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To be cited as: Eur. J. Org. Chem. 10.1002/ejoc.201601038

Link to VoR: http://dx.doi.org/10.1002/ejoc.201601038

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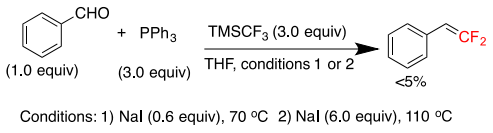
Direct Difluoromethylenation of Carbonyl Compounds Using $TMSCF_3$: The Right Conditions

Sankarganesh Krishnamoorthy, Jotheeswari Kothandaraman, Jacqueline Saldana and G. K. Surya Prakash*[a]

Dedicated to Professor George A. Olah on the occasion of his 89th birthday

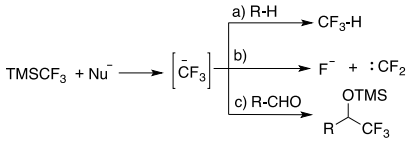
Abstract: *Using readily available, inexpensive trifluoromethyltrimethylsilane ($TMSCF_3$), LiI and PPh_3, deoxygenative difluoromethylenation of carbonyl compounds is reported. The Li^+ is proposed to prevent the unproductive exhaustion of $TMSCF_3$ by keeping the soluble free fluoride concentration in the reaction medium under control. Furthermore, solvent combination strategy to increase the reactivity and thereby reducing the reaction temperature and time is disclosed.*

The distinct electronic property and reactivity of 1,1-difluoroalkenes make them invaluable synthetic intermediates towards fluorinated[1] as well as non-fluorinated[2] synthetic scaffolds. The $C=CF_2$ has been shown to serve as a unique functionality in rational drug design[3] as a bioisoster of C=O group,[4] and therefore synthesis of difluoro ($C=CF_2$) analogues as bioactive C=O containing molecules has garnered significant attention.[5] Though there are several approaches that use various starting materials[6] and reagents[7] to synthesize 1,1-difluoroalkenes, the direct deoxygenative difluoromethylenation of carbonyl compounds via Wittig type processes [8] has been deemed efficient as it employs readily available reagents.[9] The reactive intermediate in these reactions, difluoromethylene phosphonium ylide, can be generated with phosphine and the singlet difluoromethylene. Though reagent derived from $TMSCF_3$, namely, $TMSCF_2Cl$ has been reported for such transformation, the direct use of $TMSCF_3$ has been reported to be unsuccessful (Scheme 1).[10] Therefore, direct use of $TMSCF_3$ will prove superior in terms of safety, synthetic convenience, and cost. [11] Further, Its preparation has been recently demonstrated from abundant, non-ozone depleting, Teflon^R by-product, CF_3H.[12]



Scheme 1. Previously attempted direct difluoromethylenation with $TMSCF_3$.[10]

In general, employing $TMSCF_3$ poses challenges with substrates containing fairly acidic protons or reactive electrophilic functional groups such as carbonyls[13] as the reactive intermediates (CF_3 anion or the pentavalent silicon species) are prone to pick up a proton (pKa of CF_3H = 26)[14] or react with other electrophiles (Scheme 2). In addition, for every mole equivalent of difluoromethylene formed, a mole equivalent of fluoride is produced; and the presence of the silicophilic fluoride is known to accelerate the formation of CF_3 anion from $TMSCF_3$, which generally result in autocatalytic[15] or runaway reactions producing copious amount CF_3H and other undesired singlet difluoromethylene based products. Such runaway reactions are exacerbated at the elevated temperatures and therefore limit the higher reaction temperatures that might be required to achieve some of the desirable chemical transformations. Therefore, curtailing the amount of nascent fluoride produced in the process of difluoromethylene formation will allow the non-fluoride based nucleophiles such as iodide to react with $TMSCF_3$ at higher temperatures.



Scheme 2. Typical reaction pathways of $TMSCF_3$.

