Design and Scalable Synthesis of New Chiral Selectors. Part 2: Chiral Ionic Liquids Derived from Diaminocyclohexane and Histidine

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ABSTRACT: We disclose the conception and synthesis of new chiral selectors useful for enantioselective liquid−liquid extraction processes (ELLE). We report synthetic methods giving access to substantial amounts of the compounds, at least at the multigram scale. Two series are examined, i.e. ionic liquids based on diaminocyclohexane (DACH) and histidine, respectively.

1. INTRODUCTION

Traditional methods for the separation of racemic mixtures include crystallization of diastereomeric salts, chiral chromatography and enzymatic resolution. Each method may have certain advantages (efficiency, ease of handling, economy, etc.) over the others for a particular chiral compound. However, the selection and optimization of the method can only be performed on a case-by-case basis.

Therefore, there is a continuous need for the search of both new chiral tools and alternative general strategies, able to resolve racemic mixtures in a cost, time and waste saving manner. A promising methodology relies on the ability of a chiral selector to discriminate between the two enantiomers of a racemate, thus making the enantiomeric separation of racemic mixtures possible, for example, by transport across a chiral membrane, or by liquid−liquid extraction with a chiral host, in the case of hydrophilic substrates.[1]

As part of our continuous program on the search of new chiral selectors,[2] we wish to disclose our strategies and efforts for the conception and synthesis of new tools useful for liquid phase resolution processes (so-called ELLE).[1] In all cases, we designed synthetic methods allowing access to substantial amounts of the compounds, at least at multigram scale. In this paper we focus on two series:

(i) on "chiral benzathines" (CBs), these chiral selectors being designed for enantioselective recognition either in the solid or the liquid state, and giving access to a fundamentally new class of salts belonging to the third generation of ionic liquids, i.e. "chiral ionic liquid benzathines" (CILBs). These new tools open a new possibility for resolutions processes via liquid−liquid demixtion (vide infra).

(ii) we generalized our previous studies on chiral ionic liquids derived from (S)-histidine, in order to obtain more hydrophobic salts for liquid−liquid separations.

2. BACKGROUND OF ELLE PROCESSES AND NEW INSIGHTS

A series of recent publications describes new insights in the field of optical resolution. Usually, when applied to large-scale processes, this kind of methods relies on the formation of solid diastereomeric salts that are separated by filtration. However, filtration, drying and handling of substantial amounts of solids may be uneasy.[3] New approaches on liquid-phase resolution methods may circumvent the problem of handling large amounts of solid materials. For example, in 2008 was reported the successful extraction of one enantiomer into an organic phase by selective coordination to a hydrophobic selector, leaving the uncomplexed enantiomer in the aqueous phase.[4] Thus, resolution of racemic N-benzyl α-amino acids has been achieved by a liquid−liquid extraction process using a lipophilic chiral salen−cobalt(III) acetate complex. As a result, the (S)-enantiomer predominated in the aqueous phase, while the (R)-enantiomer was driven into the organic phase by complexation to cobalt. The complexed (R)-amino acid was then quantitatively released by a reductive (CoIII−CoII) counter-extraction. Both enantiomers were obtained with more than 90% ee. The major drawback of this approach resided in the necessity to use rather harsh conditions (reduction with $NaBH_4$) to release the complexed amino acid. In 2009 was reported another new biphasic chiral extraction for the separation of mandelic acid enantiomers.[5] The segregation of mandelic acid enantiomers was studied with O,O′-dibenzoyl-(2S,3S)-4-toluoyl-tartaric acid (DTTA) in the organic phase and β-CD derivatives in the aqueous phase; the influence of the extractant types, concentrations and pH was investigated. β-CD derivatives have stronger recognition abilities for (S)-mandelic acid than for (R)-mandelic acid, while DTTA preferentially recognizes (R)-mandelic acid. The highest enantioseparation efficiency (with a maximum enantioselectivity of 1.527) is obtained at pH 2.7 and a 2:1 ratio of [D-(1)-DTTA]:[HP-β-CD]. The results indicate that the biphasic (i.e., having a chiral selector in each phase) chiral extraction is of stronger ability than

Figure 1. (*R*)-BrHPP. Benzathine salt.

Ar^1, Ar^2 = Ph, 2-pyridyl, 3-pyridyl, 4-pyridyl

Figure 2. Targeted DACH derivatives ("chiral benzathines").
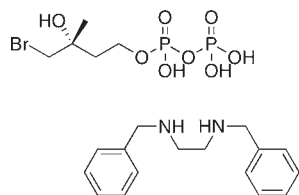
the monophasic (*i.e.* having a chiral selector in only one phase) chiral extraction. Most of these studies have been recently reviewed.[1,6]

Room-temperature ionic liquids (RTILs) are, as their name implies, low-melting salts resulting from the adequate combination of organic cations with various noncoordinating anions. They have a wide liquidus temperature range, and are able to dissolve a large range of species including organic, inorganic and organometallic compounds.[7] Interestingly, they do not show any detectable vapor pressure at near or room temperature and usually possess high thermal stability. Therefore, RTILs are often considered as novel environmentally benign solvents in chemical reactions, multiphase bioprocess operation, batteries and fuel cells investigations.
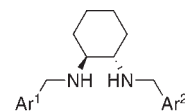
Armstrong and co-workers reported [bmim][PF$_6$]—water distribution coefficients for a set of 40 compounds including three aromatic amino acids.[8] Also interestingly, Smirnova et al. reported that in the presence of 0.05—0.10 mol L^{-1} dicyclohexano-18-crown-6, the amino acids glycine, tryptophan, leucine and alanine can be extracted efficiently by [bmim][PF$_6$] from an aqueous solution.[9] Thus, literature gives a few successful examples of liquid—liquid extraction using ionic liquids, but not in an enantiodiscriminating manner at this stage.

Our idea is to combine the two approaches described before, i.e. to benefit from RTILs properties for liquid—liquid resolution. In other terms, we are currently investigating the development of *liquid—liquid selective extraction of enantiomers by chiral ionic liquids*.[10] As discussed before, the attraction of such a method is that it may circumvent the use of excessive handling of solids, which is associated with classical resolution by crystallization of diastereomeric salts; on a production scale this is often the slowest step in the process. A very recent report describes the first successful approach in this field.[11]

3. CHIRAL IONIC LIQUIDS FROM DACH

Our interest for this series of chiral selectors is a direct consequence of a previous collaborative study between our research groups and a pharmaceutical start-up (Innate-Pharma, Marseilles, France). Indeed, we were interested at this time in the synthesis and purification of the enantiomers of BrHPP, an immunostimulant phosphoantigen (Figure 1).[12] We finally observed that nice crystallization occurred when using benzathine, a well-known biocompatible diamine, for preparing BrHPP salts (Figure 1). This allowed purification as well as easy handling and stabilization of the compound.[13]

We assumed that this behavior was due to the especially strong ionic interactions between the anionic and cationic partners of the salt. As a consequence, we imagined that if we could use chiral derivatives of benzathine, we could expect strong enantiodiscriminating properties towards the enantiomers of chiral compounds.


Compound	Ar^1	Ar^2	Nature
(*S,S*)-**1a**	Ph	2-pyridyl	*Mixed*
(*S,S*)-**1b**	Ph	3-pyridyl	*Mixed*
(*S,S*)-**1c**	Ph	4-pyridyl	*Mixed*
(*S,S*)-**1d**	2-pyridyl	2-pyridyl	*Symmetric*
(*S,S*)-**1e**	3-pyridyl	3-pyridyl	*Symmetric*
(*S,S*)-**1f**	4-pyridyl	4-pyridyl	*Symmetric*
(*S,S*)-**1g**	2-pyridyl	3-pyridyl	*Dissymmetric*
(*S,S*)-**1h**	2-pyridyl	4-pyridyl	*Dissymmetric*
(*S,S*)-**1i**	3-pyridyl	4-pyridyl	*Dissymmetric*

Figure 3. Prepared (1*S*,2*S*)-DACH-based chiral benzathines.

