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Catalytic nucleophilic fluorination by an imidazolium ionic liquid possessing trialkylphosphine oxide functionality

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ABSTRACT

The synthesis of a new alkylmethylimidazolium ionic liquid wherein the alkyl group is functionalized with dihexylphosphine oxide moiety at the terminal position has been achieved in four steps from 1-methylimidazole. This hybrid ionic liquid effectively catalyzed the nucleophilic fluorination of primary alkyl mesylates under mild conditions using CsF as the fluoride source with a faster rate compared to butylmethylimidazolium mesylate. The hybrid catalyst was recycled 5 times without compromising the yield and purity of the product. The nucleophilic fluorination has been used for the synthesis of diethyl 2-(5-fluoropentyl)-2-methyl malonate, a precursor of ^{18}F isotopomer of an apoptosis imaging agent and the protected form of *O*-(2′-fluoroethyl)-L-tyrosine, a ^{18}F isotopomer of a tumor imaging agent.

1. Introduction

Fluorinated organic molecules show improved properties especially in increasing solubility, bioavailability and metabolic stability compared to their non-fluorinated analogs [1–5]. Therefore, they have great importance in pharmaceuticals, agrochemicals, solvents, liquid crystals, dyestuffs, polymers and novel materials [6–10]. A large number of methods have been developed over last few decades for the selective introduction of fluorine into target molecules [11]. Nevertheless, development of mild, selective and environmentally more acceptable fluorination method still remains a challenge. Besides fluorinated starting materials, fluorine can be incorporated into organic molecules in a nucleophilic manner, an electrophilic manner, or electrochemically. Introduction of single fluorine into aliphatic organic compounds is very important for making ^{18}F-labeled compounds and this has been typically carried out by nucleophilic substitution of sulfonates such as tosylates, mesylates and triflates utilizing alkali-metal/tetraalkylammonium fluorides as reagents [12,13]. The limited solubility and low nucleophilicity of the fluoride salts in organic solvents require generally vigorous conditions [14]. Phase-transfer catalysis involving crown ether derivatives and quaternary ammonium salts have been used to enhance the solubility and nucleophilicity of the metal salt in organic solvent systems consequently accelerating the reaction rate [15]. Although the problem of solubility and reactivity has been solved, 'naked' fluoride generated from these phase-transfer processes can induce side reactions such as elimination and hydroxylation reactions due to strong basicity of the fluoride [16–21]. Phase-transfer catalysis is also ineffective when the metal and nucleophile form a tight ion pair [22,23].

Recently, 1,3-dialkylimidazolium salts-based ionic liquids (ILs) have frequently been used as alternative reaction media instead of conventional volatile organic solvents for reaction acceleration and easy partitioning of products and catalysts [24–28]. It was found that ionic liquids can remarkably enhance the reactivity of alkali metal fluorides in the nucleophilic fluorination [29–34]. While anionic counterparts including BF_4, PF_6, SbF_6, NTf_2, and OTf play a critical role in determining different physical properties, such as melting point, polarity and solubility, functionality in the alkyl chains has been introduced for hybrid ILs to do specific functions [35–43].

Trialkylphosphine oxides are well known to complex various cations thus enhancing the solubility of their salts in organic media [44,45]. ILs have been used as both reaction media and phase transfer catalysts, and it has been found that nucleophilic fluorination is accelerated in ILs [29–34]. We were therefore curious to uncover the outcome of hybridization of ILs and

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trialkylphosphine oxide in the nucleophilic fluorination. Also, it would be interesting to check whether this combined functionality would provide dual advantages for the acceleration of the reaction rate by IL component and interruption of tight metal fluoride ion pair to lose ion pair but not "naked one" [46]. Herein, we describe the design and synthesis of a novel, imidazolium IL-trialkylphosphine oxide hybrid and its application to nucleophilic fluorination of primary alkyl mesylates.

2. Results and discussion

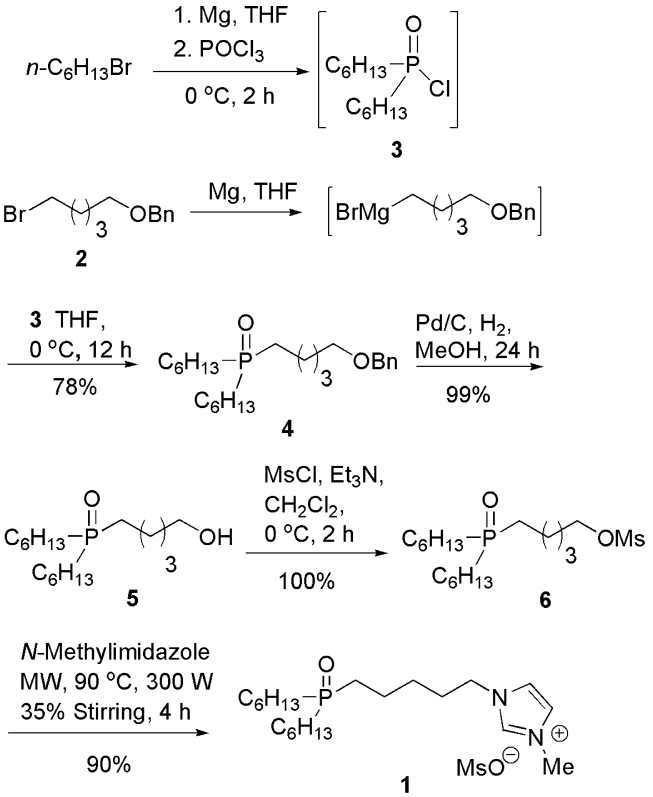
The imidazolium IL-trialkylphosphine oxide hybrid **1** having a dihexylpentylphosphine oxide moiety and methanesulfonate as a counter ion, was prepared from *N*-methylimidazole as shown in Scheme 1. For this the Grignard reagent derived from 5-benzyloxy-1-bromopentane **2** [47] was reacted with *in situ* generated dihexylphosphoryl chloride **3** in THF to give the trialkyl phosphine oxide **4** which on hydrogenolysis gave alcohol **5**. Reaction of this alcohol with methanesulfonyl chloride in the presence of triethylamine gave the mesylate **6** which on reaction with *N*-methylimidazole gave the desired hybrid IL **1** in excellent yield and purity.

For screening and optimization of nucleophilic fluorination protocol, we prepared the primary mesylate **7a** from 5-benzyloxypentanol using methanesulfonyl chloride and in the presence of triethylamine (Scheme 2). Cesium fluoride was chosen as the fluoride source as it has been reported [48–51] to give best results. We chose *t*-BuOH as the reaction medium as it is known [48–52] to suppress basicity of fluoride ion by the way of H-bonding thus minimizes the side reactions due to elimination.

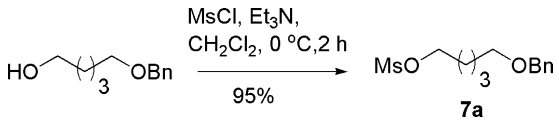
When the solution of mesylate **7a** in *t*-BuOH was heated at 60 °C with 3 equiv. of added cesium fluoride, no reaction took place (Table 1, entry 1). When the same reaction was repeated after addition of 0.5 equiv. of hybrid IL **1**, an incomplete but clean reaction took place with 48% conversion (Table 1, entry 2) of mesylate **7a** to fluoride **8a**. For comparison purpose, the fluorination reaction was carried out with 0.5 equiv. of butylmethylimidazolim mesylate ([BMIm] [OMs]) **9** instead of hybrid IL **1** under the same reaction conditions. Only 5% conversion of mesylate **7a** to fluoride **8a** was observed (Table 1, entry 3). Interestingly, when the reaction was carried out with 0.5 equiv. of phosphine oxide **4** as an additive, no fluorination took place. Only the starting mesylate **7** was recovered (Table 1, entry 4). When a mixture containing 0.5 equiv. each of [BMIm] [OMs] **9** and phosphine oxide **4** was used as an additive, a marginal rate enhancement was noticed and about 10% fluorination took place (Table 1, entry 5). Clearly, a distinctive rate enhancement was observed in the hybrid IL **1**. For establishment of optimum conditions for the catalytic fluorination using hybrid IL **1**, the reaction temperature was increased and at 100 °C within 10 min, 90% of **7a** was transformed into fluoride **8a** and the reaction was completed in 45 min (Table 1, entries 6 and 7).

