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Phase transfer catalysis: some recent applications in organic synthesis

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Abstract

A survey dealing with the use of anhydrous potassium carbonate as an efficient base for promoting organic reactions under solid–liquid phase transfer catalysis (SL-PTC) conditions is reported. In particular, the generation in situ of trifluoro- and trichloroacetamidide, and reactions of these azaanions with 2-bromocarboxylic esters and epoxides, affording protected α-amino acids and β-amido alcohols, respectively, are described. The reduction of allylic nitroderivatives with CS_2 to oximes or nitriles under SL- and liquid–liquid PTC (LL-PTC) is also presented. Finally, new preparation methods and a study of the reactivity of quaternary onium fluorides, hydrogendifluorides and dihydrogentrifluorides, together with the use of dihydrogentrifluorides as hydrofluorinating agents under SL-PTC conditions, are reported. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Phase transfer catalysis; Anhydrous potassium carbonate as PTC base; α-Amino acids and esters; β-Amido alcohols; Quaternary onium fluorides, hydrogendifluorides and dihydrogentrifluorides; Hydrofluorination reactions

1. Introduction

Some recent applications of solid–liquid (SL) and liquid–liquid (LL) phase transfer catalysis (PTC) in organic synthesis, realised in our laboratories, are presented and discussed. The first part of this report deals with the use of anhydrous potassium carbonate as a base for promoting organic reactions under SL-PTC conditions; the second part describes: (i) new methods to prepare lipophilic quaternary ammonium and phosphonium fluorides (Q^+F^-), hydrogendifluorides ($Q^+HF_2^-$) and dihydrogentrifluorides ($Q^+H_2F_3^-$); (ii) a study of the reactivity (nucleophilicity and basicity) of these fluorinated onium salts; (iii) the use of tetrabutylammonium dihydrogentrifluoride ($Bu_4N^+H_2F_3^-$) as hydrofluorinating agent under both SL-PTC and homogeneous conditions.

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2. Use of anhydrous potassium carbonate as a base under solid–liquid phase transfer catalysis (SL-PTC) conditions

The use of anhydrous potassium carbonate as an effective non-nucleophilic agent for promoting base-catalysed reactions under SL-PTC conditions was first introduced by Fedorynski et al. in 1978 [1]. After this pioneering report, many other papers appeared on this subject [2,3].

Here we describe some of our recent applications of anhydrous K_2CO_3 to organic synthesis in base-promoted reactions under SL-PTC conditions.

An important alternative to the Gabriel synthesis of primary amines was reported some years ago by Harland et al. [4]. This method involves the *N*-alkylation in anhydrous DMF of the sodium salt of trifluoroacetamide (**1**), prepared using sodium hydride as base. *N*-Alkyl trifluoroacetamides (**2**) are easily either reduced by $NaBH_4$ or hydrolysed to the corresponding primary amines (Scheme 1).

We realised the selective mono-alkylation of trifluoroacetamide using solid K_2CO_3 as a base in the presence of catalytic amounts of tetrabutylammonium bromide (TBAB) as PTC agent [5] (Eq. (1)). The highest yields (78–90%) were obtained when alkyl halides or methanesulphonates were used as alkylating agents in DMF.

$$\underset{\mathbf{1}}{CF_3CONH_2} + RX \xrightarrow[\substack{DMF\ or\ CH_3CN\\ 50-80^\circ C}]{K_2CO_{3\,solid},\,TBAB_{cat}} \underset{\mathbf{2}}{CF_3CONHR} \qquad (1)$$

All attempts to selectively synthesise *N,N*-dialkyl trifluoroacetamides **3** in a one-pot reaction, using an excess of the alkylating agent and carbonate, failed, mixtures of mono- and dialkylamides, **2** and **3** respectively, being obtained. On the contrary, the symmetrical and unsymmetrical *N,N*-dialkyl trifluoroacetamides **3** were easily prepared in good to excellent yields (50–98%) by alkylating the mono-alkyl derivatives **2** under SL-PTC conditions (Eq. (2)).

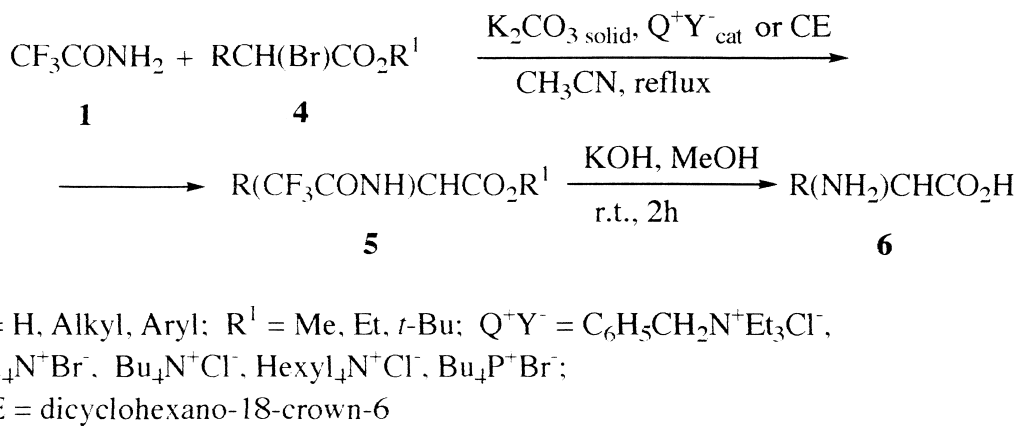
$$\underset{\mathbf{2}}{CF_3CONHR} + R^1X \xrightarrow[CH_3CN,\,80^\circ C]{K_2CO_{3\,solid},\,TBAB_{cat}} \underset{\mathbf{3}}{CF_3CONRR^1} \qquad (2)$$

The same SL-PTC protocol was followed for the selective mono *N*-alkylation of CF_3CONH_2 (**1**) by alkyl 2-bromo carboxylic esters **4**, affording the corresponding *N*-(trifluoroacetyl)-2-amino esters **5**. Since the intermediates **5** are easily hydrolysed to the corresponding α-amino acids **6** with methanolic KOH, this procedure represents a new way of synthesis of natural and unnatural α-amino acids **6** (Scheme 2) [6].

The alkylation reactions are performed by stirring, at 80°C, a heterogeneous mixture of solid K_2CO_3 (2 moles) and an acetonitrile solution of the amide **1** (1–2 moles), the 2-bromoester **4** (1 mole) and catalytic amounts of a PTC agent, generally triethylbenzylammonium chloride (TEBA) [6].

$$\underset{\mathbf{1}}{CF_3CONH_2} \xrightarrow[DMF_{\,anhy.}]{NaH} CF_3CONH^-Na^+ \xrightarrow[18\ h,\ 80^\circ C]{RX} \underset{\mathbf{2}}{CF_3CONHR} \xrightarrow[or\ KOH]{NaBH_4} RNH_2$$

Scheme 1.



Scheme 2.

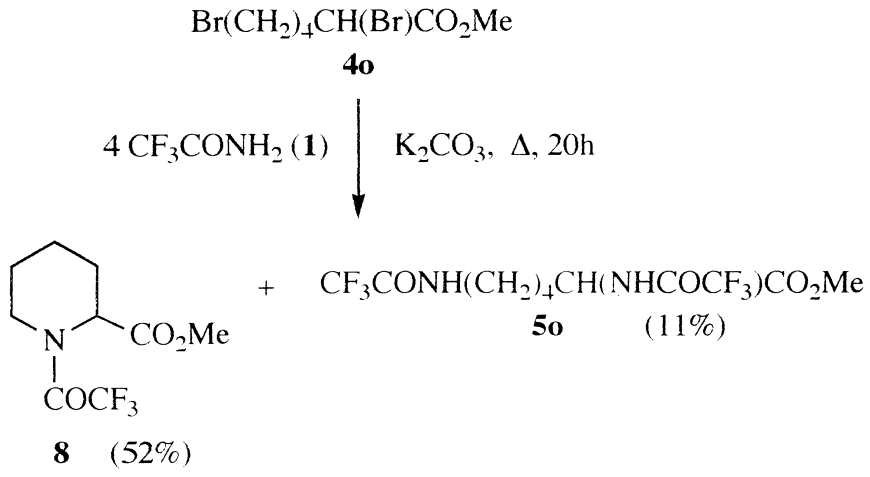
The process works for the methyl, ethyl and *t*-butyl esters of alkyl and arylalkyl carboxylic acids [7]. The *N*-(trifluoroacetyl)-2-amino carboxylic esters **5** can be isolated as pure compounds or directly converted into amino acids **6** (Table 1). No elimination products were observed, except in the case of ethyl 2-bromo-3-phenylpropanoate (**4j**) where the elimination product predominated, 60% of (*E*)-ethyl cinnamate (**7**) being isolated, together with minor amounts (16%) of the expected *N*-alkylated product (**5j**).