Scheme 1. Synthesis of symmetric DACH-based compounds

1d, Ar = 2-pyridyl
1e, Ar = 3-pyridyl
1f, Ar = 4-pyridyl
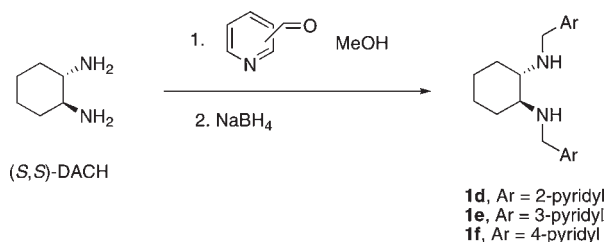
For this purpose, we selected diaminocyclohexane (DACH) as the ideal starting material, because of its availability as both enantiomers, and of the previous applications of its derivatives in various asymmetric processes.[14] The required structures must possess at least one moiety able to be either alkylated or protonated in order to obtain ionic liquids. We thus selected pyridine derivatives of DACH as targets (Figure 2). Although some examples of this series have been previously described (vide infra), literature still lacks complete information on the synthesis and comparison of all isomers. Our first set of experiments was thus devoted to the systematic preparation and study of all possible compounds in this family.

Indeed, depending on aryl substituents Ar^1 and Ar^2, the physicochemical properties of the compound itself as well as of its salts may be quite different. In our search for new chiral ionic liquids, it was thus useful to examine the structure/melting point relationship in this series, as well for symmetric as for dissymmetric derivatives.

3.1. Synthesis of the Parent Diamines. This study was one of our main goals in the frame of the INTENANT program.[15] We choose to synthesize all the possible products of reaction between (1*S*,2*S*)-diaminocyclohexane with benzene-, pyridine-2-, pyridine-3- and pyridine-4-carboxaldehydes (Figure 3). As we
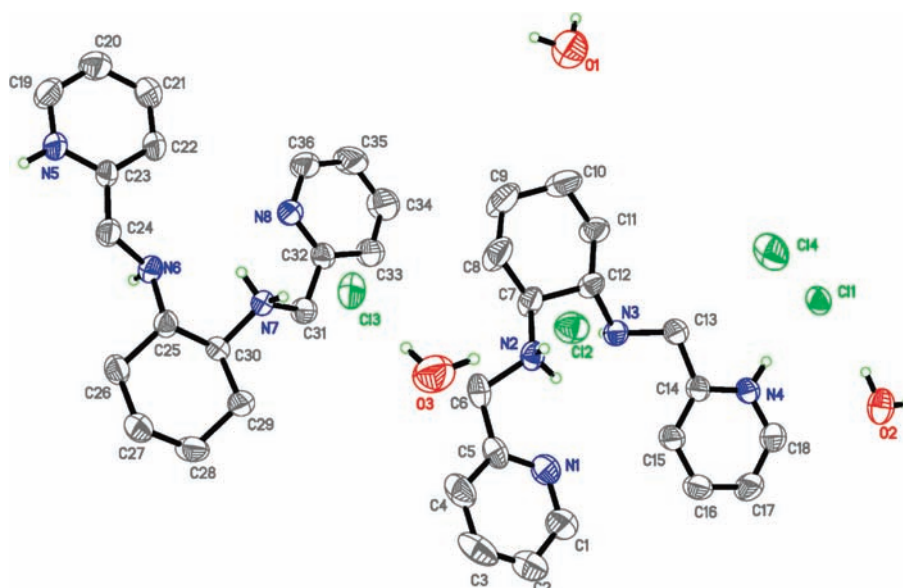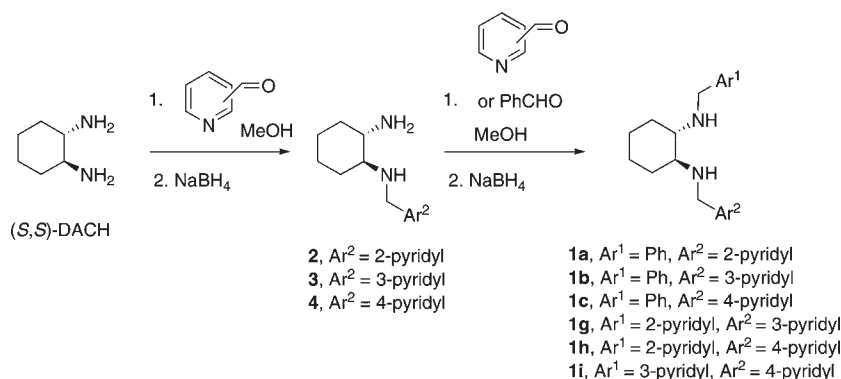
Figure 4. Ellipsoid drawing (50% probability) of the molecular structure of (1S,2S)-**1d**, HCl, H$_2$O.

Scheme 2. Synthesis of mixed and dissymmetric DACH-based diamines

were not interested by the well-known dibenzyl derivative that lacks an additional nucleophilic position, we engaged on the synthesis of the nine possible targets: three compounds are *mixed* (bearing both phenyl and pyridyl residues), three are *symmetric* (bearing two identical pyridyl residues) and another three are *dissymmetric* (bearing two different pyridyl residues). At the beginning of this project in 2008, only two compounds in this series were known, i.e. **1a** and **1d**.[16] In 2009 was reported the synthesis of (R,R)-enantiomers of compounds **1e** and **1i**.[17] Finally, this study represents the first complete data for the whole set of compounds.

The general procedure for the synthesis of symmetric 1,2-diaminecyclohexane-based compounds **1d**, **1e** and **1f** is depicted in Scheme 1. It classically relies on a reductive amination process.[16−18]

After purification by column chromatography, the preparation of the corresponding hydrochloride salts was carried out with 3 equiv of 1 M HCl. Hydrochlorides were dried under vacuum and recrystallized from *i*-PrOH. Full characterization of diamine [(S,S)-**1d**] hydrochloride was performed by single-crystal diffraction. In the asymmetric unit are present: two molecules of diamine (S,S)-**1d**, four chloride anions and three water molecules

(Figure 4). Positions of hydrogen atoms were located unambiguously by means of Fourrier difference function. Worthy of note is that only one of the secondary amine nitrogen is protonated, as is also only one of two pyridine rings. This behavior was not obvious before X-ray analysis, as we initially expected to observe two similarly protonated nitrogens, either the two secondary amines or the two pyridines. This observation was of main importance for our study since it opened the road for the construction of protic ionic liquids (vide infra). This also may explain the unexpected difficulty encountered when we tried to perform a selective alkylation on the pyridine rings.[19]

For the synthesis of mixed and dissymmetric DACH-based diamines, we modified the procedure as shown in Scheme 2. The modification consists of a sequence of two reductive amination reactions using two different aldehydes successively. Intermediate compounds **2a**−**c** were isolated and characterized. Final compounds were obtained after crystallization with overall yield 20−40% and transformed in their hydrochloride salts that proved to be much more stable than the parent diamines, which slowly decomposed when stored in free form.

3.2. Preparation of DACH-Based Diamine Ionic Liquids. An ionic liquid is a salt having a melting point below the boiling point
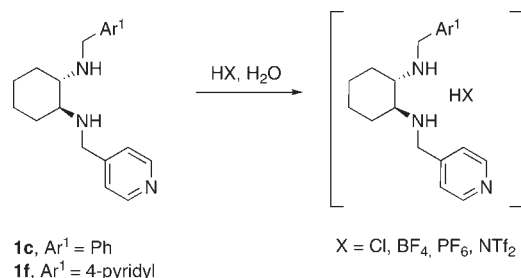
Scheme 3. Diamine salts preparation

1c, Ar^1 = Ph
1f, Ar^1 = 4-pyridyl

X = Cl, BF$_4$, PF$_6$, NTf$_2$

Table 1. Selected physical properties of diamine salts

salt	T_m or T_g °C	$[\alpha]_D$ c = 1, MeOH
1c, HPF$_6$	−18.7 (T_g)	+40.1
	79 (T_m)	
1f, HPF$_6$	−19.1 (T_g)	+41.7
	81 (T_m)	
1c, HBF$_4$	99	+69.7
1f, HBF$_4$	113	+58.5
1c, HNTf$_2$	0.3 (T_g)	+36.2
1f, HNTf$_2$	5.1 (T_g)	+58.5

of water.[7] According to this definition, any kind of salt having a melting temperature below 100 °C may be called an ionic liquid. One of the most commonly used methods to make ionic liquids is the alkylation of a heterocyclic moiety by n-alkyl chains. The melting point of the ionic liquids obtained from a given heterocycle depends both on the alkyl substituent(s) and the counteranion. Commonly used anions in ionic liquid chemistry are bis(trifluoromethanesulfonyl)imide, hexafluorophosphate and tetrafluoroborate. These noncoordinating anions efficiently delocalize the negative charge, thus lowering the melting point. Thus, we decided to synthesize the corresponding salts of our diamines with hexafluorophosphoric acid (HPF$_6$), tetrafluoroboric acid (HBF$_4$) and bis(trifluoromethanesulfonyl)imide (HNTf$_2$). Hydrochloric acid salts were also prepared to compare their melting points with those of the different salts obtained. A collection of eight diamine salts was prepared (Scheme 3) starting from two diamines 1c and 1f. We selected these two examples for comparing mixed and symmetric samples. The physical properties of received salts are compared in Table 1.

