Regioselective Reactions

DOI: 10.1002/ange.200501638

Regioselective Hypervalent-Iodine(III)-Mediated Dearomatizing Phenylation of Phenols through Direct Ligand Coupling**

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Dearomatization of phenols often constitutes an ultimate key transformation in the biogenesis of many natural products and a powerful strategy for the rapid construction of highly

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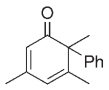
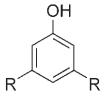
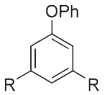
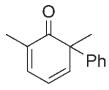
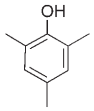
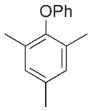
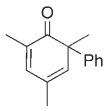
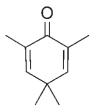
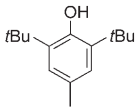
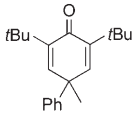
[**] We gratefully acknowledge Simafex and the Association Nationale de la Recherche Technique (CIFRE Grant N°301/2002) for their financial support and Aurélie Ozanne-Beaudenon's graduate research assistantship.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author. It includes detailed descriptions of experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra of all compounds.

functionalized intermediates in the elaboration of complex organic molecules.[1] One class of chemical reagents that is continuously finding new applications in this area of synthetic organic chemistry is composed of hypervalent λ^3- and λ^5-iodanes.[2] Herein we report a new phenol dearomatization process that involves the use diaryl λ^3-iodanes (i.e., Ar_2IL, L = Cl, BF_4, OTs)[3] to promote regioselective *ortho* phenylation to give 6-phenylcyclohexa-2,4-dienones. Diaryl-λ^3-iodane reagents have previously been used with success to give α-arylated ketones, esters, silyl enol ethers, and various 1,3-dicarbonyl compounds,[3–5] but the only products that were obtained when phenolic substrates were used under basic conditions were derived from an O-arylation process.[6] The reaction conditions unveiled herein permit us to direct the entry of an aryl group to a substituted position on the starting phenol and offer an alternative to stoichiometric processes that involve the use of toxic aryl–lead or aryl–bismuth reagents[7,8] and an alternative to transition-metal-catalyzed processes that only furnish diaryl products.[9]

We selected 2,3,5-trimethylphenol (**1a**, see Table 1) as a first model substrate to search for appropriate C-phenylation conditions and treated it with chlorodiphenyl-λ^3-iodane (Ph_2ICl) in dimethylformamide (DMF) in the presence of potassium *tert*-butoxide (*t*BuOK, 1.1 equiv) for 20 h at room temperature. Only the diaryl ether **2a** was isolated with a yield of 53%, but no formation of the desired cyclohexa-2,4-dienone **3a** was observed (Table 1, entry 1).[10] The first glimpse of success was obtained by changing the reaction solvent to a protic solvent with a low dielectric constant (i.e., *t*BuOH),[11] whereupon **3a** was isolated with a yield of 8% (Table 1, entry 1). It is worth noting that no diaryl product, which could have resulted from introduction of the phenyl group at the unsubstituted C6 position of the starting phenol **1a**, was observed. A small and weakly electron-donating substituent such as a methyl group at an *ortho* position thus appears sufficient to direct delivery of the phenyl unit to that substituted position. In accordance with this first observation, only diaryl ether products were obtained in good yields when starting from phenol (**1b**) or from the *meta*-substituted phenol, 3,5-dimethylphenol (**1c**; Table 1, entries 2 and 3). Moreover, the symmetrically *ortho*-substituted 2,6-di- and 2,4,6-trimethylphenols, **1d** and **1e**, gave rise to the formation of the desired cyclohexa-2,4-dienones, **3d** and **3e**, in 37% and 42% yields, respectively (Table 1, entries 4 and 5). Interestingly, the *para*-methylated phenol **1e** also afforded 4-phenylcyclohexa-2,5-dienone (**4e**) in 7% yield. Biasing the system with sterically demanding alkyl groups at the two *ortho* positions should lead to a quasi-exclusive phenylation at the *para*-alkylated position. This was indeed the case with 4-methyl-2,6-di-*tert*-butylphenol (**1f**), the use of which only furnished 4-methyl-4-phenylcyclohexa-2,5-dienone (**4f**) in an excellent yield of 94% (Table 1, entry 6). Further evidence of the role played by the methyl group in mediating transfer of a phenyl group from Ph_2ICl was then obtained by performing the same reaction with 2,6-di-*tert*-butylphenol (**1g**; not shown), in which case no phenylation product was isolated.

