Oxidative Dearomatization of Phenols and Anilines via $\lambda^3$- and $\lambda^5$-Iodane-Mediated Phenylation and Oxygenation

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Abstract. Treatment of 2-methylphenols with chloro(diphenyl)-$\lambda^3$-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 $\lambda^5$-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 $\lambda^3$- and $\lambda^5$-iodanes, i.e., hypervalent iodine(III) and iodine(V) compounds (Scheme 1) [4-10]. For example, the $\lambda^3$-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 $\lambda^5$-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 orthoquinolins [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 $\lambda^3$-iodanes of type Ar$_2$IL to mediate dearomatizing phenylation of methylphenols, and the second incursion has to do with experimental observations made during IBX-mediated oxidative dearomatization of anilines.

**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-$\lambda^3$-iodanes (i.e., Ar$_2$IL) do transfer, through this mechanistic path, an aryl group to enolates to furnish $\alpha$-C-arylated carbonyl compounds [17,19-21].

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†Ar$_2$IL-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 lambda iodane terminology is thus used here to name hypervalent iodine compounds [17].
Phenolates being aromatic variants of generic enolates, we thus contemplated the idea of achieving phenol dearomatization leading to 6-arylcylohexa-2,4-dienone derivatives of type 3 using diaryl-\(\lambda^3\)-iodane species (Scheme 2). The desired ligand coupling reaction could imply either passage through an aryloxy-\(\lambda^3\)-iodane intermediate of type 2c (i.e., ligand exchange path \(a\)), which would then tautomerize into a 6-\(\lambda^3\)-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)-\(\lambda^3\)-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-\(\lambda^3\)-iodane reagent to chloro(diphenyl)-\(\lambda^3\)-iodane led to some improvement in the yield of 4a, but no formation of the desired dearomatized product 3a was observed (entry 4).
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-λ3-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-λ3-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 6b and 8c) 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)-λ3-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)-$\lambda^3$-iodane-mediated phenylation of phenols

| entry | phenol$^a$ | product(s): isolated yield (%) |
|-------|------------|--------------------------------|
| 1     | ![OH](Ph)  | ![O-Ph](Ph) 4b: 75%           |
| 2     | ![OH](Ph)  | ![O-Ph](Ph) 4c: 24%           |
| 3     | ![OH](Ph)  | ![O-Ph](Ph) 4d: 7%            |
|       | 1b         |                                |
|       | 1c         | 3c: 37%                        |
|       | 1d         | 3d: 42% 6d: 7%                 |

$^a$ Reactions were carried out at room temperature using Ph$_2$ICl (1.1 equiv) and KO-t-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 $\gamma$-$\lambda^3$-iodanyl ketone of type 2f that would be formed from a direct ligand exchange between the 4-methylated carbamionic form of the starting phenolate 1d and the chloro(diphenyl)-$\lambda^3$-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.

![Scheme 3](image)

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 ArIL4 type of the λ5-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 λ3-iodanes bearing two heteroatomic nucleofugal ligands (i.e., ArIL2 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 CH2Cl2 or in a 3:1 CH2Cl2/AcOH mixture, but only intractable mixtures were obtained. However, the use of the λ5-iodane of type ArIL4 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 [CH₂Cl₂/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.

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Experimental

General

Diacetoxiodobenzene (DIB) and stabilized o-iodoxybenzoic acid (SIBX) [4] were obtained from SIMAFEX. Chloro(diphenyl)-λ³-iodane (Ph₂ICl, 97%) was purchased from Aldrich. Tetra-fluoroboro(diphenyl)-λ³-iodane (Ph₂IBF₄) [20,24] and o-iodoxybenzoic acid (IBX) [44] were prepared from DIB and 2-iodobenzoic acid, respectively. Dichloromethane (CH₂Cl₂) and tert-butyl alcohol (t-BuOH) were used as received. Tetrahydrofuran (THF) was purified by filtration through alumina under N₂ immediately before use. Moisture and oxygen sensitive reactions were carried out in flame-dried glassware under N₂. 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 λ³-Iodane-Mediated Phenylation of Phenols

To a stirred solution of KOr-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-λ³-iodane reagent, i.e., Ph₂IBF₄ [24] or Ph₂ICl (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 CH₂Cl₂ (3 × 5 mL). The combined organic extracts were washed once with water (5 mL), dried over Na₂SO₄, 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)

Ph2ICl-mediated phenylation of 2,3,5-trimethylphenol (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; ¹H-NMR (CDCl₃, 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); ¹³C-NMR (CDCl₃, 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 C₁₅H₁₆O 212.1201, found 212.1198.

4a: IR (NaCl, neat) 2929, 1489, 1224 cm⁻¹; ¹H-NMR (CDCl₃, 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); ¹³C-NMR (CDCl₃, 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 C₁₅H₁₆O 212.1201, found 212.1199.

