Solvent-Free Microwave-Assisted Preparation of Chiral Ionic Liquids from (−)-*N*-Methylephedrine

Giang Vo Thanh,*[a] Bruce Pegot,[a] and André Loupy[a]

Keywords: Solvent-free reactions / Microwave activation / Ionic liquids / Chirality / (−)-Ephedrine / Green chemistry

An efficient method for the preparation of chiral ionic liquids based on (1*R*,2*S*)-(−)-ephedrinium salts under solvent-free conditions and microwave activation is described. The influence of non-specifically thermal microwave effects – consistent with mechanistic considerations – is discussed.

Introduction

Ionic liquids (ILs), or room-temperature molten salts, are being advanced as new clean media that have attracted increasing interest over recent years, particularly in the area of green chemistry and especially in synthetic and catalytic transformations.[1] Among them, chiral ILs are particularly attractive for their potential applications to chiral discrimination, including asymmetric syntheses and optical resolution of racemates. However, very few chiral ILs, **1**−**5**, have been reported so far, lead to successful chiral discrimination[2,3] and only four of them, **2**−**5**, derived from the "chiral pool".[3,4] Recently, K. Saigo et al.[5] have designed and synthesized a novel imidazolium ionic liquid with cyclophane-type planar chirality (**6**), which showed potential as an ionic liquid chiral solvent for asymmetric synthesis and/or optical resolution. All these ionic liquids were prepared under classical conditions. Some of them are presented in Scheme 1.

Microwave (MW) activation as a non-conventional energy source has emerged as a powerful technique to promote a variety of chemical reactions and has become a very popular and useful technology in organic chemistry.[6] The combination of solvent-free conditions and MW irradiation leads to large reductions in reaction times, enhancement in conversions and, sometimes, in selectivity, and has several features of the eco-friendly approach, termed green chemistry.[7] This method was successfully applied to the synthesis of several ILs based on imidazolium salts.[8] Strict comparisons with conventional heating have been reported only rarely,[8h] so specific MW effects have not been particularly studied.

In view of the emerging importance of ILs as reaction media in organic syntheses, and our general interest in MW-assisted chemical processes, we report here the first synthesis of chiral ILs bearing chiral ephedrinium cations using solvent-free reactions and MW activation under green chemistry conditions.

Results and Discussion

The synthesis of the chiral ephedrinium cation has already been described in the literature.[3a] However, only the salt **3** was synthesized, by alkylation of (−)-*N*-methylephedrine followed by anion exchange with lithium bis(trifluoromethanesulfonyl)imide (Li[$(CF_3SO_2)_2N$]). In this case all reaction steps were performed under classical conditions and using Me_2SO_4 as alkylating agent, the use of which is now very limited for organic synthesis, especially under green chemistry conditions, owing to its carcinogenic effect (as for all alkylating agents).

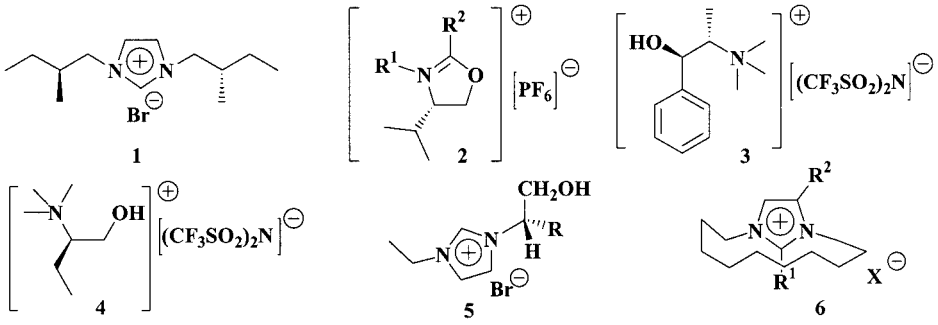
The aim of our study is to underline the potential of coupling solvent-free reaction with focused MW activation, and further to check nonthermal MW-specific effects by comparing the results with those obtained using conventional heating under identical conditions.

