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# Synthesis of novel chiral imidazolium-based ionic liquids derived from isosorbide and their applications in asymmetric aza Diels–Alder reaction

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ABSTRACT

A novel family of chiral imidazolium-based ionic liquids containing a chiral moiety and a free hydroxyl function 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 diastereoselectivities. Chiral ionic liquids are recycled while their efficiency is preserved.



## 1. 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 ILs have made 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 crystals,[6] chiral resolution and as NMR shift reagents.[7] Nowadays, the design and synthesis of novel CILs are growing rapidly. The study of CILs' applications in asymmetric synthesis presents a challenge and an opportunity to researchers. It is, therefore, essential if not interesting to synthesize different kinds of CILs from various starting materials derived from a chiral pool, especially from biorenewable sources.

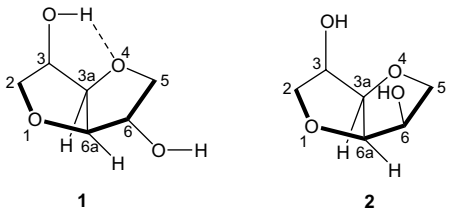
Isosorbide **1** also known as (3*R*,3a*R*,6*S*,6a*R*)-hexahydrofuro [3,2-*b*]furan-3,6-diol and isomannide **2**, (3*R*,3a*R*,6*R*,6a*R*)-hexahydrofuro[3,2-*b*]furan-3,6-diol, are renewable, and commercially available chiral carbohydrates. Isosorbide is basically two fused tetrahydrofuran rings having the 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 possible the intramolecular hydrogen bonding 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 access to 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 potentials, to date, only a few ammonium CILs derived from isomannide are reported.[14]

In a continuation of our research in the synthesis and applications of new CILs from inexpensive and commercially available natural chiral auxiliaries,[15,3a,3i] we report here the synthesis of new imidazolium family CILs derived from isosorbide and their application as chiral reaction medium as well as catalyst for an asymmetric aza Diels–Alder reaction.

## 2. Result and discussion

Our strategy is to protect one of the free hydroxyl groups as an ether while transforming the other into the imidazolium function




1 2

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

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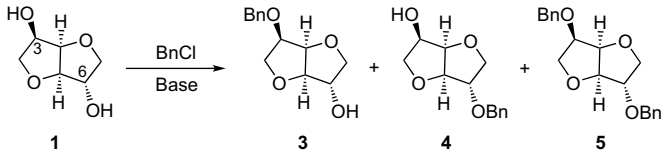
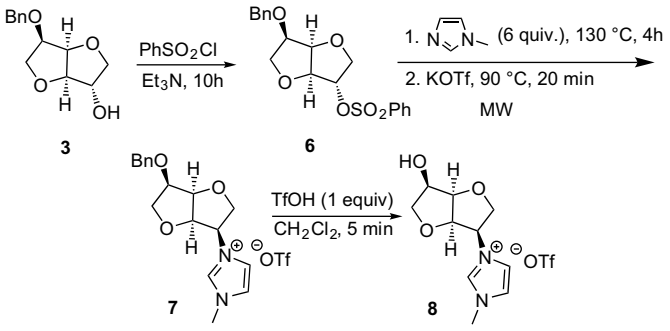
by nucleophilic substitution by *N*-methylimidazole. An anion exchange will be carried out to obtain the desired ILs.

Our synthesis was initiated by using selective monobenzylation of the hydroxyl group at the *endo* position $C_3$, 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, 3-benzyl (*endo*) **3**, 6-benzyl (*exo*) **4** and 3,6-dibenzyl ethers **5**, in ratios depending on the experimental conditions (Scheme 1).[17]




**Scheme 1.** Benzylation of isosorbide.

The best yield (56%) of compound **3** was obtained when performing the reaction using 1 equiv of benzyl chloride along with lithium hydride and lithium chloride in stoichiometric quantities. The free hydroxyl group at the *exo* position $C_6$ 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 converted to the imidazolium ether **7** by heating with a large excess of *N*-methylimidazole at 160 °C.[18] However, no trace of product was detected even after 4 days.




