Phenyl−Carbonyl Coupling Reactions Promoted by Samarium Diiodide and Hexamethylphosphoramide

Jiann-Shyng Shiue, Mei-Huey Lin, and Jim-Min Fang*

Department of Chemistry, National Taiwan University, Taipei 106, Taiwan, Republic of China

Received February 11, 1997[⊗]

By mediation of samarium diiodide and hexamethylphosphoramide, benzaldehydes and acetophenones underwent self- and cross-couplings to give the products having linkages at the *para*-carbons of phenyl rings and the carbonyl groups. The phenyl−carbonyl coupling of 2,5-dimethoxybenzaldehyde generated a Sm(III)−enolate intermediate, which was trapped by alkyl halides in a stereospecific manner to give uncommon 1,4-dialkyl-2,5-cyclohexadiene-1-carboxaldehydes. The benzaldehydes bearing tethered carbonyl chains proceeded with intramolecular phenyl−carbonyl couplings to afford fused benzocycles.

Introduction

Samarium(II) iodide is a useful one-electron-transfer reducing agent.[1] A variety of additives have been used with SmI_2 to effect organic reactions. For example,[2] bases like KOH, LiOMe, and $LiNH_2$ can be used with SmI_2 in the reductions of esters, amides, and oximes. The Lewis acids $FeCl_3$, $CoCl_2$, and $NiCl_2$ are used with SmI_2 to accelerate reductions of alkynes.[2d,3] Intramolecular halide−carbonyl and ketyl−olefin couplings are carried out by SmI_2 along with $FeCl_2$, $FeCl_3$, $Fe(acac)_3$, tris(dibenzoylmethido)iron(III), or Cp_2ZrCl_2.[4] A dipolar cosolvent HMPA is a general and effective additive to facilitate the above-mentioned and other reactions[5] such as the reduction of halides, cleavage of carbon−sulfur bonds, deoxygenation of sulfones, and halide−olefin couplings. Other dipolar cosolvents[6] such as 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) and tripiperidinophosphine oxide $(C_5H_{10}N)_3PO$ are occasionally utilized as a substitute for HMPA.

Benzaldehydes are reduced with SmI_2 in THF to give the corresponding benzyl alcohols **2** in the presence of a protic cosolvent such as MeOH or *t*-BuOH.[5a] In the absence of protic solvent, aromatic aldehydes or aromatic ketones couple readily to give pinacols **3** (the hydrodimerization products) on treatment with 1 equiv of SmI_2 in THF.[7] If less than 1 equiv of SmI_2 is employed to react with benzaldehyde, several products including benzyl alcohol, hydrobenzoin, benzoin, and benzyl benzoate are obtained.[8] We reported[9] previously that various benzaldehydes undergo phenyl−carbonyl couplings to give the dimerization products, such as **4a**−**g**, by mediation of SmI_2/HMPA in THF (Scheme 1). The coupling occurs at the *para*-carbon of benzaldehyde, differing from the *meta*-directing Friedel−Crafts reactions of the benzenes containing electron-withdrawing substituents. The yields of **4a**−**g** vary from 18 to 80% depending on substrates and reaction conditions, while significant amounts (up to 50%) of the aldehyde substrates are often recovered. An optimal yield (80%) of **4a** was obtained when the reaction was conducted with ratios PhCHO/SmI_2/HMPA = 1:2:8. The dipolar additive HMPA appears to play a crucial role to prevent the aromatic carbonyls from reduction or pinacol coupling (see Scheme 5 for discussion of the reaction mechnism). Additives such as DMF, TMEDA, *N*-methylpyrrolidinone (NMP), and *N*,*N*-dimethylacetamide (DMA) are inferior to HMPA in promoting the formation of the dimers. These additives yield black gelatinous precipitates and lower reactivity severely. Benzaldehydes bearing MeO, Me, and Cl substituents at either *ortho*- or *meta*-positions also undergo the phenyl−carbonyl couplings at the *para*-carbons, giving the dimers **4b**−**g**. However, the phenyl−carbonyl coupling reactions

[⊗] Abstract published in *Advance ACS Abstracts,* July 1, 1997.

(1) For leading reviews, see: (a) Natale, N, R. *Org. Prep. Proc. Int.* **1983**, *15*, 387. (b) Kagan, H. B.; Namy, J. L. *Tetrahedron* **1986**, *42*, 6573. (c) Kagan, H. B. *Inorg. Chim. Acta* **1987**, *140*, 3. (d) Kagan, H. B. *New J. Chem.* **1990**, *14*, 453. (e) Inanaga, J. *Rev. Heteroatom. Chem.* **1990**, *3*, 75. (f) Molander, G. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; p 251. (g) Soderquist, J. A. *Aldrichim. Acta* **1991**, *24*, 15. (h) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29. (i) Brandukova, N. E.; Vygodskii, Y. S.; Vinogradova, S. V. *Russ. Chem. Rev.* **1994**, *63*, 345. (j) *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 6, pp 4428−4432. (k) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307.

(2) (a) Zhang, Y.; Lin, R. *Synth. Commun.* **1987**, *17*, 329. (b) Honda, Y.; Inanaga, J.; Yamaguchi, M. *J. Chem. Soc., Chem. Commun.* **1989**, 298. (c) Kamochi, Y.; Kudo, T. *Tetrahedron Lett.* **1991**, *32*, 3511. (d) Inanaga, J.; Yokoyama, Y.; Baba, Y.; Yamaguchi, M. *Tetrahedron Lett.* **1991**, *32*, 5559.

(3) (a) Suginome, H.; Yamada, S. *Tetrahedron Lett.* **1987**, *28*, 3963. (b) Lannoye, G.; Sambasivarao, K.; Wehrli, S.; Cook, J. M.; Weiss, U. *J. Org. Chem.* **1988**, *53*, 2327.

(4) (a) Molander, G. A.; Etter, J. B. *J. Org. Chem.* **1986**, *51*, 1778. (b) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5763. (c) Otsubo, K.; Kawamura, K.; Inanaga, J.; Yamaguchi, M. *Chem. Lett.* **1987**, 1487. (d) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1991**, *56*, 4112.

(5) (a) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693. (b) Inanaga, J.; Ishikawa, M.; Yamaguchi, H. *Chem. Lett.* **1987**, 1485. (c) Hou, Z.; Kobayashi, K.; Yamazaki, H. *Chem. Lett.* **1991**, 265. (d) Walborsky, H. M.; Topolski, M. *J. Org. Chem.* **1992**, *57*, 370. (e) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1992**, *57*, 3132. (f) Wipf, P.; Venkatraman, S. *J. Org. Chem.* **1993**, *58*, 3455. (g) Enholm, E. J.; Jiang, S.; Abboud, K. *J. Org. Chem.* **1993**, *58*, 4061. (h) Hojo, M.; Harada, H.; Yoshizawa, J.; Hosomi, A. *J. Org. Chem.* **1993**, *58*, 6541. (i) Mazéas, D.; Skrydstrup, T.; Doumeix, O.; Beau, J.-M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1383. (j) Fukuzawa, S.-i.; Tsuchimoto, T.; Kanai, T. *Chem. Lett.* **1994**, 1981.

