REVIEW

On Novel Fluorine Reagents in Preparative Organic Chemistry

by **Helmut Vorbrüggen**

Institut für Chemie und Biochemie, Freie Universität, Takustrasse 3, D-14195 Berlin
(e-mail: helvor@chemie.fu-berlin.de)

Dedicated to Professor *Albert Eschenmoser* on the occasion of his 85th birthday

Contents

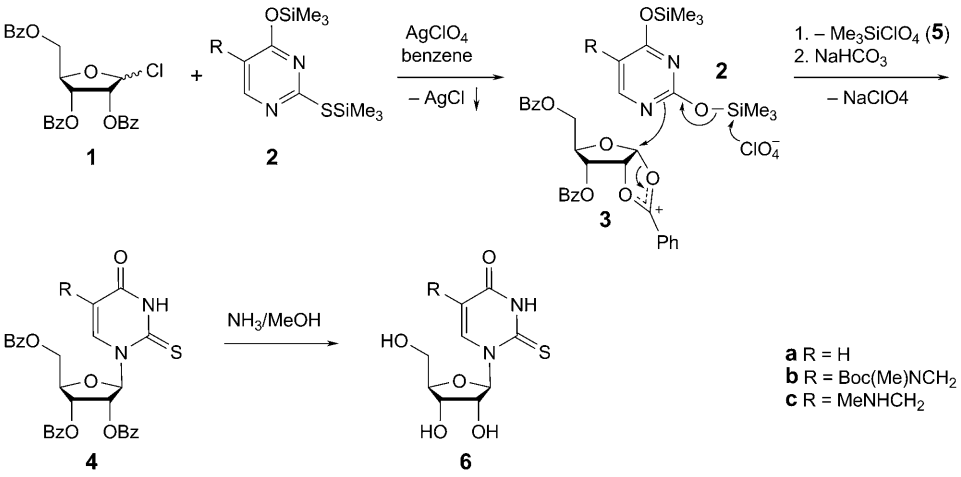
1. Introduction
2. Reactions with Trimethylsilyl Triflate (= Trimethylsilyl Trifluoromethanesulfonate; TMSOTf) and Trimethylsilyl Nonaflate (= Trimethylsilyl Perfluorobutanesulfonate; TMSONf) as Novel Mild and Selective *Lewis* Acids
   2.1. Novel Cleavage of *N*-Boc Groups
   2.2. Synthesis of Pyrimidine Nucleosides
   2.3. Synthesis of Purine Nucleosides
   2.4. Simplified One-Step – One-Pot Nucleoside Synthesis
3. Reactions with Potassium Nonaflate (NfOK)
   3.1. Synthesis of Nonaflyl (= Perfluorobutanesulfonyl) Fluoride (NfF) and Potassium Nonaflate (NfOK)
   3.2. Reactions with NfOK
4. Reactions with Nonaflyl Fluoride (NfF)
   4.1. Reactivity of NfF
   4.2. Reaction of NfF with Alcohols in the Presence of Nucleophilic Bases
   4.3. The Conversion (Dehydroxyfluorination) of Alcohols with NfF and DBU to Fluorides
   4.4. Side Reactions on Employing NfF/DBU
   4.5. Modifications of NfF Dehydroxyfluorinations by Other Groups
5. Concluding Remarks

1. Introduction. – Although the present review deals exclusively with our work on fluorine chemistry, there is some overlap in *Sects. 1*, *2*, and *4* with a former review on '*Adventures in Silicon Organic Chemistry*' published in 1995 [1], as well as with a recent review on '*The Conversion of Primary or Secondary Alcohols with Nonaflyl Fluoride into their Corresponding Inverted Fluorides*' [2], because our work in organic silicon and fluorine chemistry has always been closely related.

2. Reactions with Trimethylsilyl Triflate (= Trimethylsilyl Trifluoromethanesulfonate; TMSOTf) and Trimethylsilyl Nonaflate (= Trimethylsilyl Perfluorobutanesulfo-

nate; TMSONf) as Novel Mild and Selective *Lewis* Acids. – 2.1. *Novel Cleavage of* N-*Boc Groups.* We became involved in fluorine chemistry just by chance. When we reacted the protected 1-chloro sugar **1** and silylated 2-thiouracil **2a** in benzene with a solution of anhydrous $AgClO_4$ in dry benzene according to *Birkofer et al.* [3] and *Wittenburg* [4], AgCl was precipitated to afford the intermediate protected electrophilic sugar perchlorate **3**, which condensed with the silylated 2-thiouracil **2a** under formation of trimethylsilyl perchlorate (Me_3SiClO_4; **5**), whose intermediate formation had already been postulated by *Birkofer* [3] and *Wittenburg* [4], to give upon workup with aqueous $NaHCO_3$ solution the protected crystalline 2-thiouridine **4a** in high yield, as well as $NaClO_4$ [5]. Saponification of **4a** with NH_3 in MeOH afforded free crystalline 2-thiouridine **6a** [5] (*Scheme 1*). When we tried to synthesize 5-[(methylamino)-methyl]-2-thiouridine (**6c**), which had at that time been identified as a new rare nucleoside from t-RNA [6], we reacted the persilylated *N*-Boc-protected 5-[(methylamino)methyl]-2-thiouracil **2b** with **1** in the presence of $AgClO_4$ in dry benzene. The condensation of **2b** with **3** proceeded in high yield, yet the acid-sensitive *N*-Boc group had been lost during the reaction and subsequent aqueous workup to afford the *O*-protected nucleoside **4c**, which gave with NH_3 in MeOH in high yield the free crystalline 5-[(methylamino)methyl]-2-thiouridine **6c**, identical to an authentic sample of the natural product (*Scheme 1*) [7][8].

Scheme 1



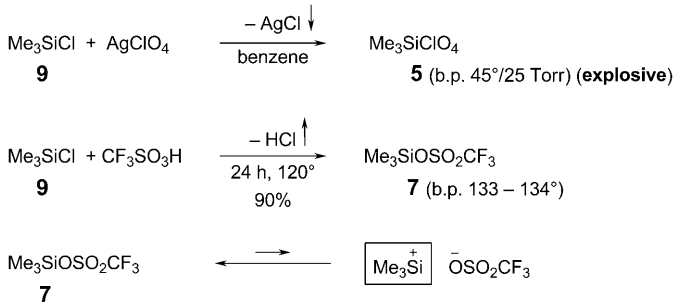
Because Me_3SiClO_4 (**5**) was obviously the only *Lewis* acid, which could have cleaved the *N*-Boc group, we looked for information on **5** and found a publication, in which a ^{29}Si-NMR study of trimethylsilyl esters of strong acids had been described [9]. Trimethylsilyl perchlorate (Me_3SiClO_4; **5**) and trimethylsilyl triflate ($Me_3SiOSO_2CF_3$, TMSOTf; **7**) showed the most pronounced downfield ^{29}Si-NMR shifts and are thus the strongest *Lewis* acids compared to other TMS esters of strong acids such as bis(trimethylsilyl)sulfate ($(Me_3Si)_2SO_4$; **8**) [9]. The corresponding pK_a values of triflic acid, $HClO_4$, and H_2SO_4 in glacial AcOH are given at the right side of *Scheme 2* [10].

Scheme 2

$Me_3SiOSO_2CF_3$ (**7**)	δ (^{29}Si) 44.6	pK_a (estim.) = –6.7	CF_3SO_3H : pK_a = –4.7 (AcOH)
Me_3SiClO_4 (**5**)	δ (^{29}Si) 43.4	pK_a (estim.) = –6.2	$HClO_4$: pK_a = –4.87 (AcOH)
$(Me_3Si)_2SO_4$ (**8**)	δ (^{29}Si) 33.7	pK_a (estim.) = –1.4	H_2SO_4: pK_a = –7.0 (AcOH)

Whereas **5** is obtained on addition of trimethylchlorosilane (Me_3SiCl, TMS-Cl; **9**) to a solution of $AgClO_4$ in dry benzene [9][11] and subsequent filtration of AgCl, TMSOTf (**7**), which had first been synthesized by reaction of TfOAg with **9** [12] or of $(Tf)_2O$ with hexamethyldisiloxane [13], is most simply prepared on boiling of TfOH and TMS-Cl (**9**) with evolution of HCl and subsequent distillation (*Scheme 3*) [9]. On dissociation of **7** (or of **5**), the hypothetic lipophilic Me_3Si^+ cation can be transferred to any present nucleophile as a lipophilic and bulky proton-equivalent (*Scheme 3*) [14].