First, we were delighted to observe that two compounds from Table 1 are liquids at room temperature, albeit quite viscous. Compound 1c, HNTf$_2$, has a glass transition temperature of +0.3 °C, and its structural analogue 1f, HNTf$_2$, has a glass transition temperature of +5.1 °C. Hexafluorophosphate salts have even lower glass transitions but crystallize after some days, while chorides (not presented in the table) are high-melting solids (mp > 150 °C). Compound 1c, HBF$_4$, is also just in the range of an ionic liquid, with a melting point of 99 °C, forming colorless monoclinic crystals in water. These kinds of low-melting-point salts, having a proton instead of an alkyl chain, are called protic ionic liquids.

All the salts of HPF$_6$, HBF$_4$ and HNTf$_2$ acids show a rather good correlation with our expectations: mixed (and thus nonsymmetrical) 1c derivatives have generally lower melting temperatures that the symmetrical 1f analogues. Also, NTf$_2^-$ is, as

Chiral histidinium-based ionic liquid

imidazole part   chiral bifunctional part
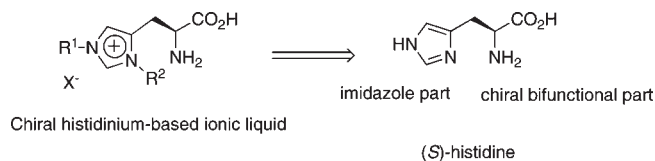
(S)-histidine

Figure 5. Conception of histidinium-based ionic liquid.

expected, the best choice to create ionic liquids, which is coherent with general observations from literature. In this series, the melting points decrease following the anion order: Cl$^-$ > BF$_4^-$ > PF$_6^-$ > NTf$_2^-$.

In addition to this study, we used hydrochloric acid to prepare mono-, bis- and tris-hydrochlorides of 1c. As expected, NMR ^{1}H analyses showed that HCl protonates at first one of the secondary amine functions, next the second secondary amine function, and finally the nitrogen atom of one pyridine ring. These observations *in solution* for 1c, nHCl, differ from those of *crystalline* 1d, HCl, X-ray analyses of which showed that both of the secondary amines and one of the pyridine rings is protonated (Figure 4). However, the actual position of proton(s) when these compounds are either dissolved in ionic liquids or in the form of ionic liquids remains unknown thus far. One can wonder if protons in an ionic environment can pass from aliphatic to aromatic nitrogen atom by diffusion processes. Current studies are engaged in our group to unravel this behavior.

4. SYNTHESIS AND PROPERTIES OF CHIRAL HISTIDINIUM-BASED IONIC LIQUIDS

Since our insights for liquid-phase resolution procedures rely on a final extraction of one enantiomer in aqueous medium, the hydrophobicity of the ionic liquids is a prerequisite. This point is the major drawback of the previously studied CILBs in which most examples are quite hydrophilic. Some years ago we envisioned (S)-histidine, a commercially available natural amino acid, as a key chiral starting material for the elaboration of dissymmetric imidazolium moieties by direct modification of the side chain, thus leaving free the amino acid function of the obtained chiral ionic liquids.[20] In the context of liquid−liquid resolution with chiral ionic liquids, the amino acid part seems to be the best candidate for separation processes because of possible strong acid−base interactions. Indeed, the side chain of histidine possesses an imidazole ring from which an imidazolium cation (one of the most commonly used cation in ionic liquids) can be constructed. The chiral bifunctional unit of the amino acid remains unchanged (Figure 5). However the histidinium salts having a free amino and/or acid function were quite hydrophilic, preventing their use as solvent for selective extraction of enantiomers from an aqueous phase.

The imidazolium cationic part can be modified by varying the substituent on the heterocyclic nitrogen atoms (without modifying the amino acid salt). Desymmetrization of the imidazolium cation generally lowers the melting point. The melting points of organic salts are closely related to the symmetry of ions: the more asymmetric, the lower the melting point. The symmetry allows efficient stacking of ions in the crystal. Conversely, the asymmetry of the cation creates a distortion in the crystal lattice, leading to a decrease in melting temperature. Histidine has three nucleophilic nitrogen atoms with different reactivities. For regioselective alkylation of the nitrogen atoms in the imidazole ring, they each must be treated independently. The chosen strategy was

Scheme 4. Protected histidinium-based ionic liquid preparation

7a[20] : R = nBu, 94%
7b : R = nOct, 98%
7c : R = nDod, 95%
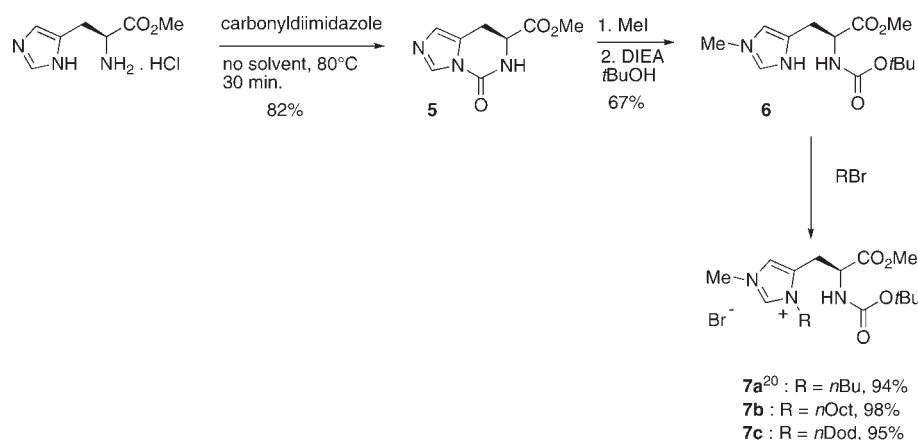
Scheme 5. One-pot deprotection of amino acids and ion metathesis
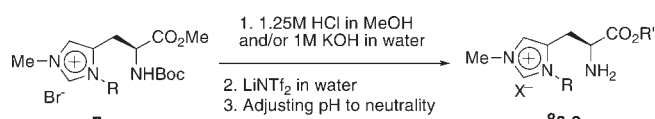
Number	Code	X	R	R'	Yield, %
8a	[mbHis-OMe]-[NTf$_2$]	NTf$_2$	n-Bu	Me	57
8b	[mbHis]-[NTf$_2$]	NTf$_2$	n-Bu	H	58
8c	[moHis-OMe]-[NTf$_2$]	NTf$_2$	n-Oct	Me	60
8d	[moHis]-[NTf$_2$]	NTf$_2$	n-Oct	H	68
8e	[mDodecHis]-[NTf$_2$]	NTf$_2$	n-Dod	H	85

Table 2. DSC analyses and optical rotations of ionic liquids 7a–c and 8a–f

number	code	T_g °C	$[\alpha]_D$ $c = 1$, MeOH
7a	[mbHis-Boc-OMe]-[Br]	−9.2	−15.8
7b	[moHis-Boc-OMe]-[Br]	−23.5	−12.4
7c	[mDodecHis-Boc-OMe]-[Br]	−37.3	−10.5
8a	[mbHis-OMe]-[NTf$_2$]	−44.6	+4.3
8b	[mbHis]-[NTf$_2$]	−16.6	+0.9
8c	[moHis-OMe]-[NTf$_2$]	−18.7	+1.8
8d	[moHis]-[NTf$_2$]	−29.6	+2.3
8e	[mDodecHis]-[NTf$_2$]	−28.5	+0.9

isoelectric point of the amino acid. All the resulting ionic liquids can be dissolved in either acidic or basic aqueous solution and then reprecipitated when shifting pH near to 7. At neutral pH, close to the isoelectric point, the amino acid exists in zwitterionic form, which decreases its solubility. Selective precipitation can be used as a suitable purification method for hydrophobic ionic liquids containing an amino acid part.

