DOI: 10.1002/anie.201101597

Organocatalysis and C–H Activation Meet Radical- and Electron-Transfer Reactions**

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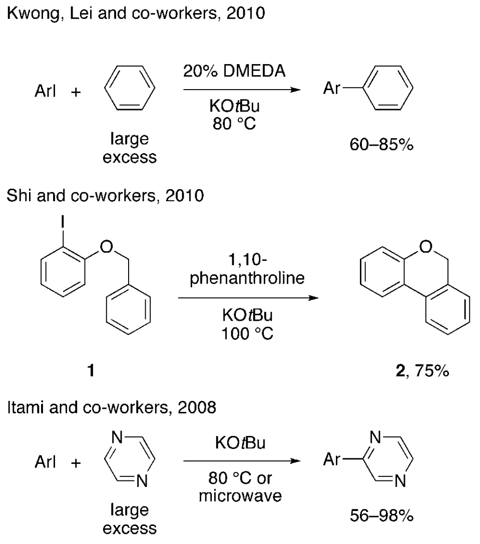
aryl radicals · C–H activation ·
homolytic radical substitutions · organocatalysis ·
radical anions

The research groups of Shi,[1] Shirakawa/Hayashi,[2] and Kwong/Lei[3] have recently reported independently on the construction of biaryl compounds from unactivated aromatic rings by direct C–H activation with the aid of organocatalysts.[4] Published in *J. Am. Chem. Soc.* and *Nature Chem.*, the results were described as "conceptual breakthroughs"[1,3] because no metal catalyst was needed.

Here we suggest that these exciting results are not best viewed in terms of C–H activation or organocatalysis, but instead in terms of homolytic radical aromatic substitution (HAS).[5–9] Although the results may not be conceptual breakthroughs from that viewpoint, they could well herald new opportunities for making organic molecules through organic radical and radical anion reactions.

Kwong, Lei, and co-workers discovered that heating aryl iodides in benzene at 80 °C with one equivalent of potassium *tert*-butoxide and 20 mol% *N,N'*-dimethylethylenediamine (DMEDA, the organocatalyst) gave biaryls in good yields (60–85%, Scheme 1).[3] The research groups of Shirakawa/Hayashi[2] and Shi[1] described similar bimolecular reactions in comparable yields, although their organocatalyst was 1,10-phenanthroline (or a substituted analogue) and used at a level of 20 and 40 mol%, respectively. In addition, Shi and co-workers reported an example of a cyclization: heating 2-iodophenyl benzyl ether (**1**) in mesitylene with potassium *tert*-butoxide (3 equiv) and 1,10-phenanthroline provided benzochromene **2** in 75% yield.


Kwong, Lei and co-workers, 2010

Shi and co-workers, 2010

Itami and co-workers, 2008

Scheme 1. Recent examples of "metal-free" direct C–H arylation. Ar = aryl.

In 2008, Itami and co-workers reported that potassium *tert*-butoxide (1.5 equiv) alone effected the addition of aryl iodides and bromides to pyridizine and other electron-poor aromatic rings.[10,11] These results are reminiscent of the Minisci reaction (addition of alkyl and other radicals to electron-poor heterocycles),[12] except that Minisci reactions are usually conducted under acidic conditions rather than basic conditions. The research groups[1,3,4] discovered these transformations through control experiments while trying to develop metal-catalyzed C–H activation reactions. They observed that with certain "ligands" and KO*t*Bu, the metal was not needed at all to effect the conversion of the aryl halide into the biaryl. Extensive control experiments and trace analyses (Shi and co-workers,[1] Itami and co-workers[10]) were performed to ensure that the conditions were indeed metal-free. Coming from this direction, the processes look like organocatalylic C–H activation reactions.