To check the reusability of the hybrid IL **1**, the fluorination reaction was repeated using same ionic liquid recovered after fluorination. After 45 min, the reaction mixture was triturated with hexanes and the hexane layer was decanted. After evaporation of the hexane solution, pure fluoride **8a** was isolated and the ionic liquid associated with CsF/CsOMs remained in the reaction pot was subjected under high vacuum and reused. In each cycle, an additional 1 equiv. of CsF was added and the yield of the fluoride **8a** was uniformly high in all the cycles (Table 2).

To enhance the utility, the IL **1** catalyzed nucleophilic fluorination was investigated with substrates having halides ($Cl^-/Br^-/I^-$) as leaving groups under the optimized conditions (Scheme 3). The reaction of chloride **10a** [53] and bromide **2** were slow and required 75 min and 60 min, respectively to undergo completion. A trace of elimination product **11** (~5%) could be seen in case of chloride substrate **10a** while bromide **2** gave about 10% of **11**. Interestingly, the reaction of iodide **10b** [54] was faster and completed within 35 min but accompanied with about 30% of alkene **11**. Although the elimination product **11** is easily separable from the desired fluoride **8a**, its yield was affected to varied extent depending on the substrate.

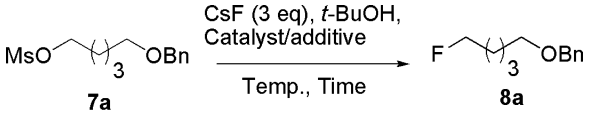


Scheme 1.



Scheme 2.

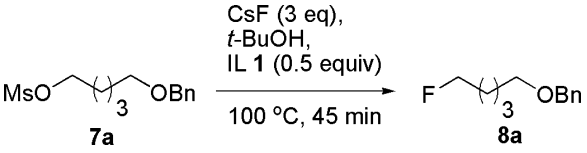
Table 1
Fluorination of mesylate **7a** with CsF in *t*-BuOH[a].



Entry	Catalyst/additive (equiv.)	Temperature (°C)/time (min)	% conversion[b]
1	Nil	60/30	0
2	**1** (0.5)	60/30	48
3	**9** (0.5)	60/30	5
4	**4** (0.5)	60/30	0
5	**9** (0.5) and **4** (0.5)	60/30	10
6	**1** (0.5)	100/10	90
7	**1** (0.5)	100/45	100

[a] All reactions were carried out using **7a** (1 mmol), cesium fluoride (3 mmol) and catalyst **1** (0.5 mmol) in *t*-BuOH (0.25 mL).
[b] Determined from ^{1}H NMR of the crude reaction mixture by integrating the peak area of CH_2 in CH_2OMs and CH_2F resonances.

Table 2
Fluorination of mesylate **7a** with recycled IL **1**[a].

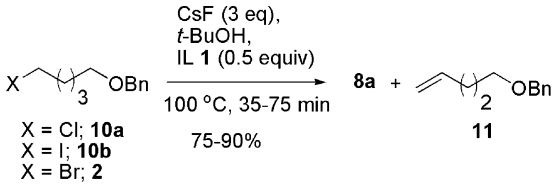


7a **8a**

Entry	Fluorination cycle	% yield of **8a**[b]
1.	1	97
2.	2	96
3.	3	98
4.	4	96
5.	5	97

[a] All reactions were carried out using **7a** (1 mmol), cesium fluoride (3 mmol) and catalyst **1** (0.5 mmol) in *t*-BuOH (0.25 mL) at 100 °C for 45 min. After each cycle, additional cesium fluoride (1 mmol) was added.
[b] Isolated yield after chromatography.

Next, the scope of the optimized protocol for nucleophilic fluorination was explored by using different primary methanesulfonates as presented in Table 3. The mesylates **7b** [55] and **7c** derived from 3-(1-napthyloxy)propanol and 3-(2-napthyloxy)propanol, respectively, gave the desired fluorinated products **8b** [56] and **8c**, respectively in very good yield and purity. The dimesylate



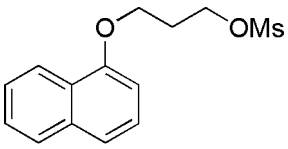
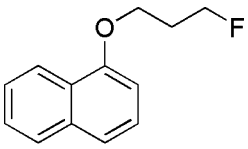
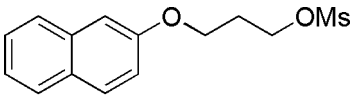
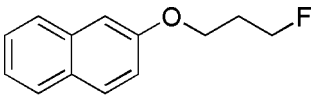
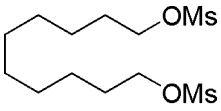
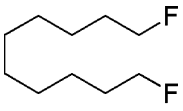
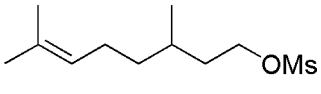
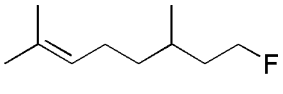
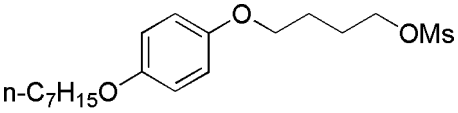
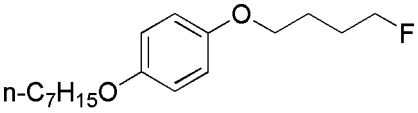
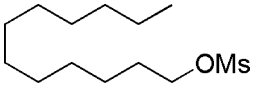
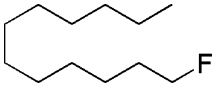
Scheme 3.

of 1,10-decanediol **7d** [57] gave the 1,10-difluorodecane **8e** [58] in excellent yield. Mesylates **7e** [59] derived from citronellol, also provided the desired fluoride **8e** [60]. Similarly, 4-aryloxy substituted butyl mesylate **7f** and dodecyl mesylate **7g** [61] gave the corresponding fluorides **8f** [56] and **8g** [62], respectively in excellent yields.

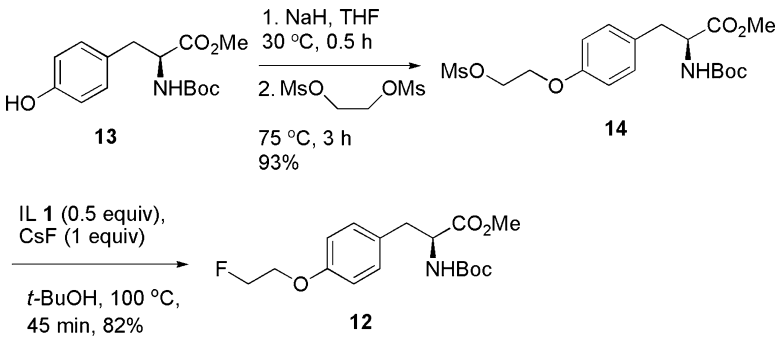
The current nucleophilic fluorination was applied for the synthesis of precursors for fluoroethyl L-tyrosine (FET) [63] and 2-(5-fluoropentyl)-2-methyl malonic acid (FPMA or ML-10) [64,65]. The ^{18}F isotopomer of FET [66] is used as a tumor imaging agent while and ^{18}F isotopomer of ML-10 [67,68] is used as apoptosis imaging agent [69–71].