The preparation of *N,N′*-bis(trifluoroacetyl)lysinate (**5o**), with 2,6-dibromohexanoate (**4o**) as alkylating agent (Scheme 3), afforded only 11% of the expected product **5o**, together with 52% of methyl *N*-(trifluoroacetyl)-2-piperidine carboxylate (**8**), produced through an intramolecular bis-alkylation reaction. Since the reactions of **5a–j** gave negligible amounts of bis-alkylated products, these results show that bis-alkylation becomes the preferred process only in the case of substrates that can undergo intramolecular cyclization.

Table 1
N-(Trifluoroacetyl)-2-amino carboxylic esters **5**, $RCH(NHCOCF_3)CO_2R^1$, prepared under SL-PTC conditions, at 80°C

5	R	R^1	Time (h)	Yield (%)
a	H	Et	0.5	65
b	Me	Et	2	72
c	$Me(CH_2)_9$	Et	3.5	75
d	Ph	Et	0.3	70
e	C_6H_4Me-2	Me	0.3	81
f	C_6H_4OMe-3	Me	0.3	70
g	C_6H_4F-4	Me	0.3	–[a]
h	C_6H_4Cl-4	Me	0.3	–[a]
i	C_6H_4Br-4	Me	0.3	–[a]
j	$PhCH_2$	Et	48	16[b]
k	Ph	Bu^t	24	82
l	Me	Bu^t	24	83
m	Bu^n	Bu^t	48	77
n	*n*-$C_{10}H_{21}$	Bu^t	48	80

[a] Not isolated, the crude was directly converted into the 2-amino acid **6**.
[b] At 25°C, 60% of (*E*)-ethyl cinnamate (**7**) is also obtained.

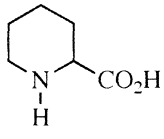


Scheme 3.

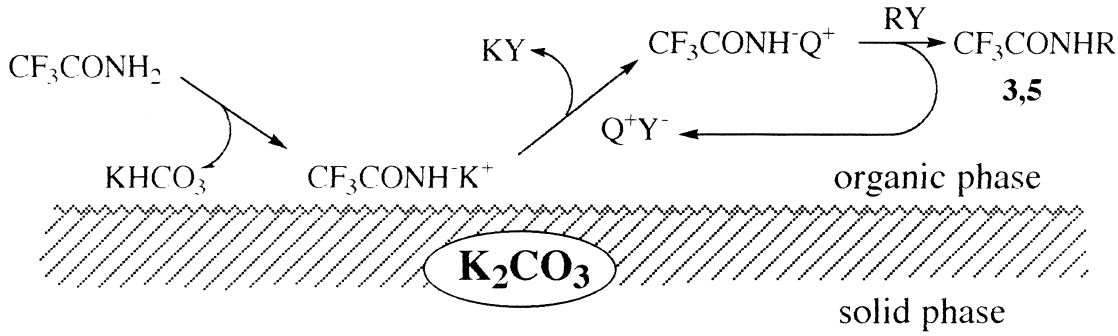
As discussed above, the hydrolysis of the trifluoroacetyl and ester groups is easily performed in quantitative yields with methanolic KOH at room temperature (Table 2).

In an attempt to give a mechanistic rationale of the *N*-alkylation under SL-PTC conditions, the following experimental facts should be considered: (i) no detectable amounts of potassium carbonate are soluble in acetonitrile, even in the presence of a lipophilic onium salt (Q^+Y^-) [8–10]; (ii) when

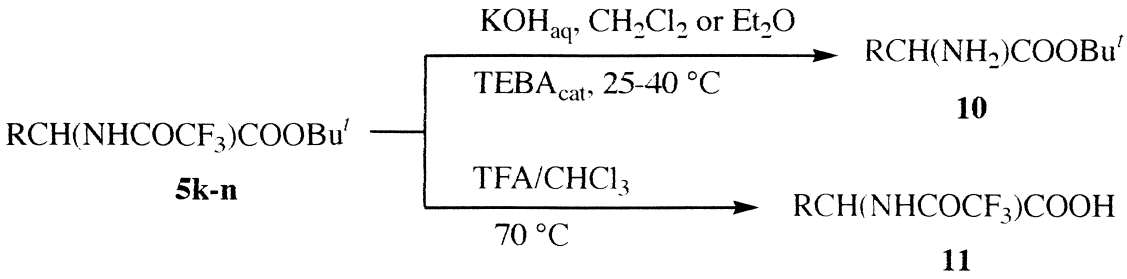
Table 2
α-Amino acids **6** prepared by hydrolysis of *N*-(trifluoacetyl)-2-amino carboxylic esters **5**[a]

5	α-Amino acid	Yield %
a	NH_2CH_2COOH	96 [b]
b	$MeCH(NH_2)COOH$	99 [b]
c	$Me(CH_2)_9CH(NH_2)COOH$	100
d	$PhCH(NH_2)COOH$	91
e	$2\text{-}MeC_6H_4CH(NH_2)COOH$	90
f	$3\text{-}MeOC_6H_4CH(NH_2)COOH$	91
g	$4\text{-}FC_6H_4CH(NH_2)COOH$	72 [c]
h	$4\text{-}ClC_6H_4CH(NH_2)COOH$	70 [c]
i	$4\text{-}BrC_6H_4CH(NH_2)COOH$	68 [c]
j	$PhCH_2CH(NH_2)COOH$	100 [b]
9		97 [b]

[a] Substrate **5** (5 mmol) in MeOH (2.5 ml) and 20% aqueous KOH (2.4 ml) at room temperature for 2 h.
[b] As hydrochloride.
[c] Overall yield referred to the 2-bromo ester **4** after hydrolysis of the crude of *N*-alkylation.



Scheme 4.



Scheme 5.

an acetonitrile solution of CF_3CONH_2 (**1**) is stirred over K_2CO_3, acid/base titrations show the actual presence of basic species (6% molar equivalents per mol of **1**) which increases when Q^+Y^- is added to the SL-system; (iii) ^{19}F-NMR measurements show the presence of the azaanion salt; (iv) the pK_a value of CF_3CONH_2 (**1**) in dipolar aprotic media is 9.7 [11].

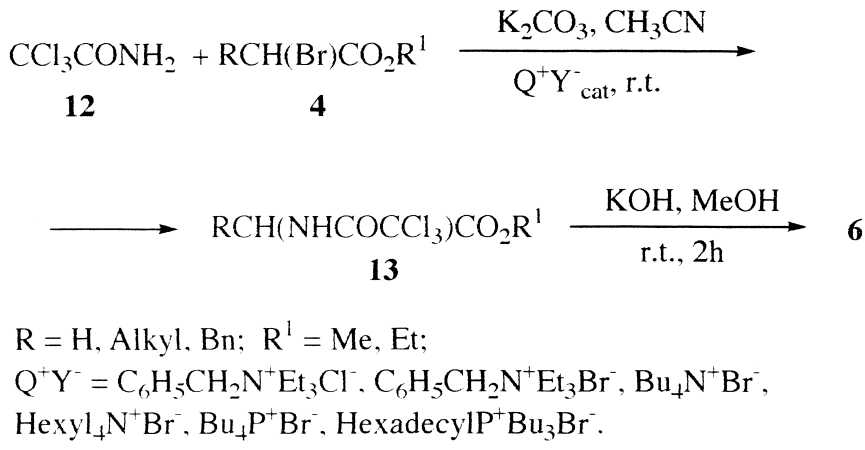
On the basis of these facts, the alkylation reaction most likely involves the following steps (Scheme 4): CF_3CONH_2 (**1**) reacts at the phase boundary, affording the corresponding potassium salt; this salt is transferred, in part, into the bulk of the organic phase, where alkylation occurs. The strong catalytic effect of the PTC agent is due to both the increased solubility of the anion reagent as quaternary salt and the higher reactivity of the $CF_3CONH^-Q^+$ species with respect to that of the K^+ salt. [9,12–16].

