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Full Paper

1-(+)-Dehydroabietylimidazolium Salts as Enantiomer Discriminators for NMR Spectroscopy

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Nine new (+)-dehydroabietylimidazolium salts were synthesised and studied as chiral solvating agents for several different racemic aromatic and non-aromatic carboxylate salts. These cationic chiral solvating agents resolve racemic ionic analytes better than non-ionic ones. Bis(dehydroabietylimidazolium) bis(trifluoromethanesulfonimide) gave the best discrimination for the enantiomers of carboxylate salts. Its resolution behaviour was studied by an NMR titration experiment, which indicated 1 : 1 complexation with the racemic analyte. The dehydroabietylimidazolium salts were also useful in enantiomeric excess (ee) determinations, and for the recognition of chirality of racemic aromatic and non-aromatic α-substituted carboxylic acids.

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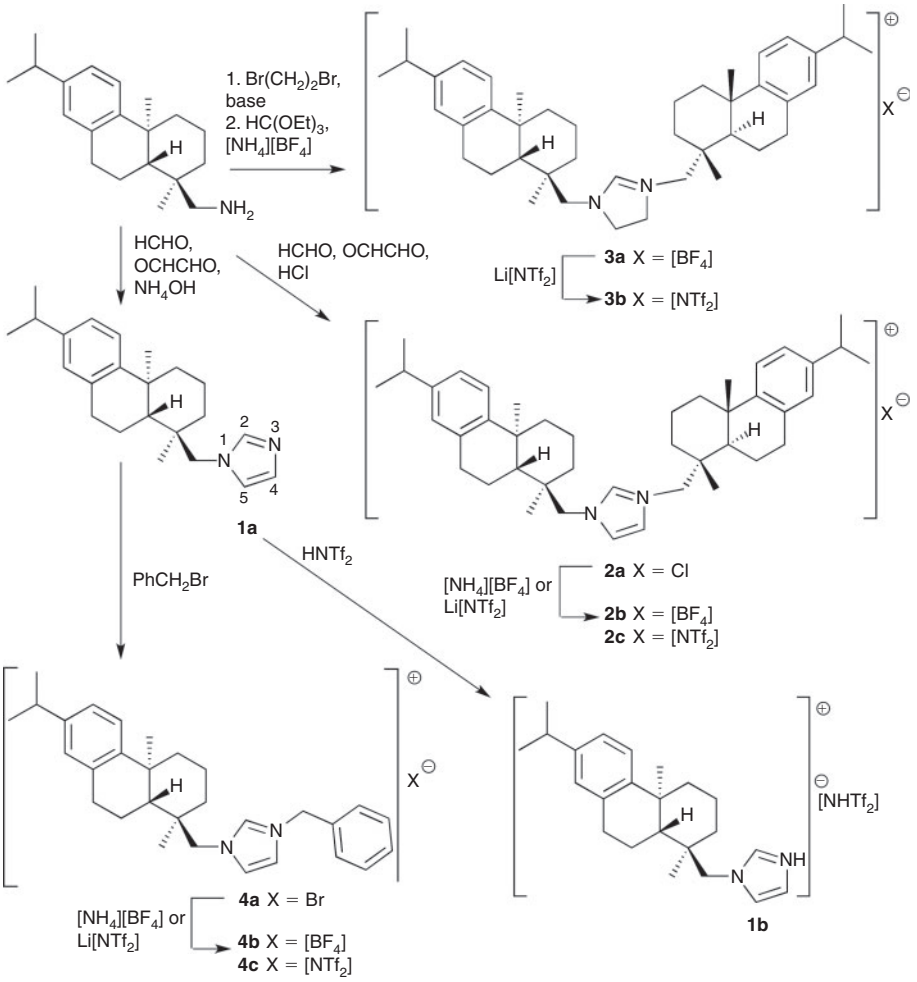
Introduction

The determination of enantiomeric purity is an important aspect of synthetic chemistry and various methods have been developed for this purpose. The two most commonly used analytical techniques to determine the enantiomeric excess (ee) of chiral compounds are the separation of enantiomers using chiral HPLC, or their treatment with chiral derivatising agents or chiral solvating agents, followed by NMR spectroscopic analysis. Owing to the development of higher-field instruments, NMR spectroscopy has become more sensitive,[1] and the ee may be determined up to a 94–99 % level.[2] This allows reliable, accurate, and expedient ee determinations,[3] required particularly in pharmaceuticals development. Minimal sample preparation, ease of use, and fast analyses make NMR spectroscopy an optimal tool for quick ee determinations.

The NMR spectra of enantiomers are indistinguishable as their chemical environments are identical. To differentiate the enantiomers, a diastereomeric environment is required. This can be created by using chiral auxiliary compounds such as chiral solvating agents, paramagnetic chiral shift reagents, chiral liquid crystals, or chiral derivatising agents.[4,5] Chiral solvating agents are most often employed owing to their ease of use. Both neutral and ionic chiral solvating agents have been developed, although the latter have gained less attention.[4,5]

The use of chiral solvating agents is based on the complexation between the chiral solvating agent (host) and the two enantiomers of the chiral substrate (guest), to generate two diastereomeric 'complexes'.[4,5] Complexation between a host and guest depends on interactions such as hydrogen bonding, π–π stacking, and ion–ion interactions.[5] Aromatic moieties in chiral solvating agents can enable π–π stacking but, more importantly, they can also provide shielding, which increases resolution.[4,6] Therefore, most of the chiral solvating agents developed are aromatic and they can be used for both aromatic and non-aromatic chiral compounds.[7] Electronegative groups and hydrogen donor and acceptor groups are able to provide the needed interaction to create a host–guest complex.[4,5] Bulky substituents are also useful, as they can obstruct complex formation for the other enantiomer, thus increasing the chemical shift difference.[1] In the case of an ionic chiral solvating agent, the counter ion will also have an effect on the degree of resolution. Counter ions with a delocalised charge are often favoured as they have been observed to increase resolution.[8]

Our aim was to develop and investigate new ionic chiral solvating agents, as they have not been widely studied. The resin derivative (+)-dehydroabietylamine is known to have an enantiomeric recognition ability towards chiral carboxylic acids[9] but, apart from recent work from our group,[10,11] (+)-dehydroabietylamine has not been used as a chiral solvating agent. As it is readily available, cheap, and derived from renewable resources, has a bulky structure, and contains both an aromatic moiety and an amino group that may also be converted to the cationic form, it should provide an ideal starting material for cationic chiral solvating agents. Although some cationic chiral solvating agents have been reported, their resolution ability has been scantily studied. In most cases, the developed chiral solvating agents have only been tested with



Scheme 1. Synthesis of (+)-dehydroabietylimidazole (**1a**), and (+)-dehydroabietylimidazolium (**1b**, **2**, and **4**) and (+)-dehydroabietylimidazolinium (**3**) salts.

one guest.[12] A lack of comparison with several compounds hinders the establishment of the full potential of a developed chiral solvating agent in enantiomeric resolutions. The resolution ability of newly developed cationic chiral solvating agents has been more extensively investigated in a few cases only,[10,13] predominantly with racemic aromatic carboxylic acids.[10,12–14] The favoured test compound has been Mosher's acid (3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid), used either as such[14] or in its anionic[12] form.

Here, 10 different (+)-dehydroabietylimidazolium or (+)-dehydroabietylimidazolinium chiral solvating agents were prepared (Scheme 1). Their effectiveness as chiral discriminators was extensively investigated, along with the effect of the anion on the resolution, the effect of the aromatic functionality, and the question as to whether it is better for the guest to be neutral or anionic. The enantiomeric resolution of neutral guests by ionic chiral solvating agents has rarely been studied, and when the guest is a carboxylic acid, it has usually been converted to the anion.[10–13] Mosher's acid was used as a test compound as it enables detection by both ^{1}H and ^{19}F NMR spectroscopy. In order to carry out a systematic study, the best-performing chiral solvating agent was used in the resolution of seven different carboxylate salts, to establish its applicability in resolving both aromatic and non-aromatic racemic carboxylic acids.

Experimental

General

All reagents and solvents were obtained from commercial suppliers (Sigma Aldrich) and were used without further purification unless otherwise stated. (+)-Dehydroabietylamine was purchased as 60 % grade (Sigma Aldrich) and purified by a method described in the literature[15] with slight modifications (see below). Flash chromatography was performed on 40–63-mesh silica gel. Microwave syntheses were performed using the CEM Focused Microwave™ Synthesis System (Model Discover). Melting points were determined on a digital melting point apparatus (Büchi B 545). Optical rotations were determined on a digital polarimeter (Jasco DIP-1000) at 22°C in trichloromethane as solvent. The exact mass measurements were performed by high-resolution mass spectrometry (HRMS) (Brucker MicroTOF LC) with electrospray ionisation (ESI).

Compound Characterisation

NMR experiments were performed using Varian Unity Inova 500 and Varian Mercury Plus 300 instruments at 27°C. ^{1}H NMR spectra were recorded with 4–16 transients, 4085–8000-Hz spectral width, and 1.9-s acquisition time at 500 MHz. ^{13}C NMR spectra were recorded with 576–1500 transients,

20000–31446-Hz spectral width, and 1.8-s acquisition time at 125 or 75 MHz. ^{19}F NMR spectra were recorded with 16–32 transients, 19047-Hz spectral width, 5.0-s relaxation delay, and 1.0-s acquisition time at 470 MHz. All 2D HSQC (heteronuclear single-quantum correlation) spectra (see Supplementary Material) were recorded using the Varian Unity Inova 500 instrument with 4 transients, 128–300 increments, 8000–4085-Hz spectral widths in the ^{1}H-dimension, 22955–31446-Hz spectral widths in the ^{13}C-dimension, 1.0–2.0-s relaxation delays, and 0.128-s acquisition time. TMS was used as the reference compound in NMR measurements. The chemical shift scale of ^{19}F was fixed by applying absolute, indirect referencing by calculating the frequency position for 0.0 ppm in the ^{19}F chemical shift scale from the ^{1}H chemical shift scale. To differentiate the proton and carbon signals of aromatic and imidazolium and 2-imidazolinium structures, the subscript Ar (CH_{Ar}) is used for aromatic and im (CH_{im}) for imidazolium and 2-imidazolinium.

