4'-methylacetophenone or its -α,α,α-d_3 isotopomer. The 1-aryl-1-cylopropylethanol and -2,2,2-d_3 precursors to **9** and **9**-d_3 cations were similarly prepared by addition of aryl Grignard reagents to cyclopropyl methyl ketone or its -α,α,α-d_3 isotopomer. All of the unlabeled precursors have been previously reported,[1b,19,21] with the exception of 1-(3',5'-dichlorophenyl)-1-cyclopropylethanol: bp 109 °C (1 mm); ^{1}H NMR ($CDCl_3$) δ 0.3-0.6 (m, 4 H), 1.1-1.3 (m, 1 H), 1.4 (s, 3 H), 2.8 (s, 1 H), 7.2 (s, 1 H), 7.4 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 0.9 (C5), 2.1 (C4), 22.4 (C3), 27.7 (C2), 72.8 (C1), 123.7 (C2',6'), 126.5 (C4'), 134.3 (C3',5'), 151.6 (C1').

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Registry No. **3**, 25954-80-7; **3** (4'-OCH_3), 53600-78-5; **3** (4'-CH_3), 53600-80-9; **3** (4'-F), 51804-52-5; **3** (4'-Cl), 53600-81-0; **3** (4'-CF_3), 53272-70-1; **3**-d_2, 128631-30-1; **3**-d_2 (4'-CH_3), 128631-28-7; **3**-d_2 (4'-F), 92720-90-6; **3**-d_2 (4'-Cl), 128631-29-8; **3**-d_2 (4'-CF_3), 128631-31-2; **4**, 59856-44-9; **4** (4'-OCH_3), 77938-38-6; **4** (4'-CH_3), 77938-39-7; **4** (4'-F), 128631-26-5; **4** (4'-Cl), 128631-27-6; **4** (4'-CF_3), 77938-40-0; **4** [3',5-$(CF_3)_2$], 77938-41-1; **4**-d_2, 59856-44-9; **4**-d_2 (4'-OCH_3), 128631-32-3; **4**-d_2 (4'-CH_3), 128631-33-4; **4**-d_2 (4'-F), 128631-34-5; **4**-d_2 (4'-Cl), 128599-40-6; **4**-d_2 (4'-CF_3), 128631-35-6; **4**-d_2 [3',5'-$(CF_3)_2$], 128631-36-7; **5**, 36043-29-5; **5** (4'-OCH_3), 35144-47-9; **5** (4'-CH_3), 36043-28-4; **5** (4'-F), 51804-42-3; **5** (4'-Cl), 41912-30-5; **5** (3'-CH_3), 84074-03-3; **5** (3'-Cl), 84074-05-5; **5** (4'-CF_3), 84074-08-8; **5**-d_3, 128599-45-1; **5**-d_3 (4'-OCH_3), 128631-37-8; **5**-d_3 (4'-CH_3), 128599-41-7; **5**-d_3 (4'-F), 128599-42-8; **5**-d_3 (4'-Cl), 128599-43-9; **5**-d_3 (3'-CH_3), 128599-44-0; **5**-d_3 (3'-Cl), 128599-46-2; **5**-d_3 (4'-CF_3), 128599-47-3; **6**, 41912-34-9; **6** (4'-OCH_3), 60665-82-9; **6** (4'-CH_3), 41912-36-1; **6** (4'-F), 39769-51-2; **6** (4'-Cl), 86766-95-2; **6** (4'-CF_3), 86766-99-6; **6**-d_3, 128599-51-9; **6**-d_3 (4'-OCH_3), 128599-48-4; **6**-d_3 (4'-CH_3), 128599-49-5; **6**-d_3 (4'-F), 128599-50-8; **6**-d_3 (4'-Cl), 128631-38-9; **6**-d_3 (4'-CF_3), 128599-52-0; **7**, 98-86-2; **7** (4'-OCH_3), 100-06-1; **7** (4'-CH_3), 122-00-9; **7** (4'-F), 403-42-9; **7** (4'-Cl), 99-91-2; **7** (3'-CH_3), 585-74-0; **7** (3'-Cl), 99-02-5; **7** (4'-CF_3), 709-63-7; **7** [3',5'-$(CF_3)_2$], 30071-93-3; **7**-d_3, 17537-31-4; **7**-d_3 (4'-OCH_3), 29268-64-2; **7**-d_3 (4'-CH_3), 128599-53-1; &-d_3 (4'-F), 101493-81-6; **7**-d_3 (4'-Cl), 128599-54-2; **7**-d_3 (3'-CH_3), 128599-55-3; **7**-d_3 (3'-Cl), 128599-56-4; **7**-d_3 (4'-CF_3), 128599-57-5; **7**-d_3 [3',5'-$(CF_3)_2$], 128599-58-6; **8**, 3441-74-5; **8** (4'-OCH_3), 53909-70-9; **8** (4'-CH_3), 56083-69-3; **8** (4'-F), 31067-67-1; **8** (4'-Cl), 56683-70-6; **8** (3'-CH_3), 128599-36-0; **8** (3'-Cl), 128599-37-1; **8** (4'-CF_3), 128599-38-2; **8** [3',5'-$(CF_3)_2$], 128599-39-3; **8**-d_3, 128599-63-3; **8**-d_3 (4'-OCH_3), 128599-59-7; **8**-d_3 (4'-CH_3), 128599-60-0; **8**-d_3 (4'-F), 101493-83-8; **8**-d_3 (4'-Cl), 128599-61-1; **8**-d_3 (3'-CH_3), 128599-62-2; **8**-d_3 (3'-Cl), 128599-64-4; **8**-d_3 (4'-CF_3), 128599-65-5; **8**-d_3 [3',5'-$(CF_3)_2$], 128599-66-6; **9**, 41912-19-0; **9** (4'-OCH_3), 15810-35-2; **9** (4'-CH_3), 15810-34-1; **9** (4'-F), 56519-31-4; **9** (4'-Cl), 15876-04-7; **9** (3'-Cl), 81390-54-7; **9** (4'-CF_3), 62586-66-7; **9** [3',5'-$(CF_3)_2$], 78195-83-2; **9**-d_3, 128599-71-3; **9**-d_3 (4'-OCH_3), 128599-67-7; **9**-d_3 (4'-CH_3), 128599-68-8; **9**-d_3 (4'-F), 128599-69-9; **9**-d_3 (4'-Cl), 128599-70-2; **9**-d_3 (3'-Cl), 128631-39-0; **9**-d_3 (4'-CF_3), 128599-72-4; **9**-d_3 [3',5'-$(CF_3)_2$], 128599-73-5; 2-phenylbicyclo[2.2.2]octanol, 53601-08-4; 2-(4'-trifluorophenyl)-2-bicyclo[2.2.2]octanol, 53272-75-6; 2-(4'-fluorophenyl)-2-bicyclo[2.2.2]octanol, 53272-74-5; 2-(4'-methylphenyl)-2-bicyclo[2.2.2]octanol, 128599-74-6; 2-(4'-chlorophenyl)-2-bicyclo[2.2.2]octanol-3,3-d_2, 128599-75-7; 2-(4'-chlorophenyl)-2-bicyclo[2.2.2]octene, 128599-76-8; 2-(4'-methoxyphenyl)-2-bicyclo[2.2.2]octene, 53601-00-6; 2-phenyl-2-bicyclo[2.1.1]hexanol, 125642-76-4; 2-[3',5'-bis(trifluoromethyl)-phenyl]2-bicyclo[2.1.1]hexanol, 128599-77-9; 2-(4'-chlorophenyl)-2-bicyclo[2.1.1]hexanol, 128599-78-0; 2-[4'-(trifluoromethyl)phenyl]-2-bicyclo[2.1.1]hexanol, 128599-79-1; 2-(4'-fluorophenyl)-2-bicyclo[2.1.1]hexanol, 128599-80-4; 2-(4'-methylphenyl)-2-bicyclo[2.1.1]hexanol, 128599-81-5; 2-(4'-methoxyphenyl)-2-bicyclo[2.1.1]hexanol, 128599-82-6.