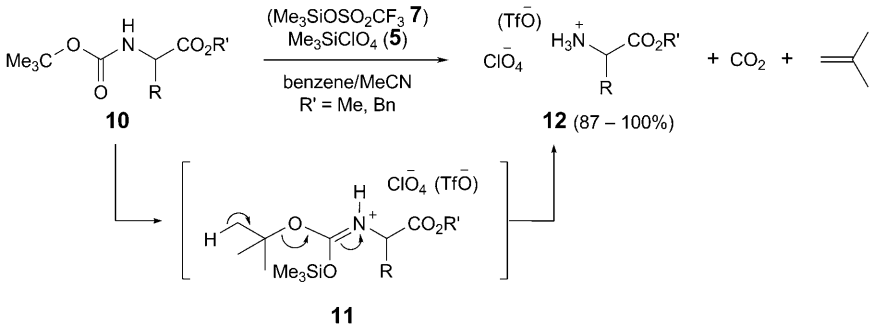
Scheme 3



We reacted a series of methyl or benzyl esters of *N*-Boc amino acids **10** or peptides with a solution of **5** in benzene, and found that the *N*-Boc groups are readily cleaved *via* *O*-silylation to the intermediate **11** in benzene/MeCN mixtures, whereupon CO_2 and isobutylene are evolved, and the perchlorate salts **12** of the ensuing esters of amino acids and peptides are precipitated on aqueous workup in yields of 87–100% (*Scheme 4*) [15]. When we learned, however, that pure, solvent free Me_3SiClO_4 (**5**) explodes on heating [16], we started using exclusively the thermally stable TMSOTf (**7**). We published a short note on the cleavage of *N*-Boc groups in amino acids **9** or peptides with **5** and emphasized in footnote 5 the analogous cleavage of *N*-Boc groups with the chemically stable TMSOTf (**7**) [15]. Subsequently, this novel cleavage of *N*-Boc-amino acids and peptides with **7** or (*t*-Bu)Me_2SiOTf has been widely applied as such or in combination, *e.g.*, with bases such as 2,6-lutidine.

2.2. *Synthesis of Pyrimidine Nucleosides.* Because we had introduced in 1969–1975 *Friedel–Crafts* catalysts such as $SnCl_4$ [17–19] in a new effective version of the silyl-*Hilbert–Johnson* synthesis of nucleosides, we tried successfully these new *Lewis* acids, the labile Me_3SiClO_4 (**5**) and, in particular, the stable TMSOTf (**7**) as new *Friedel–Crafts* catalysts in the silyl-*Hilbert–Johnson* reaction [20][21] and compared **7** with $SnCl_4$ [20][21]. The *Lewis* acids **7** and $SnCl_4$ are 'neutralized' by basic persilylated pyrimidines as σ-complexes so that a slight excess of *Lewis* acids is usually necessary to form reactive sugar cations such as **15** for nucleoside synthesis! In the ^{13}C-NMR spectra

Scheme 4



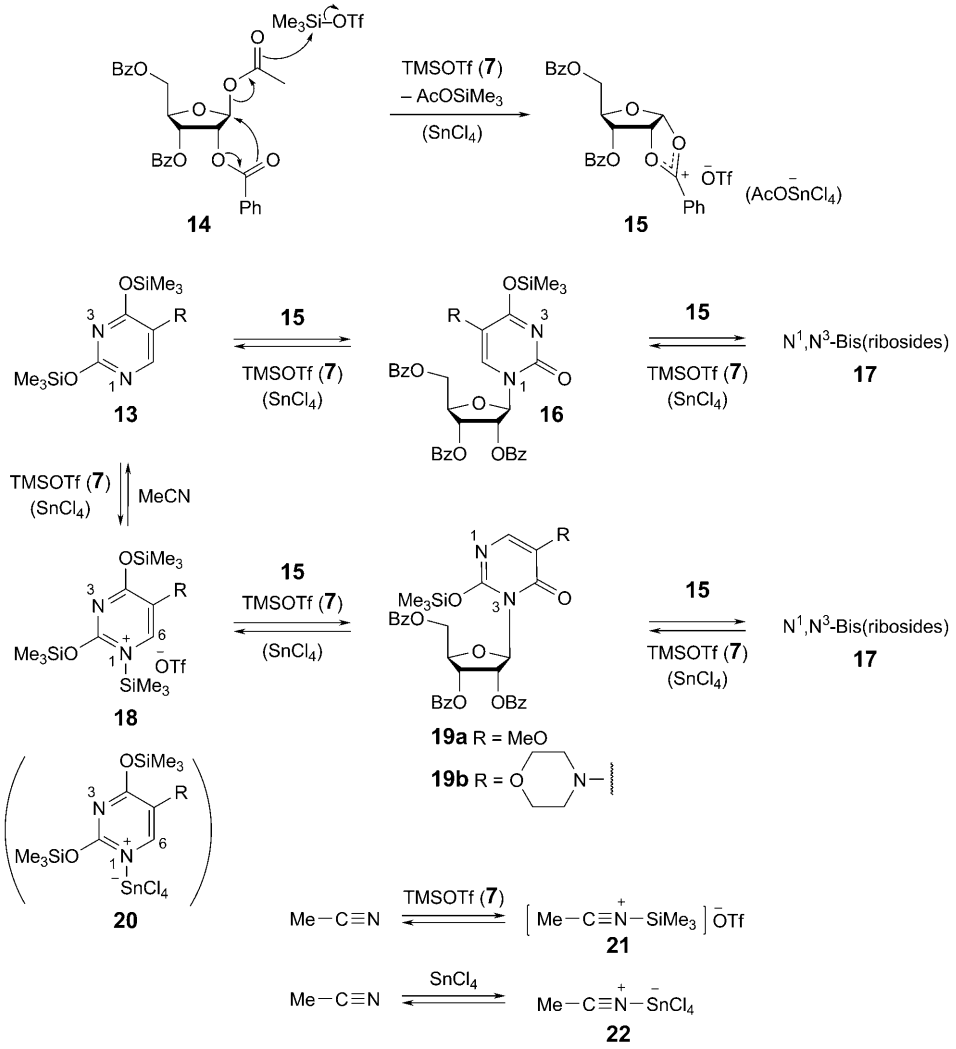
of the rather basic silylated 5-methoxyuracil **13a**, the signal of C(6) at 139 ppm is broad for the $SnCl_4$ σ-complex **20**, which proves a tight binding of $SnCl_4$ to the N^1, the center of highest electron density! The corresponding signal of the σ-complex **18** of the N^1 with **7** is sharp and indicates a rather loose binding and a rapid exchange of the weaker *Lewis* acid **7** with the N^1 of persilylated uracils (*Scheme 5*) [22][23]!

Although TMSOTf (**7**) is a much weaker *Lewis* acid than $SnCl_4$, it converts nevertheless 1-*O*-acylated sugars such as **14** by *O*-silylation of the 1-β-*O*-Ac group into TMSOAc and reactive sugar salts such as **15**. The decreased acidity of **7** results, however, in less of the σ-complexes **18** between **7** and the basic silylated heterocycles **13**, compared to the stronger *Lewis* acid $SnCl_4$, which forms with **13** much more of the corresponding σ-complex **20** as determined by ^{13}C-NMR studies following the downfield shift of C(6) [22][23]. Whereas silylated bases **13** react with the sugar salt **15** to give the desired silylated N^1-nucleosides **16**, the σ-complexes **18**, in which N^1 is blocked, can also combine in a slower reaction with the sugar salt **15** to the undesired N^3-nucleosides **19**. Since much more of the σ-complex **20** is formed with $SnCl_4$, in particular, in the rather unpolar solvent $Cl(CH_2)_2Cl$, less of the N^1-nucleosides **16** and more of the N^3-nucleosides **19** are thus obtained. Both, the silylated N^1-nucleosides **16** as well as the undesired silylated N^3-nucleoside **19** can react further with the reactive sugar salt **15** to the useless N^1,N^3-bis(ribosides) **17** (*Scheme 5*).

Because polar MeCN forms σ-complexes **21** with **7** or σ-complexes **22** with $SnCl_4$ [24] (*cf. Scheme 5*), MeCN competes with the silylated bases **13** for the *Lewis* acids TMSOTf (**7**) or $SnCl_4$ resulting in reduced formation of the σ-complexes **18** or **20**, and thus in diminished amounts of N^3-nucleosides **19** and of N^1,N^3-bis(ribosides) **17** and thus in more of the natural protected N^1-nucleosides **16** (*Scheme 6*) [21–23]!