(6) (a) Fevig, T. L.; Elliott, R. L.; Curran, D. P. *J. Am. Chem. Soc.* **1988**, *110*, 5064. (b) Curran, D. P.; Wolin, R. L. *Synlett* **1991**, 317. (c) Bennett, S. M.; Larouche, D. *Synlett* **1991**, 805. (d) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1991**, *56*, 4112.

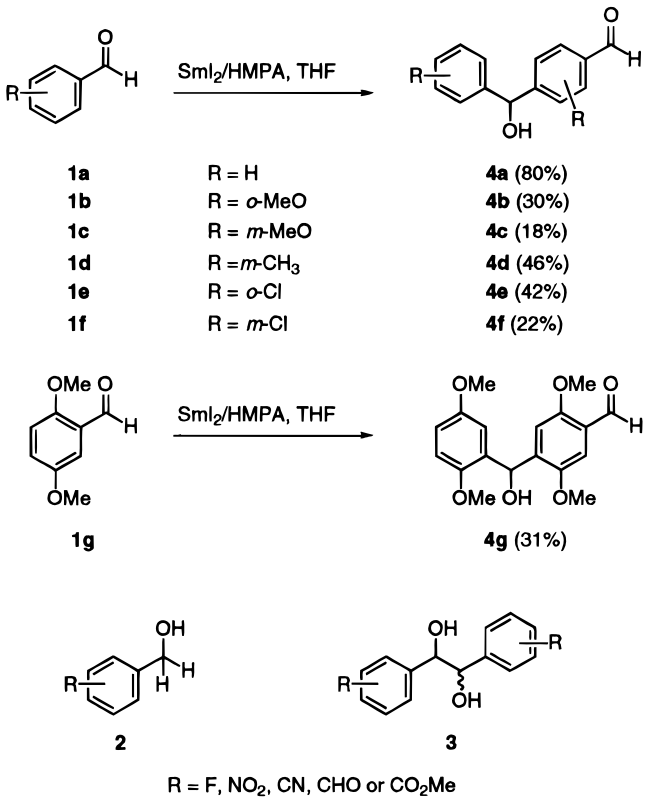
(7) (a) Namy, J. L.; Souppe, J.; Kagan, H. B. *Tetrahedron Lett.* **1983**, *24*, 765. (b) $SmCl_3$-catalyzed electrolyses of aromatic aldehydes and ketones in DMF or NMP also give pinacols. Leonard, E.; Dunbach, E.; Perichon, J. *J. Chem. Soc., Chem. Commun.* **1989**, 276.

(8) (a) Okaue, Y.; Isobe, T. *Mem. Fac. Sci. Kyushu Univ. Ser. C* **1987**, *16*, 25. The reaction of benzaldehyde with C_2H_5SmI also yields benzyl alcohol, hydrobenzoin, benzoin, and benzyl benzoate in a ratio of 10: 1:18:8. See: (b) Yokoo, K.; Fujiwara, Y.; Fukagawa, T.; Taniguchi, H. *Polyhedron* **1983**, *2*, 1101.

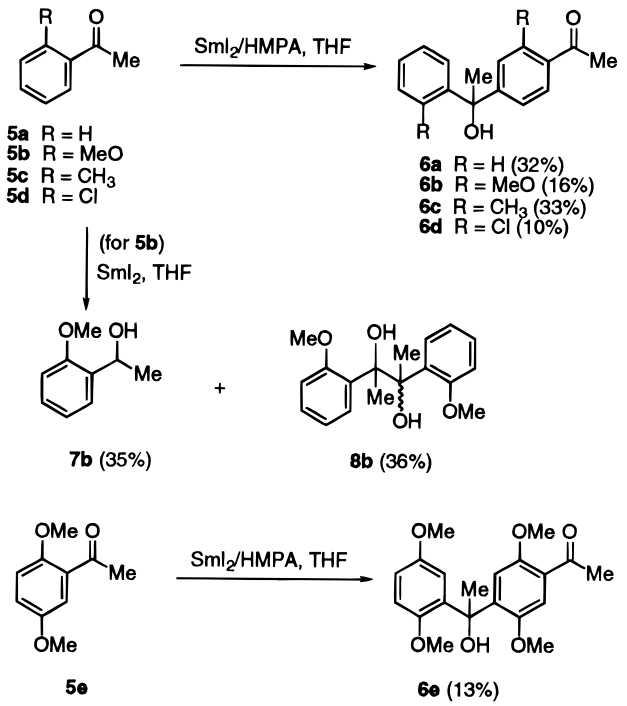
(9) (a) Shiue, J. -S.; Lin, C.-C.; Fang, J.-M. *Tetrahedron Lett.* **1993**, *34*, 335. Application to indole and thiophene systems, see: (b) Shiue, J.-S.; Fang, J.-M. *J. Chem. Soc., Chem. Commun.* **1993**, 1277. (c) Yang, S.-M.; Fang, J.-M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2669.

S0022-3263(97)00249-1 CCC: $14.00

Scheme 1



Scheme 2



did not occur in the cases of benzaldehydes bearing electron-withdrawing substituents F, NO_2, CN, CHO, or CO_2Me.

In this paper, we report our further studies of this novel type of phenyl−carbonyl coupling reactions, including the dimerizations of several acetophenones and the cross-couplings between two different aromatic carbonyls. In order to gain insight into the reaction mechanism, we also examined intra- and intermolecular trappings of the samarium intermediates.

Results and Discussion

By mediation of SmI_2/HMPA, acetophenone, its *ortho*-substituted analogs **5b**−**d**, and 2,5-dimethoxyacetophenone underwent the phenyl−carbonyl couplings in THF to give the dimers **6a**−**e** in 10−33% yields (Scheme 2). The starting acetophenones were recovered in large amounts (42−75%). In the absence of HMPA, 2-methoxyacetophenone was reduced by SmI_2 to give the benzyl alcohol **7b** (35%) and the pinacol **8b** (36%, diastereomeric ratio 1.2:1).

