Reaction Routes of Specific Decarbonylative α,α-Diarylation of 2-Methoxypropanoic Acid Analogues in P$_2$O$_5$−MsOH and the Related Reagents

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Recently, we found that 2-alkoxycarboxylic acids (**1**) undertook specific double electrophilic aromatic substitution reactions in P$_2$O$_5$−MsOH (phosphorus pentoxide−methanesulfonic acid mixture).[1,2] The corresponding 1,1-diarylalkanes (**5**) were obtained in good yields with evolution of carbon monoxide instead of formation of the suspected Friedel−Crafts acylation type adducts (Scheme 1).[2,3]

There have been some papers describing the decarbonylations of carboxylic esters and free acids[4,5] without sufficient mechanistic clarification.[6] As far as we know, only two cases have been reported concerning the decarbonylative arylation of carboxylic acids or their derivatives.[7,8] The reaction of acids **1** described above is the first example of decarbonylative α-arylation of *free carboxylic*
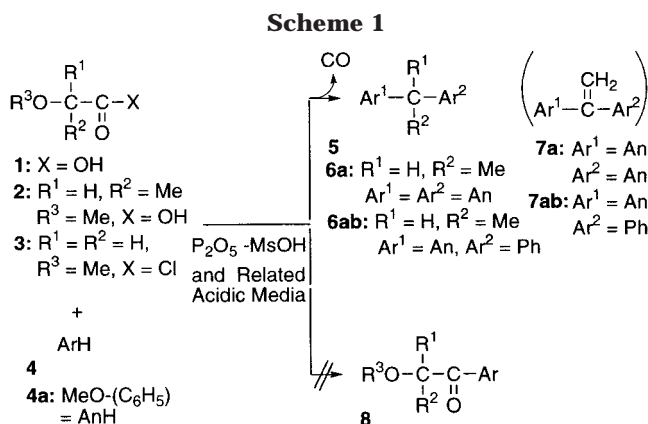
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(1) Eaton, P. E.; Carson, G. R.; Lee, J. T. *J. Org. Chem.* **1973**, *38*, 4071. The direct condensation of free carboxylic acids in P$_2$O$_5$−MsOH is explained to be induced by formation of reactive mixed acid anhydrides between phosphoric acid moieties and carboxyl groups. The anhydride is regarded as an acyl cation equivalent giving a phenone skeleton via a Friedel−Crafts acylation-type reaction.

(2) Yonezawa, N.; Tokita, Y.; Hino, T.; Nakamura, H.; Katakai, R. *J. Org. Chem.* **1996**, *61*, 3551.

(3) Yonezawa, N.; Hino, T.; Tokita, Y.; Matsuda, K.; Ikeda, T. *Tetrahedron* **1997**, *53*, 14287. The reaction of 2-methoxyacetic acid (**25**) with anisole in P$_2$O$_5$−MsOH gave the corresponding phenone (**29a**) in addition to diarylmethane (**28a**) (Scheme 3).

(4) March, J. *Advanced Organic Chemistry, Reaction, Mechanisms, and Structure*, 3rd ed.; Wiley-Interscience: New York, 1985; pp 341−342.

(5) (a) Liler, M. *Reaction Mechanisms in Sulfuric Acid*; Academic Press: New York, 1971; pp 254−259. (b) *Organic Reactions*; Bittman, R., Dauben, W. G., Fried, J., Kende, A. S., Marshall, J. A., McKusick, B. C., Meinwald, J., Trost, B. M., Eds.; John Wiley and Sons: New York, 1972, Vol. 19, pp 295−299.

(6) According to ref 4, some decarbonylation reactions were explained by S$_N$1 reaction through an acyl cation intermediate.

