The role of organic electron donors in the initiation of BHAS base-induced coupling reactions between haloarenes and arenes

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Abstract.

Coupling reactions between haloarenes and arenes (including heteroarenes) that are conducted without added transition metals but in the presence of KO^{t}Bu or NaO^{t}Bu, have been a topic of great interest since their discovery in 2008. Diverse organic structures act as additives that assist these reactions. These additives are converted into organic electron donors by the butoxide base and this leads to initiation of the coupling reactions, which proceed by radical chain mechanisms. This review provides an overview of the initiation stages of these reactions.

Keywords: Organic electron donor, potassium *tert*-butoxide, electron transfer, BHAS coupling, benzyne

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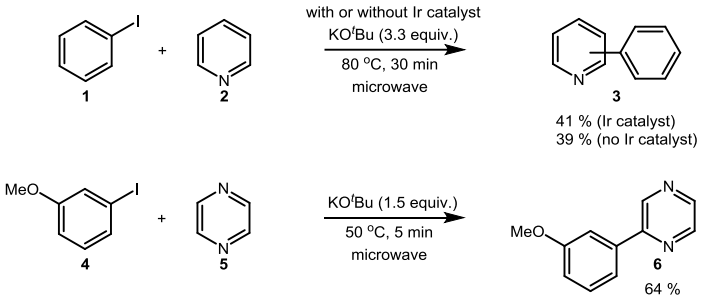
1 Introduction

Coupling reactions that are catalysed by transition metals, often palladium, are of profound importance in synthetic chemistry. Given the cost of precious metals and the toxicity of metal residues, chemists are very interested in processes that use non-precious transition metals or that avoid transition metals completely. This explains the excitement that surrounded the report of coupling of iodoarenes to heteroarenes by Itami *et al.* in 2008 (Scheme 1) in the absence of added transition metals.[1] During the exploration of iridium catalysts in the coupling of iodobenzene **1** with pyridine **2** to produce product **3** in the presence of KO^{t}Bu, it was found that the best iridium catalyst gave a comparable result to the reaction with no iridium catalyst present (41% and 39% yield respectively). The reactions, in the absence of catalysts, were extended to other electron-poor heteroarenes, *e.g.* pyrazine **5**, and were optimised to give excellent yields. By using more substituted iodoarenes *e.g.* **4**, it was established that the carbon involved in the original C-I bond in the haloarene was the carbon used to form the C-C bond to the heteroarene. The use of common radical scavengers such

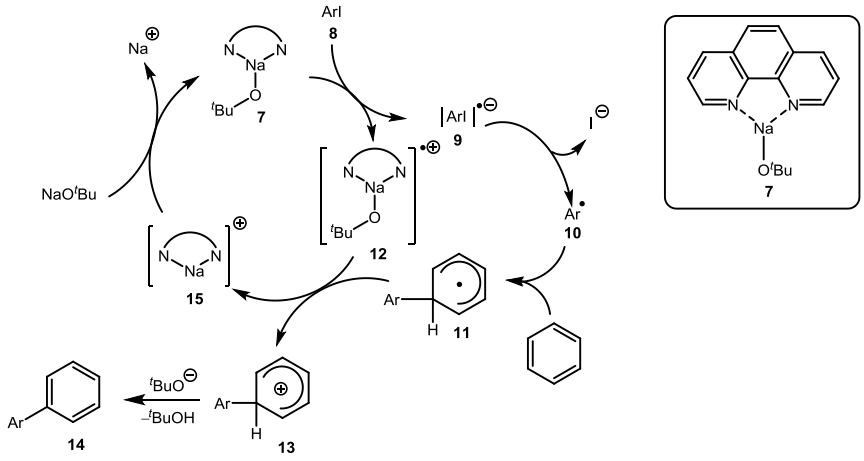
as TEMPO saw a dramatic decrease in yield (to < 1%), leading to the proposal of a radical intermediate in these reactions.

In 2010, the groups of (i) Shi *et al*.,[2] and (ii) Shirakawa and Hayashi *et al*.[3] and (iii) Kwong, Lei *et al.*[4] independently reported the use of substoichiometric amounts of organic additives, along with alkali metal *tert*-butoxides, to promote the transition metal-free coupling of a



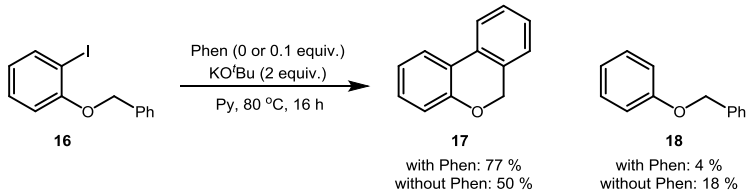
Scheme 1 – Coupling reactions reported by Itami et al.[1]

variety of iodo- and bromo-arenes with arene coupling partners. Kwong, Lei *et al*.[4] achieved high yielding couplings using 1,2-diols, 1,2-diamines, amino alcohols and also used the amino acid, proline, to facilitate coupling reactions of haloarenes to arenes in the presence of KO^{t}Bu. They also showed the involvement of radical anions as intermediates in the mechanism. Shi, and Shirakawa and Hayashi used phenanthroline as an additive. Shi proposed also that radicals were key intermediates in these reactions, although it was not clear how the radicals formed, nor what mechanism led to the coupled product. Shi also reported intramolecular coupling reactions.



Scheme 2 - Mechanism suggested by Shirakawa, Hayashi et al.[3]

In their publication, it was suggested by Shirakawa and Hayashi that the complex of NaO^{t}Bu with phenanthroline (**7**, Scheme 2) donates a single electron to the aryl halide **8** to produce a radical anion **9**. This then dissociates into an aryl radical **10** and an iodide anion. Aryl radical

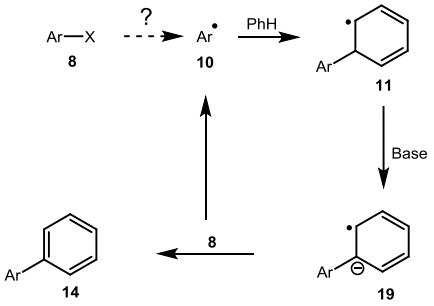


Scheme 3 - Charette's intramolecular cyclisations[5]

10 adds to benzene to produce a cyclohexadienyl radical **11**, which is subsequently oxidised by radical cation **12** to produce a *tert*-butoxide anion, complex **15** and cation **13**. Deprotonation of **13** by *tert*-butoxide affords coupled product **14** and *tert*-butanol. The sodium-phenanthroline complex **15** can then react with more sodium *tert*-butoxide to regenerate **7** and continue the cycle.

Studies by Charette in 2011 also showed intramolecular arylation of **16** with phenanthroline (phen) and KO^{t}Bu in pyridine as solvent, affording **17** and **18** (Scheme 3).[5] These reactions also afforded **17** and **18** in the absence of phenanthroline when pyridine was used as solvent, albeit in lower yield. When KO^{t}Bu was replaced with NaO^{t}Bu, no reaction occurred and only starting material was recovered. The authors proposed that this reaction proceeds via electron transfer to the aryl iodide to afford an aryl radical followed by cyclisation, but did not comment on the species responsible for the initial electron transfer.

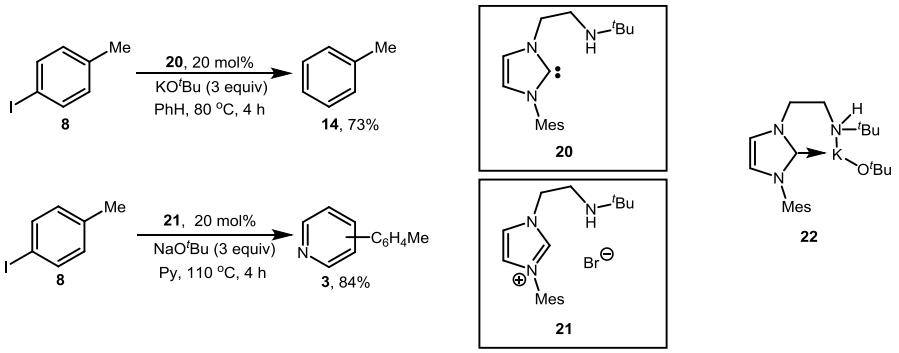
In 2011, Studer and Curran further explored the mechanism for KO^{t}Bu-mediated electron transfer reactions.[6] The common features of these coupling reactions were the coupling of a haloarene to an arene in the presence of KO^{t}Bu (or sometimes NaO^{t}Bu) and a nitrogen heterocycle; the heterocycle could either be a substrate heteroarene or simply an additive to the reaction. They proposed a key role for KO^{t}Bu in these reactions, leading to the Base-promoted Homolytic Aromatic Substitution (BHAS) mechanism shown in Scheme 4 that is now widely accepted.



