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Assessing the Role of Benzylic C—H Bonds in Suppressing Radical Chemistry Initiated by Benzynes

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ABSTRACT

Reaction of KO*t*Bu with haloarenes in arene solvent leads to the formation of biaryls through radical intermediates, and we recently (2026) showed that the radical chemistry is initiated by the formation of benzynes. Our original studies (2014) compared the reactivity of iodobenzene and 2-iodo-*m*-xylene; the latter substrate cannot form *o*-benzynes. Whereas iodobenzene led to the formation of biaryls (40%), for 2-iodo-*m*-xylene this was suppressed almost to 0%. However, in the intervening time, we came to suspect that the iodoxylene was not an ideal substrate due to the potential reactivity of the Ar-Me groups both to base and to hydrogen atom abstraction reactions. We have now examined two new substrates where the Ar-Me groups are replaced by Ar-Ph groups. These substrates cause much more efficient initiation of radical chemistry, arising from the formation of *p*- and *m*-benzynes through the reaction of iodobenzenes with base. Importantly, these substrates allow assessment of the role of the Ar-Me groups in 2-iodo-*m*-xylene in suppressing radical chemistry.

1 | Introduction

In 2008, Itami et al. reported that heating of iodoarenes, for example, **1** with KO*t*Bu in heteroarene solvents such as pyrazine **2** led to coupling of the iodoarene to the heteroarene to form the corresponding biaryl, in this case **3** [1]. This was soon extended by others to coupling between haloarenes **4** and arenes **6**, which was facilitated when the reaction was conducted in the presence of certain organic additives [2–8]. From the start, all these coupling reactions were proposed to involve attack of aryl radicals **5** onto arenes, but the mechanism of formation of the radicals and of propagation was not clear.

Studer and Curran made an important contribution by proposing that KO*t*Bu plays a key role in the mechanism, by deprotonating the intermediate arylcyclohexadienyl radical **7** to form a radical anion **8** [9]. In turn, the radical anion **8** donates an electron to substrate **4** thereby forming the coupled product **9** as well as a new radical **5**, leading to propagation of the radical chemistry. They termed these reactions "base-promoted homolytic aromatic substitutions" (BHAS) [1].

Our interest focused on the initiation of these reactions. We demonstrated that organic electron donors can initiate the chemistry [10] and further showed that many of the organic additives that had been used were converted into organic electron donors when treated with KO*t*Bu [11–13]. However, although reactions with added electron donors afford higher yields, both we and others showed that coupling could occur, albeit at a slower rate, even in the absence of recognized electron donors or their precursors [10, 14–16].

To explain the mechanism by which radicals are generated in the first place in the absence of recognized electron donors,

Dedicated to Prof. Dr. Armido Studer.

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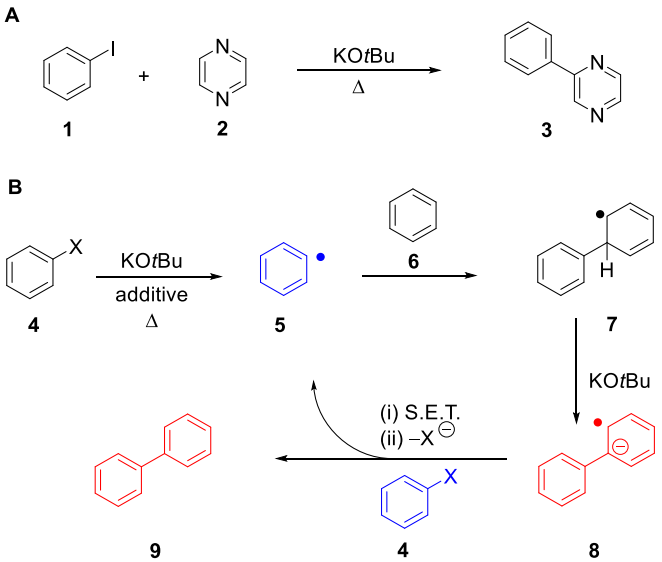


SCHEME 1 | (A) Discovery of BHAS coupling. (B) The BHAS cycle.

we proposed that the haloarene **4** was converted into an *o*-benzyne **10** and that this added to the arene solvent to generate a diradical **11** which initiated the radical chemistry [10, 17, 18]. The reactive aryl radical within **11** should react first and has two options: (i) it undergoes H-atom abstraction from benzene and forms cyclohexadienyl radical **7** together with a phenyl radical **5** (that can then enter the propagation cycle of Scheme 1B). Deprotonation of **7** would form radical anion **8** and loss of an electron would then afford product **9**. The transferred electron would convert substrate **4** into another phenyl radical **5**. (ii) Alternatively, the aryl radical within **11** could add to benzene **6** to afford diradical **12**. Deprotonation and electron transfer could occur twice to afford *o*-terphenyl **13**; the transferred electrons convert two molecules of substrate **4** into two phenyl radicals **5** (Scheme 2).

To test the proposal, we selected the xylene substrate **14**, which could not form an *o*-benzyne. In the presence of a recognized electron donor (formed from phenanthroline and KO*t*Bu, Scheme 3A) [2, 10, 19] this afforded the coupled products in 40% overall yield, comprised of **16** (8%) and **9** (32%), as well as xylene **17** (58%) [20]. Xylene would result from H-atom abstraction by radical **15** from benzene; the resulting phenyl radical then underwent BHAS coupling to the solvent, benzene, to form biphenyl **9**. However, when the reaction was conducted in the absence of a recognized electron donor, the combined yield of **16** and **9** dropped from 40% to almost 0% (in fact, 0.8%). Such a drop gave support to the "benzyne" theory of initiation in the absence of electron donors.

However, we were also concerned about the validity of our deductions arising from substrate **14**. The key feature of concern with this substrate was the benzylic methyl groups. This substrate certainly inhibited BHAS coupling, and we had attributed this to its inability to form an *o*-benzyne, but we wondered whether alternative factors might contribute to or dominate the lack of coupling. For example, simple deprotonation of substrate **14** to give anion **18** might use up some of the KO*t*Bu. (Scheme 3B). Such deprotonated molecules would interfere with the propagation of BHAS chemistry as they would be unable to accept an electron.

Deprotonation of products **16** and **17** could occur likewise. Additionally, it was likely that the benzylic methyl groups in **14**, **16**, and **17** would be good candidates for quenching reactive aryl radicals **15** by hydrogen atom transfer (HAT), thereby suppressing chain propagation of BHAS. This would afford well-stabilized benzylic radicals **21–23** that might find it challenging to propagate BHAS chemistry (see below in Section 2.1). A study by Cadogan et al. had shown the reactivity of methyl groups within bromodurene (2,3,5,6-tetramethylbromobenzene) with KO*t*Bu at the higher temperature of 225°C, although no reaction was observed at lower temperatures [21].

Because of our concerns, we determined to compare the dimethyliodobenzene substrate, **14**, with two new substrates, iodo-2,6-diphenylbenzene **24** and iodo-2,4,6-triphenylbenzene **25** that avoid these complications (Scheme 3C). The comparisons were carried out experimentally and through computational studies and are the subject of this paper.

