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$FeCl_3/SiO_2$ Reacts as Oxidant or Lewis Acid with Phenol Ethers

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Adsorption of $FeCl_3·6H_2O$ onto silica gel produces a supported reagent $FeCl_3/SiO_2$. This reagent is insoluble in CH_2Cl_2 and is used in that solvent for reaction with phenol ethers. Dimethoxy aromatics are coupled to produce biaryls in high yield. Seven examples including both inter- and intramolecular couplings are reported. The effect of various support materials is explored. An electron-transfer mechanism is proposed. Disiloxy aromatics are oxidized to quinones. Ten examples of substituted 1,4-bis(trimethylsiloxy)- or 1,4-bis(*tert*-butyldimethylsiloxy)benzene oxidations are reported. In one example the reaction is catalytic in $FeCl_3$, being driven by oxygen. Benzyloxy aromatics are cleaved to phenols. In this reaction $FeCl_3$ acts on a Lewis acid. The importance of coadsorbing the reagent and the aromatic ether in the absence of solvent is demonstrated.

We have been interested for some time in the oxidative reactions of phenol ethers performed electrochemically.[2] Such reactions have some synthetic utility, but because electrochemical equipment is not readily used by many synthetic chemists, we set out to find other heterogeneous oxidants which would perform the same reactions. This paper reports on the reactivity of ferric chloride hexahydrate adsorbed on silica gel ($FeCl_3/SiO_2$). Ferric chloride has been widely used for the oxidation of phenols and certain aromatic hydrocarbons.[3] It has, however, certain solubility disadvantages and these can be overcome by deposition of the reagent onto a silica surface prior to its use. As it has been repeatedly pointed out, such a "supported reagent" often has special reactivity and always has the advantage of being easily removed from the organic product by filtration.[4,5]

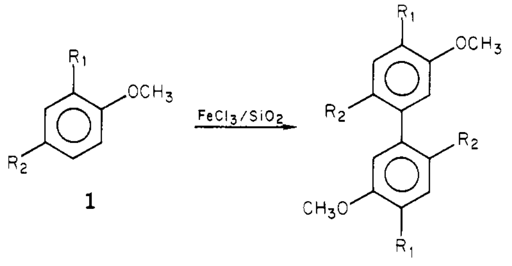
$FeCl_3/SiO_2$ was first reported by Mazur and Keinan, who used it as a Lewis acid to dehydrate and/or rearrange alcohols.[6] In a preliminary communication we have reported that $FeCl_3/SiO_2$ also has utility as an oxidant for phenol ethers.[7] As such, it is related to a group of inorganic oxidants supported on high surface area solids which have been used for phenol oxidations. It is also related to several homogeneous oxidants for phenol ethers.[8,9] In particular, the utility of $FeCl_3/SiO_2$ for oxidative coupling should be compared to the results recently reported by McKillop et al.[9]

Results and Discussion

The reagent of interest was simply prepared by dispersing $FeCl_3·6H_2O$ onto silica gel from a methanol/ether solution. Evaporation of the solvent gave $FeCl_3/SiO_2$ as a yellow powder. The amount of iron present in each batch of reagent was accurately determined by titration. Three types of reactions of $FeCl_3/SiO_2$ with phenol ethers were discovered: (1) the oxidative coupling of methoxy aromatics, (2) the oxidative conversion of 1,4-disiloxy aromatics to quinones, and (3) the cleavage of benzyloxy aromatic to phenols. We have explored the stoichiometry and scope of each of these reactions. We have also studied the role played by the solid support.

Coupling of Methoxy Aromatics. The reactions were performed by adding the aromatic ether in methylene chloride to an appropriate amount of $FeCl_3/SiO_2$. Usually, an immediate color change was observed. The solvent was removed under reduced pressure on a rotary evaporator, and the mixture was left spinning for 1 h at 30 °C. The reactions were quenched by admixture of the solid to a water/methylene chloride mixture. The color usually dissipated upon stirring this mixture for 1 min. Filtration of the spent reagent and workup gave the products.

Simple di- and trimethoxybenzenes (1) were coupled by using 1.1 equiv of $FeCl_3$ and 1.0 equiv of the aromatic compound. Yields greater than 90% based upon reacted 1 were obtained in all three cases. Gas-liquid chromatography (GLC) analysis of the crude reaction mixture showed only 1 and 2. Titration of the spent reagent with a dichromate solution indicated that less than 0.1% of the iron was present as iron(III). Use of 0.5 equiv of iron to 1.0 equiv of **1c** halved the yield of **2c**. All of these three reactions previously have been reported to proceed via chemical and/or electrochemical oxidation.[10] The $FeCl_3/SiO_2$ procedure will, however, produce isolated, pure products in about 90 min.



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a, $R_1 = OCH_3$; $R_2 = CH_3$
b, $R_1 = CH_3$; $R_2 = OCH_3$
c, $R_1 = R_2 = OCH_3$

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[1] (a) 3M Company, St. Paul, MN. (b) The Weizmann Institute of Science, Rehovot, Israel.

[2] Kerr, J. B.; Jempty, T. C.; Miller, L. L. *J. Am. Chem. Soc.* **1979**, *101*, 7338 and references therein.

[3] (a) Bouden, K.; Reece, C. H. *J. Chem. Soc.* **1950**, *2249.* (b) Erdtman, H.; Runeberg, *J. Acta Chem. Scand.* **1957**, *11*, 1060. (c) Franck, B.; Lubs, H. J. *Angew Chem., Int. Ed. Engl.* **1968**, *7*, 223. (d) Musgrave, O. C. *Chem. Rev.* **1968**, 499. (e) Fichter, F. "Organische Elektrochemie"; Theodor Steinkopff: Dresden und Leipzig, 1942. (f) Piatelli, M.; Fattorusso, E.; Nicolaus, R. A.; Magno, S. *Tetrahedron* **1965**, *21*, 3229. (g) Boekelheide, V.; Phillips, J. B. *J. Am. Chem. Soc.* **1963**, *94*, 1545.

[4] McKillop, A.; Young, D. W. *Synthesis* **1979**, *401*, 481.

[5] Posner, G. W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 487.

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[7] Jempty, T. C.; Miller, L. L.; Mazur, Y. *J. Org. Chem.* **1980**, *45*, 749.