Our synthesis was initiated by the direct alkylation of (1*R*,2*S*)-*N*-methylephedrine (**7**), easily obtained by reductive amination of (1*R*,2*S*)-ephedrine using an Eschweiler−Clark procedure,[9] to *N*-alkylmethylephedrine derivatives. A series of different alkyl chain lengths was tested. All the MW reactions were performed in the CEM Discover monomode system with strict control of power and temperature during the reaction and in the absence of any solvent (Scheme 2).

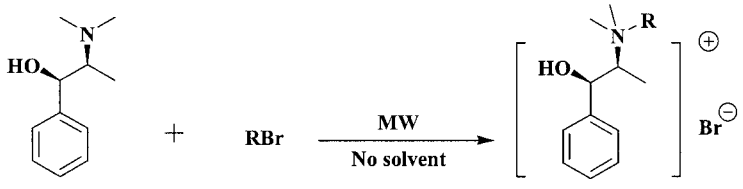
Microwaves are electromagnetic waves generated by an alternating electric field of high frequency. The energy as-

[a] Laboratoire des Réactions Sélectives sur Supports, ICMMO, CNRS UMR 8615, Bâtiment 410, Université Paris-Sud, 91405 Orsay Cedex, France
Fax: (internat.) + 33-(0)1-69154679
E-mail: gvothanh@icmo.u-psud.fr

  DOI: 10.1002/ejoc.200300601



Scheme 1



Scheme 2

sociated with a MW photon (1 J·mol^{-1} by application of Planck law $E = h\nu$ with ν = 2450 MHz) is far too small to induce any excitation of molecules. It can, however, induce thermal effects due to some internal friction between polar molecules during their changes in orientation with each alternation of the electric field. In addition, they can induce some electrostatic interactions with polar materials by dipole−dipole interactions, rather similar to the behaviour of a dipolar solvent. By analogy and extension of the interpretation of solvent effects, the carbon−halogen covalent bond rupture can be facilitated by an increase in the polarity of the system during the progress of the reaction between the ground state and the transition state. An increase in efficiency could result, therefore, from both thermal effects (which provide adequate thermal energy) and specific polar (nonspecifically thermal) effects.[6c]

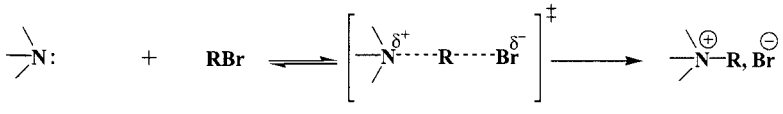
In order to check the possible intervention of nonspecifically thermal MW-specific effects, control experiments were conducted using a thermostatted oil bath (Δ = conventional heating) under identical reaction conditions (time, temperature, vessel, profile of rise in temperature). The main results are given in Table 1.

Table 1. Solvent-free *N*-alkylation of (1*R*,2*S*)-*N*-methylephedrine with *n*-alkyl bromides in open vessels under monomode microwave irradiation (CEM Discover system)

Entry	R	Time (min.)	Temperature (°C)	Isolated yield (%) MW	Δ
1	C_4H_9 [a]	10	93	83	6
2	C_8H_{17}	30	95	85	18
3		45	110	96	
4	$C_{10}H_{21}$	40	95	76	18
5		40	110	95	71
6	$C_{16}H_{33}$	120	95	81	59
7		90	110	80	

[a] Reactions were conducted in closed vessels owing to the low boiling point of C_4H_9Br (b.p. 100 °C).

Table 1 clearly shows the influence of very important non-specifically thermal MW effects. This observation is



Scheme 3

consistent with mechanistic considerations, as the mechanism involves the development of dipoles in the transition state and therefore an increase in the polarity of the system during the progress of the reaction from the ground state to the transition state, which can respond to specific MW enhancement[6c,6f] (Scheme 3). This assumption was more or less suggested by Abramovitch in the conclusion of his review in 1991[10] stating that "if the MW energy is absorbed selectively by a reactant, a complex or an intermediate on the way to rate-determining transition states, then large reaction rate increases will result".

