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ortho-Disubstituted *F*-Benzenes. V. Intramolecular Heteroatom-facilitated ortho-Substitution of *F*-Benzene Derivatives with Oxazolinyl and Oxazinyl Groups

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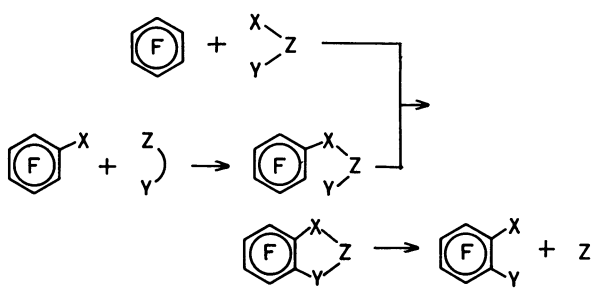
The oxazinyl and oxazolinyl substituents on an *F*-benzene ring facilitated the substitution of fluorine ortho to the heterocyclic functional groups by carbon and nitrogen nucleophiles. Alkylmagnesium halides and alkyllithium compounds were employed as the carbon nucleophile, and lithium *N*-methylanilide and *N*-methylanilinomagnesium halide as the nitrogen nucleophile. The selective ortho-substitution was accomplished by the complexing interaction between the ring-membered nitrogen on the functional substituents and the anionic nucleophile through the interposing metal cation. Effects of the substituents in the orientations and rates of the reactions depended upon the polarity of the reaction solvent and the kinds of anionic nucleophile and counter metal cation.

The reaction of monosubstituted *F*-benzene[1] with nucleophiles affords predominantly para-disubstituted derivatives, except for a few cases of the formation of meta-disubstituted products.[2] Some attempts at the specific formation of ortho-disubstituted *F*-benzenes are available in the literature. Most of them can be classified as intramolecular cyclization followed by cleavage of the resulting (*F*-benzo)-heterocyclic ring, as shown in Scheme 1.[3-16] Such heterocyclic rings, however, sometimes have been difficult to cleave.

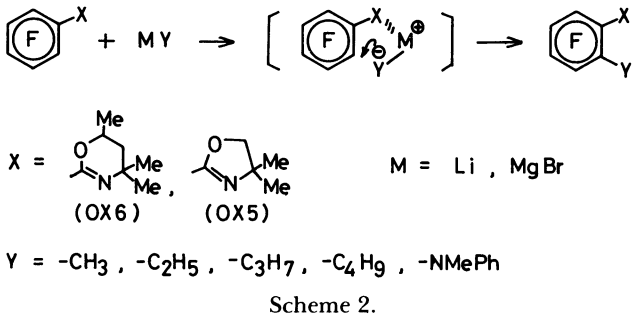


Scheme 1.

There are also some exceptional cases where the ortho-substitution dominates. Actually nitro, carbonyl, sulfone, and amine oxide substituents direct the ortho-substitution in nonpolar solvents.[2c,17] This anomalous behavior was interpreted in terms of a particular affinity of such substituents for the counter cation paired with an anionic nucleophile at the transition stage; namely, the cation is pulled towards the close neighborhood of such a substituent, so that the anionic nucleophile is oriented to attack preferentially the sterically favorable ortho-position.

Meyers and Gschwend showed that an oxazolinyl substituent on an aromatic ring was highly efficient in directing the lithiodeprotonation at the ortho-position,[18,19] and accelerated the nucleopuhilic displacement of a methoxyl group or fluorine ortho to the oxazolinyl substituent.[18,20] The ortho-activation by the oxazolinyl group in deprotonation and nucleophilic displacement was attributable to the strong ion-dipole interaction between the oxazolinyl group and lithium cation.

In the present study, 2-oxazolin-2-yl (OX5) and 1,3-oxazin-2-yl (OX6) groups on an *F*-benzene ring were examined as to how well they promoted nucleophilic attack of carbon and nitrogen nucleophiles on the ortho-position prior to the para-one (Scheme 2).



Scheme 2.

Results

The starting 2-(*F*-phenyl)-4,4,6-trimethyl-5,6-dihydro-4*H*-oxazine (**1**) and 2-(*F*-phenyl)-4,4-dimethyl-2-oxazoline (**2**) were obtained according to the methods for the preparation of the corresponding hydrocarbon analogues.[21]

Reaction with C-Nucleophile. Lithium and magnesium ions were favorable for the complex formation with the oxazoline and oxazine groups.[18] Organolithium and Grignard reagents were therefore employed as carbon nucleophiles.

Both Grignard and lithio reagents attacked exclusively the aromatic carbon ortho to the oxazolinyl and oxazinyl groups. The efficacies in the ortho-orientation caused by these functional substituents are evident in the formation of 2′-alkyl-*F*-phenyl derivatives (locations on the *F*-phenyl ring are primed) and 2′,6′-dialkyl-*F*-phenyl ones, while no 4′-monoalkylated products nor 2′,4′-dialkylated ones form at all.