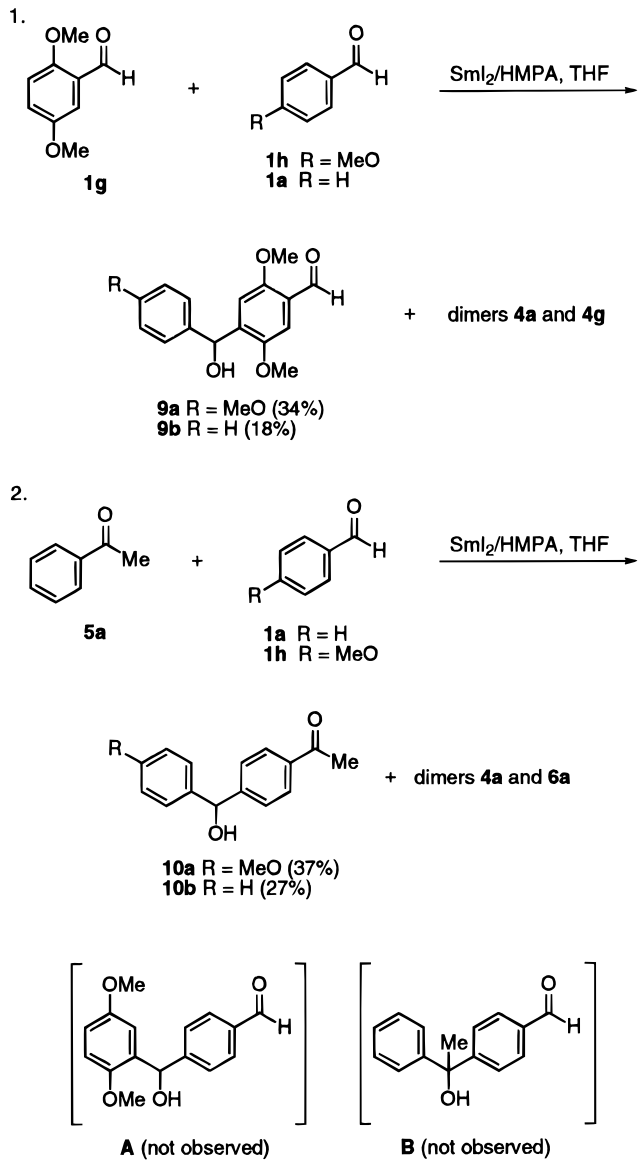
Phenyl−Carbonyl Cross-Coupling. The phenyl−carbonyl cross-couplings between two different aromatic carbonyl compounds were carried out in a substrate-selective manner (Scheme 3). A 1:1.5 mixture of 2,5-dimethoxybenzaldehyde (**1g**) and 4-methoxybenzaldehyde (**1h**) was treated with SmI_2/HMPA to give the cross-coupling product **9a** (34%), along with a small amount (3%) of dimer **4g**.

By a similar procedure, the cross-coupling product **9b** (18%) and the dimer **4a** (13%) were obtained from a 1:1 mixture of **1g** and benzaldehyde. In this instance, 2,5-dimethoxybenzaldehyde functioned as the donor substrate, whereas benzaldehyde functioned as the acceptor substrate. The other possible cross-coupling product **A**, having linkage at the *para*-carbon of benzaldehyde and the carbonyl center of **1g**, was not observed. The reaction of acetophenone with *p*-methoxybenzaldehyde (1:1.5) yielded a cross-coupling product **10a** (37%) and a dimer **6a** (11%), whereas the reaction of acetophenone with benzaldehyde (1.5:1) gave a cross-coupling product **10b** (27%) and two dimers **4a** (15%) and **6a** (10%). The putative cross-coupling product **B** was not found.

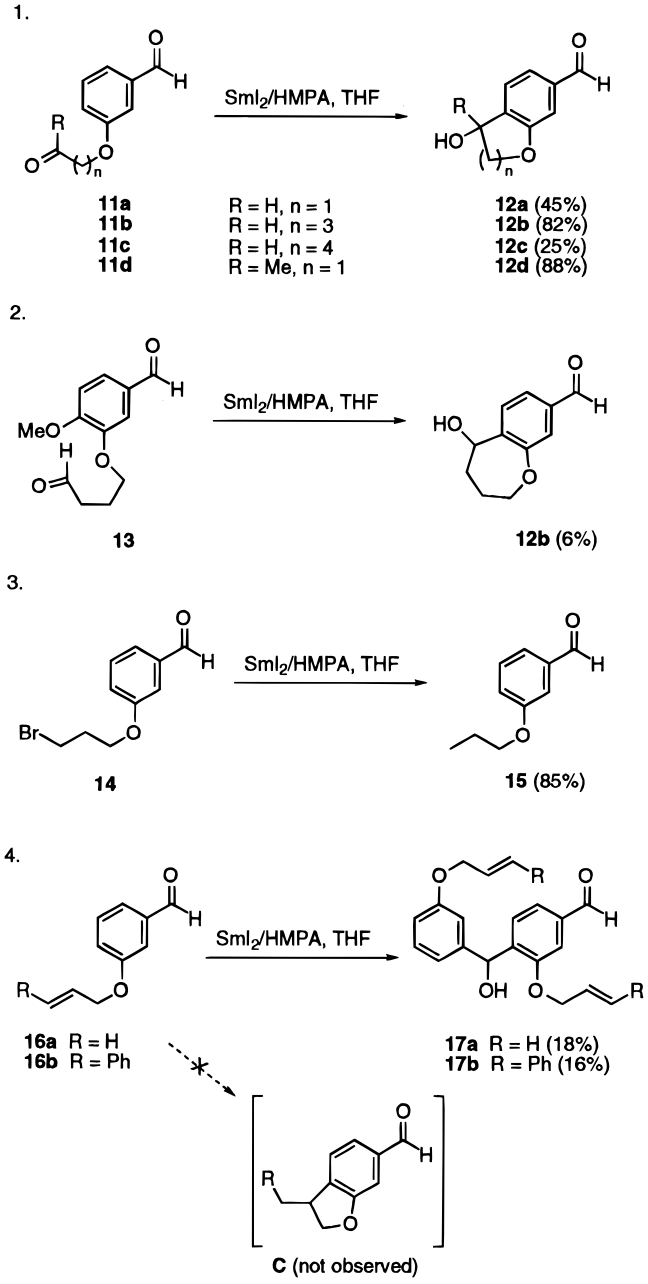
Intramolecular phenyl−carbonyl couplings of benzaldehydes **11a**−**d** bearing tethered carbonyl chains were achieved (Scheme 4). Compounds **11a**−**c** were prepared in reasonable yields by alkylations of 3-hydroxybenzaldehyde with allyl bromide, 5-bromo-1-pentene, or 6-iodo-1-hexene, followed by ozonolysis of the double bonds. Compound **11d** was prepared by a four-step sequence: (i) alkylation of 3-hydroxybenzaldehyde with chloroacetonitrile, (ii) protection of the aldehyde as the dimethyl acetal, (iii) addition of CH_3MgCl to the cyano group, and (iv) hydrolysis of the dimethyl acetal. Treatment of **11a**−**d** with SmI_2/HMPA in THF afforded benzofuran **12a** (45%), benzoxepin **12b** (82%), benzoxocin **12c** (25%), and benzofuran **12d** (88%). Benzoxepin **12b** was also obtained in a low yield (6%) from the SmI_2/HMPA-promoted intramolecular coupling reaction of 4-methoxy-3-(4-oxobutoxy)benzaldehyde (**13**). Attempts to effect the intramolecular phenyl−halide or phenyl−olefin couplings failed. Instead, 3-(3-bromopropoxy)benzaldehyde (**14**) was dehalogenated by SmI_2/HMPA to give 3-propoxybenzaldehyde (**15**). On treatment with SmI_2/HMPA, 3-alloxybenzaldehyde (**16a**) and 3-cinnamoxybenzaldehyde (**16b**) underwent intermolecular phenyl−carbonyl couplings to give the dimers **17a** (18%) and **17b** (16%). No intramolecular cyclization product **C** was formed.