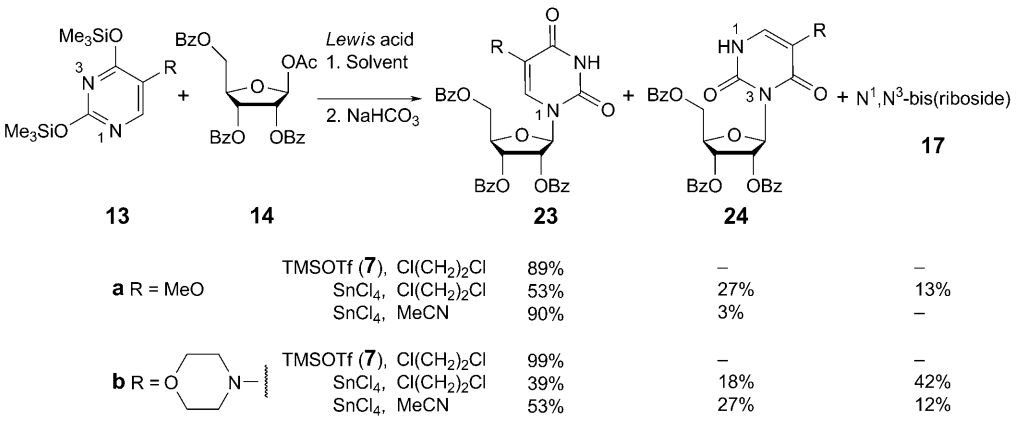
The basic silylated 5-methoxyuracil **13a** or the even more basic silylated 5-morpholinouracil **13b** give in MeCN with TMSOTf (**7**) or $SnCl_4$ as catalyst after workup high yields of the desired protected natural N^1-nucleosides **23a** and **23b**, and thus dramatically reduced formation of the undesired protected N^3-nucleosides **24a** or **24b**, and N^1,N^3-bis(ribosides) **17** [21–23]! In comparison, in $Cl(CH_2)_2Cl$ more σ-complexes **18** between the silylated bases and the *Lewis* acids are formed in the equilibria resulting in the formation of more protected N^3-nucleosides **24** and N^1,N^3-bis(ribosides) **17** (*Scheme 6*) [21–23].

Scheme 5



2.3. *Synthesis of Purine Nucleosides.* The advantages of employing TMSOTf (**7**) as catalyst compared to $SnCl_4$ are even more pronounced in the synthesis of purine or related bicyclic nucleosides. On the basis of ^{13}C-NMR studies [23] of persilylated purine bases following the downfield shift of C-atoms [8], we assume that the most basic N^1 in persilylated N^6-benzoyladenine **25** adds **7** to the σ-complex **26**, which eliminates **7** to the activated putative silylated N^6-benzoyladenine **27**. While **25** or **27** react initially, kinetically controlled, reversibly with the electrophilic sugar salt **15** to protected N^1-adenosine **28** [25] and N^3-adenosine **29**, which can be isolated at the beginning of the reaction, the subsequent reaction of **27** with the sugar salt **15** gives

Scheme 6



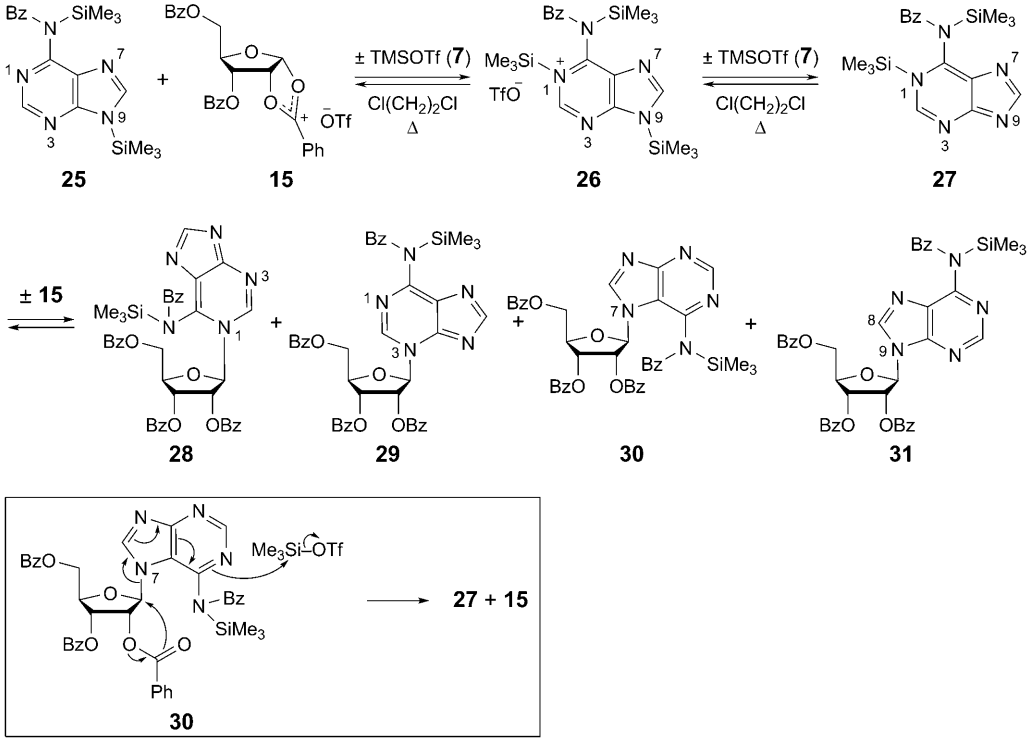
primarily the desired N^9-nucleoside **31** and the undesired protected N^7-nucleoside **30** (*Scheme 7*). On boiling the reaction mixture in the rather unpolar solvent $Cl(CH_2)_2Cl$, σ-complex formation of the undesired products **28**, **29**, and **30** with TMSOTf (**7**) and their rearrangements (*cf.* the depicted **7** catalyzed cleavage of the N^7-nucleoside **30** to **27** and **15**!) results eventually in the predominant formation of the desired and thermodynamically favored protected natural N^9-nucleoside adenosine **31**. Saponification of the mixture of **30** and **31** with NH_3 in MeOH provides free crystalline adenosine in 81% overall yield (*Scheme 7*) [21].

Persilylated N^2-acetylguanine **32** gives with **14** and **7** in boiling $Cl(CH_2)_2Cl$, followed by saponification, crystalline N^9-guanosine **33** in 66% yield [21]. These results were later confirmed, and the ratio between the desired natural N^9-guanosine **33** and the undesired N^7-guanosine **34** was determined to be 6 : 1, whereas $SnCl_4$ as catalyst leads in MeCN or $Cl(CH_2)_2Cl$, and subsequent saponification to an excess of the undesired free N^7-guanosine **34** (*Scheme 8*) [26]!

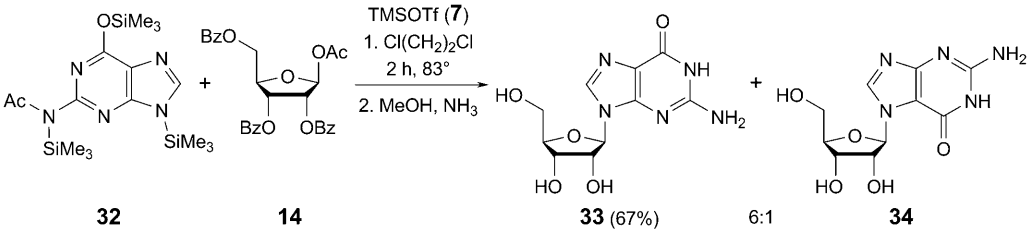
Since $Cl(CH_2)_2Cl$ as solvent favors σ-complex formation of the persilylated purine moieties with TMSOTf (**7**) and thus rearrangements of the initially formed kinetically controlled intermediates **28**, **29**, and **30** to the thermodynamically most stable natural N^9-nucleosides **31** and **33**, $Cl(CH_2)_2Cl$ is the preferred solvent for the synthesis of purine nucleosides as well as of purine nucleoside analogs [21][27][28]!

2.4. *Simplified One-Step–One-Pot Nucleoside Synthesis.* To simplify nucleoside synthesis [29][30], we have combined the acid-catalyzed silylation of the heterocyclic bases and the silylation of free triflic acid (TfOH) **36** to TMSOTf (**7**), or of NfOK (**37**) to TMSONf (**38**) with concomitant nucleoside synthesis in MeCN. Whereas free **36** can be silylated *in situ* either by a mixture of hexamethyldisilazane ($Me_3SiNHSiMe_3$, HMDS; **35**) with Me_3SiCl **9** to give **7** and NH_4Cl, which is precipitated, the stable and non-hygroscopic NfOK (**37**), which is quite soluble in boiling MeCN, (*cf. Sect. 3*) is transformed *in situ* by **9** in boiling MeCN to TMSONf (**38**) and insoluble KCl, which is likewise precipitated (*Scheme 9*) [29][30].