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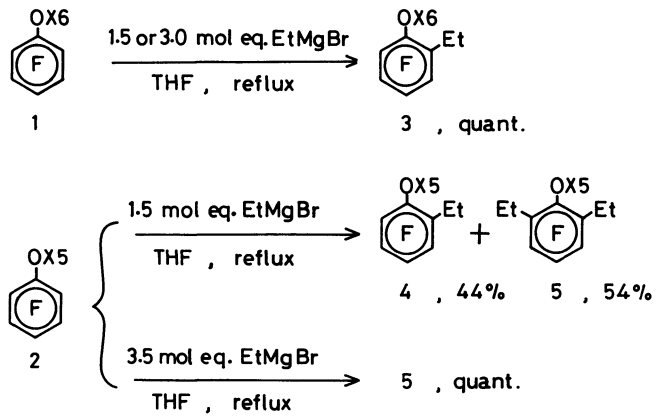
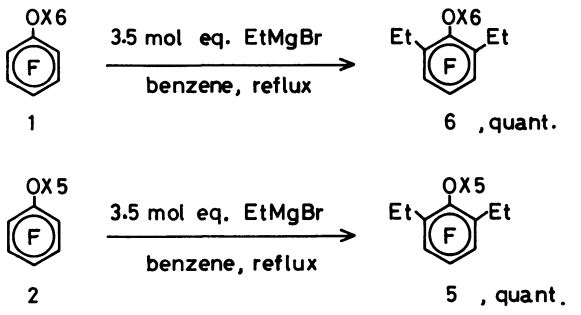


Scheme 3.

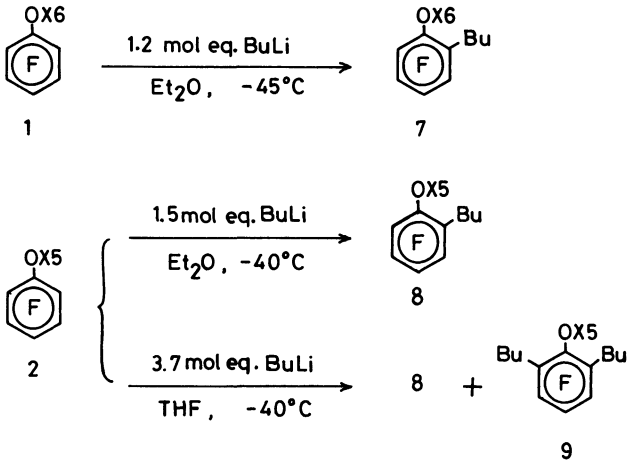
In the reaction of the oxazine **1** and the oxazoline **2** with 1.5 times molar amounts of ethylmagnesium bromide in THF, the corresponding ortho-substituted *F*-phenyl derivatives, **3**, **4**, and **5**, were exclusively afforded, as shown in Scheme 3. The ethyl derivatives **3** and **4** each show four ^{19}F-NMR signals of equal intensity. Even if an excess of ethylmagnesium bromide was added, the oxazine **1** in THF gave only the 2′-monoalkylated product **3** quantitatively, while the oxazoline **2** gave the 2′,6′-dialkylated product **5** also in quantitative yield by use of an excess of ethylmagnesium bromide. The latter product exhibits two ^{19}F-NMR signals with relative intensities of one to two. These results indicate that the oxazine **1** and the oxazoline **2** are both highly ortho-directing, no para-substituted products being formed at all.

When an excess amount of ethylmagnesium bromide was used in benzene, which is less polar and has a higher boiling point than THF, the oxazine **1** and oxazoline **2** both afforded only the 2′,6′-disubstituted products, **5** and **6**, quantitatively (Scheme 4).



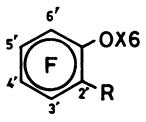
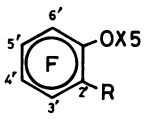
Scheme 4.

These substrates **1** and **2** reacted with butyllithium to give the corresponding ortho-substituted products, as shown in Scheme 5. The reactions with butyllithium, however, could be controlled only with some difficulty, so that the selectivity and yield of the products were less reproducible than those with the Grignard reagent.

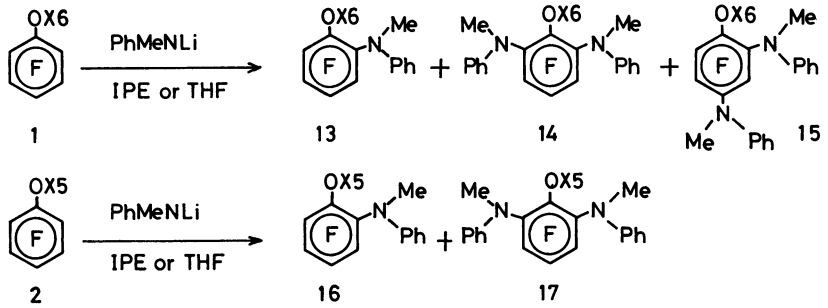


Scheme 5.

TABLE 1. ^{19}F-NMR SPECTRAL DATA OF THE (ORTHO-ALKYL-*F*-PHENYL) OXAZINES AND OXAZOLINES IN CCl_4 SOLUTIONS

	Compound	Chemical shifts/ppm against an internal C_6F_6			
		$F^{3'}$	$F^{4'}$	$F^{5'}$	$F^{6'}$
	**10**; R=Me	19.6 (m)	5.4 (ddd)	2.0 (ddd)	19.8 (m)
	3; Et	17.0 (ddd)	5.5 (ddd)	2.1 (ddd)	19.6 (ddd)
	7; *n*-Bu	17.7 (ddd)	5.3 (ddd)	2.1 (ddd)	19.5 (ddd)
	**11**; R=Me	20.4 (dddq)	8.1 (ddd)	2.9 (ddd)	23.1 (ddd)
	4; Et	17.9 (ddd)	8.3 (ddd)	3.0 (ddd)	23.2 (ddd)
	12; *n*-Pr	19.0 (ddd)	8.2 (ddd)	3.1 (ddd)	23.0 (ddd)
	8; *n*-Bu	18.8 (ddd)	8.2 (ddd)	2.9 (ddd)	23.2 (ddd)

	F-F Coupling constants/ Hz				
3′-4′	3′-5′	3′-6′	4′-5′	4′-6′	5′-6′
17.9	0.9	12.0	21.3	2.3	21.3
20.7	1.9	12.5	20.7	2.9	21.6
21.1	1.9	12.5	21.6	3.4	22.1
20.9	2.4	7.3	20.9	4.4	20.9
21.0	2.9	12.2	21.0	4.4	21.0
21.5	2.0	12.2	21.5	4.4	21.5
20.7	2.2	11.9	21.2	4.4	21.2



Scheme 6.