Previously, we disclosed that the Li^+ could be employed in preventing such runaway reactions by controlling the amount of soluble free nucleophilic fluoride present in the reaction solution,[16] which led us to re-examine the conditions reported by Hu and co-workers (Scheme 1).[10] Contrary to the reported results, we observed >60% of **2a** (Table 1, Entry 1 & 2). Further optimization of the conditions to improve the yield with NaI proved challenging. To test the effect of Li^+, NaI was replaced with LiI. As the LiI requires higher temperatures to activate $TMSCF_3$, our previously developed conditions,[16a] LiI/diglyme/170 °C, were chosen with PPh_3 as an additional reagent. The very first experiment carried out in the presence of LiI/PPh_3 produced 74% of **2a** (Entry 3) and prolonging the reaction time increased the formation of **2a** to 81% (Entry 4). When the reaction temperature was lowered to 110 °C, decrease in the reaction rate and yield were observed (Entry 5). To reduce the reaction temperature and increase the reaction rate, two strategies were considered, 1) employing electron rich phosphines such as $(Me_2N)_3P$ to increase the nucleophilicity of ylide intermediate. However, our investigation at various temperatures provided less than 15% of **2a** (Entry 6-8), which could be attributed to the competing reaction of the electron-rich phosphine with the aldehyde.[17] Further, use of dibenzothiophene (Entry 9) or $(PhO)_3P$ (Entry 10) in place of the PPh_3 resulted in less than 8% of **2a**. 2) The second strategy was to study the effect of aprotic polar solvents such as DMF, as these solvents are commonly used for nucleophilic substitution reactions involving alkali-metal halides and well known for the

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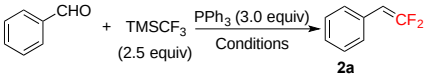
activation of silicon centers.[18] Although, $TMSCF_3$ reacted at room temperature in DMF with LiI, only 10% of the desired product **2a** was obtained (Entry 11) along with 34% of nucleophilic CF_3 addition product. Further reactions were investigated in solvent systems comprised of DMF and various less polar solvents (THF, CH_3CN, dioxane, diglyme, benzene and toluene) in different ratios (Entry 12-17). 8% DMF in dioxane and 16% DMF in toluene were found to be the optimum ratio for the reactions at 120 °C. Further optimization of reagents was carried out in 8% DMF/dioxane to obtain the conditions described in Table 2.

Table 1. Reaction conditions screening.[a]



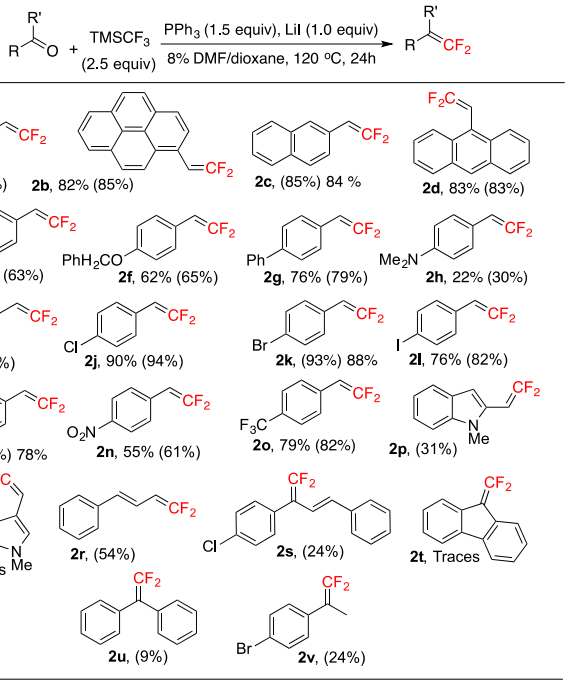
2a

Entry	Solvent	T °C	t (h)	MX (equiv)	Conv (%)[b]
[c]1	THF	70	10	NaI (0.6)	64
[c]2	THF	110	10	NaI (6)	69
3	Diglyme	170	1	LiI (2.0)	74
4	Diglyme	170	3	LiI (2.0)	81
5	Diglyme	110	37	LiI (2.0)	47
[d]6	Diglyme	70	24	LiI (2.0)	15
[d]7	Diglyme	110	7	LiI (2.0)	10
[d]8	Diglyme	170	1	LiI (2.0)	15
[e]9	Diglyme	170	3	LiI (2.0)	8
[f]10	Diglyme	170	3	LiI (2.0)	7
11	DMF	RT	20	LiI (2.0)	10
12	5% DMF/THF	70	24	LiI (2.0)	35
13	5% DMF/THF	110	24	LiI (2.0)	77
14	5% DMF/Diglyme	170	0.5	LiI (2.0)	74
15	8% DMF/dioxane	120	24	LiI (2.0)	83
16	8% DMF/CH_3CN	120	24	LiI (2.0)	78
17	16% DMF/Toluene	120	15	LiI (2.0)	83

[a] Reactions were carried out on 0.25 mmol scale with 2.5 mL of solvent. [b] Conversions were determined by ^{19}F NMR using C_6F_6 as an internal standard. [c] 3.0 equiv $TMSCF_3$ was used. [d] $(Me_2N)_3P$ (2.0 equiv) replaced PPh_3. [e] dibenzothiophene (3.0 equiv) replaced PPh_3. [f] $(PhO)_3P$ (3.0 equiv) replaced PPh_3.

