Oxidative Dearomatization of Phenols and Anilines via λ^3- and λ^5-Iodane-Mediated Phenylation and Oxygenation

Stéphane Quideau,* Laurent Pouységu, Aurélie Ozanne and Julien Gagnepain

Institut Européen de Chimie et Biologie, 2 rue Robert Escarpit, F-33607 Pessac Cedex, and Laboratoire de Chimie des Substances Végétales, Centre de Recherche en Chimie Moléculaire, Université Bordeaux 1, 351 cours de la Libération, F-33405 Talence Cedex. France. Tel. (+33) (0) 540003010, Fax (+33) (0) 540002215

* Author to whom correspondence should be addressed; e-mail s.quideau@iecb.u-bordeaux.fr

Abstract. Treatment of 2-methylphenols with chloro(diphenyl)-λ^3-iodane led to their regioselective dearomatizing 2-phenylation into cyclohexa-2,4-dienone derivatives via a proposed ligand coupling reaction. In the same vein of investigation, treatment of 2-methylanilines with the λ^5-iodane 2-iodoxybenzoic acid IBX reagent led to their regioselective dearomatization into previously undescribed *ortho*-quinol imines.
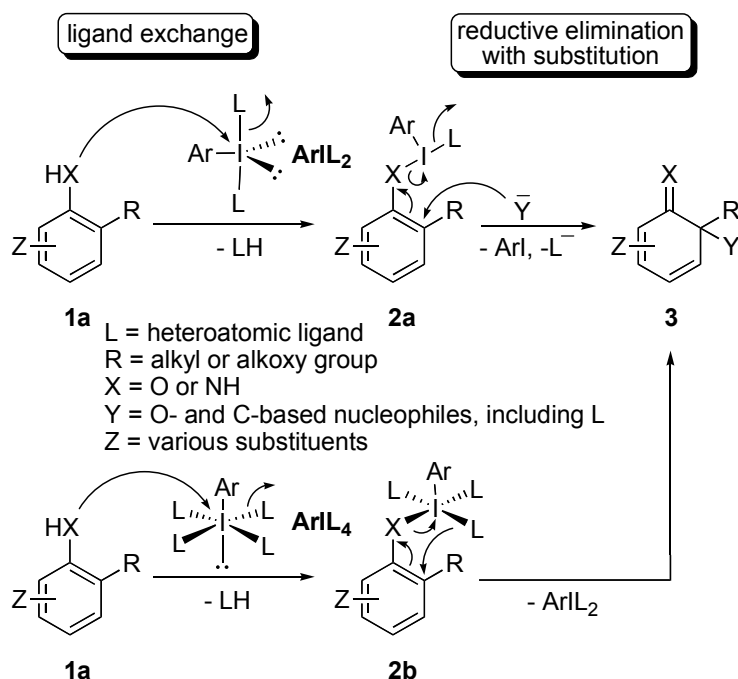
Keywords: Iodanes, phenols, anilines, dearomatization, cyclohexadienones, orthoquinol imines.

Introduction

Arene dearomatization is a powerful tactic for the construction of complex organic molecules [1-3]. Our research efforts in this arena of synthetic organic chemistry rely in part on the use of λ^3- and λ^5-iodanes, i.e., hypervalent iodine(III) and iodine(V) compounds (Scheme 1) [4-10]. For example, the λ^3-iodane of type $ArIL_2$ (L = heteroatomic ligand) (diacetoxy)iodobenzene (DIB) enables high-yielding conversion of 2-alkoxy and 2-alkylphenols into cyclohexa-2,4-dienone synthons that can then be utilized into various heterocyclization processes [7-9,11]. The [bis(trifluoroacetoxy)]iodobenzene (BTI) reagent can be used similarly to mediate regioselective carbon-carbon bond formation at substituted centers on naphthols [8,10]. The λ^5-iodane of the general type $ArIL_4$ 2-iodoxybenzoic acid (IBX), or its stabilized version SIBX [4], can be used both as an oxidant and as a source of oxygen for *ortho*-selective hydroxylation of 2-substituted arenols into orthoquinols [4,5,12]. We here wish to

describe preliminary results from two other incursions into the realm of iodane chemistry. The first one concerns the first example of the utilization of λ^3-iodanes of type Ar_2IL to mediate dearomatizing phenylation of methylphenols, and the second incursion has to do with experimental observations made during IBX-mediated oxidative dearomatization of anilines.
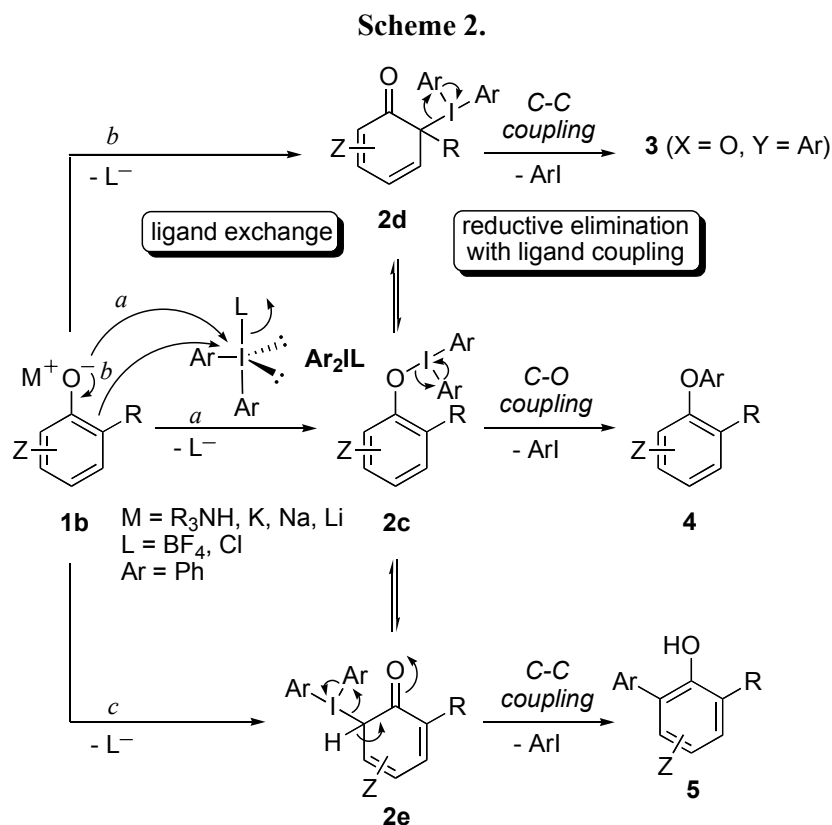
Scheme 1.

