Competing Pathways in O-Arylations with Diaryliodonium Salts: Mechanistic Insights

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Abstract: A mechanistic study of arylations of aliphatic alcohols and hydroxide with diaryliodonium salts, to give alkyl aryl ethers and diaryl ethers, has been performed using experimental techniques and DFT calculations. Aryne intermediates have been trapped, and additives to avoid by-product formation originating from arynes have been found. An alcohol oxidation pathway was observed in parallel to arylation; this is suggested to proceed by an intramolecular mechanism. Product formation pathways via ligand coupling and arynes have been compared, and 4-coordinated transition states were found to be favored in reactions with alcohols. Furthermore, a novel, direct nucleophilic substitution pathway has been identified in reactions with electron-deficient diaryliodonium salts.

Introduction

The interest in hypervalent iodine chemistry has dramatically increased over the past decade, and a plethora of novel transformations has appeared under both metal-free and metal-catalyzed conditions. Apart from being excellent oxidants, hypervalent iodine reagents can be used in carbon ligand transfer to a variety of nucleophiles. Several interesting mechanistic studies have recently been reported on reactions with iodine(III) reagents, giving new insights in some of the key aspects of these reactions. The knowledge gained from these experimental and theoretical studies will certainly be highly important for further developments in the field.

Diaryliodonium salts (diaryl-1,3-iodanes) are increasingly applied in organic synthesis as efficient electrophilic arylation reagents with a wide range of nucleophiles. Their straightforward synthesis using one-pot reactions, combined with high bench-stability and low toxicity, has made them desirable in a growing number of transformations. In metal-free reactions with nucleophiles, the generally accepted mechanism for these reagents proceeds via a ligand exchange to T-shaped Nu-I intermediates that subsequently react via a ligand coupling mechanism to provide the arylated nucleophile and the corresponding iodoarene in a regiospecific fashion (Scheme 1 a).

Aryl transfer via single electron transfer (SET) reactions is preferred under certain conditions, which has been investigated in detail by Kita and co-workers. Less studied pathways include radical reactions and arylene formation, which have been suggested to explain by-product formation in certain reactions with iodonium salts. While arylene intermediates have been applied in cycloadditions employing ortho-silylated diaryliodonium salts or strongly basic conditions (Scheme 1 b), the mechanism for arylene formation from diaryliodonium salts remains unexplored.

Our research group has gained considerable experience in metal-free arylations with these reagents using O-, N- and C-centered nucleophiles. While most of these have been efficiently arylated by the ligand coupling pathway, several intriguing indications on alternative reaction pathways have been observed, for example, by formation of regioisomeric products and oxidized byproducts. Mechanistic insights to these fascinating observations would aid further developments with diaryliodonium salts and other iodine(III) reagents, and we thus...

\[\text{Scheme 1. Mechanistic pathways in metal-free arylations.}\]
initiated an investigation on competing pathways in O-arylations using both experimental techniques and DFT calculations. Herein we report evidence for aryne intermediates as the origin of several products, as well as the use of amine additives to suppress their formation. A mechanism has been outlined to explain the unexpected oxidation of alcohols to carbonyl compounds with diaryliodonium salts, which are generally not used as oxidants. Furthermore, a novel, direct nucleophilic substitution pathway has been identified for reactions with electron-deficient iodonium salts.

The mechanistic investigations were focused on O-arylations of hydroxide and aliphatic alcohols, as the synthesis of aryl ethers is an important quest due to their abundance in natural products and pharmaceutically active compounds. Already sixty years ago, diaryliodonium salts were used to arylate alkoxides in moderate yields and with poor scope, and the reactions were later observed to suffer from severe by-product formation. We recently developed an efficient and general synthesis of diaryl ethers by arylation of phenols (Scheme 2 a). Double arylation of sodium hydroxide with strongly electron-withdrawing salt \(1a\) yielded diaryl ether \(2a\) (Scheme 2 b). Mild conditions were reported for the arylation of aliphatic alcohols \(3\) to aryl ethers \(4\) (Scheme 2 c).

Contrary to the phenol arylation, the reactions with aliphatic alcohols proved sensitive to steric hindrance, and were most efficient for primary alcohols and electron-deficient aryl groups. Unexpected oxidation of the alcohol substrate to the corresponding aldehyde/ketone or carboxylic acid was observed (Scheme 2 d), as well as formation of regioisomeric product mixtures in arylations with electron-donating iodonium salts.