Table 1: Phenylation of phenols mediated by chorodiphenyl-λ^3-iodane.[a]

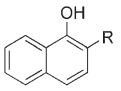
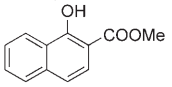
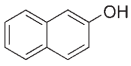
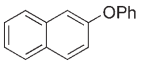
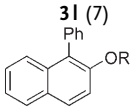
Entry	Substrate	Yield [%][b] O-phenylation	*o*-C-phenylation	*p*-C-phenylation
1	 **1a**	 **2a** (53),[c] (63)	 **3a** (0),[c] (8)	–
2	 **1b**: R = H	 **2b** (75)	–	–
3	**1c**: R = Me	**2c** (59)	–	–
4	 **1d**	 **2d** (24), (35)[d]	 **3d** (37), (44)[c]	–
5	 **1e**	 **2e** (7),[e] (63)	 **3e** (42)[e,f]	 **4e** (7)[e,f]
6	 **1f**	–	–	 **4f** (94)

[a] Reactions were carried out by adding chlorodiphenyl-λ^3-iodane (1.3 mmol) to a stirred solution of the starting phenol in *t*BuOH (4 mL) in the presence of *t*BuOK (1.4 mmol) at room temperature. [b] Yield of isolated product. [c] This reaction was carried out with DMF. [d] This reaction was carried out in (tetrafluoroboro)diphenyl-λ^3-iodane. [e] Similar results were obtained in the presence of 1,1′-diphenylethylene (2 equiv). [f] Products **3e** and **4e** could not be cleanly separated by column chromatography on silica gel, so yields were evaluated by ^{1}H NMR spectroscopic analysis of the mixture.

Having thus established the prominent role that is played by alkyl substituents in the regiocontrol of this λ^3-iodane-mediated phenylation of phenols, we turned our attention to a series of 1-naphthols, each bearing an electronically different *ortho* substituent. Experiments carried out with Ph_2ICl on 2-methyl- (**1i**), 2-methoxy- (**1j**), and 2-nitrosonaphthol (**1k**) revealed a somewhat different reactivity from that of the phenols as no diaryl ether was observed. Nevertheless, the expected dearomatization products, **3i**, **3j**, or **3k**, were isolated as the sole products in increasing yields ranging from 36 to 74% (Table 2, entries 1–3). Naphthols, as well as phenols, that bear an electron-demanding *ortho* substituent such as 2-carboxymethoxynaphthol (**1l**), 2-nitronaphthol (**1m**; see Scheme 2), 2-hydroxynaphthaldehyde, and 4-nitrophenol (**1n**, **1h**; not shown) were all found to be refractory substrates at room temperature (see below). Only the ester **1l** gave rise to the formation of the diaryl ether **2l** and the desired dearomatized phenylation product **3l**, albeit in low yields (Table 2, entry 4).

In contrast to the unsubstituted 1-naphthol (**1o**; not shown) that led to a complex product mixture, the unsubstituted 2-naphthol (**1p**) was reactive towards Ph_2ICl and underwent both O- and C-phenylation to furnish three products: the diaryl ether **2p** (9%), 1-phenyl-2-naphthol (**3p**, 18%), and the diaryl ether **4p** (22%) through trans-

Table 2: Phenylation of naphthols mediated by chorodiphenyl-λ^3-iodane.[a]

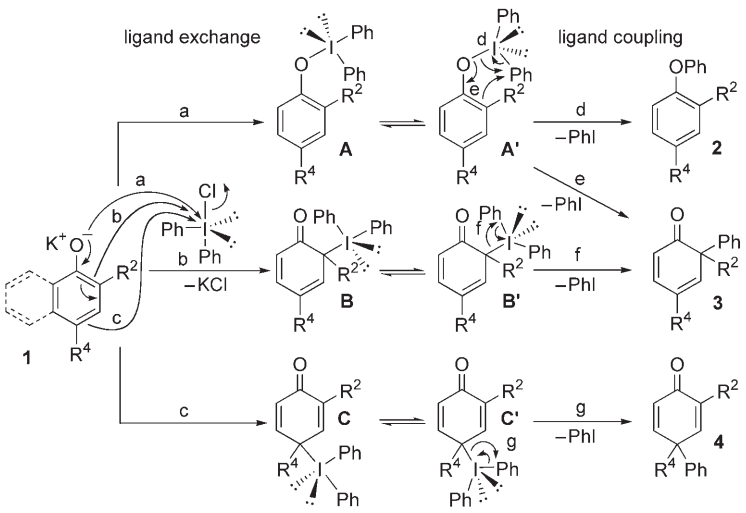
Entry	Substrate	Yield [%][b] O-phenylation	Yield [%][b] *o*-C-phenylation
1	 **1i**, R = Me	–	**3i** (36)
2	**1j**, R = OMe	–	**3j** (52)[c]
3	**1k**, R = NO	–	**3k** (74)[c]
4	 **1l**	**2l** (21)	**3l** (7)
5	 **1p**	 **2p** (9)	 **3p**: R = H (18) **4p**: R = Ph (22)

[a] Reactions were carried out by adding chlorodiphenyl-λ^3-iodane (1.3 mmol) to a stirred solution of the starting phenol in *t*BuOH (4 mL) in the presence of *t*BuOK (1.4 mmol) at room temperature. [b] Yields of isolated products. [c] Similar results were obtained in the presence of 1,1′-diphenylethylene (2 equiv).