L = heteroatomic ligand
R = alkyl or alkoxy group
X = O or NH
Y = O- and C-based nucleophiles, including L
Z = various substituents

Results and Discussion

Our previous investigation on carbon-carbon (C–C) bond-forming and dearomatizing reaction of 2-substituted arenols was accomplished by a process that was apparently intermolecular and oxidatively initiated by BTI in the presence of either an allylsilane or a silyl enol ether [8,10]. Intramolecular variants of such a transformation are known and the most effective ones rely on the use of either a lead(IV) [13,14] or a bismuth(V) [15,16] species bearing heteroatomic and aryl ligands. The starting 2-substituted arenol first reacts with the aforementioned metallic species to exchange one of its labile heteroatomic ligands. Once the aryloxy unit of the substrate is mounted onto the metallic center, a reductive elimination step can take place with a concomitant C–C ligand coupling directed at the 2-substituted position of the aryloxy unit to generate a cyclohexa-2,4-dienone product. Ligand coupling is also possible on an hypervalent iodine(III) center [17,18], and it has been proposed that diaryl-λ^3-iodanes (i.e., Ar_2IL)[†] do transfer, through this mechanistic path, an aryl group to enolates to furnish α-*C*-arylated carbonyl compounds [17,19-21].

[†]Ar_2IL-type compounds are usually referred to as diaryliodonium salts despite the fact that their geometry is not tetrahedral, but pseudotrigonal bipyramidal, as expected for hypervalent iodine(III) species. The lamba iodane terminology is thus used here to name hypervalent iodine compounds [17].

Scheme 2.

Phenolates being aromatic variants of generic enolates, we thus contemplated the idea of achieving phenol dearomatization leading to 6-arylcyclohexa-2,4-dienone derivatives of type **3** using diaryl-λ^3-iodane species (Scheme 2). The desired ligand coupling reaction could imply either passage through an aryloxy-λ^3-iodane intermediate of type **2c** (i.e., ligand exchange path *a*), which would then tautomerize into a 6-λ^3-iodanyl ketone of type **2d**, or direct formation of **2d** via participation of the 2-methylated carbanionic form of the starting phenolate **1b** (i.e., ligand exchange path *b*). In any event and to the best of our knowledge, such an iodane-mediated reaction has never been described.

We commenced our investigation of this dearomatizing arylation process by identifying the most appropriate reaction conditions to promote C–C ligand coupling (i.e., via **2d**), while minimizing the C–O ligand coupling alternative (i.e., via **2c**) that leads to diaryl ethers of type **4** (Scheme 2). This preliminary examination was carried out using 2,3,5-trimethylphenol (**1a**) with the aim of directing the introduction of a phenyl group at its substituted 2-position to enable the desired dearomatization into the cyclohexa-2,4-dienone **3a**. The presence of a methyl group at the 3-position of **1a** was chosen in order to block [4+2] dimerization of **3a** [5]. Indeed, the presence of such a small electron-releasing group at the corresponding 5-position of cyclohexa-2,4-dienones is known to block their dimerization [22,23]. Treatment of **1a** with tetrafluoroboro(diphenyl)-λ^3-iodane [24] in DMF at room temperature using weak bases such as pyridine or triethylamine failed to initiate any reaction (Table 1, entries 1 and 2). The use of a strong alkoxide base [20,25,26] was necessary to engage the reaction, but the only observed product was the diaryl ether **4a**, which was isolated in a moderate yield of 41% (entry 3) [27,28]. Change of the diphenyl-λ^3-iodane reagent to chloro(diphenyl)-λ^3-iodane led to some improvement in the yield of **4a**, but no formation of the desired dearomatized product **3a** was observed (entry 4).

Table 1. Preliminary search of reaction conditions to promote
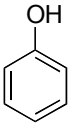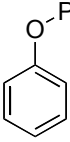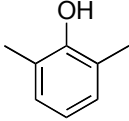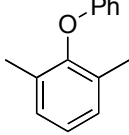dearomatizing 2-phenylation of a 2-substituted phenol
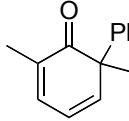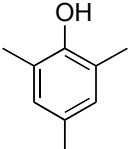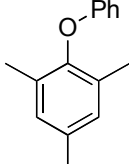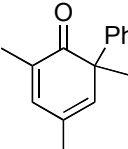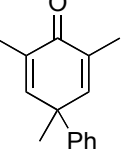
entry	L	solvent	base	temp (C)	3a (%)[a]	4a (%)[a]
1	BF$_4$	DMF	pyridine	rt	0	0
2	BF$_4$	DMF	Et$_3$N	rt	0	0
3	BF$_4$	DMF	KO*t*-Bu	rt	0	41
4	Cl	DMF	KO*t*-Bu	rt	0	53
5	BF$_4$	*t*-BuOH	KO*t*-Bu	rt	6	33
6	Cl	*t*-BuOH	KO*t*-Bu[b]	rt	8	63
7	Cl	*t*-BuOH/THF	KO*t*-Bu	- 20	6	56
8[c]	Cl	*t*-BuOH	Š	rt	6	51

[a] Isolated yields. [b] Same result using LiO*t*-Bu. [c] Using the sodium
phenoxide prepared beforehand by treating **1a** with NaOH (1.0 equiv)
in methanol.

The first glimpse of success was obtained by performing the reaction in a polar protic solvent (i.e., *t*-BuOH) at room temperature, in which case **3a** was isolated in 6% or 8% using either a tetrafluoroborate unit or a chloride atom as the ligand L on the iodine(III) of the reagent. In both cases, the major product was again the diaryl ether **4a** (entries 5 and 6). It is worth noting that no biaryl product of type **5**, which could have resulted from introduction of a phenyl residue at the unsubstituted 6-position of the starting phenol **1a** via an α-λ^3-iodanyl ketone of type **2e** (Scheme 2), was observed. It thus appears that a small alkyl group, such as a methyl group, at one phenoxy *ortho*-position plays a role in directing delivery of a phenyl residue at that substituted position and not at the unsubstituted position (*vide infra*). This observation is in agreement with a route via an α-λ^3-iodanyl ketone intermediate of type **2d** (Scheme 2). Neither performing the reaction at –20 °C (entry 7) nor using a smaller counter-cation such as Na$^+$ or Li$^+$ (entries 6[b] and 8[c]) to promote a change of chemoselectivity in favor of C–C coupling resulted in any improvement of the yield of **3a**. So, the use of chloro(diphenyl)-λ^3-iodane in the presence of potassium *tert*-butoxide in *tert*-butanol at room temperature so far emerged as the best conditions to achieve the desired transformation, albeit in low yields.

We then carried out a series of reactions under these conditions using three differently substituted phenols **1b-d** (Table 2). The unsubstituted phenol **1b** led exclusively to the formation of the diaryl ether **4b** in a good yield of 75%. This observation corroborates that made with phenol **1a** on the role of a small alkyl substituent at one phenoxy *ortho*-position (*vide supra*) not only in directing the introduction of the phenyl residue at that carbon position, but also in promoting *C*-phenylation. Hence, starting from phenols bearing the same alkyl substituent at each of two equivalent *ortho*-positions should significantly boost yields of *C*-phenylation over *O*-phenylation.

