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Fluoroform: an Efficient Precursor for the Trifluoromethylation of Aldehydes

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Abstract—Fluoroform is shown to be an efficient trifluoromethylating agent when deprotonated using standard reagents in DMF. The important role of DMF as a solvent but also as a reactant was demonstrated.

Introduction

The trifluoromethyl group is a highly important substituent in organic chemistry. Its powerful electron-withdrawing ability and small size lead to significant changes in the chemistry of substituted compounds when compared with non-fluorinated analogues. Effects reported include stabilisation of small rings,[1] as well as changes in both regioselectivity[2] and reactivity.[3] Many performance chemicals benefit from the presence of a CF_3 group. The high lipophilicity of the group gives active pharmaceutical and agrochemical compounds with improved transport characteristics in vivo and facilitates lower dosage rates. Substituted polymers that show enhanced stability, resistance to chemicals, and flame retardance have been made from trifluoromethylated precursors.[4] The light and wash fastness of dyes can be improved by the presence of CF_3.[5]

Classical methods for the synthesis of trifluoromethylated aromatics come from the beginning of this century. Indeed, Swarts discovered that antimony trifluoride could be used to convert benzotrichloride into benzotrifluoride.[6] Later, it was found that hydrogen fluoride could also fluorinate benzotrichloride to yield the trifluoride.[7] These methods are still used today, but have a number of disadvantages relating to the harsh conditions they impose and their toxicity. These facts have led to the development of milder alternative[8] reagents and particularly the synthesis of trifluoromethyl metals.[9] In Scheme 1 the different approaches to these trifluoromethyl organometallic complexes **1** are summarised.

Iodotrifluoromethane CF_3I **2** is the most common trifluoromethylating agent.[8,9] Most trifluoromethylmetals are available under mild conditions from **2** by formal insertion of a metal into the carbon–iodine bond.[8,9] On the other hand, bromotrifluoromethane **3** has a lower reactivity than that of **2**, although it can insert many metals under harsher conditions.[8,9] CF_2Br_2 **4**, introduced by Burton[10] can be used to synthesise cadmium and zinc complexes in an efficient manner. It has also been used for the direct trifluoromethylation of aromatic halides in the presence of copper.[11] Many other substrates are also effective trifluoromethylating agents and have mainly been used for the formation of copper complexes. In the presence of an aromatic halide and copper(I) salts, **5** leads to the corresponding α,α,α-trifluorotoluene.[12] Compounds **6a**,[13] **7**[14] and **8**[15] are also reliable CF_3Cu precursors and commercially available whereas **6b**,[13c,16] **6c**,[16] **9**,[17] **10**[18] and **11**[19] require a multistep synthesis. Finally, the formation of the trifluoromethylated organocopper compound CF_3Cu was postulated from trifluoromethylsilane[20] CF_3SiMe_3 by a transmetallation step[21] although the organocopper intermediate was not isolated. However, all these trifluoromethyl precursors present several drawbacks such as the cost (**2**, **6a**, **7**, **8**), imminent prohibition for ecological reasons (**2**, **3** and **4**), difficult synthesis (**6c**, **6b**, **9**, **10**, **11**) and waste of fluorinated materials (**9** and **11**). It is important to underline that among all the previous trifluoromethyl sources, CF_3SiMe_3 displays the most efficient reactivity towards numerous functionalities.[20,22] In the field of fluorine chemistry, it is still a challenge to find a new approach (safe and with the preservation of the ecological environment) for the introduction of a trifluoromethyl group on organic molecules via a trifluoromethyl metal, and we were thus interested in using fluoroform[23] as a source of the trifluoromethyl group. This gas is a side-product of the industrial synthesis of CHF_2Cl, a key intermediate in the multiple-step synthesis of Teflon® and

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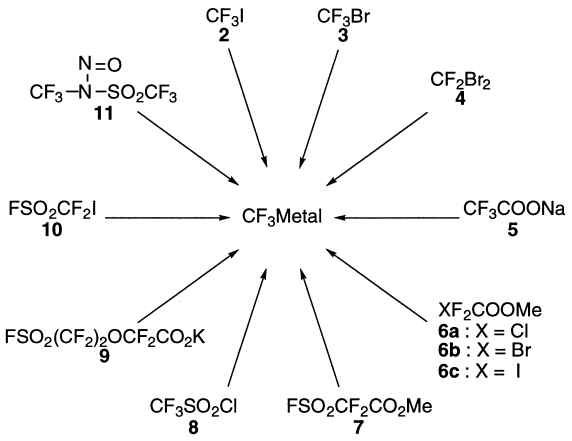
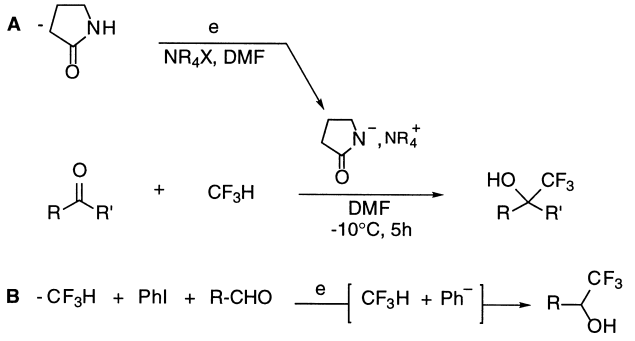


Scheme 1.

we thought it would be challenging to deprotonate it and to build trifluoromethylated organometallic complexes. However, fluoroform is the weakest acid of all the haloforms[24] (p*K*a CF_3H=28, p*K*a CCl_3H=15.5, p*K*a CBr_3H=13.7) and in a series of investigations of the mechanism of hydrolysis of mixed halomethanes,[25] Hine and co-workers have found that the basic hydrolysis of CF_3H is too slow to be measured[26] and indeed fluoroform does not undergo any deuterium exchange after 21–47 days in labelled, alkaline aqueous dioxane.[27] On the other hand, the trifluoromethyllithium (generated by the halogen–lithium exchange of iodotrifluoromethane) can not be trapped even at low temperature and decomposes to yield tetrafluoroethylene[9] (the same trend is observed for the trifluoromethyl magnesium halide[28] and trifluoromethyl sodium[29]). Then, from this overview, only the trifluoromethyl metals with M=Cu, Zn, Si, Cd, Sn, Hg and Pb are stable[8,9] (covalent organometallic) and can be used for organic transformations.