(7) DeHaan, F. P.; Djaputra, M.; Grinstaff, M. W.; Kaufman, C. R.; Keithly, J. C.; Kumar, A.; Kuwayama, M. K.; Macknet, K. D.; Na, J.; Patel, B. R.; Pinkerton, M. J.; Tidwell, J. H.; Villahermosa, R. M. *J. Org. Chem.* **1997**, *62*, 2694. Decarbonylative mono- and diarylations of methoxyacetyl chloride in the presence of Lewis acids were reported. Diarylmethane was explained to be formed from a benzyl chloride type intermediate, which was considered to be the primary product from benzene and methoxyacetyl chloride with decarbonylation.

(8) Palmer, M. H.; McVie, G. J. *J. Chem. Soc., C* **1967**, 343. Decarbonylative diarylation of phenoxyacetyl chloride with an excess amount of *p*-xylene in the presence of Lewis acids was reported. However, the yield of the 1,1-diarylated product (ArCH$_2$Ar) was very low (1%), and the phenone (PhOCH$_2$COAr) was predominantly obtained (65%).

Scheme 1

Table 1. Reactions of 2-Methoxypropanoic Acid (2) with Various Amounts of Anisole (4a) in P$_2$O$_5$−MsOH at Room Temperature for 24 h[a]

run[c]	anisole/acid **2** (mol/mol)	yield[b] (%)	
		6a	**7a**
1	2	40	44
2	5	43	13
3	10	52	18
4	20	66	tr[d]
5	40	85[e]	0
6[f]	10	0	78

[a] Reaction conditions: for 1 mmol of acid **2**, 4 mL of P$_2$O$_5$−MsOH and 40 mmol of anisole (**4a**) were used. [b] Yields were determined on the basis of ^{1}H NMR spectra. [c] Methanesulfonylated product (Ar-Ms) was also obtained except for run 1. [d] Many unidentified products were also obtained. [e] Reference 2. [f] Reaction was carried out at 80 °C for 5 h.

acids.[9] However, the mechanism, scope, and limitation of this reaction have not been fully understood yet. In this paper, the pathways of the decarbonylative α,α-diarylation of carboxylic acids **1** with and without oxidation are closely discussed.

Table 1 shows the results of the reactions of acid **2** with various amounts of anisole (**4a**) in P$_2$O$_5$−MsOH at room temperature for 24 h. The yield of 1,1-diarylethane (**6a**) increased with the amount of anisole, and that of 1,1-diarylethene (**7a**) was reduced in turn. When a 40-fold excess of anisole to acid **2** was used, alkane **6a** was solely obtained in an 85% yield and alkene **7a** was not observed (run 5). When the excess of anisole was reduced to 2−20 times, alkene **7a** was obtained as a byproduct (runs 1−4). The use of an equimolar amount of anisole gave alkene **7a** in the highest yield (44%, run 1). In particular, the reaction with a 10-fold excess of anisole at 80 °C yielded alkene **7a** without alkane **6a** (78%, run 6).

Table 2 shows the results of the reactions of acid **2** and acid chloride **3** with anisole in some acidic media under various conditions (Scheme 1). In P$_2$O$_5$−MsOH or polyphosphoric acid (PPA), acid **2** efficiently gave alkane **6a**

(9) In the previous papers (refs 2 and 3), the following features were found: (1) P$_2$O$_5$−MsOH and PPA effectively promote the reaction, (2) an alkoxy group or a hydroxy one on the α-carbon of the carboxylic acid is indispensable, (3) the reaction does not proceed when the free carboxylic acid structure is converted to ester one, (4) the relative reactivity and the selectivity are suspected to be primarily governed by the electronic property of the α-substituents on the carboxylic acids (**1**), and (5) the correlation between the structure of the arene substrates and their reactivity is almost comparable to that observed in conventional electrophilic aromatic substitution reactions.