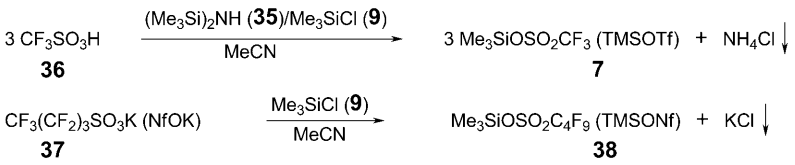
Scheme 7



Scheme 8

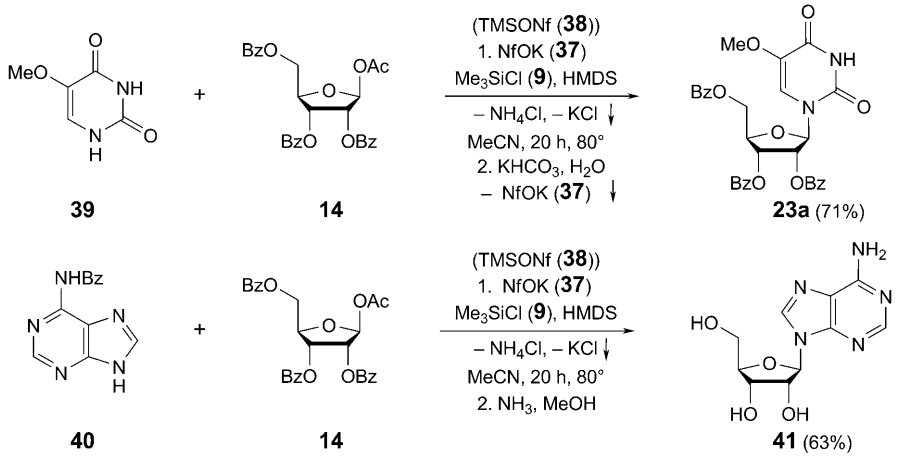


Scheme 9



5-Methoxyuracil **39** affords with **14**, in the presence of NfOK (**37**), Me_3SiCl (**9**), and HMDS (**35**) in boiling MeCN and subsequent workup with aqueous $KHCO_3$, 71% of crystalline *O*-benzoylated 5-methoxyuridine **23a**, as well as recovered NfOK (**37**), whereas N^6-benzoyladenine (**40**) gives analogously on nucleoside synthesis and subsequent saponification with NH_3 in MeOH 63% of free crystalline adenosine (**41**; *Scheme 10*) [29][30]. This one-step–one-pot procedure has been subsequently applied by numerous groups [27][28]. It turned out that this simple and rapid route is particularly suitable for the preparation of very short lived isotopically labeled fluorinated nucleosides for PET applications [31].

Scheme 10



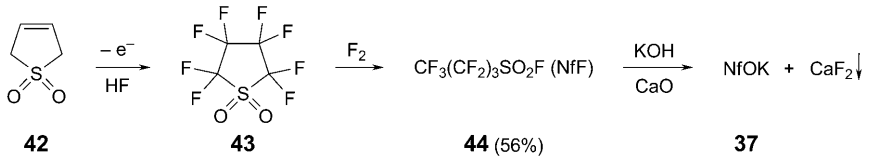
After we had introduced in 1975 Me_3SiClO_4 (**5**) and TMSOTf (**7**) as new selective *Lewis* acids for the cleavage of *N*-Boc groups [15] and, in particular, for nucleoside synthesis [20][21][23], some subsequent publications, *e.g.*, on glycoside synthesis with **7** as catalyst [32–36] referred to us, whereas two reviews on analogous applications of **7** [37][38] neglected to mention that we in fact had introduced **7** as new mild and selective *Lewis* acid into preparative organic chemistry at least one year before any other preparative applications of **7** had been published.

3. Reactions with Potassium Nonaflate (NfOK). – 3.1. *Synthesis of Nonaflyl* (= Perfluorobutanesulfonyl) *Fluoride* (NfF) *and Potassium Nonaflate* (NfOK). As discussed in *Sect. 2.4* (*cf. Schemes 9* and *10*), we started using NfOK (**37**) for the one-step–one-pot nucleoside synthesis in MeCN generating TMSONf (**38**) *in situ* as catalyst [29][30] whose reactivity is even higher than that of TMSOTf (**7**) [39].

The stable liquid NfF (**44**; b.p. 65°) [40] is obtained on a technical scale by anodic '*Simons*' fluorination of sulfolene (**42**) in liquid HF [41][42]. The fluorination proceeds *via* perfluorosulfolane (**43**) [43] and subsequent cleavage by NiF_3 or NiF_4 to give **44** in up to 56% overall yield [41][42]. Crude, technical-grade NfF (**44**) contains often 2–10% of perfluorosulfolane (**43**; b.p. 56°, m.p. 45°) [43–45]. Hydrolysis of **44** with KOH/CaO [46] affords the non-hygroscopic and very stable potassium nonaflate

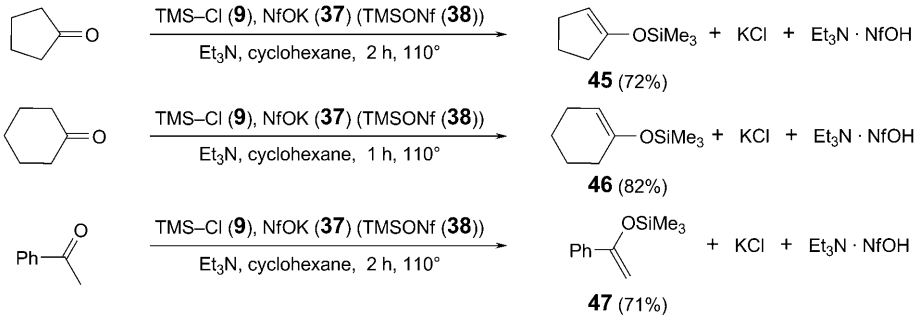
(NfOK; **37**; m.p. 271–275°), which is soluble in boiling MeCN or AcOEt [47] but rather insoluble in cold H_2O (*Scheme 11*).

Scheme 11



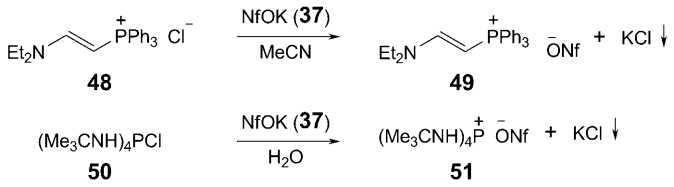
3.2. *Reactions with* NfOK (**37**). Although the non-hygroscopic NfOK (**37**) is commercially prepared and used in large amounts as additive to make organic material fire-resistant, only few additional preparative applications of **37** besides the one-step–one-pot nucleoside synthesis (*cf. Schemes 9* and *10*) have been published. Thus, ketones such as cyclopentanone, cyclohexanone, or acetophenone are readily transformed in high yields to their corresponding enol silyl ethers **45**, **46**, and **47**, respectively, on boiling ketones with a slight excess of TMS-Cl (**9**) and Et_3N with NfOK (**37**) in cyclohexane [48], generating TMSONf (**38**) *in situ*. The obtained yields of 71–82% can certainly be improved on larger-scale synthesis of enol silyl ethers (*Scheme 12*).

Scheme 12



Salts such as [2-(diethylamino)vinyl](triphenyl)phosphonium chloride (**48**) or the phosphonium chloride **50** are readily converted by NfOK (**37**) in MeCN, in nearly quantitative yield, to the nicely crystallizing nonaflates **49** [49] and **51** [50], respectively, as well as KCl (*Scheme 13*; *cf.* also the crystalline nonaflate salts **65** and **76** in *Schemes 15* and *17*, resp.).

Scheme 13



Initial attempts to convert anhydrous inorganic salts such as $CuCl_2$ with NfOK (**37**) in dry MeCN at 90° and subsequent cooling to obtain $Cu(ONf)_2$ and insoluble KCl have failed due to the formation of a crystalline supermolecular complex of **37** with MeCN. Interestingly, Li, Na as well as Cs nonaflate did not give analogous complexes with MeCN. Analogous experiments of NfOK (**37**) with salts like CuX_2 could also be carried out in boiling dry AcOEt [47].

For metal-catalyzed reactions, it might, however, be sufficient if small amounts of nonaflate salts such as $Cu(ONf)_2$ are formed *in situ* as described for the *in situ* synthesis of TMSONf (**38**; *cf. Scheme 9*), because anhydrous metal nonaflates such as $Cu(ONf)_2$ can be anticipated to have higher solubilitys in organic solvents than the hitherto mostly applied more expensive metal triflates.