In all these reports there are suggestions that aryl radicals are intermediates. The scope and conditions of the reactions (large excess of acceptor needed) and the H/D isotope effects are consistent with aryl radicals being involved. The addition of 2,2,6,6-tetramethyl-1-piperidinoxyl (TEMPO) and other inhibitors blocked the reactions,[1,3,10] and the successful cyclization of **1** to **2** is consistent with an aryl radical intermediate. Finally, high *ortho* selectivities are observed in the additions of aryl radicals to substitued benzenes.[1,2] Such

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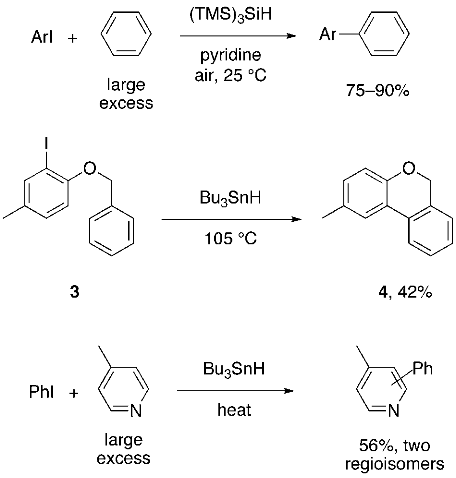
[**] We thank the Deutsche Forschungsgemeinschaft (DFG) and the US National Science Foundation (NSF) for funding. Achim Bruch and Sebastian Wertz are acknowledged for conducting control experiments.

selectivities are characteristic of additions of aryl radicals to arenes.[13]

The literature on radical chemistry abounds with related arylations of aryl halides in the presence of stoichiometric amounts of tin reagents, silicon reagents, or initiators. Sometimes, mild bases are also added. These reactions are usually called "homolytic aromatic substitutions" (HASs). Scheme 2 shows three examples of HAS reactions selected to roughly parallel those in Scheme 1.[14–16] Tris(trimethylsilyl)silane promotes reactions of aryl iodides and arenes in the presence of pyridine and air to give biaryls in good yield.[14] The cyclization of **3** with tributyltin hydride at 105 °C gives **4** in 42 % yield.[15] Addition of iodobenzene to 4-methylpyridine under similar conditions gives 2-phenyl- and 3-phenyl-substituted pyridines.[16]



Scheme 2. Selected homolytic radical aromatic substitution reactions. Ar = aryl, TMS = trimethylsilyl.

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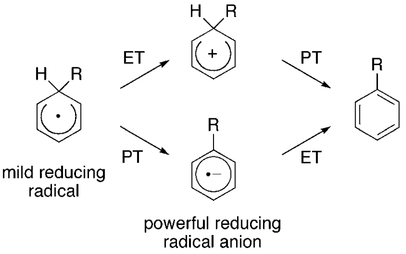
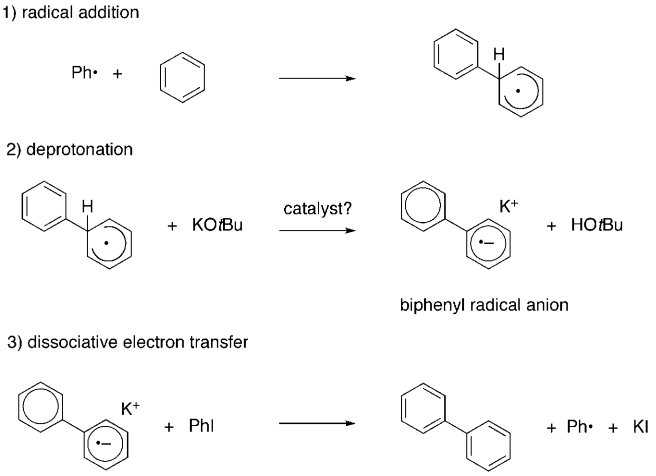
These transformations may look unusual at first glance, because reducing agents are added but a reduction is not accomplished. Nonetheless, many other related HAS transformations have been described.[5–9] There is broad agreement that a key step in all of these reactions is the addition (or cyclization) of an aryl radical to an arene. Furthermore, whenever radicals add to arenes, the resulting cyclohexadienyl-type radicals almost always find a way to rearomatize.[17–20] The net result is a "homolytic aromatic substitution". The possible mechanisms for rearomatization have been widely discussed,[21–25] and include disproportionation, reaction with an initiator by hydrogen transfer, and oxidation.

