Reaction Mechanisms

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Double Deprotonation of Pyridinols Generates Potent Organic Electron-Donor Initiators for Haloarene–Arene Coupling

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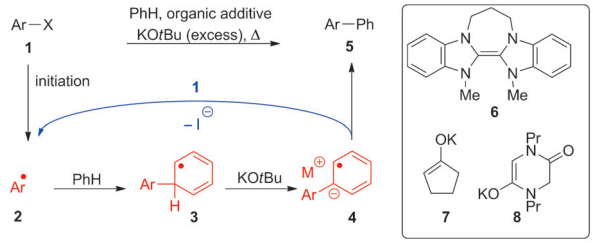
In memory of Russ Bowman

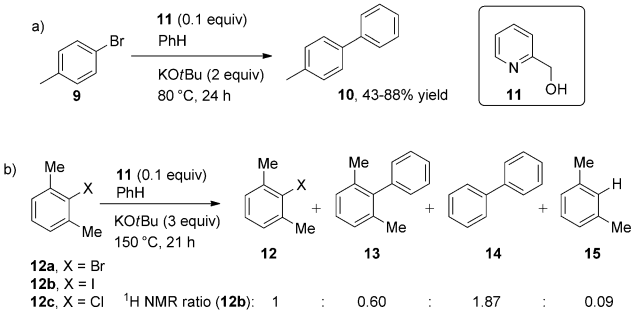
Abstract: *Transition metal-free couplings of haloarenes with arenes, triggered by the use of alkali metal alkoxides in the presence of an organic additive, are receiving significant attention in the literature. Most of the known organic additives effect coupling of iodoarenes, but not bromoarenes, to arenes. Recently it was reported that 2-pyridinecarbinol (**11**) extends the reaction to aryl bromides. This paper investigates the mechanism, and reports evidence for dianions derived from **11** as electron donors to initiate the reaction. It also proposes routes by which electron-poor benzoyl derivatives can be transformed into electron donors to initiate these reactions.*

Transition metal-free dehalogenative couplings between haloarenes and arenes have attracted significant attention from chemists. Reactions are mediated by a base (typically KO*t*Bu) and an organic additive.[1–15] The mechanism for these reactions features base-promoted homolytic aromatic substitution (BHAS; Scheme 1).[16] Here, the aryl radical **2** adds to the arene partner to yield the radical **3**. Deprotonation yields the radical anion **4**, which can propagate the chain through electron transfer to the aryl halide **1** and simultaneously release the biaryl product **5**. The majority of reports are concerned with the couplings of aryl iodides. How **2** is generated in the first place (initiation) has not been extensively explored.[14,15,17,18]



Scheme 1. Radical-chain mechanism depicting BHAS. Initiation by organic electron donors, for example, **6**–**8**.

A host of reported organic additives (amino acids, alcohols, 1,2-diamines) were analyzed in one study by our group to probe the mechanism of initiation.[18] We proposed a simple unifying mechanism for these additives, and in each case the formation of an organic electron donor was involved. Both neutral electron donors like **6** and simple enolates, for example, **7** and **8**, can activate aryl iodides under facile SET reactions (Scheme 1). The key structural component of the electron donor is an alkene which is substituted by one or more electron-donating groups. Forming the aryl radicals in this way initiates the chain reaction shown in Scheme 1. Two electron transfer steps are involved: 1) one for the initiation and 2) one for the propagation, thus converting the radical anion **4** into **5**. A crucial question relates to which electron donor is the bottleneck. Specifically, if the initiating electron donor is made stronger so that it can initiate aryl bromides, will **4** be a strong enough donor to propagate the chain? An answer to this came in a recent breakthrough with the report that the additive 2-pyridinecarbinol (**11**) initiates the coupling of aryl bromides to arenes under mild reaction conditions (Scheme 2).[4] 4-Bromotoluene (**9**) coupled efficiently in the presence of this additive, thus giving rise to the biaryl **10** in moderate to high (43–88%) yields. Clearly, a more reactive electron donor than normal is present to initiate the reaction and, after initiation, the reaction can indeed be sustained by electron transfer from **4**.



Scheme 2. a) Coupling of **9** to benzene in the presence of the additive **11** under reaction conditions reported by Kwong and co-workers.[4] b) Coupling of the electron-transfer reporters **12**, thus affording the biaryls **13** and **14**.

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In our hands, the coupling of **9** to benzene under Kwong's reaction conditions (2 equiv KO*t*Bu, 10 mol% **11**, 80°C for 24 h in benzene solvent) worked as stated and gave the biaryl product **10** in 60% yield upon isolation,[4] so we resolved to probe the mechanism of action of **11**.

