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

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

Positron emission tomography (PET) is a molecular imaging technique that non-invasively visualizes biochemical processes *in vivo*.<sup>1–3</sup> This highly sensitive technique is increasingly used for the diagnosis of diseases, evaluation of the efficacy of a drug treatment, and drug discovery.<sup>3</sup> PET radiotracers incorporate positron-emitting radionuclides, the most frequently used nuclide being fluorine-18.<sup>4</sup> Fluorine-18 has very favourable characteristics for PET imaging, such as a convenient half-life (109.7 minutes) and a low positron energy ( $E_{\text{max}} = 0.634$  MeV), making it desirable for distribution to radiochemistry laboratories and imaging centres thereby enabling multi-centre clinical trials.<sup>5–7</sup>

There is a tremendous interest in the use of fluorine-19 in drug development.<sup>8,9</sup> This is reflected by recent Food and Drug Administration (FDA) drug approvals: in 2018 almost 1/3 of the new drugs approved contained one or more fluorine atoms.<sup>10</sup> The trifluoromethyl group is a prevalent motif as it can positively influence many characteristics of a given drug, *e.g.* metabolic stability, lipophilicity, and protein binding affinity.<sup>11–13</sup>

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  $[^{18}\text{F}]\text{trifluoromethylation}$  is well established and multiple strategies have been reported.<sup>14–18</sup> However, the reported methodologies mainly rely on  $[^{18}\text{F}]\text{fluoroform}$  as  $[^{18}\text{F}]\text{trifluoromethylation}$  agent. In organic chemistry, not many trifluoromethylation procedures report the use of  $[^{19}\text{F}]\text{fluoroform}$ , as alternative trifluoromethylation agents are generally preferred. One of the most applied nucleophilic trifluoromethylation agents is the Ruppert–Prakash reagent ( $\text{Me}_3\text{SiCF}_3$ ).<sup>9</sup> It was first described in 1984 by Ruppert *et al.*<sup>19</sup> and found its first application in 1989 by Prakash *et al.*<sup>20</sup> We therefore envisioned that developing a synthesis strategy for  $^{18}\text{F}$ -labelled Ruppert–Prakash reagent would be very useful for the translation of  $\text{CF}_3$  functionalization reactions that have been developed in fluorine-19 chemistry to radiofluorination reactions and PET tracer synthesis.<sup>21</sup>

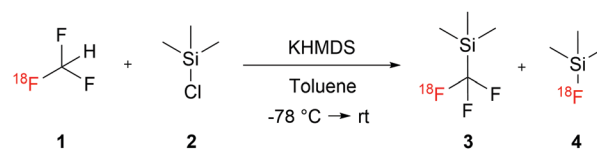
To synthesize  $[^{18}\text{F}]\text{Me}_3\text{SiCF}_3$  we followed a procedure reported by Prakash *et al.* that reacted fluoroform with trimethylsilyl chloride in presence of potassium hexamethyldisilazide (KHMDS) as the base in toluene.<sup>22</sup> Initial experiments using  $[^{18}\text{F}]\text{fluoroform}$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

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Scheme 1 Formation of  $[^{18}\text{F}]\text{Me}_3\text{SiCF}_3$  **3** and side product **4** from  $[^{18}\text{F}]\text{fluoroform}$  **1**.



The following reaction setup was used as a starting point: [ $^{18}\text{F}$ ]fluoroform **1**<sup>18</sup> was trapped in a solution of 0.6M  $\text{Me}_3\text{SiCl}$  **2** and 0.5M KHMDS in 650  $\mu\text{L}$  toluene at  $-80^\circ\text{C}$  (prepared 15 minutes before trapping [ $^{18}\text{F}$ ]fluoroform **1**, analogous to  $^{19}\text{F}$ -chemistry).<sup>22</sup> After complete distillation ( $\sim 3$  min) of [ $^{18}\text{F}$ ]fluoroform **1**, the trapping vial was either actively warmed up to  $20^\circ\text{C}$  or passively by removing it from the cooling bath.

[ $^{18}\text{F}$ ]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 [ $^{18}\text{F}$ ]fluoride). The conversion of [ $^{18}\text{F}$ ]fluoroform to [ $^{18}\text{F}$ ] $\text{Me}_3\text{SiCF}_3$  was temperature sensitive and active warming to  $20^\circ\text{C}$  resulted in complete conversion in less than 2.5 minutes, while passive warming required 15 minutes to reach completion at these reagent concentrations. Trapping at around  $-80^\circ\text{C}$  was crucial, since higher temperatures favoured the formation of the side product, [ $^{18}\text{F}$ ] $\text{Me}_3\text{SiF}$ .

