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Short communication

N-2-Iodobenzylcinchoninium bromide is effective for catalytic enantioselective trifluoromethylation of azomethine imines in Solkane® 365mfc

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ABSTRACT

Solkane® 365mfc (1,1,1,3,3-pentafluorobutane, $CF_3CH_2CF_2CH_3$) is proven to be an environmental benign alternative solvent for the catalytic enantioselective trifluoromethylation of azomethine imines **1**. High chemical yields and enantioselectivities (up to 96% ee) were achieved by employing previously unknown and structurally simple cinchona alkaloid ammonium salt, *N*-2-iodobenzylcinchoninium bromide **3d** as a catalyst.

1. Introduction

The incorporation of a trifluoromethyl group into organic or inorganic molecules has received considerable attention because they possess unique physical and chemical properties which are indispensable in the field of medicinal, agrochemical and material chemistry [1]. Thereby, tremendous effort has been directed at the introduction of trifluoromethyl groups into organic molecular frameworks [2]. Among a variety of synthetic methodologies available for the preparation of trifluoromethylated compounds, the nucleophilic trifluoromethylation reaction using the Ruppert–Prakash reagent ((trifluormethyl)trimethylsilane, Me_3SiCF_3) is the most direct method for introducing a CF_3 unit into synthetically useful compounds [2]. Thanks to the great effort of TOSOH-FTEC INC. in developing 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 [3], now a number of catalytic systems are available using Me_3SiCF_3, and stereoselective variants also have been extensively investigated in recent years under chiral catalysis. Ever since various catalytic systems were devised for asymmetric trifluoromethylation using Me_3SiCF_3 [4], several examples of enantioselective trifluoromethylation in various solvents have been reported so far, that is, using CH_2Cl_2 [5], toluene [6], ether solvents [7] or DMF [8] as a solvent. However, these solvents have some drawbacks such as toxicity and peroxide formation, and with increasingly tighter restrictions on the use of organic solvents in industrial synthesis for green chemistry [9], these facts led us to search for an alternative environmentally benign solvent for the asymmetric trifluoromethylation reaction. Recently, we developed the first enantioselective trifluoromethylation of imine equivalents, azomethine imines with Me_3SiCF_3 in toluene/CH_2Cl_2 (2/1) [10]. In this regard, we came up with the idea of investigating enantioselective trifluoromethylation in commercially available Solkane® 365mfc (1,1,1,3,3-pentafluorobutane), developed by Solvay Fluor GmbH, as an environmentally friendly liquid [11].

Solkane® 365mfc is non-toxic and has no impact whatsoever on the ozone layer. Although Solkane® 365mfc has a flash point below −27 °C, it is difficult to ignite. The minimum ignition energy is around 50 times higher than that of *n*-pentane and is 10.8 mJ (25 °C, 8 vol% in air at 1 bar). It is used as an insulating and blowing agent for polyurethane foams, whose main uses are the thermal insulation of residential and industrial buildings, as well as in cold storage. Solkane® 365mfc is now produced in a pilot plant with a capacity of several hundred tons per year. We previously reported that Solkane® 365mfc can be used as an environmentally benign alternative solvent for several transformations, namely the trifluoromethylation of carbonyl compounds [12], the catalytic asymmetric Friedel–Crafts alkylations of indoles [13], the homocoupling reaction of terminal alkynes [14], the trifluoromethanesulfonylation of indoles [15] and the Suzuki–Miyaura cross coupling reaction [16]. As part of our ongoing research project concerning the enantioselective synthesis of organofluorine compounds [4,6,10], we required the development of enantioselective trifluoromethylation of azomethine imines with Me_3SiCF_3

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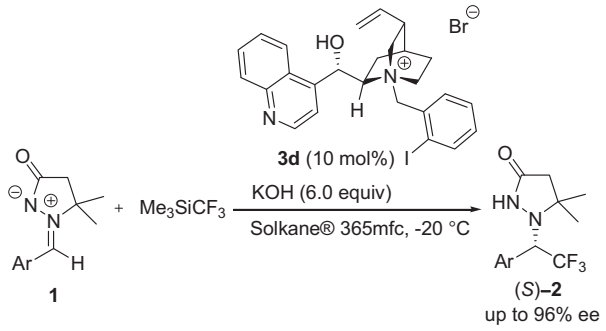


Scheme 1. Enantioselective trifluoromethylation of azomethine imines in Solkane® 365mfc.

