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# **3,5-Bis(***n***-perfluorooctyl)benzyltriethylammonium Bromide** (F-TEBA): An Efficient, Easily Recoverable Fluorous Catalyst for Solid-Liquid PTC Reactions

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**Abstract:** A readily available 3,5-bis(perfluorooctyl)benzyl bromide and triethylamine were reacted under mild conditions to give 3,5-bis(*n*-perfluorooctyl)benzyltriethylammonium bromide (**F-TEBA**), an analogue of the versatile phase-transfer catalyst, benzyltriethylammonium chloride (TEBA), containing two fluorous ponytails. This perfluoroalkylated quaternary ammonium salt was successfully employed as a catalyst in a variety of reactions run under solid-liquid phase-transfer catalysis (SL-PTC) conditions. Thus, being both hydrophobic and lipophobic, **F-TEBA** could be quickly recovered in quantitative yields, and reused without loss of activity over several reaction cycles.

**Keywords:** alkylation; amino acids; fluorous catalysis; onium salts; phase-transfer catalysis

Polyfluorinated phase-transfer (PT) catalysts, such as quaternary phosphonium salts  $R^F_3R^1P^+Y^-$  ( $R^F = C_nF_{2n+1}(CH_2)_n^-$ ,  $R^1 = R^F$ , alkyl or Bn) and crown ether derivatives with typical light or heavy fluorous characteristics, and yet having retained the ability to transfer reactive anionic species from water or from a solid surface into a second distinct organic or perfluorocarbon phase, have recently emerged on the fluorous chemistry scene.<sup>[1]</sup> These initial studies were mainly focused on proving the viability of the fluorous approach in some well known phase-transfer catalysis (PTC) reactions, such as Finkelstein-type ionic displacement reactions of simple fluorous alkyl halides  $R^F(CH_2)_n X$ ,<sup>[2]</sup> and analogous nucleophilic substitutions on purely organic substrates.<sup>[3]</sup> The ease of recovery and the recycling efficiency of PT fluorous catalysts were thus demonstrated. In addition, reactivities and selectivities comparable to those observed with classical PT agents could be achieved through careful design of the fluorous catalysts, even in the case of reactions run in extremely non-polar perfluorocarbon phases.<sup>[2c,3b]</sup>.

The true potential of fluorous catalysts in PTC reactions; however, has not been fully discovered. This was particularly the case for polyfluorinated quaternary ammonium salts, which have not been extensively investigated as PT catalysts, in spite of the wide utility and versatility of their standard counterparts. In an early, remarkable example, due to Maruoka and co-workers, an enantiopure perfluoroalkylated quaternary ammonium bromide was applied to the asymmetric synthesis of both natural and unnatural aamino acids through enantioselective liquid-liquid PTC alkylation of a protected glycine derivative in a toluene-water system.<sup>[4]</sup> Similar non-fluorous PT catalysts provided faster reactions, and afforded the alkylated products in slightly better yields and *ee* values.<sup>[4b]</sup> Nevertheless, the fluorous ammonium salt could be recovered and reused for at least two additional runs. A restricted number of structurally simple fluorous ammonium salts were also used by others in catalytic reactions, though not strictly speaking as PT agents.<sup>[5]</sup>

Herein, we report the convenient synthesis of the perfluoroalkylated quaternary ammonium salt **F**-**TEBA** (Scheme 1), which could be thought of as the analogue of the multipurpose PT catalyst, benzyltriethylammonium chloride (TEBA). The application of this salt in solid-liquid phase-transfer catalysis (SL-PTC) reactions of synthetic relevance will also be reported.

3072

Various synthetic methods were reported to generate polyfluorinated ammonium salts,  $R^{F}_{(4-m)}R^{1}_{m}N^{+}Y^{-}$  $[R^{F} = C_{n}F_{2n+1}(CH_{2})_{n}, R^{1} = R^{F} \text{ or alkyl}], \text{ which could}$ be potentially useful as PT catalysts,<sup>[1]</sup> but because of the considerably lower reactivity of tertiary amines bearing  $R^{F}$  substituents,<sup>[6]</sup> the final *N*-quaternarization step often proved to be challenging. This drawback was avoided in the case of F-TEBA, which was readily obtained in 92% yield by N-alkylation of Et<sub>3</sub>N with the highly reactive fluoroponytailed benzyl bromide, 2, a valuable building block in the synthesis of fluorous molecules.<sup>[7]</sup> The preparation of **2** from the corresponding benzyl alcohol, 1, was also improved with respect to the original procedure, thus providing this alkylating agent on a multigram scale in 90% yield (see the Supporting Information).

