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Authors: Anna Pirzer, Eva Maria Alvarez Pari, Heike Friedrich, and Markus Rolf Heinrich

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FULL PAPER

Radical carbofluorination of alkenes with arylhydrazines and Selectfluor: Additives, mechanistic pathways and polar effects

Anna S. Pirzer, Eva-Maria Alvarez, Heike Friedrich and Markus R. Heinrich*

Dedication ((optional))

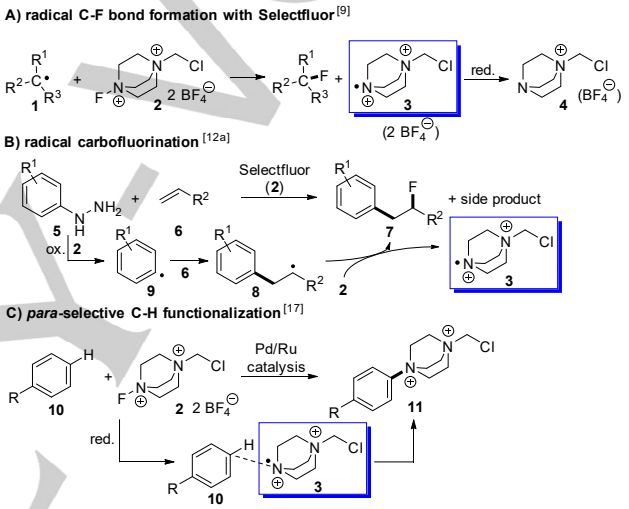
Abstract: Radical carbofluorination reactions starting from arylhydrazines and non-activated alkenes, in which the C-F bond is formed through the use of Selectfluor, can be improved through the addition of anisole. Since direct trapping products could be detected only in trace amounts, anisole does primarily act as a reversible scavenger for the highly reactive ammonium radical dication released from Selectfluor in the C-F bond forming step. As shown for three diverse substitution patterns, the main role of anisole is to prevent, or at least reduce, the undesired addition of the ammonium radical dication to the alkene, which in turn leads to an unfavorable consumption of the arylhydrazine-derived precursors required for carbofluorination. Besides the observation of remarkable polar effects in radical trapping, this study moreover shows that the Selectfluor-derived nitrogen-centered radical dication may add directly to alkenes, which has not been described so far.

Introduction

Fluorinated organic compounds are of importance in many fields of application, including agrochemistry, medicinal chemistry and materials.[1] Consequently, the development of efficient synthetic strategies for their preparation is an attractive field of research,[2] whereat the well-known approaches comprise nucleophilic[3,4] and electrophilic fluorinations[2,5,6] as well as transition metal-catalyzed or -mediated reactions.[7,8] This variety of methods was recently complemented by radical fluorinations,[9] in which the C-F bond is formed in a fluorine atom transfer step between a fluorine atom donor, such as Selectfluor (**2**),[10] and carbon-centered radical **1** (Scheme 1A).

Examples for radical reactions proceeding via C-F bond formation are decarboxylative fluorinations,[11] carbofluorina-tions,[12] and oxidative C-H functionalizations,[13],[14] whereat, among several reagents,[15] Selectfluor (**2**)[10] has evolved as the most widely used fluorine source.

Depending on the reaction type, the highly reactive ammonium radical dication **3** released in the fluorine atom transfer, may be required for further mechanistic steps,[11b,13e-l,14b,14d] e.g. the homolytic cleavage of an aliphatic C-H bond.[13] Other radical fluorinations with Selectfluor (**2**), in contrast, do not directly depend on the high reactivity of **3**, and for such cases, one can assume that a rapid reduction of radical dication **3** to cation **4**, or at least a deactivation of **3**, should be beneficial to avoid side-reactions.



Scheme 1. C-F bond formation (A), carbofluorination (B) and C-H functionalization (C) with Selectfluor (**2**).