This method was scaled up to multigram quantity and showed good results as a simple preparation of hydrophobic ionic liquids containing an amino acid part in the structure. To determine the melting points of every salt, DSC analysis was performed. All compounds 7a–c and 8a–e have glass transition points below 0 °C, confirming their ionic liquid nature (Table 2).

A clear structure/glass transition temperature relationship occurs in the series of bromides 7a–c. Increasing alkyl chain length decreases glass transition point. Optical rotation measurements confirm chirality conservation after all reaction steps (Table 2). The optical rotation of bromides 7a–c is counterclockwise, while all other ionic liquids 8a–e turn polarized light clockwise.

previously developed by our team,[20] and allowed selective alkylation of both nitrogen atoms of the imidazole ring without affecting the nitrogen atom of the amino acid part (Scheme 4, compound 7a).

In order to increase their hydrophobicity, we prepared histidinium bearing longer alkyl chains on N-3 (7b and 7c, Scheme 4). In our previous work,[20] compound 7a was directly engaged in a metathesis step with LiNTf$_2$, KPF$_6$ or NaBF$_4$. Afterwards, all NTf$_2^-$ salts were deprotected using common methods for amino acid chemistry. Nevertheless, this strategy led to several variations according to the experimental procedure. Indeed, we sometimes obtained salts that were soluble in water even when containing the hydrophobic NTf$_2^-$ anion. This was explained by the partial reformation of the very hydrophilic hydrochloride salt during the final deprotection step by means of HCl.

We thus developed a new strategy in order to obtain hydrophobic bifunctional ionic liquids in substantial amount. Ion metathesis was moved to the last step of synthesis, after the deprotection of Boc group by an acidic treatment and/or saponification of the methyl ester group (Scheme 5).

Deprotection step(s) along with anion metathesis were carried out in one pot. The resulting ionic liquid precipitated from aqueous solution when adjusting the pH to 7, near to the

5. CONCLUSION

In this paper we disclose the conception and synthesis of new chiral selectors useful for liquid-phase resolution processes. In all cases, we select synthetic methods giving access to substantial amounts of the compounds, at least at multigram scale. We first focus on "chiral benzathines" (CBs). This series gives access to a fundamentally new class of salts belonging to the third generation

of ionic liquids, i.e. "chiral ionic liquid benzathines" (CILBs). Second, we generalize and improve the access to histidine-derived ionic liquids. All these new tools open a new possibility for resolutions processes in the liquid state. Our preliminary studies for liquid-phase recognition are promising, and our studies for applications in the field of resolution processes are in progress.

6. EXPERIMENTAL SECTION

6.1. General Information. The following solvents and reagents were dried prior to use: CH_2Cl_2, Et_2O, THF, MeOH, Et_3N (distilled from calcium hydride, stored over potassium hydroxide pellets). Benzaldehyde, pyridine-2-carboxaldehyde, pyridine-3-carboxaldehyde, pyridine-4-carboxaldehyde and benzylamine were distilled before use. EtOH, petroleum ether, toluene and other starting materials were obtained from commercial suppliers or prepared according to literature procedures.

Optical rotations were measured on a Perkin-Elmer model 241 polarimeter for the sodium D line (589 nm) at RT.

Melting points were determined by Mettler Toledo MP50 automatic melting point system. Each sample was approximately 5 mg in weight and was analyzed in glass capillaries. Melting points were determined at inflection point and verified using internal video record.

Differential scanning calorimetry was performed using Mettler Toledo DSC1 STAR system. Melting points or glass transition states were determined on temperature rising curves on half-distance of baseline change. Glass transitions were measured with relaxation when it was present.

NMR spectroscopic data were obtained with Bruker Advance 300 and Bruker Advance 400. Chemical shifts are quoted in parts per million (ppm) relative to residual solvent peak using tables of chemical shifts of solvents. The chemical shifts are expressed in ppm. The coupling constants (J) are expressed in Hz. The multiplicities of the signals are abbreviated as: s (singlet), d (doublet), t (triplet), q (quadruplet), dd (doublet of doublet), etc.

Mass spectrometry (MS) data were obtained on the PE Sciex API 365 and Applied Biosystems Q Trap spectrometer.

Elemental analyses were obtained from Perkin-Elmer microanalyser CHNS series 2 for H, C and N elements.

Measurement of pH was performed using WTW 315i pH/mV pocket meter, calibrated to three points using commercial standard solutions of pH 10.01, 7.00 and 4.00.

Analytical thin layer chromatography (TLC) was performed using Merck silica gel F254_{60} precoated plates. Chromatograms were observed under UV light and/or were visualised by heating plates after dipping in 10% phosphomolybdic acid in ethanol or Dragendorff reagent. Column chromatographies were carried out with SDS 35–70 μm flash silica gel or aluminium oxide 90 active basic 0.063–0.200 mm from Merck.

6.2. Crystal Structure Determination. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-816872 (**1d**, HCl). These data can be obtained free of charge via www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033 or e-mail: deposit@ccdc.cam.ac.uk).

To determine the structures of compounds the selected crystals were mounted on a glass fiber using perfluoropolyether oil and cooled rapidly to 193 K in a stream of cold N_2. X-ray intensity data of crystals were collected with graphite-monochromated

Mo K_α radiation (wavelength = 0.71073 Å) by using ϕ- and ω-scans on a Bruker-AXS kappa APEX II Quazar diffractometer using a 30-W air-cooled microfocus source (ImS) with focusing multilayer optics at a temperature of 193(2) K. The data were integrated with SAINT,[21] and an empirical absorption correction with SADABS was applied.[22] The structure was solved by direct methods (SHELXS-97)[23] and refined against all data by the full-matrix least-squares methods on F^2 (SHELXL-97).[24]

1d, HCl, H_2O: $C_{36}H_{58}Cl_4N_8O_3$, M = 792.70, monoclinic, space group $P2_1$, a = 16.8959(13) Å, b = 7.2352(6) Å, c = 17.3497(14) Å, β = 96.293(4)°, $\alpha = \gamma$ = 90°, V = 2108.1(3)Å 3, Z = 2, crystal size 0.30 × 0.08 × 0.06 mm^3, 40826 reflections collected (9233 independent, R_{int} = 0.0556), 502 parameters, 14 restraints, R1 [$I > 2\sigma(I)$] = 0.0480, wR2 [all data] = 0.1126, absolute structure parameter: 0.02(5), largest diff. peak and hole: 0.302 and -0.264 e·Å^{-3}, respectively.

6.3. General Procedure for Synthesis of Symmetric DACH-Based Diamines. To a stirred solution of 2- or 3- or 4-pyridinecarboxaldehyde (2 equiv) in methanol was added slowly (1S,2S)-(+)-1,2-cyclohexanediamine (1 equiv) in methanol using a syringe pump. The mixture was stirred for 2 h at ambient temperature, followed by addition of anhydrous sodium sulfate, and was stirred further for another 15 min. The mixture was filtered, and with stirring was added sodium borohydride (4 equiv) in portions over a period of 30 min. The mixture was refluxed for 1 h, and then cooled to ambient temperature followed by addition of distilled water. The solvent was removed under reduced pressure leading to a white solid. The solid was dissolved in water, followed by addition of KOH 1 M solution to pH $\geq$ 10, and was extracted successively three times with dichloromethane. The combined organic layer was dried with Na_2SO_4, filtered and slowly evaporated under reduced pressure, resulting in yellow oil (75–95% yield). Purification was performed by column chromatography on SiO_2. Eluents: EtAc/MeOH/Et_3N = 88:10:2. After the column chromatography was carried out, the hydrochlorides were prepared with 3 equiv of 1 M HCl. Hydrochlorides were dried under vacuum and recrystallized from i-PrOH with total yield 30–60% starting from DACH.

