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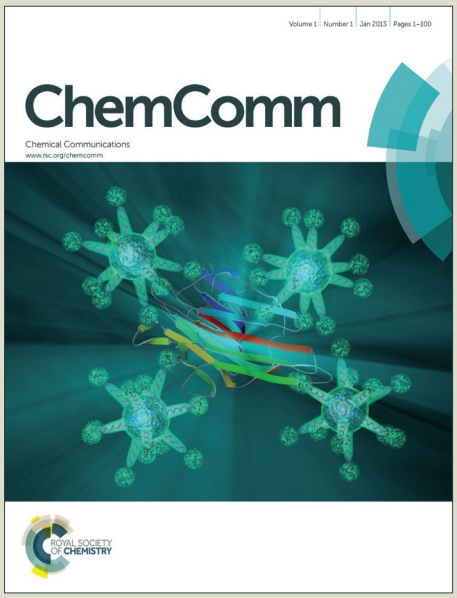

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Aluminum Oxide Mediated C-F Bond Activation in Trifluoromethylated Arenes

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Thermally activated γ-aluminium oxide was found to be very effective for C-F bond activation in trifluoromethylated arenes. Depending on the activation degree the respective arenes can be converted either to cyclic ketones or to the respective carboxylic acids with good to excellent yields.

The C-F bond is the strongest single bond to carbon and one of the most robust functionality uncounted in organic chemistry.[1] The C-F bond cleavage frequently requires harsh reaction condition leading to low selectivity and low functional group tolerance of the process. Despite significant progress in this field, a simple and effective transformation of the C-F functionality still remains a challenging task.[2-6] In this respect, the selective transformation of C-F bond leading to an effective C–C bond formation remains one of the major challenge in modern organic chemistry.[2-6] In particular, the trifluoromethyl group attached to an aromatic ring is surprisingly stable. Despite the presence of three fluorine atoms at a benzylic position examples of the conversion of respective C-F bonds to C-C bond are rare. These include: use of low-valent Nb complexes,[7-9] reaction with organoaluminium reagents,[10,11] Brønsted acid mediated activation,[12-14] electroreductive coupling,[15] lanthanoid induced activation,[16] $AlCl_3$ mediated arylation,[17] and the usage of Mg-Cu bimetal systems.[18] Recently we have found out that thermally activated γ-aluminum oxide is very effective for the activation of C_{ARYL}-F bonds under mild conditions, leading to the effective intramolecular C-C bond formation via cyclodehydrofluorination.[19-21] The process discovered characterized by an unprecedentedly high selectivity and high yields even in the case of strained polycyclic aromatic hydrocarbons (PAHs). The reaction did not require solvents, expensive reagents and/or catalysts and can be easily scaled up, which makes this approach attractive for the preparative synthesis. Moreover the solid-state synthetic strategy appears to be suitable for synthesis of highly interesting large PAH systems which are difficult to obtain by classical wet chemical techniques because of low solubility. Therefore the development of new synthetic approaches suitable for synthesis of large PAH systems which can address the solubility issues is highly desirable. Inspired by the exceptionally high selectivity and high affinity of alumina to the C-F functionality, we investigated the activation of the C_{ARYL}-CF_3 group on γ-Al_2O_3. Herein we show that the C-F bond in trifluoromethyl substituted arenes can be effectively activated using Al_2O_3 and demonstrate a general applicability of the approach for synthesis of large PAHs.

The 2-trifluoromethyl-biphenyl (**1**) was chosen as a model compound for the investigation of the intramolecular condensation via C-F bond activation. The alumina was activated by heating in vacuum according to the previously described procedure.[21] The thermal dehydration of γ-Al_2O_3 leads to the formation of reactive sites which can be described as frustrated Lewis acid-base pairs responsible for the activity.[22] It was found that the activated alumina is very reactive in respect to the C_{ARYL}-CF_3 group. Thus depositing of **1** on activated γ-Al_2O_3 at room temperature immediately resulted in color change to an intense pink (see SI). Analysis shows that already after reacting for 30 min at room temperature around 20% of **1** is converted to the 9-fluorenone **2** (5-7%) and 2-biphenyl carboxylic acid **3** (10-15%). The increase of the reaction time did not improve the conversion, indicating that the reaction at room temperature virtually stopped after several minutes. Thus after one week of exposure at room temperature, essentially the same yields of **2** (9%) and **3** (18%) were obtained. This pointed out that active sites on which coordination takes place possess different activity and only around 20% are able to activate the C-F bond at room temperature. At the same time, adsorption on less active sites completely exclude the molecular mobility on the alumina surface. The low molecular mobility can be explained by a chelate effect (triple Al···F interaction), which can be realized in an alumina nanopore. The presumable mechanism of the C-F bond activation is presented in figure 1. The

