Homolytic Base-Promoted Aromatic Alkylations by Alkyl Halides[1]

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Electron-transfer chain reactions leading to regioselective alkylations of benzenes bearing electron-withdrawing substituents can be observed with alkyl halides in the presence of the radical initiator $(Bu_3Sn)_2$ and the proton acceptor 1,4-diazabicyclo[2.2.2]octane (DABCO). Yields vary from low to high depending on the benzene derivatives. The role of DABCO is to abstract a proton from the substituted cyclohexadienyl adduct radical to form a radical anion which then transfers an electron to RX and is converted to the alkylated product itself. The rate of this electron-transfer step is probably not fast enough to sustain a good radical chain reaction so that further generation of R• from excess $(Bu_3Sn)_2$ and RX is necessary.

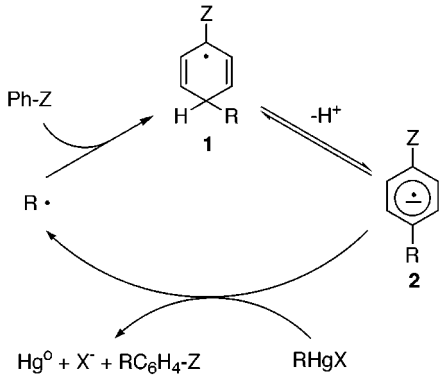
Introduction

Generally aromatic compounds are not ideal substrates in homolytic alkylation.[2] Usually the yields of substitution products are low due to side reactions, and regioselectivity is poor.[3] Among the exceptions are the protonated heteroaromatic compounds reported by Minisci, which can be alkylated efficiently by alkyl radicals.[4] Alkylmercury halides are good precursors of alkyl radicals and can undergo oxidative (substitutive) homolytic reactions with unsaturated compounds in the presence of a base, such as 1,4-diazabicyclo[2.2.2]octane (DABCO).[5] Recently we reported that alkylations of benzenes bearing electron-withdrawing substituents can proceed readily with RHgX/DABCO (R = *t*-Bu, *i*-Pr) by the mechanism shown in Scheme 1 provided the electron-withdrawing group Z (Z = CN, CHO, CO_2Et) can stabilize the radical adduct **1** and the radical anion **2**.[6] DABCO can abstract a proton from **1**, and then a chain reaction is initiated by electron transfer to RHgX with the regeneration of R•. This sequence of reactions is a novel type of homolytic aromatic alkylation.

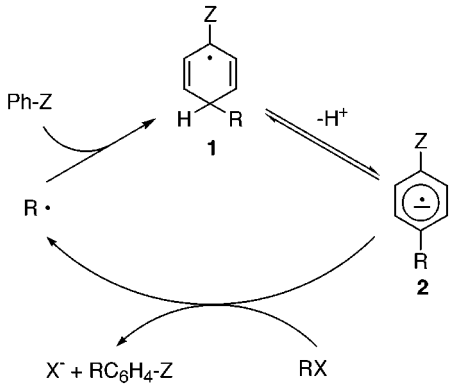
Though the *tert*-butylation of disubstituted benzenes proceeds smoothly by a chain process with *t*-BuHgX/DABCO under photolysis in dimethyl sulfoxide (DMSO),[6] we have been interested in replacing the toxic RHgX by RX to realize a similar process (Scheme 2). This modification, though simple, is mechanistically and synthetically interesting.

However, early attempts failed completely when *t*-BuBr or *t*-BuI was substituted for *t*-BuHgX.[6] No reaction is observed when the mixture of *t*-BuX and dicyanobenzene is photolyzed in the presence of 4 equiv of DABCO and 10 mol % of 2,2′-azobisisobutyronitrile (AIBN), Bz_2O_2, or $(Bu_3Sn)_2$ at 35−70 °C in dimethylformamide (DMF), DMSO, or C_6H_6. An attempt to initiate the reaction by using 20 mol % *t*-BuHgX in DMSO was also unsuccessful. The reactions stopped after the *t*-BuHgX was consumed. We think these observations are theoretically perplexing because estimated *E*°-values for *t*-BuX reductions suggest that these molecules should participate in electron transfer with the dicyanobenzene radical anions. Estimated *E*°-values (NHE) in DMSO and DMF are as follows: *t*-BuBr, −0.73, −0.82; *t*-BuI, −0.56, −0.77 V.[7]

Scheme 1



Scheme 2



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† Deceased: January 1, 1998.