Stirring of the precursor  $\text{Me}_3\text{SiCl}$  together with the base KHMDS before the trapping was not necessary for [ $^{18}\text{F}$ ] $\text{Me}_3\text{SiCF}_3$  formation, nor was stirring during the reaction. Increase of the precursor concentration as well as the total amounts of precursor, base and solvent helped to push the reaction towards completion and shorten the reaction time with passive warming up to 5 min (see Table 1).

After having established high-yielding reaction conditions for the formation of [ $^{18}\text{F}$ ] $\text{Me}_3\text{SiCF}_3$ , we turned our attention to the isolation of the product for its use in subsequent [ $^{18}\text{F}$ ]trifluoromethylation reactions. As  $\text{Me}_3\text{SiCF}_3$  has a low boiling point ( $54\text{--}55^\circ\text{C}$ )<sup>9</sup> we investigated purification by distillation. Different distillation temperatures and flow rates were tested. An overview of the conditions is given in Table 2. The distillation efficiency increased with higher flow (entry 1–7). At flow rates of  $30\text{ mL min}^{-1}$  and higher,  $>90\%$  of [ $^{18}\text{F}$ ] $\text{Me}_3\text{SiCF}_3$  could be distilled into THF. Exploring different distillation temperatures showed that temperatures  $\geq 70^\circ\text{C}$  led to the highest yields and at  $50^\circ\text{C}$  the co-distilled precursor precipitated in the tubing and led to blockage during distillation (see entry 6, 8–10). The radiochemical purity of the distilled [ $^{18}\text{F}$ ] $\text{Me}_3\text{SiCF}_3$  was determined and only minor impurities (0–2%) of [ $^{18}\text{F}$ ] $\text{Me}_3\text{SiF}$  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

**Table 1** Optimization of the [ $^{18}\text{F}$ ] $\text{Me}_3\text{SiCF}_3$  formation by variation of precursor and base

	$\text{Me}_3\text{SiCl}$ $\mu\text{mol}$	KHMDS $\mu\text{mol}$	Toluene $\mu\text{L}$	RCY $\text{CHF}_3^a$ %	RCP $\text{Me}_3\text{SiCF}_3^b$ %
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  $-80^\circ\text{C}$ , passive warmup to rt in 5 min.  
<sup>a</sup> Isolated yield, average  $\pm$  SD, decay corrected (dc),  $n = 3$ . <sup>b</sup> Determined by HPLC, average  $\pm$  SD, dc,  $n = 3$ .

**Table 2** Optimization of the [ $^{18}\text{F}$ ] $\text{Me}_3\text{SiCF}_3$  distillation

	Flow $\text{mL min}^{-1}$	Temp. $^\circ\text{C}$	RCY <sup>a</sup> $\text{Me}_3\text{SiCF}_3$ %
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  $\mu\text{mol}$   $\text{Me}_3\text{SiCl}$ , 500  $\mu\text{mol}$  KHMDS, 1 mL toluene.  
<sup>a</sup> Average  $\pm$  SD, dc,  $n = 3$ . <sup>b</sup> Distillation blocked in 2 out of 3 reactions.

suggesting that precursor  $\text{Me}_3\text{SiCl}$  (bp.  $57^\circ\text{C}$ )<sup>23</sup> and also solvent (toluene, bp.  $111^\circ\text{C}$ ) were co-distilled along with [ $^{18}\text{F}$ ] $\text{Me}_3\text{SiCF}_3$ . 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,  $\text{Me}_3\text{SiCl}$ , to avoid potential reaction with the subsequent [ $^{18}\text{F}$ ]trifluoromethylation reaction. It was found that the silica plus long Sep-Pak<sup>®</sup> was able to retain the precursor while almost all [ $^{18}\text{F}$ ] $\text{Me}_3\text{SiCF}_3$  passed the SPE. The RCY of [ $^{18}\text{F}$ ] $\text{Me}_3\text{SiCF}_3$  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, [ $^{18}\text{F}$ ] $\text{Me}_3\text{SiCF}_3$  was readily synthesized from [ $^{18}\text{F}$ ]fluoroform and obtained as a solution in THF with radiochemical yields of 85–95% and radiochemical purities of  $>95\%$ .

