Finely divided **4a** (1.1192 g, 4.88 mmol) was dissolved in 35 mL of hot acetonitrile. Cooling the solution to 5 °C produced a saturated suspension, to which was added 30 mL of saturated aqueous sodium bicarbonate solution. While holding the temperature of the reaction mixture at or below 5 °C, a solution of benzoyl chloride (3.10 g, 21.8 mmol) in 20 mL of acetonitrile was added slowly (1 drop/s). When the addition was complete, the reaction mixture was allowed to warm slowly (2 h) to room temperature and remain at that temperature for an additional 2 h. The initial precipitate was filtered off (sodium bicarbonate, 1.413 g). The mixture of two clear phases was then set aside for a few days during which time crystallization occurred. The white solid product **5a** (needles, 498.5 mg, mp 205–210 °C, uncorrected) was collected on a filter and the filtrate was evaporated to dryness. The residue was dissolved in a solvent mixture of 100 mL of water and 100 mL of chloroform. The organic layer was removed and extracted 3 times with 10% HCl and 3 times with 5% aqueous sodium bicarbonate. The organic layer was then evaporated to dryness to give crude **5a** (2.2370 g) as a tan-colored glass. Recrystallization of the crude product from acetonitrile yielded another crop of white needles (1.0665 g, mp 205–207 °C, uncorrected). The total yield was 60.3%. Mixture melting point of each crop of crystals with an authentic sample of **5a** showed no depression.

Bamberger Reaction. Isolation of Monobenzoylated Derivatives. 5-Benzoyl-4-(4-methoxyphenyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine (6a). The acid-wash solution from the previously described preparation of compound **5a** was made basic with KOH, and the tarry mass that formed was stirred in the alkaline solution until a powdery suspension remained. The nearly white powder product was collected on a filter, washed with distilled water, and dried. The yield was 63%. Recrystallization from absolute ethanol afforded white crystals, mp 215.5–218 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38–7.26 (bm, 10 H), 6.87 (s, 1 H), 6.81 (d, J = 8.6 Hz, 2 H), 3.74 (s, 3 H), 3.61 (bm, 1 H), 3.25 (bm, 1 H), 2.73 (bm, 1 H), 2.48 (m, 1 H). D_2O exchange caused a loss of a total of one NH proton absorption at δ 7.38–7.26. LRMS m/z (relative intensity) 333 (M^+, 57), 228 (100), 212 (27), 169 (19), 105 (63), 77 (23).

5-Benzoyl-4-(4-methylphenyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine (6b) was isolated as a white powder in 30% yield by basifying the acid-wash solution from the preparation of **5b**. Recrystallization from acetonitrile afforded white microcrystals mp 223–224 °C (uncorr). ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.0 (bm, 1 H), 7.34–7.07 (bm, 10 H), 6.90 (s, 1 H), 3.61 (bm, 1 H), 3.24 (bm, 1 H), 2.47 (bm, 1 H), 2.45 (m, 1 H), 2.29 (s, 3 H). D_2O exchange caused loss of a total of one NH proton absorption at δ 10.0.

5-Benzoyl-4-(4-chlorophenyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine (6c). Finely divided **4c** (467 mg, 2 mmol) was dissolved in 5 mL of warm pyridine and the solution was cooled to room temperature. Benzoyl chloride (850 mg, 6.05 mmol) was added dropwise, with stirring over a 2–3-min period. The clear pale yellow solution was heated over steam for 45 min and allowed to cool to room temperature. This solution was then added dropwise with vigorous stirring to 100 mL of aqueous 2% KOH. A white precipitate formed during the addition. After being stirred an additional 75, min the white precipitate was collected on a filter, washed with distilled water, and dried. The yield was 92%. Recrystallization from absolute ethanol afforded white microcrystals, mp 276–280 °C (uncorr.). ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.79–7.44 (bm, 12 H), 3.64 (m, 1 H), 3.18 (m, 1 H), 2.84 (m, 1 H), 2.61 (m, 1 H). LRMS m/z (relative intensity) 337 (M^+, 31), 232 (80), 169 (25), 105 (100), 77 (39).

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Registry No. **4a**, 4875-49-4; **4b**, 4875-43-8; **4c**, 4875-41-6; **5a**, 126036-46-2; **5b**, 126036-47-3; **6a**, 126036-48-4; **6b**, 126036-49-5; **6c**, 126036-50-8; **8a**, 126036-42-8; **8b**, 126036-43-9; **8c**, 126036-44-0; **9a**, 126036-45-1; **9b**, 126061-76-5; **9c**, 126061-77-6.

