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A catalytic C–C bond-forming reaction between aliphatic fluorohydrocarbons and arylsilanes

Nicole Lühmann, Robin Panisch and Thomas Müller*

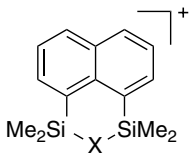
C–C coupling reactions between arylsilanes and alkylfluorides are efficiently catalyzed by disilyl cation 1. Primary as well as secondary alkylfluorides were quantitatively coupled with arylsilanes; however, in the case of tertiary fluorides, the hydrodefluorination reaction predominated. Primary alkylfluorides were found to give arenes with mostly rearranged alkyl substituents. In all cases subsequent Friedel–Crafts-type chemistry occurred.

Supporting information may be found in the online version of this article.

Keywords: C–F activation; organocatalysis; silyl cations; cross-coupling; silicon

Introduction

The catalytic activation of the very strong C–F bond is still a challenging topic in current catalysis research. Most work in this field is directed towards the stoichiometric defunctionalization of organic fluorides at transition metal sites.[1–5] Several examples of catalytic cleavage of C–F bonds[6] using transition metal complexes as catalysts have been known since the pioneering work of Milstein.[7,8] Suitable substrates are in most cases aromatic organo fluorides. A general trend in catalysis is the replacement of expensive and often toxic transition metals with main group elements.[9] During the last few years, results reported by the groups of Ozerov[10], Rosenthal[11] and our group[12] have highlighted the fascinating potential of strong Lewis acids such as sub-coordinated organosilicon and organoaluminum compounds in C–F bond activation processes.[13]

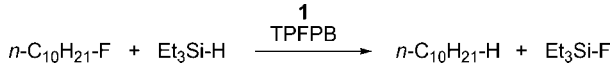


1: X = H; **2**: X = F

Figure 1. Disilylhydronium ion **1** and disilylfluoronium ion **2**.

Recently, we reported on the catalytic C–F activation of primary and benzylic fluorohydrocarbons using tetrakispentafluorophenyl borates (TPFPBs) of the bissilylated hydronium ion **1** or of the fluoronium ion **2** as catalysts and Et_3SiH as hydride source (see Figure 1).[11] In the absence of an additional solvent, the reactions yielded the corresponding alkanes as products (Scheme 1). That is, the conversion of 1-fluorodecane into *n*-decane proceeded quantitatively using **1**·TPFPB as catalyst and excess Et_3SiH as solvent. The turnover number (TON) of the strongly exothermic process was determined to be 45. Notably, no other hydrocarbons, in particular no rearranged products, were detected in this reaction.[12]

In this contribution we will report on further studies of this catalytic process using the TPFPB salt of disilyl cation **1** as catalyst. Particular attention will be paid to the development of this process from a pure hydrodefluorination reaction, which is in essence a defunctionalization process, to a synthetically preferable C–C coupling process.



Scheme 1. Catalytic hydrodefluorination reaction in excess Et_3SiH as solvent.[12]

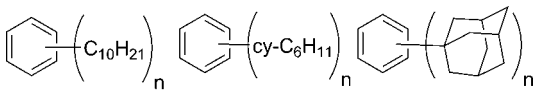
Results and Discussion

In course of our investigations of the catalyzed hydrodefluorination process (Scheme 1) we used aromatic hydrocarbons such as benzene as solvents in an attempt to control the reaction conditions of the strongly exothermic reaction more precisely. The dilution of the reaction mixture is expected to allow the effective control of experimental parameters like the reaction temperature. In a typical experiment, 0.1 mmol of the cation salt **1**·TPFPB in benzene was prepared and a solution of the fluorohydrocarbon (2.5 mmol) and triethylsilane (3 mmol) in

* *Correspondence to: Thomas Müller, Institut für Reine und Angewandte Chemie, Carl von Ossietzky Universität Oldenburg, Carl-von-Ossietzky-Str. 9-11, 26211 Oldenburg, Germany. E-mail: thomas.mueller@uni-oldenburg.de*

Institut für Reine und Angewandte Chemie, Carl von Ossietzky Universität Oldenburg, Carl-von-Ossietzky-Str. 9-11, 26211 Oldenburg, Germany

Table 1. Catalytic hydrodefluorination in the presence of benzene (catalyst **1**, 4 mol%)