[8] (a) Ronlan, A.; Parker, V. D. *J. Org. Chem.* **1974**, *39*, 1014. (b) Kupchan, S. M.; Dinghra, O. P.; Kim, C.-K.; Kameswaran, V. *Ibid.* **1978**, *43*, 252. (c) Kupchan, S. M.; Liepa, A. J.; Kameswaran, V.; Bryan, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 6861. (d) Kupchan, S. M.; Kameswaran, V.; Lynn, J. T.; Williams, D. K.; Liepa, A. J. *Ibid.* **1975**, *97*, 5622. (e) Kupchan, S. M.; Kim, C.-K. *Ibid.* **1975**, *97*, 5623. (f) Kupchan, S. M.; Dinghra, O. P.; Ramachandran, V.; Kim, C.-K. *J. Org. Chem.* **1978**, *43*, 105. (g) McKillop, A. E.; Turrell, A. G.; Taylor, E. C. *J. Org. Chem.* **1977**, *42*, 765. (h) Taylor, E. C.; Andrade, J. G.; McKillop, A. E. *J. Chem. Soc., Chem. Commun.* **1977**, 538.

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[10] (a) Reaction of **1a**: McKillop, A.; Turrell, A. G.; Taylor, E. C. *J. Org. Chem.* **1977**, *42*, 164. (b) Reaction of **1b**: Parker, V. D.; Adams, R. N. *Tetrahedron Lett.* **1969**, 1721. Fichter, F.; Ris, H. *Helv. Chim. Acta* **1924**, *7*, 803. (c) Reaction of **1c**: Erdtman, H. G. H. *Proc. R. Soc. London, Ser. A* **1934**, *143*, 191.

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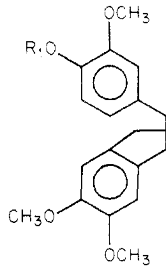
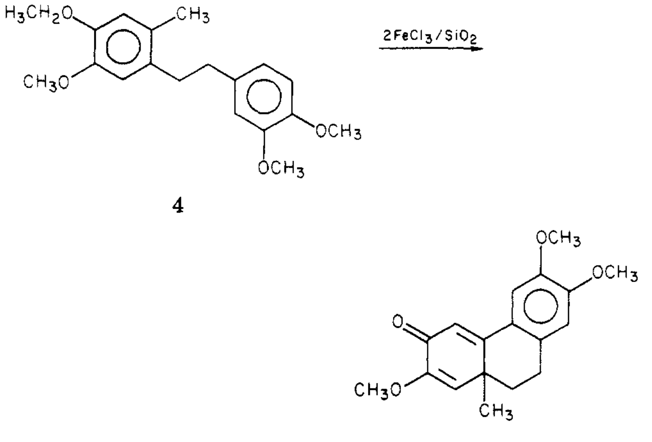
We hoped that $FeCl_3/SiO_2$ would produce intramolecular coupling of tetrahydroisoquinolines. However, reacting (±)-laudanosine, **3a** with 2.2 molar equiv of the reagent lead to quantitative recovery of the starting material. It was thought that perhaps complexation of the tertiary amine in **3a** with ferric ion was inhibiting oxidation. To test this hypothesis, (±)-*N*-formyllaudanosine, **3b**, was allowed to react with 2.2 molar equiv of $FeCl_3/SiO_2$. Despite the marked decrease in the Lewis basicity of this compound, no oxidation occurred and unreacted material was again recovered.



3a, $R_1 = CH_3$; $R_2 = CH_3$
3b, $R_1 = CH_3$; $R_2 = CHO$
3c, $R_1 = CH_2Ph$; $R_2 = CH_3$
3d, $R_1 = H$; $R_2 = CH_3$

We were able to effect the intramolecular coupling of 2-methyl-3′,4′,5′-trimethoxy-4-ethoxybibenzyl, **4**, to the rearranged dihydrophenanthrenone **5** in high yield. This reaction also takes place anodically.[2] Since such specificity of coupling using $FeCl_3/SiO_2$ was observed, it is suggested that the mechanism must be similar to that of the anodic process.[2]



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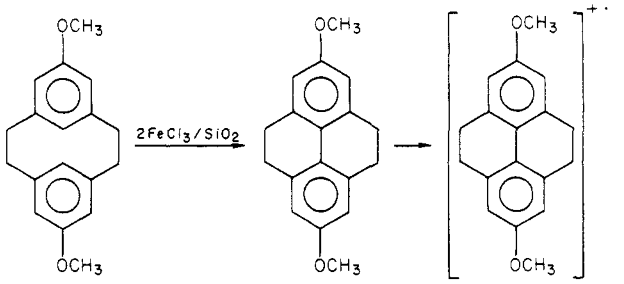
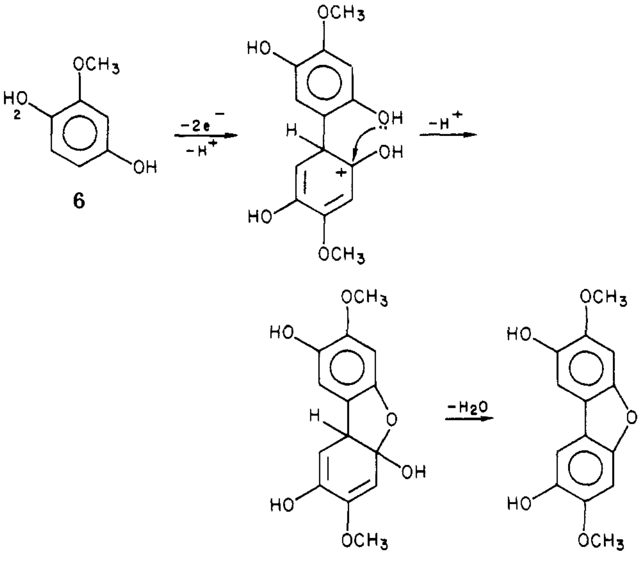
As expected from this mechanism, we have shown that for the conversion of **4** to **5**, 2 mol of ferric chloride is necessary to generate 1 mol of organic product. Equimolar amounts of reagent and organic reactant give product yields of 35–45%. An important consequence of the mechanism is that the oxidation potential of the aromatic ether is a limiting factor. It was found that silica-bound ferric chloride was not a sufficiently strong oxidant to attack anisole, *p*-methoxytoluene, or veratrole, which are known to have more positive oxidation potentials than the substrates discussed above.[11] These observations place the effective oxidation potential limit at about +1.0 V with reference to a saturated calomel electrode.

Another example of an intramolecular coupling reaction effected by $FeCl_3/SiO_2$ is the oxidation of 4,4′-dimethoxy[2.2]metacyclophane to 2,7-dimethoxy-4,5,9,10-tetrahydropyrene in 95% yield.[12] When a slight excess of the requisite 2 molar equiv was employed for this transformation, the product was further oxidized to its bright green cation radical.



Two previously unknown coupling reactions have been accomplished with this reagent. One, the oxidation of methoxyhydroquinone, **6**, leads to methoxybenzoquinone and 4,4′-dimethoxy-5,5′-dihydroxydibenzofuran, **7**, as the two major components of a complex product mixture. The formation of **7** can be rationalized in terms of electron transfer and C–C coupling para to the methoxy substituent of the phenoxonium ion intermediate.[13] Subsequent ring closure to form the furan ring and dehydration lead to the observed product.