Our deeper interest in this topic arose from a recently developed alkene functionalization (Scheme 1B).[12a] Starting from phenyl-hydrazines **5** and alkenes **6**, the first Meerwein-type carbofluorination could be put into practice, whereat the desired arylation products **7**[16] were obtained via trapping of alkyl radical **8** by Selectfluor (**2**). In this reaction, the fluorine source **2** previously also serves as an oxidant to generate aryl radicals **9** from **5**. Besides **7**, this reaction however led to an unknown by-product, which we were unable to suppress during optimization, and which, we reasoned, could be formed due the high reactivity of **3**. Further evidence for the reactivity **3** was provided by a report by Ritter[17] on an attractive new type of *para*-selective arene functionalization, in which radical dication **3** was assumed to play a key role in the attack onto arene **10** to give **11** (Scheme 1C).

Against this background, it was interesting to investigate whether a suitably substituted arene might be a beneficial additive in radical fluorination reactions with Selectfluor (**2**), as such an arene could act as a scavenger for the reactive radical dication **3**. If successful, it was our further intention to see in detail how the aromatic additive can influence the reaction pathways leading to the carbofluorination product and the related by-products.

[a] Apothekerin A. S. Pirzer, E.-M. Alvarez, H. Friedrich, Prof. Dr. M. R. Heinrich
Department of Chemistry and Pharmacy
Pharmaceutical Chemistry
Friedrich-Alexander-Universität Erlangen-Nürnberg
Nikolaus-Fiebiger-Str. 10, 91058 Erlangen, Germany
E-mail: Markus.Heinrich@fau.de

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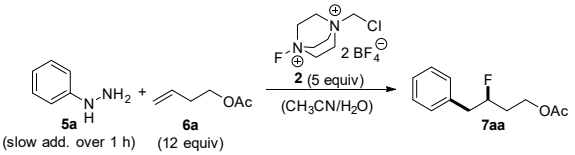
Results and Discussion

The present investigation was started with experiments in which the carbofluorination of alkene **6a** was carried out with a sufficiently soluble, donor-substituted arene as additive (Table 1).

Table 1. Evaluation of donor-substituted arenes as additives in the radical carbofluorination of 3-buten-1-yl acetate (**6a**).

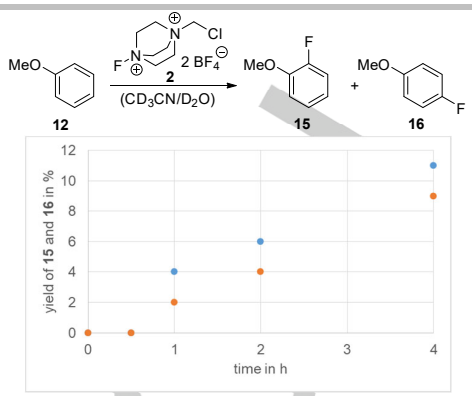


entry	variation of reaction conditions	yield **7aa** (%/%)[b],[c]
1	none (without additive)	62/57
2	anisole (**12**) (2 equiv)	41/---
3	anisole (**12**) (3 equiv)	73/69
4	anisole (**12**) (4 equiv)	54/---
5	anisole (**12**) (3 equiv), traces of oxygen[d]	**74/75**
6	Selectfluor (**2**) (3 equiv), anisole (**12**) (3 equiv)[d]	33/---
7	alkene **5a** (6 equiv), anisole (**12**) (3 equiv)[d]	70/71
8	add. of **4a** over 30 min, anisole (**12**) (3 equiv)[d]	69/---
9	1,4-dimethoxybenzene (**13**) (3 equiv.)[d]	0/---
10	1,3-dimethoxybenzene (**14**) (3 equiv.)[d]	0/---

[a] General reaction conditions: **5a** (1.0 mmol) in CH_3CN/H_2O (5:1, 4 mL) added by syringe pump over 1 h to a mixture of **6a** (12.0 mmol) and **2** (5.0 mmol) in CH_3CN/H_2O (5:1, 5 mL) under argon. [b] Yield determined by ^{1}H-NMR spectroscopy. [c] Yield after purification by column chromatography. [d] Traces of oxygen present due to incomplete degassing.