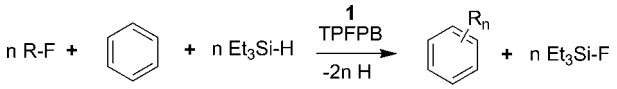


3 **4** **5**

Entry	Substrate RF	Alkylation products	Conversion RF[a]	$n = 1$	$n = 2$	$n = 3$	$n = 4$	Other products
1	n-$C_{10}H_{21}$–F	**3**	quant	91	9	–	–	–
2	cy-C_6H_{11}–F	**4**	quant	67	24	9	–	–
3[b]	cy-C_6H_{11}–F	**4**	quant	29	31	40	–	–
4	1-ad–F[c]	**5**	quant	10	–	–	–	90[d]

[a] Conversion of fluorohydrocarbon; [b] 1 equiv. benzene; [c] 1-ad: 1-adamantyl; [d] adamantane.

excess benzene (2 ml) was added at room temperature. After completion of the reaction, the product mixture was separated from the cation salt and analyzed by NMR spectroscopy and GC-MS without further purification. In all cases, the substrates, i.e. primary, secondary or tertiary fluorohydrocarbons (RF) were completely consumed. When primary and secondary alkyl fluorides were used as substrates the products of the expected hydrodefluorination reaction, simple alkanes (RH) were however not formed. Instead, alkylated arenes were found to be the main products (Table 1, Scheme 2 and, for further details, see the Supporting Information). Also in the case of the tertiary substrate 1-fluoroadamantane, 1-phenyladamantane was identified in the product mixture in detectable amounts (10%). In this case, however, adamantane, the product of the expected hydrodefluorination reaction, was found to be the major component (90%).



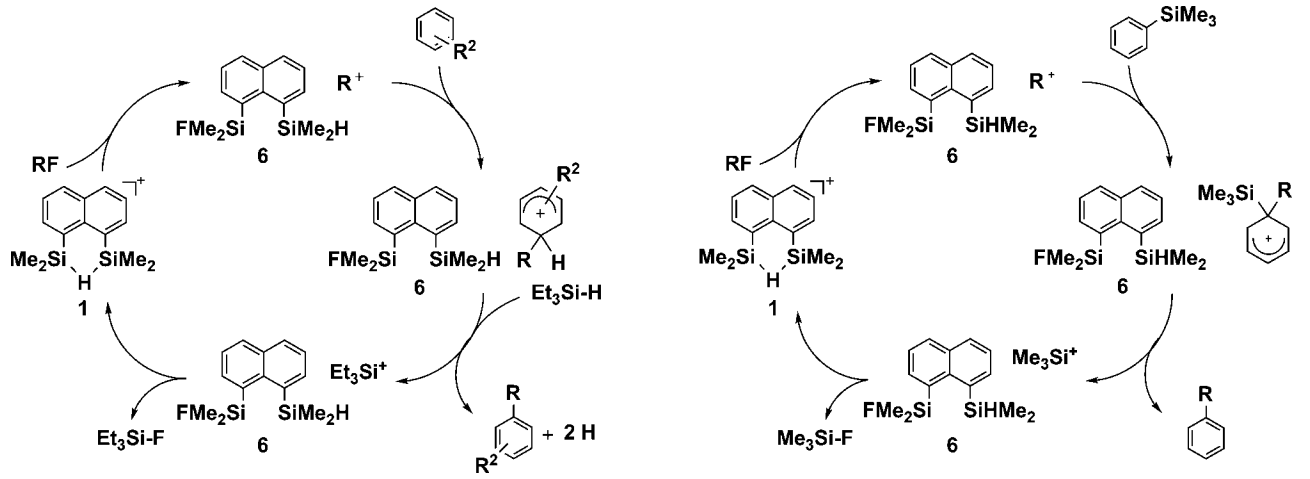
Scheme 2. C–F activation in alkyl fluorides by **1**·TPFPB with benzene.

This finding indicates the presence of highly electrophilic alkyl cations or their synthetic equivalents as intermediates in the catalytic cycle. They are formed from alkyl fluorides by reaction with the disilyl cation catalyst and they further react with the solvent benzene in an electrophilic aromatic substitution yielding alkylated arenes as products. Being towards electrophilic aromatic substitution activated species, the mono-alkylated arenes are further alkylated under the reaction conditions to give mixtures of arenes having different alkylation grades. The degree of alkylation of the arene solvent can be controlled to some degree by the concentration of the substrate. That is, high concentrations of the alkyl fluoride substrate leads to higher percentage of di- and trialkyl substituted benzenes (compare Table 1, entries 2 and 3).

