Fluorine-18 labelled Ruppert–Prakash reagent ([$^{18}$F]Me$_3$SiCF$_3$) for the synthesis of $^{18}$F-trifluoromethylated compounds†

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This article describes the first synthesis and application of fluorine-18 labelled Ruppert–Prakash reagent [$^{18}$F]Me$_3$SiCF$_3$. [$^{18}$F]Me$_3$SiCF$_3$ was synthesized from [$^{18}$F]fluoroform with radiochemical yields of 85–95% and radiochemical purities of >95% within 20 minutes. [$^{18}$F]-trifluoromethylated compounds were successfully prepared by reaction of [$^{18}$F]Me$_3$SiCF$_3$ with benzaldehydes, acetophenones and benzophenones.

Since trifluoromethyl moieties are so often found in modern pharmaceuticals, much attention has been paid to the development of synthesis strategies for introducing fluorine-18 labelled trifluoromethyl groups into PET tracers. Aromatic [$^{18}$F]trifluoromethylation is well established and multiple strategies have been reported.14–19 However, the reported methodologies mainly rely on [$^{18}$F]fluoroform as [$^{18}$F]trifluoromethylation agent. In organic chemistry, not many trifluoromethylation procedures report the use of [$^{19}$F]fluoroform, as alternative trifluoromethylation agents are generally preferred. One of the most applied nucleophilic trifluoromethylation agents is the Ruppert–Prakash reagent (Me$_3$SiCF$_3$).5 It was first described in 1984 by Ruppert et al.18 and found its first application in 1989 by Prakash et al.20 We therefore envisioned that developing a synthesis strategy for fluorine-18-labelled Ruppert–Prakash reagent would be very useful for the translation of CF$_3$ functionalization reactions that have been developed in fluorine-19 chemistry to radiofluorination reactions and PET tracer synthesis.21

To synthesize [$^{18}$F]Me$_3$SiCF$_3$ we followed a procedure reported by Prakash et al. that reacted fluoroorom with trimethylsilyl chloride in presence of potassium hexamethyldisilazide (KHMSD) as the base in toluene.22 Initial experiments using [$^{19}$F]fluoroform 1 synthesized according to our previously reported method18 showed successful formation of the desired product [$^{18}$F]Me$_3$SiCF$_3$ 3, in addition to unreacted [$^{18}$F]fluoroform 1 and formation of a side product which was identified as [$^{18}$F]trimethylsilyl fluoride 4 (see Scheme 1). To optimize the reaction towards full conversion to [$^{18}$F]Me$_3$SiCF$_3$ 3 several reaction parameters were varied.

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**Scheme 1** Formation of [$^{18}$F]Me$_3$SiCF$_3$ 3 and side product 4 from [$^{18}$F]fluoroform 1.
The following reaction setup was used as a starting point: \([^{18}F]\)fluoroform 1\(^{18}\) was trapped in a solution of 0.6M Me\(_3\)SiCl 2 and 0.5M KHMDs in 650 \(\mu\)L toluene at \(-80^\circ\)C (prepared 15 minutes before trapping \([^{18}F]\)fluoroform 1, analogous to \(^{19}\)F-chemistry).\(^{22}\) After complete distillation (~3 min) of \([^{18}F]\)fluoroform 1, the trapping vial was either actively warmed up to 20 \(^\circ\)C or passively by removing it from the cooling bath. \([^{18}F]\)fluoroform was trapped well in the toluene solution and comparable RCYs to those previously reported (trapping in DMF) were obtained (up to 44 \pm 0\% vs 44 \pm 1\%, calculated from dry \([^{18}F]\)fluoride). The conversion of \([^{18}F]\)fluoroform to \([^{18}F]\)Me\(_3\)SiCF\(_3\) was temperature sensitive and active warming to 8–10\(^\circ\)C was not necessary for \([^{18}F]\)Me\(_3\)SiCF\(_3\), but required 15 minutes before trapping \([^{18}F]\)fluoroform \(^{19}\)F-chemistry). \(^{22}\) After complete distillation of \([^{18}F]\)Me\(_3\)SiCF\(_3\) in toluene, the co-distilled precursor precipitated in 4-nitrobenzaldehyde 6g, analogous to \([^{18}F]\)Me\(_3\)SiCF\(_3\) (prepared 3 min) of 85–95\% and radiochemical purities of >95\%.