**Results and Discussion**

**Arylation of hydroxide**

Based on the conditions in Scheme 2 b, a small screening with other diaryliodonium salts \(1\) was performed. The reactions generally required elevated temperature to proceed in water, whereas room temperature proved sufficient for reactions in dichloromethane. Surprisingly, a mixture of regioisomeric diaryl ethers \(2\), as well as iodo-substituted by-products \(5\) was obtained with salts \(1\) lacking strong electron-withdrawing group (EWG) substituents in both solvents, as exemplified with di(4-tolyl)iodonium triflate \(1b\) in Scheme 3 a. As the ligand coupling mechanism is regiospecific, the formation of regioisomeric products \(2b-d\) indicated that another mechanism was operating.

Aryne intermediates are known to react with nucleophiles with poor regioselectivity in the absence of strong directing groups, and aryne formation was hence hypothesized to explain the observed regioisomeric mixture of \(2\). This was supported by a trapping experiment with excess furan, giving Diels–Alder adduct \(6a\) together with diaryl ether \(2b\) as a single regioisomer (Scheme 3 b). Contrary to the phenol arylation, the reactions with aliphatic alcohols proved sensitive to steric hindrance, and were most efficient for primary alcohols and electron-deficient aryl groups. Unexpected oxidation of the alcohol substrate to the corresponding aldehyde/ketone or carboxylic acid was observed (Scheme 2 d), as well as formation of regioisomeric product mixtures in arylations with electron-donating iodonium salts.

**Scheme 2.** Synthesis of aryl ethers and oxidation.

**Scheme 3.** Aryne trapping and mechanistic proposal.
the contrary, electron-deficient nitro salt 1a gave diaryl ether 2a as the main product with only traces of 6c,d (Scheme 3e).

The formation of by-products 5, with iodine incorporated in the ortho-position, was intriguing. While ortho-iodinated diaryl ethers recently have been obtained from phenols with other iodine(III) reagents,[16] their synthesis from diaryliodonium salts has not been reported. To simplify the analysis, diphenyliodonium trflate (1d) was employed in the investigations into the formation of this product. Treatment of sodium hydroxide with salt 1d resulted in formation of an inseparable mixture of diaryl ethers 2f and 5a (Table 1, entry 1). The product ratio was increased, at the cost of sharply reduced yield of 2f, when only 1 equivalent NaOH was used (entry 2). The addition of furan as aryne trap delivered ether 2f in diminished yield, together with the cycloaddition product 6c (entry 3). By-product 5a was only obtained in trace amount, indicating that 5a forms via an aryne pathway, whereas 2f forms both via ligand coupling and via arynes.

Other aryne scavengers were also considered, as furan did not completely suppress the formation of 5a. Amines were deemed suitable as they readily react with arynes,[19] but are difficult to arylate with diaryliodonium salts under metal-free conditions.[17] Piperidine was thus added in sub-stoichiometric amounts, which indeed inhibited the formation of 5a (entry 4). Likewise, addition of piperidine to the reaction of tolyl salt 1b with hydroxide resulted in facile isolation of diaryl ether 2b without concomitant formation of 2c, 2d, and 5.[12] In both cases, the formed N-arylated trap 7 was easily separated from 2b, making this additive useful in avoiding by-products resulting from arynes at the expense of lower isolated yield of 2b.

The product distribution was also investigated in other solvents. Reactions in water required elevated temperature to proceed, but resulted in increased yield of 2f (entry 5). Interestingly, by-product 5a was only formed in trace amounts under these conditions. The addition of piperidine considerably suppressed formation of 2f (entry 6).