N-Fluorolactams: Rapid, Mild, and Regiospecific Fluorinating Agents[1]

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Regiospecific aromatic fluorination reactions have received much attention because of the presence of fluoroaryl moieties in a large number of compounds of biological significance and potential pharmaceutical use.[2] The utility of ^{18}F-labeled aromatic compounds in positron emission tomography (PET) has elevated the interest in the field of radiofluorination reactions.[3] The relatively short half-life of the ^{18}F isotope ($t_{1/2}$ = 110 min) imposes stringent demands on the reaction times and efficient utilization of the radiolabel. Particularly noteworthy in this regard is the focus on electrophilic fluorinations of activated aromatic compounds and cleavage of several aryl–metal bonds with fluorine and acetyl hypofluorite.[3,4] The high toxicity of the starting materials, such as arylmercury derivatives, or possible isomer formation makes some of these methods less attractive.[3] Moreover, the high reactivity and oxidizing properties of various fluorinating reagents could prove to be detrimental to compounds containing sensitive functional groups.

Recently, as milder alternatives, several groups have reported *N*-fluoro compounds as useful fluorinating reagents.[5-7] Interestingly, *N*-fluoro-2-pyridone has been prepared and used as a fluorinating reagent. It is speculated that after fluorination, the tautomerization of the pyridone nucleus to 2-hydroxypyridine would be a driving force for the reaction.[8] Actually, 2-hydroxypyridine exists almost exclusively as the pyridone tautomer.[9] Hence it is likely that the pyridone nucleus is not a prerequisite, and *N*-fluoroamides in general could behave as fluorinating agents. Thus, we investigated the properties of *N*-fluoroamides as a general class of fluorinating reagents and in this report we describe our results on the preparation and reactions of *N*-fluorolactams with Grignard reagents.

N-Fluoroamides have been prepared in modest yields by the reactions of amides with CF_3OF.[10] Barton's original method[10] has recently been optimized[12] for the synthesis of fluorolactams. However, CF_3OF is expensive, not readily available, has only a finite shelf life, and is an unattractive choice for radiolabeling techniques. Also, fluorination of

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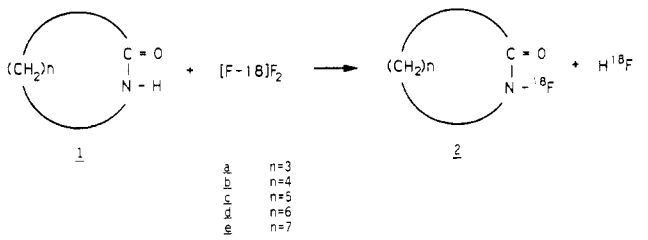
Table I. Formation of *N*-[^{18}F]Fluorolactams

[^{18}F]fluorolactam	isolated chemical yield,[a]	^{19}F NMR,[b] ppm
2a	76 (41)	-69.98
2b	61 (33)	-50.66
2c	79 (42)	-42.56
2d	71 (48)	-65.93
2e	33 (19)	-66.64

[a] Isolated chemical yields of *N*-fluorolactams are based on fluorine gas, the limiting reagent. Radiochemical yields (corrected for decay) are given in parentheses and are calculated from chromatographic data (HPLC and TLC). It should be noted that in this reaction the theoretical maximum radiochemical yield is only 50% since half of the activity is lost as H^{18}F during the formation of **2**. [b] After complete decay of the radioisotope at -20 °C (~24 h), the fluorolactams could be analyzed by ^{19}F NMR spectroscopy. These chemical shift values are identical with the literature values.[11,12]

Scheme I



cyclic amides (neat or in aqueous solution) with 100% F_2 has been reported to yield *N*-fluorolactams in low yields.[11] In this work we report that the yields of fluoroamides are excellent when the cyclic amides **1a-e** are reacted in freon with diluted ^{18}F-labeled fluorine (0.05% in neon)[13] (Table I and Scheme I).