In line with the assumption of an alkyl cation as an intermediate in the catalytic cycle, the attempted defluorination of 1-fluorodecane in the presence of benzene not only gave 1-phenyldecane as product. Instead 1,2-hydride shifts took place and 2-phenyldecane and 3-phenyldecane were identified as products by GC-MS. This result is in accordance with classical Friedel–Crafts alkylation reactions where the attempted alkylation with primary substrates leads to the rearrangement of the alkyl chain.[14–16] It is, however, in contrast to previous reports on silyl cation-catalyzed dehydrofluorination reactions of primary alkylfluorides[10a,b] and in contrast to our results using trialkylsilanes as solvents.[12] In those cases no rearranged products were detected,[10a,b] indicating the absence of a free carbocation as intermediate in the catalytic cycle. Secondary substrates such as 1-fluorocyclohexane are not subject to rearrangement reactions even in the presence of benzene, as suggested by the exclusive formation of cyclohexyl-substituted benzene derivatives (Table 1, entries 2 and 3). The poorer alkylating ability of the tertiary substrate 1-fluoroadamantane became evident by the formation of adamantane as the main product in the defluorination reaction of 1-fluoroadamantane. In this case the reduction of the intermediate tertiary 1-adamantyl cation by Et_3SiH is favored over Friedel–Crafts alkylation of the benzene solvent by the bulky carbocation.

The complete consumption of the alkyl fluorides clearly indicates the catalytic character of the observed alkylation reactions in each case. On the basis of our previous mechanistic suggestion,[12] we propose a modified catalytic cycle (Scheme 3a), according to which the alkyl fluoride is ionized by the catalyst **1**. The formed carbocation (R^+) reacts with the solvent benzene, forming an arenium ion which delivers by reaction with Et_3SiH the alkylated arene and a silyl cation (R_3Si^+). Fluoride transfer from the fluorodisilane **6** to the silyl cation affords the product Et_3SiF and recovers the catalyst **1**. The products of this catalytic reaction, alkylated arenes and Et_3SiF were unequivocally identified (see Supporting Information).

Although these alkylation reactions are not selective, they combine the challenging activation of a strong C–F bond with a highly desirable formation of a new C–C bond.[5c,10a,11,17–20] Clearly, in order to be of preparative value, it is important to enhance the selectivity of the C–C bond-forming reaction step. Therefore, trimethylsilylbenzene ($PhSiMe_3$) **7**, was chosen as a possibly suitable aromatic substrate and as the source for the silyl cation, which is needed for the propagation of the catalytic cycle (Scheme 3b). In addition, the *ipso*-directing[21] effect of the $SiMe_3$ group is expected to allow a regioselective alkylation of the arene. In a typical catalysis experiment, equimolar amounts (2 mmol) of the fluorohydrocarbon and $PhSiMe_3$ were added to a portion (0.1 mmol) of the hydronium ion salt **1**·TPFPB. The subsequent characterization of the crude product mixture by GC-MS clearly showed the formation of alkylated benzene derivatives ($R_nC_6H_{6-n}$, Table 2); alkylated Table 1 Footnote c:1-ad:1-adamantyl derivatives of $PhSiMe_3$ were not detected. The degree of alkylation varied from $n = 1$ to $n = 4$. (Complementary to the reaction in benzene trialkylsilyl fluoride and dialkylsilyl



Scheme 3. Proposed catalytic cycles of the C–F activation process (a) in the presence of arenes as solvent, and (b) in the presence of $PhSiMe_3$.

Table 2. Catalytic cross-coupling between fluorohydrocarbons and $PhSiMe_3$ **7** (catalyst **1**, 4 mol%, entries 1–3) and between *p*-trimethylsilyltoluene **9** and fluorocyclohexane (entry 4)

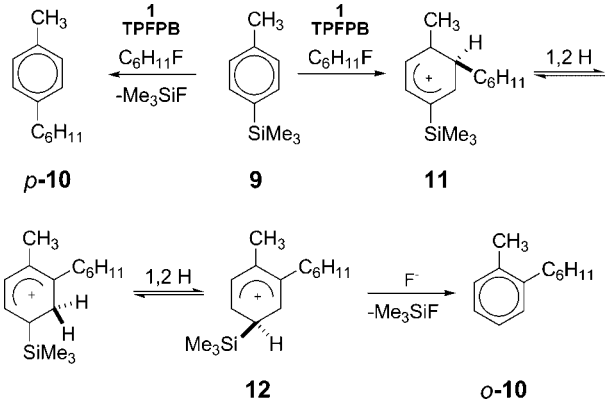
Entry	Substrate RF	Alkylation products	Conversion RF[a]	$n = 1$	$n = 2$	$n = 3$	$n = 4$	Other products
1	n-$C_{10}H_{21}$–F	**3**	quant	56	40	–[b]	–	4
2	cy-C_6H_{11}–F	**4**	quant	32	36	28	3	1
3	1-ad–F[c]	**5**	quant	21	15	–	–	64[d]
4	cy-C_6H_{11}–F	**10**	quant	36	36	28	–	0