Scheme 4 – Studer and Curran's BHAS cycle[6]

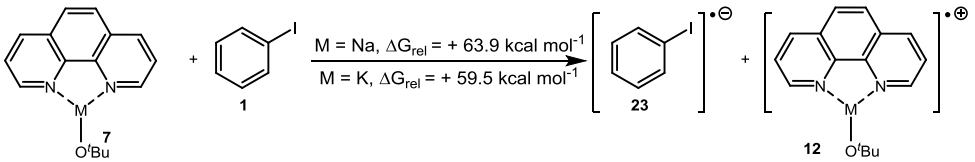
Aryl halide **8** is transformed to aryl radical **10** by a mechanism that was unknown at that time. This aryl radical undergoes addition to a molecule of benzene to produce radical **11**, which is deprotonated by potassium *tert*-butoxide to form radical anion **19**. This is a strong

electron donor, and so this is a striking example of 'upconversion' of reducing power, arising by deprotonation of a stabilised π-radical to a highly reactive radical anion where the unpaired electron is housed in a π*-orbital.[7] This radical anion can then undergo single electron transfer (SET) to another molecule of **8**, producing rearomatised coupled product **14** while regenerating another aryl radical **10**, which can propagate the chain. However, the method of initiation of the reaction through initial formation of radical **10** was still unknown at this point. The initiation of these and related coupling reactions is the focus of this review.



Scheme 5 - Arylation of benzene and pyridine by Chen, Ong et al.[8]

In 2012, Chen, Ong *et al.* reported the arylation of benzene and pyridine promoted by heterocyclic carbenes (*e.g.* **20**) or their precursor imidazolium salt precursors (*e.g.* **21**).[8] In this work, iodoarenes **8** were coupled to benzene or pyridine using KO^{t}Bu or NaO^{t}Bu and a heterocyclic carbene or imidazolium salt, to afford the products **14** and **3**. Carbene **20** and salt **21** were the most successful examples (Scheme 5). They proposed that the BHAS chemistry is initiated via SET from a complex of the carbene additive with KO^{t}Bu, *e.g.* **22**.



*Scheme 6 - Calculations of the thermodynamic barrier for ground-state electron transfer from complex **7** to iodobenzene **1**.*[9]

The studies of Chen and Ong with imidazolium salts, and those of Shi and Shirakawa and Hayashi with phenanthroline were of great interest to the Murphy team. Looking at complex **7** (M = Na), it was difficult to envisage how it could be a strong electron donor in its ground state – it features three components: (i) an electron-deficient heterocycle, phenanthroline, (ii) a sodium cation and (iii) a *tert*-butoxide anion, each of which would separately be a very reluctant electron donor. The proposal of **22** as an electron donor looks to be analogous. (i) An N-heterocyclic carbene, (ii) a potassium cation and (iii) a *tert*-butoxide anion would be unlikely to undergo electron transfer to aryl halides in the ground state. The common feature

of these two models **7** and **22** is the complexation of the metal butoxide. It might be considered that this complexation would lead to an enhanced separation of the metal ion from the *tert*-butoxide anion. This greater exposure of the charged anion in a relatively non-polar solvent like benzene, might provide some driving force for the butoxide entity to become neutral by transferring an electron, but the size of any such effect needed to be quantified.

Accordingly, in 2014, Tuttle, Murphy *et al.* reported their studies on the initiation step of the BHAS cycle.[9] Focusing on complex **7**, they calculated computationally that the free energy change (*i.e*. the thermodynamic difference, and not the kinetic barrier) for the electron transfer from the sodium ion complex with phenanthroline suggested by Shirakawa and Hayashi (**7**) to iodobenzene **1** was $\Delta G = +63.9$ kcal mol^{-1}, and $\Delta G = +59.5$ kcal mol^{-1} for the analogous potassium ion case. This ruled out **7** as the source of the initial electron transfer, and suggested that a different species must be produced *in situ* to cause the electron transfer. Similarly, they were concerned about species **22**, arising from precursor imidazolium salt **21**.

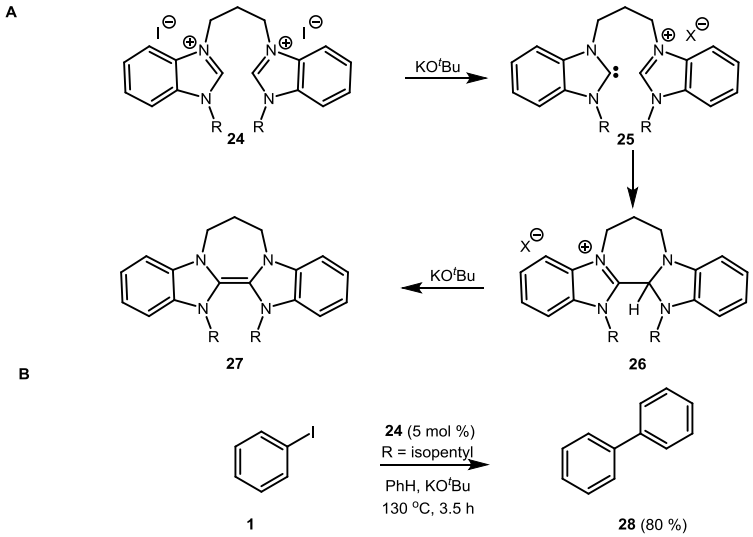
2 Providing a mechanistic picture for initiation of BHAS coupling through organic electron donors

2.1 Super Electron Donors facilitate the initiation of BHAS coupling while benzynes can provide a slower initiation

Back in 2005 and 2007, Murphy *et al.* had exploited the reactivity of tetraazafulvalene dimers, formed respectively from treatment of benzimidazolium[10] and imidazolium salts[11] with base. In the example in Scheme 7A, the base converts the imidazolium salt **24** into an N-heterocyclic carbene **25**, which then nucleophilically attacks the other imidazolium salt within the molecule. A second deprotonation then converts **26** into the tetraazafulvalene **27**. These 'dimers' were the first neutral ground-state organic molecules to reduce aryl iodides to aryl radicals or aryl anions, and were termed 'super electron donors'.[10,11] If aryl radicals, generated by compound **27** on reaction with iodobenzene **1**, could achieve coupling to benzene to form biphenyl **28** under BHAS conditions, then, in the first instance, that could allow an alternative interpretation of initiation of radical chemistry in the reactions of Chen and Ong with imidazolium salts, and later might provide a clue to the role of phenanthroline.

The initial test reaction used donor precursor salt **24**, iodobenzene **1**, and potassium *tert*-butoxide in benzene (Scheme 7B). The expected coupling product, biphenyl **28**, was formed in 80% yield, (Salt **24** forms electron donor **27** in the presence of a strong base. This donor then initiates BHAS chemistry by electron transfer to substrate **1**).

