Chiral ionic liquids derived from isosorbide: synthesis, properties and applications in asymmetric synthesis

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A novel class of chiral ammonium and imidazolium-based ionic liquids has been designed and synthesized using isosorbide as a biorenewable substrate. These chiral ionic liquids were found to catalyze the aza Diels–Alder reaction to give good yields and moderate diastereoselectivitives.

Introduction

Over the past decade, ionic liquids (ILs), or room temperature molten salts, have received considerable attention thanks to their ability to serve as effective reaction media for a wide range of organic reactions and other applications in chemistry.[1] By modifying the structure of the cations or anions of ionic liquids, it has been shown that their properties can be altered in order to influence the outcomes of reactions. Advances in IL use have made the development of chiral ionic liquids (CILs) a subject of intense study in recent years.[2] Although a limited number of CILs have been designed and synthesized, they have already found promising applications in asymmetric synthesis,[3] stereoselective polymerization,[4] chiral chromatography,[5] liquid crystal technologies,[6] chiral resolution, and as a NMR shift reagents.[7] Nowadays, the design and synthesis of novel CILs are growing rapidly. The study of CIL applications in asymmetric synthesis presents a challenge and an opportunity to researchers. It is, therefore, essential to synthesize different kinds of CILs from various starting materials derived from a chiral pool, especially from biorenewable sources.

We focused our attention on designing new chiral ammonium and imidazolium-based ionic liquids based on the structurally rigid bicyclic systems isosorbide **1**, also known as (3*R*, 3a*R*, 6*S*, 6a*R*)-hexahydrofuro[3,2-b]furan-3,6-diol, and isomannide **2**, (3*R*, 3a*R*, 6*R*, 6a*R*)-hexahydrofuro[3,2-b]furan-3,6-diol, which are renewable, and commercially available chiral carbohydrates. Isosorbide is basically two fused tetrahydrofuran rings with a *cis*-arrangement at the ring junction, giving a wedge-shaped molecule.[8] The compound bears two hydroxyl groups, one at C_6 having the *exo*-orientation with respect to the wedge-shaped molecule, and the other at C_3 having the endo-orientation, which makes intramolecular hydrogen bonding possible with the oxygen atom of the neighbouring tetrahydrofuran ring (Fig. 1). Isosorbide and isomannide are industrially obtained by dehydration of D-sorbitol and D-mannitol, and can therefore be considered as biomass products.[9] They are widely used in their nitrate ester forms in the pharmaceutical industry.[10] These commercial starting materials provide an easy and cost effective way to access optically pure functionalized compounds. Isosorbide has been used as a chiral auxiliary and chiral ligand in several reactions among which alkylation,[11] Diels–Alder reaction,[12] and asymmetric hydrogenation[13] are the most important. Surprisingly, in spite of their potential, to date, only a few ammonium CILs derived from isomannide have been reported.[14]

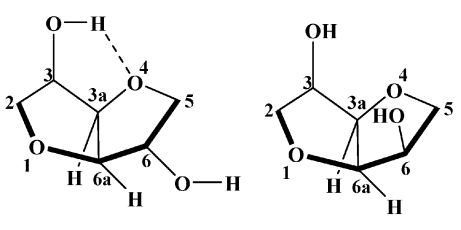
In a continuation of our research into the synthesis and applications of new CILs from inexpensive and commercially available natural chiral auxiliaries,[3a,i,15] we have managed to synthesize and formulate a novel class of chiral ammonium and imidazolium-based ionic liquids derived from isosorbide. We also report here some important physical properties of these new CILs and their application as a chiral reaction medium as well as catalyst for an asymmetric aza Diels–Alder reaction.

Results and discussion

Chiral ionic liquids: synthesis and characterisation

Our strategy is to protect one of the free hydroxyl groups as an ether while transforming the other into the ammonium or imidazolium function by nucleophilic substitution by a primary amine or *N*-methylimidazole. An anion exchange will be carried out to obtain the desired ILs.

Our synthesis was initiated by the selective monobenzylation of the hydroxyl group at the endo C_3 position, although very few protocols for isosorbide regioselective alkylation are reported in the literature.[16] In fact, the benzylation of isosorbide can lead to the formation of the three products,



1 2

Fig. 1 Structure of isosorbide **1** and isomannide **2**.

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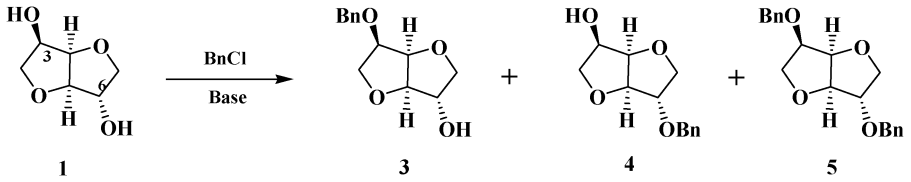


Scheme 1 Benzylation of isosorbide.

3-benzyl (endo) **3**, 6-benzyl (*exo*) **4** and 3,6-dibenzyl ethers **5**, in ratios depending on the experimental conditions (Scheme 1).[17]

The best yield (56%) of compound **3** was obtained when performing the reaction using 1 equivalent of benzyl chloride along with lithium hydride and lithium chloride in stoichiometric quantities. The free hydroxyl group at the *exo* C_6 position was then activated as its sulfonate by treatment with benzenesulfonyl chloride using an excess of triethylamine, affording the sulfonate **6** in 99% yield (Scheme 2). Subsequently, the sulfonate **6** was treated with an excess of primary aromatic and aliphatic amines in a sealed tube at 160 °C to give the corresponding amino ethers **7** *via* an S_N2 substitution reaction with complete inversion of configuration. Conversion of **7** to tertiary amines **8** was made by means of an Eschweiler–Clark reaction.[18] Generally speaking, the yields obtained were good. Amino ethers **8** were thereafter quaternized with iodomethane in refluxing dichloromethane to form the quaternary ammonium salts **9** in 85–98% yield (Scheme 2).

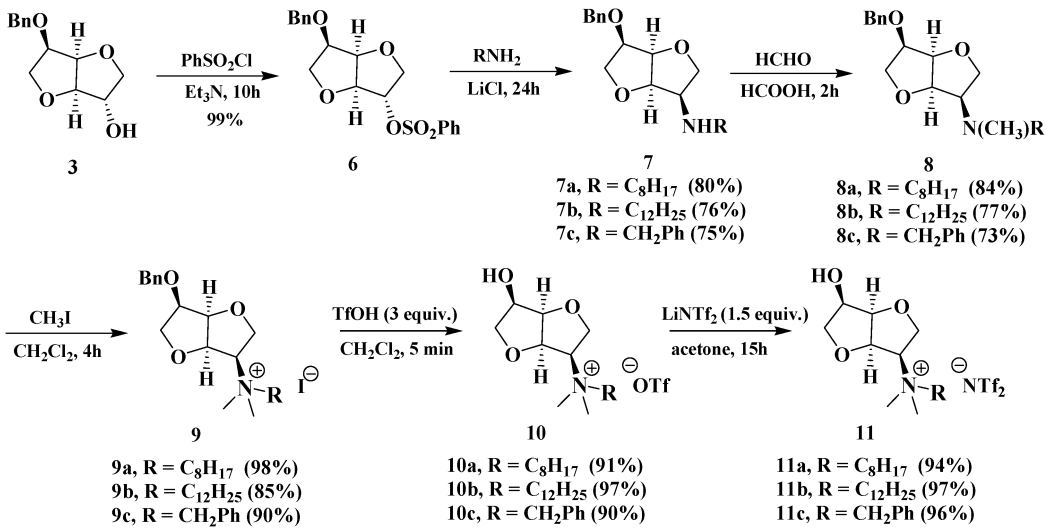
The next step in the synthesis was the transformation of ammonium iodide salts **9** into ionic liquids **10** by removing the benzyl protecting group at the endo C_3 position, followed by an anion exchange. Unfortunately, all attempts to remove the benzyl protecting group by hydrogenolysis or Lewis acid catalysis failed. In the course of our studies we found out that the use of trifluoromethanesulfonic acid in large excess in dichloromethane not only allows the cleavage of the benzyl ether protecting group but it also removes the iodide by triflate anion exchange. Ionic liquids **10** were obtained in good yields (90–97%) within a very short reaction time (5 min). On the other hand, the anion exchange of **10** with $LiNTf_2$ produced chiral ammonium *bis*(trifluoromethanesulfonyl)imides **11** in excellent yields.

We then proceeded to synthesize the chiral ammonium IL **17** in order to study the effect of 3-*exo*–6-*exo* combinations on prospective applications of these chiral ILs as new reaction media in asymmetric synthesis. Thus, ammonium salt **17** was synthesized from compound **4**, which was obtained in 40% yield by isosorbide monobenzylation (Scheme 1).[11] Using the same strategy previously described in Scheme 2, IL **17** was then obtained in 19% overall yield in 7 steps from isosorbide. Scheme 3 summarizes the synthesis of this new chiral IL.

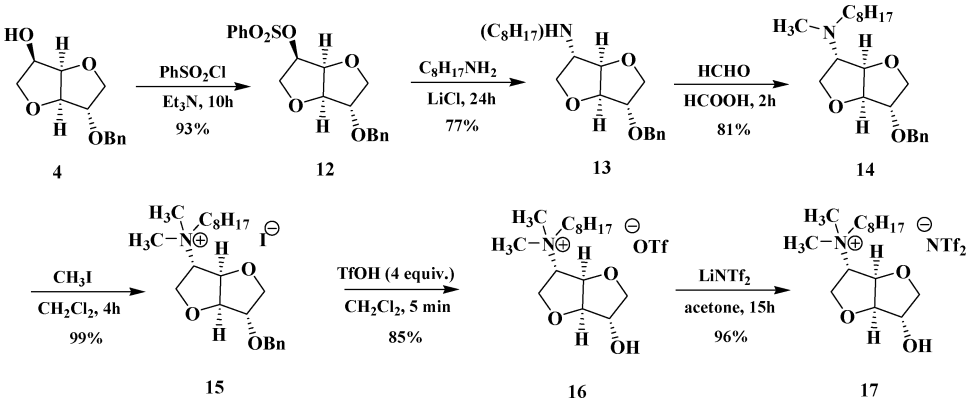
For the synthesis of imidazolium salts, using the same strategy shown in Scheme 2, the sulfonate **6** was converted to the imidazolium ether **18** by heating with a large excess of *N*-methylimidazole at 160 °C.[19] However, no product was detected even after 4 days.

We turned out our attention to the use of microwave irradiation. This technique has been developed in our laboratory and by other research groups, particularly for the synthesis of ILs.[15,20] The combination of solvent-free conditions and MW irradiation considerably reduces reaction time, enhances conversions as well as selectivity and sometimes enables the preparation of molecules which are impossible to synthesize under classic conditions.[21]

Many experiments were carried out by varying the number of equivalents of *N*-methylimidazole, the temperature and the reaction time as well as the addition of lithium salts (electrophilic assistance). The best result was obtained when performing the synthesis in a two-step but one-pot sequence reaction using solvent-free microwave activation conditions. The crude product (non isolated) resulting from the



Scheme 2 Synthesis of chiral ammonium ILs **9**, **10** and **11**.



Scheme 3 Synthesis of chiral ammonium IL **17**.

substitution reaction with 6 equivalents of *N*-methylimidazole at 130 °C for 4 h (first step) was directly submitted to an anion exchange step with KOTf at 90 °C for 20 min (Scheme 4). Purification by chromatography on alumina afforded the desired imidazolium salt **18** in 50% yield.

