Solkane® 365mfc is an environmentally benign alternative solvent for trifluoromethylation reactions[†]

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Solkane® 365mfc is introduced for the first time as a new, environmentally benign alternative solvent for nucleophilic trifluoromethylation reactions.

Trifluoromethylated compounds are finding widespread application in pharmaceuticals, agrochemicals, and liquid crystals due to their extreme properties.1 Among various methodologies available for the preparation of trifluoromethylated compounds, the nucleophilic trifluoromethylation reaction using Ruppert's reagent ((trifluormethyl)trimethylsilane, Me₃SiCF₃) is the most direct method for introducing a CF₃ unit into synthetically useful carbonyl compounds and others.² Me₃SiCF₃ was developed by Ruppert et al.,3 and in 1989, Prakash et al. found tetrabutylammonium fluoride (TBAF) to be an effective catalyst for the trifluoromethylation reaction of carbonyl compounds with Me₃SiCF₃.⁴ Me₃SiCF₃ is now becoming popular as the Ruppert-Prakash reagent and considerable efforts have been devoted to the development of efficient catalytic systems for this process.² Although Me₃SiCF₃ was initially too expensive to afford scaling up the corresponding reaction, TOSOH-FTEC INC. developed a process to make the reagent in up to ton quantities at about one-fifth of the price using a contained system avoiding problems with the ozone-depleting starting material.⁵ Since then, Me₃SiCF₃ has been widely used in both academia and industry.6-8 Among several solvents used for the trifluoromethylation reaction by Me₃SiCF₃, the most commonly used is DMF,⁷ followed by ether solvents and dichloromethane.^{6,8} An especially beneficial effect caused by DMF is believed to be responsible for the coordination of the silicon atom on Me₃SiCF₃ to stabilize the hypervalent silicate species.7e,h,i,8d However, these solvents have some drawbacks, such as toxicity and peroxide formation. Increasingly tighter restriction on the use of organic solvents in industrial synthesis9 led us to search for an environmentally benign alternative solvent for the trifluoromethylation reaction. Although solvent-free conditions seem to be suitable for green chemistry, in most cases, a solvent is often required to assist in working-up processes and transporting of materials.¹⁰ The use of ionic liquids as alternative reaction media for organic chemistry is another solution.11 Kim and Shreeve succeeded in Cu(I)-mediated nucleophilic trifluoromethylation in ionic liquid media by the use of original ionic liquids; in comparison, the corresponding trifluoromethylation did not proceed in a commercially available imidazolium ionic liquid, $[bmim][PF_6]$.¹² Fluorous technology is also attractive from a green chemistry point of view; however, issues such as the environmental impact of fluorous chemicals are a matter of debate.¹³ Curran and coworkers introduced benzotrifluoride and related compounds as new solvents for traditional organic synthesis and for fluorous synthesis.¹⁴ In this paper, we report that a hydrofluorocarbon, Solkane® 365mfc (1,1,1,3,3-pentafluorobutane) is a potentially useful alternative solvent for trifluoromethylation reactions (Scheme 1).



Scheme 1 Solkane® 365mfc is an environmentally benign alternative solvent for trifluoromethylation reactions of carbonyl compounds.

Solkane 365mfc, is a non flammable liquid developed by Solvay Fluor GmbH. Solkane 365mfc has no impact whatsoever on the ozone layer, and it passed all the necessary toxicological tests successfully.^{15,16} It is used as an insulating and blowing agent for polyurethane foams, whose main uses are thermal insulation of residential and industrial buildings as well as cold storage. Solkane 365 mfc is now produced in a pilot plant with a capacity of several hundred tons per year. Despite its environmentally attractive properties, no examples of its use for organic reactions are available. Due to the specific character that fluorinated compounds tend to dissolve well in fluorinated solvents, Solkane 365mfc might be an ideal solvent for trifluoromethylation reactions.

