Nucleophilic trifluoromethylation of some polycyclic ketones [#]

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Dedicated to Prof. Jan Epsztajn on the occasion of his 75th birthday

Abstract

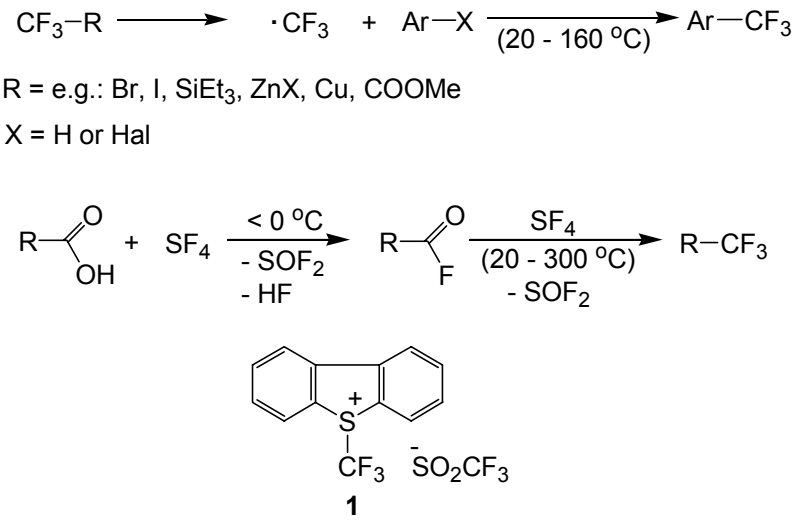
Ruppert's reagent (CF_3-$SiMe_3$) was used in the reaction with derivatives of pentacyclo-[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione ('cage' dione) in the presence of dry CsF to yield trifluoromethyl *O*-silylated products. Subsequent acidic hydrolysis gave the corresponding hydroxy derivatives. In the case of the 'cage' dione the transannular cyclization leading to oxahexacyclic (*O*-bridged) product was observed.

Keywords: Trifluoromethylation, polycyclic ketones, nucleophilic addition, transannular cyclization

Introduction

The chemistry of fluorinated compounds has been extensively explored in recent decades. It is well established that introduction of the trifluoromethyl group into a known substance results in significant changes in the chemical, physical and biological properties.[1] Direct trifluoromethylation of aromatic compounds is mostly based on the reactions of *in situ* generated ·CF_3 radical.[2] The non-direct trifluoromethylation with SF_4 used as a source of fluorine atoms has been developed by Dmowski.[3] On the other hand, there are known methods that explore an ionic CF_3-moiety, *e.g.* the sulfonium salt of type **1** is an efficient source of the trifluoromethyl cation (Scheme 1).[4] In recent times, nucleophilic trifluoromethylation has been widely explored for introduction of the CF_3-group using carbonyl substrates such as aldehydes, ketones or esters[5] and trimethyl(trifluoromethyl)silane (**3**) known as the Ruppert's reagent.[6]

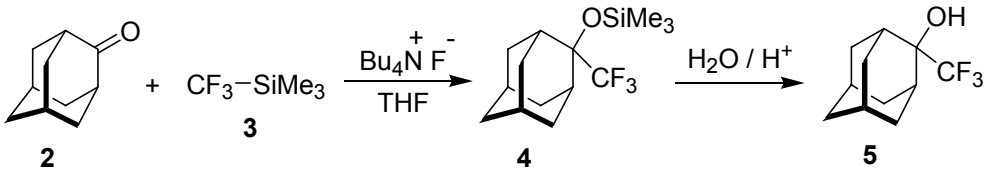
[#] For the first time presented at 14th European Symposium on Fluorine Chemistry, Poznań, Poland, July 11-16, 2004, Book of Abstracts, A-P-75, 164.



