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Identifying the Roles of Amino Acids, Alcohols and 1,2-Diamines as Mediators in Coupling of Haloarenes to Arenes

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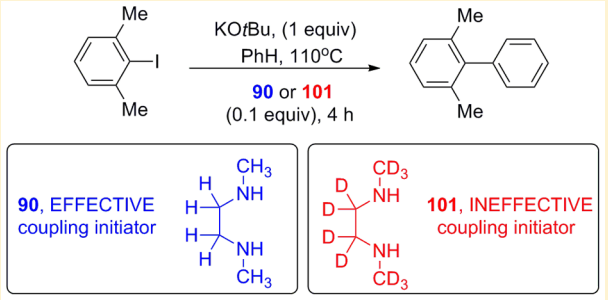
Supporting Information

ABSTRACT: Coupling of haloarenes to arenes has been facilitated by a diverse range of organic additives in the presence of KO^{t}Bu or NaO^{t}Bu since the first report in 2008. Very recently, we showed that the reactivity of some of these additives (e.g., compounds **6** and **7**) could be explained by the formation of organic electron donors in situ, but the role of other additives was not addressed. The simplest of these, alcohols, including 1,2-diols, 1,2-diamines, and amino acids are the most intriguing, and we now report experiments that support their roles as precursors of organic electron donors, underlining the importance of this mode of initiation in these coupling reactions.



INTRODUCTION

Formation of biphenyls[1] is of great importance both in industry and in academic chemistry. It has normally been achieved through coupling of arenes with the help of costly transition-metal catalysts. In pharmaceutical chemistry, purification of products from transition-metal impurities is necessary and is time-consuming, so development of alternative coupling routes is extremely worthwhile. Along these lines, Itami et al. reported[2] in 2008 the "transition-metal-free"[3] coupling of iodobenzenes with pyrazine and pyridine in the presence of KO^{t}Bu. This was followed by a large number of reports[4−36] of couplings of halobenzenes **1** with arenes or styrenes using KO^{t}Bu or NaO^{t}Bu in the presence of a range of organic additives **6**−**23** depicted in Figure 1. (In addition, a series of related couplings promoted by KO^{t}Bu has also emerged.[37−47])

A number of authors suggested that the products arose from reactions where aryl radicals were featured as intermediates.[2,4,7,9] Studer and Curran presented an overview of the area[12] and proposed that after addition of the aryl radical, **3**, to an arene, deprotonation of the resulting cyclohexadienyl radical **4** was achieved by the metal butoxide. The product would be **5**, the radical anion of a biaryl, which could then transfer an electron to another molecule of halobenzene to form the biaryl product **2**, together with a new aryl radical **3**, in a chain reaction (Scheme 1).

The mode of initiation of the reaction for most of these compounds, i.e., the origin of the initial aryl radicals, remained unknown, although a number of authors suggested that complexes formed between the metal alkoxide and additives such as phenanthroline **6**[4,9,35] or N-heterocyclic carbenes derived from imidazolium salts, e.g., **7**,[17,33] would function directly by electron transfer.

Organic electron donors have been studied intensively in recent years.[48−60] These range from TTF **24** through TDAE **25** to more recent examples **28**−**32**. In each case, an electron-rich alkene is present (shown in blue in Figure 2) that is substituted by multiple electron-releasing groups. When electron transfer occurs, the resulting radical cation [or dication, following transfer of two electrons] is stabilized by these groups. Additional driving force results from formation of new aromatic rings in the oxidized forms of most of these donors. Recently, we reported that organic electron donors, e.g., **28**, can act as initiators in coupling reactions between haloarenes and arenes,[51] forming aryl radicals by electron transfer to the haloarene. Donor **28**[52,60n] is formed *in situ* by treatment of precursor salt **26** with KO^{t}Bu. This affords an N-heterocyclic carbene **27**; attack of the carbene on the imidazolium salt within **27** gives an intermediate that, on deprotonation, affords tetraazafulvalene electron donor **28**.[61] In this and related reactions, the electron donor simply needs to initiate the aryl radical formation; the subsequent chain reaction (Scheme 1) is quite efficient, and so only an extremely low concentration of electron donor needs to be produced for a successful coupling reaction to be seen.

We proposed similarly[51] that imidazolium salts **7** could form tetraazafulvalene donors with KO^{t}Bu in the presence of a trace of ^{t}BuOH as a proton source.[17] Additionally, we showed that when the additive **6**, phenanthroline, was present, it was

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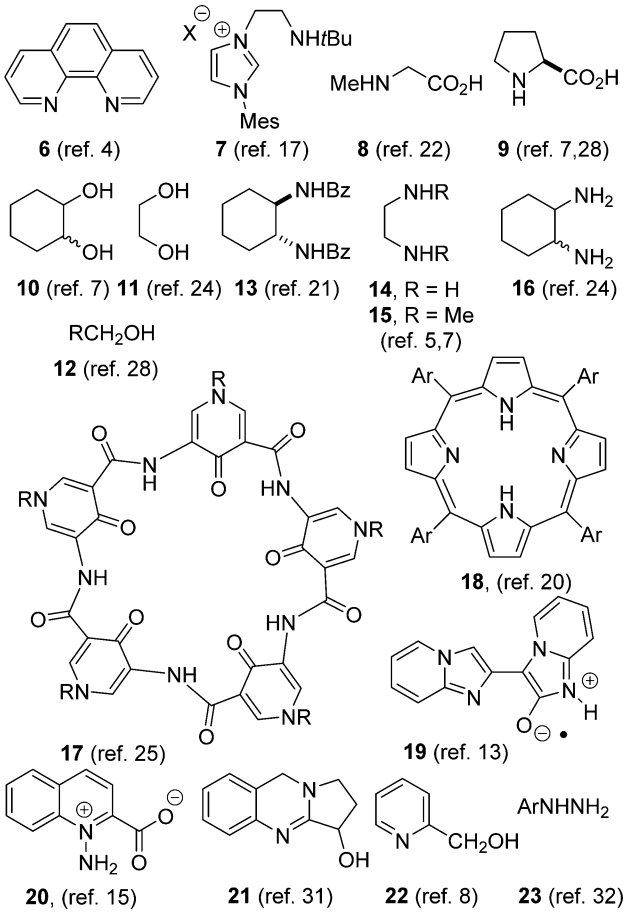
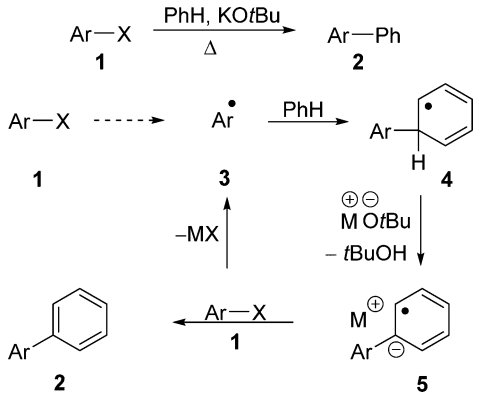


