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# Organic super-electron-donors: initiators in transition metal-free haloarene–arene coupling†

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Recent papers report transition metal-free couplings of haloarenes to arenes to form biaryls, triggered by alkali metal *tert*-butoxides in the presence of various additives. These reactions proceed through radical intermediates, but understanding the origin of the radicals has been problematic. Electron transfer from a complex formed from potassium *tert*-butoxide with additives, such as phenanthroline, has been suggested to initiate the radical process. However, our computational results encouraged us to search for alternatives. We report that heterocycle-derived organic electron donors achieve the coupling reactions and these donors can form *in situ* in the above cases. We show that an electron transfer route can operate either with phenanthrolines as additives or using pyridine as solvent, and we propose new heterocyclic structures for the respective electron donors involved in these cases. In the absence of additives, the coupling reactions are still successful, although more sluggish, and in those cases benzynes are proposed to play crucial roles in the initiation process.

## Results

An explosion of interest has arisen in dehalogenative couplings between haloarenes and arenes to form biphenyls under transition metal-free conditions[1–28] since the original report of coupling of iodobenzene with pyridine and pyrazine by Itami in 2008.[1] The excitement is easily understood, since these reactions avoid the use of costly complexes of palladium, which are the normal catalysts. A common feature of the recent reactions is the use of sodium or potassium *tert*-butoxide as base. The absence of any significant contamination with transition metals like palladium,[1,2] together with the properties of the new coupling reactions, has led to a general consensus that the reactions proceed by aryl radical intermediates.[1,6] The corollary coupling between haloarenes and styrenes, also triggered by alkali metal butoxides,[3,7,12] likely follows the same route.

The general case for a radical mechanism was well summarised in an essay by Studer and Curran[9] and an attractive proposal from that source is shown in Fig. 1A. Here, the aryl radical **2** adds to benzene to form the arylcyclohexadienyl radical **3**. Deprotonation by butoxide affords the radical anion **4**, which transfers an electron to aryl halide **1**, thereby forming biaryl **5** together with a new aryl radical **2**, ensuring the propagation of the chain. The outstanding question relates to how the initial radical **2** is generated, *i.e.* the initiation mechanism, and that is the subject of this paper.

With so many reports emerging in this area, our attention focused on four particular literature protocols that feature heterocycles as additives or substrates or solvent: (a) the Itami report[1] showed arylation of pyridine and pyrazine **7** (Fig. 1B); (b) thorough investigations by Shi and coworkers[2] and by Shirakawa, Hayashi *et al.*[6] led to intermolecular arylation of benzenes to form biphenyl **9** and analogues in the presence of phenanthrolines; (c) the team of Chen and Ong[15] showed similar success in the presence of *N*-heterocyclic carbenes, while (d) Charette[26] led the breakthrough in discovering that cyclisations, for example of substrate **10**, were significantly assisted by pyridine as solvent. Other additives have also proved useful in coupling reactions by other research groups, such as diamines,[5,25] proline,[13,21] pyridinium carboxylates,[13] porphyrin,[19] diols,[5,23] alcohols,[28] a macrocyclic pentapyridone,[24] an unusual heterocycle[11] and MOFs.[14] Although iodoarenes are used most widely in the studies, bromoarenes[2–7,13,14,18–20,24,26–28] and chloroarenes[5–7,18,23,27] have also been often used.

A number of authors have suggested that electron transfer from a complex of NaO*t*Bu or KO*t*Bu with a 'ligand' would lead to electron transfer to an aryl halide like iodobenzene.[2,3,6] Our starting point was to examine the thermodynamics for the basic electron transfer reaction between a phenanthroline complex of sodium *tert*-butoxide **12a** and iodobenzene **6** as presented in the literature.[6] The free energy change for formation of the products **13a** and **14** and iodide ion from **12a** and **6** is $\Delta G = +63.9$ kcal mol$^{-1}$,