In the case of *t*-butyl *N*-(trifluoroacetyl)-2-amino carboxylic esters **5k–n** we realised the chemoselective deprotection of the amino- or carboxylic group, affording the corresponding *t*-butyl 2-amino carboxylates **10** or *N*-(trifluoroacetyl)-2-amino acids **11**, respectively (Scheme 5) [7].

Table 3
t-Butyl 2-amino carboxylic esters **10** prepared under LL-PTC

Substrate	R	Solvent	KOH	Temperature (°C)	Time	Product	Yield (%)[a]
5k	Ph	CH_2Cl_2	2.5	25	7 d	**10k**	88
5l	Me	CH_2Cl_2	2.5	25	18 h	**10l**	89
5m	Bu^n	Et_2O	10	25	4 d	**10m**	88
5n	*n*-$C_{10}H_{21}$	Et_2O	10	35	7 d	**10n**	95
(*S*)-5q	$PhCH_2$	CH_2Cl_2	2.5	40	24 h	**(*S*)-10q**	75[b]

[a] Isolated as hydrochlorides.
[b] 77% ee.



Scheme 6.

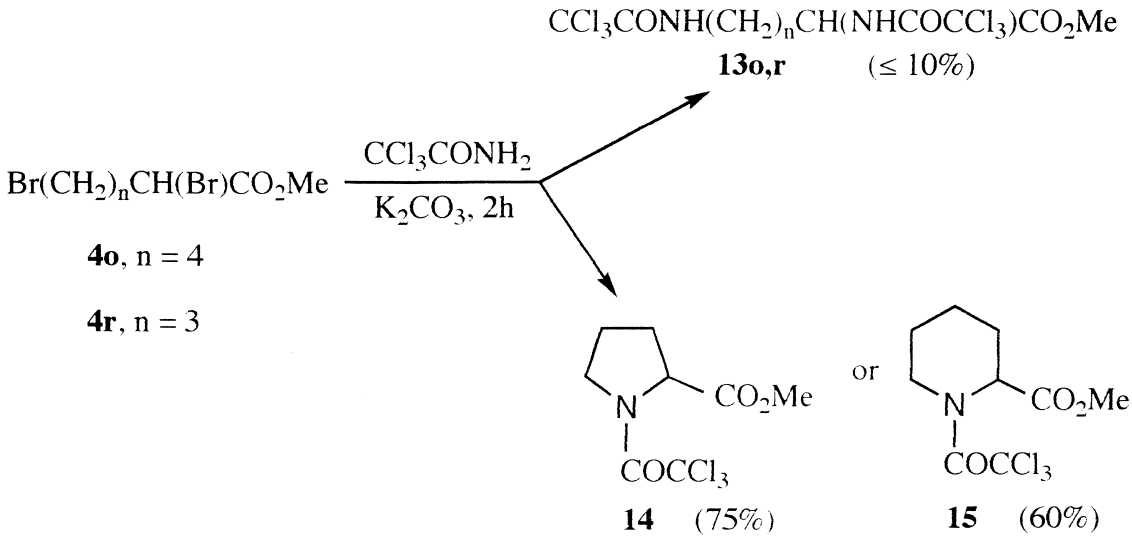
The selective hydrolysis of the amido function was accomplished under LL-PTC conditions in an aqueous KOH-dichloromethane (or diethyl ether) two phase system at 25–40°C. As shown in Table 3, the *t*-butyl 2-amino esters **10**, isolated as hydrochlorides, were obtained in 88–95% yields, together with minor amounts (4–9%) of the corresponding 2-amino acids **6**. It is interesting to note that **6** were the sole products isolated from the hydrolysis of the methyl or ethyl *N*-(trifluoroacetyl)-2-amino esters **5a–d**, under the above described LL-PTC conditions.

Moreover, the trifluoroacetyl group hydrolysis of optically pure *t*-butyl esters of (*R*)-phenylglycine and (*S*)-phenylalanine **5p** and **5q**, occurred with complete and partial racemization, respectively (Table 3). The different behaviour shown by these two substrates can be ascribed to both the different acidity of the α-protons of (*R*)-**5p** and (*S*)-**5q** and the longer reaction time required for the hydrolysis of (*R*)-**5p**.

Table 4
N-(Trichloroacetyl)-2-amino carboxylic esters **13**, R-CH(NHCOCCl$_3$)CO$_2$R^1 prepared and α-amino acids **6** derived from their hydrolysis

N-(Trichloroacetyl)-2-amino esters				**6**	α-Amino acids[a]	Yield (%)
13	R	R^1	Yield (%)			
a	H	Et	59[b]	**a**	NH_2CH_2COOH	95[c]
b	Me	Et	79	**b**	$MeCH(NH_2)COOH$	100[c]
c	*n*-$C_{10}H_{21}$	Et	76	**c**	$Me(CH_2)_9CH(NH_2)COOH$	100
j	$PhCH_2$	Et	24[d]	**j**	$PhCH_2CH(NH_2)COOH$	100[c]
s	Et	Et	95	**s**	$MeCH_2CH(NH_2)COOH$	95[c]
t	*n*-Pr	Et	73	**t**	$Me(CH_2)_2CH(NH_2)COOH$	90[c]
u	*n*-Bu	Me	79	**u**	$Me(CH_2)_3CH(NH_2)COOH$	98[c]
v	*n*-C_6H_{13}	Et	86	**v**	$Me(CH_2)_5CH(NH_2)COOH$	92
w	*n*-$C_{14}H_{29}$	Me	62	**w**	$Me(CH_2)_{13}CH(NH_2)COOH$	90
x	Me_2CHCH_2	Me	51	**x**	$Me_2CHCH_2CH(NH_2)COOH$	90[c]

[a] Substrate **13** (5 mmol) in MeOH (2.5 ml) and 20% aqueous KOH (2.4 ml) at r.t. for 20 h.
[b] When the reaction was conducted at 80°C, 75% of product was isolated after 1 h.
[c] Isolated as hydrochloride.
[d] Ethyl cinnamate (**7**) (31%) was also isolated.

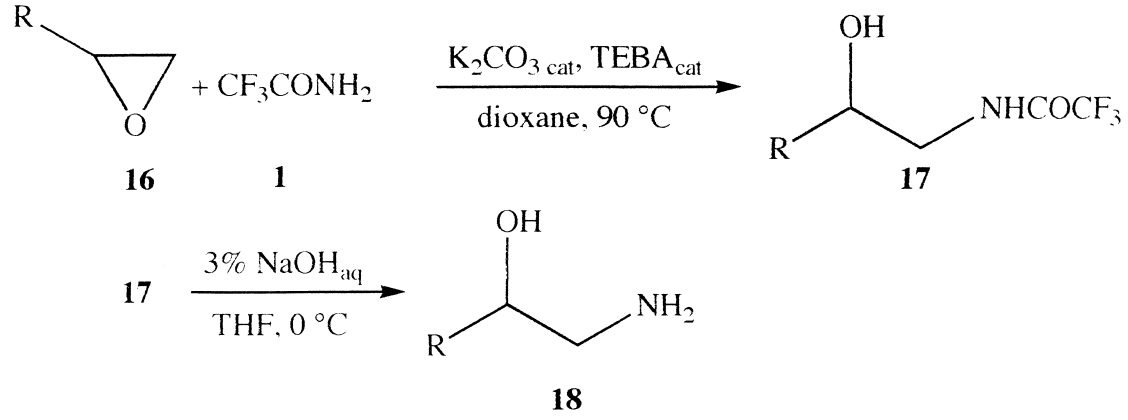


Scheme 7.

The *t*-butyl esters **5k–n** were selectively deprotected to the corresponding *N*-(trifluoroacetyl)-2-amino acids **11** in almost quantitative yields, by heating a chloroform solution containing **5k–n** and an excess of trifluoroacetic acid, according to a well known procedure [17].