The synthesis of *O*-(2-fluoroethyl) *N*-Boc-tyrosine methyl ester **12** [72], a precursor for FET was achieved in two steps from commercially available *N*-Boc-L-tyrosine methyl ester **13**

Table 3
Synthesis of primary fluorides from mesylates.[a]

Entry	Mesylate	Fluoride	% Yield[b]
1	 **7b**	 **8b**	90
2	 **7c**	 **8c**	90
3	 **7d**	 **8d**	89
4	 **7e**	 **8e**	92
5	 **7f**	 **8f**	90
6	 **7g**	 **8g**	93

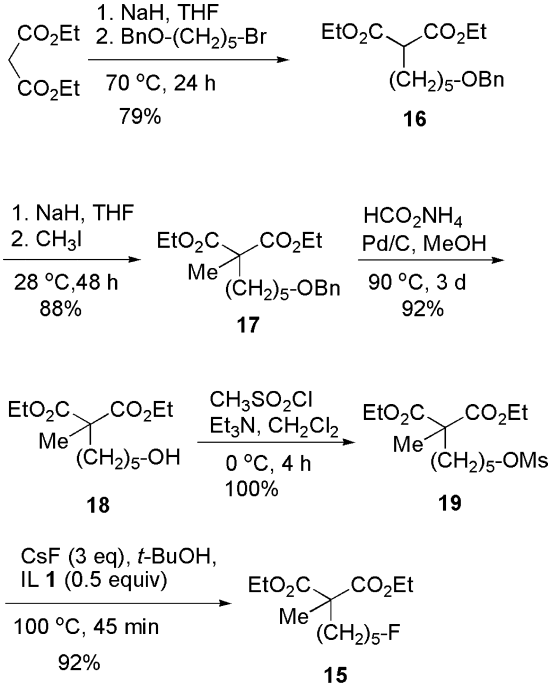
[a] All reactions were carried out using **7b–g** (1 mmol), cesium fluoride (3 mmol) and catalyst **1** (0.5 mmol) in *t*-BuOH (0.25 mL) at 100 °C for 45 min.
[b] Isolated yield after chromatography.



Scheme 4.

(enantiomeric purity 99%) (Scheme 4). For this, the tyrosine derivative **13** was reacted with 1,2-dimesyloxyethane in the presence of K_2CO_3 in refluxing acetonitrile [73] to give mesylate **14** in good yield. Unfortunately, a partial racemization (optical purity: 82% *ee*) took place at the chiral center α-to ester functionality as confirmed by HPLC analyses on a chiral stationary phase. To overcome this problem, we modified the preparation of mesylate **14** by reacting tyrosine derivative **13** first with NaH in THF at room temperature and then with 1,2-dimesyloxyethane at 75 °C. The mesylate **14** now was obtained in good yield and high enantiomeric purity (95.4% *ee*). When the optimized conditions using 3 equiv. of CsF was applied for the preparation of fluoride **12** from mesylate **14**, significant level of racemization took place at the chiral center α-to ester functionality. We ascribe this epimerization due to basic nature of the fluoride ion which was present in excess. Therefore, the fluoride **12** was subsequently obtained using 1 equiv. of CsF in our fluorination conditions in good yield with minimal additional racemization at α-to ester (90.8% *ee*) as evidenced by HPLC analyses on a chiral stationary phase.

The synthesis of 2-(5-fluoropentyl)-2-methyl malonic acid diethyl ester **15** [64] was started from diethyl malonate which on alkylation with 5-benzyloxy-1-bromopentane **2** gave monoalkylated malonate **16** (Scheme 5). Further alkylation with methyl iodide gave the dialkyl malonate **17** which on hydrogenolysis with ammonium formate in the presence of 10% Pd on charcoal gave the alcohol **18** [64]. The alcohol was converted to the mesylate **19** [64] using methanesulfonyl chloride in quantitative yield. The mesylate **19** was then subjected to our nucleophilic fluorination conditions using 0.5 equiv. of hybrid ionic liquid catalyst **1**, 3 equiv. of CsF and *t*-BuOH as the solvent at 100 °C which provided the fluorinated malonate **15** in excellent yield.



Scheme 5.

3. Conclusion

In conclusion, we have designed and synthesized a hybrid imidazolium based ionic liquid having the alkyl group is functionalized with dihexylphosphine oxide moiety at the terminal position. A distinctive rate enhancement for CsF mediated nucleophilic fluorination of primary alkyl mesylate was observed compared to [BMIm] [OMs] or trialkyl phosphine oxide alone. The rate enhancement can be attributed to the combined effect of imidazolium and phosphine oxide functionality on the stabilization of the charge built-up during substitution reaction thus accelerating the nucleophilic substitution. The ionic liquid could be recycled and the products could be easily parted with non-polar solvents. The method allowed to use halides as substrates but a competitive elimination was observed especially with iodine as leaving group. The method thus holds promise to make ^{18}F labeled radiopharmaceuticals from primary alkyl methanesulfonates. Use of excess fluoride is to be avoided for molecules with base sensitive epimerizable center(s).

4. Experimental

All reactions were performed in oven-dried (120 °C) or flame-dried glass apparatus under dry N_2 or argon atmosphere. Tetrahydrofuran (THF) was dried from sodium/benzophenone. NaH was purchased from Aldrich. Methanesulfonyl chloride and benzyl bromide were freshly distilled before use. Methyl iodide was used as obtained. *t*-BuOH, *N*-methylimidazole and alkyl bromides were used as obtained. Solvent removal was carried out using a rotary evaporator connected to a dry ice condenser. TLC (0.5 mm) was carried out using homemade silica plates with fluorescence indicator. Column chromatography was performed on silica gel (230–400 mesh). The ^1H NMR, ^{31}P NMR, ^{19}F and ^{13}C NMR spectra were recorded with Bruker 200/500/700 MHz spectrometers. The spectra were referenced to residual chloroform (δ 7.25 ppm, ^1H; δ 77.00 ppm, ^{13}C). The IR spectra were recorded with a JASCO FT IR spectrophotometer in NaCl cells or in KBr discs. Peaks are reported in cm^{-1}. Mass spectra were recorded using Bruker maXis instrument. Enantiomeric ratio (er) determinations were carried out by HPLC instrument fitted with a chiralpak AD-H column and UV detector with λ fixed at 254 nm. Optical rotations were measured in a JASCO polarimeter.

4.1. [{(5-Bromopentyl)oxy}methyl]benzene (**2**) [47]

A solution of pentane-1,5-diol (21 mL, 200 mmol) in THF (400 mL) was added drop wise to a stirred suspension of oil free sodium hydride (4.8 g, ~55% in oil, 200 mmol) in THF (100 mL) under argon atmosphere. The reaction mixture was heated under reflux for 4 h, cooled to room temperature and benzyl bromide (23.7 mL, 200 mmol) was drop wise added to it. The reaction mixture was heated under reflux overnight, cooled to room temperature and concentrated under reduced pressure. The residue was diluted with water and extracted with ethyl acetate. The organic extract was concentrated under reduced pressure and purified by fractional distillation to give 5-(benzyloxy)pentane-1-ol (25.2 g, 65%); bp 140–150 °C (bath) (0.4 mbar) as a colorless liquid.

p-Toluenesulphonyl chloride (24.8 g, 130 mmol) was added to a stirred solution of 5-(benzyloxy)pentane-1-ol (25.2 g, 130 mmol) in dry pyridine (30 mL) at 0 °C. The reaction mixture was left standing at 4 °C overnight. The reaction mixture was allowed to attain to room temperature, diluted with water and extracted with 15% ethyl acetate in hexanes. The organic extract was concentrated under reduced pressure to give 5-(benzyloxy)pentyl-1-(4-methyl)benzenesulfonate (42.5 g, 94%) as a colorless gum.

Sodium bromide (13 g, 126 mmol) was added to the stirred solution of 5-(benzyloxy)pentyl-1-(4-methyl)benzenesulfonate (42.5 g, 122 mmol) in DMF (300 mL) and the reaction mixture was heated at 45 °C for 5 h. The reaction mixture was diluted with water, and extracted with 10% ethyl acetate in hexanes. The organic extract was concentrated to give bromide **2** (31.3 g, 99%) as a colorless liquid. IR (film): $\bar{\upsilon}$ 3063, 3029, 2937, 2859, 1646, 1495, 1454, 1362, 1245, 1203, 1103, 1027, 735, 697 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.56–1.73 (m, 4H, 2 × CH_2), 1.80–1.95 (m, 2H, CH_2CH_2Br), 3.41 (t, 2H, $^3J_{HH}$ = 6.8 Hz, OCH_2), 3.49 (t, 2H, $^3J_{HH}$ = 6.4 Hz, CH_2Br), 4.51 (s, 2H, OCH_2Ph), 7.31–7.36 (m, 5H, Ph). ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.9, 28.8, 32.5, 33.7, 69.9, 72.9, 127.5, 127.6 (2C), 128.3 (2C), 138.4.