**Scheme 2.** Synthesis of imidazolium salts **7** and **8**.

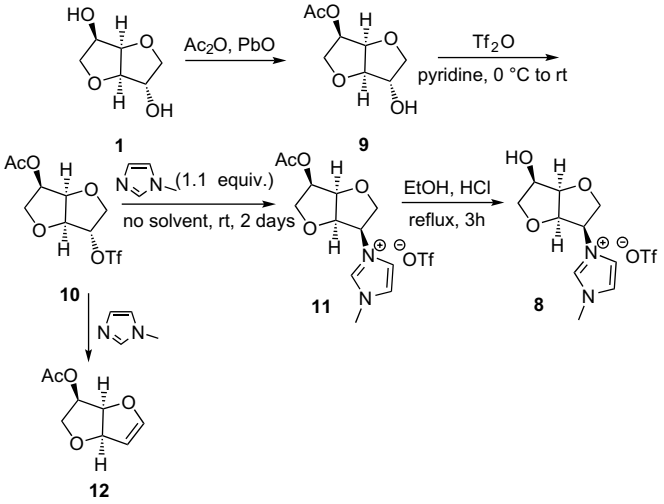
We turned out our attention to the use of microwave irradiation. This technique was widely developed in our Laboratory and other research groups, particularly for the synthesis of ILs.[15,19] The combination of solvent-free conditions and MW irradiation considerably reduces reaction time, enhances conversions as well as selectivity and sometimes allows obtaining molecules which are impossible to synthesize in classic conditions.[20]

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 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 substitution reaction with 6 equiv 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 2). Purification by chromatography on alumina afforded the desired imidazolium salt **7** in 50% of yield.

The last step in the synthesis is the removal of the benzyl ether protecting group using trifluoromethanesulfonic acid in dichloromethane. Ionic liquids **8** were obtained in good yields (97%) within very short reaction times (5 min). It is noteworthy that these chiral imidazolium salts **7** and **8** are viscous liquids at room temperature (Scheme 2).

In view of the difficulty in introducing the imidazolium skeleton on the isosorbide, it was intended 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 gaining a synthesis step.

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 be resisted to the alkylation conditions and should 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 **8** is represented in the following scheme (Scheme 3).




**Scheme 3.** Synthesis of imidazolium salt **8**.

The first step of our synthesis was realized according to the reaction conditions reported by Stoss and co-workers.[21] After purification by chromatography on silica gel, we obtained the acetate derivative **9** with 70% of yield. The free hydroxyl group in *endo* position of acetyl isosorbide **9** was then activated in the form of triflate by action of triflic anhydride and pyridine in the dichloromethane. The compound **10** was obtained with a quasi-quantitative yield. The triflate **10** was converted to imidazolium **11** 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 2 days. Imidazolium **11** was isolated with 46% yield after purification by chromatography on alumina. It is about a $S_N2$ substitution reaction with complete inversion of configuration. This was established by $^1H$ 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 **10** became a doublet of doublets in **11**. Due to this inversion of configuration, the isosorbide skeleton was converted to isomannide.

The modest yield (40%) on this alkylation could be explained by the formation of a product of elimination. The compound **12** (Scheme 3) was indeed isolated with 30% yield, resulting from the elimination of the triflate **10**, which is a very good leaving group tending to be to eliminate easily; especially, the carbocation, resulting from E1 elimination, must be stabilized in this ionic medium.

The next step in the synthesis is transforming acetylated imidazolium **11** into ionic liquids **8** by removing the acetyl protecting group at the *endo* position $C_3$. Thus, deacetylation was made in ethanol in the presence of a drop of concentrated HCl to afford the CIL **8** with 90% yield (Scheme 3).

