Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalysed *ortho*-Hydroxylative Phenol Dearomatization

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ABSTRACT: Hydroxylative dearomatization reactions of phenols (HPD) offer an efficient way to assemble complex, biologically relevant scaffolds. Despite this, enantioselective hydroxylative phenol dearomatizations for the construction of bicyclo[2.2.2]octenones are classically limited to stoichiometric chiral reagents, and a practical, enantioselective catalytic method has remained elusive. Herein, we describe a highly enantioselective, organocatalytic tandem *o*-HPD-[4+2] reaction. Our methodology utilizes a chiral oxaziridinium organocatalyst that affords high enantioselectivity for a wide range of phenol substitution patterns, and was applied in the synthesis of (+)-biscarvacrol and bis(2,6-xylenol). The practicality of our conditions were demonstrated at gram-scale, using an amine precatalyst that can be accessed in a single synthetic step.

The asymmetric dearomatization of phenols offers a valuable method towards generating biologically relevant target molecules, [1] owing to the high abundance of feedstock phenolic compounds. The hydroxylative dearomatization of *o*-alkylphenols leads to [4+2]-dimerization of the intermediate *o*-quinol, thus remarkably generating decorated bicyclo[2.2.2]octenones in a single synthetic step (Figure 1, a).[2] The dimerized *o*-quinols feature the core of several natural products, for example, the anti-pancreatic cancer compound grandifloracin,[3] bis(sesquiterpenoid) aquaticol,[4] and the bis(monoterpenoid) biscarvacrol,[5] as well as the bacterial metabolite, bis(2,6-xylenol)[6] can all logically be disconnected to their simple, phenol monomers. Therefore, methods to access such products bear noteworthy importance. The biological significance of non-natural analogues of such products has also been described,[7] further highlighting the demand for a general enantioselective *o*-hydroxylative phenol dearomatization method. However, previous efforts towards the enantioselective *o*-HPD-[4+2] reaction are limited to stoichiometric chiral reagents, and to the best of our knowledge, a general, practical, catalytic method is yet to be reported.

A pioneering example of enantioselective *o*-HPD-[4+2] reactions was reported by Porco and co-workers, using a copper-sparteine complex.[8] The reactions required an excess of Cu(I) and sparteine, as well as cryogenic temperatures (-78 °C). In addition to these shortcomings, the substrate scope was generally limited, and symmetrical, 2,6-substituted phenols were not tolerated, preventing access to compounds such as bis-(2,6-xylenol). *Ortho* substituents which were larger than methyl, such as *i*-Pr, were also not compatible, leading to S_EAr-like catechol formation. More

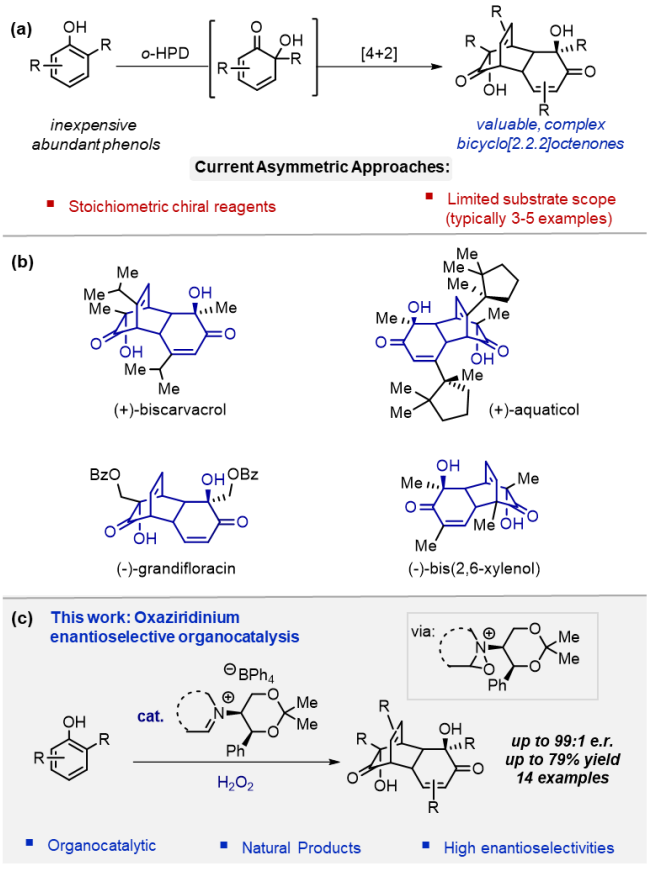
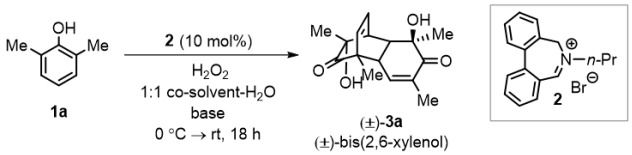