4.2. [5-(Benzyloxy)pentyl]dihexylphosphine oxide (**4**)

A solution of *n*-hexyl magnesium bromide (prepared from 13 mL, 93 mmol of *n*-bromohexane and 2.4 g, 100 mmol Mg turnings in 90 mL of THF) was cannulated to a solution of $POCl_3$ (4.3 mL, 47 mmol) in THF (30 mL) at 0 °C and stirred vigorously under argon atmosphere. After 2 h, the reaction mixture was cannulated dropwise to a solution of Grignard reagent prepared from bromide **2** (12 g, 47 mmol) and Mg turnings (1.2 g, 50 mmol) in THF (50 mL) at 0 °C. The reaction mixture was allowed to attain to room temperature and stirred overnight. The solvent was removed under reduced pressure and the residue was diluted with deionised water, extracted with 20% ethyl acetate in hexanes and the combined organic extract was washed with disodium EDTA solution. The organic extract was and evaporated under reduced pressure and the residue was purified by column chromatography to give the phosphine oxide **4** (14.3 g, 78%) as a thick liquid. IR (film): $\bar{\upsilon}$ 3402, 2930, 2858, 1723, 1640, 1452, 1366, 1270, 1205, 1141, 1104, 1024, 814, 712, 611, 509 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, 6H, $^3J_{HH}$ = 7.0 Hz, 2 × CH_3), 1.20–1.89 (m, 28H, 14 × CH_2), 3.47 (t, 2H, $^3J_{HH}$ = 6.2 Hz, OCH_2), 4.49 (s, 2H, CH_2Ph), 7.30–7.34 (m, 5H, Ph). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.7 (2C), 21.2 (d, $^3J_{PC}$ = 2.5 Hz), 21.3 (d, 2C, $^3J_{PC}$ = 4.5 Hz), 22.1 (2C), 27.4 (d, $^1J_{PC}$ = 65.0 Hz), 27.5 (d, 2C, $^1J_{PC}$ = 65.0 Hz), 27.6 (d, $^2J_{PC}$ = 14.0 Hz), 29.0, 30.5 (d, 2C, $^2J_{PC}$ = 14.0 Hz), 31.0 (2C), 69.7, 72.6, 127.2, 127.3 (2C), 128 (2C), 138.2. EIMS, 70 eV, *m/z* (rel. int.): 303 (47) $[M-Bn]^+$, 287 (11), 233 (11), 219 (13), 162 (11), 148 (18), 92 (48), 91 (100) $[Bn]^+$, 78 (30). HRMS (ESI), *m/z* calcd. for $C_{24}H_{44}O_2P^+$ 395.3073 $(M+H)^+$, found 395.3074.

4.3. Dihexyl(5-hydroxypentyl)phosphine oxide (**5**)

A solution of benzyl ether **4** (3.4 g, 8.6 mmol) in methanol (30 mL) was stirred under hydrogen atmosphere in the presence of 10% Pd/C (50 mg) for 4 days. The reaction mixture was filtered through a Celite pad and concentrated under reduced pressure to give alcohol **5** (2.6 g, 99%). IR (film): $\bar{\upsilon}$ 3394, 2930, 2958, 2716, 2360, 1973, 1458, 1036, 903 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$): δ 0.88 (t, 6H, $^3J_{HH}$ = 7.0 Hz, 2 × CH_3), 1.26–1.34 (m, 8H, 4 × CH_2), 1.36–1.40 (m, 4H, 2 × CH_2), 1.48–1.68 (m, 16H, 8 × CH_2), 1.82 (s, broad, 1H, OH), 3.64 (t, 2H, $^3J_{HH}$ = 7.0 Hz, CH_2OH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9 (2C), 21.4, 21.6 (2C), 22.3 (2C), 27.3 (d, $^2J_{PC}$ = 13.8 Hz), 27.7 (d, $^1J_{PC}$ = 64.5 Hz), 27.8 (d, 2C, $^1J_{PC}$ = 64.5 Hz), 30.8 (d, 2C, $^2J_{PC}$ = 13.8 Hz), 31.2 (2C), 32.1, 61.9. ^{31}P NMR (283 MHz, $CDCl_3$): δ 49.9. HRMS (ESI), *m/z* calcd. for $C_{17}H_{38}O_2P^+$ 305.2604 $(M+H)^+$, found 305.2603.

4.4. 5-(Dihexylphosphoryl)pentyl methanesulfonate (**6**)

Freshly distilled methanesulphonyl chloride (1.3 mL, 17 mmol) was added drop wise to a stirred solution of alcohol **5** (3.45 g, 11.3 mmol) and triethylamine (2.4 mL, 17 mmol) in dry dichloromethane (30 mL) at 0 °C. After 4 h, the reaction mixture was diluted with water and extracted with dichloromethane. The organic extract was concentrated under reduced pressure to give methane sulfonate **6** (4.2 g, 100%). IR (film): $\bar{\upsilon}$ 3399, 2930, 2859, 2209, 1641, 1464, 1411, 1352, 1265, 1242, 1209, 1175, 973, 937, 815, 732, 642, 485, 465, 437, 422, 412, 403 cm^{-1}. ^1HNMR (200 MHz, $CDCl_3$): δ 0.88 (t, 6H, $^3J_{HH}$ = 6.4 Hz, 2 × CH_3), 1.25–1.79 (m, 28H, 14 × CH_2), 3.01 (s, 3H, SO_2CH_3), 4.24 (t, 2H, $^3J_{HH}$ = 6.0 Hz, OCH_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.4 (2C), 20.6 (d, $^3J_{PC}$ = 4.0 Hz), 21.0 (d, 2C, $^3J_{PC}$ = 3.5 Hz), 21.8 (2C), 26.4 (d, $^2J_{PC}$ = 14.0 Hz), 27.0 (d, $^1J_{PC}$ = 64.5 Hz), 27.3 (2C, d, $^1J_{PC}$ = 65.5 Hz), 28.1, 30.2 (2C, d, $^2J_{PC}$ = 13.5 Hz), 30.7 (2C), 36.6, 69.3. HRMS (ESI), *m/z* calcd. for $C_{18}H_{40}O_4PS^+$ 383.2384 $(M+H)^+$, found 383.2377.

4.5. 3-{5-(Dihexylphosphoryl)pentyl}-1-methyl-1H-imidazol-3-ium methanesulfonate (**1**)

A mixture of mesylate **6** (3.9 g, 10 mmol) and 1-methyl imidazole (0.9 mL, 11 mmol) was irradiated in a microwave reactor (power 300 W) for 4.5 h at 90 °C. The reaction mixture was cooled to room temperature, washed repeatedly with dry diethyl ether (5 × 10 mL) and dried under high vacuum for 24 h to give the desired ionic liquid **1** (4.25 g, 90%) as a pale yellow thick liquid. IR (film): $\bar{\upsilon}$ 3434, 3146, 3097, 2932, 2860, 2234, 1671, 1572, 1464, 1419, 1378, 1327, 1191, 1109, 1074, 1014, 909, 769, 727, 644, 625 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.67 (t, 6H, $^3J_{HH}$ = 6.6 Hz, 2 × CH_3), 1.10–1.60 (m, 26H, 13 × CH_2), 1.60–1.78 (m, 2H, PCH_2), 2.53 (s, 3H, OSO_2CH_3), 3.82 (s, 3H, NCH_3), 4.09 (t, 2H, $^3J_{HH}$ = 7.0 Hz, NCH_2), 7.39 (s, 2H, Im), 9.55 (s, 1H, Im). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.5 (2C), 20.6 (d, $^3J_{PC}$ = 3.5 Hz), 21.2 (d, 2C, $^3J_{PC}$ = 3.5 Hz), 21.9 (2C), 26.9 (d, $^2J_{PC}$ = 15.0 Hz), 27.0 (d, $^1J_{PC}$ = 64.0 Hz), 28.5 (d, 2C, $^1J_{PC}$ = 64.5 Hz), 29.3, 30.3 (d, 2C, $^2J_{PC}$ = 13.5 Hz), 30.8 (2C), 35.8, 39.2, 48.9, 121.9, 123.3, 137.1. ESI-MS, *m/z* (rel. int.): 369 (100) $[M-MeSO_3]^+$.

