The Reactivity of 2-Fluoro- and 2-Chloropyridines toward Sodium Ethoxide: Factors Governing the Rates of Nucleophilic (Het)Aromatic Substitutions

by **Manfred Schlosser*** and **Thierry Rausis**

Institut des sciences et ingénierie chimiques, Ecole Polytechnique Fédérale, BCh, CH-1015 Lausanne
(e-mail: manfred.schlosser@epfl.ch)

Rolf Huisgen in Bewunderung und Verbundenheit

The relative displacement rates of the halide substituent from 2-fluoro- and 2-chloropyridines by EtONa in EtOH at $+25°$ were assessed by competition kinetics. The 2-fluoropyridine reacts 320 times faster than the chloro analog. A CF_3 group increases the reactivity more than single halogen atoms do, whatever the element, and the latter are superior to Me_3Si groups. Substituents accommodated at the 4-position operate through their inductive effect, whereas at the 3-position, this action may be attenuated by steric hindrance. Almost all 5-substituents enhance the rate of the nucleophilic substitution occurring at the 2-position. The sole exception concerns the F-atom at the 5-position which retards the reaction, presumably by lone-pair/lone-pair repulsion with the negative charge building up at the central C-atom of the intermediate *Meisenheimer* complex. The substituent effects are additive. Therefore, by using the increments derived from the present work, the rates of future reactions should be predictable with fair accuracy.

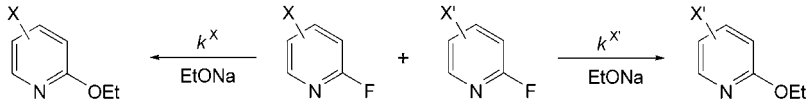
1. Introduction. – In our opinion, the regioselectivity of nucleophilic (het)aromatic substitutions did not yet receive the full attention it deserves. We came across this fundamental problem accidentally when we realized that 2,6-difluoropyridine-3-carbaldehyde reacts with lithium dimethylamide preferentially at the 6-position rather than, as previously claimed, indiscriminately at the 2- and 6-position [1]. In practical terms, more importantly, we disclosed shortly afterwards a method, the 'silyl trick', to reorient systematically the attack of nucleophiles on 2,4-dihalo- or 2,4,6-trihalopyridines from the privileged 4- to the competing 2- or 6-positions [2][3].

Absolute rates monitor reactivity, relative rates selectivity. In the following, we have assessed the ease with which structurally related 2-fluoropyridines and 2-chloropyridines undergo nucleophilic halide/ethoxide displacement. Sodium ethoxide (EtONa) is selected as the nucleophile because it is known to react with 2,4-difluorinated pyridines less regioselectively than any amine-type nucleophile would do. In other words, we expected EtONa to behave less regiodiscriminantly than, say, ammonia and thus to be more instructive.

2. Results. – To carry out competition experiments [4][5], 2-fluoropyridine (**1c**) and a substituted derivative (*e.g.*, 2,5-difluoropyridine (**1b**)) or pairs of 2-fluoropyridines of similar reactivity and carrying different substituents X and X′ (*e.g.*, 3-chloro-2-fluoropyridine (**1h**) and 4-chloro-2-fluoropyridine (**1g**)) were mixed in a 1:1 ratio. After their reaction with a stoichiometrically insufficient amount of EtONa in EtOH at ambient temperature, the concentrations of the unconsumed substrates and, as a

control, of the 2-ethoxy-substituted products **2a**–**i** were determined by gas-liquid chromatography (GLC) against a calibrated reference compound ('internal standard'). On this basis, the rate ratios $k^X/k^{X'}$ and the reaction rates k_{rel} of **1a**,**b**,**d**–**i** relative to 2-fluoropyridine (**1c**) were calculated (*Table 1*). The statistically corrected relative rates k_f^{rel} were translated into the corresponding differences in activation energies $\Delta\Delta G^{\ddagger}$ between the substituted substrate and 2-fluoropyridine (**1c**) (*Table 1*).

Table 1. *Fluoride/Ethoxide Displacement Rates Relative to 2-Fluoropyridine* (**1c**), k_{rel}, *or, after Statistical Correction,* k_f^{rel}, *and Differences in the Free Activation Energies* $\Delta\Delta G^{\ddagger}$ [kcal/mol]



2a – 2i **1a – 1i** **2a – 2i**

Compound	Substituent X	k_{rel} [a])	k_r^{rel} [b])	$\Delta\Delta G^{\ddagger}$ [c])
a	6-EtO	0.078	0.078	+1.5
b	5-F	0.67	0.67	+0.24
c	H	1.0	1.0	0.00
d	6-F	56	28	−2.0
e	4-F	86 [d])	43 [e])	−2.2
f	3-F	50	50	−2.3
g	4-Cl	69	69	−2.5
h	3-Cl	75	75	−2.6
i	5-CF_3	3100	3100	−4.8