Also, the [^{18}F]fluorolactams **2** reacted generally smoothly with various Grignard reagents to give the fluoro derivatives **4** (Table II). The mechanism for this reaction is currently under investigation. It is likely, however, that the fluorine in **2** could become slightly electron deficient due to its p-orbital electrons back-bonding into the π-electron system of the amide,[12,14,15] enabling fluorination of basic anions, e.g. Grignard reagents. On the other hand, the fluorolactams **2** failed to produce any aryl fluorides when treated with phenyllithium. This is probably due to the major side reaction of β-elimination of HF from **2** by the very strong basic anions such as phenyl lithium.[12]

In summary, we have shown that a number of *N*-fluorolactams can be prepared from readily available amides in good yields. The mild, regiospecific, and facile reaction of these *N*-fluoro derivatives with Grignard reagents are the attractive features of these electrophilic substitution reactions. The full range and limitations of these fluorination reactions are yet to be evaluated. However, *N*-fluorolactams show great promise as fluorinating agents because of their easy accessibility from F_2 and its ^{18}F-radiolabeled counterpart and they complement other related reactions reported recently.[5,6,8]

Experimental Section

Proton-decoupled ^{19}F NMR spectra in $CDCl_3$ were recorded on a Bruker WM 500 spectrometer with Freon as an internal standard. High-pressure liquid chromatography was carried out on Waters-590 solvent delivery module (Ultrasphere ODS Column, 75% CH_3OH and 25% water). The effluent from the column was monitored with a 254-nm UV detector (Altex Model 153) and a radioisotope detector (Beckman Model 170). GLC analyses were carried out with a Perkin-Elmer Model 900 gas chromatograph [DC-710 (10%) column; He Carrier gas]. Radio TLC analyses were performed with an automatic TLC analyzer [Berthold Model LB 2832; silica gel plates; hexane-ether (1:1)].

Table II. Fluorination of Grignard Reagents with *N*-[^{18}F]Fluorolactams

$$2 + RMgBr \rightarrow R^{18}F$$
$$3 \qquad 4$$

[^{18}F]fluorolactam	Grignard reagent, R =	yields,[a] %
2a	phenyl	1-2
2b	phenyl	8
2c	phenyl	20
	p-tolyl	30
	1-naphthyl	51
	cyclohexyl	19
2d	phenyl	19

[a] Isolated yields based on *N*-fluorolactams. Products identified by HPLC, GLC, and ^{19}F NMR analyses (after decay of the isotope).

General Procedure for the Preparation of [^{18}F]Fluorolactams (2). In a typical experiment, 50 mCi of [^{18}F]F_2 (specific activity 1 Ci/mmol; i.e. containing 50 μmol of nonradioactive $^{19}F_2$)[13] diluted with 100 mmol of neon was bubbled into a solution of the amide **1** (65 μmol) in freon (15 mL) at 0 °C over a period of 15 min. The solvent was evaporated at room temperature by bubbling dry argon, and the oily product was dissolved in 2 mL of dry ether. If necessary, the [^{18}F]fluorolactams **2** could by purified by HPLC.[12] However, it could be used in the next step without purification. The isolated chemical yields as well as radiochemical yields are reported in Table I.

General Procedure for the Reaction of [^{18}F]Fluorolactams with Grignard Reagents. To the [^{18}F]fluorolactam (20 μmol), as prepared above, the Grignard reagent **3** (65 μmol in 1 mL of ether) was added, vortexed for 1 min, and quenched with 1 N NH_4Cl solution (1 mL). The product **4** was isolated by semipreparatory HPLC. The overall process was carried out in less than 60 min, and the yields for the isolated ^{18}F-labeled products are given in Table II.

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Registry No. **1a**, 616-45-5; **1b**, 675-20-7; **1c**, 105-60-2; **1d**, 673-66-5; **1e**, 935-30-8; **2a**, 126063-29-4; **2b**, 126063-30-7; **2c**, 126063-31-8; **2d**, 126063-32-9; **2e**, 126063-33-0; **3** (R = Ph), 100-58-3; **3** (R = *p*-Tolyl), 4294-57-9; **3** (R = 1-naphthyl), 703-55-9; **3** (R = cyclohexyl), 931-50-0; **4** (R = Ph), 3857-04-3; **4** (R = *p*-tolyl), 2070-54-4; **4** (R = 1-naphthyl), 126063-34-1; **4** (R = cyclohexyl), 126063-35-2; $^{18}F_2$, 13981-56-1.

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Cleavage of Aldehyde Hydrazonium Iodides under Mild Conditions. A Convenient Route to Chiral Nitriles of High Enantiomeric Purity

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The combination of chiral recognition and dipole-dipole forces can have great impact on self-assembly and ordering transitions in organic phases. A remarkable example discovered not long ago was the organization of chiral

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