Ground state cross-coupling of haloarenes with arenes initiated by organic electron donors, formed *in situ* – an overview

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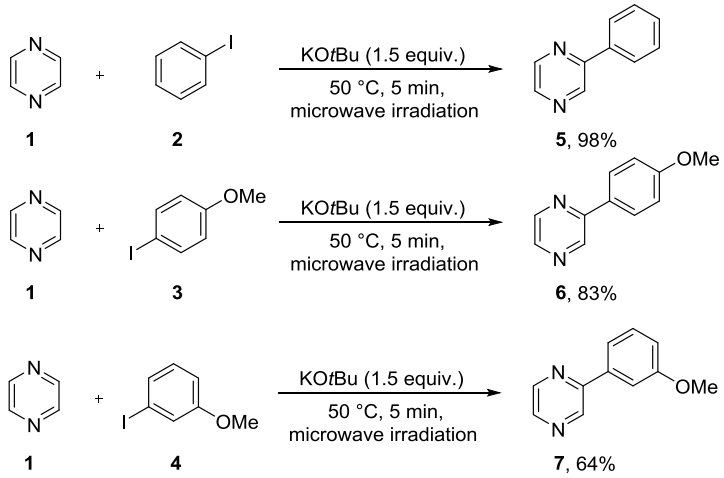
Abstract

Many reactions have been discovered that lead to coupling of haloarenes to arenes using potassium *tert*-butoxide as base, and one of a variety of organic compounds, as an additive. The organic additive reacts with the base to form a strong organic electron donor *in situ* that initiates the BHAS (base-induced homolytic aromatic substitution) coupling reaction, by converting the haloarene to an aryl radical. This brief report presents an overview of the wide range of organic additives that can be used, and the organic electron donors that they form.

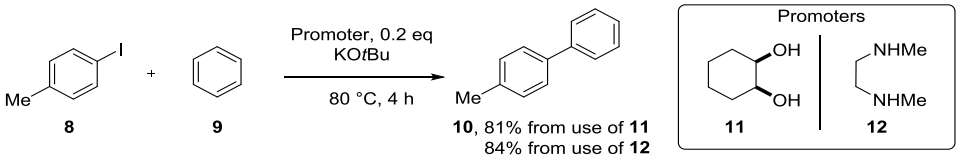
In 2008, Itami *et al.* reported a study of iridium complex-mediated coupling of iodoarenes to electron-deficient heteroarenes, mediated by potassium *tert*-butoxide.[1] During this study, they made an unusual observation *i.e.* that the coupling reaction proceeded equally well in the absence of any added iridium compound. This triggered many investigations that led to discovery of a new type of reaction mechanism for coupling haloarenes to arenes, with novel generic methods of initiation. This article provides an abridged overview of the background and the mechanism of the initiation of these reactions.



Scheme 1. The transition metal-free cross-coupling reaction of Itami *et al*.[1]

Itami *et al.* found that pyrazine **1** and related compounds (pyridine, pyrimidine *etc*.) coupled with iodobenzene **2** in good to excellent yields (Scheme 1).[1] Moreover, they found that radical scavengers such as TEMPO, galvinoxyl and acrylonitrile completely inhibited the reaction. This suggested that a radical-based process was driving the reaction. Additionally, coupling reactions between *p*- or *m*-disubstituted iodoarenes **3** or **4** and pyrazine **1** showed no formation of regioisomers from the reaction, which excluded a benzyne-mediated process as the source of the isolated products.

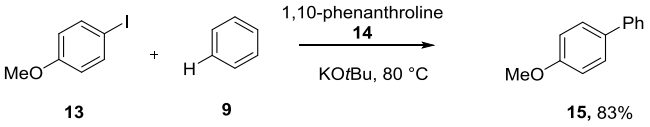
In 2010, other research groups published similar but different coupling reactions that were free from added transition metals. Lei *et al.* discovered[2] that certain organic compounds, such as *cis*-cyclohexane-1,2-diol **11** and *N,N'*-dimethylenylenediamine (DMEDA) **12**, used as additives in the reactions, promoted the transition metal-free cross-coupling of halobenzenes with benzene, as shown in Scheme 2.



Scheme 2. Lei discovered the role of some neutral compounds as promoters.[2]

Interestingly, only KO*t*Bu (as opposed to other alkali metal *tert*-butoxides) promoted the reactions. Moreover, as seen in Itami's reaction, radical scavengers completely inhibited the reaction. Dihalobenzene substrates, acting as Bunnett-Creary probes,[3] suggested that radical anions were intermediates in the process, but, at this stage, no satisfactory mechanism was proposed for these transformations.

Also in 2010, two different publications reported the use of sub-stoichiometric 1,10-phenanthroline **14** and derivatives as additives in metal-free cross-coupling reactions with aryl iodides or bromides. Shi *et al.* discovered[4] a cross-coupling between 4-iodoanisole **13** and benzene **9** in the absence of added transition metals, and in the presence of ligands capable of promoting the coupling (Scheme 3). They proposed that a radical is formed from the aryl halides by KO*t*Bu, and that 1,10-phenanthrolines might facilitate the radical generation.