Our first attempts to generate trifluoromethyl metal with M=Cu and Zn from fluoroform were based on the metallation concept with basic organocopper and organozinc derivatives in order to directly obtain the trifluoromethyl copper or zinc derivatives. However, whatever the organometallic used ($(n\text{Bu})_2\text{CuLi}$, $(n\text{Bu})_2\text{CuCNLi}_2$, $(n\text{Bu})_3\text{CuCNLi}_3$,[30] *tert*-$\text{Bu}_2\text{CuCNLi}_2$, Et_2Zn, $(n\text{Bu})_3\text{ZnLi}$, AllylZnBr,…) in different conditions (heating, sonication, in pressurised flask) or different solvents (Et_2O, THF, HMPA) no trace of the corresponding trifluoromethyl organometallic was detected by ^{19}F NMR. However, we were very intrigued by the recent results of Shono[31] who reported that the trifluoromethyl anion could be formed at −10°C in 5 h by treatment of trifluoromethane with some common bases as NaH or *tert*-BuOK in DMF, in the presence of benzaldehyde as electrophile, to give the corresponding carbinol in, respectively, 28 and 40% yield. Even better, the use of the electrogenerated anion of pyrrolidine[31] as a base led to a remarkable increase in the yield of the carbinol (75–80%) as described in Scheme 2 (path A). In a similar manner, Troupel et al.[32] showed more recently that the phenylide anion produced by electroreduction of a large excess of iodobenzene was able to deprotonate fluoroform in the presence of a series of aldehydes to afford the corresponding trifluoromethylated carbinols (Scheme 2, path B).



Scheme 2.

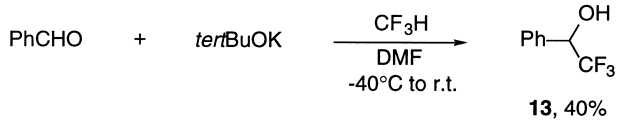
Indeed, in light of the thermal instability of the trifluoromethyl metal with M=Li, Mg and Na described above, it was difficult to understand the good results obtained by Shono[31] with these very ionic organometallics. So, we decided to investigate in detail the metallation of fluoroform with the Group IA organometallics.

Results and Discussion[33]

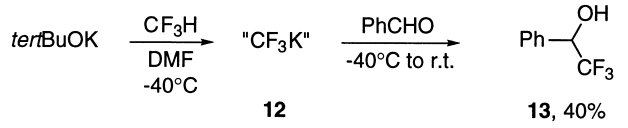
As expected, treatment of fluoroform with lithiated bases at low temperature led only to a violent exothermic reaction and then to the degradation of the starting material. If the reaction was performed in the presence of electrophiles (as benzaldehyde or zinc salt in Barbier conditions), ^{19}F NMR examination of the crude reaction mixture revealed an outstanding number of fluorinated products characteristic of the degradation of the carbenoids. However, addition of 1 equiv. of CF_3H to *tert*BuOK in DMF in the presence of benzaldehyde (Barbier conditions) at −40°C led, in agreement with Shono,[31] to a mixture of the corresponding trifluoromethyl carbinol **13** in 40% yield with 30% of benzoic acid, 22% of benzyl alcohol[34] and 8% of remaining benzaldehyde as described in Equation 1.

More importantly, when the benzaldehyde was added after the formation of the trifluoromethyl metal species (Grignard conditions), the yield in the corresponding alcohol **13** remained unchanged (Equation 2), which meant that there was no degradation of the supposed organometallic species **12** at −40°C.

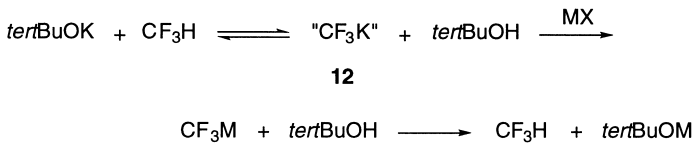
When the same reaction was performed at room temperature instead of −40°C, only the starting material was recovered.



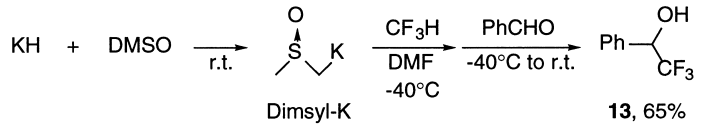
Equation 1.



Equation 2.



Equation 3.



Equation 4.

It is important to note that the presence of potassium is compulsory since the addition of one equivalent of lithium bromide (known to convert the potassium organometallic into the organolithium at very low temperature[35]) gave no trace of trifluoromethyl carbinol **13**, but intensive degradation. However, although the formation of a trifluoromethyl metal in these conditions was a very promising method for the trifluoromethylation of benzaldehyde in moderate yield, two points needed to be clarified: what was the exact mechanism of this reaction and how could we avoid the presence of one equivalent of *tert*BuOH in this transformation. Indeed, in order to increase the reactivity of the trifluoromethyl metal **12** it would be absolutely necessary to carry out some transmetallations as described in Equation 3 and then we were afraid that, once formed, the new organometallic derivative would suffer from the presence of the tertiary alcohol.

So, for these reasons we first decided to investigate an alternative route for the formation of the trifluoromethyl anion **12** and then our choice was turned to the use of potassium hydride[36] as a base. According to the same experimental conditions as described in Equation 1 but with potassium hydride instead of *tert*BuOK, only 1% of the carbinol **13** was isolated. One possible explanation for this frustrating result is that KH was totally insoluble in these experimental conditions, and then it could not react with fluoroform. In order to solve this problem, we then investigated the use of the metallated dimethylsulfoxide (dimsyl-K) as a base by treatment of DMSO with KH as described in Equation 4.

According to these new experimental conditions, the isolated yield of **13** was 65%. If we performed an analogous reaction with NaH instead of KH, **13** was obtained in 10% yield only. Once we had found suitable experimental conditions for the synthesis of **13**, we still had to investigate the mechanism of this new trifluoromethylation reaction.

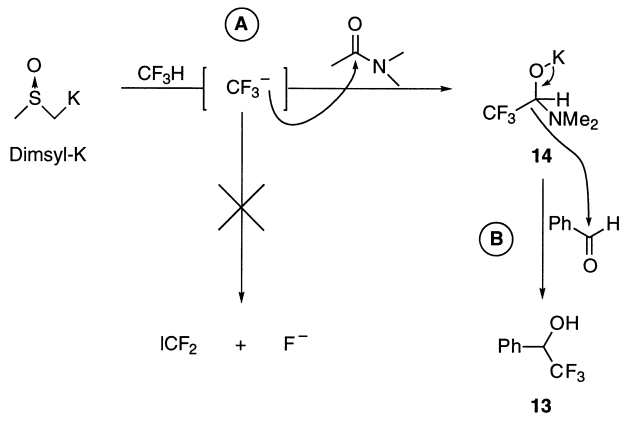
Mechanism of the trifluoromethylation

In order to determine the mechanism of this reaction, we studied the evolution of our reaction by ^{19}F NMR.