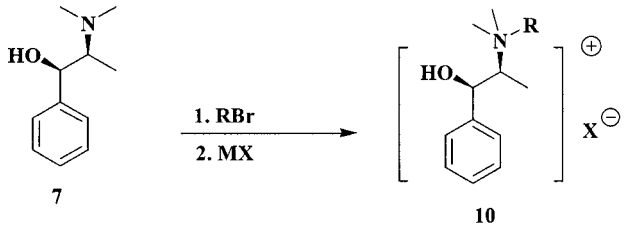
The next step in the synthesis involves transformation of ephedrinium bromide salts **9** to ionic liquids **10** by anion exchange of **9** with alkaline or ammonium salts of charge-delocalized soft anions (BF_4^-, PF_6^-, TfO^-). Generally, this step was carried out at reflux in a large excess of acetone as solvent for several hours or days.[11] Good yields were generally obtained in all cases.

As already reported by Varma et al.,[8g] anion-exchange metathesis is easily performed under MW activation using a domestic oven. In this way, 1,3-dialkylimidazolium tetrafluoroborate salts were prepared within good yields for only a few minutes of reaction time. Unfortunately, no control of power and temperature was achieved during the course of the reaction.

In order to simplify the workup of the preparation of chiral ILs, and as part of our general interest in MW-assisted chemical processes, we decided to perform this procedure in a two-step but one-pot reaction sequence. All crude products (non-isolated) resulting from the quaternisation step (first step) were directly submitted to the anion-exchange step (Scheme 4). All reactions were conducted in the CEM Discover monomode system in open vessels and under solvent-free conditions. The more significant results are given in Table 2.

The data of Table 2 generally indicate good overall yields obtained within short reaction times. In the case of the butyl chain, reactions were carried out in closed vessels owing to the low boiling point of bromobutane (b.p. 100 °C). Whereas the one-pot method A of mixing the three components seems to be satisfactory in the case of Entries 8−11 where R = C_4H_9, the one-pot two-step method B is better for R = *n*-C_8H_{17} (Entries 13 and 14). In this last case, there is no necessity to work in closed system. In order to demonstrate the MW-specific effects, one representative experiment was conducted using a thermostatted oil bath under identical reaction conditions (see Entry 9). This effect certainly arises from the first step of this sequence reaction (see Table 1). The yield obtained under conventional heating (2%) is far lower than the MW one (72%) within 10 min at 93 °C.

It is important to note that all chiral ephedrinium salts **10** are viscous liquids at room temperature (except the salts **10** where R = $C_{16}H_{33}$, C_4H_9 and X = PF_6, which are solids with m.p. of 95 and 92 °C, respectively) in contrast with the ephedrinium salt **3**, described by Wasserscheid[3a] which is a solid (m.p. 54 °C).



Scheme 4

Conclusion

In conclusion, we have developed an efficient procedure for the preparation of chiral ILs from (1*R*,2*S*)-ephedrine, a natural amino alcohol, using solvent-free reactions and MW activation under green chemistry conditions. Evidence was also obtained for an important nonthermal MW-specific effect. The preparation of optically active ILs derived from natural amino acids will be discussed in a later

Table 2. One-pot solvent-free microwave-assisted preparation of (1*R*,2*S*)-*N*-alkyl-*N*-methylephedrinium salts. Method A: reaction of the direct mixture of the three components. Method B: two-step procedure: alkylation followed by salt exchange