The catalyst/solvent systems represented by LiOAc/DMF,^{7e} TBAF/THF⁴ and P^tBu₃/DMF⁷ⁱ act as a good trigger for the trifluoromethylation of aldehyde 1a with Me₃SiCF₃; however, the catalysts were completely useless in Solkane® 365mfc (Table 1, runs 1-6), and even TBAF was ineffective for this transformation in Solkane® 365mfc, despite its big success as a catalyst for the trifluoromethylation reaction, and the desilylated 2a was obtained only in 23% yield (run 4). The K₂CO₃/DMF system is also quite effective for this type of reaction (run 7), but the result using Solkane® 365mfc was not comparable to the reported one.7h When we used a catalytic amount of K2CO3 in Solkane® 365mfc, the desired product was obtained in 64% yield after stirring for 17 h (run 8). We next focused our attention on the use of purely inorganic bases as catalysts. Reaction of 1a with Me₃SiCF₃ in the presence of catalytic amounts of NaOH in Solkane® 365mfc at rt for 4 h gave 2a in 83% yield, confirming

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 Table 1
 Trifluoromethylation of Naphthyl aldehyde (1a) in Solkane®

 365mfc

ОН		Me ₃ SiCF ₃ (2.0 equiv) additive Solkane®365mfc, rt	equiv) Me ₃ SiO CF ₃			
Ť	1a		2a			
Run	Solvent	Additive (equiv.)	Time	Yield (%)		
1	DMF	LiOAc (0.05)	10 min	98 ^{<i>b</i>}		
2	Solkane ^(R)	LiOAc (0.2)	24 h	trace		
3	THF	TBAF (0.2)	90 min	52		
4	Solkane ^(R)	TBAF (0.2)	45 min	23		
5	DMF	$P^{t}Bu_{3}(0.1)$	30 min	99°		
6	Solkane ^(R)	$P^{t}Bu_{3}(0.2)$	24 h	trace		
7	DMF	$K_2CO_3(0.2)$	5 min	85 ^d		
8	Solkane ^(R)	$K_2CO_3(0.2)$	17 h	64		
9	Solkane(R)	NaOH (0.2)	4 h	83		
10	Solkane(R)	KOH (0.2)	20 min	96		
11	Solkane(R)	$CsOH \cdot H_2O(0.2)$	10 min	94		
12	Solkane ^(R)	$CsOH \cdot H_2O(0.1)$	10 min	97		
13	Solkane ^(R)	CsF (0.2)	20 min	99		
14^{e}	Solkane ^(R)	KOH (0.2)	5 h	99.5		

^{*a*} Isolated yield by silica-gel column chromatography. ^{*b*} See ref. 7g. ^{*c*} See ref. 7i. ^{*d*} See ref. 7h. ^{*e*} The reaction was performed on a slightly large scale and the product **2a** was isolated without using any solvent by filtration and distillation. Solkane® 365mfc was recovered in 89% yield. See ESI.†

our expectations (run 9). We then examined the effect of a variety of inorganic hydroxides as catalysts for the trifluoromethylation reaction of **1a** with Me₃SiCF₃. Common bases, such as KOH and CsOH·H₂O were equally very effective as an initiator, affording the CF₃ adduct **2a** in excellent yields within 10–20 min (runs 10–12). Caesium fluoride (CsF) was also found to be efficient for this transformation to furnish **2a** quantitatively (run 13). In a slightly large-scale preparation, the product was isolated by filtration and distillation without using any solvent to give **2a** in 99.5% yield while recovering Solkane® 365mfc at 89% yield (run 14).

We then applied these conditions to the trifluoromethylation of a number of aldehydes (1b-k), and ketones (1l-o) to assess the potential scope and limitations of the method. The best results are summarized in Table 2. Aryl aldehydes, such as sterically demanding 1-naphthaldehyde (1b), conventional benzaldehyde, tolylaldehyde, o, m, or p-methoxybenzaldehyde, reacted in high yields (entries 2-7, 80-94%). Entries 8-9 further demonstrated that the present conditions tolerated functional groups on the aromatics, such as bromo and nitro groups. Selective 1,2addition was observed in the reaction of cinnamyl aldehyde (1) with Me_3SiCF_3 to furnish the trimethylsilyl ether of allyl alcohol 2j in high yield (84%, entry 10). The reactions involving enolizable aldehydes posed some additional challenges due to the possibility of proton abstraction by the hard anion. As shown in entry 11, the enolizable phenethyl aldehyde (1k) was nicely converted to the corresponding α -trifluoromethylalcohol 2k in 82% yield under the CsF condition. Ketones (11-0) also reacted nicely under similar conditions described above in good to high vields (entries 12-15).