Scheme 1

In the original protocol, tetrabutylammonium fluoride (TBAF) was used as a catalyst in the reaction of **3** with carbonyl compounds yielding the corresponding trifluoromethylated alcohols via *O*-silylated derivatives.[7] At present, cesium fluoride seems to be a catalyst of choice.[5a] However recently, an efficient application of the new catalysts in nucleophilic trifluoromethylation was described.[8]

The relatively easily available polycyclic 'cage' ketones **6** and **9** can be used as building blocks for the preparation of more complex systems, including hosts in supramolecular chemistry.[9] Adamantanone (**2**), which belongs to the polycyclic 'cage' structures, reacts easily with **3** yielding trimethylsilyl derivative **4** which after acidic hydrolysis can be easily converted to 2-(trifluoromethyl)adamantan-2-ol (**5)** (Scheme 2).[10]



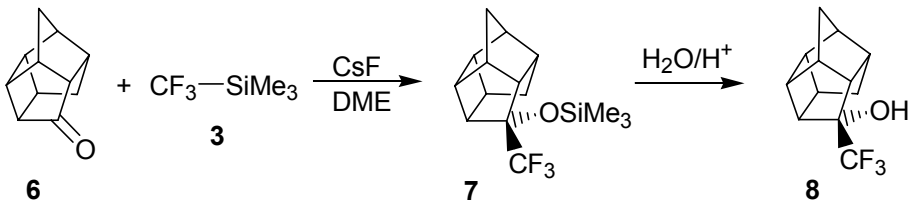
Scheme 2

In the case of the dione **9** reactions with primary amines, are reported to yield the corresponding monoimine derivatives which upon treatment with reducing agents ($NaBH_4$, $LiAlH_4$) undergo a transannular cyclization via formation of the O-bridge.[11] Reactivities of **6** and **9** have been studied in our group for some years and their ability to undergo transannular cyclization was observed in reactions with diverse O- and S-nucleophiles.[12] The aim of the

present study was to examine their reactions with Ruppert's reagent **3** and to elaborate a straightforward protocol for preparation of trifluoromethylated polycyclic alcohols.

Results and Discussion

The experiment with **3** and **6** was performed in dry 1,2-dimetoxyethane (DME) in the presence of catalytic amount of cesium fluoride (dried at 200-300 ^{o}C). The expected *O*-silylated product **7** was smoothly obtained and subsequent hydrolysis followed by crystallization from hexane led to a colorless solid identified as alcohol **8** (Scheme 3).

