Oxidative Coupling of *O*-Silyl and *O*-Alkyl Enethers: Application of the Novel Annulation Sequence to the Synthesis of Fluorinated Naphthaldehydes and Naphthyl Ketones

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Due to some surprising peculiarities of fluorine,[1] the most electronegative element, it is being used ever more frequently as a substituent in the synthesis of important pharmacologically active compounds. Fluorinated drugs have a vast range of pharmaceutical applications from anesthetics to chemotherapeutic drugs, from corticoids to neuroleptics, and are relative newcomers in the area of cardiovascular drugs.[2] Several of them hold a fluorine atom in a strategic position within an aromatic ring, so their synthesis often requires regioselective fluorination procedures. In this respect, a number of methods have been developed for the regioselective introduction of fluorine into an aromatic ring.[3] The most classical consists of replacing a NH_2 group by fluorine through the corresponding diazonium fluoborate salt (the Schiemann or Balz−Schiemann reaction).[4] More recent procedures have been developed on the basis of the ability of "naked" fluoride ion to replace other halogen atoms or nitro groups in nucleophilic aromatic substitution reactions. In such a case, the success depends on the presence of strong electron-withdrawing groups.[5] The electrophilic character of fluorine in several N−F type reagents has been also exploited in electrophilic aromatic substitution reactions which, however, are successful only in the presence of strongly electron-donating groups.[6] Alternatively, direct ortho-metalation-mediated fluorination with electrophilic fluorinating agents has been used, but once again, the reaction needs to have a directing ortho-metalation group present.[7] Here we demonstrate the use of suitable fluoroaryl derivatives as building blocks to synthesize fluorinated polycyclic aromatic compounds by electrophilic aromatic cyclization. This strategy is based on the para-orientating ability of fluorine[8] and has been employed in the synthesis of regioselectively fluorinated quinolines and 2-quinolones.[9]

In the context of our investigation of ceric ammonium nitrate (CAN)-promoted carbon−carbon bond forming reactions, we have discovered a versatile method enabling the construction of polycyclic compounds.[10] In this paper we describe an extension leading to selectively fluorinated 3,4-dihydro-(2*H*)phenanthren-1-ones, 2-acetonaphthenes, and 2-naphthaldehydes, which are valuable precursors to pharmacologically active compounds.[11] The method is based on the CAN-promoted oxidative addition of easily accessible 3-(fluoroaryl)-1-(trimethylsilyloxy)-alkenes (**1**) to ethyl vinyl ether. The reaction occurs readily in methanol at ambient temperature, affording acyclic and cyclic acetals (**2** and **3**, respectively). The latter mixture gives the expected aromatic ketones **4** by cyclization under strongly acidic conditions (see Scheme 1 and Table 1). The required *O*-silyl enol ether **1** can be easily prepared by copper-catalyzed 1,4-addition of arylmagnesium bromides to enals or enones and in situ trapping of the intermediate enolate with chlorotrimethylsilane.[12]

Without doubt, the mechanism follows the previously established pathway.[10] Upon oxidation with CAN the *O*-silyl enol ether loses consecutively an electron and the trimethylsilyl cation (Scheme 2). The α-acyl radical **5** thus generated combines with ethyl vinyl ether to produce an α-alkoxy radical **6**. The latter is instantaneously oxidized to the carbenium−oxonium ion **7**. This species is finally stabilized by addition of methanol, either directly (to give the acyclic acetal **2**) or after prior cyclization to the isomeric carbenium−oxonium ion **8** (to emerge eventually as the cyclic acetal **3**).

Aqueous 80% H_2SO_4 containing ca. 1 equiv. of DDQ proved to be the best cyclizing medium, which allowed the ketones **4** to be obtained in satisfactory overall yields.

Interestingly, with 3-fluoroaryl derivatives, the cyclization process is characterized by a remarkable regioselec-

