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Radical aromatic substitution with benzene chromiumtricarbonyl

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Abstract—Radical aromatic substitution of *tert*-butyl groups for hydrogen on simple arene chromiumtricarbonyl complexes was accomplished. Preexisting *tert*-butyl groups and methoxy groups directed incoming radicals primarily to the *meta*-position, and methoxy groups diminished the rate of substitution by roughly tenfold.

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Arene chromiumtricarbonyl complexes have been used extensively as electrophiles in organic syntheses for many years.[1] More recently, several groups have demonstrated that arene chromiumtricarbonyl complexes are also susceptible to attack by nucleophilic radicals. Schmalz[2] and Li[3] have demonstrated SmI_2-promoted ketyl addition to arene chromiumtricarbonyl complexes, which only rearomatized with the loss of previously incorporated leaving groups, such as methoxy, fluoride, or chloride. Merlic and Houk[4] demonstrated intermolecular addition of the acetone–SmI_2 ketyl, forming mixtures of isomeric cyclohexadienes. They found a 100,000:1 selectivity for radical attack at benzene chromiumtricarbonyl over uncomplexed benzene, indicating significant rate acceleration resulting from metal complexation of the arene. Our group,[5] and others,[6] have demonstrated the generation and trapping of radicals *alpha* to arene chromiumtricarbonyl complexes.

In a series of previous publications we described novel synthetic methodology whereby radical aromatic substitution could be accomplished by a process involving iodine and bromine-transfer radical addition of electrophilic radical precursors to electron-rich heteroaromatics, accompanied by spontaneous rearomatization through loss of HI.[7] We were curious to see whether this atom-transfer substitution process would prove useful in a situation where the polarity of the radicals and olefins was reversed, and the aforementioned precedent for nucleophilic radical attack on arene–chromium complexes made them an appropriate and potentially interesting reagent for a study of this type. With this goal in mind, we considered the addition of nucleophilic alkyl radicals to benzene chromiumtricarbonyl, following our previously established photolytic protocol for radical aromatic substitution. Atom transfer reactions of simple alkyl halides are not particularly common. Successful photolytic atom-transfer additions of *tert*-butyl iodide and *iso*-propyl iodide to electron-deficient olefins have been reported.[8] Atom transfer addition of 1°, 2°, and 3° alkyl iodides to CO have been demonstrated, leading to acyl iodides, which in turn were intercepted with alcohol solvents, leading to generation of esters.[9]

The specific conditions utilized in this study, the details of which have been described in greater detail in previous work from our laboratory,[7] will be briefly summarized herein: suitable alkyl halides and olefins (in this case, arene–chromium complexes) were photolyzed in a CH_2Cl_2 solution to which propylene oxide was added in excess to serve as an HI trap. Curran[8] has shown that a substoichiometric quantity of $Bu_3SnSnBu_3$ is required in I-transfer radical addition reactions in order to consume I_2, a radical chain suppressant which is generated as a byproduct of these reactions. In the course of our previous work,[7] we found that the addition of $Na_2S_2O_3$ as an I_2 reductant in the presence of the phase-transfer catalyst $Bu_4N^+I^-$ to aid in thiosulfate solubility, provided an effective alternative to the use of distannanes.

The proposed atom-transfer radical addition and associated non-radical rearomatization step are shown in Scheme 1. *tert*-Butyl iodide was chosen as a radical precursor for addition reactions with benzene chromiumtricarbonyl (**1**), as it was a source of highly nucleophilic

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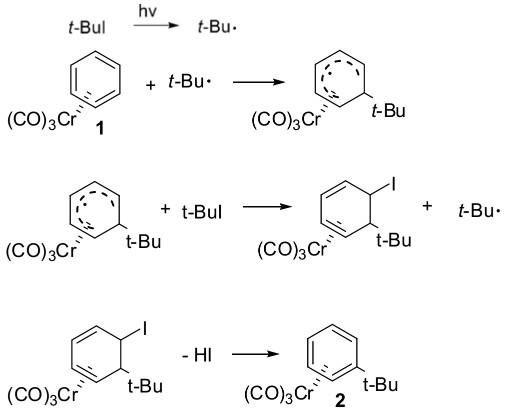


Scheme 1. Proposed mechanism for atom-transfer radical aromatic substitution with benzene chromiumtricarbonyl.

