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Rapid assembly of tetrahydrodibenzofurans and tetrahydrocarbazoles from benzene and *o*-iodophenols and *o*-iodoanilines: reductive radical arylation of benzene in action

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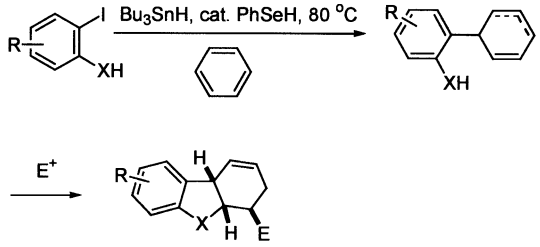
Abstract—In the presence of catalytic benzeneselenol, generated in situ from diphenyl diselenide, tributyltin hydride brings about the radical addition of *ortho*-functionalized aryl iodides to benzene giving aryl cyclohexadienes. These may then be cyclized by means of standard electrophilic reagents. The use of *o*-methoxycarbamoyliodobenzene leads to a tetrahydrocarbazole, whereas *o*-iodobenzoic acid provides a tetrahydrodibenzopyranone. *o*-Iodophenols lead, overall, to tetrahydrodibenzofurans. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

One of the most important reactions in preparative organic chemistry is the Birch reduction enabling the facile conversion of accessible, stable aromatic nuclei into versatile, reactive cyclohexadienes.[1–3] The usefulness of this reaction is enhanced when the intermediate radical anions, or anions, can be trapped with suitable electrophiles leading to concomitant arene reduction and carbon–carbon bond formation.[1–4] The value of the overall transformation is emphasized by the recent introduction of alternative methods, anionic and metal-catalyzed, for the reductive functionalization of arenes.[5,6] Here we describe a direct entry into tetrahydrodibenzofurans and tetrahydrocarbazoles, by dearomatizing addition of readily available *o*-functionalized aryl radicals onto benzene itself, followed by a simple electrophile mediated cyclization onto the cyclohexadiene (Scheme 1). Given the widespread occurrence of reduced dibenzofurans and carbazoles the overall sequence meshes nicely with a recurring theme of contemporary organic chemistry; the rapid, convergent assembly of pharmacophore-like molecular scaffolds[7] with a maximum of atom efficiency[8–10] from readily available feedstocks.



Scheme 1. Dearomatizing radial addition to benzene followed by electrophilic cyclization.

Aryl radicals add rapidly to arenes to give substituted cyclohexadienyl radicals (k=4.5×10^5 M^{-1}s^{-1} at 25°C).[11] Unfortunately, the adduct radical does not propagate chains by hydrogen abstraction from stannanes. Consequently most tin hydride mediated additions of aryl halides to arenes, intra- or intermolecular, are inefficient, require large amounts of initiator, and give rise to the fully aromatized products as a consequence of disproportionation or oxidation of the intermediate cyclohexadienyl radicals. While the usefulness of oxidative radical cyclizations in synthesis cannot be denied,[12] we contend that the inability to trap the cyclohexadienyl radical and so take advantage of the more highly functionalized, cyclohexadiene product represents a missed opportunity in preparative free radical chemistry. Recently, we described how a catalytic amount of benzeneselenol, conveniently introduced as diphenyl diselenide, serves to trap the cyclohexadienyl radicals, thereby enabling isolation of aryl substituted cyclohexadienes in moderate to good yield.[13] The present purpose is to illustrate how, through the use of *o*-functionalized aryl iodides, this reductive CC bond forming sequence may be exploited.

2. Results and discussion

In a first example (Table 1), a benzene solution of tributyltin hydride and AIBN was added dropwise to a refluxing solution of *o*-iodophenol (**1**) and 20 mol% diphenyl diselenide

Keywords: radicals and radical reactions; dienes; cyclisation; selenium and compounds.

