatsuya Mutsuga, Muhammet Uyanik, Kazuaki Ishihara
日本化学会第 97 春季年会, 2E5-41, 慶應大学, 神奈川, 2017 年 3 月（発表予定）

Poster Presentations

9. “IBS 触媒と Oxone を用いるフェノール類の酸化反応”_
◯六鹿 達矢, Uyanik Muhammet, 石原 一彰
第 45 回有機金属若手の会 夏の学校 2012, エバーグリーン富士, 山梨, 2012 年 7 月

10. “IBS 触媒と Oxone を用いるフェノールの 1,2-キノンへの選択的酸化反応”
◯Uyanik Muhammet, 六鹿 達矢, 石原 一彰
ヨウ素学会, 千葉大学, 千葉, 2012 年 11 月

11. “IBS-Catalyzed Regioselective Oxidation of Phenols with Oxone”
◯Tatsuya Mutsuga, Muhammet Uyanik, Kazuaki Ishihara
IGER Annual meeting 2012, G-16, 名古屋大学, 愛知, 2013 年 1 月

12. “超原子価ヨウ素(V)触媒と Oxone を用いるフェノール類の位置選択的酸化反応”
◯六鹿 達矢, Uyanik Muhammet, 石原 一彰
第 46 回有機金属若手の会 夏の学校 2013, 宮城蔵王ロイヤルホテル, 宮城, 2013 年 7 月

13. “Hypervalent Iodine(V)-Catalyzed *ortho*-Selective Oxidation of Phenols to 1,2-Quinols”
◯Tatsuya Mutsuga, Muhammet Uyanik, Kazuaki Ishihara
IGER Annual meeting 2013, G-33, 名古屋大学, 愛知, 2014 年 1 月

14. “超原子価ヨウ素(V)触媒と Oxone を用いる 2-置換フェノール類の 2 位選択的酸化反応とその合成的応用”
◯六鹿 達矢, Uyanik Muhammet, 石原 一彰
創薬懇話会 2014 in 岐阜, 長良川温泉ホテルパーク, 岐阜, 2014 年 7 月

15. “IBS-Catalyzed *ortho*-Selective Oxidation of Phenols with Oxone”
◯Tatsuya Mutsuga, Muhammet Uyanik, Kazuaki Ishihara
IGER Annual meeting 2014, G-19, 名古屋大学, 愛知, 2014 年 12 月

16. “IBS 触媒を用いるフェノールの *ortho* 位選択的酸化反応による 1,2-キノールの合成”
◯六鹿 達矢, Uyanik Muhammet, 石原 一彰
第 5 回 企業と博士人材の交流会, P-12, 名古屋大学, 愛知, 2015 年 9 月

17. “IBS 触媒を用いるフェノール類の位置選択的酸化反応とその合成的応用”
◯六鹿 達矢, Uyanik Muhammet, 石原 一彰
分子科学研究所リトリート研修, P06, 分子科学研究所, 愛知, 2015 年 11 月

18. “IBS-Catalyzed *site*-Selective Oxidation of Phenols to 1,2-Quinols”
◯Tatsuya Mutsuga, Muhammet Uyanik, Kazuaki Ishihara
IGER Annual meeting 2016, G-19, 名古屋大学, 愛知, 2017 年 1 月

Awards

1. 日本学術振興会特別研究員(DC1)
2. 第二回野依フォーラム若手育成塾生

Visiting Scholar

“Decarboxylative Borylation Reaction of Redox Active Esters”
Professor Varinder, K. Aggarwal, Department of Chemistry, University of Bristol.
9/1/2016–11/29/2016

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Tatsuya Mutsuga