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ortho-Functionalization of azobenzenes *via* hypervalent iodine reagents†

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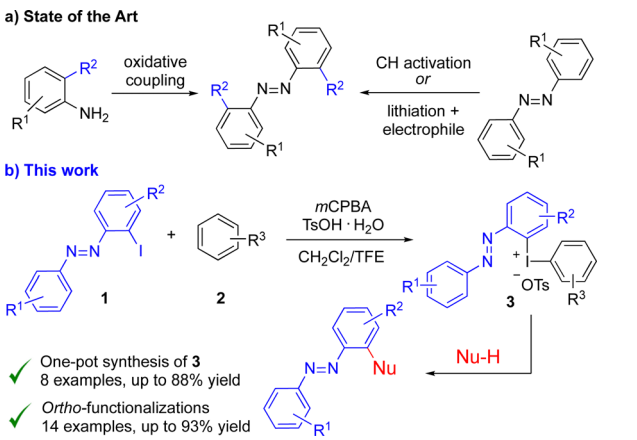
***ortho*-Functionalized azobenzenes are much sought after molecular switches, as they may be tuned to absorb in the visible range of light and the (*Z*)-isomers can have high thermal half-lives. To enable straightforward access to these targets, we have developed a synthetic route *via* novel *ortho*-substituted azobenzene-functionalized diaryliodonium salts. Selective transfer of the azobenzene moiety to O-, N-, C- and S-nucleophiles under mild, transition metal-free conditions gives access to an unprecedented range of *ortho*-substituted azobenzenes. The photoswitching properties of the reagents were investigated and the structure was determined by X-ray crystallography.**

Azobenzenes are important molecular switches that can be photochemically switched between the thermodynamically stable (*E*)-isomer and the metastable (*Z*)-isomer.[1] Exceptions exist, in which the stabilities are reversed.[2] They show a high thermal[3] and photochemical stability,[1] and the switching mechanisms are well understood.[4] Using targeted syntheses, it is often possible to obtain certain properties. Hence, there is an increasing number of applications, *e.g.* in switchable polymers with diverse purposes,[5] biomedical applications,[6] or as solar thermal fuels.[7] For each task, the azobenzene has to be finely adjusted due to two main issues.[8] The thermal stability of the less stable isomer can cause an unavoidable background isomerization[9] and the overlap of the isomers' absorption spectra results in photostationary states (PSSs) of low selectivity for either isomer at a particular wavelength.[10]

Current research focuses on *ortho*-substituted azobenzenes to reach thermally stable (*Z*)-isomers or an absorption in the visible range of light.[11] Switching occurs with wavelengths as long as 720 nm,[12] and highly selective PSS (tetra-*ortho*-fluorinated azobenzene: $PSS_{(Z)}$ 91%/$PSS_{(E)}$ 86%).[10] However, there are few synthetic methods available for their synthesis (Scheme 1a).[3,13] They can be prepared from appropriately substituted anilines[11a,14] and further functionalized *via* nucleophilic substitution,[15] or through transition metal-catalyzed C–H activation.[16] While azobenzenes decorated with carbon,[17] oxygen,[17a,18] nitrogen[19] and halide[16,19b] substituents in the *ortho*-position have been synthesized, synthetic drawbacks include the need for transition metal catalysts, long reaction times at elevated temperatures and scope limitations. Surprisingly, the literature is void of cross-coupling methods in the *ortho*-position, irrespective of whether the azobenzene moiety serves as an organometallic nucleophilic component or as an electrophilic halogenated cross-coupling partner,[13] despite access to *ortho*-metalated azobenzenes.[20]

Hypervalent iodine(III) compounds are efficient reagents for a wide range of transformations under mild reaction conditions.[21] Diaryliodonium salts have been recognized as highly reactive electrophilic arylating reagents with a variety



Scheme 1 Synthesis of *ortho*-substituted azobenzenes. (a) State of the art. (b) This work.

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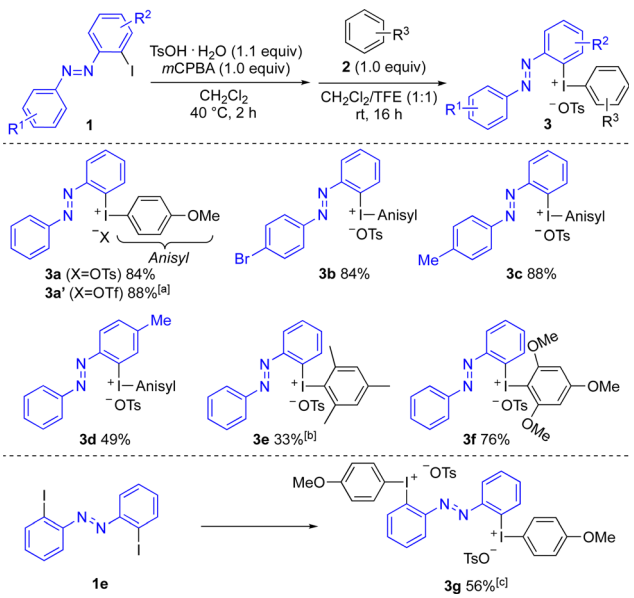
of carbon and heteroatom nucleophiles under both metal-free and metal-catalyzed conditions.[22] Furthermore, they are relatively non-toxic, bench-stable and easily synthesized through one-pot reactions of iodoarenes and arenes or arylboronic acids.[23]

