

How Alkali Metal Alkoxides Initiate Organic Radical Reactions

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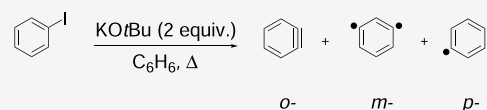
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ABSTRACT: Alkali metal alkoxides have long been known to cause hydrodehalogenation of aryl halides; this conversion of aryl halides to arenes happens when the reactions are conducted in appropriate solvents (with weak C–H bonds). More recently, when aryl halides are heated with alkoxides in arene solvents, coupling to arenes occurs. Both of these reaction types are known to involve aryl radical intermediates. The consensus has been that alkali metal alkoxides undergo electron transfer to aryl halides to form radicals, but crucial evidence has been missing. We now refute this proposal and show through deuterium isotope studies that the deprotonation of the substrates leads to benzyne that initiate radical chemistry. Surprisingly, *o*-, *m*-, *p*- and, in appropriate cases, *r*- (remote) benzyne are simultaneously formed. During reactions with potassium *tert*-butoxide, we observed for the first time low-level methylation of arenes, resulting from methyl radicals derived from *tert*-butoxide. Although methyl radicals could, in principle, arise by electron transfer from *tert*-butoxide ions, followed by known radical fragmentation, we show that a different, previously unreported mechanism applies.

Reaction affords isomeric benzyne



INTRODUCTION

Activation of aryl halides to convert the C–Hal bond to a C–H or C–C or C–heteroatom is central to organic chemistry. Conversion of aryl halides **1** to arenes **4** on heating with alkoxides **3** (Scheme 1A) has been reported since 1899.¹ In 1992, Bunnett reviewed known cases and proposed a radical mechanism for the propagation steps of the reactions but avoided any comment on the source of the radicals (i.e., the initiation of the reactions).² More recently, when aryl halides were heated with an alkali metal *tert*-alkoxide above 100 °C in an arene solvent, coupling to the arene was observed to give a biaryl. This type of coupling reaction is termed a base-promoted homolytic aromatic substitution (BHAS) reaction (Scheme 1B) and again proceeds through aryl radical intermediates. Thus, the two types of reactions, hydrodehalogenation and BHAS coupling, are linked by the reaction of alkali metal alkoxides with aryl halides and the formation of aryl radical intermediates.

Further studies on BHAS reactions showed that they are assisted by any of a wide range of additives. The reactions generally proceed in high yield.^{3–11} Propagation occurs when aryl radicals **2** add to arene **4** to give **7**. Deprotonation affords radical anion **8**, which donates an electron to another molecule of **1**, thereby propagating the chain and forming the product, biphenyl **9**.¹¹ We previously explored the role of the additives and showed that super electron donors **11**,^{12–14} formed *in situ* from additive **10**, can initiate these BHAS reactions.¹⁵ Additives other than **10** facilitate these reactions, e.g., **12–17**, and are converted *in situ* by KOtBu into strong organic electron donors that initiate the chemistry^{16–19} (Scheme 1C). Thus, it was clear for BHAS reactions that the formation of strong electron donor molecules facilitated the reaction by

converting the aryl halide substrates into aryl radicals through electron transfer.

But we also showed that a slower coupling of aryl halides to arenes can occur in the absence of additives, i.e., simply by the reaction of KOtBu **18** with the aryl halide in the presence of excess arene.¹⁵ Although not discussed in detail, the literature represents the reaction between KOtBu and an aryl halide as involving direct electron transfer from the alkoxide to the aryl halide, leading to a *tert*-butoxyl radical, an aryl radical, and a halide anion.^{7–9,20–26} However, alkali metal alkoxides are very poor electron donors. For example, for potassium *tert*-butoxide, $E_{\text{ox}} = +0.10$ V (vs. saturated calomel electrode (SCE) in dimethylformamide (DMF)),²⁷ while for Ar–I, $E_{\text{red}} \approx -2.3$ V (vs. SCE in DMF),²⁸ making outer sphere electron transfer from KOtBu to ArI impossible.²⁷

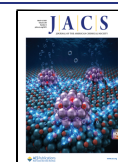
Besides the problem of incompatible redox potentials, another problem with proposing electron transfer from KOtBu as the route to the initiation of radical chemistry is the absence of evidence of methyl radicals in these reactions. If direct electron transfer from KOtBu to aryl halides occurred, the resulting *tert*-butoxyl radicals **19** would partition between hydrogen atom abstraction to form *t*BuOH **23** and fragmentation to acetone **20** and methyl radicals **21** (Scheme 2A).^{29–31} No evidence has been published of methyl radicals arising in these reactions (methyl radicals, generated by metal-