When salt 1d was treated with NaOD in deuterated water, diphenyl ether 2f-D was isolated as the only deuterated diaryl ether according to NMR and GC-MS (Scheme 4).[12] Deuterium-free product 2f was not detected, and by-product 5a was formed in 4%, corresponding well to the reaction using NaOH (Table 1, entry 5). The labeling outcome is consistent with one of the two arylation reactions taking place mainly via the aryne pathway in water.[12]

Table 1. Trapping of benzoyl.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Additive (equiv)</th>
<th>2f [%][a]</th>
<th>5a [%][b]</th>
<th>Other products[c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH2Cl2, RT</td>
<td>22 h</td>
<td>40</td>
<td>25</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>CH2Cl2, RT</td>
<td>–</td>
<td>13</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>CH2Cl2, RT</td>
<td>furan (5)</td>
<td>23</td>
<td>2</td>
<td>6c 20%</td>
</tr>
<tr>
<td>4</td>
<td>CH2Cl2, RT</td>
<td>piperidine (0.5)</td>
<td>27</td>
<td>0</td>
<td>7a 26%</td>
</tr>
<tr>
<td>5</td>
<td>H2O 80°C</td>
<td>–</td>
<td>56</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>H2O 80°C</td>
<td>piperidine (1.2)</td>
<td>17</td>
<td>0</td>
<td>7a 4%</td>
</tr>
</tbody>
</table>

[a] Isolated yields. [b] 1 equiv NaOD. [c] 1H NMR yields with 1,3,5-trimethoxybenzene (TMB) as internal standard.

Previous arylation of phenols in water did not suffer from by-product formation (cf Scheme 2a),[19] indicating that the arylation of hydroxide proceeds via arynes, followed by regiospecific phenoxy arylation by ligand coupling. Phenolic products were not detected in either solvent, supporting the hypothesis that arylation of phenol intermediates is fast compared to arylation of hydroxide.

The competition between ligand coupling and aryne formation in arylation reactions of diaryliodonium salts 1a, 1c, and 1d was studied by DFT calculations using two different functionals (B3LYP-D3, M06-2X) commonly used for hypervalent iodine reactions.[24, 26, 15] We started to investigate the reaction between 1d and hydroxide in CH2Cl2 (Figure 1). The experiment (Figure 2a) demonstrates that ligand exchange in iodine(III) compounds is considered to be facile,[20, 4e, 20] and formation of intermediate 1d-OH was followed by a large decrease in energy (–69 kJ mol\(^{-1}\)), as expected by the different pKa of TFOH and H2O. Reactions via 4-coordinated complexes have rarely been investigated in iodine(III) reactions,[20, 6, 4e, 21] but we were deemed interesting due to the stoichiometry of this transformation. Indeed, addition of a second hydroxide led to the more stable, 4-coordinated iodonium complex 1d-(OH)2 (–73 kJ mol\(^{-1}\)), whereas the mixed 4-coordinated complex 1d-(OH)OTf was higher in energy.[22]

Also complex 1d-(OH)OH, with a hydroxide coordinated to the ortho-protons of 1d-OH, is higher in energy. Due to the fast equilibrium between these three intermediates, the transition state energies are calculated with respect to 1d-(OH)2 according to the Curtin–Hammett principle.[23] The possible transitions states for deprotonation and elimination to the aryne are lower in energy than the ligand coupling transition states. External deprotonation (TS1-1d, \(+33\) kJ mol\(^{-1}\)) is favored over internal 3-coordinated (TS2-1d), 4-coordinated deprotonation (TS3-1d) or direct deprotonation of 1d, as depicted in Scheme 3b. The 3-coordinated ligand coupling (TS4-1d) and the 4-coordinated ligand coupling (TS5-1d) are significantly higher in energy. While the experimental results also show a preference for aryne formation, the calculated energy differences between the aryne formation and the ligand coupling are higher than expected with this diaryliodonium salt.

The results with methoxy-substituted salt 1c are similar to those with 1d, with three intermediates in fast equilibrium, although the 3-coordinated 1c-OH is slightly more stable than 1c-(OH)2 (Figure 2a). The transition states energies for the aryne pathway are lowest in energy, and the external deproto-
Figure 1. Free energy surface for the reaction between 1d and hydroxide in CH$_2$Cl$_2$ using B3LYP-D3. Dissociated OH and OTf are omitted for clarity. Energies are given in kJ mol$^{-1}$.

Figure 2. Free energy surface for the reaction between 1a or 1c and hydroxide in CH$_2$Cl$_2$. OH and OTf are omitted for clarity. Energies are given in kJ mol$^{-1}$. 