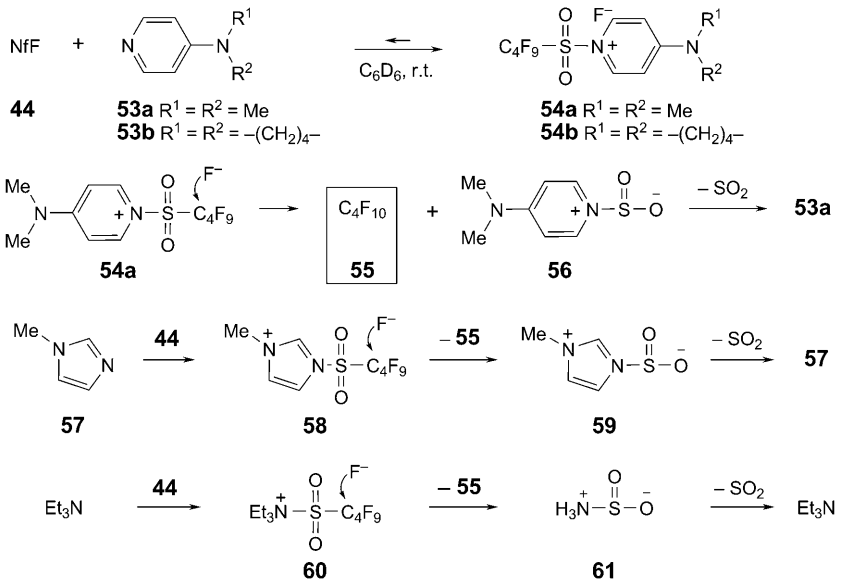
4. Reactions with Nonaflyl Fluoride (NfF). – 4.1. *Reactivity of NfF.* The readily available NfF (**44**; b.p. 65°) is the unpolar mixed anhydride between NfOH and HF, and quite stable under neutral reaction conditions. On reaction of **44** with anhydrous NH_3, however, the crystalline $C_4F_9SO_2NH_2$ as well as NH_4F is formed at +10° [51]. Likewise, **44** converts instantly O-anions such as phenolate anions, which are formed from phenols in the presence of Et_3N, to the corresponding aryl *O*-nonaflates as reported in a recent review [52]. The reaction of **44** with *O*-silylated alcohols, enols, or phenols is accelerated on addition of catalytic amounts of fluoride reagents such as CsF or $Bu_4NF \cdot (H_2O)_3$ in THF, whereupon the corresponding *O*-nonaflates and trimethylsilyl fluoride (Me_3SiF; **52**; b.p. 17°) are formed [52]. Ketones afford with **44** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), Li-HMDS, LDA, or NaH the corresponding enol *O*-nonaflates, and the salts DBU · HF, LiF, or NaF [52]. α,β-Unsaturated ketones react with NfF (**44**) and DBU on heating to 90° to *O*-dienol nonaflates [53]. Enol *O*-nonaflates or aryl *O*-nonaflates undergo readily *Suzuki*, *Stille*, or *Sonogashira* coupling reactions [52]. The chemistry of **44** has been reviewed in [52][54].

4.2. *Reactions of NfF* (**44**) *with Alcohols in the Presence of Nucleophilic Bases.* When we tried to increase the reactivity of NfF (**44**), by adding nucleophilic basic catalysts such as 4-(dimethylamino)pyridine (DMAP; **53a**), 4-pyrrolidinopyridine (PPY; **53b**), 1-methyl-1*H*-imidazole (**57**) [55], or even Et_3N to **44**, we observed with **53b** the slow formation of an equilibrium between **44**, **53b**, and the σ-complex **54b**, which can be detected by ^{19}F-NMR at room temperature [56].

The ratio **44**/**54b**, as indicated by the shift of the ^{19}F-NMR signals of the perfluorobutyl group in **54b**, is after 1 h *ca.* 1:1, whereas after 24 h the ratio **44**/**53b** changes to 1:2 (*Scheme 14*) [56]. As a consequence of the ready formation of σ-complexes such as **54**, **58**, and **60**, **44** fragments slowly already at −20° in the presence of DMAP (**53a**), PPY (**53b**), and 1-methyl-1*H*-imidazole (**57**), or Et_3N to give *via* **54**, **58**, and **60**, respectively, perfluorobutane **55** (b.p. −2°), which can be detected on GC/MS of the gaseous phase above the reaction mixture as well as in the GC inlet system in addition to SO_2, **53a**, **53b**, **57**, or Et_3N (*Scheme 14*) [57].

Reaction of neopentyl alcohol (**62**) with **44** in the presence of excess DMAP (**53a**) affords *via* the presumed intermediate neopentyl *O*-nonaflate (**63**) and $DMAP \cdot (HF)_n$ (**64**), 81% of crystalline 1-neopentyl-4-(dimethylamino)pyridinium nonaflate (**65**), small amounts of the fluorides **66** and **67**, as well as of olefins **68** and **69**, as indicated by GC/MS (*Scheme 15*) [56]. On reaction of *O*-trimethylsilylated alcohols with **44**,

Scheme 14



reactive *O*-nonaflates such as **63** are obtained as intermediates, while the competing nucleophilic anhydrous fluoride anions are removed as volatile TMS-F (**52**) [52] (*cf.* also the reactions of compounds **70** and **74b** in *Schemes 16* and *17*).

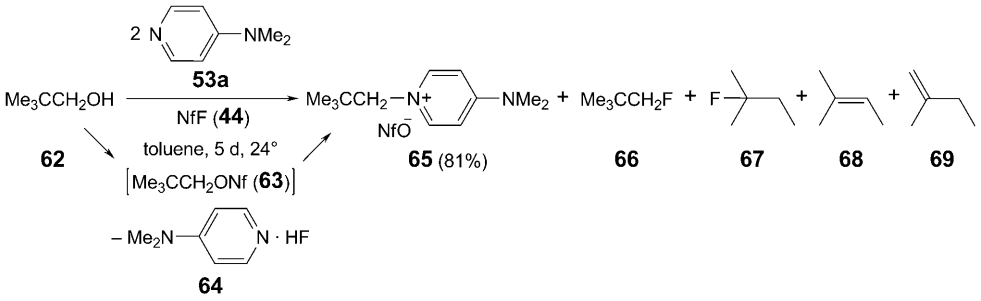
Reaction of *O*-silylated 1-(2-hydroxyethyl)-1*H*-imidazole **70** with NfF (**44**) affords TMS-F (**52**; b.p. 17°) and the intermediate *O*-nonaflate **71**, which polymerizes to an oily mixture of up to nonameric polyimidazolium nonaflates **72** (*Scheme 16*)[1]). Analogs of **70** with longer side chains ($m > 4$) can be expected to give in addition to linear structures such as **72** also monomeric bicyclic imidazolium nonaflates such as **73**.

The equatorial secondary OH group in 5α-cholestane-3β-ol (**74a**) reacts with **44** and DMAP (**53a**) to give *via* the *O*-nonaflate **75** crystalline 1-(3α-cholestan-3-yl)-4-(dimethylamino)pyridinium nonaflate (**76**) in 48% yield and a mixture of Δ^2(Δ^3)-cholestenes **77**, 3α-fluorocholestane (**78**), 3β-fluorocholestane (**78**), as well as some dimeric ether between **74a** and 5α-cholestan-3-ol, which is formed by nucleophilic

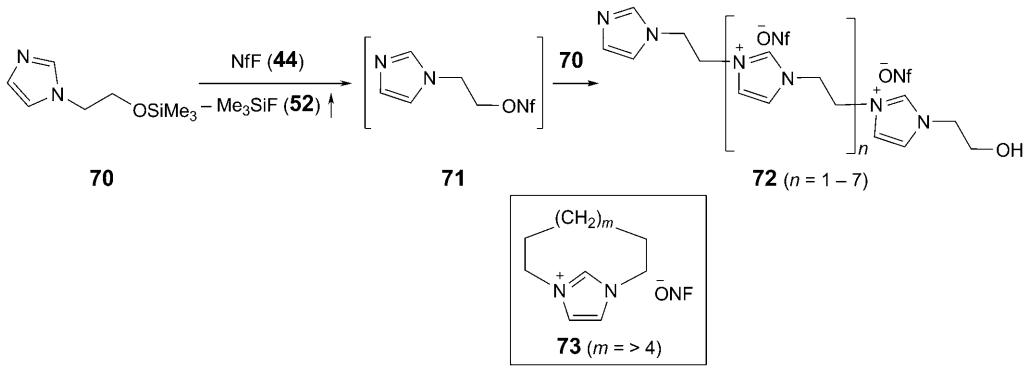
---

[1]) *H. Vorbrüggen*, *C. Schalley*, unpublished results: 1-(2-Hydroxyethyl)-1*H*-imidazole (1.16 g, 10 mmol) with hexamethyldisilazane (1.64 g; 2.1 ml) in dry xylene (40 ml) was heated at reflux for 1.5 h to afford **70**. NfF (**44**; 3.02 g; 1.8 ml) was then added within 1 h, whereupon a yellowish layer was formed, which gave on evaporation 2.85 g of yellowish oil of oligomeric imidazolium nonaflates **72**. (R_f (MeOH) 0.6; silica plates). Several fractions from the GPC separation of crude **72** were examined by positive-mode electrospray-ionization *Fourier*-transform ion-cyclotron-resonance (ESI-FT-ICR) mass spectrometry (*Bruker APEX IV* instrument with a 7 T magnet, spray solvent: THF). Several series of ions were observed, which appeared in different states of protonation and with distributions of different numbers of counter anions. Oligomer chain lengths of up to the nonamer were observed. Due to possible fragmentation reactions driven by charge repulsion, the true chain length may even be higher.