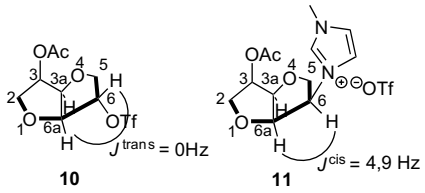


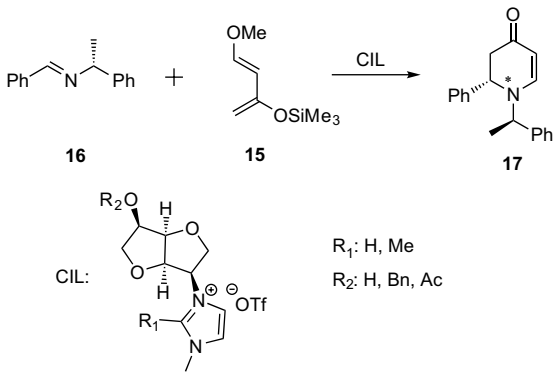

**Figure 2.** Inversion of configuration confirmed by $^1$H NMR.

We then proceeded to synthesize the imidazolium CIL **14** possessing the methyl group in position 2 of *N*-methylimidazole. Using the same strategy previously described in Scheme 3, CIL **14** was then obtained in 25% overall yield in 4 steps from isosorbide. Scheme 4 summarizes the synthesis of this new chiral IL.

After achieving the synthesis of these chiral ILs containing a chiral moiety and a free hydroxyl function, 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 **15** with a chiral imine **16** under green chemistry conditions (Scheme 5, Table 1). This reaction has proved to perform better at room temperature in ionic liquid without either Lewis acid catalyst or organic solvent[22] and with significant diastereoselectivity using an ephedrinium-based ionic liquid.[3i]

The results summarized in Table 1 show that imidazolium CILs could catalyze the aza Diels–Alder reaction. Good yields and significant diastereoselectivities are obtained when performing the experiments with 0.5 equiv of IL and 1.5 equiv 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 **17** was determined by comparison of its optical rotation and NMR spectral data with the reported values.[23]

As mentioned in the literature, the presence of the hydroxyl group is very important for reactivity and especially for chirality transfer. This fact had already been reported by Colonna and co-workers[24] in the borohydride asymmetric reduction of carbonyl compounds using a chiral phase-transfer catalyst. This observation is also supported by our studies in the asymmetric Baylis–Hillman reaction.[3a] On the other hand, imidazolium function can catalyze the Diels–Alder reaction thanks to the formation of hydrogen bonding between the mobile hydrogen in position 2 of imidazolium and the substrate as observed by Welton and his co-workers.[25] Thus, when isosorbide **1** was used as a chiral source without Lewis acid catalyst, no desired product was observed (Table 1, entry 6), a fact already mentioned in the literature.[26] On the other hand, when the hydroxyl group of the CIL **8** was protected with a benzyl group or an acetyl group (compound **7** or **11**), approximately 60% de but with only 39% or 25% yield was achieved (Table 1, entries 1 and 3). The CIL **8** turns out to catalyze in an effective way the reaction. Best yield and diastereoselectivity were observed. CILs are highly recyclable and do not lose any of their properties even when used four consecutive times (Table 1, entry 2). However, in the cases of the CIL **13**, only 5% yield was obtained, showing the 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 1, entry 5). Finally, only 32% of de was obtained when we used the chiral imine in the presence of $ZnCl_2$ as Lewis acid catalyst (Table 1, entry 7).




**Scheme 5.** Asymmetric aza Diels–Alder reaction of Danishefsky's diene **15** with imine **16**.

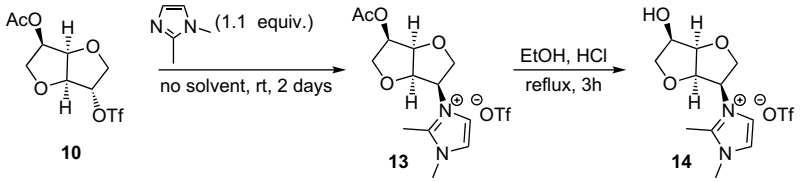
These results confirmed that not only may CILs be used as solvents and catalysts but they also play the role of chiral inductors in the asymmetric aza Diels–Alder reaction. The key to effective asymmetric induction is the existence of strong intermolecular interactions, like electrostatic attraction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

**Table 1**
Asymmetric aza Diels–Alder reaction of Danishefsky's diene **15** with imine **16**. Conditions:[a] imine **16**/diene **15**/CIL=1:1.5:0.5; temperature: 30 °C; time: 5 h

| Entry | CIL | $R_1$ | $R_2$ | Yield **17** (%) | de **17**[b] (%) |
|---|---|---|---|---|---|
| 1 | **7** | H | Bn | 39 | 60 |
| 2 | **8** | | H | 74 (74, 75, 73)[e] | 68 (66, 67, 68)[e] |
| 3 | **11** | | Ac | 25 | 59 |
| 4 | **14** | Me | H | 40 | 65 |
| 5 | **13** | | Ac | 5 | 69 |
| 6 | **1**[c] | — | — | 0 | 0 |
| 7 | —[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.