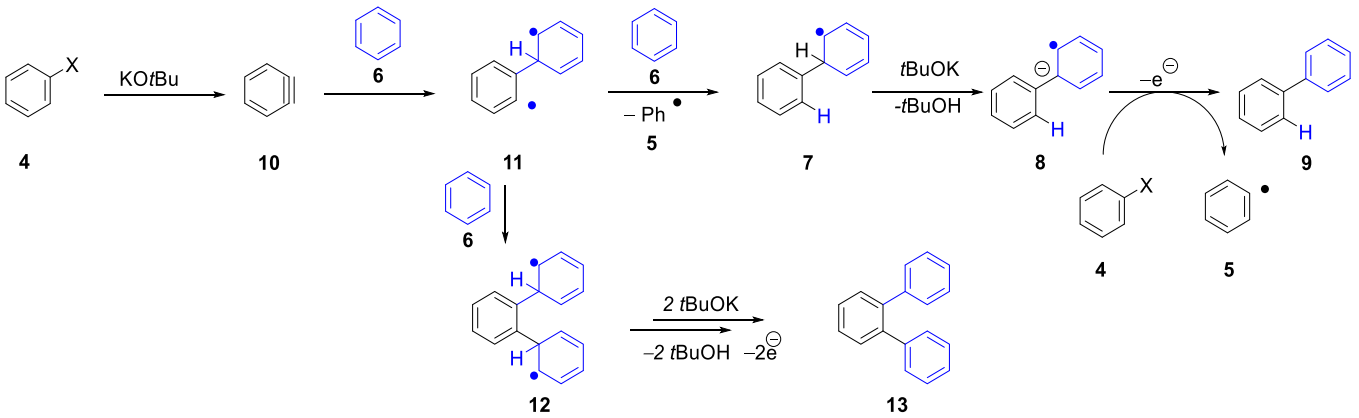
Before proceeding, we should say that since our initial publication in 2014 [10], our understanding of BHAS initiation increased when we established that treatment of iodobenzene **1** with KO*t*Bu simultaneously affords isomeric *ortho*-benzyne (**10**), *meta*-benzyne (**26**), and *para*-benzyne (**27**) [22] and that each of these can initiate BHAS chemistry. In each case, the formation of the regioisomeric benzyne involves deprotonation of the substrate together with loss of halide ion. Because we now know that *meta*- and *para*-benzynes are routinely formed, then substrate **14** should also be able to initiate the BHAS chemistry. This could explain the 0.8% of coupled products that were seen, as mentioned above. However, the very low yield of coupled products increased our suspicions about the roles of the methyl groups in **14** in suppressing BHAS coupling. A comparison with results from substrates **24** and **25** should clarify the extent to which the methyl groups of **14** inhibit the coupling.

2 | Results and Discussion

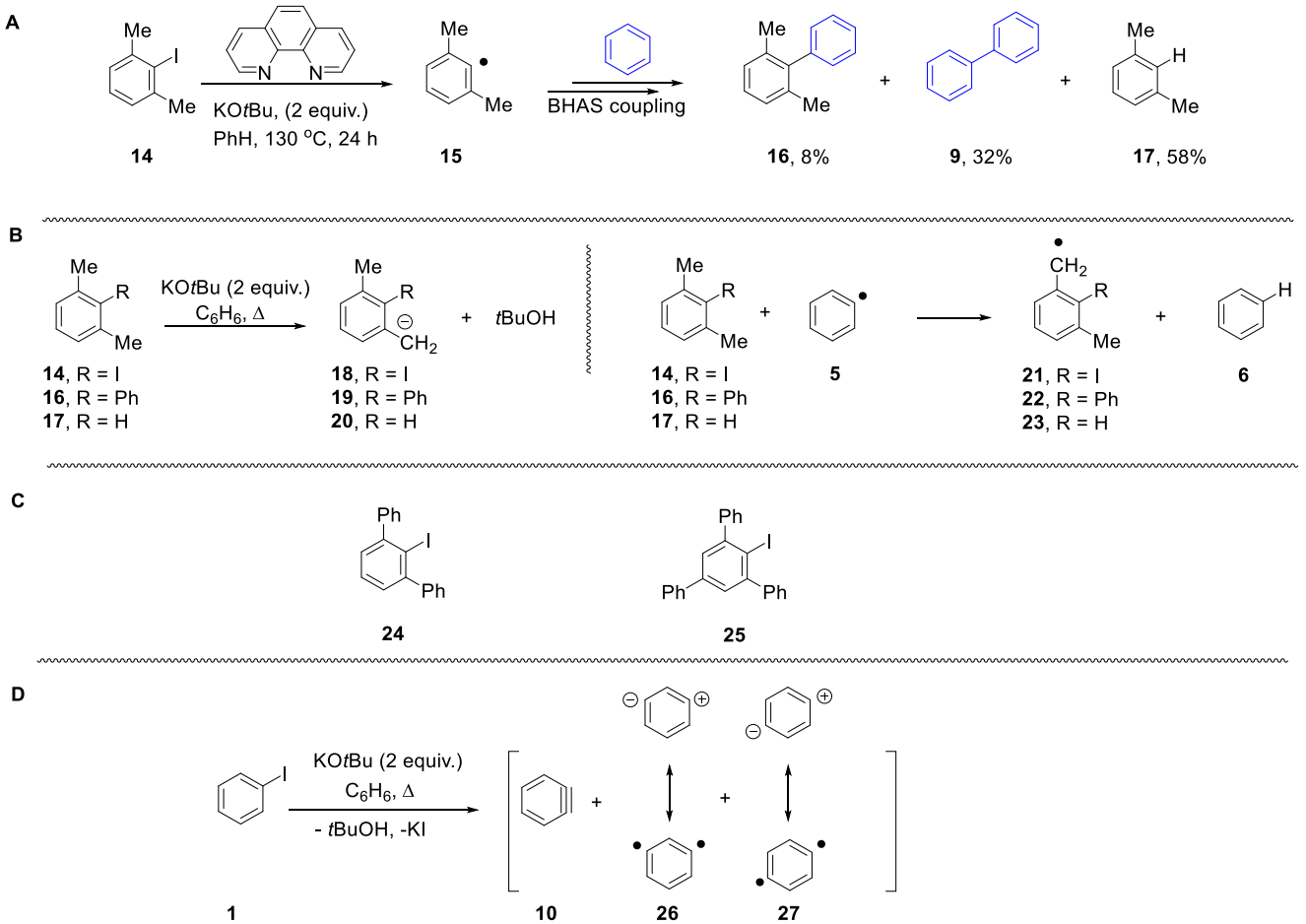
2,6-Diphenyliodobenzene **24** was prepared easily through Suzuki–Miyaura reaction on commercially available 2,6-dibromoaniline **28** to yield **29**, followed by conversion to the diazonium salt and subsequent iodination (Scheme 4) [23]. From this substrate, both *p*-benzynes and *m*-benzynes are possible. Additionally, 2,4,6-triphenyliodobenzene **25**, from which *m*-benzynes are possible, was synthesized via a similar route.

We now report the outcomes of the reactions of the two substrates with KO*t*Bu in benzene as solvent. This will then be followed by evidence (i) that these reactions arise from BHAS coupling and (ii) that the initiation of these reactions occurs through benzynes.