Scheme 15

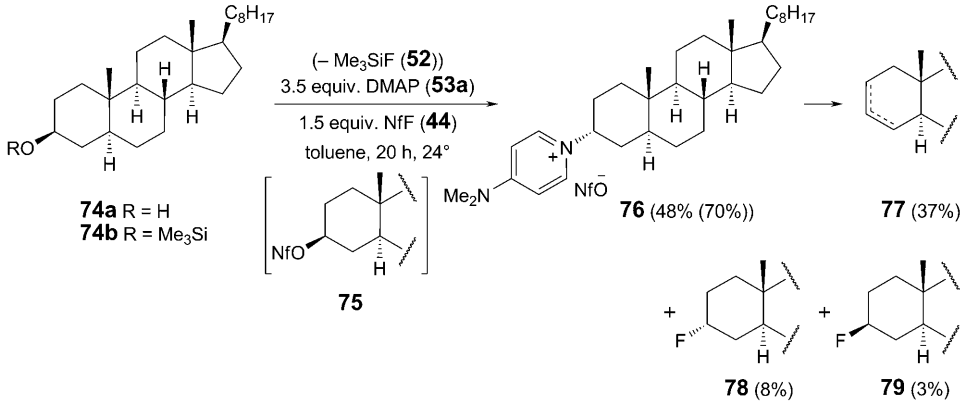


Scheme 16



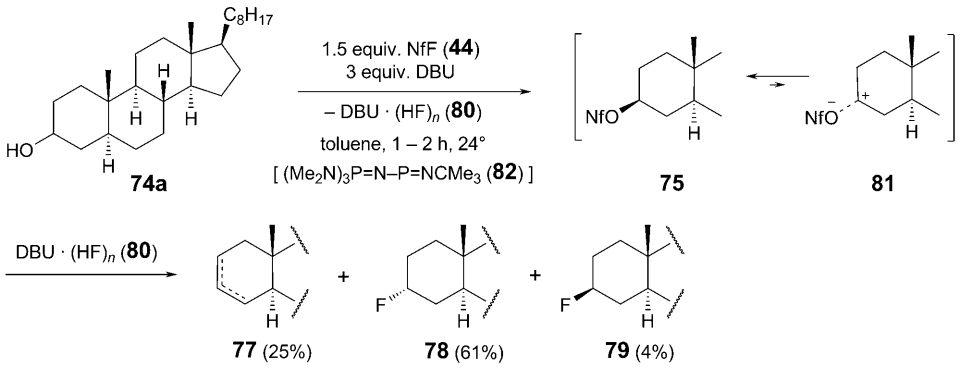
attack of the O-anion of cholestanol **74a** at the *O*-nonaflate **75**. On employing *O*-silylated 5α-cholestan-3β-ol **74b** instead of **74a** to remove the competing F^- anions as TMS-F (**52**), pyridinium nonaflate **76** is obtained in 70% yield (*Scheme 17*) [56].

Scheme 17



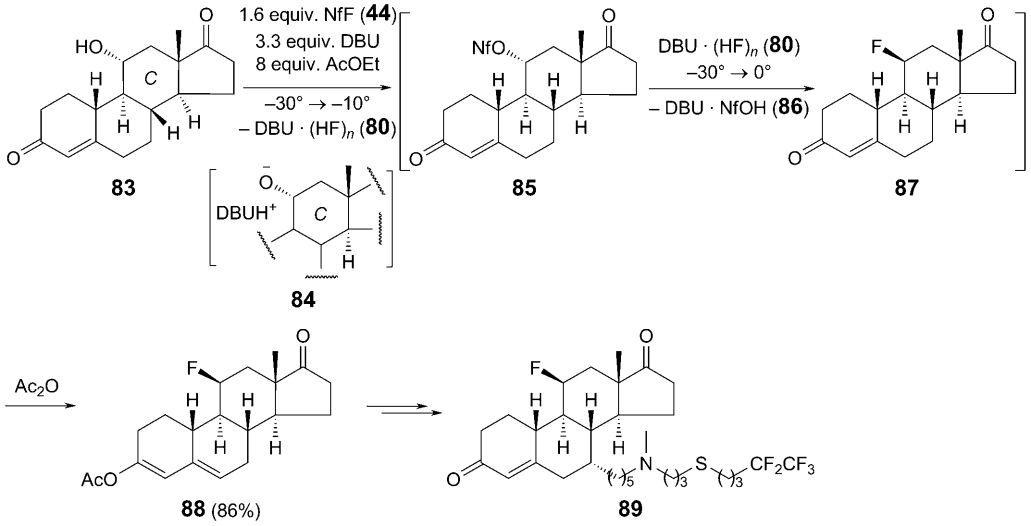
4.3. *The Conversion* (Dehydroxyfluorination) *of Alcohols with NfF and DBU to Fluorides.* When we reacted cholestan-3β-ol (**74a**) with NfF (**44**) and the much stronger base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene, we isolated the desired 3α-fluorocholestane **78** as the major product in 61% yield, which is formed by nucleophilic attack of *in situ* formed anhydrous and nucleophilic DBU · $(HF)_n$ ($n = 1-3$; **80**) at the intermediate *O*-nonaflate **75** (*Scheme 18*)! These reactions proceed in toluene already at $-40°-0°$! The strong base DBU converts the cholestanol **74a** to the corresponding DBU-alcoholate (*cf.* the O-anion **84** in *Scheme 19*), which reacts then instantly with **44** to the *O*-nonaflate **75** and the olefin mixture **77** [58]. The formation of 3β-fluorocholestane (**79**) is apparently due to temperature-dependent partial dissociation of the reactive intermediate *O*-nonaflate **75** into the intimate ion pair **81** (*Scheme 18*), which is attacked by DBU · $(HF)_n$ (**80**) or DBU from either side of the cyclohexane ring to give fluorides **78** and **79**, and olefins **77** (*Scheme 18*) [58]. On employing the much stronger *Schwesinger* base P_4-^{t}Bu, $(Me_2N)_3P{=}N{-}P{=}NCMe_3$ (**82**) [59][60] instead of DBU for the reaction of **74a** with **44**, a slightly decreased yield of 57% of 3α-fluorocholestane (**78**) is obtained, but almost no 3β-fluorocholestane (**79**). The phosphazene base **82** eliminates apparently NfOH from any intimate ion pair **81** to the olefins **77** before attack of **82** · $(HF)_n$ can occur to give any 3β-F compound **79**!

Scheme 18



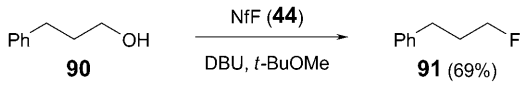
Because the conversion of 11α-hydroxy-19-norandrost-4-ene-3,17-dione (**83**) with **44**/DBU to 11β-fluoro-19-norandrost-4-ene-3,17-dione (**87**) is an important reaction step in the synthesis of new potent 11β-F estrogen-receptor antagonists such as **89**, the reaction of **83** with NfF (**44**)/DBU was reinvestigated in more detail and optimized [61]. The 11α-OH steroid **83** gives selectively, *via* the DBU-alcoholate **84** and instant subsequent reaction with **44** at *ca.* $-30°$ to $-20°$, the *O*-nonaflate intermediate **85**, which is converted by *in situ* formed DBU · $(HF)_n$ (**80**) to the 11β-F compound **87** (*Scheme 19*). High yields of **87** exceeding 80% are obtained on adding *ca.* 1.5–2 equiv. of **44** rapidly within 0.5–1 min at *ca.* $-40°$ with stirring and effective cooling to a solution of **83** and *ca.* 2–3 equiv. of DBU in *ca.* 8 equiv. of AcOEt to give DBU · NfOH (**86**) as well as **87**, which is, however, not isolated but converted *in situ* on addition of Ac_2O in an overall yield of 86% to the nicely crystallizing dienol acetate **88**, a further step towards the synthesis of potent anti-estrogens such as **89** [61].

Scheme 19



The primary alcohol **90** is converted smoothly to the corresponding volatile fluoro compound **91** [58]. Although only 69% of redistilled **91** were obtained in a first small-scale experiment, larger-scale experiments can be expected to give yields exceeding 90% for **91** (*Scheme 20*). Whereas steroidal alcohols **74a** or **83** react *via* their *O*-nonaflates with *Walden* inversion with DBU · $(HF)_n$ (**80**) to their inverted fluorides **78** or **87**, homoallylic $\Delta^{5,6}$-androstan-3β-ols are converted *via* their corresponding homoallyl cations with retention of configuration in up to 61% yield to 3-fluoro-androst-5(6)-ens [62].

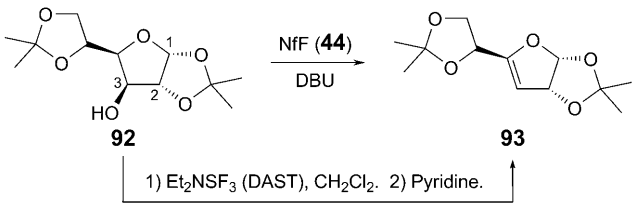
Scheme 20



Although dehydroxyfluorinations with **44**/DBU were at the time of our publication [58] not optimized, in particular the optimized [61] procedure for dehydroxyfluorinations with **44**/DBU gives consistently higher yields of inverted fluorides compared to Et_2NSF_3 (DAST), which had become the standard reagent [63] for such dehydroxyfluorinations in preparative organic chemistry. DAST is furthermore rather unstable and dangerous, particularly at temperatures exceeding 50° and *ca.* ten times more expensive than **44**. Dehydroxyfluorinations with **44** were recently reviewed [2].