Preparations

Purification of (+)-Dehydroabietylamine

Crude 60 % (+)-dehydroabietylamine (42.0 g) was dissolved in toluene (70.0 cm^3) and ethanoic acid (9.65 g) in toluene (30.0 cm^3) was slowly added. The salt was left to crystallise in the refrigerator. The product was collected by filtration and washed with hexane (30.0 cm^3). (+)-Dehydroabietylamine ethanoate was recrystallised from methanol. (+)-Dehydroabietylamine ethanoate (21.0 g) was dissolved in hot water and 10 % aqueous NaOH solution (28.0 cm^3) was added. (+)-Dehydroabietylamine was extracted with diethyl ether (50.0 cm^3) and the organic phase was washed with water until neutral, and then dried over anhydrous sodium sulfate. The solvent was evaporated, and the resultant (+)-dehydroabietylamine was dried under vacuum to yield a white solid; yield 37.0 g, 88.2 %; mp 44.2°C (lit. 44–45°C[16]). $[\alpha]^{22}_{D}$ +44.3480 (*c*, 10.0 mg cm^{-3}, $CHCl_3$). δ_H (500 MHz, $CDCl_3$) 0.89 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.22 (d, *J* 7.0, 6H, 2 × CH_3), 1.33 (m, 2H, CH_2), 1.39 (m, 1H, C*H*H), 1.52 (dd, *J* −11.8, 3.3, 1H, CH), 1.69 (m, 2H, CH_2), 1.74 (m, 2H, CH_2), 2.30 (dt, *J* −13.1, 1.7, 1H, CH*H*), 2.40 (d, *J* −13.5, 1H, C*H*H), 2.61 (d, *J* −13.5, 1H, CH*H*), 2.82 (sep., *J* 7.0, CH), 2.88 (m, 2H, CH_2), 6.89 (d, *J* 1.9, 1H, CH_{Ar}), 7.00 (dd, *J* 8.1, 1.9, 1H, CH_{Ar}), 7.18 (d, *J* 8.1, 1H, CH_{Ar}). δ_C (500 MHz, $CDCl_3$) 18.78 (CH_2), 18.90 (CH_3), 18.90 (CH_2), 24.11 (CH_3), 24.13 (CH_3), 25.37 (CH_3), 30.31 (CH_2), 33.58 (CH), 35.36 (CH_2), 37.36 (C), 37.53 (C), 38.70 (CH_2), 45.00 (CH), 53.99 (CH_2), 123.96 (CH_{Ar}), 124.38 (CH_{Ar}), 126.94 (CH_{Ar}), 134.84 (C_{Ar}), 145.67 (C_{Ar}), 147.63 (C_{Ar}). *m*/*z* (HRMS-ESI) 286.2540; calcd for $C_{20}H_{32}N$ $[M + H]^+$ 286.2529.

Synthesis of 1-Dehydroabietylimidazole (**1a**)

(+)-Dehydroabietylamine (5.0 g, 17.54 mmol, 1.0 equiv.) was dissolved in 2-propanol (10.0 cm^3) and 25 % aqueous ammonium hydroxide solution (2.70 cm^3, 17.54 mmol, 1.0 equiv.) was added. A mixture of a 40 % aqueous solution of glyoxal (2.17 cm^3, 18.94 mmol, 1.08 equiv.) and 35 % aqueous solution of methanal (1.49 cm^3, 18.94 mmol, 1.08 equiv.) in 2-propanol (20.0 cm^3) was added dropwise to the reaction mixture, which was kept at 80°C for 4 h and left to stir at room temperature overnight. Water (20.0 cm^3) was added to the reaction mixture, which was then extracted with diethyl ether (40.0 cm^3). The organic phase was washed with water until neutral and dried over anhydrous magnesium sulfate. The organic phase was filtered and the solvent evaporated; the crude product was dried under vacuum, and recrystallised from a diethyl ether/pentane mixture. Yield 2.5 g, 41.7 %; white solid; mp 107.6°C. $[\alpha]^{22}_{D}$ −25.9560 (*c*, 10.0 mg cm^{-3}, $CHCl_3$). δ_H (500 MHz, $CDCl_3$) 1.00 (s, 3H, CH_3), 1.21 (d, *J* 6.92, 6H, 2 × CH_3), 1.23 (s, 3H, CH_3), 1.28 (m, 1H, C*H*H), 1.33 (m, 1H, C*H*H), 1.35 (m, 1H, CH), 1.38 (m, 1H, CH*H*), 1.70 (m, 2H, CH_2), 1.87 (m, 2H, CH_2), 2.25 (dt, *J* −13.1, 3.5, 1H, CH*H*), 2.81 (sep., *J* 6.9, CH), 2.89 (m, 1H, C*H*H), 2.96 (ddd, *J* −16.9, 6.7, 2.4, 1H, CH*H*), 3.70 (d, *J* −14.0, 1H, C*H*H), 3.86 (d, *J* −14.0, 1H, CH*H*), 6.83 (t, *J* 1.1, 1H, CH_{im}), 6.88 (d, *J* 2.1, 1H, CH_{Ar}), 6.97 (dd, *J* 8.3, 2.1, 1H, CH_{Ar}), 6.99 (t, *J* 1.1, 1H, CH_{im}), 7.12 (d, *J* 8.3, 1H, CH_{Ar}), 7.38 (t, *J* 1.1, 1H, CH_{im}). δ_C (500 MHz, $CDCl_3$) 18.59 (CH_2), 18.77 (CH_3), 19.40 (CH_2), 24.07 (CH_3), 24.09 (CH_3), 25.69 (CH_3), 29.94 (CH_2), 33.56 (CH), 36.72 (CH_2), 37.68 (C), 38.08 (C), 38.13 (CH_2), 45.06 (CH), 58.45 (CH_2), 121.12 (CH_{im}), 124.12 (CH_{Ar}), 124.23 (CH_{Ar}), 126.97 (CH_{Ar}), 128.81 (CH_{im}), 134.19 (C_{Ar}), 138.73 (CH_{im}), 145.90 (C_{Ar}), 146.84 (C_{Ar}). *m*/*z* (HRMS-ESI) 337.2635; calcd for $C_{23}H_{33}N_2$ $[M + H]^+$ 337.2638.

Synthesis of 1-(+)-Dehydroabietylimidazolium Bis{(trifluoromethyl)sulfonyl}amide) (**1b**)

Bistriflamidic acid (80 mg, 2.97 mM, 1.0 equiv.) was added to compound **1a** (0.10 g, 2.97 mmol, 1.0 equiv.) in dichloromethane (0.5 cm^3) at 0°C. After stirring the reaction mixture for 1 h at room temperature, water (3.0 cm^3) was added, the two layers separated, and the organic phase was washed with water (3 × 2.0 cm^3). The organic solvent was evaporated and the product dried under vacuum. Yield 0.18 g, 96.8 %; amorphous solid at room temperature. $[\alpha]^{22}_{D}$ −23.2360 (*c*, 10.0 mg cm^{-3}, $CHCl_3$). δ_H (500 MHz, $CDCl_3$) 1.05 (s, 3H, CH_3), 1.21 (d, *J* 7.0, 6H, 2 × CH_3), 1.24 (s, 3H, CH_3), 1.25 (m, 1H, C*H*H), 1.29 (m, 1H, CH), 1.31 (m, 1H, C*H*H), 1.41 (dt, *J* −12.6, 2.9, 1H, CH*H*), 1.72 (m, 2H, CH_2), 1.89 (m, 2H, CH_2), 2.31 (dt, *J* −12.7, 3.2, 1H, CH*H*), 2.82 (sep., *J* 7.0, CH), 2.87 (m, 1H, C*H*H), 3.01 (ddd, *J* −17.8, 8.4, 2.2, 1H, CH*H*), 4.06 (d, *J* −14.3, 1H, C*H*H), 4.06 (d, *J* −14.3, 1H, CH*H*), 6.90 (d, *J* 1.9, 1H, CH_{Ar}), 6.99 (dd, *J* 8.1, 1.9, 1H, CH_{Ar}), 7.13 (d, *J* 8.1, 1H, CH_{Ar}), 7.14 (t, *J* 1.5, 1H, CH_{im}), 7.33 (t, *J* 1.5, 1H, CH_{im}), 8.40 (t, *J* 1.5, 1H, CH_{im}). δ_C (500 MHz, $CDCl_3$) 18.22 (CH_3), 18.31 (CH_2), 19.32 (CH_2), 24.03 (CH_3), 24.08 (CH_3), 25.57 (CH_3), 29.69 (CH_2), 33.57 (CH), 36.59 (CH_2), 37.76 (C), 37.97 (CH_2), 38.08 (C), 45.62 (CH), 60.92 (CH_2), 119.82 (q, *J* 320.8, CF_3), 120.67 (CH_{im}), 123.28 (CH_{im}), 124.14 (CH_{Ar}), 124.33 (CH_{Ar}), 127.10 (CH_{Ar}), 133.90 (C_{Ar}), 136.04 (CH_{im}), 146.23 (C_{Ar}), 146.36 (C_{Ar}). *m*/*z* (HRMS-ESI) 337.2630 calcd for $[C_{23}H_{33}N_2]^+$ $[M]^+$ 337.2638; 279.9177, calcd for $[C_2F_6NO_4S_2]^-$ 279.9167.

