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Development of L-Proline-Based Chiral Ionic Liquids for Asymmetric Michael Reaction

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Abstract: Different Chiral Ionic Liquids (CIL) based on L-proline have been developed. Simple and efficient synthetic methodologies are used, allowing preparation in good yields for twelve novel CILs using L-proline as a cation or anion combined with suitable counter-ions. A detailed physical and chemical characterization of the CILs was performed to evaluate the influence of counter-ions on the final properties. The most promissory CILs were tested as efficient chiral catalysts in IL media for asymmetric Michael addition reactions of ketones and aldehydes to nitro-olefins. Similar or even better conversions and enantioselectivities (ee up to 95%) compared to the original L-proline were achieved. Additionally, a good product extraction performance using supercritical CO_2 processes was obtained.

Keywords: chiral ionic liquids; L-proline; asymmetric Michael reaction; supercritical CO_2 extraction

Citation: Zalewska, K.; Pinto, I.; Cabrita, L.; Zakrzewska, M.E.; Noronha, J.P.; da Ponte, M.N.; Branco, L.C. Development of L-Proline-Based Chiral Ionic Liquids for Asymmetric Michael Reaction. *Catalysts* **2023**, *13*, 270. https://doi.org/10.3390/catal13020270

Academic Editor: Adriana Maria da Silva

Received: 22 September 2022
Revised: 15 January 2023
Accepted: 17 January 2023
Published: 25 January 2023

1. Introduction

Ionic Liquids (ILs) have received growing attention as the solvents of choice for organic synthesis, mainly due to their tunable features, such as their reduced volatility, high chemical and thermal stability, high ionic conductivity, large electrochemical window, insolubility in supercritical CO_2 ($scCO_2$), recyclability, and their significant dissolution performance of a large range of organic molecules and transition metal complexes [1,2]. In the case of ILs related with their high degree of organization, a transfer of chirality in these chiral media should be expected. It has been proven that many ILs possess a polymeric behavior, which are highly ordered H-bonded liquids, meaning three-dimensional networks of anions and cations are linked together by hydrogen bonds [3–5]. Following the initial work on the preparation and application of Chiral Ionic Liquids (CILs) ([Bmim][lactate] by Seddon and coworkers [6]), a number of new CILs have been synthesized and employed as chiral reaction media, catalysts, or ligands, in order to induce moderate to high enantioselectivities in several reactions, such as the asymmetric Diels–Alder [7,8], the aldol reaction [9,10], the Michael addition [11,12], and the Sharpless dihydroxylation (AD) [13,14], among others. The stunning majority of CILs are obtained from natural amino acids or their derivatives that provide a unique and essential source for chiral cations and anions [15–17].

Proline (Pro) is an abundant chiral scaffold as well as an inexpensive, secondary, and cyclic pyrrolidine-based amino acid [18] This characteristic provides the increase in pKa values (pKa_1 = 1.99 and pKa_2 = 10.60) of its amine compared to primary amino acids. Proline is a bifunctional amino acid available in both enantiomeric forms. Concerning the amino and carboxylic acid group, they can both react as an acid or base and can also facilitate further chemical transformations. Those diverse reasons contribute to proline's role in catalysis as a universal and asymmetric organocatalyst [19–21]. Taking into account the versatile properties of this stable, non-toxic, and powerful organocatalyst, it would seem daring to expect anything less than the discovery of novel, proline-based CILs. Herein,

the synthesis, characterization, and application of a new class of chiral salts derived from commercially available L-proline have been proposed.

2. Results and Discussion

2.1. Design of CILs Based on L-Proline

Synthesis and Characterization of CILs

Different structures of chiral salts developed from L-proline, including six using the amino acid unit as a cation and the other six using it as an anion, are shown in Figure 1. Two different synthetic approaches have been followed in order to develop novel L-proline-based CILs. The protonation of the secondary amine (-NH) from L-proline was performed using hydrochloride acid in a methanol solution. This hydrochloride salt was then exchanged for more appropriate organic anions, such as bis(trifluoromethanesulfonyl)imide ([NTf_2]), **1a**, docusate ([AOT]), **1b**, p-toluenesufonate ([TsO]), **1c**, and saccharinate ([SAC]), **1d**, in order to obtain room temperature CILs (Figure 2). Additionally, two enantiomers from camphorsulfonic acid sodium salt, in the form of anions (R)-CSA, **1e**, and (S)-CSA, **1f**, were combined with the L-proline cation as examples of novel chiral salts containing chirality on both ionic units.

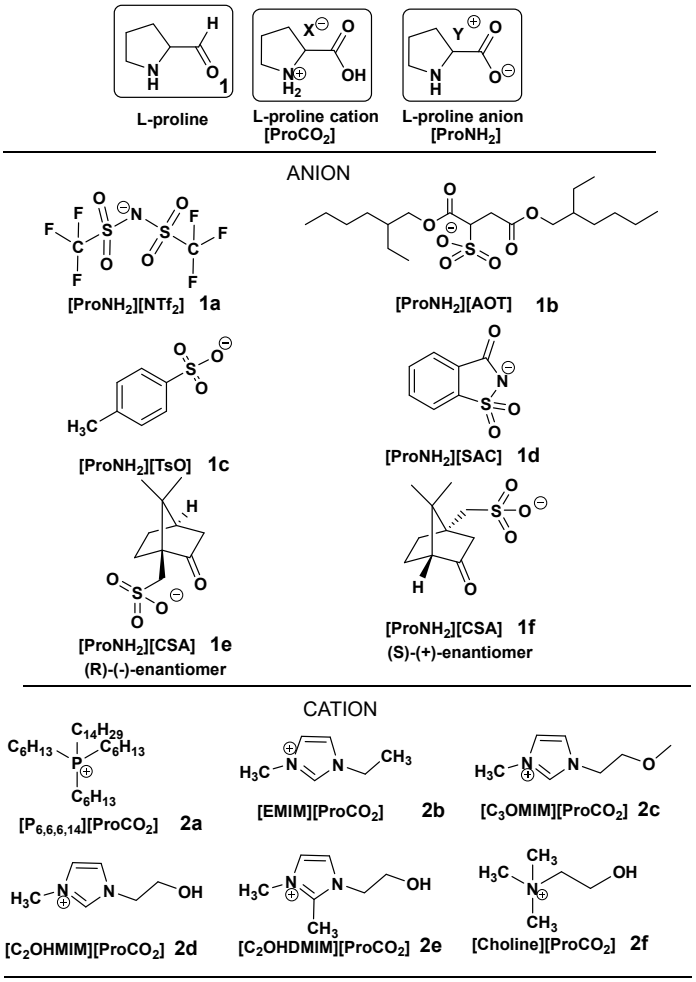


Figure 1. Structures of chiral salts developed from L-proline.

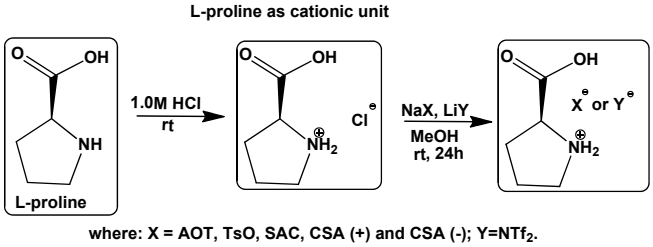


Figure 2. General strategy for the synthesis of CILs based on L-proline as cationic unit.

The selected method to synthesize the proline-based salts with the amino acid as anion was focused on the use of anion-exchange resin methodology (acid-base neutralization method) developed by Ohno and co-workers [22,23]. This strategy led to overcoming many limitations related to the conventional method (anion metathesis), in particular avoiding the contamination of halide salts, the limited variety of commercially available metal salts, and the suitable combination of amino acids to counter ions. In this work, Amberlite IRA-400 resin was efficiently used to exchange halides (bromide or chloride) to the hydroxide form and then this basic solution was neutralized by the addition of an adequate acid solution, as described in Figure 3. The direct acid–base reaction allows for the preparation of the desired proline salt combined with organic cations, such as trihexyltetradecylphosphonium ([$P_{6,6,6,14}$]), **2a**, 1-ethyl-3-methylimidazolium ([Emim]), **2b**, 1-(2-methoxyethyl)-3-methylimidazolium ([C_3Omim]), **2c**, 1-(2-hydroxyethyl)-3-methylimidazolium ([C_2OHmim]), **2d**, and 1-(2-hydroxyethyl)-2,3-dimethylimidazolium([C_2OHDmim]), **2e**. In the case of choline ([Choline]) cation, a direct acid–base reaction was performed due to the commercially available choline hydroxide in a methanol solution (40% w/w), **2f**. After the optimization of this synthetic approach, CILs based on L-proline were obtained in moderate to high yields (66 to 99%). All novel CILs based on L-proline were completely characterized by the ^{1}H and ^{13}C NMR spectroscopy, the Fourier transform infrared (FTIR) spectroscopy, the elemental analysis (C, N, H) and the differential scanning calorimetric (DSC) analysis, in order to check their chemical structure, purity, and chemical and thermal stability. Most of the novel salts derived from L-proline were obtained as colored and viscous Room Temperature Ionic Liquids (RTILs), except in the case of [ProNH_2][R-CSA], **1e**, and [ProNH_2][S-CSA], **1f**, which were developed as white crystalline solids. The color of CILs changed due to the use of L-proline as a cation or anion and the selected counter-ions between yellow, orange, and brown viscous liquids.