(1S,2S)-N^1,N^2-Bis(pyridin-4-ylmethyl)cyclohexane-1,2-diamine **1f**, 3HCl, H_2O: yield: overall 25% (4.17 g); yellow solid, mp = 210 °C; $[\alpha]_D^{20}$ = +64.5 (c 1, water); ^{1}H NMR (300.18 MHz, D_2O), ppm: 1.14–1.21 (m, 4 H); 1.67–1.76 (m, 2H); 2.12–2.26 (m, 2H); 2.75–2.84 (m, 2H); 4.16 (d, 2H, J = 15,9); 4.38 (d, 2H, J = 15,9); 7.9 (d, 4H, J = 6,3); 8.6 (d, 4H, J = 6.3); ^{13}C NMR (75.48 MHz, D_2O), ppm: 23.8; 28.6; 59.9; 126.8; 141.8; 156.4; mass, CI (NH$_3$)(MeOH/H_2O): 297; analysis, calculated for $C_{18}H_{29}Cl_3N_4O$: C, 51.01; H, 6.90; N, 13.22, found: C, 51.09; H, 7.18; N, 13.27.

(1S,2S)-N^1,N^2-Bis(pyridin-3-ylmethyl)cyclohexane-1,2-diamine **1e**, 3HCl, 2H_2O: yield: overall 39% (4.68 g); white solid, mp = 243 °C; $[\alpha]_D^{20}$ = +51.6 (c 1, water); ^{1}H NMR (300.18 MHz, D_2O), ppm: 1.14–1.21 (m, 4 H); 1.67–1.76 (m, 2H); 2.12–2.26 (m, 2H); 2.83–2.84 (m, 2H); 4.12 (d, 2H, J = 14.2); 4.35 (d, 2H, J = 14.2); 7.93 (dd, 2H, J_1 = 5.8, J_2 = 8.1); 8.51 (d, 2H, J = 8.2); 8.65 (d, 2H, J = 5.7); 8.74 (s, 2H); ^{13}C NMR (75.48 MHz, D_2O), ppm: 21.9; 26.2; 45.1; 58.6; 127.4; 132.1; 141.7; 141.8; 147.8; mass, ES$^+$ (MeOH/H_2O): 297, 189, 147; analysis, calculated for $C_{18}H_{31}Cl_3N_4O_2$: C, 48.93; H, 7.07; N, 12.68, found: C, 48.62; H, 7.44; N, 12.57.

(1S,2S)-N^1,N^2-Bis(pyridin-2-ylmethyl)cyclohexane-1,2-diamine **1d**, 3HCl, H_2O: yield: overall 22% (3.15 g); grey solid, mp = 190 °C; $[\alpha]_D^{20}$ = +50.2 (c 1, water); ^{1}H NMR (300.18 MHz,

D$_2$O), ppm: 1.16−1.32 (m, 4 H); 1.64−1.78 (m, 2H); 2.20−2.29 (m, 2H); 2.83−2.94 (m, 2H); 4.17 (d, 2H, J = 15.7); 4.40 (d, 2H, J = 15.7); 6.57 (m, 2H); 7.64 (d, 2H, J = 8.0); 8.11 (t, 2H, J = 7.8); 8.42 (d, 2H, J = 5.5); ^{13}C NMR (75.48 MHz, D$_2$O), ppm: 23.1; 28.1; 46.0; 59.5; 125.6; 125.8; 143.0; 144.5; 150.4; mass, CI (NH$_3$) (MeOH/H$_2$O): 297; analysis, calculated for C$_{18}$H$_{29}$Cl$_3$N$_4$O: C, 51.01; H, 6.90; N, 13.22, found: C, 51.00; H, 6.96; N, 13.11.

6.4. General Procedure for Synthesis of Mixed and Dissymmetric DACH-Based Diamines. To a stirred solution of 2- or 3- or 4-pyridinecarboxaldehyde (2 equiv) in methanol, (1S,2S)-(+)-1,2-cyclohexanediamine (1 equiv) in methanol was added slowly, using a syringe pump. The mixture was stirred for 2 h at ambient temperature, followed by addition of anhydrous sodium sulfate, and was stirred further for another 15 min. The mixture was filtered, and with stirring was added sodium borohydride (2 equiv) in portions over a period of 30 min. The mixture was refluxed for 1 h, and then cooled to ambient temperature followed by addition of distilled water. The solvent was removed under reduced pressure, leading to a white solid. The solid was dissolved in water, followed by addition of a 1 M KOH solution to pH ≥ 10 and extracted successively three times with dichloromethane. The combined organic layer was slowly evaporated under reduced pressure, resulting in yellow oil (85−95% yield).

To a stirred solution of precedent compound (1 equiv) in methanol was slowly added benzaldehyde (1 equiv). The mixture was stirred for 2 h at ambient temperature, followed by addition of anhydrous sodium sulfate, and was stirred further for another 15 min. The mixture was filtered, and to this mixture was added sodium borohydride (2 equiv) in portions with stirring over a period of 30 min. The mixture was refluxed for 1 h and then cooled to ambient temperature followed by addition of distilled water. The solvent was removed under reduced pressure, leading to a white solid. The solid was dissolved in water, followed by addition of KOH, 1 M solution, to pH ≥ 10 and extracted successively three times with dichloromethane. The combined organic layer was slowly evaporated under reduced pressure, resulting in yellow oil (75−85% yield). Purification was performed by column chromatography on SiO$_2$. Eluents: EtAc/MeOH/Et$_3$N = 88/10/2 for dissymmetric compounds and 96/2/2 for mixed products, i.e. containing benzyl residue. After the column chromatography was carried out, the hydrochlorides were prepared with 3 equiv of 1 M HCl. Hydrochlorides were dried under vacuum and recrystallized from i-PrOH with total yield 20−40% starting from DACH.

*(1S,2S)-N^1-Benzyl-N^2-(pyridin-4-ylmethyl)-cyclohexane-1,2-diamine **1c**, 3HCl, H$_2$O:* yield: overall 21% (7.15 g); beige solid, mp = 204 °C; [α]$_D^{20}$ = +57.8 (c 1, water); ^{1}H NMR (300.18 MHz, D$_2$O), ppm: 1.18−1.51 (m, 4 H); 1.66−1.78 (m, 2H); 2.18−2.32 (m, 2H); 2.93−3.03 (m, 1H); 3.07−3.17 (m, 1H); 4.05 (dd, 2H, J_1 = 13.1, J_2 = 16.1); 4.29 (dd, 2H, J_1 = 13.1, J_2 = 16.1); 7.31 (m, 5H); 7.87 (d, 2H, J = 6.7); 8.59 (d, 2H, J = 6.7); ^{13}C NMR (75.48 MHz, D$_2$O), ppm: 22.6; 22.8; 26.3; 27.7; 47.7; 48.5; 58.2; 58.4; 126.5; 129.3; 129.7; 130.5; 136.9; 141.3; 156.2; mass, ES$^+$ (MeOH/H$_2$O): 296, 189, 147; analysis, calculated for C$_{19}$H$_{30}$Cl$_3$N$_3$O: C, 53.97; H, 7.15; N, 9.94, found: C, 54.17; H, 7.32; N, 9.93.