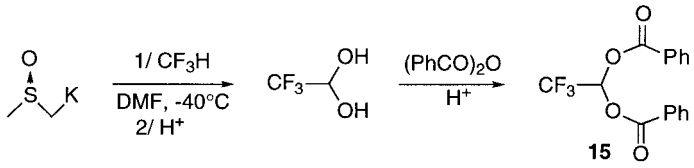
When dimsyl-K was mixed with CF_3H in DMF at −20°C, a new doublet appeared after less than 30 minutes (−78 ppm *versus* $CFCl_3$, J=7.6 Hz) in an extent of 40% (determined using α,α,α-trifluorotoluene as an internal standard). This intermediate was stable at this temperature for a very long period of time (after 14 h, 38% of this intermediate was still present in the reaction mixture) but when the reaction was warmed up to room temperature, a rapid degradation of **14** was noticed. This result could be explained by the following mechanism: deprotonation of fluoroform by potassium dimsylate afforded the trifluoromethyl anion which was trapped in situ by the carbonyl moiety of DMF[37] to form the *gem*-aminoalcoholate **14** (−78.8 ppm by ^{19}F NMR *versus* $CFCl_3$, Scheme 3 step A). This intermediate is a *masked* and *stable* form of the trifluoromethyl anion at −20°C, therefore avoiding the degradation of the carbenoid CF_3K.

In order to assess this mechanistic hypothesis, the intermediate **14** was hydrolysed at −25°C, without adding any electrophile. As expected, fluoral was identified by ^{19}F NMR (−84 ppm *versus* $CFCl_3$) (Bouveault reaction[38]). Moreover, by treatment of this latter (or its hydrate form) with benzoic anhydride, we obtained the corresponding diacylate, namely 1,1,1-trifluoro-2,2-di(phenylcarbonyloxy)ethane **15** as described in Scheme 4.

This *gem*-aminoalcoholate had already been observed by Périchon et al.[39] during electroreduction experiments of bromotrifluoromethane in DMF to form trifluoromethylzinc bromide and also by Lang et al.[40] during the formation of fluoral by reduction of iodotrifluoromethane by zinc metal in DMF.



Scheme 3.



Scheme 4.

Then the DMF solvent played the role of an in situ electrophile to give the trifluoromethylated alcoholate **14** and this latter reacted as a nucleophile with a stronger electrophile (i.e. the aldehyde) to give the corresponding carbinol (Scheme 3, step B). The second step of this reaction is the equivalent of the haloform reaction[41] with the unknown amino-alcoholate as intermediate. Moreover, it was shown from an NMR study that the reaction between the amino-alcoholate **14** and benzaldehyde is a fast and quantitative reaction (i.e. 10 mmol of **14**[42] reacted with an excess of benzaldehyde between −20°C and room temperature to give 9.7 mmol of carbinol **13**;[42] see Scheme 3, step B).

In order to have some valuable information on the importance of the DMF, trifluoromethylation of benzaldehyde was attempted using the dimethylacetal of DMF as a solvent; here, the carbonyl of DMF is masked.

In this instance, addition of fluoroform at low temperature resulted in a violent exothermic reaction and the reaction mixture immediately became black. This exothermic colour change is often characteristic of carbenoid degradation. Moreover, at the end of the reaction, no trace of the expected trifluoromethylated carbinol could be detected.

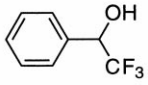
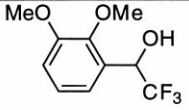
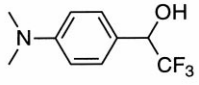
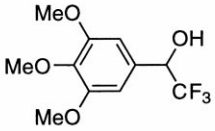
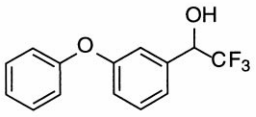
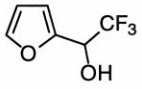
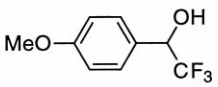
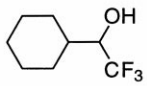
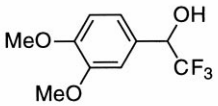
If the trifluoromethylation reaction was performed in exactly the same experimental conditions as described in Equation 3 but using THF instead of DMF as a solvent, no trace of the carbinol **13** was detected.

This simple reaction was generalised to various other aldehydes as described in Table 1.

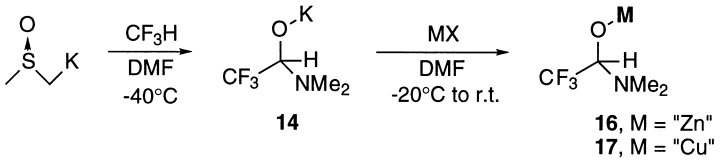
The yields of trifluoromethylated carbinols were slightly dependent on the substitution on the aromatic ring: the presence of electron-donating substituents in *para* position improved yields (entries 2–4) while their presence in *meta* position had the opposite effect (compare entry 4 and entries 5–7). This methodology was also applied to 2-furfural (entry 9) and cyclohexanecarboxaldehyde as an aliphatic aldehyde. When primary aliphatic aldehydes were involved, the major reaction to take place was aldolisation–crotonisation.

From this study, we have proved that it is possible to deprotonate fluoroform at −20°C using standard reagents and to trifluoromethylate several aldehydes with the trifluoromethyl anion so obtained. The key step of this reaction seems to be the nucleophilic addition of the trifluoromethyl anion onto the carbonyl moiety of DMF to form the intermediate trifluoromethylated amino alcoholate **14**, a masked form of the trifluoromethyl anion. In the second step, namely the reaction with a stronger electrophile, the trifluoromethyl moiety is transferred to the carbonyl via a

Table 1. Trifluoromethylation of aldehydes

Entry	Carbinol		yield (%)[a]	Entry	Carbinol		yield (%)[a]
1		**13**	65	6		**13e**	52
2		**13a**	70	7		**13f**	45
3		**13b**	61	8		**13g**	42
4		**13c**	72	9		**13h**	45
5		**13d**	51				

[a]: isolated yields.