Entry	R	Method	MX	MW system	Time (Temp.)[a]	Yield (%)
8	C_4H_9	A	NaPF	Closed	10 (93)	85
9		A	NH_4PF_6	Closed	10 (93)	72 (2)[b]
10		A	NH_4BF_4	Closed	10 (93)	77
11		A	KOTf	Closed	20 (93)	79
12	C_8H_{17}	A	NH_4PF_6	Closed	45 (95)	10
14		A	NH_4PF_6	Open	45 (95)	51
13		B	NH_4PF_6	Open	30 (110) +35 (95)	80
15		B	$NaPF_6$	Open	30 (110) +35 (95)	77
16		B	KOTf	Open	30 (110) +35 (95)	91
17	$C_{10}H_{21}$	B	$NaPF_6$	Open	40 (110) +35 (110)	85
18		B	KOTf	Open	40 (110) +35 (95)	84
19	$C_{16}H_{33}$	B	$NaPF_6$	Open	120 (95) +60 (95)	77
20		B	KOTf	Open	120 (95) +60 (95)	88

[a] Conditions for alkylation + ion exchange; time in min and temperature in °C. [b] Yield obtained by conventional heating is given in brackets.

report. Applications of chiral ILs as green media for asymmetric synthesis and catalysis are currently under investigation.

Experimental Section

General Remarks: Microwave experiments were conducted using a CEM Discover Synthesis Unit (monomode system) operating at 2450 MHz monitored by a PC computer.[12] Waves are focussed by a circular wave-guide all around the cavity. The temperature was measured by optical fibre or infrared detection with continuous-feedback temperature control, and maintained at a constant value by power modulation (0−300 W). Stirring was provided by an in situ magnetic variable speed stirrer when reactions were performed in closed vessels under controlled pressure or with mechanical stirring in the case of reactions in open vessels. Reactions were performed either in glass vessels (capacity 10 mL) sealed with a septum or in open vessels (capacity 100 mL). The pressure was controlled by a load cell connected to the vessel via a needle, which penetrated just below the septum surface.

Melting points were measured with a Kofler bank. NMR spectra were recorded in $CDCl_3$ or [D_6]acetone. ^1H NMR spectra were recorded at 250 or 200 MHz. Chemical shifts (δ) are reported in ppm relative to TMS as internal standard. *J* values are given in Hz. ^{13}C NMR spectra were recorded at 62.5 or 50 MHz. IR spectra were recorded with an FT-IR Perkin−Elmer instrument. TLC was carried out with 0.2-mm thick silica-gel plates (GF_{254}). Visualisation was accomplished by UV light or phosphomolybdic acid solution. The columns were hand packed with silica-gel 60 (200−300).

All reagents and solvents were purchased from commercial sources (Acros, Aldrich) and were used without further purification.

General Procedure for the Solvent-Free *N*-Alkylation of 7 under Microwaves:

A mixture of (1*R*,2*S*)-*N*-methylephedrine **7** (1.79 g, 10 mmol) and 1-bromoalkane (10 mmol) was irradiated with microwaves at the temperature and for the time given in Table 1. The reaction mixture was brought to room temperature and washed with EtOAc (2 × 10 mL). The crude product was dissolved in CH_2Cl_2. After filtration, the solvent was evaporated under reduced pressure to afford the solid which did not need further purification.

Reactions under conventional heating were carried out with exactly the same vessel and under similar conditions of time and temperature (see Table 1) but in a preheated oil bath.

(1*R*,2*S*)-*N*-Butyl-*N*,*N*-dimethylephedrinium Bromide 9 (R = C_4H_9): M.p. 95−96 °C. $[\alpha]_D^{25}$ = −12.1 (*c* = 1.57, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.01 (t, *J* = 7.3 Hz, 3 H), 1.19 (d, *J* = 6.8 Hz, 3 H), 1.44 (m, 2 H), 1.71 (m, 2 H), 3.30 (s, 3 H), 3.44 (s, 3 H), 3.59−3.87 (m, 3 H), 5.50 (d, *J* = 6 Hz, 1 H), 5.76 (s, 1 H), 7.26−7.53 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 6.8, 13.3, 19.2, 24.3, 49.1, 49.3, 63.2, 67.4, 72.6, 125.5, 127.1, 128.0, 140.8 ppm.