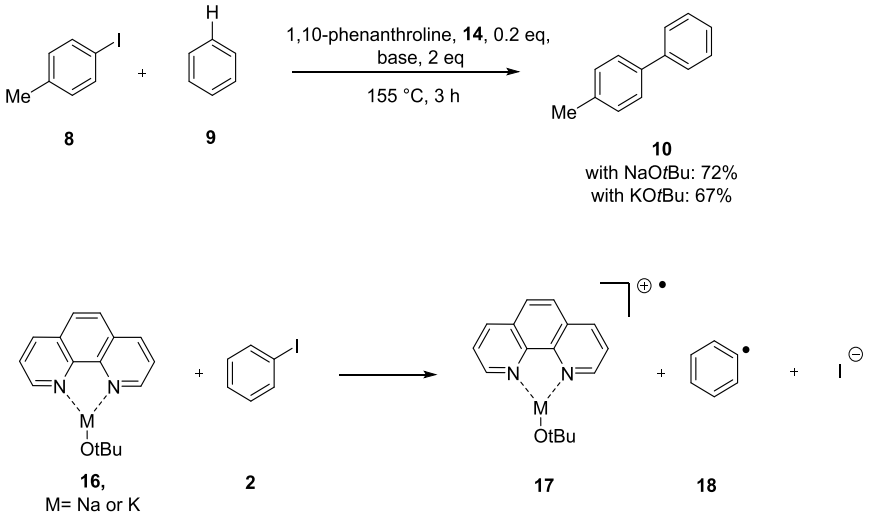


Scheme 3. Biaryl coupling assisted by 1,10-phenanthroline as reported by Shi.[4]

Shi also reported intramolecular coupling reactions with phenanthrolines. Intramolecular coupling between haloaryl and aryl rings was also reported[5] by Charette *et al.* using KO*t*Bu and phenanthrolines, with the best results arising when pyridine was used as solvent.

In addition to his work with phenanthroline, Shi also reported coupling using DMEDA, **12**, as an additive.

Simultaneously, Shirakawa, Hayashi *et al.* revealed[6] the NaO*t*Bu-mediated coupling between aryl halide **8** and benzene **9** in the presence of a small amount of 1,10-phenanthroline **14** (Scheme 4). This study showed that the choice of the base is not strictly limited to KO*t*Bu, but that NaO*t*Bu can promote these reactions as well. A notable observation was the formation of 3- and 4-butoxytoluenes (ratio 1:1), derived from the aryne intermediate, when they tested *p*-bromotoluene. This suggests that, under these conditions, benzyne is formed.



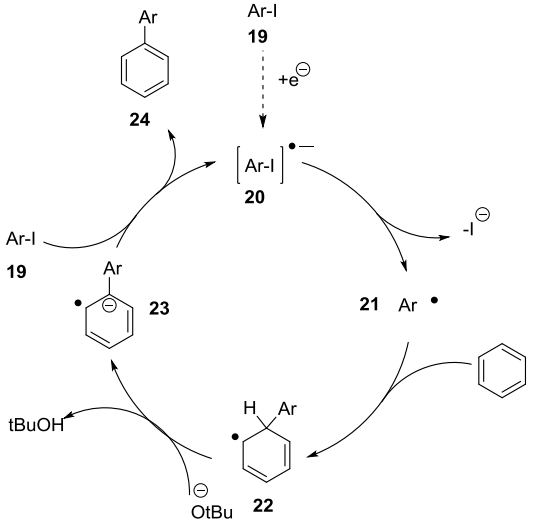
Scheme 4. Coupling reaction mediated by 1,10-phenanthroline and alkoxides as proposed by Shirakawa and Hayashi.[6]

The Shirakawa and Hayashi view sees complexation of the metal ion, M^+, from the metal butoxide, as in **16**. It was proposed that this species underwent electron transfer to iodobenzene to afford radical cation **17** and the radical anion of iodobenzene, which spontaneously dissociates into a phenyl radical **18** and iodide ion.

No rationalisation was provided, but the underlying explanation might be that complexation in **16** induces a lengthening of the bond between the metal ion and the *tert*-butoxide anion compared with the uncomplexed MO*t*Bu. In a solvent of low polarity, such as benzene, the *tert*-butoxide anion would therefore become more naked, and this might provide a driving force for electron transfer, essentially from the butoxide component of the complex, effectively to become a complexed neutral butoxyl radical. The mechanism of action of phenanthrolines will be discussed later in this report.

In many papers, these additives were reported as “catalysts”, but “catalysis” implies more than the facilitation of the reaction through a low energy transition state – it also implies no change to the structure of the additive at the end of the reaction, and none of the reports that are discussed above explored the latter point. As will be seen later, the additives are generally not catalysts, but are precursors to electron donors, which are *initiators* of radical chemistry, and quite distinct from catalysts.

An important overview, published by Studer and Curran[7] in 2011, summarised the earlier results of the teams of Itami, Shi, Shirakawa and Hayashi, and Lei. However, Studer and Curran also took matters forward in a substantive way by proposing a plausible mechanism for these transition metal-free arylations that they named as Base-promoted Homolytic Aromatic Substitution (BHAS) reactions.[7] The radical **21**, formed from iodoarene **19** by an unknown route at that time, couples with benzene to form the cyclohexadienyl radical species **22**. Studer and Curran described a role for the KO*t*Bu to deprotonate the radical **22** to form the biaryl radical anion **23**, a powerful reducing agent and keystone of the entire process. This deprotonation can occur because the presence of the radical in **22** renders the nearby sp^3 C-H more acidic, and within range of the basicity of KO*t*Bu.



Scheme 5. Base-promoted Homolytic Aromatic Substitution (BHAS) proposed by Studer and Curran[7]

The radical anion **23** propagates the process by donating an electron to another molecule of iodoarene **19**, producing the coupled product **24** and leading to another aryl radical **21**, thereby sustaining a chain reaction (Scheme 5). The mechanistic proposal explained the radical chain mechanism of propagation, but still left the initiation process to be clarified. The authors stated that presumably additives such as 1,10-phenanthroline **14** and DMEDA **12** play a crucial role, but the role could not be defined at that stage.