Oxidation of an intermediate cyclohexadienyl radical can occur by electron transfer (ET) to give a cyclohexadienyl cation, followed by proton transfer (PT), or by the reverse process of deprotonation to give a radical anion[26] followed by electron transfer (PT then ET). The two routes are shown in Scheme 3. The radical anion is a relatively good reducing radical, so direct ET from this type of intermediate deserves consideration. Related ET reactions have been proposed for (neutral) oxygen- and nitrogen-stabilized radicals.[27] Such reactions may occur by an inner sphere (atom-transfer) mechanism.[28] The striking feature of the new studies is the use of a very strong base (potassium or sodium *tert*-butoxide), sometimes with an additional catalyst. This raises the possibility that proton transfer to give a powerfully reducing radical anion intermediate could occur before electron transfer or other reactions of an intermediate cyclohexadienyl radical.

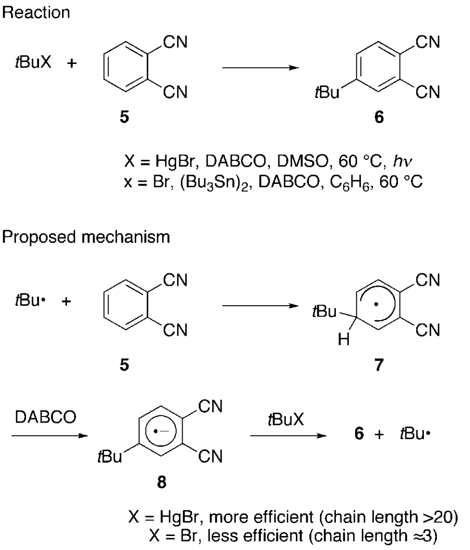


Scheme 3. PT and ET reactions of cyclohexadienyl radicals. Deprotonation of the mildly reducing cyclohexadienyl radical gives a powerfully reducing aromatic radical anion.

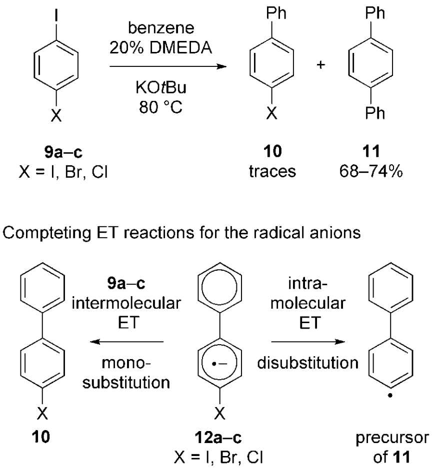
Putting these pieces together, we suggest that the reactions in Scheme 1 occur by an established mechanism called "base-promoted homolytic aromatic substitution". This is illustrated in Scheme 4 for the addition of iodobenzene to benzene to provide biphenyl. Addition of the phenyl radical to benzene gives the phenylcyclohexadienyl radical (step 1), which in turn is deprotonated by the base (step 2). The resulting biphenyl radical anion is highly conjugated and must be a powerful reducing agent. This radical anion transfers an



Scheme 4. Base-promoted homolytic aromatic substitution: A chain mechanism involving radicals and radical anions.



Scheme 5. Base-promoted homolytic aromatic substitutions with alkyl halides and alkyl mercuric halides.



Scheme 6. The use of Bunnett and Creary's probe by Kwong, Lei et al. for intramolecular ET.

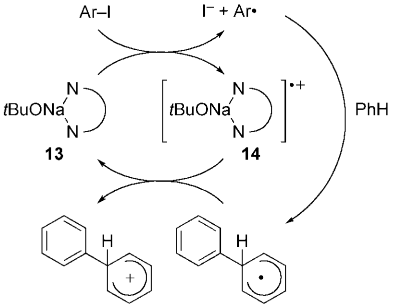
electron to the starting iodide to provide biphenyl, potassium iodide, and a new phenyl radical (step 3), thereby completing the chain. These types of electron-transfer reactions are thought to occur by dissociative (outer-sphere) electron transfer.[29,30] In other words, a long-lived aryl halide radical anion intermediate is not produced.

