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Communications

# Flow trifluoromethylation of carbonyl compounds by Ruppert-Prakash reagent and its application for pharmaceuticals, Efavirenz and HSD-016

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**The Ruppert-Prakash reagent is the most powerful and well-documented reagent for trifluoromethylation. Despite its versatility, no general method exists for its use in a flow system. Here we report the first flow trifluoromethylation of carbonyl compounds and its utility for drug synthesis of Efavirenz and HSD-016, including preliminary results of enantioselective variants.**

## Introduction

The introduction of a trifluoromethyl group ($CF_3$) into a drug candidate can greatly affect its properties, in particular bioavailability due to the alteration of the lipophilic/lipophobic balance.[1] The improvement of the chemical and physical stability of drugs by trifluoromethylation to improve oxidative degradation has also been reported.[1] Among these cases, trifluoromethyl carbinols are very impressive.[2] The strong electron-withdrawing effect of $CF_3$ strengthens the hydrogen-bonding affinity of carbinols. Consequently, trifluoromethyl carbinols have been successfully employed as components of many pharmaceuticals and drug candidates,[2] including the NK-1 receptor antagonist CJ-17493, reversible monoamine oxidase. A inhibitor Befloxatone, anti-HIV drug Efavirenz,[3] and 11β-hydroxysteroid dehydrogenase type 1 inhibitor HSD-016[4] and HSD-621,[5] among others (Figures 1 and 2). One of the most powerful and efficient methods to prepare trifluoromethyl carbinols is the direct trifluoromethylation of carbonyl compounds by (trifluoromethyl)trimethylsilane ($CF_3SiMe_3$, or Ruppert-Prakash reagent).[6] This method was reported by Prakash and co-workers using a catalytic amount of tetrabutylammonium fluoride (TBAF) over 20 years ago.[7] Nowadays, not only fluoride catalysts but also a wide variety of catalytic systems, including Lewis bases and inorganic bases, are known for this transformation. The Ruppert-Prakash reagent is available in up to ton quantities from chemical companies such as TOSOH-F TEC INC[8] and P&M Invest,[9] and has become a versatile reagent for industrial use.

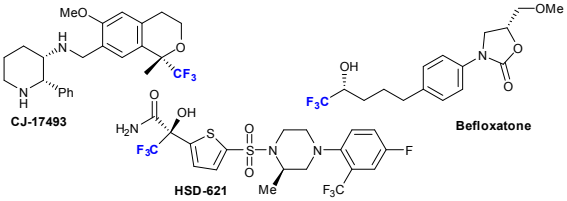


**Figure 1.** Examples of pharmaceuticals and drug candidates with trifluoromethyl carbinols.

The emergence of flow technology in organic synthesis, i.e., flow chemistry, has started to become a major contributor to process chemistry and scale-up in the pharmaceutical and chemical industries from the perspective of environmental compatibility.[10] Flow chemistry, in particular, micro-flow reactions, has several advantages over classical batch reaction systems including the speed of reactions, easy scale-up, safety, and a reduced size of the plant. Recent advances in synthetic flow chemical technology have achieved a wide variety of fundamental batch reactions for flow systems, including coupling, photo, and asymmetric reactions. Trifluoromethylation reactions have also been subjected to flow chemistry using conditions adapted from common batch conditions.[10d,11] Photochemical trifluoromethylation using $CF_3I$,[11a,b] $CF_3SO_2Na$,[11c,d] $CF_3SO_2Cl$,[11b,e] and a trifluoromethyl aromatic coupling reaction using $CF_3CO_2K$[11f] have been reported. However, there is no report on trifluoromethylation using the Ruppert-Prakash reagent, $CF_3SiMe_3$ in a flow system despite its wide versatility in industry. Herein, we disclose the trifluoromethylation of carbonyl compounds by $CF_3SiMe_3$ in a flow system for the first time. A wide variety of carbonyl compounds, including aryl ketones, alkyl ketones and aldehydes, were promptly converted into the corresponding trifluoromethyl carbinols with $CF_3SiMe_3$ in a flow system. A glass column packed with KOH/Celite was effective for flow trifluoromethylation eluted with DMF. The method enabled the flow synthesis of a key precursor of the anti-HIV drug Efavirenz, and a potent, selective, and efficacious 11β-HSD1

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inhibitor of HSD-016. Enantioselective trifluoromethylation in this flow system was also employed for the first time using a cinchona alkaloid/Celite-packed system (Figure 2).