The last step in the synthesis is the removal of the benzyl ether protecting group using trifluoromethanesulfonic acid in dichloromethane. Ionic liquids **19** were obtained in good yields (97%) within a very short reaction time (5 min). It is noteworthy that these chiral imidazolium salts **18** and **19** are viscous liquids at room temperature (Scheme 4).

In view of the difficulty encountered in introducing the imidazolium skeleton on the isosorbide, it was decided to change the leaving group. It was imagined that a triflate group could be used, on the one hand as a very good leaving group, and on the other hand as an associated anion, allowing a synthesis step to be gained. The acetate seems to be the protecting group of choice. In fact, the monoacetylation of the isosorbide was already described and offers a better yield than the monobenzylation. This protecting group should resist the alkylation conditions and be removed with no difficulty in acid as well as basic media according to the stability of the synthesized ionic liquid. The synthesis of the ionic liquid **19** by this second method is represented in the Scheme 5.

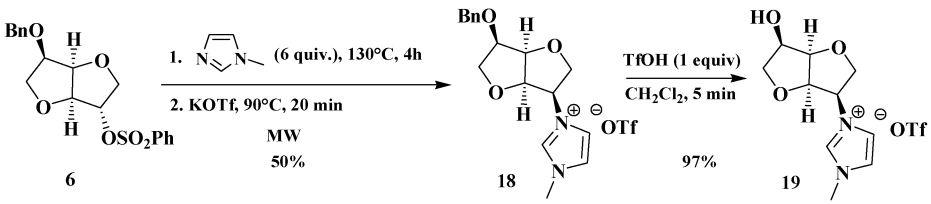
The first step of our synthesis was realized according to the reaction conditions reported by Stoss and co-workers.[22] After purification by chromatography on silica gel, we obtained the acetate derivative **20** with 70% of yield. The free hydroxyl group in the *endo* position of acetyl isosorbide **20** was then activated to the triflate form by action of triflic anhydride and pyridine in dichloromethane. The compound **21** was obtained with a quasi-quantitative yield. The triflate **21** was converted to imidazolium **22** by reaction with a slight excess of *N*-methylimidazole using no solvent at room temperature. The reaction was followed by TLC and indicated a total conversion after two days. Imidazolium **22** was isolated with 46% yield after purification by chromatography on alumina. It is again a S_N2 substitution reaction with complete inversion of configuration. This was established by ^{1}H NMR analysis based on the observation of the H_6–H_{6a} coupling constant (J^{cis} = 5 Hz and J^{trans} = 0 Hz) (Fig. 2). The doublet of H_{6a} in **21** became a doublet of doublets in **22**. Due to this inversion of configuration, the isosorbide skeleton was converted to isomannide.

The modest yield (40%) of this alkylation could be explained by the formation of a product of elimination. The compound **23** (Scheme 5) was indeed isolated with 30% yield, resulting from the elimination of the triflate **21**, which is a very good leaving group tending to be eliminated easily; especially since the carbocation, resulting from E1 elimination, must be stabilized in this ionic medium.

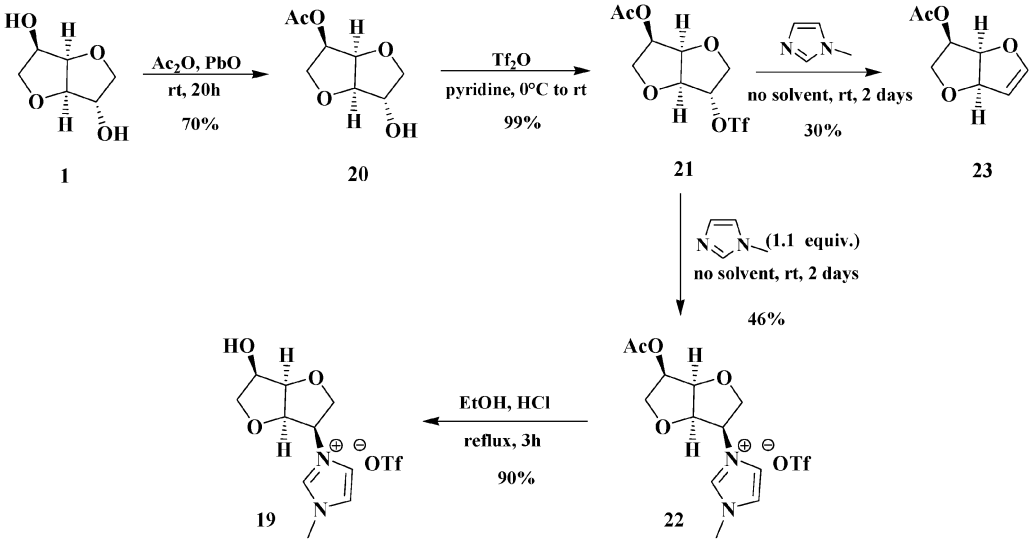
The next step in the synthesis is the transformation of the acetylated imidazolium **22** into ionic liquid **19** by removing the acetyl protecting group at the *endo* C_3 position. Thus, deacetylation was performed in ethanol in the presence of a drop of concentrated HCl to afford the CIL **19** with 90% yield (Scheme 5).

We then proceeded to synthesize the imidazolium CIL **25** possessing the methyl group in position 2 of *N*-methylimidazole. Using the same strategy previously described in Scheme 5, CIL **25** was then obtained in 25% overall yield in 4 steps from isosorbide. Scheme 6 summarizes the synthesis of this new chiral IL.

All of these CILs were characterized by ^{1}H and ^{13}C NMR spectroscopy, infrared (IR), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), optical rotation, high resolution mass spectroscopy (HRMS) and elemental analysis. Table 1 gives some physical properties of these CILs.



Scheme 4 Synthesis of imidazolium salts **18** and **19**.



Scheme 5 Synthesis of imidazolium salt **19**.

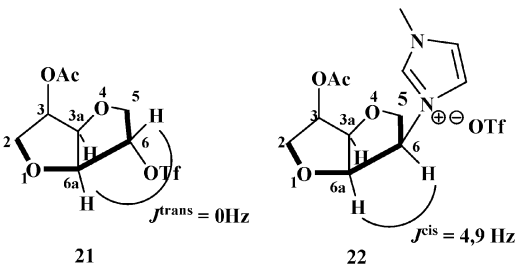


Fig. 2 Inversion of configuration confirmed by ^{1}H NMR.

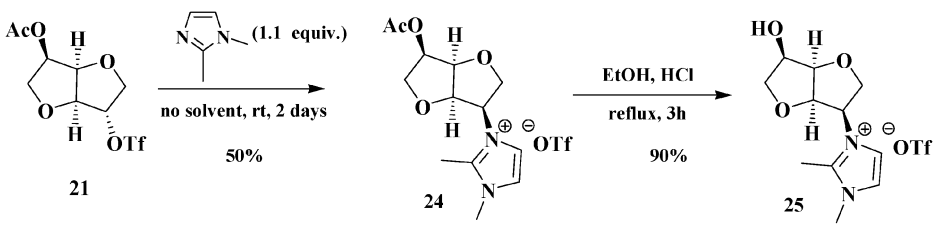
As can be seen from Table 1, most of these CILs are viscous liquids at room temperature, except the salt **10c** which is a solid with a melting point of 125 °C. Glass transition temperatures ranging from −51 to −15 °C were measured. All of these are found to be thermally stable up to 180 °C. In addition, good optical rotation was measured for all the CILs synthesized in the present work, indicating that the chirality of isosorbide has been retained in the CILs. It was observed that the chirality of all CILs remained unchanged even after 3 months or longer. This is different to some stereogenic centers in CILs, which have been reported to undergo racemization after a certain time.[23] Solubility and miscibility of these CILs depend on the alkyl chain length and the nature of the associated anion. Nevertheless, all of them are immiscible with ether and very miscible with methanol, dichloromethane or acetonitrile.

Before testing the potential of our CILs for asymmetric induction, it is advisable to make sure of their chemical stability. We proceeded to study some CILs behaviour in neutral, basic and acid aqueous media. Compounds **10a**, **11a** and **19** were chosen for this study. These compounds (30 mg) are not miscible with water; they will thus be solubilized in a small quantity of dichloromethane (30 μL). The solution was stirred with 1 mL of water distilled (neutral conditions) or with 1 mL of a saturated aqueous solution of potassium carbonate (basic conditions) or with 1 mL of a 2 N hydrochloric acid solution (acid conditions) for 2 h. For all compounds studied, after extraction of the aqueous phase by dichloromethane, dried over magnesium sulfate and concentrated under vacuum pressure, the same mass was found. ^{1}H NMR analysis and optical rotation data showed that they were intact, confirming their stability in neutral, basic and acid aqueous conditions.

Chiral ionic liquids: applications in catalysis

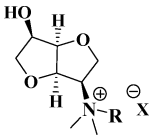
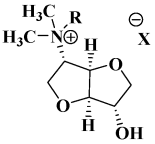
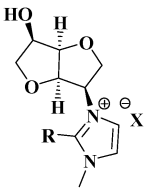
After achieving the synthesis of these ILs that contain a chiral moiety and a free hydroxyl functional group, we were interested in testing their potential for asymmetric induction. To that end, as a model reaction, we studied the asymmetric aza Diels–Alder reaction of Danishefsky's diene **26** with a chiral imine **27** in the presence of CIL (Scheme 7, Table 2). This reaction has proved to perform better at room temperature in ionic liquid without either Lewis acid catalyst or organic solvent[24] and with significant diastereoselectivity using an ephedrinium-based ionic liquid.[3i]

The results summarized in Table 2 shown that ammonium or imidazolium CILs could catalyze the aza Diels–Alder reaction. Good yields and significant diastereoselectivities

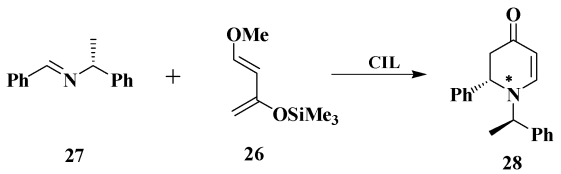


Scheme 6 Synthesis of CIL **25**.

Table 1 Properties of CILs[a]

CIL structure	R	X	CIL	T_d/°C[b]	T_m/°C[c]	T_g/°C[d]
	C_8H_{17}	OTf	**10a**	195	40	−33
		NTf_2	**11a**	180	nd	−49
	$C_{12}H_{25}$	OTf	**10b**	192	45	−51
		NTf_2	**11b**	180	nd	−47
	CH_2Ph	OTf	**10c**	210	125	−15
		NTf_2	**11c**	200	nd	−29
	C_8H_{17}	OTf	**16**	204	42	−15
		NTf_2	**17**	198	nd	−35
	H	OTf	**19**	210	nd	−40
	CH_3		**25**	214	nd	−45

[a] For optical rotation: see experimental section. [b] Decomposition temperature (T_d) was determined by thermogravimetric analysis, heating at 10 °C min^{-1}. [c] Melting point (T_m) was determined by differential scanning calorimetry, heating at 10 °C min^{-1}. nd: not detected. [d] Glass transition temperature (T_g) was determined by differential scanning calorimetry, heating at 10 °C min^{-1}.