In the following years, other authors reported neutral organic compounds as additives that were capable of promoting the coupling reactions. Examples include **14**,[2,4] **25**-**45**[1,2,3-5,8-25] shown below in Figure 1; we will comment on these examples later in this overview. The variety of additives that effect the coupling reaction in the presence of KO*t*Bu is remarkable. It would be surprising if a common theme did not underpin the pathway of initiation of many of these reactions.

Organic Electron Donors, formed *in situ*, act as initiators

Murphy *et al*. had reported[26] the first organic super electron donors in 2005. These were ground state organic electron donors that were sufficiently strong to convert aryl halides to aryl radicals by single electron transfer, or, in later cases, to aryl anions[27] by double electron transfer. Electron donor **47** was

selected to test its ability to trigger these coupling reactions; it was planned to form this compound *in situ* from its disalt precursor **46**. Before this time, conversion of the precursor to donor **47** had been achieved with strong base (*e.g.* NaH), but test reactions with KO*t*Bu, showed the vibrant yellow colour of the donor was also formed with this base in benzene as solvent, and hence it was a valid system to test for the coupling reaction of haloarenes to arenes.

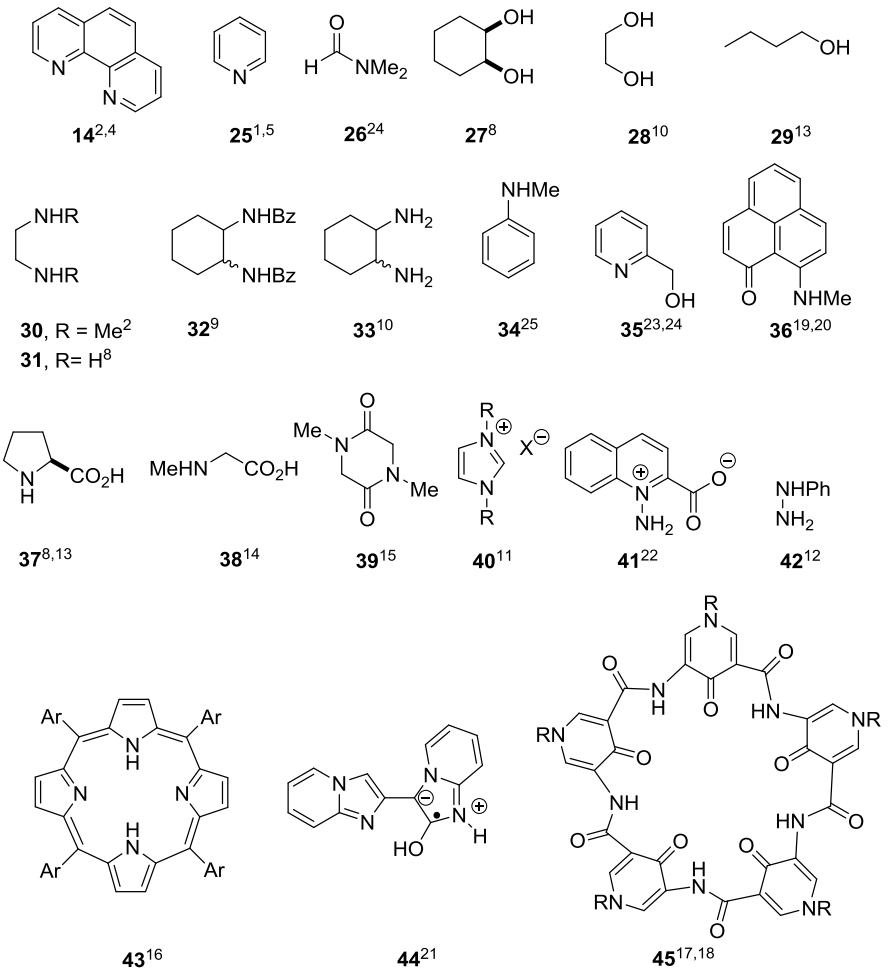
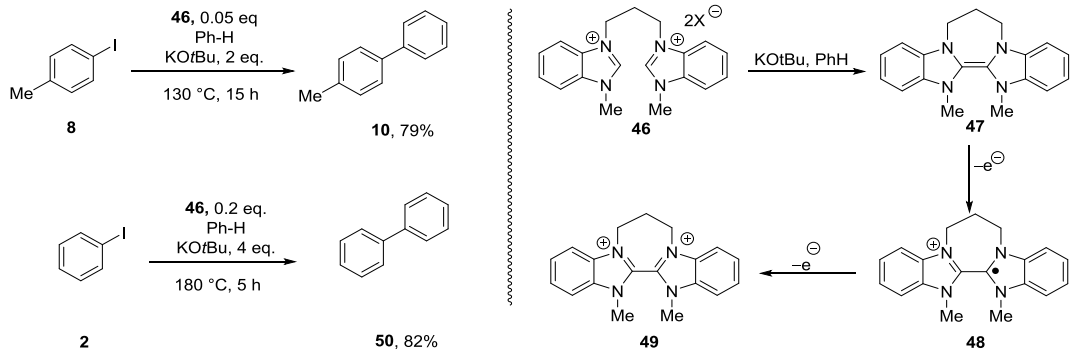


Figure 1 Some examples of organic additives that facilitate the coupling of haloarenes to arenes in the presence of KO*t*Bu.