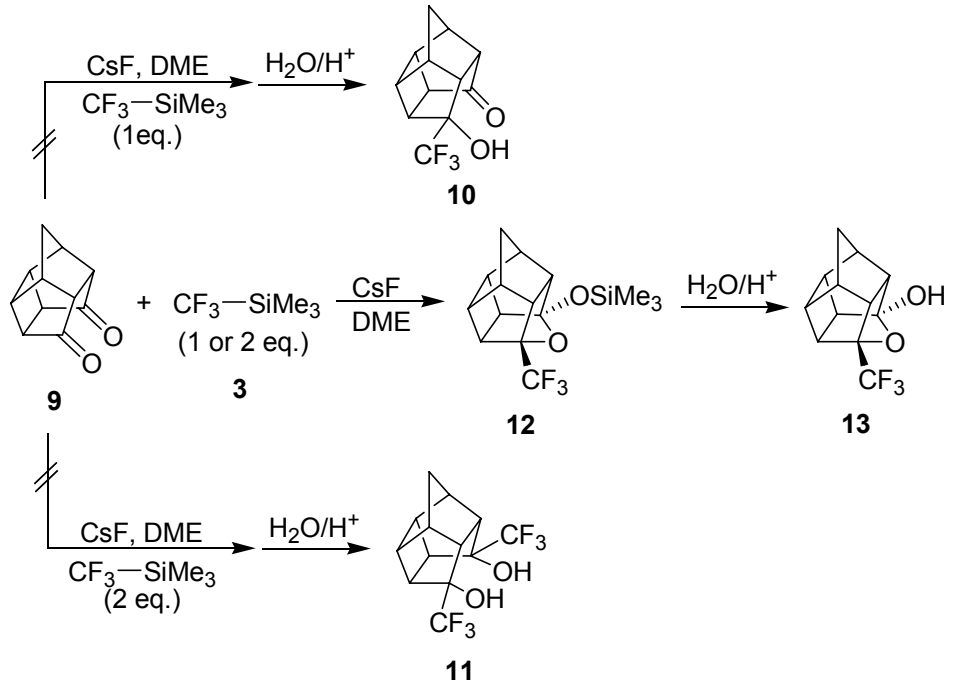


Scheme 3

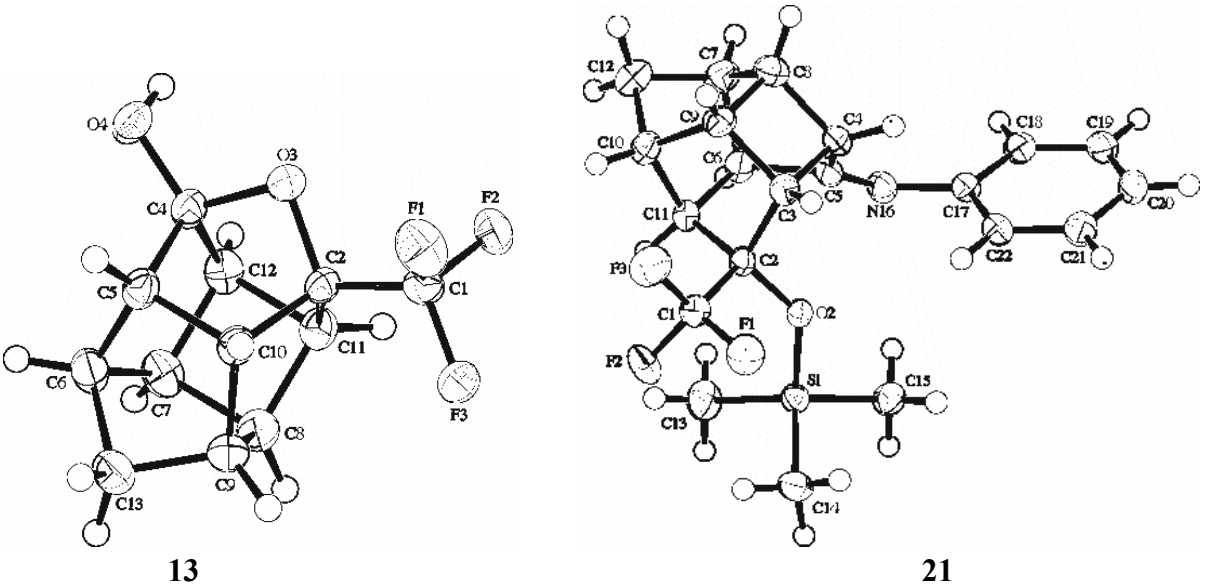
The reaction occurs stereoselectively and the trifluoromethyl anion approaches the carbonyl group from the *exo*-face exclusively. As a result, the final product **8** contained the hydroxy group placed at the *endo* position as evidenced by the X-ray study.[13]

The reaction of **3** with **9** was carried out under analogous conditions. Depending on the molar ratio of substrates dione **9** was expected to react either with one or two equivalents of CF_3-$SiMe_3$ yielding mono- or bis-trifluoromethylated alcohols **10** or **11**, respectively. The first attempted reaction of **9** with an equimolar amount of **3** was expected to yield the hydroxyketone **10** (Scheme 4).