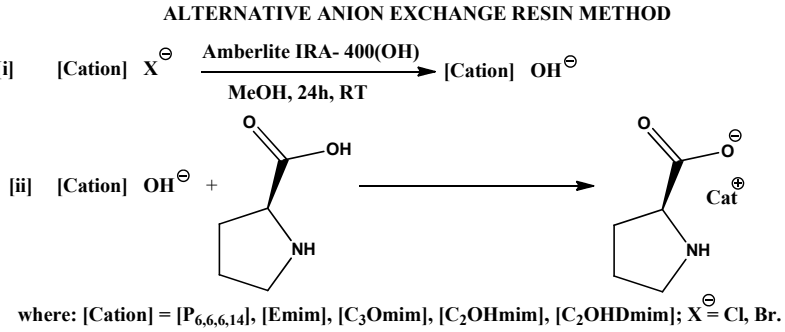


Figure 3. Synthesis of L-proline-based salts using ion exchange resins method.

2.2. Physical and Thermal Properties of CILs Based on L-Proline

Table 1 summarizes all prepared CILs based on L-proline and some of their physical properties, such as optical rotation (α_D) and density values, and thermal properties such as their melting points ™, glass-transition temperatures (Tg), and thermal decompositions (Tdec) were evaluated. The optical rotation values were measured in a methanol solution for all the CILs and the initial L-proline protonated form (1 mg·mL^{-1}) by polarimetry at 20 °C. For most of the CILs, the optical rotations oscillated between −2.0 to −12.7°, with a

±2.0° error (except **1f**). Higher optical rotations values were observed for CILs **2a** and **2e**. In general, salts derived from L-proline as a chiral anion resulted in higher optical rotation values, but these were still significantly lower when compared with the initial L-proline (−41.3 ± 2.0°). This difference can be explained by a stronger influence of organic cations combined with L-proline moiety as an anion. Another relevant observation, all proline salts combined with methylimidazolium cations showed lower optical rotations (**2b**, **2c,** and **2d** with values between −5.3 to −8.8°), except **2e** (−19.0°), compared with phosphonium and ammonium cations. The presence of an acidic proton from methylimidazolium cation can strongly interact with a proline anion compared with [C_2OHDmim] cation, where the acidic proton is replaced by a methyl group. Compounds **1e** and **1f** were developed with the idea of introducing chirality on both cation and anion units and showed the highest optical rotation values –44.0 ± 2.0° for (R) and +66.0 ± 2.0° for (S) enantiomers, respectively, (compared to the literature values: −21.0° for (R)-camphorsulfonic acid and +19.9° for (S)-camphorsulfonic acid, 2 mM in H_2O).

Table 1. Some physical and thermal properties of new, synthesized salts based on L-proline scaffold.

CIL	Physical State	Density [a] [g·cm^{-3}]	α_D [b] [cm^2 g^{-1}]	T_g [°C] [c] (Tm)	T_{dec} [°C] [d]
L-Pro **1**	white powder	—	−41.3	(228 dec.)	238.60
[ProNH_2] [NTf_2] **1a**	yellow liquid	1.63	−12.7	−58.92	287.10
[ProNH_2] [AOT] **1b**	yellow liquid	1.32	−12.0	−61.88	258.40
[ProNH_2] [TsO] **1c**	yellow liquid	0.93	−4.0	−25.07	273.90
[ProNH_2] [SAC] **1d**	white liquid	0.98	−4.5	_ [e]	299.50
[ProNH_2] [(-)CSA] **1e**	white solid	—	−44.0	_ [e] (154) [f]	292.90
[ProNH_2] [(+)CSA] **1f**	white solid	—	+66.0	_ [e] (160) [f]	292.30
[$P_{6,6,6,14}$] [ProCO_2] **2a**	orange liquid	0.93	−17.3	−70.59	290.10
[Emim] [ProCO_2] **2b**	orange liquid	1.19	−8.8	−63.44	247.80
[C_3Omim] [ProCO_2] **2c**	orange liquid	1.24	−5.3	−53.42	256.30
[C_2OHmim] [ProCO_2] **2d**	yellow liquid	1.25	−6.7	−52.60	270.40
[C_2OHDmim] [ProCO_2] **2e**	yellow liquid	1.28	−19.0	−40.30	277.50
[Choline] [ProCO_2] **2f**	brown liquid	0.97	−12.7	−70.24	[g]

[a] Density was measured by pycnometer at 25 °C. [b] Optical rotation values measured in MeOH (1 mg·mL^{-1} ± 2°) by polarimetry at 20 °C recorded on a Perkin Elmer 241MC. [c] Glass transition temperature (Tg) was determined by DSC measurements at a heating/cooling rate of 10 °C min^{-1} for all salts. [d] Decomposition temperature (Tdec) was determined by TGA studies. [e] Not observed by DSC studies. [f] Melting temperature was determined on Electrothermal Melting Point Apparatus. [g] Not determined.

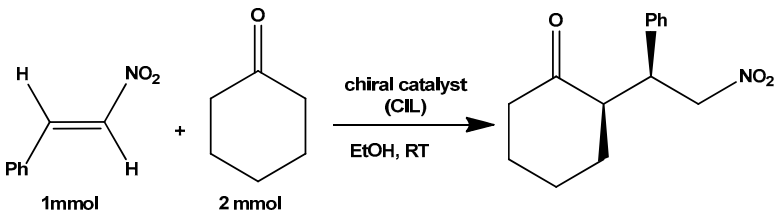
Density measurements were performed using the pycnometer at 25 °C. The higher density values were obtained for CILs **1a**, **1b,** and **2e**, because of the presence of NTf_2 or AOT anions and the imidazolium cation, respectively. In the presence of ammonium or phosphonium cations, the density values were lower than 1 g·cm^{-3}. As expected, the ILs densities decreased with the increase of the substituent's chain lengths. This fact can be attributed to the increased number of interactions between ions caused by the more bulky cations, which cannot pack closely with the anion.

Commercial L-proline, **1**, as a crystalline neutral solid with a higher melting temperature (Tm = 228 °C, decomposes), can be transformed in amorphous salts by simple changes to the counter-ions. It is important to emphasize that the CILs based on L-proline showed lower melting points than the starting materials (e.g., 198 °C to 154 °C in the case of (-) CSA and 200 °C to 160 °C for (+) CSA). In general, all salts based on L-proline were obtained as viscous liquids at room temperature, possessing a characteristic glass transition temperature (Tg) obtained by calorimetric studies (DSC analysis). In the case of L-proline as a cation, we observed a significant influence of counter-ions for Tg values: [ProNH$_2$][AOT] **1b** > [ProNH$_2$][NTf$_2$] **1a** > [ProNH$_2$][TsO] **1c**. When L-proline was used as an anion and combined with different imidazolium cations, the glass transition temperatures oscillated between −63.44 °C (**2b**) to −40.30 °C (**2e**). As expected for this type of cation, transition temperatures were recorded in the typical region. In the case of [P$_{6,6,6,14}$][ProCO$_2$] **2a** and [Choline][ProCO$_2$] **2f,** lower glass transition temperatures were obtained. Decomposition temperatures (Tdec) were analyzed by the TGA analysis for some of the synthesized compounds. As expected, these studies indicated that the selection of the organic cation influences the thermal stability of CILs based on L-proline. [P$_{6,6,6,14}$][ProCO$_2$] presented a higher thermal stability than those based on imidazolium cations. All proline-based salts showed significantly higher decomposition temperatures (258 to 299 °C) compared to the original L-proline (238.60 °C).