Equation 5.

process equivalent to the haloform reaction[41] to give, in moderate to good yields, the corresponding alcohols.

Numerous attempts to incorporate the trifluoromethyl group directly into a substrate via in situ generation and coupling of CF_3M with aryl iodides were published in the literature.[8,9,43] Having in our hands the intermediate **14**, it was interesting to study the transmetallation reaction with zinc or copper salt in order to prepare the corresponding CF_3ZnX and CF_3Cu.

When $ZnBr_2$ was added to **14** at −30°C and the reaction mixture was warmed up to room temperature, a new tetrahedral intermediate **16** was identified by ^{19}F NMR (as a doublet at −76.5 ppm *versus* $CFCl_3$, J=7.5 Hz). By acidic hydrolysis, this latter afforded fluoral (−84 ppm *versus* $CFCl_3$). Moreover, **16** had an extraordinary thermal stability and it could stand at room temperature for hours, or be heated at 60°C for 5 h without degradation. We assume that **16** arose from a transmetallation reaction of **14** with zinc salts (see Equation 5). Its high stability could be attributed to the strength of the oxygen–zinc bond.[44] However, despite all our trials, the conversion of **16** into the trifluoromethylzinc halide failed and **16** proved to be unreactive with classical electrophiles.

In a comparable manner the addition of copper iodide to a mixture of **14** at −30°C provided a new tetrahedral intermediate **17** (−76.5 ppm *versus* $CFCl_3$, J=7.5 Hz) hydrolysed to fluoral (^{19}F NMR). Once more, **17** proved to be much more stable than its analogue **14,** probably due to the strength of the oxygen–copper bond which is much higher than that of the oxygen–potassium one. **17** also proved to be less stable than **16**: its evolution at room temperature partially afforded the expected trifluoromethyl metal complex (CF_3Cu) which was observed by ^{19}F NMR as its two forms (**18**, −25 ppm and **19**, −30 ppm *versus* $CFCl_3$) in agreement with Burton's results.[45,46] Unfortunately, the total yield of trifluoromethylcopper species never exceeded 15%, either after 4 days at room temperature or after 1 h at 60°C. In the same way, when **17** was warmed in the presence of 4-iodoanisole **20**, the expected α,α,α-trifluorotoluene **21** was observed with a low yield (<10%, ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard).

The influence of the nature of the copper(I) salt in the formation of **17** and its transformation in **18**, **19** was investigated. As shown in Table 2, the presence of solvating agents such as Me_2S, TMEDA, HMPT or PBu_3 (entries 2–5) supposed to stabilise organometallic species did not improve the yield of **17**, nor that of the expected trifluoromethylcopper, CF_3Cu. In the case of CuCN.2LiBr (entry 6), the modest yield was explained by the presence of THF which could have destabilised **17** once formed. In the following work, CuI was the only copper(I) salt used. It is important to note that in any of the following experiments (Tables 3 and 4),

Table 2. Influence of the nature of Cu(I) on the formation of **17**

Entry[a]	Cu(I)	**17**(%)[b]	CF_3Cu (%)[b,c]
1	CuI	46	–
2	CuBr.Me_2S	40	3
3	CuI.TMEDA[d]	3	6
4	CuI.HMPT[d]	38	–
5	CuI.PBu_3[d]	–	–
6	CuCN.2LiBr	24	–

[a] CF_3H, KH and Cu(I) were involved in equimolar quantities in a 2/1 mixture of DMF/DMSO (v/v).
[b] Yields of fluorinated species was determined by ^{19}F NMR with α,α,α-trifluorotoluene as an internal standard.
[c] CF_3Cu under its two forms: **18**, **19**.
[d] CuI added as a suspension in 10 ml of the Lewis base.

Table 3. Replacement of DMSO by an aprotic solvent for the preparation of dimsyl-K

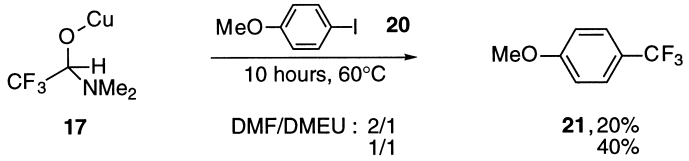
Entry[a]	Dimsyl-K[b]	Solvent	**17**(%)[c]	CF_3Cu(%)[c,d]	Total(%)[e]
1	1	Et_2O	15	–	15
2	1	Toluene	12	10	22
3	1	THF	30	–	30
4	2	THF	70	20	90

[a] Dimsyl-K was prepared in 10 ml of solvent at room temperature by addition of 1 eq. of DMSO on potassium hydride.
[b] Number of equivalents vs CF_3H.
[c] Yields of fluorinated species was determined by ^{19}F NMR with α,α,α-trifluorotoluene as an internal standard.
[d] CF_3Cu unders its two forms: **18**, **19**.
[e] Total yield in trifluoromethylated metallic species **17**, **18** and **19**.

Table 4. Influence of the presence of Lewis bases

Entry[a]	t[b]	L.B.[c]	**17** (%)	CF_3Cu[d] (%)	Total[e] (%)
1	0	None	66	14	80
2	14		20	38	58
3	0	Pyr	65	20	85
4	14		Trace	trace	Trace
5	0	TDA-1	91	–	91
6	14		27	31	58
7	0	DMEU	88	4	92
8	14		29	47	76
9	19		27	47	74

[a] CF_3H/KH/DMSO/CuI: 20/40/40/20 mmol in 20 ml of DMF. Yields of fluorinated species were determined by ^{19}F NMR with α,α,α-trifluorotoluene as an internal standard.
[b] Time at room temperature in hours.
[c] Lewis bases added at −20°C before warming up. 5 ml of pyr. and TDA-1 and 10 ml of DMEU were involved.
[d] CF_3Cu in its two forms: **18**, **19**.
[e] Total yield in trifluoromethylated metallic species **17**, **18** and **19**.



Scheme 5.

among the two copper species **18** and **19**, **18** has always appeared first, which is in total agreement with Burton's observations.[45]

Although potassium dimsylate had proved to be very useful for the deprotonation of fluoroform and the subsequent formation of the *gem*-aminoalcoholate **14**, we investigated the role of DMSO in the formation of **17**, **18**, **19** and **21**. For this purpose, dimsyl-K was formed from equimolar amounts of potassium hydride and DMSO[47] in an aprotic solvent. Diethyl ether, THF and toluene were tested (see Table 3). When one equivalent of dimsyl-K (*versus* fluoroform) was involved, yields were poor (entries 1–3). On the other hand, **17**, **18** and **19** were much less stable than in the presence of DMSO (their total disappearance took some hours at room temperature and some minutes at 60°C) which made them unreliable for subsequent coupling reactions.