(1*R*,2*S*)-*N*,*N*-Dimethyl-*N*-octylephedrinium Bromide 9 (R = C_8H_{17}): M.p. 88 °C. $[\alpha]_D^{25}$ = −13.5 (*c* = 2.00, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 0.89 (t, *J* = 6.8 Hz, 3 H), 1.13−1.40 (m, 15 H), 1.50−1.85 (m, 2 H), 3.26 (s, 3 H), 3.38 (s, 3 H), 3.55−3.95 (m, 3 H), 5.51 (d, *J* = 5.6 Hz, 1 H), 5.71(s, 1 H), 7.20−7.49 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 6.6, 13.4, 21.9, 22.2, 25.7, 28.4, 28.6, 31.0, 48.8, 49.0, 63.2, 67.2, 72.4, 125.3, 126.9, 127.8, 140.6 ppm.

(1*R*,2*S*)-*N*-Decyl-*N*,*N*-dimethylephedrinium Bromide 9 (R = $C_{10}H_{21}$): M.p. 92 °C. $[\alpha]_D^{25}$ = −13.5 (*c* = 2.00, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 0.88 (t, *J* = 6 Hz, 3 H), 1.10−1.15 (m, 19 H), 1.60−1.90 (m, 2 H), 3.29 (s, 3 H), 3.44 (s, 3 H), 3.60−3.95 (m, 3 H), 5.48 (d, *J* = 5.8 Hz, 1 H), 5.75(d, *J* = 4.8 Hz, 1 H), 7.20−7.60 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$) : δ = 6.7, 13.5, 22.0, 22.3, 25.8, 28.6, 28.7, 28.8, 28.9, 31.2, 49.0, 49.1, 63.3, 67.3, 72.5, 125.4, 127.0, 127.9, 140.7 ppm.

(1*R*,2*S*)-*N*-Hexadecyl-*N*,*N*-dimethylephedrinium Bromide 9 (R = $C_{16}H_{33}$): M.p. 86 °C. $[\alpha]_D^{25}$ = −11 (*c* = 2.00, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 0.88 (t, *J* = 6.8 Hz, 3 H), 1.05−1.50 (m, 31 H), 1.51−1.95 (m, 2 H), 3.32 (s, 3 H), 3.49 (s, 3 H), 3.55−3.90 (m, 3 H), 5.47 (d, *J* = 4.8 Hz, 1 H), 5.79(s, 1 H), 7.2−7.55 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 6.9, 13.7, 22.2, 22.5, 26.0, 27.8, 28.4, 28.9, 29.1, 29.2, 29.3, 31.5, 49.2, 49.2, 63.6, 67.5, 72.6, 125.6, 127.2, 128.1, 140.9 ppm.

General Procedure for the Solvent-free "One-pot" Preparation of Chiral Ionic Liquids 10 from 7 under Microwave Irradiation (Method A): A mixture of (1*R*,2*S*)-*N*-methylephedrine **7** (1.79 g, 10 mmol), 1-bromoalkane (10 mmol) and alkaline salt MX (10 mmol) was irradiated with microwaves at the temperature and for the time given in Table 2. The reaction mixture was brought to room temperature and washed with EtOAc (2 × 10 mL). The crude product was dissolved in acetone. After filtration, the solvent was evaporated under reduced pressure. Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH, 98:2) gave the salt **10** as a yellow viscous oil, except **10** R = C_4H_9 and X = PF_6.