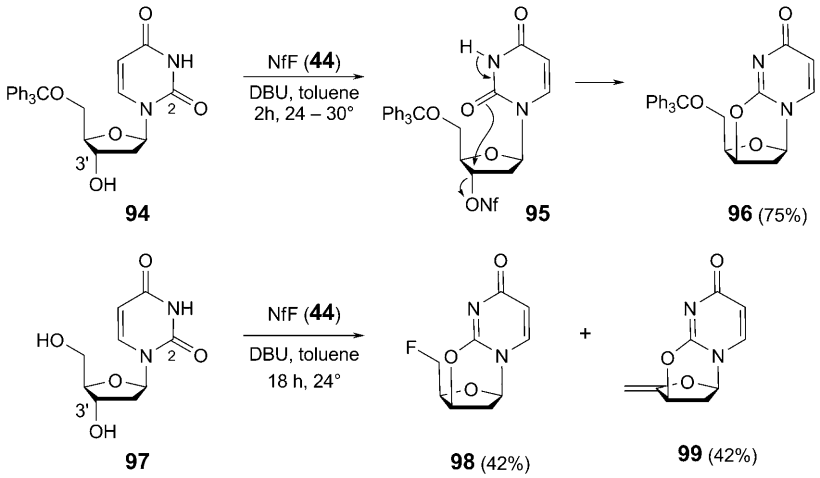
4.4. *Side Reactions on Employing NfF/DBU.* In all dehydroxyfluorinations with NfF (**44**), the base-catalyzed elimination of NfOH, *e.g.*, as DBU salts, is the most important side reaction, which can become the exclusive reaction in certain sterically favored cases. Thus, reaction of the strained 1,2,5,6-bis(acetonide) **92** with **44**/DBU affords in *ca.* 60–70% yield the crystalline dihydrofuran **93** [64], which is likewise formed by reaction of **92** with DAST and subsequent addition of pyridine (*Scheme 21*) [65].

Scheme 21



Although the anhydrous fluoride ion in $DBU \cdot (HF)_n$ (**80**) is a good nucleophile, nucleophilic bases such as DMAP and 1-alkyl-1*H*-imidazoles (*cf. Schemes 15–17* in *Sect. 4.2*) as well as adjacent (neighboring) nucleophiles will react in preference to **80**! Thus, the neighboring C(2)=O group in 5′-*O*-tritylthymidine (**94**) reacts with the intermediate 3′-*O*-nonaflate **95** to give 2,3-anhydro-5′-*O*-tritylthymidine **96**, whereas free thymidine (**97**) affords 5′-fluoro-2,3′-anhydro-5′-deoxythymidine (**98**) as well as olefin **99** (*Scheme 22*) [66].

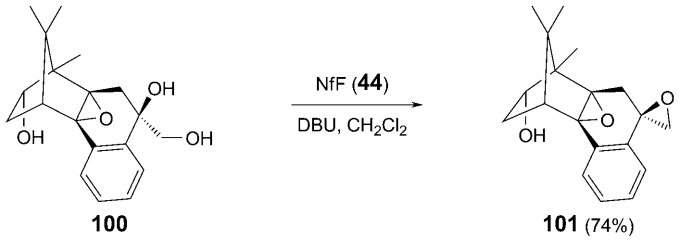
Scheme 22



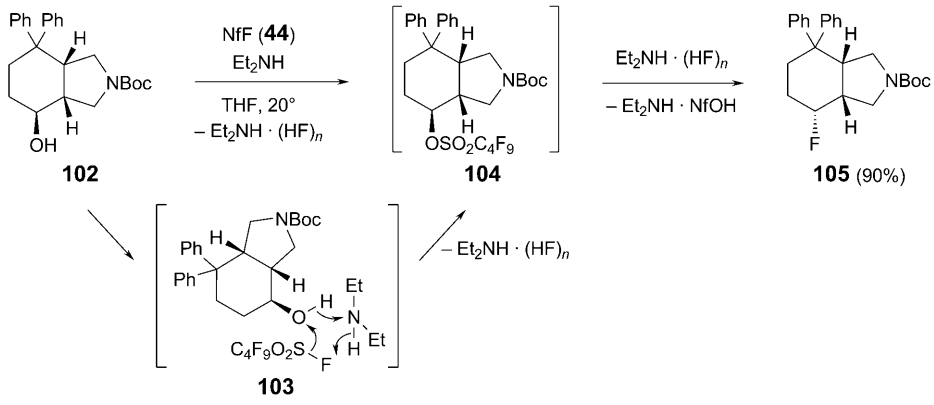
The sterically hindered borneol-triol **100** reacts with **44**/DBU in CH_2Cl_2 to the *O*-nonaflate of the primary alcoholic group in **100**, which cyclizes *via* the O-anion of the adjacent tertiary OH group to the epoxide **101**, a cyclization, which could not be achieved by any other method (*Scheme 23*) [67].

4.5. *Modifications of NfF Dehydroxyfluorinations by Other Groups.* The secondary alcohol **102** reacts with **44** in combination with Et_2NH in THF to result in the inverted fluoride **105** [68] (*Scheme 24*). The surprising reactivity of this new combination of **44** with Et_2NH (compared to **44** with Et_3N [58]) is apparently due to the transition state **103** to give the reactive *O*-nonaflate **104**, whose subsequent reaction with *in situ* formed $Et_2NH \cdot (HF)_n$ affords the inverted fluoride **105** (*Scheme 24*). Addition of $Et_3N \cdot (HF)_3$

Scheme 23



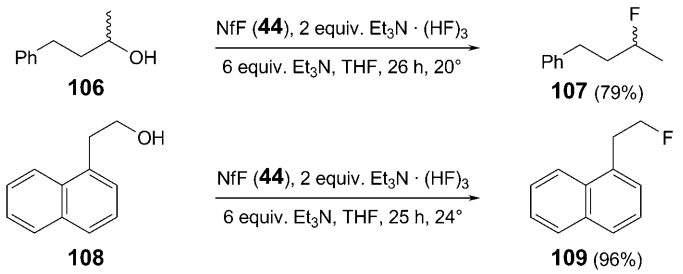
Scheme 24



to the combination of **44**/DBU converts 3,3-(ethylenedioxy)estra-5(10),9(11)-dien-17β-ol in 61% yield into the 17α-fluoro steroid [69].

On combining NfF (**44**) with a sixfold excess of Et_3N and a twofold excess of $Et_3N \cdot (HF)_3$, the secondary alcohol **106** as well as the primary alcohol **108** are converted efficiently to the fluorides **107** and **109**, respectively (*Scheme 25*) [70].

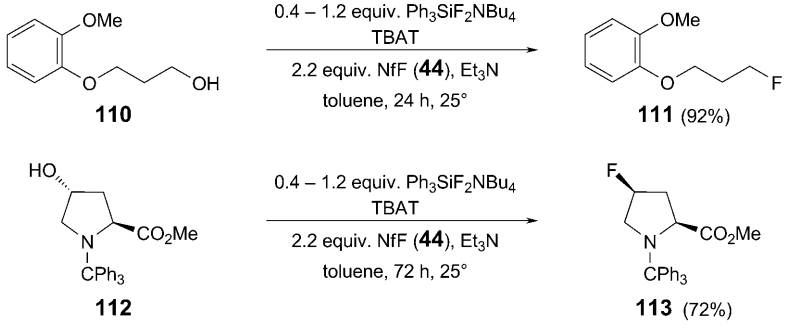
Scheme 25



Recently, *e.g.*, the primary alcohol **110** and the secondary alcohol **112** were reacted with **44** in combination with Et_3N or $^iPr_2NEt$, and the stable tetrabutylammonium

triphenyldifluorosilicate ($Ph_3SiF_2NBu_4$) [71] to afford the corresponding fluorides **111** and **113**, respectively [72] (*Scheme 26*).

Scheme 26



5. Concluding Remarks. – Whereas TMSOTf (**7**) and NfF (**44**; b.p. 65°) [52][61] have become widely used reagents, NfOK (**37**) has as yet found only rather limited preparative applications. It is hoped that the present review will stimulate further useful applications of NfF (**44**) and, in particular, also of **37** in preparative organic chemistry.

The author thanks his dedicated and very able former assistants *B. Bennua-Skalmowski* and *K. Krolikiewicz* for their excellent experimental work at the former *Schering AG* (now *Bayer–Healthcare*). The author is furthermore indebted to his former and present colleagues at the Institut für Chemie and Biochemie der Freien Universität Berlin, namely, Professors *R. Haag*, *H.-H. Limbach*, *J. Mulzer*, *H.-U. Reissig*, and *D. Schlüter*, for their generous hospitality in providing a laboratory and an office, and in particular to Prof. *H.-U. Reissig* for material support of his experimental work at the Free University.