Supplementary Material Available: Listings of additional ^{13}C chemical shifts and isotope shifts for cations **3**-**9** and NMR data for the 2-aryl-2-bicyclo[2.1.1]hexanols and 2-aryl-2-bicyclo[2.2.2]octanols (10 pages). Ordering information is given on any current masthead page.

Regioselective Reductive Electrophilic Substitution of 1,2,3-Trimethoxybenzene and Its 5-Alkyl-Substituted Homologues

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The methoxy group in the 2-position of 1,2,3-trimethoxybenzene (**1**) can be regioselectively removed by electron transfer from alkali metals and replaced with a variety of electrophiles in a one-pot procedure, affording 2-substituted resorcinol dimethyl ethers. The usefulness of this synthetic method is illustrated by numerous examples. This reaction procedure has been successfully extended to the 5-methyl-substituted homologue (**2**), but limitations occur with the higher homologue 1-pentyl-3,4,5-trimethoxybenzene (**3**). Investigations on the mechanism of demethoxylation, with the aid of labeling experiments, provided clear evidence for the intermediacy of aryl radicals and explained the low yields obtained in the reductive electrophilic substitutions of compound **3**.

Aromatic methoxy groups are considered, from a synthetic point of view, as stable linkages not suitable for transformation purposes; indeed, such groups are almost always regarded as masked phenols,[1] not as versatile synthetic functionalities. However, replacement of the methoxy group with a hydrogen atom (reductive demethoxylation) can be achieved under electron-transfer conditions; under such conditions, cleavage of the alkyl-oxygen bond (reductive demethylation) usually occurs as a competitive reaction.[2]

1,2,3-Trimethoxybenzene (**1**) is particular in that its reduction with alkali metals, in solvents of low polarity, leads to 100% regioselective demethoxylation in the 2-position in almost quantitative yields.[2-4] Such uncommon regioselectivity in the cleavage of an aryl-oxygen bond has

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0022-3263/90/1955-5386$02.50/0