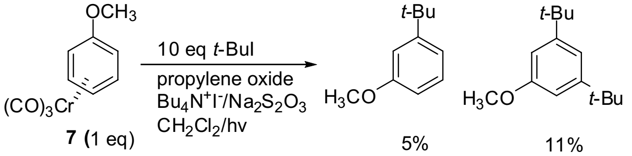
tertiary radicals, leading to enhanced addition rates to arene chromiumtricarbonyl complexes.

When these reaction conditions[10] were employed with a 1.5:1 ratio of **1**:*t*-BuI (Table 1, entry 1) and photolysis for 12 h, a mixture of mono-, di-, and tri-substituted products was obtained, with *tert*-butyl benzene as the major product. Yields were determined by GC, with product retention times determined by authentic, commercially available samples, with dodecane as an internal standard. When the experiment was repeated with an excess of *t*-BuI (1:10 **1**:*t*-BuI), the same products were observed, but with 1,3,5-tri-*tert*-tertbutylbenzene as the major product (Table 1, entry 2). No arene–chromium complexes could be observed in or isolated from the crude reaction mixture. When shorter reaction times were employed, mixtures of complexed and uncomplexed arenes were obtained, complicating the analysis. When isopropyl iodide was used as radical precursor under similar reaction conditions no substitution products were observed.

It seemed probable that the polysubstituted products formed from reaction of excess *tert*-butyl radical with *tert*-butylbenzene chromiumtricarbonyl (**2**), generated in situ. To test this premise, we subjected independently synthesized *tert*-butylbenzene chromiumtricarbonyl[11] to the reaction conditions (Table 1, entry 3), and found the ratios of 1,3-, 1,4-, disubstituted and 1,3,5-trisubstituted benzenes formed were comparable to those observed in entry 2, adding support to this presumption. We were also able to quantify decomplexed *tert*-butylbenzene, allowing us to account for most (89%) of the arene-derived products in the reaction.

In a critical control experiment, when benzene lacking chromium complexation was subjected to identical reaction conditions, none of the alkylation products listed in Table 1 were obtained. Benzene is known to be virtually unreactive with alkyl radicals,[12] and is frequently used as a solvent for reactions involving the generation and propagation of alkyl radicals. Since there are no known examples of arene chromiumtricarbonyl complexes undergoing Friedel–Crafts alkylation,[4] and benzene was unreactive under these reaction conditions, we can conclude that the observed products were indeed the result of radical addition to the chromium complex. Since uncomplexed benzene is unreactive to these conditions, the varying degrees of multiple alkylation implied that some of the reactive arene chromiumtricarbonyl intermediates remained complexed to the metal until the highest possible degree of substitution was complete. In the proposed mechanism (Scheme 1), coordinatively unsaturated 16e$^-$ and 17e$^-$ intermediates are generated, and it is likely that decomplexation occurred most readily at these intermediates, allowing for mono- and disubstituted products. Eventually, the alkyl-substituted complexes formed proved too labile under the reaction conditions, with the end result that no complexed arenes were detected at the conclusion of the reaction. Finally, the fact that aromatic substitution products, rather than addition products, were identified provided indirect evidence that the key atom-transfer step of atomic iodine to the Cr-bound pentadienyl radical, which is necessary for both rearomatization as well as radical chain propagation, was occurring as proposed.