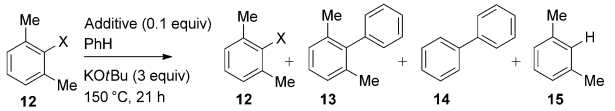
Although initiation routinely occurs through formation of an organic electron donor,[17,18] a second, more sluggish route to initiation can occur when the substrate can form benzyne, and this background mechanism can cloud the picture. Kwong et al. observed no coupling of **9** to benzene in the absence of **11**,[4] thus suggesting initiation via benzyne was not occurring under their reaction conditions. Our mechanistic studies would benefit from freedom to explore a range of conditions, and to guard against side-reactions with benzynes, we chose the coupling substrates **12a**,**b** which completely rule out benzyne formation, thus allowing us to compare additives and confidently focus solely on their ability to form electron donors in situ (Scheme 2).[17,18] Competent electron donors convert the additives **12a,b** into the corresponding aryl radical, which, because of its steric bulk undergoes competing signature reactions, namely 1) addition to benzene, thus leading to the substituted biphenyl **13** and 2) hydrogen abstraction from benzene, thus affording the volatile *m*-xylene (**15**), as well as a phenyl radical that leads to biphenyl (**14**).

Because of the steric properties of its derived aryl radical, the yields from the substrates **12a,b** are always lower than for simple substrates, such as **9** reported above, but the mechanistic information provided is invaluable. To compensate for the lower reactivity of **12**, we used harsher reaction conditions (3 equiv KO*t*Bu, 10 mol% **11**, 150°C for 21 h in benzene solvent). The substrate **12b** (Table 1, entry 3) reacted more efficiently than the bromide **12a** (entry 2), thus affording the combined biaryls (**13** and **14**) as the major component, and so we adopted **12b** as our routine substrate. The formation of **13** and **14** confirmed that electron transfer was occurring after generation of an organic electron donor from **11** (Scheme 1).

We considered how the reaction of KO*t*Bu with **11** could form an organic electron donor. Chain-reaction initiation is possible with very low concentrations of active species, thus allowing consideration of intermediates that would be ruled out for stoichiometric synthetic pathways. One mechanism[18] could involve double deprotonation of **11** by KO*t*Bu, firstly at the alcohol and secondly at the benzylic position (Scheme 3, pathway A) to afford **20**.

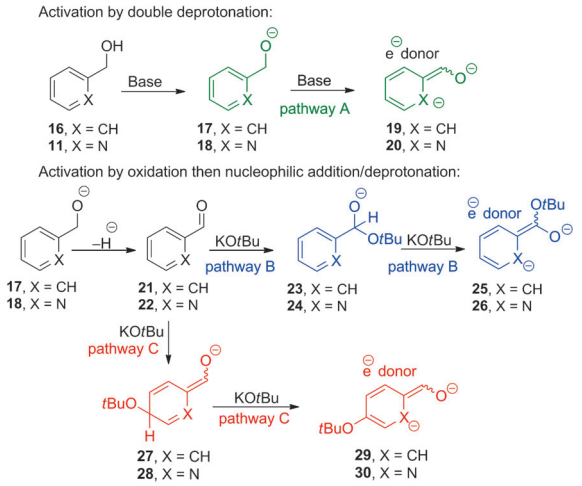
An alternative mechanism could involve oxidation of the pyridinol anion **18** by hydride loss.[18] Hydride loss from primary and secondary alcohols has been demonstrated under the reaction conditions of the coupling reactions. The resulting aromatic aldehyde **22** would not be an electron donor, of course, but it could be susceptible to nucleophilic attack either at the aldehyde function to afford **24** (Scheme 3, pathway B) or at the aromatic ring, presumably at the *ortho*- or *para*-position to give **28** (pathway C). Deprotonation of **24** and **28** respectively would give rise to the organic donors **26** and **30**. To shed light on the mechanisms of initiation of **11**, a number of analogues (Figure 1) were employed as additives in the coupling reaction of **12**. Thus heating **12** in benzene with KO*t*Bu (3 equiv) and an additive (0.1 equiv) afforded **13**, **14**, and **15**. Products are clearly identified in the ^{1}H NMR spectrum of the reaction mixture, thus allowing facile determination of the ratio of **12/13/14/15**. In key cases, **13** and **14** were isolated by chromatography (as an inseparable mixture) and the yields determined or, alternatively, quantified by the use of NMR spectroscopy using an internal standard. All reactions were performed using the same amount of **12**, (116 mg, 0.5 mmol) under identical reaction conditions, that is, temperature, number of equivalents of reagent, solvent volumes, and time. For key comparisons of

Table 1: Coupling reactions of the 2,6-dimethylhalobenzenes **12a**,**b** with benzene, facilitated by organic additives.