Scheme 7 Asymmetric aza Diels–Alder reaction of Danishefsky's diene **26** with imine **27**.

are obtained when performing the experiments with 0.5 equivalents of IL and 1.5 equivalents of Danishefsky's diene at room temperature for 5 h. The two diastereomers obtained were separated by column chromatography and the assignment of the absolute configuration of the major product **28** was determined by comparison of its optical rotation and NMR spectral data with the reported values.[25]

As mentioned in the literature, the presence of the hydroxyl group is very important for reactivity and especially for chirality transfer. This fact has already been reported by Colonna and co-workers[26] in the borohydride asymmetric reduction of carbonyl compounds using a chiral phase-transfer catalyst. This observation is also supported by our studies on the asymmetric Baylis–Hillman reaction.[3a] On the other hand, the imidazolium functionality can catalyze the Diels–Alder reaction thanks to the formation of hydrogen bonds between the mobile hydrogen in position 2 of imidazolium and the substrate as observed by Welton and co-workers.[27] Thus, when isosorbide **1** was used as a chiral source without Lewis acid catalyst, no product was observed (Table 2, entry 9), a fact already mentioned in the literature.[28] On the other hand, when the hydroxyl group of the CIL **11a** or **19** was protected with a benzyl group (compounds **29** or **18**) or an acetyl group (compounds **22**), approximately 60% de but with only around 30% yield was achieved (Table 2, entries 3, 4 and 6). The CILs **11a** and **19** turn out to catalyze in an effective way the reaction. The best yields and diastereoselectivities were thus observed. CILs are highly recyclable and do not lose any of their properties even when used four consecutive times (Table 2, entry 1 and 5). However, in the case of the CIL **24**, only 5% yield was obtained, showing a loss of catalytic reactivity due to the complete absence of mobile hydrogen on the hydroxyl function or the imidazolium nucleus. No hydrogen bonding could be formed in this case (Table 2, entry 8). Finally, only 32% de was obtained when we used the chiral imine in the presence of $ZnCl_2$ as Lewis acid catalyst (Table 2, entry 10).

These results confirmed that not only may CILs be used as catalysts but they also play the role of chiral inductors in the asymmetric aza Diels–Alder reaction. The key to effective asymmetric induction is the existence of strong intermolecular interactions, like electrostatic attraction and hydrogen bonding, between ionic solvents and intermediates or transition states on the diastereoselective reaction pathway. This observation was made by our group[3a] and further confirmed by Leitner and co-workers.[3e]

With these results in hand, we proceeded to examine the CIL effects on the reaction. To this end, a series of tests using the chiral ammonium salts with different combinations of alkyl chain length and associated anion were carried out. The best result (75% yield and 65% de) was obtained with R = C_8H_{17}. A drop in yield and in diastereoselectivity were observed with R = $C_{12}H_{25}$ and CH_2Ph (Table 3, entries 1, 3 and 5). No interpretation of these obtained results is suggested.

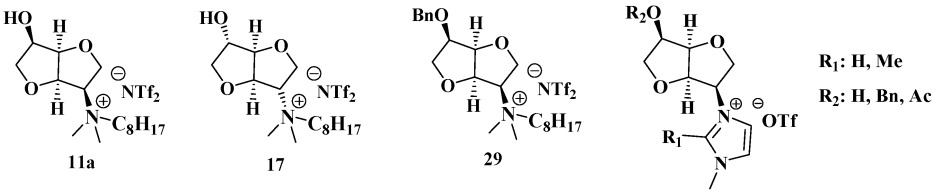
Generally speaking, better yields were observed when using OTf as opposed to NTf_2 as the associated anion. In addition, for the same alkyl chain length, a slight drop in de was detected with NTf_2. The anion nature has a significant influence on the catalytic reactivity and the asymmetric induction of this reaction. The results obtained are shown in Table 3.

Therefore, our preliminary studies on the application of these CILs for the aza Diels–Alder reaction showed that the chiral reaction medium has a significant influence on chiral induction. Further investigations to provide useful insight into the understanding of the use of these CILs in asymmetric induction are in progress in our laboratory. The results of these studies will be communicated in due course.

Conclusion

In summary, we have designed and synthesized a novel family of chiral ammonium and imidazolium-based ionic liquids that contain a chiral moiety and a hydroxyl function derived from isosorbide. The synthesis of these ionic liquids is easy and practical due to the commercially inexpensive and readily available starting materials. We have also reported some physical properties of these new CILs. These CILs can serve as chiral reaction media as well as catalysts in the asymmetric aza Diels–Alder reaction. Further improvements to the

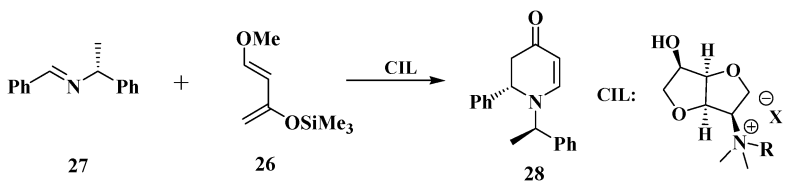
Table 2 Asymmetric aza Diels–Alder reaction of Danishefsky's diene **26** with imine **27**. Conditions[a]: imine **27**:diene **26**:CIL = 1:1.5:0.5; temperature: 30 °C; time: 5 h



Entry	CIL	R_1	R_2	Isolated yield **28** (%)	de **28**[b] (%)
1	**11a**			73 (75, 73, 75)[e]	63 (65, 62, 64)[e]
2	**17**			56	60
3	**29**			33	59
4	**18**	H	Bn	39	60
5	**19**		H	74 (74, 75, 73)[e]	68 (66, 67, 68)[e]
6	**22**		Ac	25	59
7	**25**	Me	H	40	65
8	**24**		Ac	5	69
9	**1**[c]			0	0
10	No CIL[d]			60	32

[a] Diene added into reaction medium in three phases: 0.5 equiv. at equal intervals. [b] de determined by chiral HPLC with a margin of error about 1%. [c] Compound **1** (1 equiv.) was used as a chiral source. [d] $ZnCl_2$ (10 mol%) added. [e] results obtained by reaction with recycled IL are given in brackets.

Table 3 Symmetric aza Diels–Alder reaction of Danishefsky's diene **26** with imine **27**. Conditions[a]: imine **27**:diene **26**:CIL = 1:1.5:0.5; temperature: 30 °C; time: 5 h



Entry	CIL	R	X	Isolated yield **28** (%)	de **28**[b] (%)
1	**10a**	C_8H_{17}	OTf	75	65
2	**11a**		NTf_2	41	54
3	**10b**	$C_{12}H_{25}$	OTf	56	55
4	**11b**		NTf_2	40	54
5	**10c**	CH_2Ph	OTf	48	54
6	**11c**		NTf_2	38	52

[a] Diene added into reaction medium in three phases: 0.5 equiv. at equal intervals; [b] de determined by chiral HPLC with a margin of error of about 1%.

application of CILs in asymmetric synthesis are currently underway in our laboratory.

Experimental

General information

Melting points were measured on a Kofler bank. The NMR spectra were recorded in $CDCl_3$, DMSO-d_6, MeOD-d_4 or in acetone-d_6. ^{1}H NMR spectra were recorded at 360 or 250 MHz. The chemical shifts (δ) are reported in parts per million relative to TMS as internal standard. J values are given in Hz. ^{13}C NMR spectra were recorded at 90 or 62.5 MHz. IR spectra were recorded on a FT-IR Perkin–Elmer instrument. TLC experiments were carried out in 0.2 mm thick silica gel plates (GF_{254}) and visualization 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 synthesis of compounds 6 and 12

A mixture of the alcohol **3** (or **4**) (65 mmol, 15.4 g), triethylamine (390 mmol, 55 mL) and benzenesulfonyl chloride (78 mmol, 10 mL) was stirred under an argon atmosphere for 10 h. The reaction mixture was diluted with water (200 mL), acidified with 5 N HCl (60 mL) and the hydrolysis was continued for a further 2 h. The resulting mixture was extracted with dichloromethane (3 × 120 mL). The organic phases were washed with brine, dried over anhydrous $MgSO_4$,

and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (heptane : ethyl acetate = 1 : 1) to afford **6** (or **12**).

(3*R*, 3*aR*, 6*S*, 6*aS*)-3-(benzyloxy)hexahydrofuro[3,2-b]furan-6-yl benzenesulfonate (6). Yield: 99%; white crystals, mp: 93–95 °C; $[\alpha]_D^{25}$ = +92.7 (*c* = 0.25, $CHCl_3$); IR (neat) υ = 3065, 3032, 2877, 1449, 1367, 1189, 1100, 1043, 971, 947, 902, 820, 750 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.57 (dd, *J* = 7.6; 9.0 Hz, 1H), 3.82 (dd, *J* = 6.6 and 9.0 Hz, 1H), 3.95–4.08 (m, 3H), 4.52 (d, *J* = 4.3 Hz, 1H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.68 (dd, *J* = 4.3 and 5.0 Hz, 1H), 4.73 (d, *J* = 12.0 Hz, 1H), 4.91 (m, 1H), 7.26–7.40 (m, 5H, benzyl), 7.54–7.71 (m, 3H, phenyl), 7.91–7.97 (m, 2H, phenyl). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 70.5 (CH_2), 72.5 (CH_2), 73.2 (CH_2), 78.9 (CH), 80.6 (CH), 84.2(CH), 85.8 (CH), 127.8, 127.9, 128.0, 128.5, 129.5, 134.1 (10 CH_{Ar}), 136.3 (C), 137.5 (C); anal. calcd for $C_{19}H_{20}O_6S$: C, 60.62; H, 5.36; O, 25.50; S, 8.52; found: C, 60.54; H, 5.25; O, 25.41; S, 8.49.

(3*S*, 3*aR*, 6*R*, 6*aS*)-3-(benzyloxy)hexahydrofuro[3,2-b]furan-6-yl benzenesulfonate (12). Yield: 93%; yellowish oil; $[\alpha]_D^{25}$ = +100.6 (*c* = 0.50, $CHCl_3$); IR (neat) υ = 3063, 2874, 1449, 1365, 1188, 1097, 1043, 1008, 972, 911, 850, 824 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.68 (dd, *J* = 6.3 and 9.2 Hz, 1H), 3.75–3.83 (m, 2H), 3.94 (d, *J* = 10.8 Hz, 1H), 4.00 (d, *J* = 3.2 Hz, 1H), 4.44–4.46 (m, 3H), 4.56 (dd, *J* = 4.0 and 5.8 Hz, 1H), 4.86 (q, *J* = 6.0 Hz, 1H), 7.20–7.30 (m, 5H, benzyl), 7.46 (t, *J* = 7.6 Hz, 2H, phenyl), 7.57 (t, *J* = 7.6 Hz, 1H, phenyl), 7.90 (d, *J* = 8.6 Hz, 2H, phenyl). ^{13}C NMR (90 MHz, $CDCl_3$) δ 68.8 (CH_2), 70.7 (CH_2), 72.9 (CH_2), 78.8 (CH), 79.7 (CH), 82.7 (CH), 85.3 (CH), 127.1, 127.3, 127.9, 128.8 (8 CH_{Ar}), 133.6 (2 CH_{Ar}), 135.7 (C), 137.1 (C); anal. calcd for $C_{19}H_{20}O_6S$: C, 60.62; H, 5.36; O, 25.50; S, 8.52, found: C, 60.65; H, 5.39; O, 25.38; S, 8.39.