Table 2. Chloro(diphenyl)-λ^3-iodane-mediated phenylation of phenols

entry	phenol[a]	product(s): isolated yield (%)		

1b   **4b:** 75%

1c   **4c:** 24%   **3c:** 37%

1d   **4d:** 7%   **3d:** 42%   **6d:** 7%

[a] Reactions were carried out at room temperature using Ph_2ICl (1.1 equiv) and KOt-Bu (1.05 equiv) in t-BuOH.

This hypothesis was confirmed using the di- and trimethylphenols **1c** and **1d**, which gave rise to the formation of the desired cyclohexa-2,4-dienones **3c** and **3d** in 37% and 42%, respectively (Table 2, entries 2 and 3). Moreover, these cyclohexa-2,4-dienones are stable compounds that do not spontaneously engage in [4+2] dimerization, despite the absence of an alkyl substituent at their 5-position [22,23]. Interestingly, 2,4,6-trimethylphenol (**1d**) also led to phenylation at the methylated 4-position (entry 3). Although the yield of the corresponding product **6d** was only 7%, its formation is in accordance with a ligand coupling event from a γ-λ^3-iodanyl ketone of type **2f** that would be formed from a direct ligand exchange between the 4-methylated carbanionic form of the starting phenolate **1d** and the chloro(diphenyl)-λ^3-iodane reagent (Scheme 3). Further mechanistic investigations need to be performed to confirm that the observed products are generated through ligand coupling, but the reactions described here are the first examples of iodane-mediated dearomatizing phenylation of substituted phenols.

Scheme 3.
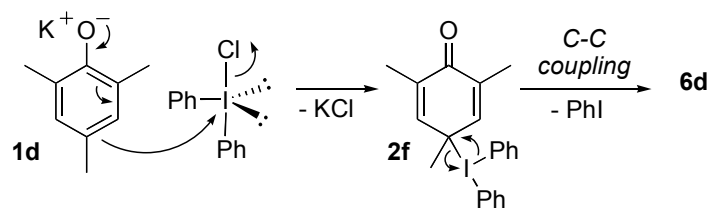
We then turned our attention to another iodane-mediated dearomatization reaction involving the oxygenation of anilines and anilides with the aim of preparing *ortho*-quinol imines. Quinonoid

compounds are powerful intermediates for organic synthesis, and those bearing a nitrogen functionality obviously expand their versatility as potential precursors and building blocks for the synthesis of biologically relevant natural and non-natural substances [29]. Among those, quinonoid imines such as quinone imines, quinone imine ketals and quinol imines occupy a valuable position as potentially useful synthons, but their imine function is unfortunately very sensitive to hydrolysis, unless the imine nitrogen is substituted by an acyl or a sulphonyl group [30,31] Most previous studies on quinonoid imines and imides have focused on *para*-compounds, and their generation was based on electrochemical or chemical oxidation of aniline and anilide parents [30,31]. Iodane reagents have seldom been used for mediating such transformations [32-34], and the only examples in the *ortho*-series [35] are those recently reported by Nicolaou and his co-workers, who exploited Dess–Martin periodinane (DMP) generated *ortho*-quinone imides in Diels–Alder reactions [29,36,37]; DMP belongs to the $ArIL_4$ type of the λ^5-iodane reagents. To the best of our knowledge, the formation of *ortho*-quinol imines by any means has never been reported. In order to achieve the preparation of such elusive species, we first went back to λ^3-iodanes bearing two heteroatomic nucleofugal ligands (i.e., $ArIL_2$ type) in order to promote the desired oxidative oxygenation process [17] starting from 2-substituted anilines or anilides.

With this consideration in mind, we attempted to perform an oxidative *ortho*-acetoxylation of aniline **7a** with DIB either in pure CH_2Cl_2 or in a 3:1 $CH_2Cl_2/AcOH$ mixture, but only intractable mixtures were obtained. However, the use of the λ^5-iodane of type $ArIL_4$ IBX at room temperature gave a 2:1 mixture of the *para*-quinone imine **10a** and the *ortho*-quinol imine **11a**, as evidenced by NMR analysis (Scheme 4). Silica gel chromatography of this mixture furnished **10a** in 42% and **11a** in 11.5%, as well as traces (i.e. < 2%) of the Diels–Alder dimer **12a** derived from **11a** (*vide infra*) [5]. Compound **10a** probably results from an initial IBX-mediated formation of the *ortho*-quinone imine **8a** (Schemes 4 and 7), which is rapidly trapped by some intact starting aniline **7a** to furnish the Schiff base **9a**. This *ortho*-quinone bisimine can then be quenched in a conjugate manner by the water released during the Schiff base formation and reoxidized to furnish the observed *para*-quinone imine **10a**. Moreover, we were pleased to isolate **11a** even in such a low yield, since, as mentioned above, such an *ortho*-quinol imine has never been described before.

Scheme 4.
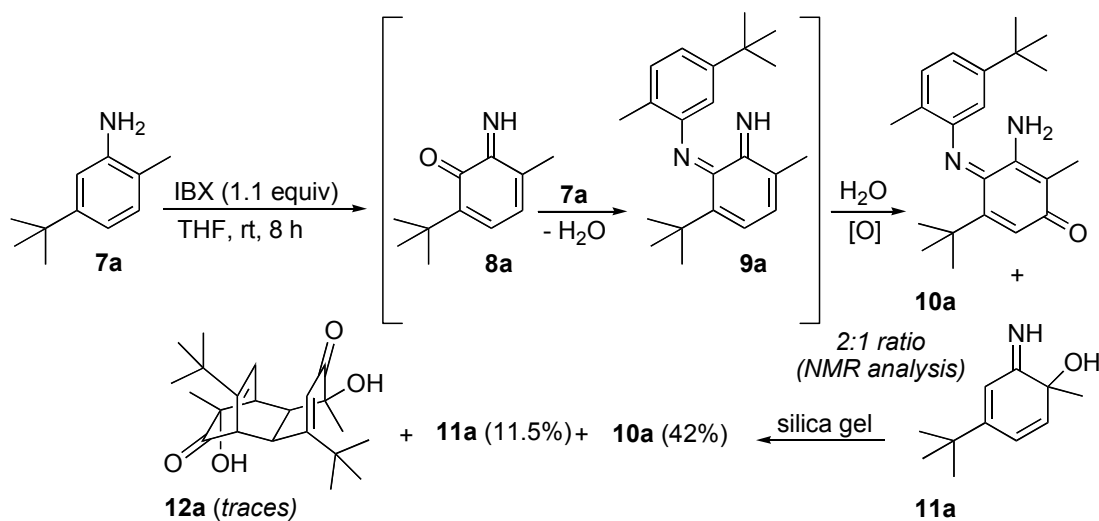
Furthermore, this first reaction with aniline **7a** showed us that IBX is capable of selectively delivering an oxygen at the positions adjacent to the amine function, in a manner probably similar to the one that we and others have suggested for analogous IBX- and SIBX-mediated *ortho*-oxygenations of phenols (Scheme 7) [4,5,12]. Having thus successfully tested the feasibility of dearomatizing an aniline into an *ortho*-quinol imine, the same reaction was performed using the anilide **7b** in the hope of improving its yield, for quinonoid imides are known to be stable enough for isolation as opposed to imines that are sensitive to hydrolysis and polymerization [29-31,37]. In addition, the lower nucleophilicity of the anilide nitrogen should preclude nucleophilic trapping of the *ortho*-quinone imine formed. For the same reason, the anilide **7b** turned out to be a very robust starting material, which necessitated a treatment with IBX for 48 h in refluxing THF to be entirely transformed, as indicated by TLC monitoring [CH$_2$Cl$_2$/MeOH (40:1)] of the reaction progress (Scheme 5). Now IBX does react with hot THF [4,38-40], therefore additional quantities of IBX were added to the reaction mixture every 12 h (see Experimental Section). These conditions led to the isolation of the *ortho*-quinone imide **8b** and the *ortho*-quinol imine **11b** in 6% and 8% yield, respectively. The acetyl group did not protect the imine double bond from hydrolysis, since dimer **12a** was again obtained, this time in 35% yield. No dimer with the two imide functions still intact was observed. However, the formation of both **11b** and its derived dimer **12a** after treating **7b** with IBX remains an interesting observation, since treatment of analogous 2-substituted anilides using DMP in the presence of water only led to *ortho*-quinone imides [29,37]. The mechanism proposed by Nicolaou and his co-workers for this *ortho*-oxygenation implies the intermolecular participation of the DMP-derived acetate of IBX (Ac-IBX) as the source of the oxygen atom [36,39], so the oxygen delivery by the bulky Ac-IBX may be indeed blocked at the 2-substituted position because of steric impediment. However, when the same authors used IBX in a mixed solvent system of THF/DMSO (10:1) at 90 °C to transform anilide derivatives tethered with an olefin unit, they only observed nitrogen/olefin cyclization products derived from one-electron oxidation at the nitrogen lone pair [39,40]. It is somewhat puzzling that they did not observe any formation of *ortho*-oxygenation products, like in the examples reported herein for which we propose that IBX acts as the oxygen source (Scheme 7).