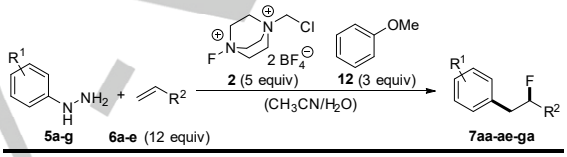
Initial experiments showed that there is indeed a beneficial effect of anisole (**12**) compared to the additive-free reaction (entries 1-4), but only at a defined excess of 3 equivalents of **12**. Whereas the amount of scavenger is probably not sufficient at 2 equivalents (entry 2), anisole (**12**) might start to compete as an aryl radical acceptor at 4 equivalents (entry 4),[18] so that lower yields are obtained in that case, too. A slight further improvement was achieved through incomplete degassing, which leaves traces of oxygen in the reaction mixture (entry 5). This effect can be rationalized by the facilitated generation of aryl radicals from **5a**, as oxygen readily decomposes phenyldiazene (ArN=NH) occuring as intermediate.[19] Whereas the optimized conditions of entry 5 do not allow a decrease of the amount of Selectfluor (**2**) to 3 equivalents (entry 6), lower amounts of the alkene (entry 7) and a faster addition of **5a** over 30 minutes (entry 8) were tolerated at an only minor drop in yield.

In further attempts, the 1,4-dimethoxybenzene (**13**) and 1,3-dimethoxybenzene (**14**) proved unsuitable, as these additives reacted readily with Selectfluor (**2**) in an electrophilic fluorination (entries 9 and 10).[20] The background reaction of anisole (**12**) with Selectfluor (**2**), on the other hand, was found to proceed quite slowly under our reaction conditions. After 1 h reaction time, which was also applied for the carbofluorinations reported in Table 1, just small amounts of 2-fluoroanisole (**15**) (2%) and 4-fluoroanisole (**16**) (4%) could be detected by ^{1}H-NMR analysis (Scheme 2). When running the experiment over a longer period of 4 h, the yield of 2-fluoroanisole (**15**) increased to 11% and the amount of 4-fluoroanisole (**16**) finally increased to 9%.



Scheme 2. The slow background reaction of Selectfluor (**2**) with anisole (**12**) to give 2-fluoroanisole (**15**) (light blue) and 4-fluoroanisole (**16**) (orange).

With optimized conditions available, the effect of anisole (**12**) was next evaluated in carbofluorination reactions starting from other aryl hydrazines **5a-g** and alkenes **6a-e** (Scheme 3).



from **5a** (R^1 = H) and **6a-e**:

7aa: R^2 = $(CH_2)_2OAc$ 75% (57%)
7ab: R^2 = $(CH_2)_2OH$ 40% (43%)
7ac: R^2 = $(CH_2)OAc$ 60% (45%)
7ad: R^2 = $(CH_2)_2COMe$ 50% (30%)
7ae: R^2 = $(CH_2)_2COOH$ 48% (40%)

from **5b-g** and **6a** (R^2 = $(CH_2)_2OAc$):

7ba: R^1 = 4-Cl 60% (39%)
7ca: R^1 = 4-Br 55% (42%)
7da: R^1 = 4-OMe 23% (11%)
7ea: R^1 = 4-CN 48% (29%)
7fa: R^1 = 3-Cl 51% (47%)
7ga: R^1 = 3-Br 59% (49%)

Scheme 3. Effect of added anisole on other substitution patterns. Yields after purification by column chromatography. Yields in brackets refer to reactions without anisole.[12a]

In the first series of experiments, in which the alkene **6** was varied, only 3-buten-1-ol (**6b**) led to a slightly lower yield of **7ab** when anisole was present. Anisole being ineffective in this case suggests that alcohols such as **6b** are even more reactive scavengers for radical dication **3**, however at the price of some destruction of reactants and related products.[21] For 5-hexen-2-one (**6d**), on the other hand, an increase in yield of **6ad** from 30% to 50% was observed upon the addition of anisole. In the second series, and under variation of the aryl hydrazine **5**, all experiments led to higher yields when anisole was present. The highest absolute increase by 21% was observed for **7ba**, the highest relative increase was determined for **7da** with a factor of 2.1.