2.3. Application of Novel CILs Based on L-Proline as a Catalyst for the Asymmetric Michael Reaction

Some of the CILs based on L-proline were tested as catalysts in the asymmetric Michael reaction. Over the last few years, many research groups have been focused on the development of more efficient and selective catalytic systems using proline derivatives for asymmetric Michael addition reactions [24,25]. It is known that one of the great advantages of using proline as a nucleophile with carbonyl groups or Michael acceptors to form iminium ions or enamines is related to its enhanced nucleophilicity compared with other amino acids, due to its secondary amine functionality and higher pKa value [26,27]. This approach using CILs based on L-proline can replace the toxic and corrosive trifluoroacetic acid [27], often added to increase the diastereo- and enantioselectivities, in enamine-based organocatalysis for asymmetric C-C bond formation. The prepared CILs based on L-proline as anions (**2a** to **2f**) could be applied as organocatalysts in the asymmetric Michael addition of cyclohexanone to trans-nitrostyrene and good conversions and selectivities up to 97% ee were obtained without additional acid. The model reaction was promoted using a chiral catalyst in a range of loading between 10 to 60 mol% using standard and optimized reaction conditions (room temperature, 24 h to 48 h) in ethanol. Table 2 summarizes the catalytic performance of different CILs compared to L-proline in the selected asymmetric Michael reaction. The initial investigation using ethanol as a solvent indicated a reduced catalytic performance using CILs based on L-proline as a cation (19 to 50% of conversion; 53% to 59% ee). Contrarily, for the cases of CILs based on L-proline as an anion, high conversions and moderate to good enantioselectivities (69% to 93%) were observed. Interestingly, Wang's group tested the asymmetric version of the Michael addition of cyclohexanone with chalcone using [Emim][ProCO$_2$] in similar conditions and obtained dr: 15:85 and 69% of ee [28]. In general, it seems that the incorporation of a protic group on the side chain of the cation, as in **2d** and **2e**, led to a decrease in both the catalytic activity and selectivity. The use of a biocompatible [Choline] cation **2f [29]** combined with the proline anion resulted in a significant increase of enantioselectivity to 97%, compared with the other cations already tested.

Table 2. Michael addition of cyclohexanone to trans-nitrostyrene catalyzed by CILs based on L-proline using EtOH as solvent.



Catalyst	Loading Catalyst [mol%]	Conversion [%]	*dr(syn: anti)* [d]	ee [%] [e]
L-PRO [a]	30	≥99	93:7	94
L-PRO [b]	60	≥99	91:9	96
$[ProNH_2][Cl]$ [b]	30	50	85:15	53
$[ProNH_2][PTSA]$ [b]	30	50	75:25	n.d. [e]
$[ProNH_2][AOT]$ [c]	30	19	73:27	55
$[ProNH_2][AOT]$ [b]	60	50	82:18	59
$[ProNH_2][NTf_2]$ [b]	30	34	80:20	58
$[Na][ProCO_2]$ [b]	30	≥99	78:22	40
$[P_{6,6,6,14}][ProCO_2]$ [b]	30	≥99	83:17	69
$[Emim][ProCO_2]$ [b]	30	≥99	86:14	78
$[Emim][ProCO_2]$ [b]	60	≥99	69:31	81
$[C_3Omim][ProCO_2]$ [a]	30	≥99	72:28	74
$[C_3Omim][ProCO_2]$ [b]	60	≥99	75:25	93
$[C_2OHmim][ProCO_2]$ [b]	30	≥99	70:30	62
$[C_2OHDmim][ProCO_2]$ [b]	30	≥99	65:35	55

[a] Reaction time: 48 h. [b] Reaction time: 90 h. [c] Reaction time: 66 h. [d] The ratio of the percentage of one diastereoisomer in a mixture to that of the other was determined using 400.13 MHz ^{1}H NMR spectroscopy comparing the known peaks of the product and the substrate in the aromatic area. [e] Enantiomeric excess and the ratio of the percent of one enantiomer (syn isomer) in a mixture to that of the other were determined by HPLC using Phenomenex Lux 5 µm i-Cellulose-250 × 4.6 Chiral Column, flow 1 mL·min^{-1}, 25 °C column oven, hexane: i-PrOH 90:10, λ = 230 nm. [e] Not determined.

Taking in mind that ILs have been extensively tested as alternative and recyclable solvents for many catalytic and non-catalytic organic transformations, $[Emim][EtSO_4]$ and [Bmim][DCA] were selected as the most promissory reaction media. The replace of ethanol by these ILs provided them with a high enhancement on both the conversions and enanselectivities in most of the cases (Table 3). Particularly, it was possible to improve the catalytic performance for the examples using docusate [AOT] and $[NTf_2]$ as counterions (from 55% to 65% ee for **1b** and from 58% to 96% ee for **1a**). In general, the use of [Bmim][DCA] as an alternative solvent showed better results when compared with $[Emim][EtSO_4]$. Figure 4 presents the model chromatogram with the enantiomers of product A using $[Choline][ProCO_2]$ as a catalyst and [Bmim][DCA] as reaction media (ee = 97%).

Table 3. Michael addition of cyclohexanone to trans-nitrostyrene catalyzed by CILs based on L-proline (30 mol%) using ILs as solvent.

Catalyst	Solvent	Conv. [%] [c]	*dr (syn: anti)* [d]	ee [%] [e]
L-PRO [a]	[Emim][$EtSO_4$]	≥99	90:10	87
L-PRO [a]	[Bmim][DCA]	≥99	93:7	96
[$ProNH_2$][Cl] [a]	[Bmim][DCA]	83	89:11	27
[$ProNH_2$][AOT] [b]	[Emim][$EtSO_4$]	92	78:22	n.d. [f]
[$ProNH_2$][AOT] [b]	[Bmim][DCA]	≥99	90:10	65
[$ProNH_2$][NTf_2] [b]	[Emim][$EtSO_4$]	92	64:36	n.d. [f]
[$ProNH_2$][NTf_2] [b]	[Bmim][DCA]	≥99	91:9	96
[Emim][$ProCO_2$] [b]	[Emim][$EtSO_4$]	≥99	94:6	94
[Emim][$ProCO_2$] [b]	[Bmim][DCA]	≥99	92:8	94
[C_3Omim][$ProCO_2$] [b]	[Emim][$EtSO_4$]	≥99	74:26	76
[C_3Omim][$ProCO_2$] [b]	[Emim][$EtSO_4$]	≥99	75:25	83
[Choline][$ProCO_2$] [b]	[Emim][$EtSO_4$]	≥99	91:9	95
[Choline][$ProCO_2$] [b]	[Bmim][DCA]	≥99	91:9	97

[a] Reaction time: 66 h. [b] Reaction time: 90 h. [c] The conversions were determined using 400.13 MHz ^{1}H NMR spectroscopy. [d] The ratio of the percentage of one diastereoisomer in a mixture to that of the other was determined from 400.13 MHz ^{1}H NMR spectroscopy. [e] Enantiomeric excess and the ratio of the percent of one enantiomer (syn) in a mixture to that of the other were determined by HPLC using Phenomenex Lux 5 µm i-Cellulose 250 × 4.6 Chiral Column, 25 °C column oven. [f] not determined.

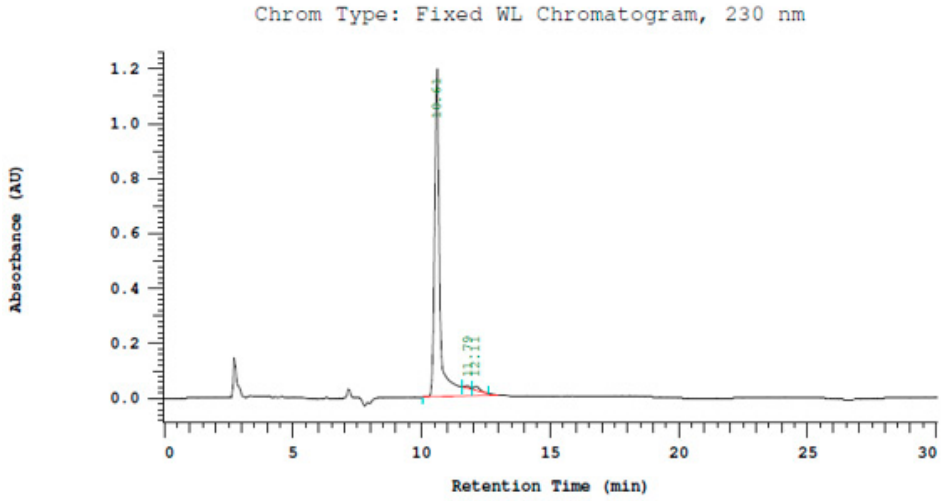
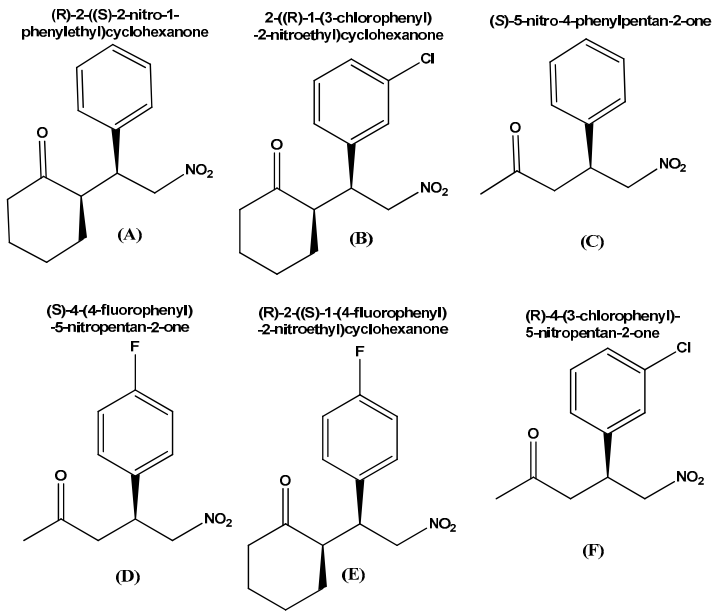