Reaction Mechanism. A possible mechanism for the formation of dimers **4a**−**g** and **6a**−**d** is proposed (Scheme 5). One-electron transfer from SmI_2 to benzaldehyde would generate the ketyl radical anion **D**, which might also exist as an intact organosamarium species or as the resonance forms **E** and **F**.[10] HMPA molecules are pro-

Scheme 3



Scheme 4



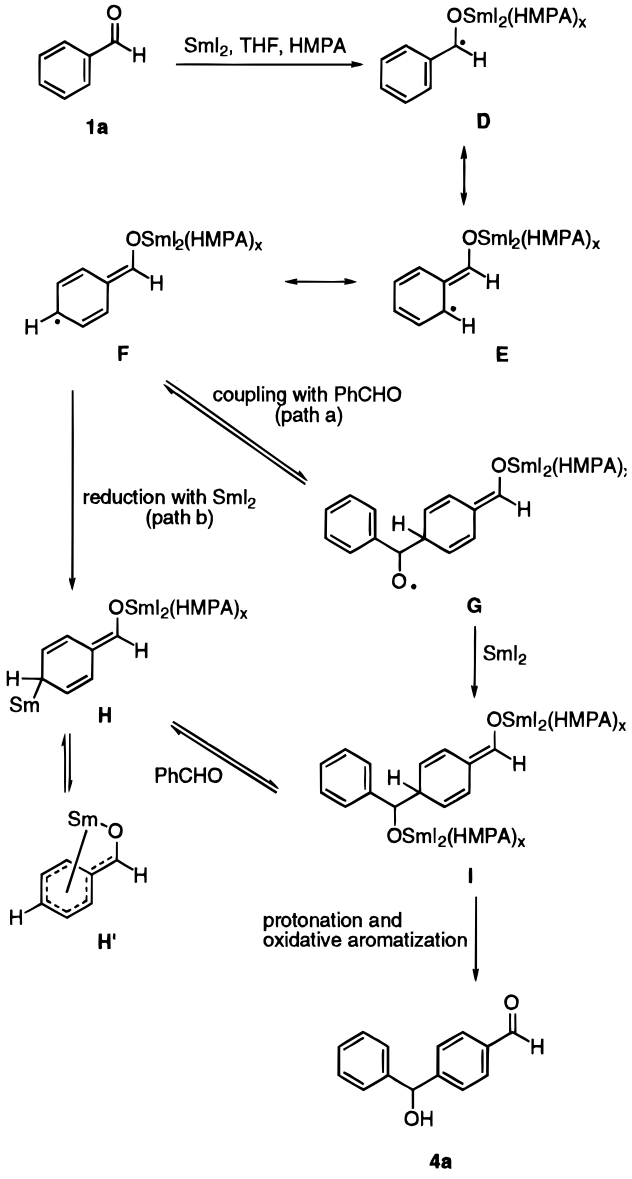
posed to coordinate with samarium ion via their oxygen atoms.[10] Because the ketyl- and *ortho*-carbons are hindered by the HMPA ligands, coupling at the *para*-carbon with a second molecule of benzaldehyde would be favored, forming an oxy radical **G** from **F** (path a). Further electron transfer from SmI_2 to **G** would give the intermediate **I**, and the subsequent protonation and oxidative aromatization, upon exposure to the air, would furnish the dimer **4a**. Alternatively (path b), the radical **F** could be reduced by SmI_2 to form an organosamarium **H** or its resonance species **H′**. The nucleophilic addition to benzaldehyde would give the intermediate **I** for the formation of **4a**. As intramolecular phenyl−olefin couplings did not occur in the reactions of alkenoxybenzaldehydes **16a**,**b**, the radical process (path a) is less likely.[11]

The transformations between **F** and **G** as well as that between **H** and **I** might be reversible processes. The remaining enolates **F** or **H** could be reoxidized to the starting substrate (benzaldehyde). As a consequence, dimerization of benzaldehydes or acetophenones was incomplete, and significant amounts of the starting materials were recovered. The substrate-selective formation of **9b** and **10b**, but not **A** or **B**, might reflect the thermodynamic preference of products or the inherent reversible nature of the phenyl−carbonyl cross couplings. Because an aromatic aldehyde group is more reactive toward SmI_2 than an aliphatic carbonyl group, intramolecular phenyl−carbonyl couplings of **11b** and **11d** could be achieved, giving **12b** and **12d** in high yields. The reaction of **11a**, giving **12a** in an inferior yield, is presumably complicated by a reduction of the α-phenoxyacetaldehyde moiety (breaking C−O bond).[1] Interestingly, (bromoalkoxy)benzaldehyde **14** underwent dehalogenation upon treatment with SmI_2/HMPA, giving the corresponding alkoxybenzaldehyde **15**, with no effect

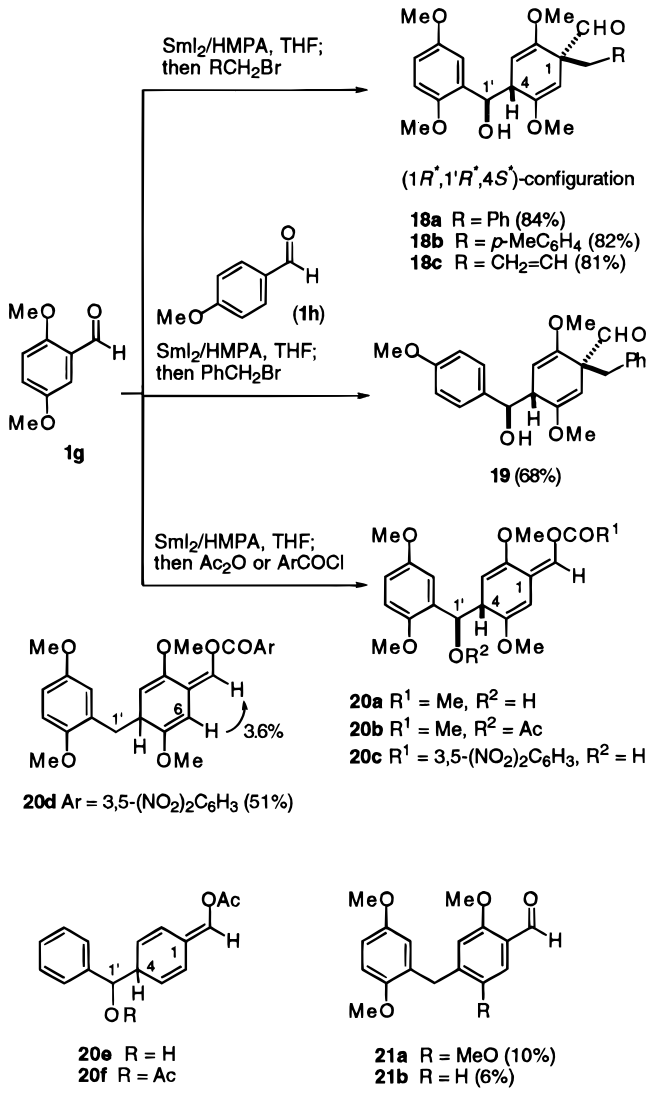
(10) (a) Donoghue, J. T.; Fernandez, E.; McMillan, J. A.; Peter, D. A. *J. Inorg. Nucl. Chem.* **1969**, *31*, 1431. Reaction of benzophenone with SmI_2/HMPA in THF, followed by protonation with 2,6-di-*tert*-butyl-4-methylphenol, gives an HMPA-ligated samarium(III) enolate of 2,5-cyclohexadienyl phenyl ketone; see: (b) Hou, Z.; Yoshimura, T.; Wakatsuki, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11169.

(11) Ketyl−olefin cyclization and the subsequent alkylation may involve either radical or organosamarium intermediates; see: (a) Kawatsura, M. Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 6900. (b) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1995**, *60*, 872.