4.6. 5-(Benzyloxy)pentyl methanesulfonate (**7a**) [47]

Freshly distilled methanesulphonyl chloride (2.3 mL, 30.9 mmol) was added drop wise to a stirred solution of 5-(benzyloxy)pentane-1-ol (4 g, 20.6 mmol) and Et_3N (4.3 mL, 31 mmol) in dry dichloromethane (45 mL) at 0 °C. After 3 h, the reaction mixture was diluted with water, and extracted with dichloromethane. The organic extract was concentrated under vacuum to give mesylate **7a** (5.3 g, 95%). IR (film): $\bar{\upsilon}$ 3427, 3034,

2943, 2860, 2519, 2315, 1959, 1732, 1460, 1352, 1172, 1096, 952, 832, 741, 695, 612, 521 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.50–1.85 (m, 6H, 3 × CH_2), 2.99 (s, 3H, OSO_2CH_3), 3.48 (t, 2H, $^3J_{HH}$ = 6.0 Hz, CH_2OCH_2Ph), 4.22 (t, 2H, $^3J_{HH}$ = 6.4 Hz, SO_2CH_2), 4.50 (s, 2H, $PhCH_2$), 7.27–7.35 (m, 5H, Ph). ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.0, 28.6, 28.8, 36.9, 69.6, 69.9, 72.6, 127.3, 127.4 (2C), 128.1 (2C), 138.3.

4.7. 3-(Naphthalene-1-yloxy)propyl methanesulfonate (**7b**) [55]

This compound has been made following the procedure described for the preparation of **7a**. Yield: 99%. ^1H NMR (500 MHz, $CDCl_3$): δ 2.34–2.40 (2H, m, CH_2), 2.95 (3H, s, SO_2Me), 4.27 (2H, t, $^3J_{HH}$ = 5.5 Hz, CH_2OSO_2Me), 4.55 (2H, t, $^3J_{HH}$ = 6.0 Hz, CH_2OAr), 6.82 (1H, d, $^3J_{HH}$ = 7.5 Hz, Ar), 7.36–7.53 (4H, m, Ar), 7.82 (1H, dd, $^3J_{HH}$ = 6.5 Hz, $^4J_{HH}$ = 2.5 Hz, Ar), 8.25 (1H, dd, $^3J_{HH}$ = 9.0, $^4J_{HH}$ = 2.0 Hz, Ar). ^{13}C NMR (125 MHz, $CDCl_3$): δ 29.3, 37.3, 63.6, 67.0, 104.9, 120.8, 121.8, 125.5, 125.6, 125.9, 126.6, 127.7, 134.6, 154.2.

4.8. 3-(Naphthalene-2-yloxy)propyl methanesulfonate (**7c**)

This compound has been made following the procedure described for the preparation of **7a**. Yield: 99%. IR (film): $\bar{\upsilon}$ 3653, 3424, 3056, 3028, 2961, 2933, 1651, 1517, 1360, 1211, 1170, 963, 831, 747 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 2.31 (2H, quint, $^3J_{HH}$ = 6.0 Hz, CH_2), 3.00 (3H, s, SO_2Me), 4.22 (2H, t, $^3J_{HH}$ = 6.0 Hz, CH_2OSO_2Me), 4.50 (2H, t, $^3J_{HH}$ = 6.0 Hz, CH_2OAr), 7.14 (1H, d, $^3J_{HH}$ = 10.0 Hz, Ar), 7.16 (1H, s, Ar), 7.37 (1H, t, $^3J_{HH}$ = 7.0 Hz, Ar), 7.47 (1H, t, $^3J_{HH}$ = 7.0 Hz, Ar), 7.74–7.80 (3H, m, Ar). ^{13}C NMR (125 MHz, $CDCl_3$): δ 29.3, 37.4, 63.4, 66.9, 107.0, 118.7, 124.0, 126.6, 126.9, 127.8, 129.3, 129.7, 134.6, 156.6. HRMS (ESI), *m/z* calcd. for $C_{14}H_{16}O_4SNa^+$ 303.0667 $(M+Na)^+$, found 303.0664.

4.9. Decane-1,10-diyl dimethanesulfonate (**7d**) [59]

This compound has been made following the procedure described for the preparation of **7a**. Yield: 99%. IR (film): $\bar{\upsilon}$ 3048, 2983, 2949, 2916, 2842, 1467, 1344, 1153, 996, 954, 847, 757, 722 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.29–1.49 (12H, m, 6 × CH_2), 1.70–1.78 (4H, m, 2 × CH_2), 3.00 (6H, s, 2 × $CH_2OSO_2CH_3$), 4.22 (4H, t, $^3J_{HH}$ = 6.3 Hz, 2 × CH_2OSO_2Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.4 (2C), 28.9 (2C), 29.1 (2C), 29.2 (2C), 37.3 (2C), 70.2 (2C).

4.10. (±)-3,7-Dimethyloct-6-en-1-yl methanesulfonate (**7e**) [57]

This compound has been made following the procedure described for the preparation of **7a**. Yield: 99%. IR (film): $\bar{\upsilon}$ 3561, 3031, 2966, 292, 2370, 1650, 1476, 136, 1170, 1053, 988, 946, 896, 739 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.92 (3H, d, $^3J_{HH}$ = 6.5 Hz, $CHCH_3$), 1.14–1.23 (1H, m, CH_AH_B), 1.29–1.38 (1H, m, CH_AH_B), 1.50–1.63 (2H, m, CH_2), 1.59 (3H, s, C=CCH_3), 1.67 (3H, s, C=CCH_3), 1.74–1.82 (1H, m, *CH*Me), 1.90–2.04 (2H, m, CH_2), 2.99 (3H, s, OSO_2CH_3), 4.20–4.30 (2H, m, CH_2OSO_2Me), 5.06 (1H, t, broad, $^3J_{HH}$ = 9 Hz, *HC*=C). ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.5, 19.0, 25.2, 25.6, 28.9, 35.8, 36.7, 37.2, 68.5, 124.2, 131.4.

4.11. 4-(4-(Heptyloxy)phenoxy)butyl methanesulonate (**7f**)

This compound has been made following the procedure described for the preparation of **7a**. Yield: 99%. IR (film): $\bar{\upsilon}$ 3031, 2924, 2842, 1526, 1459, 1344, 1228, 1153, 1054, 931, 839, 764, 664 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.89 (3H, t, $^3J_{HH}$ = 6.0 Hz, CH_3), 1.26–1.37 (6H, m, 3 × CH_2), 1.44 (2H, quint, $^3J_{HH}$ = 7.0 Hz, CH_2), 1.75 (2H, quint, $^3J_{HH}$ = 6.5 Hz, CH_2), 1.86–1.91 (2H, m, CH_2), 1.93–1.99 (2H, m, CH_2), 3.01 (3H, s, SO_2CH_3), 3.90 (2H, t, $^3J_{HH}$ = 6.5 Hz, OCH_2), 3.95 (2H, t, $^3J_{HH}$ = 6.0 Hz, OCH_2), 4.31 (2H, t, $^3J_{HH}$ = 6.0 Hz, CH_2OSO_2Me), 6.81 (4H, s, Ar). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 22.5, 25.4, 25.9, 26.1, 29.0, 29.3, 31.7, 37.3, 67.5, 68.6, 69.6, 115.3 (2C), 115.4 (2C), 152.7, 153.4. HRMS (ESI), *m/z* calcd. for $C_{18}H_{30}O_5SNa^+$ 381.1712 $(M+Na)^+$, found 381.1711.

4.12. Dodecyl methanesulfonate (**7g**) [61]

This compound has been made following the procedure described for the preparation of **7a**. Yield: 99%. IR (film): $\bar{\upsilon}$ 3041, 2908, 2849, 1467, 1360, 1178, 971, 946, 822, 747, 722 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.85 (3H, t, $^3J_{HH}$ = 6.6 Hz, CH_3), 1.15–1.49 (18H, m, 9 × CH_2), 1.72 (2H, quint, $^3J_{HH}$ = 6.3 Hz, CH_2), 2.98 (3H, s, $CH_2OSO_2CH_3$), 4.19 (2H, t, $^3J_{HH}$ = 6.3 Hz, CH_2OSO_2Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 22.7, 25.4, 29.0, 29.1, 29.3, 29.4, 29.5, 29.6 (2C), 31.9, 37.3, 70.3.

