rate under argon. Also, the rate as function of catalyst concentration passes through a maximum; e.g., the optimal catalyst concentration for the reaction of benzoylchloride with tetramethyltin is 8×10^{-4} M, the reaction being slower at both higher and lower concentrations. The active catalyst is probably $Pd(PPh_3)_2$, which is formed by reduction of **1**. Thus, the most plausible mechanism for the reaction is outlined in Scheme I. This oxidative addition-reductive elimination sequence is supported by the observation that the product of oxidative addition of benzoyl chloride to tetrakis (triphenylphosphine)palladium(0) reacts with tetramethyltin to afford acetophenone. The end point of the reaction is realized when bis(triphenylphosphine)palladium(0) undergoes disproportionation in the absence of the acid chloride (eq 2).

$$2Pd(PPh_3)_2 \rightarrow Pd(PPh_3)_4 + Pd \qquad (2)$$

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A Synthesis of *dl*-Cocaine Using Nitrone Intermediates

Sir:

We have already reported[1] an intramolecular nitrone-induced cyclization to afford pseudotropine. Herein we discuss a stereospecific synthesis of *dl*-cocaine (**1**). Previously reported[2-5] syntheses of cocaine encounter stereochemical complication in efforts to introduce the requisite carbomethoxyl group with the necessary axial geometry. Our attack on this problem focuses on the anticipated regiospecific, intramolecular cycloaddition of nitrone **2** to afford cycloadduct **3**. The *E* configuration at the olefinic center in **2** and the concerted nature of the cycloaddition compel the ester function to adopt the exo configuration denoted in **3**. We envisioned little difficulty in converting cycloadduct **3** into *dl*-cocaine by analogy to our earlier pseudotropine synthesis.[1,6]

It has been reported[7] that peracetic acid or hydrogen peroxide can oxidize isoxazolidines with concomitant ring opening to generate nitrones in modest yield. The cases studied suggested that, for those substrates lacking the appropriate symmetry, the more substituted of two possible nitrones would predominate in such oxidative openings.[7] Thus, we were surprised and gratified to find that isoxazolidine **4**, derived from 1-pyrroline 1-oxide (**5**) and styrene, undergoes oxidation with *m*-chloroperbenzoic acid in methylene chloride to give 98% of a light yellow oil, assigned structure **6** (Figure 1) on the basis of its spectral characteristics. The infrared spectrum contains a broad hydroxyl absorption at 2.8-3.2 and bands at 6.3 and

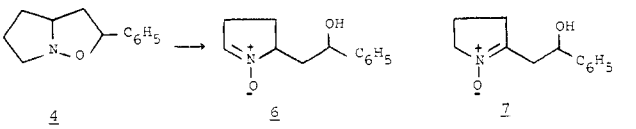
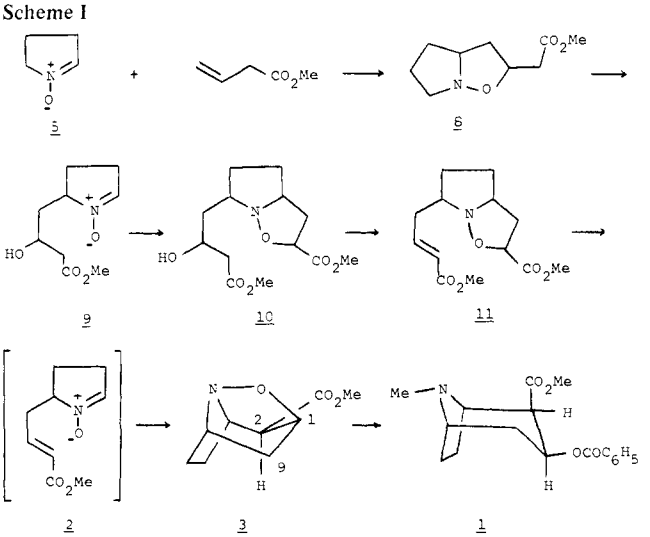


Figure 1.