Scheme 5.
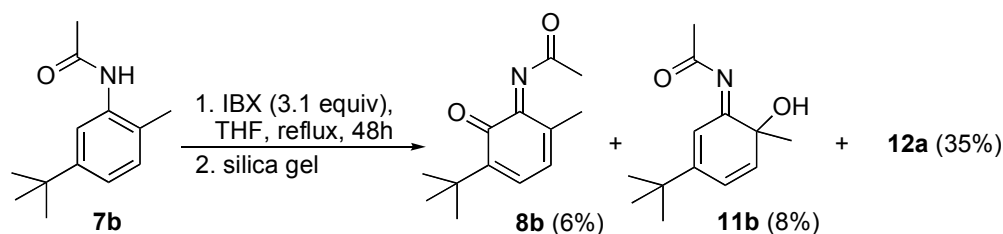
In any event, with this second dearomatization of a 2-substituted aniline derivative into an *ortho*-quinol imine accomplished (Scheme 5), we then moved on to treat 2,4,6-trimethylaniline (**7c**), having two equivalent 2-substituted *ortho*-positions, with IBX in order to boost the yield of the corresponding *ortho*-quinol imine product. This reaction led to a very clean crude product showing NMR signals assignable only to the expected *ortho*-quinol imine **11c** (Scheme 6). This quinol imine did not survive silica gel chromatography and was isolated in only 33.5% yield, together with the Diels–Alder cycloadduct **12c** in 13% yield. The use of the stabilized version of IBX (i.e., SIBX) [4] also led to the

isolation of **11c** in 35% yield, again in concert with that of the dimer **12c** (22%) (Scheme 6). This dimer has been previously prepared from 2,4,6-trimethylphenol via sodium periodate-mediated Adler oxidation [41], and via the benzeneseleninic anhydride-mediated Barton oxidation [42].

Scheme 6.
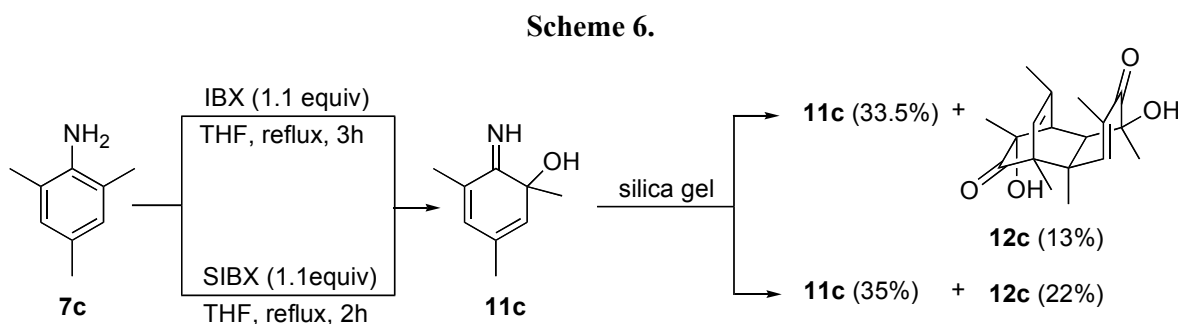
IBX is the only obvious source of oxygen in these *ortho*-oxygenations of anilines **7a** and **7c** and anilide **7b**. In analogy with our previous mechanistic proposal for related oxygenations of phenols [5,12], an ionic pathway is here depicted to rationalize these oxidative dearomatizing transformations leading to the isolation of previously undescribed *ortho*-quinol imines such as **11a-c** (Scheme 7). Thus, once the amine or amide nitrogen of **7** has attacked the IBX iodine to give **13**, reduction of this iodine(V) center could proceed via an ionic and concerted path to yield **11** and *o*-iodosobenzoic acid (IBA).

Scheme 7.
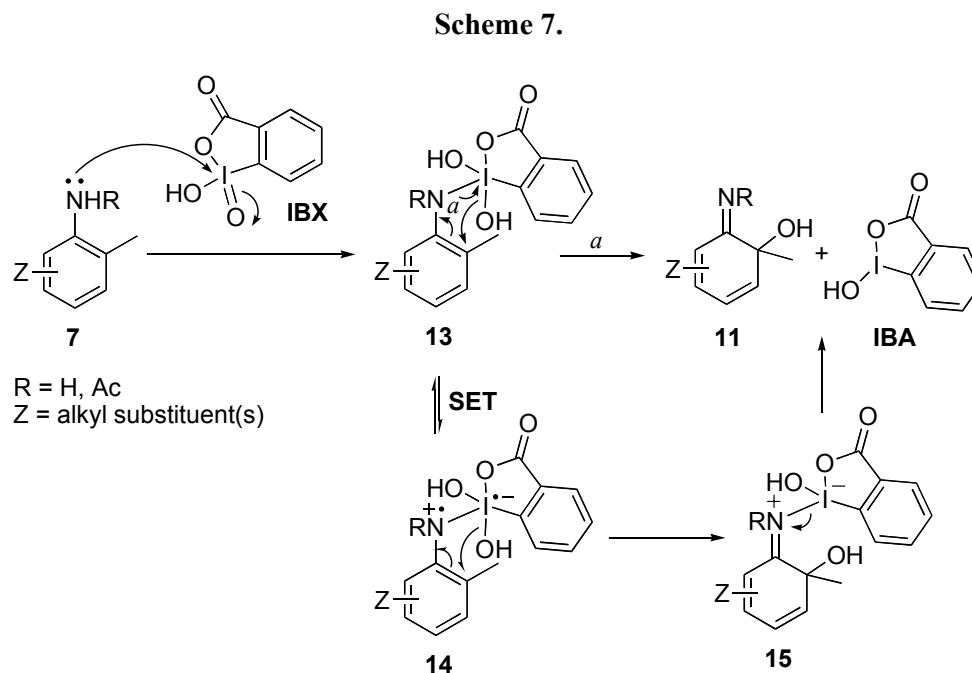
Of course, a single electron transfer (SET) mechanism [43] leading to the nitrogen radical cation **14**, followed by delivery of an hydroxyl radical to the substrate aromatic ring to give the intermediate **15**, that would then fragment into **11** and IBA, cannot be excluded at this point. Further work is in progress to delineate these mechanistic possibilities.