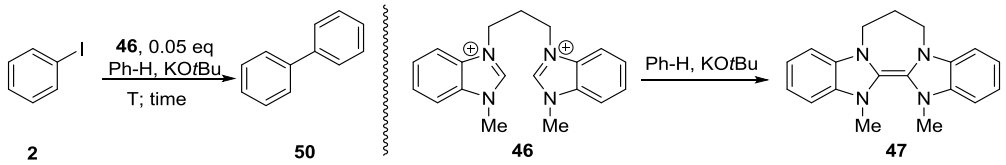
Test reactions were then performed using electron donor **47**, formed *in situ*, and different iodoarenes such as **8** and **2**. As shown in Scheme 6, the yields obtained *via* this new approach were very satisfying; when bromoarenes were tested instead, lower yields were achieved, mirroring the previous results with electron donors.[28,15] This showed, importantly, that organic electron donors can bring about the coupling reaction between halobenzenes and benzene in the presence of KO*t*Bu, and raised the prospect that organic electron donors might be formed when other additives reacted with KO*t*Bu.

To optimise conditions, Murphy *et al*. varied the temperature of the reaction and the number of equivalents of the additive **46**, the precursor to electron donor **47**. The results are shown in Table 1. Entry 1 shows that the reaction proceeded in high yield (80%) at 130 ^{o}C for 3.5 h with 5 mole% of



Scheme 6. The role of benzimidazole-derived donor **47** in mediating cross-coupling reactions.[28]

additive **46**. Dropping the temperature to 110 ^{o}C almost halved the yield (47%). Comparison with the case where **46** was not added, sees that the reaction proceeded sluggishly (27-30%) at either temperature. Thus, it appeared that the coupling reaction was dramatically accelerated by the presence of the electron donor at 130 ^{o}C, but that an alternative and more sluggish route to coupling occurred in the absence of the electron donor. The challenge was now to distinguish and understand these different routes.



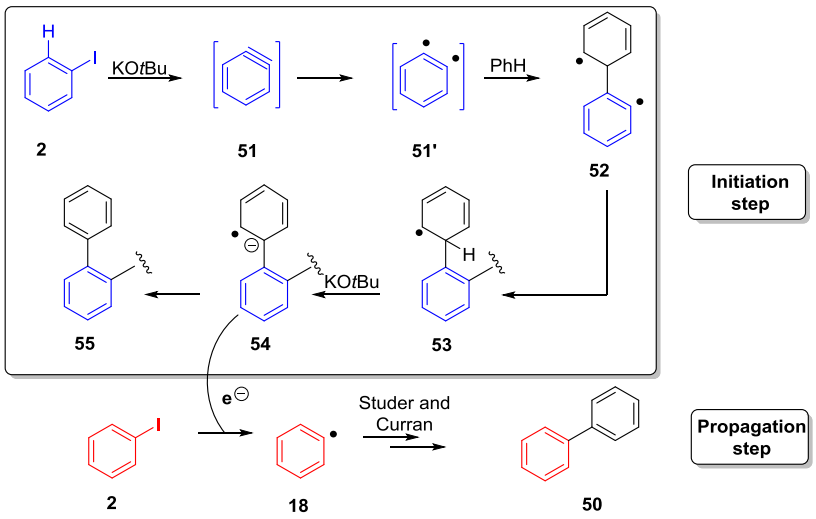
Entry	46 (eq.)	KO*t*Bu (eq.)	Reaction conditions	50 (%)
1	0.05	2	130 °C; 3.5 h	80
2	0.05	2	110 °C; 3.5 h	47
3	none	2	130 °C, 3.5 h	30
4	none	2	110 °C, 3.5 h	27

Table 1. Evaluating the effect of **46** as additive.

Given that KO*t*Bu and an aryl halide were present at high temperature in this reaction, and given that evidence was already reported for the formation of benzyne intermediates in some of the published coupling reactions,[6] then benzyne was the key suspect for the initiation of the reactions in the absence of organic additives, *i.e.* when simply KO*t*Bu, aryl halide and benzene were present. The literature already had highlighted cases where benzyne behaved as a diradical.[29-32] Accordingly, the initial task was to explain how benzyne might have played a role in these reactions, particularly

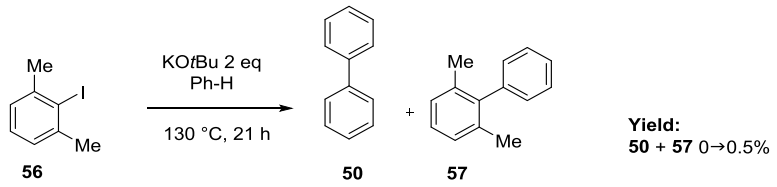
bearing in mind the earlier findings of Itami *et al.*[1] that the isolated products don't arise by a benzyne-based mechanism.

Murphy *et al*. proposed that benzyne plays a role in the initiation steps for a radical chain, but not in the propagation. As shown in Scheme 7, if the benzyne intermediate **51** acts as *o*-diradical **51'**,[28] this can add to benzene to afford diradical **52**; within this species, the aryl radical will be the more reactive radical, and may add to another arene or abstract a hydrogen, giving rise to **53**. Then, this species undergoes deprotonation by the base to form the radical anion species **54**, the electron donor species capable of donating an electron to iodobenzene, **2**. Once that happens, the propagation steps can occur as described in the proposal of Studer and Curran. If the propagation steps are considerably faster than the initiation steps, then benzyne-derived molecules will be present in such small quantities as to be undetectable, in line with experimental findings.