Figure 1. Selected organic additives that facilitate coupling of haloarenes to arenes in the presence of KO^{t}Bu or NaO^{t}Bu.

Scheme 1



converted by KO^{t}Bu into an organic electron donor, and similarly when pyridine was used as solvent in the presence of KO^{t}Bu, organic electron donors were formed.[51] The organic electron donors convert the haloarene into an aryl radical and a halide anion, thereby initiating the cycle shown in Scheme 1. The feasibilities of the observed reactions were supported by computational results. (The computational studies also showed that previously proposed electron transfer to iodobenzene from a complex of KO^{t}Bu with phenanthroline[4,9,35] would be prohibitively endergonic.[43]) Further investigation[51] showed that the coupling of iodobenzene to benzene with KO^{t}Bu occurs even in the absence of helpful additives like **28** and **6**,

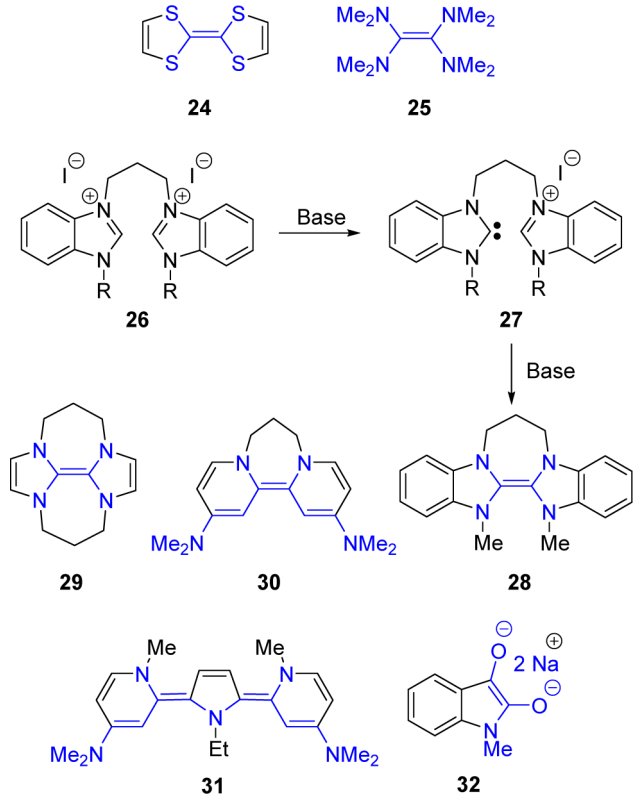


Figure 2. Organic electron donors.

although the reaction is much more sluggish. Traces of benzyne are known to be formed from reaction of butoxides with appropriate halobenzenes.[9,18] We proposed that, in the absence of additives to underpin electron-transfer chemistry, benzyne was formed and reacted as a diradical, initiating the formation of aryl radicals shown in Scheme 1. The propagation of the cycle within that scheme then secures the conversion to product.[51]

However, that still leaves a bewildering diversity of additive molecules, including **8**–**22** that facilitate the coupling reactions, and where the mode of action is not understood.[32] These include amino acids, where some examples are reported to be highly effective, while others were not at all effective. Notably, the secondary amino acids (those featuring secondary amines) sarcosine, **8**, and proline, **9**, were reported as highly active and much more so than primary amino acids.[22] Any explanation must take account of this. Alcohols,[28] including 1,2-diols,[7,24] and 1,2-diamines,[7,24] also feature prominently in the list. This paper addresses the role of amino acids and derivatives as well as alcohols, 1,2-diols and 1,2-diamines, and proposes a unifying mechanism of action for the generation of radicals from these additives.

RESULTS AND DISCUSSION

Amino Acids and their Derivatives. Looking at amino acids, the first point to establish was whether they indeed reacted by electron transfer under the conditions of the coupling reaction, as with our previous donor precursors, or by other routes. For this, we used 2,6-dimethyliodobenzene **33** as our diagnostic substrate (Scheme 2). This compound gives a characteristic ratio (approximately 4:1) of biphenyl **35** and 2,6-dimethylbiphenyl **34** by electron-transfer chemistry, as seen in our recent work.[51] The 2,6-dimethylphenyl radical **36** is