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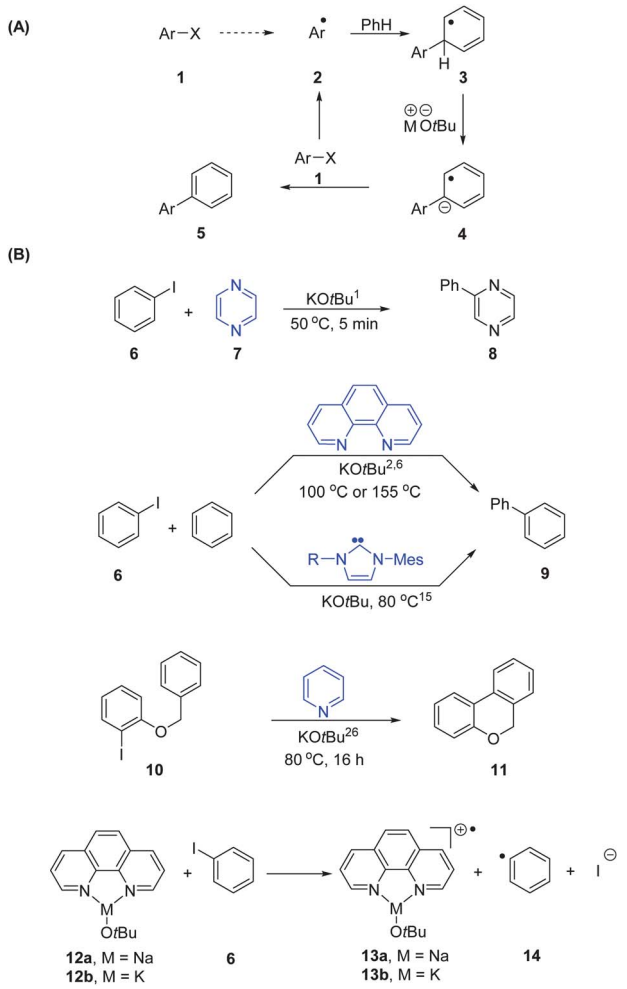


**Fig. 1** (A) Radical mechanism proposed by Studer and Curran.[9] (B) Dehalogenative couplings between halobenzenes and arenes.

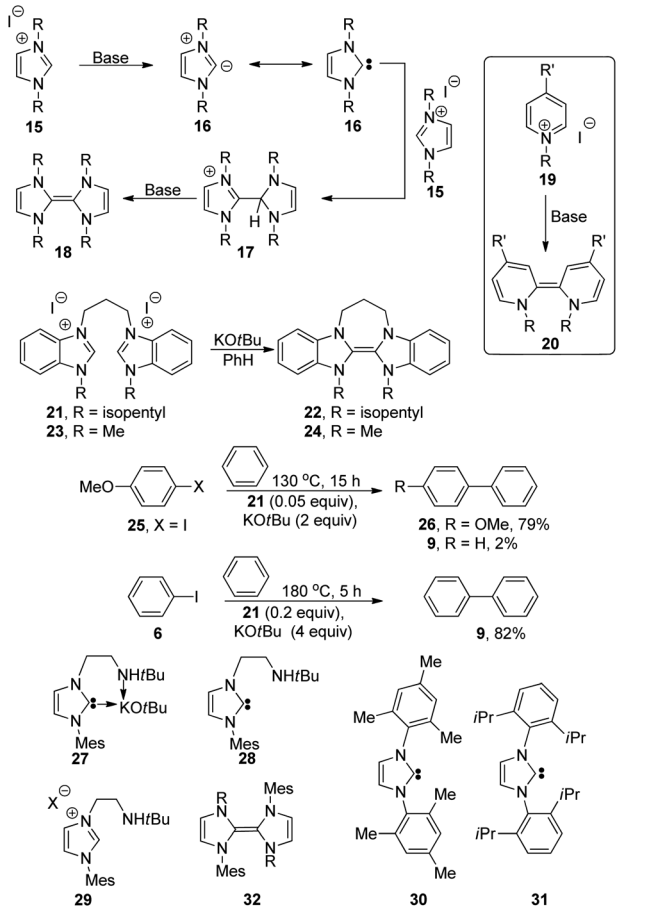


**Fig. 2** *N*-Heterocyclic carbenes and derived electron donors.

when calculated at the M06L/6-311G(d,p) level of theory using the CPCM continuum solvation method to incorporate the polarizing effect of the benzene solvent. The corresponding value for the analogous potassium case is $\Delta G = +59.5$ kcal mol$^{-1}$ (see ESI file for details†). These numbers were sufficiently large to give us grave concerns about radical initiation by this method. Of course, other unknown complexes of alkali metal *tert*-butoxides, for example involving aggregates rather than a single metal alkoxide, may be associated with less unfavourable thermodynamics for electron transfer, but the calculated values were sufficiently endergonic that they suggest other role(s) for the heterocycles that are highlighted in blue in Fig. 1B. Our findings apply to ground-state chemistry; more recently, Rossi *et al.* have reported photoactivation in the coupling of haloarenes to arenes.[27] Photoactivation can achieve remarkable transformations, and we await further information on the mechanisms of those transformations.

