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Radical Additions of Aryl Iodides to Arenes Are Facilitated by Oxidative Rearomatization with Dioxygen

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A diverse assortment of useful synthetic transformations are based on inter- and intramolecular additions of radicals to aromatic rings.[1] Such reactions are often conducted under reducing conditions with reagents such as tributyltin hydride and tris(trimethylsilyl)-silicon hydride,[2] even though the reactions are not reductions and often finish with oxidative rearomatization.[3,4] Typically, nonchain mechanisms are proposed for these formal homolytic aromatic substitution reactions, and suggestions for rearomatization pathways include reaction of an intermediate cyclohexadienyl or related radical with solvent, with initiator, with other radicals, or with itself, among other possibilities.[5]

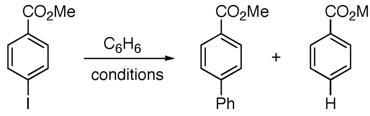
$$\mathrm{Ar{-}X + Ar^2{-}H \xrightarrow[(TMS)_3SiH,\ AIBN]{Bu_3SnH\ or} Ar^1{-}Ar^2}$$

Homolytic aromatic substitutions often require high temperatures and long reactions times and typically occur in moderate yields, perhaps because of the relative stability of cyclohexadienyl radical intermediates. We hypothesized that cyclohexadienyl radicals could be intercepted by using even more stable radicals, taking advantage of the "persistent radical effect".[6,7] We report herein the discovery that radical additions of aryl iodides to arenes can be effected under exceptionally mild conditions and in high yields in the presence of air. We suggest that the selective interception of cyclohexadienyl radicals by dioxygen, a stable triplet diradical, is a key step in this process.

We initially selected stable nitroxide radicals such as TEMPO to intercept the intermediate cyclohexadienyl radicals.[7] The identification of the air-mediated reaction conditions stemmed from control experiments for the TEMPO-mediated process. Results from several key exploratory reactions are summarized in Table 1. Under conditions typical of those used currently,[1,2] the addition of methyl *p*-iodobenzoate **1** to benzene at reflux was promoted ineffectively by tributyltin hydride and a stoichiometric quantity of AIBN (entry 1). Biphenyl-4-carboxylic acid methyl ester **2** was formed in 27% yield along with methyl benzoate **3** in 9% yield. Consistent with the results of Alvarez-Builla,[2a] a better but still moderate yield of **2** (67%) was obtained with tris(trimethylsilyl)silane (1 equiv) and AIBN (1 equiv) (entry 3). The addition of TEMPO improved both reactions, providing **2** in 68% yield in the tin hydride reaction (entry 2) and in 90% yield in the tris(trimethylsilyl)silane reaction (entry 4).

To our surprise, a routine control reaction under argon but in nondegassed benzene in the absence of both AIBN and TEMPO worked beautifully, providing **2** in 87% yield (entry 5). Further, TLC analysis showed the reaction was complete in only 3 h at room temperature. We initially had difficulty reproducing this control experiment, but soon discovered that reliable results were obtained on small scale only when nondegassed benzene was used. On larger scale, it was helpful to actually expose the reaction mixture to air. Attempted reactions under degassed conditions resulted in little or no conversion of **1**. Tributyltin hydride was not an effective substitute for tris(trimethylsilyl) silane in this ambient temperature, air-mediated process. These results showed that neither AIBN, nor TEMPO, nor high temperatures were essential for a high-yielding reaction.

Table 1. Yields of Addition of Methyl *p*-iodobenzoate to Benzene

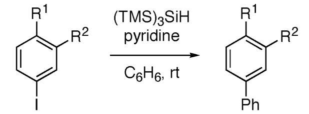


1a, 4 mM **2a** **3a**

entry	hydride 1.2 equiv	AIBN	TEMPO	temp, time	%**1**[a]	%**2**[a]	%**3**[a]
1	Bu_3SnH	1 equiv	–	80 °C, 3 h	0	27	9
2	Bu_3SnH	1 equiv	1 equiv	80 °C, 18 h	8	67	10
3	$(TMS)_3SiH$	1 equiv	–	80 °C, 14 h	0	68	6
4	$(TMS)_3SiH$	1 equiv	1 equiv	80 °C, 18 h	0	90	0[b]
5	$(TMS)_3SiH$	–	–	rt, 3 h	0	87[c]	0[d]

[a] yield determined by GC with octadecane as an internal standard; [b] not detected; [c] isolated yield; [d] not isolated

Table 2. Intermolecular Additions of Aryl Iodides to Arenes[a,b]



1a-f **2a-f**

entry	aryl iodide	R^1	R^2	product	% yield[b]
1	**1a**	CO_2Me	H	**2a**	87
2	**1b**	H	H	**2b**	75
3	**1c**	OMe	H	**2c**	90
4	**1d**	H	CO_2Et	**2d**	82
5	**1e**	*t*-Bu	H	**2e**	90
6	**1f**	H	OMe	**2f**	89

[a] rxn conds: **1**, $(TMS)_3SiH$ (1.2 equiv), and pyridine (5 equiv) were dissolved in benzene (50 mL, 4 mM); [b] isolated yields

For preparative reactions (Table 2), tris(trimethylsilyl)silane (1.2 equiv) and pyridine (5 equiv, to neutralize HI) were added to a nondegassed benzene solution of the aryl iodide **1a**−**f** (1 equiv, 0.004 M). The reaction mixture was stirred in an open flask and, if rapid precipitation of pyridine hydroiodide was not observed, then a small amount of iodine (0.02 equiv) was added.