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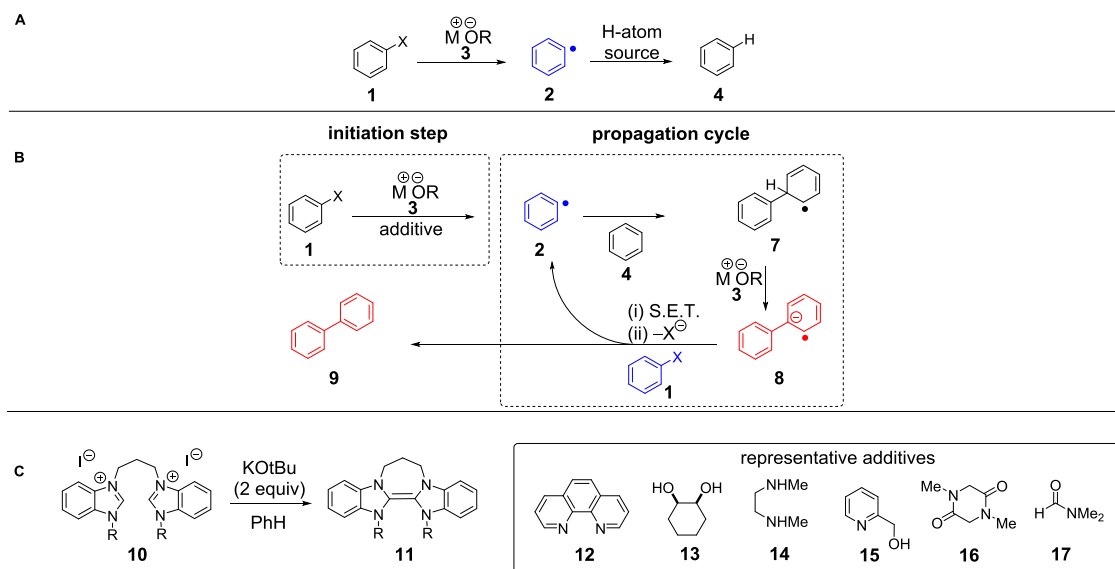
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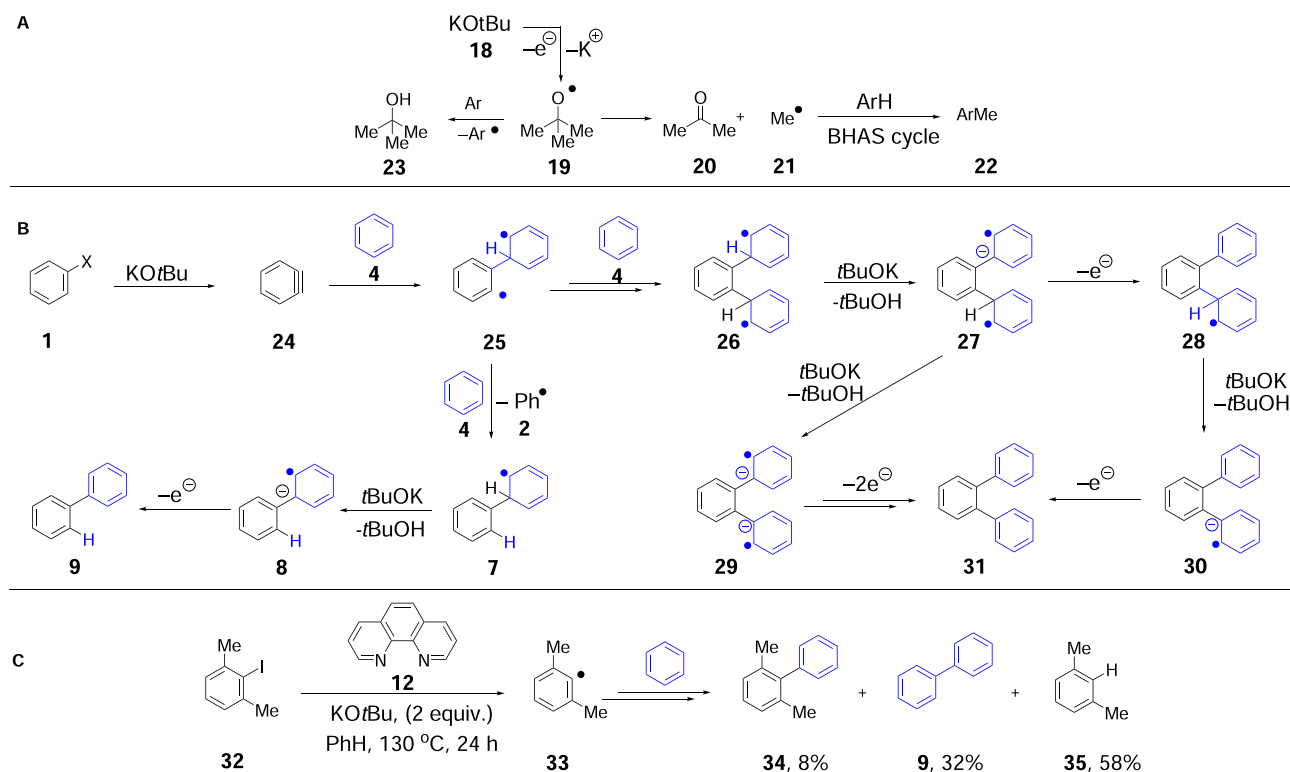
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Scheme 1. (A) Protodehalogenation of Haloarenes **1** to Arene **4**; (B) BHAS Coupling of Aryl Halide **1** to Form Biaryl **9**; and (C) Additives **10**, **12**–**17** React with KOtBu to Form Strong Organic Electron Donors



Scheme 2. (A) The Known Fragmentation of *tert*-Butoxyl Radicals **19**; (B) Potential Initiation of BHAS Coupling through Formation of *o*-Benzyne **24**; and (C) 2,6-Dimethyliodobenzene **32** as a BHAS Substrate



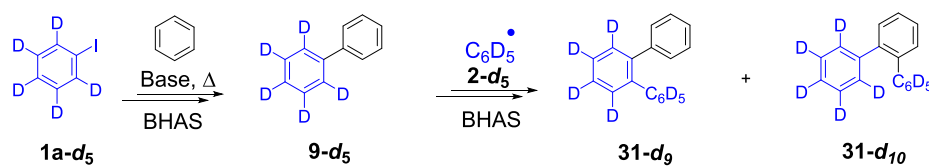
free methods from peroxides, are known to add to heteroarenes).^{32–37}

In 2014, we tentatively proposed an alternative initiation of BHAS reactions in the absence of recognized electron donors, through benzyne intermediates (Scheme 2B).¹⁵ Benzyne is known to form when aryl halides are treated with a strong base, and addition of benzyne to alkenes has been proposed to go through diradical intermediates.^{38–40} In principle, a similar addition to arenes might provide a source of radicals to initiate BHAS chemistry.¹⁵ But disruption of the aromaticity of two

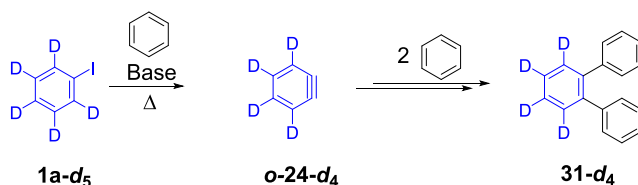
benzene rings by a ground-state *o*-benzyne to form products like **31** is unknown and would be very surprising.⁴¹ In our proposal, the addition of *o*-benzyne **24** to benzene **4** forms diradical **25**. This is both a reactive aryl radical and a less reactive cyclohexadienyl radical. The aryl radical could either add to benzene to form **26** or abstract an H atom from benzene to form **7**. Deprotonations and electron transfers would convert **7** and **26** to **9** and **31**, respectively. The electron transfer steps would activate substrate **1** as in Scheme 1B to allow the propagation of the reaction. Byproduct **31** emerging

Scheme 3. Using 1a-d₅ to Distinguish between Routes to *o*-Terphenyl 31

expected 1:1 mixture of *o*-terphenyls 31-d₉ and 31-d₁₀ not arising from benzyne-d₄



expected *o*-terphenyl 31-d₄ arising from benzyne-d₄



from the proposed initiation pathway has never been reported. That tallies with propagation being much faster than initiation, leading to very low concentrations of such byproducts.

To test the proposal, we reported the outcome of experiments with 2,6-dimethyliodobenzene **32**, which cannot form an *o*-benzyne.^{15,42} This hindered substrate affords lower yields of products, but hindrance is key to its role as an indicator of mechanism.⁴³ Using a suitable electron donor, formed from KOtBu and phenanthroline^{4,7,15} (Scheme 2C), coupling to benzene occurred, affording **34** via radical **33**. The alternative outcome for **33** was that it abstracted an H atom from benzene yielding **35**, and the resulting phenyl radical was added to benzene to form biphenyl **9** by a BHAS mechanism. Seeing these products reinforced the importance of electron transfer initiation of the reaction.