Entry	Additive	Product distribution[a]				Yield[b]
		12	**13**	**14**	**15**	**13 + 14**
1	none	1	<0.01	0.02	<0.01	1.5 (75%)
2	**11**	1	0.24	0.55	0.06	–[c]
3	**11**	1	0.60	1.87	0.09	35.0 (n.d.)[d,e]
			0.63	1.92	0.22	34.0 (n.d.)[d]
4	**31**	1	0.02	0.06	<0.01	4.0 (n.d.)[d,e]
			0.02	0.05	<0.01	3.0 (n.d.)[d]
5	**32**	1	0.015	0.04	<0.01	3.1 (65%)
6	**33**	1	0.03	0.09	<0.01	6.0 (61%)
7	**34**	1	0.42	1.34	0.36	–
8	**35**	1	0.28	0.82	0.04	–
9	**36**	1	0.16	0.53	0.10	–
10	**37**	1	0.15	0.45	0.04	–
11	**21**	1	0.17	0.50	0.04	–[f]
			0.17	0.50	0.04	
12	**38**	1	0.09	0.27	0.03	–[f]
			0.09	0.27	0.03	
13	**21**[g]	1	0.13	0.39	0.04	–[h]
14	**21**-d_6[g]	1	0.07	0.23	0.04	–[h]
15	**39**	1	0.06	0.19	0.09	–
16	**40**	1	0.01	0.03	0.01	2.1 (73%)
17	**41**	1	0.01	0.03	<0.01	2.6 (73%)
18	**42**	1	0.07	0.25	0.05	8.3 (41%)[i,j]
19	**43**	1	0.025	0.08	<0.01	4.4 (62%)[i,j]
20	**44**	1	0.015	0.04	<0.01	2.9 (72%)
21	**45**	1	0.02	0.06	0.07	3.0 (n.d.)[d,k]
22	**46**	1	0.11	0.37	0.38	9.0 (n.d.)[d,k]
23	**47**	1	0.08	0.28	0.05	–[l]
24	**48**	1	0.10	0.33	0.08	–[l]
25	none	1	<0.01	<0.01	0.09	– (60%)[m,n,o]
26	**11**	1	<0.01	0.01	0.09	0.8 (60%)[m,n]

[a] 2,6-Dimethyliodobenzene (**12b**) was used as substrate unless otherwise stated. Ratios determined by ^{1}H NMR analysis of the reaction mixture (see the Supporting Information). [b] Combined yield (mg) of biaryls (**13** and **14**) determined by NMR spectroscopy using 1,3,5-trimethoxybenzene (10 mol%) as an internal standard. The yield (%) of returned **12** is shown within parentheses. [c] **12a** was used as substrate. [d] Combined yield (mg) of the isolated biaryls **13** and **14**, which are inseparable by chromatography. [e,f] Reactions were conducted side-by-side under identical reaction conditions and the reaction pair was repeated. [g] Prepared side-by-side by CAN oxidation of toluene or toluene-d_6 (see the Supporting Information). [h,i,k,l,n] The two reactions were conducted side-by-side under identical reaction conditions. [j] Average of three runs. [m] **12c** was used as a substrate. [o] Biaryls were not detected by ^{1}H NMR spectroscopy. n.d. = not determined.



Scheme 3. Proposed mechanistic pathways for activation of additives.

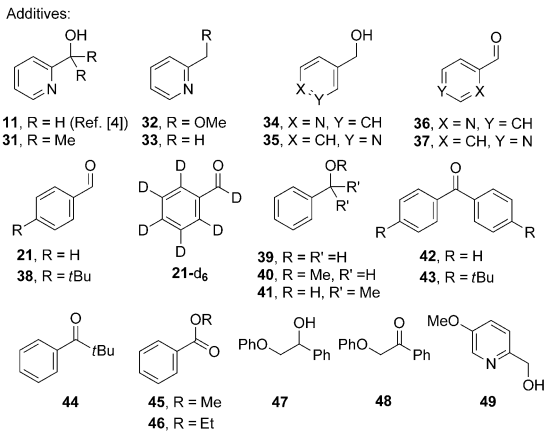


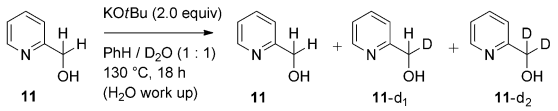
Figure 1. Unusual organic additives that facilitate coupling of haloarenes to arenes.

additives, a pair of reactions was run side-by-side and the reaction pair repeated.