Table 2. Reactions of the oxazine (**1**) and the oxazoline (**2**) with lithium *N*-methylanilide

Run No.	Substrate	Molar ratio[a)]	Solvent	Temp °C	Reaction time/h	Products (Yield/%)		
						o-mono-	*o,o'*-di-	*o,p*-di-
1	**1**	2.0	IPE[b)]	50	19.5	**13** (73)	—	—
2	**1**	3.0	IPE[b)]	50	68	**13** (3)	**14** (86)	—
3	**1**	1.6	THF	Reflux	2	**13** (12)	—	**15** (36)
4	**2**	2.0	IPE[b)]	Reflux	13.3	**16** (87)	**17** (10)	—
5	**2**	3.0	IPE[b)]	Reflux	19.5	**16** (49)	**17** (46)	—
6	**2**	1.5	THF	Reflux	4.5	**16** (17)	**17** (40)	—

a) Molar ratio of lithium *N*-methylanilide to the subtrate. b) IPE, for diisoproryl ether.

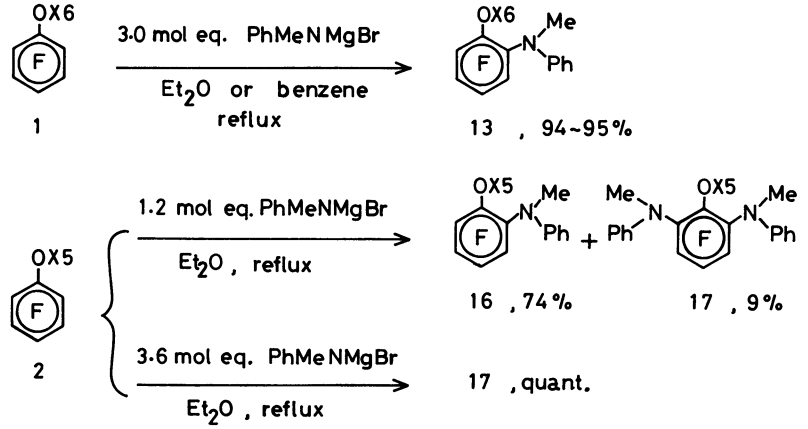
These difficulties would be due to the reactivity of alkyllithium being higher than that of the alkylmagnesium halide.

Methyl and propyl groups could be also introduced to the ortho-position on the *F*-phenyl group of the oxazine **1** and the oxazoline **2** by use of their lithio and Grignard reagent to give 2'-alkyl derivatives **10**, **11**, and **12**.[22)]

Comparisons of ^{19}F-NMR spectra of the present (2'-alkyl-*F*-phenyl)oxazines, **3**, **7**, and **10**, and -oxazolines **4**, **8**, **11**, and **12**, indicated that the chemical shifts of one fluorine varied with the alteration of the alkyl substituents, while those of the other fluorines remained within a range of 0.2 ppm, as shown in Table 1. Thus, the former signals could be assigned tentatively to the 3'-fluorine adjacent to such alkyl substituents. The assignment of fluorine chemical shifts was compatible with the relatively large downfield shifts at the adjacent 3'-fluorine caused by the monoalkylation and at the 3'- and 5'-fluorines by the dialkylation, and also the presence of the long-range coupling between 3'-fluorine and 2'-methyl hydrogens of **11** in its ^{19}F-NMR spectrum.

Reaction with N-*Nucleophile.* In the reactions with lithium *N*-methylanilide as a nitrogen nucleophile, the oxazine **1** and the oxazoline **2** gave the corresponding ortho-substituted *F*-phenyl derivatives in diisopropyl ether and THF solutions, as shown in Scheme 6.

The monoanilino derivatives, **13** and **16**, each show four ^{19}F-NMR signals of equal intensity. Their structures were interpreted on the basis of the ^{19}F-NMR chemical shifts which were assigned in an analogous manner with those of the ortho-alkylated *F*-phenyloxazines and -oxazolines. The mass spectra of **14**, **15**, and **17** indicate that the dianilino substitutions also occurred in the above reactions. ^{19}F-NMR spectra of **14** and **17**, which showed two signals of one to two in intensity ratio indicated that the disubstituted *F*-phenyloxazine and -oxazoline were of the vicinal 1',2',6'-trisubstituted *F*-benzene structure. On the other hand, three ^{19}F-signals of equal intensity of **15** indicated



Scheme 7.

that the disubstituted *F*-phenyloxazine structure was the unsymmetrical 1′,2′,4′-trisubstituted *F*-benzene structure. Lithium *N*-methylanilide in a THF solution attacked the oxazine **1** on the 2′- and 4′-positions (Run 3 in Table 2), while in diisopropyl ether, which is less polar than THF, it attacked the 2′- and 6′-positions (Run 2 in Table 2). The oxazoline **2** did not afford any 4′-substituted product, even in a THF solution (Compare Run 6 with Run 3 in Table 2), and was superior in the regioselectivity than was the oxazine **1**.

With *N*-methylanilinomagnesium bromide, on the other hand, both the reaction of the oxazine **1** and that of the oxazoline **2** proceeded, in analogy with those with alkylmagnesium bromide, to give 2′-mono- and 2′,6′-disubstituted products, **13**, **16**, and **17**, predominantly, in both diethyl ether and benzene solutions (Scheme 7).