Next, trifluoromethylation of L-phenylalanine-derived oxazolidin-5-one 3 with Me_3SiCF_3 in Solkane 365mfc to adduct 4 was examined. Adduct 4 is an intermediate for the

Table 2 Trifluoromethylation of aldehydes and ketones with Me_3SiCF_3 in Solkane® 365mfc

	0			additive (0.2 equ	_{uiv)} Me ₃ S	iO	CF ₃
R^{1}	^{⊥⊥} R²	+ Me ₃ SI-CF (2.0 equiv)	3	Solkane®365mfc	,rt	R ¹	R ²
	1	(-1- /				2	
Entry	1	\mathbf{R}^1	\mathbb{R}^2	Additive	Time/min	2	Yield (%) ^a
1	1a	2-naphthyl	Н	КОН	20	2a	96
2	1b	1-naphthyl	Н	КОН	30	2b	92
3	1c	Ph	Η	KOH	15	2c	91
4	1d	$4 - MeC_6H_4$	Н	КОН	60	2d	90
5	1e	$2-MeOC_6H_4$	Н	CsOH·H ₂ O ^b	60	2e	80
6	1f	3-MeOC ₆ H ₄	Н	KOH	60	2f	92
7	1g	4-MeOC ₆ H ₄	Н	КОН	25	2g	94
8	1h	$4-BrC_6H_4$	Н	CsOH·H ₂ O ^b	20	2h	88
9	1i	$4-NO_2C_6H_4$	Н	CsF	20	2i	94
10	1j	PhCH=CH	Н	CsOH·H ₂ O ^b	20	2j	84
11	1k	PhCH ₂ CH ₂	Н	CsF	20	2ĸ	82
12	11	2-naphthyl	Me	КОН	60	21	97
13	1m	Ph	Me	CsOH·H ₂ O ^b	20	2m	89
14	1n	Ph	Ph	CsOH·H ₂ O ^b	120	2n	93
15	10	cyclohexanor	ne	KOH	20	20	72

^{*a*} Isolated yield by silica-gel column chromatography. ^{*b*} CsOH·H₂O (0.1 equiv) was used.

synthesis of protease inhibitors. In a previous report, when oxazolidin-5-one **3** was treated with Me_3SiCF_3 and catalytic amounts of TBAF in THF, the adduct was obtained in moderate yield, and replacement of TBAF with CsF and sonication resulted in a substantial improvement of the yield (95%).¹⁷ In Solkane® 365mfc, the reaction also proceeded quite nicely in the presence of CsF without sonication to afford **4** in 97% yield (Scheme 2).



Scheme 2 Trifluoromthylation of oxazolidin-5-one 3 with Me₃SiCF₃ in Solkane® 365mfc.

Finally, nucleophilic ring-opening fluorination of aziridines¹⁸ with TBAF in Solkane® 365mfc was briefly examined. The reaction proceeded quite smoothly despite substitution of the arylsulfonyl group (Scheme 3). Our results are comparable to those previously reported on nucleophilic ring-opening fluorination of aziridines in an ionic liquid.¹⁹



Scheme 3 Nucleophilic ring-opening fluorination of aziridines with TBAF in Solkane® 365mfc.

In conclusion, Solkane(R) 365mfc is introduced as a novel and environmentally benign alternative solvent for the nucleophilic trifluoromethylation of aldehydes, ketones and oxazolidinone in the presence of inorganic bases. Solvolysis of Me₃SiCF₃ by Solkane® 365mfc via fluorophilic attraction might be responsible for this efficient transformation. It is highly advantageous that no environmentally harmful solvents, such as chlorinated alkanes or DMF, are required in any of the processes and the products, catalysts and Solkane® 365mfc are readily isolated, removed and recovered by simple filtration and distillation, respectively. This is the first example of the use of Solkane® 365mfc as a medium in an organic reaction. We believe that Solkane® 365mfc will be a green halogenated solvent for industrial use.¹⁶ Synthetic utility of this solvent will be further demonstrated by organic reactions with non-fluorinated reagents.

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