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Organocatalyzed Trifluoromethylation of Ketones and Sulfonyl Fluorides by Fluoroform under a Superbase System

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Fluoroform (HCF_3, HFC-23) is a side product in the manufacture of polytetrafluoroethylene (Teflon). Despite its attractive properties, taming HCF_3 for trifluoromethylation is quite problematic owing to its low acidity and the lability of the naked trifluoromethyl carbanion generated from HCF_3. Herein we report the organic-superbase-catalyzed trifluoromethylation of ketones and arylsulfonyl fluorides by HCF_3. The reactions were carried out by using a newly developed "superbase organocatalyst system" consisting of catalytic amounts of P_4-*t*Bu and $N(SiMe_3)_3$. A series of aryl and alkyl ketones were converted into the corresponding α-trifluoromethyl carbinols in good yields under the organocatalysis conditions in THF. The superbase organocatalytic system can also be applied to the trifluoromethylation of arylsulfonyl fluorides for biologically important aryl triflones in THF or DMF in good yields. Protonated P_4-*t*Bu, $H[P_4\text{-}tBu]^+$, is suggested to be crucial for the catalytic process. This new catalytic methodology using HCF_3 is expected to expand the range of synthetic applications of trifluoromethylation.

Organofluorine compounds have gained much attention in the research and development of pharmaceuticals, agrochemicals, and advanced materials.[1] In particular, trifluoromethyl-containing organic molecules have become primary synthesis targets in recent years given their impressive successful history in bringing new drugs to the market.[1c,e,2] Methods for the introduction of CF_3 groups into target substrates (i.e., trifluoromethylation), have therefore been actively researched worldwide.[3] A popular and convenient method for trifluoromethylation is the use of (trifluoromethyl)trimethylsilane (CF_3SiMe_3, the Ruppert–Prakash reagent).[4] The Ruppert–Prakash reagent is used in a variety of nucleophilic trifluoromethylations, and its use has been expanded to the radical or oxidative trifluoromethylation reaction. Despite its wide utility, the Ruppert–Prakash reagent is less ideal due to the expense of its preparation and the fact that it is mostly prepared from ozone-depleting bromotrifluoromethane.[5] Therefore, inexpensive and environmentally friendly alternatives to the Ruppert–Prakash reagent have long been required.

Fluoroform (HCF_3, HFC-23) is a side product in the manufacture of polytetrafluoroethylene (Teflon). In view of its attractive properties (ozone friendly, nontoxic, and inexpensive), it is not surprising that there have been many attempts to use HCF_3 for trifluoromethylation reactions.[6] However, taming HCF_3 is quite problematic due to its low acidity ($pK_a = 27$ in H_2O) and the lability of the naked trifluoromethyl carbanion generated from HCF_3.[7] During the last five years, the chemistry of HCF_3 has made significant progress with the use of organometallics as represented by Cu (Grushin), K (Prakash), and others.[8] In late 2012, we reported that a sterically demanding organic superbase, 1-*tert*-butyl-4,4,4-tris(dimethylamino)-2,2-bis[tris(dimethylamino)phosphoranylidenamino]-$2^{\lambda},5,4^{\lambda}$,5-catenadi(phosphazene) (P_4-*t*Bu) effectively generates a trifluoromethyl carbanion from HCF_3 without decomposition to difluorocarbene that undergoes successful addition to aromatic aldehydes, ketones, and disulfides.[9] Our method does not require organometallics, and the corresponding trifluoromethylation products are obtained in good to high yields. However, this reaction needs a stoichiometric amount of P_4-*t*Bu. The development of efficient organocatalytic processes for HCF_3 trifluoromethylation is considered to be one of the greatest challenges in fluorine chemistry. The seminal work by Langlois and co-workers[6e] on trifluoromethylation with HCF_3 clearly illustrates the validity of this approach. Herein we disclose a catalytic version of this HCF_3 trifluoromethylation. The key to this catalytic reaction is the combination of organic superbases. A wide variety of diaryl, aryl-alkyl, and dialkyl ketones **1** are nicely trifluoromethylated by HCF_3 under a newly developed "superbase-organocatalysis" of P_4-*t*Bu/$N(SiMe_3)_3$ in THF to provide a wide range of trifluoromethylated carbinols **2**. This superbase organocatalytic system consisting of P_4-*t*Bu and $N(SiMe_3)_3$ also realized a catalytic trifluoromethylation of arylsulfonyl fluorides **3** with HCF_3 in THF or DMF to furnish biologically important fluorinated compounds of aryltriflones **4** in good yields (Scheme 1). Protonated P_4-*t*Bu ($H[P_4\text{-}tBu]^+$) is suggested to be crucial for the catalytic process.