Discussion

The oxazinyl and oxazolinyl groups on an *F*-benzene ring are effective to facilitate the carbon-carbon and carbon-nitrogen bond formation exclusively at the ortho-position on the *F*-benzene ring relative to those heterocyclic functional groups. Such ortho-directing effects, however, seemed to be remarkable among the carbon and nitrogen nucleophiles studied so far, since the reaction with other nucleophilic reagents such as lithium aluminum hydride and lithium phenoxide took a longer reaction period and afforded an appreciable yield of the para-substituted product, though the ortho-substituted one was major.[23]

The ring-membered nitrogens of the oxazinyl and the oxazolinyl groups seem to play the indispensable role in the interacion with the metal cation, since the oxolanyl group in 2-methyl-2-(*F*-phenyl)-1,3-dioxolane (**18**) is less effective not only in the regioselectivity but also in the acceleration of reactions, as shown in Scheme 8, where the dioxolane **18** were not alkylated with ethylmagnesium bromide under reflux in benzene.

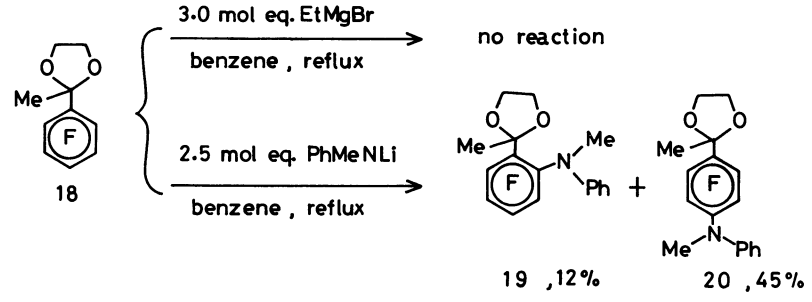
Complexation of the metal cation at the ring-membered nitrogen would lead the nucleophilic agent, which was tightly paired with the metal cation, to attack the ortho-position nearest to the heterocyclic substituent. The coordination of the nitrogen to metal cation would also induce the mesomeric polarization of the C–N double bond of the heterocyclic substituents. The effect would promote not only the nucleophilicity of the anionic agent at the beginning stage of the attack, but also the mesomeric stabilization of an intermediary anionic σ-complex at the subsequent stage, and facilitate the bond formation between the ortho-carbon and nucleophiles as illustrated in Scheme 9.

The oxazolinyl group of a smaller ring size seemed more effective in promoting the reaction than the larger oxazinyl group; once the substitution occurred on an ortho-position, the former allowed the successive substitution on the opposite ortho-position even under milder conditions, in contrast to the latter in which no additional ortho-substitution occurred.

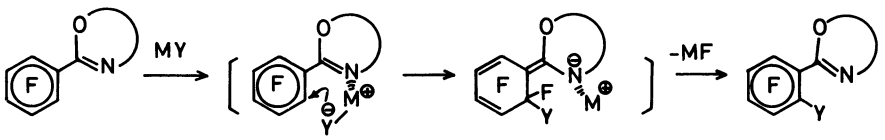
Such differences in the reactivity and selectivity might be due to the restricted rotation about the bond between the heterocyclic ring and the ortho-monosubstituted *F*-phenyl ring; *i.e.*, a coplanar conformation which would be required for mesomeric stabilization upon the subsequent substitution might be hindered by the ortho-substituent on the *F*-phenyl ring, and such a steric hindrance would be more pronounced with a larger ring size than a smaller one.

Polarity of the reaction solvent also affected the reaction path. In a less polar solvent such as benzene, the substitution proceeded to a higher extent. Such increased reactivity was understandable as follows: The less polar was the reaction solvent, the more tightly the metal cation would be coordinated with the substrate molecule at the donating nitrogen atom, so that the anionic nucleophile attacked preferably the nearest ortho-position.

The participation of the oxazinyl and oxazolinyl substituents depended also upon the kind of anionic nucleophiles; lithium amide, hydroxide, and bromide in benzene solutions caused no reactions; the starting compounds remaining intact, presumably due to very low solubility of these lithium salts in the reaction solvent.



Scheme 8.



Scheme 9.

Experimental

Melting points were uncorrected. IR spectra were measured with a JASCO DS-403G spectrometer. ^{1}H- and ^{19}F-NMR chemical shifts were recorded on a HITACHI 24-B against the internal TMS reference, and on JEOL FX-100 and HITACHI 24-F as the positive values downfield from the internal *F*-benzene reference, respectively. Mass spectra were obtained with JEOL JMS-07 and 01SG spectrometers. Electronic spectra were measured with a HITACHI 200-20 instrument. *F*-Benzonitrile[24] and *F*-benzoyl chloride[25] were prepared according to the literature methods.

2-(F-Phenyl)-4,4,6-trimethyl-5,6-dihydro-4H-oxazine (1). *F*-Benzonitrile (5.79 g, 30 mmol) was added dropwise to concentrated sulfuric acid (15 g, 220 mmol) over a 5-min period at 0 °C. To the mixture was added 2-methyl-2,4-pentanediol (3.54 g, 30 mmol) over a 15-min period at 0 °C. The resulting mixture was stirred at 0 °C for an additional 30 min, then at room temperature for another additional 30 min, and poured into ice-water. The aqueous mixture was basified by sodium hydroxide and extracted with diethyl ether. The ethereal extract was washed with water and dried over sodium sulfate. The dried extract was distilled, and the fraction boiling at 113 °C/1200 Pa gave 2-(*F*-phenyl)-4,4,6-trimethyl-5,6-dihydro-4*H*-oxazine (**1**) (4.48 g, 51%) in colorless oil. ^{1}H-NMR (neat): δ=1.05—2.10 (m, 11H, CH_3, CH_2) and 4.00—4.60 (m, 1H, CH)). ^{19}F-NMR (CCl_4): —0.7 (m, 2F, F$^{3'}$ and F$^{5'}$), 7.6 (tt, 1F, F$^{4'}$), and 20.4 ppm (m, 2F, F$^{2'}$, and F$^{6'}$), ($J_{2'4'}$=3.4 and $J_{3'4'}$=21.2 Hz). UV (EtOH): λ_{max} (log ε); 207 (2.94) and 263 nm (2.16). Found: C, 53.12; H, 4.20; N,4.50%; M$^+$, 293. Calcd for $C_{13}H_{12}NF_5O$: C, 53.25; H, 4.13; N, 4.78%; M, 293.