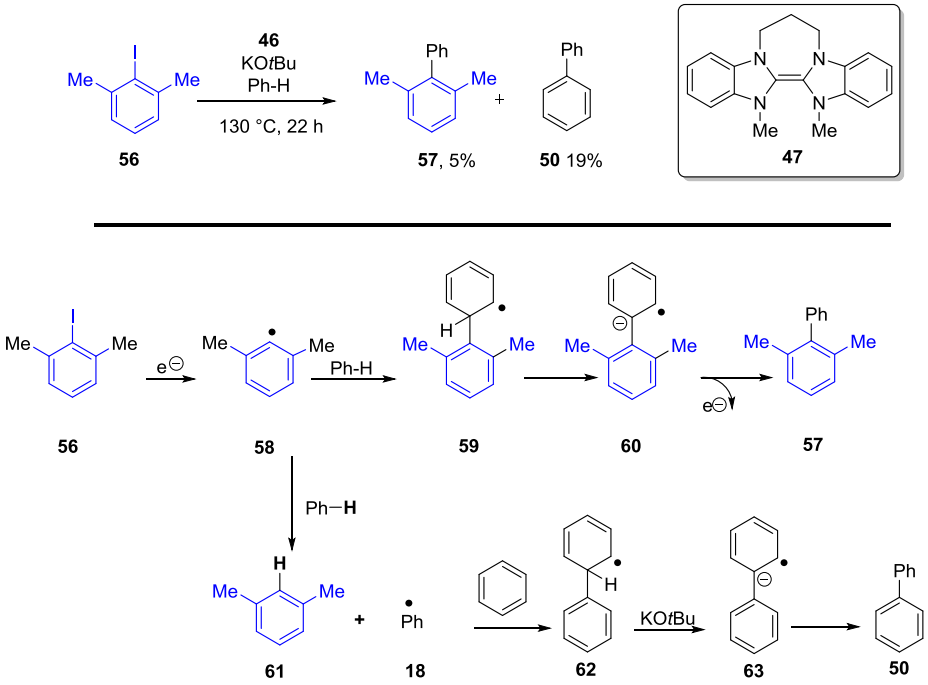
Scheme 7. Initiation promoted by the benzyne intermediate **51** proposed by the Murphy group.[28]

To establish whether benzyne initiation played a crucial role in the "additive-free" cross-coupling reactions, the substrate iodo-*m*-xylene **56**, from which a benzyne intermediate cannot form, was tested. When this substrate was reacted with KO*t*Bu in benzene, the substrate was almost unchanged, but depending on the actual experiment, 0 → 0.5% of a mixture of coupled products, biphenyl **50** and 2,6-dimethylbiphenyl **57,** was observed to be present (Scheme 8). This can be contrasted below (Scheme 9, top line) with the result when an electron donor is present. The traces of coupled product seen in Scheme 8 are attributed to minute quantities of adventitious transition metal salts or transition metal complexes. Previous analyses by Leadbeater[33] had shown that, however small their quantities, traces of such metals will always be present in reagents.



Scheme 8. Testing for coupling reactions with iodo-*m*-xylene **56** as substrate.

The reaction was then repeated under the same conditions but in the presence of organic donor **47**, formed *in situ* from KO*t*Bu and disalt **46**. This reaction led to a 1:3.8 ratio of two coupled products, 2,6-dimethylbiphenyl **57** (5%) and biphenyl **50** (19%), and also to recovery of some starting material **56**. These results, shown in Scheme 9, are explained below.



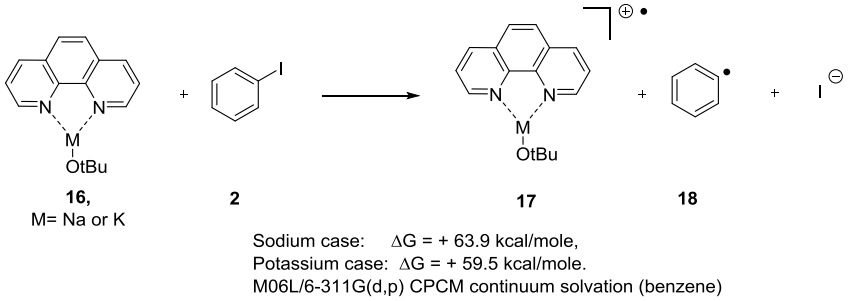
Scheme 9. Proposed benzyne-based mechanism for the formation of the two coupled products **57** and **50**.

The iodo-*m*-xylene **56** receives an electron from the electron donor **47** and then the resulting radical **58** can proceed through two different pathways: (a), radical **58** adds to benzene, giving rise to the radical **59** and, after deprotonation, radical anion **60**, which can propagate the process and promote the formation of 2,6-dimethylbiphenyl **57**; (b), the radical **58** can abstract a hydrogen from benzene and form phenyl radical **18** as well as the volatile xylene **61**. Phenyl radical **18** then follows the BHAS mechanism[7] reacting with benzene and forming biphenyl **50**. Evidently, pathway (b) progresses 3.8 times faster than pathway (a), as seen in the relative yields of **50** and **57**, likely because the radical species **58** is not an efficient coupling species due to the steric hindrance of its methyl groups; it prefers to abstract a hydrogen from the benzene and then generate the much more active coupling radical **18**.

Having established that organic super electron donors effect the coupling reaction as a result of electron transfer, the aim was now to probe whether a similar mechanism might be in play with the

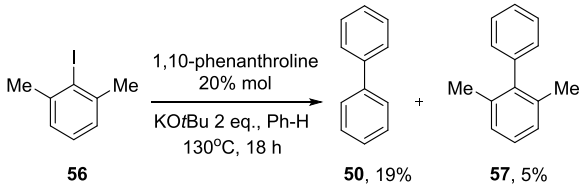
organic additives that had facilitated the coupling reactions in other laboratories. We include here a discussion of the story as it relates only to phenanthroline as an additive, and we follow that by an overview of current knowledge on the additives in Figure 1.