F-TEBA was found to be highly soluble in polar organic solvents, such as MeOH and CH<sub>3</sub>CN, while it was found to be insoluble in water and in lipophilic organic solvents, such as toluene and hexane. In other media with higher affinity for fluorous substances, such as  $CF_3C_6H_5$  (BTF) or ethers, it exhibited highly temperature-dependent solubility profiles. As an example, F-TEBA was poorly soluble in dioxane at room temperature  $(1.3 \text{ mgmL}^{-1})$ . However, by raising the temperature from 25 to 80°C, its solubility increased more than ten times. Analogously, these same thermomorphic properties were previously observed in the case of quaternary phosphonium salts  $R_{3}^{F}R^{1}P+Y^{-[2]}$  As far as non-polar perfluorocarbon phases were concerned, F-TEBA has no appreciable solubilities at room temperature, but stable colloidal dispersions were formed upon refluxing and subsequent cooling (see the Supporting Information). The

**3**  $R^{F} = -C_{8}F_{17}$ ; **4**  $R^{F} = -(CH_{2})_{2}C_{8}F_{17}$ ; **5**  $R^{F} = -C_{8}F_{17}$ 

Figure 1. Ammonium salts soluble in perfluorocarbons.

 $-NEt_3^+$  polar head of **F-TEBA**, which was instrumental for its use as a PT agent, was likely to be responsible for this particular behaviour. Indeed, related ammonium salts, 3,<sup>[5b]</sup> 4,<sup>[2c]</sup> and 5 (Supporting Information) with a  $-NH_3^+$  polar head attached to a 3,5-bis (perfluoroalkylated)aryl ring (Figure 1) were found to be soluble in perfluorocarbons. Unfortunately, the reactive nature of the  $-NH_3^+$  group imposes serious limitations on the applicability of such salts in many relevant PTC processes, especially those involving basic reagents.

To evaluate the efficiency of F-TEBA, we focused our attention on solid-liquid phase-transfer catalysis (SL-PTC), another neglected facet of fluorous PTC. Indeed, most fluorous PT catalysts described thus far were tested under liquid-liquid (water-organic solvent or water-perfluorocarbon) conditions, or in triphasic systems, consisting of a fluorous, organic, and an inorganic phase,<sup>[1]</sup> while in just one case, simple SL-PTC nucleophilic substitutions were described.<sup>[3a]</sup> Three representative reactions (Scheme 2, Scheme 3, and Scheme 4) were thus chosen, in which a reactive anion was generated on the surface of solid K<sub>2</sub>CO<sub>3</sub> suspended in an anhydrous organic solution containing the reagents and F-TEBA. The latter transferred the anion, as a reactive ion-pair, from the surface of the solid base into the organic phase.

The epoxide ring-opening reaction, shown in Scheme 2, was selected for its versatility in the preparation of aziridines and 2,6-substituted morpholines,<sup>[8]</sup> both used in stereoselective synthesis as chiral auxiliaries and ligands, while *N*-alkylation of trifluoroacet-amide with 2-bromo esters, such as ethyl 2-bromopropanoate (Scheme 3), provided access to a large number of natural and unnatural  $\alpha$ -amino acids.<sup>[9]</sup> In both cases, **F-TEBA** gave results identical to those



**Scheme 2.** Ring-opening reaction of phenyl glycidyl epoxide under SL-PTC conditions.



i) CBr<sub>4</sub>, PPh<sub>3</sub>, THF, t = 5 h, T = 20 °C, 90%; ii) Et<sub>3</sub>N, EtOH, t = 6h, reflux, 92%.

#### Scheme 1. Synthesis of F-TEBA.

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**Scheme 3.** *N*-Alkylation of trifluoroacetamide with ethyl 2bromopropanoate under SL-PTC conditions.

obtained with TEBA, the catalyst of choice for these reactions, thus showing that the introduction of the fluorous substituents had no adverse effects on the catalytic activity of these types of ammonium salts (for reaction details see the Supporting Information).