Figure 4. Chromatogram obtained for the analysis of product A using [Choline][$ProCO_2$] as catalyst and [Bmim][DCA] as reaction media (ee = 97%). The enantiomeric excess was determined using chiral HPLC (Phenomenex Lux 5 µm i-Cellulose-250 × 4.6 Chiral Column, hexane: i-propanol, 10/90, flow: 1 mL/min, λ = 230 nm): t_R = 10.61 min (major) and t_R = 12.11 min (minor).

With the success of the above reactions, we continued our study by exploring the asymmetric Michael addition of different nitro-olefins to cyclohexanone or acetone using CILs based on L-proline (Table 4). Moderate to high conversions could be obtained but not for the ee values, except in the case of (R)-4-(3-chlorophenyl)-5-nitropentan-2-one (conversion = 99% and ee = 100%).

Table 4. Asymmetric Michael reaction with CILs based on L-proline (30 mol%, 48 h) using different substrates.



Prod.	Catalyst	Solvent [a]	Conv. [%] [b]	*dr (syn: anti)* [c]	ee [%] [d]
A	L-PRO	EtOH	≥99	93:7	94
A	L-PRO	IL	≥99	91:9	96
A	[$ProNH_2$][NTf_2]	IL	≥99	94:6	94
A	[Emim][$ProCO_2$]	IL	≥99	91:9	97
B	L-PRO	EtOH	99	80:20	47
B	L-PRO	IL	≥99	75:25	31
B	[Emim][$ProCO_2$]	IL	72	69:31	29
B	[Choline][$ProCO_2$]	IL	81	66:34	28
C	L-PRO	EtOH	75	–	(nd) [e]
C	[Emim][$ProCO_2$]	IL	75	–	20
C	[Emim][$ProCO_2$]	none	71	–	33
C	[Choline][$ProCO_2$]	EtOH	79	–	86
D	L-PRO	EtOH	98	–	10
D	L-PRO	IL	94	–	rac.
D	[Emim][$ProCO_2$]	IL	93	–	10
D	[Choline][$ProCO_2$]	IL	94	–	10
E	L-PRO	EtOH	86	84:16	40
E	L-PRO	IL	≥99	84:16	4
E	[Emim][$ProCO_2$]	IL	≥99	78:22	4
E	[Choline][$ProCO_2$]	IL	≥99	94:6	4
F	L-PRO	EtOH	94	–	100
F	L-PRO	IL	≥99	–	31
F	[Emim][$ProCO_2$]	EtOH	≥99	–	19

[a] IL= [Bmim][DCA] or [Emim][EtSO4]. [b] The conversions were determined using 400.13 MHz 1H NMR spectroscopy. [c] The ratio of the percentage of one diastereoisomer in a mixture to that of the other was determined from 400.13 MHz ^{1}H NMR spectroscopy. [d] Enantiomeric excess and the ratio of the percent of one enantiomer in a mixture to that of the other were determined by HPLC using Phenomenex Lux 5 µm i-Cellulose 250 × 4.6 Chiral Column, 25 °C column oven. [e] Not determined.

2.4. Extraction of Michael Adduct with Supercritical Carbon Dioxide ($scCO_2$)

Additionally, the recovery of the product, the chiral catalyst, and the IL reaction media were studied using supercritical carbon dioxide ($scCO_2$). $scCO_2$ is a fluid state of carbon dioxide where it is held at or is above its critical temperature and critical pressure. Taking

it into account, that ILs are not soluble in $scCO_2$, there is a possibility to extract the Michael product from the reaction mixture without any traces of the IL. The use of $scCO_2$ as a more sustainable and efficient extraction and recyclable methodology has been tested. The model reaction was carried out using cyclohexanone and nitrostyrene, [Emim][ProCO_2] as the asymmetric catalyst and [Emim][EtSO_4] alternative solvent. During the extraction experiments, different parameters such as extraction time, pressure, temperature, amount of $scCO_2$, and speed of bubbling were changed in order to not only separate the 2-((D)-nitro-1-phenyl)cyclohexanone as the desired product from the reaction mixture, but also to obtain it with high yields. After optimization, the final product was successfully extracted without any IL impurities with an 80% yield. It is possible to recycle the reaction media using $scCO_2$ at least three times without any decrease in the catalytic performance (yield and enantiomeric excess).

3. Materials and Methods

Commercially available reagents L-proline (MW = 115.13 g·mol^{-1}, CAS No. 147-85-3), ionic liquids and solvents were purchased from Alfa Aestar (Haverhill, MA, USA), Aldrich (St. Louis, MO, USA), Solchemar (Alcácer Do Sal, Portugal), and were used without further purification. The basic anion-exchange resin Amberlite IRA-400-OH (ion-exchange capacity 1.4 eq.mL^{-1}) was purchased from Supelco (St. Louis, MO, USA). The 1H and 13C NMR spectra were recorded at 25 °C on a Bruker AMX400 spectrometer (Bruker, Billerica, MA, USA) with TMS as internal standard. Chemical shifts are reported downfield in ppm. IR spectra were performed by Perkin Elmer model Spectrum 1000 (PerkinElmer, Waltham, MA, USA) using KBr plates for neat liquids. DSC analysis was carried out using a TA Instruments Q-seriesTM Q200 DSC (TA Instruments, New Castle, DE, USA) with a refrigerated cooling system. The samples for elemental analysis were performed by Laboratório de Análises at REQUIMTE, Departamento de Química Faculdade de Ciências e Tecnologia (Monte da Caparica), using Thermo Finnigan-CE Instruments equipment and the model Elemental Analyzer 1112 series. Optical rotations were recorded on a Perkin Elmer 241MC. The melting point (mp) was determined using Electrothermal Melting Point Apparatus. The decomposition temperatures were measured with the Simultaneous Thermal Analyzer STA 449 F3 Jupiter, using a nitrogen atmosphere (mass changed in % or mg). Rheology studies were performed at Instituto Jean Piaget in Almada, Portugal, using a Rheometer (RS-300, Haake, Vreden, Germany). Measurements were carried out using a controlled-stress rheometer fitted with a coneplate sensor C20/2° Ti. The torque amplitude was imposed using a logarithmic ramp of shear stress, which was increased in 30 min intervals from 0.01 to 1000 Pa to decrease the initial acceleration and the effects due to instrument inertia. The temperatures of the samples were maintained at (20 ± 0.5) °C by means of a circulating water bath (DC30, Haake, Germany), and they were measured with a thermocouple attached to the stationary element. The temperature dependence of the viscosity was also studied. The ILs were heated from 20 to 70 °C (0.5 °C·min^{-1}) using a constant shear stress of 5 Pa. All the measurements were performed at least twice. High performance liquid chromatography (HPLC) analysis was carried out using a HPLC Waters® system (Milford, MA, USA) coupled with a pump and a controller (Waters® 600), an in-line degasser (X-Act-4 channels, Jour Research), an autosampler (Waters® 717 plus), and a photodiode array detector (DAD, Waters® 996). Enantiomer separations were performed with a Phenomenex Lux 5µ Cellulose-1 column (250 × 4.6 mm i.d.) coupled to a Phenomenex safety guard column (security guard cartridges, Lux Cellulose-1 4 × 3.0 mm i.d.) (Torrence, CA, USA). Depending on the final product, chiral compounds were eluted in an isocratic mode with hexane at 95% and 2-propanol at 5% or in a gradient mode (0–25 min, hexane:2-propanol 90:10; 25–30 min, hexane:2-propanol 80:20; 30–35 min, back to hexane:2-propanol 90:10 hold till 40 min). The flow rate was set at 0.8 mL·min^{-1} for the isocratic mode and 1.0 mL·min^{-1} for the gradient mode. The injection volume was between 20 to 75 µL. Before injection, samples were dissolved in 2-propanol and filtrated with GHP Acrodisc® syringe filters. The chromatograms were acquired with a MassLynxTM software

data acquisition system. Chiral products were identified at 230 nm. Reagents and materials: hexane (Sigma-Aldrich for HPLC) (St. Louis, MO, USA), 2-propanol (Sigma-Aldrich HPLC Plus) (St. Louis, MO, USA), and GHP Acrodisc® 13 mm syringe filter with 0.45 μm GHP membrane (PALL Life Sciences, Ann Arbor, MI, USA).