Acknowledgements

Experimental

General

Diacetoxyiodobenzene (DIB) and stabilized *o*-iodoxybenzoic acid (SIBX) [4] were obtained from SIMAFEX. Chloro(diphenyl)-λ^3-iodane (Ph$_2$ICl, 97%) was purchased from Aldrich. Tetra-fluoroboro(diphenyl)-λ^3-iodane (Ph$_2$IBF$_4$) [20,24] and *o*-iodoxybenzoic acid (IBX) [44] were prepared from DIB and 2-iodobenzoic acid, respectively. Dichloromethane (CH$_2$Cl$_2$) and *tert*-butyl alcohol (*t*-BuOH) were used as received. Tetrahydrofuran (THF) was purified by filtration through alumina under N$_2$ immediately before use. Moisture and oxygen sensitive reactions were carried out in flame-dried glassware under N$_2$. Evaporations were conducted under reduced pressure at temperatures less than 30 °C unless otherwise noted. Column chromatography was carried out under positive pressure using 40-63 μm silica gel (Merck) and the indicated solvents. Further drying of the residues was accomplished under high vacuum. Melting points are uncorrected. NMR spectra of samples in the indicated solvent were run at 250, 300 or 400 MHz. Carbon multiplicities were determined by DEPT-135 and *J*-MOD experiments. Electron impact (70 eV), chemical ionization and electrospray mass spectrometry low and/or high resolution (EIMS, CIMS, ESIMS and HRMS) were obtained from the mass spectrometry laboratory at the CESAMO, Université Bordeaux 1, from the mass spectrometry laboratory at the Institut Européen de Chimie et Biologie, Pessac, and from the mass spectrometry laboratory at the Centre Régional de Mesures Physiques de l'Ouest, Université de Rennes 1.

General Procedure for λ^3-Iodane-Mediated Phenylation of Phenols

To a stirred solution of KO*t*-Bu (1.4 mmol, 1.05 equiv) in *t*-BuOH (4 mL, *ca.* 0.35 M) was added the phenol **1a-d** (1.3 mmol) at room temperature, and the mixture was stirred for 1 h. The diphenyl-λ^3-iodane reagent, i.e., Ph$_2$IBF$_4$ [24] or Ph$_2$ICl (1.5 mmol, 1.1 equiv), was added in one portion to this mixture. The resulting suspension was stirred for 20 h at room temperature, after which time water (20 mL) was added, and the mixture was extracted with CH$_2$Cl$_2$ (3 × 5 mL). The combined organic extracts were washed once with water (5 mL), dried over Na$_2$SO$_4$, filtered, evaporated, and further dried under high vacuum.

3,5,6-Trimethyl-6-phenylcyclohexa-2,4-dienone (**3a**) *and 1,2,5-trimethyl-3-phenoxybenzene* (**4a**)

Ph$_2$ICl-mediated phenylation of 2,3,5-trimethyphenol (**1a**, 312 mg, 2.3 mmol) was carried out according to the general procedure to afford a crude orange oil (600 mg), which was purified by column chromatography, eluting with pentanes/EtOAc (5:1), to yield the cyclohexa-2,4-dienone **3a** as a yellow oil (40 mg, 8%), the diaryl ether **4a** as a colorless oil (309 mg, 63%), and some recovered starting phenol **1a** (50 mg, 16%).

3a: IR (NaCl, neat) 3024, 2978, 1666, 1636, 1580, 846 cm^{-1}; ^{1}H-NMR (CDCl$_3$, 300 MHz) δ 1.55 (s, 3H), 1.63 (s, 3H), 2.02 (s, 3H), 5.75 (s, 1H), 6.00 (s, 1H), 7.08-7.22 (m, 5H); ^{13}C-NMR (CDCl$_3$, 75.5 MHz) δ 203.9, 155.5, 154.6, 140.6, 128.6, 126.9, 126.6, 122.5, 120.2, 56.7, 22.9, 22.1, 19.8; EIMS *m/z* (rel intensity) 212 (M$^+$, 100), 197 (42), 184 (68), 169 (88), 154 (21), 77 (25); HRMS (EI) calcd for C$_{15}$H$_{16}$O 212.1201, found 212.1198.

4a: IR (NaCl, neat) 2929, 1489, 1224 cm^{-1}; ^{1}H-NMR (CDCl$_3$, 250 MHz) δ 2.11 (s, 3H), 2.25 (s, 3H), 2.29 (s, 3H), 6.63 (s, 1H), 6.82 (s, 1H), 6.89 (d, *J* = 7.6 Hz, 2H), 6.99-7.06 (m, 1H), 7.26-7.33 (m, 2H); ^{13}C-NMR (CDCl$_3$, 62.9 MHz) δ 158.4, 153.9, 138.4, 136.1, 129.5, 126.5, 125.5, 121.9, 118.3, 116.9, 20.8, 20.0, 11.8; EIMS *m/z* (rel intensity) 212 (M$^+$, 100), 197 (42), 135 (13), 119 (19), 77 (20); HRMS (EI) calcd for C$_{15}$H$_{16}$O 212.1201, found 212.1199.

Phenoxybenzene (**4b**)

Ph$_2$ICl-mediated phenylation of phenol (**1b**, 100 mg, 1.1 mmol) was carried out according to the general procedure to afford the diaryl ether **4b** [45] as a clean crude orange oil (140 mg, 75%), which was not further purified: IR (NaCl, neat) 3066, 3044, 1582, 1485, 1285 cm^{-1}; ^{1}H-NMR (CDCl$_3$, 300 MHz) δ 7.15-7.26 (m, 6H), 7.26-7.49 (m, 4H); ^{13}C-NMR (CDCl$_3$, 75.5 MHz) δ 157.4, 129.9, 123.4, 119.0; EIMS *m/z* (rel intensity) 170 (M$^+$, 14), 51 (31), 39 (13), 18 (100).