Conditions for the formation of **28** from **1** were studied. At 130 ^{o}C for 3.5 h with 5 mol% **24**, biphenyl **28** was formed in 80% yield (Table 1, entry 1).[9] When the reaction temperature was



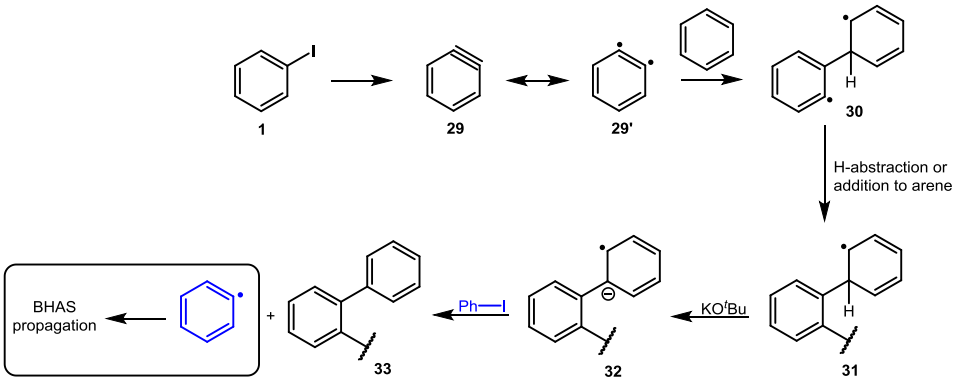
Scheme 7 – Tetraazafulvalenes can initiate coupling of iodobenzene with benzene to produce biphenyl[9]

*Table 1 – Formation of biphenyl **28** using salt **24** as precursor to electron donor **27***

Entry	**24** (Mol %)	Temperature	**28** (%)
1	5	130 ^{o}C	80
2	5	110 ^{o}C	47
3	0	130 ^{o}C	30
4	0	110 ^{o}C	27

dropped to 110 ^{o}C, the yield dropped to 47% in the presence of 5 mol% disalt **24.** When the reaction was conducted in the absence of disalt **24**, however, biphenyl was still formed but in a much lower yield (30% at 130 ^{o}C and 27% at 110 ^{o}C). These results showed that the presence of the salt **24** accelerated the reaction considerably. Murphy *et al.* therefore learned that an accelerated pathway to the product arose in the presence of the electron donor **27**, but an alternative and slower pathway still existed in its absence, *i.e.* when only ArI, PhH and KO^{t}Bu were present.

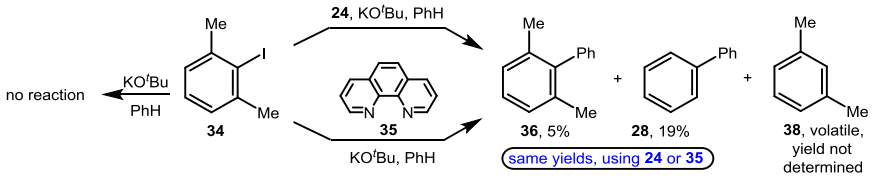
Considering firstly the slower pathway, benzyne was proposed as the initiator in the absence of the electron donor. This was supported in the literature, where a number of papers had reported the behaviour of benzyne as a 1,2-diradical.[12-14] This pathway would then see benzyne, **29'**, generated in very small quantities by the reaction of KO^{t}Bu with iodobenzene **1**, add to benzene to give distal diradical **30** (Scheme 8). The aryl radical is the more reactive of the two radicals in **30**. This could undergo rapid addition to another molecule of



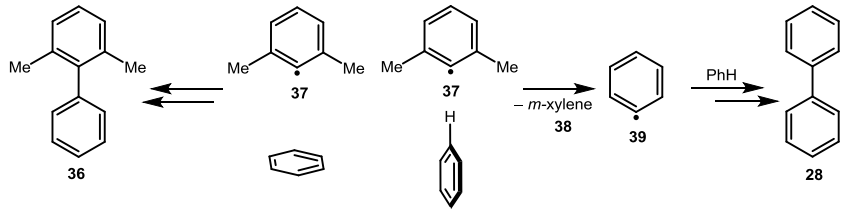
Scheme 8 - Benzyne can initiate BHAS coupling reactions[9]

benzene or hydrogen atom abstraction from benzene to afford **31**. Deprotonation would afford radical anion **32** which could then donate an electron to iodobenzene to form the phenyl radical that starts the propagation stage of the BHAS cycle. In this way, benzyne is involved in the initiation step, but not in the propagation steps. Provided that the rate of initiation is much slower than the propagation rate, no products derived from benzyne will be detected in the products.

To test this proposal and to separate the faster electron-donor induced coupling from the slower benzyne-induced coupling, substrate 2,6-dimethyliodobenzene **34**, was selected, which is blocked in the *ortho* positions by methyl groups. No reaction occurred[9] in additive-free conditions, supporting the theory that this slower coupling reaction was occurring via a benzyne mechanism. When the reaction was repeated in the presence of the salt **24**, precursor of donor **27** *in situ*, the expected coupling product **36** was formed in 5% yield, along with 19% biphenyl **28** and recovered starting material **34** (36%) (Scheme 9). The formation of **28** from this reaction is explained in Scheme 10. Electron transfer from donor **27** to substrate **34** affords radical **37** and an iodide anion. The 2,6-dimethylphenyl radical **37** is too sterically hindered to undergo efficient C-C bond formation with benzene, and is more likely to undergo hydrogen atom abstraction from benzene to form the volatile *m*-xylene **38** and phenyl radical **39**, which can undergo addition to benzene to form biphenyl **28** (Scheme 10) by BHAS chemistry. The ratio of products **28** (19%): **36** (5%) was noted.



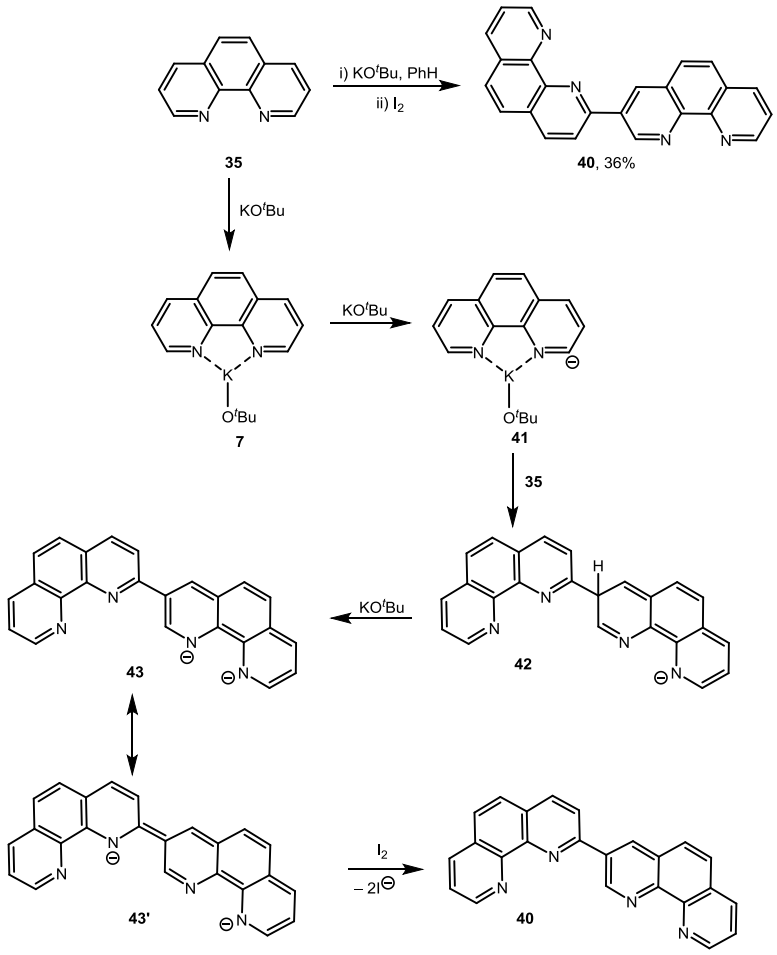
*Scheme 9 - Reaction of 2,6-dimethyliodobenzene **34***



*Scheme 10 - Different pathways of reaction for 2,6-dimethylphenyl radical **37***

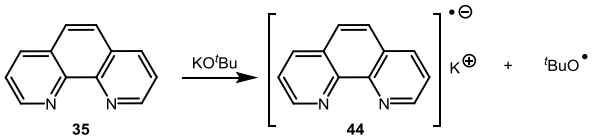
2.2 Dimerisation of phenanthroline and pyridine affords organic electron donors