(1*R*,2*S*)-*N*-Butyl-*N*,*N*-dimethylephedrinium Hexafluorophosphate 10 (R = C_4H_9, X = PF_6): M.p. 92 °C. $[\alpha]_D^{25}$ = −10 (*c* = 1.00, acetone). ^1H NMR ([D_6]acetone): δ = 1.01 (t, *J* = 7.4 Hz, 3 H), 1.35 (d, *J* = 6.8 Hz, 3 H), 1.47 (H, *J* = 7.4 Hz, 2 H), 1.97 (m, 2 H); 3.40 (s, 3 H), 3.47 (s, 3 H), 3.64−3.85 (m, 3 H), 5.28 (d, *J* = 3.4 Hz, 1 H), 5.78 (s, 1 H), 7.15−7.53 (m, 5 H) ppm. ^{13}C NMR ([D_6]acetone): δ = 7.2, 14.0, 20.9, 25.7, 49.8, 50.1, 65.6, 70.6, 74.6, 126.9, 129.0, 129.7, 142.8 ppm. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3582, 2969, 2880, 1477, 1424, 1084, 877, 726, 641, 557. $C_{15}H_{26}F_6NOP$ (381.3): calcd. C 47.24, H 6.87, F 29.89, N 3.67, P 8.12; found C 47.14, H 6.74, F 26.78, N 3.78, P, 8.12.

(1*R*,2*S*)-*N*-Butyl-*N*,*N*-dimethylephedrinium Trifluoromethanesulfonate 10 (R = C_4H_9, X = OTf): $[\alpha]_D^{25}$ = −11 (*c* = 2.00, acetone). ^1H NMR ([D_6]acetone): δ = 1.01 (t, *J* = 7.4 Hz, 3 H), 1.35 (d, *J* = 6.8 Hz, 3 H), 1.46 (H, *J* = 7.4 Hz, 2 H), 1.96 (m, 2 H), 3.38 (s, 3 H) 3.45 (s, 3 H), 3.6−3.84 (m, 3 H), 5.25 (d, *J* = 4.8 Hz, 1 H), 5.78(s, 1 H), 7.15−7.54 (m, 5 H) ppm. ^{13}C NMR ([D_6]acetone): δ = 6.4, 13.2, 19.2, 24.2, 30.5, 48.7, 49.0, 63.4, 68.5, 73.1, 125.3, 127.6, 128.3, 140.6 ppm. IR (neat, cm^{-1}): $\tilde{\nu}$ = 3418, 2968, 2880, 1495, 1455, 1278, 1163, 1030, 759, 721, 639, 574. $C_{16}H_{26}F_3NO_4S$: calcd. C 49.86, H 6.80, F 14.79, N 3.63, S 8.32; found C 50.02, H 6.68, F 14.64, N 3.87, S 8.18.

General Procedure for the Solvent-free "Two-step Sequence" Preparation of Chiral Ionic Liquids 10 from 7 under Microwaves (Method B): A mixture of (1*R*,2*S*)-*N*-methylephedrine **7** (1.79 g, 10 mmol) and 1-bromoalkane (10 mmol) was irradiated with microwaves at the temperature and for the time given in Table 2. Alkaline salt MX (10 mmol) was added and the resulting mixture was then placed under MW irradiation for an additional period of time and temperature as reported in Table 2. The reaction mixture was brought to room temperature and washed with EtOAc (2 × 10 mL). The crude product was dissolved in acetone. After filtration, the solvent was evaporated under reduced pressure. Purification by flash chro-

matography on silica gel (CH_2Cl_2/MeOH, 98:2) afforded the salt **10** as a yellow viscous oil, except **10** R = $C_{16}H_{33}$ and X = PF_6.