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Table 1. *tert*-Butylation of 1,2-Dicyanobenzene[a]

		yield[b] (%) of **3** at time given	
t-BuX (X)	DABCO (equiv)	20 h	40 h
Br, I	0	none	none
Br	0.5	63	88
Br	4	75	97
I	4	90	

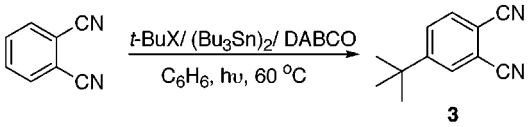
[a] Photolysis of 0.05 M substrate by a 275 W fluorescent sunlamp with 4 equiv of *t*-BuX and 2 equiv of $(Bu_3Sn)_2$. [b] Yield in C_6D_6 by ^1H NMR with $(Me_3Si)_2O$ as an internal standard.

Although the observed irreversible electrode reduction potentials are much more negative than the estimated values,[7b] they are in the range of those reported for *t*-BuHgX, e.g., for *t*-BuHgBr, $E^{1/2}$ (CH_3CN) = −1.08 V (SCE), and for *t*-BuI, $E^{1/2}$ (DMF) = −1.84 V (SCE), whereas the reduction potentials of the dicyanobenzenes are in the range of −1.5 to −1.6 V ($E°$, SCE).[7c,8]

Reminded by our former report[6] that 4 equiv of *t*-BuHgX was used for the alkylations of 1 equiv of disubstituted benzenes even though the reactions were good chain processes, we thought that the alkylations by *t*-BuX might be achieved if more than 1 equiv of *t*-Bu• is generated from *t*-BuX. Minisci also reported that when only 1 equiv of the radical source was used, the conversions of heteroaromatic compounds were as low as 15−50% in many cases, while the yields based on the converted heteroaromatic compounds were as high as 82−98%.[9] We reinvestigated the alkylation reactions with 4 equiv of alkyl halides in the presence of 2 equiv of $(Bu_3Sn)_2$ and 4 equiv of DABCO and report the results herein.

Results and Discussion

1. 1,2-Disubstituted Benzenes. We have found that 1,2-dicyanobenzene can be *tert*-butylated upon photolysis with 4 equiv of *t*-BuX, 2 equiv of $(Bu_3Sn)_2$, and 4 equiv of DABCO at 60 °C (eq 1 and Table 1).



(1)

3

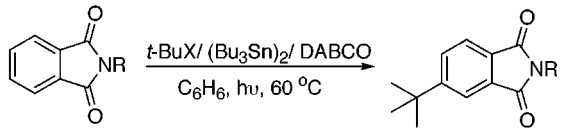
A higher yield of **3** was formed at a faster rate when *t*-BuX was *t*-BuI rather than *t*-BuBr. This observation is accounted for by the different rates of formation of the *t*-Bu• from the two *tert*-butyl halides. Alkylation by RX gives comparable yields of alkylated products to that by RHgX but requires a much longer reaction time. The dibutylated product which is formed when *t*-BuHgX is used was not found. Without DABCO, no alkylated product (such as **3**) was found. This shows that without a base the corresponding adduct radical which is probably formed reversibly is converted to **3** slowly. Also, no reaction was observed when AIBN or Bz_2O_2 was used instead of $(Bu_3Sn)_2$ or when DBU was used instead of DABCO. The initial kinetic chain length of the reaction was 7.0 with *t*-BuI as measured by the $(t\text{-Bu})_2NO$• (DTBN) inhibition method.[10] All of these results are consistent with the electron-transfer chain process presented in Scheme 2.