After addition of CF_3-$SiMe_3$ an exothermic reaction started and after 1.5 h the conversion was complete. The initially formed trimethylsilyl derivative was hydrolyzed without isolation and crude product was purified by crystallization from hexane to give colorless crystals with a narrow melting point. The second experiment with two equivalents of CF_3-$SiMe_3$ should have led to **11**, but unexpectedly the isolated product was identical with the substance obtained in the first entry; this result was confirmed by the absence of mixed melting point depression and by comparison of spectroscopic data. The IR-spectrum did not show the absorption band of the C=O group suggesting that a transannular process took place. In the ^{13}C-NMR spectra the characteristic signals appeared at 89.3 (q, $^{2}J_{C\text{-}F}$ = 34 Hz) and 120.0 (s, O-C-O) ppm, respectively. The MS-CI exhibited a molecular peak at m/z 262 $[M+1+NH_3]^+$. Finally, the structure of trifluoromethylated hemiacetal **13** was unambiguously confirmed by the X-ray single crystal diffraction analysis (Fig.1).[13]



Scheme 4

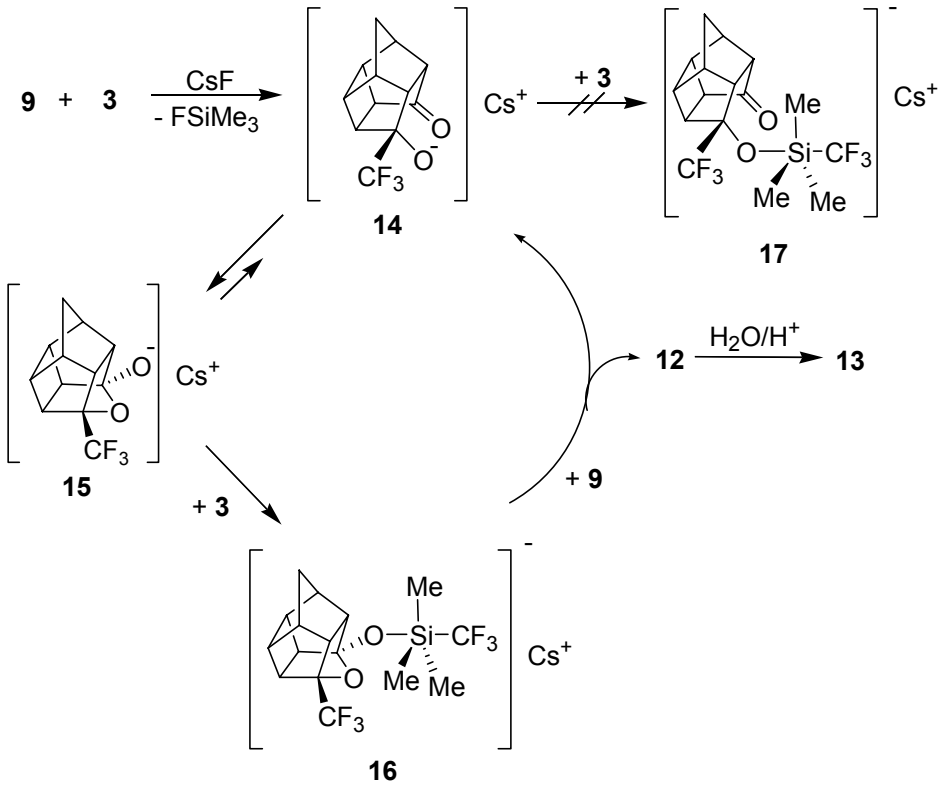


13 **21**

Figure 1. ORTEP-plots for compounds 13 and 21.[13]

Noteworthy, the transannular cyclization under trifluoromethylation conditions was previously reported for the reaction of a 1,5-dione (*i.e.* bicyclo[3.3.1]nonane-2,6-dione) but in this case the successful formation of the product of bis-trifluoromethylation was reported.[14]

According to an other report the reaction of 1,4-dione (*i.e.* hexane-2,5-dione) with one or two equivalents of **3** did not afford the product of transannular cyclization.[15] Recently, we have found that **9** easily reacts at low temperatures with amines as a nucleophilic agent and the formation of transannular cyclization products was established,[16] instead of already reported aminoalcohol derivatives.[11]