Scheme 5



Scheme 6



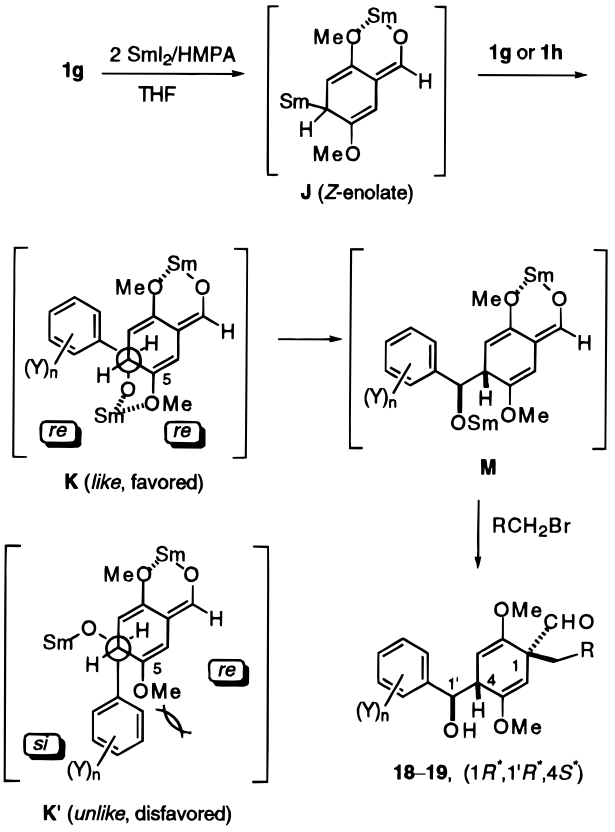
on the carbonyl group. This result might be attributed to formation of an intermediate samarium enolate, similar to **F** or **H**, to protect the aldehyde group from reduction.

Sequential Coupling−Alkylation. The proposed Sm(III)−enolate intermediates,[12] such as **I**, were successfully trapped by alkylating or acylating agents (Scheme 6). Thus, 2,5-dimethoxybenzaldehyde treated with SmI_2/HMPA in THF, followed by alkylation with benzyl bromide, gave a single product **18a** in 84% yield. The structure of **18a** was unambiguously assigned to have the (1*R**,1′*R**,4*S**) configuration by X-ray analysis. The formyl proton appeared at an unusually high field δ 8.44. The ORTEP drawing of **18a** also showed that the formyl proton was oriented above the cyclohexadiene ring, in the shielding region of the enol ether [MeO−C(2)=C(3)]. Similarly, trapping with 4-methylbenzyl bromide and allyl bromide occurred in a regio- and stereospecific manner to afford (cyclohexadiene)carboxaldehydes **18b** (82%) and **18c** (81%). A cross-coupling between 2,5-dimethoxybenzaldehyde (**1g**) and 4-methoxybenzaldehyde (**1h**), followed by alkylation with benzyl bromide, gave exclusively **19** (68%). The formyl protons of **18b**, **18c**, and **19** also occurred at relatively high fields of δ 8.41, 8.32, and 8.33, respectively. Although self-coupling of **1g** and cross-coupling of **1g** with **1h** afforded dimers **4g** (31%) and **9a** (34%) in lower yields, trapping the intermediates with alkylating agents drives the coupling reaction through an irreversible last step, thus giving **18a**−**c** and **19** in much higher yields. The reaction using 2,5-dimethoxybenzyl bromide as the alkylating agent proceeded differently. On treating a THF solution of **1g** and 2,5-dimethoxybenzyl bromide with SmI_2/HMPA, the reaction gave the dimer **4g** (16%) and a product **21a** (10%) by direct alkylation at the *para*-carbon of **1g**. Treatment of 2-methoxybenzaldehyde (**1b**) and 2,5-dimethoxybenzyl bromide with SmI_2/HMPA also afforded a small amount (6%) of *para*-alkylation product **21b** and the dimer **4b** (24%).

The self-coupling of 2,5-dimethoxybenzaldehyde, followed by *O*-acylation with acetic anhydride, gave the enol

(12) The reactions of samarium enolates are known: (a) Vougioukas, A. E.; Kagan, H. B. *Tetrahedron Lett.* **1987**, *28*, 5513. (b) Zhang, Y.; Liu, T.; Lin, R. *Synth. Commun.* **1988**, *18*, 2003. (c) Molander, G. A.; Etter, J. B.; Harring, L. S.; Thorel, P.-J. *J. Am. Chem. Soc.* **1991**, *113*, 8036. (d) Van de Weghe, P.; Collin, J. *Tetrahedron Lett.* **1993**, *34*, 3881. (e) Aoyagi, Y.; Yoshimura, M.; Tsuda, M.; Tsuchibuchi, T.; Kawamata, S.; Tateno, H.; Asano, K.; Nakamura, H.; Obokata, M.; Ohta, A.; Kodama, Y. *J. Chem. Soc., Perkin Trans. 1* **1995**, 689. A recent report of samarium dienolate: (f) Yang, S.-M.; Fang, J.-M. *Tetrahedron Lett.*, in press.

Scheme 7



acetate **20a** and the diacetate **20b** in 52% and 27% crude yields. These acetates were unstable and decomposed upon silica gel chromatography. The similar reaction using the acylating agent 3,5-dinitrobenzoyl chloride at 0 °C gave an enol carboxylate **20c** (45% crude yield) and a 1′-deoxy compound **20d** (3%). If 2,5-dimethoxybenzaldehyde was treated with SmI_2/HMPA, followed by reaction with 3,5-dinitrobenzoyl chloride at 30 °C for a prolonged period (4 h), only the deoxy compound **20d** was obtained in 51% yield. Compound **20c** decomposed on standing in $CDCl_3$, and its structure was inferred from the ^1H NMR analysis. The signals at δ 3.63 (H-4), 4.69 (H-1′), 5.04 (H-3), and 5.81 (H-6) were characteristic. The exact mechanism for formation of **20d** is unclear. An NOE study, *i.e.*, irradiation of H-6 (δ 5.50), caused a 3.6% enhancement of the vinyl proton (δ 7.57) geminal to the carboxyl group, indicating that the *exo* double bond of **20d** had the (*Z*)-configuration. The reaction of benzaldehyde with SmI_2/HMPA, followed by acylation with acetic anhydride, also produced unstable enol acetates **20e** and **20f**.

The resulting stereochemistry for the formation of **18** and **19** is interpreted as follows (Scheme 7). Reduction of 2,5-dimethoxybenzaldehyde with 2 equiv of SmI_2 would give the samarium enolate **J**, presumably existing as the (*Z*)-form as implied from the configuration of **20d**. The preference of (*Z*)-enolate might account for the chelation effect of the adjacent methoxy group. The phenyl−carbonyl coupling via a *like* transition state **K**, giving **M**, would be favored as it would be stabilized by chelation with the methoxy group at C-5. The *unlike* transition state **K′** is disfavored due to the repulsion between the C-5 methoxy group and the other phenyl ring. Alkylation of **M** should occur at the less hindered face to afford the observed products **18**−**19**.