*(1S,2S)-N^1-Benzyl-N^2-(pyridin-3-ylmethyl)-cyclohexane-1,2-diamine **1b**, 3HCl, H$_2$O:* yield: overall 29% (3.96 g); white solid, mp = 225 °C; [α]$_D^{20}$ = +41.6 (c 1, water); ^{1}H NMR (300.18 MHz, D$_2$O), ppm:: 1.45 (m, 2H); 1.68 (m, 2H); 1.87 (m, 2H); 2.43−2.47 (m, 2H); 3.55 (m, 2H); 4.24 (d, 1H, J = 13.0); 4.38

(d, 1H, J = 13.7); 4.51 (d, 1H, J = 13.0); 4.67 (d, 1H, J = 13.7); 7.48 (m, 5H); 8.13 (dd, 1H, J_1 = 5.8, J_2 = 8.2); 8.74 (d, 1H, J = 8.2); 8.86 (d, 1H, J = 5.8); 8.95 (s, 1H); ^{13}C NMR (75.48 MHz, D$_2$O), ppm: 22.0; 22.1; 26.0; 26.5; 45.4; 49.1; 57.7; 58.3; 127.7; 129.3; 129.8; 130.2; 132.8; 142.0; 142.1; 148.0; mass, ES$^+$ (MeOH/H$_2$O): 296, 189, 147; analysis, calculated for C$_{19}$H$_{30}$Cl$_3$N$_3$O: C, 53.97; H, 7.15; N, 9.94, found: C, 54.40; H, 7.28; N, 9.94.

*(1S,2S)-N^1-Benzyl-N^2-(pyridin-2-ylmethyl)-cyclohexane-1,2-diamine **1a**, 3HCl, H$_2$O:* yield: overall 21% (2.68 g); light-violet solid, mp = 209 °C; [α]$_D^{20}$ = +41.3 (c 1, water); ^{1}H NMR (300.18 MHz, D$_2$O), ppm: 1.21−1.35 (m, 3 H); 1.44−1.55 (m, 1H); 1.77−1.89 (m, 2H); 2.27−2.36 (m, 2H); 2.84 (m, 1H); 3.13 (m, 1H); 4.13 (dd, 2H, J_1 = 16.5; J_2 = 13.2); 4.35 (dd, 2H, J_1 = 16.6; J_2 = 13.2); 7.37−7.45 (m, 5H); 7.76 (m, 2H); 8.31−8.40 (m, 2H); ^{13}C NMR (75.48 MHz, D$_2$O), ppm: 23.2; 23.5; 26.8; 29.7; 46.5; 47.8; 58.1; 59.2; 125.5; 125.6; 129.3; 129.7; 130.8; 141.9; 145.3; 153.3; mass, ES$^+$ (MeOH/H$_2$O): 296, 189, 144; analysis, calculated for C$_{19}$H$_{30}$Cl$_3$N$_3$O: C, 53.97; H, 7.15; N, 9.94, found: C, 54.30; H, 7.48; N, 10.09.

*(1S,2S)-N^1-(Pyridin-3-ylmethyl)-N^2-(pyridin-4-ylmethyl)-cyclohexane-1,2-diamine **1i**, 3HCl, 2H$_2$O:* yield: overall 29% (2.94 g); beige solid, mp = 194 °C; [α]$_D^{20}$ = +65.6 (c 1, water); ^{1}H NMR (300.18 MHz, D$_2$O), ppm: 1.16−1.38 (m, 4 H); 1.64−1.78 (m, 2H); 2.18−2.30 (m, 2H); 2.78−3.03 (m, 2H); 4.09 (d, 2H, J = 16.2); 4.23 (d, 2H, J = 14.0); 4.37 (d, 2H, J = 16.2); 4.43 (d, 2H, J = 14.0); 7.95 (m, 3H); 8.53 (d, 1H, J = 8.4); 8.60−8.68 (m, 3H); 8.78 (s, 1H); ^{13}C NMR (75.48 MHz, D$_2$O), ppm: 23.1; 27.4; 28.3; 45.1; 47.9; 59.3; 59.9; 126.5; 126.6; 127.7; 133.6; 141.3; 142.0; 147.5; 147.6; mass, ES$^+$ (MeOH/H$_2$O): 297, 189, 147; analysis, calculated for C$_{18}$H$_{31}$Cl$_3$N$_4$O$_2$: C, 48.93; H, 7.07; N, 12.68, found: C, 48.13; H, 7.90; N, 12.43.

*(1S,2S)-N^1-(Pyridin-2-ylmethyl)-N^2-(pyridin-4-ylmethyl)-cyclohexane-1,2-diamine **1h**, 3HCl, 2H$_2$O:* yield: overall 20% (2.48 g); beige solid, mp =173 °C; [α]$_D^{20}$ = +44 (c 1, H$_2$O); ^{1}H NMR (300.18 MHz, D$_2$O), ppm: 1.12−1.39 (m, 4 H); 1.66−1.79 (m, 2H); 2.16−2.31 (m, 2H); 2.73 (m, 1H); 3.00 (m, 1H); 4.05 (d, 1H, J_1 = 16.3); 4.35 (d, 1H, J = 15.4); 4.37 (d, 1H, J = 16.3); 4.57 (d, 1H, J = 15.4); 7.66 (m, 2H); 8.02 (d, 2H, J = 6.6); 8.22 (t, 1H, J = 7.9); 8.42 (d, 1H, J = 5.1); 8.7 (d, 2H, J = 6.7); ^{13}C NMR (75.48 MHz, D$_2$O), ppm: 23.3; 23.4; 26.9; 29.8; 46.6; 46.9; 58.7; 61.5; 125.7; 126.1; 127.2; 141.4; 141.8; 146.1; 152.6; 153.4; mass, ES$^+$ (MeOH/H$_2$O): 297; analysis, calculated for C$_{18}$H$_{31}$Cl$_3$N$_4$O$_2$: C, 48.93; H, 7.07; N, 12.68, found: C, 48.73; H, 6.78; N, 11.89.

*(1S,2S)-N^1-(Pyridin-2-ylmethyl)-N^2-(pyridin-3-ylmethyl)-cyclohexane-1,2-diamine **1g**, 3HCl, 2H$_2$O:* yield: overall 29% (2.89 g); white solid, mp = 221 °C; [α]$_D^{20}$ = +60.9 (c 1, water); ^{1}H NMR (300.18 MHz, D$_2$O), ppm: 1.08−1.47 (m, 4 H); 1.64−1.80 (m, 2H); 2.21−2.32 (m, 2H); 2.68 (m, 1H); 3.04 (m, 1H); 4.03 (d, 1H, J_1 = 16.2); 4.33 (dd, 2H, J_1 = 16.3, J_2 = 13.8); 4.54 (d, 1H, J_2 = 13.8); 7.74 (dd, 2H, J_1 = 16.8, J_2 = 17.5); 8.00 (t, 1H, J = 6.5); 8.25 (t, 1H, J = 8.3); 8.40 (d, 1H, J = 6.0); 8.58 (d, 1H ; J=8.1); 8.73 (d, 1H, J = 8.0) ; 8.84 (s, 1H); ^{13}C NMR (75.48 MHz, D$_2$O), ppm: 23.3; 23.4; 26.8; 29.7; 44.5; 46.8; 58.6; 61.2; 125.8; 126.2; 127.9; 131.9; 141.3; 142.3; 146.2; 148.4; 153.1; mass, ES$^+$ (MeOH/H$_2$O): 297, 189, 144; analysis, calculated for C$_{18}$H$_{31}$Cl$_3$N$_4$O$_2$: C, 48.93; H, 7.07; N, 12.68, found: C, 48.96; H, 7.29; N, 12.59.

6.5. Preparation of DACH Diamine-Based Ionic Liquids. The corresponding DACH diamine-based compound, in the form of hydrochloride hydrate, was added to 1 M water solution

of KOH up to pH ≥ 12. The resulting mixture was extracted three times with CH$_2$Cl$_2$. Combined organic layers were evaporated and dried under vacuum line. As a typical example, the preparation of **1f**, HNTf$_2$, was carried out by adding one equivalent of bis(trifluoromethanesulfonyl)imide (5 mmol, 1.4 g) in CH$_3$CN to 1.48 g (5 mmol) of the compound **1f** in the form of free base. The obtained mixture was stirred for 30 min, evaporated and dried under vacuum line. The same procedure was repeated for all other compounds of this series.