We initiated our investigations with the reaction of benzophenone (**1a**) and HCF_3 (Table 1). First, trifluoromethylation of **1a** in THF took place under our previous stoichiometric conditions,[9] but with a catalytic amount of P_4-*t*Bu (30 mol%); owing to the superbase character of P_4-*t*Bu, this trifluoromethylation

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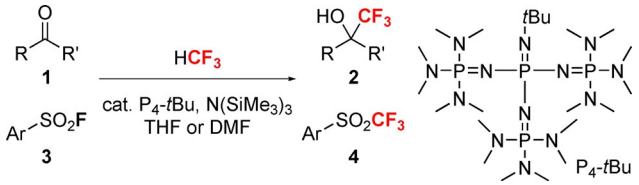
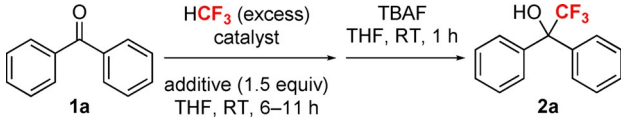


Scheme 1. Catalytic trifluoromethylation of ketones **1** and sulfonyl fluorides **3** by HCF_3 under the organocatalytic superbase system, P_4-*t*Bu/$N(SiMe_3)_3$.

Table 1. Optimization of catalyst, additive, and concentration for the trifluoromethylation of benzophenone (**1a**).



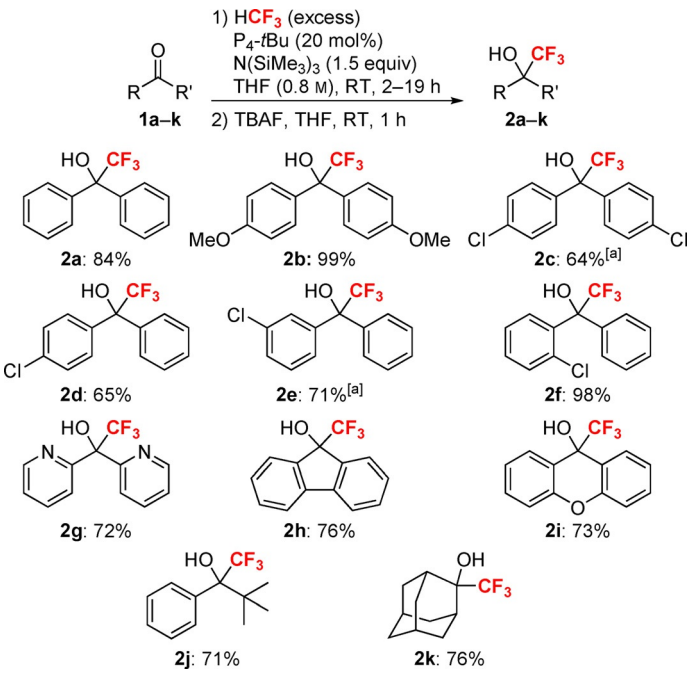
Run	Catalyst (mol%)	Additive	THF [M]	Yield [%][a]
1	P_4-*t*Bu (30)	–	0.4	20
2	P_4-*t*Bu (30)	$Me_3SiC{\equiv}CMe$	0.4	21
3	P_4-*t*Bu (30)	Me_3SiNMe_2	0.4	14
4	P_4-*t*Bu (30)	$N(SiMe_3)_3$	0.4	71
5	P_4-*t*Bu (20)	$N(SiMe_3)_3$	0.4	34
6	P_4-*t*Bu (20)	$N(SiMe_3)_3$	0.8	84
7	P_4-*t*Bu (10)	$N(SiMe_3)_3$	0.8	24
8	P_4-*t*Bu (10)	$N(SiMe_3)_3$	2.0	34
9[b]	P_4-*t*Bu (20)	$N(SiMe_3)_3$	0.8	79
10	P_2-Et (30)	$N(SiMe_3)_3$	0.8	NR
11	CsF (30)	$N(SiMe_3)_3$	0.8	NR
12	KHMDS (30)	$N(SiMe_3)_3$	0.8	NR
13	*t*BuOK (30)	$N(SiMe_3)_3$	0.8	NR