Table 2. Reactions of 2-Methoxypropanoic Acid (2) and 2-Methoxypropanoyl Chloride (3) with Anisole (4a) in Some Acidic Media[a]

| | substrate (conditions) | | | | | |
| | **2** (rt, 24 h) yield[b] (%) | | **2** (60 °C, 3.5 h) yield[b] (%) | | **3** (rt, 24 h) yield[b] (%) | |
acidic medium	**6a**	**7a**	**6a**	**7a**	**6a**	**7a**
P_2O_5–MsOH	85[c]	0	78	3	41[d]	0
PPA	76[c]	0	67	14	61	0
MsOH	2	0	24	2	50	0
TFA	0	0	0	0	86	0

[a] Reaction conditions: for 1 mmol of substrate **2** or **3**, 4 mL of acidic media and 40 mmol of anisole (**4a**) were used. [b] Yields were determined on the basis of ^{1}H NMR spectra. [c] Reference 2. [d] Many unidentified products were also obtained.

in 85% and 76% yields at room temperature, respectively. The yield of the reaction in MsOH was very low (2%). No diarylated products were obtained by the reaction in TFA. At 60 °C, the reactions in P_2O_5–MsOH and in PPA gave alkane **6a** in yields almost the same as those at room temperature (78% and 67%). The yield in MsOH at 60 °C was higher than that at room temperature (24%). The reaction in TFA yielded neither alkane **6a** nor alkene **7a** even at 60 °C. When acid chloride **3** was used in place of acid **2** in the reaction with anisole in P_2O_5–MsOH at room temperature, the yield of alkane **6a** was ca. 40% lower than that of acid **2**. The reaction in TFA gave alkane **6a** in the highest yield among all runs (86%). The yield of the reaction of acid chloride **3** in MsOH at room temperature (50%) was approximately 2 times that of acid **2** at 60 °C (24%).

These reaction behaviors show that the decarbonylative α,α-diarylations of acid **2** and acid chloride **3** took place with strong reagent dependence. The combination of free carboxylic acid **2** and phosphoric (methanesulfonic) acid moiety in P_2O_5–MsOH or PPA, or that of acid chloride **3** and TFA, is assumed to have a suitable reactivity. Accordingly, mixed acid anhydride **9** is considered to be formed at the initial step in the reaction of acid **2** in P_2O_5–MsOH. After the formation of acid
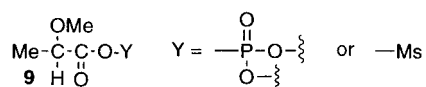
anhydride **9**, the following four cases are considered to be possible: (1) First arylation proceeds before replacement of the methoxy group. Two possible structures are proposed for the first case: (a) aryl α-methoxyethyl ketone (**10a**) by Friedel–Crafts acylation type reaction, and (b) α-arylethyl methyl ether (**12a**) by decarbonylative α-arylation reaction. (2) Substitution of the methoxy group on anhydride **9** occurs as the first arylation proceeds. (3) Replacement of the methoxy group by phosphoryloxy or methanesulfonyloxy group takes place before the first α-arylation.
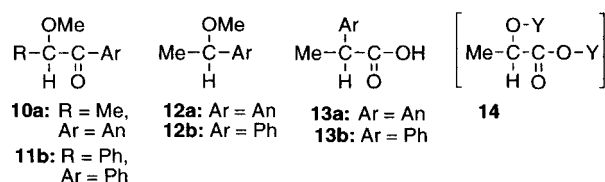

We first investigated the plausibility of the former two cases. The reactions of α-methoxy-α-phenylacetophenone

Table 3. Reactions of Model Compounds (12b and 17b) with Anisole (4a) in P_2O_5–MsOH or MsOH at Room Temperature for 24 h[a]

| | | substrate | |
| | | **12b** | **17b** |
acidic medium	anisole/substrate (mol/mol)	yield[b] (%) **6ab**	yield[b] (%) **18b**
P_2O_5–MsOH	1	36	71
	5	70	83
	10	87	73
	40	52	82
MsOH	40	70	

[a] Reaction conditions: for 1 mmol of substrate, 4 mL of acidic medium was used. [b] Yields were determined on the basis of ^{1}H NMR spectra.