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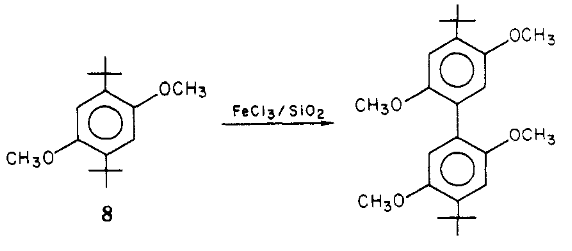
The observed oxidative coupling of 2,5-di-*tert*-butyl-1,4-dimethoxybenzene (**8**) is also new. The sole product, 4,4′-di-*tert*-butyl-2,2′,5,5′-tetramethoxybiphenyl (**9**), whose structure proof assumes that the remaining substituents retain their initial arrangement, arises from ipso substi-



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9

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(12) Becker, J. Y.; Miller, L. L.; Boekelheide, V.; Morgan, T. *Tetrahedron Lett.* **1976**, 2939.

(13) The same reaction producing **7** has been accomplished by Dr. R. F. Stewart via anodic oxidation. Unpublished results, University of Minnesota.

Table I. Oxidation of 1,2,5-Trimethoxybenzene

entry no.	reagent	% yield of **2c**[a]
1	4.4% $FeCl_3/SiO_2$	76
2	4.5% $FeCl_3/SiO_2$ L.V.[e]	45
3	4.4% $FeCl_3/SiO_2$	78[b]
4	5.0% $FeCl_3$/Celite	80
5	5.0% $FeCl_3$/Chromosorb A	80
6	5.0% $FeCl_3$/Chromosorb W	96
7	5.0% $FeCl_3/Al_2O_3$	0[c]
8	4.4% $FeCl_3/SiO_2$ (slurry)	43 (60)[d]

[a] These yields were determined by GLC analysis and are not corrected for unreacted starting material. [b] This reagent was prepared from anhydrous ferric chloride in place of the usual ferric chloride hexahydrate. [c] Starting material was recovered in a quantitative yield. [d] In this experiment, after 1 h as a slurry, one-half of the crude reaction mixture was quenched and worked up, whereas the yield in brackets is that observed for the other half of the reaction, which was then taken to dryness prior to workup. [e] L.V. signifies that the solvent was removed from the reagent under a low vacuum at room temperature.

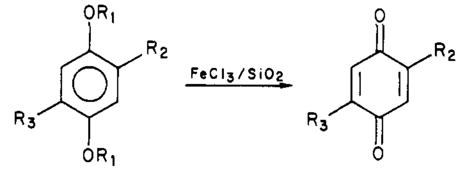
tution for the *tert*-butyl groups. Similar ipso de-*tert*-butylation reactions have been observed.[14] Compound **8** reacted incompletely even with excess $FeCl_3/SiO_2$. Conducting the reaction of elevated temperatures lead to chlorinated products as determined by mass spectroscopy.

Having explored the scope of this reaction we were also interested in the relative utility of other supported ferric chloride reagents, and compound **1c** was used to explore this problem. The results are summarized in Table I. Those conditions which inhibit production of **2c** do so by a decrease in conversion, since in all cases the only materials present were starting material and the biaryl product.

Entry 1 is the standard reaction reported above. Entry 2 refers to an experiment in which the reagent was prepared by using a weak vacuum (~20 torr) to remove the solvent and water at ambient temperature. This reagent is clearly less reactive. Entry 3 refers to an experiment in which anhydrous ferric chloride was used to prepare the reagent instead of ferric chloride hexahydrate. This made no difference and it is clear that the waters of hydration of the ferric chloride are not important to the structure or reactivity of the supported reagent. Entries 4, 5, 6, and 7 refer to experiments in which the support was changed. Alumina is not a suitable support, but Celite (a diatomaceous earth) and Chromosorb (silylated silica) are as useful as silica gel. Finally, in entry 8 are results for a modified procedure using the usual $FeCl_3/SiO_2$. In this experiment the mixture of reactant and reagent was first evaporated to a slurry. After 1 h, half of the mixture was quenched and worked up, giving a 43% yield of **2c**. The other half was taken to dryness and then quenched and worked up, giving 60% of **2c**. It is thus clear that coadsorbing the reagent and reactant on the silica support for 1 h improves the conversion and that the reaction is really a heterogeneous one, not one in which $FeCl_3$ desorbs and reacts in solution.

Quinones from Disiloxy Aromatics. It has recently been shown that 1,4-disiloxy aromatics can be anodically cleaved to produce quinones.[15] It was our interest in the present study to see if this transformation could be accomplished with $FeCl_3/SiO_2$. This oxidative desilylation reaction is of some synthetic interest since it provides a way to unmask a quinone function which has been protected as a disiloxy group. Complex quinones are of some importance.[16]

Table II. Quinones from Disiloxy Aromatics



10 **11**

reactant **10**	% yield of **11**[a]
a, R_1 = Me_3Si; R_2 = R_3 = H	57
b, R_1 = *t*-Bu$(CH_3)_2Si$; R_2 = R_3 = H	52
c, R_1 = H; R_2 = R_3 = *t*-Bu	99
d, R_1 = Me_3Si; R_2 = R_3 = *t*-Bu	99
e, R_1 = *t*-Bu$(CH_3)_2Si$; R_2 = R_3 = *t*-Bu	99
f, R_1 = Me_3Si; R_2 = R_3 = CH_3	98
g, R_1 = *t*-Bu$(CH_3)_2Si$; R_2 = R_3 = CH_3	99
h, R_1 = Me_3Si; R_2 = H; R_3 = CH_3	76
i, R_1 = *t*-Bu$(CH_3)_2Si$; R_2 = H; R_3 = CH_3	59
j, R_1 = R_2 = H; R_3 = Cl	80

[a] These oxidations employed 2.2 molar equiv of 4.4% $FeCl_3/SiO_2$. The yields were determined by GLC analysis.

The bis(trimethylsilyl) ethers were prepared by treatment of hydroquinones with trimethylsilyl chloride and hexamethyldisilazine in acetonitrile.[17] The bis(*tert*-butyldimethylsilyl) ethers were prepared by treatment of hydroquinones with *tert*-butyldimethylsilyl triflate and triethylamine in chloroform.[17] A summary of the oxidation of these substrates (**10**) and their parent hydroquinones with $FeCl_3/SiO_2$ using the same method outlined for methoxyaromatics is presented in Table II. Although high yields of quinones **11** were observed for disubstituted disiloxyaromatics, the mono- and unsubstituted compounds **10a,b,i–k** gave mixtures of products. For example, it was determined by GLC that in the oxidation of 1,4-bis(trimethylsiloxy)benzene another product, in addition to benzoquinone (57%), was formed. Mass spectral analysis revealed that this byproduct contained one more oxygen than expected for the quinone product. This product probably arises during aqueous quenching of the reaction since the yield of this byproduct was diminished when this step was omitted from the workup procedure.