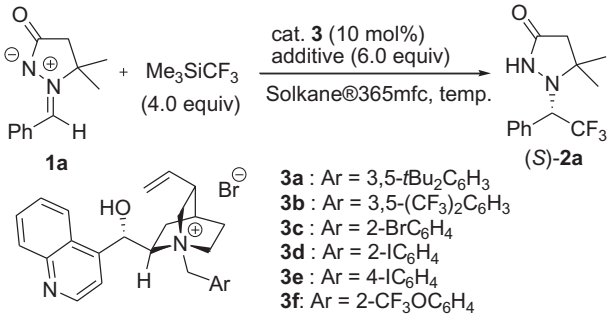
using Solkane® 365mfc as a green medium in organic reactions. This reaction was previously achieved by *N*-3,5-bis(*tert*-butylbenzyl)cinchoninium bromide (**3a**) as a catalyst in toluene/CH_2Cl_2 [10]; however, **3a** is not efficient enough for this transformation in Solkane® 365mfc. We herein report that previously unknown *N*-2-iodobenzylcinchoninium bromide **3d** is effective as a chiral catalyst for enantioselective trifluoromethylation of azomethine imines in Solkane® 365mfc. The novel catalyst **3d** has a very simple structure and is readily synthesized in one step from commercially available cinchonine and *o*-iodobenzyl bromide in high yield (Scheme 1).

2. Results and discussion

First, our original catalytic system for enantioselective trifluoromethylation of **1a** in toluene/CH_2Cl_2 (2/1) was tested in Solkane® 365mfc as a medium. A stoichiometric amount of KOH was added to a mixture of **1a** and 4.0 equiv. of Me_3SiCF_3 in Solkane® 365mfc in the presence of a catalytic amount of *N*-3,5-bis(*tert*-butylbenzyl) cinchoninium bromide (**3a**) at −10 °C, affording the trifluoromethylated adduct **2a** in 96% with 78% ee (Table 1, run 1). This result was inferior to chiral induction using toluene/CH_2Cl_2 (2/1) as a solvent under the same reaction condition (81%, 82% ee, run 2). We next investigated other additives in an attempt to improve enantioselectivity (runs 3–5); however, none of the additives provided a better result in terms of reactivity and enantioselectivity. We then turned our attention to screening a broad range of ammonium bromides derived from cinchona alkaloids to find a proper catalyst for the transformation in Solkane® 365mfc (runs 6–10). We were pleased to find that the reaction with novel *N*-2-iodobenzylcinchoninium bromide **3d** in Solkane® 365mfc gave a superior result to the *ee* value of the reaction catalyzed by either **3a** and **3d** in toluene/CH_2Cl_2 (2/1) (87%, 83% ee, run 8 vs. runs 2, 9). The best result was obtained by treating **1a** with Me_3SiCF_3 (4.0 equiv.) at −20 °C in Solkane® 365mfc in the presence of **3d** (10 mol%) and KOH (6.0 equiv.), leading to the isolation of **2a** in 99% yield with 86% ee (run 11). It should be noted that the catalyst **3d** is very efficient in spite of its simple structure, and can be prepared in one step from commercially available cinchonine and *o*-iodobenzyl bromide. *N*-2-Trifluoroethoxybenzylcinchoninium bromide **3f** also proved to be an almost equally effective catalyst, affording **2a** in 97% yield with 84% ee (run 12).