Synthesis of 1,3-Bisdehydroabietylimidazolium Chloride (**2a**)

Formaldehyde (35 % aqueous solution; 0.14 cm^3, 1.75 mmol, 1.0 equiv.) was added dropwise to (+)-dehydroabietylamine (1.0 g, 3.51 mmol, 2.0 equiv.) in toluene (10.0 cm^3) at 0°C and the reaction mixture was allowed to warm to room temperature. A mixture of aqueous hydrochloric acid (35 %, 0.16 cm^3, 1.75 mmol, 1.0 equiv.) and 40 % glyoxal (0.20 cm^3, 1.75 mmol, 1.0 equiv.) was added dropwise to the reaction mixture at 0°C, which was allowed warm to room temperature, and then heated for 24 h at 80°C. The solvent was removed by evaporation and the crude product dried under vacuum, purified by column chromatography (1 : 9 methanol/CH_2Cl_2), and crystallised from a CH_2Cl_2/EtO_2CMe mixture. Yield 0.73 g, 64.5 %; white solid;

mp 220.5°C. $[\alpha]^{20}_D$ −66.4120 (*c*, 10.0 mg cm^{-3}, $CHCl_3$). δ_H (500 MHz, $CDCl_3$) 1.03 (s, 6H, 2 × CH_3), 1.11 (m, 2H, 2 × C*H*H), 1.15 (m, 2H, 2 × C*H*H), 1.19 (s, 6H, 2 × CH_3), 1.21 (d, *J* 6.9, 12H, 4 × CH_3), 1.24 (m, 2H, 2 × CH), 1.43 (dt, *J* −12.7, 2.8, 2H, 2 × CH*H*), 1.53 (m, 2H, 2 × C*H*H), 1.62 (m, 2H, 2 × CH*H*), 1.88 (m, 2H, 2 × C*H*H), 2.05 (m, 2H, 2 × CH*H*), 2.19 (dt, *J* −13.0, 3.2, 2H, 2 × CH*H*), 2.81 (sep., *J* 6.9, 2H, 2 × CH), 2.89 (m, 2H, 2 × C*H*H), 2.99 (dd, *J* −17.4, 6.7, 2H, 2 × CH*H*), 4.13 (d, *J* −14.0, 2H, 2 × CH*H*), 4.37 (d, *J* −14.0, 2H, 2 × C*H*H), 6.89 (d, *J* 1.9, 2H, 2 × CH_{Ar}), 6.96 (dd, *J* 8.2, 1.9, 2H, 2 × CH_{Ar}), 7.07 (d, *J* 8.2, 2H, 2 × CH_{Ar}), 7.11 (s, 2H, 2 × CH_{im}), 10.78 (s, 1H, CH_{im}). δ_C (500 MHz, $CDCl_3$) 18.22 (2 × CH_3), 18.42 (2 × CH_2), 19.22 (2 × CH_2), 24.04 (2 × CH_3), 24.08 (2 × CH_3), 25.50 (2 × CH_3), 29.72 (2 × CH_2), 33.53 (2 × CH), 36.61 (2 × CH_2), 37.65 (2 × C), 37.97 (2 × CH_2), 38.19 (2 × C), 45.43 (2 × CH), 60.50 (2 × CH_2), 122.75 (2 × CH_{im}), 124.03 (2 × CH_{Ar}), 124.09 (2 × CH_{Ar}), 126.98 (2 × CH_{Ar}), 134.09 (2 × C_{Ar}), 140.99 (CH_{im}), 146.00 (2 × C_{Ar}), 146.51 (2 × C_{Ar}). *m*/*z* (HRMS-ESI) 605.4824; calcd for $[C_{43}H_{61}N_2]^+$ $[M]^+$ 605.4829.

Synthesis of N,N′*-Bisdehydroabietyl-1,2-diaminoethane*

(+)-Dehydroabietylamine (1.0 g, 3.51 mmol, 2.0 equiv.), 1,2-dibromoethane (0.15 cm^3, 1.75 mmol, 1.0 equiv.), and Na_2CO_3 (0.18 g, 1.75 mmol, 1.0 equiv.) were added to a microwave tube with 2-propanol. The reaction mixture was microwave-irradiated (110 W at 110°C) for 2 h. The solvent was evaporated and the solid triturated with diethyl ether, collected by filtration, and then mixed with diethyl ether (20.0 cm^3) and aqueous sodium hydroxide (2.0 M, 10.0 cm^3). The organic phase was washed with water until neutral and dried over anhydrous sodium sulfate. The organic phase was filtered and the solvent evaporated. The solid product was dried under vacuum and purified by flash chromatography (1 : 9 MeOH/CH_2Cl_2). Yield 0.78 g, 74.3 %; white solid; mp 63.8°C. $[\alpha]^{22}_D$ +43.3160 (*c*, 10.0 mg cm^{-3}, $CHCl_3$). δ_H (500 MHz, $CDCl_3$) 0.91 (s, 6H, 2 × CH_3), 1.20 (s, 6H, 2 × CH_3), 1.23 (d, *J* 7.0, 12H, 4 × CH_3), 1.37 (m, 2H, 2 × C*H*H), 1.38 (m, 4H, 2 × CH_2), 1.57 (dd, *J* −12.3, 2.7, 2H, 2 × CH), 1.60 (m, 4H, 2 × CH_2), 1.71 (m, 2H, 2 × C*H*H), 1.75 (m, 2H, 2 × CH*H*), 2.23 (dt, *J* −12.8, 3.3, 2H, 2 × CH*H*), 2.32 (d, *J* −11.8, 2H, 2 × C*H*H), 2.51 (d, *J* −11.8, 2H, 2 × CH*H*), 2.70 (s, 4H, 2 × CH_2), 2.82 (sep., *J* 7.0, 2H, 2 × CH), 2.88 (m, 4H, 2 × CH_2), 6.87 (d, *J* 1.7, 2H, 2 × CH_{Ar}), 6.98 (dd, *J* 8.1, 1.6, 2H, 2 × CH_{Ar}), 7.16 (d, *J* 8.1, 2H, 2 × CH_{Ar}). δ_C (500 MHz, $CDCl_3$) 18.98 (4 × CH_2), 19.35 (2 × CH_3), 24.14 (4 × CH_3), 25.47 (2 × CH_3), 30.46 (2 × CH_2), 33.58 (2 × CH), 36.39 (2 × CH_2), 37.18 (2 × C), 37.55 (2 × C), 38.58 (2 × CH_2), 45.62 (2 × CH), 50.02 (2 × CH_2), 61.61 (2 × CH_2), 123.91 (2 × CH_{Ar}), 124.41 (2 × CH_{Ar}), 126.89 (2 × CH_{Ar}), 134.88 (C_{Ar}), 145.54 (2 × C_{Ar}), 147.64 (2 × C_{Ar}). *m*/*z* (HRMS-ESI) 597.5132; calcd for $C_{42}H_{65}N_2$ $[M + H]^+$ 597.5142.

*Synthesis of 1,3-Bisdehydroabietyl-2-dihydroimidazolinium Tetrafluoroborate (**3a**)*

A microwave tube was loaded with *N*,*N*′-bisdehydroabietyl-1,2-diaminoethane (0.5 g, 0.84 mmol, 1.0 equiv.), triethylorthoformate (0.14 cm^3, 0.84 mmol, 1.0 equiv.), ammonium tetrafluoroborate (88 mg, 0.84 mmol, 1.0 equiv.), and 2-propanol (1.0 cm^3). The reaction mixture was irradiated (140 W at 110°C) for 40 min. The solvent was removed by evaporation and diethyl ether (5.0 cm^3) was added. The mixture was then filtered and the resultant solid dried under reduced pressure followed by recrystallisation from a methanol/ethanenitrile mixture. Yield 0.41 g, 66.8 %; white solid; mp 210.4°C. $[\alpha]^{22}_D$ −45.1400 (*c*, 10.0 mg cm^{-3}, $CHCl_3$). δ_H (500 MHz, $CDCl_3$) 0.97 (s, 6H, 2 × CH_3), 1.20 (s, 6H, 2 × CH_3), 1.21 (m, 2H, 2 × C*H*H), 1.22 (d, *J* 6.9, 12H, 4 × CH_3), 1.30 (m, 2H, 2 × CH), 1.31 (m, 2H, 2 × C*H*H) 1.50 (dt, *J* −13.1, 2H, 2 × CH*H*), 1.63 (m, 4H, 2 × CH_2), 1.76 (m, 2H, 2 × C*H*H), 1.84 (m, 2H, 2 × CH*H*), 2.28 (dt, *J* −13.5, 3.3, 2H, 2 × CH*H*), 2.79 (m, 2H, 2 × C*H*H), 2.82 (sep., *J* 6.9, 2H, 2 × CH), 2.97 (m, 2H, 2 × CH*H*), 3.40 (d, *J* −14.8, 2H, 2 × C*H*H), 3.44 (d, *J* −14.8, 2H, 2 × CH*H*), 4.03 (m, 4H, 2 × CH_2), 6.88 (d, *J* 2.0, 2H, 2 × CH_{Ar}), 6.98 (dd, *J* 8.2, 2.0, 2H, 2 × CH_{Ar}), 7.12 (d, *J* 8.2, 2H, 2 × CH_{Ar}), 7.91 (m, 1H, CH). δ_C (500 MHz, $CDCl_3$) 18.26 (2 × CH_2), 18.45 (2 × CH_3), 18.67 (2 × CH_2), 23.81 (2 × CH_3), 23.87 (2 × CH_3), 25.28 (2 × CH_3), 29.54 (2 × CH_2), 33.32 (2 × CH), 36.65 (2 × CH_2), 37.40 (2 × C), 37.91 (2 × CH_2), 38.21 (2 × C), 45.29 (2 × CH), 52.54 (2 × CH_2), 59.55 (2 × CH_2), 123.92 (2 × CH_{Ar}), 123.98 (2 × CH_{Ar}), 126.78 (2 × CH_{Ar}), 133.78 (C_{Ar}), 145.80 (2 × C_{Ar}), 146.45 (2 × C_{Ar}), 161.75 (CH). *m*/*z* (HRMS-ESI) 607.4995; calcd for $[C_{43}H_{63}N_2]^+$ $[M]^+$ 607.4986.