When the experiment was repeated without an electron donor,¹⁵ i.e., in the presence of KOtBu alone, we expected that the combined yield of coupled products, **34** + **9**, would be 0%. Although the combined yield dropped significantly from 42 to <1%, nevertheless, the fact that the coupled products **34** and **9** were still formed to any extent indicated that an additional mechanism for their formation was in play.

Returning to Scheme 2B, our motivation was to search for terphenyl byproduct **31** and to see if that might give evidence of the involvement of benzyne in the initiation process. If **31** could be identified, (i) it might simply arise through further BHAS reaction of phenyl radicals **2** with biphenyl **9**, or alternatively, (ii) it could arise from the reaction of benzyne **24** with two molecules of benzene solvent. The two routes might be distinguished by reacting deuterated iodobenzene, 1-d₅, with a base, in benzene as a solvent, and observing the products that are formed (Scheme 3). In this case, if labeled phenyl radicals 2-d₅ are produced, then they should routinely lead to labeled biphenyl, 9-d₅, through reaction with benzene solvent; reaction of another radical 2-d₅ with 9-d₅ would yield equal amounts of terphenyls 31-d₉ and 31-d₁₀. On the other hand, if the terphenyl arises from labeled benzyne 24-d₄ reacting with two molecules of benzene solvent, this would afford 31-d₄. As will be seen below, deuterium isotope studies provide strong evidence in support of *o*-terphenyl formation from *o*-benzyne **24**, but they will also provide evidence of simultaneous formation of *m*- and *p*-benzynes from iodobenzene as a substrate. Further important information about the regiochemistry of benzyne formation will then be explored using isotopologues of 9-bromoanthracene and 9,10-dibro-

moanthracene. Our strategy also involves studying the outcomes of such reactions with the deuterated solvent C₆D₆ and deuterated base KOtBu-d₉ to provide further important mechanistic information.

RESULTS AND DISCUSSION

Evidence of Benzynes

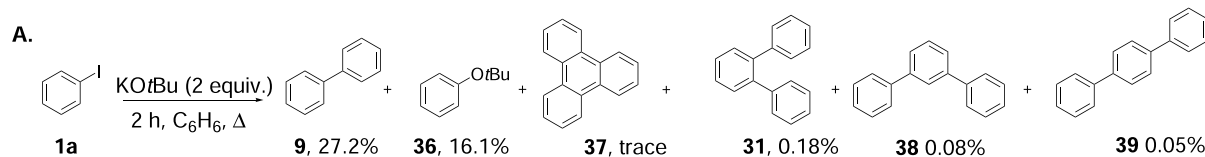
As mentioned in the Introduction, our study began with a search for terphenyl product **31** in the reaction of iodobenzene **1a** (X = I), with KOtBu in benzene as a solvent. This reaction afforded *tert*-butoxybenzene, **36** (16.1%), from attack by butoxide on benzyne and traces of triphenylene **37** from the trimerization of benzyne⁴⁴ (Scheme 4a). In addition, biphenyl **9** (27.2%) from the propagation steps in Scheme 1B starting material, and iodobenzene **1a**, X = I (36.7%), were quantified by gas chromatography-flame ionization detection (GCFID) or NMR. Three terphenyls, **31** (0.18%), **38** (0.08%), and **39** (0.05%), were also identified by GC mass spectrometry (GCMS) (see SI, pp S6–S10), quantified by GCFID, and correlated with authentic samples of *o*-, *m*-, and *p*-terphenyl (Scheme 4A).

These terphenyls might simply have arisen through the BHAS reaction of the standard propagation product of the reaction, biphenyl **9**, with further phenyl radicals in solution. However, this was disproved when the experiment was repeated with iodobenzene-d₅, where the deuteration patterns of the products revealed important information.

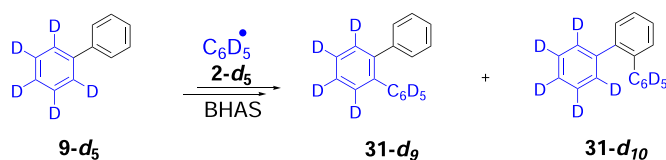
In this reaction, phenyl radicals 2-d₅ might react with the biphenyl formed in this reaction, i.e., 9-d₅; *o*-, *m*-, and *p*-terphenyls could form in this way. Scheme 4B focuses only on the *o*-terphenyl products and shows the two isotopologues that would arise. The radical attack of 2-d₅ can occur on either ring of the biphenyl, ultimately giving a ~1:1 mixture of *o*-terphenyls, 31-d₉ and 31-d₁₀. Likewise, d₉ and d₁₀ isotopologues would be seen for the *m*- and *p*-terphenyls. However, the observed labeling patterns were quite different; d₉ isotopologues were seen, but d₁₀ isotopologues were not seen. The other isotopologues seen were d₄ isotopologues. While both these d₄ and d₉ isotopologues were easily seen for the *ortho*- and *para*-isomers, **31** and **39**, the *meta*-case formed almost exclusively 38-d₉ (see SI, pp S14 and S15). Scheme 4C shows how they arise from benzyne intermediates.

First, we focus on *o*-benzyne, *o*-24-d₄. This led to the terphenyls 31-d₄ and 31-d₉. As shown in the inset, 31-d₄ would