1a $\rightarrow$ OTf $\rightarrow$ Ph $\rightarrow$ Ph

1c $\rightarrow$ OTf $\rightarrow$ Ph $\rightarrow$ Ph

1a $\rightarrow$ OTf $\rightarrow$ Ph $\rightarrow$ Ph

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nation via TS1-1a\((-36\,\text{kJ mol}^{-1})\) is again slightly favored over the internal deprotonation via TS2-1a\((-46\,\text{kJ mol}^{-1})\). The 4-coordinated ligand coupling (TS3-1c), the 3-coordinated ligand coupling (TS4-1c) and the 4-coordinated ligand coupling (TS5-1c), are all much higher in energy, in agreement with the experimental results where coupling product 2e was not detected (Scheme 3d).

The reaction of nitro salt 1a with hydroxide shows a rather different energy profile, with a clear preference for the 4-coordinated intermediate 1a-(OH)2 over the 3-coordinated 1a-OH (Figure 2b). Surprisingly, the obtained transition state energies did not match the experimental results, where formation of product 2a is strongly favored (Scheme 3e). Instead, the external deprotonation via TS1-1a\((+30\,\text{kJ mol}^{-1})\) is slightly favored over the 4-coordinated ligand coupling (TS5-1a, \(+38\,\text{kJ mol}^{-1}\)). While the barriers between the pathways are more similar than for 1c and 1d, aryne formation is still favored according to these calculations.

This unexpected finding inspired us to search for alternative mechanisms with salt 1a, and a direct C-attack of the hydroxide on the iodonium salt 1a, without prior coordination to the iodine, indeed proved to have a very low barrier. TS6-1a (\(E_{b} = 3.2\,\text{kJ mol}^{-1}\)) is only 6 kJ mol\(^{-1}\) higher in energy than 1a, which explains the product distribution seen in Scheme 3e. This is not a normal nucleophilic aromatic substitution (SNAr), as no Meisenheimer complex could be identified. Instead, TS6-1a directly leads to the phenol in a concerted nucleophilic aromatic substitution (CSNAr),\(^{24}\) similar to previous reports for vinyliodonium salts and ethynylbenziodoxolones.\(^{2c,25}\)

To fully compare this pathway to the alternative paths in Figure 2, we would need to calculate the barrier to attack of hydroxide directly on iodine, leading to 1a-(OH)OTf. We have been unable to locate this transition state; the energy change on approach is monotonous, indicating that this is a diffusion-controlled reaction. Harvey and co-workers have estimated on approach to TS1-1c the 3-coordinated ligand coupling (TS4-1c) and the 4-coordinated ligand coupling (TS5-1c), are all much higher in energy, in agreement with the experimental results where coupling product 2e was not detected (Scheme 3d).

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Based on the experimental and theoretical results, we propose that the formation of diaryl ethers 2 from hydroxide takes place via three competing mechanisms. Ethers 2 are partly formed via the traditional ligand coupling mechanism that is depicted in Scheme 5a, with ligand exchange to 1d-OH followed by regiospecific ligand coupling (LC). The intermediate phenol (A) quickly undergoes another arylation by LC. Diarylodonium salts lacking strong EWG substituents partly react via the aryne mechanism shown in Scheme 5b, and this pathway dominates with electron-donating salts such as 1c. In this pathway, a hydroxide deprotonates intermediate 1d-OH, (rather than salt 1d directly, cf. Scheme 3c), with concomitant elimination of iodobenzene to give benzene B, which is attacked by a hydroxide to form anionic intermediate C.

A solvent-mediated proton shift delivers phenoxide (D) followed by facile O-arylation via LC to yield diaryl ether 2f. Contrary to the ligand coupling, the intermediate and TS for the aryne pathway involves two hydroxides, which is in line with the observed product ratio variation with the stoichiometry of the reaction (cf. Table 1, entries 1–2). The competition between these pathways is solvent dependent, and reactions in CH\(_2\)Cl\(_2\) proceed via both mechanisms whereas product formation in water takes place mainly via arynes.\(^{26}\) Reactions with strongly electron-deficient salts result in regioselective product formation, which could either proceed via ligand coupling, or via a low energy, direct substitution mechanism. This pathway was only found for nitro salt 1a (Scheme 5c), explaining the facile reactions with this salt.

The observed diaryl ether by-products could be formed via several aryne pathways from intermediate C, as illustrated in Scheme 5d. Aryne-derived intermediates similar to C have been reported to attack the iodine of iodobenzene.\(^{26}\) Should C react with PhI, which is produced in the aryne formation step, the hypervalent iodine (ate) complex E could fragment to...
iodophenol \( F \) and a high-energy phenyl carbanion. \( F \) could then be arylated by LC to give 5a. However, the addition of another iodoarene did not alter the ratio between 2f and 5a, and as a high energy intermediate would be formed, this pathway seems unlikely.