Support for the ET step of this mechanism comes from several sources. Ketyl and related radical anions readily transfer electrons to halides, including aryl halides.[31] Aromatic radical anions generated electrochemically have also been shown to reduce alkyl halides.[28] Furthermore, stable radical anions such as lithium di-*tert*-butylbiphenylide ("Freeman reagent") and lithium dimethylaminonaphthalenide are commonly used as organic electron-transfer reagents.[32,33]

Analogous base-promoted alkylations of electron-poor arenes by alkyl mercuric halides and alkyl halides have been reported by the research groups of Russell, Trahanovsky, and Kim et al.[34–36] They showed that adduct **6** was formed by a radical chain reaction (chain lengths of over 20) of *tert*-butylmercuric halides with 1,2-dicyanobenzene in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO, 60 °C, DMSO; Scheme 5). A ditin reagent was required to keep the reaction with *tert*-butylbromide from stopping. However, experiments still showed that a short chain (≈ 3) was operating. Here, DABCO is presumably a strong enough base to deprotonate radical **7**, since a rather stable radical anion **8** results.

The type of electron-transfer reaction proposed in Scheme 4—from a stabilized radical anion to a halide—is also very common in $S_{RN}1$ reactions of aryl halides.[37,38] Indeed, Kwong, Lei and co-workers made some very unusual observations by using Bunnett and Creary's dihalide probe for radical anion mechanisms in $S_{RN}1$ reactions.[39] Specifically, 1,4-halo-iodobenzenes **9a–c** were all directly converted into the disubstituted product (*para*-terphenyl, **11**) under their conditions.[3] Only small amounts of monosubstitution product **10** were formed, even at very short reaction times (Scheme 6). These obervations can readily be accommodated by a base-promoted HAS mechanism because the electron-transfer step from the first-formed radical anion **12a–c** can occur intramolecularly or intermolecularly. If the intramolecular ET reaction is faster, then the precursor **9** is railroaded directly to the disubstituted product **11**.

Electron-transfer reactions were also suggested in a mechanistic proposal for such reactions by Shirakawa, Hayashi et al.[2] as shown (in a simplied fashion) in Scheme 7. They suggested that ET from a complexed sodium *tert*-butoxide **13** (the ligand is represented schematically) produces an aryl radical, iodide, and complexed radical cation **14**. The addition of the aryl radical to benzene is followed by back ET from the resulting phenylcyclohexadienyl radical to the radical cation **14** to generate a phenylcyclohexadienyl cation and the starting *tert*-butoxide complex **13**. The phenylcyclohexadienyl cation is deprotonated by *tert*-butoxide (not shown).



Scheme 7. A simplified version of the Sharakawa/Hayashi mechanism, with the ligand represented schematically.

In some ways, this mechanism ressembles the type of mechanism that we suggest, but with ET before PT (see Scheme 3). However, there is a major difference—this mechanism is not a radical chain reaction. This can be seen because there is no need to invoke either initiation or termination steps. There are two problems with this mechanism from a radical standpoint. First, the reduction of complex **14** by a phenylcyclohexadienyl radical is a reaction between two transient intermediates. Even when such reactions have extremely high rate constants, they are inherently unlikely because of concentration effects. Such reactions are second-order overall—first-order in two species present in very low concentrations. Second, the initial stage of the reaction (**13**→**14**) is a reduction of an aryl halide by *tert*-butoxide to give two radicals (Ar$^•$ and *t*BuO$^•$). This reaction is very endothermic, so complexation would have to dramatically reduce the energy of the intermediates. Such endothermic reactions look much better as initiation steps than as steps in a nonchain catalytic cycle.