To probe the role of phenanthroline in these coupling reactions, computational investigations were undertaken by Tuttle and Murphy[28] on the pathway described by Shirakawa, Hayashi *et al*. in 2010. Primarily, the thermodynamics for the electron transfer reaction between the complex **16** of 1,10-phenanthroline with alkali metal alkoxides and iodobenzene **2** were evaluated (Scheme 10). The calculated free energy change (this is not the *kinetic* barrier) was found to be ΔG_{rel} = +63.9 kcal mol^{-1} for NaO*t*Bu and ΔG = +59.5 kcal mol^{-1} for KO*t*Bu.[28] These large values led the Murphy and Tuttle[28,15]



Scheme 10. Thermodynamics for electron transfer for the reaction between a complex of [1,10-phenanthroline with alkali metal alkoxides] and iodobenzene.

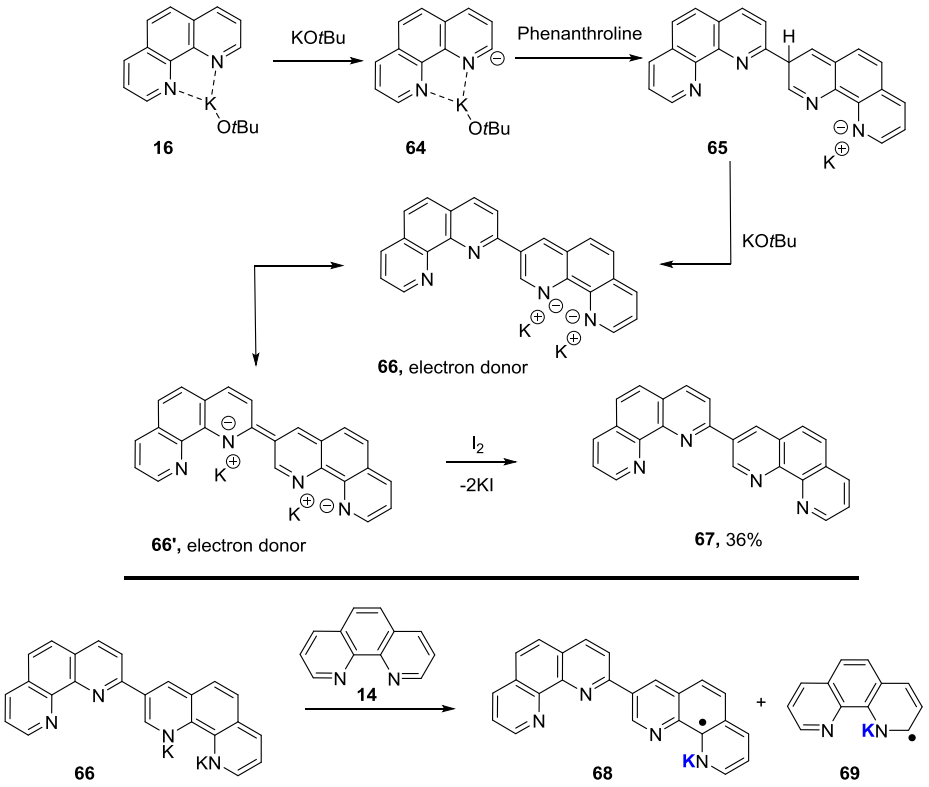
group to conclude that the pathway shown for complex **16** is not responsible for the observed ground-state chemistry. To test whether electron transfer chemistry might be involved, substrate **56** was again used (Scheme 11). If an electron transfer mechanism was in play, then the reaction might offer a similar result to the experiment with the super electron donor **47** (Scheme 9). Interestingly, the results obtained from this reaction exactly mirrored the results displayed by the donor **47**, with formation of **50** (19%) and **57** (5%); the ratio of the two coupled products was identical to that seen for the organic super electron donor. But how could phenanthroline + KO*t*Bu behave as an electron donor, in the light of the calculations described above?



Scheme 11. The importance of the presence of an additive in metal-free cross-coupling reaction involving **56**.

It was noted that in all coupling reactions where phenanthroline was used with KO*t*Bu, a deep green[28] solid was afforded, and this seemed to hold the key to the chemistry. A blank experiment was conducted where only KO*t*Bu, phenanthroline and benzene were present (no haloarene substrate), and the precipitate was again produced. This material was pyrophoric in air in a similar vein to

previously made super electron donors. To identify the dark-green solid, the reaction was repeated and quenched with iodine, an electron acceptor, affording 2,3'-bis-phenanthroline (**67**, 36%). Murphy *et al.* then proposed a possible mechanism for this observation, as shown in Scheme 12. The phenanthroline complex **16** undergoes deprotonation by KO*t*Bu, and the resulting anion **64** then nucleophilically attacks a neutral phenanthroline to afford the species **65** which, after further deprotonation, forms **66** and, upon oxidation by iodine, gives rise to the dimer **67**. The dianion **66** would then likely promote the initiation step for the coupling process, donating an electron to the iodoarene and triggering the radical cycle.]