[a] Yield of isolated product; NR: no reaction. [b] 5.0 equiv of HCF_3 was used.

was difficult to achieve via catalytic reaction, and product **2a** resulting from the amount of P_4-*t*Bu used was obtained in 20% yield (run 1). To effect catalytic turnover, the removal of a proton from the protonated superbase H[P_4-*t*Bu]$^+$, or re-activation of H[P_4-*t*Bu]$^+$ in some manner, is crucial. Kondo and co-workers reported a deprotonating functionalization of heteroaromatic molecules with carbonyl compounds using an organic superbase catalyst.[10] After screening silylated additives, trimethylsilylpropyne ($Me_3SiC{\equiv}CMe$) was found to be the key to the catalytic cycle. We therefore examined our trifluoromethylation reaction using $Me_3SiC{\equiv}CMe$ (1.5 equiv) as an additive. However, no improvement was observed, and **2a** was obtained in 21% yield (run 2).[11] We further investigated various silylated additives to activate the catalyst. Whereas *N*-(trimethylsilyl)dimethylamine (Me_2NSiMe_3) was not useful (14% yield, run 3), tris(trimethylsilyl)amine ($N(SiMe_3)_3$) was found to effectively activate the catalyst, providing **2a** in 71% yield (run 4). Upon decreasing the amount of catalyst to 20 mol%, the yield decreased to 34% (run 5), but a higher concentration of the reaction produced a good result, with 84% yield (run 6). In an attempt with P_4-*t*Bu at 10 mol%, the yields of **2a** decreased considerably, regardless of their concentration (runs 7 and 8). The amount of HCF_3 could be decreased to 5.0 equiv without a major loss of chemical yield, furnishing **2a** at 79% (run 9). In all cases, silylated trifluoromethylated carbinol was detected in the reaction before treatment with tetra-*n*-butylammonium fluoride (TBAF). The inclusion of another phosphazene base, 1-ethyl-2,2,4,4,4-pentakis(dimethylamino)-2$^{\lambda}$5,4$^{\lambda}$5-catenadi(phosphazene) (P_2-Et) or other bases such as CsF, *t*BuOK, or KHMDS in the presence of $N(SiMe_3)_3$ under similar reaction conditions did not lead to an effective transformation (runs 10–13). Run 11 is of interest because CsF was previously reported to be an active base toward HCF_3 with $N(SiMe_3)_3$, but only in DMF.[6e,12]

With suitable conditions in hand, the scope of trifluoromethylation of ketones **1** using HCF_3 was explored with a variety of substrates selected in order to establish the generality of the process (Scheme 2). Aromatic rings substituted with either electron-donating or -withdrawing substituents, such as methoxy and chloro, were tolerated independent of the substituted positions on the benzene ring (**2b** and **2c**–**f**). A heteroaromatic di(2-pyridyl) ketone was compatible with the same reaction conditions to provide **2g** in 72% yield. The corresponding trifluoromethylated carbinols (**2h** and **2i**) from cyclic ketones were obtained in good isolated yields. Furthermore, the alkyl-substituted ketones produced the desired products **2j** and **2k** in 71–76% yield.

Figure 1 shows a proposed catalytic cycle for the trifluoromethylation of **1** with HCF_3. As mentioned in our previous report,[9] the CF_3 adducts $RCCF_3(O^-)R'$ are initially formed as ion pairs with H[P_4-*t*Bu]$^+$. Next, delivery of the trimethylsilyl group of $N(SiMe_3)_3$ to the alkoxides $RCCF_3(O^-)R'$ proceeds, providing



Scheme 2. Trifluoromethylation of ketones **1** by HCF_3. Yield values shown are for isolated product. [a] P_4-*t*Bu used at 30 mol%.