(1*R*,2*S*)-*N*,*N*-Dimethyl-*N*-octylephedrinium Hexafluorophosphate 10 (R = C_8H_{17}, X = PF_6): $[\alpha]_D^{25} = -5.5$ (c = 2.00, acetone). ^{1}H NMR ([D$_6$]acetone): δ = 0.89 (t, J = 6.7 Hz, 3 H), 1.21−1.43 (m, 15 H), 1.85−2.05 (m, 2 H), 3.19 (s, 3 H), 3.34 (s, 3 H), 3.59−3.82 (m, 3 H), 5.19 (s, 1 H), 5.75(s, 1 H), 7.25−7.55 (m, 5 H) ppm. ^{13}C NMR ([D$_6$]acetone): δ = 5.5, 12.9, 21.6, 25.4, 27.8, 28.1, 29.0, 30.9, 48.0, 48.2, 63.1, 68.5, 72.4, 125.1, 127.1, 127.7, 140.7 ppm. IR (neat, cm^{-1}) $\tilde{\nu}$ = 3582, 2929, 2859, 1492, 1454, 1047, 998, 839, 739, 720, 676, 558. $C_{19}H_{34}F_6NOP$: calcd. C 52.17, H 7.83, F 26.06, N 3.20, P 7.08; found C 52.41, H 7.87, F 23.54, N 3.11, P 6.80.

(1*R*,2*S*)-*N*,*N*-Dimethyl-*N*-octylephedrinium Trifluoromethanesulfonate 10 (R = C_8H_{17}, X = OTf): $[\alpha]_D^{25} = -7.0$ (c = 2.00, acetone). ^{1}H NMR ([D$_6$]acetone): δ = 0.88 (t, J = 6.6 Hz, 3 H), 1.05−1.63 (m, 15 H),1.90−2.05 (m, 2 H), 3.41 (s, 3 H), 3.48 (s, 3 H), 3.60−3.90 (m, 3 H), 5.37 (d, J = 3.8 Hz, 1 H), 5.78 (s, 1 H), 7.25−7.55 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 6.4, 13.8, 22.3, 22.4, 25.9, 28.7, 28.8, 30.6, 31.3, 48.8, 49.0, 63.6, 68.5, 73.2, 125.4, 127.6, 128.3, 140.7 ppm. IR (neat, cm^{-1}) $\tilde{\nu}$ = 3410, 2957, 2930, 1494, 1469, 1278, 1225, 1164, 1030, 759, 720, 639, 573. $C_{20}H_{34}F_3NO_4S$: calcd. C 54.40, H 7.76, F 12.91, N 3.17, S 7.26; found C 54.43, H 7.87, F 12.86, N 3.31, S 7.14.

(1*R*,2*S*)-*N*-Decyl-*N*,*N*-dimethylephedrinium Hexafluorophosphate 10 (R = $C_{10}H_{21}$, X = PF_6): $[\alpha]_D^{25} = -9.0$ (c = 2.00, acetone). ^{1}H NMR ([D$_6$]acetone): δ = 0.87 (t, J = 6.4 Hz, 3 H), 1.22−1.47 (m, 19 H), 1.92−2.06 (m, 2 H), 3.40 (s, 3 H), 3.47 (s, 3 H), 3.65−3.87 (m, 3 H), 5.26 (d, J = 4 Hz, 1 H), 5.78 (s, 1 H); 7.30−7.55 (m, 5 H) ppm. ^{13}C NMR ([D$_6$]acetone): δ = 6.4, 14.0, 22.5, 22.6, 26.0, 29.0, 29.2, 29.3, 29.4, 31.8, 49.0, 49.2, 64.2, 69.4, 73.0, 125.4, 128.0, 128.7, 140.2 ppm. IR (neat, cm^{-1}) $\tilde{\nu}$ = 3537, 2993, 2917, 2853, 1493, 1478, 1058, 845, 764, 721, 634, 558. $C_{21}H_{38}F_6NOP$: calcd. C 54.18, H 8.23, F 24.49, N 3.01, P 6.65; found C 54.38, H 8.19, F 22.83, N 2.95, P 6.60.