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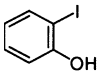
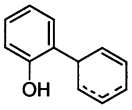
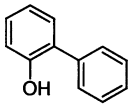
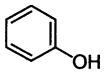
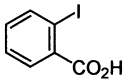
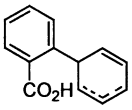
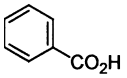
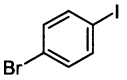
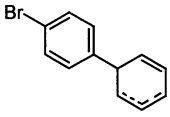
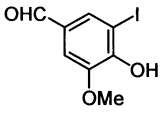
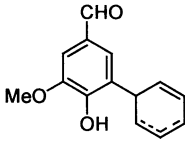
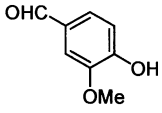
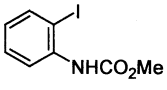
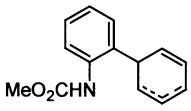
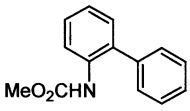
Table 1. Addition of functionalized aryl radicals to benzene

Entry	Substrate	Cyclohexadiene (skipped/conjugated)	Aromatized adduct	Deiodination
1				
	1	**2**, 48%, 10/1	**3**, 5%	16%
2			Not isolated	
	4	**5**, 54%, 10/1		23%
3			Not isolated	Not isolated
	6	**7**, 43%, 4/1		
4			Not isolated	
	8	**9**, 44%, 10/1		15%
5				Not isolated
	10	**11**, 41%, 3/2	**12**, 10%	

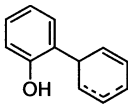
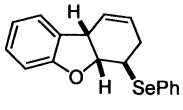
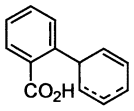
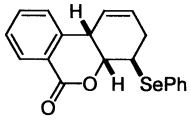
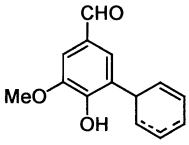
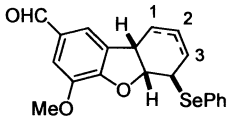
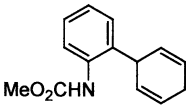
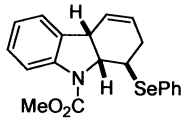
in benzene at reflux over a period of 12 h. After removal of the volatiles, silica gel chromatography enabled the isolation of the desired adduct **2** in 48% yield together with 5% of the rearomatized product **3** and 16% of phenol. The substrate (**1**) was completely consumed under these conditions whereas in the absence of diphenyl diselenide large amounts of **1** were recovered and the major products were phenol, the result of simple deiodination, and the aromatized adduct (**3**). The presence of benzeneselenol, derived by in situ reduction of the diphenyl diselenide,[14] is clearly important for the smooth operation of these reactions: it functions by trapping of the intermediate cyclohexadienyl radical, thereby ensuring chain propagation.[13] The ratio of non-conjugated to conjugated diene product resembles that seen in the earlier examples,[13] and reflects on the preferential kinetic trapping of the cyclohexadienyl radical at the internal site. The predominant formation of the non-conjugated diene in this example argues against intramolecular quenching of the intermediate cyclohexadienyl radical by the phenol.[15]

In a second example (Table 1) the *o*-cyclohexadienyl benzoic acid **5** was isolated in 54% yield from the selenol catalyzed addition of **4** to benzene. The third example (Table 1) takes advantage of the greater reactivity of aryl–iodine bonds over aryl–bromine bonds and provides **7**, poised for further functionalization perhaps by organometallic means. The use of *o*-iodovanillin (**8**) as substrate (Table 1) illustrates the further functional group compatibility typical of free radical chain reactions and demonstrates application to more complex substrates. Finally, the last example of Table 1 confirms the applicability of the process to *o*-iodoanilines, provided that they are protected in the form of carbamates. In this last example analysis of the crude reaction mixture, before passage over silica gel, by ^{1}H NMR revealed the non-conjugated diene to be formed in a ratio of >10:1. The ratio of 3:2 reported in Table 1 is therefore the result of partial equilibration occurring on chromatographic purification.[16]

Although the isolated yields in the above additions are typically only 40–50%, we believe that they represent synthetically useful processes given that the products are derived from very readily available starting materials, namely benzene and an *o*-functionalized iodoarene, and because of the considerable increase in complexity obtained in a single reaction step. The functionality present in the adducts is most readily exploited by cyclization reactions as illustrated by the selenium bromide mediated ring closures of Table 2.