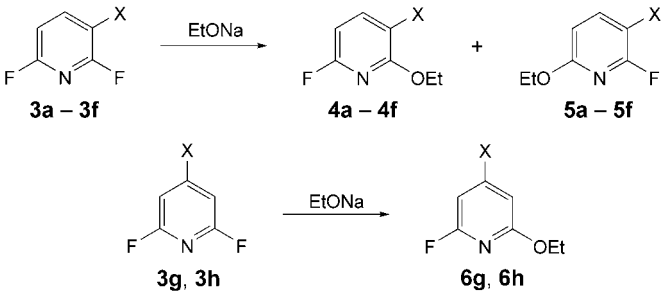
[a]) Substitution rate relative to 2-fluoropyridine (**1c**). [b]) The same relative rate after statistical correction. [c]) $\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger}(\mathbf{1}\text{-X}) - \Delta G^{\ddagger}(\mathbf{1c}) = -4.575 \cdot 0.298 \cdot \log k_f^{rel}$. [d]) Total rate of consumption of 2,4-difluoropyridine (**1e**) by concomitant substitution at both the 2- and the 4-position in a 1 : 1 ratio. [e]) Relative rate of nucleophilic substitution occurring at the 2-position of 2,4-difluoropyridine (**1e**).

In the same way, the substitution rates k_{rel} or k_f^{rel} of substituted 2,6-difluoropyridines **3a**,**b**,**d**–**h** relative to 2,6-difluoropyridine (**3c**) and the corresponding relative activation energies $\Delta\Delta G^{\ddagger}$ were determined (*Table 2*). In all cases, when the extra substituent was located at the 3-position, both F-atoms underwent nucleophilic substitution simultaneously even when mostly in quite unequal proportions (→ **4a**–**f** + **5a**–**f**; **3g**,**h** → **6g**,**h**).

Finally the kinetic study was extended to 2-chloropyridine (**7a**) and congeners **7b**–**d** → **8a**–**d**; *Table 3*). The recorded substituent effects fell in the expected range. The most remarkable result concerns the reactivity of 2-chloropyridine (**7a**) which itself underwent the nucleophilic substitution with EtONa 320 times more slowly than 2-fluoropyridine (**1c**) does ($\Delta\Delta G^{\ddagger} = 3.4$ kcal/mol).

The $\Delta\Delta G^{\ddagger}$ values have to be conceived as increments which quantify to what extent a given substituent accelerates or retards the nucleophilic displacement proceeding in its vicinity. The quasi-identity between such increments (in particular of 3-Cl, 3-F, and 5-CF_3) extracted from the relative rates measured in the 2-fluoropyridine, 2,6-difluoropyridine, and 2-chloropyridine series (*Tables 1–3*) suggests the substituent effects to be additive for the entire scope of the investigated reactions. Further comparisons support this assumption.

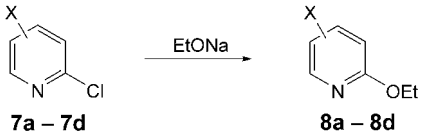
Table 2. *Fluoride/Ethoxide Displacement Rates* k_{rel} *or, after Statistical Correction,* k_f^{rel} *of Congeners Relative to 2,6-Difluoropyridine* (**3c**) *and Differences in the Corresponding Free Activation Energies* $\Delta\Delta G^{\ddagger}$ [kcal/mol]



Compound	Substituent X	k_{rel}[a])	k_f^{rel}[b])	$\Delta\Delta G^{\ddagger}$[c])
a	3-Me_3Si	0.042[d])	0.084	+1.5
b	5-F	0.25[e])	0.50	+0.41
c	H	1.0	1.0	0.00
a	5-Me_3Si	1.4[d])	2.7	−0.59
d	5-Cl	4.2[f])	8.3	−1.3
e	5-Br	9.8[g])	20	−1.8
f	5-I	13[h])	25	−1.9
g	4-F	44[i])	44	−2.2
b	3-F	25[e])	50	−2.3
f	3-I	25[h])	50	−2.3
d	3-Cl	33[f])	66	−2.5
h	4-I	75	75	−2.6
e	3-Br	50[g])	100	−2.7

[a]) Substitution rate relative to 2,6-difluoropyridine (**3c**). [b]) The same relative rate after statistical correction. [c]) $\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger}(\mathbf{3}\text{-X}) - \Delta G^{\ddagger}(\mathbf{3c}) = -4.576 \cdot 0.298 \cdot \log k_f^{rel}$. [d]) Nucleophilic attack at the 2- and 6-position in a 1:32 ratio; total relative rate $k_{tot}^{rel} = 1.4$. [e]) Nucleophilic attack at the 2- and 6-position in a 99:1 ratio; $k_{tot}^{rel} = 25$. [f]) Nucleophilic attack at the 2- and 6-position in a 8:1 ratio; $k_{tot}^{rel} = 38$. [g]) Nucleophilic attack at the 2- and 6-position in a 5:1 ratio; $k_{tot}^{rel} = 59$. [h]) Nucleophilic attack at the 2- and 6-position in a 2:1 ratio; $k_{tot}^{rel} = 38$. [i]) Not considering the substitution which occurs at the 4-position, affording 4-ethoxy-2,6-difluoropyridine (**6i**), concomitantly with the reaction at the 2(6)-position in a ratio of 1:4; $k_{tot}^{rel} = 55$.