There has been considerable interest in the development of efficient procedures for the synthesis of enantiomerically pure N-alkyl amino acids and esters, due to their importance as intermediates in the synthesis of biologically active products. A functional methodology, amenable to large-scale applications, was reported by one of us, and was based on the selective N-monoalkylation of N-(2-nitrobenzenesulfonyl)- $\alpha$ -amino acid esters, 6, under mild SL-PTC conditions to give compounds of the general formula, 7 (Scheme 4).<sup>[10]</sup> The same reaction applied to N-(4-nitrobenzenesulfonyl)- $\alpha$ -amino esters, 8, allowed a convenient access to compounds, 9, the starting materials the synthesis of  $\alpha$ -4-nitrobenzene- $\alpha$ -amino for acids,<sup>[11]</sup> which have attracted considerable attention for the design of new oligopeptidic fragments. F-**TEBA** proved to be a suitable catalyst for this PTC process, as shown by the results collected in Table 1 and Table 2.

The reaction between the L-phenylalanine derivative, **6a**, and a slight excess of allyl bromide (1.1 mol equiv.), in the presence of anhydrous  $K_2CO_3$  (1.5 mol equiv.), was chosen in order to determine the suitable conditions for the use of **F-TEBA** (Table 1).

In both the case of TEBA (entry 5) and **F-TEBA** (entry 8), the best results were obtained with a catalyst loading of 10 mol% with respect to the substrate, in refluxing CH<sub>3</sub>CN (entry 8). The reaction with **F-TEBA** was considerably slower in other solvents, such as toluene (entry 6) and BTF (entry 7). Solubility issues were not a convincing explanation for this finding. Indeed, at 80 °C, **F-TEBA** readily dissolved in BTF, and the lipophilic ion-pair formed by anion ex-

**Table 1.** *N*-Alkylation of *N*-(2-nitrobenzenesulfonyl)- $\alpha$ -amino acid ester **6a** with  $R^2X = CH_2 = CHCH_2Br$ , solvent =  $CH_3CN$ .

Entry	Catalyst	mol% <sup>[a]</sup>	<i>T</i> [°C]	<i>t</i> [h]	Yield <sup>[b]</sup> [%]
1	_	_	30	10	traces <sup>[c]</sup>
2	F-TEBA	5	30	10	75
3	F-TEBA	10	30	10	86
4	TEBA	10	30	10	87
5	TEBA	10	80	1.5	98
6 <sup>[d]</sup>	F-TEBA	10	80	12	98
7 <sup>[e]</sup>	F-TEBA	10	80	7	97
8	F-TEBA	10	80	1.5	98
9 <sup>[f]</sup>			80	1.5	99
10			80	1.5	98
11			80	1.5	98
12			80	1.5	98

<sup>[a]</sup> With respect to **6a**.

<sup>[b]</sup> Isolated yields.

<sup>[c]</sup> Detected by <sup>1</sup>H NMR.

<sup>[d]</sup> Solvent = toluene.

<sup>[e]</sup> Solvent = BTF.

change between **F-TEBA** and the deprotonated substrate, was equally soluble in toluene. This reinforced the idea, which first emerged in the case of fluorous crown ethers,<sup>[3b]</sup> that the choice of the solvent in SL-PTC reactions cannot only be dictated by its affinity for the fluorous PT agents.

The work-up of the reaction mixture and the separation of **F-TEBA** were operationally simple. For example, fluorous solid-phase extraction, without using any fluorous solvent, allowed us to obtain the reaction product, **7a**, in excellent yields and purity without any additional purification step. The catalyst could also be conveniently recovered by washing the cartridge with MeOH, with no apparent degradation, and was reused. However, **F-TEBA** was partly retained on fluorous silica (see the Supporting Information), and the optimal work-up method found entailed the evaporation of the clear CH<sub>3</sub>CN phase, followed by the addition of toluene. The solid catalyst was then quantitatively recovered by filtration, and was reused.<sup>[12]</sup> Five



**ba**  $\mathbf{K} = \mathbf{D}\mathbf{I}, \ \mathbf{D}\mathbf{I}, \ \mathbf{K} = \mathbf{I} + \mathbf{I}, \ \mathbf{D}\mathbf{a} + \mathbf{K} = \mathbf{M}\mathbf{e}, \ \mathbf{D}\mathbf{D} + \mathbf{K} = (3) - \mathbf{O}\mathbf{I}_3 + \mathbf{O}\mathbf{I}_2 + \mathbf{O}\mathbf{I}_3 + \mathbf{O}\mathbf{I}_2 + \mathbf{O}\mathbf{I}_3 + \mathbf{O}\mathbf{I}$ 

**Scheme 4.** *N*-alkylation of *N*-[2-(4-nitrobenzenesulfonyl)]- $\alpha$ -amino acid esters.

3074 asc.wiley-vch.de

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<sup>&</sup>lt;sup>[f]</sup> Entries 9–12=subsequent reaction runs performed with recovered **F-TEBA**.