In conclusion, we have provided methodology for the addition of *o*-functionalized aryl radicals to benzene under reductive conditions that enables the isolation of arylated cyclohexadienes in moderate yield. These functionalized cyclohexadienes are ideally set up for cyclization reactions

Table 2. Selenium bromide medicated cyclizations

Entry	Substrate	Product, % yield
1[a]	 **2**	 **13**, 76%
2[a]	 **5**	 **14**, 79%
3[b]	 **9**	 **15**, 71%
4[c]	 **11**	 **16**, 69%

[a] Reaction performed with the inseparable 10/1 mixture of non-conjugated/conjugated diene.
[b] Reaction performed with the inseparable 10/1 mixture of non-conjugated/conjugated diene. The product was a ~8:1 inseparable mixture of 1,2- and 2,3-alkene arising from cyclization of the mixture.
[c] Reaction performed with a pure sample of non-conjugated diene.

leading to the formation of tetrahydrodibenzofurans and tetrahydrocarbazoles, thereby providing a very rapid means of entry into these nuclei from commodity chemicals. Finally, we note that in the ultimate cyclized products (Table 2) three adjacent sites of the original benzene ring are directly functionalized, while the remaining three are set up for immediate exploitation.

3. Experimental

3.1. Typical protocol for radical addition to benzene

A flask fitted with a condensor is charged with $(PhSe)_2$ (0.2 mmol), the aryl iodide (1 mmol) and benzene (20 mL) is flushed thoroughly with argon by sparging for 30 min. The solution is brought to reflux, then a solution of AIBN (0.1 mmol) and Bu_3SnH (1.2 mmol) in degassed benzene (10.0 mL) is added via a syringe pump over 12 h with care being taken that the needle tip is not placed in the hot refluxing vapors. After completion of addition, the reaction mixture is refluxed for an additional hour, then cooled down to room temperature and the volatiles are removed under vacuum. The crude reaction mixture is redissolved in acetonitrile (30.0 mL) and washed with hexane (3×7 mL). The acetonitrile layer is concentrated and the residue purified by chromatography on silica gel using a mixture of ethyl acetate–hexane as eluent. Mixtures of regioisomers were not separated but were characterized as such.

3.1.1. 2-(Cyclohexadienyl)phenol (2). Ratio 10:1. HRMS Calcd for $C_{12}H_{12}O$ $[M]^{+\cdot}$: 172.0888, found: 172.0878. Major isomer: ^1H NMR ($CDCl_3$) δ 2.78–2.85 (m, 2H), 4.15–4.21 (m, 2H), 5.60 (br s, 1H), 5.79–5.86 (m, 2H), 5.92–6.00 (m, 2H), 6.81 (d, J=7.5 Hz, 1H), 6.91 (t, J=7.5 Hz, 1H), 7.3–7.4 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.8, 38.6, 115.9, 120.7, 125.3, 127.4, 128.8, 130.4, 138.4, 154.8. The minor isomer was distinguished in the ^1H NMR spectrum by signals at δ 2.30–2.42 (m, 1H), 2.50–2.62 (m, 1H), 3.80–3.96 (m, 1H).

3.1.2. 2-(Cyclohexadienyl)benzoic acid (5). Ratio 7:1. HRMS Calcd for $C_{13}H_{12}O_2$ $[M]^{+\cdot}$: 200.0837, found: 200.0818. Major isomer: ^1H NMR ($CDCl_3$) δ 2.77 (m, 2H), 5.05 (m, 1H), 5.71–5.84 (m, 4H), 7.30 (d, J=7.8 Hz, 1H), 7.47 (t, J=7.8 Hz, 1H), 7.52 (t, J=7.8 Hz, 1H), 8.00 (d, J=7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.9, 38.0, 124.1, 126.3, 127.8, 128.6, 130.6, 131.2, 133.3, 147.3, 172.5. The minor isomer was distinguished in the ^1H NMR spectrum by signals at δ 2.35 (m, 1H), 4.58–4.70 (m, 1H).