The scope of the optimized conditions on several aromatic aldehydes was investigated (Table 2). The simple polycyclic aromatic aldehydes provided greater than 80% yield (**2a-2d**). Substrates with electron-donating substituents such as -OMe, -OCH_2Ph and -Ph yielded greater than 60% of the corresponding 1,1-difluoroalkenes (**2e-2g**). Typically amino groups are sensitive functional groups for reaction with $TMSCF_3$. However, under the present conditions, the *N,N*-dimethylamino benzaldehyde underwent reaction to give 30% of **2h**. Excellent yields of products, **2i-2l**, were obtained with halogen containing aldehydes. The substrates with electron-withdrawing groups such as -CN, -NO_2 and –CF_3 groups also furnished good product yields (**2m-2o**). Among the nitrogen containing heterocyclic aldehydes investigated, 31% of **2p** was obtained with indole-2-carboxaldehyde, whereas only traces of **2q** was detected with indole-3-carboxaldehyde and no product was observed with pyridine-3-carboxaldehyde. The α,β-unsaturated carbonyls like cinnamaldehyde and 4'-chlorochalcone underwent reaction to provide the difluoroalkenes **2r** (54%) and **2s** (24%); in these cases no CF_3 addition to carbonyl groups or cyclopropanation of double bonds was seen. Under the present conditions, fluorenone produced traces of **2t**, whereas benzophenone yielded 9% of **2u**. When the enolizable 4-bromoacetophenone was investigated, only 24% of **2v** was observed.

Table 2. Substrate scope of aromatic aldehydes and ketones (**Condition A**).[a]



[a] Reactions were carried out on 0.25 mmol scale with 2.5 mL solvent. Isolated yield is presented without parenthesis. Conversions in parenthesis were determined by ^{19}F NMR using C_6F_6 as an internal standard.

We surmised that the enolization and consequent side reactions are pronounced at elevated temperatures and therefore milder conditions might be needed for sensitive functional groups containing aldehydes and ketones. Thus, the solvent combination strategy to lower the reaction temperature was further explored. As we discussed earlier, the singlet difluoromethylene can be generated with the right combination of solvent system at various temperatures. Therefore, various ratios of DMF/THF and DMF/toluene were investigated with 4-bromoacetophenone as a model substrate to carry out the reaction around the boiling point of $TMSCF_3$, to avoid $TMSCF_3$ staying in vapour phase in the reaction vessel's headspace, 30% DMF in toluene or 20% DMF in THF appeared to have similar reactivity in terms of unreacted $TMSCF_3$. However, 30% DMF in toluene seemed to produce higher yield of the desired product. Hence, DMF/toluene combination was chosen for further optimization. However, the reaction at room temperature

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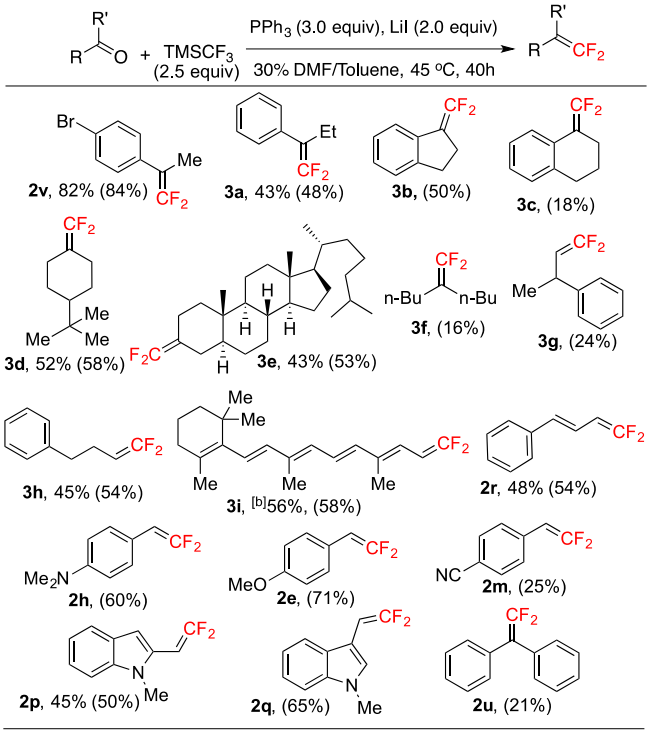
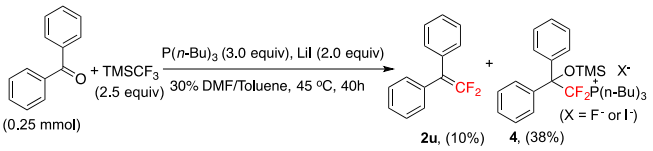
proceeded rather slowly. Therefore, reactions at various temperatures (45, 55, 65, & 75 °C) were investigated, and 45 °C found to be the optimum temperature with 84% conversion to **2v** over 40 hours (Table 3). Further, reducing the amount of PPh_3 or LiI decreased the reaction rate.