We have recently shown[29–34] that aryl iodides can be activated to form aryl radicals, and even aryl anions, in the presence of organic electron donors derived from pyridines and imidazoles. This raised an initial question of whether our electron donors could trigger haloarene–arene coupling reactions. Imidazolium salts **15**[29,30,32,35,36] can be deprotonated with strong bases like sodium hydride to form imidazolylidenes **16** (Fig. 2). Reaction between an imidazolylidene and an imidazolium salt **15** leads to C–C bond formation, and deprotonation of the intermediate by NaH affords intensely yellow electron donors **18**. In like manner, pyridinium salts *e.g.*, **19** were converted into bipyridinylidenes **20**, which are strong electron donors that can reduce halobenzenes.[31] However, the formation of these electron donors had not been demonstrated with metal butoxides as base nor in benzene as solvent. To this end, *N*-isopentylbenzimidazolium salt **21** was treated with potassium *tert*-butoxide in benzene, immediately affording the vibrant yellow solution characteristic of the bibenzimidazolylidene donor **22**. In this case, **21** was selected rather than our previously used salt **23**,[29] because of our finding that the solubility of **24** was not high in benzene. As will be seen below in later experiments, where lower concentrations of disalt were employed, **23** was used then with no difficulty.

## Super-electron-donors (derived from 21 and 23) as initiators, and the relevance to *N*-heterocyclic carbenes as additives

Test reactions were then performed in benzene as solvent with salt **21** and KO*t*Bu, using (a) *p*-iodoanisole **25** and (b) iodobenzene **6** as substrates, to explore possible coupling with benzene. Heating *p*-iodoanisole **25** with **21** (5 mol%) and KO*t*Bu

(2 equiv.) in benzene at 130 °C for 15 h afforded the desired 4-methoxybiphenyl **26** (79%), together with biphenyl **9** (2%). [Similar observations of small amounts of biphenyl in transition metal-free coupling reactions of substituted iodobenzenes with benzene have been made by Kappe and coworkers[17] and will be discussed below.] Likewise, heating iodobenzene **6** at 180 °C for 5 h with **21** (20 mol%) and KO*t*Bu (4 equiv.) in benzene and 130 °C for 3.5 h afforded biphenyl, **9**, in very good yield (82% and 72% respectively). [Whereas these conditions were effective for coupling iodoarenes, bromobenzenes reacted very sluggishly. Thus reacting 4-bromotoluene with **23** (20 mol percnt;) and KO*t*Bu in benzene at 185 °C for 2.5 h afforded 4-methyl-1,1′-biphenyl (3%, not shown in scheme). This lower reactivity with aryl bromides mirrored our prior reactions of benzimidazole-derived donors[29] with halobenzenes.]

These findings are consistent with our previous chemistry of neutral organic electron donors. Our results may have particular relevance to the findings of Chen and Ong,[15] who proposed that a complex **27** (Mes = 2,4,6-trimethylphenyl) between potassium butoxide and *N*-heterocyclic carbene **28**, which derives from imidazolium salt **29** on treatment with KO*t*Bu, could undergo electron transfer to an iodobenzene as part of the reaction mechanism for its coupling to benzene. They reported that carbenes **30** and **31**, substituted by two bulky substituents led to very poor yields, while carbene **28** bearing one bulky substituent and one much less bulky substituent, operated very successfully. They attributed this success to the fact that the less bulky substituent in **28** featured an amine unit that might help to complex the metal, forming **27** and facilitating electron transfer, but an alternative interpretation would be that this substituent permitted the formation of the recognized super-electron-donor skeleton within **32** (R = *t*BuNHCH$_2$CH$_2$); formation of analogous structures from **30**, **31** would be much more difficult for steric reasons.

Studer and Curran[9] had proposed that radical generation might be required simply to initiate the reaction and that a chain reaction might then be sustained through electron transfer from an arene radical anion **4**. In line with this, iodobenzene was heated at 180 °C in benzene for 6 h with KO*t*Bu (3 equiv.) and decreasing amounts of salt **23** (0.1 equiv., 0.05 equiv. and 0.01 equiv.); biphenyl **9** was still formed in 65%, 67% and 73% yield respectively, consistent with the proposal that these electron donors are important simply for initiation of the radical process.