With substrate **34** now identified as a probe for electron transfer initiation, we were curious to test whether the phenanthroline conditions would indicate electron transfer, or whether a different mechanism would be required. Reaction of substrate **34** with 1,10-phenanthroline **35** (20 mol %) and potassium *tert*-butoxide (2 equiv.) in benzene produced coupled products **36** (5 %) and biphenyl **28** (19 %) not only in the same ratio, but in the same yields as seen with salt **24**. This supported the idea that electron transfer was involved in initiation when phenanthroline **35** was the additive. The question was: how could the presence of phenanthroline lead to formation of an electron donor?[15]



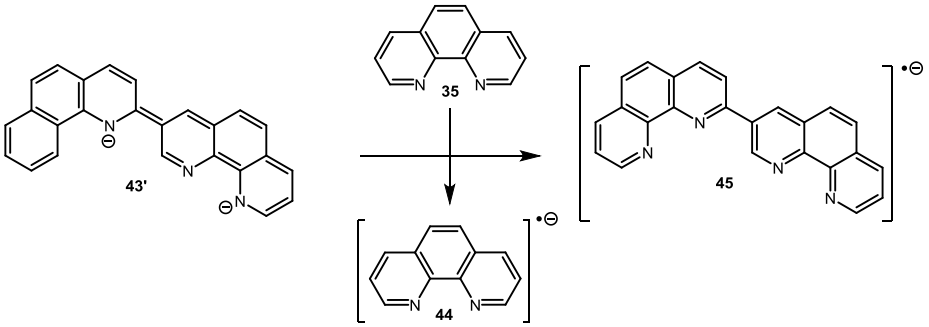
*Scheme 11 - Formation of phenanthroline dimer **43** as an in situ electron donor*[9]

These phenanthroline reactions always gave rise to a dark-green, almost black, precipitate.[9,15] To find out what was the origin of this precipitate, phenanthroline **35** and potassium *tert*-butoxide were heated in the absence of the haloarene substrate, and still gave rise to the formation of the dark-green solid. When this solid was exposed to air, it was found to be pyrophoric. The experiment was repeated and this time the green solid was instead quenched under milder conditions with iodine (as an electron acceptor), leading to isolation of phenanthroline dimer **40** (Scheme 11). Here, **35** complexes to potassium *tert*-butoxide to form **7**, which is subsequently deprotonated to form anion **41**. Anion **41** can then act as a nucleophile and attack at the 3-position of another molecule of phenanthroline **35** to form intermediate **42** which, upon further deprotonation, forms dianion **43**. The similarity of **43** to other super electron donors, such as **27**, is clear, as they contain an electron-rich alkene which is capable of donating an electron to an aryl iodide to initiate the BHAS cycle. This provides an explanation for initiation occurring in Shi's and Shirakawa and Hayashi's work.



Scheme 12 - Jutand and Lei's suggestion for the role of phenanthroline[17]

Electron transfer from KO^{t}Bu to 1,10-phenanthroline complex was also proposed by Wilden *et al.*[16] and by Jutand, Lei *et al*.[17] Jutand and Lei used electrochemical methods and electron paramagnetic resonance (EPR) spectroscopy to determine that radicals are present when KO^{t}Bu and 1,10-phenanthroline react with each other. They found that the combination of these two reagents led to an EPR signal, consistent with the formation of radicals, and proposed that these radicals must be the relatively long-lived species **44**, formed from electron transfer from the butoxide anion to phenanthroline **35** (Scheme 12). They proposed that this species is the one that then reduced the aryl iodide to an aryl radical, and initiated the coupling reaction. Their EPR spectrum is similar to that of a phenanthroline radical anion, but the asymmetry of the spectrum would be more consistent with the presence of two similar, but not identical, radical anions (see below).



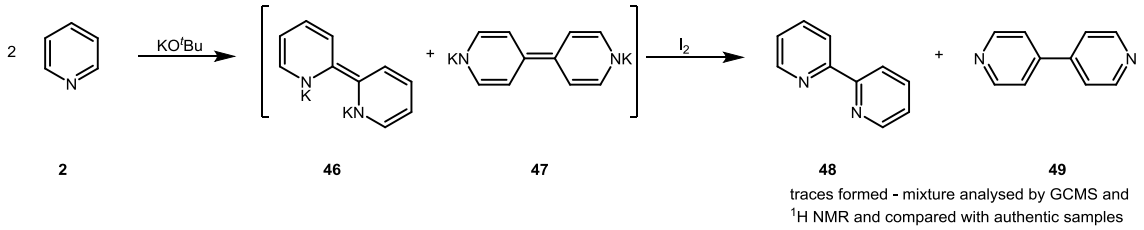
*Scheme 13 - Murphy's proposal for the formation of radicals with phenanthroline **35** and KO^{t}Bu*

Moreover, their electrochemical studies do not support their proposal, as they show that the tert-butoxide anion (with an oxidation potential of + 0.10 V vs. SCE in DMF) is not capable of reducing aryl iodides (reduction potential of – 2.0 V vs. SCE in DMF). It is therefore unlikely that the butoxide anion will reduce phenanthroline (first reduction potential of – 2.06 V vs. SCE in DMF) as the authors suggest. The authors propose that this reduction might occur due to the formation of a phenanthroline-KO^{t}Bu complex where the complexation with a potassium cation brings the butoxide close to the phenanthroline, aiding the electron transfer.

Murphy *et al.* have suggested that if the phenanthroline dimer **43'** forms, then this is a strong enough electron donor to reduce a neutral molecule of phenanthroline **35** (reduction potential of – 2.05 V vs. SCE in DMF) to its radical anion **44**, and this co-existence of the two radical anions **42** and **45** is the reason for the observation of radical species in the complex EPR spectra of Jutand and Lei (Scheme 13).

This use of phenanthroline + KO^{t}Bu as a donor has recently been deployed in further coupling reactions.[18]

All of the discussions above relate to ground state reactivity, but it should be borne in mind from the work of Yuan et al.[19] that irradiation of the phenanthroline/KO^{t}Bu system with a strong source of visible light can lead to direct electron transfer from KO^{t}Bu to phenanthroline.



*Scheme 14 - Dimerization of pyridines provides donors **46** and **47**.*

This phenanthroline example provided further evidence that an organic electron donor could be the initiator for the coupling reaction, and so this became a theme in our work. The next example was pyridine, which had been used as an initial substrate by Itami and which was a key solvent in the results of Charette *et al.* Structural similarity meant that pyridine was likely to behave like phenanthroline, and so it was treated with potassium *tert*-butoxide followed by quenching with iodine. This led to dimeric products **48** and **49**, analogous to those seen for phenanthroline, albeit in much lower yield. Therefore, **46** and **47** are produced *in situ* and act as electron donors to initiate coupling. Thus, it seemed that initiation through *in situ* formation of organic electron donors could rationalise the coupling results of Itami, Shi, Shirakawa and Hayashi, and Charette.