All ^{1}H and ^{13}C NMR; and HPLC data are included in the Supplementary information.

3.1. Synthesis of (L)-Proline Hydrochloride—Cationic Approach

In the first step, (L)-proline 1 (1 g; 8.69 mmol) was dissolved in 15 mL of methanol and 1M solution of HCl in MeOH (1:1 eq., 8.69 mL) was slowly added in order to protonate the amine group. The reaction mixture was stirred at room temperature for 24 h. The solution was evaporated and dried in vacuum for ~5 h. The (L)-proline hydrochloride 2 was obtained as a viscous yellow liquid (1.31 g, 100%). ^{1}H NMR (400.13 MHz, D_2O) δ 4.27 (t, 3J H-H = 8 Hz, 1H), 3.32–3.20 (m, 2H), 2.32–2.27 (m, 1H), 2.06–2.00 (m, 1H), and 1.95–1.86 (m, 2H). ^{13}C NMR (100.61 MHz, D_2O) δ 172.12, 59.69, 46.20, 28.31, and 23.37.

Synthesis of (L)-2-carboxypyrrolidin-1-ium bis((trifluoromethyl)sulfonyl)amide (1a). After the protonation was finished, the isolated L-proline hydrochloride (0.4 g; 2.64 mmol) was dissolved in 5 mL of methanol and Li[NTf_2] was added to perform the ion exchange (0.79 g; 2.77 mmol). The reaction was stirred for 24 h at room temperature. Then the solvent was evaporated, and the crude was re-dissolved in acetone in order to remove the inorganic salts and the desired product was filtrated from the solution. The solution was evaporated and dried in vacuum for 8 h. The product was obtained as a viscous yellow liquid (0.94 g, 90%). Tg = −77.67 °C; $[\alpha]_D$= −12.7 ± 2° (c = 1 mg·mL^{-1} in MeOH); ^{1}H NMR (400.13 MHz, D_2O) δ 4.27 (t, 3J H-H = 8 Hz, 1H), 3.38–3.25 (m, 2H), 2.38–2.278 (m, 1H), 2.13–2.02 (m, 1H), 1.99–1.92 (m, 2H). ^{13}C NMR (100.61 MHz, D_2O) δ 172.12, 120.79, 59.69, 46.20, 28.31, and 23.37. ^{19}F NMR (376 MHz, DMSO) δ −79.19. FTIR (KBr) υ = 3414, 2362, 2345, 2067, 1638, 1350, 1199, 1133, 1056, 793, 766, 743, and 666 cm^{-1}. Elemental analysis (%) calcd for $C_7H_{10}F_6N_2O_6S_2$ (MW = 396.28 g·mol^{-1}): C 21.22, H 2.54, N 7.07, and S 15.48; found: C 21.12, H 2.52, N 7.04, and S 15.40.

Synthesis of (L)-2-carboxypyrrolidin-1-ium 1,4-bis((2-ethylhexyl)oxy)-1,4-dioxobutane-2-sulfonate (1b). The protonated L-proline (0.5 g; 3.30 mmol) was dissolved in 5 mL of methanol and sodium docusate Na[AOT] was added to perform the ion exchange (1.76 g; 1.96 mmol). The reaction was stirred for 24 h at room temperature. Then the solvent was evaporated, and the crude was re-dissolved in acetone in order to remove the inorganic salts and the desired product was filtrated from the solution. The solution was evaporated and dried in vacuum for 8 h. The product was obtained as a viscous yellow liquid (1.73 g, 97%). Tg = −61.88 °C; $[\alpha]_D$ = −12.0 ± 2° (c = 1 mg·mL^{-1} in MeOH); ^{1}H NMR (400.13 MHz, DMSO) δ 4.26 (t, 3JH-H = 8 Hz, 1H), 3.92–3.87 (m, 4H), 3.62 (dd, 2J H-H = 4 Hz, 3J H-H = 8 Hz, 1H), 3.23–3.19 (m, 1H), 2.89 (m, 1H), 2.80 (dd, 2J H-H = 4 Hz, 3J H-H = 8 Hz, 1H), 2.25 (m, 1H), 2.03–1.82 (m, 3H), 1.49 (m, 2H), 1.41–1.15 (m, 16H), and 0.84 (m, 12H). ^{13}C NMR (100.61 MHz, DMSO) δ 171.49, 170.99, 168.81, 66.65, 66.58, 61.88, 59.42, 49.05, 45.92, 30.20, 30.02, 28.80, 28.36, 23.62, 23.47, 22.86, 14.35, and 11.24. FTIR (KBr) υ = 3450, 2960, 2932, 2874, 2861, 2362, 2343, 1736, 1638, 1508, 1460, 1414, 1390, 1356, 1243, 1091, 1041, 855, 768, 730, and 666 cm^{-1}. Elemental analysis (%) calcd for $C_{25}H_{47}NO_9S$ (MW = 537.71 g·mol^{-1}): C 55.84, H 8.81, and N 2.60; found: C 55.57, H 8.87, and N 2.57.

Synthesis of (L)-2-carboxypyrrolidin-1-ium 4-methylbenzenesulfonate(1c). The protonated L-proline (0.30 g; 1.98 mmol) was dissolved in 5 mL of methanol and p-toluenosulfonic sodium salt Na[*p*-TSA] was added to perform the ion exchange (0.39 g; 2.0 mmol). The reaction was stirred for 24 h at room temperature. Then the solvent was evaporated, and the crude was re-dissolved in acetone in order to remove the inorganic salts and the desired product was filtrated from the solution. The solution was evaporated and dried in vacuum for 8 h. The product was obtained as a viscous yellow gel (0.38 g, 66%). Tg = −25.07 °C; $[\alpha]_D$ = −4.0 ± 2° (c = 1 mg·mL^{-1} in MeOH); ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.70 (d, 3J = 7.5 Hz, 2H), 7.16 (d, 3J = 7.5 Hz, 2H), 4.48 (t, 3JH-H = 8 Hz, 1H), 3.43 (m, 2H, H5), 3.33 (m, 1H), 2.34 (s, 3H), 2.08 (m, 1H), and 1.90 (m, 2H). ^{13}C NMR (100.61 MHz,

$CDCl_3$) δ 171.17, 141.01, 140.83, 129.07, 125.84 (Cb), 59.76 (C2), 46.52 (C5), 28.48 (C3), 23.51 (C4), and 21.35. FTIR (KBr) υ = 3430, 2361, 2343, 2092, 1736, 1639, 1458, 1181, 1126, 1036, 1012, 819, 750, 689, and 666 cm^{-1}. Elemental analysis (%) calcd for $C_{12}H_{17}NO_5S$ (MW = 287.33 $g \cdot mol^{-1}$): C 50.16, H 5.96, N 4.87, qne S 11.16; found: C 50.01, H 5.98, N 4.85, and S: 11.12.

Synthesis of (L)-2-carboxypyrrolidin-1-ium 3-oxo-3H-benzo[d]isothiazol-2-ide 1,1-dioxide(1d). The protonated L-proline (0.5 g; 3.30 mmol) was dissolved in 5 mL of methanol and 5 mL water and sodium saccharin Na[SAC] was added to perform the ion exchange (0.82 g; 3.96 mmol). The reaction was stirred for 24 h at room temperature. Then the solvent was evaporated, and the crude was re-dissolved in acetone in order to remove the inorganic salts and the desired product was filtrated from the solution. The solution was evaporated and dried in vacuum for 8 h. The product was obtained as a viscous yellow gel (0.96 g, 98%). $[\alpha]_D = -4.5 \pm 2^\circ$ (c = 1 $mg \cdot mL^{-1}$ in MeOH); ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.74 (m, 4H), 4.65–4.62 (t, 3JH-H3 = 8 Hz, 1H), 4.47–4.44 (t, 3JH2-H3 = 8 Hz, 1H, H2), 3.61–3.46 (m, 2H, H5, H5´), 2.51–2.30 (m, 1H, H3), 2.24–2.13 (m, 1H), and 2.10–1.96 (m, 2H). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 169.86, 167.82, 142.36, 133.09, 131.54, 124.13, 120.43, 59.30, 46.30, 29.00, and 24.24. FTIR (KBr) υ = 3430, 2960, 1720, 1630, 1335, 1258, 1148, 1120, 1053, 951, 758, and 681 cm^{-1}. Elemental analysis (%) calcd for $C_{12}H_{14}N_2O_5S$ (MW = 298.31 $g \cdot mol^{-1}$): C 48.31; H 4.73; N 9.39; and S 10.75; found: C 48.25, H 4. 57, N 9.35, and S: 10.80.