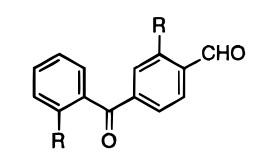
Functional Group Elaboration. The only previous preparation of **4a** is from the addition of PhMgBr to terephthaldehyde bound to a polymer.[13] Our present SmI_2/HMPA-promoted phenyl−carbonyl coupling reaction provides a novel method to obtain various dimers of benzaldehydes and acetophenones, such as **4a**−**g** and **6a**−**d**, though the yields are usually modest due to the reversible nature of these reactions. High yields were attainable in the intramolecular phenyl−carbonyl coupling reactions, as shown in the formations of tetrahydrobenzoxepin **12b** and dihydrobenzofuran **12d**. The dimers **4a** and **4b** were oxidized with PDC to give diaryl ketones **22a** and **22b** in 80% and 85% yields, respectively.

Using our present SmI_2/HMPA procedure, uncommon 1,4-dialkyl-2,5-cyclohexadiene-1-carboxaldehydes **18a**−**d** and **19** were obtained. This dearomatization method for aromatic carbonyls is unprecedented, though partial reduction of substituted benzenes (Birch reduction)[14] is well documented. In order to expand the potential of this methodology, the chemical properties of **18** were investigated. On treatment with $SOCl_2$ in pyridine, **18a** or **18b** underwent dehydration to give an unstable alkylidenecyclohexadiene **23a** or **23b**, which readily decarbonylated and rearomatized to yield a 1,4-dibenzylbenzene **24a** (71%) or **24b** (67%). The rearomatization of **24** is most likely the driving force for the deformylation in **23**. Following a similar pathway, the acetate **25b** derived from **18c** also reacted with DBU to furnish a small amount (5%) of 1-allyl-4-benzylbenzene **26**. The reaction of **18a** with MnO_2 in CH_2Cl_2 (21 °C, 5 h) did not give the desired phenone; instead, 2,5-dimethoxybenzaldehyde (**1g**, 30%) and 1-benzyl-2,5-dimethoxybenzene (**27**, 23%) were obtained along with a recovery of **18a** (47%). The reaction of **18a** with PDC afforded **1g** (62%) and **27** (29%) as well as diaryl ketones **28** (5%) and **29** (14%). Treatment of acetate **25a** with *t*-BuOK in THF (25 °C, 18 h) afforded **1g** (18%) and **27** (12%). Reduction of **18a** with $LiAlH_4$ gave the corresponding alcohol **30** (78%), which might be converted to the *p*-quinodimethine **31** on treatment with $SOCl_2$−pyridine (0 °C, 1 h). Several diagnostic proton resonances for the quinodimethine moiety were found at δ 4.32, 4.89, 5.48, and 5.81 in the ^1H NMR spectrum; however, the reaction was complicated by other intractable products and **31** was too unstable to be verified.

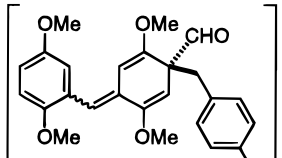
Summary

We have demonstrated the phenyl−carbonyl self- and cross-coupling reactions of various benzaldehydes and acetophenones. The method is beneficially conducted intramolecularly for the preparation of fused benzocycles. Sequential coupling−alkylations are achieved to afford high yields of uncommon 1,4-dialkyl-2,5-cyclohexadiene-1-carboxaldehydes. This method can be applied to heteroaromatic systems such as indolecarboxaldehydes[9b] and thiophenecarboxaldehydes,[9c] of which aryl−carbonyl coupling products are potentially useful in the synthesis of drugs or natural products.

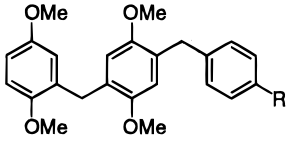
(13) Leznoff, C. C.; Wong, J. Y. *Can. J. Chem.* **1973**, *51*, 3756.
(14) (a) Birch, A. J.; Subba Rao, G. *Adv. Org. Chem.* **1972**, *8*, 1. (b) Kaiser, E. M. *Synthesis* **1972**, 91. (c) Harvey, R. G. *Synthesis* **1980**, 161. (d) Schultz, A. G.; Macielag, M. *J. Org. Chem.* **1986**, *51*, 4983. (e) Hook, J. M.; Mander, L. N. *Nat. Prod. Rep.* **1986**, *3*, 35. (f) Rabideau, P. W. *Tetrahedron* **1989**, *45*, 1599.



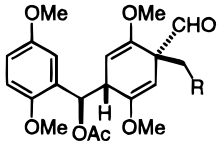
22a R = H (80%)
22b R = MeO (85%)



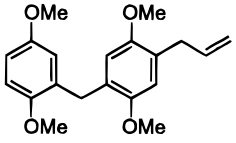
23a R = H
23b R = CH_3



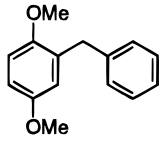
24a R = H
24b R = CH_3



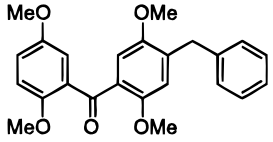
25a R = Ph
25b R = $CH{=}CH_2$



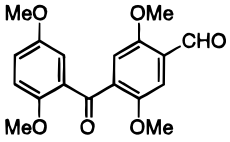
26



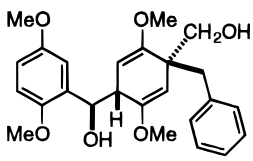
27



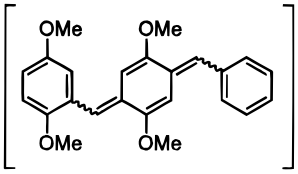
28



29



30



31

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra were recorded at 200, 300, or 400 MHz; ^{13}C NMR spectra were recorded at 50, 75, or 100 MHz. Tetramethylsilane (δ = 0 ppm) was used as internal standard in ^{1}H NMR spectra. Mass spectra were recorded at an ionizing voltage of 70 or 20 eV. Merck silica gel 60F sheets were used for analytical thin-layer chromatography. Column chromatography was performed on SiO_2 (70−230 mesh); gradients of EtOAc and *n*-hexane were used as eluents. High-pressure liquid chromatography was carried out on a liquid chromatograph equipped with UV (254 nm) and refractive index detectors.

Typical Procedure for Phenyl−Carbonyl Coupling Reactions. Samarium metal (0.31 g, 2 mmol) and 1,2-diiodoethane (0.38 g, 1.35 mmol) in anhydrous THF (20 mL) were stirred at room temperature (27 °C) under an atmosphere of argon for 1 h to give a dark blue solution. HMPA (1.4 mL, 8 mmol) was added, after 5 min the resulting dark blue solution was cooled to 0 °C in an ice bath, and benzaldehyde (106 mg, 1 mmol) in THF (2 mL) was added dropwise over a period of 2 min. The mixture was stirred at 0 °C for 1 h and warmed to room temperature over a period of 0.5−2 h. The serum cap was removed, and the reaction mixture was exposed to air to furnish the final steps of protonation and oxidative aromatization. The mixture was filtered, the filtrate was concentrated under reduced pressure, and the residue was chromatographed on a silica gel column by elution with EtOAc/hexane (2:8) to give 4-(α-hydroxybenzyl)benzaldehyde[13] (**4a**, 81 mg, 80%): oil; TLC (EtOAc/hexane (15:85)) R_f = 0.15; IR (neat) 3425, 1689 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.45 (1 H, d, J = 1.9 Hz, OH), 5.90 (1 H, d, J = 1.9 Hz), 7.26−7.37 (5 H, m), 7.57 (2 H, d, J = 8.2 Hz), 7.85 (2 H, d, J = 8.2 Hz), 9.98 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 75.9, 126.7, 126.9 (2 C), 128.1 (2 C), 128.8 (2 C), 130.0 (2 C), 135.6, 143.0, 150.4, 191.9 (d); MS *m*/*z* (rel intensity) 212 (30, M$^+$), 105 (100).