8.12 μ, which are typical of nitrones. The NMR spectrum has a multiplet at δ 6.00 (br m) and the nitrone proton (2 position) at 6.70 ppm (m, 1 H). We could uncover no evidence to suggest that any detectable quantity of the more substituted nitrone **7** was formed. This finding suggested to us an efficient synthesis of the desired nitrone (**2**)

The reaction of 1-pyrroline 1-oxide (**5**) with methyl 3-butenoate in refluxing toluene produced ester isoxazolidine **8** (Scheme I) regiospecifically (96%). A quintet at δ 4.47 ppm (1 H, J = 7 Hz) in the NMR spectrum, assigned to the hydrogen at the 5 position of the isoxazolidine ring, supports the structural assignment. Addition of 1 equiv of *m*-chloroperbenzoic acid to adduct **8** in methylene chloride gave an 89% yield of nitrone **9** as a clear oil. The IR spectrum displays a hydroxyl stretching band at 2.9-3.2 and an intense carbonyl absorption at 5.80 μ. The NMR spectrum exhibits a multiplet at δ 7.07 (1 H), assigned to the nitrone 2 proton, and a multiplet at 4.32 ppm (2 H). The latter multiplet is comprised of signals from the 5 hydrogen and the alcohol proton (exchangeable, D_2O). Successful dehydration of hydroxy nitrone **9** was expected to afford the long sought ester nitrone **2.** The former was remarkably resistant to dehydration, however. Forcing conditions led to resinous material. Clearly, the nitrone function was interfering with the dehydration process. At this point, a nitrone blocking function was deemed desirable. While we were unaware of the use of blocking groups in the synthetic applications of nitrones, several possible approaches suggested themselves. The most direct and precedented of these involves the addition of an appropriate alkene since these cycloadditions are, in principle, capable of reversal.[8,9] Since methyl acrylate is a low boiling, activated olefin, it was chosen as our blocking alkene. Cyclization of nitrone **9** with methyl acrylate in refluxing benzene gave the isoxazolidine ester **11,** as a mixture of stereoisomers, in 77% overall yield from **8.** The IR spectrum of **10,** with bands at 2.89 (hydroxyl) and 5.81 μ (carbonyl), and the NMR spectrum, indicating the disappearance of the nitrone 2 proton, are supportive of the assigned structure. The methanesulfonate of **10** was prepared (95%) with methanesulfonyl chloride in pyridine. Upon reaction with 1,5-diazabicyclo[4.3.0]non-5-ene in benzene,[10] the methanesulfonate of **10** afforded exclusively the trans olefin **11** in 86% yield. A strong carbonyl band (5.85 μ) is observed in the IR spectrum

Scheme I



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of **11.** The NMR spectrum shows a doublet at δ 5.92 ppm (J = 16 Hz) indicative of the trans geometry of the double bond. With **11** in hand, successful deblocking would now afford nitrone ester **2.** Indeed, we were able to deblock **11** under conditions which would simultaneously promote the intramolecular cycloaddition to follow and thereby produce cycloadduct **3.** Thus, a dilute solution of the unsaturated isoxazolidine **11** was refluxed in xylene to produce **3** in 66% yield. A one-proton doublet at δ 4.94 ppm (J = 5 Hz) was assigned to the C-1 proton. A one-proton doublet of doublets at δ 1.24 (J = 3, 12.5 Hz) was assigned to the endo proton at C-9. In addition, one-proton multiplets at δ 3.52 and 3.86 ppm were assigned to the methine protons at C-6 and C-3, respectively. The spectrum also contains a three-proton singlet at δ 3.67 ppm due to the carbomethoxyl group. The IR spectrum exhibits the expected carbonyl band at 5.79 μ.

The route described above provides adduct **3** in 40% overall yield from the readily available methyl 3-butenoate. This adduct has already been converted by us[6] into *dl*-cocaine by methylation, hydrogenolytic cleavage of the nitrogen–oxygen bond, and benzoylation.[3] The overall approach provides a stereospecific synthesis of *dl*-cocaine in very high overall yield.