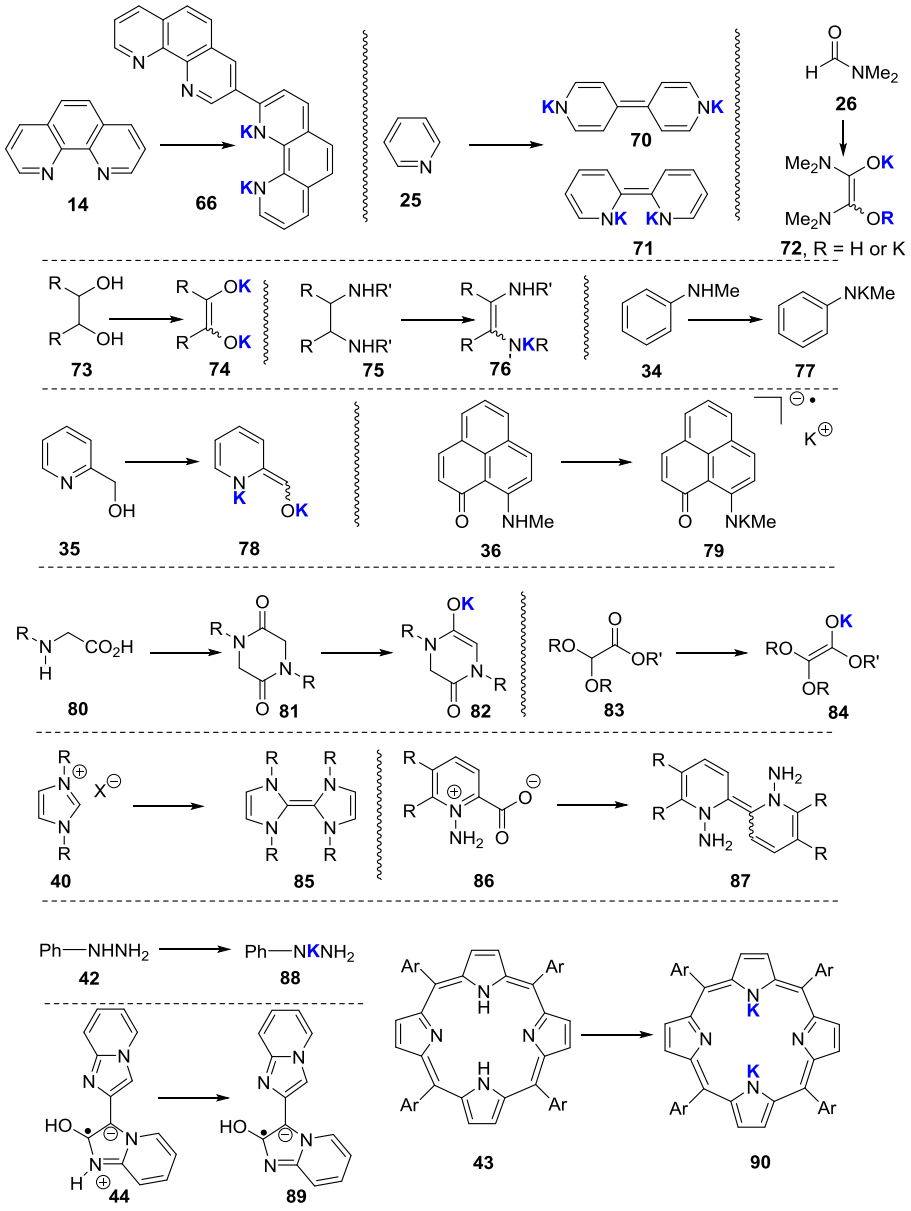
Scheme 12. Formation of dimer **67** derived from the electron donor species **66**.[28]

Wilden *et al.* had earlier taken the view[34] that KO*t*Bu directly transfers an electron to phenanthroline. Lei and Jutand subsequently published[35] further thoughts on the phenanthroline/KO*t*Bu coupling system. Their interesting observation was that the mixture of KO*t*Bu and phenanthroline affords radical signatures by EPR that look similar to a phenanthroline radical anion. They concluded that KO*t*Bu must be donating an electron to phenanthroline. However, their paper revealed the oxidation potential of KO*t*Bu to be = +0.14 V vs SCE, and the reduction potential of phenanthroline to be −2.0V, so an outer sphere electron transfer[35] is clearly not feasible. Careful examination of the EPR spectrum arising from the reaction of KO*t*Bu with phenanthroline showed that the EPR signature was not symmetrical but rather looked like a superposition of two similar but not identical spectra. Murphy *et al*. attribute this to an electron transfer equilibrium between the hexacyclic dianion **66** and unreacted phenanthroline **14** (or its complexed form **16**). This would afford two similar radical anions **68** and **69**, likely accounting for the observed EPR spectrum. Thus phenanthroline could be converted into an

organic electron donor by the action of KO*t*Bu. Further applications of the phenanthroline/KOtBu system have recently been reported. [36,37]

More generally, the formation of electron donors by dimerization of compounds, following deprotonation by base, has also been extended even to some solvents DMF **26**[15] (see Scheme 13) when KO*t*Bu is base and, when KH is the base, to benzene.[38]

In like manner, Murphy *et al*., investigated the reactions of KO*t*Bu with a range of other additives,[28,15] establishing evidence for the *in situ* formation of organic electron donors (Scheme 13). Phenanthroline has been discussed in detail, but pyridine behaved similarly, with dimeric dianions **70** and **71** acting as electron donors. Pyridine **25**, and related heterocycles like pyrazine **1**, were substrates in Itami's initial report[1] and pyridine was a crucial solvent in Charette's studies[5] of coupling reactions. This therefore rationalises how those reactions were initiated through electron transfer.



Scheme 13. The *in situ* formation of organic electron donors in the presence of KO*t*Bu.