To explore the applicability of \([^{18}F]\)Me\(_3\)SiCF\(_3\) as \([^{18}F]\)trifluoromethylation reagent, we demonstrated its use by reaction with aldehydes and ketones and adapted the procedure for \(^{19}\)F-reactions reported by Prakash \textit{et al.}\(^{20}\) In this procedure, the aldehyde or ketone was reacted with Me\(_3\)SiCF\(_3\) under addition and obtained as a solution in THF with radiochemical yields of 85–95\% and radiochemical purities of >95\%.

The RCY of \([^{18}F]\)Me\(_3\)SiCF\(_3\) was comparable to distillation without SPE (86 \pm 1\% vs. 88 \pm 6\%). However, the distillation time increased from 5 minutes to 10 minutes (see ESI\(^{†}\) for more details). In summary, \([^{18}F]\)Me\(_3\)SiCF\(_3\) passed the SPE. The RCY of \([^{18}F]\)Me\(_3\)SiCF\(_3\) was determined and only minor impurities (0–2\%) of \([^{18}F]\)Me\(_3\)SiF were found.

At higher flow rates and higher temperatures we noted a significant decrease of the volume in the first reaction vessel and the formation of a precipitate in the second vessel suggesting that precursor Me\(_3\)SiCl (bp. 57 \(^\circ\)C)\(^{23}\) and also solvent (toluene, bp. 111 \(^\circ\)C) were co-distilled along with \([^{18}F]\)Me\(_3\)SiCF\(_3\). Subsequently, we explored the possibility of further purification by distillation over solid phase extraction (SPE) cartridges. Our primary focus was on the removal of the precursor, Me\(_3\)SiCl, to avoid potential reaction with the subsequent \([^{18}F]\)trifluoromethylation reaction. It was found that the silica plus long Sep-Pak\(^{\text{®}}\) was able to retain the precursor while almost all \([^{18}F]\)Me\(_3\)SiCF\(_3\) passed the SPE. The RCY of \([^{18}F]\)Me\(_3\)SiCF\(_3\) was 88–95\%.

| Flow mL min\(^{-1}\) | Temp. \(^\circ\)C | RCY\(^a\) Me\(_3\)SiCF\(_3\) % |
|-------------------|-------------|------------------|
| 1                 | 5           | 70               | 52 \pm 6 |
| 2                 | 10          | 70               | 69 \pm 3 |
| 3                 | 20          | 70               | 86 \pm 3 |
| 4                 | 30          | 70               | 93 \pm 1 |
| 5                 | 40          | 70               | 94 \pm 1 |
| 6                 | 50          | 70               | 95 \pm 1 |
| 7                 | 70          | 70               | 95 \pm 1 |
| 8                 | 50          | 50               | 75 \pm 21\(^b\) |
| 9                 | 50          | 60               | 88 \pm 6 |
| 10                | 50          | 80               | 95 \pm 1 |

Conditions: 1182 \(\mu\)mol Me\(_3\)SiCl, 500 \(\mu\)mol KHMDs, 1 mL toluene. \(^{a}\) Average \pm SD, dc, n = 3. \(^{b}\) Distillation blocked in 2 out of 3 reactions.