Figure 1. (a) *o*-HPD-[4+2] dimerization concept and current limitations. (b) Representative natural products from dimerized *o*-quinols. (c) Our organocatalytic enantioselective method.

recently, chiral hypervalent iodine reagents have been utilized for the *o*-HPD-[4+2] reaction. Birman and co-workers reported an *o*-oxazoline derived iodine(V) reagent, which could invoke the bicyclo[2.2.2]octenone synthesis,[9] however only moderate enantioselectivity (up to 88.5:12.5 e.r.) was achieved. Pouységu, Quideau and co-workers then published the use of an axially chiral bis-iodine(V) reagent, which afforded the reaction with selectivities ranging from 70:30 e.r. up to 97:3 e.r., offering only moderate enantioselectivity for most substrates.[10]

With a general, practical, catalytic method for the enantioselective *o*-HPD-[4+2] reaction still yet to be discovered, we postulated that the dearomatization could be invoked by a catalytically generated electrophilic oxygen atom source, in the form of an oxaziridinium cation. The potential ion pairing between a phenolate and the oxaziridinium aimed to promote high enantioselectivity. We speculated that suitable conditions would therefore allow facile access to enantioenriched natural and non-natural *o*-quinol dimers. Since oxaziridinium organocatalysis is classically employed in epoxidation reactions,[11] our strategy additionally aimed to extend the synthetic capabilities of this class of catalyst.

Table 1. Initial Optimization Summary of the Synthesis of (±)-bis(2,6-xylenol) Using an Achiral Catalyst

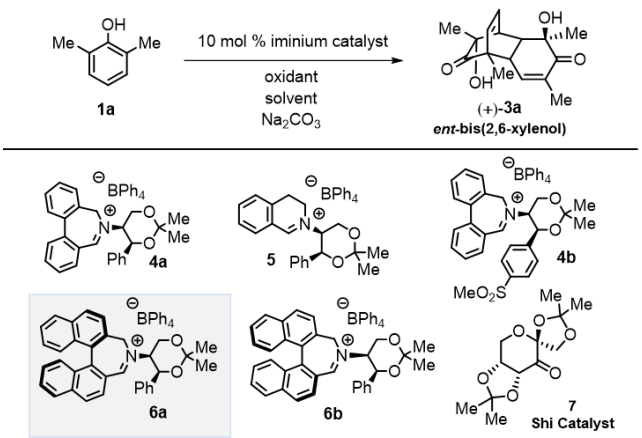


Entry	Solvent	Base[a]	H_2O_2 eq.[b]	Yield[c]
1[d]	MeCN-H_2O (1:1)	Na_2CO_3	1.5	17%
2	MeCN-H_2O (1:1)	Na_2CO_3	2.0	34%
3	MeCN-H_2O (1:1)	Na_2CO_3	3.0	65%
4	MeCN-H_2O (1:1)	NaOH	3.0	< 5%
5	MeOH-H_2O (1:1)	Na_2CO_3	3.0	< 10%
6	CH_2Cl_2-H_2O (1:1)	Na_2CO_3	3.0	< 5%
7	THF-H_2O (1:1)	Na_2CO_3	3.0	< 5%
8	PhCN-H_2O (1:1)	Na_2CO_3	3.0	55%
9	MeCN-H_2O (1:1)	none	3.0	< 5%
10	MeCN-H_2O (9:1)	Na_2CO_3	3.0	< 5%

Reactions performed on a 0.4 mmol scale. [a]2.5 mmol. [b]Used as a 30% aq. solution. [c]Isolated yields after chromatography. [d]4 h reaction time.

