

trans-N-Methyl-3-(2-(cyanomethyl)-4,5-(methylenedioxy)phenyl)-4-methyl-7,8-(methylenedioxy)-3,4-dihydro-1-(2H)-isoquinolone (12). A 1:2 mixture of 10 and 11 (645 mg, 1.53 mmol) was dissolved in dry Me₂SO and heated at 160 °C for 0.5 h. The solvent was evaporated from the dark brown solution, and the resulting residue was dissolved in CHCl₃. The CHCl₃ was then evaporated from the filtered solution to give a brown oil, which was subjected to column chromatography over silica gel (60 g), eluting with 9:1 mixture of EtOAc and hexane, respectively. Evaporation of solvent from the fractions containing the first component eluted from the column afforded compound 12 (218 mg). The analytical sample was recrystallized twice from CHCl₃-Et₂O, which gave pale yellow crystals: mp 250–253 °C; IR (CHCl₃) 2940, 2890, 2240, 1635, 1590, 1475, 1365, 1070, 1020, 910 cm⁻¹; NMR δ 6.80 (s, 1 H), 6.78 (d, 1 H, *J* = 7.8 Hz), 6.42 (d, 1 H, *J* = 7.8 Hz), 6.37 (s, 1 H), 6.16 (d, 1 H, *J* = 1.2 Hz), 6.13 (d, 1 H, *J* = 1.3 Hz), 5.92 (d, 1 H, *J* = 1.3 Hz), 5.87 (d, 1 H, *J* = 1.3 Hz), 4.49 (d, 1 H, *J* = 1.6 Hz), 3.65 (s, 2 H), 3.02 (s, 3 H), 2.91 (d of q, 1 H, *J* = 1.6, 7.0 Hz), 1.45 (d, 3 H, *J* = 7.0 Hz); CIMS *m/e* (relative intensity) 379 (MH⁺, 100).

Anal. Calcd for C₂₁H₁₈N₂O₅·1/2H₂O: C, 65.12; H, 4.91; N, 7.24. Found: C, 65.09; H, 4.65; N, 7.02.

cis-N-Methyl-3-(2-(cyanomethyl)-4,5-(methylenedioxy)phenyl)-4-methyl-7,8-(methylenedioxy)-3,4-dihydro-1-(2H)-isoquinolone (13). Continued elution of the column above gave a 5:7 mixture of 12 and 13 (131 mg), respectively, followed by isomer 13, which was isolated as a white solid after evaporation of solvent and recrystallization from CHCl₃-Et₂O: 33 mg, mp 241–244 °C; IR (CHCl₃) 2940, 2880, 2230, 1630, 1590, 1470, 1445, 1365, 1105, 1010, 910 cm⁻¹; NMR δ 6.85 (d, 1 H, *J* = 8.1 Hz), 6.78 (s, 1 H), 6.52 (d, 1 H, *J* = 8.1 Hz), 6.25 (s, 1 H), 6.14 (s, 2 H), 5.88 (s, 2 H), 4.65 (d, 1 H, *J* = 6.4 Hz), 4.00–3.41 (m, 3 H), 3.01 (s, 3 H), 1.12 (d, 3 H, *J* = 7.0 Hz); CIMS, *m/e* (relative intensity) 379 (MH⁺, 100).

Anal. Calcd for C₂₁H₁₈N₂O₅·1/2H₂O: C, 65.12; H, 4.91; N, 7.24. Found: C, 64.72; H, 4.69; N, 7.12.