Having observed the beneficial effect of anisole in the Meerwein-type carbofluorination, the yet unknown hydrophilic by-product was reinvestigated using the reaction of **5b** and **6a** to give **7ba** (Scheme 4).[12a]

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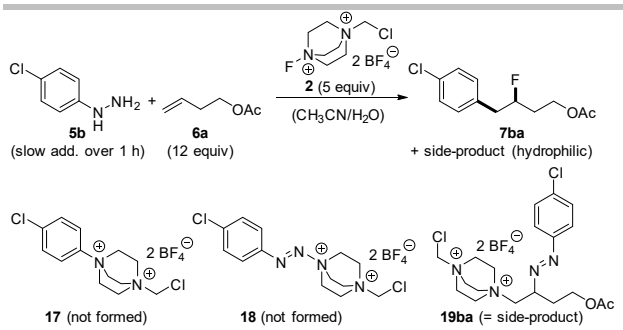
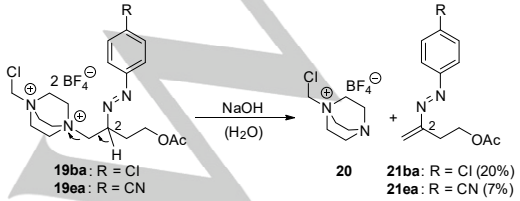


Scheme 4. Identification of the hydrophilic key by-product of the carbofluorination reaction.[12a]

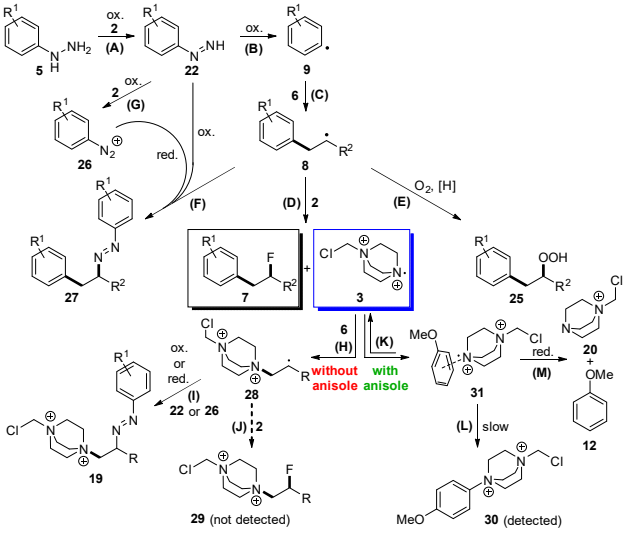
To obtain the by-product in high quantity, the reaction was now again conducted in the absence of anisole (**12**). While the desired carbofluorination product **7ba** can easily be separated from the reaction mixture by extraction with an organic solvent such as diethyl ether, the by-product was always found in the aqueous phase and could not be extracted due to its high polarity. Although attempts to separate or purify the by-product failed due to a certain instability of the compound, some insight could be gained by ^{1}H-NMR analysis, which indicated the presence of an acceptor-substituted, arylhydrazine-derived 4-chlorophenyl moiety as well as a Selectfluor-derived diammonium unit as structural elements. Combining these two substructures, our first suggestion was compound **17**, which could however readily be ruled out by the synthesis of an authentic sample.[17] The next candidate, which appeared plausible to due to its assumable instability, and which might result from an undesired attack of radical dication **3** on hydrazine **5b** was compound **18**. As **18** should however also be formed in the absence of the alkene **6a**, we conducted a control reaction comprising only 4-chlorophenylhydrazine (**5b**) and Selectfluor (**2**). This control reaction did not provide the sought-after by-product, nor compound **18**, so that it became clear that the former alkene **6a** needed to be a structural component of the by-product as well. Based on what was known about the by-product from ^{1}H-NMR analysis of the original reaction (Scheme 4), the 4-chlorophenyl has to be bound to an electron-accepting unit, so that compound **19ba** now appeared plausible. Reinvestigation of the aqueous phase by HPLC-MS did indeed support this suggestion, and the presence of the acetate unit could be confirmed by ^{1}H-NMR. To unambiguously prove the formation of **19ba** in the carbofluorination reaction, the aqueous phase containing the by-product was treated with sodium hydroxide (Scheme 5). In the presence of a base, we reasoned that deprotonation should easily occur at position 2, then leading to elimination of the single charged diazabicycle **20** and formation of vinyldiazene **21**.[22]



Scheme 5. Conversion of by-products **19ba** and **19ea** to vinyldiazenes **21ba** and **21ea**.