4.13. [{(5-Fluoropentyl)oxy}methyl]benzene (**8a**)

Cesium fluoride (456 mg, 3 mmol) was added to a stirred solution of mesylate **7a** (272 mg, 1 mmol) and ionic liquid **1** (232 mg, 0.5 mmol) in *t*-BuOH (0.25 mL) and the mixture was heated at 100 °C for 45 min. The reaction mixture was diluted with water and extracted with 15% ethyl acetate in hexanes. The organic extract was concentrated under reduced pressure and the residue was purified by silica gel column chromatography using 5% ethyl acetate in hexanes to give compound **8a** (190 mg, 97%) as a colorless oil.

This compound has also been prepared from chloride **10a**. The procedure is same as from mesylate **7a** except the mixture was heated at 100 °C for 75 min which provided a mixture of fluoride **8a** and alkene **11** in a ratio of 95:5. Yield of **8a**: 94% as a colorless oil. This compound has also been prepared from bromide **2**. The procedure is same as from mesylate **7a** except the mixture was heated at 100 °C for 60 min which provided a mixture of fluoride **8a** and alkene **11** in a ratio of 90:10. Yield of **8a**: 87% as a colorless oil. This compound has also been prepared from iodide **10b**. The procedure is same as from mesylate **7a** except the mixture was heated at 100 °C for 30 min which provided a mixture of fluoride **8a** and alkene **11** in a ratio of 70:30. Yield of **8a**: 68% as a colorless oil. Yield of **11**: 23%.

Data for **8a**: IR (film): $\bar{\upsilon}$ 3334, 2493, 2866, 2367, 1960, 1723, 1600, 1454, 1362, 1277, 1208, 1101, 1024, 909, 749, 717, 649 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.50–1.82 (m, 6H, 3 × CH_2), 3.49 (t, 2H, $^3J_{HH}$ = 6.2 Hz, OCH_2), 4.45 (dt, 2H, $^2J_{HF}$ = 47.2 Hz, $^3J_{HH}$ = 6.2 Hz, CH_2F), 4.51 (s, 2H, $PhCH_2$), 7.30–7.36 (m, 5H, Ph). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.9 (d, $^3J_{CF}$ = 5.5 Hz), 29.3, 30.1 (d, $^2J_{CF}$ = 19.5 Hz), 70.0, 72.8, 83.8 (d, $^1J_{CF}$ = 163.5 Hz), 127.4, 127.5 (2C), 128.2 (2C), 138.5. HRMS (ESI), *m/z* calcd. for $C_{12}H_{17}FONa^+$ 219.1156 $(M+Na)^+$, found 219.1157.

Data for **11**: ^1H NMR (500 MHz, $CDCl_3$): δ 1.73 (2H, quint, $^3J_{HH}$ = 6.5 Hz), 2.14–2.18 (2H, m, CH_2), 3.50 (2H, t, $^3J_{HH}$ = 6.5 Hz, CH_2OAr), 4.51 (2H, s, CH_2OAr), 4.97 (1H, d, $^3J_{HH}$ = 10.0 Hz, CH=CH_ACH_B), 5.03 (1H, dd, $^3J_{HH}$ = 17.0 Hz, $^4J_{HH}$ = 1.5 Hz, CH=CH_ACH_B), 5.79–5.87 (1H, m, *CH*=CH_2), 7.28–7.37 (5H, m, Ar). ^{13}C NMR (125 MHz, $CDCl_3$): δ 29.0, 30.3, 69.7, 72.9, 114.7, 127.5, 127.6 (2C), 128.3 (2C), 138.3, 138.6.

4.14. 1-(3-Fluoropropoxy)naphthalene (**8b**) [56]

This compound has been made from **7b** following the procedure described for the preparation of **8a** from **7a**. Yield: 90%. ^1H NMR (500 MHz, $CDCl_3$): δ 2.33 (2H, dquint, $^3J_{HF}$ = 25.5 Hz, $^3J_{HH}$ = 6.0 Hz, CH_2CH_2F), 4.30 (2H, t, $^3J_{HH}$ = 6.5 Hz, CH_2OAr), 4.77 (2H, dt, $^2J_{HF}$ = 47.0 Hz, $^3J_{HH}$ = 6.0 Hz, CH_2F), 6.84 (1H, d, $^3J_{HH}$ = 7.5 Hz, Ar),

7.36–7.51 (4H, m, Ar), 7.81 (1H, dd, $^3J_{HH}$ = 9 Hz, $^4J_{HH}$ = 1.5 Hz, Ar), 8.26 (1H, d, $^3J_{HH}$ = 8.0 Hz, Ar). ^{13}C NMR (125 MHz, $CDCl_3$): δ 30.7 (d, $^2J_{CF}$ = 20.0 Hz), 63.9 (d, $^3J_{CF}$ = 5.0 Hz), 81.1 (d, $^1J_{CF}$ = 163.8 Hz), 104.9, 120.6, 122.0, 125.3, 125.8, 126.0, 126.6, 127.7, 134.7, 154.6. ^{19}F NMR (470 MHz, C_6F_6): δ 225.2. HRMS (ESI): *m/z* calcd. for $C_{13}H_{13}FO^+$ 204.0950 $(M)^+$, found 204.0952.

4.15. 2-(3-Fluoropropoxy)naphthalene (**8c**)

This compound has been made from **7c** following the procedure described for the preparation of **8a** from **7a**. Yield: 90%. IR (film): $\bar{\upsilon}$ 3056, 3024, 2949, 2908, 2395, 2328, 1641, 1575, 1516, 1467, 1376, 1252, 1202, 1177, 1637, 971, 846, 757 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.26 (2H, dquint, $^3J_{HF}$ = 25.6 Hz, $^3J_{HH}$ = 6.0 Hz, CH_2CH_2F), 4.24 (2H, t, $^3J_{HH}$ = 6.0 Hz, CH_2OAr), 4.72 (2H, dt, $^2J_{HF}$ = 47.2 Hz, $^3J_{HH}$ = 6.0 Hz, CH_2F), 7.18 (2H, d, $^3J_{HH}$ = 1.6 Hz, Ar), 7.38 (1H, t, $^3J_{HH}$ = 7.2 Hz, Ar), 7.48 (1H, t, $^3J_{HH}$ = 6.8 Hz, Ar), 7.75–7.81 (3H, m, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.5(d, $^2J_{CF}$ = 19.0 Hz), 63.7 (d, $^3J_{CF}$ = 5.0 Hz), 80.9 (d, $^1J_{CF}$ = 163.0 Hz), 106.9, 118.9, 123.8, 126.5, 126.9, 127.8, 129.2, 129.5, 134.7, 156.8. ^{19}F NMR (470 MHz; C_6F_6,): δ 225.2. HRMS (ESI): *m/z* calcd. for $C_{13}H_{14}FO^+$ 205.1023 $(M+H)^+$, found 205.1025.

4.16. 1,10-Difluorodecane (**8d**) [60]

This compound has been made from **7d** following the procedure described for the preparation of **8a** from **7a** and using double the amount of CsF, catalyst **1** and *t*-BuOH. Yield: 89%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.24–1.41 (12H, m, 6 × CH_2), 1.59–1.77 (4H, m, 2 × CH_2), 4.42 (4H, dt, $^2J_{HF}$ = 47.4 Hz, $^3J_{HH}$ = 6.0 Hz, 2 × CH_2F). ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.1 (2C, d, $^3J_{CF}$ = 5.5 Hz), 29.2 (2C), 29.4 (2C), 30.4 (2C, d, $^2J_{CF}$ = 19.5 Hz), 84.2 (2C, d, $^1J_{CF}$ = 162.9 Hz).

4.17. (±)-8-Fluoro-2,6-dimethyloct-2-ene (**8e**) [58]

This compound has been made from **7e** following the procedure described for the preparation of **8a** from **7a**. Yield: 92%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.51 (3H, d, $^3J_{HH}$ = 7.0 Hz, CH_3CH), 1.16–1.59 (4H, m, 2 × CH_2), 1.62 (3H, s, CH_3), 1.69 (3H, s, CH_3), 1.70–1.82 (1H, m, CH), 1.92–2.70 (2H, m, CH_2), 4.47 (1H, dt, $^2J_{HF}$ = 47.5 Hz, $^3J_{HH}$ = 7.5 Hz, CH_AH_BF), 4.48 (1H, dt, $^2J_{HF}$ = 47.5 Hz, $^3J_{HH}$ = 6.0 Hz, CH_AH_BF), 5.10 (1H, t, $^3J_{HH}$ = 7.0 Hz, *HC*=C). ^{13}C NMR (175 MHz, $CDCl_3$): δ 17.6, 19.3, 25.4, 25.6, 28.9 (d, $^3J_{CF}$ = 3.4 Hz), 37.0, 37.3 (d, $^2J_{CF}$ = 18.6 Hz), 82.7 (d, $^1J_{CF}$ = 162.4 Hz), 124.5, 131.3.