2-(F-Benzoylamino)-2-methyl-1-propanol (21). A solution of *F*-benzoyl chloride (1.74 g, 7.6 mmol) in anhydrous dichloromethane (5 cm^3) was added dropwise to a stirred solution of 2-amino-2-methyl-1-propanol (1.35 g, 15 mmol) in anhydrous dichloromethane (10 cm^3) over a 30-min period at 0 °C. The mixture was kept stirred at room temperature for an additional 12 h, and then evaporated to dryness *in vacuo*. The residue was washed with water, and recrystallization from benzene gave 2-(*F*-benzoylamino)-2-methyl-1-propanol (**21**) (1.86 g, 87%) in colorless plates, mp 126 °C. IR (KBr): 3350 and 3200 (OH, NH), and 1660 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$–DMSO-d_6): δ=1.34 (s, 6H, CH_3), 3.54 (d, J=5.3 Hz, 2H, CH_2), 4.28 (br. t, J=5.3 Hz, 1H, OH), and 7.25 (br. s, 1H, NH). Found: M$^+$, 283. Cacld for $C_{11}H_{10}NF_5O_2$: M, 283.

2-(F-Phenyl)-4,4-dimethyl-2-oxazoline Hydrochloride (22). A mixture of the propanol **21** (9.52 g, 33.7 mmol) and thionyl chloride (7.1 cm^3, 100 mmol) was stirred at room temperature for 1 d. The mixture was poured into diethyl ether, and evaporated to dryness *in vacuo*. The residue was 2-(*F*-phenyl)-4,4-dimethyl-2-oxazoline hydrochloride (**22**) (7.47 g, 72%) in a colorless solid, mp 119—120 °C. ^{1}H-NMR ($CDCl_3$): δ=1.45 (s, 6H, CH_3), 3.85 (s, 2H, CH_2), and 6.15 (br. s, 1H, HCl). Found: M$^+$, 303 and 301. Calcd for $C_{11}H_9NClF_5O$: M, 303 and 301.

2-(F-Phenyl)-4,4-dimethyl-2-oxazoline (2). A solution of the hydrochloride **22** (3.35 g, 11.1 mmol) in anhydrous THF (10 cm^3) was added dropwise to a stirred mixture of sodium hydride (17.7 mmol) and anhydrous THF (10 cm^3) over a 5-min period at room temperature under a dry nitrogen atmosphere. The mixture was stirred at room temperature for an additional 10 min and poured into diethyl ether. The ethereal solution was washed with water, dried over sodium sulfate, and evaporated *in vacuo*. The residue was distilled, and the fraction boiling at 96—97 °C/1600 Pa gave 2-(*F*-phenyl)-4,4-dimethyl-2-oxazoline (**2**) (2.68 g, 91%) in colorless oil. ^{1}H-NMR (CCl_4): δ=1.32 (s, 6H, CH_3), and 4.03 (s, 2H, CH_2). ^{19}F-NMR (CCl_4): 0.3 (m, 2F, F$^{3'}$ and F$^{5'}$), 10.5 (tt, 1F, F$^{4'}$), and 24.6 ppm (m, 2F, F$^{2'}$ and F$^{6'}$), ($J_{2'4'}$=2.1 and $J_{3'4'}$=21.1 Hz). UV (EtOH): λ_{max} (log ε); 211 nm (2.92). Found: C, 49.66; H, 3.06; N, 5.26%; M$^+$, 265. Calcd for $C_{11}H_8NF_5O$: C, 49.82; H, 3.04; N, 5.28%; M, 265. Isolation of the free oxazoline **2** from the hydrochloride **22** failed with aqueous and methanolic alkalis.

Reaction of the Oxazine 1 with Ethylmagnesium Bromide. The Reaction in THF: A solution of the oxazine **1** (1.17 g, 4.0 mmol) in anhydrous THF (10 cm^3) was added dropwise to a stirred mixture of ethylmagnesium bromide (6.0 mmol) and anhydrous THF (20 cm^3) over a 5-min period at room temperature under a dry nitrogen atomosphere. The mixture was refluxed for 10 h with stirring, poured into water after being cooled, and extracted with dichloromethane. The extract was washed with water, dried over sodium sulfate, and evaporated *in vacuo*. The residue was developed on a silica-gel TLC plate with dichloromethane. The fraction of R_f=0.15—0.20 afforded 2-(2-ethyl-*F*-phenyl)-4,4,6-trimethyl-5,6-dihydro-4*H*-oxazine (**3**) (1.16 g, 93%) in colorless oil. Found: M$^+$, 303. Calcd for $C_{15}H_{17}NF_4O$: M, 303. Elemental analysis was carried out in the form of its hydrochloride monohydrate. Found: C, 50.34; H, 5.63; N, 3.91%. Calcd for $C_{15}H_{18}NClF_4O \cdot H_2O$: C, 50.36; H, 5.63; N, 3.92%.