*Synthesis of 3-Benzyl-1-dehydroabietylimidazolium Bromide (**4a**)*

(+)-Dehydroabietylimidazole (0.3 g, 0.891 mmol, 1.0 equiv.), benzyl bromide (0.168 g, 0.117 cm^3, 0.981 mmol, 1.1 equiv.), and $CHCl_3$ (0.3 cm^3) were added to a microwave tube. The reaction mixture was irradiated (110 W at 110°C) for 1 h. The product was quenched with diethyl ether, filtered, and dried under vacuum. Yield 0.42 g, 93.7 %; white solid; mp 152.9°C. $[\alpha]^{22}_D$ −27.0920 (*c*, 10.0 mg cm^{-3}, $CHCl_3$). δ_H (500 MHz, $CDCl_3$) 1.07 (s, 3H, CH_3), 1.22 (d, *J* 6.9, 6H, 2 × CH_3), 1.22 (s, 3H, CH_3), 1.23 (m, 1H, CH), 1.28 (m, 1H, C*H*H), 1.30 (m, 1H, C*H*H), 1.48 (m, 1H, CH*H*), 1.71 (m, 2H, CH_2), 1.89 (m, 1H, C*H*H), 2.27 (dt, *J* −13.0, 1H, CH*H*), 2.62 (dd, *J* −13.5, 7.6, 1H, CH*H*), 2.82 (sep., *J* 6.9, CH), 2.82 (m, 1H, C*H*H), 3.01 (dt, *J* −17.6, 6.3, 1H, CH*H*), 4.16 (d, *J* −14.1, 1H, C*H*H), 4.26 (d, *J* −14.1, 1H, CH*H*), 5.60 (s, 2H, CH_2), 6.89 (d, *J* 1.2, 1H, CH_{Ar}), 6.98 (dd, *J* 8.2, 1.2, 1H, CH_{Ar}), 7.11 (d, *J* 8.2, 1H, CH_{Ar}), 7.15 (m, 1H, CH_{im}), 7.21 (m, 1H, CH_{im}), 7.34 (m, 3H, 3 × CH_{Ar}), 7.46 (m, 2H, 2 × CH_{Ar}), 10.75 (m, 1H, CH_{im}). δ_C (500 MHz, $CDCl_3$) 18.32 (CH_2), 18.46 (CH_3), 19.31 (CH_2), 24.05 (CH_3), 24.09 (CH_3), 25.56 (CH_3), 29.84 (CH_2), 33.55 (CH), 36.60 (CH_2), 37.75 (C), 37.98 (CH_2), 38.14 (C), 45.49 (CH), 53.50 (CH_2), 60.86 (CH_2), 121.09 (CH_{im}), 123.74 (CH_{im}), 124.07 (CH_{Ar}), 124.21 (CH_{Ar}), 127.12 (CH_{Ar}), 129.15 (CH_{Ar}), 129.58 (CH_{Ar}), 129.64 (CH_{Ar}), 132.99 (C_{Ar}), 134.11 (C_{Ar}), 138.78 (CH_{im}), 146.09 (C_{Ar}), 146.47 (C_{Ar}). *m*/*z* (HRMS-ESI) 427.3118; calcd for $[C_{30}H_{39}N_2]^+$ $[M]^+$ 427.3108.

Synthesis of Guests

N-Acetylation of phenylalanine was performed according to the literature procedure.[17] Preparation of tetrabutylammonium salts of acids was performed by adding tetrabutylammonium hydroxide (1.0 M in methanol, 1.0 equiv.) to the racemic acid (1.0 equiv.) in methanol. After stirring for 3 h, the solvent was removed by evaporation and the product was dried under vacuum.

General Procedure for Anion Exchange

Anion-exchange reactions were performed according to literature procedures.[14a] Li[NTf_2] (NTf_2 = bis(trifluoromethane) sulfonamide) or ammonium tetrafluoroborate solution (1.0 M, 1.0 equiv.) was added to the chiral solvating agent (1.0 equiv. in

dichloromethane) at room temperature and the mixture stirred for 1 h. The phases were separated by gravity and the organic phase was washed with water ($3 \times 10\,cm^3$). The organic phase was concentrated and dried under vacuum.

*1,3-Bisdehydroabietylimidazolium Tetrafluoroborate (**2b**)*

Yield 0.21 g, 94.2 %; white solid; mp 186.9°C (recrystallised from CH_2Cl_2/EtOCOMe). $[\alpha]^{20}_D$ −67.5760 (*c*, 10.0 mg cm^{-3}, $CHCl_3$). δ_H (500 MHz, $CDCl_3$) 0.99 (s, 6H, 2 × CH_3), 1.03 (m, 2H, 2 × C*H*H), 1.10 (m, 2H, 2 × C*H*H), 1.14 (m, 2H, 2 × CH), 1.18 (s, 6H, 2 × CH_3), 1.21 (d, *J* 7.0, 12H, 4 × CH_3), 1.35 (dt, *J* −12.6, 3.2, 2H, 2 × CH*H*), 1.46 (m, 2H, 2 × C*H*H), 1.60 (d, *J* −13.6, 3.2, 2H, 2 × CH*H*), 1.84 (m, 2H, 2 × C*H*H), 1.98 (m, 2H, 2 × CH*H*), 2.14 (dt, *J* −13.1, 3.6, 2H, 2 × CH*H*), 2.82 (sep., *J* 7.0, 2H, 2 × CH), 2.86 (m, 2H, 2 × C*H*H), 2.98 (dd, *J* −17.5, 6.7, 2H, 2 × CH*H*), 4.09 (d, *J* −13.2, 2H, 2 × CH*H*), 4.16 (d, *J* −13.2, 2H, 2 × C*H*H), 6.90 (d, *J* 1.9, 2H, 2 × CH_{Ar}), 6.97 (dd, *J* 8.2, 1.9, 2H, 2 × CH_{Ar}), 7.06 (d, *J* 8.2, 2H, 2 × CH_{Ar}), 7.10 (d, *J* 1.6, 2H, 2 × CH_{im}), 9.20 (s, 1H, CH_{im}). δ_C (500 MHz, $CDCl_3$) 18.21 (2 × CH_3), 18.35 (2 × CH_2), 18.99 (2 × CH_2), 24.06 (2 × CH_3), 24.09 (2 × CH_3), 25.51 (2 × CH_3), 29.64 (2 × CH_2), 33.54 (2 × CH), 36.38 (2 × CH_2), 37.61 (2 × C), 37.95 (2 × CH_2), 38.06 (2 × C), 45.29 (2 × CH), 60.27 (2 × CH_2), 123.12 (2 × CH_{im}), 124.06 (4 × CH_{Ar}), 126.96 (2 × CH_{Ar}), 134.10 (2 × C_{Ar}), 139.70 (CH_{im}), 145.95 (2 × C_{Ar}), 146.53 (2 × C_{Ar}). *m/z* (HRMS-ESI) 605.4837; calcd for $[C_{43}H_{61}N_2]^+$ $[M]^+$ 605.4829.

*1,3-Bisdehydroabietylimidazolium Bis{(trifluoromethyl) sulfonyl}amide (**2c**)*

Yield 0.25 g, 92.6 %; white solid; mp 199.0°C (recrystallised from CH_2Cl_2/pentane). $[\alpha]^{22}_D$ −31.8200 (*c*, 10.0 mg cm^{-3}, $CHCl_3$). δ_H (500 MHz, $CDCl_3$) 0.99 (s, 6H, 2 × CH_3), 1.04 (m, 2H, 2 × C*H*H), 1.05 (m, 2H, 2 × C*H*H), 1.16 (m, 2H, 2 × CH), 1.19 (s, 6H, 2 × CH_3), 1.21 (d, *J* 6.9, 12H, 4 × CH_3), 1.36 (dt, *J* −12.3, 2H, 2 × CH*H*), 1.49 (m, 2H, 2 × C*H*H), 1.63 (m, 2H, 2 × CH*H*), 1.90 (m, 4H, 2 × CH_2), 2.17 (dt, *J* −12.8, 2.3, 2H, 2 × CH*H*), 2.82 (sep., *J* 6.9, 2H, 2 × C*H*), 2.84 (m, 2H, 2 × C*H*H), 3.01 (ddd, *J* −17.3, 6.0, 1.7, 2H, 2 × CH*H*), 4.09 (d, *J* −13.9, 2H, 2 × C,H*H*), 4.16 (d, *J* −13.9, 2H, 2 × C*H*H), 6.89 (d, *J* 1.8, 2H, 2 × CH_{Ar}), 6.97 (dd, *J* 8.1, 1.8, 2H, 2 × CH_{Ar}), 7.06 (d, *J* 8.1, 2H, 2 × CH_{Ar}), 7.10 (s, 2H, 2 × CH_{im}), 8.62 (s, 1H, CH_{im}). δ_C (500 MHz, $CDCl_3$) 17.92 (2 × CH_2), 18.11 (2 × CH_3), 18.81 (2 × CH_2), 23.83 (2 × CH_3), 23.86 (2 × CH_3), 25.26 (2 × CH_3), 29.32 (2 × CH_2), 33.33 (2 × CH), 36.30 (2 × CH_2), 37.41 (2 × C), 37.69 (2 × CH_2), 37.94 (2 × C), 44.98 (2 × CH), 60.45 (2 × CH_2), 119.95 (q, *J* 321.0, CF_3), 123.22 (2 × CH_{im}), 123.86 (2 × CH_{Ar}), 123.97 (2 × CH_{Ar}), 126.76 (2 × CH_{Ar}), 133.59 (2 × C_{Ar}), 138.00 (CH_{im}), 145.92 (2 × C_{Ar}), 146.10 (2 × C_{Ar}). *m/z* (HRMS-ESI) 605.4814; calcd for $[C_{43}H_{61}N_2]^+$ $[M]^+$ 605.4829; 279.9160; calcd for $[C_2F_6NO_4S_2]^-$ 279.9167.