Table 3. *Chloride/Ethoxide Displacement Rates* k_{rel} *or, after Statistical Correction,* k_f^{rel} *of Congeners Relative to 2-Chloropyridine* (**7a**) *and Differences in the Corresponding Free Activation Energies* $\Delta\Delta G^{\ddagger}$ [kcal/mol]

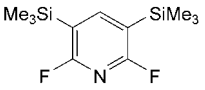
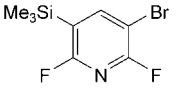
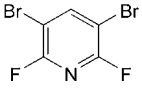


Compound	Substituent X	k_{rel}[a])	k_f^{rel}[b])	$\Delta\Delta G^{\ddagger}$[c])
a	H	1.0	1.0	0.00
b	6-Cl	65	32	−2.1
c	3-CF_3	220	220	−3.2
d	5-CF_3	2800	2800	−4.7

[a]) Substitution rate relative to 2-chloropyridine (**7a**). [b]) The same relative rate after statistical correction. [c]) $\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger}(\mathbf{7}\text{-X}) - \Delta G^{\ddagger}(\mathbf{7a}) = -4.576 \cdot 0.298 \cdot \log k_f^{rel}$.

The 2,6-difluoro-3,5-bis(trimethylsilyl)pyridine (**9**) reacts with EtONa at a rate of $4.1 \cdot 10^{-1}$ relative to the 2,6-difluoropyridine (**3c**) reference (*Table 4*). This corresponds to an experimental $\Delta\Delta G^{\ddagger}$ value of $+0.53$ kcal/mol. Summing up the increments of 3-Me_3Si and 5-Me_3Si of $+1.47$ and -0.59 kcal/mol (see *Table 2*) gives a $\Delta\Delta G^{\ddagger}$ estimate of $+0.88$ kcal/mol. In the same way, 3-bromo-2,6-difluoro-5-(trifluoromethyl)pyridine (**10**) ($k_f^{rel} = 2.3 \cdot 10^2$) and 3,5-dibromo-2,6-difluoropyridine (**11**) ($k_f^{rel} = 1.6 \cdot 10^3$) can be treated. The agreement between the kinetically measured and increment-derived $\Delta\Delta G^{\ddagger}$ values is excellent (*Table 4*).

Table 4. *Nucleophilic Substitution of Tetrasubstituted Pyridines by EtONa: Differences in Free Activation Energies Relative to 2,6-Difluoropyridine as Assessed by Competition Kinetics* ($\Delta\Delta G^{\ddagger}_{exp}$) *and, for Comparison, Estimated on the Basis of Additively Used Increments* ($\Delta\Delta G^{\ddagger}_{incr} \equiv \Delta\Delta G^{\ddagger}$ in *Table 2*)

		k_f^{rel}	$\Delta\Delta G^{\ddagger}_{exp}$	By increments
	**9**	0.41	+0.53	+0.88
	**10**	230	−3.2	−3.3
	**11**	1600	−4.4	−4.5

The coincidence between experimental and increment-inferred substituent effects is equally quite satisfactory in the chloropyridine series (*Table 5*). The 2-chloro-4-iodo-5-(trifluoromethyl)pyridine (**12**), being more reactive by $5.8 \cdot 10^4$ towards EtONa than 2-chloropyridine (**7a**) itself, has an experimental $\Delta\Delta G^{\ddagger}$ value of -6.5 kcal/mol. Adding the -4.7 kcal/mol increment for 5-CF_3 (see *Table 3*) and a 4-I increment of -2.6 kcal/mol (assimilated from *Table 2*) gives a total of -7.3 kcal/mol. The 2,6-dichloro-3-(trifluoromethyl)pyridine (**13**) reacts with rates of $9.7 \cdot 10^3$ and $5.8 \cdot 10^4$ at the 2- and 6-position, respectively. This corresponds to a $\Delta\Delta G^{\ddagger}$ of -5.4 and -6.5 kcal/mol, respectively. The additivity-postulating increment approach, using -2.1 kcal/mol for 6-Cl, -3.2 kcal/mol for 3-CF_3, and -4.7 kcal/mol for 5-CF_3 (all in *Table 3*), leads to -5.3 and -6.8 kcal/mol, respectively.