With use of 1,4-bis(trimethylsiloxy)-2,5-di-*tert*-butylbenzene (**10d**) as the reactant, several aspects of the reactions were explored. First, it was shown that finely ground, insoluble ferric chloride was nearly as effective as the supported reagent. Second, it was shown that silica gel alone did not hydrolyze the silyl ether function. Thus, in this reaction the silica plays a minor role. A more interesting set of experiments was initiated by the observation that the yellow reagent was white at the end of the reaction but returned to yellow after filtration. This suggested reoxidation to iron(III) by air. The hypothesis was tested by recycling the reagent and eventually by making the reaction catalytic. Specifically, 0.1 equiv of

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(14) (a) Tashiro, M.; Fukata, G. *J. Org. Chem.* **1977**, *42*, 1208 and references therein. (b) Olah, G. A.; Kuhn, S. J.; Flood, H. *J. Am. Chem. Soc.* **1962**, *84*, 1688. (c) Olah, G. A.; Kuhn, S. J.; Flood, S. H. *Ibid.* **1972**, *94*, 7488. (d) Olah, G. A. *Acc. Chem. Res.* **1971**, *4*, 240. (e) Tsuge, O.; Tashiro, M. *Bull. Chem. Soc. Jpn.* **1965**, *38*, 185. (f) Tsuge, O.; Tashiro, M. *Ibid.* **1967**, *40*, 115, 119, 125.

(15) Miller, L. L.; Stewart, R. F. *J. Am. Chem. Soc.* **1980**, *102*, 4999.

(16) (a) Patai, S., Ed. "The Chemistry of the Quinoid Compounds"; Wiley: New York, 1974; Vol. 1 and 2. (b) Cason, J. *Org. React.* **1957**, *4*, 305.

(17) Oxidative debenzylations are well-known. See, for example, Boyd, J. W.; Schmalzl, P. W.; Miller, L. L. *J. Am. Chem. Soc.* **1980**, *102*, 3856.

Table III. Debenzylation Reactions Using $FeCl_3/SiO_2$

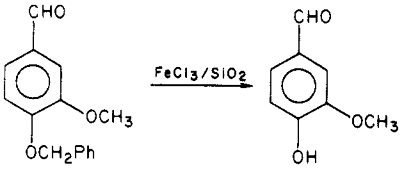
entry	compound	product	procedure[a]	% yield[b]
1	(±)-*O*-benzylpseudocodamine (**1c**)	(±)-pseudocodamine **1d**	A	40
2	4-(benzyloxy)-3-methoxybenzaldehyde (**12**)	vanillin (**13**)	A	99
3	3-(benzyloxy)-4-methoxybenzaldehyde (**14**)	isovanillin (**15**)	A	99
4	4-(benzyloxy)benzaldehyde (**16**)	4-hydroxybenzaldehyde (**17**)	A	22
5	4-(benzyloxy)benzaldehyde (**16**)	4-hydroxybenzaldehyde (**17**)	B	99
6	3-(benzyloxy)benzaldehyde	3-hydroxybenzaldehyde	A	24
7	3-(benzyloxy)benzaldehyde	3-hydroxybenzaldehyde	B	99

[a] Method A: 1.1 molar equiv of 4.4% $FeCl_3/SiO_2$; the reactant was adsorbed onto the reagent once, and remained spinning on the rotary evaporator in vacuo for 1 h at ≃30 °C. Method B: 2.2 molar equiv of 4.4% $FeCl_3/SiO_2$ for 30 min at ≃80 °C. [b] Isolated yields of recrystallized or distilled materials.

4.4% $FeCl_3/SiO_2$ and 1.0 equiv of **10d** were reacted for 2 h in a CH_2Cl_2 slurry at room temperature by bubbling air through the mixture. A 74% yield of **11d** was obtained. Of all the reactants studied, this was the only one which reacted catalytically. Even **10e** did not behave this way.

Cleavage of Benzyl Ethers. As part of this study of phenol ether oxidations we attempted to oxidize *O*-benzylpseudocodamine (**3c**) with $FeCl_3/SiO_2$. The sole product was isolated and identified as the debenzylated (±)-pseudocodamine **3d** in 40% yield. All further attempts to generate any oxidation products failed. In fact, by increasing the amount of reagent to 5 molar equiv and leaving the reaction mixture of $\simeq$80 °C on the rotary evaporator overnight, a new product was isolated which contained at least four chlorine atoms as determined by mass spectral analysis.

In an attempt to determine the scope and limitations of $FeCl_3/SiO_2$ for the cleavage of benzyl ethers, a number of simple benzyl ethers were treated with this reagent. The procedure was the same as for oxidations except that the phenol products were isolated by aqueous base extraction, subsequent acidification of the aqueous phase, and back-extraction with a volatile organic solvent. Pure phenols were always obtained in this manner, often in high yield (Table III). It was shown, for example, that compounds **12** and **14** gave excellent yields of vanillin (**13**) and isovanillin (**15**), using 1.1 equiv of $FeCl_3$ at 30 °C for 1 h. Dichromate titration showed that no Fe(II) was generated. These are not oxidative cleavages.[17] Use of 0.5 equiv of reagent gave a 43% yield of **13** and **12**, indicating that the $FeCl_3$ is reacting stoichiometrically.



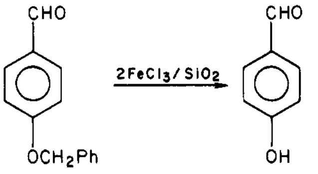
12 13

Table IV. Variations of Reaction Conditions for the Debenzylation of 12

entry	reagent	time, min	% yield[a]
1	$FeCl_3\cdot 6H_2O$	60	5
2	SiO_2	60	0
3	9% $FeCl_3/SiO_2$	60	99
4	9% $FeCl_3/SiO_2$	1	99
5	9% $FeCl_3/SiO_2$ (slurry)	1	6
6	9% $FeCl_3/SiO_2$ (slurry)	60	6
7	entry 6 now taken to dryness[b]		99
8	9% $FeCl_3/SiO_2$ L.V.[c]	60	22

[a] These are yields based upon the amount of substrate reacted. [b] After 1 h as a slurry the reaction mixture was taken to dryness and immediately worked up in the usual manner. [c] L.V. signifies that the solvent was removed from the reagent under a low vacuum at room temperature.