Therefore, our preliminary studies on the application of these CILs for the title reaction showed that the chiral reaction medium has a significant influence on chiral induction. Further investigations to provide useful insights 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.




**Scheme 4.** Synthesis of CIL **14**.

## 3. Conclusion

In summary, we have designed and synthesized a novel family of chiral imidazolium-based ionic liquids containing 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 available starting materials. These new CILs can serve as chiral reaction media as well as catalysts in asymmetric aza Diels–Alder reaction. Further improvements of the application of CILs in asymmetric synthesis are currently underway in our laboratory.

## 4. Experimental section

### 4.1. 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-$d_6$. $^1H$ NMR spectra were recorded at 360 or 250 MHz. The chemical shifts ($\delta$) are reported in parts per million relative to TMS as internal standard. $J$ values are given in hertz. $^{13}C$ 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.

### 4.2. Synthesis of CILs 8 and 14

#### *4.2.1. (3R,3aR,6S,6aS)-3-(Benzyloxy)hexahydrofuro[3,2-b]furan-6-yl benzenesulfonate* ***6***

A mixture of the alcohol **3** (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 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** as white crystals in 99% yield. Mp: 93–95 °C; $[\alpha]_D^{25}$ +92.7 (*c* 0.25, $CHCl_3$); IR (neat) $\nu$=3065, 3032, 2877, 1449, 1367, 1189, 1100, 1043, 971, 947, 902, 820, 750 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 3.57 (dd, $J$=7.6 and 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, $CDCl_3$) $\delta$ 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 ($10CH_{Ar}$), 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.

#### *4.2.2. 3-Methyl-1-(3R,3aR,6S,6aR)-[6-(benzyloxy)-hexahydrofuro [3,2-b]furan-3-yl]imidazolium trifluoromethanesulfonate* ***7***

A mixture of the sulfonate **6** (300 mg, 0.8 mmol) and *N*-methylimidazole (392 mg, 4.7 mmol) was irradiated under microwaves 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 **7** as a yellow viscous oil in 50% yield. $[\alpha]_D^{25}$ +103.4 (*c* 0.53, acetone); IR (neat) $\nu$=3425, 3426, 3152, 3099, 1638, 1560, 1456, 1429, 1368, 1254, 1224, 1166, 1074, 1030 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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 ($5CH_{Ar}$), 137.4 (C); HRMS (M−OTf) $m/z$ (%) calcd for $[C_{17}H_{21}N_2O_3]^+$: 301.1547, found: 301.1556.

#### *4.2.3. 3-Methyl-1-(3R,3aR,6S,6aR)-[6-(hydroxy)-hexahydrofuro [3,2-b]furan-3-yl]imidazolium trifluoromethanesulfonate* ***8***

Trifluoromethanesulfonic acid (3 mL, 36 mmol) was added under an argon atmosphere to a solution of benzylated imidazolium salt **7** (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 **8** as a yellow viscous oil in 97% yield. $[\alpha]_D^{20}$ +62.5 (*c* 0.70, acetone); IR (neat) $\nu$=3500, 3518, 3119, 2965, 2891, 1634, 1580, 1558, 1259, 1171, 1031, 851, 760, 639 $cm^{-1}$; $^1H$ NMR (360 MHz, acetone-$d_6$) $\delta$ 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-$d_6$) $\delta$ 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.

#### *4.2.4. (3R,3aR,6S,6aS)-3-(Acetoxy)hexahydrofuro[3,2-b]furan-6-yl trifluoromethanesulfonate* ***10***

Pyridine (3.8 mL, 47 mmol) was added to a solution of acetate **9** (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 mmol). 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 **10** as a colourless oil (13.5 g, 99%). $[\alpha]_D^{20}$ +86.2 (*c* 0.52, $CHCl_3$); IR (neat) $\nu$=2987, 2937, 2881, 1745, 1415, 1372, 1243, 1212, 1146, 1098, 948, 908 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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.