With conditions optimized, several families of azomethine imines differing in the nature of their aryl groups were submitted to the action of our trifluoromethylation system, to explore the scope of the chiral ammonium bromide **3d**/KOH catalyst in Solkane® 365mfc (Table 2). A series of azomethine imines **1a–h** were nicely converted to the corresponding trifluoromethylated adducts **2a–h** in high yield in 85–99% yield with high enantioselectivities up to 96% ee, these being almost independent of the functional groups on the aromatic ring (entries 1–8). What is more, in a slightly large-scale preparation, the product was isolated by filtration and distillation to give **2a** (86% ee), and 72% yield after recrystallization, while Solkane® 365mfc was recovered in 72% (entry 9).

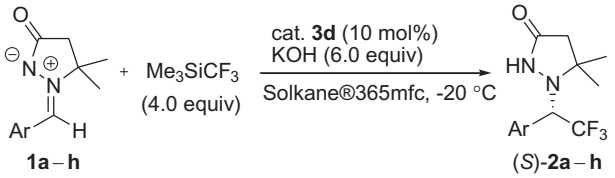
Table 1
Optimization of reaction conditions for the enantioselective trifluoromethylation of **1a** with Me_3SiCF_3 in Solkane® 365mfc.



Run	Catalyst	Additive	Time (h)	Yield (%)	ee[a]
1	**3a**	KOH	8	96	78
2[b]	**3a**	KOH	12	81	82
3	**3a**	NaOH	16	15	80
4	**3a**	CsF	10	57	78
5	**3a**	KOPh	10	20	76
6	**3b**	KOH	15	76	11
7	**3c**	KOH	12	85	63
8	**3d**	KOH	12	87	83
9[b]	**3d**	KOH	7	70	82
10	**3e**	KOH	14	56	37
11[c]	**3d**	KOH	14	99	86
12[c]	**3f**	KOH	12	97	84

[a] Determined by chiral HPLC.
[b] Toluene/CH_2Cl_2 (2/1) was used as solvent.
[c] The reaction was carried out at −20 °C.

Table 2
Enantioselective trifluoromethylation of azomethine imines **1a–h** with Me_3SiCF_3 catalyzed by **3d** in Solkane® 365mfc.



Entry	1	R	Time (h)	Yield (%)	ee[a]
1	**1a**	Ph	14	99	86
2[b]	**1b**	3-$MeOC_6H_4$	10	80	84
3[b,c]	**1c**	4-$MeOC_6H_4$	18	65	89
4[b]	**1d**	3-MeC_6H_4	12	87	89
5[b]	**1e**	4-MeC_6H_4	12	95	86
6	**1f**	4-*i*PrC_6H_4	17	90	96
7[b]	**1g**	4-*t*BuC_6H_4	21	94	96
8[b]	**1h**	4-FC_6H_4	21	84	74
9[d]	**1a**	Ph	18	72	86[e]

[a] Determined by chiral HPLC.
[b] Me_3SiCF_3 (6.0 equiv.) and KOH (10.0 equiv.) were used.
[c] **3f** was used instead of **3d**.
[d] The reaction was performed at a slightly large scale and product **2a** was isolated by filtration, distillation and recrystallization. Solkane® 365mfc was recovered in 72% yield.
[e] Before recrystallization.

3. Conclusion

In conclusion, Solkane® 365mfc was introduced as an environmentally benign alternative solvent for the enantioselective trifluoromethylation reaction of imine equivalents, azomethine imines **1**. The trifluoromethylated adducts can be readily converted into pharmaceutically important trifluoromethylated amines [10]. High chemical yields and enantioselectivities (up to 96% ee) were achieved by employing previously unknown *N*-2-iodobenzylcinchoninium bromide **3d** as a chiral catalyst. The novel catalyst **3d** has a very simple structure and is readily synthesized in one step from commercially available cinchonine and *o*-iodobenzyl bromide in high yield.