In the presence of two equivalents of dimsyl-K prepared in THF (entry 4), yields increased dramatically (**17**, 70% and **18**, 20%). Unfortunately, **17** and **18** suffered from the same lack of stability. It was possible to stabilise these two trifluoromethylated complexes at room temperature by adding HMPT to the reaction mixture, but at 60°C, the stabilising effect seemed to disappear: after 0.5 h, none of **17**, **18** or **19** was present.

Aprotic cosolvents were therefore suppressed and dimsyl-K was prepared by addition of 1.1 equiv. of DMSO on potassium hydride at room temperature (see Table 4). In the absence of any Lewis base, **17** was obtained in 66% yield along with **18** (entry 1). After 14 h at room temperature, the total yield in trifluoromethylated species was still 58% (entry 2). The presence of TDA-1[48] (tris(2-(2-methoxyethoxy)ethyl)amine) or pyridine, expected to stabilise **18** and **19** once formed was quite disappointing: after 14 hours, **17**, **18** and **19** had almost disappeared in the latter case (entry 4) while in the former, their total yield was the same as in the absence of any chelating agent (entry 6). On the other hand, when DMEU[49] was involved as a cosolvent, **17** and **18** were formed in a 92% total yield and were still present in a 74% yield after 19 h, with a 47% yield in the expected trifluoromethylcopper species (**18** and **19**) (entry 9). Thus, the destabilising effect of THF, diethyl ether or toluene quoted in Table 3 had been overridden by the use of DMEU.

Given these results, we then investigated the reactivity of the obtained CF_3Cu (**18** and **19**) on aromatic halides. When 4-iodoanisole **20** was introduced in a solution of **18** and **19** in a mixture of DMF/DMEU (formed as described in Table 4, entry 8) and heated at 60°C for 10 h, the expected 4-trifluoromethylated anisole **21** was formed in a 15% yield (*versus* **20**, determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard). On the other hand, when **20** was heated directly in the presence of **17** in the same solvents system, **22** was obtained in a 20% yield. Finally, when the same experiment was attempted in a 1/1 DMF/DMEU mixture, **21** was formed in a 40% yield (see Scheme 5).

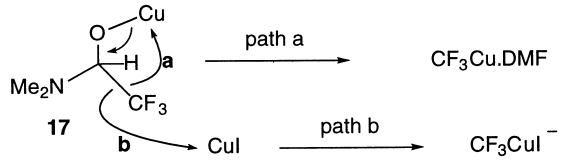
From this study, we have demonstrated that **17**, arising from a transmetallation reaction of **14** in the presence of copper iodide, afforded the trifluoromethylated copper complex CF_3Cu. Even if the mechanism of this transformation is not precisely known, we assume that **17** could both rearrange (Scheme 6, path a) or transfer a trifluoromethyl moiety on copper iodide (Scheme 6, path b). Moreover, these two pathways could account for the two forms of CF_3Cu observed by ^{19}F NMR, namely **18** and **19**.

Thus, when heated in the presence of **17**, 4-iodoanisole afforded its trifluoromethylated analogue in a 40% yield, probably via in situ formation of a trifluoromethylcopper species and Ullmann coupling reaction. Despite the modest observed yields, an aromatic halide was for the first time to our knowledge trifluoromethylated starting from fluoroform as a trifluoromethyl source.

These reactions seem to be solvent-sensitive and the reaction, as well as the role of solvents in the formation of **17**, **18**, **19** and then **20**, are still under investigation in our laboratory.

Conclusion

We have demonstrated the efficiency of fluoroform in trifluoromethylating reactions. Its deprotonation by potassium dimsylate in the presence of DMF afforded the *gem*-aminoalcoholate **14**, a stable form of the trifluoromethyl anion. This latter exhibited an interesting reactivity. In the presence of an aldehyde, it transferred its trifluoromethyl moiety, affording the corresponding carbinol. On the other hand, in the presence of copper iodide, it was transmetallated to **17**. In the presence of a stabilising agent like DMEU, **17** was transformed to trifluoromethylcopper CF_3Cu. And finally, when heated in the presence of an aromatic compound and DMEU, it afforded the corresponding α,α,α-trifluorotoluene. These first results are more than



Scheme 6.

promising and many aspects of this new reaction are still under study in our laboratory.

Experimental

General

^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Brüker ARX-400 at 400, 100 and 380 MHz respectively. For ^{19}F NMR, $CFCl_3$ was taken as an internal reference. Microanalyses and mass spectroscopy were accomplished at Paris VI University. Infrared (IR) spectra were recorded on a Perkin–Elmer 1420 Spectrophotometer.

DMF, DMSO and DMEU were distilled from calcium hydride under reduced pressure. Reactions were carried out under inert atmosphere of nitrogen and fluoroform was added through a gazometer. Merck plates (Silica gel 60 GF_{254}, 0.25 mm) were used for thin layer chromatography (TLC) and the crudes were purified by column chromatography on silica gel (Silica Gel Geduran Si 60, 43–60 μm)

General preparation of a solution of potassium dimsylate in DMSO

A flask equipped with a nitrogen inlet was charged with potassium hydride in suspension in mineral oil. The mineral oil was removed by washing with pentane (15 ml) and DMSO was added. The obtained mixture was then stirred for 1 h at room temperature.

Preparation of 1,1,1-trifluoro-2,2-di(phenylcarbonyloxy)ethane 15

The solution of potassium dimsylate was prepared in a four-necked flask (equipped with mechanical stirring, nitrogen inlet and internal thermometer) according to the above procedure from KH in mineral oil (1 ml, 10 mmol) and DMSO (1.42 ml, 20 mmol).

It was frozen at −40°C and DMF (20 ml) and fluoroform (440 ml, 20 mmol) were added. The mixture was stirred for 1 h at −25°C: during this period, the frozen potassium dimsylate was slowly solubilised. Then, a mixture of benzoic anhydride (2.26 g, 10 mmol) in DMF (5 ml) was added and the reaction mixture allowed to reach room temperature within 2 h before being quenched by a 2N HCl aqueous solution (10 ml). The crude product was poured in Et_2O (40 ml) and washed with 2N HCl (2×20 ml). Et_2O was removed from organic layers by evaporation under reduced pressure and replaced by pentane (15 ml). Most of the benzoic acid present in the crude product was then removed by precipitation at −20°C and filtration. The filtrate was condensed and purified by column chromatography on silica gel (cyclohexane/ethyl acetate: 4/1). The product was isolated as a colourless oil (0.58 g, 18%). IR (neat): 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 8.15 (m, 4H), 7.72 (q, 1H, J_{HF}=3.6 Hz), 7.68 (m, 2H), 7.51 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm): 163.31, 161.12 (q, J_{CF}=291 Hz), 134.52, 130.51, 128.82, 127.66, 83.25 (q, J_{CF}=39 Hz); ^{19}F NMR ($CDCl_3$) δ(ppm): −81.28 (d, J_{HF}=3.6 Hz); MS (i.e.): m/z=324 (M^+).