2,6-Dimethyl-6-phenylcyclohexa-2,4-dienone (**3c**) *and 1,3-dimethyl-2-phenoxybenzene* (**4c**)

Ph$_2$ICl-mediated phenylation of 2,6-dimethylphenol (**1c**, 155 mg, 1.3 mmol) was carried out according to the general procedure to afford a crude orange oil (367 mg), which was purified by column chromatography, eluting with cyclohexane/EtOAc (9:1), to yield the cyclohexa-2,4-dienone **3c** [16] as a yellow oil (93 mg, 37%) and the diaryl ether **4c** [46] as a colorless oil (60 mg, 24%).

3c [16]: IR (NaCl, neat) 3034, 2978, 1660, 742, 692 cm^{-1}; ^{1}H-NMR (CDCl$_3$, 300 MHz) δ 1.62 (s, 3H), 1.88 (s, 3H), 6.26 (dd, *J* = 6.0, 9.4 Hz, 1H), 6.37 (d, *J* = 9.4 Hz, 1H), 6.89 (d, *J* = 6.0 Hz, 1H), 7.21-7.33 (m, 5H); ^{13}C-NMR (CDCl$_3$, 75.5 MHz) δ 203.9, 145.3, 140.9, 138.0, 132.5, 128.6, 127.2, 126.6, 119.8, 54.2, 23.8, 15.6; EIMS *m/z* (rel intensity) 198 (M$^+$, 100), 183 (60), 170 (63), 155 (93).

4c [46]: IR (NaCl, neat) 3040, 2921, 1490, 1224, 750 cm^{-1}; ^{1}H-NMR (CDCl$_3$, 300 MHz) δ 2.04 (s, 6H), 6.65-6.69 (m, 2H), 6.85-6.95 (m, 1H), 6.97-7.03 (m, 3H), 7.13-7.19 (m, 2H); ^{13}C-NMR (CDCl$_3$,

75.5 MHz) δ 157.8, 151.0, 131.5, 129.6, 128.9, 124.9, 121.2, 114.6, 16.3; EIMS *m/z* (rel intensity) 198 (M[+], 31), 183 (18), 77 (97), 76 (75).

2,4,6-Trimethyl-6-phenylcyclohexa-2,4-dienone (**3d**)*, 1,3,5-trimethyl-2-phenoxybenzene* (**4d**) *and 2,4,6-trimethyl-4-phenylcyclohexa-2,5-dienone* (**6d**)

Ph$_2$ICl-mediated phenylation of 2,4,6-trimethylphenol (**1d**) (172 mg, 1.3 mmol) was carried out according to the general procedure to afford a crude orange oil (503 mg), which was purified by column chromatography, eluting with cyclohexane/EtOAc (99:1), to yield the diaryl ether **4d** [47] as a colorless oil (18 mg, 7%), the cyclohexa-2,4-dienone **3d** [15] as a yellow oil (84 mg, 31%), and a 3:2 mixture of **3d**/**6d** as a yellow oil (47 mg, 18%).

3d [15]: IR (NaCl, neat) 3030, 2978, 1656, 1458, 710 cm^{-1}; ^{1}H-NMR (CDCl$_3$, 300 MHz) δ 1.63 (s, 3H), 1.91 (s, 3H), 2.03 (s, 3H), 6.08 (s, 1H), 6.80 (s, 1H), 7.25-7.34 (m, 5H); ^{13}C-NMR (CDCl$_3$, 75.5 MHz) δ 203.8, 142.7, 141.9, 139.9, 132.1, 128.8, 127.4, 127.3, 126.9, 53.7, 24.4, 21.5, 15.9; EIMS *m/z* (rel intensity) 212 (M[+], 100), 184 (42), 169 (35), 154 (9).

4d [47]: IR (NaCl, neat) 3022, 2926, 1592, 1490, 1223 cm^{-1}; ^{1}H-NMR (CDCl$_3$, 300 MHz) δ 2.00 (s, 3H), 2.22 (s, 6H), 6.66-6.69 (m, 2H), 6.82 (s, 2H), 6.84-6.89 (m, 1H), 7.13-7.18 (m, 2H); ^{13}C-NMR (CDCl$_3$, 75.5 MHz) δ 158.0, 148.7, 134.4, 131.0, 129.5, 121.1, 114.6, 20.8, 16.2; EIMS *m/z* (rel intensity) 212 (M[+], 59), 197 (60), 120 (100).

6d: ^{1}H-NMR (CDCl$_3$, 300 MHz) δ 1.66 (s, 6H), 1.96 (s, 3H), 6.73 (s, 2H), 7.23-7.35 (m, 5H); ^{13}C-NMR (CDCl$_3$, 75.5 MHz) δ 187.5, 151.2, 132.9, 129.0, 127.5, 126.6, 44.6, 24.6, 16.5. These NMR data were read on the spectrum of the 3:2 mixture of the *ortho-* and the *para*-phenylated products **3d** and **6d**.

4-tert-Butyl-2-methylaniline (**7a**)

To a stirred solution of 4-*tert*-butyltoluene (500 mg, 3.4 mmol) in Ac$_2$O (15 mL) was added dropwise HNO$_3$ (598 μL, 8.4 mmol) in AcOH (800 μL, 13.5 mmol) [48]. The solution turned slowly bright yellow, and was stirred at room temperature for 1 h. The reaction mixture was diluted with ice-cold water, and extracted with CH$_2$Cl$_2$ (2 × 20 mL). The combined organic extracts were washed with 20% aqueous NaOH (3 × 10 mL), brine (3 × 10 mL), dried over Na$_2$SO$_4$, filtered and evaporated. Purification by column chromatography, eluting with hexane, afforded 4-*tert*-butyl-2-nitrotoluene [49,50] as a bright yellow oil (479 mg, 73%): IR (NaCl) 2972, 1532, 1354 cm^{-1}; ^{1}H-NMR (CDCl$_3$, 400 MHz) δ 1.36 (s, 9H), 2.57 (s, 3H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 8.01 (s, 1H); ^{13}C-NMR (CDCl$_3$, 100 MHz) δ 150.5, 148.9, 132.3, 130.4, 130.1, 121.3, 34.5, 30.9, 19.8; EIMS *m/z* (rel intensity) 193 (M[+], 117), 178 (100). Hydrogenation of this material, collected from two runs (500 mg, 2.6 mmol) in dry THF (10 mL) was carried out under H$_2$ for 8 h at room temperature in the presence of 10% Pd/C as a catalyst (50 mg) using an autoclave (5 bars) with mechanical stirring. The reaction mixture was filtered through Celite, and the solid was washed with Et$_2$O. Evaporation of the combined filtrates and washings furnished a crude product, which was submitted to column

chromatography, eluting with hexane/Et$_2$O (4:1), to give the aniline **7a** [51] as a colorless oil (360 mg, 85%), which was immediately protected from light: IR (NaCl) 3260, 2574, 1633, 1056 cm^{-1}; ^{1}H-NMR (CDCl$_3$, 250 MHz) δ 1.41 (s, 9H), 2.24 (s, 3H), 3.62 (s, 2H), 6.83 (d, *J* = 1.8 Hz, 1H), 6.87 (dd, *J* = 1.8, 7.9 Hz, 1H), 7.1 (d, *J* = 7.9 Hz, 1H); ^{13}C-NMR (CDCl$_3$, 62.9 MHz) δ 150.0, 144.0, 130.0, 119.4, 115.6, 112.1, 34.2, 32.0, 16.8; EIMS *m/z* (rel intensity) 163 (M$^+$, 47), 148 (100).