We envisioned that the combination of azobenzenes with iodine(III) chemistry could overcome the limitations in the synthesis of *ortho*-functionalized azobenzenes. Herein, we showcase the successful synthesis and applications of *ortho*-azobenzene diaryliodonium salts in metal-free arylations to access hitherto unobtainable products (Scheme 1b).

The study commenced by investigating suitable conditions for the synthesis of diaryliodonium salts **3** from the corresponding *ortho*-iodoazobenzenes **1**.[24] Our standard one-pot conditions with *m*CPBA and triflic or tosic acid and a suitable arene failed,[23b,d] as did one-pot reactions of **1** with arylboronic acids.[23c] To our delight, a sequential one-pot reaction[25] with oxidation of iodoarene **1** using *m*CPBA and tosic acid at 40 °C, followed by the addition of arene **2** at room temperature was successful for the synthesis of the novel iodonium salts **3** (Scheme 2). In this way, the otherwise unsubstituted *ortho*-azobenzene iodonium salt **3a** was obtained in 84% isolated yield from **1a**. A stepwise synthesis of **3a** with isolation of the corresponding [hydroxy(tosyloxy)iodo]arene before treatment with anisole gave **3a** in 78% overall yield.[24] Anion exchange to the corresponding triflate salt **3a′** could be performed by *in situ* treatment with triflic acid or workup with NaOTf.[24,25b]

The scope investigations were focused on the synthesis of unsymmetric diaryliodonium salts (Ar^1Ar^2IX) to avoid wasting a precious azobenzene moiety in subsequent arylations. The anisyl moiety is often an efficient "dummy group" in chemoselective arylations with Ar^1Ar^2IX under metal-free conditions.[26] Anisole



Scheme 2 Scope of *ortho*-azobenzene(aryl)iodonium salts **3** (isolated yields after precipitation). [a] After workup with NaOTf. [b] TFE as the only solvent. [c] TsOH·H_2O (2.2 equiv.), *m*CPBA (2.0 equiv.) and anisole (2.0 equiv.).

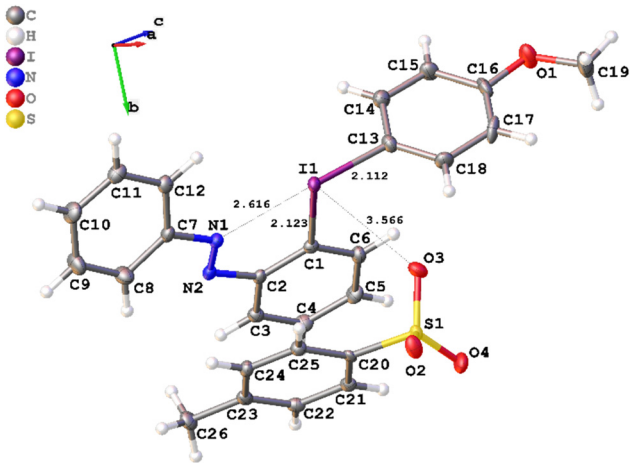
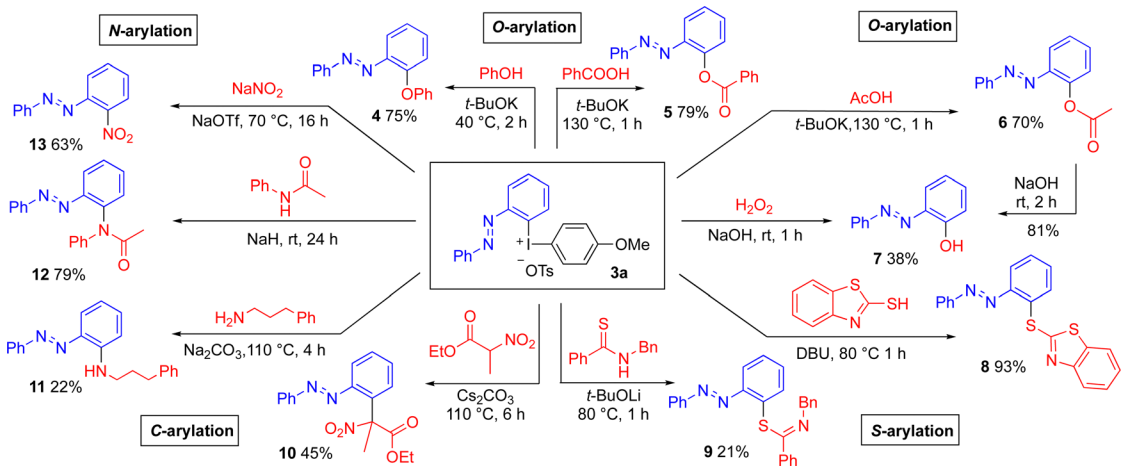