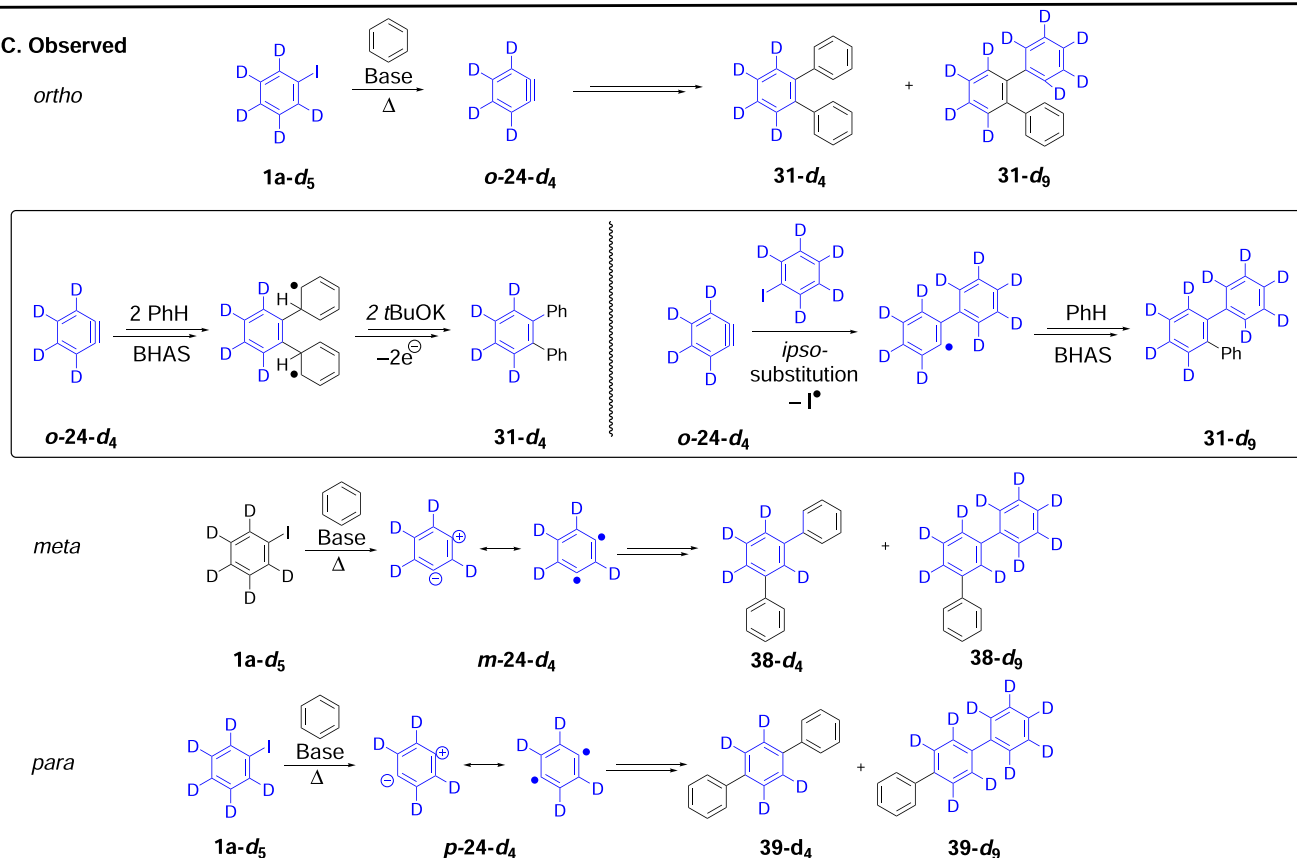
Scheme 4. (A) Products from the Reaction of PhI with KOtBu in PhH; (B) From Reaction of C₆D₅I with KOtBu in PhH, Terphenyls Might Arise from Attack of Phenyl Radicals 2-d₅ on Biphenyl Product 9-d₅;^a and (C) The Observed *o*-, *m*-, and *p*-Terphenyl Products and How They Arise from *o*-, *m*-, and *p*-Benzynes



B. The 2 isotopologues of *o*-terphenyl expected if no benzenes



C. Observed



^aOnly the *o*-terphenyl products expected **31-d₉** and **31-d₁₀** are shown here.

arise from sequential BHAS reactions with two benzene molecules. The route to **31-d₉**, on the other hand, would involve an *ipso*-substitution^{45,46} reaction on C₆D₅I, together with a BHAS reaction with PhH. Similar outcomes for the *m*- and *p*-terphenyls would fit with the proposal. Our experiment therefore surprisingly establishes that the terphenyl products formed in this reaction arise because *o*-, *m*-, and *p*-benzenes are being formed in solution. (*m*- and *p*-Benzenes may alternatively be referred to as “arenediyls” or as “dihydroarenes”, but we will use the benzyne terminology in this paper.)

These reactions also show the following:

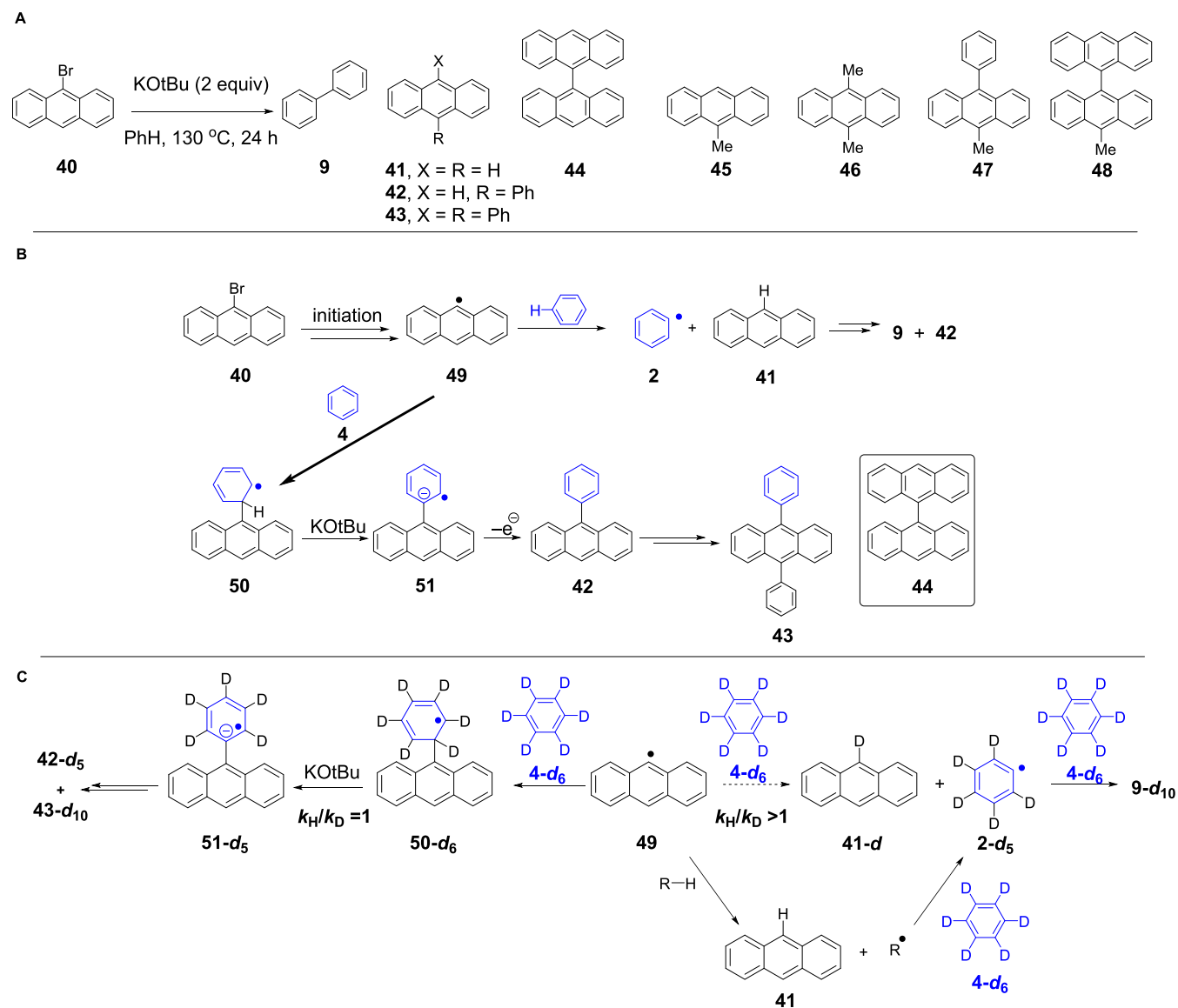
- (i) *m*- and *p*-benzenes are formed through base-treatment of a simple halobenzene (until now, only *o*-benzenes were

known to form in this way).⁴⁷ Perrin et al. have recently pioneered the nonradical chemistry of *p*-benzenes and widely investigated the reverse reaction, i.e., addition of halide anion to *p*-benzenes.^{48,49}