Alternatively, C could attack the much better electrophile 1d to give the T-shaped triaryl intermediate \( G \). Ligand coupling from \( G \) would deliver phenol H and iodozenbenzene, as depicted in pathway II.

Subsequent arylation of H by LC would yield either 8, which has indeed been detected in minor amounts by GC-MS. The other possible ligand coupling from triaryl intermediate \( G \) would give iodophenol \( F \) and biphenyl (pathway III). Subsequent arylation of F with 1d by a ligand coupling would give 5a. As only a trace amount of biphenyl has been detected, this cannot be the major pathway to 5a.

To account for the observed formation of iodo ethers 5, we instead propose the novel mechanism depicted in pathway IV. Triaryl intermediate \( G \) is in fast equilibrium with the other T-shaped intermediate \( G \), having the phenolic moiety in the equatorial position. In this conformation, a facile collapse of \( G \) into benzene and the zwitterionic intermediate I is plausible. Such iodonium phenolates are well known to undergo intra-molecular rearrangement leading to ortho-iodo substituted diaryl ethers like 5a under mild conditions. The suppressed formation of 5a in water compared to CH\(_2\)Cl\(_2\) (Table 1, entries 1, 5) is explained by the facile proton shift from C to D in aqueous media, leading to product 2f rather than 5a.

### Arylation of aliphatic alcohols

The competition between ligand coupling and aryne formation was also found when primary aliphatic alcohols were arylated with electron-donating diaryliodonium salts. This is exemplified by the arylation of 1-pentanol (3a) with \( p \)-tolyl salt 1b under our reported conditions, which resulted in a regioisomeric mixture of ethers 4a-4b (Table 2, entry 1). Contrary to reactions with hydroxide, only traces of iodo-substituted by-products were formed. The product ratio between 4a and 4b indicates that ligand coupling and aryne intermediates yield ethers in a 60:40 ratio. Diels–Alder adduct 6a was indeed formed upon addition of furan to the reaction mixture, supporting the presence of arynes (entry 2). As by-product 4b could still be detected, the reaction was examined with amine additives to suppress the by-product formation.

The use of piperidine changed the reaction outcome, and ether 4a was isolated as the only regiosomer (entry 3). Other amines were also screened, but piperidine proved best. When piperidine was employed as both base and aryne trap, no ether was formed (entry 4). The use of the stronger base NaHMDS, which gives an amine after the initial deprotonation and might act as an internal trap, unfortunately delivered a regiosomeric mixture of the product (entry 5).

Similar types of by-products, derived from aryne intermediates, were detected in arylations of both secondary and tertiary alcohols with electron-donating diaryliodonium salts. Furthermore, primary and secondary alcohols suffered from partial oxidation of the alcohol to the corresponding aldehyde/ketone or carboxylic acid. Diaryliodonium salts are generally poor oxidents, in contrast to iodine(III) reagents with two heteroaromatic ligands and McCewan and co-workers suggested a radical pathway to explain the observed oxidation products in this type of transformation.

We envisioned that the oxidation could either proceed via radicals, arynes or the T-shaped intermediate, which is formed prior to the ligand coupling. The oxidation was especially prominent with benzylic and allylic alcohols, and the reaction was hence investigated using secondary benzylic alcohol 3b (Table 3). Ketone 9 was indeed formed as major product in the attempts to arylate 3b with salt 1d, delivering ether 4c in poor yield under the reaction conditions optimized for primary and tertiary alcohols (entries 1 and 3). Only traces of an ortho-iodo by-product was identified, and the Diels–Alder adduct 6d could barely be detected (<5%) upon addition of furan. Addition of piperidine to the reaction only slightly changed the reaction outcome, (entries 2 and 4), indicating...