At the onset of our investigations, we wished to understand whether the hypothesized oxaziridinium-mediated hydroxylative dearomatization could occur. To achieve this, we prepared achiral catalyst **2**, derived from a simple linear amine. We then studied its ability to dearomatize our model substrate, 2,6-dimethylphenol (**1a**), in order to synthesize (±)-bis-(2,6-xylenol) **3a** (Table 1). It was of significant importance to develop the reaction using H_2O_2 as the stoichiometric oxidant, in order to ensure simplicity of the reaction conditions. Initial experiments showed that iminium salt catalyst **2** (10 mol%) could achieve the synthesis of (±)-**3a** in low yield (17%, Table 1, Entry 1).

Table 2. Optimization Summary of The Catalytic Enantioselective *o*-HPD-[4+2] Reaction



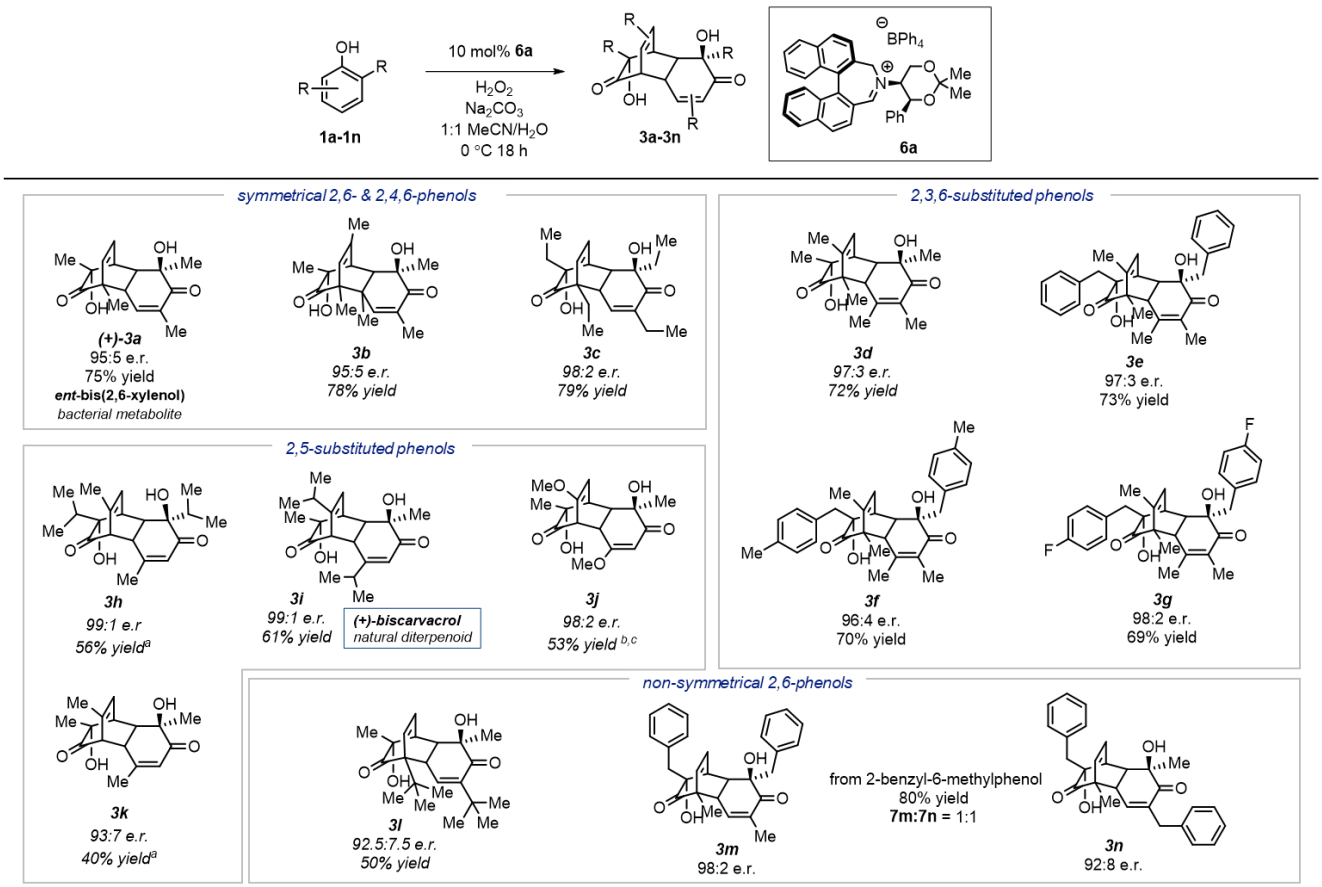
Entry	Oxidant[a]	Solvent	Catalyst	*T* (°C)	Yield	e.r.[c]
1	H_2O_2	MeCN-H_2O (1:1)	**4a**	r.t.	86%	79:21
2	H_2O_2	MeCN-H_2O (1:1)	**5**	r.t.	90%	60:40
3	Oxone	MeCN-H_2O (1:1)	**4a**	r.t.	14%	76:24
4	H_2O_2	MeCN-H_2O (1:1)	**4b**	r.t.	96%	79:21
5	H_2O_2	MeCN-H_2O (1:1)	**4a**	0 °C	91%	85.5:14.5
6	UHP/$PhSe_2$[b]	$CHCl_3$	**4a**	0 °C	52%	88:12
7	H_2O_2	MeCN-H_2O (1:1)	**6a**	0 °C	75%	**95:5**
8	UHP/$PhSe_2$[b]	$CHCl_3$	**6a**	0 °C	53%	87:13
9	H_2O_2	MeCN-H_2O (1:1)	**6b**	0 °C	56%	10:90
10[d]	H_2O_2	MeCN-H_2O (1:1)	**6a**	0 °C	40%	91:9
11[e]	H_2O_2	MeCN-H_2O (2:1)	**7**	0 °C	29%	42:58