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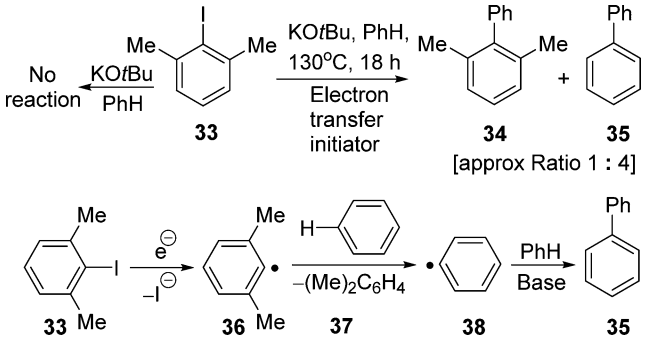
Scheme 2



sterically hindered, and this particularly slows its attack on the π-system of benzene that leads to formation of a C–C bond en route to **34**. In contrast, it can react more easily by hydrogen-atom abstraction from benzene to form a phenyl radical **38** (together with the volatile *meta*-xylene **37**). The phenyl radical then takes the place of the 2,6-dimethylphenyl radical **36** in carrying out coupling to benzene, leading to formation of biphenyl **35**. This indirect process is less efficient than that seen with less hindered iodobenzenes, and so while the yields of coupled product with unhindered iodobenzenes are high with efficient electron donors, they are routinely lower with this substrate, affording a mixture of **34** and **35** typically in about 25% combined yield. This does not detract from the value of substrate **33** as a diagnostic tool; it is not susceptible to benzyne formation and therefore is an unambiguous reporter of electron transfer. Moreover, as seen in the literature and as will be shown below, less hindered aryl halides provide excellent yields in coupling reactions with many types of initiator discussed here.

In the following experiments, 2,6-dimethyliodobenzene **33** (1 mmol) was used as the haloarene in benzene as solvent with KO^{t}Bu (2 equiv) and additive (0.2 equiv), unless otherwise stated. (For additives with an X–H bond, where X is a heteroatom, e.g., carboxylic acids or alcohols, 3 equiv of KO^{t}Bu were used.) The reactions were all performed under identical conditions of time and temperature, and the mass of 2,6-dimethylbiphenyl **34** + biphenyl **35** is noted below in brackets as 'a'; in experiments where low amounts of these products were produced, the reactions generally afforded high percentages of recovered starting material, and in each experiment this percentage is reported below as 'b'. The theoretical yield, based on a 1:4 ratio of the coupled products is 160 mg, so the "effective" electron donors gave 'a' >25 mg with this hindered substrate, and reactions that gave 0–0.5 mg of coupled products were classified as "not active" by electron-transfer initiation. A blank reaction where KO^{t}Bu was added to the substrate in the absence of additives gave a minute amount (<0.5 mg) of coupled products. It might be imagined that this background reactivity should be 0 rather than <0.5 mg, but it is clear that a very small amount of background reaction arises from other less prevalent pathways.[62]

The two amino acid test cases, sarcosine **8** (a = 44, b = 25%) and proline **9** (a = 32, b = 54%) (Figure 3), were indeed able to bring about the coupling reaction (with substrate **33** in benzene as solvent), and so we interpret their reactions as being due to electron transfer. The simplest source of electron transfer would be the enolate of these amino acids, present as a dianion—the dianion of sarcosine is shown as **39**. To test this, the C,C-dimethylamino acid **41** was tested and, as would be

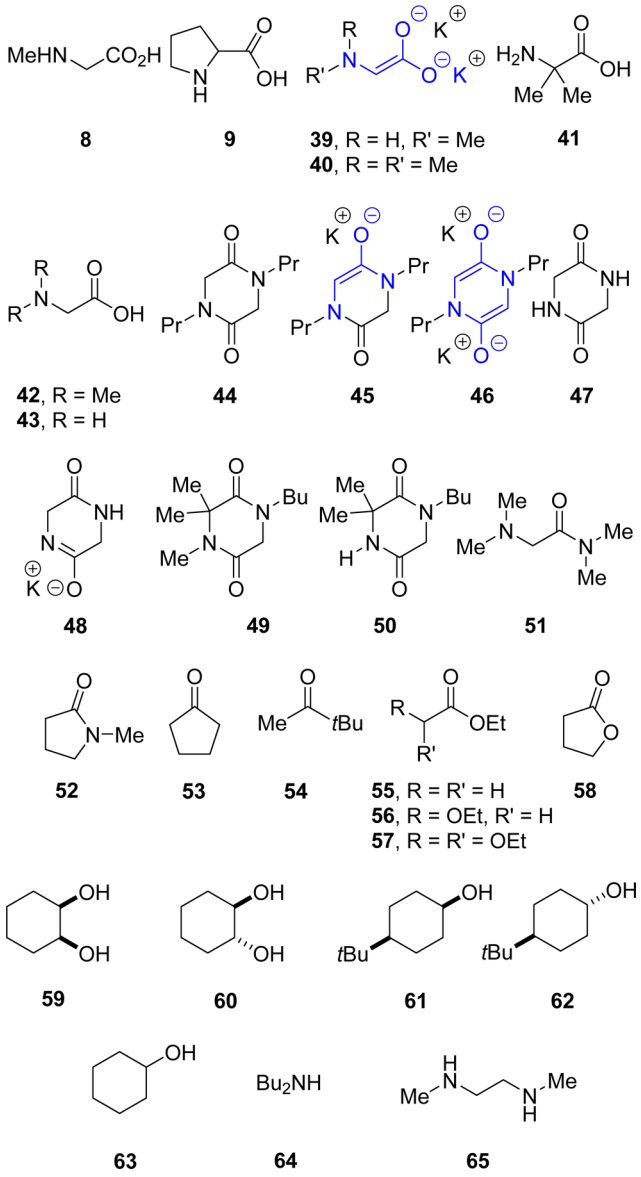


Figure 3. Additives tested as precursors to electron donors through reaction of substrate **33**.

predicted, gave no product (a = <0.5, b = 92%). If the amino acids had an alternative general mode of activity that did not rely on deprotonation of the α-carbon, for example, through formation of a coordination complex with KO^{t}Bu, followed by direct electron transfer from the butoxide anion, then coupling products might have been expected when **41** was used as organic additive. Interestingly, the *N*,*N*-dimethylglycine **42** gave no product (a = <0.5, b = 94%), and this suggested that a double deprotonation of this amino acid, as in **40**, was more difficult to achieve, perhaps for steric reasons. However, it was notable that glycine **43** (a = 14; b = 76%) showed some electron-transfer activity under our conditions.