The Reaction in Benzene: A solution of the oxazine **1** (1.17 g, 4.0 mmol) in dry benzene (20 cm^3) was added dropwise to a stirred mixture of ethylmagnesium bromide (14 mmol) and anhydrous diethyl ether (30 cm^3) over a 10-min period at room temperature under a dry nitrogen atmosphere. Diethyl ether was distilled out of the mixture by adding portions of dry benzene. The resulting benzene solution was refluxed for an additional 10 h and worked up in a similar manner. 2-(2,6-Diethyl-*F*-phenyl)-4,4,6-trimethyl-5,6-dihydro-4*H*-oxazine (**6**) was obtained quantitatively, in colorless oil. ^{19}F-NMR (CCl_4): 1.1 (t, 1F, F$^{4'}$) and 18.9 ppm (d, 2F, F$^{3'}$ and F$^{5'}$), ($J_{3'4'}$=21.2 Hz). Found: M$^+$, 313. Calcd for $C_{17}H_{22}NF_3O$: M, 313. Found: (Hydrochloride monohydrate): C, 55.41; H, 6.83; N, 3.77%. Calcd for $C_{17}H_{23}NClF_3O \cdot H_2O$: C, 55.51; H, 6.85; N, 3.81%.

Reaction of the Oxazoline 2 with Ethylmagnesium Bromide. The Reaction in THF: The oxazoline **2** (1.06 g, 4 mmol) reacted with ethylmagnesium bromide (6 mmol) in anhydrous THF (30 cm^3) like the oxazine **1** did. The reaction mixture was distilled, and the fraction boiling at 95—96 °C/1200 Pa gave colorless oily 2-(2-ethyl-*F*-phenyl)-4,4-dimethyl-2-oxazoline (**4**) in 44% yield. Found: C, 56.85; H, 4.91; N, 4.94%; M$^+$, 275. Calcd for $C_{13}H_{13}NF_4O$: C, 56.73; H, 4.76; N, 5.09%; M, 275. The residue was developed on a silica-gel TLC plate with dichloromethane. The fraction of R_f=0.2—0.3 afforded 2-(2,6-diethyl-*F*-phenyl)-4,4-dimethyl-2-oxazoline (**5**) in 54% yield, colorless oil. ^{19}F-NMR (CCl_4): 3.5 (t, 1F, F$^{4'}$) and 19.7 ppm (d, 2F, F$^{3'}$ and F$^{5'}$), ($J_{3'4'}$=21.6 Hz). Found: M$^+$, 285. Calcd for $C_{15}H_{18}NF_3O$: M, 285. Found (Hydrochloride): C, 56.06; H, 6.02; N, 4.26%. Calcd for $C_{15}H_{19}NClF_3O$: C, 55.99; H, 5.95; N, 4.35%.

The Reaction in Benzene: The reaction in dry benzene was carried out in a similar manner to that in diethyl ether. The residue was purified by TLC on a silica-gel plate. The fraction of R_f=0.2—0.3 gave the diethyl derivative **5** quantitatively.

Reaction of the Oxazine 1 with Butyllithium. A mixture of butyllithium (1.17 mmol, *ca.* 15% hexane solution) and anhydrous diethyl ether (3 cm^3) was added dropwise to a stirred solution of the oxazine **1** (298 mg, 1 mmol) in anhydrous diethyl ether (5 cm^3) over a 5-min period at —45 °C under a dry nitrogen atmosphere. The mixture was kept stirred at —45 °C for 21 h and at room temperature for an additional 3 h, and poured into diethyl ether. The ethereal solution was washed with water, dried over sodium sulfate, and evaporated *in vacuo*. The residue was purified by TLC to give 2-(2-butyl-*F*-phenyl)-4,4,6-trimethyl-5,6-dihydro-4*H*-oxazine (**7**) in 65%

yield, a colorless oil. Found: M+ 331. Calcd for $C_{17}H_{21}NF_4O$: M, 331. Found (Hydrochloride): C, 55.41; H, 6.05; N, 3.76%. Calcd for $C_{17}H_{22}NClF_4O$: C, 55.51; H, 6.03; N, 3.81%.

Reaction of the Oxazoline **2** *with Butyllithium.* A mixture of butyllithium (2.3 mmol, *ca.* 15% hexane solution) and anhydrous diethyl ether (5 cm³) was added dropwise to a stirred mixture of the oxazoline **2** (396 mg, 1.5 mmol) and anhydrous diethyl ether (5 cm³) over a 25-min period at −40 °C under a dry nitrogen atmosphere. The mixture was stirred at −40 °C for 6.5 h and then at room temperature for an additional 3 h, and then was worked up as above. The residue was chromatographed on a silica-gel column. The earlier fraction eluted with dichloromethane gave 2-(2-butyl-*F*-phenyl)-4,4-dimethyl-2-oxazoline (**8**) (49 mg, 11%) in colorless oil. Found: C, 59.33; H, 5.69; N, 4.50%; M+, 303. Calcd for $C_{15}H_{17}NF_4O$: C, 59.40; H, 5.65; N, 4.62%; M, 303. The later fraction eluted with dichloromethane was the starting compound **2** (266 mg, 67%).

When treated with 3.7 times molar amounts of butyllithium, the compound **8** (40%) and 2-(2,6-dibutyl-*F*-phenyl)-4,4-dimethyl-2-oxazoline (**9**) (15%) was obtained. ^{19}F-NMR (CCl_4): 3.1 (t, 1F, F$^{4'}$) and 19.4 ppm (d, 2F, F$^{3'}$ and F$^{5'}$), ($J_{3'4'}$ = 21.5 Hz). Found: C, 66.86; H, 7.63; N, 4.11%; M+, 341. Calcd for $C_{19}H_{26}NF_3O$: C, 66.84; H, 7.68; N, 4.10 %; M, 341.