Reactions performed on a 0.4 mmol scale. [a]3.0 eq . [b]5 mol% $PhSe_2$, 3.0 eq. UHP. [c]determined by chiral stationary phase HPLC. [d]reaction buffered to pH 10. [e]Employed using original conditions reported by Shi (see ref 12). substrate (0.5 mmol), MeCN (1 mL), 0.5 mL 1.0 M K_2CO_3 in 0.4 mM EDTA, H_2O_2 (1.5 mmol), 30 mol% D-epoxone (Shi catalyst **7**).

By increasing the amount of H_2O_2, the desired racemic product was afforded with 65% yield (Table 1, Entry 3). The use of MeCN, and a carbonate base was crucial to facilitate the reaction. Since non-nitrile co-solvents (MeOH, CH_2Cl_2, THF) all failed in the reaction, we speculate that the use of MeCN activates H_2O_2, as proposed in the Payne oxidation.[12] This enables oxaziridinium formation through the attack of peroxyimidic acid. The use of PhCN also facilitated the reaction, albeit with a slightly reduced yield (Table 1, Entry 8).

With preliminary optimization achieved using the arbitrary achiral catalyst, we turned our attention to the development of the enantioselective variant of the reaction. Again, 2,6-dimethylphenol (**1a**) was selected as the model substrate, since symmetrical phenols are particularly challenging/non-compatible with the aforementioned litera-

Scheme 1. Scope of The Catalytic Enantioselective *o*-HPD-[4+2] Reaction.



Reactions ran at 0.26-0.41 mmol scale. e.r. = enantiomeric ratio. [a]performed at room temp. [b]performed using tertiary amine pre-catalyst **8** (*see Figure 2*). [c]crude mixture was heated at 70 ^{0}C for 1 h to allow for the [4+2] cycloaddition. Enantioselectivities determined by chiral stationary phase HPLC (see SI).