The fact that secondary amino acids **8** and **9** were effective, while tertiary amino acid **42** was not, suggested that the single N-alkyl substitution of the secondary amino acids was useful and important. For now, our minds focused on ways in which the N-monosubstitution of amino acids might assist the coupling reactions. A literature search showed that condensation of amino acids can occur simply on heating. Condensation

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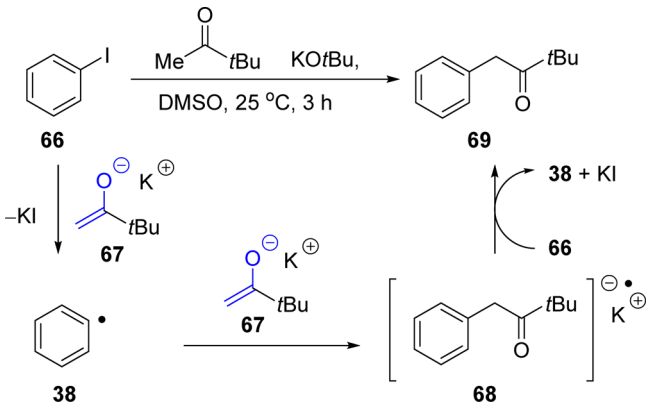
of secondary amines with carboxylic acids forms linear N-alkyl amides or cyclic piperazinedione dimers, simply on heating.[63] In our hands, heating of the amino acids with KO^{t}Bu in benzene at 150 °C did not afford detectable amounts of condensation products, such as piperazinediones, but being aware that even trace amounts of reactive compounds could form and could initiate coupling chemistry through efficient chain reactions, we explored the chemistry of piperazinediones, prepared by other routes. Under the conditions of the coupling reaction, *N*,*N*′-dialkyl piperazinedione **44** behaved as a good electron donor (a = 45, b = 22%), while **47**, an analogue featuring free N−H groups, which would form from the primary amino acid, glycine, was totally ineffective (a = <0.5, b = 92%). In this compound, **47**, competition between deprotonation of the CH_2 protons and an amide N−H would be in play, and the experiments agree with expectations that the amide N−H is more acidic.[64] In the resulting amide anion, **48**, the CH_2 would not be deprotonated, and no electron-rich alkene would form. Hence no electron transfer would be observed. Thus, deprotonation of *N*,*N*′-dialkylpiperazinediones may be relevant to the special success of secondary amino acids in facilitating the coupling reactions, but the minor reactivity arising from primary amino acid glycine **42** cannot be due to such a piperazinedione and may instead result from formation of a small amount of dianion of glycine **43**. Cyclic piperazinedione **44** likely forms electron-rich enolate, **45**, but we also considered the possible formation of low concentrations of the anti-aromatic dianion in **46**, which could be an even more powerful electron donor. Computational studies (see Supporting Information) showed that the structure **46** would indeed be planar and hence qualify as being anti-aromatic. This should make it an exceptionally strong electron donor. To calibrate the reactivity of **44** in the presence of KO^{t}Bu, we also prepared **49** which can only form a mono-enolate, to check for differences from **44**. Piperazinedione **49** worked as efficiently (a = 53, b =15%) as **44**, so dianion formation, as in **46**, is not required. If disalt **46** can be formed, it should be an excellent electron donor compared to monosalt **45** and capable of initiating the coupling of tougher substrates than iodobenzenes. Accordingly, we tested **44** on chloroarene substrates[58] but saw no coupling reactivity under our standard conditions. The final piperazinedione prepared was **50**, an analogue of **49** but featuring a single free carboxamide N−H. Consistent with results from the other N−H containing piperazinedione, **47**, this final example again showed no activity (a = <0.5, b = 93%). Accordingly, the presence of an amide N−H seems to decrease or remove electron-transfer-initiated coupling activity completely. To explore whether a simple N-alkylamide could trigger the coupling reactions in the presence of KO^{t}Bu, the *N*′,*N*′-dimethylcarboxamide, **51**, was tested, giving moderate electron-transfer activity (a = 22, b = 57%). This was similar to *N*-methylpyrrolidone **52** (a = 18, b = 52%).

Regardless of whether uncondensed amino acid derivatives or derivatives of condensation products like piperazinediones are involved, the electron-rich component that is formed following base treatment in both cases is an enolate. Here reference must be made to literature precedents by Scamehorn and Bunnett,[65] developing from findings of Rossi and Bunnett,[66] who reported that the enolate of pinacolone **67** reacted by electron transfer with iodobenzene **66** in DMSO as solvent to form a phenyl radical **38**; that radical coupled with a further molecule of enolate **67** in a classic example of the $S_{RN}1$ reaction, forming radical anion **68**; in turn, **68** acted as electron donor to another molecule of iodobenzene **66**, thereby forming ketone product **69** (Scheme 3). The authors reported that this

Scheme 3



chemistry can be accelerated by photoactivation. Recently, the team of Rossi has elegantly developed room-temperature methods to extend this chemistry,[47] but they have also achieved the photoactivated coupling of haloarenes to arenes in the presence of KO^{t}Bu in DMSO as solvent.[27]

To see if enolates of simple esters and ketones would behave as electron donors for the coupling of iodoarenes to arenes, under our conditions in the nonpolar solvent benzene and in the absence of photoactivation, they were now tested in the coupling reaction between iodoarene **33** and benzene (Figure 3). Cyclopentanone **53** (a = 42, b = 0%) and pinacolone **54** (a = 32, b = 3%) were active in this electron-transfer reaction. Bearing in mind that π-releasing substituents on the α-carbon should also assist, compounds **55**−**58** were investigated. Of these esters, the α-ethoxy **56** (a = 44, b = 0%) and α,α-diethoxy **57** (a = 35, b = 0%) esters were most successful. The simpler esters, ethyl acetate **55** (a = 19, b = 41%), and γ-butyrolactone **58** (a = 9, b = 74%), which would afford less electron-rich enolates, were less effective.