(**11b**) and α-phenylpropanoic acid (**13b**) as the model compounds gave the corresponding phenones (**15a** and **16b**), respectively. Resulting phenones **15a** and **16b** gave
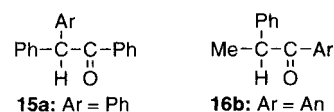
no further products. In this stage, routes 1a and 2 were considered to be excluded. Consequently, the first α-arylation is explicated to proceed via decarbonylative α-arylation.[10] However, the reaction behavior of ether **12b** also differed from that of acid **2** as described below.

In the reaction of ether **12b** with various amount of anisole in P_2O_5–MsOH or MsOH (Table 3), alkane **6ab** was solely obtained. The corresponding alkene **7** was not produced at all from ether **12b** even under the same conditions in which alkene **7a** was obtained from acid **2**. In addition, the reaction of ether **12b** gave alkane **6ab** in a rather low yield (52% in Table 3) even under the optimum conditions in which the highest yield of alkane **6a** (85%, run 5 in Table 1) was achieved. Furthermore, inversion of the product distributions in P_2O_5–MsOH and in MsOH was observed; the yield of alkane **6a** in the reaction of acid **2** in P_2O_5–MsOH at room temperature was far higher than that in MsOH (Table 2). In contrast, the yield of alkane **6ab** in the reaction of ether **12b** in MsOH (70%) was higher than that in P_2O_5–MsOH (52%) under the same conditions (Table 3). These results strongly suggest that ether **12b** is neither the sole intermediate nor the major one. The existence of other intermediates having a similar structure to ether **12b** is strongly manifested.

Though the type of reaction about the decarbonylative α,α-diarylation of acid **2** with oxidation yielding alkene **7a** remains unspecified as yet, strong cation sources are speculated to take part in this oxidation step under such reaction conditions. Hence, we assume that the reaction proceeds through abstraction of hydride ions by such strong cation sources. In practice, the reaction of arenes in P_2O_5–MsOH generally produces methanesulfonylated compound (Ar-Ms) as one of the byproducts. In this reaction system, it is possible to propose that the cation sources such as sulfonium cation and/or phosphoryl cation are generated by disproportionation of the acidic medium. The dependence of the product distribution on the ratio of the substrates, the acidic medium used, and/ or the reaction temperature supports the above interpretation.

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(10) Whether this first arylation step with decarbonylation proceeds by a concerted manner or a stepwise one has not been specified yet.

The formation of alkene **7a** (Tables 1 and 2) is accounted for as follows. An adequate concentration of cation sources is considered to remain in the reaction of acid **2** with an equimolar or small excess amount of anisole, because the consumption of these cations by the formation of Ar-Ms is estimated to be more gentle than that with an excess amount of arene. However, attempts at conversion of alkane **6a** to alkene **7a** in P_2O_5–MsOH at room temperature were unsuccessful, and substrate **6a** was recovered quantitatively. Accordingly, the oxidation (abstraction of hydride ions) is assumed to be efficiently induced by these cation species during the course of the formation of alkane **6a** from acid **2**. Particularly, the absence of Ar-Ms products in the reaction with an equimolar amount of anisole strongly indicates the participation of the cation species (such as Ms^+) in the formation of alkene **7a** (run 1 in Table 1). However, the disproportionation of acidic medium is rationally supposed to be accelerated at elevated temperature because the yield of Ar-Ms byproduct generally tends to increase with temperature. This accounts for the acceleration of the oxidation reaction at elevated temperature (Table 2).

The possibilities of the intermediary of ether **17a** were also excluded as follows. The reaction of compound **17b** with various amounts of anisole in P_2O_5–MsOH gave triarylethane (**18b**) exclusively, and alkene **7b** was not obtained (Table 3). Triarylethane **18b** was never attained

17a: Ar = An
17b: Ar = Ph
**18a:** Ar = An
18b: Ar = Ph
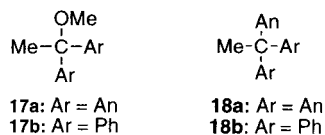
in the reaction of acid **2**. No alkene **7ab** was obtained in the reaction of ether **17b** with anisole in P_2O_5–MsOH. Consequently, none of three types of the supposed intermediates (**6a**, **12a**, and **17a**) were concluded to be the actual intermediates in the present reaction.