Table I. Reductive Electrophilic Substitution of Compounds 1–3

entry	compd	metal	electrophile	T, °C	t, h	product, E =	yield,[a] %
1	1	K	MeI (1.5)	0	4	**10a**, Me	85[b]
2	1	K	EtBr (1.5)	0	4	**10b**, Et	81[b]
3	1	K	*n*-BuBr (1.5)	0	4	**10c**, *n*-Bu	70[b]
4	1	K	*i*-PrI (1.5)	0	24	**10d**, *i*-Pr	0[b]
5	1	K	heptane-2-Br (1.5)	0	24	**10e**, 2-heptyl	0[b,c]
6	2	K	MeI (1.5)	0	4	**11a**, Me	72[b]
7	2	K	*n*-BuBr (1.5)	0	4	**11b**, *n*-Bu	56[b]
8	2	K	*n*-dodecylBr (1.5)	0	4	**11c**, *n*-dodecyl	52[b]
9	3	K	*n*-BuBr (1.5)	0	24	**12a**, *n*-Bu	15[d]
10	1	K	I_2 (3)	−30	2[e]	**10f**, I	61
11	1	Na	I_2 (3)	−30	2[e]	**10f**, I	53
12	1	K	Br_2 (3)	−78	4	**10g**, Br	21
13	1	K	Me_3SiCl (1.5)	−50	6	**10h**, $SiMe_3$	68
14	1	K	PhCHO (1.5)	0	4	**10i**, CHOHPh	71
15	1	K	*t*-BuCHO (1.5)	0	4	**10j**, CHOH*t*-Bu	91
16	1	Na	*t*-BuCHO (1.5)	0	4	**10j**, CHOH*t*-Bu	64
17	1	K	EtCHO (1.5)	0	4	**10k**, CHOHEt	0
18	1	K	EtCHO (1.5)	−60	4	**10k**, CHOHEt	21
19	1	K	EtCHO (1.5)	−78	4	**10k**, CHOHEt	45
20	1	Na	EtCHO (1.5)	−78	4	**10k**, CHOHEt	23
21	2	K	*t*-BuCHO (1.5)	0	4	**11d**, CHOH*t*-Bu	65
22	1	K	PhCOCl (3)	−20	5	**10l**, COPh	79
23	1	K	MeCOCl (3)	−78	4	**10m**, COMe	0
24	1	Na	MeCOCl (3)	−78	4	**10m**, COMe	0
25	1	K	CO_2 (gaseous)	0	4	**10n**, COOH	23
26	1	K	ClCOOMe (3)	−30	3	**10o**, COOMe	96
27	1	Na	ClCOOMe (3)	−30	3	**10o**, COOMe	62
28	2	K	ClCOOMe (3)	−30	3	**11e**, COOMe	76
29	3	K	ClCOOMe (3)	−30	3	**12b**, COOMe	25
30	1	K	NMF[f] (3)	0	4	**10q**, CHOHAr[g]	71
31	1	K	NMF[f] (3)	−20	4	**10p**, CHO	21[d,h]
						10q, CHOHAr[g]	41[d,h]
32	1	K	HCOOEt (3)	−20	2	**10q**, CHOHAr[g]	65

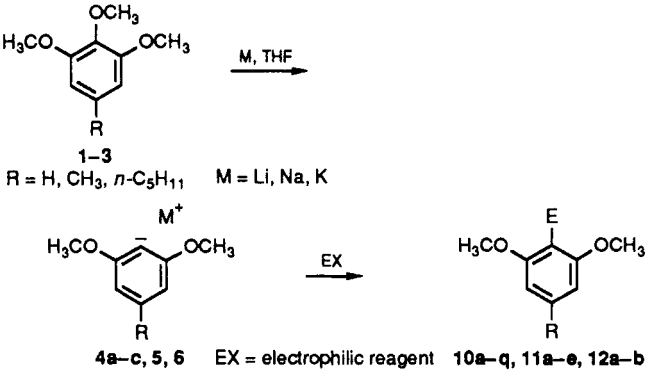
[a] Determined on isolated products, unless otherwise stated. [b] From ref 12. [c] At 66 °C, elimination to olefin took place. [d] Determined by GLC. [e] Stirring was continued for 3 h at room temperature. [f] NMF = *N*-methylformanilide. [g] Ar = 2,6-dimethoxyphenyl. [h] 22% **7** also recovered.

been attributed to twisting of the leaving methoxy group out of the plane of the aromatic ring caused by the two ortho substituents[2,5,6] the reaction is likely influenced also by the combined electronic effects of the two *o*-methoxy groups.

We have further investigated the synthetic usefulness of this reaction, and describe here a one-pot procedure allowing the regioselective replacement of the methoxy group in the 2-position of **1**, as well as of 3,4,5-trimethoxytoluene (**2**) and 1-pentyl-3,4,5-trimethoxybenzene (**3**), by a variety of electrophilic reagents (Scheme I), thus allowing a new synthetic approach to 2-substituted resorcinols, a class of products with potential biological and pharmacological properties;[7-11] a preliminary report concerning the reductive alkylation of compounds **1** and **2** has already appeared.[12]

Our approach to the indirect electrophilic substitution of the 2-methoxy group in compounds **1–3** relied upon the assumption that the reductive cleavage of the aryl–oxygen bond would lead, according to a two-electron reduction process, to the quantitative formation of the corresponding anion, from which quenching with water should lead to

Scheme I



dimethoxy derivatives **7–9** (Scheme II).

Besides mechanistic considerations,[2,13] this hypothesis was supported by the known relatively high stability of 2,6-dimethoxyaryl anions.[7,8,14] However, the difficulties encountered in the extension of our reaction to compound **3** prompted us to investigate in greater detail on this assumption; deuteration experiments showed that the formation of the postulated aryl anion is not quantitative in the case of the 5-alkyl-substituted substrates.