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mechanism previously proposed for Al_2O_3 mediated HF elimination in fluoroarenes via an aromatic transition state,[20] can be excluded, since in this case no carboxylic acid formation is expected. The intense coloring of the alumina phase indicates that the reaction passes through the formation of a carbenium ion, generated as a result of heterolytic C-F bond dissociation typical for Lewis acid mediated C-F bond activation.[6] The respective carbenium ion **4** is strongly stabilized by the pore environment, resulting in an exceptionally long lifetime as indicated by no color change over several weeks. Such high degree of stabilization is probably a collaborative effect of α-stabilizing effect of fluorine substituent,[22] and effective electrostatic stabilization inside the nanopore. The electrophilic center of the cation can be attacked either by the π system of the neighboring phenyl group or by the closely placed hydroxyl groups leading finally to the fluorenone **2** or to the acid **3** (Fig. 1). In the first case the intramolecular ring closure results in the formation of σ-complex **5**. Further deprotonation of **5** leads to difluoro-fluorene which quickly undergoes further C-F bond hydrolysis yielding **2**. The efficiency of the hydrolysis process is strongly depended on the concentration of the OH groups on the alumina surface, which is in good agreement with the proposed mechanism. The density of OH groups strongly depends on the activation degree which is known to be key for generating reactive Lewis acid-base pairs on alumina.[23] Thus, it was found out that after activation of alumina at 400°C (containing around 3-5 OH groups nm^{-2},[24]) the hydrolysis dominates over the intramolecular cyclization. An efficient conversion to the fluorenone can be achieved only on properly activated alumina (600°C). On the other hand the hydrolysis cannot be supressed completely because the exhaustive dehydration of γ-Al_2O_3 is not possible since at higher temperatures the alumina loses activity due to transition to δ-Al_2O_3 and θ-Al_2O_3 forms.[24] Thus, after activation at 600°C the density of OH groups on the alumina surface is still rather high (1-0.5OH nm^{-2}).[24] Since the reactive cationic intermediates are enclosed in a "single molecule nanoreactor" the temperature increase practically does not affect the selectivity of the reaction. The reaction at 100°C for 30 min leads to the formation of compounds **2** (38%) and **3** (29%). Condensations at 150°C for 30 min shows full conversion of **1** with up to 80% yield of fluorenone **2**. (Further increase of the reaction temperature to 200 and 250°C shows similar results.

Interestingly that **3** which is formed during hydrolysis of **1**, cannot be converted further to **2** either by elongation of the reaction time or by increasing of the reaction temperature. On the other hand directly deposited on activated aluminium oxide acid **3** undergoes effective intramolecular cyclization to **2** already at 150°C. Such behaviour more probably resulted from the limited number of active centres inside the pore. According to HPLC and NMR analyses no evidences of intermolecular condensations and formation of any side products were detected during the reaction of **1** on alumina even at high temperatures. The optimal condition at which effective conversion of **1** to **2** can be achieved in a short time were found to be 30 min at 150°C (all following activation experiments were carried out at this conditions if not stated otherwise). Importantly, product **2** can be obtained in a highly pure form by simple extraction with MeOH (figure 2). The acid **3** (in a form of Al salt) remains adsorbed on the alumina and can be extracted only after treatment with acetic acid.