3. Discussion. – The results reported above provide some practical guidance when the reaction conditions for nucleophilic substitutions of halopyridines are to be selected or optimized. In this respect, it may be helpful to know that the replacement of a Cl- by an F-atom as the nucleofugal leaving group enhances the reactivity by two and a half powers of ten.

The superior reactivity of fluorinated as opposed to chlorinated aromatic substrates towards nucleophiles has been previously established in numerous cases (*Table 6*). However, as already *Sauer* and *Huisgen* have pointed out in their authoritative review [6], the reason for this remains obscure. Textbooks use to invoke differences in the

Table 5. *Nucleophilic Substitution of CF_3-Bearing Chloropyridines: Differences in Free Activation Energies Relative to 2-Chloropyridine as Assessed by Competition Kinetics* ($\Delta\Delta G^{\ddagger}_{exp}$) *and, for Comparison, as Estimated on the Basis of Additively Used Increments* ($\Delta\Delta G^{\ddagger}_{incr}$, taken from *Tables 2* and *3*)

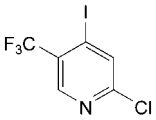
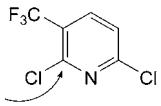
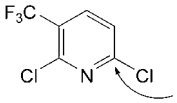
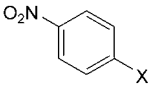
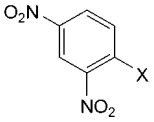
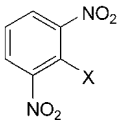
		k_f^{rel}	$\Delta\Delta G^{\ddagger}_{exp}$	By increments
	**12**	58000	– 6.5	– 7.3
	**13**	9700	– 5.4	– 5.3
	**13**	58000	– 6.5	– 6.8

Table 6. *Halogenated Nitroarenes as Substrates of Nucleophilic Aromatic Substitution Reactions: Rates* k_{rel} *Relative to the Chloro Compound as a Function of the Nucleofugal Leaving Group*

Substrate						
Nucleophile X	$C_5H_{10}NH$[a]) k^{rel}_{323} [9]	MeONa k^{rel}_{323} [10]	$C_5H_{10}NH$[a]) k^{rel}_{273} [11]	MeONa k^{rel}_{273} [12]	PhSNa k^{rel}_{273} [12]	$PhNH_2$[b]) k^{rel}_{298} [13]
F	410	310	770	880	27	81
Cl	1.0	1.0	1.0	1.0	1.0	1.0
Br	1.2	0.75	1.0	0.67	1.7	1.8
I	0.26	0.37	0.23	1.5	1.3	0.46
NO_2	8.7	–	210	–	–	3300
MeO	0.0017	–	–	–	–	–
CN	*ca.* 0.0010	–	–	–	–	–

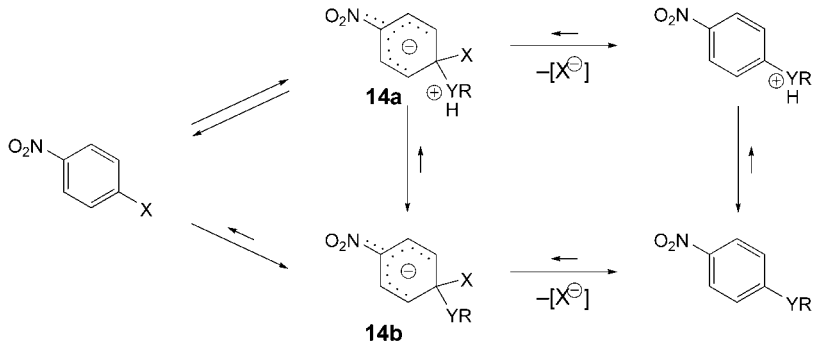
[a]) $C_5H_{10}NH$ = piperidine. [b]) $PhNH_2$ = aniline.

electronegativity of the halogen atoms when addressing this issue. But the F-atom surpasses the Cl-atom in this respect mainly on the *Pauling* scale [7][8] which reflects bond strength and is unrelated to reactivity.

One aspect that has not been taken into account so far is how the space requirements of the various nucleofugal leaving groups depend on bond hybridization. As revealed by model compounds such as fluoromethane [9], difluoromethane [14], 2-fluoro-2-methylpropane [10] ('*tert*-butyl fluoride'), and fluoroamine [11][12], the F-atom needs to be surrounded by less conical empty space than any other element. Thus, the smallest halogen atom can be most easily accommodated at the tetragonal center of

the *Meisenheimer* complex (*e.g.*, **14a** or **14b** in *Scheme 1*) as it can better tolerate the spatial requirements of the ring segment the C–C–C angle of which is far wider than tetrahedral. The *Meisenheimer* complex, in general a high-energy species, is the mechanistically crucial intermediate.

Scheme 1



The same causality may be at the origin of the exceptional nucleophilic mobility of NO_2 groups in nucleophilic aromatic substitution reactions (*Table 6*). However, a switch from a polar to a single-electron-transfer ($S_{RN}1$) mechanism [13][14] may provide an alternative, perhaps more-plausible explanation.