Similarly to CF_3CONH_2 (**1**), the cheaper CCl_3CONH_2 (**12**) was selectively mono-alkylated by 2-bromo carboxylic esters **4** under SL-PTC conditions [18]. The highest yields (60–95%) of *N*-(trichloroacetyl)-2-amino esters **13** were obtained by stirring, at room temperature, an acetonitrile solution of 2-bromo esters **4** (1 mol), CCl_3CONH_2 (**12**) (3–4 mol) and a PTC agent (0.1 mol) over solid K_2CO_3 (4 mol) (Scheme 6, Table 4).

The excess of **12** can be quantitatively recovered at the end of the reaction. Poor yields (51%) were obtained with the sterically hindered 2-bromo-4-methyl pentanoate **4x4s**; moreover ethyl *trans*-cinnamate (**7**) was the major product of the reaction of ethyl 2-bromo-3-phenylpropionate (**4j**) (Table 4).



Scheme 8.

Table 5
β-Amido alcohols **17** R-CH(OH)$CH_2NHCOCF_3$, prepared under SL-PTC conditions, in dioxane at 90°C

Epoxide	R	Time (h)	Product	Yield (%)
16b	CH_2OPh	7.5	**17b**	75
		18	**17b**	30[a]
16c	CH_2OBOM	18	**17c**	76
16d	$CH_2OAllyl$	27	**17d**	55
16e	(*S*)-(+)-CH_2OBn	9	**17e**	58[b]
16f	*n*-C_6H_{13}	24	**17f**	75
16g	Ph	48	**17g**	58

[a] Without TEBA.
[b] Enantiopure compound.

The methyl esters of 2,5-dibromopentanoic acid **4r** and 2,6-dibromohexanoic acid **4o** react with CCl_3CONH_2 (**12**), affording the *N*-(trichloroacetyl)-2-pyrrolidinecarboxylate **14** and the *N*-(trichloroacetyl)-2-piperidinecarboxylate **15** in 75 and 60% yields, respectively, together with small amounts of the *N,N′*-bis-(trichloroacetyl)-α,ω-diaminocarboxylates **13o** and **13r** (Scheme 7).

These results clearly indicate that, once again, with the compounds **4o,r** the intramolecular bis-alkylation is the favoured process.

As found for the *N*-(trifluoroacetyl)-2-amino esters **5**, the *N*-(trichloroacetyl)-2-amino derivatives **13** are easily hydrolysed in nearly quantitative yields to amino acids **6** with methanolic potassium hydroxide at room temperature (Table 4) [18].

Anhydrous potassium carbonate under SL-PTC conditions was found to be an efficient base for promoting the ring opening of epoxides **16** with CF_3CONH_2 (**1**), affording β-trifluoroacetamido alcohols **17** (Scheme 8) [19].

The opening reaction was performed by heating, at 90°C, a dioxane solution of the epoxide **16** (1 mol), trifluoroacetamide (**1**) (2 mol) and TEBA (0.1 mol), over catalytic amounts of K_2CO_3 (0.1 mol). Under these conditions the β-amido alcohols **17**, deriving from the attack of the trifluoroacetamidide to the less substituted carbon atom of the oxirane ring, were isolated in 55–76% yields (Table 5).

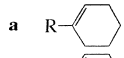
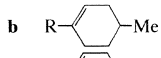
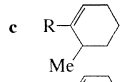
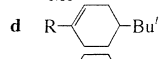
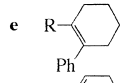
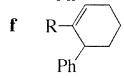
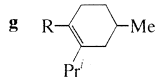
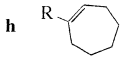
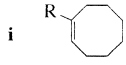
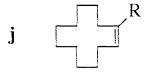
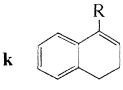
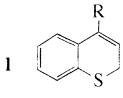
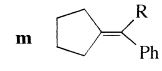
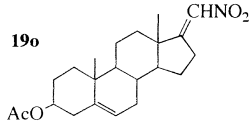
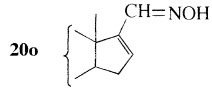
Owing to the complete regioselectivity of the ring opening, the stereocenter of chiral epoxides, such as (*S*)(+)-benzyl glycidyl ether (**16e**), was not affected during the process. In addition, the high stability of *O*-protected glycidols, like **16b–e**, under the above reaction conditions, and the availability of both the enantiomers of glycidol (**16a**) [20] enable the use of the corresponding β-amido alcohols **17b–e** as polyfunctionalized C_3 building blocks bearing a stereocenter of known configuration.

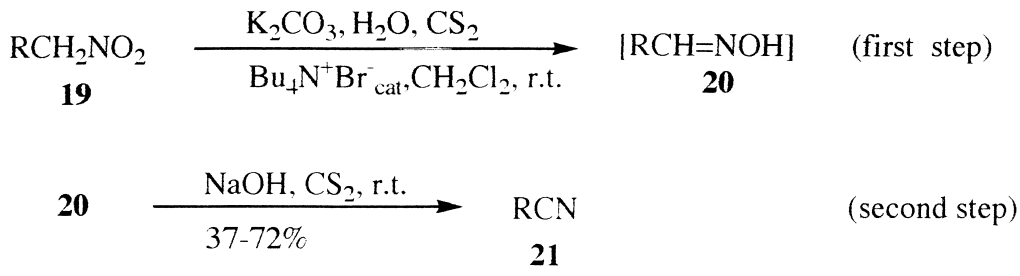
Finally, the trifluoroacetyl group of **17** can be easily removed by mild alkaline hydrolysis, affording in almost quantitative yields [19] β-amino alcohols **18** (Scheme 8), important starting materials for the preparation of pharmaceuticals and chiral ligands for asymmetric catalysis [21].

Notes to Table 6:
[a] Reduction conditions: nitro compound **19** (0.1 mol), CS_2 (0.15 mol), K_2CO_3 (0.05 mol), H_2O (0.02 mol), TEBA (0.01 mol), CH_2Cl_2 (100 ml), at room temperature.
[b] 60% Conversion of the substrate **19g**.
[c] 88% Conversion of the substrate **19m**.
[d] 72% Conversion of the substrate **19o**.

Another reaction promoted by solid K_2CO_3, under SL-PTC conditions is the reduction of allylic nitro compounds **19** to oximes **20** by CS_2 (Eq. (3)) [22]. This reaction was previously described by

Table 6
Reduction of nitro compounds **19** to oxime **20** with carbon disulphide catalysed by wet potassium carbonate under SL-PTC conditions[a]

19 R = CH_2NO_2 **20** R = CH=NOH	**20** Reaction Time (h)	**20** Yield (%)
a 	7	52
b 	8	60
c 	5	68
d 	14	60
e 	25	79
f 	25	51
g 	112 [b]	25
h 	24	60
i 	168	60
j 	157	56
k 	8	60
l 	24	45
m 	76 [c]	50
n *n*-$C_7H_{15}R$	120	no reaction
19o 	200 [d]	29
20o 		



Scheme 9.

Barton et al. [23] (Eq. (4)) under homogeneous conditions using triethylamine as a base. The choice of the base is a crucial factor for a good outcome of the reaction. The best PTC conditions are the following: a CH_2Cl_2 solution of 1 mole of the substrate **19**, 1.5 moles of CS_2, 0.5 moles of solid wet K_2CO_3 and catalytic quantities of TEBA at room temperature.

$$\underset{\mathbf{19}}{RCH_2NO_2} \xrightarrow[TEBA_{cat},CH_2Cl_2]{\text{wet } K_2CO_3,CS_2,\text{r.t.}} \underset{\mathbf{20}}{RCH=NOH} \quad (45\text{–}79\%) \tag{3}$$

$$\underset{\mathbf{19}}{RCH_2NO_2} \xrightarrow[Et_2O \text{ or } CH_2Cl_2]{R_3N,CS_2,\text{r.t.}} \underset{\mathbf{20}}{RCH=NOH} \quad (30\text{–}83\%) \tag{4}$$

As shown in Table 6, the oximes **20** are obtained in 45–79% yields. Under the above conditions, 1-nitrooctane does not react. Under LL-PTC conditions the reaction rate is higher, but the yields are poorer (5–10%).