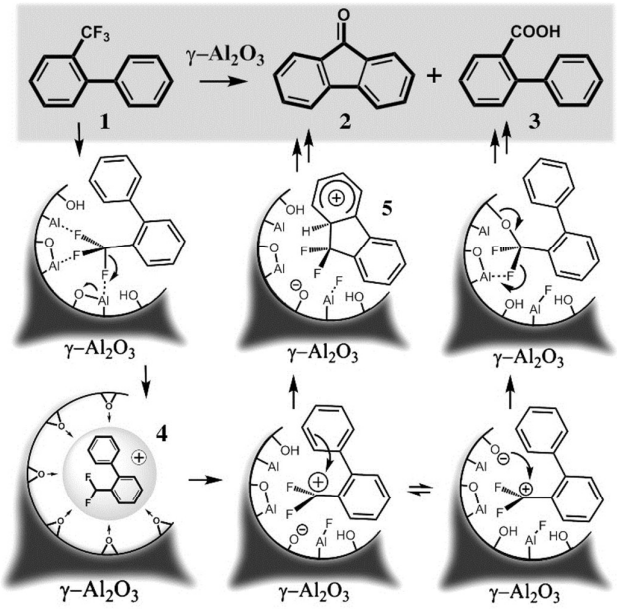

Fig. 1 Presumable mechanism of C-F activation in trifluoromethylated arenes in alumina nanopores.

The cationic mechanism and formation of cations in nanopores was confirmed by the capturing experiment with benzene where the formation of expected compounds **6** and **7** was observed (Fig. 2). Interestingly fluorenone **2** was found to be the major product despite the big excess of benzene (refluxing in benzene). These experiments show that the penetration of benzene molecule into the confined and highly polar environment of the nanopore is difficult and the local concentration of the benzene inside the pore is very low. Indeed, similar experiments with more bulky mesitylene show virtually no formation of arylation products. Thus the nanopores can be considered as nanoreactors which are "loaded" with a single substrate molecule preventing possible intermolecular reactions. The single molecule "chemistry" in the confined space of the nanopore is in good agreement with exceptionally high selectivity of the process which is atypical for reactions involving cationic intermediates. Further it was found that the reaction can be also conducted under ambient atmosphere (deposition under Ar atmosphere) demonstrating very effective encapsulation of molecules into nanopores. In this case fluorenone **2** was obtained with slightly lower yields (60-70%) which is probably connected with air moisture, leading to hydrolysis. As it was shown previously 2-trifluoromethyl-biphenyl **1** can be in general converted to fluorenone **2** under superacid conditions.[13] Thus, treatment of **1** for 48h with 10 equivalents of trifluoromethansulfonic acid in anhydrous dichlormethane yielded 50% of fluorenone.[13] Unfortunately the scope of this reaction is limited to the

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synthesis of simple cyclic ketones. Thus, attempts to convert structurally related methylated homolog **8** to the methyl-fluorenone **9** resulted in a messy unidentified products mixture.[13] In contrast, our experiments on the activated alumina showed clean conversion of **8** to **9** with 72% yield.

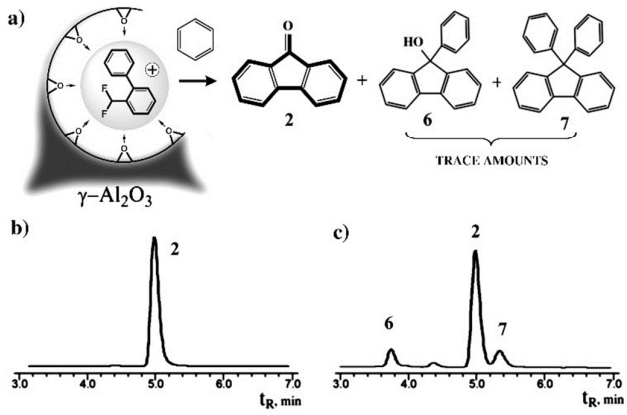

Fig. 2 a) Capturing of the pore trapped carbenium ions by benzene molecule; b) Condensation of **1** on activated alumina. HPLC profile of the MeOH extract as obtained after reaction showing high selectivity of the process; c) HPLC profile of the reaction mixture as obtained after reaction (condensation of **1** in presence of benzene) showing low reactivity of the pore trapped carbenium ions in respect to benzene. (HPLC conditions: 5PYE column, eluent MeOH:cyclohexane 4:1, 30°C, flow rate 1 mL/min, detection 300 nm).