General procedure for the synthesis of compounds 7a–c and 13

A solution of the sulfonate **6** (or **12**) (64 mmol), freshly distilled amine (386 mmol) and lithium chloride (32 mmol) was heated at 160 °C in a sealed tube for 24 h. The contents were cooled to room temperature and the excess of amine was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2 : MeOH = 98 : 2) to afford **7a–c** (or **13**) as a yellowish oil (75–80%)

(3*R*, 3*aR*, 6*R*, 6*aS*)-6-benzyloxy-3-(octylamino)hexahydrofuro[3,2-b]furan (7a). Yield: 80%; $[\alpha]_D^{[25]}$ = +123.5 (*c* = 1.83, $CHCl_3$); IR (neat) υ = 3322, 3064, 3031, 2926, 2855, 1496, 1455, 1367, 1309, 1207, 1143, 1084, 1027, 826, 736, 698 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.87 (t, *J* = 6.7 Hz, 3H), 1.20–1.40 (m, 10H), 1.40–1.60 (m, 2H), 1.96 (s br, NH), 2.47–2.57 (m, 1H), 2.63–2.73 (m, 1H), 3.25–3.43 (m, 2H), 3.62 (dd, *J* = 8.0 and 8.5 Hz, 1H), 3.88 (dd, *J* = 8.5 and 6.75 Hz, 1H), 4.00–4.05 (m, 1H), 4.12 (dd, *J* = 7.5 and 7.25 Hz, 1H), 4.43 (dd, *J* = 4.25 and 4.5 Hz, 1H), 4.51 (d, *J* = 11.5 Hz, 1H), 4.57 (dd, *J* = 4.5 and 4.5 Hz, 1H), 4.72 (d, *J* = 11.5 Hz, 1H), 7.25–7.45 (m, 5H phenyl). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.7 (CH_3), 22.3 (CH_2), 26.9 (CH_2), 28.9 (CH_2), 29.1 (CH_2), 30.2 (CH_2), 31.4 (CH_2), 48.3 (CH_2), 62.7 (CH), 70.9 (CH_2), 72.0 (CH_2), 72.4 (CH_2), 79.6 (CH), 80.1 (CH), 80.8 (CH), 127.4, 127.5, 128.0 (5 CH_{Ar}), 137.5 (C); HRMS (MH^+) *m*/*z* (%) calcd for $[C_{21}H_{33}NO_3]^+$: 348.2533, found: 348.2539.

(3*R*, 3*aR*, 6*R*, 6*aS*)-6-benzyloxy-*3*-(docecylamino)hexahydrofuro[3,2-b]furan (7b). Yield: 76%; Yellowish oil; $[\alpha]_D^{20}$ = +99.9 (*c* = 3.91, $CHCl_3$); IR (neat) υ = 3321, 2924, 2853, 1674, 1496, 1466, 1456, 1367, 1309, 1206, 1142, 1071, 1084, 970, 825, 735, 698 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.2 Hz, 3H), 1.20–1.36 (m, 18H), 1.43–1.53 (m, 2H), 1.90 (s br, NH), 2.51–2.58 (m, 1H), 2.66–2.73 (m, 1H), 3.30–3.36 (m, 1H), 3.41 (dd, *J* = 10.1 and 8.0 Hz, 1H), 3.64 (dd, *J* = 7.9 and 8.3 Hz, 1H), 3.91 (dd, *J* = 6.1 and 8.3 Hz, 1H), 4.05–4.11 (m, 1H), 4.14 (dd, *J* = 8.0 and 7.2 Hz, 1H), 4.46 (dd, *J* = 4.3 and 4.3 Hz, 1H), 4.54 (d, *J* = 12.8 Hz, 1H), 4.61 (dd, *J* = 4.3 and 4.7 Hz, 1H), 4.75 (d, *J* = 12.8 Hz, 1H), 7.23–7.40 (m, 5H phenyl). ^{13}C NMR (90 MHz, $CDCl_3$) δ 13.8 (CH_3), 22.4 (CH_2), 27.0 (CH_2), 29.1 (CH_2), 29.4 (5 CH_2), 30.3 (CH_2), 31.6 (CH_2), 48.4 (CH_2), 62.8 (CH), 71.0 (CH_2), 72.1 (CH_2), 72.4 (CH_2), 79.7 (CH), 80.2 (CH), 80.9 (CH), 127.6, 128.1 (5 CH), 137.6 (C); anal. calcd for $C_{25}H_{41}NO_3$: C, 74.40; H, 10.24; N, 3.47; O, 11.89, found: C, 74.26; H, 10.21; N, 3.48; O, 12.09.

(3*R*, 3*aR*, 6*R*, 6*aS*)-3-benzylamino-6-(benzyloxy)hexahydrofuro[3,2-b]furan (7c). Yield: 75%; yellowish oil; $[\alpha]_D^{20}$ = +145.3 (*c* = 1.47, $CHCl_3$); IR (neat) υ = 3321, 3087, 3062, 3029, 2942, 2871, 1955, 1880, 1815, 1695, 1604, 1586, 1496, 1463, 1455, 1367, 1312, 1259, 1206, 1136, 1084, 1045, 1027, 970 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.27 (s br, NH), 3.27–3.46 (m, 2H), 3.62 (dd, *J* = 7.7 and 8.5 Hz, 1H), 3.72 (d, *J* = 12.3 Hz, 1H), 3.85 (d, *J* = 12.3 Hz, 1H), 3,87 (dd, *J* = 8.5 and 6.8 Hz, 1H), 3.98–4.11 (m, 2H), 4.40 (dd, *J* = 4.0 and 4.3 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.51–4.54 (m, 1H), 4.71 (d, *J* = 12.0 Hz, 1H), 7.14–7.40 (m, 10H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 52.3 (CH_2), 62.1 (CH), 71.1 (CH_2), 72.4 (CH_2), 72.6 (CH_2), 79.8 (CH), 80.2 (CH), 81.1 (CH), 127.0, 127.8, 128.0, 128.3 (10 CH_{Ar}), 137.7 (C), 140.0 (C); anal. calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30, O, 14.75, found: C, 73.52; H, 7.11; N, 4.46; O, 14.77.

(3*S*, 3*aR*, 6*S*, 6*aS*)-6-benzyloxy-3-(octylamino)hexahydrofuro[3,2-b]furan (13). Yield: 77%; yellowish oil; $[\alpha]_D^{25}$ = +21.8 (*c* = 0.5, $CHCl_3$); IR (neat) υ = 3315, 3064, 3031, 2926, 2855, 1497, 1455, 1366, 1341, 1207, 1082, 1029, 857, 914, 841, 783, 735, 697 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.5 Hz, 3H), 1.20–1.35 (m, 10H), 1.40–1.50 (m, 2H), 2.60–2.65 (m, 2H), 3.25–3.30 (m, 1H), 3.66 (dd, *J* = 2.7 and 9.6 Hz, 1H), 3.85–3.90 (m, 3H), 4.03–4.06 (m, 1H), 4.51–4.64 (m, 4H), 7.25–7.35 (m, 5H phenyl). ^{13}C NMR (90 MHz, $CDCl_3$) δ 13.9 (CH_3), 22.5 (CH_2), 27.1 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 30.0 (CH_2), 31.7 (CH_2), 48.0 (CH_2), 64.7 (CH), 71.3 (CH_2), 72.0 (CH_2), 72.8 (CH_2), 82.9 (CH), 85.4 (CH), 87.0 (CH), 127.6, 128.3 (5 CH_{Ar}), 137.5 (C); anal. calcd for $C_{21}H_{33}NO_3$: C, 72.58; H, 9.57; O, 13.81; N, 4.03, found: C, 72.52; H, 9.61; O, 13.91; N, 4.02.

General procedure for the synthesis of compounds 8a–c and 14

To a solution of formaldehyde (79 mmol), and formic acid (79 mmol) was added at 0 °C the secondary amine 7 (or **13**)

(49 mmol). After being refluxed for 2 h, the reaction mixture was allowed to warm at 0 °C and 5 N HCl (64 mmol) was added. Water and the excess formic acid were removed under reduced pressure. The residue was treated with excess 2 N NaOH (98 mmol) and the aqueous phase was extracted with ethyl acetate (3 × 60 mL). The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, and then concentrated under reduced pressure. The resulting residue was finally purified by flash column chromatography on silica gel (CH_2Cl_2 then EtOAc) to afford **8a–c** (or **14**) as a yellowish oil or white solid (73–84%).

(3*R*, 3*aR*, 6*R*, 6*aS*)-6-benzyloxy-3-(*N*-methyl-*N*-octylamino)-hexahydrofuro[3,2-b]furan (8a). Yield: 84%; yellowish oil $[\alpha]_D^{25}$ = +95.8 (*c* = 2.40, $CHCl_3$); IR (neat) υ = 3031, 2928, 2855, 2788, 1496, 1455, 1368, 1304, 1208, 1134, 1087, 1026, 823, 735, 698 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.87 (t, *J* = 6.4 Hz, 3H), 1.16–1.36 (m, 10H), 1.40–1.60 (m, 2H), 2,32 (s, 3H), 2.37–2.57 (m, 2H), 2.83–2.91 (m, 1H), 3.75 (dd, *J* = 10.5 and 8.5 Hz, 1H), 3.79 (dd, *J* = 9.0 and 8.0 Hz, 1H), 3.95 (dd, *J* = 6.25 and 9.0 Hz, 1H), 4.04–4.15 (m, 2H), 4.48 (dd, *J* = 3.75 and 3.75 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.60 (dd, *J* = 3.75 and 3.75 Hz, 1H), 4.72 (d, *J* = 12.0 Hz, 1H), 7.25–7.40 (m, 5H phenyl). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.0 (CH_3), 22.5 (CH_2), 25.0 (CH_2), 27.5 (CH_2), 29.1 (CH_2), 29.4 (CH_2), 31.7 (CH_2), 40.7 (CH_3), 56.7 (CH_2), 69.1 (CH), 71.1 (CH_2), 72.3 (2 CH_2), 79.6 (CH), 81.3 (CH), 81.6 (CH), 127.7, 128.3 (5 CH_2), 137.7 (C); HRMS (MH^+) *m*/*z* (%) calcd for $[C_{22}H_{35}NO_3]^+$: 362.2690, found: 362.2692.

(3*R*, 3*aR*, 6*R*, 6*aS*)-6-benzyloxy-3-(*N*-dodecyl-*N*-methylamino)-hexahydrofuro[3,2-b]furan (8b). Yield: 77%; yellowish oil; $[\alpha]_D^{20}$ = +89.9 (*c* = 0.89, $CHCl_3$); IR (neat) υ = 3064, 3031, 2925, 2853, 2788, 1496, 1466, 1455, 1368, 1342, 1304, 1237, 1207, 1134, 1087, 1073, 1026, 735, 698 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.7 Hz, 3H), 1.14–1.36 (m, 18H), 1.44–1.54 (m, 2H), 2.31 (s, 3H), 2.38–2.51 (m, 2H), 2.82–2.88 (m, 1H), 3.73–3.81 (m, 2H), 3.94 (dd, *J* = 9.0 and 6.8 Hz, 1H), 4.04–4.13 (m, 2H), 4.47 (dd, *J* = 4.3 and 3.6 Hz, 1H), 4.56 (d, *J* = 12.2 Hz, 1H), 4.59–4.61 (m, 1H), 4.72 (d, *J* = 12.2 Hz, 1H), 7.25–7.42 (m, 5H phenyl). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.9 (CH_3), 22.5 (CH_2), 25.0 (CH_2), 27.4 (CH_2), 29.1 (CH_2), 29.4 (5 CH_2), 31.7 (CH_2), 40.7 (CH_3), 56.7 (CH_2), 69.2 (CH), 71.1 (CH_2), 72.2 (2 CH_2), 79.5 (CH), 81.2 (CH), 81.6 (CH), 127.6, 128.2 (5 CH_{Ar}), 137.6 (C); HRMS (M-H) *m*/*z* (%) calcd for $[C_{26}H_{43}NO_3]$: 417.3237, found: 417.3233.