The combination of SL- and LL-PTC techniques allowed the one-pot synthesis of allylic nitriles **21**, starting from the allylic nitro derivatives **19** (Scheme 9) [24].The nitro compounds **19** are first converted to oximes **20** under SL-PTC, as previously described, and then, by addition of 15% aqueous NaOH and more CS_2, **20** are dehydrated to the corresponding nitriles **21** in 37–72% overall yield (Table 7).

Table 7
One-pot conversion of nitro compounds **19** to nitriles **21** with carbon disulphide under PTC conditions[a]

Substrate	Time		Product	Yield (%)
	t_1 (h)[b]	t_2 (h)[c]		
19a	8	2	**21a**	37
19b	8	2	**21b**	54
19c	5	3	**21c**	55
19d	14	4	**21d**	60
19e	25	2	**21e**	60
19h	24	2	**21h**	60
19i	168	3	**21i**	64
19j	166	2	**21j**	72
19k	8	2	**21k**	63
19m	72	24	**21m**	56

[a] Reaction conditions. First step: **19** (0.1 mol), CS_2 (0.15 mol), K_2CO_3 (0.05 mol), H_2O (0.02 mol), TBAB (0.01 mol), CH_2Cl_2 (100 ml). Second step: CS_2 (0.67 mol), aqueous 15% NaOH (0.44 mol).
[b] Time for the conversion **19** → **20**, from the end of addition of CS_2.
[c] Time for the conversion **20** → **21**, from the end of addition of aqueous NaOH.

Table 8
Quaternary onium fluorides **22**, hydrogendifluorides **23** and dihydrogentrifluorides **24** prepared

Q^+		$Q^+F^-\cdot 3H_2O$	Yield (%)	$Q^+HF_2^-$	Yield (%)	$Q^+H_2F_3^-$	Yield (%)
a	$(n\text{-}C_4H_9)_4N^+$	**22a**	100	**23a**	100	**24a**	100
b	$(n\text{-}C_6H_{13})_4N^+$	**22b**	100	**23b**	100	**24b**	100
c	$(n\text{-}C_7H_{15})_4N^+$	**22c**	99	–	–	–	–
d	$(n\text{-}C_8H_{17})_4N^+$	**22d**	100	–	–	–	–
e	$(n\text{-}C_4H_9)_4P^+$	–	–	**23e**	98	**24e**	100
f	$n\text{-}C_{16}H_{33}P^+(C_4H_9\text{-}n)_3$	–	–	**23f**	99	**24f**	98
g	$(C_6H_5)_4P^+$	–	–	**23g**	100	**24g**	100

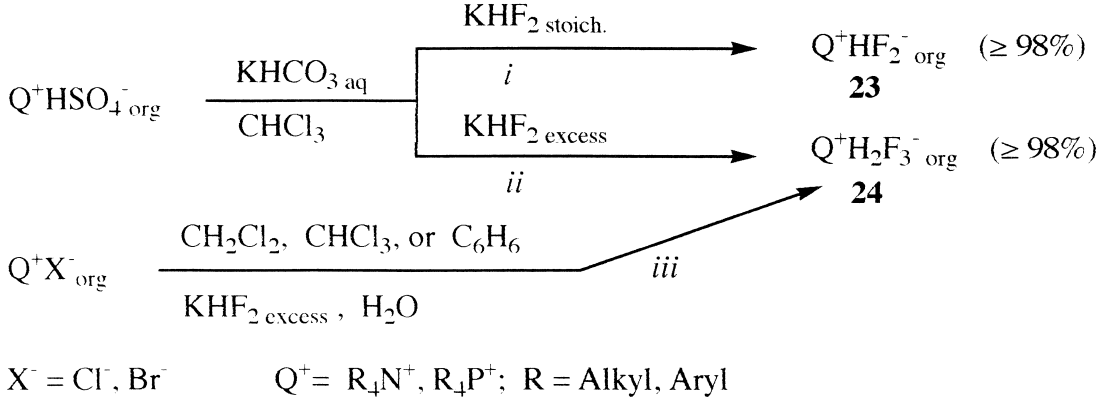
For this process catalysts more lipophilic than TEBA, e.g., TBAB, are needed. Furthermore, the second step, due to the lower acidity of oximes (pK_a 11–12) [23], requires a base stronger than potassium carbonate in order to generate the oximate anion, $RCH=NO^-Na^+$.

3. Synthesis of lipophilic quaternary onium fluorides (Q^+F^-), hydrogendifluorides ($Q^+HF_2^-$) and dihydrogentrifluorides ($Q^+H_2F_3^-$)

The importance of lipophilic quaternary onium fluorides (Q^+F^-) **22**, hydrogendifluorides ($Q^+HF_2^-$) **23** and dihydrogentrifluorides ($Q^+H_2F_3^-$) **24**, as organic-soluble sources of fluoride and polyfluoride ions for various purposes in synthetic chemistry, is well documented [25]. In particular tetrabutylammonium fluoride (TBAF) (**22a**) finds a widespread use as a promoter of organic reactions involving organosilyl derivatives, and a number of elimination, condensation and fluorination reactions [25].

Lipophilic quaternary onium hydrogendifluorides ($Q^+HF_2^-$) **23** provide anhydrous nucleophilic HF_2^-. In fact $Q^+HF_2^-$ is easily prepared anhydrous, differently from Q^+F^- which cannot be obtained as the naked material [26]. In turn, lipophilic quaternary onium dihydrogentrifluorides ($Q^+H_2F_3^-$) **24** have been used as easy to handle sources of HF for hydrofluorination and other important reactions [25].

The main synthesis methods for tetraalkylammonium fluorides **22** are: (i) neutralisation of an aqueous solution of quaternary hydroxides with hydrofluoric acid in a non-glass apparatus; (ii)



Scheme 10.

Table 9
Influence of the specific hydration of Hexyl$_4$N$^+$ F$^-\cdot n$H$_2$O (**22b**) on the reaction rate for nucleophilic substitution of methanesulphonate by fluoride ion in *n*-octyl methanesulphonate in chlorobenzene at 60°C[a]

Hydration state *n* of Hexyl$_4$N$^+$ F$^-\cdot n$H$_2$O (**22b**)	10^3k, M^{-1} s^{-1}	k_{rel}
8.5	2.3	1
6.0	2.4	1
4.0	4.3[b]	2
3.0	21[b]	9
2.6	46[b]	20
1.8	120[b]	52
1.5	220[b]	96
0.0	1890[c]	822

[a][Substrate] = 2–4×10^{-2} M; [Q$^+$ F$^-$] = 3–4×10^{-2} M.
[b]Initial rate constants.
[c]Extrapolated value by plotting log *k* vs. *n*.

metathesis X$^-\rightarrow$ F$^-$ (X = Cl, Br) through protracted ion exchange chromatography; (iii) treatment of quaternary chlorides, bromides or iodides with the expensive silver fluoride. All these methods work for onium salts substantially soluble in water, such as the tetrabutyl derivatives, but their extension to less lipophilic compounds is not straightforward.

We found that lipophilic tetraalkylammonium fluorides **22** [25] can be easily obtained, in almost quantitative yields, by preparative ion-pair extraction from the corresponding hydrogen sulphate ($Q^+HSO_4^-$) in a saturated aqueous KF-benzene two-phase system, in the presence of a molar equivalent of a base (KOH, NaOH, $NaHCO_3$, etc.) (Eq. (5)). The onium fluorides are isolated as trihydrate compounds with a purity ≥ 98% (Table 8) [25].

$$Q^+HSO_{4\,org}^- + KF_{aq} \underset{C_6H_6,\,r.t.}{\overset{KOH}{\rightarrow}} \underset{\mathbf{22}}{Q^+F^-\cdot BH_2O_{org}} + K_2SO_{4\,aq} \qquad (5)$$

With the same technique quaternary ammonium or phosphonium hydrogendifluorides **23** can be prepared by reacting a chloroform solution of $Q^+HSO_4^-$, previously neutralised with $KHCO_3$, with a stoichiometric amount of aqueous KHF_2 (Scheme 10, path (i)). The use of a slight excess of KHF_2 gave a mixture of hydrogendifluoride **23** and dihydrogentrifluoride **24**, whereas only the onium dihydrogentrifluoride salts **24** were obtained by using a large excess (50 mol/mol) of KHF_2 (Scheme 10, path (ii)). Alternatively **24** can be obtained directly from commercially available quaternary

Table 10
Effect of the specific hydration of fluoride ion on its basicity for the elimination reaction of Hexyl$_4$N$^+$ F$^-\cdot n$H$_2$O (**22b**) in chlorobenzene at 60°C[a]

Hydration state *n* of Hexyl$_4$N$^+$ F$^-\cdot n$H$_2$O (**22b**)	10^5k, s^{-1}	k_{rel}
6.0	–	–[b]
4.6	0.005	1
3.2	0.035	7
2.4	1.7[c]	340
2.0	9.5[c]	1900
1.7	38[c]	7600
0.0	1.17×10^5[d]	2.34×10^7

[a][Q$^+$ F$^-$] = 3–4×10^{-2} M.
[b]No elimination reaction occurred within 2 weeks.
[c]Initial rate constants.
[d]Extrapolated value by plotting log *k* vs. *n*.