The results of the model reactions using these candidate compounds manifest that the precursor of alkane **7a** does not have an α-methoxy group. This consideration suggests that the C–OMe bond on the substrate is converted to another bond at the early stage, and the resulting compound has a concern in the core oxidation step during the course of reaction. Accordingly, for the formation of alkene **7a** in P_2O_5–MsOH, the arylation is considered to proceed after the methoxy moiety on the substrate is replaced by a phosphoryloxy or methanesulfonyloxy group. However, it is difficult to specify whether the actual hydride abstraction occurs before or after the first arylation (Scheme 2).

The above conclusion about the order of the steps in the route to alkene **7a** suggests that the methoxy group on acid **2** is also replaced by a phosphoryloxy or methanesulfonyloxy group in non-oxidative and decarbonylative diarylation in P_2O_5–MsOH under the similar reaction conditions. The yield of alkane **6ab** in the reaction of ether **12b** with a 40-fold excess of anisole in P_2O_5–MsOH was lower by ca. 30% than that of acid **2** (Table 3, cf. run 5 in Table 1). This fact implies that the substitution of the methoxy group on acid **2** for a phosphoryloxy or methanesulfonyloxy one proceeds no later than the first α-arylation step.[11]
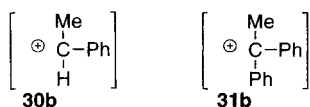
Scheme 2
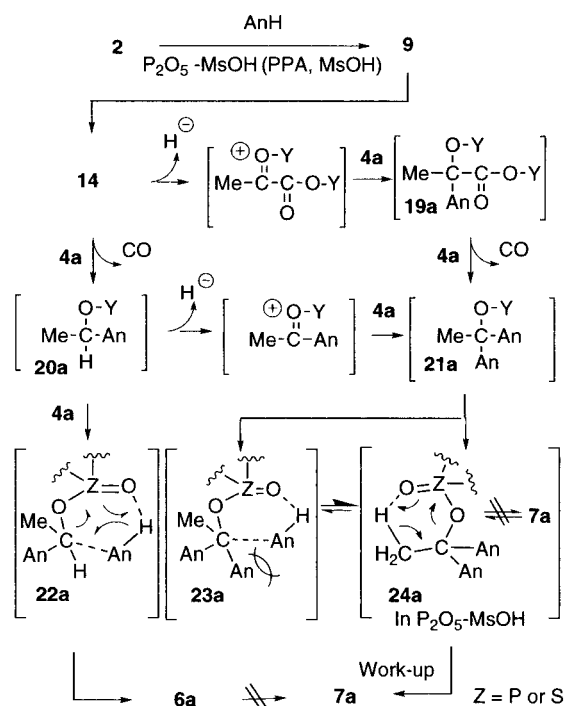
Scheme 3
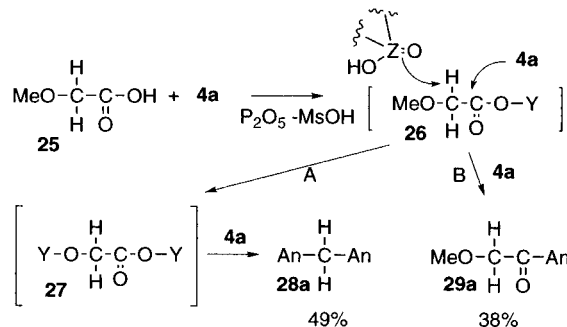
This interpretation is also supported by the previous results that the reaction of 2-methoxyacetic acid (**25**) with anisole in P_2O_5–MsOH gave not only diarylalkane (**28a**, 49%) but also the corresponding α-methoxyphenone (**29a**, 38%) and tetraarylethene (1%, $An_2CHCHAn_2$).[3] This case is rather exceptional because most other α-alkoxyacids gave 1,1-diarylated adducts specifically. The difference is explained as follows. The substitution of the methoxy group on acid **25** for a phosphoryloxy or methanesulfonyloxy group is considered to be rather disadvantageous compared to that of other 2-methoxycarboxylic acids (**1**: $R^3 = Me$), because the absence of an alkyl group on the α-carbon of acid **25** is suspected to retard the displacement electronically. In the case of acid **25**, two routes of reactions (A and B in Scheme 3) are supposed to occur competitively. Thus, when a Friedel–Crafts acylation-type reaction proceeded prior to the replacement of the methoxy group by a phosphoryloxy or methanesulfonyloxy group, phenone **29a** having a methoxy group at the α-carbon was obtained. Compared with α-methoxyphenone **8** ($R^3 = Me$, Scheme 1), phenone **29a** is considered to have a larger partial positive charge at the α-position, making the corresponding cation somewhat unstable to