Table 2. *tert*-Butylation of Phthalimides[a]

			product yield[b] (%) at time given		
substrate	X	product	20 h	60 h	100 h
4a	Br	**5a**	14	28	
4a	I	**5a**	15		
4b	Br	**5b**	27	57	75
4b	I	**5b**	31		

[a] See footnote *a* of Table 1. [b] See footnote *b* of Table 1.

Phthalimides also can be alkylated by *t*-BuX (eq 2, Table 2). Compound **4b** is more reactive than **4a**, and both are less reactive than 1,2-dicyanobenzene. Higher yields of products (such as **5a**,**b**) were obtained with *t*-BuBr than with *t*-BuI. With *t*-BuI, it is likely that *t*-Bu• was generated so rapidly that most of it went to disproportionation, leaving most starting material unreacted.



(2)

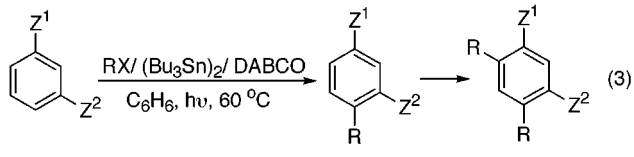
4, **a**, R = H
b, R = Me

5, **a**, R = H
b, R = Me

Phthalic anhydride failed to undergo reaction under the same conditions, probably because it has a more negative reduction potential than phthalimide (−1.16 vs −0.70 V, SCE, in H_2O).[11] As Minisci pointed out,[4] the transition state for attack of the nucleophilic *t*-Bu• upon an aromatic ring should be stablized by $t\text{-Bu}^+Ar^{\bullet-}$, and this is unfavored for phthalic anhydride which has the more negative reduction potential.

2. 1,3-Disubstituted Benzenes. Results for the formation of the mono and di-*tert*-butylated products **6a** and **7a** from 1,3-dicyanobenzene are summarized in Table 3. The initial chain length was only 3.0 with *t*-BuI, measured by using 20 mol % DTBN. This is much shorter than that with *t*-BuHgCl which is 22.[6]

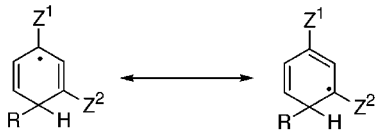
Even though for 1,3-disubstituted benzenes the adduct radicals **8** can be stablized by both substituents, 1,3-dicyanobenzene is less reactive than 1,2-dicyanobenzene, as shown by the comparison of their alkylation yields at 20 h.



(3)

6 **7**

a, R = *t*-Bu, $Z^1 = Z^2$ = CN
b, R = *i*-Pr, $Z^1 = Z^2 = CO_2Et$
c, R = *t*-Bu, Z^1 = CN, $Z^2 = CO_2Et$



Diethyl isophthalate cannot be *tert*-butylated by *t*-BuBr or *t*-BuI in the presence of $(Bu_3Sn)_2$ and DABCO.

(8) The electrode potential SCE value is +0.241 V greater than the NHE value.
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Table 3. *tert*-Butylation of 1,3-Dicyanobenzene[a]

t-BuX (X)	DABCO (equiv)	time (h)	**6a**[b] (%)	**7a**[b] (%)
Br, I	0	20	none	none
Br	0.5	20	23	
Br	0.5	60	38	
Br	4	20	33	
Br	4	60	65	15
I	4	20	66	18

[a] See footnote *a* of Table 1. [b] See footnote *b* of Table 1.