Looking first at 2,4,6-triphenyliodobenzene **25**, this substrate was reacted with KO*t*Bu (2 equiv.) at 130°C in C_6H_6, where it was found that a reaction time of 48 h was required for the reaction to near completion. The reaction was carried out twice, with the average yields given below (Scheme 5). BHAS product 1,2,3,5-tetraphenylbenzene **32** was produced (12.0%), along with biphenyl **9** (42.8%) and 1,3,5-triphenylbenzene **33** (82.0%). Iodobenzene **1** (5.3%) was produced via halogen atom



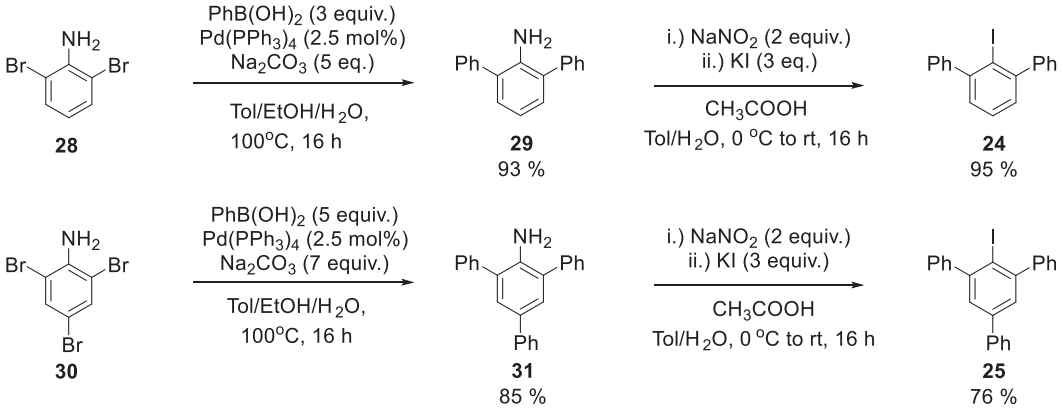
SCHEME 2 | Proposal for initiation of BHAS radical chemistry by benzynes.



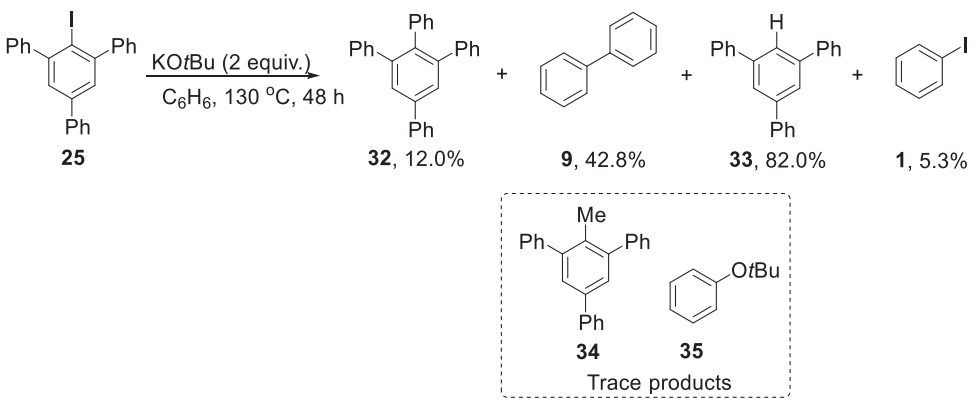
SCHEME 3 | (A) Reaction of substrate **14**. (B) Potential side-reactions with substrate **14** and products **16** and **17**. (C) Planned substrates **24** and **25**. (D) Formation of regioisomeric benzynes **10**, **26**, and **27**.

transfer (XAT) reaction of phenyl radicals with **25**, and 2,4,6-triphenyltoluene **34** was also observed (see below).

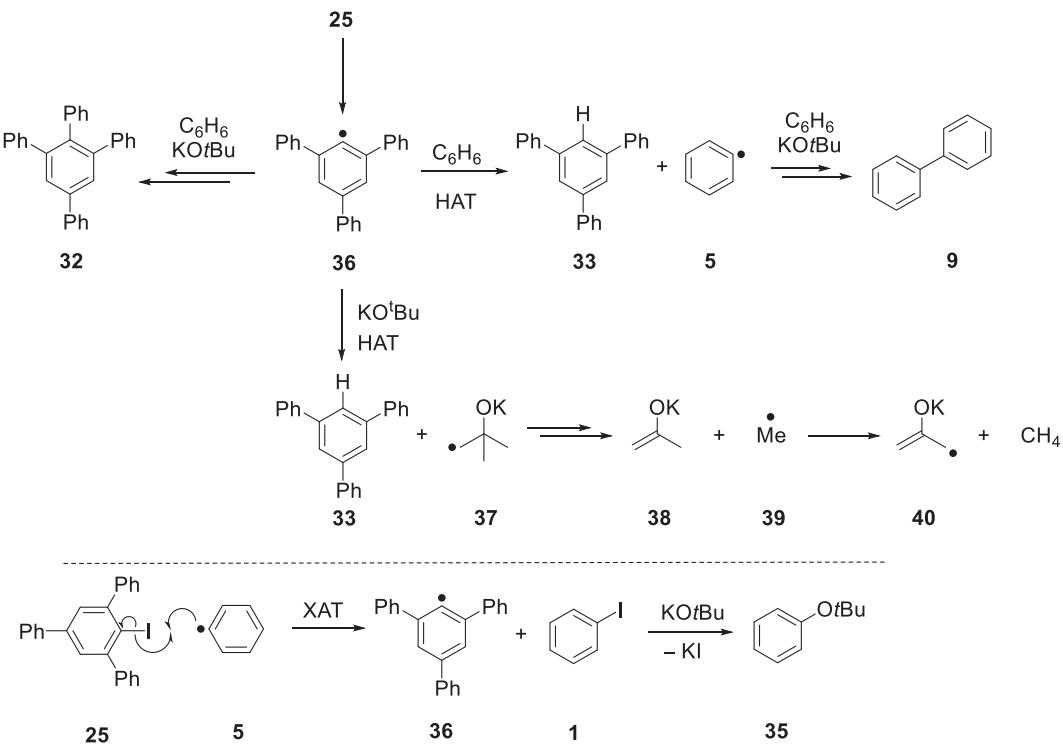
Aryl radical **36** derived from **25** is very sterically hindered, making C—C bond formation to benzene difficult and thus favoring HAT from benzene to yield **33** and phenyl radicals **5**, which go on to form biphenyl **9** (Scheme 6). The high conversion of **25** under these conditions suggests that the poor reactivity of iodoxylene **14** (with reactions of both substrates **14** and **25** being carried out in the absence of added electron-donor initiators) was likely due to its relatively reactive benzylic positions, rather than its inability to form *o*-benzynes. The yield of 1,3,5-triphenylbenzene **33** from the reaction of substrate **25** is far higher than the yield of biphenyl **9**, suggesting an additional alternative source of HAT for aryl radical **36** (Scheme 6). As shown in our recent paper [20], this hydrogen source is likely KO*t*Bu. The resulting radical **37** fragments easily



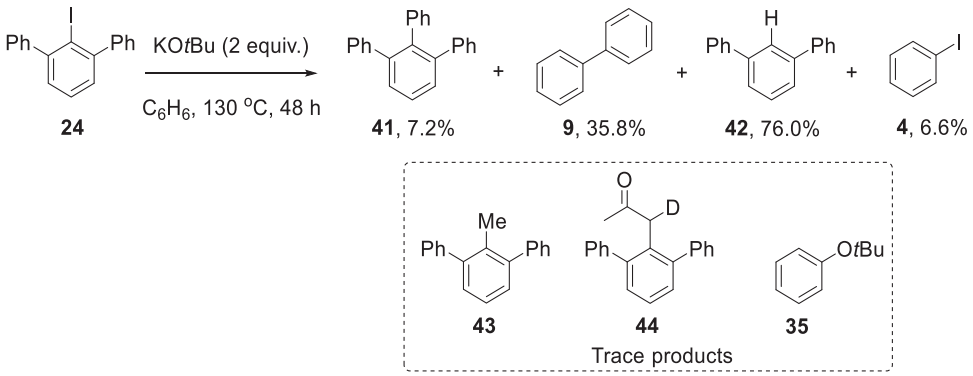
SCHEME 4 | Synthesis of 2,6-diphenyliodobenzene **24** and 2,4,6-triphenyliodobenzene **25**.