Results

The regioselective demethoxylation in the 2-position of **1–3** has been performed by the action of finely divided K

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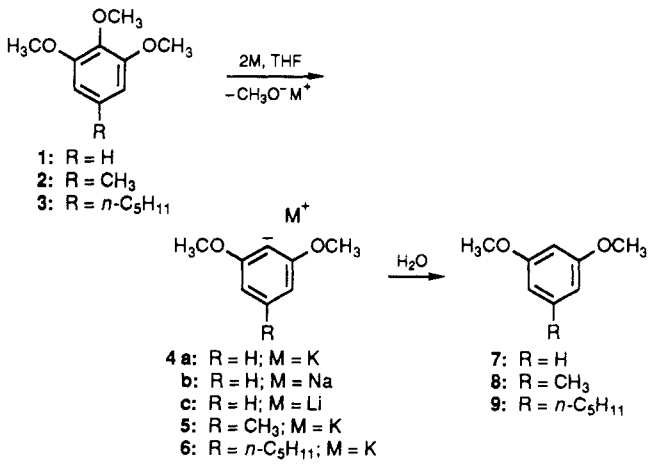
Scheme II



metal (3 equiv) in anhydrous THF at room temperature during 24 h. At this stage, as previously reported,[3] compounds **7–9** can be obtained in high yields by quenching with water (Scheme II). Under similar reaction conditions, **1** afforded compound **7** in 85% yield by reduction with Na metal, while reduction with Na of compounds **2** and **3** led to the formation of complex reaction mixtures. Reduction of **1** with Li metal afforded **7** as the main product, but the reaction was very sluggish (50% conversion after 7 days); the reduction with Li of **2** and **3** was not investigated.

The results obtained in the reductive electrophilic substitution of compounds **1–3** are reported in Table I.

Reaction with Alkyl Halides and Halogens. Alkylation of **4a** and **5** with primary alkyl halide (Table I, entries 1–4 and 6–8) could be achieved under mild reaction conditions: an excess (1.5 equiv) of the alkyl halide was added at 0 °C to the reaction mixture obtained by the action of potassium metal on the appropriate trimethoxy-substituted arene; after stirring for several hours, standard workup afforded good to high yields of the alkylated product, as well as different amounts of the product of reductive demethoxylation. Interestingly, alkylation of **6** under the same conditions (Table I, entry 9) afforded only a low yield of the alkylated product.

Secondary alkyl halides did not react at 0 °C with **4a**, even after prolonged reaction times (Table I, entry 5); similarly, no reaction occurred at room temperature. At reflux temperature, dehydrohalogenation of the secondary alkyl halide in the highly basic reaction medium took place; a mixture of heptenes was recovered after reaction with 2-bromoheptane.[12]

The reactivity of **4a** and **4b** has been also tested toward halogens and Me_3SiCl (Table I, entries 10–13). Good yields were obtained in the reaction of **4a** with both I_2 and Me_3SiCl at low temperature, whereas a somewhat lower yield was obtained in the reaction of the latter with **4b**. Reaction of **4a** with Br_2 afforded the aryl bromide **10g** in low yield; this result has analogy with a literature report on the reaction of Br_2 with (2,6-dimethoxyphenyl)lithium (**4c**), prepared by the action of BuLi on 1,3-dimethoxybenzene.[8]

Reaction with Aldehydes. Addition of **4a** and **4b** to the carbonyl group of nonenolizable aldehydes proceeded in good yields within few hours at 0 °C (Table I, entries 14–16). Good results were also obtained in the reductive electrophilic substitution of **2** with 2,2-dimethylpropionaldehyde (Table I, entry 21).

On the contrary, reaction of **4a** with propionaldehyde, i.e., with an enolizable carbonyl derivative, did not lead to the formation of the desired product unless the addition of the aldehyde was performed at low temperature (Table I, entries 17–20); indeed, the carbinol **10k** was formed to an appreciable extent only below –60 °C and was obtained in 45% yield at –78 °C. Under similar conditions, the arylsodium derivative **4b** gave a somewhat lower yield. Enolization of propionaldehyde under the reaction conditions reported above was inferred from the results of quenching the reaction mixtures with D_2O; GC/MS analysis showed no incorporation of deuterium in the recovered product of reductive demethoxylation, i.e., **7**.

Table II. Product Distribution in Deuterium Labeling Experiments

R	quencher	ArD/ArH[a,b]
H	D_2O	95.4/4.6
Me	D_2O	88.7/11.3
n-pentyl	D_2O	64.9/35.1

[a] Determined by GC–MS from the $M^{\bullet+}$ + 1/$m^{\bullet+}$ ratio, taking into account isotopic abundancies; the results are the average of three determinations. [b] Ar = 1,3-dimethoxyphenyl (R = H) or 2,6-dimethoxy-4-alkylphenyl (R = Me or *n*-pentyl).

Reaction with Carboxyl Derivatives. The reductive electrophilic substitution of compounds **1–3** has been tested with acyl halides, esters, CO_2, and an amide, usually employing K as reducing agent and a large excess (3 equiv) of the electrophilic reagent (Table I, entries 22–32).

As in the case of aldehydes, reaction of **4a** with an acyl chloride not bearing hydrogen(s) in the 2-position, i.e., benzoyl chloride, afforded a good yield of ketone **10l**; on the contrary, reaction both **4a** and **4b** with acetyl chloride did not afford the expected ketone **10m**, even at –78 °C, but led to recovery of **7**.

Carboxylation of **4a** with gaseous CO_2 afforded, after aqueous workup, the corresponding 2,6-dimethoxybenzoic acid (**10n**) in low yield; as the introduction of the carboxylic function could be easily achieved in high yield by the reaction of both **4a** and **4b** with ClCOOMe, we have not attempted to improve the yield of this reaction.

