Relative Electrophilic Fluorinating Power as Assayed by Competitive Catalytic Halogenation Reactions

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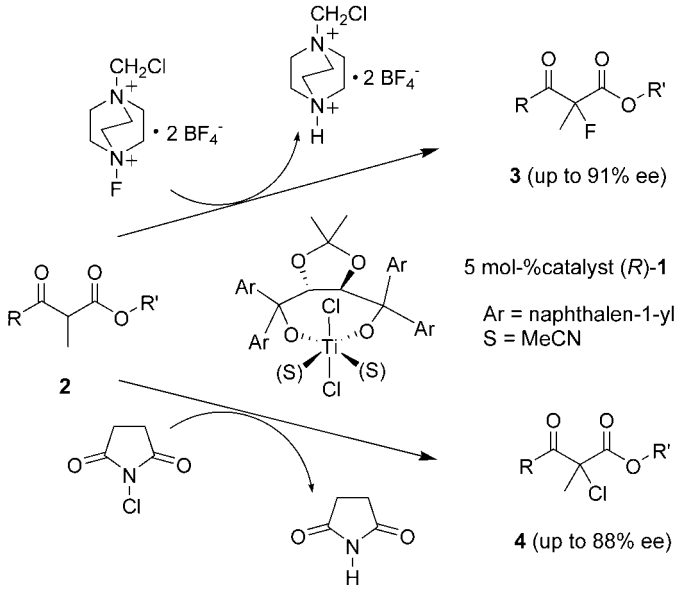
Catalytic fluorination/chlorination competition experiments of β-keto ester **5** were used to assess the relative fluorinating activity of various electrophilic N–F reagents (containing an N–F bond). Thus, in the halogenation reactions catalyzed by the [Ti(TADDOLato)] complex **1** (= bis(acetonitrile)dichloro[(4*R*,5*R*)-2,2-dimethyl-α,α,α',α'-tetra(naphthalen-1-yl)-1,3-dioxolane-4,5-dimethanolato(2–)-κO,$\kappa O'$]titanium), the activity range of a series of commercially available reagents spans more than two orders of magnitude. *Selectfluor*™ (= 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate); **9**; also called F-TEDA; TEDA = triethylenediamine) reacts more than 100 times faster than 1-fluoropyridinium tetrafluoroborate.

1. Introduction. – Selective fluorination of organic compounds has been and still is a matter of great interest. This is due to the far-reaching implications in terms of reactivity, solubility, and stability of organic compounds containing F-atoms. Even a single F-substituent may be responsible for the improved resistance against metabolic degradation of biologically active compounds, in particular drugs and crop-protection agents (see, *e.g.*, [1]).

There are a variety of methods for the selective introduction of F-atoms into organic molecules [2], but electrophilic fluorinations relying on the use of compounds containing an N–F bond (N–F reagents) have been particularly successful in recent years [3]. This class of reagents is easily prepared, chemically and thermally stable, easy to handle, and comprises several commercially available representatives. Progresses in asymmetric fluorination as it has taken place in most recent years would not have been possible without these reagents [4]. So far, extensive qualitative information has been obtained concerning the fluorinating power of different N–F reagents through their chemical reactivity (see, *e.g.*, [5]). Electrochemical studies have shown that the electrophilic fluorinating strength is qualitatively correlated to the oxidizing power of the reagent [6]. However, accessing accurate data concerning the fluorinating power is often precluded by experimental problems encountered when determining the standard redox potential of these reagents. Computational studies have also been carried out to establish the order of reactivity of different pyridinium cations, but the method does not seem to be applicable to a wider set of reagents [7]. In fact, an accurate and comprehensive method for the quantitative determination of the fluorinating power of different classes of fluorinating agents is still very desirable. We previously reported both enantioselective electrophilic fluorinations [8] and chlorinations [9] of β-keto esters **2** effectively catalyzed by [Ti(TADDOLato)]

complexes such as (*R*)-**1**. These reactions give high yields of **3** and **4**, respectively, and afford enantioselectivities of up to *ca.* 90% ee (*Scheme 1*). This concept was further extended to an asymmetric α-heterodihalogenation of β-keto esters [10].