- (ii) Addition of a ground state *o*-benzyne to an arene, benzene, does indeed lead to products derived from diradical intermediates.^{50,51} Ground state *o*-benzenes do not routinely show diradical behavior with closed shell molecules, but recent results showed that they can be attacked by persistent radicals like TEMPO.^{52,53}

Haloanthracene Substrates

Having observed that the deprotonation of iodobenzene could occur at *ortho*, *meta*, and *para*-sites to lead to *o*-, *m*-, and *p*-

Scheme 5. (A) Reaction of 9-Bromoanthracene, 40; (B) Formation of the Non-methylated Products from 9-Bromoanthracene 40; and (C) Expected Reactions of Radical 49 with C₆D₆^a

^aIn the actual experiment, the product anthracene 41 was unlabeled.

benzynes, we were keen to explore the regiochemistry of deprotonation of other substrates, namely, 9-haloanthracenes 40, 40^{Cl}, and 40^I that cannot form *o*-benzynes (Scheme 5A). 9-Iodoanthracene 40^I and 9-bromoanthracene 40 reacted most efficiently, while 9-chloroanthracene 40^{Cl} was less reactive (see SI, pp S59–S68).⁵⁴ For these substrates, while *o*- and *m*-benzynes cannot form, a *p*-benzyne could be possible. Focusing on the reaction with 9-bromoanthracene, this afforded anthracenes 41–44, as well as biphenyl 9, as detailed below. Notably, methylated compounds 45–48 were also identified (Scheme 5A and see SI, p. S25).

The methylated products will be discussed below, while Scheme 5B illustrates the formation of the other products. 9-Anthracenyl radical 49 could (a) abstract an H atom from benzene to afford anthracene 41 and a phenyl radical 2 or (b) add to benzene 4 (shown) or to anthracene 41 (not shown) by the BHAS mechanism or to bromoanthracene 40 by *ipso*-substitution of the bromine atom (not shown) to afford 9-

phenylanthracene 42 and 9,9'-bianthracene 44 (inset in Scheme 5B), respectively. In turn, further BHAS reaction of phenylanthracene 42 with phenyl radical 2 would form diphenylanthracene 43, while 2 and 41 undergo further reactions to form products 9 and 42.

Isotope Effects with 9-Bromoanthracene 40

The above reaction of 40 in C₆H₆ was repeated under identical conditions in a side-by-side reaction in C₆D₆ as a solvent. First, we describe what was expected when the anthracenyl radical 49 reacts with C₆D₆ in relation to isotope effects. Two possibilities exist:

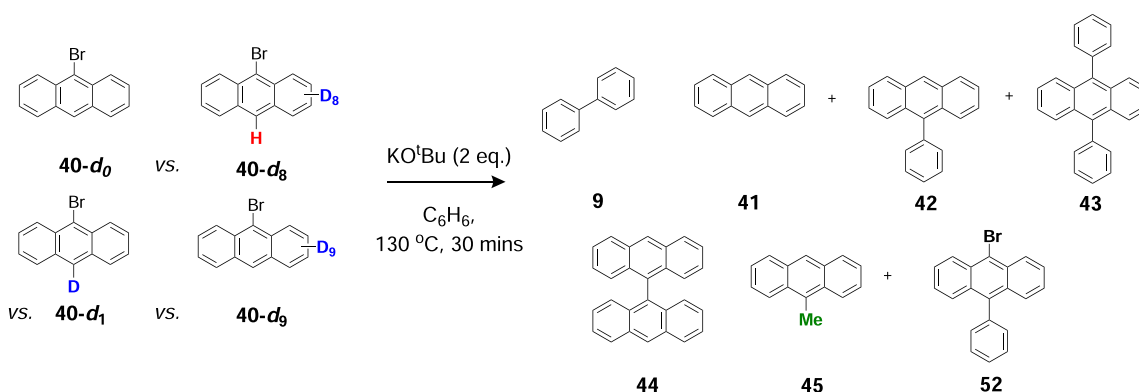
- The radical adds to C₆D₆ to form arylcyclohexadienyl radical 50-d₆ and this undergoes loss of D⁺ to afford 51-d₅ en route to products (Scheme 5C). Deprotonations of cyclohexadienyl radicals (like 50) to form cyclohexadienyl radical anions in BHAS chemistry are known not to be rate-determining steps.^{7,23,55}

Table 1. Reactions of 40 Using Isotopologues of the Solvent and KOtBu

$$40 \xrightarrow[\text{C}_6\text{H}_6, 130^\circ\text{C}, 24\text{ h}]{\text{KOtBu (2 equiv)}} \text{products}$$
 see table for variations in conditions

entry	conditions	40	9 or 9- <i>d</i> ₁₀ ^b (%)	41 (%)	42 or 42- <i>d</i> ₅ ^b (%)	43 or 43- <i>d</i> ₁₀ ^b (%)	44 (%)	45 or 45- <i>d</i> _n (%)
1 ^a	KOtBu, C ₆ H ₆	0	28.2	39.2	20.4	1.4	5.8	3.2
2 ^a	KOtBu, C ₆ D ₆	0	5.2 ^b	20.4	20.1 ^b	0.4 ^b	6.8	6.2
3	KOtBu- <i>d</i> ₉ , C ₆ H ₆	0	26.8	29.0	18.9	1.5	4.7	0.7 ^b
4	KOtBu- <i>d</i> ₉ , C ₆ D ₆	0	5.0 ^b	8.3	18.1 ^b	0.4 ^b	3.8	2.5 ^b

^aReactions were conducted in triplicate (entry 1) and in duplicate (entry 2). ^bIndicates deuterated product.

Table 2. Reactions of Isotopologues of 40 with C₆H₆ and KOtBu

entry	substrate	% yield ^{a,b}							
		40	9	41	42	43	44	45	52
1	40- <i>d</i> ₀	45.1	12.4	17.6	7.1	0.5	2.0	1.7	0.8
2	40- <i>d</i> ₁	65.2	5.7	8.7	3.3	0.2	1.1	0.9	0.5
3	40- <i>d</i> ₈	75.7	2.2	3.5	1.4	0.1	0.5	0.4	0.2
4	40- <i>d</i> ₉	81.0	1.8	2.8	1.1	0.1	0.3	0.3	0.2

^aIsotopologue yields determined using GC/FID calibrations for nondeuterated compounds. ^bReactions were performed in triplicate; averaged values are presented in this table.