With alcohols[13] (not tertiary) and 1,2-diols, **73**, Murphy *et al.* found evidence of oxidation to carbonyl compounds by loss of hydride, and enolate formation from these carbonyl compounds could trigger the initial formation of radicals through electron transfer (see below also for enolates). 1,2-Diols **73** have the opportunity to form the especially electron-rich potassium enediolate salts **74** as organic electron donors. Likewise for 1,2-diamines **75**, Murphy *et al.* proposed the formation of potassium salts of enediamines, **76**, and evidence for these species was reported by Jiao *et al*.[25] Jiao's group refined the mechanism of reaction of 1,2-diamines, and went on to illustrate their ideas proposing and verifying that ArNHMe **34** should act as precursor to organic electron donor **77**.[39,40]

With the hydroxymethylpyridine, **35**, strong evidence was amassed that the disalt **78** was produced[24] and was responsible for initiating the coupling reaction through electron transfer. Likewise, Mandal *et al*.[19,20] established that phenalenone **36** was converted by KO*t*Bu into electron donor radical dianion **79**.

The scope of the study was then expanded to probe how amino acids facilitated the coupling reaction. Amino acids that feature a secondary amine *e.g.* **80** are uniquely successful in initiating coupling through electron transfer.[8,13,14] An explanation for this may be found in condensation in solution to linear oligomers or to cyclic dimers (piperazinediones). Murphy *et al*. showed[15] that piperazinediones **81** react with KO*t*Bu to form strong electron donors, **82**. When the piperazinediones are derived from secondary amino acids, **80**, R = alkyl, then N,N-dialkylpiperazinediones **81** are formed by deprotonation on carbon, and act as precursors to **82** which triggers successful coupling reactions. However, similar piperazinediones but with R = H (i.e. derived from primary amino acids) undergo deprotonation on nitrogen in the presence of KO*t*Bu, and do not promote coupling reactions.

The piperazinediones feature electron-rich enolates of tertiary amides **82** as the electron donor. Esters *e.g.* **83** and ketones with electron-rich substituents on their α-carbon also form electron-rich enolates (here **84**) and prove also to be good electron donors. In fact, this simply illustrates a new use for these electron donors that were historically explored in $S_{RN}1$ reactions in DMSO by the teams of Bunnett,Scamehorn, Rossi and others.[41-43]

Murphy's work began with his knowledge of organic electron donors derived from imidazolium salts **40**.[26,27,11] Here the deprotonated form, an N-heterocyclic carbene, attacked another molecule of imidazolium salt under the basic conditions of the reaction to form dimer **85**. Carbenes are intermediates in that dimerization but also in the decarboxylative dimerisation of **86**. It is already known that pyridine carboxylates **86** form dimers **87** through thermal reaction that involves decarboxylation.

Phenylhydrazine **42** has also been used to promote coupling. A mechanism has been proposed by Studer *et al*. that sees the formation of strong electron donor **88**. The electron donating properties of the product of reaction of KO*t*Bu with a stable zwitterionic radical has been reported.[21] The structure for the zwitterionic radical shown in the publication is not compatible with the multiplicity proposed, so I use structure **44** as a working hypothesis. Deprotonation of this species in KO*t*Bu would afford radical anion **89**, (or the radical dianion resulting from a further deprotonation of the OH group) an

excellent candidate electron donor. The mechanism of action of porphyrins **43** has not been investigated, but it is easy to imagine the deprotonated form **90** being electron-rich enough to act as a powerful electron donor. This means that the activity in coupling of haloarenes to arenes of almost all of the structures shown in Figure 1 can be explained by electron transfer initiation. The remaining molecule is the macrocyclic polyamide **45**, and related structures from the Zeng laboratory.[17,18] Again, electron transfer of a likely deprotonated potassium complex is proposed to trigger the coupling chemistry, but it is difficult with such a complex structure to identify a unique anionic electron donor. This is not the sole structure where mechanism can benefit from further investigation.[44]

In summary, the mechanism of action of the plethora of structures that assisted coupling reactions of haloarenes to arenes and that appear in Figure 1 posed major questions some years ago. The mechanisms by which these compounds initiate BHAS chemistry now appears quite logical through the *in situ* formation of organic electron donors that can initiate the formation of aryl radicals by activation of the haloarene. The fact that these electron donors simply need to initiate the radical cycles of the BHAS coupling reactions means that they only require to be formed in small amounts. This exercise has been useful for identifying a previously unidentified but very common theme, the *in situ* formation of electron donors through reaction of base with many types of common organic chemicals. We expect many more instances of this phenomenon to appear in the literature in the coming years.

The work discussed above has emerged from experimental studies, but no X-ray structures of the proposed strong organic donors have yet been published. Many of these are potassium salts, and the full structural picture would provide valuable information on the ligands on the potassium ions as well as any evidence of aggregation in the electron donor structures. In the absence of X-ray structures, valuable computational studies have been provided[45] by Patil, whose studies examine the importance of aggregation in facilitating electron transfer in the initiation reactions.

The experiments discussed above reflect ground state chemistry, but the situation may be different and even more extensive for excited state reactions. Rossi *et al*. have been chief proponents of the use of light in BHAS-type coupling reactions, particularly in the presence of DMSO.[46,47] and authors have proposed that DMSO anion may be the electron donor in certain reactions[48-50] In relation to phenanthroline, Yuan *et al.* showed[51] that besides thermal activations, visible light can be used effectively to generate electron donor species by *direct* reaction of phenanthrolines with KO*t*Bu within a complex. Similarly, Nocera *et al.* showed[52] that visible light-promoted direct electron transfer from KO*t*Bu to benzophenone form the corresponding blue potassium ketyl, a known strong electron donor. These interventions of visible light including routine daylight can lead to reactions that are otherwise completely unexpected.

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