3.1.3. 4-Bromophenylcyclohexadiene (7). Ratio 4:1. HRMS Calcd for $C_{12}H_{11}$ $[M-Br]^+$: 155.0861, found: 155.0861. Major isomer: ^1H NMR ($CDCl_3$) δ 2.71–2.80 (m, 2H), 3.82–3.90 (m, 1H), 5.62–5.71 (m, 2H), 5.78–5.82 (m, 2H), 7.11 (d, J=8.4 Hz, 2H), 7.42 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 26.0, 41.7, 124.3, 128.1, 128.7, 131.6, 131.7, 136.7. The minor isomer was distinguished in the ^1H NMR spectrum by signals at (2.22–2.32 (m, 1H), 2.41–2.60 (m, 1H), 3.51–3.61 (m, 1H), 5.92–6.11 (m, 2H), 7.15 (d, J=8.4 Hz, 2H).

3.1.4. 5-(Cyclohexadienyl)vanillin (9). Ratio 4:1. HRMS Calcd for $C_{14}H_{14}O_3$ $[M]^{+\cdot}$: 230.0942, found: 230.0945. Mp 112–114°C. Major isomer: ^1H NMR ($CDCl_3$) δ 2.73–2.76 (m, 1H), 3.96 (s, 3H), 4.45–4.52 (m, 1H), 5.70–5.98 (m, 4H), 6.41 (s, 1H), 7.26 (d, J=1.8 Hz, 1H), 7.51 (d, J=1.8 Hz, 1H), 9.82 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.9, 34.4, 56.4, 106.7, 124.1, 124.9, 125.5, 126.9, 127.6, 148.8, 172.2, 191.4. The minor isomer was distinguished in the ^1H NMR spectrum by signals at: δ 2.31–2.48 (m, 1H), 2.52–2.68 (m, 1H), 3.99–4.08 (m, 1H), 5.99–6.01 (m, 2H), 6.20–6.25 (m, 2H), 6.41 (s, 1H), 7.25 (d, 1H, J=1.8 Hz, 1H), 7.40 (d, J=1.8 Hz, 1H), 9.83 (s, 1H).

3.1.5. Cyclohexadienyl-2-methoxycarbamoylbenzene (11). Ratio 3:2. MS Calcd for $C_{14}H_{16}N0_2$ $[MH]^{+\cdot}$: 130.1, found 130.1. Major isomer: ^1H NMR ($CDCl_3$) δ 2.80–2.85 (m, 2H), 3.79 (m, 3H), 4.08–4.18 (m, 1H), 5.62–5.75 (m, 2H), 5.82–5.98 (m, 2H), 7.00–7.31 (m, 4H), 7.80 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.7, 41.3, 52.4, 125.0, 125.2, 127.2, 127.9, 128.5, 129.0, 130.0, 136.8, 154.6. The minor isomer was distinguished in the ^1H NMR spectrum by signals at δ 2.22–2.58 (m, 2H), 3.78 (m, 1H), 3.79 (s, 3H), 5.70 (m, 1H), 5.81 (m, 1H), 5.95 (m, 1H), 6.12 (m, 1H), 6.71 (br s, 1H), 7.15 (t, J=7.8 Hz, 1H), 7.22–7.35 (m, 2H), 7.38–7.40 (m, 1H).

3.2. Typical protocol for selenocyclization

To a cooled (−78°C) solution of the cyclohexadiene (0.4 mmol) in CH_2Cl_2 (2.0 mL) is added a solution of PhSeBr (1.1 mmol). The reaction mixture is stirred under

argon for 5 h, then warmed to 0°C and quenched with saturated aqueous $NaHCO_3$. The organic layer is dried (Na_2SO_4), concentrated and purified by column chromatography over silica gel using ethyl acetate–hexane as an eluent.