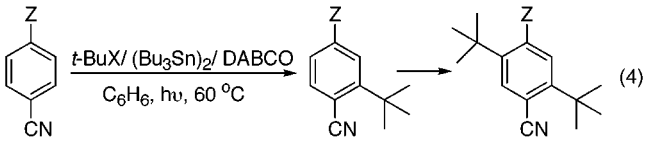
Table 4. *tert*-Butylation of 1,4-Dicyanobenzene[a]

t-BuX (X)	DABCO (equiv)	time (h)	**9a**[b] (%)	**10a**[b] (%)
Br, I	0	100	none	none
Br	0.5	20	6	
Br	0.5	100	27	
Br	4	20	17	
Br	4	100	74	10
I	4	20	38	
I	8	20	51	3

[a] See footnote *a* of Table 1. [b] See footnote *b* of Table 1.

However, with *i*-Pr•, which is smaller than *t*-Bu•, the alkylation takes place. Compound **6b** was produced in a yield of 18% in 20 h with 4 equiv of *i*-PrI and in a yield of 35% in 100 h with 4 equiv of *i*-PrBr. No dialkylated product **7b**, which was observed with *t*-BuHgX, was found. However, with *n*-BuBr or *n*-BuI, no alkylated products can be formed from diethyl isophthalate in 3 days. Ethyl 3-cyanobenzoate reacted slowly with 4 equiv of *t*-BuBr, 2 equiv of $(Bu_3Sn)_2$, and 4 equiv of DABCO. Compound **6c** was formed in yields of 25 and 82% upon photolysis in 20 and 100 h, respectively. The *tert*-butyl group is always introduced ortho to the −CN group, which is less sterically hindered than the position ortho to $-CO_2Et$. Replacement of *t*-BuBr by *t*-BuI yielded only a trace of **6c**.

3. 1,4-Disubstituted Benzenes. The 1,4-disubstituted benzenes are much less reactive than the 1,3-derivatives (eq 4). Table 4 summarizes the results for the alkylations of 1,4-dicyanobenzene. The dialkylated product **10a** was also formed as well as the monoalkylated product **9a**. The initial kinetic chain length was only 1.3 with *t*-BuI, measured by using 20 mol % DTBN. Obviously, this reaction did not proceed by an efficient chain process.



9, **a**, Z = CN
b, Z = CO_2Et **10**

Ethyl 4-cyanobenzoate yielded only a trace of **9b** with *t*-BuI. However, with *t*-BuBr, **9b** was formed in yields of 39, 57, and 70% upon photolysis for 20, 60, and 100 h, respectively. No **10b** was found. The *tert*-butyl groups were always introduced ortho to the −CN group. Unlike the significant reactivity difference between 1,3- and 1,4-dicyanobenzenes, the reactivity difference between ethyl 3- and 4-cyanobenzoates is small.

Conclusion

Overall, we find that homolytic base-promoted aromatic alkylations can be observed with alkyl halides, $(Bu_3Sn)_2$, and DABCO in C_6H_6 at 60 °C. These results suggest that base-promoted homolytic aromatic substitution may be a rather general process for aromatic compounds bearing electron-withdrawing substituents. This alkylation method can to some extent serve as a complementary methodology to the well-known Friedel−Crafts reaction, which can alkylate benzene derivatives bearing electron-donating substituents. Alkylations by alkyl halides have a much shorter kinetic chain length than those involving alkylmercury halides[6] and usually need a longer reaction time. Yields vary from low to high, depending on the substrates, and are much higher if the recovered starting substrates are taken into account. In most reactions unreacted aromatic compounds remained after the RX was consumed. The lower reactivity of *t*-BuX compared to *t* -BuHgX is probably due to the slower electron-transfer rate from the radical anions to *t*-BuX. Lund has estimated the rate of electron transfer from aromatic radical anions to *t*-BuBr to be only 10 L/(mol•s) at 25 °C for an aromatic compound with $E° = -1.5$ V (SCE).[12] This rate is too slow to sustain an efficient chain process.

Usually the reactivity and initial kinetic chain length decrease from 1,2- to 1,3- to 1,4-disubstituted benzenes. For reactive substrates such as 1,2-dicyanobenzene, alkylations by *t*-BuI give higher yields of products than those by *t*-BuBr. Otherwise, alkylations by *t*-BuBr give higher yields of the products.