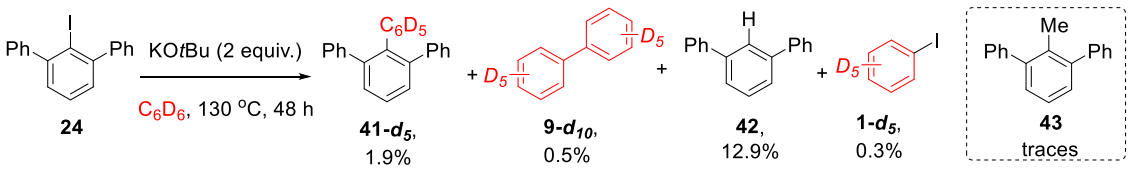
SCHEME 5 | Reaction of 2,4,6-triphenyliodobenzene **25** with KO*t*Bu in benzene.



SCHEME 6 | Proposed reaction paths for radical **36**, and the formation of iodobenzene **1** and *tert*-butyl phenyl ether **35**.



SCHEME 7 | Reaction of 2,6-diphenyliodobenzene **24** with KOtBu in benzene.



SCHEME 8 | Reaction of 2,6-diphenyliodobenzene **24** with KO*t*Bu in deuterated benzene.

to afford acetone enolate **38** and a methyl radical **39**. Indeed, small quantities of the methylated product 2,4,6-diphenyltoluene **34** were observed, derived from attack of methyl radicals onto **25**. Methyl radicals can add to arenes, but an easier reaction results in HAT from enolate **38** to yield stabilized radical **40** (see Section 2.1). The reaction of **25** also afforded iodobenzene **1** (5.3%). This is formed when phenyl radical **5** undergoes halogen atom transfer (XAT) with **25** in an energetically favorable reaction that releases steric strain [24]. Formation of *o*-benzyne from **1**, followed by attack by *tert*-butoxide leads to **35**, which was also observed in trace amounts.

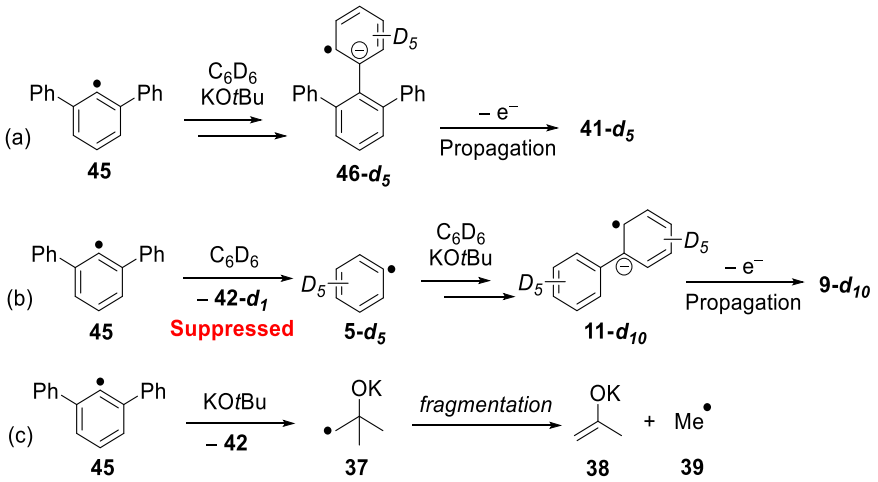
Reaction with 2,6-diphenyliodobenzene **24** proceeded very similarly, and the results are shown in Scheme 7. Thus, 1,2,3-triphenylbenzene **41** (7.2%), biphenyl **9** (35.8%), 1,3-diphenylbenzene **42** (76%), together with iodobenzene (6.6%) were the main products. In this case, traces of methylated product **43** and of acetonylated product **44** were also detected. (The workup of this reaction was conducted by quenching with D_2O; accordingly, **44-*d*** was detected). The latter likely arose when acetone enolate either (i) underwent a facile HAT to reactive radicals in solution, and the resulting radical **40** reacted with substrate **24** (see Section 2.1) or (ii) underwent single-electron transfer to trigger an $S_{RN}1$ reaction [25–28]. Ether **35** was also detected in trace amounts, arising from iodobenzene, as noted above.

Overall, substrates **24** and **25** thus gave similar results. To provide supporting evidence that the products arose through BHAS chemistry, **24** was then reacted with KO*t*Bu in C_6D_6, with the average yields of two runs given in Scheme 8. In this case, the reaction was heavily retarded, with the majority of starting material **24** recovered (81.3%), so that only about one-fifth of the substrate was converted. The fall in yield of **9-*d*$_{10}$** (35.8% → 0.5%) compared to the yield of **9** from reactions in C_6H_6 was expected (due both to conversion of one-fifth of substrate **24** in C_6D_6, and to the isotope effect arising from a more challenging abstraction from C_6D_6 by radical **45**) [20]. The fall in yield of **41-*d*$_5$** (7.2% → 1.9%) fits with the low 20% conversion of the substrate (no isotope effect is expected here). The yield of *m*-terphenyl **42** has also fallen considerably (76.0% → 12.9%) again consistent with the low 20% conversion; notably, this product was almost entirely unlabeled.

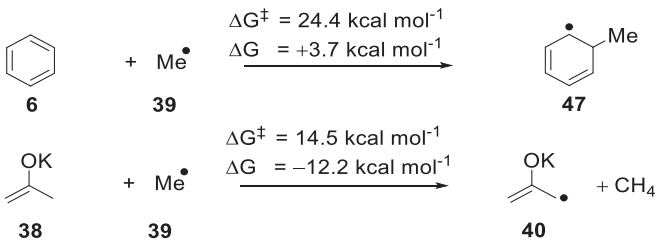
A plausible explanation for the inefficient reaction is chain-termination, due to HAT by **45** from KO*t*Bu (Scheme 9). The major reaction pathways for radical **45** are (a) C—C bond formation with benzene to form **46-*d*$_5$**, (b) HAT with benzene, or (c) HAT with KO*t*Bu. In C_6D_6, paths (a) and (c) should be unaffected, but path (b) is almost entirely suppressed. While path (a) can still propagate BHAS (*via* radical anion **46**), path (c) leads to radical **37**, with subsequent fragmentation to enolate **38** and methyl radical **39**.

Methyl radicals are observed to add to arenes, which after deprotonation will lead to radical anions capable of propagating BHAS. Our calculations show that C—C bond formation by methyl radicals **39** with benzenes is difficult, making this a less likely route to BHAS propagation in our reactions of **24** (Scheme 10). Alternatively, methyl radical **39** can abstract a hydrogen from enolate **38** relatively easily, yielding allylic radical **40**. **40** is a stabilized radical, making disruption of the benzene aromatic ring more challenging (see Section 2.1). Therefore, the propensity for **45** to undergo chain-terminating HAT with KO*t*Bu is a plausible explanation for the low reactivity of 2,6-diphenyliodobenzene **24** in C_6D_6.

If the reactions of **24** and **25** with KO*t*Bu are indeed initiated through the formation of benzynes, a decrease in the rate of initiation would be expected when deuterated analogues are employed. This difference in rate would most clearly be seen



SCHEME 9 | Proposal for the inhibition of reaction of 2,6-diphenyliodobenzene **24** observed in C_6D_6.