3.2.1. 4*S,4a*S**,9b*R**-4-Phenylseleno-3,4,4a,9b-tetrahydrodibenzofuran (13).** ^{1}H NMR ($CDCl_3$) δ 2.35–2.42 (m, 1H), 2.62–2.78 (m, 1H), 3.68–3.77 (m, 1H), 4.08 (m, 1H), 5.01 (t, J=7.1 Hz, 1H), 5.75–5.82 (m, 2H), 6.75 (d, J=8.1 Hz, 1H), 6.86 (t, J=7.2 Hz, 1H), 7.10–7.25 (m, 5H), 7.58–7.62 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 27.4, 39.9, 40.8, 84.0, 110.2, 121.0, 124.5, 125.4, 126.9, 127.8, 127.9, 128.4, 129.3, 131.1, 134.8, 158.7. HRMS Calcd for $C_{18}H_{16}OSe$ $[M]^{+\cdot}$: 328.0366, found: 328.0350.

3.2.2. 4*S,4a*S**,10b*R**-4-Phenylseleno-3,4,4a,10b-tetrahydrobenzo[*b*,*d*]pyran-6-one (14).** ^{1}H NMR ($CDCl_3$) δ 2.40–2.46 (m, 1H), 3.08–3.15 (m, 1H), 3.92 (t, J=4.5 Hz, 1H), 4.11–4.15 (m, 1H), 4.81 (t, J=3.9 Hz, 1H), 5.49 (d, J=10.2 Hz, 1H), 5.72–5.81 (m, 1H), 7.21–7.25 (m, 2H), 7.30–7.45 (m, 4H), 7.57–7.62 (m, 2H), 8.10 (d, J= 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 26.9, 34.9, 38.9, 72.4, 124.1, 125.1, 125.3, 127.6, 128.2, 128.8, 129.8, 130.6, 134.5, 134.7, 141.9, 164.9. Calcd for $C_{19}H_{16}O_2SeNa$ $[M+Na]^+$: 379.0213, found: 379.0230.

3.2.3. 4*S,4a*S**,9b*R**-6-Methoxy-4-phenylseleno-3,4,4a,9b-tetrahydrodibenzofuran-8-carboxaldehyde (15).** Ratio 8:1. HRMS Calcd for $C_{20}H_{18}O_3Se$ $[M]^{+\cdot}$: 386.0421, found 386.0430. Major isomer: ^{1}H NMR ($CDCl_3$) 2.40–2.45 (m, 1H), 2.80–2.87 (m, 1H), 3.80–3.85 (m, 1H), 3.95 (s, 3H), 4.18 (m, 1H), 5.17 (dd, J=6.0, 7.05 Hz, 1H), 5.71–5.80 (m, 2H), 7.21–7.48 (m, 5H), 7.52–7.61 (m, 2H), 9.75 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 26.3, 40.0, 42.2, 56.2, 86.2, 111.6, 121.0, 125.6, 125.7, 126.4, 128.1, 129.4, 132.0, 132.1, 133.8, 134.5, 145.3, 190.6. The minor isomer was distinguished in the ^{1}H NMR spectrum by signals at δ 1.90 (m, 1H), 2.40 (m, 1H), 3.98 (s, 3H), 4.68–4.70 (m, 1H), 5.30 (m, 1H), 6.18–6.22 (m, 1H), 6.30–6.33 (m, 1H), 9.76 (s, 1H).

3.2.4. 1*S,9a*S**,4a*R**-9-Methoxycarbonyl-1-phenylseleno-1,2,4a,9a-tetrahydrocarbazole (16).** ^{1}H NMR ($CDCl_3$) δ 2.38–2.42 (m, 2H), 3.72–3.80 (m, 1H), 3.80 (s, 3H), 4.11–4.20 (m, 1H), 4.81 (t, J=9 Hz, 1H), 5.75–5.82 (m, 1H), 5.91–6.08 (m, 1H), 7.02 (t, J=7.8 Hz, 1H,), 7.15–7.18 (d, J=7.5 Hz, 1H), 7.19–7.23 (m, 4H), 7.50–7.58 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.7, 26.8, 29.3, 40.7, 52.4, 122.4, 124.4, 125.1, 127.2, 127.6, 127.9, 128.1, 128.6, 129.4, 130.1, 130.3, 136.8, 154.6. ESI-HRMS Calcd for $C_{20}H_{19}NNaO_2Se$ $[M+Na]^+$: 408.0479, found: 408.0494.

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16. It is interesting to note that the isomerization gives the 2,4-conjugated diene and not the 1,3-diene in conjugation with the aromatic ring.