(3*R*, 3*aR*, 6*R*, 6*aS*)-3-(*N*-benzyl-*N*-methylamino)-6-(benzyloxy)-hexahydrofuro[3,2-b]furan (8c). Yield: 73%; White solid; mp: 54–55 °C; $[\alpha]_D^{20}$ = +119.7 (*c* = 1.09, $CHCl_3$); IR (neat) υ = 3086, 3062, 3029, 2944, 2874, 2788, 1495, 1454, 1367, 1304, 1208, 1133, 1110, 1087, 1073, 1040, 937, 913, 891, 849, 823, 741 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.24 (s, 3H), 2.86–2.94 (m, 1H), 3.52 (d, *J* = 13.2 Hz, 1H), 3.72–3.87 (m, 3H), 3.98 (dd, *J* = 6.5 and 8.8 Hz, 1H), 4.05–4.18 (m, 2H), 4.54–4.63 (m, 3H), 4.74 (d, *J* = 12.3 Hz, 1H), 7.20–7.40 (m, 10H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 40.6 (CH_3), 60.7 (CH_2), 68.6 (CH), 71.1 (CH_2), 71.9 (CH_2), 72.1 (CH_2), 79.3 (CH), 80.9 (CH), 81,5 (CH), 126.9, 127.6, 127.9, 128.1, 129.2 (10 CH_{Ar}), 137.2 (C), 137.6 (C); anal. calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13, O, 14.14, found: C, 74.16; H, 7.23; N, 4.17; O, 14.07.

(3*S*, 3*aR*, 6*S*, 6*aS*)-6-benzyloxy-3-(*N*-methyl-*N*-octylamino)-hexahydrofuro[3,2-b]furan (14). Yield: 81%; yellowish oil; $[\alpha]_D^{25}$ = +30.1 (*c* = 0.50, $CHCl_3$); IR (neat) υ = 3065, 3031, 2965, 2855, 2798, 1497, 1455, 1367, 1340, 1312, 1207, 1084, 1045, 941, 959, 919, 772, 735, 697 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.20–1.40 (m, 10H), 1.40–1.58 (m, 2H), 2.23 (s, 3H), 2.26–2.32 (m, 1H), 2.47–2.55 (m, 1H), 2.92–2.98 (m, 1H), 3.64 (dd, *J* = 7.7 and 8.5 Hz, 1H), 3.83–3.92 (m, 2H), 3.98–4.02 (m, 2H), 4.51–4.61 (m, 3H), 4.64–4.67 (m, 1H), 7.25–7.45 (m, 5H phenyl). ^{13}C NMR (90 MHz, $CDCl_3$) δ 13.8 (CH_3), 22.4 (CH_2), 26.8 (CH_2), 27.1 (CH_2), 29.0 (CH_2), 29.2 (CH_2), 31.5 (CH_2), 39.3 (CH_3), 55.4 (CH_2), 70.8 (CH_2), 71.0 (CH_2), 71.3 (CH), 71.5 (CH_2), 82.8 (CH), 85.6 (CH), 86.3 (CH), 127.4, 128.1 (5 CH_{Ar}), 137.4 (C); anal. calcd for $C_{22}H_{35}NO_3$: C, 73.09; H, 9.76; O, 13.28; N, 3.87, found: C, 72.94; H, 9.88; O, 12.99; N, 3.81.

General procedure for the synthesis of compounds 9a–c and 15

To a solution of the amine **8** (or **14**) (41 mmol) in dichloromethane (100 mL) was added iodomethane (2.8 mL, 45 mmol). After refluxing the mixture for 4 h the solvent was removed under reduced pressure. The residue was washed with ether to give **9a–c** (or **15**) as an orange oil or white solid (85–98%). The products were used for the next step directly without further purification.

(3*R*, 3*aR*, 6*R*, 6*aS*)-*N*-[6-(benzyloxy)hexahydrofuro[3,2-b]-furan-3-yl]-*N*,*N*-dimethyl-*N*-octylammonium iodide (9a). Yield: 98%; Orange oil; $[\alpha]_D^{25}$ = +67.2 (*c* = 5.29, $CHCl_3$); IR (neat) υ = 3460, 2954, 2926, 2857, 1455, 1372, 1135, 1104, 1027 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.7 Hz, 3H), 1.20–1.43 (m, 10H), 1.75–1.90 (m, 2H), 3.38 (s, 3H), 3.47 (s, 3H), 3.54–3.62 (m, 1H), 3.79–3.86 (m, 1H), 3.89 (d, *J* = 6.1 Hz, 2H), 4.17–4.20 (m, 1H), 4.24 (dd, *J* = 8.6 and 9.7 Hz, 1H), 4.36 (dd, *J* = 8.6 and 7.9 Hz, 1H), 4.52 (d, *J* = 11.5 Hz, 1H), 4.73 (d, *J* = 11.5 Hz, 1H), 4.84–4.92 (m, 2H), 4.98 (dd, *J* = 4.7 and 4.3 Hz, 1H), 7.27–7.41 (m, 5H phenyl). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.9 (CH_3), 22.4 (CH_2), 23.0 (CH_2), 26.0 (CH_2), 28.9 (CH_2), 29.0 (CH_2), 31.5 (CH_2), 51.0 (CH_3), 51.3 (CH_3), 65.2 (CH_2), 66.7 (CH_2), 72.5 (CH_2), 72.8 (CH_2), 78.4 (CH), 80.3 (CH), 82.2 (CH), 127.8, 127.9, 128.4 (5 CH_{Ar}), 137.2 (C); HRMS (M-I) *m*/*z* (%) calcd for $[C_{23}H_{38}NO_3]$: 376.2846, found: 376.2849.

(3*R*, 3*aR*, 6*R*, 6*aS*)-*N*-[6-(benzyloxy)hexahydrofuro[3,2-b]-furan-3-yl]-*N*,*N*-dimethyl-*N*-dodecylammonium iodide (9b). Yield: 85%; Orange oil; $[\alpha]_D^{20}$ = +73.1 (*c* = 1.04, $CHCl_3$); IR (neat) υ = 3445, 2925, 2854, 1615, 1470, 1456, 1373, 1211, 1135, 1105, 1071, 1027, 891, 845, 740, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.87 (t, *J* = 6.6 Hz, 3H), 1.20–1.40 (m, 18H), 1.72–1.91 (m, 2H), 3.37 (s, 3H), 3.47 (s, 3H), 3.51–3.63 (m, 1H), 3.76–3.84 (m, 1H), 3.89 (d, *J* = 8.3 Hz, 1H), 4.16–4.27 (m, 2H), 4.37 (dd, *J* = 8.8 and 7.2 Hz, 1H), 4.52 (d, *J* = 11.6 Hz, 1H), 4.74 (d, *J* = 11.6 Hz, 1H), 4.86 (dd, *J* = 5.0 and 3.8 Hz, 1H), 4.89–4.99 (m, 2H), 7.30–7.42 (m, 5H phenyl). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.9 (CH_3), 22.4 (CH_2), 22.9 (CH_2), 26.0 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 29.2

(2 CH_2), 29.3 (2 CH_2), 31.6 (CH_2), 50.9 (CH_3), 51.3 (CH_3), 65.1 (CH_2), 66.7 (CH_2), 72.4 (CH_2), 72.7 (CH_2), 78.3 (CH), 80.1 (CH), 82.1 (CH), 127.7, 127.8, 128.3 (5 CH_{Ar}), 137.1 (C); HRMS (M-I) m/z (%) calcd for $[C_{27}H_{46}NO_3]$: 432.3472, found: 432.3475

(3*R*, 3*aR*, 6*R*, 6*aS*)-*N*-benzyl-*N*-[6-(benzyloxy)hexahydrofuro-[3,2-b]furan-3-yl]-*N*,N-dimethylammonium iodide (9c). Yield: 90%; White solid; mp: 137–138 °C; $[\alpha]_D^{20}$ = +97.9 (c = 0.75, $CHCl_3$); IR (neat) υ = 3455, 3029, 2952, 2882, 1605, 1584, 1495, 1477, 1454, 1410, 1372, 1323, 1312, 1272, 1243, 1216, 1134, 1104, 1071, 1027, 922, 881, 851, 741, 703 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.26 (s, 3H), 3.43 (s, 3H), 3.91 (d, J = 6.1 Hz, 2H), 4.15–4.25 (m, 3H), 4.51 (d, J = 11.5 Hz, 1H), 4.73 (d, J = 11.5 Hz, 1H), 4.81 (dd, J = 4.3 and 4.3 Hz, 1H), 4.94–5.00 (m, 2H), 5.15–5.21 (m, 1H), 5.28 (d, J = 12.6 Hz, 1H), 7.32–7.57 (m, 4H), 7.44–7.53 (m, 4H), 7.67–7.70 (d, J = 7.9 Hz, 2H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 49.6 (CH_3), 50.2 (CH_3), 65.2 (CH_2), 69.0 (CH_2), 72.2 (CH), 72.3 (CH_2), 72.4 (CH_2), 78.2 (CH), 80.2 (CH), 81.4 (CH), 126.4 (C), 127.6, 128.2, 129.0, 130.7, 133.1 (10 CH_{Ar}), 137.1 (C); HRMS (M-I) m/z (%) calcd for $[C_{22}H_{28}NO_3]$: 354.2064, found: 354.2072.

(3*S*, 3*aR*, 6*S*, 6*aS*)-*N*-[6-(benzyloxy)hexahydrofuro[3,2-b]furan-3-yl]-*N*,*N*-dimethyl-*N*-octylammonium iodide (15). Yield: 99%; yellowish oil; $[\alpha]_D^{25}$ = +29.7 (c = 0.50, $CHCl_3$); IR (neat) υ = 3436, 2967, 2857, 1606, 1471, 1455, 1372, 1213, 1084, 1005, 915, 745, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.88 (t, J = 7.0 Hz, 3H), 1.26–1.46 (m, 10H), 1.70–1.80 (m, 2H), 3.37 (s, 3H), 3.40 (s, 3H), 3.56–3.73 (m, 2H), 3.95–4.02 (m, 2H), 4.07–4.09 (m, 1H), 4.22–4.28 (m, 2H), 4.30–4.35 (m, 1H), 4.53 (d, J = 11.3 Hz, 1H), 4.63 (d, J = 11.3 Hz, 1H), 4.81 (d, J = 5.4 Hz, 1H), 5.20 (d, J = 5.0 Hz, 1H), 7.27–7.36 (m, 5H phenyl). ^{13}C NMR (90 MHz, $CDCl_3$) δ 13.9 (CH_3), 22.4 (CH_2), 22.5 (CH_2), 25.9 (CH_2), 28.8 (CH_2), 28.9 (CH_2), 31.4 (CH_2), 49.9 (CH_3), 50.7 (CH_3), 65.3 (CH_2), 66.6 (CH_2), 71.4 (CH_2), 71.9 (CH_2), 77.1 (CH), 81.0 (CH), 82.2 (CH), 86.8 (CH),127.8, 128.3 (5 CH_{Ar}), 137.0 (C); anal. calcd for $C_{23}H_{38}NO_3I$: C, 54.87; H, 7.61; O, 9.53; N, 2.78; I: 25.21, found: C, 54.91; H, 7.71; O, 9.53; N, 2.81; I: 25.05.

General procedure for the synthesis of compounds 10a–c and 16

Trifluoromethanesulfonic acid (10 mL, 113 mmol) was added under an argon atmosphere to a solution of ammonium iodide **9** (or **15**) (36 mmol) in dichloromethane (150 mL). After stirring the mixture for 5 min at room temperature, the solvent was removed under reduced pressure. The residue was washed with ether and dried under vacuum to give **10a–c** (or **16**) as a yellowish oil or white solid (90–97%).