SCHEME 10 | Calculations assessed the ability of methyl radicals **39** to attack arenes or to undergo HAT with enolate **38**.

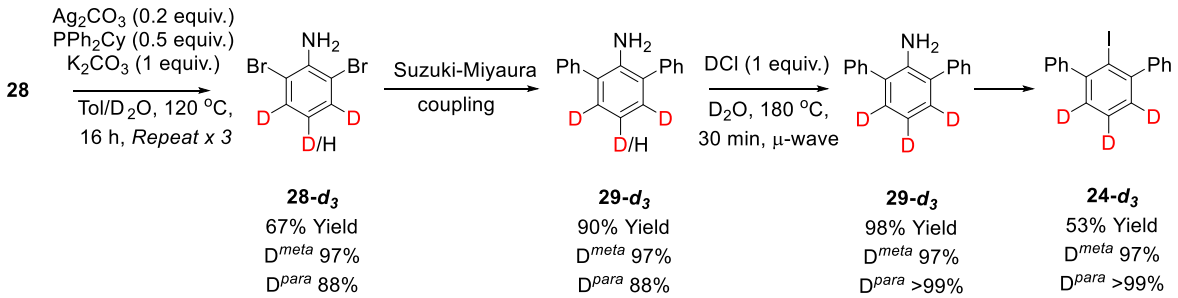
when the reactions are sampled early in their course. Therefore, **24-*d*$_3$** was prepared for this purpose (Scheme 11). Firstly, 2,6-dibromoaniline **28** was deuterated according to the method of Zhang et al. [29], which after 3 repeats gave excellent deuterium incorporation in the *meta*-positions (97% D^{meta}), but failed to adequately deuterate the *para*-position (88% D^{para}) where *meta*- and *para*- are referenced relative to the amino group. It was planned to further deuterate the *para*-position by S_EAr [30], but to avoid debromination, **28-*d*$_3$** was first converted to **29-*d*$_3$** by Suzuki coupling. The subsequent S_EAr reaction completely deuterated the *para*-position, which after conversion to the diazonium salt and subsequent iodination yielded **24-*d*$_3$** (97% D^{meta}, >99% D^{para}).

With **24-*d*$_3$** in hand, side-by-side reactions of **24** and **24-*d*$_3$** were carried out at shortened reaction times, for which 6 h was found to be appropriate. The reactions were each carried out twice, with the average yields summarized in Table 1. The rate of reaction for **24-*d*$_3$** (entry 2) is slower than for **24** (entry 1). This suggests that initiation is inhibited by incorporation of deuterium onto the haloarene, consistent with more difficult removal of D^+ over H^+ as a prerequisite for benzyne formation and in line with our recent observations on other classes of substrates [22].

Experiments were then carried out with a 50:50 ratio of **24** and **24-*d*$_3$** (i.e., 0.5 equiv. of each substrate in the same reaction), which gave yields that were intermediate between those of the individual isotopologues (entry 3). From the GC–MS trace of this reaction, it was observed that products **41** and **42** (and traces of methylated product **43**) are produced in *ca*. 1:1 ratio of ***d*$_0$** and ***d*$_3$** isotopologues, which suggests that the lower yields (compared to entry 1) are due to slightly slower initiation of the reaction due to less unlabeled **24** available for deprotonation and subsequent benzyne formation. However, once initiation occurs, both substrates are activated equally easily.

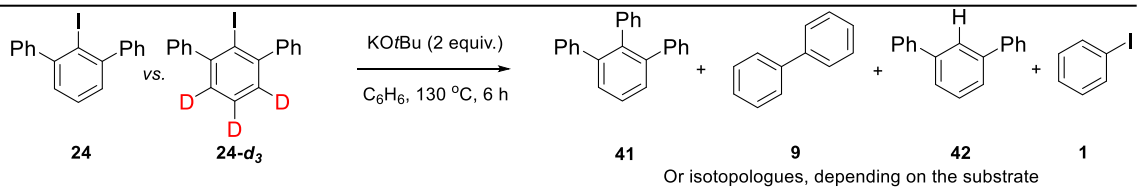
2.1 | Computational Studies

Our selection of substrates **24** and **25** for comparison with substrate **14** bears scrutiny through computational chemistry. Computational studies were carried out at the M06-2X-D3/ma-Def2-QZVP/CPCM(benzene)//M06-2X/6-311++G(d,p),SDD(iodine)/CPCM(benzene) level using Gaussian16; full details can be found in the Supporting Information. Thus Equation 1 shows the comparative kinetic and thermodynamic values for HAT from benzene by radicals **15** and



SCHEME 11 | Preparation of deuterated 2,6-diphenyliodobenzene **24-*d*$_3$**.

TABLE 1 | Short timescale reactions of 2,6-diphenyliodobenzene isotopologues.



Entries	Substrates	% yield[a,b]				
		24 or 24-d_3	**41 or 41-d_3**	**9**	**42 or 42-d_3**	**1**
1	**24**	81.0 ± 0.8	1.5 ± 0.2	4.7 ± 0.8	17.1 ± 1.5	3.1 ± 0.7
2	**24-d_3**	91.3 ± 1.2	0.7 ± 0.1	1.9 ± 0.1	7.0 ± 0.7	1.5 ± 0.1
3	50:50 **24: 24-d_3**	85.1 ± 0.3	1.0 ± 0.1	3.0 ± 0.4	10.9 ± 1.0	2.1 ± 0.1

[a]Yields determined by GC–FID calibrated with authentic samples, isotopologue yields were calculated using calibrations for non-deuterated standards.
[b]Averaged yields of 2 runs per isotopologue, with the deviation from the average given.

45. Equation 2 (Scheme 12) shows that the barriers for abstraction of deuterium from C_6D_6 by both these radicals are 1.1 kcal mol^{-1} higher than from C_6H_6 in line with the expected kinetic isotope effect. Equation 3 shows that formation of a C—C bond through addition to benzene faces barriers of about 25 kcal mol^{-1} for both radicals. These barriers are achievable under the conditions of the reaction but are higher than those for HAT from benzene, in line with our observations. Our reactions showed evidence of formation of iodobenzene through abstraction of iodine atoms from the substrates by phenyl radicals **5**, and Equation 4 shows that this reaction is easily achieved for both substrates **14** and **24**.

Equations 5 and 6 show that iodine atom exchange between the substrates and their derived aryl radicals is also easily achieved. Equation 7 shows the HAT from ArMe groups by aryl radicals is also easily achieved. This reaction quenches the aryl radicals by forming much less reactive benzylic radicals, thereby potentially quenching the BHAS chemistry of substrate **14**. Equation 8 shows that benzyl radicals, using the simple benzyl radical **48** as a model, can add to benzene, but that this is rather endergonic and faces a considerable barrier, while Equation 9 shows a similar barrier for addition to benzene of the stabilized radical **40**.