Preparation of 2,2,2-trifluoroethanols 13

The solution of potassium dimsylate was prepared in a two-necked flask (equipped with magnetic stirring and nitrogen inlet) according to the above procedure from KH in mineral oil (2 ml, 20 mmol) and DMSO (10 ml).

It was added to a solution of fluoroform (440 ml, 20 mmol) in DMF (20 ml) at −40°C. After 30 mins, a solution of aldehyde (10 mmol) in DMF (5 ml) was added dropwise and after 30 mins more the mixture was allowed to warm to 0°C and quenched by 2N HCl (10 ml). It was poured into Et_2O (40 ml) and washed with 2N HCl (2×20 ml). Organic layers were dried over $MgSO_4$ and Et_2O removed by evaporation under reduced pressure. The obtained oil was purified by column chromatography on silica gel.

The physical properties and analytical data for the trifluoromethylated carbinols are listed below.

2,2,2-Trifluoro-1-(4-dimethylaminophenyl)ethanol 13a. IR (neat): 3460, 2820 cm^{-1}; ^1H NMR ($CDCl_3$) δ(ppm): 7.34 (d, 2H, J=8.6 Hz), 6.74 (d, 2H, J=8.6 Hz), 4.93 (dq, 1H, J_{HF}=6.4 Hz et J_{HH}=4.4 Hz), 3.00 (s, 6H), 2.38 (d, 1H, J=4.4 Hz); ^{13}C NMR ($CDCl_3$) δ(ppm): 151.65, 128.79, 124.94 (q, J_{CF}=282 Hz), 121.84, 112.52, 73.14 (q, J_{CF}=32 Hz), 40.76; ^{19}F NMR ($CDCl_3$) δ(ppm): −78.82 (d, J_{HF}=6.4 Hz).; Anal. calculated for $C_{10}H_{12}F_3NO$: C, 54.79; H, 5.52. Found: C, 54.82 H, 5.47.

2,2,2-Trifluoro-1-(3-phenyloxyphenyl)ethanol 13b[39]. ^1H NMR ($CDCl_3$) δ(ppm): 7.39 (m, 3H), 7.23 (m, 1H), 7.19 (m, 2H), 7.16 (m, 1H), 7.06 (m, 3H), 4.99 (q, 1H, J_{HF}=6.6 Hz), 2.95 (s, 1H); ^{13}C NMR ($CDCl_3$) δ(ppm): 157.55, 156.68, 135.82, 129.99, 129.91, 123.98 (q, J_{CF}=290 Hz), 123.72, 122.07, 119.61, 119.11, 117.80, 72.45 (q, J_{CF}=32 Hz); ^{19}F NMR ($CDCl_3$) δ(ppm): −78.67 (d, J_{HF}=6.6 Hz); Anal. calculated for $C_{14}H_{11}F_3O_2$: C, 62.69; H, 4.13. Found: C, 62.70; H, 4.11.

2,2,2-Trifluoro-1-(4-methoxyphenyl)ethanol 13c. ^1H NMR ($CDCl_3$) δ(ppm): 7.39 (d, 2H, J=8.6 Hz), 6.94 (d, 2H, J=8.6 Hz), 4.92 (q, 1H, J_{HF}=6.7 Hz), 3.82 (s, 3H), 3.42 (s, 3H); ^{13}C NMR ($CDCl_3$) δ(ppm): 160.74, 129.22, 126.69, 124.90 (q, J_{CF}=290 Hz), 114.40, 72.73 (q, J_{CF}=32 Hz), 55.67; ^{19}F NMR ($CDCl_3$) δ(ppm): −78.64 (d, J_{HF}=6.7 Hz; Anal. calculated for $C_9H_9F_3O_2$: C, 52.43; H, 4.40. Found: C, 52.42; H, 4.40.

2,2,2-Trifluoro-1-(3,4-dimethoxyphenyl)ethanol 13d[31]. ^1H NMR ($CDCl_3$) δ(ppm): 7.03 (m, 2H), 6.90 (m, 1H), 5.0 (q, 1H, J_{HF}=7.5 Hz), 3.93 (s, 3H), 3.92 (s, 3H), 2.54 (s, 1H); ^{13}C NMR ($CDCl_3$) δ(ppm): 149.86, 149.02, 126.59, 124.80 (q, J_{CF}=290 Hz), 120.33, 110.86, 110.17, 72.55, 55.91; ^{19}F NMR ($CDCl_3$) δ(ppm): −78.86 (d, J_{HF}=7.5 Hz); Anal. calculated for $C_{10}H_{11}F_3O_3$: C, 50.85; H, 4.69. Found: C, 50.92; H, 4.65.

2,2,2-Trifluoro-1-(2,3-dimethoxyphenyl)ethanol 13e. ^1H NMR ($CDCl_3$) δ(ppm): 7.07 (t, 1H, J=8 Hz), 7.00 (d, 1H, J=8 Hz), 6.92 (d, 1H, J=8 Hz), 5.28 (dq, 1H, J_{HH}=7.2 Hz, J_{HF}=7.2 Hz), 4.08 (d, 1H, J=7.2 Hz), 3.89 (s, 3H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$) δ(ppm): 158.58, 152.49, 127.44,

124.72 (q, J_{CF}=280 Hz), 124.34, 120.57, 113.46, 69.30 (q, J_{CF}=33 Hz), 61.25, 55.84; ^{19}F NMR ($CDCl_3$) δ(ppm): −78.46 (d, J_{HF}=7.2 Hz); Anal. calculated for $C_{10}H_{11}F_3O_3$: C, 50.85; H, 4.69. Found: C, 50.89; H, 4.65.