*(1S,2S)-N^1-Benzyl-N^2-(pyridin-4-ylmethyl)cyclohexane-1,2-diamine **1c**, HBF$_4$:* yield: 99% (1.92 g); brown solid, mp = 99 °C; [α]$_D^{20}$ = +69.7 (*c* 1, MeOH); ^{1}H NMR (300,18 MHz, MeOD), ppm: 1.04−1.52 (m, 4H); 1.81 (m, 2H); 2.27 (m, 2H); 2.49 (dt, 1H, J$_1$ = 11 Hz, J$_2$ = 4 Hz); 2.79 (dt, 1H, J$_1$ = 11 Hz, J$_2$ = 4 Hz); 3.72 (d, 1H, J = 14.7 Hz); 3.98 (d, 1H, J = 14.7 Hz); 4.21 (AB, 2H, J$_{AB}$ = 13.2); 7.42 (m, 6H); 8.45 (d, 2H, J = 6.2 Hz); ^{13}C NMR (75,48 MHz, MeOD), ppm: 23.9; 24.2; 27.2; 30.2; 58.1; 60.2; 123.9; 129.0; 129.2; 129.3; 131.9; 147.5; 152.2; ^{31}B NMR (96, 29 MHz, MeOD), ppm: −0.83 (s); ^{19}F NMR (282,37 MHz, MeOD), ppm: −154.0 (s); mass, ES$^+$ (MeOH): 296, 216, ES$^-$ (MeOH): 87; analysis, calculated for C$_{19}$H$_{26}$BF$_4$N$_3$: C, 59.55; H, 6.84; N, 10.96, found: C, 59.16; H, 6.68; N, 10.74.

*(1S,2S)-N^1-Benzyl-N^2-(pyridin-4-ylmethyl)cyclohexane-1,2-diamine **1c**, HPF$_6$:* yield: 100% (2.22 g); light-brown solid, mp = 79 °C; [α]$_D^{20}$ = +40.1 (*c* 1, MeOH); ^{1}H NMR (300,18 MHz, MeOD), ppm: 1.13−1.54 (m, 4H); 1.87 (m, 2H); 2.34 (m, 2H); 2.62 (td, 1H, J$_1$ = 10.8, J$_2$ = 3.9); 2.89 (td, 1H, J$_1$ = 11.1, J$_2$ = 3.8); 3.85 (d, 1H, J = 15.6 Hz); 4.16 (d, 1H, J = 15.6 Hz); 4.24 (d, 1H, J = 13.2 Hz); 4.34 (d, 1H, J = 13.2 Hz); 7.43−7.53 (m, 5H); 7.77 (d, 2H, J = 6.0 Hz); 8.61 (d, 2H, J = 5.8 Hz); ^{13}C NMR (75,48 MHz, MeOD), ppm: 23.8; 24.1; 27.1; 30.2; 48.4; 58.1; 60.1; 124.6; 129.1; 129.2; 129.4; 131.6; 145.1; 149.5; ^{31}P NMR (121,49 MHz, MeOD), ppm: −143.2 (sept, J = 708.5 Hz); ^{19}F NMR (282,37 MHz, MeOD), ppm: −72.7 (d, J = 708.8 Hz); HRMS (DCI, CH$_4$): calcd for C$_{19}$H$_{26}$N$_3$ (M + H$^+$) 296.2127; found 296.2117.

*(1S,2S)-N^1,N^2-Bis(pyridin-4-ylmethyl)cyclohexane-1,2-diamine **1f**, HPF$_6$:* yield: 100% (2.21 g); light-brown solid, mp = 81 °C; [α]$_D^{20}$ = +41.7 (*c* 1, MeOH); ^{1}H NMR (300,18 MHz, MeOD), ppm: 1.36−1.41 (m, 4H); 1.84 (m, 2H); 2.33 (m, 2H); 2.74 (m, 2H); 4.07 (d, 2H, J = 14.5 Hz); 4.25 (d, 2H, J = 14.3 Hz); 7.60 (d, 4H, J = 5.5 Hz); 8.59 (s, 4H); ^{13}C NMR (75,48 MHz, MeOD), ppm: 24.0; 28.7; 59.5; 124.2; 148.2; 154.3; ^{31}P NMR (121,49 MHz, MeOD), ppm: −143.2 (sept, J = 708.6 Hz); ^{19}F NMR (282,37 MHz, MeOD), ppm: −72.7 (d, J = 708.7 Hz); HRMS (DCI, CH$_4$): calcd for C$_{18}$H$_{25}$N$_4$ (M + H$^+$) 297.2079; found 297.2072.

*(1S,2S)-N^1-Benzyl-N^2-(pyridin-4-ylmethyl)cyclohexane-1,2-diamine **1c**, HNTf$_2$:* yield: 100% (2.89 g); yellow viscous wax, DSC = +0.3 °C (glass transition); [α]$_D^{20}$ = +36.2 (*c* 1, MeOH); ^{1}H NMR (300.18 MHz, CDCl$_3$), ppm: 0.95−1.54 (m, 4H); 1.80 (m, 2H); 2.17 (m, 2H); 2.44 (m, 1H); 2.41 (m, 1H); 3.62 (d, 1H, J = 14.0 Hz); 3.83 (d, 1H, J = 14.0 Hz); 4.04 (d, 1H, J=13.2 Hz); 4.18 (d, 1H, J = 13.2 Hz); 7.19 (d, 2H, J = 5.9 Hz); 7.36 (m, 5H); 8.15 (d, 2H, J = 5.9 Hz); ^{13}C NMR (75.48 MHz, CD$_3$CN), ppm: 24.0; 24.3; 27.3; 30.5; 48.6; 48.7; 57.7; 60.7; 113.3−126.1 (q, 2C, J = 317 Hz); 123.9; 129.3; 129.7; 130.1; 130.6; 148.4; 149.8; ^{19}F NMR (282.37 MHz, CD$_3$CN), ppm: −80.15 (s); mass, ES$^+$ (MeOH): 296, 216, ES$^-$ (MeOH): 280; analysis, calculated for C$_{21}$H$_{26}$F$_6$N$_4$O$_4$S$_2$: C, 43.75; H, 4.55; N, 9.72, found: C, 44.23; H, 4.85; N, 9.34.

*(1S,2S)-N^1,N^2-Bis(pyridin-4-ylmethyl)cyclohexane-1,2-diamine **1f**, HNTf$_2$:* yield: 100% (2.88 g); yellow viscous wax,

DSC = +5.1 °C (glass transition); [α]$_D^{20}$ = +38.5 (*c* 1, MeOH); ^{1}H NMR (300.18 MHz, CD$_3$CN), ppm: 1.31 (m, 4H); 1.84 (m, 2H); 2.33 (m, 2H); 2.64 (m, 2H); 3.93 (d, 2H, J = 14.1 Hz); 4.18 (d, 2H, J = 14.1 Hz); 7.40 (d, 4H, J = 6.0 Hz); 8.57 (d, 4H, J = 6.0 Hz); ^{13}C NMR (75.48 MHz, CD$_3$CN), ppm: 23.9; 28.5; 47.6; 59.6; 120.1 (q, 2C, J = 320 Hz); 123.8; 145; 149.8; ^{19}F NMR (282.37 MHz, CD$_3$CN), ppm: −80.12 (s); mass, ES$^+$ (MeOH): 297, 189, ES$^-$ (MeOH): 280; analysis, Calculated for C$_{20}$H$_{25}$F$_6$N$_5$O$_4$S$_2$: C, 41.59; H, 4.36; N, 12.13, found: C, 41.45; H, 4.31; N, 11.82.

6.6. Chiral Ionic Liquids Based on Histidinium Salts. *Alkylation Step.* The synthesis, purification and full analytical data for compounds **5**, **6** and **7a** have been previously published.[20] To the compound **6** (3.3 mmol, 0.95 g) was added *n*-octylylbromide (16.5 mmol, 2.9 mL). The reaction medium was heated at 90 °C overnight. The resulting biphasic mixture was concentrated in vacuo and dried over the vacuum line at 60 °C for 10 h to give yellow, viscous oil. The same procedure was repeated for compounds **7a** and **7c**.