[a] Conversion of fluorohydrocarbon substrate; [b] detected, but less than 1%; [c] 1-ad: 1-adamantyl; [d] 56% Ph_2SiMe_2, 5% (Ad-C_6H_4)$SiMe_3$, 3% adamantane.

fluoride could be detected.) This finding indicates that the first reaction step was the desired *ipso*-substitution of the $SiMe_3$ group by the intermediate R^+ (Scheme 3b). The activating effect of the alkyl group facilitated further Friedel–Crafts-like alkylation reactions, leading to the observed multiple substitution products. Notably, the reaction of 1-fluorodecane with $PhSiMe_3$ gave in addition products resulting from rearrangement reactions of the alkyl chain as well as a small amount of 1-phenyldecane. In the case of cyclohexyl fluoride no products resulting from rearrangements of the cyclohexyl ring were detected. This was supported by the isolation of 1,2,4,5-tetracyclohexylbenzene from the reaction mixture and its spectroscopic identification.[22,23]

While the reaction of fluorodecane and fluorocyclohexane gave alkylated benzene derivatives as products, the attempted C–C coupling of fluoroadamantane and $PhSiMe_3$ was more complicated. Unexpectedly, the main product is Ph_2SiMe_2, the desired product phenyladamantane was only formed as a minor product. The larger steric demand of the adamantyl substrate made the *ipso*-substitution at the substrate $PhSiMe_3$ unfavorable; instead a Si–C bond of the $SiMe_3$ group was cleaved by the electrophile. However, the exact mechanism of this unexpected reaction remains unknown.

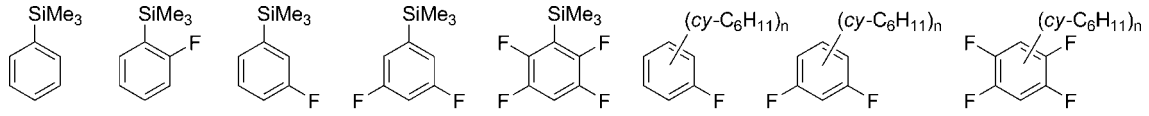
The regioselectivity of the catalyzed C–C coupling reaction was tested for the reaction of *p*-trimethylsilyltoluene **9** with fluorocyclohexane. Using the standard procedure, in this case not only the product of *ipso*-substitution of the trimethylsilyl group was detected but subsequent electrophilic alkylation reactions also gave higher alkylated products in considerable yields (Table 2, entry 4). Moreover, even the monoalkylated product was not produced regioselectively, but two different isomers were



Scheme 4. Cross-coupling reaction of *p*-trimethylsilyltoluene **9** to give *p*-**10** and suggested mechanism for the formation of *o*-**10**.

detected by GC-MS. The expected isomer *p*-**10** which results from *ipso*-substitution (C_6H_{11} vs $SiMe_3$) was formed in an equal amount relative to the *ortho* isomer *o*-**10**. The *meta* regio-isomer *m*-**10** was not found in the product mixture.[24] In a test reaction applying the reaction conditions of the catalyzed C–C coupling reaction (*p*-**10**, excess fluorocyclohexane, 4% **1**·TPFPB), it was shown that pure *p*-**10** did not rearrange to *o*-**10**. This suggests that the *ortho* isomer was formed in a competitive reaction to the *ipso*-substitution. A possible mechanistic rationalization for the formation of the *ortho* regio-isomer is put forward in Scheme 4. The formation of an arenium ion **11** under kinetic control might be envisaged after two 1,2-H shifts to the thermodynamically

Table 3. Catalytic cross-coupling between fluorohydrocarbons and fluorinated arenes **13** (catalyst **1**, 4 mol%)