*1,3-Bisdehydroabietyl-2-dihydroimidazolinium Bis {(trifluoromethyl)sulfonyl}amide (**3b**)*

Yield 0.45 g, 82.7 %; white solid; mp 88.8°C. $[\alpha]^{22}_D$ −31.8520 (*c*, 10.0 mg cm^{-3}, $CHCl_3$). δ_H (500 MHz, $CDCl_3$) 0.978 (s, 6H, 2 × CH_3), 1.17 (m, 2H, 2 × C*H*H), 1.21 (s, 6H, 2 × CH_3), 1.22 (d, *J* 6.9, 12H, 4 × CH_3), 1.29 (m, 2H, 2 × C*H*H), 1.30 (m, 2H, 2 × CH), 1.47 (dt, *J* −12.3, 3.0, 2H, 2 × CH*H*), 1.62 (m, 4H, 2 × CH_2), 1.75 (m, 2H, 2 × C*H*H), 1.84 (m, 2H, 2 × CH*H*), 2.29 (dt, *J* −13.2, 3.2, 2H, 2 × C*H*H), 2.78 (m, 2H, 2 × CH*H*), 2.82 (sep., *J* 6.9, 2H, 2 × CH), 2.99 (dd, *J* −17.1, 7.0, 2H, 2 × C*H*H), 3.35 (d, *J* −14.8, 2H, 2 × C*H*H), 3.44 (d, *J* −14.8, 2H, 2 × CH*H*), 4.03 (m, 4H, 2 × CH_2), 6.89 (d, *J* 1.7, 2H, 2 × CH_{Ar}), 6.99 (dd, *J* 8.3, 1.7, 2H, 2 × CH_{Ar}), 7.12 (d, *J* 8.3, 2H, 2 × CH_{Ar}), 7.75 (m, 1H, CH). δ_C (500 MHz, $CDCl_3$) 18.43 (2 × CH_2), 18.65 (2 × CH_3), 18.96 (2 × CH_2), 24.06 (2 × CH_3), 24.12 (2 × CH_3), 25.51 (2 × CH_3), 29.70 (2 × CH_2), 33.58 (2 × CH), 37.05 (2 × CH_2), 37.65 (2 × C), 38.14 (2 × CH_2), 38.56 (2 × C), 45.54 (2 × CH), 52.78 (2 × CH_2), 59.89 (2 × CH_2), 119.96 (q, *J* 320.6, CF_3), 124.16 (2 × CH_{Ar}), 124.31 (2 × CH_{Ar}), 127.03 (2 × CH_{Ar}), 133.87 (C_{Ar}), 146.16 (2 × C_{Ar}), 146.56 (2 × C_{Ar}), 161.37 (CH). *m/z* (HRMS-ESI) 607.4967; calcd for $[C_{43}H_{63}N_2]^+$ $[M]^+$ 607.4986; 279.9157; calcd for $[C_2F_6NO_4S_2]^-$ 279.9167.

*3-Benzyl-1-dehydroabietylimidazolium Tetrafluoroborate (**4b**)*

Yield 0.099 g, 97.5 %; white solid; mp 113.4°C. $[\alpha]^{22}_D$ −29.9880 (*c*, 10.0 mg cm^{-3}, $CHCl_3$). δ_H (500 MHz, $CDCl_3$) 1.01 (s, 3H, CH_3), 1.19 (m, 1H, CH), 1.20 (s, 3H, CH_3), 1.22 (d, *J* 6.8, 6H, 2 × CH_3), 1.23 (m, 1H, C*H*H), 1.28 (m, 1H, C*H*H), 1.40 (dt, *J* −12.5, 1H, CH*H*), 1.68 (m, 2H, CH_2), 1.87 (m, 2H, CH_2), 2.26 (dt, *J* −13.4, 1H, CH*H*), 2.74 (m, 1H, C*H*H), 2.82 (sep., *J* 6.8, 1H, CH), 2.96 (dd, *J* −13.5, 6.1, 1H, CH*H*), 4.04 (d, *J* −14.3, 1H, C*H*H), 4.11 (d, *J* −14.3, 1H, CH*H*), 5.36 (s, 2H, CH_2), 6.88 (d, *J* 1.8, 1H, CH_{Ar}), 6.98 (dd, *J* 8.1, 1.8, 1H, CH_{Ar}), 7.11 (d, *J* 8.1, 1H, CH_{Ar}), 7.15 (m, 1H, CH_{im}), 7.18 (m, 1H, CH_{im}), 7.33 (m, 3H, 3 × CH_{Ar}), 7.38 (m, 2H, 2 × CH_{Ar}), 9.07 (m, 1H, CH_{im}). δ_C (500 MHz, $CDCl_3$) 18.17 (CH_3), 18.34 (CH_2), 19.12 (CH_2), 24.08 (CH_3), 24.12 (CH_3), 25.57 (CH_3), 29.75 (CH_2), 33.58 (CH), 36.38 (CH_2), 37.74 (C), 37.97 (C), 38.00 (CH_2), 45.62 (CH), 53.60 (CH_2), 61.00 (CH_2), 121.50 (CH_{im}), 124.11 (CH_{im}), 124.22 (CH_{Ar}), 124.26 (CH_{Ar}), 127.12 (CH_{Ar}), 129.08 (CH_{Ar}), 129.63 (CH_{Ar}), 129.66 (CH_{Ar}), 132.92 (C_{Ar}), 134.11 (C_{Ar}), 137.43 (CH_{im}), 146.07 (C_{Ar}), 146.52 (C_{Ar}). *m/z* (HRMS-ESI) 427.3118; calcd for $[C_{30}H_{39}N_2]^+$ $[M]^+$ 427.3108.

*3-Benzyl-1-dehydroabietylimidazolium Bis{(trifluoromethyl)sulfonyl}amide (**4c**)*

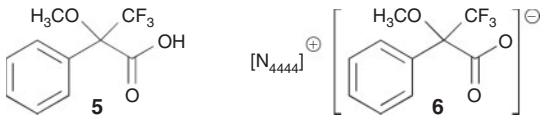
Yield 0.13, g 92.7 %; amorphous solid at room temperature. $[\alpha]^{22}_D$ −25.3600 (*c*, 10.0 mg cm^{-3}, $CHCl_3$). δ_H (500 MHz, $CDCl_3$) 1.02 (s, 3H, CH_3), 1.18 (m, 1H, C*H*H), 1.19 (m, 1H, CH), 1.22 (d, *J* 6.9, 6H, 2 × CH_3), 1.22 (s, 3H, CH_3), 1.29 (m, 1H, C*H*H), 1.41 (m, 1H, CH*H*), 1.71 (m, 2H, CH_2), 1.87 (m, 2H, CH_2), 2.29 (dt, *J* −12.4, 1H, CH*H*), 2.73 (m, 1H, C*H*H), 2.82 (sep., *J* 6.9, 1H, CH), 2.96 (dt, *J* 17.1, 3.7, 1H, CH*H*), 4.06 (d, *J* −14.1, 1H, C*H*H), 4.10 (d, *J* −14.1, 1H, CH*H*), 5.34 (s, 2H, CH_2), 6.88 (d, *J* 1.6, 1H, CH_{Ar}), 6.99 (dd, *J* 8.3, 1.6, 1H, CH_{Ar}), 7.12 (d, *J* 8.3, 1H, CH_{Ar}), 7.14 (m, 2H, 2 × CH_{im}), 7.24 (m, 1H, CH_{Ar}), 7.32 (m, 2H, 2 × CH_{Ar}), 7.37 (m, 2H, 2 × CH_{Ar}), 8.80 (m, 1H, CH_{im}). δ_C (300 MHz, $CDCl_3$) 18.21 (CH_3), 18.30 (CH_2), 19.14 (CH_2), 24.06 (CH_3), 24.10 (CH_3), 25.58 (CH_3), 29.68 (CH_2), 33.58 (CH), 36.52 (CH_2), 37.77 (C), 37.99 (C), 38.07 (CH_2), 45.46 (CH), 53.92 (CH_2), 61.12 (CH_2), 119.96 (q, *J* 320.6, CF_3), 121.45 (CH_{im}), 124.11 (CH_{im}), 124.22 (CH_{Ar}), 124.31 (CH_{Ar}), 127.14 (CH_{Ar}), 129.00 (CH_{Ar}), 129.82 (CH_{Ar}), 129.99 (CH_{Ar}), 132.16 (C_{Ar}), 133.93 (C_{Ar}), 137.16 (CH_{im}), 146.22 (C_{Ar}), 146.38 (C_{Ar}). *m/z* (HRMS-ESI) 427.3122; calcd for $[C_{30}H_{39}N_2]^+$ $[M]^+$ 427.3108; 279.9167; calcd for $[C_2F_6NO_4S_2]^-$ 279.9167.

Results and Discussion

The syntheses of (+)-1-dehydroabietylimidazole (**1a**) and the nine derived imidazolium salts **1b–4c** were performed as shown in Scheme 1. To obtain **1a**, (+)-dehydroabietylamine was treated with aqueous NH_3, glyoxal, and aqueous formaldehyde in 2-propanol at 80°C (41 %). The salt **1b** was formed (96 %) from **1a** by reaction with $HNTf_2$ in CH_2Cl_2 at 0°C. Compound **2a** was obtained from (+)-dehydroabietylamine, glyoxal, aqueous formaldehyde, and aqueous hydrochloric acid (64 %) in toluene. **3a** was prepared via *N*,*N*′-bisdehydroabietyl-1, 2-diaminoethane, in a one-pot reaction from (+)-dehydroabietylamine, 1,2-dibromoethane, and Na_2CO_3 in 2-propanol with microwave heating (74 %), followed by the addition of $CH(OEt)_3$ and $[NH_4][BF_4]$ in 2-propanol (66 %). For improved shielding ability, **1a** was quaternised with benzyl bromide under microwave irradiation to give **4a**. It is known that more delocalised and bulky anions generally enhance binding between the cationic chiral solvating agent and (ionic or molecular) chiral substrate owing to weaker binding between the cation and anion of the chiral solvating agent.[8] To tune the binding properties of **2a**, **3a**, and **4a**, anion exchange was performed with $[NH_4][BF_4]$ and $Li[NTf_2]$ to obtain **2b–c**, **3b**, and **4b–c** in high yield. The delocalisation and increased size of the anion also affect the physical properties of the ionic chiral solvating agents.[8] For instance, the melting points of **4a**, **4b**, and **4c** decrease as the bulkiness and delocalisation of anion increase (mp of $Br > [BF_4] > [NTf_2]$).