Both substrates **12** and **14** have a methoxy group ortho to the benzyl ether being cleaved. This orientation of the two oxygen atoms has been reported to efficiently coordinate Lewis acids, and the chelation of a Lewis acid reagent by a catechol ether has been suggested by Kametani et al. as a probable enhancing feature in the reductive cleavage of benzyl ethers using an alkoxyaluminohydride.[18] To determine if coordination of this type was an important feature for the cleavage of benzyl ethers with $FeCl_3/SiO_2$, two monoethers were subjected to the usual reaction conditions. Both 4-(benzyloxy)benzaldehyde (**16**) and 3-(benzyloxy)benzaldehyde were incompletely cleaved to the corresponding phenols in separate experiments. Even with greatly prolonged reaction times and elevated temperatures cleavage was incomplete. Both monoethers were, however, completely cleaved to the corresponding phenols when 2 molar equiv of reagent was employed. One explanation for these results is that the aldehyde group competes with the isolated aryl alkyl ether function for the complexation of ferric ion, thus requiring an excess of iron(III). In contrast, chelation with a catechol functionality in **12** should be more stable than the aldehyde–ferric chloride complex and **12** could react with 1 equiv.



16 17

The relative reactivities were tested by mixing 1 molar equiv each of **12** and **16** with a molar equivalent of $FeCl_3/SiO_2$. It was found by GLC that **12** was 80% debenzylated, whereas only a trace of 4-hydroxybenzaldehyde was detected in the crude product mixture. It is thus clear that the ortho diethers react more quickly than monoethers. This is in concert with the chelation hypothesis.

The debenzylation of **12** was chosen as the model system to study what effect variation of reaction conditions might exert on this reaction. The gamut of experiments performed on this substrate appears in Tables IV and V. In Table IV, entries 1 and 2 show that a minimal amount of debenzylation occurred when the substrate was reacted on either finely ground ferric chloride hexahydrate or chromatographic grade silica gel.

Entries 3 and 4 indicate the time frame in which the reaction takes place. These times were measured after

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(18) Kametani, T.; Huang, S.-P.; Ihara, M.; Fukomoto, K. *J. Org. Chem.* **1976**, *41*, 2545.

Table V. Comparative Effectiveness of Various Supports for the Debenzylation of 12

support	% $FeCl_3$ [a]	% yield of 13 [b]
10 Å molecular sieves	10	0 [c]
3 Å molecular sieves	0.3	0
Celite Filter Aid	5	80
Chromosorb A	5	99
Chromosorb W [d]	5	91
activated charcoal	5	0
activity I alumina	5	0
DMS [d] treated silica gel	9	45

[a] The percentage of ferric ion on the support was determined by titration of the reagent with a dichromate solution. [b] The reactions were conducted as follows: 1.1 molar equiv of reagent was reacted with 12, the substrate was adsorbed onto the reagent once, and the flask remained spinning on the rotary evaporator for 1 h at ≅30 °C. The yield is based upon 12 reacted and is an isolated yield of 13. [c] A quantitative recovery of starting material was observed. [d] Both Chromosorb W and chromatographic grade silica gel were treated with dichlorodimethylsilane prior to deposition of ferric chloride.

mixing and evaporation, from the instant that the solvent was no longer visible and the reagent appeared powderlike. Clearly, the benzyl ether cleavage is very fast once the solvent is *completely* removed. Further testimonies to this are found as entries 5 and 6 where the reactions were performed as slurries, i.e., a minimum of solvent was still present, and the reaction was monitored by thin-layer chromatography. It should be noted that in entry 6, after 1 h as a slurry, only 6% reaction had occurred. A quantitative yield was then immediately obtained by merely drying that slurry. *This is, therefore, truly a reaction in a "dry medium".* Another example of a reaction which occurs sans solvent is the oxidation of amines to nitro groups with ozone impregnated silica gel.[20]

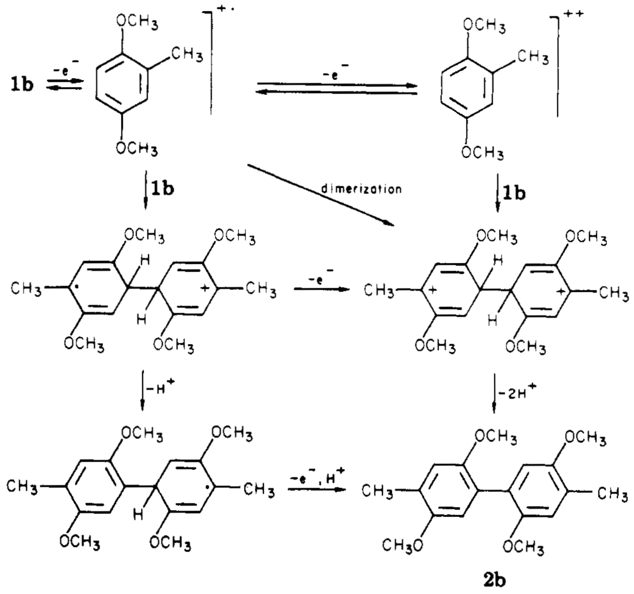
Mazur reported that a high water content in $FeCl_3/SiO_2$ could greatly inhibit this reagent's ability to effect either dehydration or epimerization of alcohols.[6] Similar inhibition has been observed for the cleavage of benzyl ethers with this reagent (see entry 8).

Since previous experiments with alcohols[6] have not explored the role of the silica gel in $FeCl_3/SiO_2$, we prepared several $FeCl_3$ supported reagents and used them for the cleavage of 12. The results are summarized in Table V. Chromatographic grade silica gel appears to be the most effective support for this debenzylation. However, both Celite Filter Aid (a diatomaceous earth) and Chromosorb A were also quite effective. In contrast, alumina, charcoal, or molecular sieves were useless. Clearly, high surface area silicates are important to this process. It was suspected that surface silanol functions might be involved, and to test this hypothesis we performed an experiment in which the silica gel was silylated with dichloromethylsilane before ferric chloride was adsorbed.[21] This, indeed, decreased the reactivity of the reagent. Interpretation of the result is clouded because some $FeCl_3$ could have been consumed by reaction with surface silyl ethers or silyl chlorides. In this regard it is noted that Chromosorb W, a silylated silica support, was an effective reagent.

Comparative Summary

Synthetic Utility. This study has demonstrated that $FeCl_3/SiO_2$ rapidly oxidizes dimethoxy aromatics and disiloxy aromatics. The former compounds couple to form biaryls, often in high yield. Such coupling reactions can be achieved with other oxidants,[8,9] but $FeCl_3/SiO_2$ gives exceptionally fast and clean reactions, the workup is trivial, and toxic or expensive metal oxidants are not used. The disiloxy aromatic to quinone transformation is of more limited utility, since high yields are only obtained for highly substituted reactants. Pyridium chlorchromate[22] or anodic oxidation[17] would appear to have more generality.