### Table 2. Arylation of 1-pentanol.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive (equiv)</th>
<th>Ratio 4a:4b [%]</th>
<th>Other products [%]</th>
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<tbody>
<tr>
<td>1</td>
<td>–</td>
<td>51</td>
<td>80:20</td>
</tr>
<tr>
<td>2</td>
<td>furan (5)</td>
<td>36</td>
<td>nd</td>
</tr>
<tr>
<td>3</td>
<td>piperidine (0.5)</td>
<td>27</td>
<td>100:0</td>
</tr>
<tr>
<td>4</td>
<td>piperidine (1.2)</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>NaHMDS (1.2)</td>
<td>52</td>
<td>80:20</td>
</tr>
</tbody>
</table>

[a] Isolated yields.
[b] \( ^1H \) NMR yield with TMB as internal standard.
[c] No \( rtBuONa \) was added. nd = not determined due to overlapping peaks, mainly 4a.

### Table 3. Phenylation and oxidation of alcohol 3b.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Additive (equiv)</th>
<th>4c [%]</th>
<th>9 [%]</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>( rtBuONa )</td>
<td>toluene</td>
<td>–</td>
<td>21</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>( rtBuONa )</td>
<td>toluene</td>
<td>piperidine (1.2)</td>
<td>14</td>
<td>54</td>
</tr>
<tr>
<td>3</td>
<td>NaHMDS</td>
<td>pentane</td>
<td>–</td>
<td>9</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>NaHMDS</td>
<td>pentane</td>
<td>piperidine (1.2)</td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>NaH</td>
<td>TBME</td>
<td>–</td>
<td>30</td>
<td>53</td>
</tr>
<tr>
<td>6</td>
<td>NaH</td>
<td>TBME</td>
<td>–</td>
<td>11</td>
<td>65</td>
</tr>
<tr>
<td>7</td>
<td>( rtBuONa )</td>
<td>THF</td>
<td>–</td>
<td>10</td>
<td>31</td>
</tr>
<tr>
<td>8</td>
<td>( rtBuONa )</td>
<td>THF</td>
<td>DPE (1.2)</td>
<td>21</td>
<td>39</td>
</tr>
<tr>
<td>9</td>
<td>( rtBuONa )</td>
<td>THF</td>
<td>TEMPO (1.2)</td>
<td>24</td>
<td>43</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: see the Supporting Information. [b] \( ^1H \) NMR yields using TMB as internal standard. [c] 3b in excess, 50 °C for 1 h, isolated yields. [d] Ph(Mes)IBr was used instead of 1d, chemoselectivity Ph:Mes 2:1.
that arynes are not the main pathway in the oxidation mechanism.

In Stuart’s recent methodology to arylate primary and secondary aliphatic alcohols, benzyl alcohol was arylated using aryldimethyl)dium salts with only trace formation of benzaldehyde. However, submission of 3b to these conditions, with either salt 1d or unsymmetric Ph(Mes)IBr, delivered the oxidized product 9 as a major product and ether 4c as a minor product (entries 5–6). Furthermore, the arylation chemoselectivity was only 2:1 in favor of phenyl over mesityl, illustrating the need for electron-deficient aryl groups when using the mesityl as a dummy group.

The effect of radical traps was examined in THF, as traps in toluene had no effect. While the yield of ether 4d increased in the presence of 1,1-diphenylethylene (DPE) or TEMPO (entries 7–9), the oxidation product 9 formed in similar amounts. This indicates that the oxidation does not take place via radicals, while radical pathways leading to other by-products could play a role in THF.

Reactions between alcohol 3b and ortho-blocked dimethyl salt 1e resulted in considerably higher arylation yields than with salts having ortho-protons (Scheme 6a). This could be rationalized by facilitated ligand coupling due to the ortho-effect and arylene formation being impossible with 1e. Importantly, the oxidation to ketone 9 still competed with the ether formation, and the combined yield of ether 4d and 9 corresponds well to reactions with salt 1d.

### Scheme 6. Arylations with ortho-blocked salt 1e.

The deuterated substrate 3b-D was aryalted to ether 4d-D in higher yield, with less of ketone 9 compared to reactions with 3b (Scheme 6b). Deuterated mesitylene was detected by GC-MS. A reaction containing both alcohols 3b and 3b-D gave a good average yield of ethers 4d and 4d-D in a 1:1 ratio, whereas the unreacted starting materials contained more of 3b-D (Scheme 6c). The yield of 9 was affected in a similar fashion.

Having ruled out both arynes and radicals as oxidation promoters, we envisioned two possible mechanisms for the oxidation (Scheme 7). Both pathways go via the T-shaped intermediate J, which forms from the deprotonated alcohol and salt 1d. The benzylic proton could either be transferred to the phenyl ring in an intramolecular, concerted fashion to release 9, iodo-benzene and benzene (Scheme 7a), similar to mechanisms involving iodine(VI) reagents.