Synthesis of (L)-2-carboxypyrrolidin-1-ium ((1D, 4D)-7,7-dimethyl-2-oxobicyclo [2.2.1] heptan-1-yl)methanesulfonate (1e). First, the (1D)-(-)-10-camphorsulfonic acid was transformed in a sodium salt. Then, the acid (0.5 g, 2.12 mmol) was dissolved in 15 mL of ethanol and 0.5 M solution of NaOH in EtOH (1 eq., 4.31 mL) was added dropwise. The mixture was stirred overnight at room temperature. The final salt was isolated and used for ion exchange in the second step with [ProNH_2]Cl. The protonated L-proline (0.34 g; 2.24 mmol) was dissolved in 5 mL of methanol and camphorsulfonic acid sodium salt Na[CSA] was added to perform the ion exchange (0.57 g; 2.24 mmol). The reaction was stirred for 24 h at room temperature. Then the solvent was evaporated, and the crude was re-dissolved in acetone in order to remove the inorganic salts and the desired product was filtrated from the solution. The solution was evaporated and dried in vacuum for 8 h. The product was obtained as a white solid (0.78 g, 99%); Tm = 154 °C; $[\alpha]_D = -44.0 \pm 2^\circ$ (c = 1 $mg \cdot mL^{-1}$ in MeOH); ^{1}H NMR (400.13 MHz, D_2O) δ 4.27 (t, 3JH-H = 8 Hz, 1H), 3.34–3.29 (m, 2H), 3.17 (d, 2JH-H = 16Hz, 1H), 2.75 (d, 2JH-H = 16Hz, 1H), 2.30 (m, 3H), 2.03–1.84 (m, 6H), 1.52 (m, 1H), 1.33 (m, 1H), 0.91 (s, 3H), and 0.71 (s, 3H). ^{13}C NMR (100.61 MHz, D_2O) δ 210.0, 172.19, 59.73, 58.43, 48.15, 47.09, 46.18, 42.54, 28.35, 26.15, 24.51, 23.22, and 18.67. Elemental analysis (%) calcd for $C_{15}H_{25}NO_6S$ (MW = 347.43 $g \cdot mol^{-1}$): C 51.86, H 7.25, N 4.03, and S 9.23; found: C 51.70, H 7.22, N 3.99, and S 9.18.

Synthesis of (L)-2-carboxypyrrolidin-1-ium ((1L, 4D)-7,7-dimethyl-2-oxobicyclo[2.2.1] heptan-1-yl)methanesulfonate (1f). First, the (1L)-(+)-10-camphorsulfonic acid was transformed in a sodium salt. Then, the acid (0.5 g, 2.12 mmol) was dissolved in 15 mL of ethanol and 0.5M solution of NaOH in EtOH (1 eq., 4.31 mL) was added dropwise. The mixture was stirred overnight at room temperature. The final salt was isolated and used for ion exchange in the second step with [ProNH_2]Cl. The protonated L-proline (0.3 g; 2.24 mmol) was dissolved in 5 mL of methanol and camphorsulfonic acid sodium salt Na[CSA] was added to perform the ion exchange (0.57 g; 2.24 mmol). The reaction was stirred for 24 h at room temperature. Then the solvent was evaporated, and the crude was re-dissolved in acetone in order to remove the inorganic salts and the desired product was filtrated from the solution. The solution was evaporated and dried in vacuum for 8 h. The product was obtained as a white solid (0.74 g, 95%); Tm = 155–160 °C; $[\alpha]_D = +66.0 \pm 2^\circ$ (c = 1 $mg \cdot mL^{-1}$ in MeOH); ^{1}H NMR (400.13 MHz, D_2O) δ 4.27 (t, 3JH-H = 8 Hz, 1H), 3.34–3.29 (m, 2H), 3.17 (d, 2JH-H = 16 Hz, 1H), 2.75(d, 2JH-H = 16 Hz, 1H), 2.30 (m, 3H), 2.03–1.84 (m, 6H), 1.52 (m, 1H), 1.33 (m, 1H), 0.91 (s, 3H), and 0.71 (s, 3H). ^{13}C NMR (100.61 MHz, D2O) δ 210.0, 172.19, 59.73, 58.43, 48.15, 47.09, 46.18, 42.54, 28.35, 26.15, 24.51, 3.22, and 18.67. Elemental

analysis (%) calcd for $C_{15}H_{25}NO_6S$ (MW = 347.43 g·mol^{-1}): C 51.86, H 7.25, N 4.03, and S 9.23; found: C 51.80, H 7.25, N 4.00, and S 9.19.

Synthesis of trihexyl(tetradecyl)phosphonium (L)-pyrrolidine-2-carboxylate (2a). For the preparation of trihexyl(tetradecyl)phosphonium (L)-pyrrolidine-2-carboxylate, a column ion exchange method was used. The phosphonium chloride $[P_{6,6,6,14}]Cl$ (2.26 g; 4.34 mmol) was first transformed into hydroxide by the use of an ionic exchange column (Amberlite IRA-400 OH) in methanol, and then this basic solution was neutralized by reacting with the (L)-proline (0.5 g; 4.34 mmol) in methanol solution. The mixture was stirred at room temperature for 24 h. After the indicated time, the established water was evaporated and dried in vacuum for 8 h. The final product was obtained as a viscous yellow liquid (2.52 g, 97%). Tg = −74.40 °C; $[\alpha]_D$= −17.3 ± 2° (c = 1 mg·mL^{-1} in MeOH). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 3.56 (t, 3JH-H = 8 Hz, 1H), 3.07 (m, 1H), 2.82 (m, 1H), 2.32 (m, 8H), 2.03 (m, 1H), 1.66 (m, 1H), 1.45 (m, 2H), 1.27 (m, 16H), 1.26–1.20 (m, 32H,), and 0.83 (m, 12H). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 178.50, 62.49, 47.06, 31.79, 30.99, 30.45, 26.00, 22.52, 22.22, 21.77, 13.82. FTIR (KBr) υ = 3400, 2956, 2927, 2856, 2361, 1586, 1458, 1414, 1310, 1268, 1214, 1173, 1112, 1044, 986, 917, 862, 820, 721, and 667 cm^{-1}. Elemental analysis (%) calcd for $C_{37}H_{76}NO_2P$ (MW = 597.98 g·mol^{-1}): C 74.32; H 12.81; N 2.34; found: C 73.97, H 12.87, N 2.30.

Synthesis of 1-ethyl-3-methyl-1H-imidazol-3-ium pyrrolidine-2-carboxylate (2b). For the preparation of 1-ethyl-3-methyl-1H-imidazol-3-ium pyrrolidine-2-carboxylate, a column ion exchange method was used. The 1-ethyl-3-methyl-1H-imidazol-3-ium bromide chloride [Emim]Br (0.83 g; 4.34 mmol) was first transformed into hydroxide by the use of an ionic exchange column (Amberlite IRA-400 OH) in methanol, and then this basic solution was neutralized by reacting with the (L)-proline (0.5 g; 4.34 mmol) in methanol solution. The mixture was stirred at room temperature for 24 h. After the indicated time, the established water was evaporated and dried in vacuum for 8 h. The final product was obtained as a viscous yellow liquid (1.08 g, 100%). Tg = −77.57 °C; $[\alpha]_D$ = −8.8 ± 2° (c = 1 mg·mL^{-1} in MeOH). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.28 (m, 3H), 4.36 (q, 3JH-H =10Hz, 2H), 4.05 (s, 3H), 3.60 (t, 3JH-H = 8 Hz, 1H), 3.12 (m, 1H), 2.83 (m, 1H), 2.13 (m, 1H), 1.88 (m, 1H), 1.66 (m, 2H), 1.66 (m, 2H), and 1.56 (t, 3JH-H = 4 Hz, 3H). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 179.63, 122.69, 120.73, 62.62, 47.04, 44.99, 36.26, 31.45, 26.17, 15.44. FTIR (KBr) υ = 3400, 3154, 3108, 2973, 2876, 2361, 2343, 1578, 1390, 1171, 1092, 1032, 959, 917, 856, 766, 702, 667, 649, and 623 cm^{-1}. Elemental analysis (%) calcd for $C_{11}H_{19}N_3O_2$ (MW = 225.29 g·mol^{-1}): C 58.64; H 8.50; and N 18.65; found: C 58.40, H 8.53, and N 18.57.