Formylation of **4a** with *N*-methylformanilide (NMF) or with HCOOEt did not lead to high yields of the desired 2,6-dimethoxybenzaldehyde (**10p**); the main reaction product was in both cases the symmetric carbinol (**10q**), likely due to the high reactivity of the intermediate **10p** toward **4a** (eq 1).

$$\mathbf{4a} \xrightarrow{\text{HCOOEt or NMF}} \underset{\mathbf{10p}}{\text{ArCHO}} \xrightarrow{\mathbf{4a}} \underset{\mathbf{10q}}{(\text{Ar})_2\text{CHOH}} \qquad (1)$$

Ar = 2,6-dimethoxyphenyl

Good results were obtained in the reductive electrophilic substitution of **1** or **2** with ClCOOMe; however, the same reaction with **3** gave the corresponding 2,6-dimethoxy-4-pentylbenzoic acid methyl ester (**12b**) in low yield.

Deuterium Incorporation Studies. A comparison of the results obtained in the reductive alkylation of compounds **1–3** with butyl bromide (Table I, entries 3, 7, and 9), as well as of the results obtained with ClCOOMe (Table I, entries 26, 31, and 32), shows a decrease of the yields with the increase of the length of the alkyl chain in the 5-position of the aromatic substrate.

This can be due to a decrease in the reactivity of the intermediate arylpotassium derivatives, as already observed for the corresponding lithium derivatives,[10] but also to their incomplete formation in the reduction step. Indeed, the low yield obtained in the reductive electrophilic substitution of **3** with a powerful electrophile like ClCOOMe supported the last hypothesis, which was confirmed by D_2O quenching experiments; the results (GC–MS) clearly showed decreasing incorporation of deuterium

on going from products **7** to **9** (Table II). Since in our highly basic reaction conditions a protonation process is likely excluded, this behavior strongly suggests the formation of intermediate aryl radicals, which may abstract hydrogen atoms from components of the reaction medium.[13,15,16]

Discussion

Among the various synthetic applications of the Birch reduction of aromatic compounds, reductive electrophilic substitution is meant as the alkali metal reduction of an aromatic substrate leading to the formation of a carbanion which is subsequently allowed to react with an electrophilic reagent, such as an aldehyde or an alkyl halide, to form substituted 1,4-cyclohexadienyl derivatives; an appropriate substituent, usually a carboxylic function, directs the electrophilic attack in the *ipso* position.[17] In a subsequent step the compound can be easily rearomatized with loss of the group originally present in the aromatic nucleus. As an example, 3,5-dimethoxybenzoic acid treated with Li in liquid NH_3 affords a carbanion which is allowed to react with 1-bromopentane, affording 3,5-dimethoxy-1-pentyl-2,5-cyclohexadiene-1-carboxylic acid; afterward, the latter is oxidatively decarboxylated to 3,5-dimethoxy-1-pentylbenzene.[18]

The synthetic procedure described herein represents a new entry to this reaction, in that the reduction of the substituted substrate, followed by loss of the directing group, leads to an aryl anion; in a subsequent step the aryl anion is treated with an electrophilic reagent to afford directly the substituted aromatic product. The comparison of the two procedures emphasizes the novelty of our reaction, based not only on the preservation of the aromatic nucleus, thus excluding the rearomatization step, but also on the unusual leaving group.

Furthermore, our synthetic procedure, whose first step resembles the formation of an arylmetal derivative by halogen–metal exchange, represents a useful alternative to the known synthesis of 2-substituted resorcinols dimethyl ethers via the regioselective lithiation at the 2-position of 1,3-dimethoxybenzene with alkyl- or aryllithium derivatives.[7,8,14] From this point of view, it is possible to make a comparison between the results obtained in this work with the potassium and sodium derivatives **4a** and **4b** and the literature results obtained, via the metalation procedure, with the lithium derivative **4c**. Comparable behavior of the three alkali metal derivatives has been found in the reaction with alkyl halides,[7,8] halogens,[8] and nonenolizable carbonyl derivatives;[8] on the contrary, while **4c** reacts at the carbonyl function of enolizable ketones and acyl chlorides at room temperature,[8] **4a** and **4b** react at the carbonyl function of propionaldehyde only partially and at very low temperatures and do not undergo the substitution reaction with acetyl chloride even at −78 °C. These results suggest a higher basicity of **4a** and **4b** in comparison with **4c**.

Mechanistic Implications. Two reactions pathways are usually considered for the cleavage of the aryl–oxygen bond of aryl ethers under reductive electron-transfer conditions,[2,15,16] both starting with the formation of a radical anion (eq 2).

$$\mathrm{ArOR} + e^- \rightarrow \mathrm{ArOR}^{\bullet -} \quad (2)$$

$$\mathrm{ArOR}^{\bullet -} \rightarrow \mathrm{Ar}^\bullet + \mathrm{RO}^- \quad (3)$$

$$\mathrm{Ar}^\bullet + e^- \rightarrow \mathrm{Ar}^- \quad (4)$$

$$\mathrm{Ar}^\bullet + \mathrm{SH} \rightarrow \mathrm{ArH} + \mathrm{S}^\bullet \quad (5)$$

$$\mathrm{ArOR}^{\bullet -} + e^- \rightarrow \mathrm{ArOR}^{2-} \quad (6)$$

$$\mathrm{ArOR}^{2-} \rightarrow \mathrm{Ar}^- + \mathrm{RO}^- \quad (7)$$

In the first case the reaction proceeds through cleavage of the radical anion, with formation of an aryl radical (eq 3), which can be reduced to an aryl anion (eq 4) or abstract a hydrogen atom from the reaction medium (eq 5). Alternatively, the radical anion is further reduced to the dianion (eq 6), mainly by disproportionation;[15] cleavage of the latter affords the aryl anion (eq 7).