(3*R*, 3*aR*, 6*R*, 6*aS*)-*N*-[6-(benzyloxy)hexahydrofuro[3,2-b]-furan-3-yl]-*N*,*N*-dimethyl-*N*-octylammonium trifluoromethanesulfonate (10a). Yield: 91%; yellowish oil; $[\alpha]_D^{20}$ = +46.5 (c = 3.25, $CHCl_3$); IR (neat) υ = 3445, 2958, 2930, 2860, 1634, 1488, 1471, 1418, 1258, 1226, 1163, 1100, 1031, 975, 834, 758, 640 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.87 (t, J = 6.5 Hz, 3H), 1.20–1.40 (m, 10H), 1.70–1.86 (m, 2H), 3.24 (s, 3H), 3.29 (s, 3H), 3.37–3.45 (m, 1H), 3.54–3.62 (m, 1H), 3.73 (s br, OH), 3.82 (dd, J = 5.8 and 9.0 Hz, 1H), 3.89 (dd, J = 5.8 and 9.0 Hz, 1H), 4.21 (dd, J = 7.2 and 9.0 Hz, 1H), 4.29–4.39 (m, 3H), 4.67 (dd, J = 4.3 and 4.7 Hz, 1H), 4.78 (dd, J = 4.3 and 3.6 Hz, 1H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 13.8 (CH_3), 22.3 (2 CH_2), 25.9 (CH_2), 28.8 (2 CH_2), 31.4 (CH_2), 50.1 (CH_3), 51.0 (CH_3), 64.7 (CH_2), 66.6 (CH_2), 71.6 (CH), 72.4 (CH), 73.8 (CH_2), 79.6 (CH), 83.0 (CH), 112.7, 117.8, 122.8, 127.9 (C); HRMS (M-OTf) m/z (%) calcd for $[C_{16}H_{32}NO_3]$: 286.2377, found: 286.2389.

(3*R*, 3*aR*, 6*R*, 6*aS*)-*N*-[6-(benzyloxy)hexahydrofuro[3,2-b]-furan-3-yl]-*N*,*N*-dimethyl-*N*-dodecylammonium trifluoromethanesulfonate (10b). Yield: 97%; yellowish oil; $[\alpha]_D^{20}$ = +41.4 (c = 0.97, $CHCl_3$); IR (neat) υ = 3445, 2956, 2923, 1488, 1469, 1258, 1255, 1162, 1030, 831, 639 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.88 (t, J = 6.1 Hz, 3H), 1.15–1.50 (m, 18H), 1.78 (m, 2H), 3.24 (s, 3H), 3.29 (s, 3H), 3.36–3.50 (m, 1H), 3.52–3.64 (m, 1H), 3.79–3.83 (m, 1H), 3.91–3.95 (m, 1H), 4.13 (s br, OH), 4.22–4.43 (m, 4H), 4.64–4.72 (m, 1H), 4.76–4.84 (m, 1H). ^{13}C NMR (62.5 MHz, MeOD-d_4) δ 14.4 (CH_3), 23.6 (CH_2), 23.7 (CH_2), 27.4 (CH_2), 30.2 (CH_2), 30.4 (CH_2), 30.5 (CH_2), 30.6 (CH_2), 30.7 (2 CH_2), 33.1 (CH_2), 51.2 (CH_3), 51.7 (CH_3), 66.0 (CH_2), 68.5 (CH_2), 73.3 (CH), 73.8 (CH), 75.0 (CH_2), 81.1 (CH), 84.8 (CH); HRMS (M-OTf) m/z (%) calcd for $[C_{20}H_{40}NO_3]$: 342.3003, found: 342.3010.

(3*R*, 3*aR*, 6*R*, 6*aS*)-*N*-benzyl-*N*-[6-(benzyloxy)hexahydrofuro[3,2-b]furan-3-yl]-*N*,N-dimethylammonium trifluoromethanesulfonate (10c). Yield: 90%; White solid; mp: 125–126 °C; $[\alpha]_D^{20}$ = +58.8 (c = 1.56, acetone); IR (neat) υ = 3459, 3040, 2965, 1637, 1480, 1475, 1415, 1259, 1225, 1161, 1130, 1099, 1067, 1030, 744, 706, 638 cm^{-1}; ^1H NMR (360 MHz, DMSO-d_6) δ 3.10 (s, 3H), 3.13 (s, 3H), 3.65 (dd, J = 6.8 and 9.0 Hz, 1H), 3.85 (dd, J = 6.1 and 9.0 Hz, 1H), 4.02–4.08 (m, 1H), 4.14 (dd, J = 8.6 and 10.8 Hz, 1H), 4.23–4.27 (m, 2H), 4.46 (dd, J = 5.4 and 4.3 Hz, 1H), 4.61 (d, J = 12.6 Hz, 1H), 4.71 (d, J = 12.6 Hz, 1H), 4.82 (dd, J = 4.3 and 4.3 Hz, 1H), 5.21 (s br, OH), 7.53–7.60 (m, 5H phenyl). ^{13}C NMR (62.5 MHz, MeOD-d_4) δ 50.8 (CH_3), 50.9 (CH_3), 66.1 (CH_2), 71.2 (CH_2), 73.3 (CH), 74.4 (CH), 75.0 (CH_2), 81.3 (CH), 84.6 (CH), 119.3, 124.4 (C), 128.4 (C), 130.5 (2 CH_{Ar}), 132.2 (CH_{Ar}), 134.4 (2 CH_{Ar}); HRMS (M-OTf) m/z (%) calcd for $[C_{15}H_{22}NO_3]$: 264.1594, found: 264.1589.

(3*S*, 3*aR*, 6*S*, 6*aS*)-*N*-[6-(benzyloxy)hexahydrofuro[3,2-b]-furan-3-yl]-*N*,*N*-dimethyl-*N*-octylammonium trifluoromethanesulfonate (16). Yield: 85%; yellowish oil; $[\alpha]_D^{20}$ = +42.0 (c = 0.50, $CHCl_3$); IR (neat) υ = 3436, 2930, 1485, 1256, 1226, 1165, 1093, 1031, 640 cm^{-1}; ^1H NMR (360 MHz, acetone) δ 0.86 (t, J = 6.5 Hz, 3H), 1.20–1.50 (m, 10H), 1.92–1.99 (m, 2H), 3.31 (s, 3H), 3.34 (s, 3H), 3.62 (dd, J = 10.1 and 7.2 Hz, 2H), 3.80 (d, J = 9.3 Hz, 1H), 3.91 (dd, J = 9.5 and 3.4 Hz, 1H), 4.18–4.34 (m, 4H), 4.58 (d, J = 5.0 Hz, 1H), 5.20–5.31 (m, 1H). ^{13}C NMR (90 MHz, MeOD-d_4) δ 14.4 (CH_3), 23.3 (CH_2), 23.6 (CH_2), 27.2 (CH_2), 30.0 (2 CH_2), 32.7 (CH_2), 49.6 (CH_3), 49.9 (CH_3), 66.6 (CH_2), 67.1 (CH_2), 74.9 (CH_2), 76.4 (CH), 78.8 (CH), 82.2 (CH), 90.5 (CH); HRMS (M-OTf) m/z (%) calcd for $[C_{16}H_{32}NO_3]$: 286.2377, found: 286.2389.

General procedure for the synthesis of compounds 11a–c and 17

Lithium *bis*(trifluoromethanesulfonyl)imide (5.6 mmol) was added to a solution of ammonium trifluoromethanesulfonate

10 (or **16**) (3.7 mmol) in acetone (5 mL). After stirring for 16 h at room temperature, the solvent was removed under reduced pressure. The residue was washed with ether (3 x 10 mL) and thereafter purified by flash column chromatography on silica gel (CH_2Cl_2 : MeOH = 9 : 1) to afford **11a–c** (or **17**) as a colorless oil (94–97%)

(3*R*, 3*aR*, 6*R*, 6*aS*)-*N*-[6-(benzyloxy)hexahydrofuro[3,2-b]-furan-3-yl]-*N*,*N*-dimethyl-*N*-octylammonium *bis*(trifluoromethanesulfonyl)imide (11a). Yield: 94%; $[\alpha]_D^{20}$ = +39.8 (c = 0.83, $CHCl_3$); IR (neat) υ = 3516, 2960, 2932, 2861, 1488, 1471, 1418, 1352, 1194, 1135, 1057, 975, 834, 790, 741cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.88 (t, J = 7.0 Hz, 3H), 1.20–1.50 (m, 10H), 1.70–1.85 (m, 2H), 3.18 (s, 3H), 3.25 (s, 3H), 3.31–3.40 (m, 1H), 3.44–3.52 (m, 1H), 3.81 (dd, J = 9.7 and 4.0 Hz, 1H), 3.91 (dd, J = 9.7 and 5.4 Hz, 1H), 4.04–4.14 (m, 1H), 4.18 (dd, J = 8.3 and 9.7 Hz, 1H), 4.29 (dd, J = 8.3 and 7.9 Hz, 1H), 4.34–4.41 (m, 1H), 4.65 (dd, J = 5.0 and 4.3 Hz, 1H), 4.75 (dd, J = 4.3 and 4.3 Hz, 1H). ^{13}C NMR (90 MHz, MeOD-d_4) δ 14.3 (CH_3), 23.4 (2 CH_2), 27.0 (CH_2), 29.9 (2 CH_2), 32.6 (CH_2), 51.1 (CH_3), 51.6 (CH_3), 65.8 (CH_2), 68.4 (CH_2), 73.1 (CH), 73.6 (CH), 74.7 (CH_2), 80.9 (CH), 84.5 (CH), 113.4, 118.5, 123.6, 128.7 (2 C); HRMS (M-NTf_2) m/z (%) calcd for [$C_{16}H_{32}NO_3$]: 286.2377, found: 286.2378.

(3*R*, 3*aR*, 6*R*, 6*aS*)-*N*-[6-(benzyloxy)hexahydrofuro[3,2-b]-furan-3-yl]-*N*,*N*-dimethyl-*N*-dodecylammonium *bis*(trifluoromethanesulfonyl)imide (11b). Yield: 97%; colorless oil; $[\alpha]_D^{20}$ = +34.4 (c = 1.07, $CHCl_3$); IR (neat) υ = 3513, 2927, 2856, 1488, 1469, 1420, 1351, 1194, 1135, 1057, 832, 789, 740, 654, 618, 601, 571 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.20–1.50 (m, 18H), 1.72–1.85 (m, 2H), 3.19 (s, 3H), 3.26 (s, 3H), 3.31–3.40 (m, 1H), 3.47–3.54 (m, 1H), 3.82–3.92 (m, 2H), 4.09–4.12 (m, 1H), 4.18 (dd, J = 10.8 and 7.6 Hz, 1H), 4.31 (dd, J = 7.6 and 8.3 Hz, 1H), 4.37–4.40 (m, 1H), 4.67 (dd, J = 4.3 and 5.4 Hz, 1H), 4.75 (dd, J = 4.3 and 4.3 Hz, 1H). ^{13}C NMR (90 MHz, MeOD-d_4) δ 14.5 (CH_3), 23.6 (CH_2), 23.7 (CH_2), 27.3 (CH_2), 30.1, 30.5, 30.6, 30.7 (6 CH_2), 33.0 (CH_2), 51.2 (CH_3), 51.7 (CH_3), 65.9 (CH_2), 68.5 (CH_2), 73.2 (CH), 73.7 (CH), 75.0 (CH_2), 81.0 (CH), 84.7 (CH), 113.6, 118.6, 123.8, 128.8 (2 C); HRMS (M-NTf_2) m/z (%) calcd for [$C_{20}H_{40}NO_3$]: 342.3003, found: 342.3010.