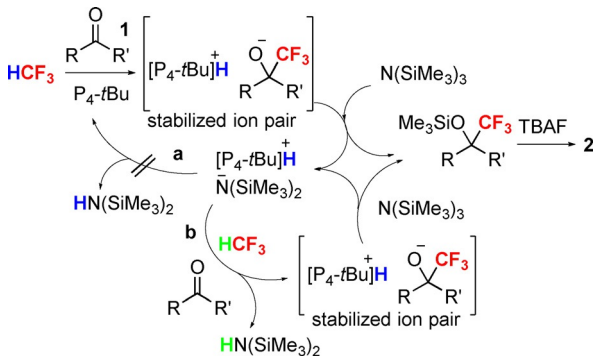


Figure 1. Proposed catalytic process for the trifluoromethylation of **1** with HCF_3 under the P_4-*t*Bu/$N(SiMe_3)_3$ system.

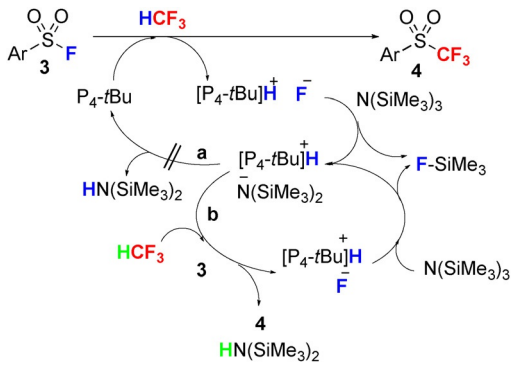


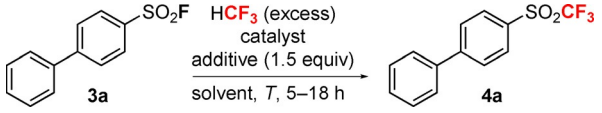
Figure 2. Proposed catalytic process for the trifluoromethylation of **3** with HCF_3 to aryl triflones **4** under the P_4-*t*Bu/$N(SiMe_3)_3$ system.

trimethylsilyl ethers accompanied with the same amount of $[N(SiMe_3)_2]^-$. The $[N(SiMe_3)_2]^-$ species might extract a proton from $H[P_4\text{-}tBu]^+$ to activate P_4-*t*Bu for a catalytic process (route a). However, activation of P_4-*t*Bu by deprotonation of $H[P_4\text{-}tBu]^+$ with $[N(SiMe_3)_2]^-$ should be difficult, given their basicity (P_4-*t*Bu pK_{BH}: 28.0 (THF), 30.3 (DMSO); $HN(SiMe_3)_2$ pK_a = 25.8 (THF), 26 (DMSO)).[13] Another possibility is that $[N(SiMe_3)_2]^-$ directly deprotonates HCF_3, allowing a shunt catalytic cycle to provide the ion pairs of $RCCF3(O^-)R'$ and $H[P_4\text{-}tBu]^+$ (route b). The alkoxides $RCCF_3(O^-)R'$ should attack the silyl group of $N(SiMe_3)_3$ to furnish products of trimethylsilyl ethers accompanied by the same amount of $[N(SiMe_3)_2]^-$ as an ion pair with $H[P_4\text{-}tBu]^+$. Hence, $H[P_4\text{-}tBu]^+$ should play an important role in this catalytic cycle. The $H[P_4\text{-}tBu]^+$ species forms a stabilized ion pair with the alkoxides $RCCF_3(O^-)R'$. This stabilization should be a driving force for the catalytic cycle mediated by $[N(SiMe_3)_2]^-$, because no reaction was observed with the use of CsF instead of P_4-*t*Bu (Table 1, run 11).