2,2,2-Trifluoro-1-(3,4,5-trimethoxyphenyl)ethanol 13f. ^{1}H NMR ($CDCl_3$) δ(ppm): 6.54 (s, 2H), 4.80 (q, 1H, J_{HF}=6.6 Hz), 3.76 (s, 6H), 3.71 (s, 3H); ^{13}C NMR ($CDCl_3$) δ(ppm): 153.30, 138.37, 130.76, 124.66 (q, J_{CF}=282 Hz), 104.87, 72.93 (q, J_{CF}=32 Hz), 61.2, 56.34; ^{19}F NMR ($CDCl_3$) δ(ppm): −78.61 (d, J_{HF}=6.6 Hz); Anal. calculated for $C_{11}H_{13}F_3O_4$: C, 49.63; H, 4.92. Found: C, 49.52; H, 4.91.

2,2,2-Trifluoro-1-(2-furyl)ethanol 13g[39]. ^{1}H NMR ($CDCl_3$) δ(ppm): 7.45 (m, 1H), 6.51 (m, 1H), 6.41 (m, 1H), 5.02 (q, 1H, J_{HF}=6.4 Hz), 3.34 (s, 1H); ^{13}C NMR ($CDCl_3$) δ(ppm): 147.32, 143.70, 123.56 (q, J_{CF}=280 Hz), 110.81, 110.18, 67.23 (q, J_{CF}=34 Hz); ^{19}F NMR ($CDCl_3$) δ(ppm): −78.42 (d, J_{HF}=6.4 Hz); Anal. calculated for $C_6H_5F_3O_2$: C, 43.39; H, 3.03. Found: C, 43.35; H, 3.08.

2,2,2-Trifluoro-1-(cyclohexyl)ethanol 13h[50]. ^{1}H NMR ($CDCl_3$) δ(ppm): 3.64 (m, 1H), 2.74 (m, 1H), 1.82 (m, 1H), 1.77−1.58 (m,5H), 1.28−1.03 (m, 5H); ^{13}C NMR ($CDCl_3$) δ(ppm): 125.74 (q, J_{CF}=284 Hz), 74.63 (q, J_{CF}=29.2 Hz),38.58, 29.60, 27.15, 26.37, 26.33, 26.07; ^{19}F NMR ($CDCl_3$) δ(ppm): −75.98 (d, J_{HF}=7.5 Hz).

Preparation of 4-trifluoromethylanisole 21

The solution of potassium dimsylate was prepared in a four-necked flask (equipped with mechanical stirring, nitrogen inlet and internal temperature) according to the above procedure from KH in mineral oil (4 ml, 40 mmol) and DMSO (3.12 ml, 44 mmol).

It was frozen at −40°C and DMF (20 ml) and fluoroform (440 ml, 20 mmol) were added. The mixture was stirred for one hour at −25°C: during this period, the frozen potassium dimsylate was slowly solubilised. Copper Iodide (3.81 g, 20 mmol) was added and the mixture was allowed to warm up to room temperature. Then DMEU (20 ml) and 4-iodoanisole (2.34 g, 10 mmol) were added and the mixture was warmed at 60°C for 10 h. After cooling to room temperature, it was quenched with NH_3/sat. NH_4Cl (2/1 v/v, 30 ml) and filtered through a celite pad. It was then extracted by Et_2O (2×30 ml). Combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The product was purified by column chromatography on silica gel (Pentane/Et_2O: 9/1). ^{1}H NMR ($CDCl_3$) δ(ppm): 7.58 (d, 2H, J=8.8 Hz), 6.98 (d, 2H, J=8.8 Hz), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$) δ(ppm): 160.97, 125.85, 123.45 (q, J_{CF}=270 Hz), 121.78 (q, J_{CF}=32 Hz), 112.90, 54.37; ^{19}F NMR ($CDCl_3$) δ(ppm): −61.8; MS (i.e.): m/z=176 (M^+).

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References

1. Banks, R. E.; Tatlow, J. C. *Fluorine—The First Hundred Years, 1886–1986*; Banks, R. E., Sharp, D. W. A.; Tatlow, J. C., Eds.; Elsevier Sequoia: New York, 1986, p 233 Chapter 11.
2. Gautshi, M.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1083.
3. Alverbhe, G.; Langlois, B.; Laurent, A.; Le Drean, I.; Selmi, A. *Tetrahedron Lett.* **1991**, *32*, 643.
4. (a) Maier, G.; Hecht, R.; Nuyken, O.; Burger, K.; Helmreich, B. *J. Fluorine Chem.* **1991**, *54*, 90. (b) Reynolds, D. W.; Cassidy, P. E.; Greg Johnson, C.; Cameron, M. L. *J. Org. Chem.* **1990**, *55*, 4448.
5. Wolfrum, G. *Organofluorine Chemicals and their Industrial Applications*; Banks, R. E., Ed.; Ellis Horwood: Chichester, UK, 1979, Chapter 10.
6. Hudlicky, M. *Chemistry of Organic Fluorine Compounds*, 2nd ed.; Ellis Horwood: Chichester, UK, 1976.
7. Simons, J. H.; Lewis, C. J. *J. Am. Chem. Soc.* **1938**, *60*, 492.
8. Burton, D. J.; Yang, Z. Y. *Tetrahedron Lett.* **1992**, *48*, 189.
9. McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555.
10. Burton, D. J.; Wiemers, D. *J. Am. Chem. Soc.* **1985**, *107*, 5014.
11. Clark, J. H.; McClinton, M. A.; Jones, C. W.; Landon, P.; Bishop, D.; Blade, R. J. *Tetrahedron Lett.* **1989**, *30*, 2133.
12. Carr, G. E.; Chambers, R. D.; Holmes, T. F. *J. Chem. Soc., Perkin Trans. I* **1988**, 921.
13. (a) Su, D. B.; Duan, J. X.; Chen, Q. Y. *Tetrahedron Lett.* **1991**, *32*, 7689. (b) McNeil, J. G.; Burton, D. J. *J. Fluorine Chem.* **1991**, *55*, 225. (c) Chen, Q. Y.; Duan, J. X. *Tetrahedron Lett.* **1993**, *64*, 4241.
14. Duan, J. X.; Su, D. B.; Wu, J. P.; Chen, Q. Y. *J. Fluorine Chem.* **1994**, *66*, 167.
15. Heaton, C. A.; Powell, R. L. *J. Fluorine Chem.* **1989**, *45*, 86.
16. Duan, Q. Y.; Su, D. B.; Chen, Q. Y. *J. Fluorine Chem.* **1989**, *45*, 86.
17. Long, Z. Y.; Duan, J. X.; Lin, Y. B.; Guo, C. Y.; Chen, Q. Y. *J. Fluorine Chem.* **1996**, *78*, 177.
18. Chen, Q. Y.; Wu, S. W. *J. Chem. Soc., Perkin Trans. I* **1989**, 2385.
19. Umemoto, T.; Ando, A. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 447.
20. (a) Ruppert, I.; Schlich, K.; Volbach, W. *Tetrahedron Lett.* **1984**, *25*, 2195. (b) Krishnamurti, R.; Bellew, D. R.; Prakash, K. S. *J. Org. Chem.* **1991**, *56*, 984. (c) Aymard, F.; Nedelec, J.-Y.; Perichon, J. *Tetrahedron Lett.* **1994**, *35*, 8623. (d) Walter, M. W.; Adlington, R. M.; Baldwin, J. E.; Chuhan, J.; Schofield, C. J. *Tetrahedron Lett.* **1995**, *36*, 7761.
21. Urata, H.; Fuchikami, T. *Tetrahedron Lett.* **1991**, *32*, 91.
22. Prakasch, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757–786.
23. Generously provided by Rhone-Poulenc. This gas has a low boiling point (−82°C) but is very soluble in polar solvents as DMF.
24. Reutov, O. A.; Butin, K. P.; Beletskaya, I. P. *Usp. Khim.* **1974**, *43*, 35.
25. Klabunde, K. P.; Burton, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 5985.
26. (a) Hine, J.; Dowell, A. M.; Singley, J. E. *J. Am. Chem. Soc.* **1956**, *78*, 479. (b) Hine, J.; Langford, P. B. *J. Am. Chem. Soc.* **1957**, *79*, 5497.
27. (a) Slaugh, L. H.; Bergman, E. *J. Org. Chem.* **1961**, *26*, 3158. (b) Andreades, S. *J. Am. Chem. Soc.* **1964**, *86*, 2003.
28. (a) Haszeldine, R. N. *J. Chem. Soc.* **1954**, 1273. (b) McBee,