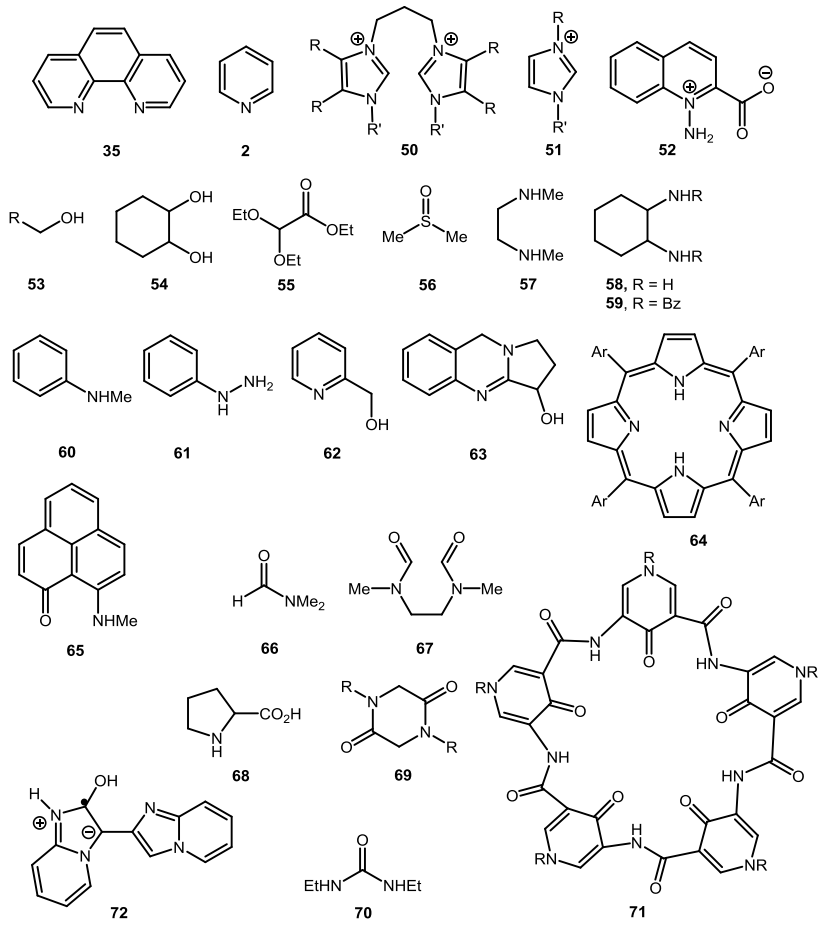
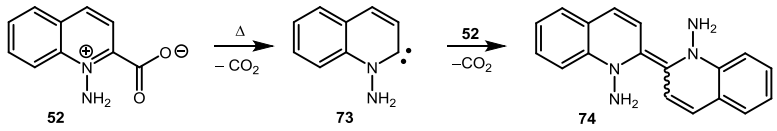


Figure 1 - A selection of additives that promote coupling reactions

A wide range of other organic additives is known to promote the coupling of iodoarenes to arenes, including alcohols, amines, amino acids, pyridinols, formamides, and DMSO, amongst others. (Figure 1). The role of a large number of these additives was identified by Murphy *et al.*[9,15] It was proposed that these additives react with KO^{t}Bu to form electron donors, and it is these electron donors which initiate the coupling reactions.

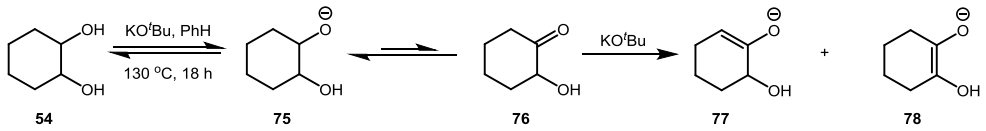
The current list features some common themes. Phenanthroline **35** and pyridine, **2**, just discussed, are electron-poor heterocycles that undergo deprotonation followed by dimerization. Imidazolium salts **50** and **51** also undergo dimerization following deprotonation but, in this case, an N-heterocyclic carbene is an intermediate. The zwitterionic heterocycle, **52**,[20] is in the same family, since it is known to undergo decarboxylative dimerization to afford species **74**, featuring an electron-rich alkene (Scheme 15). Product **74** is also a hydrazine, where deprotonation of the NH_2 group(s) could enhance the electron donor nature of the compound (see below for phenylhydrazine **61**).



*Scheme 15 - Formation of electron donor **74***

2.3 Primary and secondary alcohols, 1,2-diols and diamines are oxidised by loss of hydrides; the products are precursors to organic electron donors

Simple aliphatic alcohols[21] (not tertiary) **53** and 1,2-diols such as 1,2-dihydroxycyclohexane[4] (**54**, both *cis*- and *trans*- isomers) form *in situ* electron donors on treatment with KO^{t}Bu. Thermal studies on cyclohexanediols **54** showed oxidation to ketone **76** by hydride ion expulsion (Scheme 16).[15] The same occurs for monoalcohols **53**. Alkoxides **75** are normally oxidised to ketones via the Oppenauer oxidation, but it was shown many decades ago by Woodward *et al.* that hydride loss also occurred on heating with potassium *tert*-butoxide in toluene.[22] Deprotonation of the resulting ketone **76** then gave enolates of type **77** and/or **78**, which are likely initiators of electron transfer. It is proposed that **78** is a better electron donor than **77**, as it features a more electron-rich alkene. The deprotonation states of these enolates have not been explored; both may form dianions by a second deprotonation on the hydroxyl group.

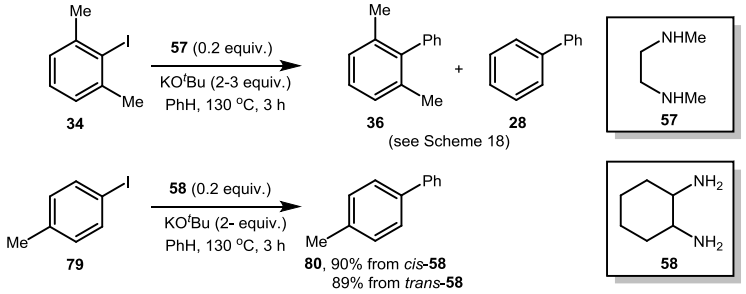


*Scheme 16 – Formation of Electron Donors **77** and **78** from **54***

Previous reports by Bunnett, Scamehorn and Rossi had shown that enolates of simple ketones such as pinacolone or acetone can act as efficient electron donors to aryl halides in ground-state $S_{RN}1$ reactions, and this explains their facilitation of coupling reactions here.[23-25] Esters such as **55** form enolates that are substituted by additional electron-releasing ethoxy groups and so it is not too surprising that they are particularly effective as electron donors.

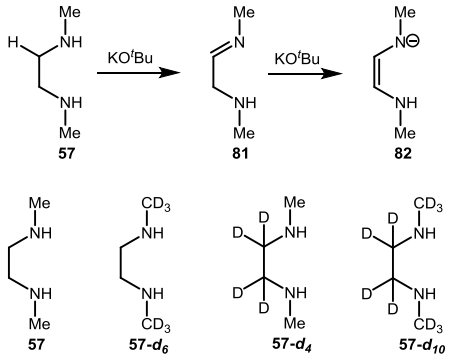
DMSO **56** has also previously been reported to act as an electron donor to aryl halides via formation of the dimsyl anion.[26]

Simple amines, such as di-*n*-butylamine were found to exhibit no activity in the coupling of haloarenes to arenes; however 1,2-diamines such as *N*,*N*'-dimethylethylenediamine **57**, and **58** formed effective electron donors (Scheme 17).[4] Cyclohexane-1,2-diamine **58** was precursor to one of the best electron donors, allowing the coupling of 4-iodotoluene **79** to benzene to give 4-methylbiphenyl **80** in 89% and 90% yields for the *trans*- and *cis*- isomers respectively.



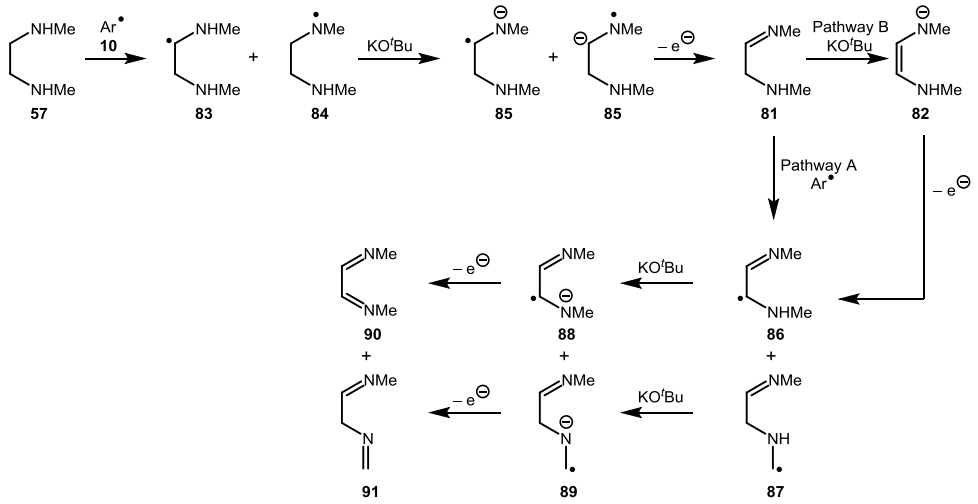
*Scheme 17– Amine additives **57** and **58** in transition metal-free coupling reactions*

The mechanism proposed for the formation of the active electron donor from amines involves the generation of the corresponding imine **81** from amine **57** by deprotonation and expulsion of a hydride. Upon deprotonation of **81**, electron-rich alkene **82** can be formed, and this is proposed as an electron-donating species. This is further backed up by use of deuterated isotopomers of **57** (Scheme 18). When **57**, **57-*d*$_6$**, **57-*d*$_4$**, and **57-*d*$_{10}$** were compared in side-by-side reactions involving coupling of iodoarene **34** to benzene, **57** outperformed all of the deuterated analogues, with **54-*d*$_4$**, and **54-*d*$_{10}$** returning only trace amounts of coupled products. This is consistent with the cleavage of a methylene C-H (or C-D) in the diamine being involved in the rate determining step of the initiation, in line with Scheme 18.