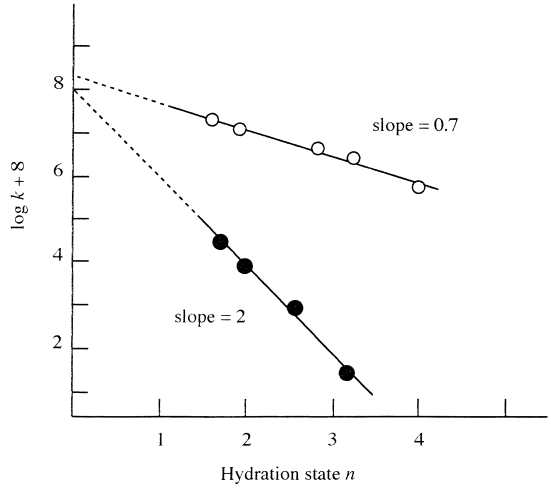


Fig. 1. Correlation between log k and the hydration state n of quaternary ammonium flouride $Q^+F^-\cdot n\,H_2O$ (**22b**) for the nucleophilic substitution (Eq. (6)) (○) and the elimination reaction (Eq. (7)) (●).

chlorides or bromides Q^+X^- (X = Cl, Br) under the above reaction conditions (Scheme 10, path (iii)) [25].

As shown in Table 8, the salts **23** and **24** are isolated in quantitative yields, purity $\geq 98\%$, as anhydrous, non-hygroscopic and stable compounds.

The quaternary onium fluorides **22** and polyfluorides **23** and **24** can be differentiated by ^{19}F-NMR spectroscopy [25].

4. Reactivity (nucleophilicity and basicity) of quaternary onium fluorides (Q^+F^-), hydrogendifluorides ($Q^+HF_2^-$) and dihydrogentrifluorides ($Q^+H_2F_3^-$)

In low polarity media bulky quaternary onium fluorides **22** give rise to loose ion pairs in which the F^- anion is poorly solvated and hence highly reactive. Anion reactivity is dramatically reduced, however, in the presence of even small quantities of protic species (water, methanol, etc.) which specifically solvate the anion, resulting in strong hydrogen bonds [27].

In order to quantitatively define this behaviour, we performed a kinetic study of how specific hydration affects both the nucleophilic reactivity and the basicity of the fluoride anion of $Hexyl_4N^+F^-$ (**22b**) in the low polar chlorobenzene, 1,2-dichlorobenzene and benzene [26].

Table 9 shows that the nucleophilicity of $Hexyl_4N^+F^-\cdot nH_2O$ (**22b**), studied in a typical S_N2 reaction (Eq. (6)), increases by about 3 powers of ten on diminishing the hydration number 'n' from

Table 11
Reactivity of $Hexyl_4N^+F^-$ (**22b**), $Hexyl_4N^+HF_2^-$ (**23b**) and $Hexyl_4N^+H_2F_3^-$ (**24b**) in the nucleophilic substitution of methanesulphonate by fluoride ion in 1,2-dichlorobenzene at 90°C

$Hexyl_4N^+Y^-$	Y^-	10^3k ($M^{-1}\,s^{-1}$)	k_{rel}
22b	F^-	6.5×10^{4a}	8.5×10^5
22b	$F^-\cdot4H_2O$	155	2×10^3
23b	HF_2^-	9.4	122
24b	$H_2F_3^-$	0.077	1

[a] Extrapolated value for the hypothetical anhydrous **22b**.

8.5 to an extrapolated 0 value. Such enhancement is much higher ($\sim$ 100 times) than that obtained by dehydrating the other halides (11 times for Cl^-, 2.5 for Br^- and 1.5 for I^-) [28,29] in agreement with the increasing stabilisation of these anions due to their specific solvation, in the order $I^- < Br^- < Cl^- < F^-$ [30]. Interestingly, the nucleophilicity sequence found in chlorobenzene for anhydrous anions ($I^- < Br^- < Cl^- \ll F^-$) is the same as that found in the gas phase, even if the absolute rates are still orders of magnitude lower [29,31].

$$n\text{-}C_8H_{17}OMs + \underset{\mathbf{22b}}{Hexyl_4N^+F^-} \rightarrow n\text{-}C_8H_{17}F + Hexyl_4N^+MsO^- \quad (6)$$

Also the basicity of F^- is found to depend strongly on the specific hydration of the anion [26,27]. As reported in Table 10, the rate of the Hofmann-like elimination reaction of $Hexyl_4N^+F^- \cdot nH_2O$ (**22b**), increases by more than seven orders of magnitude by completely removing the hydration sphere n of fluoride (Eq. (7) and Table 10) [26].

$$2\,\underset{\mathbf{22b}}{Hexyl_4N^+F^-} \rightarrow \text{Hex-l-ene} + Hexyl_3N + \underset{\mathbf{23b}}{Hexyl_4N^+HF_2^-} \quad (7)$$

Comparison in the same range of hydration ($n = 0$–3) shows that the basicity of the F^- ion is much more affected by specific hydration than its nucleophilicity is ($\Delta k_{\text{basicity}} \cong 10^4\ \Delta k_{\text{nucleophilicity}}$), as clearly indicated by their plots log k vs. n (Fig. 1).

Extension of this study to quaternary ammonium poly(hydrogen fluorides) $Hexyl_4N^+(HF)_nF^-$ (**23b** and **24b**) ($n = 1,2$), in order to evaluate their ability as alternative sources of F^- (Eq. (8)), gave the following reactivity scale: $F^- \gg F^- \cdot nH_2O > HF_2^- > H_2F_3^-$ [26]. The data of Table 11 indicate that the reactivity of the hypothetical anhydrous F^- dramatically diminishes when the anion is solvated by one or two molecules of HF as in hydrogendifluoride HF_2^- (7000 times) and dihydrogentrifluoride $H_2F_3^-$ (about 10^6 times). It is noteworthy that the tetrahydrate $Hexyl_4N^+F^- \cdot 4H_2O$ (**22b**) is 400 times less reactive than the anhydrous salt but still more reactive than $Hexyl_4N^+HF_2^-$ (**23b**) and $Hexyl_4N^+H_2F_3^-$ (**24b**) (17- and 2000-fold respectively) [32]. The different stabilisation of the fluoride anion by H_2O and HF accounts for the scale, in line with literature H bond energy values [33–36] for these species: HOH $\cdots$ $F^- \cong 23$ kcal mol^{-1} and F $\cdots$ H $\cdots$ $F^- \cong 39$ kcal mol^{-1}.

$$n\text{-}C_8H_{17}OMs + 2\,\underset{\mathbf{23b},\,\mathbf{24b}\ n=1,2}{Hexyl_4N^+F^-(HF)_n} \rightarrow n\text{-}C_8H_{17}F + Hexyl_4N^+MsO^- + \underset{\substack{\mathbf{24b}\ m=2\\ \text{or } m=4}}{Hexyl_4N^+F^-(HF)_m} \quad (8)$$

Results indicate that the partially hydrated $Q^+F^- \cdot nH_2O$ **22** ($n = 3,4$) can always be considered the fluorinating agent of choice in low polarity solvents [37]. However, given the difficulties in preparing anhydrous quaternary ammonium fluorides, the less reactive $Q^+HF_2^-$ **23** can be alternatively used as F^- source in reactions where rigorous anhydrous conditions are needed [38,39].