Fig. 1 X-ray crystal structure of the (*E*)-isomer of **3a** with selected bond lengths. Selected angles: C(13)–I(1)–O(3) 81.84(10)°; O(3)–I(1)–C(1) 90.45(9)°; N(1)–I(1)–O(3) 107.47°; C(1)–I(1)–N(1) 69.2(1)°; C(13)–I(1)–C(1) 94.56(12)°; N(1)–I(1)–C(13) 8.54(5).

was hence utilized as the standard arene in reactions with substituted *ortho*-iodoazobenzenes **1b–d** to provide iodonium salts **3a–d** in good to high yields. Substituents were well tolerated on the *para*-azo aryl moiety, with bromo-substituted salt **3b** well positioned for further late-stage functionalizations. Further substituents on the iodo-substituted aryl group were also tolerated, as shown by methyl-substituted product **3d**. Mesitylene and trimethoxybenzene could be utilized to provide iodonium salts **3e** and **3f** bearing a mesityl or trimethoxyphenyl (TMP) dummy group, which are reported to give chemoselective arylations with certain nucleophiles.[26] Bis(diaryliodonium) salt **3g** was obtained in good yield through difunctionalization of the corresponding diiodo-azobenzene **1e**.

It was possible to grow single crystals of the (*E*)-isomer of salt **3a**, suitable for X-ray diffraction analysis (Fig. 1, CCDC number: 2215795). Diaryliodonium salts generally have the typical T-shape of iodine(III) compounds, where one aryl group and the counterion reside in the hypervalent bond.[21] Interestingly, the X-ray structure of **3a** displays an N–I-aryl hypervalent bond with an N–I interaction of 2.616 Å, whereas the tosylate anion coordinates perpendicular to the hypervalent bond (bond angles: C(13)–I(1)–O(3) 81.84(10)°; O(3)–I(1)–C(1) 90.45(9)°). While azo-coordination to iodine(III) is unknown, Nachtsheim and coworkers have recently reported on related N–I interactions in iodine(III) reagents.[27] Preliminary calculations indicate that the pseudocyclic structure is favored for the (*E*)-isomer, whereas the (*Z*)-isomer lacks the N–I stabilizing interaction and the expected I–OTs coordination is favored.[24]

The influence of the hypervalent iodine moiety on the photoswitching behavior of the azobenzene was examined by ^{1}H NMR and UV/vis spectroscopy in $CDCl_3/CHCl_3$, comparing iodonium salt **3a** and the parent azobenzene **1a**. Under ambient conditions, both molecules existed exclusively as the (*E*)-isomer. Upon irradiation with UV light (340 nm), both molecules switched to the corresponding (*Z*)-isomer ((*E*)/(*Z*) ratio: 32/68 (**1a**), 29/71 (**3a**)). Re-isomerization occurred upon irradiation



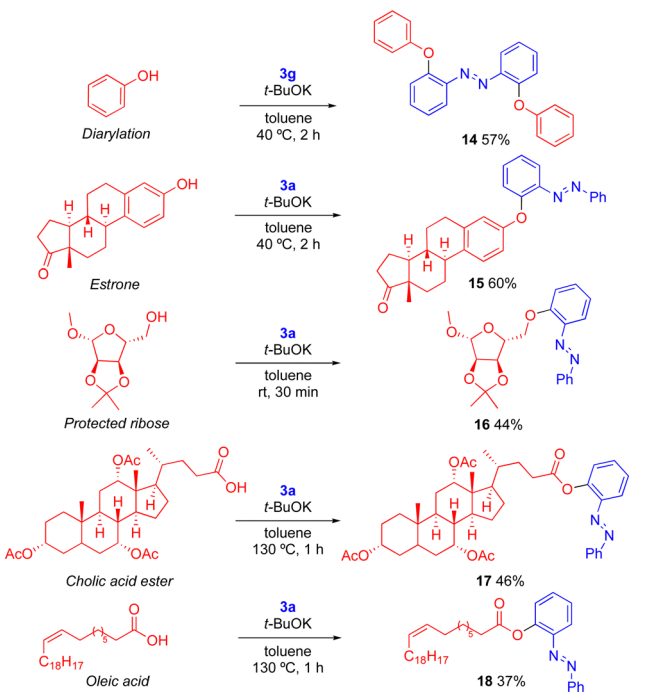
Scheme 3 Metal-free arylations of C, N, O and S-nucleophiles with reagent **3a**.