Blank reactions without an additive (entry 1) confirmed the non-reactivity of **12** resulting from the inability of KO*t*Bu to act as an electron donor to haloarenes, as evidenced previously.[17–20] To investigate the effect of blocking the benzylic position of **11**, the *gem*-dimethyl additive **31** was tested under the reaction conditions side-by-side with **11** (the reactions were repeated to confirm reproducibility; entries 3 and 4). It is clearly seen that the *gem*-dimethyl additive **31** is not capable of effecting the coupling, and is consistent with an important role for benzylic C–H deprotonation.[21] Blocking the hydroxy proton as its methyl ether in the additive **32** halted the reaction, and removing the hydroxy group as in additive **33** resulted in significant loss of reactivity (entries 5 and 6). These results strongly suggest that double deprotonation (Scheme 3, pathway A) is the major pathway for electron-donor formation from **11**.

Next, 4-pyridinecarbinol (**34**) and 3-pyridinecarbinol (**35**; entries 7 and 8) were investigated and displayed a decrease in reactivity in that order. Upon deprotonation, **11** can delocalize its negative charge onto the pyridine N, whereas **35** cannot. Deprotonation at the benzylic position was confirmed when **11** was treated (in the absence of **12**) with KO*t*Bu (2 equiv) in PhH/D_2O (1:1) at 130 °C for 18 hours, thus resulting in deuteration at the benzylic position (see the Supporting Information). Next, 2-pyridinecarboxaldehyde (**36**) and 4-pyridinecarboxaldehyde (**37**) were tested (entries 9 and 10) and resulted in appreciably lower reactivity than the corresponding carbinols **11** and **34**. If the pyridinecarbinols underwent hydride loss (as evidenced for other alcohol additives)[18] as the main pathway for generating single electron donors, then the pyridinecarboxaldehyde additives (**36** and **37**) should be more reactive than the pyridinecarbinol additives (**11** and **34**).

To further probe mechanisms, benzaldehyde (**21**) and either the corresponding substituted or deuterated analogues were subjected to the reaction conditions (Scheme 4). **21** was tested side-by-side with 4-(*tert*-butyl)benzaldehyde (**38**; the reaction pair was repeated to confirm reproducibility; entries 11 and 12), thus demonstrating that blocking the *para*-position halved the conversions. To investigate the effect of deuteration, **21**-d_6, synthesized from toluene-d_8, was compared side-by-side (entries 13 and 14) with **21** (synthesized in exactly the same way from toluene;[24] see the Supporting Information). Deuteration halved the conversion seen with **21**, thus indicating that formation of the initiator likely involves breaking of a C–H/C–D bond in the rate-determining step.



Scheme 4. KO*t*Bu-mediated benzylic deuteration of 2-pyridincarbinol (**11**) in the presence of D_2O.

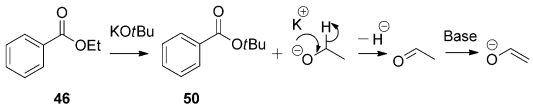
An interesting observation is that benzyl alcohol (**39**) gave rise to lower reactivity than **21** (entry 15), thus contrasting with the difference in reactivity between pyridinecarbinols (**11** and **34**) and their corresponding pyridinecarboxaldehydes (**36** and **37**). The electron-deficiency of **11**, **34**, and **35** renders them more susceptible to the double deprotonation mechanism (Scheme 3, pathway A) than **39**. Oxidation followed by nucleophilic addition/deprotonation (Scheme 3, pathways B and C) may be the preferred mechanism for electron donor formation from **39**, hence reactivity is enhanced with **21**, which is already an oxidation state higher. This proposal was confirmed through use of the additives **40** and **41** (entries 16 and 17), which are blocked to both double deprotonation and oxidation, thereby halting the reaction.

To investigate whether an aldehyde function was required, benzophenone (**42**) was tested side-by-side with 4,4′-di-*tert*-butylbenzophenone (**43**; entries 18 and 19). **42** gave similar reactivity to that of **39** and the fact that coupling was observed supports the proposal for the pathway involving nucleophilic addition to the arene followed by deprotonation (Scheme 3, pathway C). Furthermore, blocking the *para*-positions to

nucleophilic attack in the form of additive **43** halved the reactivity, thus mirroring the difference in reactivity between additives **21** and **38**.