The examples above shed light on the ability of a broad range of enolates to act as electron-donor initiators in the coupling reactions. As mentioned, the yields are low when using substrate **33** relative to normal substrates, because of steric hindrance. Accordingly we now investigated what happens with normal substrate *p*-iodotoluene **70** (Figure 4). In this case, small amounts of coupling reaction can occur through the benzyne route,[51] as seen in the blank reaction (inset, Figure 4) where no additive is present, where 4% of the coupling product **71** was isolated. In contrast, reagents that afforded greater than 80% yield of *p*-methylbiphenyl **71** by electron transfer include sarcosine **8**, proline **9**, *N*,*N*′-di-*n*-propylpiperazinedione **44** and esters **55**−**57**. Although mechanisms have not yet been discussed for diamines (see below), the diamines **72** and **73** were also highly effective initiators in these coupling reactions.[5,7,24]

Alcohols and 1,2-Diols. To test whether these substrates reacted by electron transfer, our first experiments studied *cis*-1,2-dihydroxycyclohexane **59** and *trans*-1,2-dihydroxycyclohexane **60**,[7] using substrate **33** in benzene as solvent (Scheme 2). These experiments duly formed coupled products **34** + **35** (a = 32, b = 0% for **59**; a = 64, b = 0% for **60**), showing that both isomers operate as efficient electron donors. *Cis*- and *trans*-4-*t*-butylcyclohexanol **61** (a = 10, b = 50%) and **62** (a = 5, b =

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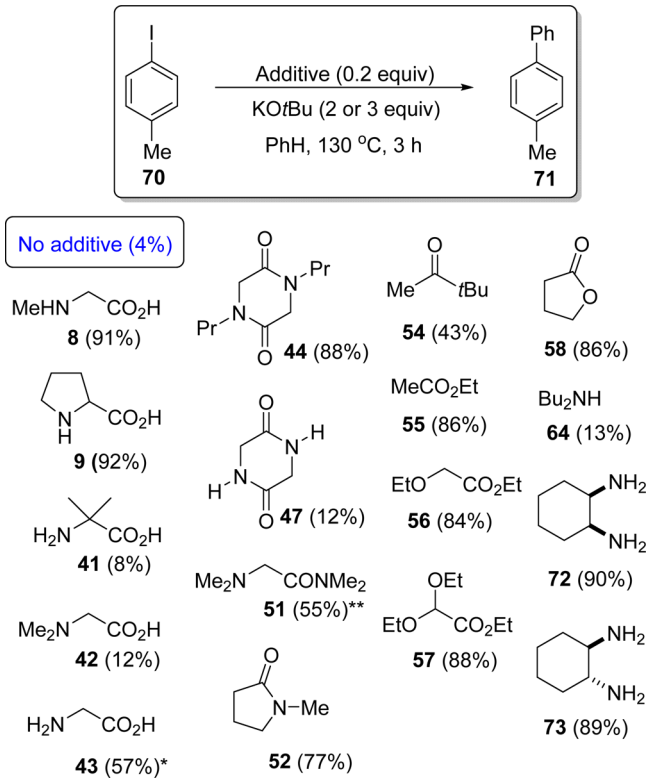


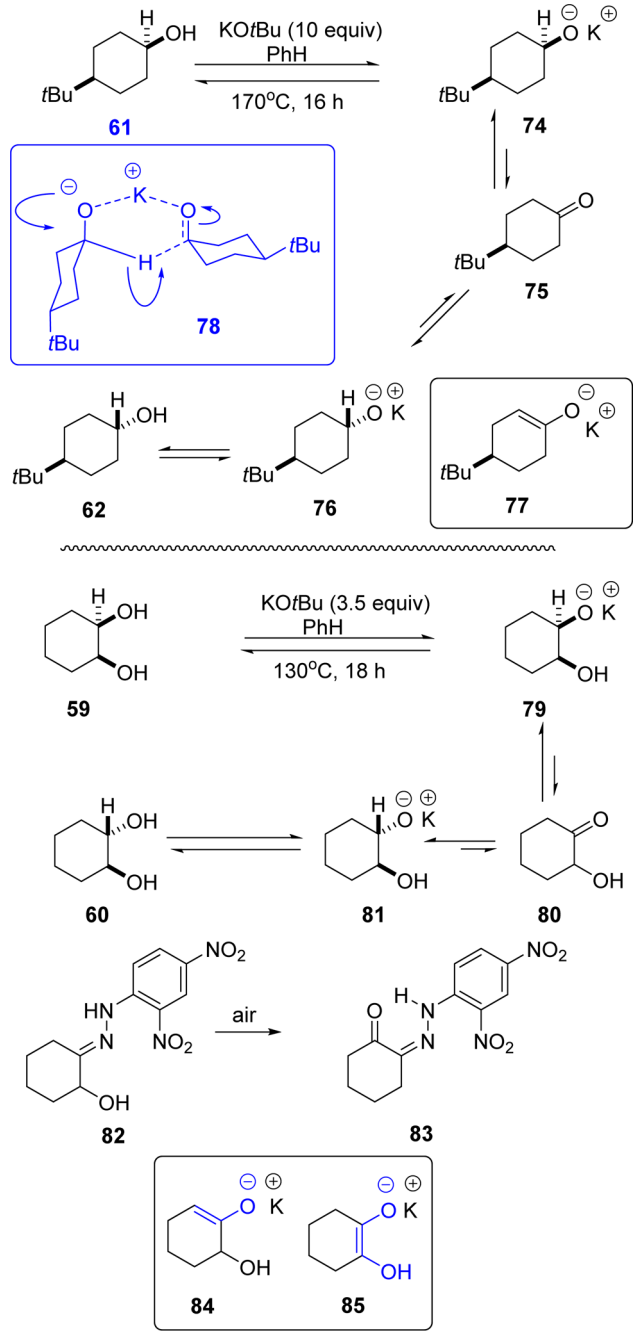
Figure 4. Coupling reactions of *p*-iodotoluene **70** with benzene, facilitated with various additives. Yields in the parentheses are isolated yields of **71**. *Reacting for 5 h gave 89%; **reacting for 5 h gave 86%.

