°C for 7 h. After evaporation of the solvent under reduced pressure, the residue was purified by a silica gel column chromatography (1.1 × 15 cm), eluting with hexane/ethyl acetate (3:1), to give a mixture (10.3 mg) of the chromenol derivative 11 and its 9-epimer: ^{1}H NMR ($CDCl_3$) δ 1.00 (3 H, d, J = 7 Hz), 1.01 (3 H, s), 1.46 (3 H, s), 2.31 (1 H, m), 3.77 (3 H, s), 3.80 (3 H, s), 4.65 (0.5 H, s), 4.66 (0.5 H, s), 4.70 (0.5 H, s), 4.72 (0.5 H, s), 5.19 (1 H, s), 5.72 (1 H, d, J = 9.9 Hz), 6.47 (1 H, s), and 6.56 (1 H, d, J = 9.9 Hz); EIMS, m/z 372 (M^+), 221, 207, and 191. The mixture (8.3 mg) of 11 and 9-*epi*-11 was treated with an excess of diazomethane in an ether solution (15 mL) in the presence of silica gel (Wako gel C-300, 4 mg) at room temperature for 19 h. Evaporation of the solvent and purification by a silica gel column chromatography (1.1 × 17 cm), eluting with hexane/ethyl acetate (4:1), afforded a mixture (1.8 mg) of trimethoxychromenol derivative 9 and its 9-epimer: ^{1}H NMR ($CDCl_3$) δ 1.01 (3 H, s), 1.02 (3 H, d, J = 6.4 Hz), 1.45 (3 H, s), 3.79 (3 H, s), 3.83 (3 H, s), 3.84 (3 H, s), 4.66 (0.5 H, s), 4.67 (0.5 H, s), 4.72 (0.5 H, s), 4.73 (0.5 H, s), 5.68 (1 H, d, J = 10.1 Hz), 6.47 (1 H, s), and 6.67 (1 H, d, J = 10.1 Hz); EIMS, m/z 386 (M^+), 263, 235, 220, 205, 147, and 123.

Bioassay Methods. Rabbits (2–3 kg) were sacrificed by cervical dislocation and the hearts were excised in cold Krebs-Ringer bicarbonate solution of the following composition (mM): NaCl, 120; KCl, 4.8; $CaCl_2$, 1.2; $MgSO_4$, 1.3; KH_2PO_4, 1.2; $NaHCO_3$, 25.2; and glucose, 5.8; pH 7.4. The coronary artery was excised and cut into helical strips, ~1 mm in width and 10 mm in length. The strip was tied at each end by surgical silk. One end was connected to a force-displacement transducer and the other end was secured to a glass tissue holder. The 20-mL organ bath containing the solution was gassed with 95% O_2:5% CO_2 and the temperature was maintained at 36 °C. A resting tension of 800 mg was applied to each strip. Isometric force was monitored continuously by a polygraph.

The assay method of antitumor activity in vitro has been previously reported.[3a]

Acknowledgment. We thank Mr. Z. Nagahama for help with collections, Mr. T. Hayase of Central Research Laboratories, Mitsubishi Chemical Industries Ltd., for help with NMR measurements, and Ms. M. Hamashima and A. Muroyama of this institute for technical assistance.

A Simple Direct Procedure for the Regiospecific Preparation of Chloro Aromatic Compounds

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A common problem facing organic chemists is the regiospecific chlorination of aromatic rings. One practical solution to this problem is the substitution of aromatic nitro groups by chlorine. The Sandmeyer reaction[1] is normally used to accomplish this conversion. The nitro group is reduced to an amine, diazotized, and reacted with copper chloride to give the corresponding chloro aromatic. A number of variations on this basic reaction are also known.[2] Other methods of taking aromatic nitro to chloro functions include irradiation in chloroform/hydrogen chloride solution,[3] alkylative reduction by Grignard reactions quenched with sodium hypochlorite,[4] and treatment with chlorine or thionyl chloride in the vapor phase.[5] Here we report the successful application of two readily available organophosphorus reagents to accomplish the same transformation. Thus, phosphorus pentachloride and phenyltetrachlorophosphorane[6] (PTCP) have each been used to convert nitro aromatics directly to the analogous chloro aromatic materials. Prior to our work, PTCP was almost unknown as a reagent for organic synthesis. Timokhin et al.[7] reported the reaction of cyclohexene with PTCP to give *trans*-1,2-dichlorocyclohexane and 3-chlorocyclohexene. Mitrasov et al.[8] found that treatment of aliphatic aldehydes and ketones with PTCP produced geminal dichlorides. PTCP has also been used to form tetrazines from hydrazides.[9] Most recently, we have used PTCP in phenylphosphonic dichloride at 170 °C to convert nitro aromatics to chloro aromatics. The reaction is straight-forward and high-yielding and offers a simple, inexpensive alternative to the less desirable processes mentioned previously. We have tested our procedure on a variety of substrates and our results are recorded in

Table I. Chloro Aromatics from Nitro Aromatics Using PPTC/BPOD

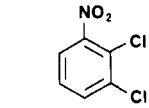
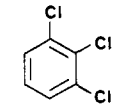
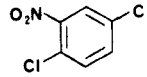
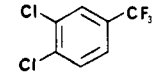
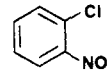
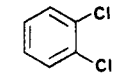
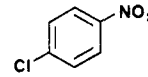
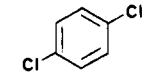
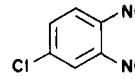
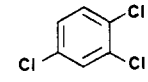
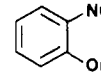
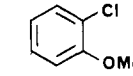
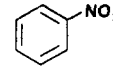
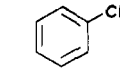
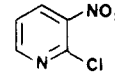
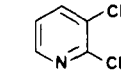
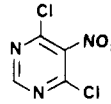
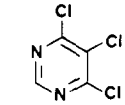
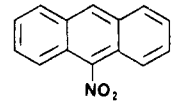
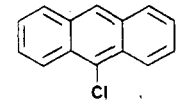
starting material	product	% yield
		94
		67
		78
		73
		86
		66
		93
		81
		82
		90