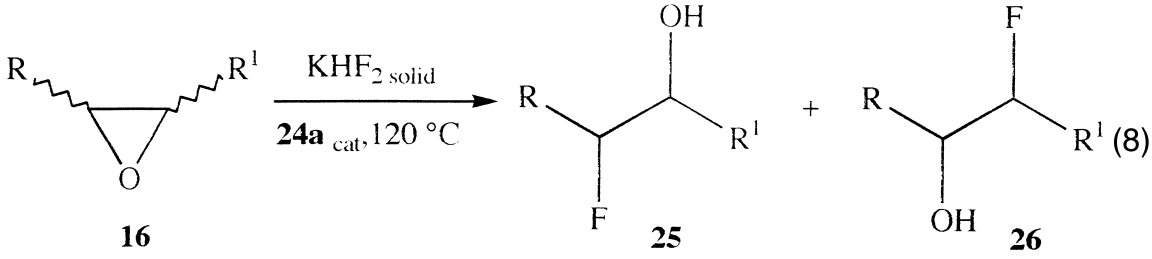
Our data on the F^- basicity clearly show the virtual impossibility of obtaining perfectly 'naked' tetraalkylammonium fluorides due to their instability both as pure substances and in solutions of anhydrous aprotic solvents, as later 'discovered' by other authors [40,41].

5. Tetrabutylammonium dihydrogentrifluoride ($Bu_4N^+H_2F_3^-$) as a catalyst in hydrofluorination reactions under SL-PTC conditions

The dihydrogentrifluoride anion, $H_2F_3^-$ associated with a lipophilic onium cation Q^+ combines acceptable nucleophilicity with a good tendency to provide an electrophilic H^+. For these reasons,

quaternary dihydrogentrifluorides $Q^+H_2F_3^-$ **24** are particularly suitable reagents for the acid catalysed introduction of fluorine atoms into organic molecules [26,42,43]. Furthermore, differently from Olah's reagent, $Py \cdot (HF)_n$, or $R_2NH \cdot 3HF$, **24** are excellent non-corrosive source of HF and can be used in normal Pyrex flasks.

We found that $Bu_4N^+H_2F_3^-$ (**24a**), used under SL-PTC conditions, promotes the conversion of epoxides **16** to the corresponding fluorohydrins **25** and **26** [44,45]. The reaction (Eq. 9) was carried out by heating, at 120°C, and stirring the epoxide **16** (1 mol) over solid KHF_2 (2 mol) in the presence of catalytic amounts of **24a**.



16 **25** **26**

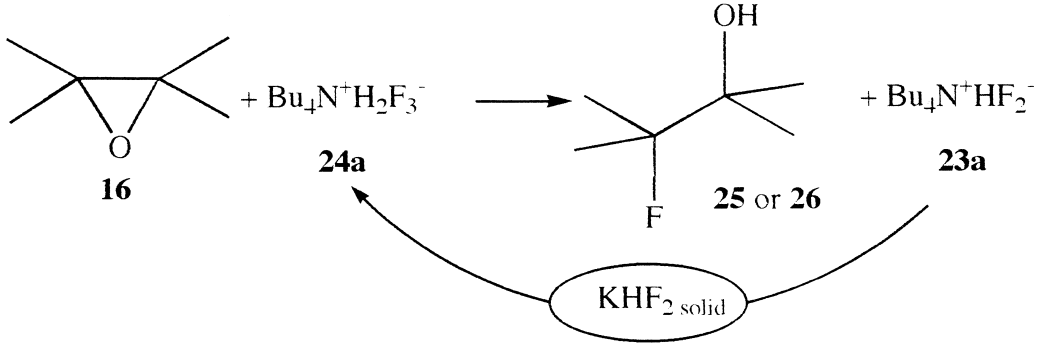
Whereas the PTC agent **24a** provides the HF required by the stoichiometry of the reaction, solid KHF_2 regenerates the onium dihydrogentrifluoride, realising the SL-PTC catalytic cycle (Scheme 11) [44].

As reported in Table 12, the reaction is quite general and affords the fluorohydrins **25** and **26** in comparable or better yields (45–90%) than those reported for other known procedures. In the case of more crowded substrates, such as stilbene oxides **16j**,**k** and epoxycholestane (**16u**), the use of a molar equivalent of **24a** gave better results than the catalytic process.

The reaction is *trans*-stereoselective: (*Z*)-cyclohexene oxide (**16i**), gave exclusively (*E*)-2-fluorocyclohexanol (**25i**); (*Z*)- and (*E*)-stilbene oxide (**16j**) and (**16k**) afforded *threo*- and *erythro*-1,2-diphenyl-2-fluoroethanol (**25j**) and (**25k**), respectively.

The reaction is highly regioselective, affording the fluorohydrins **26** deriving from the attack of the F^- anion at the less substituted carbon atom of the oxirane ring (Table 12), as the sole or largely prevalent regioisomers. Similar behaviour was found in the reaction of epoxides **16** with *i*-$Pr_2NH \cdot 3HF$ [46], which is opposite that observed using $Py \cdot (HF)_n$ [47].

Several functional or protective groups, such as methyl, benzyl, triptyl, allyl, phenyl, MEM, tetrahydropyranyl, are tolerated [44,45]. Acyl derivatives, such as benzoyl **16t**, react affording the expected fluorohydrins (e.g., **26t**, 45%), together with minor amounts of 2,3-diacyl-1-fluoroglycerols



16 **24a** **25** or **26** **23a**

Scheme 11.

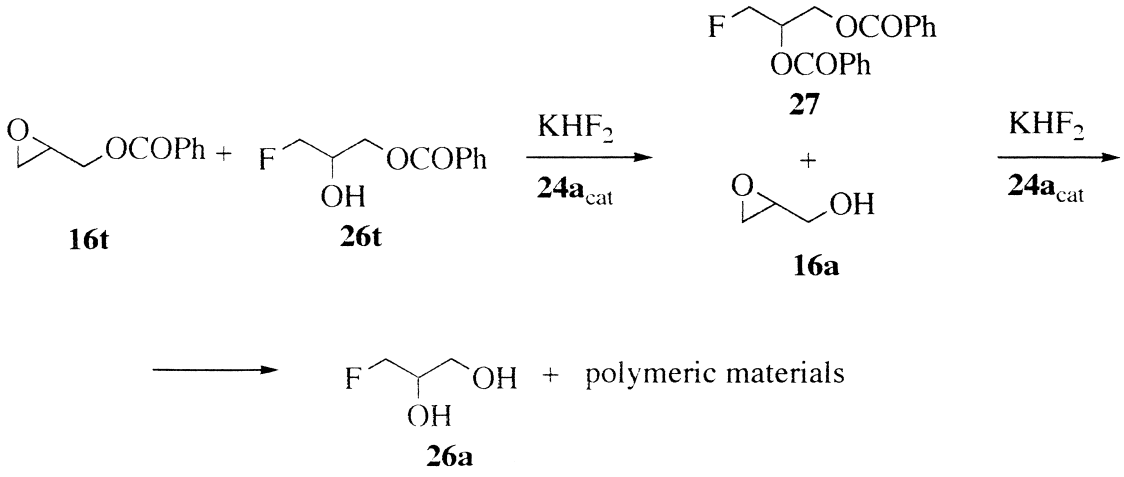
Table 12
Fluorohydrins **25** and **26** prepared by hydrofluorination of epoxides **16**, under SL-PTC conditions at 120°C[a]