#### *4.2.5. General procedure for the synthesis of compounds* ***11*** *and* ***13***

A mixture of the triflate **10** (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 **11** (or **13**) as a yellow oil.

*4.2.5.1. 3-Methyl-1-(3R,3aR,6S,6aR)-[6-(acetoxy)-hexahydrofuro[3,2-b]furan-3-yl]imidazolium trifluoromethanesulfonate **11**.* Yield: 46%; $[\alpha]_D^{25}$ +82.0 (*c* 0.65, acetone); IR (neat) $\nu$=3521, 3156, 3120, 2984, 2888, 1739, 1580, 1558, 1375, 1258, 1164, 1030, 639 $cm^{-1}$; $^1H$ NMR (360 MHz, MeOD-$d_4$) $\delta$ 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-$d_6$) $\delta$ 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.

*4.2.5.2. 2,3-Dimethyl-1-(3R,3aR,6S,6aR)-[6-(acetoxy)-hexahydrofuro[3,2-b]furan-3-yl]imidazolium trifluoromethanesulfonate **13**.* Yield: 50%; $[\alpha]_D^{25}$ +131.7 (*c* 0.50, acetone); IR (neat) $\nu$=3508, 3147, 2961, 2890, 1591, 1532, 1374, 1739, 1259, 1163, 1031, 639 $cm^{-1}$; $^1H$ NMR (360 MHz, MeOD-$d_4$) $\delta$ 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-$d_4$) $\delta$ 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.

*4.2.6. General procedure for the synthesis of compounds **8** and **14***

Concentrated HCl (2 drops) were added to a solution of acetate **11** (or **13**) (3.6 mmol) in ethanol (60 mL). The mixture was heated in 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 **8** (or **14**) as a yellow oil.

*4.2.6.1. 3-Methyl-1-(3R,3aR,6S,6aR)-[6-(hydroxy)-hexahydrofuro[3,2-b]furan-3-yl]imidazolium trifluoromethanesulfonate **8**.* Yield: 90%.

*4.2.6.2. 2,3-Dimethyl-1-(3R,3aR,6S,6aR)-[6-(hydroxy)-hexahydrofuro[3,2-b]furan-3-yl]imidazolium trifluoromethanesulfonate **14**.* Yield: 90%; $[\alpha]_D^{20}$ +112.3 (*c* 0.50, acetone); IR (neat) $\nu$=3479, 3148, 2960, 2888, 1634, 1591, 1538, 1423, 1253, 1170, 1032, 758, 639 $cm^{-1}$; $^1H$ NMR (360 MHz, MeOD-$d_4$) $\delta$ 2.66 (s, 3H, $H_m$), 3.49 (dd, *J*=9.0 and 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-$d_4$) $\delta$ 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.

*4.2.7. General procedure for the asymmetric aza Diels–Alder reaction of Danishefsky's diene with imine **22***

A mixture of imine **16** (1 mmol), chiral ionic liquid (0.5 equiv) and Danishefsky's diene **15** (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 **17**.

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, $^1H$ and $^{13}C$) were identical to the initial ionic liquid sample. This IL was reused without loss of efficiency (Table 1, entry 2).

*4.2.7.1. (2S)-2,3-Dihydro-2-phenyl-1-[(R)-1-phenylethyl]pyridine-4-(1H)-one **17**.* Mp: 74 °C; $[\alpha]_D^{26}$ +183.7 (*c* 1.96, $CHCl_3$) (de=97% determined by chiral HPLC); IR (neat): 3029, 2975, 1639, 1590, 1494, 1451, 1393, 1294, 1152, 762, 700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 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 and 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 ($CDCl_3$) $\delta$ 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.

*4.2.7.2. (2R)-2,3-Dihydro-2-phenyl-1-[(R)-1-phenylethyl]pyridine-4-(1H)-one (**17** diastereomer).* IR (neat): 3029, 2975, 1639, 1590, 1494, 1451, 1393, 1294, 1152, 762, 700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 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 and 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 ($CDCl_3$) $\delta$ 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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