E.T.; Battershell, R. D.; Braendlin, H. P. *J. Org. Chem.* **1963**, *28*, 1131.
29. Seyferth, D.; Mui, J. Y. P.; Gordon, M. E.; Burlitch, J. M. *J. Am. Chem. Soc.* **1965**, *87*, 681.
30. Although we have no evidence of the formation of these species, this formulae represents the relative stoichiometry of the reactants.
31. Shono, T.; Ishifune, M.; Okada, T.; Kashimura, S. *J. Org. Chem.* **1991**, *2* (56), 2.
32. Barhadi, R.; Troupel, M.; Périchon, J. *Chem. Commun.* **1998**, 1251.
33. Preliminary results of this work have already been published: Folléas, B.; Marek, I.; Normant, J. F.; Saint-Jalmes, L. *Tetrahedron Lett.* **1998**, *39*, 2973, and more recently, a parallel study from Rhône-Poulenc Company has been disclosed concerning the potassium trifluoromethylide: Russell, J.; Roques, N. *Tetrahedron* **1998**, *54*, 13771.
34. Formed probably by the Tishchenko reaction, followed by saponification in the work-up; see Kamm, O.; Kamm, F. *Org. Synth.* **1948**, *1*, 104.
35. Schlosser, M.; Hartmann, J. *Angew. Chem. Int.. Ed. Engl.* **1973**, *12*, 508.
36. After metallation, one equivalent of hydrogen is formed which will not react with the trifluoromethyl metal.
37. The reaction of several organometallics with DMF as a formylating agent is a well known reaction.
38. Olah, G.; Prakash, G. K. S.; Arvanaghi, M. *Synthesis* **1978**, 228.
39. Sibille, S.; Mcharek, S.; Perichon, J. *Tetrahedron* **1989**, *45*, 1423.
40. Lang, R. W. *Helv. Chim. Acta* **1988**, *71*, 369.
41. Hudlicky, P. *Chemistry of Organic Fluorine Compounds*; Macmillan: New York, 1962, p 208.
42. Determined by using α,α,α-trifluorotoluene as an internal standard.
43. (a) Mc Loughlin, V. C. R.; Thrower, J. *Tetrahedron* **1969**, *25*, 5921. (b) Kobayashi, Y.; Kumadaki, I. *Tetrahedron Lett.* **1969**, 4095. (c) Kobayashi, Y.; Kumadaki, I.; Sato, S.; Hara, N.; Chidami, E. *Chem. Pharm. Bull.* **1970**, *18*, 2334. (d) Kobayashi, Y.; Kumadaki, I.; Hanzawa, Y. *Chem. Pharm. Bull.* **1977**, *25*, 3009. (e) Kobayashi, Y.; Kumadaki, I.; Ohsawa, A. *Chem. Pharm. Bull.* **1972**, *20*, 1839. (f) Kobayashi, Y.; Yamamoto, Y.; Kumadaki, I. *Tetrahedron Lett.* **1979**, 4071. (g) Kobayashi, Y.; Kumadaki, I. *J. Chem. Soc., Perkin Trans. 1* **1980**, 661. (h) Kobayashi, Y.; Yamamoto, Y.; Asai, T.; Nakano, M.; Kumadaki, I. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2755. (i) Kondratenko, N. V.; Vechirko, E. P.; Yagupolskii, L. M. *Synthesis* **1980**, 932. (j) Matsui, K.; Tobita, E.; Ando, M.; Kondo, K. *Chem. Lett.* **1981**, 1719. (k) Suzuki, H.; Yoshida, Y.; Osuka, A. *Chem. Lett.* **1982**, 135. (l) Leroy, J.; Rubinstein, M.; Wakselman, C. *J. Fluorine Chem.* **1985**, *27*, 291.
44. Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117.
45. Wiemers, D. M.; Burton, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 832.
46. Moreover, in the presence of I_2, **18** and **19** afforded almost instantaneously Iodotrifluoromethane (^{19}F NMR).
47. In above studies, dimsyl-K was formed in DMSO as a solvent.
48. (a) Soula, G. J. *J. Org. Chem.* **1985**, *50*, 3717. (b) Greiner, A. *Synthesis* **1989**, 312.
49. This environmentally friendly urea has a polarity comparable to that of HMPT and can replace it in many cases. See: Sakurai, H.; Kondo, F. *J. Organomet. Chem.* **1975**, *92*, C46.
50. Note added in proof: During our corrections, a recent publication (Mispelaere, C.; Roques, N. *Tetrahedron Letters* **1999**, *40*, 6411) showed that our postulated mechanism involving **14** as the trifluoromethylating intermediate is indeed viable.