The chiral discrimination of racemic carboxylic acids and their respective carboxylate anions by (+)-1-dehydroabietylimidazole (**1a**) and its imidazolium salt derivatives (**1b–4c**) was examined with Mosher's acid (**5**; $F_3CC(OCH_3)(Ph)COOH$) and its tetrabutylammonium ($[N_{4444}]^+$) salt (**6**). The effect of the concentration of the chiral solvating agent was also investigated, because it is known that higher concentrations generally enhance the enantiomeric resolution between *R* and *S* enantiomers (Δδ).[4,5] As polar solvents can dissolve salts, and protic solvents may interfere in hydrogen-bond formation,[13a] $CDCl_3$ was chosen as a solvent for the NMR studies, performed by dissolving the chiral solvating agent (1.0 or 2.0 equiv.) in a stock solution containing **5** or **6** (0.5 cm^3; 1.0 equiv., 22.0 mM). According to the results obtained from the NMR experiments (Table 1 and Fig. 1), the chiral solvating agents **1b–4c** resolved the enantiomers of **6** very efficiently (Δδ 11.4–49.9 Hz). The best results were obtained with **2c** (0.11 ppm, 49.8 Hz). Also, the enantiomers of **5** were resolved, but with a Δδ less than that with **6**. Only **1a** gave notably better discrimination for **5** (19.3 Hz) compared with **1b–4c** (0.88–7.0 Hz). This indicates that resolution using **1b–4c** is highly dependent on the ionic nature of the guest and vice versa in the case of **5**. Although ionic hosts (**1b–3b** and **4c**) were able to discriminate **5**, the neutral **1a** failed to discriminate **6**, making the ionic chiral solvating agents more versatile than a neutral one as the former also discriminate neutral species. For **6** and **5**, Δδ was found to be larger in the ^{19}F NMR spectra than in the ^1H NMR spectra. The ionic **1b–4c** gave larger resolutions in ^1H NMR spectra in the case of **5** compared with **6**. This may be due to a different host–guest complex structure formed between the neutral guest and the ionic host, compared with the situation when both are ionic. The increase of chiral solvating agent concentration to 2.0 equiv. did not cause a significant increase in Δδ (~0.0–8.0 Hz). Also, in some cases (**1b**, **2c**, **3b**, and **4c**), the resolution was decreased owing to an increased host concentration.

Table 1. The ^1H and ^{19}F NMR chemical shift differences (Δδ) between the *R* and *S* enantiomers of racemic Mosher's acid 5 and its tetrabutylammonium salt 6 in the presence of various (+)-dehydroabietylimidazole chiral solvating agents (500 MHz) in $CDCl_3$ at 27°C



	Host : guest	**5**: Δδ/ppm; (Hz)		**6**: Δδ/ppm; (Hz)	
		^1H (OCH_3)	^{19}F (CF_3)	^1H (OCH_3)	^{19}F (CF_3)
1a	1 : 1	0.0092 (4.6)	0.031 (14.8)	0.000	0.000
	2 : 1	0.011 (5.7)	0.041 (19.3)	0.000	0.000
1b	1 : 1	0.002 (0.99)	0.000	0.0044 (2.2)	0.024 (11.4)
	2 : 1	0.000	0.000	0.0042 (2.1)	0.026 (12.2)
2a	1 : 1	0.0056 (2.8)	0.000	0.000	0.074 (35.0)
	2 : 1	0.0091 (4.5)	0.000	0.000	0.080 (37.7)
2b	1 : 1	0.0071 (3.5)	0.000	0.000	0.092 (43.5)
	2 : 1	0.0099 (5.0)	0.000	0.000	0.102 (47.9)
2c	1 : 1	0.002 (1.0)	0.000	0.0029 (1.5)	0.110 (49.8)
	2 : 1	0.000	0.000	0.0061 (3.0)	0.110 (49.9)
3a	1 : 1	0.000	0.007 (3.3)	0.000	0.060 (28.1)
	2 : 1	0.000	0.015 (7.0)	0.000	0.077 (36.4)
3b	1 : 1	0.0019 (1.0)	0.000	0.000	0.065 (30.6)
	2 : 1	0.000	0.000	0.000	0.074 (34.7)
4a	1 : 1	0.000	0.000	0.000	0.028 (13.4)
	2 : 1	0.000	0.000	0.000	0.033 (15.7)
4b	1 : 1	0.000	0.000	0.000	0.034 (15.7)
	2 : 1	0.000	0.000	0.000	0.036 (17.0)
4c	1 : 1	0.0017 (0.8)	0.000	0.000	0.034 (15.8)
	2 : 1	0.000	0.000	0.000	0.032 (15.3)

To determine which features affect the resolution of **5** and **6** by an ionic host (**1b–4c**), the effect of the structure of the cation and its counter anion was examined. The discrimination of enantiomers of **6** was enhanced by a bulky chiral substituent on the imidazolium N-3, an aromatic ionic unit, and an anion with a more delocalised charge ($[NTf_2]^-$ versus Cl^-). In the case of **5**, resolution was enhanced by a bulky substituent at the N-3 site, a non-aromatic ionic unit, and an anion with a more localised charge (Cl^- versus $[BF_4]^-$). For example, **1b**, lacking a substituent at N-3, resolves the enantiomers of **6** less efficiently than **4c**, which has a benzyl group as the N-3 substituent. This indicates that the presence and nature of an imidazolium N-3 substituent is important for resolution. When comparing **4a–c** with **3a**, **b** and **2a–c**, where the imidazolium nucleus carries two (+)-dehydroabietyl groups, the discrimination is distinctly improved. An additional contribution to binding comes from hydrophobic and π–π stacking effects due to the substituents on the imidazolium unit. This can be seen from the simplified models in Fig. 2, illustrating a tentative complex structure. On comparing **3a**, **b** and **2a–c**, it is clearly seen that the aromaticity of the ionic centre has a beneficial influence on Δδ (e.g. **2c** versus **3b**). Similar behaviour was noted with **5**, and also in this case, a bulky side chain at N-3 enhanced the resolution. The non-aromatic ionic centre (**3a**, 7.0 Hz) was noted to give a better resolution for **5** than for an aromatic one (**2a–2c**, 1.0–5.0 Hz).

No explicit counter anion effects on the discrimination of molecular guests could be seen. In a 1 : 1 stoichiometry, $[NTf_2]^-$ (**2c**, **3b**, and **4c**) gave the best resolution, as non-hydrogen-bonding anions (such as $[NTf_2]^-$) allow bonding between the

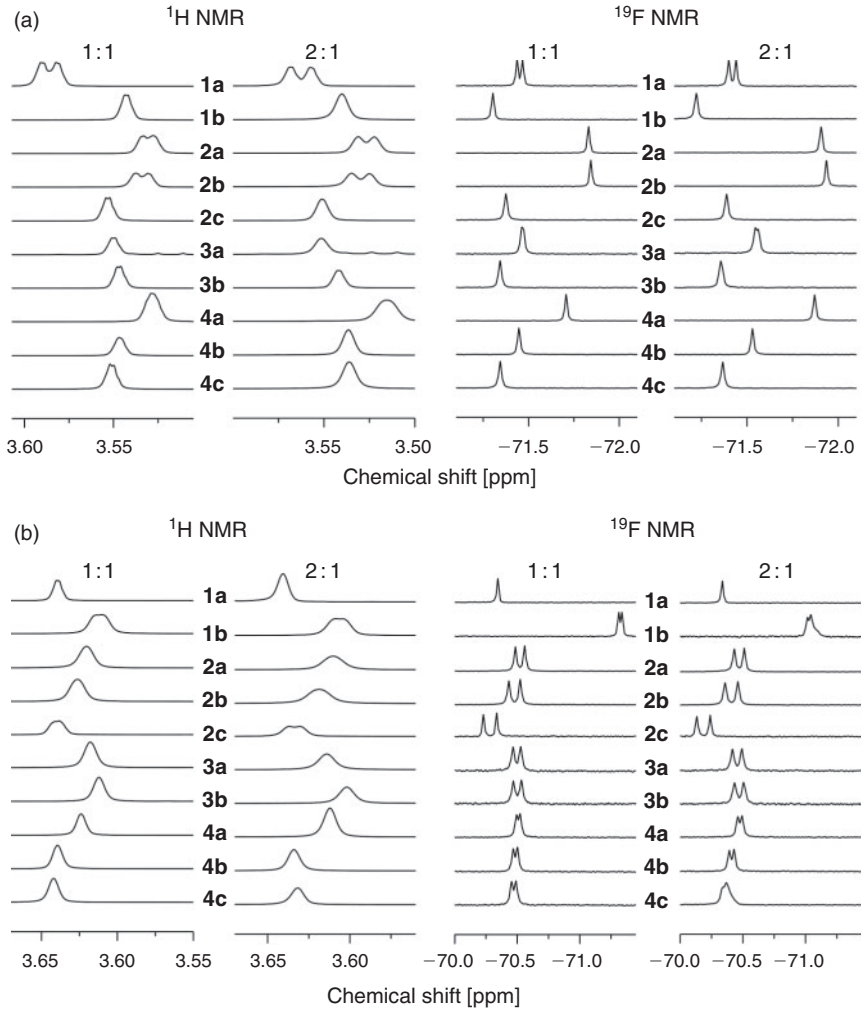


Fig. 1. ^{1}H (OCH_3) and ^{19}F (CF_3) NMR spectra of (a) **5**, and (b) **6** from the resolution of enantiomers with chiral solvating agents **1a–4c** in 1 : 1 and 2 : 1 host : guest ratio.

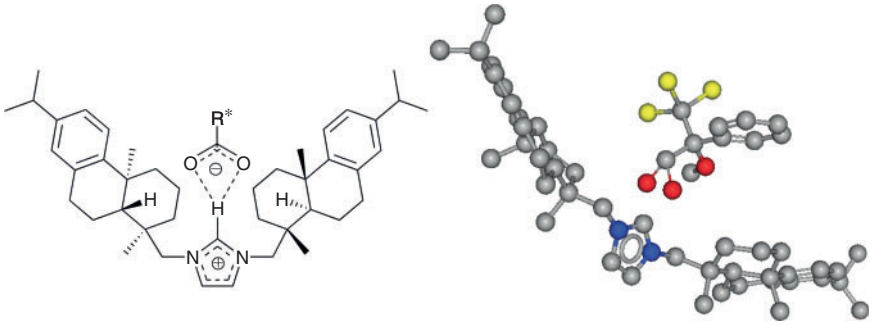


Fig. 2. A model illustrating how the cation of **2c** may interact with (left) a carboxylate anion, and (right) Mosher's carboxylate. Hydrogen atoms have been omitted for clarity.

host and the carboxylate to occur more efficiently due to their 'loose' association with the host cation. However, when the concentration was increased, $[BF_4]^-$ gave slightly better results in the case of **3a** and **4a**. This phenomenon may be due to aggregation between the host and guest due to the increased concentration of host. In the case of **5**, the effect of a counter anion was also noted, although in this case, the delocalisation of charge in the anion did not seem to increase resolution. An anion with a more localised charge favoured resolution, and among those, the size of the anion (Cl^- versus $[BF_4]^-$) seemed to play a crucial role.