The substituent effects monitored with our structurally simple 2-fluoropyridines (**1c**) and 2-chloropyridines (**7a**) cover four and a half powers of ten between the least-reactive and most-reactive substrate (*Table 1*). The rate alterations previously encountered in a series of polyhalogenated pyridines (in particular pentafluoropyridine, 4-chloro-2,3,5,6-tetrafluoropyridine, tetrafluoropyridines, and 4-chloro-2,3,6-trifluoropyridine) were less pronounced [15][16]. More importantly, it was for the first time possible to derive from the measured substituent effects a self-consistent set of 'increments'. As these increments proved to be applicable to all substrates investigated and furthermore are linearly additive, they may now be used to predict the rates of new reactions. This makes our work unprecedented and of general significance.

What remains to be done is the most difficult part of the data analysis. We have to rationalize the substituent effects or their equivalents, the increments (the $\Delta\Delta G^{\ddagger}_{incr}$ values extracted from *Tables 1–3* and compiled in *Table 7*), in terms of electronic interactions and to describe their nature in detail. While attempting to do this, we proceed in three steps.

The 6-ethoxy-2-fluoropyridine (=2-ethoxy-6-fluoropyridine; **1a**) (see *Table 7*, first line) represents a special case. It can be regarded as an imino analog of an ester. As such it benefits from resonance stabilization. Upon addition of a nucleophile at the 2-position, the N-atom becomes electron-rich and no longer acts as an electron-withdrawing center. The +1.5 kcal/mol are the price to pay for the loss of zwitterionic polarization.

All of the following data can be rationalized by a superposition of steric, inductive, and repulsive interactions. Substituents attached to the 3-position do not only display electronic but also steric effects. Bulky groups such as Me_3Si can thus substantially

Table 7. *Substituent Parameters* ('increments') $\Delta\Delta G^{\ddagger}_{incr}$ [kcal/mol] *Taken from* Tables 1–3

Substituent	6-position	5-position	4-position	3-position
EtO	+1.5	[a])	[a])	[a])
Me_3Si	[a])	−0.6	[a])	+1.5
F	−2.0	+0.3[b])	−2.2	−2.3
Cl	−2.1	−1.3	−2.5	−2.6
Br	[a])	−1.8	[a])	−2.7
I	[a])	−1.9	−2.6	−2.3
CF_3	[a])	−4.8	[a])	−3.2

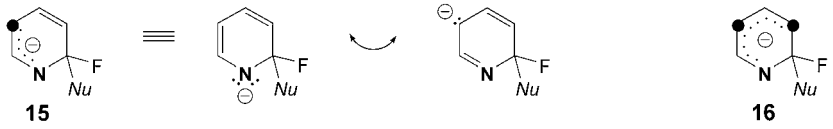
[a]) Not determined. [b]) Average between +0.24 and +0.41 (*Tables 1* and *2*).

retard the nucleophilic displacement at the neighboring reaction center ($\Delta\Delta G^{\ddagger}_{incr} = +1.5$ kcal/mol; see *Table 7*, second line), whereas at the remote 5-position, it exerts only its moderate charge-stabilizing effect [17][18]. The strongly electron-withdrawing CF_3 group accelerates the nucleophilic substitution at both the 5- and 3-position although less markedly if located at the latter site where it causes congestion of the adjacent reaction center ($\Delta\Delta G^{\ddagger}_{incr} = -4.8$ *vs.* -3.2 kcal/mol; see *Table 7*, last line).

The opposite trend is observed with I, Br, and Cl as substituents. When connected to the 3-position, they accelerate respectively 2, 5, and 8 times more than at the 5-position (average $\Delta\Delta G^{\ddagger}_{incr} = -2.5$ *vs.* -1.6 kcal/mol; *Table 7*). Evidently, the electronic effect now outweighs the steric hindrance.

The F-atom provided once more a surprise. Whereas it facilitates the substitution to approximately the same extent as the other halogen atoms when accommodated at the 3-position, it diminishes the reaction rate by a factor ranging from 1.5 (*Table 1*) to 4.0 (*Table 2*) when at the 5-position. The F-atom is known to raise the free energy of planar (and only planar) carbanions by lone-pair/lone-pair repulsion (conjugative destabilization [19]) [20–22]. That this effect manifests itself at the 5- but not the 3-position must mean an unequal distribution of the electron excess, perhaps in the sense of the transient intermediate being better visualized as an azaallyl anion **15** as opposed to the azapentadienyl anion **16** (see *Scheme 2*). In fact, C(3) may well be depleted of electrons as the electronegative N-atom should attract a fair amount of the charge and as in cyclohexadienyl anions, the electron density appears to accumulate at the central C-atom as one can judge from the regioselectivity of protonation [23][24] and the ^{13}C-chemical shifts [25]. Thus, the F-atom has once again confirmed its role as a diagnostic probe.