(3*R*, 3*aR*, 6*R*, 6*aS*)-*N*-benzyl-*N*-[6-(benzyloxy)hexahydrofuro-[3,2-b]furan-3-yl]-*N*,N-dimethylammonium *bis*(trifluoromethanesulfonyl)imide (11c). Yield: 96%; colorless oil; $[\alpha]_D^{20}$ = +45.9 (c = 0.91, $CHCl_3$); IR (neat) υ = 3515, 3065, 2959, 2932, 2862, 1486, 1417, 1352, 1194, 1135, 1057, 1021, 975, 920, 834, 790, 741, 706, 654, 617 cm^{-1}; ^{1}H NMR (360 MHz, DMSO-d_6) δ 3.11 (s, 3H), 3.13 (s, 3H), 3.66 (dd, J = 6.8 and 9.0 Hz, 1H), 3.87 (dd, J = 6.1 and 9.0 Hz, 1H), 4.01–4.07 (m, 1H), 4.16 (dd, J = 9.7 and 9.4 Hz, 1H), 4.24–4.28 (m, 2H), 4.47 (dd, J = 4.7 and 5.7 Hz, 1H), 4.60 (d, J = 12.2 Hz, 1H), 4.70 (d, J = 12.2 Hz, 1H), 4.82 (dd, J = 4.7 and 4.3 Hz, 1H), 5.17 (d, J = 4.7 Hz, OH), 7.50–7.63 (m, 5H phenyl). ^{13}C NMR (90 MHz, DMSO-d_6) δ 49.4 (CH_3), 49.6 (CH_3), 64.4 (CH_2), 68.9 (CH_2), 71.4 (CH), 72.0 (CH), 73.1 (CH_2), 79.4 (CH), 82.6 (CH), 117.7, 121.2 (2 C), 127.4 (C), 129.0 (2 CH_{Ar}), 130.6 (CH_{Ar}), 133.2 (2 CH_{Ar}); anal. calcd for $C_{17}H_{22}N_2O_7S_2F_6$: C, 37.50; H, 4.07; N, 5.14; S, 11.78; F, 20.84, found: C, 37.28; H, 3.96; N, 5.14; S, 11.88; F, 20.67.

(3*S*, 3*aR*, 6*S*, 6*aS*)-*N*-[6-(benzyloxy)hexahydrofuro[3,2-b]-furan-3-yl]-*N*,*N*-dimethyl-*N*-octylammonium *bis*(trifluoromethanesulfonyl)imide (17). Yield: 96%; colorless oil; $[\alpha]_D^{20}$ = +49.4 (c = 0.51, $CHCl_3$); IR (neat) υ = 3532, 3050, 2958, 2931, 2861, 1484, 1470, 1350, 1329, 1195, 1135, 1057, 618; ^{1}H NMR (250 MHz, acetone) δ 0.88 (t, J = 6.7 Hz, 3H), 1.20–1.48 (m, 10H), 1.90–2.10 (m, 2H), 3.34 (s, 3H), 3.38 (s, 3H), 3.64 (dd, J = 11.0 and 6.0 Hz, 2H), 3.82 (d, J = 9.2 Hz, 1H), 3.94 (dd, J = 10.1 and 3.9 Hz, 1H), 4.18–4.32 (m, 4H), 4.59 (d, J = 5.0 Hz, 1H), 5.31–5.33 (m, 1H). ^{13}C NMR (250 MHz, MeOD-d_4) δ 14.4 (CH_3), 23.3 (CH_2), 23.5 (CH_2), 27.1 (CH_2), 30.0 (CH_2), 32.7 (CH_2), 49.6 (CH_2), 49.6 (CH_3), 49.7 (CH_3), 66.7 (CH_2), 67.0 (CH_2), 74.8 (CH_2), 76.3 (CH), 78.7 (CH), 82.1 (CH), 90.4 (CH), 113.4, 118.5, 123.6, 128.7 (2 C); HRMS (M-NTf_2) m/z (%) calcd for [$C_{16}H_{32}NO_3$]: 286.2377, found: 286.2385.

Synthesis of (3*R*, 3*aR*, 6*R*, 6*aS*)-*N*-[6-(benzyloxy)hexahydrofuro-[3,2-b]furan-3-yl]-*N*,*N*-dimethyl-*N*-octylammonium *bis*(trifluoromethanesulfonyl)imide (29)

Lithium *bis*(trifluoromethanesulfonyl)imide (5.6 mmol) was added to a solution of ammonium iodide **9a** (3.7 mmol) in acetone (5 mL). After stirring for 16 h at room temperature, the solvent was removed under reduced pressure. The residue was washed with ether (3 × 10 mL) and thereafter purified by flash column chromatography on silica gel (CH_2Cl_2 : MeOH = 9 : 1) to afford **29** as a yellowish oil.

Yield: 95%; $[\alpha]_D^{25}$ = +81.3 (c = 0.50, $CHCl_3$); IR (neat) υ = 3445, 2957, 2929, 2859, 1487, 1455, 1470, 1417, 1263, 1224, 1153, 1030 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.89 (t, J = 6.8 Hz, 3H), 1.25–1.37 (m, 10H), 1.76–1.82 (m, 2H), 3.30 (s, 3H), 3.38 (s, 3H), 3.44–3.54 (m, 1H), 3.67–3.75 (m, 1H), 3.86–3.94 (m, 1H), 4.17–4.24 (m, 2H), 4.33 (dd, J = 7.9 and 8.3 Hz, 1H), 4.53 (d, J = 11.3 Hz, 1H), 4.67–4.72 (m, 1H), 4.75 (d, J = 11.3 Hz, 1H), 4.83 (dd, J = 4.7 and 4.7 Hz, 1H), 4.92 (dd, J = 4.7 and 5.4 Hz, 1H), 7.31–7.40 (m, 5H phenyl). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.9 (CH_3), 22.4 (CH_2), 22.7 (CH_2), 26.0 (CH_2), 28.8 (2 CH_2), 31.4 (CH_2), 50.5 (CH_3), 51.0 (CH_3), 65.0 (CH_2), 66.7 (CH_2), 72.4 (CH_2), 72.7 (CH_2), 78.4 (CH), 80.1 (CH), 82.1 (CH), 127.8, 127.9, 128.4 (5 CH_{Ar}), 137.2 (C); HRMS (M-NTf_2) m/z (%) calcd for [$C_{23}H_{38}NO_3$]: 376.2846, found: 376.2851.

Synthesis of 3-methyl-1-(3*R*, 3*aR*, 6*S*, 6*aR*)-[6-(benzyloxy)-hexahydrofuro[3,2-b]furan-3-yl] imidazolium trifluoromethanesulfonate (18)

A mixture of the sulfonate **6** (300 mg, 0,8 mmol) and *N*-methylimidazole (392 mg, 4.7 mmol) was placed under microwave irradiated at 130 °C for 4 h. Potassium trifluoromethanesulfonate (180 mg, 9.6 mmol) was added and the resulting mixture was then placed under microwave irradiation at 90 °C for 20 min. The reaction mixture was brought to room temperature and filtered on silica gel (CH_2Cl_2 : MeOH = 80 : 20). Solvents were evaporated under reduced pressure and the obtained oil was successively washed with toluene (3 × 5 mL), with cyclohexane (3 × 5 mL), then with ethyl ether (3 × 5 mL). Purification by flash chromatography on alumina

(CH_2Cl_2 : MeOH gradually from 7% to 15%) afforded the salt **18** as a yellow viscous oil in 50% yield. $[\alpha]_D^{25} = +103.4$ (c = 0.53; acetone); IR (neat) υ = 3425, 3426, 3152, 3099, 1638, 1560, 1456, 1429, 1368, 1254, 1224, 1166, 1074, 1030cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.77–3.92 (m, 2H), 4,09 (t, J = 8.7 Hz, 1H), 4.14–4.20 (m, 1H), 4.33 (dd, J = 9.3 and 7.2 Hz, 1H), 4.52 (d, J = 11.4 Hz, 1H), 4.67 (m, 3H), 5.07–5.14 (m, 1H), 7.27 (s, 1H), 7.49 (s, 1H), 9.10 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.2 (CH_3), 61.7 (CH), 71.0 (CH_2), 72.4 (CH_2), 72.8 (CH), 79.0 (CH), 81.1 (CH), 82.4 (CH), 122.8, 122.9, 126.8 (5 CH_{Ar}), 137.4 (C); HRMS (M-OTf) m/z (%) calcd for $[C_{17}H_{21}N_2O_3]^+$: 301.1547, found: 301.1556.

Synthesis of 3-methyl-1-(3*R*, 3*aR*, 6*S*, 6*aR*)-[6-(hydroxy)-hexahydrofuro[3,2-b]furan-3-yl] imidazolium trifluorométhanesulfonate (19)

Trifluoromethanesulfonic acid (3 mL, 36 mmol) was added under an argon atmosphere to a solution of benzylated imidazolium salt **18** (36 mmol) in dichloromethane (80 mL). After stirring the mixture for 5 min at room temperature, the solvent was removed under reduced pressure. The residue was washed with ether and dried under vacuum to give **19** as a yellow viscous oil in 97% yield. $[\alpha]_D^{20} = +62.5$ (c = 0.70, acetone); IR (neat) υ = 3500, 3518, 3119, 2965, 2891, 1634, 1580, 1558, 1259, 1171, 1031, 851, 760, 639 cm^{-1}; ^{1}H NMR (360 MHz, acetone-d_6) δ 3.73 (dd, J = 9.0 and 6.5 Hz, 1H), 3.94 (dd, J = 9.0 and 6.1 Hz, 1H), 4.08 (s, 3H), 4.21 (t, J = 9.0 Hz, 1H), 4.41–4.46 (m, 2H), 4.70 (t, J = 4.9 Hz, 1H), 4.84 (t, J = 4.7 Hz, 1H), 5.28–5.34 (m, 1H), 7.72 (t, J = 2.0 Hz, 1H), 7.83 (t, J = 2.0 Hz, 1H), 9.17 (s, 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ 36.8 (CH_3), 63.0 (CH), 71.2 (CH_2), 73.4 (CH_2), 74.7 (CH), 81.8 (CH), 84.4 (CH), 124.0 (CH), 124.1 (CH), 138.0 (CH); HRMS (M-OTf) m/z (%) calcd for $[C_{10}H_{15}N_2O_3]$: 211.1077, found: 211.1080.

Synthesis of (3*R*, 3*aR*, *6S*, 6*aS*)-3-(acetoxy)hexahydrofuro[3,2-b]-furan-6-yl trifluoromethane sulfonate (21)

Pyridine (3.8 mL, 47 mmol) was added to a solution of acetate **20** (8 g, 42.5 mmol) in dichloromethane (100 mL). The reaction mixture was stirred in an ice-bath at 0–5 °C followed by slow addition of trifluoromethanesulfonic anhydride (7.8 mL, 47 mml). The resulting mixture was stirred at room temperature for 2 h. The organic phase was successively washed with water (20 mL), a solution of 5 N HCl (20 mL) and a solution of saturated NaCl (20 mL). The organic layer was then dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (pentane : AcOEt = 1 : 1) to give **21** as a colorless oil (13.5g, 99%). $[\alpha]_D^{[20]} = +86.2$ (c = 0.52, $CHCl_3$); IR (neat) υ = 2987, 2937, 2881, 1745, 1415, 1372, 1243, 1212, 1146, 1098, 948, 908 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.11 (s, 3H), 3.80 (dd, J = 5.0 and 10.1 Hz, 1H), 3.97 (dd, J = 5.8 and 10.1 Hz, 1H), 4.04 (dd, J = 3.4 and 11.9 Hz, 1H), 4.21 (d, J = 11.9 Hz, 1H), 4.67 (d, J = 4.7 Hz, 1H), 4.93 (t, J = 5.0 Hz, 1H), 5.18 (q, J = 5.5 Hz, 1H), 5.30–5.33 (m, 1H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 20.5 (CH_3), 70.7 (CH_2), 72.8 (CH_2), 73.4 (CH), 80.8 (CH), 85.4 (CH), 89.3 (CH), 123.7 (Cq), 170,0 (Cq); HRMS (MNa^+) m/z (%) calcd for $[C_9H_{11}O_7SF_3]$: 343.0070, found: 343.0078.