Reaction of the Oxazine **1** *with Lithium* N-*Methylanilide.* A solution of the oxazine **1** (0.1 g, 0.36 mmol) in anhydrous diisopropyl ether (6 cm³) was added dropwise over a 10-min period at room temperature under a dry nitrogen atmosphre to a stirred mixture of lithium *N*-methylanilide (0.72 mmol), which was prepared from *N*-methylaniline and lithium amide in anhydrous diisopropyl ether (7 cm³). The mixture was stirred at 50 °C for an additional 19.5 h, and poured into diethyl ether after being cooled. The ethereal solution was washed with water. The aqueous washings were acidified and again extracted with diethyl ether. The ethereal extract and the original ethereal solution were combined, washed with water, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on a silica-gel column. The fraction eluted with dichloromethane gave 2-[2-(*N*-methylanlino)-*F*-phenyl]-4,4,6-trimethyl-5,6-dihydro-4*H*-oxazine (**13**) (73%) in pale yellow oil. ^{19}F-NMR ($CDCl_3$): 3.89 (ddd, 1F, F$^{5'}$), 7.59 (ddd, 1F, F$^{4'}$), 15.79 (ddd, 1F, F$^{3'}$), and 20.44 ppm (ddd, 1F, F$^{6'}$) ($J_{3'4'} = J_{4'5'} =$ 22.59, $J_{3'6'} = 10.99$, and $J_{4'6'} = J_{3'5'} = 2.44$ Hz). Found: C, 63.30; H, 5.45; N, 7.29%; M+, 380. Calcd for $C_{20}H_{20}N_2F_4O$: C, 63.14; H, 5.31; N, 7.37%; M, 380.

When 3.0 times molar amounts of the reagent were used in the same solvent, a mixture of the monoanilino derivative **13** and 2-[2,6-bis(*N*-methylanilino)-*F*-phenyl]-4,4,6-trimethyl-5,6-dihydro-4*H*-oxazine (**14**) was obtained in the yields of 13 and 86%, respectively. The latter was a yellow oil. ^{19}F-NMR ($CDCl_3$): 6.79 (t, 1F, F$^{4'}$) and 20.28 ppm (d, 2F, F$^{3'}$ and F$^{5'}$), ($J_{3'4'}$ = 21.97 Hz). Found M+, 467. Calcd for $C_{27}H_{28}N_3F_3O$; M, 467. Found (Hydrochloride): C, 64.41; H, 5.84; N, 8.42%. Calcd for $C_{27}H_{29}N_3ClF_3O$: C, 64.35; H, 5.80; N, 8,34%.

When the reaction was carried out in anhydrous THF with 1.5 times molar amounts of the reagent, the mixture of the monoanilino derivative **13** and 2-[2,4-bis(*N*-methylanilino)-*F*-phenyl]-4,4,6-trimethyl-5,6-dihydro-4*H*-oxazine (**15**) was afforded in the yields of 12 and 36%, respectively. ^{19}F-NMR (CCl_4) of the latter **15**: 20.6 (dd, 1F, F$^{6'}$), 21.0 (d, 1F, F$^{5'}$), and 33.9 ppm (d, 1F, F$^{3'}$), ($J_{3'6'} = 13.0$, $J_{5'6'} = 24.0$ Hz). Found: M+ 467. Calcd for $C_{27}H_{28}N_3F_3O$: M, 467.

Reaction of the Oxazoline **2** *with Lithium* N-*Methylanilide.* The reaction was carried out in anhydrous diisopropyl ether with 2.0 times molar amounts of the reagent as described above. The reaction mixture was chromatographed on a silica-gel column, then eluted with dichloromethane. The earlier fraction gave 2-(2-*N*-methylanilino-*F*-phenyl)-4,4-dimethyl-2-oxazoline (**16**) (87%), which was isolated in the form of the yellow picrate, mp 149—150 °C (decomp). ^{19}F-NMR ($CDCl_3$): 4.17 (ddd, 1F, F$^{5'}$), 12.15 (ddd, 1F, F$^{4'}$), 17.27 (ddd, 1F, F$^{3'}$) and 24.43 ppm (ddd, 1F, F$^{6'}$), ($J_{3'4'} = J_{4'5'} = J_{5'6'} = 21.97$, $J_{3'6'} = 10.98$, $J_{3'5'} = 4.88$, and $J_{4'6'} = 2.44$ Hz). Found (Picrate): C, 49.71; H, 3.31; N, 12.02%. Calcd for $C_{24}H_{19}N_5F_4O_8$: C, 49.58; H, 3.29; N, 12.05%. The later fraction afforded 2-[2,6-bis(*N*-methylanilino)-*F*-phenyl]-4,4-dimethyl-2-oxazoline (**17**) (10%) in pale yellow powder, mp 102—103.5 °C. ^{19}F-NMR ($CDCl_3$): 9.41 (t, 1F, F$^{4'}$) and 21.16 ppm (d, 2F, F$^{3'}$ and F$^{5'}$, ($J_{3'4'}$ = 21.97 Hz). Found: C, 68.26; H, 5.66; N, 9.32%; M+, 439. Calcd for $C_{25}H_{24}N_3F_3O$: C, 68.31; H, 5.52; N, 9.56%; M, 439.

When 3.0 times molar amounts of the reagent were used in the same reaction solvent, a mixture of the same products, **16** and **17**, was obtained, while the yields varied to 49 and 46%, respectively; these values were determined by GLC peak areas and ^{19}F-NMR signal intensities. The reaction which was carried out in anhydrous THF with 1.5 times molar amounts of the reagent, also afforded the same products, **16** and **17**, in the yields of 17 and 40%, respectively.