	Substrate **16**		Isolated	Products (%)	
	R	R^1	Yield (%)	**25**	**26**
a	$HOCH_2$	H	47[b]	–	100
b	$PhOCH_2$	H	90	–	100
c	$PhCH_2OCH_2OCH_2$	H	77	6	94
d	$CH_2=CH-CH_2OCH_2$	H	70	9	91
g	Ph	H	74	39	61
h	*n*-$C_{10}H_{21}$	H	84	26	74
i	$(CH_2)_4$		71	(*E*)-2-F-cyclohexanol	
j	(*Z*)-Ph	Ph[c]	71	*threo* PhCHF–CH(OH)Ph	
k	(*E*)-Ph	Ph[c]	72	*erythro* PhCHF–CH(OH)Ph	
l	$MeOCH_2$	H	74	–	100
m	$PhCH_2OCH_2$	H	73	11	89
n	Ph_3COCH_2	H	89	–	100
o	$MEMOCH_2$	H	63	–	100
p	$THPOCH_2$	H	76	3	97
q	$MsOCH_2$	H	5	–	100
r	$TsOCH_2$	H	6	–	100
s	$BrCH_2$	H	48	–	100
t	$PhCOOCH_2$	H	45	–	100
u	3β-Hydroxy-5α, 6α-epoxycholestane		47	3β,5α-Dihydroxy-6β-fluorocholestane	

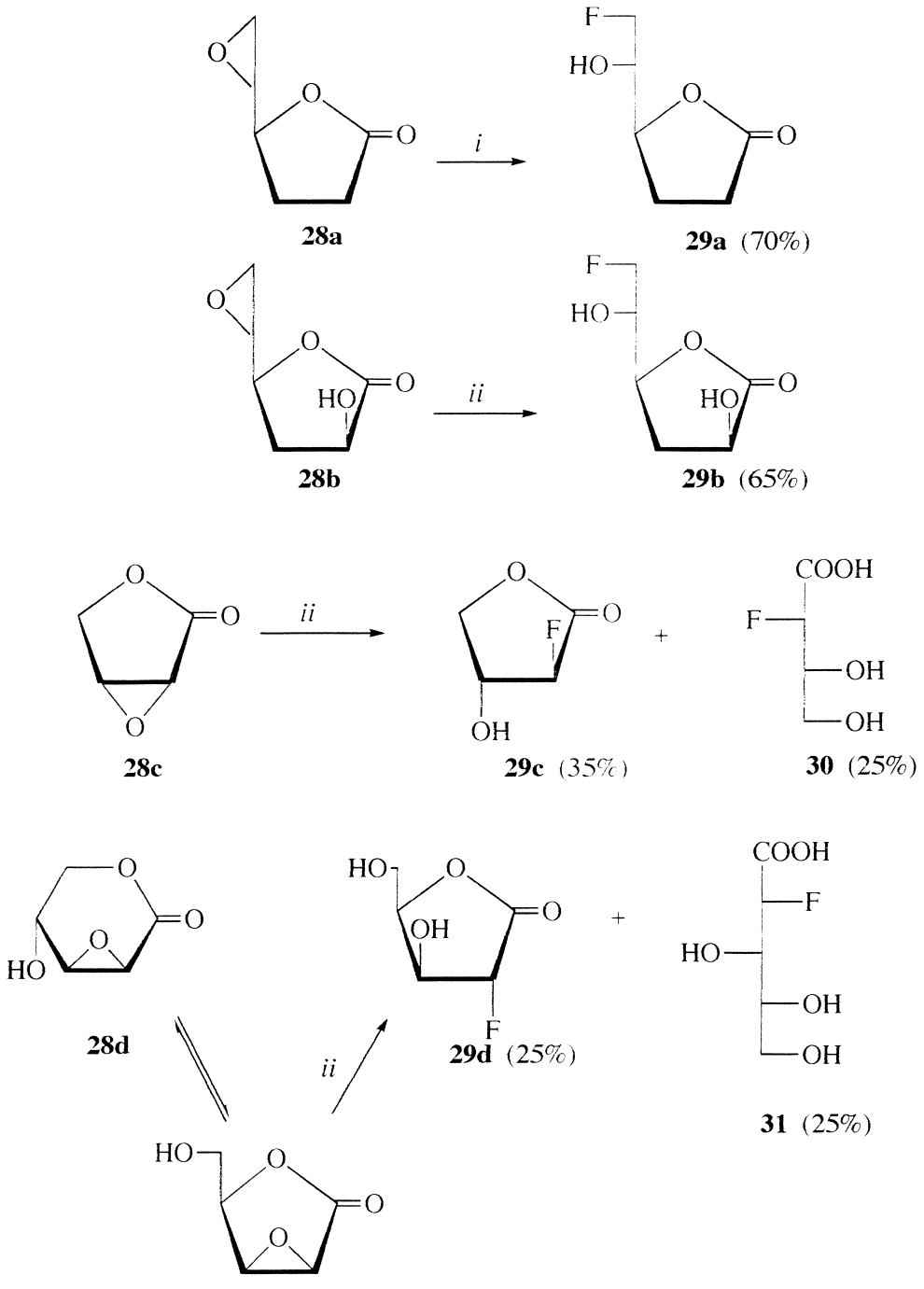
[a] Epoxide **16** (1 mol), $Bu_4N^+H_2F_3^-$ (**24a**) (0.1 mol), KHF_2 (2 mol).
[b] At 80°C.
[c] In the presence of 1 mol of **24a**/mol substrate.

(e.g., **27**, 17%) and traces of 1-fluoroglycerol (**26a**), remainders being polymeric materials (Scheme 12). These products most likely derive from an acid-catalysed transesterification process between the starting epoxide **16t** and the initially formed fluorohydrin **26t**. The presence of glycidol (**16a**) detected during the process, together with the derivative **26a**, accounts for this rationale [45].

On the other hand, transesterification reactions of *O*-acylglycidols [20,48] and *O*-glycerols [49] have been reported. Moreover, the hydrofluorination of glycidol (**16a**) gave mainly polymeric



Scheme 12.



i) **28a** (1 mol), (**1**) (0.1 mol), KHF_2 (2 mol), 75°C.
ii) **28b-d** (1 mol), **1** (1 mol), 75 °C.

Scheme 13.

products and only minor amounts of 3-fluoro-1,2-propandiol (**26a**). Higher yields (47%) of **26a** were obtained by operating at 80°C instead of 120°C (Table 12).

According to the good nucleofugacity of methanesulphonyl (mesyl) and 4-toluensulphonyl (tosyl) groups, glycidyl mesylate (**16q**) and tosylate (**16r**) were found to be largely unstable under the above hydrofluorinating conditions. Indeed, from the reaction mixture of **16q**, only 5% of 3-fluoro-1,2-propanediol 1-*O*-mesylate (**26q**) was obtained, whereas from **16r** 6% of 3-fluoro-2,3-propanediol 1-*O*-tosylate (**26r**) was isolated [45].

Hydrofluorination of optically pure (+)-(2*R*)-(triphenylmethoxy)methyl oxirane (***R*-16n**), promoted by **24a**, afforded optically pure (+)-(2*R*)-1-fluoro-3-(triphenylmethoxy)propan-2-ol (***R*-26n**) in 83% yield, showing that the stereocenter was not affected [45]. Thus, due to the recent commercial availability of both the enantiomers of glycidol (**16a**) [20], optically active polyfunctionalized building blocks, bearing a fluorine atom and a stereocenter of known configuration, can be easily synthesised by this method.

The same procedure of hydrofluorination has been applied to a series of epoxylactones **28a–d**, having a 5,6- or 2,3-epoxy function (Scheme 13) [50]. Lactones **28** are chiral compounds which could lead to fluorodeoxylactones **29**. Compounds **29** can be converted into fluorodeoxy-sugars or alditols, very interesting compounds in a biological context [51–53].

Hydrofluorination reactions were performed under PTC conditions, by stirring at 75°C the epoxyaldonolactone **28** (1 mol) and $Bu_4N^+H_2F_3^-$ (**24a**) (0.1 mol) over solid KHF_2 (2 mol), without solvent. Under these conditions only the unsubstituted 5,6-epoxy-hexono-1,4-lactone **28a** gave the corresponding fluorohydrin **29a** in high yield (70%). In the case of the substrates **28b–d**, the catalytic procedure gave scarce results, and therefore an equimolar amount of the hydrofluorinating agent **24a** was needed in order to obtain the corresponding fluorohydrins **29b–d** in acceptable yields (25–65%). Moreover, from the reactions of **28c** and **28d** the fluoroacid **30** and **31** were respectively also isolated. In all cases the process is completely regio- and stereoselective, affording 6-deoxy-6-fluoro-hexono lactones **29a,b** and 2-deoxy-2-fluoro-aldono lactones **29c,d**.

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