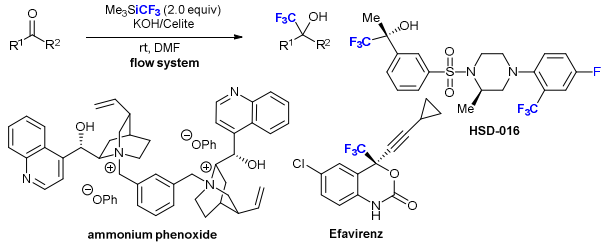



**Figure 2.** Flow trifluoromethylation of carbonyl compounds by $CF_3SiMe_3$ and its application to pharmaceuticals, Efavirenz and HSD-016, including preliminary attempts of an enantioselective reaction.

## Results and discussion

We devised a simple Pasteur pipette flow reactor packed with base/Celite for the trifluoromethylation of benzophenone (**1a**) with $CF_3SiMe_3$ (Figure 3).

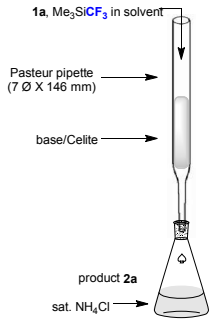
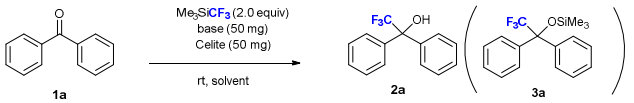



**Figure 3.** System diagram of flow reactor for trifluoromethylation.

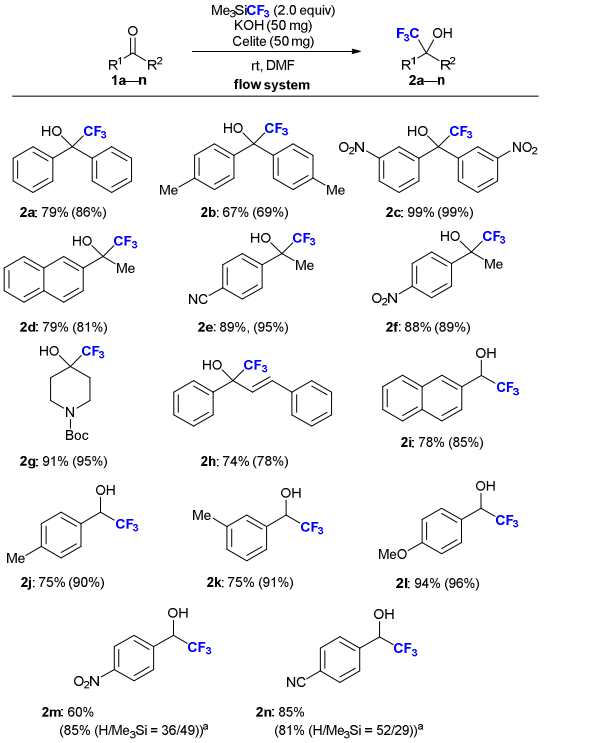
First, KOH was selected as a packed base in Celite (50 wt.%) for the flow-trifluoromethylation of **1a** by $Me_3SiCF_3$, since KOH is an inexpensive and good initiator of trifluoromethylation in a greener solvent, Solkane®365 in a common batch system.[12] However, the reaction did not take place in Solkane®365 under flow conditions (run 1, Table 1). Toluene, THF and dichloromethane were also not suitable (runs 2—4), while DMSO showed a good result of 48%, yielding trifluoromethyl carbinol **2a** (run 5). We thus attempted the reaction in a polar aprotic solvent, DMF, and **2a** was obtained in 95% yield (run 6). The base was next screened in DMF (runs 7—9). The reaction proceeded smoothly in DMF with PhOK, LiOAc and CsF, but the yields were not higher than when KOH was used. Interestingly, **2a** was solely obtained by potassium salts, KOH and PhOK (runs 6 and 7), while a mixture of **2a** and its trimethylsilyl ether **3a** was observed using lithium and cesium salts (runs 8 and 9). The formation of **3a** suggested that a catalytic process was partially involved in the reaction. We thus reduced the amount of KOH in Celite for flow trifluoromethylation (runs 10—11). As expected, the formation of **3a** was dependent upon the amount of KOH, i.e., as the amount of KOH decreased, the amount of **3a** increased, while the total yields of **2a** and **3a** remained as the majority.