Entry <sup>[a]</sup>	Substrate	R <sup>2</sup> X	<i>t</i> [h]	Yield <sup>[b]</sup> [%]
1	6a	CH <sub>2</sub> =CHCH <sub>2</sub> Br	1.5	98
2	6a	MeI	1.5	98
3	6a	HC≡CCH <sub>2</sub> Br	1.5	94
4	6a	<i>n</i> -PrI	12	93
5	6a	<i>n</i> -BuBr	24	89
6	6a	$n - C_{10} H_{21} I$	40	84
7	6b	CH <sub>2</sub> =CHCH <sub>2</sub> Br	4	95
8	8a	CH <sub>2</sub> =CHCH <sub>2</sub> Br	3	91
9	8b	CH <sub>2</sub> =CHCH <sub>2</sub> Br	1.5	98

**Table 2.** *N*-Alkylation of *N*-(2-nitrobenzenesulfonyl)- $\alpha$ -amino acid esters **6** and **8** (Scheme 4) catalyzed by **F-TEBA**.

<sup>[a]</sup> *Reaction conditions:* see Experimental Section.

<sup>[b]</sup> Isolated yields.

subsequent reaction runs (entries 8–12) were conducted with no apparent loss of activity.

The scope of the SL-PTC *N*-alkylation catalyzed by **F-TEBA** was also briefly investigated (Table 2). The reaction was very sensitive to the steric hindrance of the alkylating agent (entries 1–5), and to a lesser extent, the nature of the protected  $\alpha$ -amino acid esters (entries 6 and 7). In any event, the corresponding *N*-alkylated products were obtained in excellent isolated yields (84–98%), after a minimal work-up procedure.

In conclusion, we have shown, for the first time, that a readily accessible perfluorolakylated ammonium salt, **F-TEBA**, could be conveniently employed as a recyclable PT catalyst in a series of synthetically useful reactions that were conducted under SL-PTC conditions. Further investigations on the use of fluorous ammonium salts in PTC are underway in our laboratories, and will be reported in the future.

## **Experimental Section**

### **Preparation of F-TEBA**

To a stirred suspension of 3,5-bis(*n*-perfluorooctyl)benzyl bromide 2 (2.01 g, 2.00 mmol) in dry EtOH (20 mL) a solution of freshly distilled Et<sub>3</sub>N (1.62 g, 2.23 mmol) in dry EtOH (5 mL) was added dropwise. The reaction mixture was heated to reflux until 2 was completely consumed (6 h, TLC monitoring:  $PE/Et_2O$ , 9/1). The solvent was then evaporated under reduced pressure, and the solid residue was washed with cold Et<sub>2</sub>O and dried overnight in a vacuum oven at 40°C to give pure F-TEBA, as a white solid; yield: 2.01 g (90.7%); mp 168–170 °C; <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD):  $\delta$ =1.45 (t, *J*=7.2 Hz, 9H), 3.35 (q, *J*=7.2 Hz, 6H), 4.81 (s, 2H), 8.09 (br s, 1H), 8.21 (br s, 2H); <sup>13</sup>C NMR (100.8 MHz, CD<sub>3</sub>OD):  $\delta = 9.0$ , 55.4, 61.4, 105.0–121.8 (m,  $\hat{R}_{F}$ ), 129.50, 133.0 (t,  ${}^{2}J_{C,F}$ =24.5 Hz), 133.1, 137.1;  ${}^{19}F$  NMR (282 MHz, CD<sub>3</sub>OD):  $\delta = -78.9$  (t,  $J_{FF} = 10.5$  Hz, 6F), -108.5 $(t, J_{EF} = 14.2 \text{ Hz}, 4\text{F}), -118.4 \text{ (br s, 4F)}, -119.2 \text{ (m, 12F)},$ -120.2 (br s, 4F), -123.7 (br s, 4F); anal. calcd. for  $[C_{29}H_{20}F_{34}N]Br$  (1108.33): C 31.43, H 1.82, N 1.26; found C 31.01, H 1.95, N 1.22%.