Scheme I



Mechanism. The analogy to electrochemistry has been mentioned above at several points, and, indeed, the data point to similar mechanisms for anodic and $FeCl_3/SiO_2$ coupling. Such mechanisms will involve one-electron transfer steps and chemical steps as illustrated by a scheme for the oxidation of **1b** (Scheme I). It should be understood that each iron(III) can accept only one electron. The second electron (steps labeled $-e^-$) required to complete certain mechanisms could come at the surface, where a second iron(III) is the acceptor, or in the solution, near the surface, where a high concentration of oxidized and oxidizing organic intermediates exists. Support for such mechanisms is seen in the anodic analogies.[2] Thus, the same coupled products can be obtained from dimethoxy aromatics by using electrochemistry, $FeCl_3/SiO_2$, or other reagents proposed to utilize electron-transfer oxidation routes. Of particular interest is the rearrangement product from oxidation of 4. This same product is obtained at an anode and strongly supports the hypothesis. In a study of $FeCl_3$ oxidations of durene or naphthalene in solution, Nyberg has made a similar mechanistic proposal.[23] The rate of oxidations which involve electron transfer are usually correlated with the anodic oxidation potential. In the present study it is seem that only those compounds whose oxidation potential (cyclic voltammetry) is less than about 1.0 V vs. SCE react by an oxidation mode. Monoalkoxy aromatics are, for example, not oxidized.

The oxidative formation of quinones from disiloxy aromatics also has an anodic analogue and it is possible that $FeCl_3/SiO_2$ utilizes an electron-transfer mechanism in this case as well. Onn the other hand, it has been shown that pyridinium chlorochromate oxidation of disiloxy aromatics

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to quinones is unlikely to involve electron transfer.[22] Due to the limited data, further speculation about the $FeCl_3/SiO_2$ mechanism is unwise.

The reactions of benzyloxy aromatics are not analogs of electrochemistry, for here the iron(III) acts as a Lewis acid. The acidity of iron(III) can also account for the lack of oxidation of the alkaloids **3**. Since it is known that amines and even amides are effective ligands for iron(III), it seems likely that the alkaloids complex on nitrogen with iron, and this prevents aromatic oxidation.

Role of the Support. Although alumina as a support stops all reactivity, the silica appears to play a minor role in the oxidation reactions. The surface is, on the other hand, quite important for debenzylation. Most interesting is the extreme difference in reactivity of concentrated slurries and "dry" mixtures in which iron and the reactant are coadsorbed.

Experimental Section

General Procedures. All melting points recorded are uncorrected, open capillary measurements, using a Mel-Temp melting point apparatus. Pressures were measured on a Conolab MacLeod vacuum meter. Nuclear magnetic resonance spectra were recorded on a Varian CFT-20 instrument. Chemical shifts, reported in δ units, were measured relative to either tetramethylsilane or chloroform as the internal standard in deuteriochloroform except where noted. ^{13}C spectra were recorded on a Varian XL-100-15, operating at 25.16 MHz with proton broad band decoupling of 9 W. Infrared spectra were recorded on a Perkin-Elmer infrared spectrophotometer Model 727B. Mass spectra (MS) were recorded on an AEI MS-30, while gas chromatography mass spectrometry (GC–MS) analysis were obtained on a Hitachi RMU-60DX instrument coupled to a Varian Aerograph gas chromatograph. All product spectra were compared with spectra of authentic samples taken on the same instrument whenever possible. Combustion analyses were obtained from M-H.W. Laboratories, Phoenix, AZ.

Analytical thin-layer chromatography was performed by using either 0.25 mm thick precoated Polygram SIL G/UV_{254} plastic sheets with fluorescent indicator distributed by Brinkmann Instruments, Inc., or Baker-flex Silica Gel 1B plates with fluorescent indicator distributed by J. T. Baker Chemical Co. Preparative thin-layer chromatography was performed by using either 1.0 mm or 2.0 mm thick precoated SIL G-100 UV_{254} glass plates with fluorescent indicator distributed by Brinkmann Instruments, Inc.

Gas–liquid chromatography (GLC) analyses of product mixtures were carried out on either a Varian Model 3700 gas chromatograph utilizing a flame-ionization detector coupled to a Perkin-Elmer M-2 calculating integrator or a Hewlett-Packard Model 5840A gas chromatograph using a Hewlett-Packard Model 5840A terminal to determine peak areas. Preparative gas–liquid chromatography (PGLC) was performed by using a thermal conductivity detector.

High-pressure liquid chromatograph (HPLC) was performed by using two Waters Associates Model 6000A solvent delivery systems, a Waters Associates Model 660 solvent programmer, and a Waters Associates Model 440 absorbance (254 nm) detector. Peaks were recorded on a Linear recorder and peak areas were calculated by using a Perkin-Elmer M-2 calculating integrator. The column used was an analytical Waters μ-Bondapak C-18 reverse-phase column.

Low-pressure liquid chromatography (LPLC) was performed with Altex columns, fittings, and tubing. A FMI Model RP-Sy solvent pump and ISCO Model 273 fraction collector were also used. The silica gel used was Woelm Keiselguhr (60 μm).

All solvents were reagent grade and used as received. The following solid supports were used as received from their respective manufacturers: Celite Filter Aid (Johns-Manville), Chromosorb A and Chromosorb W (Johns-Manville), activated charcoal (Mallinckrodt), activated alumina of activity I (EM Laboratories), and 3 and 10 Å molecular sieves (Davison). Silica gel powder (Baker AR, 60–200 mesh) was dried at 240 °C for 2 days prior to use in the reagent. Silica gel for column chromatography was used as received from Baker. Unless noted, all organic compounds and the $FeCl_3 \cdot 6H_2O$ (Mallinckrodt AR) were commercial samples used without purification.

Preparation of $FeCl_3/SiO_2$. An appropriate amount of ferric chloride is dissolved in a 90% anhydrous ether, 10% anhydrous methanol solution. Enough solvent is added to assure the complete dissolution of the ferric chloride. To this is added the appropriate amount of dried chromatographic grade silica gel (or other solid support). The solvent is removed under reduced pressure ($\simeq$20 mmHg) in a water bath at $\simeq$30 °C. Once the reagent appears to be free of clumps, the flask is transferred to a vacuum ($\simeq$0.5 mmHg). This is reported to be stringent enough conditions to remove >80% of all of the SiOH groups on the surface of the silica gel.[25] The reagent at this point is reproducibly a homogeneous, free flowing, yellow powder which is moisture and light sensitive. Storage under an inert, dry atmosphere and in a brown bottle appears to greatly increase the shelf life of the reagent. Prolonged heating under vacuum produced a red powder of no utility for the reactions reported here.