Table 1. Optimization of base and solvent for trifluoromethylation of **1a**




| Run | base | solvent | **2a** Yield (%)[a] |
|---|---|---|---|
| 1 | KOH | Solkane®365 | 0 |
| 2 | KOH | toluene | 0 |
| 3 | KOH | THF | 0 |
| 4 | KOH | $CH_2Cl_2$ | 0 |
| 5 | KOH | DMSO | 48 |
| 6 | KOH | DMF | 95 |
| 7 | PhOK | DMF | 68 |
| 8 | LiOAc | DMF | 77[b] (**2a**/**3a**=78/22) |
| 9 | CsF | DMF | 75[b] (**2a**/**3a**=72/28) |
| 10 | KOH[c] | DMF | 89[b] (**2a**/**3a**=94/ 6) |
| 11 | KOH[d] | DMF | 80[b] (**2a**/**3a**=59/41) |

[a]Determined by $^{19}$F-NMR using a crude mixture with trifluorotoluene as the internal standard. [b]Total yields of **2a** and **3a**. The ratios of **2a**/**3a** are indicated in parentheses. [c]20 mg of KOH was used. [d]5 mg of KOH was used.




**Scheme 1.** Trifluoromethylation of carbonyl compounds **1** by the flow reaction. The values indicate isolated yield after desilylation and the values in parentheses are $^{19}$F-NMR yields. [a]LiOAc was used instead of KOH.

With a suitable condition in hand (run 6, Table 1), the substrate scope for trifluoromethylation in the flow system was explored (Scheme 1). Diarylketones **1a—c** were nicely converted to the corresponding α-trifluoromethyl alcohols **2a—c** in good to high isolated yields (67%—99%). Aryl methyl ketones **1d—f** with an enolizable proton and cyclic aliphatic ketone **1g** were also accepted in the flow system to provide the corresponding trifluoromethylated carbinols **2d—g** in up to

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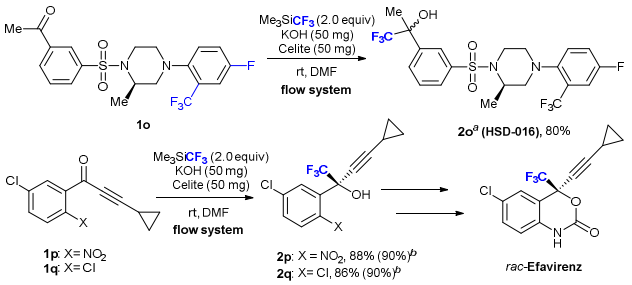
91% isolated yields. Chalcone (**1h**) was transformed exclusively into 1,2-trifluoromethyalted adduct **2h** in 74% yield. We next examined the reaction of aldehydes **1i—n**. A variety of substituents at their aromatic ring of aldehydes such as methyl, and methoxy, nitro cyano were well tolerated to provide the corresponding α-trifluoromethyl alcohols **2i—n** in good to high yields, with up to 94% isolated yield. Although the aldehydes **1m—n** having electron-withdrawing $NO_2$ and $CF_3$ groups decomposed in KOH, this was overcome by using LiOAc to provide **2** in 60–81% yield as a mixture with its silyl ethers **3m—n**.

We next focused on the synthesis of pharmaceuticals using our flow trifluoromethylation (Scheme 2). Flow reactions have long been used for the preparation of simple materials in the chemical industry, while the technology has just recently gained special attention by the pharmaceutical industry to realize the on-demand synthesis of drugs.[10e,f, 13] In this context, we were interested in the flow synthesis of a potent and efficacious 11β-HSD1 inhibitor, HSD-016.[4] HSD-016 was developed by Pfizer and shows attractive pharmaceutical profiles in human studies. Although HSD-016 can be prepared in multigram quantities in batch synthesis, the flow synthesis of HSD-016 has not been examined. We found that our flow trifluoromethylation was well-adapted for the synthesis of HSD-016 from corresponding ketone **1o** by $Me_3SiCF_3$ under our flow-system to furnish **2o** (HSD-016) in 80% yield as a mixture of diastereoisomers. The next target was Efavirenz.[3] Efavirenz is an anti-HIV drug, and its production is carried out in a batch system by Merck[14] and Lonza,[15] and a flow protocol for the synthesis of Efavirenz is the next challenge.[16] We thus examined the flow trifluoromethylation of 1-(5-chloro-2-nitrophenyl)-3-cyclopropylprop-2-yn-1-one (**1p**) with $Me_3SiCF_3$ through our KOH/Celite packed reactor. As expected, the reaction proceeded rapidly to provide a desired trifluoromethylated carbinol **2p** in 88% yield. 1-(2,5-Dichlorophenyl)-3-cyclopropylprop-2-yn-1-one (**1q**) was also nicely converted into trifluoromethylated adduct **2q** in 86% yield in the flow system. Both trifluoromethylated carbinols **2p**[17] and **2q**[15] are key intermediates for the synthesis of *rac*-Efavirenz.