50%), respectively, as well as cyclohexanol **63** (a = 7, b = 50%) behaved as less effective donors. The mechanism by which alcohols and diols might initiate couplings by electron transfer was now considered. One possibility involved transformation of the alcoholate to an enolate. If so, then electron-transfer pathways mentioned above would be accessible to the enolates.

For these cyclohexanols, enolate formation could come about after oxidation of the alcoholate to the ketone, followed by deprotonation. Conversion of alkoxides to ketones is normally associated with the aluminum alkoxide in the Oppenauer oxidation and features hydride ion delivery to an electrophile (a ketone or aldehyde). Woodward showed[67] that this chemistry could also be triggered by KO^{t}Bu in toluene, although this reaction has rarely been used since his work.

We examined a blank reaction of *cis-tert*-butylcyclohexanol **61** in benzene in the presence of KO^{t}Bu by NMR spectroscopy (Scheme 4). This very rapidly gave rise to a mixture of the *cis*-**61** and *trans*-**62** diols as the major components, together with a small amount of *tert*-butylcyclohexanone **75** (ratio: 1.00:6.54:0.32). The fact that the mixture was not converted exclusively to the ketone implies that delivery of the hydride by **74** or **76** to the ketone carbonyl group once formed, as in complex **78**, is easier than deprotonation by the alkoxide of ^{t}BuOH or 4-*tert*-butylcyclohexanol to form H_2[68] (for computational support, see Supporting Information). When the *trans-tert*-butylcyclohexanol **62** was treated similarly with KO^{t}Bu, it also gave rise to the same mixture of **61**, **62**, and **75**, although in slightly different ratio (ratio: 1.00:8.63:0.11). This supports the idea that the intermediate ketone is formed, which can act as precursor to the enolate **77** as electron donor.[67] To verify that a structurally determined enolate can bring about such reactions, enolate **77** was also formed separately and isolated, following

Scheme 4



reaction of KH with ketone **75**; the enolate formation was verified by quenching a small aliquot with D_2O, and this gave rise to monodeuterated **75**-d^1. The isolated enolate was indeed shown to trigger coupling reactions with benzene of substrates **33** and **78**. (Details are included in the Supporting Information file).

The experiments were repeated with *cis*- and *trans*-cyclohexane-1,2-diols **59** and **60**. Treatment of *cis*-cyclohexane-1,2-diol **59** at 130 °C with KO^{t}Bu afforded a mixture of both diols and 2-hydroxycyclohexanone **80**. The latter was isolated as its 2,4-dinitrophenylhydrazone **82**. This compound is not stable when exposed to air, undergoing oxidation, over some hours, of the alcohol group to a ketone **83**, which was also characterized and compared to a sample prepared by an independent route.

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Comparing the reactivity of the diol isomers **59** and **60** with cyclohexanols **61**−**63** in the coupling reactions, the diols are far more reactive. This could be explained if the reactive initiator for radical formation is the enediolate **85** (a dianion resulting from deprotonation of the hydroxyl group in **85** is also conceivable) rather than the less electron-rich eneolate **84**. The former, **85**, should be more electron-rich and more reactive than its regioisomer, **84**.

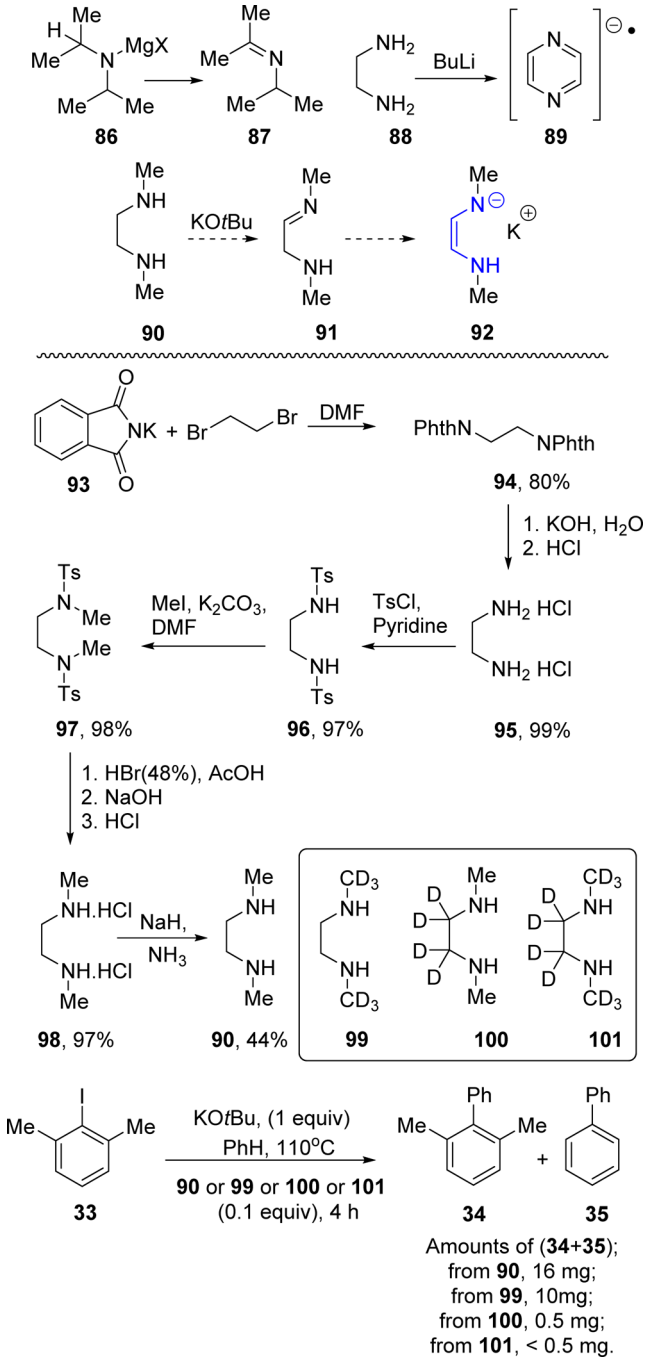
1,2-Diamines. Finally, we considered amines and 1,2-diamines. Simple amine **64** showed no electron-transfer activity (Figure 3, a = <0.5, b = 92) in the coupling reaction with substrate **33**. However, in complete contrast, *N*,*N*′-dimethylethylenediamine **65** was an effective donor (Figure 3, a = 46, b = 0), and Figure 4 shows that cyclohexane-1,2-diamines, **72** and **73**, were among the most effective additives in promoting the coupling of aryl halide **70** to benzene. In the coupling reaction triggered by *N*,*N*′-dimethylethylenediamine **65** and by cyclohexane-1,2-diamines **72** and **73**, successful coupling reactions are accompanied by formation of colored reaction mixtures, indicative of the formation of conjugated substances, and so we began to consider whether conversion of the diamines to electron donors might be analogous to the oxidation of diols **59** and **60**. However, all attempts by us to isolate discrete products in blank reactions of KO^{t}Bu with these amines in benzene led to no success.