REFERENCES

[1] H. Vorbrüggen, *Acc. Chem. Res.* **1995**, *28*, 509.
[2] H. Vorbrüggen, *Synthesis* **2008**, 1165.
[3] L. Birkofer, A. Ritter, H.-P. Kühlthau, *Chem. Ber.* **1964**, *97*, 934.
[4] E. Wittenburg, *Chem. Ber.* **1968**, *101*, 1095.
[5] H. Vorbrüggen, P. Strehlke, *Chem. Ber.* **1973**, *106*, 3039.
[6] J. Carbon, H. David, M. H. Studier, *Science* **1968**, *161*, 1146.
[7] H. Vorbrüggen, K. Krolikiewicz, *Angew. Chem., Int. Ed.* **1975**, *14*, 255.
[8] H. Vorbrüggen, K. Krolikiewicz, *Liebigs Ann. Chem.* **1980**, 1438.
[9] H. C. Marsmann, H. G. Horn, *Z. Naturforsch.* **1972**, *27b*, 1448.
[10] A. Engelbrecht, B. M. Rode, *Monatsh. Chem.* **1972**, *103*, 1315.
[11] U. Wannagat, F. Brandmair, W. Liehr, H. Niederprüm, *Anorg. Allg. Chemie.* **1959**, *302*, 185.
[12] M. Schmeißer, P. Sartori, B. Lippsmeier, *Chem. Ber.* **1970**, *103*, 868.
[13] H. W. Roesky, H. H. Giere, *Z. Naturforsch.* **1970**, *25b*, 773.
[14] J. R. Hwu, J. M. Wetzel, *J. Org. Chem.* **1985**, *50*, 3946.
[15] H. Vorbrüggen, K. Krolikiewicz, *Angew. Chem., Int. Ed.* **1975**, *14*, 818.
[16] U. Wanagat, W. Liehr, *Angew. Chem.* **1957**, *69*, 783.
[17] U. Niedballa, H. Vorbrüggen, *J. Org. Chem.* **1974**, *39*, 3664.
[18] U. Niedballa, H. Vorbrüggen, *J. Org. Chem.* **1974**, *39*, 3668.
[19] U. Niedballa, H. Vorbrüggen, *J. Org. Chem.* **1976**, *41*, 2084.

[20] H. Vorbrüggen, K. Krolikiewicz, *Angew. Chem., Int. Ed.* **1975**, *14*, 421.
[21] H. Vorbrüggen, K. Krolikiewicz, B. Bennua, *Chem. Ber.* **1981**, *114*, 1234.
[22] H. Vorbrüggen, U. Niedballa, K. Krolikiewicz, B. Bennua, G. Höfle, in 'Chemistry and Biology of Nucleosides and Nucleotides', Eds. R. E. Harman, R. K. Robins, L. B. Townsend, Academic Press, New York, 1978, p. 251.
[23] H. Vorbrüggen, G. Höfle, *Chem. Ber.* **1981**, *114*, 1256.
[24] I. R. Beattie, L. Rule, *J. Chem. Soc.* **1964**, 3267.
[25] J. Boryski, G. Framski, *Collect. Czech. Commun., Symposium Series* **2005**, *7*, 177.
[26] P. Garner, S. Ramakanth, *J. Org. Chem.* **1988**, *53*, 1294.
[27] H. Vorbrüggen, C. Ruh-Pohlenz, 'Organic Reactions', J. Wiley & Sons Inc., New York, 2000, Vol. 55.
[28] H. Vorbrüggen, C. Ruh-Pohlenz, ' Handbook of Nucleoside Synthesis', Wiley & Sons Inc., New York, 2001.
[29] H. Vorbrüggen, B. Bennua, *Tetrahedron Lett.* **1978**, *19*, 1339.
[30] H. Vorbrüggen, B. Bennua, *Chem. Ber.* **1981**, *114*, 1279.
[31] H. Anderson, N. Pillarsetty, M. Cantorias, J. S. Lewis, *Mol. Med. Biol.* **2010**, in print.
[32] T. Ogawa, K. Beppu, S. Nakabayashi, *Carbohydr. Res.* **1981**, *93*, C6 – C9.
[33] E. M. Nashed, C. P. J. Glaudemans, *J. Org. Chem.* **1989**, *54*, 6116.
[34] M. Numata, M. Sugimoto, Y. Ito, T. Ogawa, *Carbohydr. Res.* **1990**, *203*, 205.
[35] M. Mori, Y. Ito, T. Ogawa, *Carbohydr. Res.* **1990**, *195*, 199.
[36] C. Kolar, G. Kneißl, *Angew. Chem.* **1990**, *102*, 827.
[37] H. Emde, D. Domsch, H. Feger, U. Frick, A. Götz, H. H. Hergott, K. Hofmann, W. Kober, K. Krägeloh, T. Oesterle, W. Steppan, W. West, G. Simchen, *Synthesis* **1982**, 1.
[38] R. Noyori, S. Murata, M. Suzuki, *Tetrahedron* **1981**, *37*, 3899.
[39] L. R. Subramanian, M. Hanack, *Chem. Ber.* **1972**, *105*, 1465.
[40] T. Gramstad, R. N. Haszeldine, *J. Chem. Soc.* **1957**, 2640.
[41] M. Wechsberg, Ger. Offen 2.319.078; *Chem. Abstr.* **1975**, *82*, 57463a.
[42] V. Beyl, H. Niederprüm, P. Voss, *Liebigs Ann.* **1970**, *731*, 58.
[43] I. N. Rozhkov, A. V. Buktiarov, I. L. Knunyants, *Izv. Akad. Nauk USSR* **1969**, 945.
[44] T. Abe, J. M. Shreeve, *J. Fluorine Chem.* **1973**, *3*, 17.
[45] H. Bürger, F. Heyder, P. Pawelke, H. Niederprüm, *J. Fluorine Chem.* **1979**, *13*, 251.
[46] H. N. Huang, R. J. Lagow, H. Roesky, *Inorg. Chem.* **1991**, *30*, 789.
[47] I. Brüdgam, D. Lentz, H. Vorbrüggen, *Cryst. Eng. Commun.* **2010**, *12*, 795.
[48] H. Vorbrüggen, K. Krolikiewicz, *Synthesis* **1979**, 34.
[49] H. Vorbrüggen, K. Krolikiewicz, *Helv. Chim. Acta* **1993**, *76*, 819.
[50] R. Schwesinger, J. Willaredt, H. Schlemper, M. Keller, D. Schmitt, H. Fritz, *Chem. Ber.* **1994**, *127*, 2435.
[51] H. W. Roesky, *Inorg. Nucl. Chem. Lett.* **1970**, *6*, 807.
[52] J. Högermeier, H.-U. Reissig, *Adv. Synth. Catal.* **2009**, *351*, 2747.
[53] Z. Zhu, W. Tian, Q. Liao, *Tetrahedron Lett.* **1996**, *37*, 8553.
[54] R. Zimmer, M. Webel, H.-U. Reissig, *J. Prakt. Chem.* **1998**, *340*, 274.
[55] G. Höfle, W. Steglich, H. Vorbrüggen, *Angew. Chem., Int. Ed.* **1978**, *17*, 569.
[56] B. Bennua-Skalmowski, K. Krolikiewicz, H. Vorbrüggen, *Bull. Soc. Chim. Belg.* **1994**, *103*, 453.
[57] B. Bennua-Skalmowski, U. Klar, H. Vorbrüggen, *Synthesis* **2008**, 1175.
[58] B. Bennua-Skalmowski, H. Vorbrüggen, *Tetrahedron Lett.* **1995**, *36*, 2611.
[59] R. Schwesinger, *Chimia* **1985**, *39*, 269.
[60] R. Schwesinger, C. Hasenfratz, C. Schlemper, L. Walz, E.-M. Peters, K. Peters, H. G. von Schnering, *Angew. Chem., Int. Ed.* **1993**, *32*, 1361.
[61] O. Petrov, M. Schneider, R. Bohlmann, S. Vettel, PCT-int. Appl. WO 2009/053008; *Chem. Abstr.* **2009**, *150*, 472960.
[62] R. A. Decréau, C. M. Marson, *Synth. Commun.* **2004**, *34*, 4369.
[63] M. Hudlicky, *Org. React.* **1988**, *35*, 513.
[64] B. Bennua-Skalmowski, H. Vorbrüggen, unpublished.
[65] T. J. Tewson, M. J. Welch, *J. Org. Chem.* **1978**, *43*, 1090.

[66] B. Bennua-Skalmowski, H. Vorbrüggen, *Nucleosides, Nucleotides Nucleic Acids* **1996**, *15*, 739.
[67] U. Klar, G. Neef, H. Vorbrüggen, *Tetrahedron Lett.* **1996**, *37*, 7497
[68] S. Daubié, S. Mutti, *Tetrahedron Lett.* **1996**, *43*, 7743.
[69] F. Nique, C. Moratille, P. Roessel, J. Bousque, FR 25854403; *Chem. Abstr.* **2004**, *11*, 809.
[70] J. Yin, D. S. Zarkowski, D. W. Thomas, M. M. Zhao, M. A. Huffman, *Org. Lett.* **2004**, *6*, 1465.
[71] A. S. Picher, H. L. Ammon, P. DeShong, *J. Am. Chem. Soc.* **1995**, *117*, 5166.
[72] X. Zhao, W. Zhuang, D. Fang, X. Xue, J. Zhou, *Synlett* **2009**, 779.

Received January 27, 2011