ture methods. We investigated the oxaziridinium catalysts originally developed by Page and co-workers for asymmetric epoxidation, derived from a chiral (*S*,*S*)-(+)-acetonamine.[13] When biphenylazepinium **4a**, which is directly analogous to catalyst **2**, was employed, *ent*-bis-(2,6-xylenol) ((+)-**3a**) was afforded with a promising 79:21 e.r. and in 86% yield (Table 2, entry 1). Changing the catalyst backbone to a dihydroisoquinoline (**5**) caused a significant decrease in selectivity (60:40 e.r. Table 2, Entry 2). Alteration of the electronics of the catalyst was also investigated, by introducing a sulfonyl group within the (*S*,*S*)-(+)-acetonamine to afford catalyst **4b**. This approach has previously proven useful in asymmetric epoxidation,[14] although had no effect on the observed enantioselectivity of the HPD-[4+2] reaction (79:21 e.r., Table 2, Entry 4). The reaction could also be facilitated using a non-aqueous, dual-catalytic system,[15] using $PhSe_2$, UHP and an iminium catalyst (Table 2, Entry 6). The described system, employed with $CHCl_3$ as the solvent, offered a small increase in selectivity relative to the H_2O_2-MeCN system, albeit with reduced yield (88:12 e.r., 52% yield). With various conditions explored for the biphenylazepinium catalyst **4a**, we turned to binaphthylazepinium catalyst **6a**. Since a clear influence of the catalyst backbone was observed (**4a** vs. **5**, Table 2, Entries 1 and 2), we anticipated that the larger, rigid binaphthyl backbone could increase the enantioselectivity of the reaction. Pleasingly, it was found that the *o*-HPD-[4+2] reaction could be achieved with 95:5 e.r., and 75% yield using the MeCN-H_2O_2 system with catalyst **6a** (Table 2, Entry 7). Attempts to further increase selectivity with a catalyst that features an increased biaryl dihedral angle due to the presence of an axial methyl group (see SI Table S1),[16] were unsuccessful. The diastereomeric catalyst **6b**, in which the binaphthalene backbone of the catalyst is the opposite configuration, gave access to the natural (-) isomer of the metabolite bis-(2,6-xylenol) in 56% yield and 10:90 e.r. (Table 2, Entry 9). Reducing the pH also offered no further improvement in selectivity and diminished the yield. This observation acts as further evidence for the role of the peroxyimidic acid formation between H_2O_2 and MeCN, which has been found to be pH dependent.[12b] For comparison of oxaziridinium catalysts with other oxygen-transfer organocatalysts, we found that the Shi catalyst **7** affords a low yield of product, with almost no enantiocontrol (Table 2, Entry 11).

Using our optimized enantioselective conditions for the *o*-HPD-[4+2] reaction, we evaluated the performance of alternative phenol substrates (Scheme 1). 2,4,6-trimethylphenol, another highly symmetrical substrate, was successful (**3b**) with similarly high enantioselectivity and yield. Larger *ortho*- substituents on symmetrical phenols are also compatible, as shown by the reaction of 2,6-

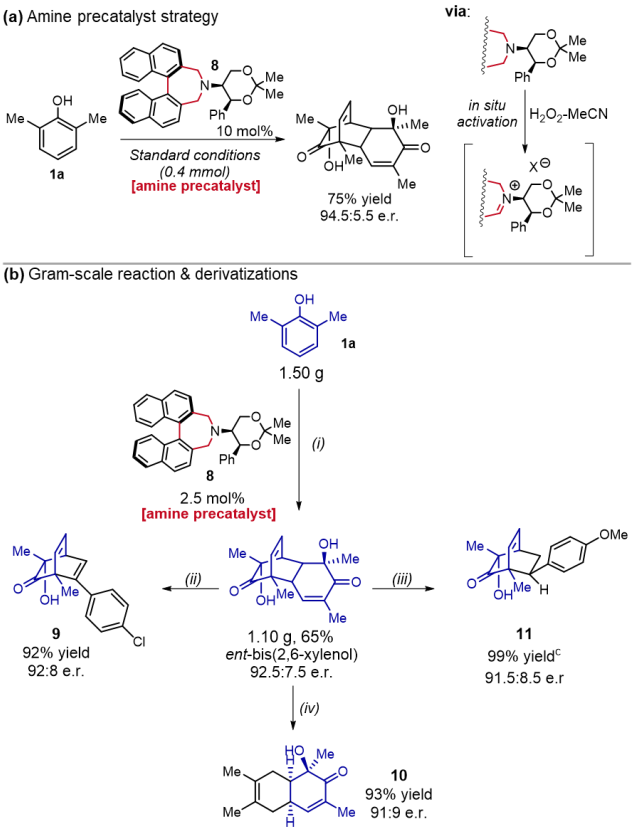


Figure 2. (a) Direct use of amine **8** as a pre-catalyst in the dearomatization reaction. (b) Gram-scale preparation of *ent*-bis(2,6-xylenol) using amine **8**, with reduced loading, and subsequent retro-[4+2]-[4+2] transformations. [c]ca. 10:1 regiomeric ratio. i) aq. H_2O_2 (3.0 eq.), 1:1 MeCN-H_2O, 2.5 mol% **8**, Na_2CO_3 (5 eq.), 0 ^{0}C, 18 h. (ii) 15 eq. 4-chlorophenylacetylene, μW 140 ^{0}C, 3.5 h. (iii) 10 eq. 4-vinylanisole, μW 130 ^{0}C, 2 h. (iv) 15 eq. 2,3-dimethyl butadiene, μW 130 ^{0}C, 4 h.