- (ii) The radical abstracts a D atom from C₆D₆. This would form 41-*d* together with a C₆D₅ radical, 2-*d*₅. This breaking of an Ar–D bond is a kinetically challenging step in BHAS chemistry and would give rise to a primary deuterium isotope effect.⁴³

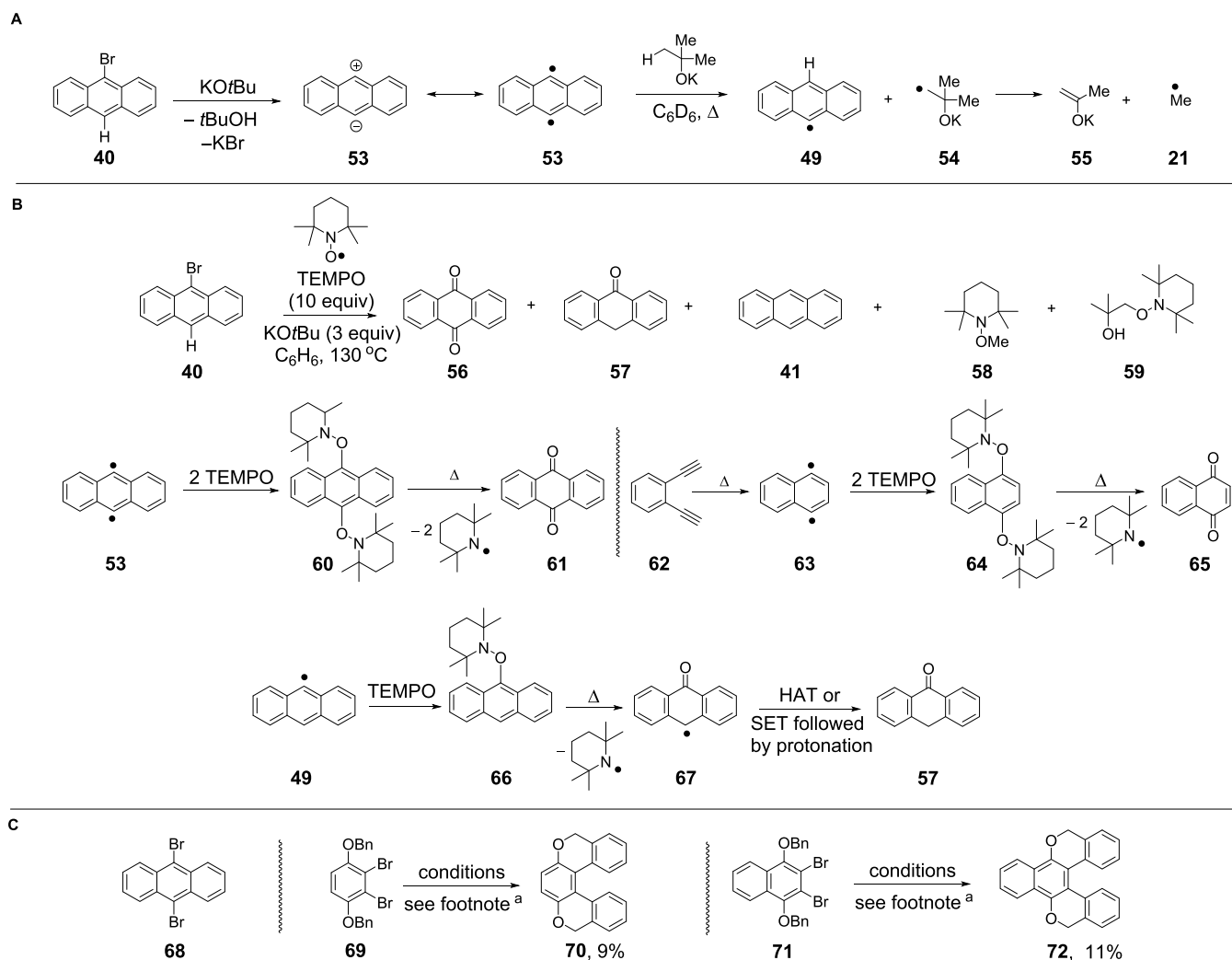
The results are shown in Table 1, entries 1 and 2. Similar products were formed in both reactions, but the labeled products that formed in C₆D₆ were 9-*d*₁₀, 42-*d*₅, and 43-*d*₁₀. Unlabeled anthracene 41 was formed in that reaction rather than 41-*d*. This implies that 49 abstracts an H atom from a source, R–H, other than deuterobenzene 4-*d*₆, and that the resulting radical is responsible for the subsequent formation of the phenyl radical, 2-*d*₅. The nature of R–H is discussed later in this paper.

The amount of biphenyl 9-*d*₁₀ produced from the C₆D₆ reaction was greatly decreased compared to that of the corresponding compound in C₆H₆ (28.2 → 5.2%), reflecting that the formation of biphenyl 9 was occurring through the

expected BHAS process. The amount of phenylanthracene 42-*d*₅ produced remained constant relative to its isotopologue in the C₆H₆ reaction (20.1 → 20.4%), which would be expected, as no kinetic isotope effect (KIE) should be associated with the deprotonation of radical 50. The same applies to the formation of bianthracene 44 (entries 3 and 4 of Table 1 will be discussed later).

Further information was gathered by preparing a range of selectively deuterated isotopologues of 40, namely, 40-*d*₁, 40-*d*₈, and 40-*d*₉, and comparing their reactivity with that of undeuterated 40. In these experiments, the duration of the reaction is shorter (30 min) to ensure that none of the substrates is fully converted into product and hence that the differences in their reactivity are evident. The substrates were tested under identical conditions in side-by-side reactions (*d*₀, *d*₁, *d*₈, *d*₉) (Table 2).

The results show that an increasing level of deuteration in 40 slows the reaction. The amount of the particular isotopologue

Scheme 6. (A) A Role for KO t Bu in Hydrogen Atom Transfer (HAT) Reactions; (B) TEMPO Studies; and (C) Double BHAS Reactions on Substrates 68, 69, and 71^a

^aConditions: KO t Bu (2 equiv), PhH, 130 °C, 24 h.