3 | Conclusions

Support for our early proposal that benzyne formation could initiate BHAS coupling of haloarenes to arenes, (when the reactions are conducted without the addition of recognized electron-donors or molecules that could be converted in situ into such electron-donors) was originally partly based on the suppression of BHAS coupling by the substrate 2-iodo-*m*-xylene **14**. Here, the formation of an *o*-benzyne is precluded by the presence of the methyl substituents. More recently, we have published compelling evidence supporting initiation of BHAS coupling by benzynes, using a range of substrates including those that cannot form *o*-benzynes [22]. As our familiarity with the chemistry grew over intervening years, we developed concerns related to the potential reactivity of the Ar-Me groups both toward KO*t*Bu as base (proton removal by KO*t*Bu) and with reactive radicals like aryl radicals (H-atom removal by the radicals). In this paper, two substrates **24** and **25**, that cannot form *o*-benzynes, but that avoid the complications associated with Ar-Me groups, have been examined. Both substrates led to BHAS coupling reactions with benzene, and at much higher levels than seen with substrate **14** (Scheme 13). Evidence supports the reactions of substrates **24** and **25** being initiated by benzyne formation through deprotonation followed by loss of iodide ion. Comparison of substrates **24** and **25** with substrate **14** shows that the extent of BHAS coupling seen with substrate **14** was curtailed due to the reactivity of its Ar-Me substituents. This study has thus provided valuable insight into the reactive nature of Ar-Me groups in BHAS chemistry.

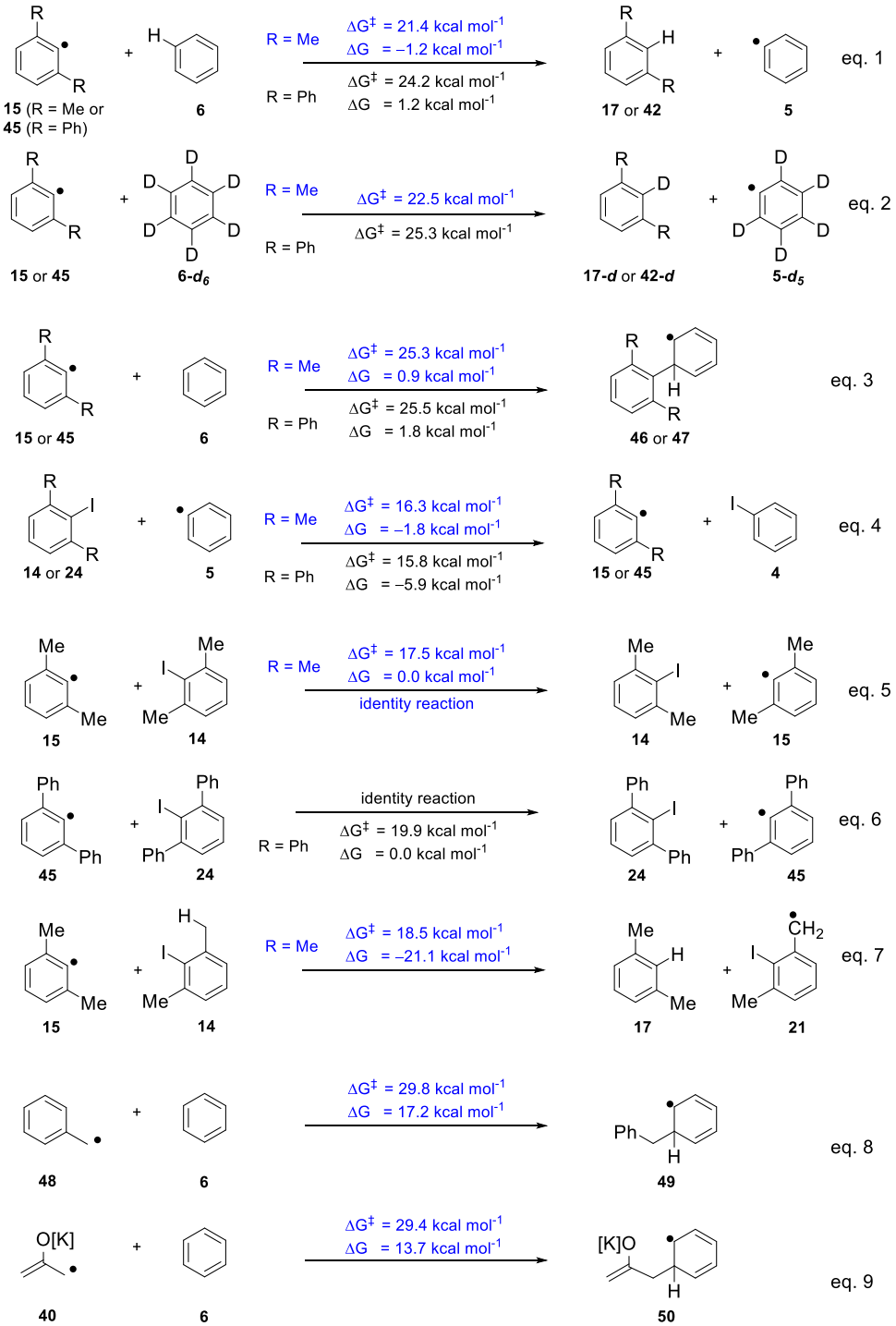
4 | Experimental Section

4.1 | General Information

All reagents and solvents were obtained from commercial suppliers and were used without further purification unless mentioned otherwise. THF was dried using a Pure-Solv 400 solvent purification system (Innovative Technology Inc., USA). Anhydrous benzene (C_6H_6) was obtained from Sigma Aldrich, while benzene-d_6 99.5%D (C_6D_6) was obtained from Eurisotop. For mechanistic reactions, new microwave vials and Teflon stirbars were used in the first instance, after which between each use they were soaked overnight in a NaOH/^{i}PrOH base bath, and then rinsed thoroughly with aqueous HCl, water and acetone before drying overnight in an oven set to 150°C.

4.2 | Syntheses

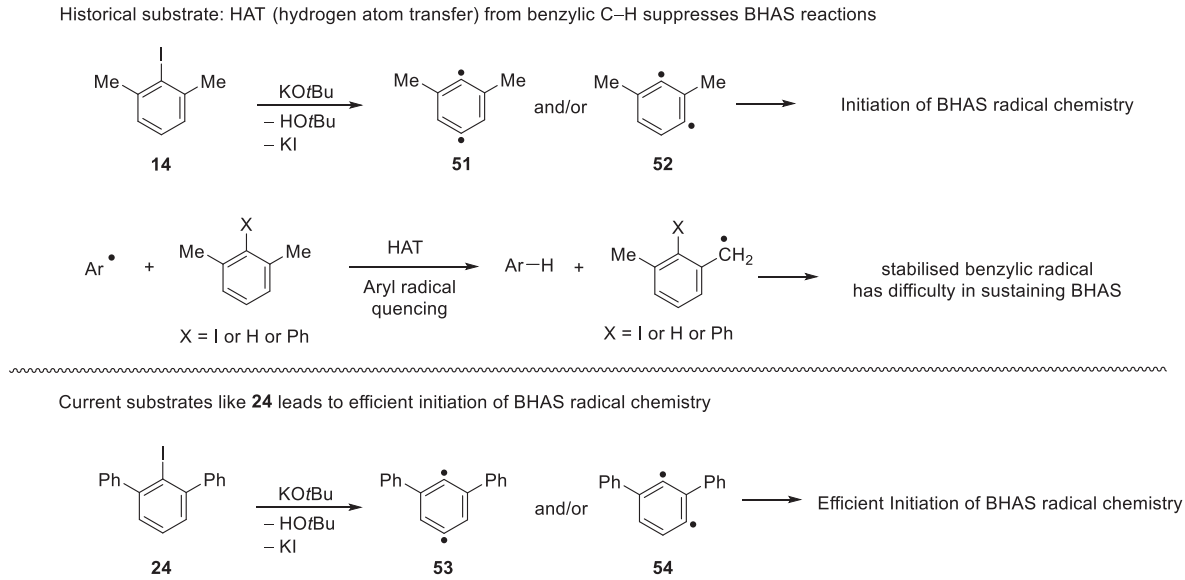
2,6-diphenylaniline **29**: The reaction was carried out according to a literature procedure [23]. A 250 mL Schlenk flask was charged with 2,6-dibromoaniline **28** (2.51 g, 10.0 mmol, 1 equiv.), $PhB(OH)_2$ (3.66 g, 30.0 mmol, 3 equiv.), Na_2CO_3 (5.30 g, 50.0 mmol, 5 equiv.), toluene (40 mL), EtOH (12.5 mL), H_2O (12.5 mL), and a stirbar. The mixture was then degassed thoroughly by bubbling with argon for 30 min before the flask