4.18. 1-(4-Fluorobutoxy)-4-(heptyloxy)benzene (**8f**) [56]

This compound has been made from **7f** following the procedure described for the preparation of **8a** from **7a**. Yield: 90%. IR (film): $\bar{\upsilon}$ 3006, 2941, 2834, 1484, 1452, 1394, 1245, 1021, 806, 732, 640 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (3H, t, $^3J_{HH}$ = 6.4 Hz, CH_3CH_2), 1.25–1.39 (6H, m), 1.39–1.49 (2H, m), 1.76 (2H, quint, $^3J_{HH}$ = 7.6 Hz), 1.80–1.98 (4H, m), 3.91 (2H, t, $^3J_{HH}$ = 6.4 Hz, OCH_2), 3.96 (2H, t, $^3J_{HH}$ = 6.0 Hz, OCH_2), 4.52 (2H, dt, $^2J_{HF}$ = 47.6 Hz, $^3J_{HH}$ = 6.0 Hz, CH_2F), 6.83 (4H, s, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 22.8, 25.5 (d, $^3J_{CF}$ = 5.0 Hz), 26.2, 27.4 (d, $^2J_{CF}$ = 20.0 Hz), 29.2, 29.5, 31.9, 68.1, 68.8, 83.9 (d, $^1J_{CF}$ = 163.0 Hz), 115.5 (2C), 115.6 (2C), 153.1, 153.5. ^{19}F NMR (470 MHz, C_6F_6): δ 221.7.

4.19. 1-Fluorododecane (**8g**) [62]

This compound has been made from **7g** following the procedure described for the preparation of **8a** from **7a**. Yield: 93%. IR (film): $\bar{\upsilon}$ 3429, 2958, 2908, 2849, 1641, 1459, 1385, 1054, 996 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, t, $^3J_{HH}$ = 6.8 Hz, CH_2CH_3), 1.20–1.42 (18H, m, 9 × CH_2), 1.69 (2H, dquint, $^2J_{HF}$ = 24.4 Hz, $^3J_{HH}$ = 6.0 Hz, CH_2CH_2F), 4.43 (2H, dt, $^2J_{HF}$ = 47.6 Hz, $^3J_{HH}$ = 6.0 Hz, CH_2F). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.2, 22.8, 25.3 (d, $^3J_{CF}$ = 5.0 Hz), 29.4, 29.5, 29.6, 29.7 (2C), 29.8, 30.6 (d, $^2J_{CF}$ = 20.0 Hz), 32.1, 84.4 (d, $^1J_{CF}$ = 162.5 Hz). ^{19}FNMR (470 MHz, C_6F_6): δ 221.2. HRMS (ESI): *m/z* calcd. for $C_{12}H_{25}FNa^+$ 211.1838 $(M+Na)^+$, found 211.1840.

4.20. (S)-Methyl 2-[(tert-butoxycarbonyl)amino]-3-(4[2{(methylsulfonyl)oxy}ethoxy]phenyl)propanoate (**14**) [73]

A solution of *N*-BOC-L-tyrosine methyl ester (475 mg, 1.6 mmol) in dry THF (5 mL) was added to a stirred suspension of NaH (52 mg, 60% in oil, 1.3 mmol) in THF (2 mL) and the mixture was stirred at room temperature. After 0.5 h, 1,2-bis(mesyloxy)ethane (283 mg, 1.3 mmol) in dry THF (3 mL) was added to the reaction mixture and heated under reflux for 4 h. The solvent was removed under reduced pressure, the residue was diluted with water and extracted with 50% ethyl acetate in hexanes. The organic extract was concentrated under reduced pressure and purified by silica gel column chromatography using 30% ethyl acetate in hexanes to give compound **14** (504 mg, 93%) as a colorless oil. $[\alpha]_D^{26}$ = +38.9 (*c* 1.03, $CHCl_3$). The *ee* was determined by HPLC using a chiralpak AD-H column [hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 43.71 min (97.7%), τ_{minor} = 34.55 min (2.3%). IR (film): $\bar{\upsilon}$ 3404, 3048, 2974, 2859, 1766, 1724, 1616, 1501, 1434, 1369, 1253, 1177, 1054, 1029, 921, 789, 747 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41 (9H, s, 3 × CH_3), 2.85–3.10 (2H, m, CH_2CHN), 3.09 (3H, s, OSO_2CH_3), 3.71 (3H, s, OCH_3), 4.14–4.25 (2H, m, $OCH_2CH_2OSO_2Me$), 4.45–4.59 (3H, m, CH_2OSO_2Me, CHN), 4.90–5.01 (1H, s, broad, NH), 6.82 (2H, d, $^3J_{HH}$ = 9.0 Hz, Ar), 7.04 (2H, d, $^3J_{HH}$ = 8.1 Hz, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.3 (3C), 37.5, 37.8, 52.3, 54.5, 65.8, 68.1, 80.0, 114.6 (2C), 129.1, 130.5 (2C), 155.1, 157.0, 172.4. HRMS (ESI): *m/z* calcd. for $C_{18}H_{27}NO_8SNa^+$ 440.1355 $(M+Na)^+$, found 440.1357.

4.21. (S)-Methyl 2-[(tert-butoxycarbonyl)amino]-3-[4-(2-fluoroethoxy)phenyl]propanoate (**12**) [72]

Cesium fluoride (72 mg, 0.47 mmol) was added to a stirred solution of mesylate **14** (197 mg, 0.47 mmol) and ionic liquid **1** (109 mg, 0.24 mmol) in *tert*-butyl alcohol (0.15 mL) and the mixture was heated at 100 °C for 45 min. The reaction mixture was diluted with water and extracted with 25% ethyl acetate in hexanes. The organic extract was concentrated under reduced pressure and purified by silica gel column chromatography using 5% ethyl acetate in hexanes to give compound **12** (130 mg, 82%). M.p. 105–106 °C. $[\alpha]_D^{26}$ = +42.6 (*c* 0.57, $CHCl_3$). The *ee* was determined by HPLC using a chiralpak AD-H column [hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 24.55 min (95.4%), τ_{minor} = 18.87 min (4.6%). IR (film): $\bar{\upsilon}$ 3454, 3031, 2974, 2916, 1749, 1716, 1608, 1517, 1452, 1369, 120, 1211, 1170, 1063, 988, 747, 665 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (9H, s, 3 × CH_3), 2.92–3.09 (2H, m, CH_2CHN), 3.70 (3H, s, OCH_3), 4.18 (2H, dt, $^2J_{HF}$ = 27.6 Hz, $^3J_{HH}$ = 4.4 Hz, CH_2O), 4.52–4.54 (1H, m, *CH*N), 4.73 (2H, dt, $^2J_{HF}$ = 47.2 Hz, $^3J_{HH}$ = 4.4 Hz CH_2F), 4.97 (1H, d, ^3J = 7.2 Hz, NH), 6.84 (2H, d, $^3J_{HH}$ = 6.6 Hz, Ar), 7.04 (2H, d, $^3J_{HH}$ = 8.4 Hz, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.4 (3C), 37.6, 52.3, 54.7, 67.3 (d, $^2J_{CF}$ = 20.0 Hz), 80.0, 82.0 (d, $^1J_{CF}$ = 170.0 Hz), 114.9, 128.3, 130.5 (3C), 155.2, 157.7, 172.5. ^{19}F NMR (470 MHz, C_6F_6): δ 225.2. HRMS (ESI): *m/z* calcd. for $C_{17}H_{24}FNO_5Na^+$ 364.1536 $(M+Na)^+$, found 364.1538.