trans-N-Methyl-3-(2-(methoxycarbonyl)methyl)-4,5-(methylenedioxy)phenyl)-4-methyl-7,8-(methylenedioxy)-3,4-dihydro-1-(2H)-isoquinolone (14). Compound 12 (36 mg, 0.095 mmol) was suspended in MeOH (3 mL). Hydrogen chloride gas was passed through a CaCl₂ drying tube into the suspension, which was kept at a temperature of -40 °C to -20 °C for 1 h. The resulting clear solution was stored at 0 °C for 12 h. The solution was concentrated to half the original volume. The residue was stirred with H₂O (4 mL). The white precipitate was extracted into EtOAc (3 × 3 mL). The organic solution was washed with H₂O (4 mL), 5% aqueous NaHCO₃ (3 mL), and finally H₂O (4 mL). The organic extract was then dried and filtered, and the solvent was evaporated to yield the methyl ester 14 (32 mg, 82%). The analytical sample was recrystallized from CHCl₃-Et₂O: mp 190–192 °C; IR (CHCl₃) 2970, 2940, 1730, 1720, 1630, 1590, 1470, 1165 cm⁻¹; NMR δ 6.67 (d, 1 H, *J* = 7.8 Hz), 6.69 (s, 1 H), 6.40 (d, 1 H, *J* = 7.8 Hz), 6.34 (s, 1 H), 6.14 (d, 1 H, *J* = 1.2 Hz), 6.11 (d, 1 H, *J* = 1.3 Hz), 5.87 (d, 1 H, *J* = 1.4 Hz), 5.82 (d, 1 H, *J* = 1.4 Hz), 4.62 (d, 1 H, *J* = 1.3 Hz), 3.72 (s, 3 H), 3.58 (s, 2 H), 3.00 (s, 3 H), 2.88 (d of q, 1 H, *J* = 1.3, 7.1 Hz), 1.40 (d, 3 H, *J* = 7.1 Hz); CIMS *m/e* (relative intensity) 412 (MH⁺, 100).

Anal. Calcd for C₂₂H₂₁NO₇: C, 64.23; H, 5.11; N, 3.41. Found: C, 63.94; H, 5.11; N, 3.62.

Corydalic Acid Methyl Ester (15). Compound 14 (40 mg, 0.097 mmol) was heated at 55–60 °C in POCl₃ (0.3 mL) for 3 h. The mixture was then concentrated by evaporation in vacuo, and dry 1,2-dimethoxyethane (0.4 mL) was added to the residue. The resulting solution was cooled in an ice bath and treated with a solution of NaBH₄ in EtOH (0.7 M, 0.42 mL). After being stirred at room temperature for 3.5 h, the reaction mixture was cooled in an ice bath and treated again with a solution of NaBH₄ in EtOH (0.7 M, 0.42 mL). After stirring at room temperature for 12 h, a 2% aqueous HCl solution (0.54 mL) was added. The mixture was concentrated by evaporation and H₂O (2 mL) was added to the residue. The mixture was then extracted with Et₂O (2 × 1 mL). The aqueous layer was basified with 20% aqueous K₂CO₃ (1.6 mL) as the mixture was cooled in an ice bath. The mixture was then extracted with EtOAc (3 × 2 mL). The organic extract was combined with the Et₂O extract above. The solution was dried and filtered, and the solvent was evaporated to yield a pale yellow

oil (39 mg). The oil was subjected to preparative TLC (silica gel, 3:1 EtOAc-hexane) to afford the starting material 14 (8 mg, 20%) and the product 15, which was crystallized from CHCl₃-hexane: 22 mg, 57%; mp 144–147 °C; NMR δ 6.88 (s, 1 H), 6.70 (s, 3 H), 5.93 (s, 4 H), 4.03 (d, 1 H, *J* = 15.6 Hz), 3.71 (s, 2 H), 3.64 (s, 3 H), 3.36 (d, 1 H, *J* = 15.7 Hz), 3.15–3.06 (m, 2 H), 2.06 (s, 3 H), 1.03 (d, 3 H, *J* = 6.3 Hz). The synthetic compound cochromatographed with the natural product on silica gel TLC in the following solvent systems: 3:1 EtOAc-hexane (*R_f* 0.68), CHCl₃ (*R_f* 0.19), Et₂O (*R_f* 0.95), 1:1 Me₂CO-benzene (*R_f* 0.93).

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Registry No. (±)-8, 82929-74-6; 9, 75283-81-7; (±)-10, 88610-26-8; (±)-11, 88610-27-9; (±)-12, 88610-28-0; (±)-13, 88610-29-1; (±)-14, 88610-30-4; (±)-15, 88610-31-5.