The role of temperature in these reactions was next investigated. At 130 °C for 3.5 h, in the presence of salt **21** (5 mol%), and KO*t*Bu (2 equiv.), biphenyl product **9** (80%) was still formed. Dropping the temperature to 110 °C and keeping the concentration of the salt and base constant afforded biphenyl **9** (47%) together with recovered iodobenzene **6** (26%). Repeating this last experiment but dropping the concentration of salt **21** to 2.5 mol% and keeping the duration at 3.5 h still afforded product **9** (27%). These last experiments were then compared with 'blank' experiments at 130 °C and 110 °C respectively, *i.e.* where no salt **21** was present. In these cases, biphenyl **9** was still isolated in 30% and 27% yield respectively, indicating that the reaction occurs even in the absence of salt **21**. Thus, at the lowest temperature, 110 °C, a comparison of the yields (27% in the presence of 2.5 mol% salt **21** and 27% in its absence) indicates that salt **21** is ineffective at assisting the reaction. In our previous work in DMF/toluene,[29] our related electron donor **24** needed thermal activation to accomplish dehalogenation of arenes, and the threshold here for donor **22** appears to be in the 110–130 °C range.

To see if the reaction would become more efficient at higher temperature in the absence of salt **21**, biphenyl **9** was isolated in 48% yield when iodobenzene **6** and KO*t*Bu (4 equiv.) were heated at 185 °C for 14 h.

### Initiation in the presence of KO*t*Bu, but no additional additives

In these "additive-free" cases, only KO*t*Bu, iodobenzene and benzene were present. Given the thermodynamic barrier for electron transfer mentioned above, butoxide cannot be the direct initiator of the radical chemistry, and this suggested that

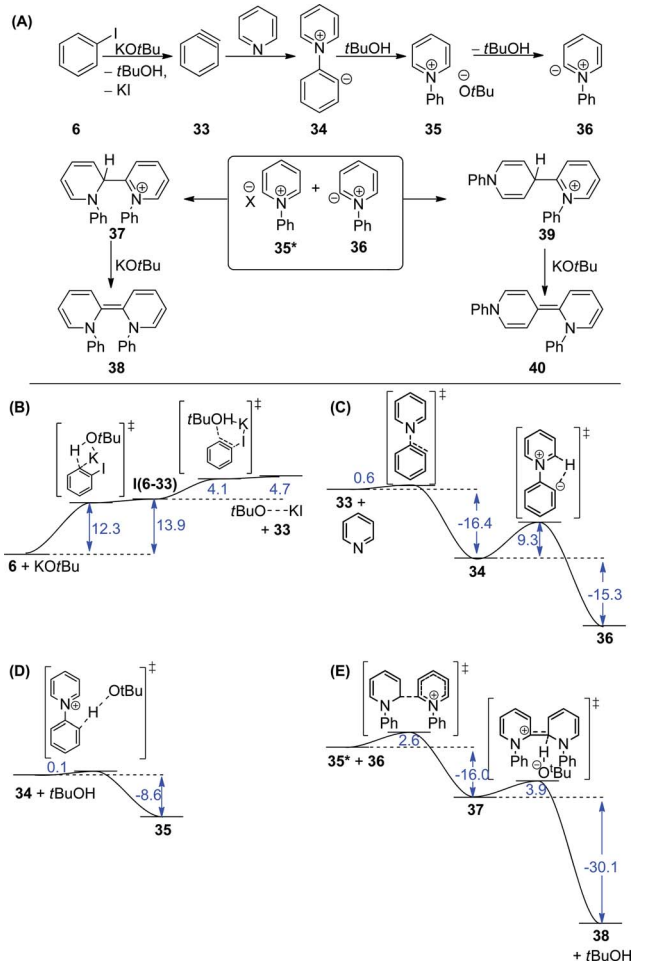


**Fig. 3** (A) Benzyne reacts with pyridine and base to form organic electron donors. (B) Reaction free energy (Δ*G*) profile for the formation of **33** from **6**. (C) Reaction free energy (Δ*G*) profile for the formation of **36** from pyridine and **33**. (D) Reaction free energy (Δ*G*) profile for the formation of **35** from **34**. (E) Reaction free energy (Δ*G*) profile for the formation of **38** from the cation **35*** and **36**. Δ*G* values are reported in kcal mol$^{-1}$.