diethylphenol, which provided **3c** (79% yield, 98:2 e.r.). 2,3,6-Substituted phenols also readily reacted under the reaction conditions, showing selective dearomatization at the less-hindered 6-position (**3d**). Benzyl groups were also tolerated as *ortho*-substituents, as shown by product 3**e**. Electron donating (-Me) and electron withdrawing (-F) substituents on the 6-benzyl group afforded **3f** and **3g** respectively. Our methodology could also furnish the reaction on substrates with only a single *ortho*-subsituent from 2,5-substituted phenols, as depicted in examples **3h**-**3k**. This allowed the synthesis of the natural diterpenoid (+)-biscarvacrol **3i** (61% yield, 99:1 e.r.). Thymol, a substrate with a sterically demanding isopropyl substitutent at the *ortho*-position, was also tolerated well, giving the desired dimer **3h** with 99:1 e.r. by performing the reaction at room temperature. Substitution at the 5-position with an electron donating methoxy group was also tolerated, affording the bicyclo[2.2.2]octenone **3j**, with similarly high selectivity (98:2 e.r.). Non-symmetrical 2,6-substituted phenols were also successful in the reaction. For example, 2-methyl-6-*tert*-butyl phenol was converted into bicyclo[2.2.2]octenone **3l**, by selective dearomatization at the 2-position. However, dearomatization at both the 2- and 6-position occurred with 2-benzyl-6-methylphenol, giving rise to homo-dimer **3m** and hetero-dimer **3n** in a 1:1 ratio. Phenol substitution patterns which are known to prevent the subsequent [4+2] dimerization were avoided. Suprisingly, a 2,4-substitution pattern on the phenol led to a low yielding *para* hydroxylative dearomatization, with poor enantiocontrol. Unsuccessful substrates (see SI) also include highly hindered 2,6-diisopropyl phenol. The phenolic precursor to grandifloracin was also not tolerated under our conditions.

To further highlight the utility of our methodology, we were able to perform the synthesis of *ent*-bis-(2,6-xylenol), using the amine **8** as a pre-catalyst, wherein the amine is oxidized under the reaction conditions to form the active iminium ion.[17] The tertiary amine pre-catalyst successfully facilitated the desired dearomatization of 2,6-dimethylphenol **1a** with near-identical yield and enantioselectivity to the parent iminium (75% yield, 94.5:5.5 e.r., Figure 2, a). This approach was also employed in a gram-scale reaction, with reduced catalyst loading (2.5 mol %). This allowed for the synthesis of 1.10 g of *ent*-bis(2,6-xylenol), with a small reduction in yield and selectivity compared to the original conditions (65% yield, 92.5:7.5 e.r.).

The described bicyclo[2.2.2]octenone products can be further utilized in the synthesis of complex organic scaffolds. One of the most useful transformations of such compounds is retro-[4+2]-[4+2] chemistry,[18] in which the dimers can be used as masked *o*-quinols. Following our gram-scale synthesis, *ent*-bis(2,6-xylenol) was derivatized using retro-[4+2]-[4+2] reactions (Figure 3), using a modified method reported by Porco.[19] This demonstrates a range of further enantioenriched scaffolds that can be accessed from the bicyclo[2.2.2]octenones. A terminal alkene, as well as a terminal alkyne successfully behaved as dienophile partners to form compounds **9** and **11**. 1,3-dimethyl butadiene engaged in the retro-[4+2]-[4+2] reaction leading to the *cis*-decalin framework **10**. All of the described reactions proceeded with excellent retention of enantiopurity.