N-acetyl-5-tert-butyl-2-methylaniline (**7b**)

Hydrogenation of 4-*tert*-butyl-2-nitrotoluene (300 mg, 1.55 mmol) in 2:1 Ac$_2$O/AcOH (30 mL) was carried out under H$_2$ for 3 h at room temperature in the presence of 10% Pd/C as a catalyst (30 mg) using an autoclave (5 bars) equipped with mechanical stirring [52]. The reaction mixture was filtered through Celite, and the solid was washed with Et$_2$O (50 mL). The combined filtrates and washings were washed successively with saturated aqueous NaHCO$_3$ (3 × 10 mL) and brine (2 × 10 mL), dried over Na$_2$SO$_4$, filtered and evaporated to furnish an amorphous solid, which was purified by crystallization from Et$_2$O, to yield the anilide **7b** [51] as white fine needles (284 mg, 89%): mp 102 °C (lit. [51] mp 97-98 °C); IR (neat) 3268, 2925, 1661 cm^{-1}; ^{1}H-NMR (CDCl$_3$, 400 MHz) δ 1.29 (s, 9H), 2.08 (s, 3H), 2.15 (s, 3H), 7.07 (d, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 1H), 7.57 (s, 1H), 7.82 (s, 1H); ^{13}C-NMR (CDCl$_3$, 100 MHz) δ 168.6, 149.6, 135.2, 130.0, 127.4, 122.6, 121.2, 34.4, 31.2, 24.0, 17.3; EIMS m/z (rel intensity) 205 (M$^+$, 75), 190 (100), 163 (42), 148 (90).

2,4,6-trimethylaniline (**7c**)

To a stirred ice-cold solution of mesitylene (5.0 g, 41.7 mmol) in Ac$_2$O (10 mL) was added fuming HNO$_3$ (6.5 mL, 145.6 mmol). The mixture was stirred for 1 h at 0 °C, and then poured into ice-cold water (30 mL). The aqueous phase was extracted with Et$_2$O (3 × 30 mL), and the combined organic extracts were washed successively with 20% aqueous NaOH (6 × 20 mL), water (20 mL), and brine (20 mL), dried over MgSO$_4$, filtered, and evaporated to furnish a crude yellow solid (6.6 g). Purification by column chromatography, eluting with a cyclohexane/Et$_2$O gradient (100:0 → 95:5), afforded 2-nitromesitylene as pale yellow crystals (5.5 g, 80%): mp 43 °C (lit. [53] mp 44 °C); IR (NaCl) 2928, 2871, 1604, 1521, 1367, 1041 cm^{-1}; ^{1}H-NMR (CDCl$_3$, 250 MHz) δ 2.26 (s, 6H), 2.30 (s, 3H), 6.90 (s, 2H); ^{13}C-NMR (CDCl$_3$, 62.9 MHz) δ 149.7, 140.2, 129.3, 20.9, 17.4; EIMS *m/z* (rel intensity) 165 (M$^+$, 16), 148 (31), 91 (100). To a stirred ice-cold solution of 2-nitromesitylene (4.2 g, 25.5 mmol) in MeOH/H$_2$O (9:1) (30 mL) were added successively NH$_4$Cl (4.1 g, 76.4 mmol) and Zn dust (16.0 g, 250 mmol) [54,55]. The resulting suspension was stirred overnight at room temperature, filtered through a pad of Celite, and concentrated. The aqueous residue was taken up with Et$_2$O (30 mL), washed with saturated aqueous Na$_2$CO$_3$ (20 mL) and brine (20 mL), dried over MgSO$_4$, filtered and evaporated to give the aniline **7c** [56] as a colorless oil (3.1 g, 90%), which was not further purified, but immediately stored in the dark. IR (NaCl) 3462, 3379, 2923, 1626, 1491 cm^{-1}; ^{1}H-NMR (CDCl$_3$, 250 MHz) δ 2.22 (s, 6H), 2.28 (s, 3H), 3.45 (bs, 2H), 6.84 (s, 2H); ^{13}C-NMR (CDCl$_3$, 62.9 MHz) δ 140.0, 128.7, 127.0, 121.7, 20.3, 17.5; EIMS *m/z* (rel intensity) 135 (M$^+$, 79), 120 (100).

3-Amino-5-tert-butyl-4-[5-tert-butyl-2-methylphenylimino]-2-methylcyclohexa-2,5-dienone (**10a**) *and 4-tert-butyl-6-imino-1-methylcyclohexa-2,4-dienol* (**11a**).

To a stirred solution of the aniline **7a** (56 mg, 0.34 mmol) in anhydrous THF (2.5 mL) was added IBX (105 mg, 0.38 mmol) as a solid in one portion. The resulting suspension was vigorously stirred at room temperature for 8 h, after which time it was diluted with EtOAc (10 mL), washed with 5% aqueous NaHCO$_3$ (5 mL) and brine (5 mL), dried over Na$_2$SO$_4$, filtered, and evaporated. The resulting brown oil (71 mg) was submitted to column chromatography, eluting with hexane/Et$_2$O (95:5 → 1:1), and then CH$_2$Cl$_2$/MeOH (6:1), to furnish the *p*-quinone imine **10a** as a dark red solid (24 mg, 42%), the *o*-quinol imine **11a** as a pale red oil (7 mg, 11.5%), and traces of dimer **12a** [5].

10a: mp 88 °C; IR (NaCl) 3483, 3382, 2957, 1633, 1601, 1566 cm^{-1}; ^{1}H-NMR (CDCl$_3$, 250 MHz) δ 1.18 (s, 9H), 1.29 (s, 9H), 2.14 (s, 3H), 4.42 (s, 2H), 6.52 (d, *J* = 1.8 Hz, 1H), 6.73 (s, 1H), 7.07 (dd, *J* = 1.8, 7.9 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 1H); ^{13}C-NMR (CDCl$_3$, 62.9 MHz) δ 182.6, 156.4, 148.8, 148.0, 141.0, 129.8, 126.7, 123.7, 121.3, 117.5, 113.7, 35.0, 34.4, 31.4, 29.1, 17.6, 10.1; EIMS *m/z* (rel intensity) 338 (M$^+$, 60), 323 (100), 281 (76), 163 (29), 148 (75); HRMS (EI) calcd for C$_{22}$H$_{30}$N$_2$O 338.2358, found 338.2352.