*(S)-4-(2-(tert-Butoxycarbonylamino)-3-methoxy-3-oxopropyl)-1-methyl-3-octyl-1H-imidazol-3-ium bromide **7b** [moHis-Boc-OMe]-[Br]:.* yield: 98% (1.96 g); yellow viscous oil, DSC = −23.5 °C (glass transition); [α]$_D^{20}$ = −12.4 (*c* 1, MeOH); ^{1}H NMR (300.18 MHz, MeOD), ppm: 0.90 (3H, t); 1.31 (9H, s); 1.41 (12H, m); 1.88 (2H, m); 3.07−3.29 (2H, m); 3.78 (3H, s); 3.88 (3H, s); 4.17 (2H, m); 4.47 (1H, m); 7.37 (1H, s); 8.92 (1H, s); ^{13}C NMR (75.48 MHz, MeOD), ppm: 13.1; 22.3; 26.1; 27.2; 28.8; 28.9; 29.5; 31.5; 35.1; 51.8; 52.2; 118.4; 121.7; 131.6; 171.1; mass ESI$^+$ (MeOH): 396; 340; analysis, calculated for C$_{21}$H$_{38}$BrN$_3$O$_4$: C, 52.94; H, 8.04; N, 8.82, found: C, 52.73; H, 7.94; N, 8.77.

*(S)-4-(2-(tert-Butoxycarbonylamino)-3-methoxy-3-oxopropyl)-3-dodecyl-1-methyl-1H-imidazol-3-ium bromide **7c** [mDodecHis-Boc-OMe]-[Br]:* yield: 95% (1.69 g); yellow viscous oil, DSC = −37.3 °C (glass transition); [α]$_D^{20}$ = −10.5 (*c* 1, MeOH); ^{1}H NMR (300.18 MHz, acetone-d_6), ppm: 0.90 (3H, t); 1.30 (9H, s); 1.41 (18H, m); 2.06 (2H, m); 2.95 (1H, m); 3.37 (2H, m); 3.75 (3H, s); 4.06 (s, 3H); 4.38 (2H, m); 4.47 (1H, m); 7.72 (1H, s); 9.99 (1H, s); ^{13}C NMR (75.48 MHz, MeOD), ppm: 13.1; 22.4; 25.5; 26.0; 27.2; 28.8; 29.1; 29.3; 29.4; 31.7; 32.6; 33.0; 35.1; 51.8; 52.2; 81.6; 121.7; 131.7; 153.8; 171.0; mass ESI$^+$ (MeOH): 452; 396; analysis, calculated for C$_{25}$H$_{46}$BrN$_3$O$_4$: C, 56.38; H, 8.71; N, 7.89, found: C, 56.49; H, 8.34; N, 7.59.

Synthesis of Histidiniums-Based Ionic Liquids (Amino Ester Derivatives). A solution of HCl, 1.25 N in methanol (10 equiv), was added to a stirred solution of histidinium bromide in dry methanol. The mixture was stirred at room temperature for 3 h. The solvents were evaporated, and the residue was partitioned between water and dichloromethane. After separation, the aqueous phase was concentrated under reduced pressure to afford the product as yellow oil. To the resulting oil was added distilled water and LiNTf$_2$ (1 equiv). The resulting mixture was neutralized to precipitate yellow oil-like compound, which was decanted, washed with distilled water and dried under vacuum line. The synthesis, purification and full analytical data for compounds **8a** have been previously published.[20]

*(S)-4-(2-Amino-3-methoxy-3-oxopropyl)-1-methyl-3-octyl-1H-imidazol-3-ium, NTf$_2$ **8c** [moHis-OMe]-[NTf$_2$]:* yield: 60% (1.77 g); yellow viscous oil, DSC = −18.7 °C (glass transition); [α]$_D^{20}$ = +1.8 (*c* 1, MeOH); ^{1}H NMR (300.18 MHz, DMSO-d_6), ppm: 0.85 (t, 3 H); 1.25 (m, 10 H); 1.73 (m, 2H); 3.30 (m, 2H); 3.18 (m, 1 H); 3.75 (s, 3 H); 7.53 (s, 1 H), 9.09 (s, 1 H);

^{13}C NMR (75.48 MHz, CDCl$_3$), ppm: 17.0; 26.2; 28.5; 30.0; 32.7; 32.8; 33.4; 35.4; 39.1; 55.0; 56.3; 117.4−130.1 (q, 2C, J = 311 Hz); 126.3; 126.6; 133.8; 174.1; ^{19}F NMR (282.37 MHz, MeOD), ppm: −79.5 (s); mass ESI$^+$ (MeOH): 296, ESI$^−$ (MeOH): 280.

Synthesis of Histidinium-Based Ionic Liquids (Amino Acid Derivatives). Procedure for the compound **8d**, which was repeated for all other compounds of this series: a solution of 1 M HCl in water (6.5 mmol, 6.5 mL) was added to a stirred solution of histidinium bromide **7b** (3.25 mmol, 1.55 g). The mixture was stirred at room temperature for 3 h. To the resulting mixture was added KOH, 1 M water solution (6.5 mmol, 6.5 mL), and the mixture was stirred at room temperature for 3 h. After that, 1 equiv of LiNTf$_2$ was added. The solution was stirred for 2 h at room temperature. Then, it was neutralized to pH = 7 using HCl solution to precipitate the oil-like yellow substance, which was separated from the water layer, washed with distilled water and dried in vacuo. The synthesis, purification and full analytical data for compound **8b** have been previously published.[20]

(S)-4-(2-Amino-2-carboxyethyl)-1-methyl-3-octyl-1H-imidazol-3-ium, NTf$_2$ **8d** *[moHis]-[NTf$_2$]:* yield: 68% (1.73 g); yellow viscous oil, DSC = −29.6 °C (glass transition); [α]$_D^{20}$ = +2.3 (c 1, MeOH); ^{1}H NMR (300.18 MHz, D$_2$O), ppm: 0.93 (t, 3 H); 1.34−1.43 (m, 12 H); 1.90 (m, 2H); 3.33 (m, 2H); 3.78 (m, 1 H); 3.92 (s, 3 H); 7.45 (s, 1 H); 8.43 (s, 1H); ^{13}C NMR (75.48 MHz, MeOD), ppm: 13.0; 22.3; 26.1; 28.8; 28.9; 29.5; 31.5; 35.1; 47.0; 53.0; 113.5−126.2 (q, 2C, J = 320.4 Hz); 121.9; 122.2; 130.4, 136.2; ^{19}F NMR (282.37 MHz, MeOD), ppm: −79.5 (s); mass ESI$^+$ (MeOH): 282, ESI- (MeOH): 280; analysis, calculated for C$_{17}$H$_{28}$F$_6$N$_4$O$_6$S$_2$: C, 36.30; H, 5.02; N, 9.96, found: C, 36.26; H, 4.80; N, 9.62.

(S)-4-(2-Amino-3-methoxy-3-oxopropyl)-3-dodecyl-1-methyl-1H-imidazol-3-ium, NTf$_2$ **8e** *[mDodecHis]-[NTf$_2$]:* yield: 85% (1.73 g); yellow viscous oil, DSC = −28.5 °C (glass transition); [α]$_D^{20}$ = +0.9 (c 1, MeOH); ^{1}H NMR (300.18 MHz, MeOD), ppm: 0.89 (t, 3 H); 1.29−1.41 (m, 20 H); 1.87 (m, 2H); 3.07 (m, 1 H); 3.77 (s, 3 H); 4.16 (m, 2 H); 7.32 (s, 1 H), 8.83 (s, 1 H); ^{13}C NMR (75.48 MHz, MeOD), ppm: 13.1; 22.4; 26.1; 27.2; 27.3; 28.8; 29.1; 29.3; 29,3; 29.4; 31.1; 35.0; 46.8; 52.9; 117.7−122.0 (q, 2C, J = 320.4 Hz); 117.7; 121.7; 132.2, 136.2; 173.6; ^{19}F NMR (282.37 MHz, MeOD), ppm: −79.5 (s); mass ESI$^+$ (MeOH): 338, ESI$^−$ (MeOH): 280; analysis, calculated for C$_{21}$H$_{36}$F$_6$N$_4$O$_6$S$_2$: C, 40.77; H, 5.87; N, 9.06, found: C, 40.46; H, 5.94; N, 8.84.

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