We next extended the organocatalyzed trifluoromethylation reaction using HCF_3 for the synthesis of aryl triflones, i.e., trifluoromethyl aryl sulfones.[14] Aryl triflones are recognized as important structural units in bioactive molecules, chiral catalysts, and functional materials[15] because of the unique properties of the SO_2CF_3 moieties, such as high electronegativity (σ_m = 0.96) with moderate lipophilicity (π = 0.55).[16] To generate an optimal catalytic process, a new working hypothesis for the transformation should first be considered, as shown in Figure 2. The key to this transformation is the use of aryl fluorides **3**. Specifically, after the initial formation of aryl triflones **4** from **3** and HCF_3 with P_4-*t*Bu, $H[P_4\text{-}tBu]^+$ is formed as an ion pair with the fluoride ion, F^-, which spontaneously attacks the silicon atom of $N(SiMe_3)_3$ to form F-$SiMe_3$ and $[N(SiMe_3)_2]^-$. Regeneration of P_4-*t*Bu by $[N(SiMe_3)_2]^-$ should be difficult (route a); thus $[N(SiMe_3)_2]^-$ should remove the proton of HCF_3 with the help of $H[P_4\text{-}tBu]^+$ to regenerate the ion pair of $H[P_4\text{-}tBu]^+$ and F^-. $H[P_4\text{-}tBu]^+$ acts directly as a true catalyst on the reaction cycle (route b), as predicted for the trifluoromethylation of ketones in Figure 1.

4-Biphenylsulfonyl fluoride (**3a**) was selected as a model substrate for the trifluoromethylation, and the effect of bases and their amounts, additives, solvents, and temperature on the product formation of **4a** was examined (Table 2). The use of

Table 2. Optimization of catalysts, additives, solvents, and temperature for the trifluoromethylation of 4-biphenylsulfonyl fluoride (**3a**) with HCF_3.



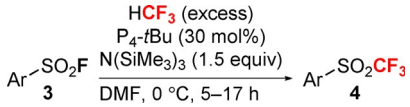
Run	Catalyst (mol%)	Additive	Solvent	*T* [°C]	Yield [%][a]
1	P_4-*t*Bu (30)	$N(SiMe_3)_3$	THF	RT	61
2	P_4-*t*Bu (30)	$N(SiMe_3)_3$	DMF	RT	60
3	P_4-*t*Bu (30)	$Me_3SiC{\equiv}CMe$	DMF	RT	45
4	P_4-*t*Bu (30)	Me_3SiNMe_2	DMF	RT	23
5	P_4-*t*Bu (30)	$N(SiMe_3)_3$	THF	0	72
6	P_4-*t*Bu (30)	$N(SiMe_3)_3$	DMF	0	84
7	P_4-*t*Bu (30)	$N(SiMe_3)_3$	DMF	−20	9
8[b]	P_4-*t*Bu (30)	$N(SiMe_3)_3$	DMF	0	70
9	P_4-*t*Bu (20)	$N(SiMe_3)_3$	DMF	0	17
10	P_4-*t*Bu (10)	$N(SiMe_3)_3$	DMF	0	14
11	P_4-*t*Bu (10)	$N(SiMe_3)_3$	DMF	RT	7
12	P_1-*t*Bu (30)	$N(SiMe_3)_3$	DMF	RT	NR
13	CsF (30)	$N(SiMe_3)_3$	DMF	RT	NR
14	KHMDS (30)	$N(SiMe_3)_3$	DMF	RT	NR
15	*t*BuOK (30)	$N(SiMe_3)_3$	DMF	RT	NR

[a] Yield of isolated product; NR: no reaction. [b] 5.0 equiv of HCF_3 was used.

the same superbase and additive, P_4-*t*Bu (30 mol%) and $N(SiMe_3)_3$ (1.5 equiv), with excess HCF_3 gave good yields in the trifluoromethylation of **3a** in THF (61%, run 1) or DMF (60%, run 2) at RT, and higher yields were obtained in THF (72%) and in DMF (84%) at 0 °C (runs 5 and 6). The product was obtained in 70% yield under the best conditions, but with 5 equiv of HCF_3 (run 8). Other bases, including a strong alkoxide of *t*BuOK, were not effective (runs 12–15). The results (runs 13–15) again suggested that $H[P_4\text{-}tBu]^+$ is crucial to the catalytic cycle proposed in route b (Figure 2).