Table 3. Substrate scope of a variety of aldehydes and ketones (**Condition B**).[a]



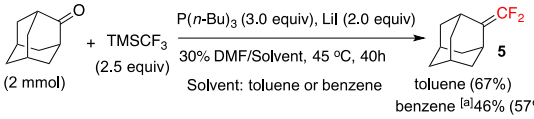
[a] Reactions were carried out on 0.25 mmol scale with 2.5 mL solvent. Isolated yield is presented without parenthesis. Conversions in parenthesis were determined by ^{19}F NMR using C_6F_6 as an internal standard. [b] Light was excluded.

With milder optimized conditions, several enolizable and sensitive group containing carbonyl compounds were studied (Table 3). Propiophenone reacted moderately well to provide **3a** (43%), whereas the cyclic aryl alkyl ketones, indanone and α-tetralone, furnished **3b** and **3c**, in moderate and poor yields, respectively. Cyclic alkyl ketones such as 4-*tert*-butylcyclohexanone and 5α-cholestan-3-one yielded greater than 50% products (**3d** & **3e**). However, the open chain ketone, 5-nonanone, performed poorly to give 16% of **3f.** Aliphatic enolizable aldehydes such as 2-phenylpropanal and 3-phenylpropanal also reacted under these conditions, producing **3g** (24%) and **3h** (54%), respectively. Non-enolizable cinnamaldehyde yielded 54% of **2r**. The difluoromethylene analogue of polyene containing retinal (**3j**) was obtained in 56% isolated yield. The poorly performing aromatic aldehydes (Table 2) at 120 °C, namely, 4-(dimethylamino)benzaldehyde, indole-2-carboxaldehyde and indole-3-carboxaldehyde performed well under these conditions to provide **2h** (60%), **2p** (50%) and **2q** (65%) products, accordingly. However, no product was obtained in the case of pyridine-3-carboxaldehyde. Only, 25% of **2m** was obtained with 4-cyanobenzaldehyde. Furthermore, no desired product was observed in the reactions with *N*-methyl and *N*-phenyl succinimides and the simple aromatic carboxylic ester, ethyl benzoate. When benzophenone was investigated under the present milder conditions (**B**), 21% of **2u** was formed. To avoid steric crowding, which may be an inhibiting factor in the formation of oxaphosphatane intermediate; the tributylphosphine (cone angle (θ) = 132°) was employed instead of PPh_3 (cone angle (θ) = 145°).[19] Consequently, 10% of the expected product along with the 38% of the TMS protected intermediate **4** was observed in NMR analyses (Scheme 3; also see SI).[20] One can speculate that the oxaphosphatane formation is hindered and therefore the betaine picks up a TMS group leading to the formation of **4**. Our attempts to increase the conversion by increasing the temperature resulted in little improvement in the yield. For instance, only 17% **2u** was obtained at 75 °C. No product was observed when dibenzothiophene, diphenylsulfide and tetrahydrothiopyran were employed in place of $(n\text{-Bu})_3P$. Scalability and ease of the experiments were also demonstrated on the bench top on a gram scale (20 mmol) using 4-bromoacetophenone to obtain 76% isolated yield (3.46 g) of **2v** (see SI).[21]



Scheme 3. Difluoromethylenation of benzophenone. Conversions in parentheses were determined by ^{19}F NMR using C_6F_6 as an internal standard.