Scheme 1. *Enantioselective Halogenation Reactions Catalyzed by the [Ti(TADDOLato)] Complex* **1**

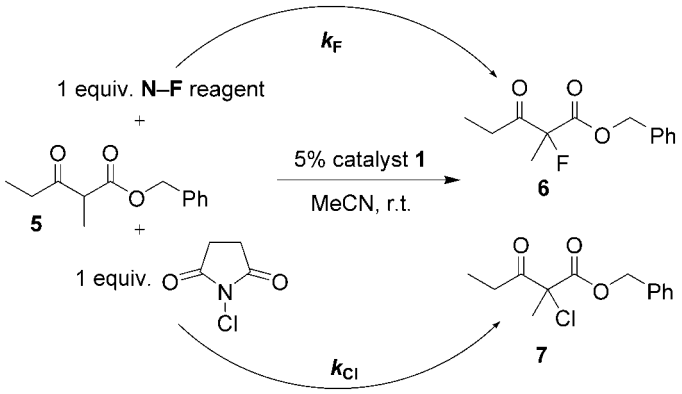


2. Results and Discussion. – Considering the new related reactions mentioned above, we present here a protocol for the assessment of the fluorinating activity of different N–F reagents based on competitive halogenations of β-keto esters. Thus, halogenation experiments were conducted in the presence of a mixture of 1 equiv. of *N*-chlorosuccinimide (NCS) and 1 equiv. of a chosen fluorinating agent as shown in *Scheme 2*. After full consumption of the β-keto ester **5**, the composition of the resulting mixture **6**/**7** of α-halogenated β-keto esters was determined by chiral HPLC. Under the reasonable assumption that the chlorination reaction occurs at the same rate (k_{Cl}) independently from the fluorinating agent used for the concomitant fluorination process, the molar ratio of the two halogenated products is a relative measure of the rate of fluorination with a given N–F reagent, as described by *Eqn. 1*, where the rate constants $k_{F/Cl}$ represent the rates of fluorination/chlorination, and the parameters $n_{F/Cl}$ are the molar amounts of fluorination/chlorination products formed.

$$k_{rel} = \frac{k_F}{k_{Cl}} = \frac{n_F}{n_{Cl}} = \frac{[\mathbf{6}]}{[\mathbf{7}]} \quad (1)$$

The choice of the catalytic reaction (catalyst and β-keto ester) is crucial to avoid overestimation of the amount of chlorinated product due to oxidation of the chloride

Scheme 2. *Competitive Halogenation Reactions Catalyzed by the [Ti(TADDOLato)] Complex* **1**



from the catalyst by strong fluorinating agents [9][11]. By using β-keto ester **5** and catalyst **1**, it was ascertained that fluorination with F-TEDA **9** alone (shown below to be the strongest F-transfer reagent tested) does not lead to more than 1% of the chlorinated product. Furthermore, control experiments indicated that NCS did not react with any of the fluorinating agents under the reaction conditions.

As our primary goal was to find the most-active fluorinating reagent compatible with our catalytic system, we turned our attention to N–F derivatives already known to exhibit the desired reactivity with β-keto esters. Thus, 1,4-diazabicyclo[2.2.2]octane salt derivatives such as F-TEDA (see **9**) [12] (also called *Selectfluor*™), or NFTh (see **10**) [13] (also called *Accufluor*™), the activated pyridinium salts **11** [14], **12** [5a][15], and **13** (also called *Synfluor*™) [16], as well as neutral activated fluoroamine derivatives such as NFSI (see **14**) [17] and perfluoropiperidine **15** [18] were chosen for this study (*Fig.*). The results of the competitive halogenations are summarized in the *Table*. All reactions proceeded with total consumption of β-keto ester **5**. According to this procedure, the dicationic derivatives **9** and **10** are the most-powerful fluorinating reagents tested. Activated *N*-fluoropyridinium salts show moderately good reactivity when one takes into account that the parent *N*-fluoropyridinium tetrafluoroborate afforded only *ca.* 30% conversion under similar reaction conditions and was, therefore, not included in this study. Neutral amine derivatives, finally, act as very slow fluorinating agents, NFSI, **14**, being *ca.* 40 times slower than **9**.