Scheme 2



The rate-retarding effect of the F-atom in the *para* position of the center undergoing nucleophilic (het)aromatic substitution has already been postulated [26] before and quantified for the reaction of polyhalopyridines with MeONa [27].

However, the latter work was based on a comparison of 4-chloro-2,3,5,6-tetrafluoropyridine and 4-chloro-2,3,5-trifluoropyridine being attacked at the 2-position, whereas the reactivity-enhancing effect of the *meta*- and *ortho*-located F-atom was derived in the same study [27] from substitution occurring at the 4-position. In contrast, our data are deduced from simple model compounds and refer consistently to nucleophilic displacement at the N-adjacent 2(or 6)-position.

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Experimental Part

1. *General.* Air- and moisture-sensitive materials were stored in *Schlenk* tube or *Schlenk* burettes. They were protected by and handled under 99.995% pure N_2, by using appropriate glassware (*Glasgerätebau Pfeifer*, D-98711 Frauenfeld). NMR Spectra: *Bruker DPX-400* spectrometer; 400 (^{1}H) and 101 MHz (^{13}C; ^{1}H-decoupled); $CDCl_3$ solns.; δ in ppm rel. to $SiMe_4$, J in Hz.

2. *Starting Materials.* The preparations of *2,3-*, *2,4-*, and *2,5-difluoropyridine* (**1f**, **1e**, and **1b**) [28], *2,3,6-* and *2,4,6-trifluoropyridine* (**3b** and **3g**) [28], *3-chloro-2-fluoro-* and *4-chloro-2-fluoropyridine* (**1h** and **1g**) [29], *3-bromo-2,6-difluoro-*, *3-chloro-2,6-difluoro-*, *2,6-difluoro-3-iodo-*, *2,6-difluoro-4-iodo-*, *2,6-difluoro-3-(trimethylsilyl)-*, *3-bromo-2,6-difluoro-5-(trimethylsilyl)-*, *2,6-difluoro-3,5-bis(trimethylsilyl)-*, and *3,5-dibromo-2,6-difluoropyridine* (**3e**, **3d**, **3f**, **3h**, **3a**, **10**, **9**, and **11**) [1], *2-chloro-4-iodo-5-(trifluoromethyl)pyridine* (**12**) [30], and *2-fluoro-5-(trifluoromethyl)pyridine* (**1i**) [31] have already been described. All other starting materials, except one, are commercially available; *2-fluoropyridine* (**1c**) and *2,6-difluoropyridine* (**1d**≡**3c**) were purchased from *Apollo Scientific* (UK-SK6-2QR Stockport), and *2-chloropyridine* (**7a**), *2,6-dichloro-*, *2,6-dichloro-3-(trifluoromethyl)-*, *2-chloro-3-(trifluoromethyl)-*, and *2-chloro-5-(trifluoromethyl)pyridine* (**7b**, **13**, **7c**, and **7d**) from *Acros Organics* (B-2440 Geel).

2-Ethoxy-6-fluoropyridine (**1a**≡**2d**). Sodium (1.2 g, 50 mmol) was dissolved in EtOH (50 ml) and 2,6-difluoropyridine (4.5 ml, 5.8 g, 50 mmol) added subsequently. After 2 h at 50°, distillation afforded **1a** (6.07 g, 86%). Colorless liquid. M.p. 0–1°. B.p. 81–83°/52 Torr. $n_{20}^{D} = 1.4721$. $d_{20}^{4} = 1.100$. ^{1}H-NMR: 7.62 (q, $J = 8.0$, 1 H); 6.57 (dd, $J = 8.0$, 1.9, 1 H); 6.44 (dd, $J = 7.7$, 2.5, 1 H); 4.32 (q, $J = 7.0$, 2 H); 1.38 (t, $J = 7.0$, 3 H). ^{13}C-NMR: 163.0 (d, $J = 14$); 162.2 (d, $J = 240$); 142.3 (d, $J = 8$); 107.0 (d, $J = 5$); 99.5 (d, $J = 35$); 62.2 (s), 14.2 (s). Anal. calc. for C_7H_8FNO (141.14): C 59.57, H 5.71; found: C 59.48, H 5.79.

3. *Materials for Comparison*. The preparation of *2,6-difluoro-4-ethoxypyridine* (**6i**, see *Footnote i* in *Table 2*) has already been described [3].

4-Chloro-2-ethoxypyridine (**2g**). As described for **1a**, with 4-chloro-2-fluoropyridine (**1g**; 3.3 g, 25 mol): **2g** (3.19 g, 81%). Colorless liquid [32]: m.p. −1 to 1°). B.p. 74–76°/1 Torr. $n_{20}^{D} = 1.5031$. ^{1}H-NMR: 8.04 (d, $J = 5.4$, 1 H); 6.85 (dd, $J = 5.4$, 1.6, 1 H); 6.74 (d, $J = 1.6$, 1 H); 4.35 (q, $J = 7.0$, 2 H); 1.38 (t, $J = 7.0$, 3 H).