with visible light (450 nm) ((*E*)/(*Z*) ratio: 90/10 (**1a**), 72/28 (**3a**)). A complete conversion to the (*E*)-isomer could not be achieved photochemically but no significant photodegradation was detected for **1a** and **3a** upon repeated switching. The incorporation of the hypervalent moiety had almost no influence on the absorption maxima of the azobenzene switch: (π–π*: 325 nm (**1a**), 338 nm (**3a**); n–π*: 434 nm (**1a**), 436 nm (**3a**)). However, the thermal half-life was significantly decreased ($t_{1/2}$: 124.6 h (**1a**), 5.83 h (**3a**)). This can be attributed to the strong electron acceptor character of the iodine(III) moiety, and the N–I stabilizing interaction in the (*E*)-isomer of **3a**.

To demonstrate the utility of the novel reagents, well-established methods for transition metal-free arylation of various nucleophiles with diaryliodonium salt **3a** were utilized to provide a range of *ortho*-substituted azobenzene products. The transformations proceeded with complete chemoselectivity and retained (*E*)-configuration (Scheme 3). *O*-Arylation of phenol and carboxylic acids[28] delivered the azobenzene-functionalized diaryl ether **4** and aryl esters **5** and **6** in good yields. The aryl ester **6** could be hydrolyzed under mild conditions into 2-hydroxyazobenzene **7** in 81% yield, which has excellent features as a structural motif in pharmaceutical and materials science.[18b] The synthesis of product **7** was also feasible through the hydroxylation of **3a** with hydrogen peroxide[29] in a moderate yield. As Pd-catalyzed *ortho*-acyloxylation and hydroxylation of azobenzenes is reported,[17a,18] we were eager to evaluate the reactivity of **3a** with other types of nucleophiles.

To our delight, *S*-arylation with a mercaptothiazole[30] delivered the novel, heterocyclic azobenzene product **8** in excellent yield (93%). The arylation of thioamide[31] to thioimidates **9** was more difficult. Even the *C*-arylation of a substituted nitroester[32] could be performed to provide the sterically congested product **10**. Methods for *N*-arylation were next explored, and the arylation of a primary amine[33] proved to be challenging. The novel, amino-substituted product **11** was obtained in 22% yield due to partial decomposition of **3a** under the reaction conditions. On the other hand, the arylation of acetanilide[34] proceeded smoothly to give the tertiary amide **12** in 79% yield. Furthermore, arylation of sodium nitrite[35] delivered *ortho*-nitro azobenzene (**13**) in 63% yield.

The *O*-arylation methodology[28] was subsequently employed to achieve more advanced *ortho*-functionalized azobenzene products that should be relevant in supramolecular chemistry, materials science[14,36] and biological chemistry[37] (Scheme 4). The reaction of bis(diaryl)iodonium salt **3g** with phenol gave the *ortho*-diphenoxylated azobenzene **14** and the steroid estrone was arylated with reagent **3a** to diaryl ether **15** in 60% yield. Moreover, the *O*-arylation of protected ribose[38] delivered the arylated derivative **16**. Arylation of acetyl-protected cholic acid produced ester **17** in moderate yield, as the basic conditions caused partial hydrolysis of the acetate groups, with



Scheme 4 *O*-Arylations to provide complex *ortho*-substituted azobenzenes. Conditions: **3** (1.0 equiv.), nucleophile and *t*BuOK (1.2–2.1 equiv.), in toluene.

competing arylation to give byproduct **6** in 20% yield.[24] Finally, the *O*-arylation of oleic acid produced the functionalized ester **18**. It should be noted that **8–11** and **15–18** are novel *ortho*-azobenzenes, illustrating the utility of the method to quickly reach a variety of targets. In comparison with literature methods to reach the known products **4–7** and **12–14**, our method often has milder conditions and shorter reaction times.[24]

In conclusion, the synthesis of *ortho*-azobenzene-derived diaryliodonium salts was achieved in high yields. The novel iodonium reagents were demonstrated as chemoselective arylation reagents with a range of C, N, O and S-nucleophiles under mild and metal-free conditions. The X-ray crystal structure revealed that the nitrogen is involved in hypervalent bonding with the iodine(III) center. The photoswitching properties of the azobenzene were retained in the hypervalent azobenzene derivatives but the incorporation of the hypervalent iodine bond influenced the position of the absorption maxima and drastically reduced the half-life time.

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A.S. and B.O. conceived the project; E.M.D.T. and M.W. performed the experiments and analyzed the data; all authors contributed to writing the manuscript; A.S. and B.O. supervised the project and acquired the funding. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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