4. Experimental

4.1. Preparation of N-2-iodobenzylcinchoninium bromide 3d

A solution of cinchonine (200 mg, 0.68 mmol) and *o*-iodobenzyl bromide (222 mg, 0.75 mmol, 1.1 equiv.) in THF (20 mL)/MeCN (5 mL) was refluxed under a nitrogen atmosphere. After 12 h, the reaction mixture was concentrated under reduced pressure and recrystallized from CH_2Cl_2/diethyl ether to give **3d** (330 mg, 82%) as a solid with a bisque color; ^{1}H NMR (CD_3OD, 300 MHz) δ 1.07 (m, 1H), 1.89–1.96 (m, 4H), 2.47 (t, J = 11.7 Hz, 1H), 2.64 (q, J = 8.3 Hz, 1H), 3.27–3.34 (m, 1H), 3.48 (t, J = 11.3 Hz, 1H), 4.12–4.16 (m, 2H), 4.71–4.77 (m, 1H), 5.26–5.45 (m, 4H), 6.05 (ddd, J = 7.0, 10.4, 17.3 Hz, 1H), 6.69 (s, 1H), 7.29 (t, J = 7.5 Hz, 1H), 7.61 (t, J = 7.5 Hz, 1H), 7.84 (t, J = 3.8 Hz, 2H), 7.98 (d, J = 4.8 Hz, 2H), 8.14 (t, J = 9.0 Hz, 2H), 8.42 (d, J = 6.0 Hz, 1H), 8.96 (d, J = 4.5 Hz, 1H); ^{13}C NMR (CD_3OD, 150.9 MHz) δ 22.3, 24.7, 28.2, 38.9, 57.2, 58.2, 67.1, 67.4, 69.2, 106.4, 117.8, 121.1, 124.5, 126.1, 129.3, 130.2, 131.2, 132.2, 133.4, 136.6, 137.6, 142.7, 147.4, 148.7, 151.0; IR (KBr) 3382, 3163, 3089, 2884, 1639, 1587, 1509, 1459, 1424, 1329, 1281, 1206, 1169, 1130, 1053, 998, 932, 858, 760, 630, 551 cm^{-1}; mp = 230 °C (decomposed) (CH_2Cl_2/Et_2O); MS (ESI, m/z) 511 (M^+-Br).

4.2. Trifluoromethylation of azomethine imine 1a in Solkane® 365mfc catalyzed by 3d

To a stirred solution of azomethine imine **1a** (20.2 mg, 0.1 mmol), catalyst **3d** (5.9 mg, 0.010 mmol, 10 mol%) and KOH (33.7 mg, 0.60 mmol, 6.0 equiv.) in Solkane® 365mfc (1.0 mL) Me_3SiCF_3 (59.1 μL, 0.40 mmol, 4.0 equiv.) was added at −20 °C under a nitrogen atmosphere. After the reaction mixture was stirred at the same temperature for 14 h, it was quenched with sat. NH_4Cl aq. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 1/1) to give trifluoromethylated compounds (*S*) – **2a** (27.2 mg, 99%, 86% ee) as a white solid; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.32 (s, 3H), 1.48 (s, 3H), 1.62, 1.77 (AB quartet, J = 16.1 Hz, 2H), 4.51 (q, J = 8.9 Hz, 1H), 7.35–7.42 (m, 3H), 7.46–7.51 (m, 2H), 7.58 (brs, 1H); ^{13}C NMR (CD_3OD, 150.9 MHz) δ 25.0, 30.9, 44.9, 67.5 (q, J = 28.2 Hz), 67.6 127.7 (q, J = 280.2 Hz), 130.6, 131.3, 133.2, 133.5, 180.2; ^{19}F NMR ($CDCl_3$, 188 MHz) δ −70.7 (d, J = 9.2 Hz, 3F); IR (KBr) 3186, 3086, 2980, 2929, 1694, 1497, 1455, 1360, 1275, 1242, 1167, 1124, 1088, 1033, 898, 846, 710, 658 cm^{-1}; mp = 191–192 °C (CH_2Cl_2/hexane); MS (EI, m/z) 272 (M^+), HRMS calcd. for $C_{13}H_{15}F_3N_2O$: 272.1136, Found: 272.1138; the ee of the product was determined by HPLC using an OJ-H column (*n*-hexane/*i*-PrOH = 95/5, flow rate 0.5 mL/min, λ = 254 nm, τ_{maj} = 16.7 min, τ_{min} = 21.6 min).

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