4.22. Diethyl 2-[5-(benzyloxy)pentyl]malonate (**16**)

Freshly distilled diethyl malonate (4.2 mL, 27.3 mmol) was added drop wise to a stirred suspension of oil free sodium hydride (872 mg, 20 mmol) in THF (55 mL) under argon atmosphere. After 1.5 h of stirring, bromide **2** (5 g, 19.5 mmol) was slowly added to

the reaction mixture and then heated at 70 °C for 12 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic extract was concentrated under reduced pressure and the residue was purified by column chromatography (25% ethyl acetate in hexanes) to give compound **16** (5.13 g, 79%) as colorless oil. IR (film): $\bar{\upsilon}$ 2936, 2859, 1731, 1454, 1368, 1153, 1098, 1029, 862, 736, 698, 423, 412 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.26 (t, 6H, $^3J_{HH}$ = 7.0 Hz, 2 × CH_3), 1.30–1.50 (m, 4H, 2 × CH_2), 1.53–1.70 (m, 2H, CH_2), 1.84–1.95 (m, 2H, $CHCH_2$), 3.31 (t, 1H, $^3J_{HH}$ = 7.2 Hz, CH), 3.45 (t, 2H, $^3J_{HH}$ = 6.2 Hz, $PhCH_2OCH_2$), 4.18 (q, 4H, $^3J_{HH}$ = 7.2 Hz, 2 × OCH_2), 4.49 (s, 2H, $PhCH_2$), 7.28–7.34 (m, 5H, Ph). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9 (2C), 25.7, 27.0, 28.5, 29.3, 51.8, 61.0 (2C), 70.0, 72.6, 127.3, 127.4 (2C), 128.1 (2C), 138.4, 169.3 (2C). HRMS (ESI), *m/z* calcd. for $C_{19}H_{28}O_5Na^+$ 359.1834 $(M+Na)^+$, found 359.1832.

4.23. Diethyl 2-methyl-2-[5′-(bezyloxy)pentyl]malonate (**17**)

A solution of compound **16** (3.7 g, 11.02 mmol) in THF (35 mL) was added drop wise to a stirred suspension of oil free sodium hydride (582 mg, ~50% in oil, 12.1 mmol) in THF (10 mL) under argon atmosphere. After 30 min, methyl iodide (1.5 mL, 24 mmol) was added drop wise to the reaction mixture and stirred for 2 days. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic extract was concentrated under reduced pressure and the residue was purified by column chromatography to give compound **17** (3.4 g, 88%). IR (film): $\bar{\upsilon}$ 3057, 3036, 2988, 2938, 2865, 2796, 1733, 1497, 1455, 1365, 1120, 1028, 858, 754, 698, 666 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.23 (t, 6H, $^3J_{HH}$ = 7.0 Hz, 2 × CH_3), 1.38 (s, 3H, CH_3), 1.29–1.65 (m, 6H, 3 × CH_2), 1.81–1.89 (m, 2H, CH_2), 3.45 (t, 2H, $^3J_{HH}$ = 6.4 Hz, $PhCH_2OCH_2$), 4.16 (quint, 4H, $^3J_{HH}$ = 7.0 Hz, 2 × OCH_2), 4.49 (s, 2H, $PhCH_2$), 7.28–7.34 (m, 5H, Ph). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8 (2C), 19.6, 23.9, 26.3, 29.3, 35.2, 53.3, 60.8 (2C), 69.9, 72.6, 127.2, 127.3 (2C), 128.1 (2C), 138.4, 172.1 (2C). HRMS (ESI), *m/z* calcd. for $C_{20}H_{30}O_5Na^+$ 373.1991 $(M+Na)^+$, found 373.1992.

4.24. Diethyl 2-methyl-2-[5′-hydroxypentyl]malonate (**18**) [64]

Palladium on charcoal (10%, 600 mg) was added to a stirred solution of benzyl ether 17 (1.2 g, 3.7 mmol) and ammonium formate (1.15 g, 18.3 mmol) in methanol (25 mL) and the mixture was heated under reflux for 3 days. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was diluted with water and extracted with 5% ethyl acetate in hexanes. The organic extract was concentrated under reduced pressure to give compound 18 (870 mg, 92%) as colorless liquid. R_f (hexane–EtOAc, 70:30) = 0.5; IR (film): $\bar{\upsilon}$ 3402, 2936. 2867, 1722, 1465, 1388, 1256, 1122, 1029, 857, 749, 703. ^1H NMR (200 MHz, CDCl3): δ 1.23 (6H, t, $^3J_{HH}$ = 7.0 Hz, 2 × CH_3), 1.26–1.37 (2H, m, CH_2), 1.38 (3H, s, CH_3), 1.52–1.64 (4H, m, 2 × CH_2), 1.80–1.89 (2H, m, CH_2), 3.62 (2H, t, $^3J_{HH}$ = 6.4 Hz, CH_2OH), 4.16 (4H, quint, $^3J_{HH}$ = 7.2 Hz, 2 × OCH_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0 (2C), 19.8, 24.0, 26.0, 32.4, 35.4, 53.6, 61.1 (2C), 62.8, 172.5 (2C).

4.25. Diethyl 2-methyl-2-[5′-(methanesulfonyloxy)pentyl]malonate (**19**) [64]

Freshly distilled methanesulphonyl chloride (0.18 mL, 2.28 mmol) was added drop wise to a stirred solution of alcohol **18** (400 mg, 1.5 mmol) and triethylamine (0.3 mL, 2.3 mmol) in dry dichloromethane (6 mL) at 0 °C. After 4 h, the reaction mixture was diluted with water and extracted with 40% ethyl acetate in hexanes. The organic extract was concentrated under reduced pressure to give mesylate **19** (514 mg, 100%) as pale yellow liquid. R_f (hexane–EtOAc, 70:30) = 0.5; IR (film): $\bar{\upsilon}$ 3652, 3566, 3465, 2990, 2944, 2874, 1730, 1637, 1473, 1349, 1263, 1178, 1123, 944, 827, 764 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.22 (6H, *t*, $^3J_{HH}$ = 7.2 Hz, 2 × CH_3), 1.30–1.48 (4H, m, 2 × CH_2), 1.37 (3H, s, CH_3), 1.67–1.87 (4H, m, 2 × CH_2), 2.99 (3H, s, CH_3), 4.16 (4H, quint, $^3J_{HH}$ = 7.2 Hz, 2 × $CO_2CH_2CH_3$), 4.19 (2H, t, $^3J_{HH}$ = 7.2 Hz, OCH_2). ^{13}C NMR (50 MHz, $CDCl_3$): 13.8 (2C), 19.6, 23.5, 25.4, 28.6, 35.0, 37.0, 53.3, 60.9 (2C), 69.7, 172.1 (2C).

4.26. Diethyl 2-methyl-2(5′-fluoropentyl)malonate (**15**) [64]

Cesium fluoride (106.33 mg, 0.7 mmol) was added to a stirred solution of mesylate **19** (78 mg, 0.2 mmol) and ionic liquid **1** (46 mg, 0.1 mmol) in *t*-BuOH (0.1 mL) and the mixture was heated at 100 °C for 45 min. The reaction mixture was diluted with water and extracted with 15% ethyl acetate in hexanes. The organic extract was concentrated under reduced pressure and purified by silica gel column chromatography using 5% ethyl acetate in hexanes to give compound **15** (56 mg, 92%) as a colorless oil. R_f (hexane–EtOAc, 95:5) = 0.4; IR (film): $\bar{\upsilon}$ 3465, 2944, 2867, 1737, 1465, 1371, 1247, 1122, 1021, 952, 858, 756, 718 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.21 (6H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.36 (3H, s, CH_3), 1.24–1.46 (4H, m, 2 × CH_2), 1.64–1.89 (4H, m, 2 × CH_2), 4.14 (4H, quint, $^3J_{HH}$ = 7.2 Hz, 2 × OCH_2), 4.39 (2H, dt, $^2J_{HF}$ = 47.2 Hz, $^3J_{HH}$ = 6.0 Hz, CH_2F). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9 (2C), 19.7, 23.8, 25.3 (d, $^3J_{CF}$ = 5.0 Hz), 30.1 (d, $^2J_{CF}$ = 19.0 Hz), 35.2, 53.5, 61.0 (2C), 83.8 (d, $^1J_{CF}$ = 163.5 Hz), 172.3 (2C). HRMS (ESI), *m/z* calcd. for $C_{13}H_{23}FO_4Na^+$ 285.1473 $(M+Na)^+$, found 285.1474.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2015.06.022.

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