Motivated by the fact that the adamantyl skeleton, referred in medicinal chemistry as a lipophilic-bullet motif for its compact nature, found as a key structure in seven approved drugs in the market,[22] difluoromethylenation of 2-adamantanone was investigated. Under the conditions **A** (Table 2) and **B** (Table 3)**,** the 2-admantanone failed to react. Interestingly, when $(n\text{-Bu})_3P$ was employed, 67% **5** was obtained (Scheme 4). However, the product was volatile, therefore benzene was employed as a co-solvent for its easy separation.



Scheme 4. Difluoromethylenation of 2-adamantanone. Conversions in parentheses were determined by ^{19}F NMR using C_6F_6 as an internal standard. [a] isolated yield.

In the control experiments carried out under the conditions **A** and **B** with 2-napthaldehyde and 4-bromoacetophenone, respectively, in the absence of DMF or LiI or PPh_3, no desired product was observed. Similarly, when the LiI was replaced with Ph_3PO or LiF, the reactions failed to produce product. In all these cases, majority of the $TMSCF_3$ remained unreacted. Though the LiF failed to react with $TMSCF_3$ under the reaction conditions, TMSF was observed in all the reactions, which is likely formed by the reaction of the in situ formed, more reactive TMSI or the $[Ph_3POTMS]^+$ intermediates. Consequently, the

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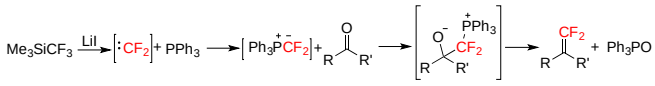
reactions should only require catalytic amount of LiI. When catalytic amount of LiI (10 mol%) was employed under the conditions **A** with 2-napthaldehyde, 68% of the desired alkene (**2c**) was obtained. However, prolonging the reaction time did not improve the product formation. Furthermore, the TMSI produced in the reaction mixture could be consumed by reacting with the solvents.[23] Therefore, it is safe to say that the Li^+ lowers reactivity of fluoride such that it only reacts with more Lewis acidic silicon center before it reacts with $TMSCF_3$. In the experiments carried out with 2-napthaldehyde in the presence of 1,1-diphenylethylene, the difluoromethylenation of carbonyl prevailed over the cyclopropanation of the alkene—traces of *gem*-difluorocyclopropane. On the other hand, in the absence of 2-napthaldehyde and PPh_3, >30% of such product was observed. Based on the above observations and control experiments, the following mechanism was proposed (Scheme 5).



Scheme 5. Proposed mechanism.

In conclusion, this work emphasizes the effect of Li^+ in the singlet difluoromethylene generation and prevention of undesired decomposition of $TMSCF_3$. Furthermore, by finding the right conditions to activate $TMSCF_3$ in the presence of phosphines at various temperatures (RT to 170 °C), we have achieved a practical and versatile one-pot procedure for the synthesis of a series of functionalized *gem*-difluoroalkenes, including difluoro analogs of biologically active compounds, from aldehydes and ketones. The work also demonstrates that the mixed solvent system can be critical to achieve controlled depletion of $TMSCF_3$. We believe that the results presented in this paper will, in addition to providing access to interesting *gem*-difluoroalkenes, propel the researchers to discover useful direct difluoromethylene transfer methods using the readily available Ruppert-Prakash reagent.

Acknowledgements

Financial Support from the Loker Hydrocarbon Research Institute is gratefully acknowledged.

Keywords: *gem*-Difluoroolefins • Carbonyls • LiI • Triphenylphosphine • Ruppert-Prakash reagent

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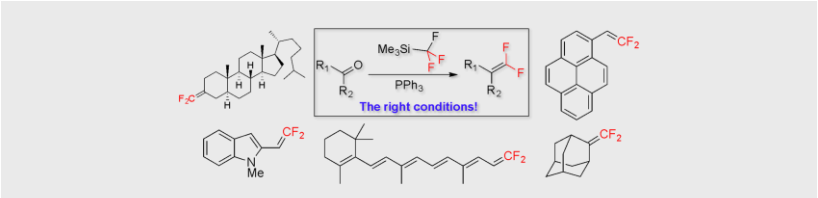

What can Li^+ do? When Me_3SiCF_3 is reacted with LiI for the formation of singlet difluoromethylene, LiF formed is less soluble in the reaction medium allowing controlled depletion of Me_3SiCF_3. Such an understanding has offered us the right conditions for the direct difluoromethylenation of carbonyl compounds using $TMSCF_3$ with phosphines at various temperatures in a Wittig type reaction.

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Direct Difluoromethylenation of Carbonyl Compounds Using $TMSCF_3$: The Right Conditions

KEY TOPIC: *gem*-Difluoroolefin Synthesis

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