The scope of trifluoromethylation of sulfonyl fluoride **3** with HCF_3 under the best conditions is given in Table 3. Good to high yields of aryl triflones **4** were obtained under these conditions almost independent of the electronic nature of substitution on the benzene ring (chloro, bromo, iodo, isopropyl, *tert*-butyl) as well as their positions (*ortho*, *meta*, *para*) (entries 2–8). The sterically demanding naphthyl-substituted alkynes **3i**

Table 3. Trifluoromethylation of sulfonyl fluorides **3** with HCF_3.



Run	Ar	Product **4**	Yield [%][a]
1	4-PhC_6H_4	**4a**	84 (72)[b]
2[c]	4-ClC_6H_4	**4b**	57
3	2-BrC_6H_4	**4c**	62
4[d]	3-BrC_6H_4	**4d**	50
5[e]	4-BrC_6H_4	**4e**	79
6[e]	4-IC_6H_4	**4f**	79
7[c,e]	4-*i*PrC_6H_4	**4g**	54
8	4-*t*BuC_6H_4	**4h**	78
9[e,f]	1-naphthyl	**4i**	78
10[g]	2-naphthyl	**4j**	60

[a] Yield of isolated product. [b] Yield for the reaction having been performed in THF. [c] The reaction was carried out at −10 °C. [d] The reaction was carried out at 5 °C. [e] 20 mol% of P_4-*t*Bu was used. [f] The reaction was carried out at room temperature. [g] 40 mol% of P_4-*t*Bu was used.

and **3j** also afforded the corresponding products **4i** and **4j** in 60–78% yield (entries 9 and 10).

In conclusion, we have developed an organic-superbase-catalyzed trifluoromethylation of ketones and arylsulfonyl fluorides using fluoroform (HCF_3), a catalytic amount of P_4-*t*Bu, and $N(SiMe_3)_3$. Wide substrate generalities were observed in good yields for both ketones and arylsulfonyl fluorides. The most innovative aspect of the work is the use of $H[P_4\text{-}tBu]^+$ as the cation for stabilization of the presumed intermediate ion pair. Conclusive mechanistic/stability studies of this ion pair would be potentially useful for the application of other types of transformation. The role of protonated P_4-*t*Bu ($H[P_4\text{-}tBu]^+$) should be investigated in detail with the help of molecular calculations. Extending trifluoromethylation with HCF_3 to other substrates and asymmetric trifluoromethylation reactions under superbase catalysis are two subsequent challenges that we are currently exploring.

Experimental Section

Synthesis of 2: A Schlenk tube containing ketones **1** (0.20 mmol) and tris(trimethylsilyl)amine (70.1 mg, 0.30 mmol, 1.5 equiv) in THF was charged with HCF_3 by cooling in liquid nitrogen under vacuum. This tube was warmed to room temperature, and P_4-*t*Bu (50.0 μL, 0.8 M in hexane, 0.040 mmol, 20 mol%) was added. HCF_3 was then bubbled for 1 min at the same temperature. After stirring the reaction mixture at the same temperature for 2–19 h and monitoring by TLC analysis, it was quenched with saturated aqueous NH_4Cl (5 mL). The aqueous layer was extracted with CH_2Cl_2,(20 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The trimethylsilyl ether was treated with *n*Bu_4NF (62.6 mg, 0.24 mmol, 1.2 equiv) in THF (2.0 mL) at room temperature for 1 h. The resulting mixture was concentrated under reduced pressure and purified by column chromatography on silica gel to give α-trifluoromethyl alcohol **2**.

Synthesis of 4: A Schlenk tube containing sulfonyl fluorides **3** (0.10 mmol) and tris(trimethylsilyl)amine (35.0 mg, 0.15 mmol, 1.5 equiv) in DMF was charged with HCF_3 by cooling in liquid nitrogen under vacuum. This tube was warmed to 0 °C, and P_4-*t*Bu (37.5 μL, 0.8 M in hexane, 0.030 mmol, 30 mol%) was added. HCF_3 was then bubbled for 1 min at the same temperature. After stirring the reaction mixture at the same temperature for 5–17 h and monitoring by TLC analysis, it was quenched with saturated aqueous NH_4Cl (5 mL). The aqueous layer was extracted with Et_2O,(20 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give triflones **4**.

Acknowledgements

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Keywords: fluoroform · organocatalysis · phosphazene base · triflone · trifluoromethylation

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