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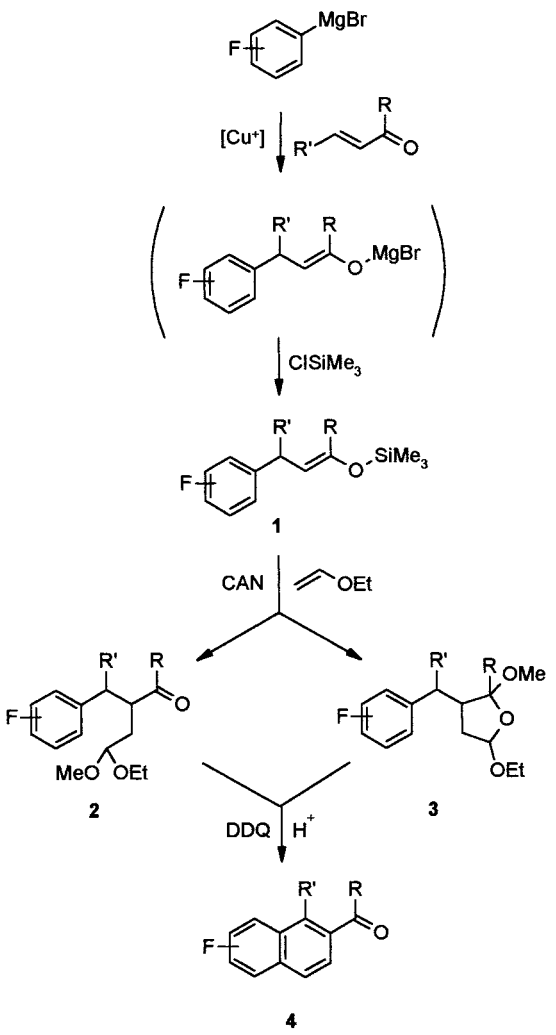
Scheme 1



tivity; 6-fluoro-3,4-dihydrophenanthren-1-one, 7-fluoro-2-acetonaphthones, and 7-fluoro-2-naphthaldehydes are exclusively formed when 3-(3-fluorophenyl)silyloxyalkenes are used as starting materials (**4a,c,e,h**). This is in agreement with the high sensitivity of the electrophilic aromatic substitution to electronic effects, especially in the presence of weak electrophiles such as a protonated carbonyl group.[13]

Moreover, depending on the structure of the α,β-unsaturated carbonyl compound precursor of the starting silyl enol ether, selectively alkylated fluoroarylaldehydes and ketones can be obtained, endowing the method with a certain versatility. Thus, 3-penten-2-one and crotonaldehyde allow the corresponding fluorinated 1-methyl-2-acetonaphthones and 1-methyl-2-naphthaldehydes, respectively, to be obtained in satisfactory overall yield (**4e,f,h,i**).

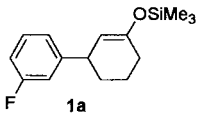
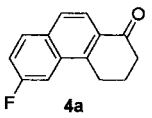
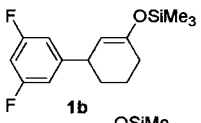
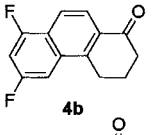
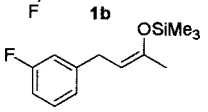
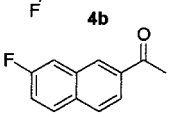
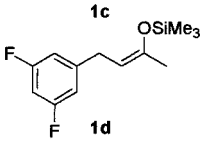
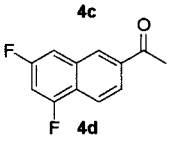
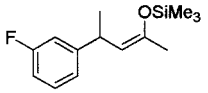
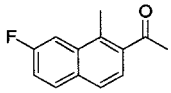
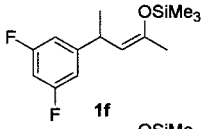
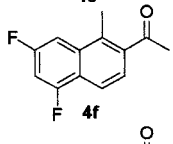
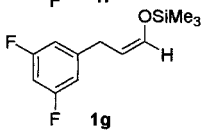
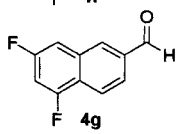
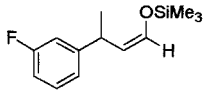
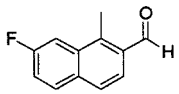
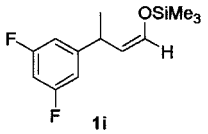
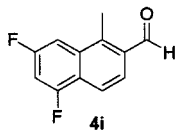
Experimental Section

^{1}H and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, using TMS as internal standard. IR spectra were registered in $CHCl_3$ in the 4000−625 cm^{-1} range. GLC. analyses were performed on two capillary columns employing two different stationary phases: cross-linked 5% PH ME syloxane (HP-5MS) and poly(ethylene glycol) (HP-Innowax). Mass spectra were registered at 70 eV. Melting points are corrected after calibration performed with authentic standards.

Reagents and Solvents. With the exception of ethyl vinyl ether, which was distilled before use, all the organic reagents, of the highest grade of purity, were used as received. Ceric ammonium nitrate (Baker 99%) was dried by heating at 80 °C for 1 h before use. Absolute methanol (Carlo Erba, ACS grade) was used without further purification. Tetrahydrofuran and diethyl ether were distilled from KOH in the presence of CuCl and redistilled from sodium wire in the presence of benzophenone.