Determination of Iron(III) Present in the Reagent. A weighed sample of reagent was analyzed for the amount of iron present by a series of redox reactions which have been outlined by Fritz and Schenk.[25] The final step consists of a titration with a dichromate solution.[26]

General Procedure for the Oxidative Coupling Reactions. To a methylene chloride solution (25 mL) of the substrate (3–5 mmol) was added a slight excess of solid supported reagent. The amount of reagent depends upon whether the reaction was intermolecular or intramolecular. The former, a dimerization, only requires 1.1 molar equiv of reagent per substrate molecule. The latter required 2.1 molar equiv of reagent per substrate molecule. Usually an immediate color change was observed. The solvent was then removed under reduced pressure. To this crude reaction mixture was added methylene chloride (25 mL) and distilled water (1 mL) to quench the reaction as well as destroy any inorganic complexes that may have formed during the reaction. This mixture was stirred for 1 min and then suction filtered. The spent reagent was washed twice with methylene chloride (25 mL). The combined organics were dried over magnesium sulfate, and the solvent was removed under reduced pressure. This crude reaction mixture was analyzed and purified in a conventional manner. Compounds were identified by comparison of NMR, IR, and MS with authentic samples whenever they were available.

2,2′-Dimethyl-4,4′,5,5′-tetramethoxybiphenyl (2a). The oxidative coupling of 4-methylveratrole (**1a**) was performed as outlined in the general procedure. The crude product mixture was analyzed by GLC (10% Carbowax 20M on Chromosorb W, column length 3 m, flow rate 33 mL min^{-1}). The chromatogram contained only two peaks, unreacted starting material **1a** (retention time 431 s) and the biphenyl product **2a** (retention time 2062 s). The yield of biphenyl **2a** corrected for unreacted starting material was 95%. The product could be crystallized from the crude product mixture with petroleum ether (60–70) in 64% isolated yield based upon added starting material: mp 113–114 °C (lit.[8a] mp. 113 °C); NMR (acetone-d_6 + 1% Me_4Si) δ 1.98 (s, 3 H, $ArCH_3$), 3.76 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 6.64 (s, 1 H, ArH), 6.85 (s, 1 H, ArH); low-resolution mass spectrum (70 eV), *m/e* (relative intensity) 302 M^+, 100), 287 ($M^+ - 15$, 16), 272 ($M^+ - 30$, 6); high-resolution mass spectrum (70 eV), *m/e* 302.1528, observed for $C_{18}H_{22}O_4$ (calcd 302.1540).

4,4′-Dimethyl-2,2′,5,5′-tetramethoxybiphenyl (2b). The oxidative coupling of 2-methyl-1,4-dimethoxybenzene (1b) was performed as outlined in the general procedure. The crude reaction mixture was analyzed by GLC (10% Carbowax 20 M on Chromosorb W, column length 3 m, flow rate 30 mL min^{-1}). The chromatogram of this crude mixture contained only two major peaks; unreacted starting material **1b** (retention time 513 s) and the desired biphenyl product **2b** (retention time 2118 s). The yield

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(26) A reagent which was prepared and found to contain 3.5% iron(III) by weight, using the titration procedure, was found to contain 4.5% iron by weight by elemental analysis. The iron to chlorine ratio was 1:3 and the silicon to oxygen ratio was determined to be 1:2, as expected.

for 4,4′-dimethyl-2,2′,5,5′-tetramethoxybiphenyl (**2b**) corrected for unreacted starting material was 90%. The product could be crystallized from the crude reaction mixture with a minimum of hot petroleum ether (60–70) in 82% based upon the amount of material reacted: mp 129–131 °C (lit.[10b] mp 133 °C); NMR ($CDCl_3$ + 1% Me_4Si) δ 2.26 (s, 3 H, $ArCH_3$), 3.72 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 6.76 (s, 1 H, ArH), 6.80 (br s, 1 H, ArH); low-resolution mass spectrum (70 eV) *m/e* (rel intensity) 302 (M^+, 14), 287 ($M^+ - 15$, 3), 272 ($M^+ - 30$, 12), 256 ($M^+ - 46$, 4), 151 ($M^+ - 151$, 2), 28 ($M^+ - 274$, 100); high-resolution mass spectrum (70 eV), *m/e* 302.1516, $C_{18}H_{22}O_4$ (calcd 302.1540, $C_{18}H_{22}O_4$).

2,2′,4,4′,5,5′-Hexamethoxybiphenyl (2c). The oxidative coupling of 1,2,4-trimethoxybenzene (**1c**) was performed as outlined in the general section. The crude reaction mixture was analyzed by GLC (10% OV-101 on Chromosorb W, column length 4 m, flow rate 36 mL min^{-1}). The chromatogram contained only two peaks, unreacted starting material **1c** (retention time 9.57 min) and the desired biphenyl product **2c** (retention time 17.70 min). The yield corrected for unreacted starting material was 99%. The product was crystallized from the crude reaction product mixture with a minimum of hot petroleum ether (60–70) in 89% yield: mp 175–176.5 °C (lit.[10c] mp 177 °C); NMR ($CDCl_3$ + 1% Me_4Si) δ 3.74 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 6.62 (s, 1 H, ArH), 6.82 (s, 1 H, ArH); low-resolution mass spectrum (70 eV), *m/e* (relative intensity) 334 (M^+, 100), 319 ($M^+ - 15$, 22), 288 ($M^+ - 46$, 36), 167 ($M^+ - 167$, 9); high-resolution mass spectrum (70 eV), *m/e* 334.1395, $C_{18}H_{22}O_6$ (calcd 334.1376, $C_{18}H_{22}O_6$).

9,10-Dihydro-10a-methyl-2-ethoxy-6,7-dimethoxy-3(10a)-phenanthrenone (5). The intramolecular oxidative coupling of **4** was performed as outlined above. The crude reaction mixture was determined to contain two major peaks by HPLC (water/methanol, μ-Bondapak C-18). The crude reaction product could be crystallized from wet ethanol to yield 90% of pure **5** based upon the amount of **4** reacted: mp 178–179 °C (lit.[2] mp 178–179.5 °C); NMR ($CDCl_3$ + 1% Me_4Si) δ 1.21 (s, 3 H, CH_3), 1.45 (t, 3 H, OCH_2CH_3), 1.95 (m, 2 H, aliphatics), 2.95 (m, 2 H, aliphatics), 3.80 (q, 2 H, OCH_2CH_3), 3.90 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 5.79 (s, 1 H, vinyl), 6.60 (s, 1 H, ArH), 6.68 (s, 1 H, vinyl), 7.08 (s, 1 H, ArH). The IR, MS, and UV data of **5** were as expected as compared to those of a sample made via anodic oxidation.