SCHEME 12 | Calculated barriers and energy changes for plausible fundamental steps. All energies are Gibbs free energies at the M06-2X-D3/ma-Def2-QZVP/CPCM(benzene)//M06-2X/6-311++G(d,p),SDD(iodine)/CPCM(benzene) level of theory at 403.15 K.

was sealed and transferred into a glovebox. $Pd(PPh_3)_4$ (290 mg, 0.25 mmol, 0.025 equiv.) was then added, with the flask subsequently sealed and removed from the box, then stirred at 100°C for 16 h. The reaction was then allowed to cool to room temperature and diluted with EtOAc (100 mL), then washed with H_2O (2 × 50 mL) and brine (50 mL). The organics were then dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography (0 → 20% DCM in hexane) of the crude yielded 2,6-diphenylaniline **29** as a white solid (2.28 g, 9.27 mmol, 93%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54–7.50 (m, 4H), 7.49–7.44 (m, 4H), 7.39–7.34 (m, 2H), 7.13 (d, J = 7.5 Hz, 2H), 6.89 (t, J = 7.4 Hz, 1H), 3.85 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.0, 139.9, 129.9, 129.5, 129.0, 128.1, 127.4, and 118.3. **GC–MS (EI)**: 245.1 ([M^+]). **M.p**: 84°C–88°C. The data are in agreement with the literature [23].

2,6-diphenyliodobenzene **24**: The reaction was carried out according to a literature procedure [23]. To a 100 mL round-bottom



SCHEME 13 | Replacing Ar-Me groups in **14** by Ar-Ph groups in **24** affords efficient initiation of BHAS chemistry.

flask were added 2,6-diphenylaniline **29** (2.28 g, 9.27 mmol, 1 equiv.) and a stirbar. The solid was dissolved in toluene (5 mL) and cooled in an ice bath, then glacial acetic acid (17.5 mL) was added. The solution was stirred for 15 min, at which point a solution of $NaNO_2$ (1.28 g, 18.5 mmol, 2 equiv.) in H_2O (1 mL) was added dropwise, yielding a yellow solution which was left to stir at 0°C for 30 min. After this time, a solution of KI (4.62 g, 27.8 mmol, 3 equiv.) in H_2O (2 mL) was slowly added dropwise, immediately causing the solution to darken with gas evolution. After addition was complete the reaction was allowed to stir at 0°C for 4 h, then at room temperature for 12 h. After this time, the reaction was slowly quenched with dropwise addition of sat. Na_2CO_3, then diluted with EtOAc (100 mL) and washed with $Na_2S_2O_3$ (2 × 50 mL), water (50 mL), and brine (50 mL). The organics were then dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography (1% DCM in hexane) of the crude and subsequent recrystallization from hot hexane yielded 2,6-diphenyliodobenzene **24** as white needle-like crystals (3.12 g, 8.77 mmol, 95%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50–7.38 (m, 11H), 7.29 (d, J = 7.3 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.1, 145.7, 129.5, 128.6, 127.9, 127.6, and 103.7. **GC–MS (EI)**: 356.0 ([M^+]). **M.p**: 111°C–112°C. The data are in agreement with the literature [23].

2,4,6-triphenylaniline **31**: The reaction was carried out according to a modified literature procedure [23]. A 250 mL Schlenk flask was charged with 2,4,6-tribromoaniline **30** (1.65 g, 5.0 mmol, 1 equiv.), $PhB(OH)_2$ (3.05 g, 25.0 mmol, 5 equiv.), Na_2CO_3 (3.71 g, 35 mmol, 7 equiv.), toluene (20 mL), EtOH (6.5 mL), H_2O (6.5 mL), and a stirbar. The mixture was then degassed thoroughly by bubbling with argon for 30 min before the flask was sealed and transferred into a glovebox. $Pd(PPh_3)_4$ (114 mg, 0.125 mmol, 0.025 equiv.) was then added, with the flask subsequently sealed and removed from the box, then stirred at 100°C for 16 h. The reaction was then allowed to cool to room temperature and diluted with EtOAc (70 mL), then washed with H_2O (2 × 40 mL) and brine (40 mL). The organics were then dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography (0 → 20% DCM in hexane) of the crude yielded 2,4,6-triphenylaniline **31** as a pale orange solid (1.37 g, 4.25 mmol, 85%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62–7.55 (m, 6H), 7.51–7.46 (m, 4H), 7.42–7.36 (m, 6H), 7.30–7.24 (m, 1H), 3.92 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.0, 140.5, 139.8, 131.2, 129.5, 129.1, 128.8, 128.5, 128.5, 127.6, 126.6, and 126.5. **GC–MS (EI)**: 321.2 ([M^+]). **M.p**: 136°C–139°C. The data are in agreement with the literature [31].

2,4,6-triphenyliodobenzene **25**: The reaction was carried out according to a modified literature procedure [23]. To a 100 mL round-bottom flask was added 2,4,6-diphenylaniline **31** (1.37 g, 4.25 mmol, 1 equiv.) and a stirbar. The solid was dissolved in toluene (2 mL) and cooled in an ice bath, then glacial acetic acid (8 mL) was added. The solution was stirred for 20 min, at which point a solution of $NaNO_2$ (587 mg, 8.50 mmol, 2 equiv.) in H_2O (1 mL) was added dropwise, yielding a yellow solution which was left to stir at 0°C for 30 min. After this time, a solution of KI (2.17 g, 12.8 mmol, 3 equiv.) in H_2O (2 mL) was slowly added dropwise, immediately causing the solution to darken with gas evolution. After addition was complete the reaction was allowed to stir at 0°C for 4 h, then at room temperature for 16 h. After this time, the reaction was slowly quenched with dropwise addition of sat. Na_2CO_3, then diluted with EtOAc (100 mL) and washed with $Na_2S_2O_3$ (2 × 50 mL), water (50 mL) and brine (50 mL). The organics were then dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography (0 → 10% DCM in hexane) of the crude and subsequent recrystallization from hot hexane yielded 2,4,6-triphenyliodobenzene **25** as white crystals (1.40 g, 3.23 mmol, 76%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 (d, J = 7.3 Hz, 2H), 7.51 (s, 2H), 7.49–7.40 (m, 12H), 7.36 (t, J = 7.3 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.7, 145.7, 140.7, 139.7, 129.6, 129.1, 128.1, 128.0, 127.8, 127.4, 127.2, and 102.4. **GC–MS (EI)**: 432.2 ([M^+]). **M.p**: 116°C–118°C. The data are in agreement with the literature [32].