6-Ethoxy-2-fluoro-3-(trimethylsilyl)pyridine (**5a**). As described for **1a**, with 2,6-difluoro-3-(trimethylsilyl)-pyridine (**3a**; 9.4 g, 50 mmol), except that the reaction time at 50° was extended from 2 h to 6 h. **5a** (9.92 g, 93%). Colorless liquid. B.p. 76–78°/11 Torr. $n_{D}^{20} = 1.4787$. $d_{4}^{20} = 1.012$. ^{1}H-NMR: 7.66 (dd, $J = 8.6$, 7.7, 1 H); 6.57 (dd, $J = 7.7$, 2.2, 1 H); 4.33 (q, $J = 7.0$, 2 H); 1.38 (t, $J = 7.0$, 3 H); 0.29 (d, $J = 1.0$, 9 H). ^{13}C-NMR: 166.1 (d, $J = 236$); 164.5 (d, $J = 14$); 147.9 (d, $J = 11$); 108.7 (d, $J = 44$); 107.2 (d, $J = 5$); 62.3 (s); 14.5 (s); −1.2 (s, 3 C). Anal. calc. for $C_{10}H_{16}FNOSi$ (213.32): C 56.30, H 7.56; found: C 56.28, H 7.47.

3-Chloro-2-ethoxy-6-fluoropyridine (**4d**), *and 3-Chloro-6-ethoxy-2-fluoropyridine* (**5d**). Sodium (1.2 g, 50 mmol) was dissolved in EtOH (25 ml). At 0°, a soln. of 3-chloro-2,6-difluoropyridine (**3d**; 7.5 g, 50 mmol) in EtOH (25 ml) was added. After 2 h, evaporation of the volatiles followed by distillation afforded a colorless liquid: 8:1 mixture **4d**/**5d** (6.41 g, 73%). B.p. 70–72°/12 Torr. GLC (30 m, *DB-1*, 100°; 30 m, *DB-WAX*, 100°; internal standard tridecane): **4d** (85%) and **5d** (11%).

Data of **4d**: ^{1}H-NMR: 7.67 (dd, $J = 8.3$, 7.0, 1 H); 6.44 (dd, $J = 8.3$, 3.2, 1 H); 4.42 (q, $J = 7.04$, 2 H); 1.44 (t, $J = 7.04$, 3 H). ^{13}C-NMR: 160.0 (d, $J = 241$); 157.7 (d, $J = 15$); 141.8 (d, $J = 8$); 113.3 (d, $J = 7$); 100.5 (d, $J = 38$); 63.5 (s); 14.2 (s).

Data of **5d**: ^{1}H-NMR: 7.63 (dd, $J = 9.3$, 8.6, 1 H); 6.55 (d, $J = 8.3$, 1 H); 4.31 (q, $J = 7.04$, 2 H); 1.37 (t, $J = 7.04$, 3 H). ^{13}C-NMR: 161.0 (d, $J = 12$); 156.7 (d, $J = 239$); 142.2 (d, $J = 2$); 108.5 (d, $J = 6$); 106.2 (d, $J = 33$); 62.9 (s); 14.2 (s). Anal. calc. for C_7H_7ClFNO (175.59): C 47.88, H 4.02; found: C 47.89, H 3.85.

4. *General Competition Protocol*. At 25°, EtONa (5.0 mmol) in EtOH (3.2 ml) was added to a soln. containing pairs of substrates A and B (*ca.* 5.0 mmol each) and the 'internal standard' tridecane (0.30 g, 1.6 mmol) in Et_2O (6.8 ml). A sample (*ca.* 2 ml) was collected and treated with H_2O (1 ml) and Et_2O (2 ml). The org. phase was dried (Na_2SO_4) and filtered. Unconsumed starting materials and the ethoxy derivatives formed were identified by GLC (30 m, *DB-1*, 50° (7 min) → 125° (15 min); heating rate 30°/min; 30 m, *DB-WAX*, 50°, identical temp. program) by comparing their t_R with those of authentic materials, and their concentrations were determined by monitoring their peak areas relative to that of the 'internal standard' tridecane and by using calibration factors to correct differences in detector responses. The relative rates k_A/k_B were calculated by applying the standard logarithmic formula [4][5] (*Table 8*).