*Scheme 18 – Transformation of additive **57** and listing of isotopomers deployed to explore mechanism.*

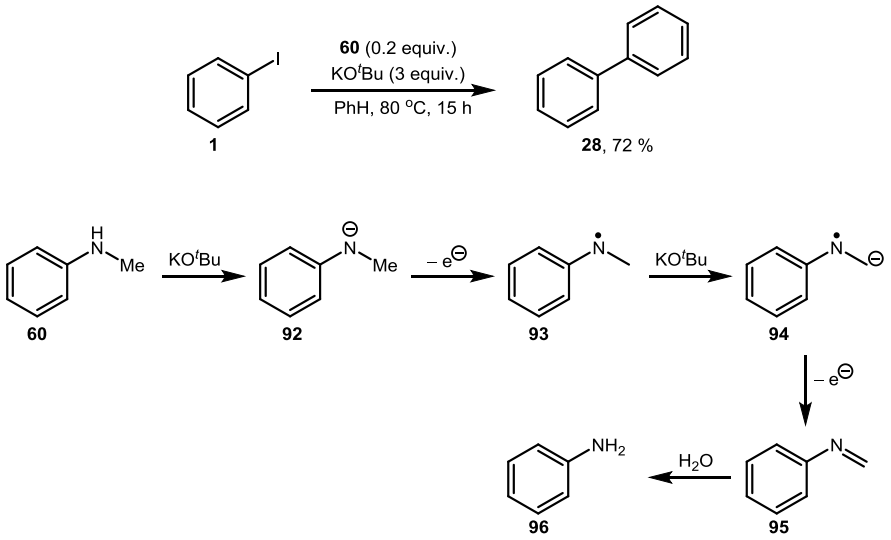
The mechanism of the diamine initiation was also studied by Jiao *et al.*, who proposed a modified and refined mechanism after experimental and computational studies (Scheme 19).[27] They proposed that, after formation of aryl radicals had started, the diamine **57** acted as hydrogen atom donor to aryl radicals **10**, forming radicals **83** and/or **84**, which undergo deprotonation by KO^{t}Bu to form radical anion **85**.



*Scheme 19 - Jiao's proposal for initiation with diamine **57***[27]

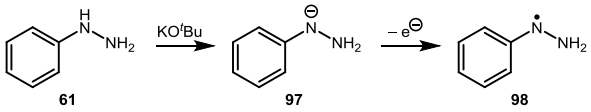
This radical anion **85** can then transfer an electron to the aryl iodide **8** to form the aryl radical **10** and join in the initiation of the reaction. The resulting compound **81** can then either transfer a hydrogen atom to an aryl radical to form the arene and radicals **86** and/or **87** via pathway A, or can be deprotonated to form electron-rich alkene **82**. Species **82** can also transfer an electron to the aryl iodide to initiate the coupling reactions, as previously proposed by Murphy *et al*., via pathway B. The resulting radicals **86** and/or **87** can be deprotonated and generate radical anions **88** and **89**, which are capable of further initiating the coupling reactions by electron transfer, forming imines **90** and **91**.

Developing the theme, Jiao *et al.* showed that *N*-methylaniline derivatives **60** promote the coupling reaction between aryl iodides and benzene (Scheme 20).[28] They proposed that deprotonation of *N*-methylaniline **60** to form anion **92** occurs, and this species is the active electron donor, donating an electron to the aryl iodide to initiate the chain process. The resulting radical **93**, formed after oxidation, can be deprotonated to form radical anion **94**, which can donate a second electron to a second molecule of aryl iodide, resulting in imine **95**. This imine could then hydrolyse upon work-up to produce aniline **96**, which was detected in the reaction mixture by GCMS. More recently, Jiao *et al.* have shown that indoline is an aryl amine precursor to a particularly effective organic electron donor that allows the coupling of aryl chlorides as well as bromides and iodides.[29]



*Scheme 20 - Formation of an electron donor from N-methylaniline **60***[28]

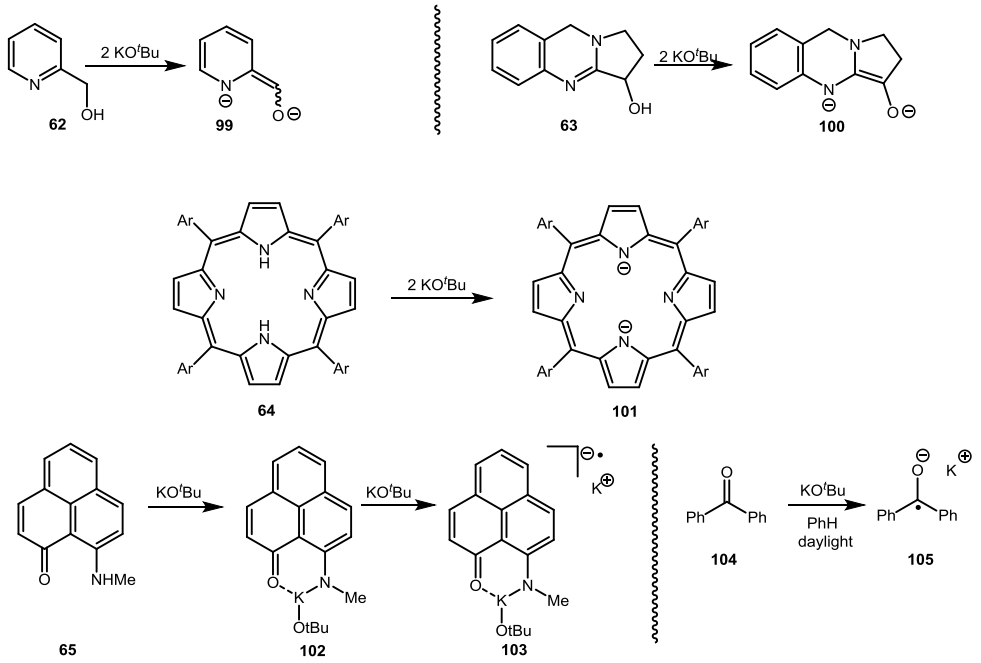
Curran, Studer *et al.* have shown that phenylhydrazine **61** (Scheme 21) is also effective in the coupling of iodoarenes to benzene.[30] Phenylhydrazines were proposed to be good initiators due to the α-effect from the lone pair of electrons on the adjacent nitrogen atoms which can stabilise the resulting radical after electron transfer. They propose that deprotonation of phenylhydrazine **61** occurs to form phenylhydrazide **97**, which can then act as an electron donor and form stabilised radical **98**. The aryl iodide radical anion, formed by the electron transfer, can then fragment and propagate as previously, ultimately forming biaryl products.



*Scheme 21 - Phenylhydrazide **97** as an electron donor*

Moving on to pyridinol **62**, this compound reacts with KO^{t}Bu to facilitate the coupling of haloarenes to benzene (Scheme 22).[31,32] Extensive investigation showed[32] that the electron donor resulted from double deprotonation of **62**, forming **99** as the electron donating initiator, reducing both aryl iodides and aryl bromides to aryl radicals.