Looking at relevant cases in the literature where dehydrogenation of amines occurs under basic conditions, it is known that magnesium diisopropylamide **86** can expel hydride to form an imine **87**.[69−72] In our case, with potassium butoxide as the base, the equilibrium for formation of the amide anion KNHR is expected to be very unfavorable from a simple primary amine, although it might well be more favorable for a 1,2-diamine. However, it has been shown that ethylenediamine **88**, on treatment with base, affords pyrazine radical anion **89**,[73] and this likely results from condensation reactions with imines that are initially formed through loss of hydride.[72]

If such reactions are occurring under our conditions with vicinal diamines, they may lead to a complex mixture of condensed or uncondensed enamine-type products, present at low concentration, each of which could function by electron transfer. However, the necessary gate to those substances would be formation of an imine through expulsion of hydride. This could then undergo further deprotonation to afford an enamine salt. The simplest scenario (no condensations) is represented in Scheme 5 with transformation of diamine **90** to representative imine **91** that on deprotonation gives electron-rich alkene **92**. Loss of hydride to form the imine is likely to have a very high activation barrier and likely to be the rate-determining step in formation of the initiating electron donor(s). (We emphasize that we are speaking about the slow step in the process of forming the initiator, not the slow step in the main chain reaction shown in Scheme 1.) We proposed to test for this using deuterium-labeled analogs of diamine **90**.

In detail, our plan was to prepare the unlabeled *N*,*N*′-dimethylethylenediamine **90** by an efficient route that could be adapted to the synthesis of deuterated analogues in good yield. If hydride loss is associated with the rate-determining step for the formation of the initiator, then changing the relevant C−H to C−D should slow down the formation of the initiator(s). Conducting parallel reactions with deuterated and undeuterated additives under the same conditions and for a given period should result in formation of less initiator in the deuterated case, and therefore a smaller number of radical chains would have initiated in the deuterated amine case, resulting in much less effective arene−arene coupling under defined conditions.

Scheme 5



The synthesis that we developed for this purpose is shown in Scheme 5, starting with potassium phthalimide, **93**. Using this route, the unlabeled diamine **90**, the tetradeutero **100**, hexadeutero **99**, and decadeutero **101** analogues were all prepared. (Where deuterium analogues were prepared, d_4-1,2-dibromoethane and/or d_3-iodomethane were used in place of their non-deuterated counterparts in Scheme 5). The diamines **90**, **99**−**101** were then tested side-by-side in four parallel reactions of identical scale and under identical conditions. The conditions were chosen through preliminary work with the unlabeled diamine **90**, using a relatively mild temperature (110 °C) and short reaction time (4 h) to give just about half of the

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normal conversion from substrate **33**. Stopping short of full conversion was important in allowing realistic assessment of differences between the isotopomers. Under these conditions the products (**34** + **35**) isolated from the four reactions were: 16 mg from **90**, 10 mg from **99**, 0.5 mg from **100**, and <0.5 mg from **101** (see Supporting Information for additional tests at 135 °C). These reactions clearly show that a primary isotope effect is in place for breakage of a methylene C−H(D) bond here, so that formation of the active promoter(s) of the coupling reaction definitely involves cleavage of a C−H/C−D bond in the rate-determining step. Given that (i) these coupling reactions operate through electron transfer, as seen in the conversion of substrate **33**, and therefore that electron donors require to be prepared in situ; (ii) when the coupling reactions with diamines are successful, the reaction mixtures become brown-colored, indicating the formation of conjugated compounds (in this respect, the reactions of additives **90** and **99** contrast with the additives **100** and **101**, where no color developed); (iii) there is literature precedent for conversion of diamine **88**, under basic conditions, to a pyrazine radical anion;[73] and (iv) deuterium isotope effects are observed, when conducting the coupling of **33** in benzene, particularly for labeled methylene groups in *N*,*N*′-dimethylethylenediamine, **90**, the most satisfactory conclusion is that these reactions are initiated by organic electron donors that are formed following oxidation of the amines under basic conditions. The results are definitely not consistent with a simple complexation of potassium *tert*-butoxide followed by electron loss from the butoxide.[43]