Table 8. *Relative Reaction Rates* k_A/k_B (without statistic correction) *Calculated with the Amounts of Two Competing Pyridines A and B before* ($[A]_0$ and $[B]_0$) *and after* ($[A]_t$ and $[B]_t$) *Their Simultaneous Reaction with NaOEt.* $k_A/k_B = (\log A_\infty - \log A_0)/(\log B_\infty - \log B_0)$

Pyridine A	Pyridine B	$[A]_0$	$[B]_0$	$[A]_d^t$	$[A]_i^{t\,a)}$	$[B]_d^t$	$[B]_i^{t\,a)}$	k_A/k_B
2-F	3-CF_3, 2-Cl	5.18	5.10	3.21	(3.36)	3.72	(3.56)	1.5
2-F	2,5-F_2	5.51	5.26	2.96	(2.83)	3.49	(3.35)	1.5
2-F, 6-EtO	2-Cl	5.16	5.11	0.52	(0.58)	4.67	(4.25)	25.5
2,3-F_2	5-CF_3, 2-Cl	5.08	5.07	1.19	(1.08)	3.94	(3.77)	5.7
2,4-F_2	5-CF_3, 2-Cl	5.56	5.27	1.02	(1.09)	4.46	(4.31)	10.1
2,6-Cl_2	2-F, 6-EtO	5.29	5.17	4.50	(4.51)	4.84	(4.85)	2.5
2,6-F_2, 3-I	5-CF_3, 2-Cl, 4-I	5.14	5.07	1.24	(1.30)	4.50	(4.66)	11.9
2,6-F_2, 4-I	2,6-F_2, 3-I	2.51	2.53	1.11	(1.20)	1.65	(1.63)	2.0
2,6-F_2, 3-Me_3Si	5-CF_3, 2-Cl	4.99	5.01	1.12	(1.15)	4.25	(4.21)	9.1
2,6-F_2, 3-Me_3Si	2,6-F_2	5.08	5.10	2.06	(2.23)	2.66	(2.75)	1.4
2,6-F_2, 3,5-$(Me_3Si)_2$	5-CF_3, 2-Cl	2.54	2.53	0.94	(1.02)	1.77	(1.61)	2.7
2,3,6-F_3	5-CF_3, 2-Cl, 4-I	5.22	5.06	1.00	(1.06)	4.33	(4.27)	10.6
2,4,6-F_3	5-CF_3, 2-Cl, 4-I	4.89	3.97	0.27	(0.30)	3.35	(3.40)	16.9
2,4,6-F_3, 3-Me_3Si	5-CF_3, 2-F	5.06	5.16	4.20	(4.43)	4.55	(4.51)	1.5
3-CF_3, 2-Cl	2,6-Cl_2	5.00	5.06	3.43	(3.17)	4.54	(4.56)	3.5
3-CF_3, 2-Cl	2,5-F_2	5.00	5.16	3.13	(2.84)	3.34	(3.03)	1.1
3-CF_3, 2-Cl	2-F, 6-EtO	5.10	5.13	2.57	(2.60)	4.65	(4.81)	7.0
3-CF_3, 2,6-Cl_2	5-CF_3, 2-Cl, 4-I	5.09	5.23	2.74	(2.78)	3.10	(3.23)	1.2
3-Br, 2,6-F_2	5-CF_3, 2-Cl, 4-I	5.34	5.04	0.88	(0.93)	4.57	(4.52)	18.4
3-Br, 2,6-F_2, 5-Me_3Si	5-CF_3, 2-F	2.55	2.55	0.98	(1.07)	1.60	(1.47)	2.1
3-Cl, 2-F	5-CF_3, 2-Cl	5.16	5.09	1.02	(0.94)	4.22	(4.28)	8.6
3-Cl, 2,6-F_2	5-CF_3, 2-Cl, 4-I	5.07	5.11	1.13	(1.17)	4.49	(4.53)	11.6
3-Cl, 2,6-F_2	2,3,6-F_3	5.14	5.11	2.23	(2.33)	3.05	(3.23)	1.6
3,5-Br_2, 2,6-F_2	2,6-F_2, 4-I	2.62	2.51	0.40	(0.45)	2.30	(2.25)	21.4
4-Cl, 2-F	5-CF_3, 2-Cl	5.20	5.13	1.35	(1.27)	4.33	(4.42)	8.0
5-CF_3, 2-Cl	3-CF_3, 2-Cl	5.43	5.10	1.09	(1.18)	4.50	(4.58)	12.6
5-CF_3, 2-F	5-CF_3, 2-Cl, 4-I	5.02	5.00	0.77	(0.69)	4.49	(4.42)	17.4
5-CF_3, 2-F	2,3,6-F_3	5.75	5.11	2.55	(2.34)	3.51	(3.59)	2.2
5-CF_3, 2-Cl, 4-I	2,6-F_2, 3-Me_3Si	5.19	5.04	2.84	(3.04)	3.88	(3.89)	2.3

[a]) $[A]_d^t$ and $[B]_d^t$ stand for the amount of substrates A and B present after the reaction as directly determined by GLC, whereas $[A]_i^t$ and $[B]_i^t$ are indirectly determined by subtracting from the initial amounts $[A]_0$ and $[B]_0$ the amount of the corresponding ether obtained after the reaction and quantified again by GLC.

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