(11) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.: Pergamon Press: Oxford, 1988.

afford the prolonged product. Consequently, α-arylation of phenone **29a** is not supposed to proceed under such mild conditions. This substituent dependence strongly suggests the important role of the displacement of the α-methoxy group by a phosphoryloxy or methanesulfonyloxy one in this decarbonylative α,α-diarylation.

Though compound **17b** was exclusively converted to triarylethane (**18b**) (Table 3), none of triarylethane **18a** was obtained in the reaction of acid **2** (Table 1). The opposite results clearly manifest that the route to alkene **7a** does not pass through an ether intermediate analogous to compound **17b**. The arylation of ether **17b** is considered to proceed by a stepwise manner through the trivalent carbonium intermediate (**31b**) under such conditions. Furthermore, the reaction of ether **12b** with anisole in MsOH afforded alkane **6ab** in a yield approximately 20% higher than that in P$_2$O$_5$—MsOH under the same reaction conditions (Table 3). Hence, in MsOH, formation of the carbonium ion from ether **12b** is considered to be very likely, compared to that in P$_2$O$_5$—MsOH. On the basis of these results, in P$_2$O$_5$—MsOH the chemical species of phosphoryloxy (methanesulfonyloxy) diarylethane intermediate (**21a**) is suggested to remain unchanged, and the formation of alkene **7a** via elimination is interpreted to take place mainly during the workup process. The absence of the free olefin of alkene **7a** in the reaction system is supposed to inhibit the formation of triarylethane **18a**. This explanation is rationalized on the assumption that, because of the large steric hindrance and electronic stabilization, the reaction intermediate (**23a**) is prevented from attack by anisole. In addition, intramolecular decomposition via transition state **24a** yielding alkene **7a** is assumed to be disadvantageous on account of the large stability of intermediate **21a** or its more stable derivative in P$_2$O$_5$—MsOH.

The reaction of intermediate **20a** yielding alkane **6a** is suspected to proceed through a special transition state, such as the electrocyclic transition state (**22a**), which accelerates the approach of the arene molecule (**4a**), whereas the reaction of ether **12b** was proved to proceed through the trivalent carbonium intermediate (**30b**) under such conditions. Particularly, for the formation of alkene **7a** from acid **2**, the steric hindrance is considered to affect considerably the determination of the reaction route. The second arylation step for the formation of ethane **6a** in P$_2$O$_5$—MsOH is reasonably estimated to proceed via an intermolecular concerted reaction.

$$\left[\begin{array}{c} \text{Me} \\ | \\ \overset{\oplus}{\text{C}}-\text{Ph} \\ | \\ \text{H} \end{array}\right] \quad \left[\begin{array}{c} \text{Me} \\ | \\ \overset{\oplus}{\text{C}}-\text{Ph} \\ | \\ \text{Ph} \end{array}\right]$$