Alternatively, intermediate J could be deprotonated by an external base, releasing 9, iodo-benzene and benzene carbanion K, which is quickly protonated to benzene (Scheme 7b).

To distinguish between these mechanisms, excess base was added to the reaction of alcohol 3b with mesityl salt 1e. This neither affected the yield nor the ratio of 4d and 9. The amount of oxidized product 9 also remained the same upon dilution of the reaction. The reaction mixtures were heterogeneous in toluene, but comparable ratios were obtained in homogenous solution (toluene/DMF). This indicates that the two processes are of the same order. As the ligand coupling mechanism is considered to be a concerted process (see Scheme 1a), the oxidation should proceed via the intramolecular pathway shown in Scheme 7a.

Further investigations were conducted using DFT. The arylation of 1-phenylethoxide with mesityl salt 1e was investigated, to avoid alternative pathways via arynes. The 4-coordinated intermediate 1e-(OR)2 was found to be considerably lower in energy than the 3-coordinated 1e-OR (Figure 3a). Likewise, the TS corresponding to the 4-coordinated coupling (TS7-1e) is strongly favored over any other TS corresponding to coupling or oxidation (TS8-1e to TS11-1e). The internal oxidation (TS9-1e) is much more favorable compared to the external pathway (TS11-1e). The same trends were observed using both the B3LYP-D3 and the M06-2X functional.

Considering that the experimental conditions (0.1 M) diverge from the standard state conditions (1 M), this accounts for an energy penalty of around 7.9 kJ mol⁻¹ for the reactions that are binmolecular with respect to the alkoxide. Taking this into account, the energy for the 4-coordinated TSs and intermediates increase and hence the gap between ligand coupling and oxidation (TS7-1e vs. TS9-1e) decreases to 10 kJ mol⁻¹ using B3LYP-D3 (Figure 3b). This difference indicates a selectiv-
ity of >10:1 in favor of coupling, which is not experimentally observed.

The deviations between the experimental results (Scheme 6) and the DFT investigations could be caused by the chosen DFT method being insufficiently accurate in the current context. Discrepancies between DFT and experimental results are not uncommon. In particular, continuum solvation models can be unreliable for anions,[36] In the current case, the relative energies of small anions (like hydroxide) and distributed anions (like square planar iodine(III) complexes) would be expected to be unreliable. Calculations with explicit water molecules around the nucleophile could provide more reliable energies,[37] but were beyond our computational capacity. Within a set of similar compounds, errors will cancel to a large extent, but between sets, we have relied on experimental results to judge which of several manifolds that best describe the studied transformations.

Based on the combination of experimental and theoretical results, we believe that 4-coordinated intermediates and transition states are favored in reactions with alcohols and diaryliodonium salts to give aryl ethers (Scheme 8). The ligand coupling pathway proceeds regiospecifically via intermediate 1d-(OR), (Scheme 8a). Arynes were formed in reactions with diaryliodonium salts lacking EWG substituents. This pathway also yields aryl ethers, albeit with poor regioselectivity when substituted salts are employed. In another competing reaction pathway, the alcohol is oxidized to the corresponding ketone or aldehyde via an intramolecular mechanism (Scheme 8b). The computational barriers for the 4- and 3-coordinated TSs are similar. Still, we suggest that the oxidation mainly proceeds via the 4-coordinated TS, since the experimental results show that oxidation and ligand coupling are of the same order. This side reaction is most prominent with allylic and benzylic alcohols.

**Figure 3.** (a) Free energy surface for the reaction between 1e and 1-phenylethoxide in toluene using the B3LYP-D3 functional (b) Free energy surface with an applied standard state correction. Free alkoxides and triflates are omitted for clarity. Energies are given in kJ mol⁻¹.