To explore the applicability of [ $^{18}\text{F}$ ] $\text{Me}_3\text{SiCF}_3$  as [ $^{18}\text{F}$ ]trifluoromethylation reagent, we demonstrated its use by reaction with aldehydes and ketones and adapted the procedure for  $^{19}\text{F}$ -reactions reported by Prakash *et al.*<sup>20</sup> In this procedure, the aldehyde or ketone was reacted with  $\text{Me}_3\text{SiCF}_3$  under addition of catalytic amounts of TBAF in THF. After hydrolysis with aqueous HCl, the desired trifluoromethylated product was obtained. 4-Nitrobenzaldehyde **6g** was selected as a model substrate and the following reaction parameters were varied: reaction time and temperature, quantities of TBAF and precursor as well as the scale of the reaction. [ $^{18}\text{F}$ ] $\text{Me}_3\text{SiCF}_3$  was found to readily react with 4-nitrobenzaldehyde: Reaction of an aliquot of the [ $^{18}\text{F}$ ] $\text{Me}_3\text{SiCF}_3$  in THF (300  $\mu\text{L}$ ) with 100  $\mu\text{mol}$  4-nitrobenzaldehyde **6g** and 200  $\mu\text{mol}$  TBAF for 5 minutes at room temperature in a total of 0.5 mL THF resulted in  $39 \pm 4\%$  RCY. [ $^{18}\text{F}$ ] $\text{CHF}_3$  was formed as a side product, likely resulting from reaction of [ $^{18}\text{F}$ ] $\text{Me}_3\text{SiCF}_3$  with traces of water present in THF or the TBAF solution. The 1M TBAF solution in THF was therefore stored in small batches (10–20 mL) over molecular sieves ( $3\text{\AA}$ ) to minimize the water content as much as possible.<sup>23</sup>

Variation of reaction time (2.5–20 min) and temperature ( $0\text{--}80^\circ\text{C}$ ) did not have an effect on the radiochemical yield under our conditions. The control of the TBAF concentration however was important since low concentrations ( $\leq 200\ \mu\text{M}$ ) resulted in incomplete release of [ $^{18}\text{F}$ ] $\text{CF}_3^-$  from [ $^{18}\text{F}$ ] $\text{Me}_3\text{SiCF}_3$  and therefore lower yields, whereas high concentrations ( $\geq 600\ \mu\text{M}$ ) were not



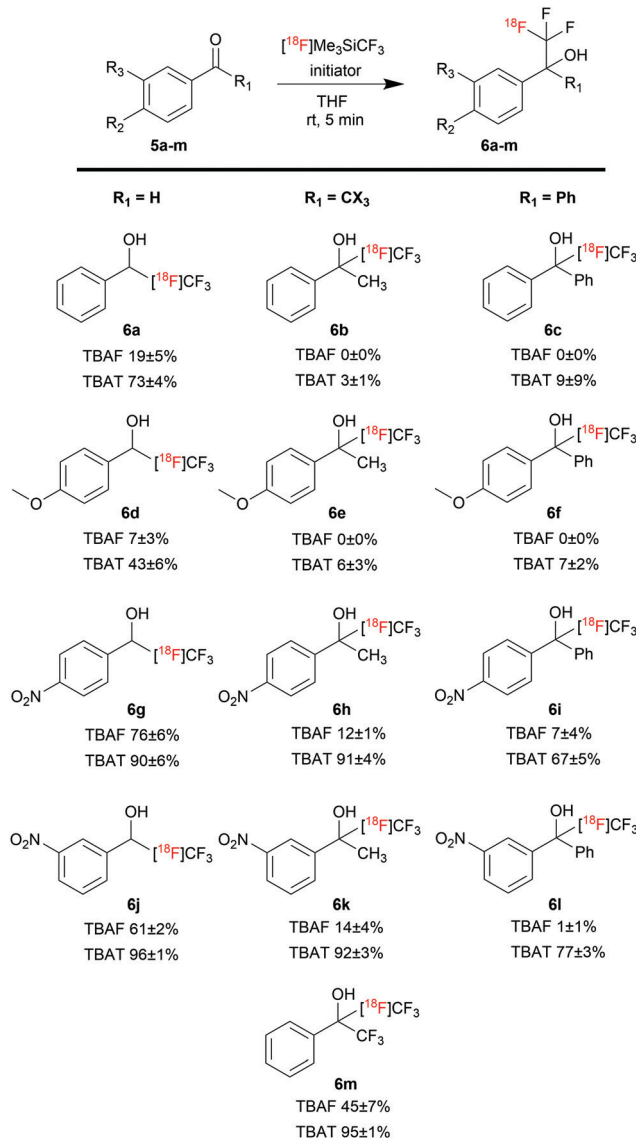
beneficial for the reaction, and is likely attributed to increasing amounts of water in the TBAF solution which is responsible for promoting  $[^{18}\text{F}]\text{CHF}_3$  formation.