Utilization of Magnesium Chelates in the Synthesis of 3-Nitro- and 3-(Methoxycarbonyl)-Substituted 2-Arylchromones

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Although a wide variety of flavones are available as natural products, the 3-nitro-, 3-carboxy-, and 3-(alkoxy-carbonyl)-substituted flavones are rare substances. The treatment of flavone (1, Chart I) with lithium diisopropylamide and carbon dioxide recently provided the first synthesis of 3-carboxyflavone (2), while the corresponding ethyl ester 3 was obtained by using ethyl chloroformate in the acylation step.¹ The nitrosation of flavanone (4) and subsequent oxidation has previously afforded 3-nitroflavanone (5), which on bromination followed by dehydrobromination gave 3-nitroflavone (6).² Intermediate 5 has also been prepared by the condensation of 2-hydroxy- α -nitroacetophenone (10) with benzaldehyde.³ However, the conversion of 5 to 6 in this synthesis is of limited scope because of the required use of bromine, which causes bromination of the aromatic rings when activating substituents are present.³ It is anticipated that the chemistry of 3-substituted chromones will be of interest during the utilization of these compounds as intermediates in the synthesis of novel heterocyclic systems. Certain 3-nitrochromones have already been converted to dihydrobenzopyrans⁴ as well as benzoxepins.⁵

Our interest in 2-aryl-3-substituted chromones stems from their potential use in the preparation of pyridines.⁶ This paper describes a novel one-pot procedure for the conversion of 2-hydroxy- α -nitroacetophenones and 2-hydroxy- α -(methoxycarbonyl)acetophenones (A, Scheme I) to 2-aryl-3-nitrochromones and 2-aryl-3-(methoxycarbonyl)chromones (E). This method avoids preformed

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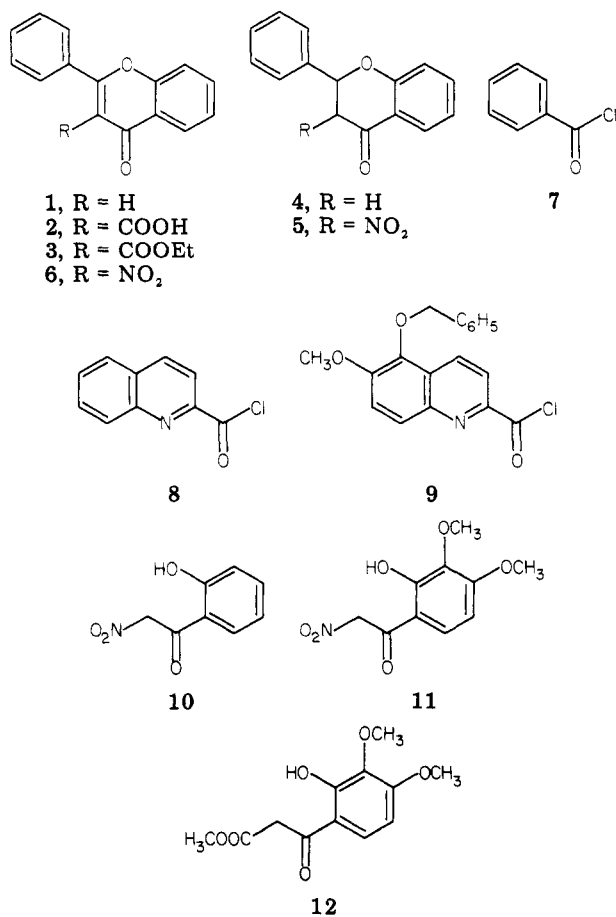
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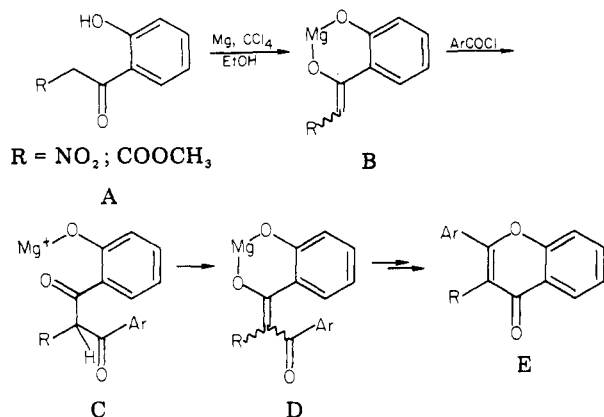
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Chart I



Scheme I

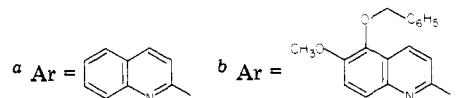


flavones as well as the troublesome dehydrogenations of 3-substituted flavanones.