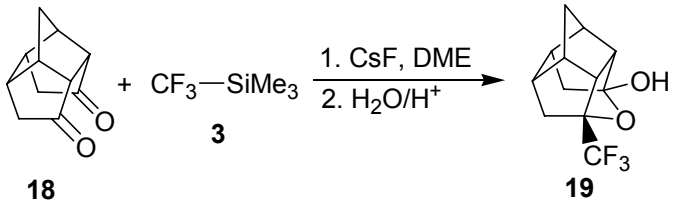


Scheme 5

The formation of **13** strongly supports the mechanistic pathway of the CF_3-group addition to the carbonyl group formulated by Prakash *et al*.[17] The first step of the reaction is the replacement of the CF_3-group by the fluorine anion and trifluoromethide anion (F_3C^-) attacks the carbonyl group to form the salt of type **14**. Apparently, the following transannular cyclization leading to **15** is faster than the addition of another molecule of **3** leading to the intermediate **17** which could give hydroxyketone **10**. In the next step, reaction with another molecule of **3** generates a transient species **16** bearing pentacoordinated silicon atom. This intermediete rapidly transfers F_3C-group to the next molecule of **9** and the formation of the *O*-silylated acetal **12** is observed (Scheme 5).

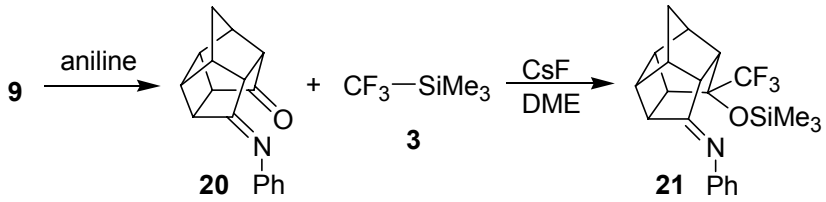
In an extension of the above presented study, the C-C *back*-bond in the dione **9** was selectively reduced with zinc dust in refluxing glacial acetic acid yielding the 'released' ketone **18** (tetracyclo[6.3.0.0^{4,11}.0^{5,9}]undecane-2,7-dione).[18] This ketone was treated with **3** in order to

examine the limitation of transannular cyclization in this less strained structure. The distance between the two carbonyl groups, as evidenced by the X-ray study, is larger in comparison with 'cage' dione **9**.[19,21b] The product isolated after reaction with **3** and subsequent hydrolysis exhibited no C=O absorption, indicating the formation of hemiacetal **19**; additional spectroscopic data are comparable with those registered for compound **12**.



Scheme 6

In another experiment the imine **20** prepared in the reaction of aniline with **9**,[20] was treated with **3** and in this case the formation of silylated ether **21** was observed. The transannular process has not been observed and even with an excess of **3** the C=N-group did not react. The X-ray analysis[13] showed that the CF_3-group is placed at *exo*-position (Fig.1).



Scheme 7

In summary, the synthesis of new derivatives of trifluoromethylated polycyclic compounds **8**, **13** and **19** using Ruppert's reagent was presented. Transannular cyclization led to hemiacetals **13** and **19**, but it was not observed in the reaction with monoimine **20**. In all cases the trifluoromethylation process proceeded stereoselectively and the trifluoromethyl group is placed at the *exo* position, exclusively.

Experimental Section

General Procedures. Melting points were determined in a capillary by using a MelTemp 2 apparatus and are uncorrected. IR spectra were obtained using a NEXUS FT-IR apparatus. MS spectra were obtained using a Varian MAT-112S spectrometer, which was operated in the CI mode. ^{1}H-, ^{13}C- and ^{19}F-NMR spectra were recorded with a Bruker 300 MHz in $CDCl_3$ using

TMS (δ = 0 ppm) or $CFCl_3$, respectively, as an internal standards. Elemental analysis and HRMS (Finnigan MAT95) data were obtained at Polish Academy of Sciences.