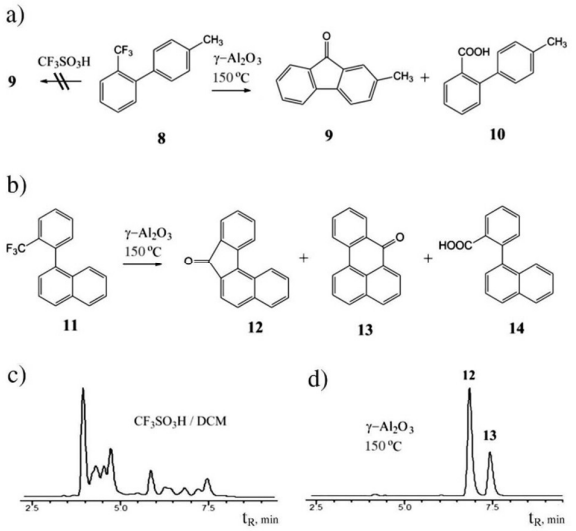

Fig. 3 a) Condensation of **8**; b) condensation of **11**; c) HPLC profile of the reaction mixture as obtained after reaction of **11** with triflic acid in DCM; d) HPLC profile of the reaction mixture as obtained after reaction of **11** on alumina at 200°C for 30 min (MeOH extract). HPLC conditions: 5PYE column, eluent MeOH, 30°C, flow rate 1 mL/min, detection 300 nm.

According to the HPLC-UV analysis no side products were detected in the reaction mixture (remaining 25% are converted to the respective acid). In order to demonstrate the efficiency of the approach we chose more reactive 1-[2-(trifluoromethyl)phenyl]- naphthalene (**11**) as a model compound. In the test experiment, compound **11** was treated with 10 equivalents of triflic acid in anhydrous dichloromethane according to the reported procedure.[13] The reaction resulted in a complex mixture, in which none of the desired ketones was detected by HPLC-UV analysis (Fig. 3). At the same time the condensation of **11** on activated alumina showed clean conversion to **12** (18%) and **13** (40%), and to the respective acid **14** (40%) (Fig. 3).

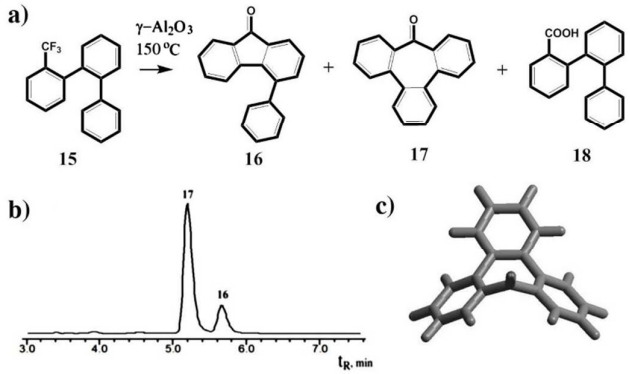

Fig. 4 a) Condensation of **15**; b) HPLC profile of the reaction mixture as obtained after reaction on alumina at 200°C for 30 min (MeOH extract). HPLC conditions: 5PYE column, eluent MeOH, 30°C, flow rate 1 mL/min, detection 300 nm; c) Projection view of DFT (B3LYP) optimized structure of **17** showing high degree of deviation from planarity.