2,6-dibromoaniline **28-*d*$_3$**: The reaction was carried out according to an adapted literature procedure [29]. A 20 mL microwave vial was charged with **28** (1.00 g, 4.0 mmol, 1 equiv.), Ag_2CO_3 (220 mg, 0.80 mmol, 0.2 equiv.), PPh_2Cy (537 mg, 2 mmol, 0.5 equiv.),

K_2CO_3 (553 mg, 4 mmol, 1 equiv.), toluene (2 mL), and D_2O (4 mL) under air. The vial was capped and stirred at 120°C for 16 h. After this time, the reaction was quenched with sat. NH_4Cl (20 mL) and extracted into DCM (2 × 20 mL). The combined organics were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by column chromatography (0 → 5% DCM in hexane) yielding a white fluffy solid. The above procedure was repeated twice more, yielding partially deuterated 2,6-dibromoaniline **28-*d*$_3$** (683 mg, 2.69 mmol, 67% over 3 steps). Deuterium incorporation as determined by ^{1}H NMR: *D% meta* = 97%, *D% para* = 88%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43–7.30 (m, 0.06H), 6.48 (s, 0.12H), 4.50 (br, 2H). **^{2}H NMR** (61 MHz, $CHCl_3$) δ 7.38, 6.50. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.0, 133.5–129.3 (m), 119.2, 108.8. **GC–MS (EI)**: 254.0, 252.0, and 255.6 (2:1:1 [M^+]). **M.p**: 83°C–87°C.

2,6-diphenylaniline **29-*d*$_3$**: The reaction was carried out according to an adapted literature procedure [23]. A 250 mL Schlenk flask was charged with 2,6-dibromoaniline **28-*d*$_3$** (628 mg, 2.70 mmol, 1 equiv.), $PhB(OH)_2$ (988 mg, 8.10 mmol, 3 equiv.), Na_2CO_3 (1.43 g, 13.5 mmol, 5 equiv.), toluene (11 mL), EtOH (3.4 mL), H_2O (3.4 mL), and a stirbar. The mixture was then degassed thoroughly by bubbling with argon for 30 min before the flask was sealed and transferred into a glovebox. $Pd(PPh_3)_4$ (78 mg, 0.068 mmol, 0.025 equiv.) was then added, with the flask subsequently sealed and removed from the box, then stirred at 100°C for 16 h. The reaction was then allowed to cool to room temperature and diluted with EtOAc (50 mL), then washed with H_2O (2 × 25 mL) and brine (25 mL). The organics were then dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography (0 → 20% DCM in hexane) of the crude yielded **29-*d*$_3$** as a white solid (603 mg, 2.42 mmol, 90%). Deuterium incorporation was retained from the previous step. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55–7.50 (m, 4H), 7.49–7.43 (m, 4H), 7.39–7.33 (m, 2H), 7.14 (s, 0.06H), 6.92 (s, 0.12H), 4.02 (br, 2H). **^{2}H NMR** (61 MHz, $CHCl_3$) δ 7.17, 6.94. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.1, 139.7, 129.5, 129.0, 128.4, and 127.5. **GC–MS (EI)**: 248.2 ([M^+]). **M.p**: 83°C–86°C.

Further deuteration of 2,6-diphenylaniline **29-*d*$_3$**: The reaction was carried out according to a literature procedure [30]. A microwave vial was charged with **29-*d*$_3$** (601 mg, 2.4 mmol, 1 equiv.), 20% DCl in D_2O (4 mL, 2.4 mmol, 1 eq.) and D_2O (8 mL). The vial was capped and heated to 180°C in a microwave reactor for 30 min. The mixture was then washed with 1 M NaOH and extracted into DCM (3 × 30 mL). The combined organics were washed with brine, dried over $MgSO_4$ and concentrated. Recrystallization from hot hexane yield **29-*d*$_3$** as a white crystalline solid (584 mg, 2.35 mmol, 98%). Deuterium incorporation as determined by ^{1}H NMR: D% *meta* = 97%, D% *para* = >99%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54–7.51 (m, 4H), 7.49–7.44 (m, 4H), 7.39–7.34 (m, 2H), 7.14 (s, 0.06H), 6.91 (s, 0.01H), 3.99 (br, 2H). **^{2}H NMR** (61 MHz, $CHCl_3$) δ 7.18, 6.95. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.3, 139.7, 129.5, 129.0, 128.3, 127.5, 118.7–117.6 (m). **GC–MS (EI)**: 248.2 ([M^+]). **M.p**: 85°C–87°C.

2,6-diphenyliodobenzene-*d3* **24-d$_3$**: The reaction was carried out according to an adapted literature procedure [23]. To a 25 mL round-bottom flask was added 2,6-diphenylaniline-d_3 (**29-*d*$_3$**) (584 mg, 2.35 mmol, 1 equiv.) and a stirbar. The solid was dissolved in toluene (1 mL) and cooled in an ice bath, then glacial acetic acid (5 mL) was added. The solution was stirred for 15 min, at which point a solution of $NaNO_2$ (324 mg, 4.70 mmol, 2 equiv.) in H_2O (0.5 mL) was added dropwise, yielding a yellow solution which was left to stir at 0°C for 30 min. After this time, a solution of KI (1.17 g, 7.05 mmol, 3 equiv.) in H_2O (1 mL) was slowly added dropwise, immediately causing the solution to darken with gas evolution. After addition was complete the reaction was allowed to stir at 0°C for 4 h, then at room temperature for 12 h. After this time, the reaction was slowly quenched with dropwise addition of sat. Na_2CO_3, then diluted with EtOAc (50 mL) and washed with $Na_2S_2O_3$ (2 × 20 mL), water (20 mL), and brine (20 mL). The organics were then dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography (1% DCM in hexane) of the crude and subsequent recrystallization from hot hexane yielded 2,6-diphenyliodobenzene-d_3 **24-d$_3$** as white needle-like crystals (447 mg, 1.24 mmol, 53%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47–7.36 (m, 10H), 7.27 (s, 0.05H). **^{2}H NMR** (61 MHz, $CHCl_3$) δ 7.40, 7.27. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.2, 145.8, 129.6, 128.1, 127.7, and 103.8. **GC–MS (EI)**: 359.1 ([M^+]). **M.p**: 110°C–112°C. Deuterium incorporation leads to splitting in ^{13}C NMR, leading to some peaks becoming lost in the baseline.

4.3 | General Procedure for the Reactions of Aryl Halides With KO^{t}Bu in Benzene

To an oven-dried 20 mL microwave vial, primed with a stirrer bar, in a glovebox was added the aryl halide (0.350 mmol, 1 equiv.), KO*t*Bu (79 mg, 0.7 mmol, 2 equiv.), and solvent (either C_6H_6 or C_6D_6, 3.5 mL). The vial was subsequently sealed with a PTFE/silicone crimp cap, removed from the glovebox and stirred at 130°C in a pre-heated oil bath for a given time. The crude mixture was then cooled to room temperature, then D_2O (0.2 mL) and an accurately weighed amount of a dodecane internal standard in EtOAc (5 mL) were added. An aliquot of the crude mixture was then analyzed by both GC–MS and GC–FID. The identity and yields of reaction products were determined by calibration against authentic samples (for calibration information, see Supporting Information, page S29).

Author Contributions

Seb Tyerman performed the laboratory experiments, **David. J. Nelson** performed the computational chemistry, and **Craig M. Robertson** and **John A. Murphy** supervised the work. All authors analyzed the results and contributed to the drafting of the paper and the Supporting Information file.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are openly available in Helvetica Chimica Acta at https://onlinelibrary.wiley.com/journal/15222675.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

The authors have cited additional references within the Supporting Information [31-38].

Supporting File 1: hlca70089-sup-0001-SuppMat.docx.

Supporting File 2: hlca70089-sup-0002-Data.zip.