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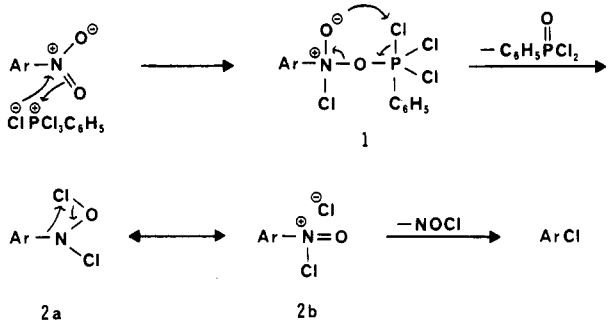
Table I. These data illustrate that substituted benzenes, pyrimidines, pyridines, and anthracenes all undergo this reaction with ease.

From a mechanistic point of view, this conversion could be considered to be the result of a nucleophilic displacement of nitro anion. Although such reactions are unusual, they are not without precedent.[10] However, we are in favor of an alternative reaction pathway with the mechanism proposed below. Initial attack of PTCP on the nitro group gives the zwitterion **1**. Fragmentation of **1** with the loss of phenylphosphonic dichloride could produce the covalent intermediate **2a** or perhaps the ionic form **2b**. The



structure proposed for **2** may be represented by a resonance hybrid of the covalent and ionic forms **2a** and **2b**, respectively. The ionic representation bears a striking resemblance to the aromatic diazo salt intermediates of the Sandmeyer reaction. Since there is clear evidence that the halogenodediazonization step of the Sandmeyer reaction is a radical process,[11] it is also possible that the halogenation of **2** occurs by a radical mechanism.

In order to test our proposed mechanism, we performed an experiment in which we replaced PTCP with freshly generated phosphorus pentachloride. Phosphorus pentachloride was chosen because phosphorus oxychloride would be formed as a byproduct. Using PTCP as the chlorine source produces phenylphosphonic dichloride, which is undetectable in the phenylphosphonic dichloride solvent. Indeed, when nitrobenzene was treated with phosphorus pentachloride in phenylphosphonic dichloride at 110 °C, chlorobenzene and phosphorus oxychloride were the products observed. These data support the first steps of our proposed mechanism.

To gain a better understanding of the second half of our proposed mechanism we carried out the chlorodenitration of nitrobenzene in the presence of copper bromide. Thus, radical decomposition of **2** would be expected to give a product mixture containing bromobenzene and chlorobenzene. Analysis of the reaction mixture revealed only the presence of chlorobenzene. Another test for radical character was carried out by adding hydroquinone to the reaction as a radical trap. No inhibition of product formation was observed. On the basis of these two experiments, we suggest that **2** does not undergo radical decomposition. Rather we feel that **2** gives up nitrosyl chloride via a heterolytic bond-cleavage process to produce aryl chloride products.[13] With this discovery, we feel that we have only scratched the surface with regard to the synthetic potential of PTCP and a host of other little known organophosphorus compounds. We hope that continued work in this area will lead to additional valuable synthetic methodologies.

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(12) Phosphorus pentachloride was generated in situ by bubbling chlorine gas into a solution of phosphorus trichloride in phenylphosphonic dichloride.

(13) Although we favor a heterolytic bond cleavage mechanism, fragmentation via a "tight" radical pair is also possible.

Experimental Section

The following procedure for the preparation of 1,2,3-trichlorobenzene is typical. All reaction products were identified by comparison to authentic samples.

1,2,3-Trichlorobenzene. Chlorine gas (400 mg, 5.61 mM) was bubbled into a solution of dichlorophenyl phosphine (789 μL, 5.73 mM) in phenylphosphonic dichloride (10 mL) at room temperature. The reaction warmed slightly but did not rise above 30 °C. The initially clear, colorless solution turned pale yellow but remained clear. To this mixture was added 1,2-dichloro-3-nitrobenzene (1.0 g, 5.23 mM), and the reaction was heated to 170 °C for 5 h. The cooled reaction was then poured onto crushed ice/water (100 mL) and neutralized with 50% aqueous sodium hydroxide. After extraction with ether, (100 mL) the ether extracts were washed with brine and dried over anhydrous magnesium sulfate. Concentration in vacuo gives 1,2,3-trichlorobenzene (880 mg, 93%).

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Free Radicals in Organic Synthesis. A Novel Synthesis of Glycerol Based on Ethylene Glycol and Formaldehyde

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Introduction

The free-radical addition of alcohols,[1] amines,[2] and carboxylic acids[3,4] and derivatives[5] to olefins is well known as a synthetic method for the formation of carbon–carbon bonds. The formation of carbon–carbon bonds by the free-radical addition of various substrates to formaldehyde is less well known.[6,7] This type of reaction is, however, quite useful synthetically.[8]

Although cyclic formals undergo reaction with formaldehyde in the presence of free radicals, the yield is reduced due to β-scission of the initially formed radical[9] (eq

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