Table 1

| Me\(_3\)SiCl \(\mu\)mol | KHMDs \(\mu\)mol | Toluene \(\mu\)L | RCY CHF,\(^a\) % | RCP Me\(_3\)SiCF\(_3\),\(^b\) % |
|------------------------|------------------|----------------|----------------|------------------|
| 1                      | 394              | 325            | 650            | n.d.             | 0 \pm 0 |
| 2                      | 788              | 325            | 650            | 28 \pm 1         | 74 \pm 28 |
| 3                      | 1576             | 650            | 1300           | 39 \pm 0         | 95 \pm 4 |
| 4                      | 1182             | 488            | 975            | 44 \pm 0         | 98 \pm 2 |
| 5                      | 1182             | 500            | 1000           | 43 \pm 3         | 97 \pm 3 |

Conditions: Trapping at \(-80^\circ\)C, passive warmup to rt in 5 min. \(^{a}\) Isolated yield, average \pm SD, decay corrected (dc), n = 3. \(^{b}\) Determined by HPLC, average \pm SD, dc, n = 3.
beneficial for the reaction, and is likely attributed to increasing amounts of water in the TBAF solution which is responsible for promoting $[^{18}\text{F}]\text{CHF}_3$ formation.

Next, the effect of precursor concentration was investigated and showed that the higher the concentration of precursor, the higher the radiochemical yield (64 ± 5% RCY with 400 μmol precursor; see ESI† for details). To adapt the reaction for relevance to PET tracer syntheses the scale of the reaction was reduced compared to the initial conditions. It was observed that scaling down the reaction to 250 μL and 125 μL total volume resulted in comparable to even slightly higher radiochemical yields than the initial conditions (see Table S6 in ESI†). Due to easier handling and abundance of the model precursors we moved on to explore the substrate scope with the following conditions: 250 μL THF, 200 μmol precursor, 100 μmol TBAF (ESI†, Table S6, entry 7).

Three different groups of substrates were investigated, benzaldehydes, acetophenones and benzophenones, each with no substituents, electron withdrawing (4-MeO-) and electron donating (3-NO2-, 4-NO2-) substituents. An overview of all products and the corresponding RCYs is shown in Scheme 2. Two general trends were observed: 1. Electron withdrawing groups had a positive influence on the RCY. 2. Benzaldehydes reacted very well whereas benzophenones only resulted in low RCYs (<10%). The first observation can be explained by the electron density. The trifluoromethyl group attacks the positively polarised C atom of the carbonyl group. Electron withdrawing groups reduce the electron density of the carbonyl C atom and facilitate the nucleophilic attack whereas electron donating groups exert the opposite effect. The second observation can be explained by the reaction kinetics. It has been described that the rate constants of trifluoromethylation reactions observe the following rank order: $k$(benzaldehyde) > $k$(acetophenone) > $k$(benzophenone); and a competing reaction is the formation of fluoroform by reaction of Me$_3$SiCF$_3$ with trace amounts of water. Due to easier handling and abundance of the model precursors we moved on to explore the substrate scope with the following conditions: 250 μL THF, 200 μmol precursor, 100 μmol TBAF (ESI†, Table S6, entry 7).

Attempts to increase the RCY of the benzophenone reactions by further optimization of the previously varied reaction conditions [temperature, time, TBAF amount] were not fruitful. We therefore turned our attention to alternative initiators. Based on work of Johnston et al. we chose two initiators, KOPh and TBAT. Reactions initiated by K$^+$-containing initiators were expected to have a faster turnover rate than with NH$_4$+, and could improve the RCY of the slow-reacting benzophenones. Anhydrous TBAT was reported to result in more reproducible yields compared to TBAF, due to lower water content.

Under our radiochemistry conditions KOPh resulted in very low yields for all substrate groups, and is likely due to poor solubility of KOPh in THF. However, TBAT proved to be an excellent initiator (see Scheme 2). Reactions with nitro-substituted benzaldehydes and acetophenones resulted in ≥90% RCY of the corresponding products. It is noteworthy that three of these compounds previously failed to label using $[^{18}\text{F}]\text{fluoroform}$. Furthermore, the unsubstituted and methoxy-substituted benzaldehydes were $[^{18}\text{F}]$trifluoromethylated with decent to good yields (73 ± 4% and 43 ± 6%, respectively). Unsubstituted and methoxy-substituted acetophenones and benzophenones still showed low yields (∼10%). On the contrary to the nitro-substituted derivatives, these substrates are reported to react very well with $[^{18}\text{F}]\text{fluoroform}$.