It is of interest to our work to point out that in the case of formation of aryl radicals their decay according to eq 5 competes with their reduction to aryl anions (eq 4), i.e., with the formation of the species able to suffer electrophilic attack in the subsequent step. Indeed, the labeling experiments strongly suggest that the decay of aryl radicals according to eq 5 is a major reaction pathway at least in the reductive cleavage of compound **3** and, to a lower extent, also in the case of compounds **2**. Indeed, the solvent (THF),[15] the methoxide ion[19] formed during the reductive cleavage, and, perhaps, the alkyl chain on the aromatic nucleus can act as hydrogen atom donors toward aryl radicals; however, at the present stage of the research we cannot say anything conclusive on this matter.

The observation that the amount of aryl anion formed in our reactions decreases with the increase of the length of the alkyl chain in the 5-position of the substrate indicates that the delicate competition at the aryl radical level between eqs 4 and 5 is influenced, inter alia, by the nature of the 5-substituent; this constitutes, at the present, a limit to the extension of this substitution reaction to other alkyl-substituted substrates.

Experimental Section

General Procedures. All the products and reagents were of the highest commercial quality from freshly opened containers. Deuterium oxide, minimum isotopic purity 99.8 atom % deuterium, was purchased from Aldrich. Tetrahydrofuran was distilled from Na immediately prior to use. Compound **3** was synthesized as described in ref 3. All reactions were run under nitrogen, except for the reduction of compound **1** with Li metal, which was run under argon. The ^1H NMR spectra were recorded on a Varian EM 360 (60 MHz) spectrometer in $CDCl_3$ solution with Me_4Si as internal standard; coupling constants are reported in hertz. Mass spectra were recorded on a Finnigan Mat 1020-B mass spectrometer operating at 70 eV, interfaced with a Perkin-Elmer Sigma 3 gas-chromatograph, equipped with a Supelco SP-2100 30-m capillary column (i.d. 0.25 mm). GC analyses were performed with a Hewlett-Packard Model 5890 gas chromatograph equipped with a similar SP-2100 capillary column; the chromatograms were recorded with a Perkin-Elmer LC 100 integrator. The IR spectra were recorded on a Perkin-Elmer 983 spectrophotometer. Elemental analyses were performed by the Microanalytical Laboratory of the Dipartimento di Chimica, Università di Sassari. Boiling and melting points are uncorrected.

General Procedure for the Reductive Electrophilic Substitution of Compounds 1–3. A solution of the appropriate 1,2,3-trimethoxybenzene derivative (28 mmol) in anhydrous THF (5 mL) was added dropwise to a mixture of the freshly cut metal (0.084 g-atom) in anhydrous THF (20 mL) and vigorously stirred at room temperature. The mixture was stirred for 24 h at room temperature and then chilled to the reported temperature; the appropriate amount of the electrophile dissolved in anhydrous

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THF (5 mL) was slowly added, and the resulting mixture was stirred for several hours (Table I). The reaction was quenched by slow dropwise addition of H_2O (10 mL) (*caution!*) and extracted with Et_2O (3 × 30 mL). The organic phase was collected, washed with H_2O (50 mL), dried ($CaCl_2$), and evaporated to afford the crude product which was purified by distillation, flash chromatography, or recrystallization. The products were characterized as follows.

1,3-Dimethoxy-2-methylbenzene (10a): bp 120–122 °C (30 Torr) (lit.[20] bp 110–115 °C (20 Torr)); ^1H NMR δ 2.05 (s, 3 H, CH_3), 3.73 (s, 6 H, 2 OCH_3), 6.40 (d, J = 7, 2 H, phenyl), 6.80–7.26 (m, 1 H, phenyl); mass spectrum, m/e (relative intensity) 152 ($M^{\bullet+}$, 100), 137 ($M^{\bullet+}$ - CH_3, 20.3).

1,3-Dimethoxy-2-ethylbenzene (10b): mp 54–55 °C (from iPrOH–H_2O) (lit.[8] mp 59–60 °C)); ^1H NMR δ 1.12 (t, J = 7, 3 H, CH_3), 2.71 (q, J = 7, 2 H, CH_2), 3.83 (s, 6 H, 2 OCH_3), 6.53 (d, J = 7, 2 H, phenyl), 6.90–7.29 (m, 1 H, phenyl). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.45; H, 8.53.

1,3-Dimethoxy-2-butylbenzene (10c): bp 116 °C (15 Torr) (lit.[8] bp 107–107.5 °C (3–4 Torr)); ^1H NMR δ 0.73–1.09 (br m, 3 H, CH_3), 1.19–1.65 (m, 4 H, 2 CH_2), 2.44–2.80 (m, 2 H, CH_2), 3.73 (s, 6 H, 2 OCH_3), 6.34 (d, J = 7, 2 H, phenyl), 6.73–7.26 (m, 1 H, phenyl); mass spectrum, m/e (relative intensity) 194 ($M^{\bullet+}$, 19.2), 151 ($M^{\bullet+}$ - C_3H_7, 100).