Synthesis of 1-(2-methoxyethyl)-3-methyl-1H-imidazol-3-ium (L)- pyrrolidine-2-carboxylate (2c). For the preparation of 1-(2-methoxyethyl)-3-methyl-1H-imidazol-3-ium (L)-pyrrolidine-2-carboxylate, a column ion exchange method was used. The 1-(2-methoxyethyl)-3-methyl-1H-imidazol-3-ium chloride $[C_3Omim]Cl$ (0.77 g; 4.34 mmol) was first transformed into hydroxide by the use of an ionic exchange column (Amberlite IRA-400 OH) in methanol, and then this basic solution was neutralized by reacting with the (L)-proline (0.5 g; 4.34 mmol) in methanol solution. The mixture was stirred at room temperature for 24 h. After the indicated time, the established water was evaporated and dried in vacuum for 8 h. The final product was obtained as a viscous yellow liquid (0.83 g, 99%). Tg = −83 °C; $[\alpha]_D$ = −5.3 ± 2° (c = 1 mg·mL^{-1} in MeOH). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.34 (m, 1H), 7.12 (m, 2H), 4.56 (t, 3J H-H = 4 Hz, 2H), 4.01 (s, 3H), 3.75 (t, 3J H-H = 4 Hz, 2H), 3.56 (t, 3JH-H = 4 Hz, 1H), 3.33 (s, 3H), 3.15 (m, 1H), 2.80 (m, 1H), 2.11 (m, 1H), and 1.84–1.65 (m, 3H). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 179.91, 122.84, 121.90, 70.62, 62.68, 58.91, 49.65, 47.08, 36.24, 31.49, and 26.21. FTIR (KBr) υ = 3402, 2359, 2341, 2136, 1622, 1574, 1428, 1353, 1311, 1171, 1118, 1081, 1035, 1013, 833, 750, 666, and 623 cm^{-1}. Elemental analysis (%) calcd for $C_{12}H_{21}N_3O_3$ (MW = 255.31 g·mol^{-1}): C 56.45; H 8.29; and N 16.46; found: C 56.18, H 8.32, and N 16.38.

Synthesis of 1-(2-hydroxyethyl)-3-methyl-1H-imidazol-3-ium (L)-pyrrolidine-2-carboxylate (2d). For the preparation of 1-(2-hydroxyethyl)-3-methyl-1H-imidazol-3-ium (L)-pyrrolidine-2-carboxylate, a column ion exchange method was used. The 1-(2-hydroxyethyl)-

3-methyl-1H-imidazol-3-ium chloride [C_2OHmim]Cl (0.71 g; 4.34 mmol) was first transformed into hydroxide by the use of an ionic exchange column (Amberlite IRA-400 OH) in methanol, and then this basic solution was neutralized by reacting with the (L)-proline (0.5 g; 4.34 mmol) in methanol solution. The mixture was stirred at room temperature for 24 h. After the indicated time, the established water was evaporated and dried in vacuum for 8 h. The final product was obtained as a viscous yellow liquid (0.94 g, 80%). Tg = −52.06 °C; $[\alpha]_D = -6.7 \pm 2°$ (c = 1 mg·mL^{-1} in MeOH). ^{1}H NMR (400.13 MHz, D_2O) δ 7.37 (m, 3H), 4.20 (t, 3J H-H = 4 Hz, 2H), 4.01 (s, 3H), 3.79 (t, 3J H-H = 4 Hz, 2H), 3.45 (t, 3JH-H = 4 Hz, 1H), 3.33 (s, 3H), 3.15 (m, 1H), 2.73 (m, 1H), 2.11(m, 1H), and 1.84–1.65 (m, 3H). ^{13}C NMR (100.61 MHz, D_2O) δ 180.85, 136.28, 123.52, 61.42, 59.70, 51.46, 45.94, 35.61, 30.37, and 24.81. FTIR (KBr) υ = 3410, 2361, 2342, 2142, 1630, 1578, 1420, 1168, 1073, 947, 872, 751, 667, and 622 cm^{-1}. Elemental analysis (%) calcd for $C_{11}H_{19}N_3O_3$ (MW = 241.29 g·mol^{-1}): C 54.76; H 7.94; and N 17.41; found: C 54.50, H 7.91, and N 17.31.

Synthesis of 1-(2-hydroxyethyl)-2,3-dimethyl-1H-imidazol-3-ium (L)-pyrrolidine-2-carboxylate (2e). For the preparation of 1-(2-hydroxyethyl)-2,3-dimethyl-1H-imidazol-3-ium (L)-pyrrolidine-2-carboxylate, a column ion exchange method was used. The 1-(2-hydroxyethyl)-2,3-dimethyl-1H-imidazol-3-ium chloride [C_2OHDmim]Cl (0.76 g; 4.34 mmol) was first transformed into hydroxide by the use of an ionic exchange column (Amberlite IRA-400 OH) in methanol, and then this basic solution was neutralized by reacting with the (L)-proline (0.5 g; 4.34 mmol) in methanol solution. The mixture was stirred at room temperature for 24 h. After the indicated time, the established water was evaporated and dried in vacuum for 8 h. The final product was obtained as a viscous yellow liquid (0.82 g, 75%). Tg = −40.30 °C; $[\alpha]_D = -19.0 \pm 2°$ (c = 1 mg·mL^{-1} in MeOH). ^{1}H NMR (400.13 MHz, D_2O) δ 7.24 (m, 3H), 4.20 (t, 3J H-H = 4 Hz, 2H), 4.01 (s, 3H), 3.79 (t, 3J H-H = 4 Hz, 2H), 3.45 (t, 3JH-H = 4 Hz, 1H), 3.33 (s, 3H), 3.15 (m, 1H), 2.73 (m, 1H), 2.45 (s, 3H), 2.11 (m, 1H), and 1.84–1.65 (m, 3H). ^{13}C NMR (100.61 MHz, D_2O) δ 180.85, 136.28, 123.52, 61.42, 59.70, 51.46, 45.94, 35.61, 30.37, 24.81, and 8.97. FTIR (KBr) υ = 3390, 2360, 2339, 2142, 1630, 1588, 1416, 1169, 1076, 872, 771, and 666 cm^{-1}. Elemental analysis (%) calcd for $C_{13}H_{25}N_3O_3$ (MW = 271.36 g·mol^{-1}): C 57.54; H 9.29; and N 15.49; found: C 57.27, H 9.26, and N 15.48.

Synthesis of 2-hydroxy-N,N,N-trimethylethanaminium (L)-pyrrolidine-2-carboxylate (2f). For the synthesis of 2-hydroxy-N,N,N-trimethylethanaminium (L)-pyrrolidine-2-carboxylate, a simple acid base reaction was performed. The choline hydroxide in MeOH 45% (0.25 g; 2.06 mmol) was diluted with additional 10 mL of methanol and next, 20 mL methanol was added dropwise to the solution of (L)-proline. The mixture was stirred at room temperature for 24 h. After the indicated time, the established water was evaporated and dried in vacuum for 8 h. The final product was obtained as a viscous brown liquid (0.65 g, 100%). Tg = −79.85 °C; $[\alpha]_D = -12.7 \pm 2°$ (c = 1 mg·mL^{-1} in MeOH). ^{1}H NMR (400.13 MHz, DMSO) δ 5.26 (m, 1H), 3.84 (m, 2H), 3.43 (m, 2H), 3.47 (m, 1H), 3.12 (s, 9H), 2.88 (m, 2H), 2.11 (m, 1H), and 1.84–1.65 (m, 3H). ^{13}C NMR (100.61 MHz, DMSO) δ 182.41, 67.49, 61.48, 55.56, 53.85, 45.94, 30.64, and 24.99. FTIR (KBr) υ = 3401, 2360, 2341, 2134, 1633, 1574, 1488, 1417, 1352, 1204, 1134, 1086, 1052, 957, 865, 750, and 667 cm^{-1}. Elemental analysis (%) calcd for $C_{11}H_{26}N_2O_3$ (MW = 234.34 g·mol^{-1}): C 56.38; H 11.18; and N 11.95; found: C 56.12, H 11.12, and N 11.92.

3.1.1. General Procedure for the Michael Reaction of Cyclohexanone and β–Nitrostyrene

To a suspension of catalyst (10–30 mol%) and cyclohexanone (210 μL, 2 mmol) in 1 mL of solvent (EtOH, [Emim][$EtSO_4$] or [Bmim][DCA]) and trans-β-nitrostyrene (0.149 g, 1.0 mmol) were added. The resulting mixture was allowed to stir at room temperature for 48–90 h, and was then evaporated in vacuum and the resulting residue was purified by extraction with Et_2O and flash column chromatography using ethyl acetate/hexane (1:2), giving the desired product. If necessary, the product was purified by filtration using neutral alumina and Et_2O as washing solvent. Relative and absolute configurations of the products were determined by comparison with the known ^{1}H NMR and chiral HPLC analysis. The enantiomeric excess was determined by chiral HPLC analysis on a Phenomenex Lux 5 um

250 × 10 cellulose column, flow 1 mL.min^{-1}, 25 °C column oven, hexane: i-PrOH 90:10, λ = 230 nm. t(major) = 13.7 min and t(minor) = 15.0 min.