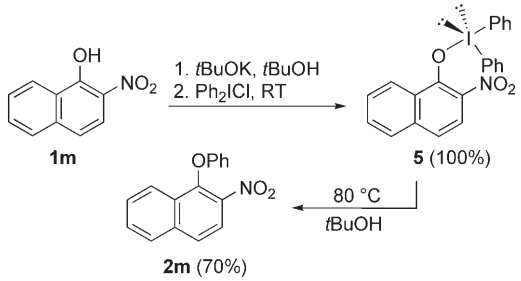
ferring a second phenyl unit to **3p** (Table 2, entry 5). The C-phenylation course is thus globally favored over the O-phenylation alternative for this unsubstituted 2-naphthol treated under basic conditions in a protic solvent.[11] It is interesting to note that 2-naphthol (**1p**) was also the only phenol among those we used to furnish a diaryl product through phenylation at its unsubstituted C1 center. This is probably due to the more pronounced ambident character of the delocalized 2-naphthoxide anion relative to that of unsubstituted phenoxide anions[11] and to the aromaticity retained when this anion engages itself in bond formation at C1, but not at C3.

We next wondered about the mechanism that is operative in these phenylation reactions of phenols and naphthols as they constitute a novel aspect of hypervalent iodine chemistry. The first experimental observations of mechanistic relevance were that iodobenzene was formed as a by-product and that no reaction took place in the absence of a base strong enough to deprotonate the starting phenol. The delocalized phenolate nucleophile can then attack the iodine(III) center of Ph_2ICl in a ligand-exchange step, thus displacing the chloride anion ligand to furnish (aryloxy)diphenyl-λ^3-iodanes of type **A** (Scheme 1, path a) and/or their C-iodanylated cyclohexadienone variants of types **B** and **C** (Scheme 1 paths b and c) depending upon the electronic and steric demands of the substituents on the starting phenol.

Alternatively, the phenolate anion could engage itself in an aromatic nucleophilic-substitution reaction (i.e., S_NAr) and directly attack Ph_2ICl at one of its two phenyl carbon atoms bonded to the iodine(III) center. This S_NAr mechanistic path is generally proposed to rationalize the reactivity of species such as Ph_2ICl towards nucleophiles.[12] It must be recalled that these species are not tetrahedral diaryliodonium salts, as commonly thought, but 10-I-3 T-shaped pseudotrigonal bipyramidal entities, as expected for hypervalent I^{III} species.[3] To find evidence for one or the other mechanistic alternative, we revisited some of the reactions we had performed with the aim of characterizing any stable reaction intermediates. This was accomplished by isolating an intermediate from the reaction performed at room temperature with the apparently refractory substrate, 2-nitronaphthol (**1m**, see above). This intermediate was characterized as the type-**A** (2-nitronaphthoxy)diphenyl-λ^3-iodane, **5** (see Supporting Information and Scheme 2). In contrast to reactions



Scheme 1. Mechanistic description of the phenol phenylation reactions through direct ligand coupling. **A**, **B**, and **C**: 10-I-3 trigonal-bipyramidal intermediates; **A**′, **B**′, and **C**′: tetragonal-pyramidal intermediates. R^2, R^4: various substituents.



Scheme 2. Evidence of ligand exchange: isolation of type-**A** intermediate **5** and its heat-induced conversion into the diaryl ether **2m**.

carried out with phenols bearing electron-releasing *ortho* substituents, this intermediate does not further evolve at room temperature but gives the starting naphthol **1m** upon chromatography on silica gel. However, compound **5** furnishes the O-phenylated product **2m** in 70% yield when heated to reflux in *t*BuOH for 8 h (Scheme 2).