In comparison to the $-CO_2Et$ group, the −CN group is a much better activating group with a smaller steric requirement. The introduction of alkyl substituents is very regioselective, and usually monoalkylated products are the major products. Since Bu_3Sn• is incompatible with the aldehyde group,[13] no aldehyde-substituted benzenes can be alkylated by this method.

Dialkylated products were formed from the less reactive 1,3- and 1,4-dicyanobenzenes but not from the more reactive 1,2-dicyanobenzene. This observation shows that the formation of dialkylated products is not strongly related to the reactivity of the starting benzene derivatives but to the reactivity difference between the starting aromatic compounds and the corresponding monoalkylated products.

Even though there are many literature methods available for removal of the tin compounds from the desired products,[14] the use of excess $(Bu_3Sn)_2$ in this method is still a drawback in preparative applications. Further work on replacing the tin radical initiator is highly desired.

Experimental Section

General Procedures. The aromatic substrates (0.5 mmol) and reagents were dissolved in 5 mL of C_6H_6 under a nitrogen atmosphere in a Pyrex test tube and irradiated with a 275 W Sylvania fluorescent sunlamp which was approximately 10 cm away from the reaction tube. After the reaction stopped, the solution was concentrated to about 2 mL and cooled to 0 °C, and some precipitate was removed by filtration. Then 2 mL of 1 M NaOH solution was added to the filtered solution, and the mixture solution was stirred for 30 min at room temperature for further removal of the tin compounds.[14a] After the ethereal extract was dried by $MgSO_4$ and concentrated, the

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reaction products were isolated by thin layer chromatography (TLC) using hexanes−ethyl acetate as the eluent.

For reactions monitored by ^{1}H NMR spectroscopy, the substrate (0.05 mmol) and added reagents were dissolved in 0.6 mL of C_6D_6 in a 5 mm NMR tube with 2 μL of $(Me_3Si)_2O$ (bp ∼ 101 °C) as an internal standard. A 0.01 mmol amount of DTBN was added to the solution for inhibition reactions to measure the initial kinetic chain length.[10]

^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ at 400 and 100 MHz with δ measured relative to $CHCl_3$ (7.27 ppm) or the central ^{13}C peak of $CDCl_3$ (77.23 ppm).

Products **6b**,**c** and **9a**,**b** have ^{1}H and ^{13}C NMR spectral data consistent with those reported[6] and give HRMS consistent with their structure. Additional data for these products and data for all other products are listed below.

1,2-Dicyano-4-(1,1-dimethylethyl)benzene (3) was isolated as a white solid, mp 57−59 °C. FTIR (cm^{-1}) 3103, 2962, 2874, 2234, 1596; ^{1}H NMR δ 7.82 (t, J = 1.2 Hz, 1H), 7.75 (d, J = 1.2 Hz, 2H), 1.37 (s, 9H); ^{13}C NMR δ 157.91, 133.57, 131.11, 130.60, 116.02, 115.94, 115.79, 113.03, 35.82, 30.91; HREIMS *m*/*z* (rel intens) 184.1002 (20; calcd for $C_{12}H_{12}N_2$, 184.1001), 169 (100), 141 (51), 114 (7).

4-(1,1-Dimethylethyl)phthalimide (5a) was isolated as a white solid, mp 130−132 °C. FTIR (cm^{-1}) 3250, 3050, 2868, 1748, 1700; ^{1}H NMR δ 7.91 (s, 1H), 7.85 (brs, 1H), 7.78−7.79 (m, 2H), 1.39 (s, 9H); ^{13}C NMR δ 168.73, 168.31, 159.26, 133.03, 131.62, 130.13, 123.65, 120.95, 36.00, 31.35; HREIMS *m*/*z* (rel intens) 203.0947 (23; calcd for $C_{12}H_{13}NO_2$, 203.0946), 188 (100), 169 (39), 145 (12), 115 (6).