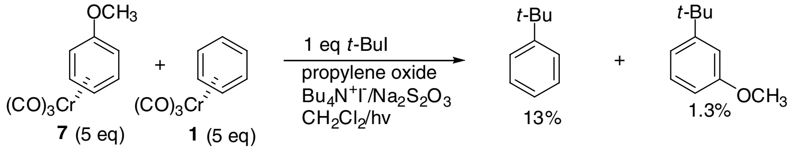
The regiochemistry of nucleophilic additions to substituted arene–chromium complexes have been extensively studied. Prediction of regiochemistry proved quite complex, depending on sterics, LUMO coefficients, charge, nucleophile strength, and rotamer conformations of the arene–Cr(CO)$_3$ bond.[13] In our examples, the absence of any *ortho*-disubstitution is not surprising due to steric effects. *meta*-Substitution accounted for most of the polyalkylated products observed, with *meta*:*para* ratios (**4** + **6**:**5**) of 6.5:1 (entries 1 and 3) and 7.8:1 (entry 2) being observed. The LUMO coefficients of alkylbenz-



Scheme 2. Addition to anisole chromiumtricarbonyl.

Table 1. Products and yields

Entry	Precursor (equiv)	*t*-BuI (equiv)		Yields (%)			
				t-Bu benzene (**3**)	1,3-Di-*t*-Bu benzene (**4**)	1,4-Di-*t*-Bu benzene (**5**)	1,3,5-Tri-*t*-Bu benzene (**6**)
1	**1** (1.5)	1	$\xrightarrow[\text{propylene oxide}]{t\text{-BuI}}$ $Bu_4N^+I^-/Na_2S_2O_3$ CH_2Cl_2/hv 12 h	23	7	2	6
2	**1** (1)	10		12	5	5	34
3	**2** (1)	10		29	9	8	43



Scheme 3. Competitive radical additions.

ene–$Cr(CO)_3$ complexes favored *ortho* and *meta* addition of nucleophiles, and polarization effects favored *para* attack.[13] The predominance of *meta*-substitution seen in our work with *tert*-butyl radicals can be understood in light of this model, by recognizing the neutral nature of the radical, greatly diminishing the influence of polarization effects. Predominate *meta*-direction by methyl groups has also been observed in the radical substitution of SmI_2 ketyls for halides.[3]

When anisole chromiumtricarbonyl (**7**) was submitted to these reaction conditions, 3-*tert*-butyl and *3,5*-di-*tert*-butyl anisole were obtained (Scheme 2), accompanied by significant quantities of unreacted anisole chromiumtricarbonyl. Arene complexes bearing electron donors are apparently more robust than those lacking such functionality, allowing for recovery of some unreacted starting material **7**. In order to assess the electronic influence of a methoxy substituent on the rate of radical attack, we subjected an equimolar mixture of **7** and **1** to limiting *tert*-butyl iodide, leading to the formation of a 10:1 ratio of *tert*-butylbenzene to 3-*tert*-butylanisole (Scheme 3). Thus, we concluded that the rate of radical attack on **1** occurs at 10 times the rate as that observed with **7**. This makes qualitative sense in light of the fact that nucleophilic radicals are known to react more rapidly with more electron-deficient alkenes, making the deactivating effect of a methoxy substituent reasonable.

In summary, we have found that our methodology for radical aromatic substitution can be used effectively with benzene chromiumtricarbonyl and highly nucleophilic *tert*-butyl radicals. The observed regioselectivity is reasonable in light of the established literature dealing with nucleophilic attack on arene chromiumtricarbonyl data.

Acknowledgments

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10. Typical reaction conditions: In a screw-top Pyrex test tube, the chromium complex **1** (0.270 g, 1 mmol), *tert*-butyl iodide (1.839 g, 10 mmol), propylene oxide (0.515 g, 10 mmol), $Na_2S_2O_3$ (0.158 g, 1 mmol), and $Bu_4N^+I^-$ (0.0369 g, 0.1 mmol) were combined with 3 mL of dichloromethane. The reaction mixture was deoxygenated at 0 °C for 10 min and photolyzed with a 450-W medium pressure Hanovia lamp for 12 h. Analysis was performed by GC/FID on an HP-5 capillary column. The identities of all products were determined by comparison of retention times with authentic samples. Response factors and yields were determined relative to dodecane (~100 mg) added as an internal standard prior to GC/FID analysis (Hewlett-Packard 5890) gas chromatograph for yield determination.
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