These observations are in agreement with an initial ligand-exchange step, but not with a direct S_NAr-type mechanism. Furthermore, the isolation of the 10-I-3 species **5** is particularly revealing of the mechanistic path followed in this process as the presence of a strongly electron-withdrawing *ortho* substituent on the starting phenol is usually

associated with the stabilization of S_NAr Meisenheimer-type intermediates.[12,13]

Hence, the phenylation products observed with concomitant reductive elimination of iodobenzene can, in principle, result either from collapse of the λ^3-iodanyl intermediate into a phenyl and a phenoxy radical, which would then pair off, or from a concerted ligand coupling on the iodine(III) center itself.[4,13] To address this question, the efficient phenyl radical trapping agent, 1,1-diphenylethylene (DPE)[5g,8d,8e] was added to the reaction medium during the phenylation of **1e, 1j**, and **1k** (Table 1, entry 5 and Table 2, entries 2 and 3). The presence of DPE did not affect the outcome of the reaction, thus showing that no radical-based intermediate plays any determinant role in the process. These observations are in agreement with the proposal of an exclusive nonradical ligand-coupling mechanism. Thus, the 10-I-3 intermediates of types **A**, **B**, and **C** may evolve through coupling of their phenolate-derived ligand with one of the phenyl groups. Ligand coupling is symmetry-forbidden on these trigonal-bipyramidal structures, but bond-forming events can occur from tetragonal-pyramidal transient species of types **A′**, **B′**, and **C′** during ligand pseudorotation around the iodine(III) center (Scheme 1).[3,12,13]

Formation of diaryl ethers of type **2** would then result from intermediates of type **A′** through a nonsynchronous *ipso–ipso* coupling (path d) with a polar transition state as a consequence of the difference of polarity between the two ligands (i.e., LC_N-type coupling).[13] The formation of cyclohexa-2,4-dienone products of type **3** could either also arise from intermediates of type **A′** through an *ipso–allyl* $LC_{N'}$-type coupling (path e) or from **B′** through a quasi-synchronous *ipso–ipso* LC-type coupling (path f).[13] The fact that Ph_2ICl was also capable of transferring one of its phenyl ligands to the *para* position of 2,4,6-trimethylphenol (**1e**) and 4-methyl-2,6-di-*tert*-butylphenol (**1f**) to furnish cyclohexa-2,5-dienone products of type **4** (Table 1, entries 5 and 6) can only be rationalized in terms of a passage through intermediates of type **C′**, which then evolve through an *ipso–ipso* LC-type coupling (path g).

Semiempirical and Hartree–Fock calculations that we performed at the AM1 and 6-31G* levels to determine the electrostatic charge distribution and the relative magnitudes of the atomic coefficients of the highest occupied molecular orbital (HOMO) of the phenolate forms of **1a, d–g** illustrate the contribution of *ortho* and *para* methyl groups in controlling the regiochemical outcome of these phenylation reactions (see Supporting Information). In all cases, the negative charge is mostly localized on the oxygen atom, and the presence of a methyl group at one *ortho* position (**1a**) reinforces partial localization of the charge at the unsubstituted *ortho* and *para* positions (i.e., C6 and C4). Similarly, when comparing data for **1d** versus **1e** and **1f** versus **1g**, it can be read that the presence of a methyl group at the *para* position decreases the extent of partial localization of the charge at this locus. Hence, the O-phenylation path of the reaction may benefit from this charge distribution, but not its C-phenylation alternatives. However, the presence of a methyl group at C2 of **1a** or at C4 of **1e** and **1f** renders the relative magnitudes of the HOMO atomic coefficients at these centers larger in comparison to those at the unsubstituted *ortho* position in **1a** and at the unsubstituted *para* position in **1d** and **1g**, respectively. The dearomatizing C-phenylation path of the reaction would thus seem to be essentially under this orbital control. The results obtained with naphthols **1i–l** are in agreement with this substituent-controlled modulation of reactivity, since the more electron-releasing the substitutent at C2, the better is the yield of the dearomatizing *ortho*-phenylation reaction (Table 2, entries 1–3).

In conclusion, the work described herein presents a novel aspect of the versatility of hypervalent iodine(III) reagents in organic synthesis, which is illustrated by the use of the diaryl-λ^3-iodane Ph_2ICl to promote regioselective C-phenylation of *ortho*- and/or *para*-substituted phenols to give cyclohexadienone derivatives under basic conditions. The presence of a small electron-donating substituent at the *ortho* and/or *para* positions of the starting phenol determines the efficacy and regioselectivity of the process, which involves a nonradical coupling of the phenolate-derived and phenyl ligands directly around the iodine(III) center. Evidence of such a direct ligand-coupling mechanism is also given for the competitive O-phenylation process, which is commonly thought to follow an intermolecular aromatic nucleophilic-substitution reaction path.

Received: May 12, 2005
Revised: July 13, 2005
Published online: October 6, 2005

Keywords: aromaticity · hypervalent compounds · iodine · reaction mechanisms · regioselectivity

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