(3*R*, 3*aS*, 6*aR*)-2,3,3a,6a-tetrahydrofuro[3,2-b]furan-3yl acetate (23)

Yield: 30% $[\alpha]_D^{20} = +42.5$ (c = 0.3, $CHCl_3$); IR (neat) υ = 2985, 2920, 2815, 1745, 1415, 1372, 1253, 1225, 1198, 952 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.2 (s, 3H), 3.30 (dd, J = 5.0 and 10.4 Hz, 1H), 3.85 (dd, J = 5.5 and 10.4 Hz, 1H), 4.15 (dd, J = 3.5 and 11.6 Hz, 1H), 4.80 (m, 1H), 5,1 (dd, J = 4.7 and 10.2 Hz, 1H), 5.35 (m 1H), 6.7 (d, J = 3.5 Hz, 1H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 20.8 (CH_3), 64.8 (CH_2), 79.3 (CH), 80.6 (CH), 84.7 (CH), 100.2 (CH), 151.5 (CH), 170,0 (Cq); HRMS (MNa^+) m/z (%) calcd for $[C_8H_{10}O_4]$: 193.0477, found: 193.0480.

General procedure for the synthesis of compounds 22 and 24

A mixture of the triflate **21** (6 g, 19 mmol) and *N*-methylimidazole (or 1,2-dimethylimidazole) (21 mmol) was stirred under an argon atmosphere at 40 °C for 2 days. Water (10 mL) was added before saturating the aqueous phase with potassium carbonate until obtaining a white dough. The resulting mixture was then extracted with dichloromethane (3 × 40 mL). After evaporation of the solvent, the residue was washed with toluene (3 × 30 mL), cyclohexane (3 × 30 mL) and ethyl ether (3 × 30 mL). The crude product was purified by flash chromatography on alumina (CH_2Cl_2 then CH_2Cl_2 : MeOH gradually from 1% to 15%) to give **22** (or **24**) as a yellow oil.

3-methyl-1-(3*R*, 3*aR*, 6*S*, 6*aR*)-[6-(acetoxy)-hexahydrofuro-[3,2-b]furan-3-yl] imidazolium trifluoromethanesulfonate (22). Yield: 46%; $[\alpha]_D^{25} = +82.0$ (c = 0.65, acetone); IR (neat) υ = 3521, 3156, 3120, 2984, 2888, 1739, 1580, 1558, 1375, 1258, 1164, 1030, 639 cm^{-1}; ^{1}H NMR (360 MHz, MeOD-d_4) δ 2.11 (s, 3H), 3.95 (s, 3H), 3.99–4.01 (m, 2H), 4.05 (t, J = 9,2 Hz, 1H), 4.34 (dd, J = 9.0 and 6.8 Hz, 1H), 4.71 (t, J = 4.9 Hz, 1H), 4.67 (t, J = 5.0 Hz, 1H), 5.02–5.08 (m, 1H), 5.26 (q, J = 4.9 Hz, 1H), 7,58 (t, J = 1.8 Hz, 1H), 7.70 (t, J = 1.8 Hz, 1H), 9.04 (s, 1H). ^{13}C NMR (75 MHz, acetone-d_6) δ 20.5 (CH_3), 36.7 (CH_3), 62.1 (CH), 70.2 (CH_2), 72.6 (CH_2), 75.0 (CH), 81.5 (CH), 83.0 (CH), 124.0 (2CH), 137.9 (CH), 170.8 (Cq); HRMS (M-OTf) m/z (%) calcd for $[C_{12}H_{17}N_2O_4]$: 253.1183, found: 253.1185.

2,3-dimethyl-1-(3*R*, 3*aR*, 6*S*, 6*aR*)-[6-(acetoxy)-hexahydrofuro[3,2-b]furan-3-yl] imidazolium trifluoromethanesulfonate (24). Yield: 50%; $[\alpha]_D^{25} = +131.7$ (c = 0.50, acetone); IR (neat) υ = 3508, 3147, 2961, 2890, 1591, 1532, 1374, 1739, 1259, 1163, 1031, 639 cm^{-1}; ^{1}H NMR (360 MHz, MeOD-d_4) δ 2.10 (s, 3H), 2.69 (s, 3H), 3.84 (s, 3H), 3.84–3.89 (m, 1H), 3.92–3.98 (m, 1H), 4.19–4.29 (m, 2H), 4.80 (t, J = 5.0 Hz, 1H), 4.88 (t, J = 5.2 Hz, 1H), 5.03–5.09 (m, 1H), 5.19 (q, J = 5,3 Hz, 1H), 7.46 (d, J = 2.2 Hz, 1H), 7.62 (d, J = 2.2 Hz, 1H). ^{13}C NMR (62.5 MHz, MeOD-d_4) δ 21.0 (CH_3), 35.9 (CH_3), 60.9 (CH), 70.8 (CH_2), 73.0 (CH_2), 75.4 (CH), 82.5 (CH), 83.6 (CH), 121.8 (CH), 123.4 (CH), 147.1 (Cq), 171.9 (Cq); HRMS (M-OTf) m/z (%) calcd for $[C_{13}H_{19}N_2O_4]$: 267.1339, found: 267.1345.

General procedure for the synthesis of CILs 19 and 25

Concentrated HCl (2 drops) were added to a solution of acetate **22** (or **24**) (3.6 mmol) in ethanol (60 mL). The mixture was heated under reflux for 4 h. After cooling, the reaction mixture was neutralized with a solution of saturated Na_2CO_3. Solvents were evaporated and the residue was dissolved in acetone. The organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product was purified by flash chromatography alumina (CH_2Cl_2 then CH_2Cl_2 : MeOH gradually from 5% to 20%) to give **19** (or **25**) as a yellow oil.

3-methyl-1-(3*R*, 3*a*R, 6*S*, 6*a*R)-[6-(hydroxy)-hexahydrofuro-[3,2-b]furan-3-yl] imidazolium trifluorométhanesulfonate (19). Yield: 90%.

2,3-dimethyl-1-(3*R*, 3*a*R, 6*S*, 6*a*R)-[6-(hydroxy)-hexahydrofuro-[3,2-b]furan-3-yl] imidazolium trifluoromethanesulfonate (25). Yield: 90%; $[\alpha]_D^{20} = +112.3$ ($c = 0.50$; acetone); IR (neat) $\upsilon = 3479, 3148, 2960, 2888, 1634, 1591, 1538, 1423, 1253, 1170, 1032, 758, 639$ cm^{-1}; ^{1}H NMR (360 MHz, MeOD-d_4) δ 2.66 (s, 3, H_m) ; 3.49 (dd, $J = 9.0$; 7.6 Hz, 1H, H_f) ; 3.82–3.86 (m, 1H, H_f) ; 3,84 (s, 3H, H_k) ; 4.23–4.38 (m, 3H, H_{c+e}) ; 4,58 (t, $J = 4.9$ Hz, 1H, H_d) ; 4.83 (t, $J = 5.2$ Hz, 1H, H_a) ; 5.10 (q, $J = 6.1$ Hz, H_b); 7.46 (d, $J = 2.2$ Hz, 1H, H_i) ; 7.65 (d, $J = 2.0$ Hz, 1H, H_j).. ^{13}C NMR (90 MHz, MeOD-d_4) δ 10.1 (CH_3), 35.6 (CH_3), 61.9 (CH), 71.4 (CH_2), 73.3 (CH), 74.2 (CH_2), 82.8 (CH), 84.9 (CH), 121.4 (CH), 123.3 (CH), 147.1 (CH); HRMS (M-OTf) m/z (%) calcd for $[C_{11}H_{17}N_2O_3]$: 225.1234, found: 225.1241.

General procedure for the asymmetric aza Diels–Alder reaction of Danishefsky's diene with imine 27

A mixture of imine **27** (1 mmol), chiral ionic liquid (0.5 equiv.) and Danishefsky's diene **26** (1.5 equiv. added in three portions) was stirred at 30 °C for 5 h. The reaction mixture was extracted from the ionic liquid phase with Et_2O (3 × 10 mL). The combined ether fractions were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by flash column chromatography (AcOEt : pentane = 10 : 90 to 70 : 30) to provide **28**.

The chiral ionic liquid was dissolved in dichloromethane (20 mL) and then recycled by washing with water (10 mL × 2). The organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* to afford the recycled ionic liquid. Spectra data (IR, ^{1}H and ^{13}C) were identical to the initial ionic liquid sample. This IL was reused without loss of efficiency (Table 1, entry 2).

(2*S*)-2,3-dihydro-2-phenyl-1-[(*R*)-1-phenylethyl]pyridine-4-(1*H*)-one (28). Mp: 74 °C; $[\alpha]_D^{26}$: + 183.7 (c 1.96, $CHCl_3$) (ed = 97% determined by chral HPLC). IR (neat) $\upsilon = 3029, 2975, 1639, 1590, 1494, 1451, 1393, 1294, 1152, 762, 700$ cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.45 (d, 3H, $J = 6.8$ Hz), 2.55–2.88 (m, 2H), 4.43 (q, 1H, $J = 6.8$ Hz), 4.70 (dd, 1H, $J = 6.8$, 8.8 Hz), 5.04 (d, 1H, $J = 7.0$ Hz), 7.06 (d, 1H, $J = 7.0$ Hz), 7.09–7.42 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 17.4 (CH_3), 43.2 (CH_2), 59.0 (CH), 60.2 (CH), 98.0 (CH), 125.8, 126.4, 127.3, 128.0, 128.3, 128.8 (10 CH_{Ar}), 138.7 (C), 139.6 (C), 149.0 (CH), 189.8 (C); HRMS (EI) calcd. for $C_{19}H_{19}NO$ (M^+) 277.1461, found 277.1460.

(2*R*)-2,3-dihydro-2-phenyl-1-[(*R*)-1-phenylethyl]pyridine-4-(1*H*)-one (28 diastereomer). IR (neat) $\upsilon = 3029, 2975, 1639, 1590, 1494, 1451, 1393, 1294, 1152, 762, 700$ cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.60 (d, 3H, $J = 7.0$ Hz), 2.55–2.88 (m, 2H), 4.28 (q, 1H, $J = 6.8$ Hz), 4.70 (dd, 1H, $J = 6.8$, 8.8 Hz), 5.14 (d, 1H, $J = 7.5$ Hz), 7.61 (d, 1H, $J = 7.7$ Hz), 7.09–7.42 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 21.4 (CH_3), 43.9 (CH_2), 59.9 (CH), 60.6 (CH), 99.5 (CH), 125.9, 126.6, 127.8, 128.2, 128.7, 128.9 (10 CH_{Ar}), 139.3 (C), 141.8 (C), 152.0 (CH), 190.4 (C); HRMS (EI) calcd. for $C_{19}H_{19}NO$ (M^+) 277.1461, found 277.1460.

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