Kumar *et al*. reported that alcohol **63** facilitates the coupling of various iodo- and bromoarenes to benzene with KO^{t}Bu. The authors propose a direct electron transfer from a KO^{t}Bu-**63** complex.[33] However, in view of the structural similarity to pyridinol **62**, we suggest that **63** is a prime candidate for double-deprotonation to form electron donor **100**, complexed with a potassium cation. Similarly, porphyrin **64** has two readily removable protons; double-deprotonation would afford **101** as an excellent candidate for *in situ* electron donor to initiation of BHAS reactions.[34]



*Scheme 22 – Proposed formation of dianionic electron donors **99**-**101** and **103**.*

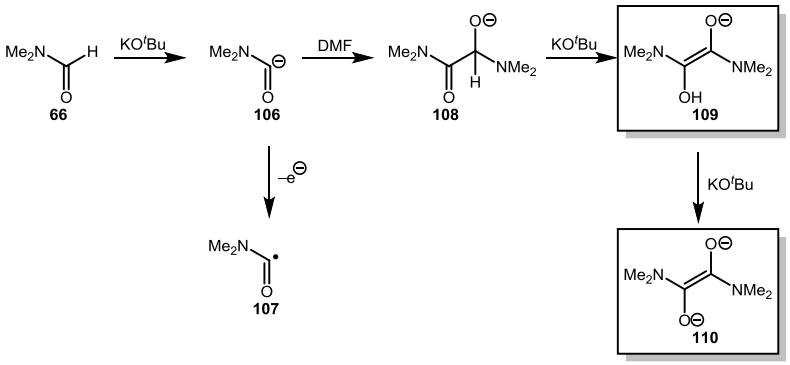
Mandal has vigorously pursued the chemistry of phenalenone **65** and related compounds, and this has been used for the coupling of haloarenes to arenes and to heteroarenes.[35,36] Treatment with KO^{t}Bu results in formation of a complex **102**, where the π-framework then receives an electron to form a radical dianion **103**. This compound is thought to be the active electron donor to aryl halides to initiate BHAS coupling. As **103** is powerful enough to donate an electron to the aryl halide and KO^{t}Bu is able to donate an electron to salt **102**, the question arises as to why KO^{t}Bu does not directly donate an electron to the aryl halide. This raises the question of whether the conversion of **102** to **103** may be subject to photo-assistance from daylight. If so, this would be analogous to the photoreaction of KO^{t}Bu[19] with phenanthroline, and to the conversion of **104** to **105**, reported recently.[37]

2.4 Dimerisation of DMF and other formamides affords organic electron donors

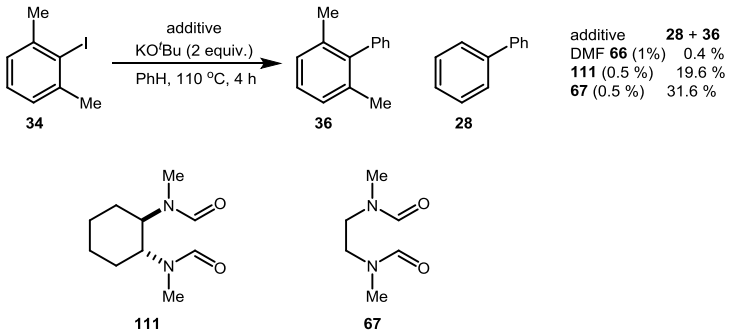
Formamides have been shown to be effective additives in the coupling of iodoarenes to benzene. Previous literature had suggested that the anion of DMF (**106**), formed after deprotonation with KO^{t}Bu, could act as an electron donor to various substrates, including to aryl iodides[38] or to another molecule of DMF (Scheme 23).[39] The latter proposal is untenable in view of recent calculations that indicate a kinetic barrier of > 50 kcal mol^{-1} [40]

Murphy *et al.* proposed[41] that the anion of DMF **106** can act as a nucleophile to a neutral molecule of DMF **66**, forming dimer **108**, based on literature precedent. Proton transfer would afford the enolate **109**, which has the electron-rich alkene structure reminiscent of a strong electron donor. Alternatively, further deprotonation could afford dianion **110**, which

could be an even more powerful electron donor (Scheme 23). Evidence for the formation of this dimer was given by the use of formamides **111** and **67** (Scheme 24). These formamides were found to be more active in the electron transfer to **34** than DMF, even at half the



Scheme 23 - Formation of an electron donor from DMF as proposed by Murphy et al.[41]



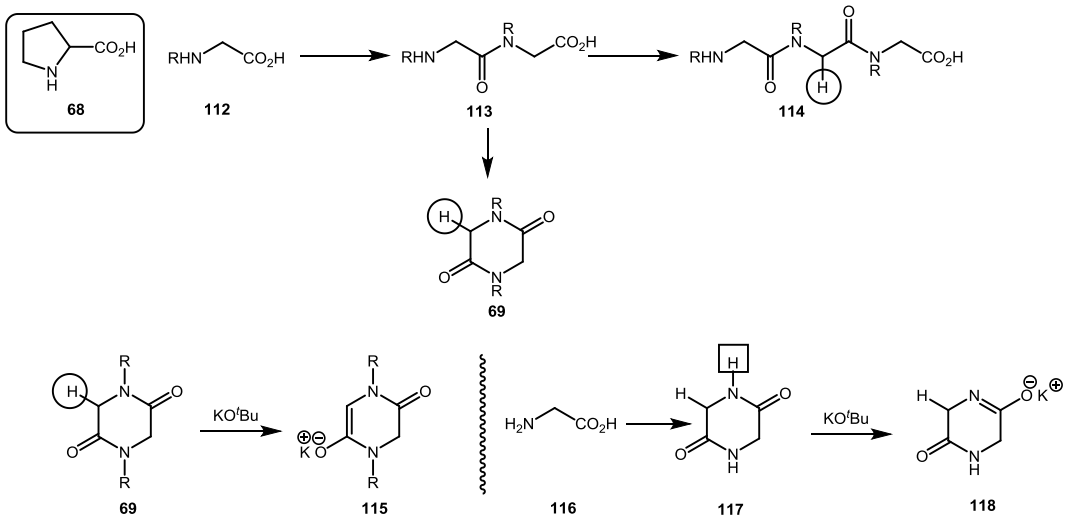
Scheme 24 - Comparison of formamides in electron transfer reactions[41]

concentration, suggesting that facilitating the reaction between two formamide groups really assists the formation of the active electron donor (it would be easier to form a dimer from **111** and **67** than from DMF **66** due to the intramolecular 1,6-relationship of the formamide groups).

2.5 N,N'-disubstituted piperazine-2,5-diones, derived from secondary aminoacids, are precursors to organic electron donors

Secondary amino acids such as proline, **68**, are also precursors to efficient electron donors, whereas primary amino acids are less effective and tertiary amino acids are ineffective.[4,42] As secondary amines are able to undergo condensation reactions with acids on heating, we envisaged forming small amounts of linear oligomers **113** and **114** or cyclic piperazinedione dimers **69**. Under the conditions of the coupling reactions, it is thought that small amounts of these compounds could form and that the enolate of such a species, formed by deprotonation, could act as a powerful electron donor. *N*,*N*'-dialkylpiperazinedione **69** was prepared independently and was shown to be a good electron donor[15] *via* enolate **115** (Scheme 25), whereas analogue **117** was ineffective, via enolate **118**. This is thought to be

due to the competing deprotonation between the CH_2 and the NH groups. As the NH is more acidic, that will be the site of deprotonation when an NH is present. When an amide enolate **118** is formed, it features an electron-poor imine into which some electron density is pumped by the oxyanion. On the other hand, enolate **115** is an alkene rather than an imine, and three electron-rich atoms (O, N, N) endow it with electron density. This explains why **115** is an excellent electron donor while **118** does not work as an electron donor.