Starting materials

Trimethyl(trifluorometylhyl)silane (**3**), pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione (**9**), cesium fluoride and dry dimethoxyethane (DME) are commercialy avialable. Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8-one[21] (**6**) and tetracyclo[6.3.0.0^{4,11}.0^{5,9}]undecane-2,7-dione[18] (**18**) were obtained according to described procedures.

Reaction of Ketones 6, 9 and 18 with Ruppert's Reagent - General Procedure

The corresponding ketone **6**, **9** or **18** (1 mmol) was dissolved in dry DME (3 ml) and to the solution catalytic amount of CsF (approx. 5 mg, dried at 200-300 ^{o}C) was added under argon atmosphere. The mixture was protected against the moisture. Trimethyl(trifluorometylhyl)silane (**3**) (1.1 mmol) was added in small portions through the septum and the mixture was stirred for 1.5 h at ambient temp. After this time 4N HCl (1 ml) was added and stirring was continued for an additional 1 h. Then the reaction mixture was diluted with water (5 ml) and extracted with dichloromethane (3x5 ml). Combined organic layers were dried over anhydrous magnesium sulfate. The solvent was removed in *vacuo* and crude products were purified by crystallization.

8-(Trifluoromethyl)pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8-ol (8). mp 126–127 ºC (hexane), yield 60 % (0.14 g, 0.6 mmol). ^{1}H NMR ($CDCl_3$) δ: 1.06-1.13(m, 1H), 1.24(AB, J_{AB}=11 Hz, 1H), 1.70(AB, J_{AB}=11Hz, 1H), 1.97(br. s, 1H, OH), 2.30-2.39(m, 2H), 2.40-2.68(m, 6H), 2.83-2.86(s, 1H). ^{13}C NMR ($CDCl_3$) δ: 29.2(t), 34.7(t), 36.0(d), 38.3(d), 41.7(d), 42.1(d), 43.2(d), 43.5(d), 45.7(d), 46.3(d), 82.3(q, $^{2}J_{C-F}$=27 Hz), 126.4(q, $^{1}J_{C-F}$=285 Hz). ^{19}F NMR ($CDCl_3$) δ: -76.4(s). IR (KBr) cm^{-1}: 3346vs, 2978s, 2867s, 1454w, 1393m, 1308s, 1288s, 1264s, 1158vs, 1143vs, 1127s, 1080s, 1026s, 967m, 700s. Anal. Calcd for $C_{12}H_{13}F_3O$: C 62.60; H 5.69. Found: C 62.61; H 5.57. MS (m/z): 248 $(M+1+NH_3)^+$

5-(Trifluoromethyl)-4-oxahexacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]dodecane-3-ol (13). mp 116–117 º C (methanol), yield 65 % (0.16 g, 0.65 mmol). ^{1}H NMR ($CDCl_3$) δ: 1.59(AB, J_{AB}=11Hz, 1H), 1.95(AB, J_{AB}=11Hz, 1H), 2.61-2.81(m, 6H), 2.83-3.11(m, 2H). ^{13}C NMR ($CDCl_3$) δ: 41.9(d), 42.0(d), 43.4(d), 43.5(t), 45.3(d), 45.5(d), 47.1(d), 55.3(d), 57.0(d), 89.3(q, $^{2}J_{C-F}$ = 34 Hz), 120.0(s),124.7(q, $^{1}J_{C-F}$=275 Hz). ^{19}F NMR ($CDCl_3$) δ: -80.0(s). IR (KBr) cm^{-1}: 3348vs, 2993vs, 2976vs, 2881m, 1722m, 1396s, 1351s, 1307m, 1191vs, 1176vs, 1138s, 1035s, 861m, 715m. Anal. Calcd for $C_{12}H_{11}F_3O_2$: C 59.02; H 4.54. Found: C 59.29; H 4.21. MS (m/z): 262 $(M+1+NH_3)^+$.