As **2c** gave the best resolution (49.9 Hz), its enantiomeric discriminating power was further investigated by titration to find the optimum conditions for complexation. It is important to establish the structure of the complex in order to evaluate how much chiral solvating agent will be needed for optimal

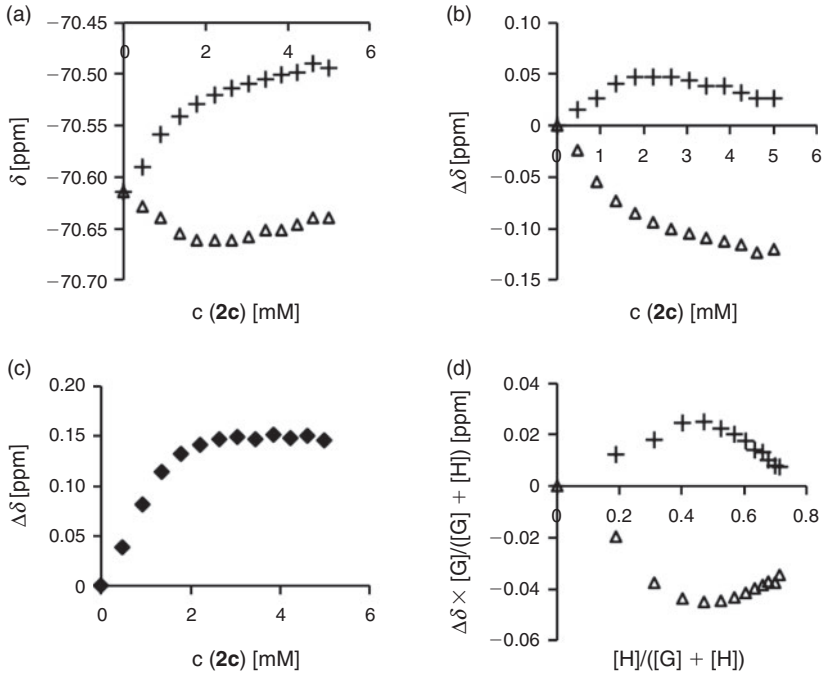


Fig. 3. (a) The chemical shifts of *S* (+) and *R* (Δ) enantiomers of **6** (*c*, 2.0 mM); (b) the change of chemical shift of *R* and *S* enantiomers of **6**; (c) Δδ between *R* and *S* enantiomers of **6** as a function of concentration of **2c**; (d) Job's plot ([H], concentration of host; [G], concentration of guest).

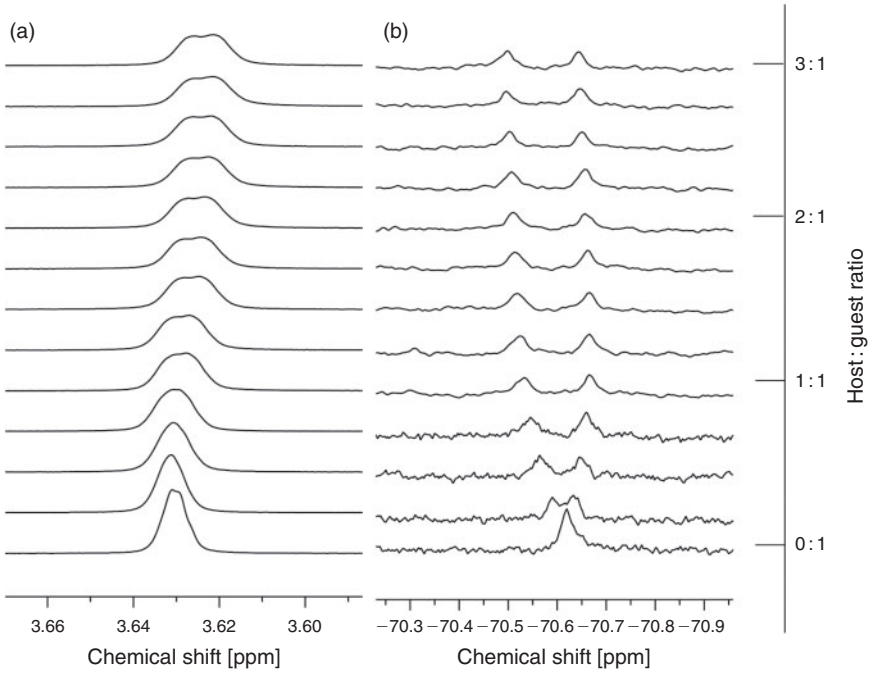


Fig. 4. The change of chemical shift of *R* and *S* enantiomers of **6** in (a) the ^{1}H NMR spectra, and (b) the ^{19}F NMR spectra.

resolution. It also helps to evaluate if it is practical to increase the amount of host over the stoichiometric amount. A solution of guest **6** (0.5 cm^3, 2.0 mM) was measured into an NMR tube and titrated with 0.5 mm^3 doses of a host solution of **2c** (46.6 mM). Figs 3a and 4 show the chemical shifts of *S* and *R* enantiomers as a function of host concentration. Also, the change in the chemical shifts of enantiomers was determined (Fig. 3b) from the titration experiment. The Δδ was not large enough in the ^{1}H NMR spectra (Fig. 4) for a reliable indication of complexation and only data from ^{19}F NMR spectra were used. The Δδ change between *S* and *R* enantiomers as a function of host concentration (Fig. 3c) suggests that maximal resolution is obtained when the concentrations of host and guest are the same (2.0 mM, 1.0 equiv.), corresponding to 1 : 1 complexation. Also, a Job's

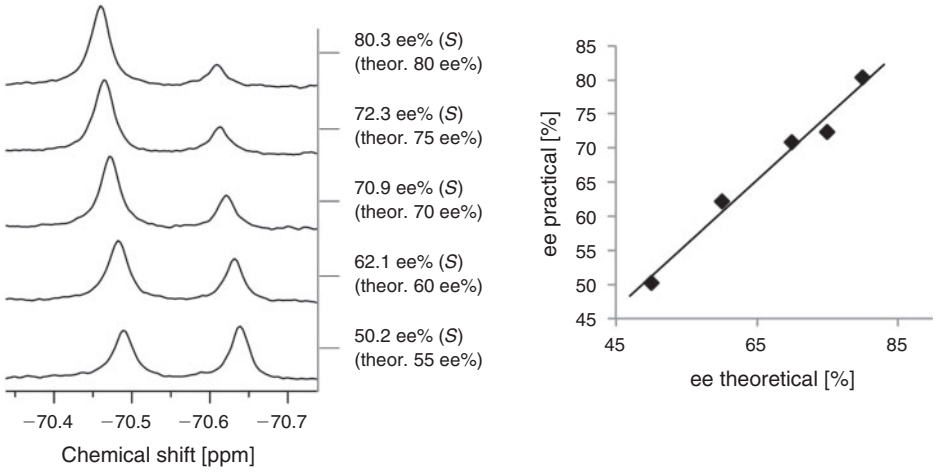


Fig. 5. Correlation between theoretical and experimental ee% values of enantiomerically enriched samples of **6** (**2c** used as chiral solvating agent) by ^{19}F NMR spectroscopy (470 MHz, $CDCl_3$, 27°C). Measured values are based on the peak areas from line fitting of the CF_3 peak.

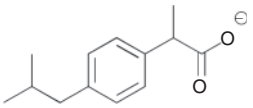
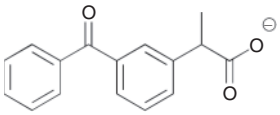
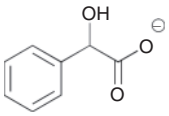
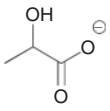
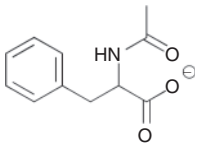
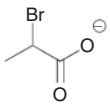
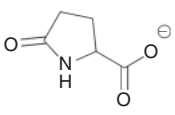
plot[18] based on data obtained from a titration experiment (Fig. 3d) confirmed the 1 : 1 complex stoichiometry.

The applicability of **2c** in ee measurements by NMR spectroscopy was investigated employing a solution of racemic **6** and enantiomerically pure *S*-**6** (2.0 mM). Mixtures of enantiomerically enriched samples were prepared in an NMR tube (0.5 cm^3, 1.0 equiv.) and **2c** (22.5 cm^3, 46.6 mM, 1.0 equiv.) was added. The determined ee% values are in line with the expected values (Fig. 5), showing that **2c** can be reliably used in ee determinations.

To obtain more information about the resolution behaviour of **2c,** its ability to discriminate between enantiomers of various α-substituted racemic carboxylic acids was studied. Acids were converted to their tetrabutylammonium salts, as **2c** showed better resolution towards ionic species, due to stronger interactions through ionic and hydrogen bonding. The experiments were performed by adding a solution of **2c** (46.6 mM, 22.5 cm^3, 1.0 equiv.) to a solution of the guest (2.0 mM, 0.5 cm^3, 1.0 equiv.). The results indicate (Table 2) that **2c** can resolve both aromatic and non-aromatic α-substituted carboxylic acids. The best resolution was obtained with **11** but no essential differences between the Δδ values of **7–10**, **12**, and **13** were detected. This is in contrast to a previous study[7a] suggesting that the presence of an aromatic ring (in the carboxylic acid) is necessary for good signal separation. In addition, **2c** not only resolved the proton at the chiral centre of **7,** but also the prochiral CH_2 and isopropyl groups. Such long-range effects are rare because usually only the nuclei close to the chiral centre and the nuclei adjacent to the site of association of the chiral reagent can be resolved.[1] The long-range effect may indicate the asymmetric shape of the pseudo-cavity present in the host (Fig. 2). According to the results, **2c** efficiently resolves chiral carboxylic acids with a large polar group at the α-position (e.g. **11**) or those with a crowded α-position (e.g. **6**).