Next, the effect of precursor concentration was investigated and showed that the higher the concentration of precursor, the higher the radiochemical yield ( $64 \pm 5\%$  RCY with 400  $\mu\text{mol}$  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  $\mu\text{L}$  and 125  $\mu\text{L}$  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  $\mu\text{L}$  THF, 200  $\mu\text{mol}$  precursor, 100  $\mu\text{mol}$  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-NO<sub>2</sub>-, 4-NO<sub>2</sub>-) 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:  $k(\text{benzaldehyde}) > k(\text{acetophenone}) > k(\text{benzophenone})$ ; and a competing reaction is the formation of fluoroform by reaction of  $\text{Me}_3\text{SiCF}_3$  with trace amounts of water.<sup>24</sup> The reaction with benzaldehydes is likely fast enough to outcompete the  $[^{18}\text{F}]\text{fluoroform}$  formation whereas with benzophenones  $[^{18}\text{F}]\text{fluoroform}$  formation predominates.

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.*<sup>24</sup> we chose two initiators, KOPh and TBAT. Reactions initiated by K<sup>+</sup>-containing initiators were expected to have a faster turnover rate than with  $\text{NH}_4^+$  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  $\geq 90\%$  RCY of the corresponding products. It is noteworthy that three of these compounds previously failed to label



Scheme 2 Reaction of  $[^{18}\text{F}]\text{Me}_3\text{SiCF}_3$  with aldehydes and ketones; Reaction conditions: 200  $\mu\text{mol}$  precursor, 250  $\mu\text{L}$  THF, 5 min, rt, 100  $\mu\text{mol}$  TBAF or 80  $\mu\text{mol}$  TBAT; RCY = average  $\pm$  SD,  $n = 3$ .

using  $[^{18}\text{F}]\text{fluoroform}$ .<sup>16</sup> Furthermore, the unsubstituted and methoxy-substituted benzaldehydes were  $[^{18}\text{F}]\text{trifluoromethylated}$  with decent to good yields ( $73 \pm 4\%$  and  $43 \pm 6\%$ , respectively). Unsubstituted and methoxy-substituted acetophenones and benzophenones still showed low yields ( $\leq 10\%$ ). 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  $[^{18}\text{F}]\text{trifluoromethylation}$  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  $[^{18}\text{F}]\text{fluoride}$ . 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  $\mu\text{mol}$ ) were required to fully



release  $\text{CF}_3^-$  from  $[\text{F}^{18}]\text{Me}_3\text{SiCF}_3$ , but the precursor amount could be kept at 200  $\mu\text{mol}$ . 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  $[\text{F}^{18}]\text{fluoride}$ ) was  $11 \pm 3\%$  (dc) and the molar activity was  $13 \pm 2 \text{ GBq}/\mu\text{mol}$  ( $n = 3$ ). The molar activity compares well to the  $A_m$  reported for  $[\text{F}^{18}]\text{fluoroform}^{18}$  at the same starting amount of  $[\text{F}^{18}]\text{fluoride}$ . The low overall yield is mainly due to losses during  $[\text{F}^{18}]\text{fluoroform}$  formation. Details on the reaction procedure and molar activity calculations can be found in the ESI.†

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

In conclusion, we report the first synthesis and application of fluorine-18 labelled Ruppert–Prakash reagent.  $[\text{F}^{18}]\text{Me}_3\text{SiCF}_3$  was synthesized with radiochemical yields of over 90% and radiochemical purities of  $> 95\%$  (starting from  $[\text{F}^{18}]\text{fluoroform}$ ) within 20 minutes. Reaction with benzaldehydes, acetophenones and benzophenones provided a complementary substrate scope to the previously reported method using  $[\text{F}^{18}]\text{fluoroform}$ ,<sup>25</sup> enabling the synthesis of compounds that were not previously accessible. It should be noted that the relatively high amounts of precursor (200  $\mu\text{mol}$ ) 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  $[\text{F}^{18}]\text{Me}_3\text{SiCF}_3$  will open doors to the development of many new  $[\text{F}^{18}]\text{trifluoromethylation}$  strategies.

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## Conflicts of interest

There are no conflicts to declare.

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