radicals could be formed in another way. Literature shows that potassium *tert*-butoxide can convert iodobenzene to benzyne **33** (Fig. 3A).[37] Indeed, evidence for benzyne formation is cited in a number of the current publications relating to haloarene–arene coupling,[6,17] although the regiochemistry of the observed products of haloarene–arene coupling, and other properties of the coupling reactions, mean that the isolated biphenyls do not derive from benzynes in any appreciable measure. We envisage that a very small concentration of benzyne could be formed, as part of the *initiation* process solely. The process is supported by the calculated energetics of the reaction (Fig. 3B). The abstraction of a proton and subsequent formation of KI is calculated to be an endergonic reaction ($\Delta G = 18.6$ kcal mol$^{-1}$). The products and intermediates of this mechanism were characterized as true minima on the potential energy surface and connected to the corresponding transition states. However, the inclusion of thermal and entropic effects results in the reverse reaction (**33** → **6**) occurring in a barrierless process and as such only a very low concentration of **33** will be present *in situ*.

The literature also shows that benzyne is attacked by pyridines as nucleophiles.[38] With this in mind, we envisaged a scenario where pyridine, under Charette's conditions,[26] and possibly phenanthroline, under the conditions of Shi[2] and of Shirakawa and Hayashi[6] could similarly add to benzyne. In the case of pyridine, (Fig. 3) this would create a zwitterion **34** that could undergo proton transfer intramolecularly to form **36** (see Fig. 3C). Alternatively *tert*-butanol could protonate **34** (Fig. 3D), and the resulting salt **35** would then closely resemble the pyridinium salts **19** that were used by us previously as precursors of strong bipyridinylidene electron donors **20**. Deprotonation by KO*t*Bu could then lead to **36**. The addition of the cation **35*** to **36** results in the transformation to electron donors **38** and **40** (Fig. 3E). The rate-limiting step in the reaction is the formation of benzyne (**33**), which is thermodynamically unfavourable. However, once produced, the reaction to form the electron donor **38** is both kinetically and thermodynamically favourable. The formations of the various intermediates are all exergonic with the largest barrier encountered for the intramolecular proton transfer to form **36** from **34** ($\Delta G^* = 9.3$ kcal mol$^{-1}$, Fig. 3C), which is easily accessible under the reaction conditions. To test this idea, *N*-phenylpyridinium chloride **35*** (X = Cl) (0.2 equiv.) was treated with iodobenzene **6** and KO*t*Bu (4 equiv.) in benzene at 180 °C for 8 h. This did indeed afford a good yield of biphenyl **9** (68%) showing that pyridinylidenes like **36** are possible intermediates in these reactions. Hence the reaction might be operating with benzyne as an intermediate. This would be attacked by pyridine (and possibly phenanthroline), ultimately resulting in the synthesis of bipyridinylidene (biphenanthrolylidene) super electron donors to initiate the radical chemistry.

However, the results that were seen above in the "additive-free" cases *i.e.*, simply with iodobenzene, benzene and KO*t*Bu still require an explanation of how these reactions can lead to radical chemistry. Benzyne reacts with benzene to form biphenyl as well as other products.[40] Although detailed mechanistic studies of this reaction have not been carried out, the likely mechanism can be deduced from the reaction of benzyne