11a: IR (NaCl) 3388, 2920, 2857, 1597 cm^{-1}; ^{1}H-NMR (CDCl$_3$, 250 MHz) δ 1.16 (s, 9H), 2.29 (s, 3H), 5.21 (d, *J* = 1.1 Hz, 1H), 6.35 (dd, *J* = 1.1, 12.2 Hz, 1H), 6.45 (d, *J* = 12.2 Hz, 1H); ^{13}C-NMR (CDCl$_3$, 62.9 MHz) δ 197.5, 170.9, 136.0, 132.4, 117.4, 93.8, 37.7, 30.1, 28.7; CIMS *m/z* (rel intensity) 197 (MNH$_4^+$, 30), 195 (100); HRMS (ESI) calcd for C$_{11}$H$_{15}$NONa 200.1051, found 200.1060.

6-tert-Butyl-3-methyl-1,2-benzoquinone-2-(N-acetyl)imine (**8b**) *and 6-(N-acetylimino)-4-tert-butyl-1-methyl-cyclohexa-2,4-dienol* (**11b**)

To a stirred solution of the anilide **7b** (50 mg, 0.24 mmol) in anhydrous THF (2.5 mL) was added IBX (74 mg, 0.26 mmol) as a solid in one portion. The resulting suspension was brought to reflux for 48 h, and further additions of IBX (0.5 equiv) were carried out every 12 h. The reaction mixture was then allowed to cool down to room temperature, diluted with EtOAc (10 mL), washed with 5% aqueous NaHCO$_3$ (5 mL) and brine (5 mL), dried over Na$_2$SO$_4$, filtered, and evaporated. The residue was submitted to column chromatography, eluting with CH$_2$Cl$_2$/MeOH (100:0 → 100:1), to furnish the *o*-quinone imine **8b** as a bright orange oil (3 mg, 6%), the *o*-quinol imine **11b** as a brown oil (4 mg, 8%), and the dimer **12a** [5] as a beige solid (15 mg, 35%).

8b: IR (NaCl) 3388, 2920, 2857, 1597 cm^{-1}; ^{1}H-NMR (CDCl$_3$, 250 MHz) δ 1.19 (s, 9H), 2.04 (d, *J* = 1.5 Hz, 3H), 2.29 (s, 3H), 6.53 (dq, *J* = 1.5, 7.0 Hz, 1H), 6.83 (d, *J* = 7.0 Hz, 1H); ^{13}C-NMR (CDCl$_3$, 62.9 MHz) δ 186.4, 178.0, 150.0, 146.1, 138.9, 135.8, 131.4, 34.9, 29.1, 23.1, 17.2; CIMS *m/z* (rel intensity) 222 ([MH + 2]$^+$, 100); HRMS (ESI) calcd for C$_{13}$H$_{17}$NO$_2$Na 242.1157, found 242.1155.

11b: IR (NaCl) 2959, 1698, 1602, 1196 cm^{-1}; ^{1}H-NMR (CDCl$_3$, 250 MHz) δ 1.18 (s, 9H), 1.38 (s, 3H), 2.07 (s, 3H), 6.05 (dd, *J* = 0.6, 1.8 Hz, 1H), 6.22 (dd, *J* = 0.6, 10.0 Hz, 1H), 6.38 (dd, *J* = 1.8, 10.0 Hz,

1H); ^{13}C-NMR (CDCl$_3$, 62.9 MHz) δ 199.2, 186.6, 163.4, 140.9, 122.3, 119.4, 78.0, 35.4, 28.2, 23.8, 23.2; CIMS *m/z* (rel intensity) 222 (MH$^+$, 100); HRMS (ESI) calcd for C$_{13}$H$_{18}$DNO$_2$Na 245.1376, found 245.1377.

6-Imino-1,3,5-trimethyl-cyclohexa-2,4-dienol (**11c**) *and 3,10-dihydroxy-3,5,7,8,10,12-hexamethyl-tricyclo[6.2.2.0$^{2.7}$]dodeca-5,11-diene-4,9-dione* (**12c**).

To a stirred solution of the aniline **7c** (56 mg, 0.415 mmol) in anhydrous THF (2.5 mL) was added IBX (130 mg, 0.46 mmol) as a solid in one portion. The resulting suspension was brought to reflux for 3 h, after which time it was allowed to cool down to room temperature, diluted with EtOAc (10 mL), washed with 5% aqueous NaHCO$_3$ (5 mL) and brine (5 mL), dried over Na$_2$SO$_4$, filtered, and evaporated. The resulting brown oil was submitted to column chromatography, eluting with hexane/acetone (6:1), and then with CH$_2$Cl$_2$/MeOH (6:1), to furnish the *o*-quinol imine **11c** as a red gum (21 mg, 33.5%) and the dimer **12c** [42] as a brown solid (8 mg, 13%). The SIBX-mediated oxygenation of aniline **7c** (135 mg, 1.0 mmol) in refluxing THF (6 mL) was carried out for 2 h, according to our previously described procedure [4]. Purification by column chromatography, eluting with hexane/acetone (6:1), and then with CH$_2$Cl$_2$/MeOH (6:1), yielded the *o*-quinol imine **11c** as a red gum (53 mg, 35%) and the dimer **12c** [42] as a brown amorphous solid (33 mg, 22%).

11c: IR (NaCl) 2959, 2213, 1682, 1577, 1177 cm^{-1}; ^{1}H-NMR (CDCl$_3$, 250 MHz) δ 2.08 (d, *J* = 1.5 Hz, 3H), 2.19 (s, 3H), 2.25 (d, *J* = 1.5 Hz, 3H), 6.16 (s, 1H), 7.65 (s, 1H); ^{13}C-NMR (CDCl$_3$, 62.9 MHz) δ 198.0, 145.4, 142.0, 129.3, 118.7, 111.5, 31.7, 22.7, 22.2; CIMS *m/z* (rel intensity) 169 (MNH$_4^+$, 16), 168 (31), 167 (100), 150 (38), 108 (22); HRMS (ESI) calcd for C$_9$H$_{12}$NO 150.0919, found 150.0907.

Dimer **12c**: mp 158 °C (lit. [41,42] mp 181-183 °C); IR (NaCl) 3481, 2972, 2927, 1719, 1681, 1448, 1361 cm^{-1}; ^{1}H-NMR (CDCl$_3$, 250 MHz) δ 1.16 (s, 3H), 1.23 (s, 6H), 1.36 (s, 3H), 1.70 (d, *J* = 1.5 Hz, 3H), 1.83 (d, *J* = 1.5 Hz, 3H), 2.8 (d, *J* = 2.1 Hz, 1H), 3.13 (m, 1H), 3.93 (bs, 1H), 5.03 (m, 1H), 6.02 (s, 1H); ^{13}C-NMR (CDCl$_3$, 62.9 MHz) δ 214.1, 202.4, 145.2, 145.1, 133.1, 127.6, 76.5, 73.7, 72.2, 57.7, 48.7, 48.6, 45.3, 32.4, 25.2, 23.2, 21.4, 16.2, 12.4; EIMS *m/z* (rel intensity) 304 (M$^+$, 10), 153 (26), 152 (42), 135 (100), 110 (40), 109 (52).

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