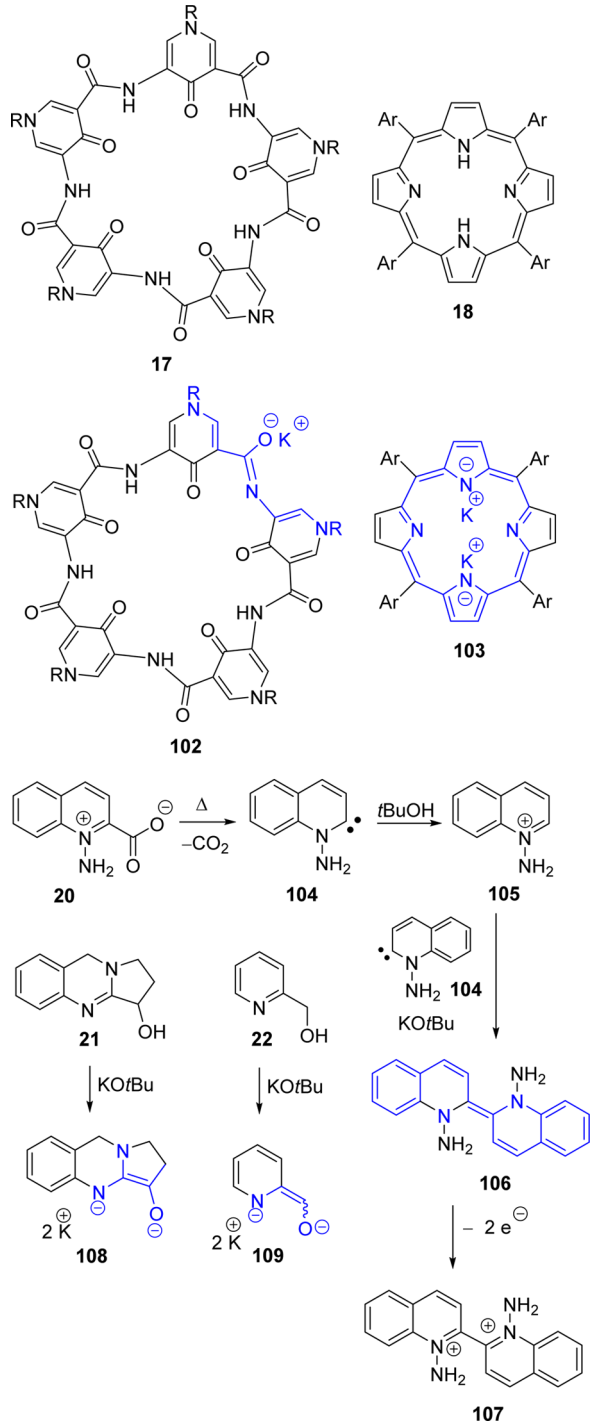
The difference in yield in these reactions, notably the difference in yield between using **99** and using **101** reflects differences in concentration of the electron donors, which may be 20-fold less in the labeled reactions. This does not mean that a kinetic isotope effect of 20 or more is associated with the breaking of a methylene C−H bond here, since the active electron donor(s) may be formed in a scheme where two or more imine-derived molecules play a role, e.g., in forming a dihydropyrazine donor.

CONCLUSIONS

At the end of 2013, many organic additives were known to trigger coupling of haloarenes to arenes in the presence of KO^{t}Bu or NaO^{t}Bu, but their modes of action were unknown. In our earlier paper,[51] we showed that fully characterized organic electron donors like **28** can initiate the coupling reactions between haloarenes and arenes in the presence of KO^{t}Bu in benzene as solvent. We also proposed and presented evidence that the couplings that were facilitated by N-heterocyclic carbenes, by phenanthroline, or by pyridine as solvent or that used pyridines or pyrazines as substrates were all due to the in situ formation of organic electron donors. Now, we present evidence that amino acids also act as precursors to organic electron donors, which are likely to be enolates, and that this chemistry, conducted in benzene, builds on the observations of Scamehorn and Bunnett[65,66] for $S_{RN}1$ reactions that had been conducted in DMSO; the special effectiveness of amino acids that feature secondary amines may be due to intermolecular condensation reactions of amino acids to form cyclic *N*,*N*-dialkylpiperazinediones or related compounds.

We present direct evidence in favor of oxidation of 1,2-diols and alcohols to ketones under the conditions of our coupling reactions, with the ketones acting as precursors of electron-rich enolates.[67] 1,2-Diamines are also shown to be precursors to

Scheme 6



electron donors under the conditions of the coupling reactions. Comparison between deuterium labeled analogues and unlabeled diamine **90** shows that C−H bond cleavage within the diamines is absolutely required for the synthesis of the electron donor initiator(s), and we propose that electron-rich enamines or related compounds, such as their deprotonated analogues, e.g., **92**, are the active electron donors.

With this foundation now in place, a number of the remaining mysteries relating to coupling reactions, facilitated by organic additives, can be addressed predictively. Deprotonation of macrocyclic pentapyridone **17** would afford **102**, where the amide enolate linked to two enamine structures is shown in

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blue, would be a candidate electron donor (Scheme 6). Similarly deprotonation of porphyrin **18** would produce an electron-rich structure; the doubly deprotonated porphyrin shown as **103** is likely to be a superb electron donor. Thermal decarboxylation of salt **20** would afford carbene **104**.[15,74,75] Combination of carbene **104** with its protonated form **105** would afford the highly electron-rich structure **106** that can become an aromatic bis-quinolinium salt **107** on losing two electrons. Compounds **21** and **22** can be deprotonated to afford the organic electron donors **108** and **109**. Many other organic structures can therefore be predicted to be able to initiate C−C coupling reactions. Since they are simply initiators for the efficient radical chains shown in Scheme 1, the important point is that they do not need to be formed in high yield; formation reactions that would afford far less than 1% of the initiating electron donors are quite likely to be able to trigger excellent yields of coupled products.

■ ASSOCIATED CONTENT

Supporting Information

Additional examples and experimental procedures as well as analytical, spectroscopic and computational data are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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