All optimization reactions were carried out using aliquots of a $[^{18}\text{F}]\text{Me}_3\text{SiCF}_3$ stock solution. To confirm that the $[^{18}\text{F}]$trifluoromethylation reactions work using the full batch of $[^{18}\text{F}]\text{Me}_3\text{SiCF}_3$ and to determine the overall RCY and molar activity ($A_m$), $[^{18}\text{F}]\text{Me}_3\text{SiCF}_3$ was synthesized from 5 GBq $[^{18}\text{F}]$fluoride. It was trapped after distillation in a reaction vessel containing THF, TBAT and 4-nitrobenzaldehyde and reacted for 5 min at rt after complete trapping. It was found that higher TBAT amounts (556 μmol) were required to fully
release $\text{CF}_3^-$ from $[^{18}\text{F}]\text{Me}_3\text{SiCl}$, but the precursor amount could be kept at 200 $\mu$mol. The product was purified by preparative HPLC and the collected product fraction was measured for radioactivity and analysed by HPLC. The overall radiochemical yield (with regard to aqueous $[^{18}\text{F}]$fluoride) was 11 $\pm$ 3% (dc) and the molar activity was 13 $\pm$ 2 GBq/μmol ($n = 3$). The molar activity compares well to the $A_m$ reported for $[^{18}\text{F}]$fluoroform$^{18}$ at the same starting amount of $[^{18}\text{F}]$fluoride.

The low overall yield is mainly due to losses during $[^{18}\text{F}]$fluoroform formation. Details on the reaction procedure and molar activity calculations can be found in the ESI.$^{\dagger}$

As a final note it should be mentioned that for the chosen model reaction it was not necessary to distill $[^{18}\text{F}]\text{Me}_3\text{SiCF}_3$ over a silica SPE cartridge to remove co-distilling Me$_3$SiCl since RCYs of the subsequent $[^{18}\text{F}]$trifluoromethylation reaction were comparable with and without Me$_3$SiCl present. Surprisingly, without any intermediate purification of $[^{18}\text{F}]\text{Me}_3\text{SiCF}_3$ the $[^{18}\text{F}]$trifluoromethylation of 4-nitrobenzaldehyde still proceeds very well. We were able to $[^{18}\text{F}]$trifluoromethylate 4-nitrobenzaldehyde in a one-pot synthesis from $[^{18}\text{F}]$fluoroform that was synthesized on a commercial automated radiofluorination platform (Neptis module)$^{18}$ with RCYs of 58 $\pm$ 10% ($n = 3$, determined by HPLC, with regard to $[^{18}\text{F}]$fluoroform) (see ESI). The purification might be a crucial point of consideration when developing trifluoromethylation reactions for other substrates where Me$_3$SiCl, KHMDMS and/or toluene could contaminate the desired reaction.

In conclusion, we report the first synthesis and application of fluorine-18 labelled Ruppert–Prakash reagent. $[^{18}\text{F}]\text{Me}_3\text{SiCF}_3$ was synthesized with radiochemical yields of over 90% and radiochemical purities of > 95% (starting from $[^{18}\text{F}]$fluoroform) within 20 minutes. Reaction with benzaldehydes, acetoephones and benzophenones provided a complementary substrate scope to the previously reported method using $[^{18}\text{F}]$fluoroform,$^{25}$ enabling the synthesis of compounds that were not previously accessible. It should be noted that the relatively high amounts of precursor (200 μmol) require further optimization for routine application in PET tracer synthesis, and will be the focus of our future work. Since Ruppert–Prakash reagent is a widely used trifluoromethylation agent in organic synthesis, the development of $[^{18}\text{F}]\text{Me}_3\text{SiCF}_3$ will open doors to the development of many new $[^{18}\text{F}]$trifluoromethylation strategies.

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Conflicts of interest

There are no conflicts to declare.

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