4-(1,1-Dimethylethyl)-*N*-methylphthalimide (5b) was isolated as a white solid, mp 87−89 °C. FTIR (cm^{-1}) 2968, 2871, 1765, 1709, 1602; ^{1}H NMR δ 7.87 (d, J = 1.6 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 1.6 Hz, 1H), 3.16 (s, 3H), 1.37 (s, 9H); ^{13}C NMR δ 169.16, 168.76, 158.64, 132.60, 131.00, 129.70, 123.17, 120.60, 35.98, 31.33, 24.08; HREIMS *m*/*z* (rel intens) 217.1105 (23; calcd for $C_{13}H_{15}NO_2$, 217.1103), 202 (100), 174 (20), 145 (20), 115 (8).

2,4-Dicyano-1-(1,1-dimethylethyl)benzene (6a) was isolated as a white solid, mp 56−58 °C. FTIR (cm^{-1}) 3119, 3044, 2988, 2878, 2237, 2230, 1602; ^{1}H NMR δ 7.96 (d, J = 2.0 Hz, 1H), 7.80 (dd, J = 8.4, 2.0 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 1.55 (s, 9H); ^{13}C NMR δ 159.07, 138.77, 135.95, 127.88, 118.29, 116.97, 112.76, 112.24, 36.57, 30.02; HREIMS *m*/*z* (rel intens) 184.1002 (21; calcd for $C_{12}H_{12}N_2$, 184.1001), 169 (100), 141 (26), 114 (5), 57 (4).

Diethyl 4-(1-Methylethyl)isophthalate (6b) was isolated as a colorless liquid.[6] FTIR (cm^{-1}) 2990, 2906, 2872, 1731, 1717, 1305, 1229.

Ethyl 3-Cyano-4-(1,1-dimethylethyl)benzoate (6c) was isolated as a colorless liquid.[6] FTIR (cm^{-1}) 2990, 2910, 2225, 1731, 1607, 1298, 1129.

2,4-Dicyano-1,5-bis(1,1-dimethylethyl)benzene (7a) was isolated as a white solid, mp 176−178 °C. FTIR (cm^{-1}) 2959, 2873, 2224, 1593; ^{1}H NMR δ 7.94 (s, 1H), 7.64 (s, 1H), 1.54 (s, 18H); ^{13}C NMR δ 158.37, 141.83, 125.10, 118.45, 109.57, 36.77, 30.03; HREIMS *m*/*z* (rel intens) 240.1626 (13; calcd for $C_{16}H_{20}N_2$, 240.1627), 225 (100), 210 (4), 197 (6), 57 (5).

1,4-Dicyano-2-(1,1-dimethylethyl)benzene (9a) was isolated as a white solid, mp 150−152 °C (lit.,[6] 150−151 °C). FTIR (cm^{-1}) 3115, 2988, 2875, 2231, 2226, 1558.

Ethyl 4-Cyano-3-(1,1-dimethylethyl)benzoate (9b) was isolated as a white solid, mp 44−46 °C (lit.,[6] liquid). FTIR (cm^{-1}) 2970, 2873, 2223, 1733.

1,4-Dicyano-2,5-bis(1,1-dimethylethyl)benzene (10a) was isolated as a white solid, mp 172−174 °C. FTIR (cm^{-1}) 2959, 2874, 2223; ^{1}H NMR δ 7.48 (s, 2H), 1.52 (s, 18H); ^{13}C NMR δ 151.80, 133.60, 119.30, 114.93, 35.57, 30.05; HREIMS *m*/*z* (rel intens) 240.1626 (12; calcd for $C_{16}H_{20}N_2$, 240.1627), 225 (100), 210 (4), 197 (9), 182 (5), 57 (5).

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Supporting Information Available: ^{1}H and ^{13}C NMR, and HREIMS data for **6b**,**c** and **9ab** and ^{1}H and ^{13}C NMR spectra of **5a,b**, **6a**−**c**, **7a**, **9a,b**, and **10a** (37 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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