1,3-Dimethoxy-2-iodobenzene (10f): mp 102–103 °C (from EtOH) (lit.[8] mp 103 °C); ^1H NMR δ 3.83 (s, 6 H, 2 OCH_3), 6.37 (d, J = 7, 2 H, phenyl), 6.90–7.26 (m, 1 H, phenyl); mass spectrum, m/e (relative intensity) 264 ($M^{\bullet+}$, 100).

1,3-Dimethoxy-2-bromobenzene (10g): mp 91–93 °C (from Et_2O) (lit.[8] mp 93–94 °C); ^1H NMR δ 3.86 (s, 6 H, 2 OCH_3), 6.40 (d, J = 7, 2 H, phenyl), 6.86–7.23 (m, 1 H, phenyl); mass spectrum, m/e (relative intensity) 218 ($M^{\bullet+}$ + 2, 96.2), 216 ($M^{\bullet+}$, 100).

(2,6-Dimethoxyphenyl)trimethylsilane (10h): bp 131 °C (10 Torr) (lit.[21] bp 51–52 °C (0.1 Torr)); ^1H NMR δ 0.30 (s, 9 H, 3 CH_3), 3.73 (s, 6 H, 2 OCH_3), 6.34 (d, J = 7, 2 H, phenyl), 6.93–7.29 (m, 1 H, phenyl); mass spectrum, m/e (relative intensity) 210 ($M^{\bullet+}$, 7), 195 ($M^{\bullet+}$ - CH_3, 67), 135 (100).

(2,6-Dimethoxyphenyl)phenylmethanol (10i): mp 98–100 °C (from Et_2O/isooctane); IR (CCl_4) 3561 (OH) cm^{-1}; ^1H NMR δ 2.86 (br s, 1 H, OH), 3.80 (s, 6 H, 2 OCH_3), 6.23–6.51 (m, 1 H, CH), 6.59–6.80 (m, 2 H, phenyl), 7.03–7.42 (m, 6 H, phenyl); mass spectrum, m/e (relative intensity) 244 ($M^{\bullet+}$, 21.4), 227 ($M^{\bullet+}$ - OH, 100). Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.74; H, 6.61. Found: C, 74.13; H, 7.05.

1-(2,6-Dimethoxyphenyl)-2,2-dimethyl-1-propanol (10j): mp 104–105 °C (from EtOH–H_2O); IR (CCl_4) 3562 (OH) cm^{-1}; ^1H NMR δ 0.82 (s, 9 H, 3 CH_3), 2.95 (br s, 1 H, OH), 3.76 (s, 6 H, 2 OCH_3), 4.82 (s, 1 H, CH), 6.53 (d, J = 8, 2 H, phenyl), 7.15 (t, J = 8, 1 H, phenyl); mass spectrum, m/e (relative intensity) (no molecular ion) 207 ($M^{\bullet+}$ - OH, 5.2), 167 ($M^{\bullet+}$ - C_4H_9, 100). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.60; H, 9.01. Found: C, 69.21; H, 9.14.

1-(2,6-Dimethoxyphenyl)-1-propanol (10k): mp 55.5–57 °C; purified by flash chromatography (AcOEt/hexane = 1:1); IR (CCl_4) 3572 (OH) cm^{-1}; ^1H NMR δ 0.94 (t, J = 7, 3 H, CH_3), 1.68–1.97 (br m, 2 H, CH_2), 2.87 (br s, 1 H, OH), 3.83 (s, 6 H, 2 OCH_3), 5.0–5.12 (br m, 1 H, CH), 6.56 (d, J = 8, 2 H, phenyl), 7.17 (t, J = 8, 1 H, phenyl); mass spectrum, m/e (relative intensity) (no molecular ion) 179 ($M^{\bullet+}$ - OH, 100), 167 ($M^{\bullet+}$ - CH_3, 14.7). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.31; H, 8.23. Found: C, 66.95; H, 8.17.

2,6-Dimethoxybenzophenone (10l): bp 93 °C (2 Torr); mp 108–110 °C (from $CHCl_3$/isooctane); IR (CCl_4) 1763 (CO) cm^{-1}; ^1H NMR δ 3.66 (s, 6 H, 2 OCH_3), 6.50 (d, J = 7, 2 H, phenyl), 7.00–7.82 (m, 6 H, phenyl); mass spectrum, m/e (relative intensity) 242 ($M^{\bullet+}$, 19.0), 165 ($M^{\bullet+}$ - C_6H_5, 100). Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.34; H, 5.84. Found: C, 74.72; H, 6.26.

2,6-Dimethoxybenzoic acid (10n): mp 192–194 °C (from EtOH) (lit.[20] mp 190 °C); IR (Nujol) 1694 (CO) cm^{-1}; ^1H NMR δ 3.93 (s, 6 H, 2 OCH_3), 6.66 (d, J = 7, 2 H, phenyl), 7.23–7.59 (m, 1 H, phenyl), 11.0 (s, 1 H, COOH).

Methyl 2,6-dimethoxybenzoate (10o): mp 93–94 °C (from Et_2O) (lit.[22] mp 88–90 °C); IR (CCl_4) 1740 (CO) cm^{-1}; ^1H NMR δ 3.79 (s, 6 H, 2 OCH_3), 3.89 (s, 3 H, $COOCH_3$), 6.50 (d, J = 7, 2 H, phenyl), 7.02–7.39 (m, 1 H, phenyl); mass spectrum, m/e (relative intensity) 196 ($M^{\bullet+}$, 18.5), 165 ($M^{\bullet+}$ - OCH_3, 100). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.21; H, 6.18. Found: C, 61.58; H, 6.07.