The fluorination with **9** alone and chlorination with NCS alone give 71 and 59% ee, respectively. It is, therefore, worth noting that the enantioselectivities of both electrophilic halogenations differ when changing the combination of halogenating agents, although not very significantly (at least in terms of $\Delta\Delta G^{\ddagger}$). However, one should take into account that the substrate/catalyst adduct exists in different diastereoisomeric forms [19]. Since these will display different reaction rates with different halogenating agents, it is not surprising that the observed ee in the different experiments are only comparable but not identical.

Conclusions. – The k_{rel} values determined in this study not only are a manifestation of the intrinsic fluorinating power of the reagents **9**–**15** but also convey possible steric,

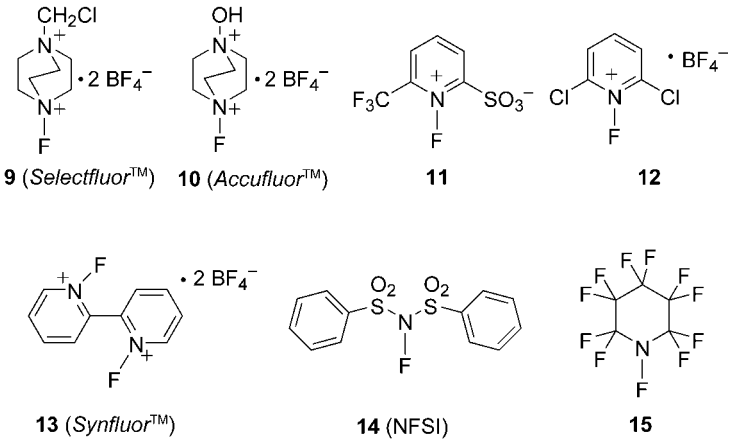


Figure. *Electrophilic fluorinating agents tested in this study*

Table 1. *Results of Competitive Halogenations of β-Keto Ester* **5**

Fluorinating agent[a])	**6**		**7**		k_{rel}
	yield [%][b])	ee [%][b])	yield [%][b])	ee [%][b])	
9 (*Selectfluor*™)	73	70	27	57	2.72
10 (*Accufluor*™)	65	60	35	49	1.84
11	45	74	55	38	0.81
12	13	53	87	49	0.15
13 (*Synfluor*™)	6	45	94	62	0.06
14 (NFSI)	4	67	96	63	0.04
15	3	74	97	64	0.03

[a]) Systematic names: **9**, 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate); **10**, 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate); **11**, 1-fluoro-2-sulfo-6-(trifluoromethyl)pyridinium inner salt; **12**, 2,6-dichloro-1-fluoropyridinium tetrafluoroborate; **13**, 1,1′-difluoro-2,2′-bipyridinium bis(tetrafluoroborate); **14**, *N*-fluoro-*N*-(phenylsulfonyl)benzenesulfonamide; **15**, undecafluoropiperidine. [b]) As determined by HPLC.

charge, and solvation effects influencing the reactivity. The type of experiment we disclosed involving the system constituted by catalyst **1** and β-keto ester **5** is very simple. Nevertheless, it affords a reactivity ranking of the most-common, commercially available, electrophilic fluorinating agents that was not available before.

Experimental Part

General. Reactions with air- or moisture-sensitive materials were carried out under Ar by using *Schlenk* techniques. Complex **1**, bis(acetonitrile)dichloro[(4*R*,5*R*)-2,2-dimethyl-α,α,α′,α′-tetra(naphthalen-1-yl)-1,3-dioxolane-4,5-dimethanolato(2-)-κ*O*,κ*O*′]titanium, was prepared as reported [20]. HPLC: determination of enantiomer excess (ee) by using the *Agilent 1050* series system equipped with a *DAICEL Chiralcel OB-H* column (4.6 × 250 × 5); t_R in min. ^{1}H, ^{13}C, and ^{19}F-NMR Spectra: *Bruker Avance* spectrometers *AC-200*, *DPX-250*, and *DPX-300*; δ(H) and δ(C) in ppm downfield from $SiMe_4$; internal standard $CFCl_3$ for ^{19}F-NMR; *J* in Hz. Elemental analyses were carried out by the Laboratory of Microelemental Analysis (ETH Zürich).