(L)-2-(D)-2-nitro-1-phenylethyl)cyclohexanone: colourless solid; mp 128–130 °C; conversion 100%; and dr (syn/anti): 93:7, 99% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.26 (m, 3H), 7.17 (d, 4JH-H = 8 Hz, 2H), 4.94 (dd, 2JH-H = 4 Hz, 3JH-H = 8 Hz, 1H), 4.64 (dd, 2JH-H = 4 Hz, 3JH-H = 8 Hz, 1H), 4.19 (dt, 3JH-H = 8 Hz, 3JH-H = 10 Hz, 1H), 3.76 (ddd, 3JH-H = 8 Hz, 3JH-H = 8 Hz, 3JH-H = 10 Hz, 1H), 2.74–2.67 (m, 2H), 2.51–2.36 (m, 1H), 1.81–1.59 (m, 4H), and 1.30–1.20 (m, 1H). ^{13}C NMR (101 MHz, CDCl3) δ 211.88, 137.73, 128.90, 128.14, 127.74, 78.86, 52.51, 43.91, 42.71, 33.18, 28.49, and 25.00 ppm.

(R)-5-nitro-4-phenylpentan-2-one: colourless solid; conversion 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ NMR 7.43–7.31 (m, 4H), 4.74 (dd, 2JH = 4 Hz, 3JH´ = 8 Hz, 1H´), 4.65 (dd, 2JH = 4 Hz, 3JH = 8 Hz, 1H), 4.06 (dt, 3JH = 8 Hz, 3JH = 10 Hz, 1H), 2.95 (m, 2H), and 2.15 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.81, 129.09, 127.93, 127.39, 79.46, 46.14, 39.94, 39.06, and 29.71 ppm.

(R)-2-((S)-1-(4-fluorophenyl)-2-nitroethyl)cyclohexanone: yellow gel; conversion 100%; and 40% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.15 (m, 2H), 7.06–7.02 (m, 2H), 4.97 (dd, 2JH2 = 4 Hz, 3JH = 8 Hz, 1H), 4.65 (dd, 2JH = 4 Hz, 3JH = 8 Hz, 1H´), 3.82 (dt, 3JH1 = 8 Hz, 3JH = 10 Hz, 1H), 2.71 (ddd, 3JH = 8 Hz, 3JH = 8 Hz, 3JH = 10 Hz, 1H), 2.52–2.36 (m, 2H), 2.13–2.09 (m, 1H), 1.84–1.59(m, 4H), and 1.30–1.20 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.14, 163.43, 160.98, 134.62, 129.06, 115.98, 79.43, 46.15, 38.34, 30.34, 27.4, 25.4, and 24.8 ppm.

(S)-4-(4-fluorophenyl)-5-nitropentan-2-one: yellow gel; conversion 98%; and 10% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.20 (m, 2H), 7.06–7.02 (m, 2H), 4.71 (dd, 2JH = 4 Hz, 3JH´ = 8 Hz, 1H), 4.60 (dd, 2JH = 4 Hz, 3JH = 8 Hz, 1H), 4.03 (dt, 3JH = 8 Hz, 3JH = 10 Hz, 1H), 2.93 (m, 2), and 2.15 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.15, 162.12, 139.24, 129.36, 128.69, 117.29, 114.99, 82.67, 45.35, 36.67, and 29.65 ppm.

2-((R)-1-(3-chlorophenyl)-2-nitroethyl)cyclohexanone: yellow gel; conversion 99%; and 47% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 1H), 7.19 (m, 2H), 7.10 (m, 1H), 4.98 (dd, 2JH = 4 Hz, 3JH = 8 Hz, 1H), 4.66 (dd, 2JH = 4 Hz, 3JH2 = 8 Hz, 1H), 3.97 (dt, 3JH1 = 8 Hz, 3JH = 10 Hz, 1H), 3.78 (ddd, 3JH = 8 Hz, 3JH = 8 Hz, 3JH = 10 Hz, 1H), 2.77–2.64 (m, 2H), 2.51–2.34(m, 1H), 2.19–2.10 (m, 2H), 1.88–1.54 (m, 2H), and 1.31–1.21 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.38, 143.87, 133.51, 128.87, 128.78, 128.59, 125.76, 81.10, 54.24, 45.00, 39.34, 28.76, 25.53, and 23.53 ppm.

(R)-4-(3-chlorophenyl)-5-nitropentan-2-one: yellow gel; conversion 99%; and 100% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 1H), 7.23 (m, 2H), 7.15 (m, 1H), 4.73 (dd, 2JH = 4 Hz, 3JH = 8 Hz, 1H), 4.61 (dd, 2JH = 4 Hz, 3JH = 8 Hz, 1H), 4.05 (dt, 3JH = 8 Hz, 3JH = 10 Hz, 1H), 2.93 (m, 2H), and 2.15 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.15, 145.39, 133.80, 128.57, 127.68, 126.64, 126.43, 82.67, 45.35, 36.50, and 29.65 ppm.

3.1.2. General Procedure for Extraction Using $scCO_2$

The $scCO_2$ extraction was carried out in the apparatus schematically presented in ESI. The core of the apparatus is a 3.5 mL high-pressure cell, with two sapphire windows allowing visualization of the internal volume. In order to perform the extraction, the cell is charged with a desired amount of the reaction mixture (0.9 mL), placed inside a constant temperature (40 °C) water bath, and pressurized with CO_2 until the desired pressure (250 bar) is brought into the cell. Supercritical extraction starts by carefully opening the venting valves and allowing the extract to be collected in a cold trap filled with ethanol and cooled with ice. The drop of pressure is continuously compensated by the introduction of fresh CO_2. The total quantity of CO_2 passed through the system is measured by a gas flow meter placed at the exit of an ethanol trap. The extraction is considered finished when 0.55 mol of CO_2 passes through the system. After a careful depressurization of the system, some additional solvent (ethanol) is injected through the expansion lines to ensure that all the solute is recovered in the trap.

4. Conclusions

In this work, a series of novel CILs based on L-proline, a naturally derived and inexpensive material, as an organic cation or anion have been developed. As expected, according to the selection of the counter-ions, it is possible to tune the physical, chemical, and thermal properties of the different CILs. Using the simple and efficient synthetic protocols, it was possible to obtain the required CILs in good yields and purities. The optical rotation, glass transition, decomposition temperatures (Tg, Tdec), density, and rheological profile of some CILs were evaluated. In contrast to the initial crystalline L-proline, in most of the cases, amorphous salts possessing a characteristic glass transition temperature were detected. Strong chiral interactions, in combination with the tunable properties of ionic liquids, reveal new solutions for an important carbon–carbon bond forming reaction, such as the asymmetric Michael reaction. Cyclohexanone could react with trans-nitrostyrene to give Michael adducts with a complete conversion and moderate to good enantioselectivities (53–97% ee), particularly in the presence of CILs [Emim][ProCO_2], [C_3Omim][ProCO_2], [C_2OHmim][ProCO_2], and [Choline][ProCO_2] in selected IL media. In addition, recovery of the product as well as the recycling of the catalytic reaction media (CILs and ILs) using scCO_2 have been performed. The extracted product was found to contain no detectable amount of ILs. These results provide a good perspective and open the door to discovering new and more efficient organocatalyst-based ILs for asymmetric catalytic processes.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/catal13020270/s1.

Author Contributions: Conceptualization, L.C.B.; Methodology, K.Z.; Validation, L.C.; Formal analysis, I.P., L.C., M.E.Z. and L.C.B.; Writing—original draft, K.Z.; Writing—review & editing, I.P., M.E.Z., J.P.N., M.N.d.P. and L.C.B.; Supervision, L.C.B.; Funding acquisition, L.C.B. All authors have read and agreed to the published version of the manuscript.

Funding: The authors thank the technical support from the Associate Laboratory for Green Chemistry LAQV, which is funded by national funds from FCT/MEC (UIDB/50006/2020) and co-financed by the ERDF under the PT2020 Partnership agreement (POCI-01-0145-FEDER–007265) and the FCT project (PTDC/QUI-QOR/32406/2017). The NMR spectrometers are part of the National NMR Network (PTNMR) and are partially supported by the Infrastructure Project N° 022161 (co-financed by FEDER through COMPETE 2020, POCI and PORL and FCT through PIDDAC).

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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