### N-Alkylation of N-(n-Nitrobenzenesulfonyl)-α-amino Acid Esters 6, 8, and Catalyst Recycling: Typical Procedure

In an oven-dried screw-cap vial, anhydrous potassium carbonate (104 mg, 0.75 mmol) was added to a solution of starting sulfonamide 6a (183 mg, 0.50 mmol), F-TEBA (55 mg, 0.05 mmol), and allyl bromide (67 mg, 0.55 mmol) in anhydrous acetonitrile (3 mL). The heterogeneous reaction mixture was magnetically stirred at 80°C and the consumption of 6a was followed by TLC analysis (PE/AcOEt, 2/1). After cooling to room temperature, the mixture was filtered on Celite to remove the inorganic salts. The filtrate was evaporated under reduced pressure and the catalyst was removed by addition of cold toluene (2 mL) followed by filtration. The solid catalyst was washed with  $2 \times 0.5$  mL of toluene, dried at 40°C under vacuum for 5 h and then reused. The combined filtrate and washing phases were evaporated under reduced pressure affording 7a ( $R^2$  = allyl) in quantitative yield.

The *N*-alkylation reactions summarized in Table 2 were similarly performed. Spectroscopic data for **7a** and all previously reported compounds were identical to those reported in ref.<sup>[10]</sup> For all other compounds (Table 2, entries 6, 8, 9) see the Supporting Information.

## References

- For an overview of fluorous PTC see: G. Pozzi, S. Quici, R. H. Fish, J. Fluorine Chem. 2008, 129, 920– 929.
- [2] a) C. Emnet, K. M. Weber, J. A. Vidal, C. S. Consorti, A. M. Stuart, J. A. Gladysz, *Adv. Synth. Catal.* 2006, 348, 1625–1634; b) C. S. Consorti, M. Jurisch, J. A. Gladysz, *Org. Lett.* 2007, *9*, 2309–2312; c) D. Mandal, M. Jurisch, C. S. Consorti, J. A. Gladysz, *Chem. Asian J.* 2008, *3*, 1772–1782.
- [3] a) A. M. Stuart, J. A. Vidal, J. Org. Chem. 2007, 72, 3735–3740; b) G. Pozzi, S. Quici, R. H. Fish, Adv. Synth. Catal. 2008, 350, 2425–2436.
- [4] a) S. Shirakawa, Y. Tanaka, K. Maruoka, Org. Lett.
  2004, 6, 1429–1431; b) S. Shirakawa, M. Ueda, Y. Tanaka, T. Hashimoto, K. Maruoka, Chem. Asian J.
  2007, 2, 1276–1281.
- [5] a) G. Maayan, R. H. Fish, R. Neumann, Org. Lett.
  2003, 5, 3547–3550; b) L. Mercs, G. Pozzi, S. Quici, Tetrahedron Lett. 2007, 48, 3053–3056; c) W. Shen, L.-M. Wang, H. Tian, J. Fluorine Chem. 2008, 129, 267–273.
- [6] Z. Slávik, G. Tárkányi, Á Gömöry, G. Tarczay, J. Rábai, J. Fluorine Chem. 2001, 108, 7–14.
- [7] R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, G. Pozzi, *Eur. J. Org. Chem.* **2003**, 1191–1197.
- [8] a) D. Albanese, D. Landini, M. Penso, *Tetrahedron* 1999, 55, 6387–6394; b) M. Penso, V. Lupi, D. Albanese, F. Foschi, D. Landini, A. Tagliabue, *Synlett* 2008, 2451–2454.
- [9] D. Landini, M. Penso, J. Org. Chem. 1991, 56, 420-423.

- [10] D. Albanese, D. Landini, V. Lupi, M. Penso, Eur. J. Org. Chem. 2000, 1443–1449.
- [11] V. Lupi, M. Penso, F. Foschi, F. Gassa, V. Mihali, A. Tagliabue, *Chem. Commun.* 2009, 5012–5014.
- [12] The resting state of the catalyst features Br<sup>-</sup> as the counterion, and was verified by potentiometric titra-

tions with AgNO<sub>3</sub>. Indeed, multiply charged anions such as  $CO_3^{2-}$  were extracted with great difficulty by quaternary ammonium salts: F. Montanari, D. Landini, F. Rolla, *Top. Curr. Chem.* **1982**, *101*, 147–200.