7-(Trifluoromethyl)-12-oxapentacyclo[6.3.1.0^{2,6}.0^{3,10}.0^{5,9}]dodecane-1-ol (19). mp 90-92 º C (hexane), yield 57 % (0.14 g, 0.57 mmol). ^{1}H NMR ($CDCl_3$) δ: 1.65-1.79(m, 2H), 1.92-2.12(m, 4H), 2.23-2.61(m, 5H), 2.78-3.15(m, 2H). ^{13}C NMR ($CDCl_3$) δ: 35.5(t), 37.7(t), 41.7(d), 42.6(d), 43.3(t), 47.8(d), 49.3(d), 55.2(d), 58.9(d), 89.5(q, $^{2}J_{C-F}$ = 31 Hz), 117.3(s),125.8(q, $^{1}J_{C-F}$=278 Hz). IR (KBr) cm^{-1}: 3399brs, 2971s, 2947m, 1377m, 1388s, 1299s, 1219s, 1170vs, 1145vs, 1119s,

1102s, 1062s, 1042s, 1012m, 947m. HRMS: Calcd. for $C_{12}H_{13}F_3O_2$: 246.0868; Found: 246.0863. MS-EI (m/z): 246 (M^+, 32), 224(100), 186(72), 91(50).

Phenyl(11-trifluoromethyl-11-trimethylsilanyloxypentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undec-8-ylidene)amine (21). Dione **9** (250 mg, 1.15 mmol) was dissolved in THF (10 ml) and cooled down in ice-bath. To this solution aniline (0.5 ml, excess) was added dropwise and after approx. 30 min. white precipitate was filtered off. This half-product was suspended in benzene and dehydrated in boiling toluene using Dean-Stark aparatus. After 1h toluene was removed in vacuo and obtained imine **20** (200 mg, 0.80 mmol, 70%) was dissolved in dry DME (3 ml). To this solution catalytic amount of CsF (approx. 5 mg) was added under argon atmosphere and the mixture was protected against the moisture. The Ruppert's reagent **3** (1.0 mmol) was added in small portions through the septum and the mixture was stirred for 1.5 h at ambient temp. After this time water (1 ml) was added and stirring was continued for additional 1 h. Than the reaction mixture was diluted with water (5 ml) and extracted with dichloromethane (3x5 ml). Combined organic layers were dried over anhydrous magnesium sulfate. The solvent was removed in *vacuo* and crude product was purified by chromatography on preparative plates (SiO_2, CH_2Cl_2/hexane, 1:4). Obtained product **21** was recrystalized from MeOH to give colorless crystalls (150 mg, 0.38 mmol, 48%), mp 140-142 ^oC.

^1H NMR ($CDCl_3$) δ: 0.14(s, 9H), 1.50(AB, J_{AB}=11Hz, 1H), 1.89(AB, J_{AB}=11Hz, 1H), 2.46-2.96(m, 8H), 6.92-7.11(m, 3H), 7.26-7.34(m, 2H). ^{13}C NMR ($CDCl_3$) δ: 33.3(d), 37.4(t), 38.9(d), 41.4(d), 42.2(t), 50.7(d), 51.1(d), 82.7(q, $^2J_{C-F}$ = 27 Hz), 122.4(d), 124.0(d), 126.9(q, $^1J_{C-F}$=286 Hz), 128,3(d), 149.7(s), 178.8(s). ^{19}F NMR ($CDCl_3$) δ: -75.2(s). IR (KBr) cm^{-1}: 2997s, 2898m, 2870m, 1672m 1604m, 1596m, 1488m, 1406m, 1339s, 1307m, 1254vs, 1159vs, 1140vs, 1042s, 886s, 864s, 846s, 756m 701m. Anal. Calcd for $C_{21}H_{24}F_3NOSi$: C 64.43; H 6.18. Found: C 64.18; H 6.07. MS (m/z): 392 $(M+1)^+$.

Acknowledgements

Authors thank the Rector of University of Lodz for financial support (Grant nr 505/712).

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