As soon as the aryl iodide was consumed (TLC analysis), the mixture was filtered, the solvent was removed, and the crude product was directly subjected to flash chromatography to provide the target biaryls **2a**−**f**. Reactions were rapid (15−30 min) and clean and isolated yields of biaryl adducts **2a**−**f** were uniformly high (75−90%).

Although these conditions are much milder and the yields are higher than typical bimolecular additions of aryl radicals to arenes, standard limitations presumably apply: the arene acceptor must

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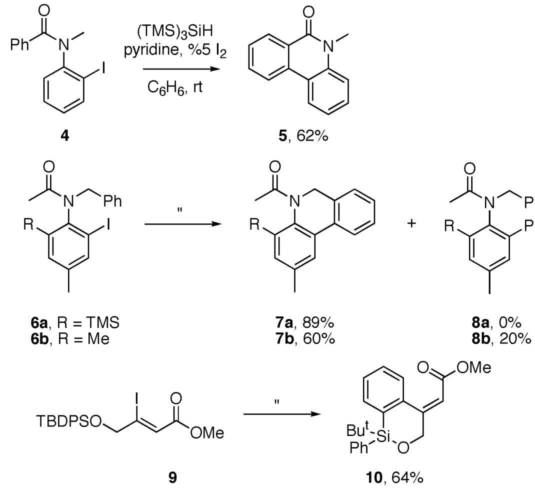
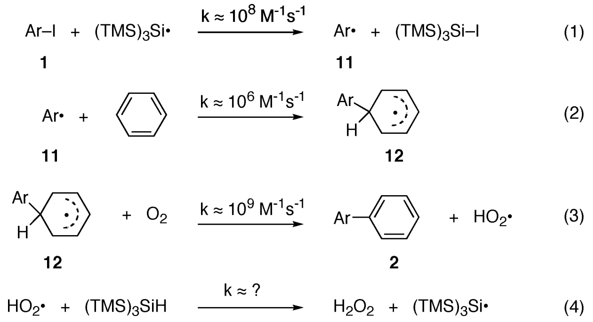
Scheme 1. Intramolecular Additions to Arenes



Scheme 2. Proposed Mechanism for Homolytic Aromatic Substitution Mediated by TTMSS/O$_2$



be used in large excess and regioselectivity is low for substituted benzenoid acceptors (see Supporting Information).

These limitations should be overcome in the intramolecular variant, and several early examples are shown in Scheme 1. The cyclization reactions were conducted under the standard conditions in benzene with iodine (0.02 equiv) as initiator. Reactions of **4** and **6a** provided exclusively the corresponding cyclized products **5** (62%) and **7a** (89%), while the reaction of **6b** provided a major cyclized product **7b** (60%) alongside a minor benzene adduct **8b** (20%). Alkenyl iodide precursor **9** was selected to probe whether alkenyl radical additions to benzene were possible, but we learned instead that 1,6-cyclization to the phenyl ring of the *tert*-butyldiphenylsilyl group was preferred; **10** was isolated as a single *E*-isomer in 64% yield. This transformation could form the basis of a generally useful intramolecular aryl transfer reaction.[8]

A mechanistic pathway for the oxygen-promoted, bimolecular radical addition to benzene is suggested in Scheme 2. Abstraction of iodine from the aryl iodide **1** by tris(trimethylsilyl)silyl radical provides aryl radical **11** (step 1),[9] which in turn adds to benzene to provide cyclohexadienyl radical **12** (step 2).[10] Oxygen reacts rapidly with both tris(trimethylsilyl)silyl[11] and aryl radicals ($k \approx 10^9$ M^{-1} s^{-1}), but these side reactions will not compete with the proposed reactions if the concentration of oxygen in the solution is sufficiently low.[12] The relatively stable cyclohexadienyl radical **12** will not react with the silane to propagate a chain; however, it will react very rapidly with triplet oxygen (step 3).[13]

The reaction of the parent cyclohexadienyl radical with oxygen is believed to occur not by the usual addition pathway to form a cyclohexadienylperoxy radical but instead by hydrogen transfer to produce benzene and the hydroperoxy radical (HOO$^\bullet$).[13] Accordingly, we propose that the reaction of **12** with oxygen directly provides the aromatized product **2** and the hydroperoxy radical. In turn, HOO$^\bullet$ can abstract hydrogen from the silane to transfer the chain.[14] The so-formed hydrogen peroxide may be capable of oxidizing another cyclohexadienyl radical **12**.[15]

These results have important implications for both synthetic and mechanistic radical chemistry. First, the mild reaction conditions may be generally applicable to a diverse range of inter- and intramolecular additions of aryl and alkenyl radicals to arenes and heteroarenes. Though such transformations are commonly used, they can often be stubbornly slow and low yielding. Second, the role of oxygen and its unique reaction path with cyclohexadienyl radicals have not been appreciated in these types of formal homolytic aromatic substitution reactions. Such reactions are often conducted with degassing to prevent premature interception of intermediate radicals by O$_2$. However, in cases where radical generation and addition are fast enough, oxygen is actually likely to promote the target reaction by providing a rapid and productive path for aromatization of the intermediate cyclohexadienyl radical. Further work will be needed to confirm the proposed path, and such work could ultimately open the door to a general new approach to formal homolytic aromatic substitution.

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Supporting Information Available: Full details of experiments and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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