The assumed conversion of **19ba** to **21ba** did indeed occur and could also be reproduced for the by-product **19ea** (previously formed along with **7ea**) to give vinyldiazene **21ea**. Investigation of the vinyldiazenes **19ba** and **19ea** by ^{1}H-NMR spectroscopy revealed that both compounds exhibit only a very low stability, which was found to be even lower for the acceptor-substituted cyano derivative **21ea**.[22] Due to the fact that the diazabicycle **20** is already formed in reasonable amounts during the carbofluorination reaction, and cannot be removed from the aqueous phase, which also contains **19**, it is not possible to distinguish analytically in between the previously formed diazabicycle **20** and one that is newly formed during the elimination of **19** to give **21**.

As the structure of the key by-product had been determined, it is now possible to give a more complete ovierview over the multiple pathways occurring during carbofluorination (Scheme 6). Starting from phenylhydrazine **5**, oxidation by Selectfluor (**2**) at first provides the phenyldiazene **22** (step **(A)**). The formation of **22** under the typical carbofluorination conditions could be confirmed through trapping of **22b** with 2,5-dimethylfuran (**23**), which led to the pyridazinium salt **24b** in 51% yield (Scheme 7).[19] The further oxidation of **22** to **9** under loss of dinitrogen represents one of the critical steps in the carbofluorination (step **(B)**, Scheme 6), as it is greatly facilitated by the presence of dioxygen,[19] but a large amount dioxygen would later on promote the undesired formation of the hydroperoxide **25** from **8** (step **(E)**).[12a,23] This background thus explains why partial degassing, so that a limited but defined amount of dioxygen is available, was found to be beneficial. Addition of aryl radical **9** to the alkene **6** furnishes the central and typical intermediate **8** of Meerwein arylation reactions (step **(C)**). Besides the desired trapping of **8** by fluorine atom transfer from **2** to give **7** (step **(D)**), **8** may also react with dioxygen (step **(E)**), see above), or it be trapped by a diazonium ion **26** or diazene **22** to finally give azo compound **27** (step **(F)**).[22] Both **26** and **27** could be identified as by-products, whereat **26** most likely results from over-oxidation of **22** by Selectfluor (**2**) (step **(G)**).



Scheme 6. Overview over mechanistic pathways.

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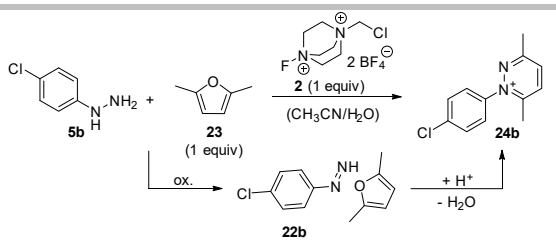
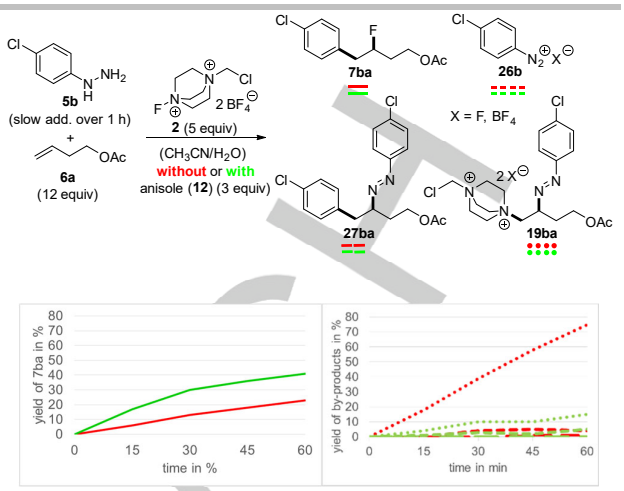


Scheme 7. Trapping of the phenyldiazene intermediate **22b** by cycloaddition to 2,5-dimethylfuran (**23**).