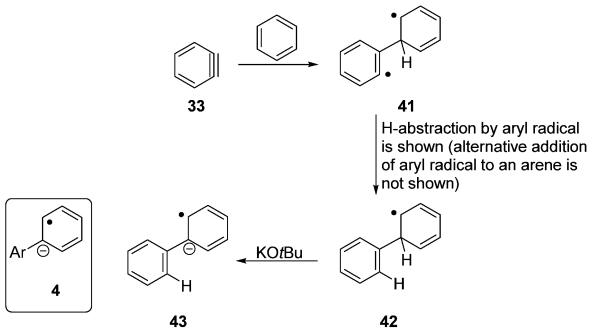


**Fig. 4** Proposed pathway from benzyne to an electron donor in the absence of "additives".

with alkenes and thiones. Benzynes undergo reactions with alkenes to form benzocyclobutanes. At least two detailed studies of benzocyclobutane formation on reaction of benzyne with alkenes have shown that this is not a concerted reaction, but proceeds through a diradical intermediate.[41,42] Similarly, addition to thiones affords diradical intermediates.[43,44] Applying a similar reactivity to addition of benzyne to benzene would afford a diradical **41** (Fig. 4), and its similarity to phenylcyclohexadienyl radical **3** is apparent. Further reaction of the aryl radical in **41**, by hydrogen atom abstraction from benzene (see below), followed by deprotonation of the cyclohexadienyl radical by base is a likely sequence to afford species, **43**, that can act as an excellent electron-donor. As in the case of the reaction of benzyne with pyridine, the formation of the benzyne is the limiting step in this reaction. The calculated energetics show that the electron donor **43** will be formed in an exergonic reaction ($\Delta G = -29.1$ kcal mol$^{-1}$) with a maximum barrier of 12.2 kcal mol$^{-1}$, once the reactive benzyne species is formed (see Fig. S2 in ESI†).

Our aim was now to focus on the role of electron transfer, in experiments that would preclude the formation of benzyne. Plainly, benzyne cannot form from iodobenzenes that are blocked in both *ortho*-positions, so 2,6-dimethyliodobenzene **44** was selected (Fig. 5) and treated with KO*t*Bu and benzene (130 °C, 22 h). This led to no reaction (*cf.* the "additive-free" reaction above using iodobenzene **6**). This experiment supports a role for benzyne under these "additive-free" conditions, for substrates like iodobenzene where benzyne formation is possible. The lack of reaction with **44** also showed that under these conditions KO*t*Bu was not able to trigger electron transfer. It might have been argued that 2,6-dimethyliodobenzene **44** was too hindered to undergo electron transfer-mediated loss of iodide to form radical **47**, but this argument was quashed when it was reacted with the benzimidazolium salt **21** (20 mol%) in the presence of KO*t*Bu and benzene (130 °C, 22 h). This led to an inseparable mixture of 2,6-dimethylbiphenyl **46** (5%) and biphenyl **9** (19%) as well as recovery of **44** (36%). This suggests that the 2,6-dimethylphenyl radical **47** is not an efficient coupling agent, which is understandable for steric reasons, but also shows that this radical can abstract a hydrogen atom from the solvent, benzene, to form a phenyl radical **48**,[45] explaining the origin of the biphenyl **9** here and also from *p*-iodoanisole **25** reported above and also in the literature.[17]

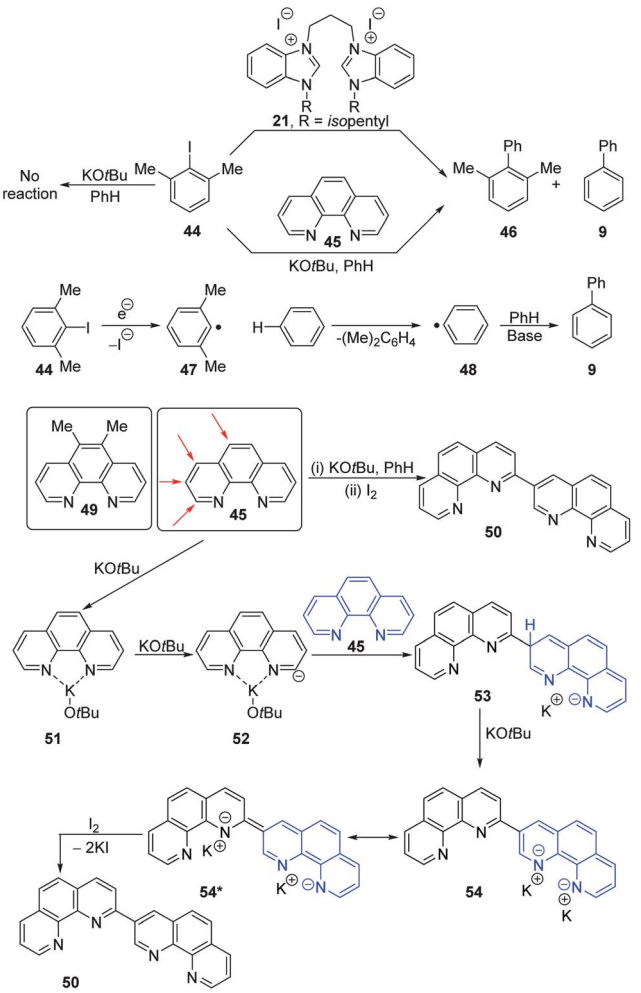


**Fig. 5** Reactivity of 2,6-dimethyliodobenzene with organic electron donors.

It was now of interest to revisit additives, such as phenanthroline and pyridine. If they could convert substrate **44** to coupled product, then this would be evidence in favour of an electron-transfer capability in their reactions. Phenanthrolines were examined first.