To confirm the mechanism of our dearomatization reaction, we sought to provide evidence of the active oxaziridinium ion being formed. Isolation of the oxaziridinium ion derived from catalyst **6a** proved unsuccessful. However, direct HRMS injection of the iminium catalyst **6a** after exposure to oxone proved fruitful in observing the elusive oxaziridinium cation **12** (Figure 3, a), confirming its formation under oxidative conditions. Oxaziridinium tetrafluoroborate[20] **14** is inherently more stable than **12**, allowing for its isolation. Therefore, **14** was employed in a stoichiometric reaction with phenol **1a**, furnishing (±)-**3a** in 37% yield. Since the oxaziridinium salt was the sole oxidant in the reaction, this demonstrates the ability of the oxaziridinium ion, as a structural motif, to perform the hydroxylative dearomatization.

With these findings, we can propose a mechanism as shown in Figure 3, in which H_2O_2 is activated by reacting with MeCN, in an analogous manner to the Payne oxidation.[12] The intermediate peroxyimidic acid **13** can attack the iminium catalyst **6a**, to form oxaziridinium **12**. This oxaziridinium formation is believed to be diastereoselective, as described by Page and co-workers.[21] Nucleophilic attack on the oxaziridinium by the phenolate gives rise to the *o*-quinol, in the enantiodetermining step of the reaction. The *o*-quinol then dimerizes in a regio- and diastereoselective manner,[22] giving rise to the bicyclo[2.2.2]octenone products.

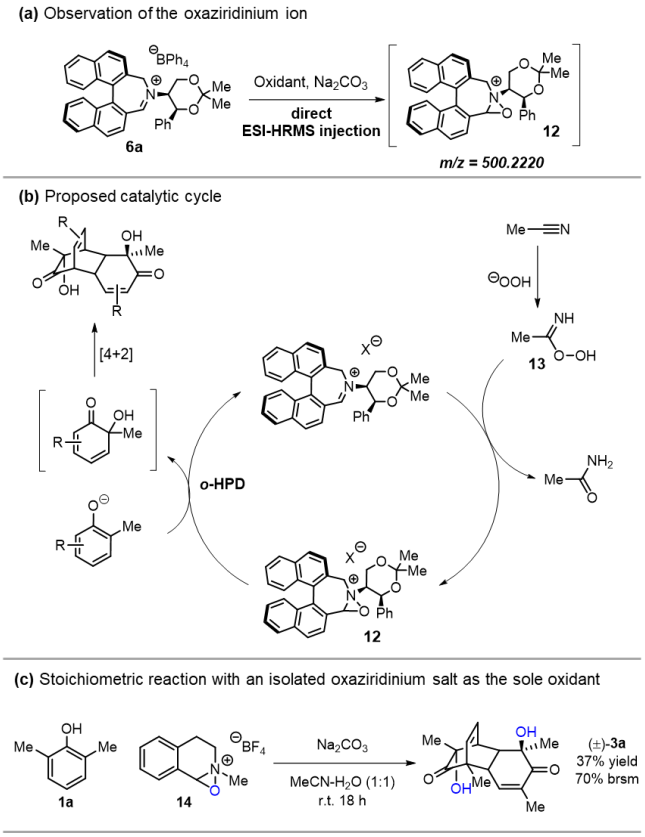


Figure 3. (a) Observation of the reactive oxaziridinium ion by direct HRMS. (b) Proposed catalytic cycle. (c) Stoichiometric dearomatization with oxaziridinium salt **14**.

In summary, we have developed an organocatalytic, highly enantioselective method for hydroxylative phenol dearomatization reactions. Notoriously challenging substrates, such as highly symmetrical phenols, are successfully oxidized in high enantiomeric purity with our conditions. We applied our chemistry to natural products such as (+)-biscarvacrol, and bis-(2,6-xylenol). Non-natural analogues could also be accessed with high selectivity. We demonstrated the practicality of our conditions by the use of a simpler, amine precatalyst alternative, which can be synthesized in one step from commercial materials, and could be used at reduced loading on a gram scale. Several retro-[4+2]-[4+2] reactions were performed on *ent*-bis(2,6-xylenol), to highlight that previously inaccessible enantioenriched bicyclo[2.2.2]octenones can be further manipulated into alternative scaffolds whilst retaining enantiopurity. We hope the reported dearomatization methodology offers a useful tool when studying biologically active *o*-quinol dimers. Due to this newly found use for oxaziridinium catalysts in dearomative chemistry, we hope to extend our research to further enantioselective oxaziridinium-catalysed dearomatization reactions.

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Notes

The authors declare no competing financial interest.

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