The procedure utilizes magnesium chelates as depicted in Scheme I. Treatment of the starting materials A⁷ with magnesium ethoxide yielded the magnesium chelates B, which were isolated as solid materials after evaporation of the solvent. The chelates were then suspended in benzene and reacted with the acid chlorides. Although intermediates B possess three nucleophilic sites, it is to be expected that the coordination of the two oxygen atoms with the magnesium retards acylation at these sites, forcing it to occur at carbon to yield intermediates C and D.⁸ It

Table I. Synthesis of 3-Nitro- and 3-(Methoxycarbonyl)-2-arylchromones

reactants	product	Ar	R ¹	R ²	yield, %
7 + 10	6	C ₆ H ₅	NO ₂	H	53
7 + 12	13	C ₆ H ₅	COOCH ₃	OCH ₃	61
8 + 10	14	Ar ^a	NO ₂	H	63
8 + 12	15	Ar ^a	COOCH ₃	OCH ₃	60
8 + 11	16	Ar ^a	NO ₂	OCH ₃	54
9 + 11	17	Ar ^b	NO ₂	OCH ₃	54
9 + 12	18	Ar ^b	COOCH ₃	OCH ₃	51



is well-known that magnesium enolates give a greater proportion of C-acylation than sodium or lithium enolates⁹ and that this effect is most pronounced in nonpolar solvents.^{8a} The requirement for the magnesium chelates appears to be critical for the success of the reaction, since it failed to occur under a variety of other basic conditions including treatment with lithium diisopropylamide, sodium hydride, or sodium acetate in tetrahydrofuran, ammonium or sodium acetate in acetic acid, and either neat pyridine or pyridine in chloroform.

The products listed in Table I were prepared from various combinations of the acid chlorides 7–9 with substituted acetophenones 10–12.¹⁰

Experimental Section

All reactions were performed under a nitrogen atmosphere. Melting points were determined on a Thomas-Hoover Unimelt or on a Meltemp apparatus and are uncorrected. NMR spectra were recorded on a Varian FT-80 80-MHz spectrometer in CDCl₃. Chemical shifts are reported in parts per million relative to Me₄Si as internal standard. IR spectra were recorded on a Beckman IR-33 spectrophotometer with CHCl₃ as the solvent. Chemical ionization mass spectra (CIMS) were determined on a Finnegan 4000 spectrometer using an ionization potential of 70 eV with isobutane as the reagent gas.

Typical Procedure. 7,8-Dimethoxy-3-(methoxycarbonyl)-2-phenyl-4H-benzopyran-4-one (13). A mixture containing the starting material 12 (127 mg, 0.5 mmol), magnesium metal turnings (12 mg, 0.5 mg-atom), absolute EtOH (3 mL), and CCl₄ (3 drops) was heated at 50–55 °C until all of the magnesium had dissolved. The solvent was evaporated, and benzene (3 mL) and freshly distilled benzoyl chloride (7, 71 mg, 0.5 mmol) were added. The reaction mixture was heated at reflux for 4 h and then cooled to room temperature. Aqueous AcOH (10%, 5 mL) was added and the mixture stirred until all of the solid dissolved. The mixture was extracted with CHCl₃ (2 × 10 mL), and the organic extract was washed with brine, dried, and evaporated. The residue was subjected to preparative thin-layer chromatography on silica gel with CHCl₃ as solvent to yield the substituted flavone 13 (104 mg, 61%): mp 124–125 °C; IR 1720, 1630, 1610, 1590, 1370 cm⁻¹; NMR δ 7.97 (d, 1 H, J = 9.0 Hz), 7.83–7.46 (m, 5 H), 7.05 (d, 1 H, J = 9.0 Hz), 3.99 (s, 3 H), 3.97 (s, 3 H), 3.78 (s, 3 H); CIMS, m/e (relative intensity) 341 (M⁺ + 1, 100), 309 (33).