**Scheme 8.** Mechanistic summary with alcohols.
Conclusion

A mechanistic investigation of O-arylations of hydroxide and aliphatic alcohols with diaryliodonium salts under metal-free conditions has been performed to understand the pathways that compete with ligand coupling. The study involved both experimental techniques and DFT calculations to understand the different reaction outcomes depending on the electronic properties of the diaryliodonium salt. Trapping experiments with furan were consistent with the formation of aryne intermediates under mild conditions. Piperidine proved to be a more efficient trap to avoid by-products, which demonstrates an important proof of principle. While the aryne formation presently cannot be avoided in arylation of hydroxide and aliphatic alcohols with electron-donating salts, the use of piperidine enables the synthesis and easy isolation of aryl ethers as single regioisomers in moderate isolated yields.

The oxidation of alcohols by diaryliodonium salts was found to proceed via a novel cyclic transition state, ruling out the involvement of arynes and radicals. Small differences in substrate and reagent structures were found to have large impacts on the reaction outcome with competing pathways via arynes, ligand coupling and oxidation. Furthermore, a direct substitution mechanism was found for arylation with nitrophenyl salt 1a, explaining the facile synthesis of aryl ethers with this salt. We believe that the mechanistic insights presented herein, as well as the piperidine trap technique, can be utilized to develop novel reactions with iodine(III) reagents and to overcome the present limitations with these reagents.

Experimental Section

Arylation of hydroxide

Sodium hydroxide (1.6 mmol, 2 equiv) was added to a 10–20 mL or 2–5 mL microwave vial and CH₂Cl₂ or deionized H₂O (3 mL) was added. The indicated additive was added followed by immediate addition of diaryliodonium salt 1 (0.8 mmol, 1 equiv). The reagents were rinsed down from the walls of the vial with solvent (1 mL). The vial was capped and stirred at RT for 22 h, or stirred in a preheated oil bath at 80 °C for 22 h. The reaction mixture was quenched with sat. NH₄Cl and then extracted with CH₂Cl₂ (x 3). The combined organic phases were dried over MgSO₄, filtrated and the solvent removed in vacuo. The crude mixture was then submitted to column chromatography.

Arylation of alcohols

A dry 10 mL Schlenk tube was evacuated and backfilled with argon three times. tBuONa (58 mg, 0.6 mmol, 1.2 equiv) was added, followed by anhydrous toluene (1.5 mL). The mixture was cooled to 0 °C and 1-pentanol (54 μL, 0.5 mmol, 1 equiv) was added and rinsed down using toluene (0.5 mL). After stirring at RT for 15 min the mixture was cooled to 0 °C and additive (0.3–5.0 equiv) was added followed by salt 1 (0.6 mmol, 1.2 equiv). After rinsing down using toluene (0.5 mL) the mixture was left to stir at RT for 3 hours. The reaction was quenched using sat. NH₄Cl, extracted with CH₂Cl₂ (3 × 10 mL) dried over MgSO₄, filtered and concentrated in vacuo. The crude was then submitted to flash column chromatography to obtain the product.

Computational methods

Geometry optimizations and energy calculations were carried out with the Becke Three-Parameter Lee–Yang–Parr functional[38] with the dispersion correction by Grimme[39] (B3LYP-D3) or the Minnesota functional, M06-2X[12, 40] as implemented by Gaussian09. The SDD basis set with an applied effective core potential (MWB46) was used for iodine,[41] Pople’s triple-zeta basis set with added polarization and diffuse functions (6–311+G(d,p))[42a] were used for N, O, F, Cl and Na atoms while the triple-zeta basis set with added polarization (6–31G(d,p)) were used for the H, C and S atoms. Several iodine(III) reactions have recently been studied by DFT using similar setups.[2a, 8b, 15c, 18] The systems were studied in both CH₂Cl₂ and H₂O using the polarizable continuum model (PCM, solvent = SES, Radii = UFF).[43] and the results in H₂O are given in the Supporting Information. Structures were optimized with the applied solvation model and true transition states were verified via frequency analysis and the presence of one, and only one, imaginary frequency.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: aryl ethers · arynes · hypervalent iodine · mechanistic study · oxidation

Put a ring on it! The arylation of aliphatic alcohols and hydroxide with diaryliodonium salts, to give alkyl aryl ethers and diaryl ethers, has been studied using experimental techniques and DFT calculations. Aryne formation and alcohol oxidation pathways were observed in parallel to arylation, and additives to avoid by-product formation originating from arynes have been found. A novel, direct nucleophilic substitution pathway has been identified in reactions with electron-deficient diaryliodonium salts.

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Competing Pathways in O-Arylations with Diaryliodonium Salts: Mechanistic Insights