Representative Competitive Halogenation Experiment. Benzyl 2-methyl-3-oxopentanoate (**5**; 44 mg, 0.2 mmol) and complex **1** (8 mg, 0.01 mmol) are placed in a 10-ml *Schlenk* tube under Ar, and dist. MeCN (2 ml) is added *via* a syringe. *N*-Chlorosuccinimide (27 mg, 0.2 mmol) and the fluorinating agent (0.2 mmol) are placed in a second *Schlenk* tube under Ar, and dist. MeCN (2 ml) is added *via* a syringe. The first soln. is added to the second under vigorous stirring, and then the mixture is stirred at r.t. until complete consumption of the starting **5** (TLC monitoring). The MeCN is evaporated, and the resultant oil purified by chromatography (silica gel, hexane/^{t}BuOMe 96:4): unseparated **6**/**7** as a colorless oil. The ratio **6**/**7** as well as the ee of each **6** and **7** are determined by chiral HPLC (hexane/^{i}PrOH 98:2, flow 0.8 ml/min) after calibration with pure **6** and **7**: t_R 18.0 (major enantiomer) and 20.9 (minor enantiomer) for **6**, and t_R 12.4 (minor enantiomer) and 14.8 (major enantiomer) for **7**.

Benzyl 2-Fluoro-2-methyl-3-oxopentanoate (**6**). A pure sample of **6** is obtained according to our reported procedure [8]. TLC (^{t}BuOMe/hexane 1:10): R_f 0.30. $[\alpha]_D = +32.5$ ($c = 0.905$, MeOH; 70.8% ee). IR (film, NaCl): 3067*w*, 3035*w*, 2982*m*, 2942*m*, 1758*s*, 1736*s*, 1498*w*, 1456*m*, 1406*w*, 1378*m*, 1353*w*, 1277*s*, 1135*s*, 1093*s*, 1030*m*, 949*m*, 908*w*, 752*m*, 698*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.04 (*t*, *J* = 7.2, 3 H); 1.70 (*d*, *J*(F,H) = 22.2, 3 H); 2.53–2.79 (*CD* of *A*$_3$*CDX*, 2 H); 5.23 (*s*, 2 H); 7.27–7.45 (*m*, 5 H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 7.0 (*d*, *J*(F,C) = 2, Me); 20.1 (*d*, *J*(F,C) = 23, Me); 30.6 (CH_2); 67.8 (CH_2); 97.8 (*d*, *J*(F,C) = 194, CF); 128.1 (CH); 128.6 (CH); 128.6 (CH); 134.7 (C); 166.8 (*d*, *J*(F,C) = 26, CO); 204.9 (*d*, *J*(F,C) = 27, CO). ^{19}F-NMR (188.3 MHz, $CDCl_3$): −159.5 (*qt*, *J*(F,H) = 22.2, 3.1). EI-MS (pos.): 238 (0.02, M^+), 162 (5), 136 (7), 104 (3), 91 (100), 57 (42), 28 (32). Anal. calc. for $C_{13}H_{15}FO_3$ (238.255): C 65.54, H 6.35; found: C 65.28, H 6.30.

Benzyl 2-Chloro-2-methyl-3-oxopentanoate (**7**). A pure sample of **7** is obtained according to our reported procedure [9]: As described for **6**/**7**, with **5** (44 mg, 0.2 mmol), **1** (8 mg, 0.01 mmol), dist. MeCN (2 ml), and *N*-chlorosuccinimide (27 mg, 0.2 mmol) (without fluorinating agent): **7** (46 mg, 90%; after chromatography). Colorless oil. TLC (^{t}BuOMe/hexane 5:95): R_f 0.42. $[\alpha]_D = -1.0$ ($c = 2.1$, CH_2Cl_2; 62% ee). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.06 (*t*, *J* = 7.2, 3 H); 2.60 (*dq*, *J* = 18.3, 7.2, 1 H); 2.77 (*dq*, *J* = 18.3, 7.2, 1 H); 5.19 (*d*, J_{AB} = 12.2, 1 H); 5.28 (*d*, J_{AB} = 12.2, 1 H); 7.3–7.5 (*m*, 5 H). ^{13}C-NMR (300 MHz, C_6D_6): 8.32; 24.67; 31.10; 68.20; 71.15; 128.46; 128.70; 128.77; 135.28; 168.06; 201.67. Anal. calc. for $C_{13}H_{15}ClO_3$ (254.71): C 61.30, H 5.94; found: C 61.58, H 5.87.

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