Although the peaks of **7–10**, **12**, and **13** were not properly baseline-resolved (Δδ 2.3–4.8 Hz), the determinations of ee were nevertheless feasible with special techniques. For instance, the recently published pure shift experiments,[19,20] or *J*-resolved,[21] RESolved-TOCSY (RES-TOCSY),[22,10c] and ^1H homonuclear decoupling experiment (HOMODEC)[23,24]

Table 2. Determination of chiral discrimination of seven racemic tetrabutylammonium carboxylate salts in the presence of 2c, using ^1H NMR (500 MHz, $CDCl_3$, 27°C) spectroscopy

Compound	$[N_{4444}]^+$ salt of racemic carboxylic acid		Δδ [ppm]	Δδ [Hz]
7		Me	0.000	0.0
		$CHMe_2$	0.0096	4.8
		H	0.0087	4.4
		CH_2	0.006	3.0
8		Me	0.0065	3.2
		H	0.0047	2.3
9		H	0.0077	3.9
10		Me	0.000	0.0
		H	0.0055	2.8
11		Me	0.041	20.6
		H	0.000	0.0
		NH	0.019	9.7
12		Me	0.0021	1.1
		H	0.0033	1.6
13		H	0.0044	2.19

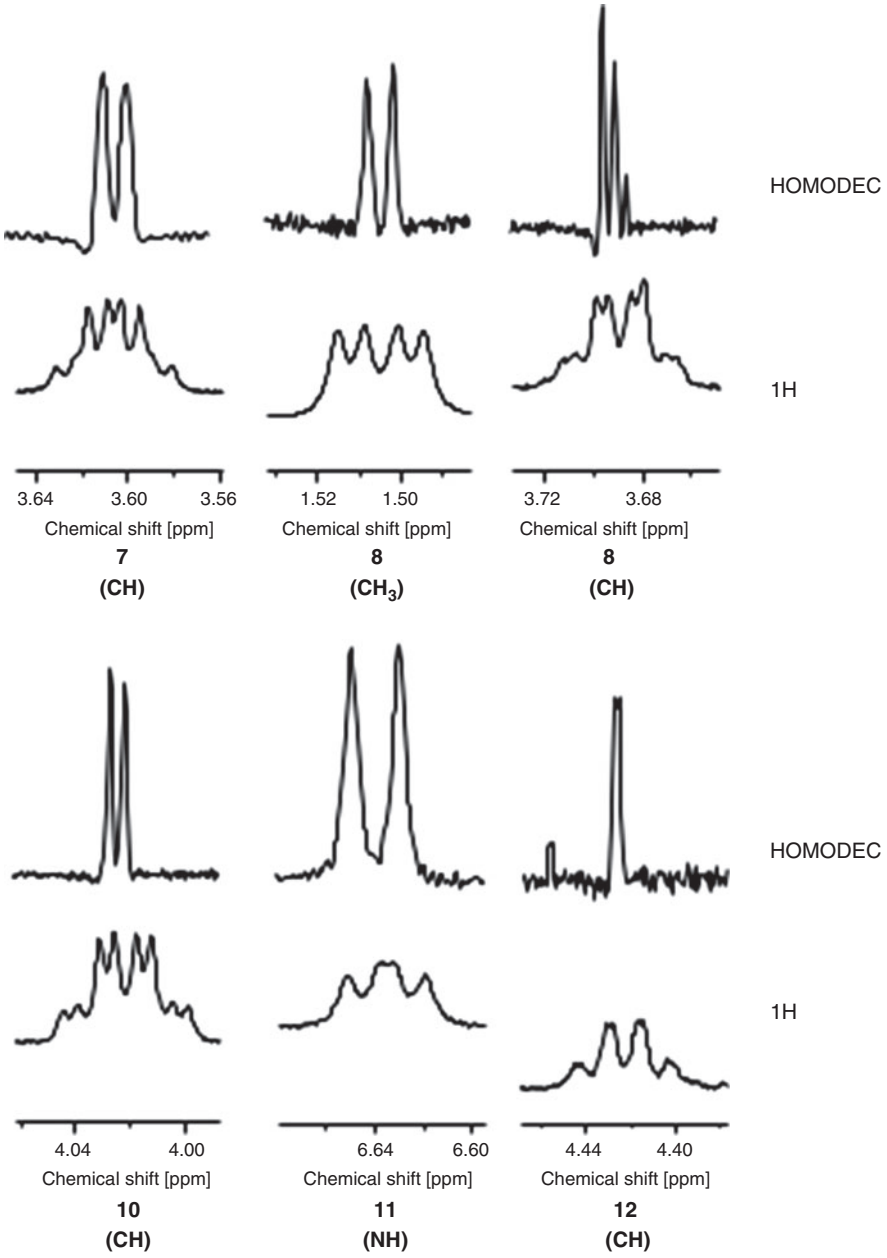


Fig. 6. HOMODEC spectra of carboxylic acids **7**, **8**, **10–12** with their ^{1}H spectra. All HOMODEC spectra have been processed by using Gaussian enhancement.

techniques can be used for ee determinations in cases where the baseline resolution is insufficient for integration in the ^{1}H NMR spectra. To demonstrate the use of specialised NMR techniques in situations where baseline resolution has not been achieved, we used a ^{1}H homonuclear decoupling experiment (HOMODEC) with carboxylic acids **7**, **8**, and **10–13** (Figs 6 and 7). In addition, we inspected the possible enantiomeric resolution of three carboxylic acids (**7**, **11**, **12**) by using HSQC (2.0 mM solution). Only in the case of **11** could resolution be detected (6.15 Hz, 0.049 ppm) (see Supplementary Material).

In HOMODEC, multiplicity can be simplified by decoupling one coupling partner (or more, depending on the hardware and software available). The advantage of HOMODEC compared with pure shift is that the former gives well-resolved spectra with low signal-to-noise ratio from low-molarity samples in shorter time (Fig. 7). In general, when using of these types of experiments (e.g. RES-TOCSY, pure shift, HOMODEC), the success of baseline resolution is dependent on the peak resolution and peak width. When resolution is higher than peak width (dependent on shimming quality, sample, and natural line width), baseline resolution can be achieved. When the peak width is larger than the achieved resolution, baseline resolution may be achieved by utilising window functions. However, there are some limitations that can be seen in the spectra of **8** (CH) and **12** (Fig. 6). In the cases where multiplicity edition does not work owing to overlap, techniques such as RES-TOCSY can be applied. Also, when HOMODEC-type experiments cannot be used owing to several coupling partners (carboxylic acid **13**) and hardware limitations, RES-TOCSY can be used for solving the problem (Fig. 7)

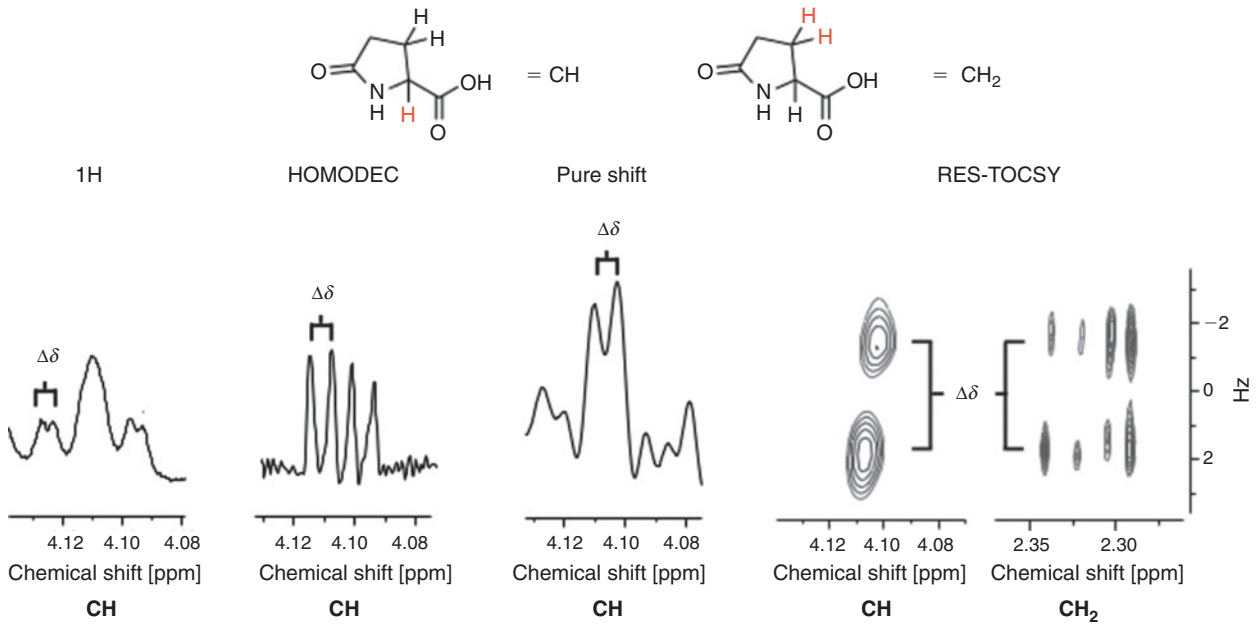


Fig. 7. Ordinary ^{1}H (~2 min), HOMODEC (~7 min), pure shift (~1 h), and RES-TOCSY (~1 h) NMR spectra from carboxylic acid **13** (2.0 mM solution).

Conclusions

New (+)-dehydroabietylimidazolium chiral solvating agents were synthesised and tested for the resolution of Mosher's acid (**5**) and its tetrabutylammonium salt (**6**). All nine cationic chiral solvating agents resolved **6** highly efficiently. The best resolution of the enantiomers of **6** was obtained with **2c**. The enantiomers of **5** were also resolved and gave better resolution in the ^{1}H NMR spectra compared with **6**, which was better resolved in the ^{19}F NMR spectra. The behaviour of **6** in resolution was further studied by titration, which indicated a 1 : 1 complexation between the host and guest. Further studies also showed that cationic chiral solvating agents such as **2c** can be expediently used for the determination of enantiomeric excesses of other chiral racemic carboxylates. The enantiomeric resolution of seven racemic α-substituted carboxylic acids was carried out with **2c**, showing that acids containing polar group(s) at the α-site can be resolved efficiently. Additionally, there is no strict requirement for the presence of an aryl substituent in the carboxylic acid, allowing a wider diversity of the guest substrates. The new (+)-dehydroabietylimidazolium chiral solvating agents constitute a biorenewable approach to ee determination.

Supplementary Material

Data of ^{1}H and ^{13}C NMR spectra and HSQC spectra of synthesised products **1a–4c** are available on the Journal's website.

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