3-Nitro-2-phenyl-4H-benzopyran-4-one (6). The magnesium chelate of the nitro ketone 10 was prepared by using a mixture

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of EtOH and benzene (1:1) as solvent. The crude product was purified by preparative thin-layer chromatography on silica gel with hexane-CHCl₃ as solvent to yield a solid: mp 137-139 °C; IR 1660, 1540, 1365 cm⁻¹; NMR δ 8.24-7.36 (m, 9 H); CIMS, *m/e* (relative intensity) 268 (M⁺ + 1, 100), 105 (87).

2-(2-Quinoly)-3-nitro-4H-benzopyran-4-one (14). The crude material was recrystallized from MeOH: mp 239-241 °C; IR 1655, 1540, 1360 cm⁻¹; NMR δ 8.46-7.50 (m, 10 H); CIMS, *m/e* (relative intensity) 319 (M⁺ + 1, 100).

7,8-Dimethoxy-3-(methoxycarbonyl)-2-(2-quinoly)-4H-benzopyran-4-one (15). The final residue was recrystallized from MeOH: mp 216-217 °C; IR 1730, 1630, 1620 cm⁻¹; NMR δ 8.34-7.69 (m, 6 H), 8.02 (d, 1 H, *J* = 9.0 Hz), 7.08 (d, 1 H, *J* = 9.0 Hz), 4.06 (s, 3 H), 4.05 (s, 3 H), 4.02 (s, 3 H); CIMS, *m/e* (relative intensity) 392 (M⁺ + 1, 100), 360 (74).

7,8-Dimethoxy-3-nitro-2-(2-quinoly)-4H-benzopyran-4-one (16). The magnesium chelate of the nitro ketone 11 was prepared by using a mixture of EtOH and benzene (1:1) as solvent. The crude product was recrystallized from a mixture of MeOH and CHCl₃: mp 236-237 °C; IR 1640, 1590, 1535, 1365, 1280, 1090 cm⁻¹; NMR δ 8.41 (d, 1 H, *J* = 9.2 Hz), 8.16 (d, 1 H, *J* = 9.7 Hz), 8.06 (d, 1 H, *J* = 9.8 Hz), 8.20-7.64 (m, 4 H), 7.14 (d, 1 H, *J* = 9.2 Hz), 4.06 (s, 3 H), 4.03 (s, 3 H); CIMS, *m/e* (relative intensity) 379 (M⁺ + 1, 100).

7,8-Dimethoxy-3-nitro-2-[5-(benzyloxy)-6-methoxy-2-quinoly]-4H-benzopyran-4-one (17). In this case, the magnesium chelate was prepared by using a benzene-EtOH mixture (1:1) as solvent. The crude product was recrystallized from MeOH: mp 236-237 °C; IR 1650, 1590, 1280, 1080 cm⁻¹; NMR δ 8.57 (d, 1 H, *J* = 8.9 Hz), 8.06 (d, 1 H, *J* = 9.0 Hz), 8.05 (d, 1 H, *J* = 9.1 Hz), 7.91 (d, 1 H, *J* = 9.3 Hz), 7.59 (d, 1 H, *J* = 9.3 Hz), 7.50-7.30 (m, 5 H), 7.12 (d, 1 H, *J* = 9.1 Hz), 5.21 (s, 2 H), 4.06 (s, 3 H), 4.05 (s, 3 H), 4.03 (s, 3 H); CIMS, *m/e* (relative intensity) 515 (M⁺ + 1, 100), 482 (12), 424 (19), 91 (32).

7,8-Dimethoxy-3-(methoxycarbonyl)-2-[5-(benzyloxy)-6-methoxy-2-quinoly]-4H-benzopyran-4-one (18). The final residue was recrystallized from MeOH: mp 210-211 °C; IR 1725, 1720, 1630, 1590 cm⁻¹; NMR δ 8.55 (d, 1 H, *J* = 9.5 Hz), 8.11 (d, 1 H, *J* = 8.8 Hz), 8.01 (d, 1 H, *J* = 8.8 Hz), 7.86 (d, 1 H, *J* = 9.2 Hz), 7.57 (d, 1 H, *J* = 9.6 Hz), 7.51-7.27 (m, 5 H), 7.05 (d, 1 H, *J* = 9.1 Hz), 5.22 (s, 2 H), 4.06 (s, 3 H), 4.04 (s, 6 H), 4.01 (s, 3 H); CIMS, *m/e* (relative intensity) 528 (M⁺ + 1, 100), 437 (30), 91 (67).