Interestingly, a higher degree of hydrolysis in comparison to condensation of **1** was observed, despite the higher nucleophilicity of the naphthyl moiety. Further it was found that the molar ration of **12**/**13** is virtually not influenced by the reaction temperature. Thus essentially the same **12**/**13** values were obtained at different reaction temperatures (250, 200, 150, 100 and 50°C). Such behaviour can be explained by the low flexibility of the naphthalene moiety inside the pore. The molecule inside the pore cannot change its configuration as easily as it is required for the energetically more favourable electrophilic attack. To prove this assumption, a condensation of compound **15** was examined. The formal intramolecular Friedel-Crafts acylation of **15** may lead to two ketones **16** and **17**, from which the formation of ketone **17** bearing a seven membered ring is highly unlikely.[25] It was found that the condensation of **15** on activated alumina indeed shows an effective formation of tribenzoheptanone **17** (52% yield) which dominates over the formation of **16** (8%)(Fig. 4). These results demonstrate that the confined space of the alumina pore does not only effectively prevent side reactions, but also dictates the regiochemistry of the process. As it was mentioned above, the reaction on alumina can be directed to the hydrolysis of the trifluoromethyl group, if "badly" activated alumina is used. Further we have found that the hydrolysis of the CF_3 group can be realized very effectively even on non-activated alumina at 150°C. The activity of non-activated alumina towards CF_3 groups at 150°C is highly unexpected, since according to previous studies no active Lewis acid-base pairs can be formed below 400°C.[23] At 200°C complete hydrolysis can be achieved in several minutes. At this conditions, compounds **1**, **8**, **11** and **15** were converted to the respective acids (**3**, **10**, **14** and **18**) with close to quantitative yield without any sign of side product formation. The selective transformation of robust CF_3 groups to the carboxyl groups appears to be very useful from

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the synthetic point of view. Although trifluoromethylbenzene can be in general hydrolyzed to benzoic acid by the action of concentrated sulfuric acid at 100°C or by using of superacids,[26] these conditions cannot be applied for extended PAHs, because of the polymerization and numerous side reactions.

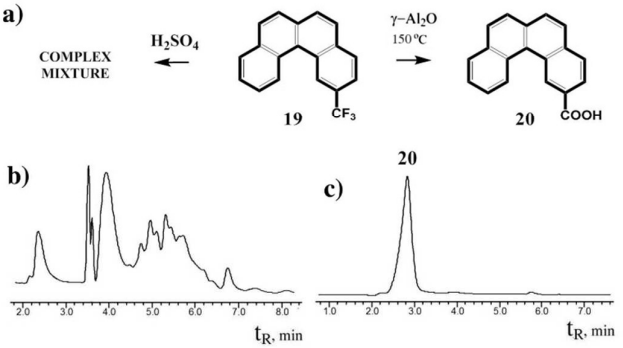

Fig. 5 a) Hydrolysis of **19**; b) HPLC profile of the reaction products after reaction of **19** with sulphuric acid at 100°C; c) HPLC profile of the reaction mixture as obtained after reaction of **11** on alumina at 150°C for 120 min (MeOH/AcOH extract). HPLC conditions: 5PYE column, eluent MeOH:toluene 4:1, 30°C, flow rate 1 mL/min, detection 300 nm.

To demonstrate the efficiency of our approach the relative large trifluoromethylated benzophenanthrene **19** was used as a model compound.[27] Hydrolysis experiments with sulfuric acid and triflic acid gave complex mixtures in both cases. In contrast the hydrolysis of **19** on non-activated alumina at 150°C for 120 min resulted in clean CF_3 to COOH conversion with 96% yield (Fig. 5).

Summing up we have demonstrated that the C-F bond in CF_3 group can be effectively activated at mild conditions. The presented approach is practical, because it can be scaled up and does not require expensive reagents. Because of the high tolerance of the CF_3 group to many organic reactions this functionality can be easily introduced into the PAH system. Direct intramolecular cyclization in *ortho* trifluoromethylarenes on activated alumina allows facile synthesis of cyclic ketones. As a result of unprecedentedly high selectivity respective products can be obtained in highly pure form by simple extraction. The high selectivity of the reaction is a consequence of an effective encapsulation of the reagent in to the alumina nanopore environment. Further, taking into account the possibility to perform effective hydrolysis of the CF_3 group, the presented approach opens a way for simple access to various carboxylated large PAHs molecules. In general our finding demonstrates that the CF_3 functionality can be reconsidered as synthetically useful functionality and an effective synthon for carboxyl groups. Further applications of alumina assisted C-F bond activation are under investigation in our laboratory.

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