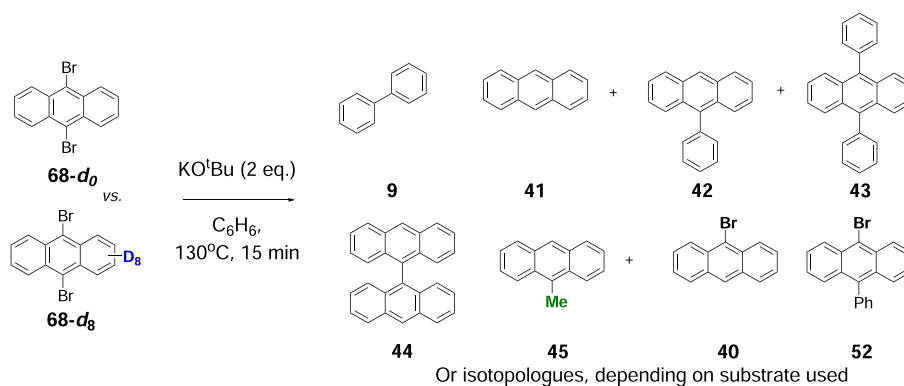
of 9 (or of anthracene 41) formed in each experiment represents the radical flux. Comparing experiments in Table 2 (entries 1 and 2) shows that the yield of 9 from 40- d_1 (5.7%) is significantly lower than that from 40- d_0 (12.4%). This shows that the amount of phenyl radical being produced in these reactions is dependent on the C–H/C–D bond in the 10-position of the anthracene. This is not at all consistent with the radical chemistry being driven by single electron transfer (SET) from KO t Bu 18 (Scheme 2A). Instead, it suggests that removal by KO t Bu of H⁺/D⁺ from this C–H/C–D bond controls the level of initiation of radical chemistry. This makes sense if this step is followed by the loss of a bromide anion affording a *p*-benzyne. More surprising information emerges from the reactions of the d_8 and d_9 isotopologues (entries 3 and 4), which have progressively stronger inhibitory effects. This shows that breaking the C–H at sites other than at position 10 also contributes to the flux of radical chemistry. This suggests that the site of deprotonation and loss of halide do not need to be on the same ring, i.e., that “remote benzyne” (“distal diradicals” resulting from loss of HBr from substrates; we suggest that distal diradicals is the better term) can also trigger these reactions.

Explaining the Methylated Products

Now returning to consider the methylated products from Scheme 5A, the structure of methylanthracene 45 was confirmed by ¹H NMR and by high-resolution MS (HRMS), and its retention time on GCMS was confirmed by comparison with that of authentic 9-methylanthracene. The positions of the methyl groups in the other methylated products 46–48 have not been determined but are proposed by analogy to 45. These compounds arise through the BHAS reaction of methyl radicals 21 with the anthracenes present in the reaction mixture. Methyl radicals might arise through fragmentation of *tert*-butoxyl radicals 19, which, in turn, might form following electron transfer from KO t Bu 18 (Scheme 2A), and so SET from KO t Bu seemed at least a possible explanation.

Comparing the reactions conducted in C₆D₆ versus C₆H₆ (Table 1), the amount of 9-methylanthracene 45 formed in C₆H₆ was much lower compared to the reaction in C₆D₆ (3.2 vs 6.3%). If *tert*-butoxyl radicals 19 were present and were fragmenting as in Scheme 2A, this could explain the data. In C₆H₆, the methyl radicals would (i) add to anthracenes or (ii) abstract an H from the solvent in a defined ratio. In C₆D₆, it would be more difficult to abstract a D atom, resulting in a

Table 3. Reaction of 9,10-Dibromoanthracene



entry	substrate	% yield ^a								
		68	9	40	41	42	43	44	45	52
1	68- <i>d</i> ₀	41.0	19.1	22.1	0.7	2.4	0.4	3.7	0.4	3.7
2	68- <i>d</i> ₈	85.1	2.8	4.1	0.0	0.3	0.0	0.0	0.0	4.1

^aIsotopologue yields determined using GC/FID calibrations for nondeuterated compounds.

higher percentage of addition to anthracenes. However, please note that an alternative rationale for this chemistry is provided below.

As mentioned above, the anthracene **41** generated from the reaction of 9-bromoanthracene **40** with KOtBu in C₆D₆ was unlabeled, suggesting KOtBu as the most likely source of the abstracted H atom. To investigate this, KOtBu-*d*₉ was used in a repeat experiment (Table 1, entry 3; spectra pp S38–S40). Treatment of 9-bromoanthracene **40** with KOtBu-*d*₉ in C₆H₆ still led to the formation of unlabeled anthracene **41**, suggesting that, in this case, the hydrogen atom transfer (HAT) is solely or predominantly occurring from the solvent. That would mean that the selectivity for abstraction of an H versus a D atom was good, with KOtBu being used as a source of HAT when the solvent is C₆D₆, and C₆H₆ being used when KOtBu-*d*₉ is the base. In view of this, we reacted **40** with a combination of C₆D₆ and KOtBu-*d*₉, which yielded predominantly anthracene **41-d**₁ along with undeuterated anthracene (Table 1, entry 4; spectra pp S41–S43). The undeuterated anthracene component shows that intermolecular hydrogen abstraction from anthracene C–H bonds competed with the abstraction of C–D from KOtBu-*d*₉ and C₆D₆. In this case, when faced with both deuterated reagents, then labeling did indeed occur; the yield of the anthracene was significantly decreased compared to the parent reaction (entry 1) with KOtBu in C₆H₆ (39.2 → 8.3%).

The information that KOtBu is used for hydrogen atom transfer (HAT) by the aryl radicals is very important and it raises the question of what happens to the product radicals **54** (Scheme 6A). The answer to that comes from comparing entries 1 and 3 or 2 and 4 in Table 1. Comparing entries 1 and 3, we see that using C₆H₆ as the solvent and changing from KOtBu to KOtBu-*d*₉ decrease the amount of methylanthracene isotopologue **45** 4-fold (3.2 → 0.7%). This results from a 4-fold decrease in the flux of methyl radicals. This number represents a primary kinetic isotope effect associated with C–H/C–D bond cleavage in KOtBu in the rate-determining step (Scheme 6A). That is completely inconsistent with the picture shown in Scheme 2A. There, the reactions would simply involve electron transfer from KOtBu or KOtBu-*d*₉ to substrate **40**. This could involve a minor quantitative change but far

smaller than what is seen here. Similarly comparing entries 2 and 4 in Table 1 shows that a primary deuterium isotope effect is evident. A primary deuterium isotope effect would align with HAT from KOtBu by diradicals **53** (or aryl radicals) and fragmentation of the resulting alkyl radical **54** to afford methyl radicals **21** and the potassium enolate of acetone, **55**. Computational studies show that both the hydrogen atom abstraction from potassium *tert*-butoxide and the fragmentation of the resulting radical are easily achieved under the reaction conditions (see pp. S144–S146). That therefore means that electron transfer from KOtBu was NOT driving the reaction, but rather that formation of anthracenyl radicals **49** controls the formation of methyl radicals **21**, in line with our other evidence for the role of benzynes.

Turning now to results in Table 2, the yield of 9-methylanthracene **45** also decreases with an increasing level of deuteration of the bromoanthracene substrate. Again, this is completely inconsistent with the electron transfer from KOtBu. If that were controlling the initiation, then no notable change in the level of initiation would be expected with the different isotopologues. Instead, the level of radical flux is controlled by the speed of the removal of HBr/DBr from the substrate by KOtBu.