Typical Procedure for Sequential Coupling−Alkylation. The SmI_2 (2 mmol) solution in HMPA (1.4 mL) and THF (20 mL) was prepared by a procedure described for **4a**. A solution of 2,5-dimethoxybenzaldehyde (1 mmol) in THF (1 mL) was added dropwise over a period of 1 min at 0 °C. The light violet solution was stirred for 10 min, after which a solution of benzyl bromide (0.25 mL, 2 mmol) in THF (1 mL) was added. The light green solution was stirred at 0 °C for 30 min and at room temperature for 48 h. Et_2O (20 mL) was then added, the precipitates were filtered off, and the filtrate was concentrated under reduced pressure. The residue was chromatographed on a silica gel column by elution with EtOAc/hexane (3:7) to give 1-benzyl-2,5-dimethoxy-4-(2,5-dimethoxy-α-hydroxybenzyl)-2,5-cyclohexadiene-1-carboxaldehyde (**18a**, 180 mg, 84%). The (1*R**,1′*R**,4*S**) configuration was assigned by X-ray diffraction analysis: solid; mp 118−119 °C; TLC (EtOAc/hexane (3:7)) R_f = 0.26; IR (neat) 3500, 1716, 1643 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.76 (1 H, d, J = 13.5 Hz), 3.15 (1 H, dd, J = 5.4, 4 Hz), 3.21 (1 H, d, J = 13.5 Hz), 3.46 (3 H, s), 3.53 (3 H, s), 3.70 (3 H, s), 3.72 (3 H, s), 4.11 (1 H, s), 4.62 (1 H, d, J = 4 Hz), 5.10 (1 H, t, J = 5.2 Hz), 6.72−6.74 (3 H, m), 6.98−7.03 (2 H, m), 7.11−7.17 (3 H, m), 8.44 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 37.1, 46.6, 54.2, 54.6, 55.6, 55.7, 58.7, 74.1, 93.0, 95.7, 111.3, 113.0, 114.4, 125.9, 127.5 (2 C), 129.4, 130.1 (2 C), 137.3, 151.1, 151.5, 153.4, 157.6, 198.8; MS *m*/*z* (rel intensity) 424 (1, M$^+$), 167 (100); HRMS calcd for $C_{25}H_{28}O_6$ 424.1886, found 424.1876.

Typical Procedure for Sequential Coupling−Acylation. By a procedure similar to that for **18a**, a solution of 2,5-dimethoxybenzaldehyde (1 mmol) was treated with SmI_2 (2 mmol) in HMPA (8 mmol) and THF (20 mL) at 0 °C for 10 min, followed by reaction with a solution of 3,5-dinitrobenzoyl chloride (460 mg, 2 mmol) in THF (1 mL) at 0 °C for 30 min, to give [2,5-dimethoxy-4-(2,5-dimethoxy-α-hydroxybenzyl)-2,5-cyclohexadienylidene]methyl 3,5-dinitrobenzoate (**20c**, 110 mg, 45%) and [2,5-dimethoxy-4-(2,5-dimethoxybenzyl)-2,5-cyclohexadienylidene]methyl 3,5-dinitrobenzoate (**20d**, 7 mg, 3%) after chromatography (silica gel, EtOAc/hexane (2:3)). If the reaction mixture was stirred at room temperature (30 °C) for 4 h, after addition of 3,5-dinitrobenzoyl chloride, only **20d** was obtained in 51% yield. Compound **20c** decomposed on standing in $CDCl_3$.

20c: yellow oil; ^{1}H NMR ($CDCl_3$) δ 3.52 (3 H, s), 3.60−3.65 (1 H, m), 3.71 (3 H, s), 3.72 (6 H, s), 4.69 (1 H, d, J = 4.6 Hz), 5.04 (1 H, d, J = 6.0 Hz), 5.81 (1H, s), 6.73 (2 H, br s), 6.84 (1 H, d, J = 2.1 Hz), 7.58 (1H, d, J = 1.7 Hz), 9.20−9.24 (3 H, m); ^{13}C NMR ($CDCl_3$) δ 47.3, 54.5, 54.9, 55.7, 55.8, 73.8, 91.3, 97.3, 111.4, 113.3, 113.6, 118.1, 122.6, 127.2, 129.5, 130.1, 133.1, 148.7, 149.7, 150.9, 153.5, 159.2.

20d: yellow solid; mp 167−168 °C; TLC (EtOAc/hexane (1:3)) R_f = 0.23; IR (KBr) 2952, 1741, 1625, 1548, 1348 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.98 (1 H, d, J = 10.5 Hz), 2.65 (1H, dd, J = 10.5, 4.4 Hz), 3.18 (3 H, s), 3.28 (1 H, br s), 3.55 (3 H, s), 3.68 (3 H, s), 3.79 (3 H, s), 5.50 (1 H, d, J = 1.2 Hz, H-6), 5.65 (1 H, d, J = 3.6 Hz, H-3), 6.71 (2 H, d, J = 1.2 Hz), 6.92 (1 H, d, J = 3 Hz), 7.57 (1 H, s), 9.19−9.23 (3 H, m); ^{13}C NMR ($CDCl_3$) δ 36.2, 46.7, 49.8, 55.0, 55.9 (2 C), 80.0, 91.0, 106.7, 110.4, 112.4, 112.9, 122.5, 125.6, 127.5, 128.4, 129.5 (2 C), 133.4, 148.7 (2 C), 150.6, 153.3, 159.4, 161.6; MS *m*/*z* (rel intensity) 512 (1), 167 (100); HRMS calcd for $C_{25}H_{24}N_2O_{10}$ 512.1431, found 512.1425.

4-Formylbenzophenone (22a). Under an atmosphere of argon, compound **4a** (220 mg, 1 mmol) in CH_2Cl_2 (15 mL) was treated with PDC (1 g, 2.4 mmol) in the presence of molecular sieves (4 Å, 3 g) for 3 h. The mixture was filtered, the filtrate was concentrated, and the residue was purified by column chromatography (silica gel, EtOAc/hexane (3:7)) to give **22a**

(190 mg, 80%): solid; mp 54−55 °C; TLC (EtOAc/hexane (2:8)) R_f = 0.32; IR (KBr) 1695, 1654 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43−7.60 (3 H, m), 7.75 (2 H, d, J = 7 Hz), 7.86 (2 H, d, J = 8 Hz), 7.95 (2 H, d, J = 8 Hz), 10.07 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 128.4 (2 C), 129.4 (2 C), 130.0 (2 C), 130.2 (2 C), 133.0, 136.6, 138.4, 142.4, 191.5, 195.7; MS m/z (rel intensity) 210 (51, M^+), 105 (100); HRMS calcd for $C_{14}H_{10}O_2$ 210.0681, found 210.0681.