30b   **31b**

In summary, the reaction routes of specific decarbonylative α,α-diarylation of acid **2** giving alkane **6a** and alkene **7a** were concluded as follows. (1) Mixed acid anhydride **9** is formed from acid **2** and the phosphoric (methanesulfonic) acid moiety at the initial step. (2) The replacement of the methoxy group on the substrate by a phosphoryloxy or methanesulfonyloxy group takes place before the first α-arylation. (3) The first α-arylation is

ascertained to proceed with evolution of carbon monoxide, and the second α-arylation yielding alkane **6a** proceeds mainly through a phosphoryloxyarylethane (sulfonyloxyarylethane) intermediate (**20a**). The reaction features are distinctively different from those of the related methyl ethers. The reaction is considered to propagate through the electrocyclic transition state **22a** rather than the trivalent carbonium intermediate (**30b**). (4) The formation of alkene **7a** proceeds through the phosphoryloxydiarylethane intermediate (**21a**). The reaction is considered to proceed through the electrocyclic transition state **24a** rather than the trivalent carbonium intermediate (**31b**).

These findings also suggest the possibility that the direct condensation of free carboxylic acid mediated by P$_2$O$_5$—MsOH or PPA progresses via an electrocyclic reaction of the mixed acid anhydride between carboxylic acid and phosphoric acid moiety instead of the electrophilic attack of acylium cation formed from the mixed acid anhydride.

Experimental Section

Methods and Materials. Purification of the reagents was performed according to the literature.[11] NMR spectra were recorded at 200 or 500 MHz for ^{1}H and at 50 or 125 MHz for ^{13}C in CDCl$_3$ or DMSO-d_6 using TMS as an internal reference. P$_2$O$_5$—MsOH,[1] 2-methoxypropanoic acid (**2**),[2] and 2-methoxypropanoyl chloride (**3**)[12] were prepared by literature procedures.

Typical Procedure for Reactions of Acids 1 or Acid Chloride 3 and Arene (4). Reaction of Acid 2 and Anisole (4a) in P$_2$O$_5$—MsOH. P$_2$O$_5$—MsOH (6 mL) was added to an ice-cooled mixture of acid **2** (156 mg, 1.5 mmol) and the noted amount of anisole (**4a**) under vigorous stirring. The mixture was stirred at the prescribed temperature for the stated time and poured into ice—water. The aqueous solution was extracted with ether (40 mL × 2). The combined organic layer was washed with aqueous 1 M NaOH solution (30 mL × 1) and brine (30 mL × 1), dried over MgSO$_4$ overnight, and concentrated under reduced pressure. An isomeric mixture of alkane **6a** was obtained. Under some specific conditions, alkene **7a** was also produced. These products were separated by silica gel column chromatography (eluent: benzene/hexane = 1/1 v/v).

***p,p′*-Dimethoxy-1,1-diphenylethane (6a):**[2] ^{1}H NMR δ (CDCl$_3$) 1.60 (3H, d, $J = 7.5$ Hz), 3.80 (6H, s), 4.10 (1H, q, $J = 7.5$ Hz), 6.85 (4H, d, $J = 8$ Hz), 7.15 (4H, d, $J = 8$ Hz). ***o,p′*-Dimethoxy-1,1-diphenylethane (6a):** ^{1}H NMR δ (CDCl$_3$) 1.56 (3H, d, $J = 7.5$ Hz), 3.79 (3H, s), 3.80 (3H, s), 4.55 (1H, q, $J = 7.5$ Hz), 6.80—6.98 (4H, m), 7.10—7.23 (4H, m). **1,1-Dianisylethene (7a):**[13] ^{1}H NMR δ (CDCl$_3$) 3.83 (6H, s), 5.30 (2H, s), 6.83 (4H, dd, $J = 8$ and 2 Hz), 7.24 (4H, dd, $J = 8$ and 2 Hz). IR (KBr) 843, 897, 1028, 1250, 1510, 1606, 2955 cm^{-1}. Anal. Calc for C$_{16}$H$_{16}$O$_2$: C, 79.97; H, 6.72. Found: C, 79.65; H, 6.71.

Supporting Information Available: Synthesis of α-methyl methylbenzyl ether (**12b**) and spectral date for compounds **2**, **3**, **6ab**, **7ab**,[14] **15a**, **16b**, and **18b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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