As mentioned in the introduction, and as verified by the structure of the by-products **19ba** and **19ea** (Scheme 5), the reactivity of the radical dication **3** does indeed play a major role in the carbofluorination reaction described herein. In the absence of anisole (**12**), **3** does readily attack alkene **6** to give **28** (step **(H)**). Interestingly, alkyl radical **28** is then almost exclusively trapped by **22** or **26** to give **19** (step **(I)**), but not by Selectfluor (**2**) to provide **29** (step **(J)**), since **29** could not be detected among the hydrophilic products by ^{19}F-NMR or LC-MS. Given that the two secondary alkyl radicals **8** and **28** should possess a comparable reactivity, but **8** preferably reacts with **2** to give **7** (step (**D**)), whereas **28** chooses **22** or **26** to give **19** (step **(I)**), we assume that a strong polar effect (lipophilic phenyl group in **8** *vs.* doubly charged diazabicycle in **28**) is responsible for this remarkable selectivity. At this point, it is worth to mention that the direct attack of radical dication **3** onto an alkene has so far not been reported, so that this observation could be an interesting starting point for future developments.[24], [25]

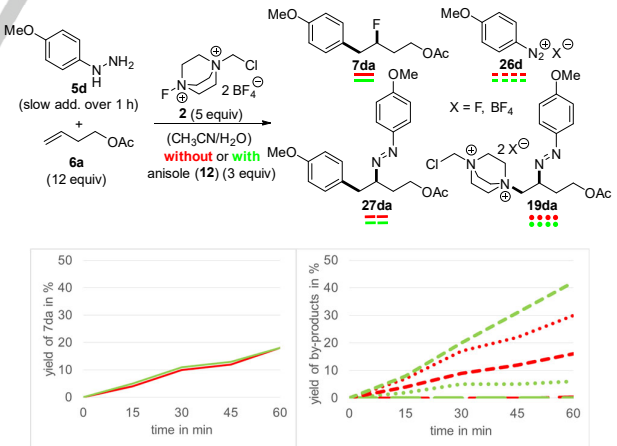
In the presence of anisole (**12**), **19** is most often formed in much lower amounts, so that one can assume that the reactivity of radical dication **3** gets reduced. Since no degradation products related to anisole (**12**) could however be detected in the reaction mixture besides a small amount of **30** (steps **(K)** and **(L)**) it appears plausible that a reversible complex such as **31** is responsible for the reduced reactivity of **3**.[26] The substitution of **12** to give **30** (step **(L)**), which is identical to one of the products recently reported by Ritter,[17] obviously occurs slowly in comparison to the reductive decay of the complex **31** leading to **12** and **20**. The reductive step **(M)** is thereby most probably coupled to one of the oxidative steps **(A)**, **(B)**, **(F)** or **(I)**.

Against the background of these multiple pathways, we next studied the particular influence of the substitution on the arylhydrazine using the more or less electron-neutral arylhydrazine **5b** (4-Cl), the donor-substituted hydrazine **5d** (4-OMe) as well as the acceptor substituted hydrazine **5e** (4-CN) (Schemes 8-10). Samples from the individual reaction mixtures were drawn after 15, 30, 45 and 60 minutes to get insights into product and by-product formation depending on the presence of anisole (**12**). Note that, due to the multiple sample acquisitions, the final yields in this study do not exactly match those of the undisturbed reactions reported in Scheme 3. The resulting graphs should thus be preferably seen as a qualitative than an absolutely quantitative representation.



Scheme 8. Influence of anisole (**12**) on the carbofluorination using 4-chlorophenylhydrazine (**5b**).

Regarding the formation of the carbofluorination product **7ba** from arylhydrazine **5b** and alkene **6a** (Scheme 8), a strong effect of anisole (**12**) could be observed (bottom left), which resulted in an almost doubled yield for the anisole-containing reaction. On the part of the by-products (bottom right), and in agreement with the above made assumptions, the presence of anisole led to sharp drop in yield for the adduct **19ba** arising from the addition of radical cation **3** onto alkene **6a**. The main damage to the reaction related to adduct **19** is thereby generally not done due to the incorporation of the alkene, which is present in sufficient excess, but due to the consumption of diazene **22**, which could otherwise form the desired product **7**. Regarding the further by-products in the reaction of the 4-chloro-substituted phenylhydrazine **5b**, neither diazonium salts **26b** nor the azo compound **27ba** play a major role.



Scheme 9. Influence of anisole (**12**) on the carbofluorination using 4-methoxyphenylhydrazine (**5d**).