TEMPO Studies

Given the role of radicals in these reactions, we next used TEMPO to probe the intermediates (Scheme 6B). When bromoanthracene **40** was heated with KOtBu in benzene in the presence of TEMPO, this led to products including anthraquinone **56** and anthrone **57** in addition to TEMPO-trapped products **58** and **59**. Anthraquinone arises by thermolysis of bis-TEMPO intermediate **60**, which, in turn, comes from trapping of the *p*-benzyne **53** from the initiation of the reaction. This has clear direct analogy in the literature when Bergman cyclization of *o*-benzenediyne **62** led to formation of naphthalen-1,4-diyl **63**; the initial bis-TEMPO-trapped intermediate **64** thermolyzed *in situ* to afford *p*-naphthoquinone **65**.⁵⁶ The anthrone **57** formed in our experiment would similarly form from thermolysis of **66**, which in turn arises from trapping anthracenyl radical **49**.

Studies with Different Bases

Given the outcome of the experiments of 9-bromoanthracene with KO t Bu in C₆H₆, we also explored a number of variants that are detailed in the SI (pp S45–S59). The reaction worked well when KOEt was used, establishing that the reaction was not confined to KO t Bu as the base (see SI). This was important because it showed that nontertiary alkoxides promote this reaction. Unlike *tert*-butoxide, ethoxide contains weak H–CO bonds that can quench aryl radicals, and so, in this case, quenching of anthracenyl radicals to form anthracene, a hydrodehalogenation reaction, was more prevalent than in reactions with KO t Bu. The hydrodehalogenation reactions reviewed by Bunnett² invariably used primary or secondary alkoxides and this therefore links the mechanism for radical formation in those reactions to our observations on BHAS reactions here.

When KOEt₃ was used instead of KO t Bu, the reaction was again successful. As expected, KOEt₃ afforded traces of ethylated products rather than the methylated products seen with KO t Bu. No reaction was seen with NaO t Bu or LiO t Bu, but this may have been due to the low solubility in benzene. Adding 15-crown-5 to the NaO t Bu experiment allowed conversion to the expected products, including the BHAS products. 15-Crown-5 is an excellent H atom donor, and so anthracene **41** was the major product in this case (see pp S50–S52). A control reaction using KO t Bu (but carried out while in darkness (under foil)) also afforded the products seen under normal daylight conditions, so the reaction was not light-dependent.

Dihalo-Substrates

Having studied the reactivities of monohalo substrates, we then explored the reactivity of three dibromo substrates **68**, **69**, and **71** (Scheme 6C). 9,10-Dibromoanthracene **68** was of interest because benzyne-type activation of this substrate specifically could only be achieved by deprotonation at a site remote from the C–Br bonds (i.e., not *o*-, *m*-, or *p*- to these bonds). Here, we compared the reaction of the parent to the reaction of its *d*₈-isotopologue (Table 3). Side-by-side reactions (15 min) of the two isotopologues were conducted under identical conditions. The yield of **9** dropped from 19.1% in the parent substrate to 2.8% in the deuterated substrate. This provides strong backing to the generality of the benzyne activation in this case, where no *o*-, *m*-, or *p*-benzyne can form. In this case, deprotonation at the periphery must lead to an “*r*-benzyne” (or “*r*-diyl”).

The remaining substrates that we discuss here are vicinal dibromides **69** and **71**. These substrates were interesting as *o*-dibromides that offered opportunities for intramolecular BHAS reactions. In **69**, deprotonation can occur at *m*- and *p*- to the bromides, while in **71**, deprotonation at a remote ring site is needed. Comparing the outcomes allows for an assessment of any penalty in **71** for requiring deprotonation in a remote ring. The complex multistep reactions lead to similar yields, suggesting that the need for remote deprotonation does not necessarily impede the reaction.

CONCLUSIONS

The route by which base-treatment of haloarenes affords aryl radicals, which has puzzled chemists since 1899, is now revealed.

- (i) Deuterium labeling establishes that treatment of iodobenzene with KO t Bu in benzene affords simulta-

neously *o*-, *m*-, *p*-benzynes through deprotonation and loss of halide anion but, starting from C₆D₅I, the formation of specifically deuterated *o*-, *m*-, and *p*-terphenyl products shows that each type of benzyne is able to trap two benzenes regiospecifically through radical reactions and thereby they act as initiators of radical chain chemistry. As initiators, they only need to be present in minute quantities.

- (ii) A study of specifically deuterated haloanthracenes shows that base-induced removal of H⁺/D⁺ does not need to occur in the ring that bears the halogen substituent but can happen in a neighboring ring, thereby giving rise to distal diradicals that are effectively “*r*-benzynes” (remote benzynes).
- (iii) When KO t Bu is used as a base, low levels of methylated arenes are also formed that arise from methyl radicals. These are generated when aryl radicals or diradicals abstract an H atom from a C–H bond in KO t Bu and the resulting carbon radical undergoes a previously unreported fragmentation.

The results are completely at odds with suggestions that KO t Bu acts as an electron donor to haloarenes. They rationalize the initiation pathway for the protodehalogenations observed since 1899 as reviewed by Bunnett.²

Wider Applications?

Questions arise about how widespread our observations may prove to be. Clearly, any case in which alkoxides encounter aryl halides could lead to benzynes that trigger further reactions. Some colleagues report on preferences for sodium alkoxides over potassium alkoxides as bases in synthetic transformations such as Buchwald–Hartwig aminations. It may be that potassium alkoxides are more effective bases on aryl halides and promote byproducts to a greater extent, but this would require detailed analysis. The role of alkoxides in deprotonating arenes is not necessarily confined to aryl halides but can also be manifested in other arenes that may be subject to deprotonation.

One case in which KO t Bu was suggested to act as an electron donor to a surprising substrate was reported by Lei and Jutand. They showed that the reaction of KO t Bu $E_{ox} = +0.10$ V (vs. SCE in DMF)²⁷ with phenanthroline $E_{red} \approx -2.06$ V (vs. SCE in DMF) afforded radical anions derived from phenanthroline. They proposed that electron transfer from KO t Bu was taking place despite the large gap in potentials. We proposed an alternative explanation, where deprotonation of phenanthroline by KO t Bu led to an electron-rich dimeric product and, in turn, to formation of radical anion organic electron donors.^{15,57} The take-home message is a reassuring one, that KO t Bu is a notably poor electron donor in its ground state^{58–60} and that its radical-forming properties derive from its ability to deprotonate aryl halides and to convert them to benzynes/arenediyls, or to deprotonate other arenes.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.5c22122>.

Experimental procedures and spectroscopic data in support of the results are reported; X-ray data for compound **69** are available (Database ref number is

CCDC 2211274) Computational data underpinning this study can be downloaded from the ioChem-BD database^{61,62} at the following URL: <https://doi.org/10.19061/iochem-bd-6-628> (PDF)

Accession Codes

Deposition Number 2211274 contains the supporting crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe [Access Structures service](#).

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Notes

Traces of acetonylantracene were detected. The potassium enolate of acetone can undergo easy abstraction of an H atom, and the resulting radical may react to form acetonylantracene or the enolate could undergo electron transfer to the aryl halide (see [pp S45 and S46](#)).

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