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Substrate Selectivity and Orientation in Aromatic Substitution by Molecular Fluorine

Sir:

In sharp contrast to the wealth of information on aromatic substitution by other molecular halogens,[1] and despite the theoretical relevance of the problem,[2] no kinetic or mechanistic data are currently available concerning aromatic substitution by elemental fluorine. Apparently, the widespread and time-honored[3] notion that interaction of F_2 with organic compounds is a violent and uncontrollable process, leading frequently to explosions and almost invariably to the destruction of the substrate, has hampered mechanistic studies, despite substantial improvements of the experimental techniques to tame the reactivity of F_2,[4] and reports of successful preparative approaches to direct liquid-phase fluorination of aromatics.[5]

Table I. Reactivity Relative to Benzene and Isomeric Composition of Products in Aromatic Substitution by Dilute Elemental Fluorine in CCl_3F at −78 °C

Substrate C_6H_5X, X	$k_{C_6H_5X}/k_{C_6H_6}$	Isomeric composition of C_6H_4XF, %		
		Ortho	Meta	Para
CH_3[a]	4.70 ± 0.05[b]	60 ± 2	11 ± 1.5	29 ± 2
NO_2[c]	0.017 ± 0.004	9 ± 2	80 ± 3	11 ± 2
OCH_3[d]	54 ± 2	76 ± 3	0.5 ± 0.1	23.5 ± 2

[a] The search for reaction products, and their identification, was carried out with several columns. For instance, in the analysis of the fluorination products from the C_6H_6/C_7H_8 pair, the following columns were used: 12 m, Carbowax 20M, packed; 200 m, squalane, capillary; 1 m, SE-30, packed; 50 m, OV-17, capillary; 100 m, DC 702, capillary; 33 m, Carbowax 20M, SCOT, with mass spectrometric analysis of effluents. Quantitative analysis was achieved with a 76-m Carbowax 20M SCOTT column at 75 °C, until fluorotoluenes were eluted, then at 130 °C for elution of benzyl fluoride. Analysis with a short SE-30 column at high flow rates operated at 300 °C failed to detect any other high boiling or relatively nonvolatile products. These numerous column systems were used to avoid fortuitous lack of detection of other volatile products, if any, under solvent peaks. [b] Referred exclusively to ring fluorination. Benzyl fluoride was also identified in amounts corresponding to ~20% of the combined yields of ring substituted fluorotoluenes. It is a minor product under these reaction conditions. [c] Quantitative analysis on a 61-m Carbowax 20M SCOT column at 130 °C. [d] Quantitative analysis on a 30-m Carbowax 20M SCOT column, in series with a 15-m DEGS capillary column at 90 °C.

We wish to report the preliminary results of a study on substrate selectivity and orientation in aromatic substitution by elemental fluorine. Fluorine (Matheson Co.) having a stated purity of 98.5 mol %, containing N_2 and O_2 as the major impurities, was diluted with a large excess of an inert gas (Ar or N_2), the F_2 concentration being typically 0.75 mol % (determined by iodometric titration[6]). The gas scrubbed of HF by passage through a NaF trap was slowly bubbled through a dilute (0.01–0.1 M) solution of the aromatic substrate(s) in inert solvents (CCl_3F, CH_3CN, C_6F_6, or C_7F_8) maintained at low temperature (typically −78 °C). The purity of the solvent and of the substrate(s) was determined by GLC, on the same columns used for the analysis of products. The reactions were carried out in the dark, at extremely low [F_2]:[substrate] ratios, calculated to obtain correspondingly low substrate conversions, approaching the limit of analytical sensitivity. Typical conversions were below 0.01%, rising only in a few cases to 0.1–0.3%. Such stringent conditions were chosen to minimize further interaction between F_2 and primary fluorination products, to achieve effective *local* control of temperature, and to reduce *local* modifications of the reaction medium by products, e.g., HF.

It should be emphasized that the results reported in this contribution are typical of aromatic fluorination carried out at low temperatures, in the dark, at nearly "infinite" F_2 dilution, and at substrate conversions approaching zero. An entirely different product pattern is obtained from reactions performed under photochemical, or preparative conditions, or at considerably higher [F_2]:[substrate] ratios, characterized by the occurrence of polymerization, addition, predominant side-chain attack, etc., at the expense of ring substitution.[4,5]

When the desired conversion was accomplished, the cold solution was thoroughly outgassed with dry N_2 and allowed to come to room temperature and the products were analyzed by GLC, using a Model 900 Perkin-Elmer chromatograph equipped with capillary columns and an FI detector.

The products were identified by comparison of their retention volumes with those of authentic samples, and their yields