As shown in Scheme 9 (bottom left), the carbofluorination reaction starting from 4-methoxyphenylhydrazine (**5d**) does not strongly benefit from the addition of anisole (**12**). A closer inspection of the by-products revealed that although anisole (**12**) can again suppress the formation of the adduct **19da** to a large extent, it is however unable to inhibit the undesired over-oxidation of the

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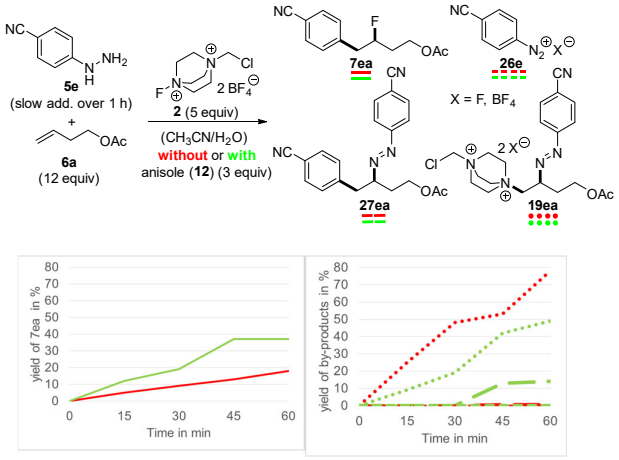
diazene **22** to the diazonium salts **26d** (Scheme 9, botton right). Taking into account that the electron-donating character of the 4-methoxy group does strongly facilitate the oxidation of diazene **22d** to diazonium salts **26d**, it is not surprising that oxidative carbofluorinations are difficult to carry out with electron-rich arylhydrazines as starting materials.



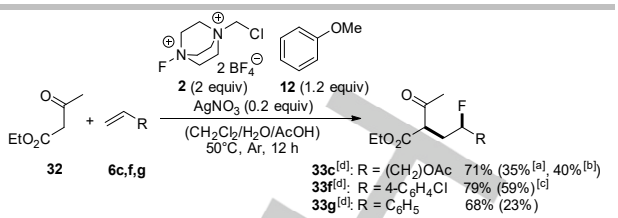
Scheme 10. Influence of anisole (**12**) on the carbofluorination using 4-cyanophenylhydrazine (**5e**).

In the case of the acceptor-substituted 4-cyanophenylhydrazine (**5e**), the yield of the carbofluorination product **7ea** could again be considerably increased through the addition of anisole (**12**) (Scheme 10, bottom left). On the side of the by-products (bottom right), it however became obvious that the amount of adduct **19** was not decreased to the same extent as it had been the case for the 4-chloro- and the 4-methoxy derivatives (Schemes 8 and 9). A plausible explanation for the reduced effect of anisole (**12**) is, that the anisole-radical cation complex **31** can no longer decay rapidly enough to cation **20** and anisole (**12**) (Scheme 6, step **(M)**) as the available oxidation steps **(A)**, **(B)**, **(F)** and **(I)** have become more difficult due to the presence of the cyano group on the aromatic core. Complex **31** can thus reversibly give back radical dication **3**, which in turn limits the overall effect.

On the other hand, the electron-accepting cyano group turns diazene **22** and diazonium **26** into very good scavengers for nucleophilic alkyl radicals such as **8** (Scheme 6), now giving rise to an increased amount of azo compound **27**. The fact that the formation of **27** is exclusively observed in the anisole-containing reaction, whereat diazonium ions **26** were not detected, suggests that especially the lifetime of the 4-cyanophenyldiazene **22** gets increased through anisole addition.

As a concluding remark related to all six time course reactions depicted in Schemes 8 to 10, it is worth to mention that product as well as by-product formation mainly occurred in a linear fashion. This means that inhibitory and accelerating effects of the newly formed compounds do not play a major role in the reaction course.

Finally, we evaluated the effect of anisole (**12**) in another type of carbofluorination that was recently reported by Li[12b] (Scheme 11). In this reaction, radicals that are oxidatively generated from ethyl acetoacetate (**32**), or similar compounds, add to alkenes **6**, and the related adducts are ultimately trapped by Selectfluor (**2**) to give carbofluorinaton products **33**.