General Procedure for the Preparation of 3-Fluoroaryl-1-trimethylsilyloxyalkenes 1.[10] A few drops of a solution of fluorinated bromobenzene (24 mmol) in dry THF (20 mL) were added, under nitrogen, to magnesium chips (0.58 g, 24 mmol) under dry THF (3.0 mL). The mixture was gently heated and, once the reaction was triggered, the addition could be continued slowly if the temperature was kept below 30 °C. After the addition was completed, the mixture was allowed to react at 25

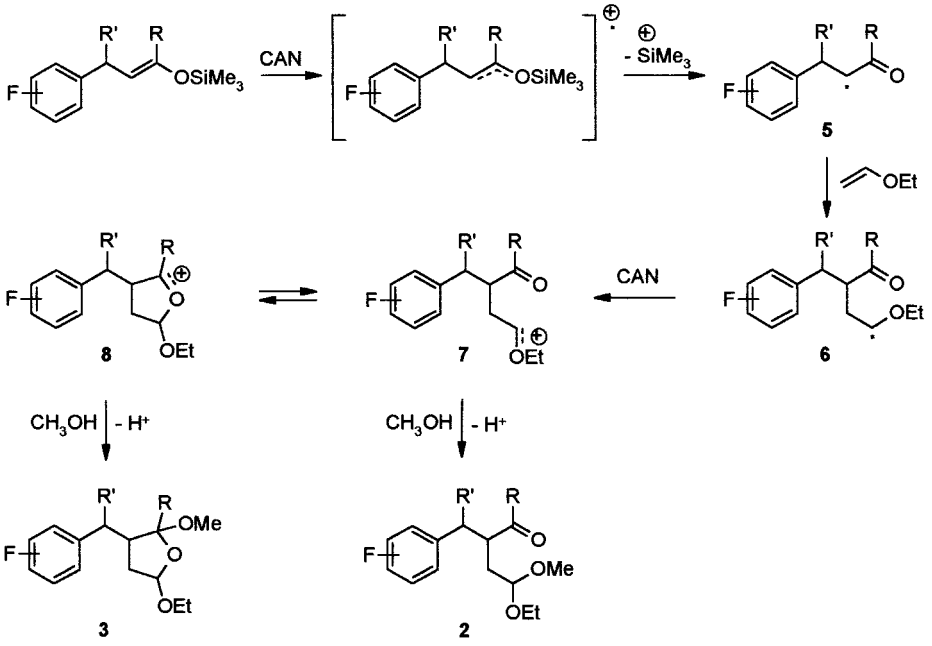
Table 1. Regioselectively Fluorinated Polycyclic Aromatic Carbonyl Compounds (4a−i) by CAN−Promoted Oxidative Addition of Fluoroaryl-1-trimethylsilyloxyalkenes (1a−i) to Ethyl Vinyl Ethers

Silyl Enol Ether	Aromatic Carbonyl Comp.	Overall [a] Yield, (%)
 **1a**	 **4a**	70
 **1b**	 **4b**	65
 **1c**	 **4c**	53
 **1d**	 **4d**	48
 **1e**	 **4e**	50
 **1f**	 **4f**	51
 **1g**	 **4g**	38
 **1h**	 **4h**	42
 **1i**	 **4i**	37

[a] Yield of isolated product calculated with respect to trimethylsilyloxyalkene.

(13) A fluorine atom in the para position with respect to the attacked carbon exerts a weak activating mesomeric effect ($\sigma_p^+ = -0.073$), whereas, due to the strong electronegativity of the element, a deactivating inductive effects would largely dominate in the ortho position.[8]

Scheme 2



°C, while stirring, until the disappearance of magnesium (2.5 h). In a second Schlenk tube, CuI (0.50 g, 2.6 mmol) and LiCl (0.25 g, 5.9 mmol) were added, under nitrogen, to dry THF (100 mL), and the mixture was kept at 20 °C until a pale yellow solution was obtained. The carbonyl compound (24 mmol) and chlorotrimethylsilane (4.0 mL, 31 mmol) were then added at 0 °C, and the mixture was stirred until an orange color was observed (20 min). After cooling to −40 °C, the previously prepared solution of fluorophenylmagnesium bromide was slowly added using a syringe. The reaction was made to proceed at −40 °C for 0.5 h (after an initial bleaching, the mixture became deep-yellow), then the cold bath was removed and the temperature was allowed to rise slowly to 20 °C. The solvent was evaporated under vacuum (1 mmHg) and the yellow residue was extracted four times with 20 mL portions of petroleum ether. The collected extracts were washed with cold 10% aqueous $NaHCO_3$ (50 mL) and dried over Na_2SO_4. The solvent was evaporated at reduced pressure (15 mmHg) and pure 3-fluoroaryl-1-trimethylsilyloxy-alkenes were recovered and characterized by their ^{1}H NMR spectra. They were used in the successive reaction without further purification.