Anal. Calcd for C₃₀H₂₅NO₈: C, 68.31; H, 4.78; N, 2.66. Found: C, 68.50; H, 5.00; N, 2.71.

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Registry No. 6, 10524-88-6; 7, 98-88-4; 8, 50342-01-3; 9, 88685-87-4; 10, 29378-60-7; 10 (Mg chelate), 88685-95-4; 11, 82222-78-4; 11 (Mg chelate), 88685-96-5; 12, 88685-88-5; 12 (Mg chelate), 88685-97-6; 13, 88685-89-6; 14, 88685-90-9; 15, 88685-91-0; 16, 88685-92-1; 17, 88685-93-2; 18, 88685-94-3.

Base-Catalyzed Autoxidation of Weak Carbon Acids Using Poly(ethylene glycols) as Phase-Transfer Catalysts

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Base-catalyzed autoxidations using phase-transfer catalysts are known only for relatively strong carbon acids, *pK* < 25. Cryptands, crown ethers,¹ and quaternary ammonium salts² have been used as catalysts for this reaction.

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Scheme I

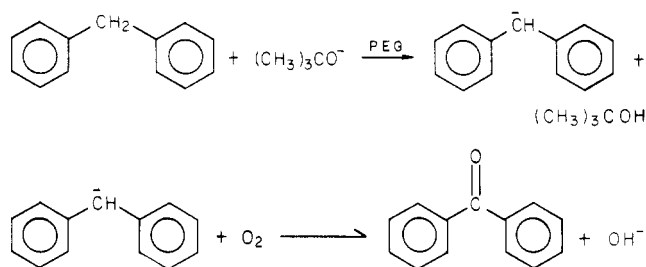


Table I. Autoxidation of Various Carbon Acids^a

substrate	<i>pK</i>	conversion, ^b		product
		<i>pK</i>	%	
fluorene	22.5		87	fluorenone
α-picoline	31		30	picolinic acid
β-picoline	30		36	nicotinic acid
γ-picoline	29		48	isonicotinic acid
diphenylmethane	34		50	benzophenone
triphenylmethane	32		62	triphenylcarbinol
toluene	35		0	
ethylenebenzene	35		0	

^a Reaction conditions: *T* = 25 °C, 0.025 mol of substrate, 0.05 mol of potassium *tert*-butoxide, 0.00033 mol of PEG 6000, 30 mL of benzene, *P*_{O₂} = 75 psi, time 2 h.

^b These are fundamentally maximum conversion because after 2 h there was no further absorption of oxygen.

Oxidation of weaker carbon acids, *pK* ≥ 30, is unknown under these conditions. Previously, oxidations of this type have been preformed by using expensive aprotic polar solvents. Picolines, *pK* ~ 30, have been oxidized by using DMF as solvent and potassium *tert*-butoxide as base.³ Diphenylmethane, *pK* ~ 33, and triphenylmethane, *pK* ~ 32, have been oxidized by using the same base in solvents such as Me₂SO⁴ and HMPA.⁵

Poly(ethylene glycols) and their alkyl ethers, RO-(CH₂CH₂O)_{*n*}R (R = H, alkyl), have received attention in recent years as phase-transfer catalysts in a variety of reactions, for example, aliphatic nucleophilic substitution,⁶ oxidation by permanganate,⁷ reductions,⁸ and Williamson ether syntheses,⁹ but have never been used in autoxidation reactions.

We have oxidized weak carbon acids in simple nonpolar solvents, e.g., benzene, by using solid potassium *tert*-butoxide as base and various poly(ethylene glycols) (PEG) as phase-transfer catalysts at ambient temperatures. In a solid-liquid phase-transfer system the general reaction scheme using diphenylmethane as the substrate is shown in Scheme I. We have investigated the scope of the reaction and the effect of the catalyst's molecular weight and compared alkylated and nonalkylated catalysts. In addition a comparison has been made with other common phase-transfer catalysts.

Results and Discussion

The results of the autoxidation of a variety of carbon acids are summarized in Table I. Significant yields were

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