**Scheme 2.** Application of flow trifluoromethylation for the preparation of pharmaceuticals, HSD-016 and Efavirenz. [a]A mixture of diastereomers was obtained (the ratio was not determined.) [b] $^{19}$F-NMR yield.

To show the potential of large-scale synthesis of trifluoromethyl carbinols, the flow trifluoromethylation of **1p** was also successfully performed with a microflow reactor under similar conditions (KOH/Celite, 50% wt, glass packed column) providing Efavirenz intermediate **2p** in high yield of 91% (Figure 4). Hence, our method can be easily extended to the continuous-flow process which realizes the large scale preparation of corresponding trifluoromethyl carbinols.

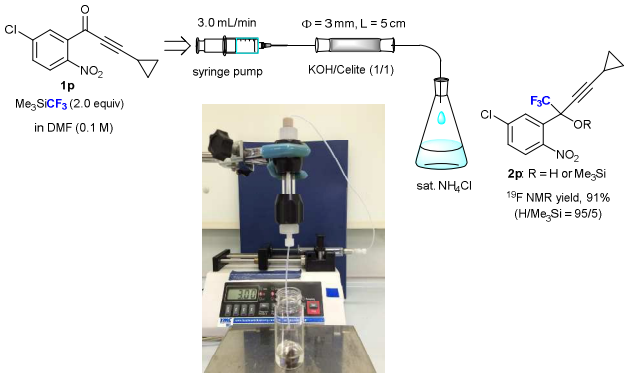



**Figure 4**. System diagram of microflow reactor for trifluoromethylation of **1p** to **2p**.

Finally, enantioselective trifluoromethylation was attempted under the flow system (Scheme 3). We devised a cinchona alkaloid/Celite packed Pasteur pipette. DMF was unsuitable for this flow system due to the high solubility of cinchona alkaloids packed with Celite in a column. We first attempted the enantioselective trifluoromethylation of ketones **1** with $Me_3SiCF_3$ using our previously reported batch system, the combination of ammonium bromide of cinchona alkaloids and tetramethylammonium fluoride (TMAF),[17,18] however, the method also failed. After many trials, we found that the system consisting of cinchona alkaloid ammonium phenoxides packed with Celite and eluted with $CH_2Cl_2$/toluene (1/1) was useful for this transformation. Namely, a mixture of 2-naphthaldehyde (**1i**) and $Me_3SiCF_3$ in $CH_2Cl_2$/toluene (1/1) was directly eluted through the cinchona alkaloid catalyst A[18a]/Celite pack to afford **2i** in 52% yield with 36% ee. The enantioselective flow trifluoromethylation of Efavirenz was also successful through a cinchona alkaloid catalyst B[17a]/Celite pack from alkynyl ketone **1p** and **1q** with $Me_3SiCF_3$ to afford **2p** in 41% yield with 36% ee, and **2q** in 47% yield with 30% ee, respectively. Enantioenriched **2q** and **2p** can be converted to Efavirenz by methods described in the literature. These are the first examples of enantioselective trifluoromethylation in a flow system.

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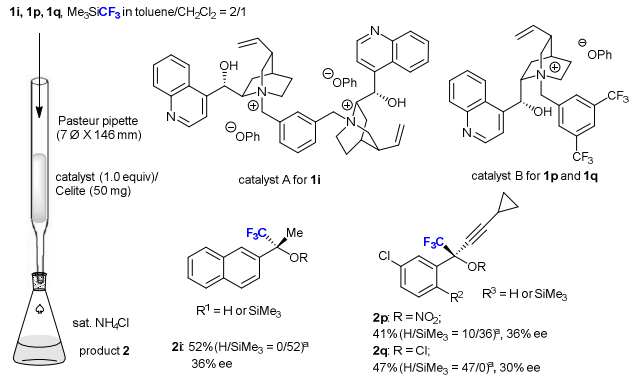


**Scheme 3.** Enantioselective trifluoromethylation of **1i**, **1p** and **1q** by a flow system. [a]Mixtures (R=H and $SiMe_3$) were obtained, and ratios were determined by $^{19}F$-NMR.

## Conclusions

We have developed a flow method for the trifluoromethylation of carbonyl compounds by the Ruppert-Prakash reagent. The KOH/Celite packed column is easy to set up and trifluoromethylation can be performed under air. The reaction is rapid and can be applied to the synthesis of pharmaceuticals such as Efavirenz and HSD-016. A microflow reactor is also useful for this flow trifluoromethylation. We also devised a cinchona alkaloid ammonium phenoxides/Celite packed column and disclose preliminary results of enantioselective flow trifluoromethylation. Improvement of enantioselectivity in the flow system is currently underway.

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