### Initiation with phenanthrolines as additives

Reaction of substrate **44** with phenanthroline **45** (20 mol%), KO*t*Bu (2 equiv.) at 130 °C for 18 h afforded an inseparable mixture of biphenyl **9** (19%) and 2,6-dimethylbiphenyl **46** (5%) in the same yield and ratio as had been seen with the salt **21**, precursor of the organic electron donor **22**, supporting an electron transfer mechanism for reactions involving phenanthroline **45**. Also recovered was **44** (41%).

Next, 5,6-dimethylphenanthroline **49** (100 mol%) was reacted. Complete conversion was seen after heating at 130° C for 15 h, affording the same mixture of biphenyl **9** (27%) and 2,6-dimethylbiphenyl **46** (8%). Repeating the experiment with dimethylphenanthroline **49** (20 mol%) led to biphenyl **9** (17%) and 2,6-dimethylbiphenyl **46** (5%), together with recovered **44** (31%). In these reactions with phenanthrolines, we noted that significant quantities of a deep green solid material were produced during the reactions, and this was now investigated.

Phenanthroline[2–4,6–8] **45** is an electron-poor arene, and an obvious way to convert it into a π-electron-rich species would be by addition of a nucleophile to its periphery. We considered the possibilities shown in Fig. 5; addition of a nucleophile at any of the atoms indicated by the red arrows on boxed structure **45** would afford electron-rich anionic adducts that ultimately might convert into electron donors resembling those already discussed in this paper. To probe this, phenanthroline was heated in benzene in the presence of potassium *tert*-butoxide. As in the previous reactions, deep-green solid material was produced, and at the end of the reaction, this was analysed. When removed from the glove-box and exposed to air, this material was pyrophoric, reminiscent of our previous organic electron donors. When the material was instead quenched with iodine, as electron acceptor, and was then examined by $^1$H NMR, it appeared to be an almost pure single compound. Rigorous purification through column chromatography gave pure (2,3′-bis)phenanthroline **50** as a red oil (36%); a key feature of its spectrum was the presence at $\delta$ 9.42 and $\delta$ 9.84 of two doublets each with $J$ = 2.2 Hz, indicating *meta* coupling. To rationalize its formation, complexation of phenanthroline with a potassium ion would give structure **51** (KO*t*Bu is represented as monomeric here, but we recognize that aggregation may occur in benzene). Some of these molecules are then deprotonated to form **52**. This anion then acts as a nucleophile on the 3-position of another phenanthroline molecule to afford intermediate **53**. Further deprotonation by KO*t*Bu would afford the dianion **54**, with the charge highly delocalized over the six rings, and undoubtedly complexed to potassium. The analogy is clear between canonical form **54** and super-electron donors **20** and **38**, all of which feature very electron-rich nitrogen heterocycles, where loss of two electrons restores full aromaticity in all three cases. The energetics of this reaction mechanism were investigated computationally (see Fig. S3 in the ESI†). The rate-limiting step in the reaction was found to be the initial *ortho* deprotonation of phenanthroline (**51**) to form **52**. This reaction is endergonic by 15.8 kcal mol$^{-1}$, however in analogy to the formation of benzyne, the reverse reaction from **52** to form **51** is barrierless and as such only very small amounts of **52** are present *in situ*. However, once **52** is formed, a subsequent reaction with phenanthroline can readily occur. The maximum barrier ($\Delta G^*$) for the addition to the *meta* position of phenanthroline is 10.5 kcal mol$^{-1}$. This is slightly more favourable than the addition to the *para* (10.6 kcal mol$^{-1}$) or *ortho* (11.5 kcal mol$^{-1}$) positions. Overall, the formation of **54** is strongly favourable with a reaction energy of −30 kcal mol$^{-1}$.

Since phenanthroline had converted substrate **44** to products **46** and **9**, pyridine (1 equiv.) was also reacted with KO*t*Bu (2 equiv.) at 130 °C for 15 h. However, no reaction was observed.