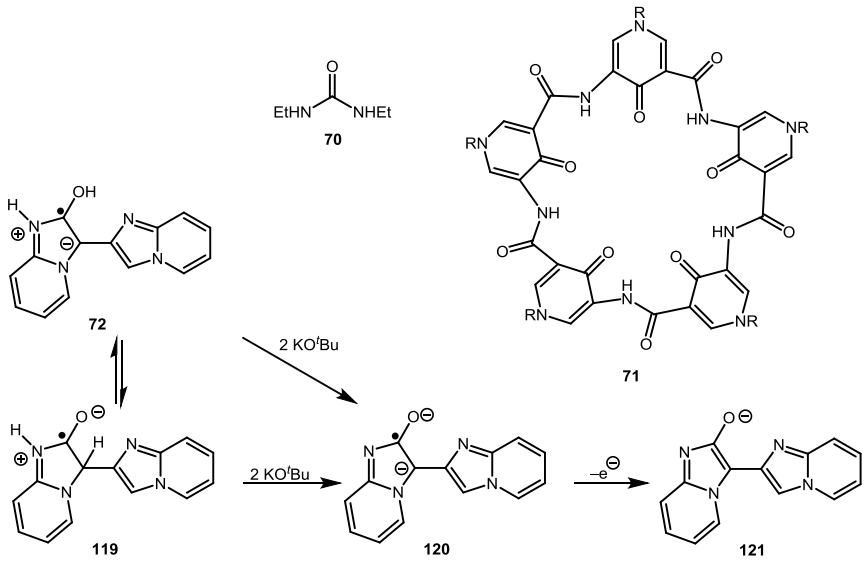
*Scheme 25 - Formation of electron donor **115** and structure of inactive piperazinedione precursor **117**.*[40]

2.6 Ongoing mechanistic challenges

Amide deprotonation likely also features in the two examples **70**[43] and **71**.[44,45] For the diethylurea **70**[46], no mechanistic investigation has been carried out, to our knowledge, although the authors claim that it follows the general guidelines for initiation of the reaction by electron transfer. Substrate **34** would be the ideal assay for initiation by electron transfer. Additive **71** and related compounds are known to bind potassium cations[44,45] and are thought to form an electron donor in the presence of KO^{t}Bu, but the precise structure has not yet been investigated.

More clarity also needs to arise about the mechanism of the coupling reactions that are triggered by KO^{t}Bu in the presence of some MOFs.[47]

Finally, additive **72** is an interesting zwitterion[48] - the problem is that the structure that represents it in the literature cannot feature the correct bonding. We suggest that the structure may be one or both of the isomeric structures **72** and **119** (Scheme 26). It is easily seen that treating this compound with base would form the radical dianion **120**, which is extremely electron-rich. Loss of an electron enhances the aromaticity of the system, by formation of **121**, supporting the role of **120** as a strong electron donor.



*Scheme 26 – Additives **70**-**72***

2. 7 Summary

This review shows that KO^{t}Bu, and sometimes NaO^{t}Bu, reacts with many classes of organic compounds to form strong electron donors that initiate BHAS coupling reactions. The common structural patterns of electron donors are represented in Figure 1. This behaviour is now widely accepted and replaces earlier proposals that KO^{t}Bu or NaO^{t}Bu were themselves good electron donors in the ground state. That error arose from the early work of Ashby *et al.*[49] involving misinterpretation of electron transfer from KO^{t}Bu to benzophenone as a ground state reaction. It is not, but it instead results from a visible light-induced photoelectron transfer[37] within a KO^{t}Bu-benzophenone complex.

Whereas the principles that underlie the formation of organic electron donors are discussed above, the details of structure still need to be better understood. For example, it is not clear why KO^{t}Bu is superior to NaO^{t}Bu in almost all of the cases discussed. This will be revealed as we understand more about the details of structure. Patil[50] has identified another factor relating to structure from his computational studies. There, he has explored the effect of aggregation in electron transfer complexes which may be very important for the future.

Chemists have traditionally focussed on reactions that afford high yields of products. This overview indicates that the generation of even very small yields of strong electron donors can divert reactivity into unexpected pathways, when these compounds act as *initiators* (it is important to stress that they are not catalysts) for BHAS chain reactions. Hence it is not only the high yielding reactions that we need to study.

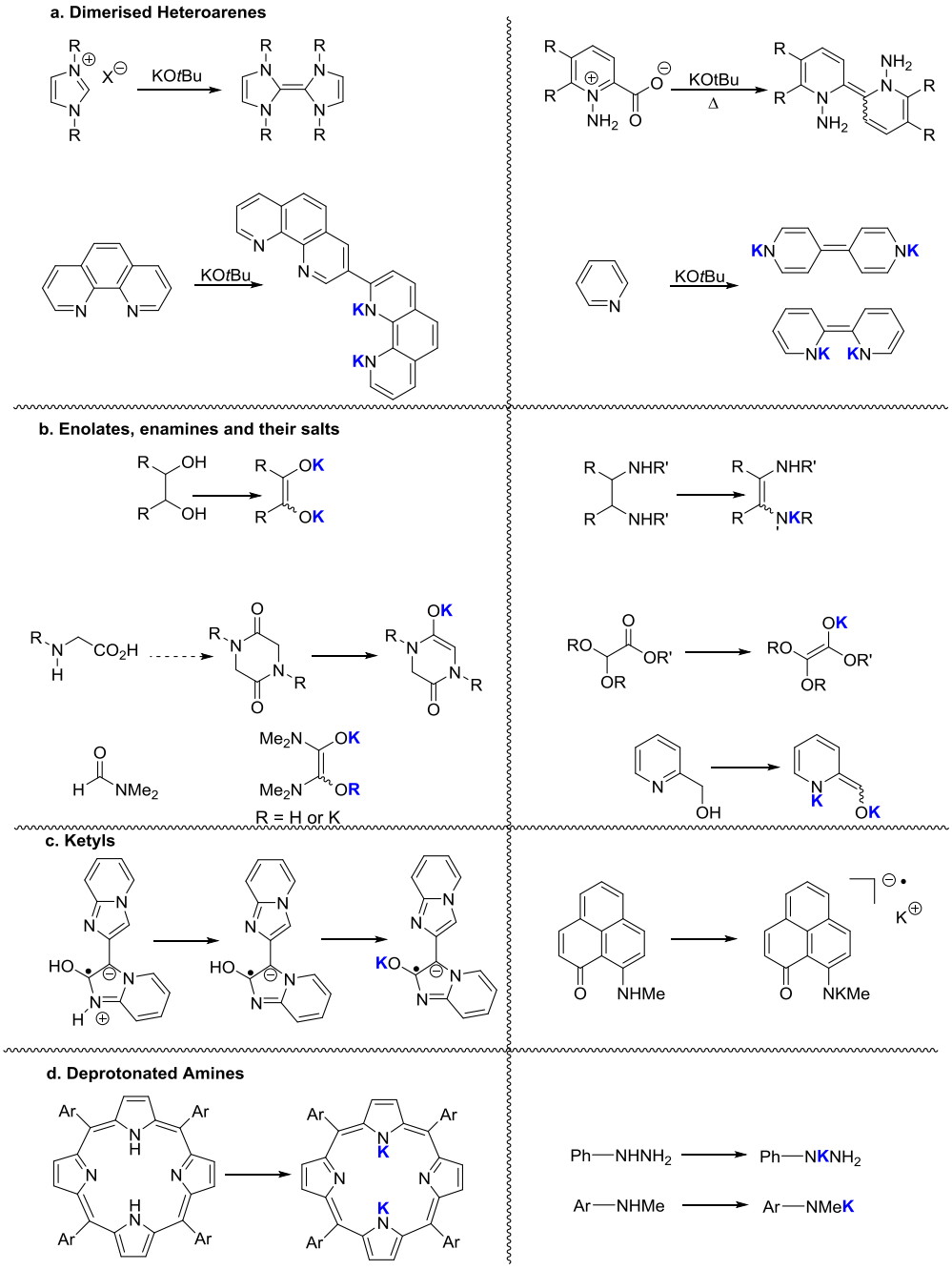


Figure 1. Types of organic electron donors, formed *in situ* in BHAS reactions, and their chemical precursors.

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Graphical abstract.

The role of organic electron donors in the initiation of BHAS base-induced coupling reactions between haloarenes and arenes

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