7 **13a** **13b** **13c** **13d** **14a** **14b** **14c**

Entry	Substrate Me_3Si-Ar	Substrate RF	Alkylation products	$n = 0$	$n = 1$	$n = 2$	$n = 3$	$n = 4$
1	**7**	*cy*-C_6H_{11}–F	**4**	8	30	34	26	3
2	**13a**	*cy*-C_6H_{11}–F	**14a**	28	35	21	15	1
3	**13b**	*cy*-C_6H_{11}–F	**14a**	52	22	16	10	–
4	**13c**	*cy*-C_6H_{11}–F	**14b**	100	–	–	–	–
5	**13d**	*cy*-C_6H_{11}–F	**14c**	100	–	–	–	–

more stable β-silyl substituted arenium ion **12**. An intermolecular deprotonation/reprotonation sequence, which would directly give cation **12** from arenium ion **11**, cannot, however, be excluded. Finally, desilylation of arenium ion **12** occurs to form the isomer *o*-**10**.[25]

In order to inhibit the unwanted multiple alkylation products in the C–C coupling reaction, fluorinated phenylsilanes **13** were chosen as alternative substrates. The fluorine substitution was expected not only to block possible substitution sites, but also to significantly deactivate the aromatic ring towards electrophilic aromatic substitution. The results of a series of C–C coupling experiments using fluorinated phenylsilanes with cyclohexyl fluoride as reagent are summarized in Table 3. Monofluorsubstitution as in **13a,b** significantly decreased the reactivity in the C–C coupling reaction, i.e. the conversion of the phenylsilane was not quantitative. As expected, the deactivation was more efficient for the *meta* regio-isomer **13b** than for *ortho*-fluoro-phenylsilane **13a**. In both cases, however, the formation of multiple substitution products was not suppressed. Compounds **13c,d** with additional fluorine substituents were unreactive under the applied reaction conditions.

Conclusion

Catalytic activation of C–F functionalities in fluoroalkanes using the TPFPB salt of disilylcation **1** is a very efficient process which proceeds at room temperature in high rates with reasonable turnover numbers in trialkylsilanes as solvent.[12] In aromatic solvents the high reactivity of the catalyst prevails; however, Friedel–Crafts-type reactions between intermediate carbocations and the arene solvent become predominant and result in mixtures of different alkyl arene regio-isomers with partially rearranged alkyl substituents. Therefore, the intriguing combination between activation of an aliphatic C–F bond and a C–C bond forming process in this reaction is obscured by the intractable reaction mixture obtained. This dichotomy can be resolved using arylsilanes as substrates and as the source for the silyl cation, which is needed for the propagation of the catalytic cycle. The reaction of trimethylphenylsilane with primary, secondary and tertiary alkylfluorides which yields C–C coupling products indeed demonstrates in principle the validity of this approach. The high reactivity of the so-formed alkyl arenes towards Friedel–Crafts-type alkylation processes, however, leads to subsequent reactions which will severely hamper the use of this C–C coupling reaction in synthetic organic chemistry.

Experimental

General

Benzene and benzene-d_6 were distilled from sodium. Et_3SiH was distilled freshly from calcium hydride. 1-Fluorocyclohexane and 1-fluorodecane were distilled from P_4O_{10}. All reactions were carried out under inert conditions. **1**·TPFPB was prepared as described previously.[12] NMR spectra were recorded on a Bruker Avance 250 spectrometer at $T = 300$ K. GC-MS analyses were carried out on a coupled system, with a Thermo Focus gas chromatograph (DB5 column, length 25 m, inner diameter 0.2 mm) and a Thermo DSQ (EI) mass spectrometer.

Catalyzed hydrodefluorination reaction of alkylfluorides in the presence of benzene

A solution of 0.1 mmol **1**·TPFPB in 2 ml benzene was added to a mixture of 2.5 mmol fluorohydrocarbon (1-fluorodecane, fluorocyclohexane, 1-fluoroadamantane) and 3 mmol Et_3SiH at room temperature. The crude product mixture was characterized by NMR spectroscopy and GC-MS.

Catalyzed C–C cross coupling between arylsilanes and alkylfluorides

An equimolar mixture of 2.5 mmol fluorohydrocarbon and 2.5 mmol phenyltrimethylsilane was added to 0.1 mmol **1**·TPFPB at −10 °C and stirred for 2 min. The reaction mixture was warmed to room temperature and stirred for 30 min. The crude product mixture was characterized by NMR spectroscopy and GC-MS.

Because of the low solubility of 1-fluoroadamantane in phenyltrimethylsilane, a solution of 2 mmol 1-fluoroadamantane in 3.5 ml phenyltrimethylsilane was added to 0.1 mmol **1**·TPFPB at −10 °C. After warming to room temperature, the crude product mixture was characterized by NMR spectroscopy and GC-MS.

Acknowledgments

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Supporting information

Supporting information can be found in the online version of this article.

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