(1*R*,2*S*)-*N*-Decyl-*N*,*N*-dimethylephedrinium Trifluoromethanesulfonate 10 (R = $C_{10}H_{21}$, X = OTf): $[\alpha]_D^{25} = -6.5$ (c = 2.00, acetone). ^{1}H NMR ([D$_6$]acetone): δ = 0.87 (t, J = 6.4 Hz, 3 H), 1.20−1.47 (m, 19 H), 1.95−2.05 (m, 2 H), 3.40 (s, 3 H), 3.47 (s, 3 H), 3.60−3.90 (m, 3 H), 5.37 (d, J = 4.3 Hz, 1 H), 5.78 (d, J = 3.8 Hz, 1 H), 7.25−7.60 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 6.4, 13.9, 22.4, 25.9, 28.9, 29.0, 29.1, 29.2, 30.6, 31.6, 48.8, 49.0, 63.7, 68.5, 73.2, 125.4, 127.6, 128.3, 140.7 ppm. IR (neat, cm^{-1}) $\tilde{\nu}$ = 3411, 2927, 2856, 1494, 1468, 1278, 1225, 1164, 1030, 759, 721, 640, 573. $C_{22}H_{38}F_3NO_4S$: calcd. C 56.27, H 8.16, F 12.14, N 2.98, S 6.83; found C 56.31, H 7.94, F 12.41, N 2.93, S 6.86.

(1*R*,2*S*)-*N*-Hexadecyl-*N*,*N*-dimethylephedrinium Hexafluorophosphate (R = $C_{16}H_{33}$, X = PF_6): M.p. 95 °C. $[\alpha]_D^{25} = -4.5$ (c = 2.00, acetone). ^{1}H NMR ([D$_6$]acetone): δ = 0.88 (t, J = 6.8 Hz, 3 H), 1.15−1.45 (m, 31 H), 1.95−2.05 (m, 2 H), 3.42 (s, 3 H), 3.49 (s, 3 H), 3.65−3.90 (m, 3 H), 5.31 (d, J = 3.8 Hz, 1 H), 5.79 (d, J = 3.4 Hz, 1 H), 7.30−7.55 (m, 5 H) ppm. ^{13}C NMR ([D$_6$]acetone): δ = 6.6, 13.84, 22.8, 29.0, 29.3, 29.6, 32.1, 49.4, 49.6, 64.4, 69.8, 73.6, 126.2, 128.0, 128.8, 141.9 ppm. IR (KBr, cm^{-1}) $\tilde{\nu}$ = 3534, 2994, 2916, 2848, 1493, 1476, 1419, 1051, 856, 765, 720, 557. $C_{27}H_{50}F_6NOP$: calcd. C 59.00, H 9.17, F 20.74, N 2.55, P 5.64; found C 58.85, H 9.06, F 18.94, N 2.52, P 5.60.

(1*R*,2*S*)-*N*-Hexadecyl-*N*,*N*-dimethylephedrinium Trifluoromethanesulfonate 10 (R = $C_{16}H_{33}$, X = OTf): $[\alpha]_D^{25} = -5.5$ (c = 2.00, acetone). ^{1}H NMR ([D$_6$]acetone): δ = 0.88 (t, J = 6.2 Hz, 3 H), 1.15−1.50 (m, 31 H),1.90−2.07 (m, 2 H,), 3.40 (s, 3 H), 3.47 (s, 3 H), 3.60−3.90 (m, 3 H), 5.38 (d, J = 4.8 Hz, 1 H), 5.77 (s, 1 H), 7.30−7.55 (m, 5 H) ppm. ^{13}C NMR ([D$_6$]acetone): δ = 6.4, 14.0, 22.5, 26.0, 29.0, 29.2, 29.3, 29.4, 29.5, 29.6, 30.7, 31.8, 48.97, 48.99, 63.85, 68.64, 73.29, 126.0, 127.7, 128.5, 140.8 ppm. IR (neat, cm^{-1}) $\tilde{\nu}$ = 3400, 2921, 2852, 1468, 1279, 1225, 1157, 1031, 764, 720, 638, 572. $C_{28}H_{50}F_3NO_4S$: calcd. C 60.73, H 9.10, F 10.29, N 2.53, S 5.79; found C 60.76, H 9.42, F 10.22, N 2.48, S 5.91.

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Received September 25, 2003