To explore further, we employed pivalophenone (**44**). ^{1}H NMR spectroscopy (see the Supporting Information) indicates that **44** experiences diminished conjugation between the carbonyl and the arene. Hence we predicted that the nucleophilic addition/deprotonation mechanism (Scheme 3, pathway C) would be less available to **44**. In line with this, subjecting **44** to the coupling reaction of **12** gave no more reactivity than the blank reaction (entry 20).

Overall, the benzophenone-type additives **42** and **43** were less effective than the benzaldehyde-type additives **21** and **38**, where the aldehyde function was available to react. To further probe the role of benzoyl groups, the esters **45** and **46** were studied side-by-side (entries 21 and 22). Whilst the **45** provided results that were similar to the blank reaction, we were surprised at appreciably higher reactivity for **46**. We rationalized that transesterification under the reaction conditions would liberate ethoxide (Scheme 5) and Bi[11] reported



46 50

Scheme 5. Mode of activation for ethyl benzoate **46**.

ethanol as a good promoter of KO*t*Bu-mediated cross-couplings. Ethoxide would form the enolate of acetaldehyde, which can act as electron donor, through the previously reported mechanism.[18] When ethyl benzoate (**46**) was subjected at room temperature to the reaction conditions in the absence of **12**,[25] full conversion of **46** occurred, thus forming the *tert*-butyl ester **50** as the sole product (see the Supporting Information). Additives **47** and **48** were employed in the coupling reaction of **12** (entries 23 and 24). The alcohol **47** initiated the reaction (with similar efficacy to additives **39** and **42**), and was thought to proceed via oxidation to **48**. This proposal was supported when **48** gave similar (if marginally higher) activity.

In this study, it is the double-deprotonation of **11** that forms the most potent electron donor (**20**), which can initiate reactions of bromoarenes. However, it is ineffective at initiating reactions of chloroarenes. When 2,6-dimethylchlorobenzene (**12c**) was treated with **11** under our reaction conditions, only trace amounts of biaryl were observed. The reaction was run side-by-side with a blank reaction where **11** was omitted (entries 25 and 26). Our findings mirrored those of Kwong and co-workers[4] when 4-chlorotoluene was used under their reaction conditions, thus giving a very low 8% yield of **10** as determined by ^{1}H NMR spectroscopy using an internal standard. An analogue of **11** with an additional alkoxy-substituent (**49**; which mimics dianion **30** upon double deprotonation) was no more effective. Cyclic voltammetry studies suggest that the thermodynamics for the reduction of chloroarenes by these dianions are favorable (see the Supporting Information).[26] Similarly, the oxidation potentials for biphenyl radical anions (e.g. **4**)[27] are sufficiently negative to reduce chloroarenes, so that it is the kinetics of the chloroarene reactions (probably associated with the loss of chloride ion from the chloroarene radical anion) that constitute the bottleneck.

To conclude, the reaction of 2-pyridinecarbinol (**11**) with KO*t*Bu affords a potent electron donor which facilitates coupling of bromobenzenes to arenes.[4] Double deprotonation plays a key role in coupling reactions initiated by **11**. This paper identifies a secondary pathway for conversion of benzylic alcohols into electron donors, and involves initial in situ oxidation of the alcohol. Understanding the initiation of transition metal-free cross-coupling reactions is key to unlocking milder reaction conditions and to coupling more challenging substrates in these reactions.

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Keywords: arenes · cross-coupling · electron transfer · radicals · reaction mechanisms

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[20] The blank reaction was performed under the published conditions.[18] The ratio of **12**/**13**/**14**/**15** was $1: < 0.01: < 0.01: < 0.01$, which corresponded with a biaryl yield of 0.3 mg (using 10 mol % 1,3,5-trimethoxybenzene as an internal standard), and is consistent with previous findings.[18] 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. In this regard, pyridine + KO*t*Bu affords electron donors,[17] although the process is very inefficient, and requires pyridine in great excess, as solvent, to work well.[7]
[21] The possibility for additives such as **11** initiating the coupling reactions by complexing potassium *t*-butoxide to yield an electron donor[2,5,14,15] is inconsistent with the non-reactivity of additive **31**.
[22] Although deprotonated forms of both **11** and **34** can delocalize their charges onto the pyridine N, the difference in reactivity observed may be due to enhanced complexation of K^+ afforded by **11** (compared to **34**), thus increasing the acidity of its hydroxy and benzylic protons.
[23] Blocking the *para*-position in the form of the additives **38** and **43** still gave some reactivity over the blank reaction. This reactivity suggests that attack at the aldehyde function and/or *ortho*-position of **38** are important. Similarly, attack at the *ortho*-position of **43** might occur.
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