Like all radical chain reactions, the base-promoted HAS reactions (Scheme 4) require an initiation step. Such steps are typically endothermic and can even be difficult to identify when the chains are long. The oxidation of (complexed) *tert*-butoxide is a plausible intitiation step. Indeed, the combination of KO*t*Bu with photolysis—a process called entrainment—is one of the most commonly used methods to initiate $S_{RN}1$ reactions.[37,38] Furthermore, under phase-transfer conditions hydroxide can act as a reducing reagent (by ET) in radical chain reactions.[40] Once hydroxide is transported into the organic phase, electron transfer becomes less difficult because the hydroxide anion is poorly solvated relative to the hydroxy radical.

Beyond fundamental interest, the base-promoted homolytic substitution mechanism in Scheme 4 provides a framework for evaluating both the limitations and opportunities as the new process is extended. On the limitation front, aryl radicals are highly reactive species. In addition to participating in assorted C–C bond-forming reactions, they abstract hydrogen atoms from the solvent (if any is used) or just about anything else that is present in the medium at suitable concentrations (including the substrate and the product). So it might not be possible, for example, to perform high-yielding bimolecular additions such as those in Scheme 1 with only one equivalent of arene acceptor.

Nonetheless, there are rich opportunities in intramolecular reactions, and variation of the radical precursor and acceptor can now be readily evaluated on the basis of previous findings.[41] The many rate constants that are available for elementary radical reactions provide a rich source of information for planning new base-promoted HAS transformations.

Coming full circle to the original premise in Scheme 1: Do these reactions involve C–H activation? Furthermore, is this organocatalysis? Defining "C–H activation" is difficult, and different views exist.[42] Essentially, any substitution of a C–H bond can be said to involve a C–H activation at some point. That said, the base-promoted HAS mechanism resembles the Friedel–Crafts reaction, where deprotonation follows the addition of a reactive intermediate to an arene. Friedel–Crafts reactions are not usually said to involve C–H activation. Likewise, we do not think that the term is especially appropriate for HAS reactions in general.

On the other hand, the "organocatalysis" moniker could fit. The role of additives such as DMEDA and 1,10-phenanthroline is not clear at this point. They could help in the initiation step, in which case they might or might not be catalysts. Or they could assist one of the propagation steps, presumably either by helping with deprotonation or electron transfer. In this case, they probably would be catalysts. Organocatalysis is common in radical reactions. Polarity-reversal catalysis, for example, is an important method to bypass slow hydrogen transfer or other reactions with more rapid catalytic alternatives.[43] Redox catalysts are also common in electron-transfer reactions because many direct ET reactions often have high barriers despite being very exothermic.[44] In short, the role of the additives merits further study, but we do not object to calling them organocatalysts at this point.

If there is organocatalysis of base-promoted HAS reactions, then presumably there can be metal catalysis as well. Along these lines, several very recent publications are striking in their similarity to the reactions in Scheme 1 and 2, except that metal salts (Fe, Cu, Co, etc) are added.[45-49] We suggest that such reactions might be metal-catalyzed or (perhaps more likely) metal-initiated base-promoted HAS reactions.

To summarize, we have interpreted recent "organocatalytic C–H activation reactions" within the framework of an established mechanism called base-promoted homolytic substitution. Within that framework, the results are not conceptual breakthroughs (in the sense that some fundamentally new process must be invoked). However, they could be breakthroughs nonetheless. Base-promoted HAS substitution reactions may have a much broader scope of application in organic synthesis than is currently recognized. The recent results (Scheme 1) combined with the new mechanistic understanding presented herein (Scheme 4) could provide a launching pad for the rapid development of improved reaction conditions and new synthetic methods.

Received: March 4, 2011

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[13] For example, we conducted additions of 4-iodoanisole to two substituted arenes under the conditions used in Ref. [14] and obtained ratios very similar to those reported by Shi and coworkers in Ref. [1]: 1) addition to toluene: according to Ref. [1], 58% yield, *o*/*m*/*p*, 57:23:20; according to Ref. [14], 27%, 64:23:13; 2) addition to anisole: according to Ref. [1], 70%, 63:23:14; according to Ref. [14], 52%, 74:13:13.

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