Scheme 11. Effect of anisole on carbofluorination developed by Li.[12b] Yields after purification by column chromatography. Yields in brackets refer to reactions without anisole. [a] Yield determined by ^{1}H-NMR spectroscopy. [b] Yield according to ref. 12b. [c] $K_2S_2O_8$ (1.00 mmol) added.[12b] [d] Product shows *cis/trans* isomerism and keto-enol tautomerism.

With allyl acetate (**6c**), a remarkable increase in the yield of **33c** from 40% to 71% was observed upon the addition of anisole to the reaction mixture. In contrast to that, the effect of anisole on the carbofluorination of styrenes appears to be dependent on the substitution pattern on the aromatic core. While only a smaller raise of 20% was achieved for **33f**, the yield of **33g** could be increased by 45%. Thus, the free *para*-position on styrene (**6g**) plays a role in the sensitivity of this type of alkene towards the reactive radical dication **3**. Under the conditions of Li[12] the background reaction of anisole (**12**) and Selectfluor (**2**) led to an almost complete consumption of **12** with only 7% remaining after the typical reaction time of 12 h. This shows that carbofluorination reactions such as the one developed by Li should be completed within a few hours to benefit from the addition of anisole (**12**), as the negative effect of Selectfluor consumption will otherwise prevail.

Conclusions

In summary, it has been shown that carbofluorination reactions, in which C-F bond formation is achieved through the use of Selectfluor, benefit from the addition of anisole to the reaction mixture. All obtained experimental results support the assumption that the reactive ammonium radical dication **3**, released in the fluorine atom transfer step, is only trapped to a very minor extent by anisole in an electrophilic aromatic substitution. Instead, a complex of **3** with anisole is most likely formed, through which the reactivity of radical dication **3** is sufficiently reduced to prevent its undesired addition to the alkene. Anisole can thus be a useful additive for all those radical fluorinations with Selectfluor that do not further depend on the reactivity of the ammonium radical dication **3**. Moreover, the hitherto unknown ability of the ammonium radical dication **3** to add onto alkenes can serve as a promising starting point for future developments in the field of alkene functionalization and related experiments are currently underway in our laboratory.

Experimental Section

General Procedure for carbofluorination reaction (GP1): To an undegassed, stirred solution of Selectfluor (**2**) (1.77 g, 5.00 mmol) and the alkene **6** (12.0 mmol) in a mixture of CH_3CN/H_2O (5:1, 5 mL), anisole (**12**) (3.00 mmol) was added at room temperature under argon atmosphere in a Schlenk flask shortly before the next step. Subsequently an undegassed solution of the aryl hydrazine **5** (1.00 mmol) in CH_3CN/H_2O (5:1, 4 mL) was

added dropwise to the reaction mixture over a period of 1 h. Stirring was continued for 5 min and the reaction mixture was diluted with Et_2O (10 mL). The organic layer was separated, and after a further extraction with Et_2O (10 mL), the combined organic phases were washed with water (30 mL) and brine (30 mL) and dried over Na_2SO_4. The solvents were removed under reduced pressure and the products were purified by column chromatography on silica gel.

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Keywords: Fluorination • Radical reaction • Selectfluor • Anisole • Alkene functionalization

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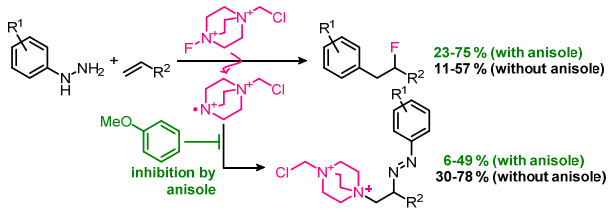

Tamed by anisole. Anisole was found to be a beneficial additive in two types of radical carbofluorination reactions using Selectfluor. Given that the ammonium radical dication arising from the fluorine atom transfer step is not required for the reaction course, anisole can serve as a scavenger for this reactive intermediate to prevent side-reactions such as the addition of the radical cation to the alkene.

*Anna S. Pirzer, Eva-Maria Alvarez, Heike Friedrich, Markus R. Heinrich **

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Radical carbofluorination of alkenes with arylhydrazines and Selectfluor: Additives, mechanistic pathways and polar effects