Phenoxybenzene (4b)

Ph₂ICl-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; ¹H-NMR (CDCl₃, 300 MHz) δ 7.15-7.26 (m, 6H), 7.26-7.49 (m, 4H); ¹³C-NMR (CDCl₃, 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)

Ph₂ICl-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; ¹H-NMR (CDCl₃, 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); ¹³C-NMR (CDCl₃, 75.5 MHz) δ 203.9, 145.3, 140.9, 134.0, 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; ¹H-NMR (CDCl₃, 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); ¹³C-NMR (CDCl₃,
75.5 MHz) δ 157.8, 151.0, 131.5, 129.6, 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)

Ph₂ICl-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; ¹H-NMR (CDCl₃, 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); ¹³C-NMR (CDCl₃, 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 (100).

4d [47]: IR (NaCl, neat) 3022, 2926, 1592, 1490, 1223 cm⁻¹; ¹H-NMR (CDCl₃, 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); ¹³C-NMR (CDCl₃, 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: ¹H-NMR (CDCl₃, 300 MHz) δ 1.66 (s, 6H), 1.96 (s, 3H), 6.73 (s, 2H), 7.23-7.35 (m, 5H); ¹³C-NMR (CDCl₃, 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 Ac₂O (15 mL) was added dropwise HNO₃ (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 CH₂Cl₂ (2 × 20 mL). The combined organic extracts were washed with 20% aqueous NaOH (3 × 10 mL), brine (3 × 10 mL), dried over Na₂SO₄, 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; ¹H-NMR (CDCl₃, 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); ¹³C-NMR (CDCl₃, 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 H₂ 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 Et₂O. Evaporation of the combined filtrates and washings furnished a crude product, which was submitted to column
chromatography, eluting with hexane/Et₂O (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; ¹H-NMR (CDCl₃, 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); ¹³C-NMR (CDCl₃, 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 Ac₂O/AcOH (30 mL) was carried out under H₂ 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 Et₂O (50 mL). The combined filtrates and washings were washed successively with saturated aqueous NaHCO₃ (3 × 10 mL) and brine (2 × 10 mL), dried over Na₂SO₄, filtered and evaporated to furnish an amorphous solid, which was purified by crystallization from Et₂O, 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; ¹H-NMR (CDCl₃, 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); ¹³C-NMR (CDCl₃, 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 Ac₂O (10 mL) was added fuming HNO₃ (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 Et₂O (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 MgSO₄, filtered, and evaporated to furnish a crude yellow solid (6.6 g). Purification by column chromatography, eluting with a cyclohexane/Et₂O 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; ¹H-NMR (CDCl₃, 250 MHz) δ 2.26 (s, 6H), 2.30 (s, 3H), 6.90 (s, 2H); ¹³C-NMR (CDCl₃, 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/H₂O (9:1) (30 mL) were added successively NH₄Cl (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 Et₂O (30 mL), washed with saturated aqueous Na₂CO₃ (20 mL) and brine (20 mL), dried over MgSO₄, 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; ¹H-NMR (CDCl₃, 250 MHz) δ 2.22 (s, 6H), 2.28 (s, 3H), 3.45 (bs, 2H), 6.84 (s, 2H); ¹³C-NMR (CDCl₃, 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 NaHCO₃ (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered, and evaporated. The resulting brown oil (71 mg) was submitted to column chromatography, eluting with hexane/Et₂O (95:5 → 1:1), and then CH₂Cl₂/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; ¹H-NMR (CDCl₃, 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); ¹³C-NMR (CDCl₃, 62.9 MHz) δ 182.6, 156.4, 148.8, 148.0, 140.0, 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 C₂₂H₃₀N₂O 338.2358, found 338.2352.

11a: IR (NaCl) 3388, 2920, 2857, 1597 cm⁻¹; ¹H-NMR (CDCl₃, 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); ¹³C-NMR (CDCl₃, 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 (MNH₄⁺, 30), 195 (100); HRMS (ESI) calcd for C₁₁H₁₅NONa 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 NaHCO₃ (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered, and evaporated. The residue was submitted to column chromatography, eluting with CH₂Cl₂/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; ¹H-NMR (CDCl₃, 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); ¹³C-NMR (CDCl₃, 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 C₁₃H₁₉NO₂Na 242.1157, found 242.1155.

11b: IR (NaCl) 2959, 1698, 1602, 1196 cm⁻¹; ¹H-NMR (CDCl₃, 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,
6-Imino-1,3,5-trimethyl-cyclohexa-2,4-dienol (11c) and 3,10-dihydroxy-3,5,7,8,10,12-hexamethyltricyclo[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 NaHCO₃ (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered, and evaporated. The resulting brown oil was submitted to column chromatography, eluting with hexane/acetone (6:1), and then with CH₂Cl₂/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 CH₂Cl₂/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; ¹H-NMR (CDCl₃, 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); ¹³C-NMR (CDCl₃, 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 (MNH₄⁺, 16), 168 (31), 167 (100), 150 (38), 108 (22); HRMS (ESI) calcd for C₉H₁₂NO 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; ¹H-NMR (CDCl₃, 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); ¹³C-NMR (CDCl₃, 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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Sample Availability: Available from the authors.

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