4,4′-Di-*tert*-butyl-2,2′,5,5′-tetramethoxybiphenyl (9). The oxidative coupling of **8** was performed as outlined in the general section. The crude product mixture was found to contain **9** (20%) as determined by GLC (SE-30 on Chromosorb W, column length 3 m, flow rate 25 mL min^{-1}) as well as unreacted starting material. The desired product, **9**, was isolated from the crude reaction mixture by crystallization from ethanol: mp 196–198.5 °C; NMR (acetone-d_6 + 1% Me_4Si) δ 1.42 (s, 18 H, t-Bu), 3.69 (s, 6 H, OCH_3), 3.81 (s, 6 H, OCH_3), 6.79 (s, 2 H, ArH), 6.92 (s, 2 H, ArH); low-resolution mass spectrum (70 eV), *m/e* (absolute intensity) 238 ($M^+ - 58$, 63), 213 ($M^+ - 173$, 119), 198 ($M^+ - 188$, 84), 185 ($M^+ - 201$, 100), 91 ($M^+ - 295$, base peak); high-resolution mass spectrum (70 eV), *m/e* 386.2462, $C_{24}H_{34}O_4$ (calcd 386.4269, $C_{24}H_{34}O_4$).

3,6-Dihydroxy-2,7-dimethoxydibenzofuran (7). The oxidative coupling reaction of **6** was performed as outlined in the general section procedure. The crude reaction product was crystallized from chloroform to yield **7** in 35% yield: mp 179–181 °C (lit.[13] mp 180–181 °C); NMR (acetone-d_6 + 1% Me_4Si) δ 3.95 (s, 6 H), 7.15 (s, 2 H), 7.25 (s, 2 H), 7.28 (s, 2 H); mass spectrum (20 eV), *m/e* (relative intensity) 260 (M^+, 62), 246 ($M^+ - 14$, 16), 245 ($M^+ - 15$, 100), 230 ($M^+ - 30$, 22), 217 ($M^+ - 43$, 10), 202 ($M^+ - 58$, 15), 44 ($M^+ - 216$, 30).

General Procedure for the Oxidative Desilylations of the 1,4-Bis(trialkylsiloxy)benzenes. The substrate (3–5 mmol) was dissolved in dry methylene chloride (10 mL). To this was added 2.2 molar equiv of 4.4% silica bound ferric chloride. The solvent was removed under reduced pressure. To this powder were added methylene chloride (10 mL) and distilled water (1 mL). This mixture was stirred for 1 min and then the spent reagent was filtered away. The spent reagent was consistently a white powder at this point. The spent reagent was washed with methylene chloride twice (25 mL). The combined organics were dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The crude reaction products at this point were always crystalline. They were analyzed by GLC (9% OV-275 and 1% OV-101 on Chromosorb W. Pure quinones were isolated quickly and in high yield by either of two methods: direct crystallization of the crude reaction mixture or passing the material down a short column of Florasil with anhydrous ether as the solvent. Compounds were identified by comparison of NMR, IR, and MS data with those of authentic samples.

General Debenzylation Procedure. With the exceptions noted below, all benzylations were performed as follows. The substrate (3–5 mmol) was dissolved in 10 mL of dry methylene chloride. To this was added 1.1 molar equiv of solid supported reagent. The solution usually changed color immediately. The solvent was removed under vacuum on a rotary evaporator and the flask remained there for 1 h at ≃30 °C. At this point the free flowing solid was admixed with methylene chloride (25 mL) and distilled water (1 mL). After the mixture was stirred for 1 min, the solution usually returned to the color of the original reagent. The mixture was then suction filtered to remove the reagent and dried over anhydrous magnesium sulfate and the solvent removed under pressure. At this point the crude yields were determined either by weight or GLC. The phenolic products were isolated via successive aqueous hydroxide extraction, acidification of the aqueous layer, and repeated extraction of this solution with methylene chloride. The combined organic layers were dried, and the solvent was removed under reduced pressure. Phenols were isolated in this manner as pure materials. All phenols were identified by comparison of the NMR, IR, and MS data with those of authentic samples.

Competitive Debenzylation of 12 and 16. To a stirred solution of **12** (0.0921 g, 0.38 mmol) and **16** (0.0806 g, 0.38 mmol) in dry methylene chloride was added 1.54 g of 4.4% $FeCl_3/SiO_2$ (0.38 mmol). An immediate deep red color formed on the surface of the reagent. The solvent was removed under reduced pressure on the rotary evaporator and remained spinning for 15 min. At this point the reaction mixture was a red-brown powder. This was admixed with methylene chloride (10 mL) and distilled water (1 mL). This mixture was stirred for 2 min and the color dissipated and returned to the original yellow of the fresh reagent. The spent reagent was filtered away and washed twice with methylene chloride (10 mL). The combined organics were dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The TLC analysis (SiO_2, $EtOAc/CH_2Cl_2$ (1:1), 5 drops of AcOH) indicated the presence of **12**, **16**, and **13**. The crude reaction mixture was redissolved in methylene chloride (25 mL) and extracted 3 times with 15 mL of 1 M sodium hydroxide solution. The organic layer was dried and the solvent removed under reduced pressure. This yielded 0.116 g of unreacted starting materials, and the yield was determined to contain mostly **16** as well as a small amount of **12** by TLC (same conditions as above). The combined aqueous extracts were acidified with 1 M hydrochloric acid solution until acidic to indicator paper. This solution was extracted 3 times with methylene chloride (25 mL). The combined organic layers were dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The resulting colorless solid (0.040 g, 70%) crystallized upon cooling to room temperature and was found to contain only **13** by TLC.

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Registry No. **1a**, 494-99-5; **1b**, 24599-58-4; **1c**, 135-77-3; **2a**, 62012-51-5; **2b**, 13341-00-9; **2c**, 1702-67-6; **3c**, 41182-99-4; **3d**, 79026-55-4; **4**, 52711-85-0; **5**, 52711-86-1; **6**, 824-46-4; **7**, 72442-70-7; **8**, 7323-63-9; **9**, 72428-45-6; **10a**, 2117-24-0; **10b**, 78018-57-2; **10c**, 88-58-4; **10d**, 18724-29-3; **10e**, 73759-45-2; **10f**, 78018-52-7; **10g**, 78018-55-0; **10h**, 78018-53-8; **10i**, 78018-56-1; **10j**, 615-67-8; **11a**, 106-51-4; **11c**, 2460-77-7; **11f**, 137-18-8; **11h**, 553-97-9; **11j**, 695-99-8; **12**, 2426-87-1; **13**, 121-33-5; **14**, 6346-05-0; **15**, 621-59-0; **16**, 4397-53-9; **17**, 123-08-0; ferric chloride, 7705-08-0; 3-(benzyloxy)benzaldehyde, 1700-37-4; 3-hydroxybenzaldehyde, 100-83-4.