CAN−Promoted Oxidative Addition of 1a to Ethyl Vinyl Ether. Powdered calcium carbonate (9.2 g, 92 mmol) and ethyl vinyl ether (4.0 mL, 3.0 g, 42 mmol) were added to a solution of ceric ammonium nitrate (25 g, 46 mmol) in methanol (70 mL). To the resulting suspension was added a solution of 1-trimethylsilyloxy-3-(3-fluorophenyl)cyclohexene (5.0 g, 19 mmol) in ethyl vinyl ether (11 mL, 8.3 g, 0.12 mol) dropwise in 2 min under vigorous stirring, and the mixture was allowed to react at 25 °C until it became colorless (30 min). The solid was filtered on a 1 cm Celite layer and the filtrate was concentrated at reduced pressure (15 mmHg) to one-fourth of its initial volume. The resulting thick mixture was slowly poured, under vigorous stirring, into 1:1 v/v diethyl ether−10% aqueous $NaHCO_3$, the precipitate was filtered off, the ethereal solution was separated, and the solvent was evaporated at reduced pressure (15 mmHg).

Cyclization of the Acetals 2+3 in 80% Aqueous H_2SO_4. The resulting oil (a mixture of acyclic and cyclic acetals) was dissolved in methanol (10 mL) and added dropwise, over 30 min, to a suspension of dichlorodicyanobenzoquinone (DDQ) (5.0 g, 22 mmol) in 80% aqueous sulfuric acid (50 mL) cooled to 0 °C. After the addition was completed, the ice bath was removed and stirring was continued for 30 min. The mixture was poured into ice water (100 mL); the resulting brown precipitate was filtered and dissolved in acetone (100 mL). SiO_2 was added to the solution and the solvent was removed at reduced pressure (15 mmHg). The resulting powder was put on the top of a silica gel chromatographic column and eluted with 2:1 petroleum ether−$CHCl_3$ mixture. Crystallization of the recovered orange solid from ethyl acetate, after treatment with active coal, gave pure aromatic ketones having the following spectroscopic and analytical characteristics.

6-Fluoro-3,4-dihydrophenanthren-1(2*H*)-one (4a): 2.85 g, 70% from **1a**; mp 141−142 °C; ^{1}H NMR δ 8.05 (d, J = 8.7 Hz, 1 H), 7.83 (dd, J = 8.9 and 5.8 Hz, 1 H), 7.72 (d, J = 8.7 Hz, 1 H), 7.70 (dd, J = 10.8 and 2.5 Hz, 1 H), 7.35 (ddd, J = 8.9, 8.2 and 2.5 Hz, 1 H), 3.27 (t, J = 6.1 Hz, 2 H), 2.72 (dd, J = 7.4 and 5.9 Hz, 2 H), 2.28 (quint., J = 6.5 Hz, 2 H); ^{13}C NMR δ 198.3, 161.1 (d, J = 245 Hz), 142.0, 131.1 (d, J = 8 Hz), 130.9, 130.6, 126.7, 122.1, 118.2 (d, J = 25 Hz), 107.7 (d, J = 21 Hz), 38.2, 25.6, 22.6; IR ($CHCl_3$) 3060, 2997, 2951, 2871, 1709, 1672, 1629, 1597, 1451, 1437, 1330, 1189, 1106, 856 cm^{-1}; MS m/z (%) 214 (M^+, 86), 200 (6), 186 (70), 172 (11), 158, (100), 138 (7). Anal. Calcd. for $C_{14}H_{11}FO$ (214.24): C, 78.49; H, 5.17. Found C, 78.63; H, 5.28.

By the same way, the fluorinated aromatic ketones and aldehydes **4b**−**i** were prepared from **1a**−**i** and characterized by ^{1}H NMR, ^{13}C NMR, IR, mass spectra, and elemental analysis.

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Supporting Information Available: Data about properties and identification (^{1}H NMR, ^{13}C NMR, IR, mass spectra, and elemental analysis) for newly synthesized compounds **1a**−**i** and **4a**−**i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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