Reaction of the Oxazine **1** *with* N-*Methylanilinomagnesium Bromide.* A solution of the oxazine **1** (0.3 g, 1.19 mmol) in anhydrous diethyl ether (8 cm³) was added dropwise to the solution of *N*-methylanilinomagnesium bromide (3.57 mmol), which was prepared by adding ethereal *N*-methylaniline into ethylmagnesium bromide in diethyl ether over a 10-min period under a dry nitrogen atmosphere. The mixture was refluxed for 14.5 h, and the formation of the product **13** was determined by GLC to be in 96% yield. When the reaction solvent was altered into dry benzene, the same product **13** was formed in 95% yield.

Reaction of the Oxazoline **2** *with* N-*Methylanilinomagnesium Bromide.* The reaction was carried out in anhydrous diethyl ether with 1.2 times molar amounts of the reagent, and the resulting mixture was worked up as above. The yields of ortho-substituted products, **16** and **17**, were 74 and 9%, respectively, and the starting oxazoline **2** was recovered in 17% yield; the yields were determined by the ^{19}F-NMR signal ratio of the reaction mixture.

When 3.0 times molar amounts of the reagent was used, 2′,6′-disubstituted product **17** was obtained quantitatively.

2-Methyl-2-(F-phenyl)-1,3-dioxolane (18). A solution of 2,3,4,5,6-pentafluoroacetophenone (4.62 g, 22 mmol), ethylene glycol (1.24 g, 20 mmol), and *p*-toluenesulfonic acid (0.1 g, 1 mmol) in anhydrous methanol (50 cm³) was refluxed for 22 h under a nitrogen atmosphere. Cyclohexane (230 cm³) was added to the resulting mixture, which was distilled to remove water as an azeotropic mixture. The residue was then distilled and the fraction boiling at 113 °C/6300 Pa gave 2-methyl-2-(*F*-phenyl)-1,3-dioxolane (**18**) (1.85 g, 36%). IR (neat): 1208 and 1168 cm^{-1} (C–O–C). ^{1}H-NMR (neat): δ = 1.7 (s, 3H, CH_3) and 3.8—4.4 (m, 4H, CH_2). ^{19}F-NMR (neat): —0.3 (m, 2F, F$^{3'}$ and F$^{5'}$), 6.7 (tt, 1F, F$^{4'}$), and 21.4 ppm (m, 2F, F$^{2'}$ and F$^{4'}$), ($J_{2'4'} = 3.7$, $J_{3'4'} = 20.8$ Hz). Found: C, 47.25; H, 2.79%; M+, 254. Calcd for $C_{10}H_7F_5O_2$: C, 47.26; H, 2.77%; M, 254.

Reaction of the Dioxolane **18** *with Ethylmagnesium Bromide.* The dioxolane **18** (0.4 g, 1.6 mmol) reacted with ethylmanesium bromide (4.8 mmol) in anhydrous benzene like the oxazine **1** did. The starting dioxolane **18** was confirmed by GLC to remain intact under such conditions.

Reaction of the Dioxolane **18** *with Lithium* N-*Methylanilide.* A solution of the dioxolane **18** (0.3 g, 1.2 mmol) in dry benzene (5 cm³) was added dropwise to a stirred mixture of lithium *N*-methylanilide (3.0 mmol) and anhydrous benzene (5 cm³) over a 10-min period at room temperaure under a nitrogen atmosphere. The mixture was refluxed for 29 h, and poured into diethyl ether (50 cm³) after being cooled. The ethereal solution was washed with water, dried over

magnesium sulfate, and evaporated *in vacuo*. An addition of a small amount of heptane into the residue afforded the precipitates of 2-methyl-2-(4-*N*-methylanilino-*F*-phenyl)-1,3-dioxolane (**20**), mp 113—115°C. ^{19}F-NMR ($CDCl_3$): 16.89 dd, 2F, $F^{2'}$ and $F^{6'}$) and 18.72 ppm (dd, 2F, $F^{3'}$ and $F^{5'}$), ($J_{2'3'}$ = 21.97 and $J_{2'5'}$ = 10.99 Hz). Found: C, 59.94; H, 4.51; N, 4.18%. Calcd for $C_{17}H_{15}NF_4O_2$: C, 59.82; H, 4.44; N, 4.10%. The residue after separating the dioxolane **20** contained 2-methyl-2-(2-*N*-methylanilino-*F*-phenyl)-1,3-dioxolane (**19**), which could not be isolated in its pure form; the structure was assigned by its ^{19}F-NMR spectrum. ^{19}F-NMR ($CDCl_3$): 3.99 (dd, 1F, $F^{5'}$), 10.43 (ddd, 1F, $F^{4'}$), 16.80 (dd, 1F, $F^{3'}$), and 23.89 ppm (ddd, 1F, $F^{6'}$), ($J_{3'4'} = J_{4'5'} = J_{5'6'} = 21.97$, $J_{3'6'} = 10.79$, and $J_{3'5'} = 4.89$ Hz). Overall yields of **19** and **20** were 12 and 45%, respectively.

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22) Reactions of the oxazine (**1**) with methyllithium and the oxazoline (**2**) with methylmagnesium iodide and propylmagnesium bromide were performed like those with butyllithium and ethylmagnesium bromide, respectively, and afforded 2-(2-methyl-*F*-phenyl)-4,4,6-trimethyl-5,6-dihydro-4*H*-oxazine (**10**), and 2-(2-methyl-*F*-phenyl)- and 2-(2-propyl-*F*-phenyl)-4,4-dimethyl-2-oxazoline, (**11**) and (**12**), in 95, 15, and 25% yields, respectively. Enough of these alkyl derivatives could not be isolated in their pure forms for elemental analyses, so their structures were assigned by ^{19}F-NMR and mass spectra.

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