1,4-Dimethoxy-2-(2,5-dimethoxybenzyl)-5-(4-methylbenzyl)benzene (24b). Under an atmosphere of argon, a solution of **18b** (250 mg, 0.57 mmol) in CH_2Cl_2 (15 mL) was treated with pyridine (0.08 mL, 1 mmol) and $SOCl_2$ (0.05 mL, 0.7 mmol) at 0 °C for 2 h. The yellow solution was poured into water (10 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined organic phase was dried (Na_2SO_4), concentrated, and chromatographed on a silica gel column by elution with EtOAc/hexane (1:9) to give **23b**. Compound **23b** was unstable and yielded to **24b** (150 mg, 67%) on standing at room temperature for 30 min.

23b: ^1H NMR ($CDCl_3$) δ 2.56 (3 H, s), 2.63 (1 H, d, J = 13.6 Hz), 3.10 (1 H, d, J = 13.6 Hz), 3.45 (3 H, s), 3.64 (3 H, s), 3.67 (3 H, s), 3.72 (3 H, s), 3.97 (1 H, s), 5.04 (1 H, d, J = 3.9 Hz), 5.88 (1 H, d, J = 3.9 Hz), 6.64−6.97 (7 H, m), 7.87 (1 H, s).

24b: solid; mp 99−100 °C; TLC (EtOAc/hexane (1:4)) R_f = 0.81; IR (KBr) 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30 (3 H, s), 3.67 (3 H, s), 3.69 (6 H, s), 3.79 (3 H, s), 3.89 (4 H, s), 6.61−6.80 (5 H, m), 7.08 (4 H, br s); ^{13}C NMR ($CDCl_3$) δ 21.0, 29.8, 35.3, 55.5, 56.0, 56.1, 56.2, 110.8, 111.0, 113.4, 113.8, 116.7, 127.2, 128.1, 128.7 (2 C), 128.9 (2 C), 130.7, 135.1, 138.0, 151.2, 151.4, 151.8, 153.4; MS m/z (rel intensity) 392 (100, M^+); HRMS calcd for $C_{25}H_{28}O_4$ 392.1988, found 392.1985.

1-Allyl-2,5-dimethoxy-4-(α-acetoxy-2,5-dimethoxybenzyl)-2,5-cyclohexadiene-1-carboxaldehyde (25b) and 5-Allyl-1,4-dimethoxy-2-(2,5-dimethoxybenzyl)benzene (26). Compound **18c** (187 mg, 0.5 mmol) was treated with Ac_2O (1 mL, 10 mmol) in Et_3N (5 mL) at room temperature for 23 h to give the corresponding acetate **25b** (168 mg, 80%). This sample was dissolved in THF (15 mL) and treated with DBU (0.14 mL, 0.9 mmol) at reflux for 19 h to give **26** (7 mg, 5%) and other intractable compounds.

25b: oil; TLC (EtOAc/hexane (25:75)) R_f = 0.27; IR (neat) 1742, 1722 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.09 (3 H, s), 2.15 (1 H, dd, J = 8, 14 Hz), 2.55 (1 H, dd, J = 8, 14 Hz), 3.49 (3 H, s), 3.51 (3 H, s), 3.58 (1 H, dd, J = 4, 4 Hz), 3.68 (3 H, s), 3.70 (3 H, s), 3.93 (1 H, s), 4.84 (1 H, d, J = 4 Hz), 4.90−4.99 (2 H, m), 5.51 (1 H, m), 6.51 (1 H, d, J = 4 Hz), 6.68−6.80 (3 H, m), 7.90 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 21.2, 35.9, 44.5, 54.5, 54.8, 55.8, 56.0, 57.1, 71.4, 93.0, 94.6, 111.1, 112.7, 115.5, 117.2, 126.8, 133.9, 151.1, 152.8, 153.5, 156.1, 169.6, 199.0; MS m/z (rel intensity) 416 (2, M^+), 167 (100); HRMS calcd for $C_{23}H_{28}O_7$ 416.1835, found 416.1827.

26: oil; TLC (EtOAc/hexane (15:85)) R_f = 0.40; IR (neat) 2949, 1501, 1217, 1047, 996, 915 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.33 (2 H, d, J = 6.5 Hz), 3.67 (3 H, s), 3.68 (3 H, s), 3.75 (3 H, s), 3.78 (3 H, s), 3.89 (2 H, s), 5.02 (1 H, dd, J = 4, 2 Hz), 5.07 (1 H, d, J = 2 Hz), 5.96 (1 H, m), 6.60−6.69 (4 H, m), 6.77 (1 H, d, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 29.8, 34.2, 55.6, 56.0, 56.2 (2 C), 110.9, 111.1, 113.0, 113.9, 115.3, 116.7, 126.9, 127.3, 130.8, 137.2, 151.1, 151.6, 151.8, 153.5; MS m/z (rel intensity) 328 (100, M^+); HRMS calcd for $C_{20}H_{24}O_4$ 328.1674, Found 328.1678.

1-Benzyl-2,5-dimethoxy-1-(hydroxymethyl)-4-(2,5-dimethoxy-α-hydroxybenzyl)-2,5-cyclohexadiene (30). A solution of aldehyde **18a** (300 mg, 0.75 mmol) in THF (10 mL) was treated with $LiAlH_4$ (100 mg, 2.8 mmol) at room temperature for 20 min. After addition of water, the mixture was extracted with Et_2O (10 mL × 2). The organic phase was dried (Na_2SO_4), concentrated, and chromatographed on a silica gel column by elution with EtOAc/hexane (3:7) to give the alcohol **30** (250 mg, 78%): solid; mp 145−146 °C; TLC (EtOAc/hexane (45:55)) R_f = 0.25; IR (KBr) 3382, 1652, 1492, 1223, 1043 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.44 (1 H, d, J = 12.9 Hz), 2.97 (1 H, d, J = 12.9 Hz), 3.00 (1 H, dd, J = 5.4, 4.2 Hz), 3.20 (1 H, d, J = 10.2 Hz), 3.43 (3 H, s), 3.46 (3 H, s), 3.71 (3 H, s), 3.73 (3 H, s), 3.74 (1 H, d, J = 10.2 Hz), 4.31 (1 H, s), 4.35 (1 H, d, J = 4.2 Hz), 4.37 (1 H, d, J = 5.4 Hz), 6.72−6.76 (2 H, m), 6.91 (1 H, d, J = 2.4 Hz), 6.92−7.18 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 41.3, 45.7, 48.5, 54.0, 54.2, 55.7, 56.0, 68.1, 73.2, 96.2, 98.4, 111.5, 112.8, 113.0, 125.8, 127.4 (2 C), 130.1 (2 C), 131.4, 137.5, 150.5, 153.7, 154.1, 156.0; MS m/z (rel intensity) 426 (1, M^+), 260 (100); HRMS calcd for $C_{25}H_{30}O_6$ 426.2042, found 426.2041.

Acknowledgment. We thank the National Science Council for financial support (Grant No. NSC84-2113-M002-010).

Supporting Information Available: NMR spectra of new compounds, ORTEP drawing of compound **18a**, and an additional experimental procedure and data (57 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS, see any current masthead page for ordering information.

JO9702498