2,6-Dimethoxybenzaldehyde (10p): mp 96–98 °C (from aqueous EtOH) (lit.[20] mp 97–99 °C); mass spectrum, m/e (relative intensity) 166 ($M^{\bullet+}$, 66.1), 165 ($M^{\bullet+}$ - 1, 55.4), 107 (100); the compound was characterized by Ag_2O oxidation to **10n**.

2,2',6,6'-Tetramethoxydiphenylmethanol (10q): mp 189–191 °C (from Et_2O–hexane); IR (Nujol) 3510 (OH) cm^{-1}; ^1H NMR δ 2.86 (br s, 1 H, OH), 3.73 (s, 12 H, 4 OCH_3), 5.36–5.80 (m, 1 H, CH), 6.43 (d, J = 7, 4 H, phenyl), 6.89–7.20 (m, 2 H, phenyl). Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.08; H, 6.64. Found: C, 67.28; H, 6.97.

1,3-Dimethoxy-2,5-dimethylbenzene (11a): bp 105 °C (10 Torr); solidifies on standing (lit.[9] mp 49–50 °C); ^1H NMR δ 2.11 (s, 3 H, CH_3), 2.38 (s, 3 H, CH_3), 3.79 (s, 6 H, 2 OCH_3), 6.34 (s, 2 H, phenyl); mass spectrum, m/e (relative intensity) 166 ($M^{\bullet+}$, 100), 151 ($M^{\bullet+}$ - CH_3, 35.3).

1,3-Dimethoxy-2-butyl-5-methylbenzene (11b): bp 121 °C (10 Torr); ^1H NMR δ 0.78–1.11 (m, 3 H, CH_3), 1.19–1.65 (m, 4 H, 2 CH_2), 2.31 (s, 3 H, CH_3), 2.45–2.80 (m, 2 H, CH_2), 3.74 (s, 6 H, 2 OCH_3), 6.40 (s, 2 H, phenyl); mass spectrum, m/e (relative intensity) 208 ($M^{\bullet+}$, 13.0), 165 ($M^{\bullet+}$ - C_3H_7, 100).

1,3-Dimethoxy-2-dodecyl-5-methylbenzene (11c): mp 47–48 °C (from EtOH); ^1H NMR δ 0.87–1.65 (m, 23 H, aliphatic), 2.31 (s, 3 H, CH_3), 2.34–2.80 (m, 2 H, CH_2), 3.76 (s, 6 H, 2 OCH_3), 6.27 (s, 2 H, phenyl); mass spectrum, m/e (relative intensity) 320 ($M^{\bullet+}$, 15), 165 (100). Anal. Calcd for $C_{21}H_{36}O_2$: C, 78.54; H, 11.41. Found: C, 77.98; H, 11.48.

1-(2,6-Dimethoxy-4-methylphenyl)-2,2-dimethyl-1-propanol (11d): bp 142 °C (2.5 Torr); mp 75–77 °C (from MeOH); IR (CCl_4) 3687 (OH) cm^{-1}; ^1H NMR δ 0.86 (s, 9 H, 3 CH_3), 2.27 (s, 3 H, CH_3), 3.00–3.21 (m, 1 H, OH), 3.73 (s, 6 H, 2 OCH_3), 4.39–4.59 (m, 1 H, CH), 6.20 (s, 2 H, phenyl); mass spectrum, m/e (relative intensity) (no molecular ion) 221 ($M^{\bullet-}$ - OH, 100), 181 ($M^{\bullet-}$ - C_4H_9, 44). Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.54; H, 9.32. Found: C, 70.63; H, 9.74.

Methyl 2,6-dimethoxy-4-methylbenzoate (11e): bp 132–134 °C (1 Torr); solidifies on standing (lit.[23] mp 84–85 °C); IR (CCl_4) 1736 (CO) cm^{-1}; ^1H NMR δ 2.24 (s, 3 H, CH_3), 3.70 (s, 6 H, 2 OCH_3), 3.77 (s, 3 H, $COOCH_3$), 6.20 (s, 2 H, phenyl); mass spectrum, m/e (relative intensity) 210 ($M^{\bullet+}$, 73), 179 ($M^{\bullet+}$ - OCH_3, 100).

1,3-Dimethoxy-2-butyl-5-pentylbenzene (12a): bp 134–135 °C (2 Torr) (lit.[24] bp 131 °C (2 Torr)); ^1H NMR δ 0.75–1.08 (m, 6 H, 2 CH_3), 1.15–1.73 (m, 10 H, aliphatic), 2.40–2.80 (br m, 4 H, 2 CH_2 benzylic), 3.80 (s, 6 H, 2 OCH_3), 6.28 (s, 2 H, phenyl); mass spectrum, m/e (relative intensity) 264 ($M^{\bullet+}$, 28), 221 ($M^{\bullet+}$ - C_3H_7, 100).

Methyl 2,6-dimethoxy-5-pentylbenzoate (12b): high-boiling colorless oil (bulb-to-bulb distillation in vacuo); mass spectrum, m/e (relative intensity) 266 ($M^{\bullet+}$, 57), 235 ($M^{\bullet+}$ - OCH_3, 52), 210 (100); the compound was not further characterized.

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