### Initiation with pyridine as solvent and relevance to pyridines or pyrazines as substrates

The lack of reactivity of pyridine is noteworthy, at least under these conditions where it is present at this limited

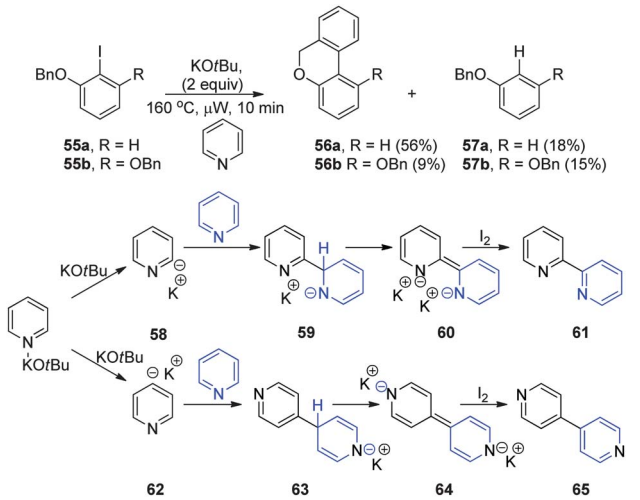


**Fig. 6** Base-induced formation of organic electron donors from pyridine.

concentration. Under the Charette conditions,[26] where pyridine has been shown to facilitate intramolecular coupling reactions, pyridine is present in great excess as the solvent, and so substrate **55a** was now tested under these conditions (Fig. 6). The 2-benzyloxyiodobenzene **55a** underwent complete conversion and afforded an inseparable mixture of two products, **56a** (56%) and **57a** (18%), identified by NMR and mass spectrometry. Both of these products are consistent with intermediate aryl radicals; product **56a** is the expected cyclisation product from the Charette conditions,[26] and **57a** should result from quenching of the intermediate aryl radical by hydrogen abstraction from pyridine, analogous to the reaction of aryl radical **47** with benzene shown in Fig. 5. The studies were then extended to the 2,6-dibenzyloxyiodobenzene **55b**. This behaved in a qualitatively similar way, affording an inseparable mixture of two products, **56b** (9%) and **57b** (15%).

Under these conditions, and with this substrate **55b**, benzyne cannot be an intermediate, and so initiation results from electron transfer. Based on the phenanthroline studies above, it appeared likely that a similar reaction occurs to form an organic electron donor. Pyridine may be much more difficult to deprotonate than phenanthroline, since the complex between pyridine and KO*t*Bu should be a lot weaker than the complex between the chelating phenanthroline and KO*t*Bu; hence lower concentrations of pyridine-derived super electron donor would be formed. A blank experiment was again conducted in which potassium *tert*-butoxide was heated in pyridine as solvent. On work-up with iodine as electron acceptor, this led to very small quantities of a residue. This residue was initially examined by GCMS and gave two peaks that showed the correct *m*/*z* for (two isomers of) bipyridine. Purification provided mass spectra and $^1$H NMR spectra indicating 2,2′-bipyridine **61** (the major product) and 4,4′-bipyridine **65** (no 2,4′-bipyridine was isolated). The origin of **61** is not difficult to rationalize: pyridine is deprotonated in the 2-position to form **58**. Addition of **58** to the electrophilic 2-position of pyridine would afford intermediate **59** that, on further deprotonation by KO*t*Bu, would afford dianions **60**. Finally, oxidation with iodine affords bipyridine **61**. Similarly, **62** resulting from deprotonation of pyridine in the 4-position[39] can lead to **65**. Compounds **60** and **64** again contain the signature properties of a super-electron-donor, *i.e.* a very electron-rich nitrogen-containing heterocyclic structure that can become completely aromatic by loss of two electrons.

These reactions relate to the use of pyridine as solvent, as seen in the work of Charette's team,[26] but also to the initial observations of Itami,[1] where pyridines and pyrazines were reacted in the presence of iodoarenes and KO*t*Bu.

## Conclusions

In summary, we propose that initiation of coupling reactions between haloarenes and arenes in the absence of transition metals can occur, based on formation of heterocycle-derived organic electron donors *in situ* by different pathways. Importantly, they avoid the requirement for KO*t*Bu, or a simple derived complex, to act as an electron donor. Our findings provide a rationale, based on the developing chemistry of organic super electron donors, for the generation of radicals to initiate transition metal-free coupling reactions under four different protocols; here, the heterocycles do not form organocatalysts, but rather, organic initiators, whose reactions add to the growing litany of reactions that are accomplished by organic electron donors. A final interesting point is that the coupling of simple iodobenzenes and benzene proceeds also in the absence of additives – here a role for benzyne in the *initiation* of the radical chemistry is proposed.

## Acknowledgements

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