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Article

# Beneficial Contribution of Biosourced Ionic Liquids and Microwaves in the Michael Reaction

Katia Bacha, Kawther Aguib, Jean-Pierre Mbakidi and Sandrine Bouquillon \*

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**Abstract:** We developed a synthesis of chiral ionic liquids from proline and one of its derivatives. Nine chiral ionic liquids were synthesized with yields from 78% to 95%. These synthesized ionic liquids played two roles in Michael reactions, as solvents, and as basic catalysts, where the ionic phase could also be reused at least five times without loss of activity. The yields up to 99% were improved by increasing the amount of dimethylmalonate from 1.2 equivalents to 3 or 4 equivalents. Furthermore, the reaction time could be reduced from 24 h to 45 min through microwaves activation.

**Keywords:** ionic liquids; biomass; microwaves; Michael reaction; chalcone; dimethylmalonate

## 1. Introduction

The impact of chemical solvents on the environment is an increasingly debated subject. Indeed, most of these solvents are volatile organic compounds and can, therefore, be easily dispersed in the environment. Risks often accompany this because they are flammable. In addition, they are generally harmful from an ecological and health point of view [1]. Over the past fifteen years, green chemistry, which has become a priority area for academic and industrial research, has undergone considerable development. In this context, much research is focused on alternative, environmentally friendly solvents that can replace some highly volatile and environmentally harmful solvents [2].

These include water [3–9], supercritical CO<sub>2</sub> [10–14], and ionic liquids (ILs) [15–21]. Ionic liquids are of particular interest because they are a new class of solvents that offer interesting opportunities as a reaction medium for cleaner chemistry due to their multiple properties.

Ionic liquids are salts consisting solely of ions, whose melting point is below an arbitrary temperature, often 100 °C. They consist of generally bulky organic cations and organic or inorganic anions, which gives them an asymmetry of shape and charge, as well as great flexibility [22,23]. In general, cations have a voluminous and asymmetric nature [15]. The most commonly represented are composed of ammoniums, phosphoniums, or heteroaromatic systems such as imidazolium, pyridinium, pyrrolidinium, oxazolium, thiazolium, pyridazinium, triazolium, and tetraalkylammonium. Different ionic liquids can be formed either by the appropriate combination of cations and anions or by the chemical modification of the cation or anion. This offers a choice of considerable combinations, and the literature now reports the possible synthesis of at least 10<sup>6</sup> different ILs [19].

Their synthesis is generally carried out in two steps: the formation of the cation followed by an anion exchange step called anionic metathesis [24].

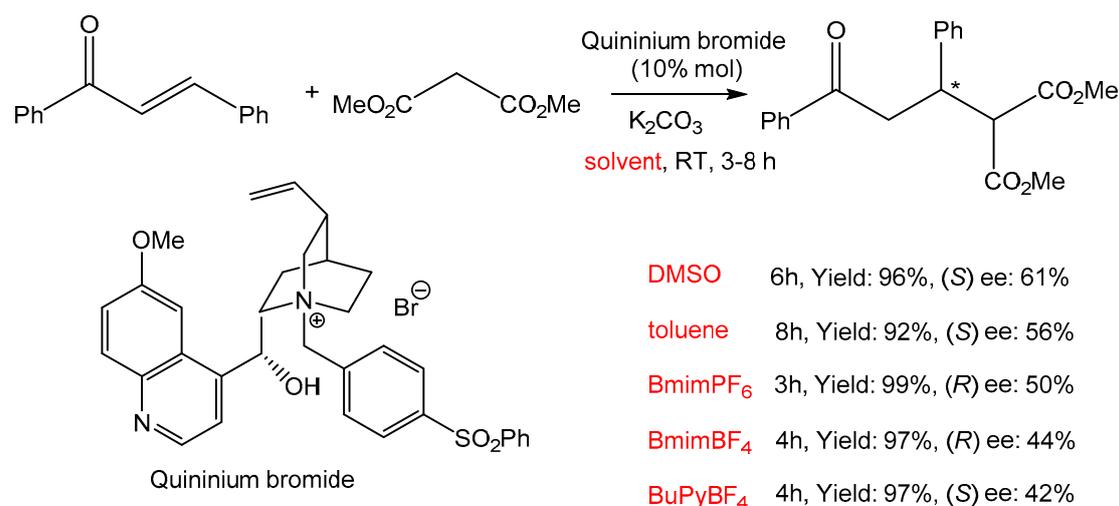
The properties of the ILs are also very large [19,25,26]: low vapor tension, high decomposition temperature, high solubilizing power, and a wide variety of the structures that allow different polarities [27,28].

The ILs are commonly used in the domain of (bio)catalysis [18,29], organic synthesis [30,31], electrochemistry [32], or extraction [33] as recently described in the appropriate reviews [34–36]. Catalyses (hydrogenation, oxidation, Pd-catalyzed couplings, Friedel-Crafts, Diels-Alder, etc.) in ILs are also largely developed [37] and the use of these new solvents generally led to higher kinetics and better selectivity's.

However, the low biodegradability and the toxicity of the ionic liquids, in general, led the scientific community to reduce their use or to find other greener alternatives by using renewable resources as starting materials such as acids, amino acids, amino alcohols, and sugars which could improve the green character of ILs [38–42]. Catalyses (hydrogenation, heck reactions) have also been performed in such ILs [43–45].

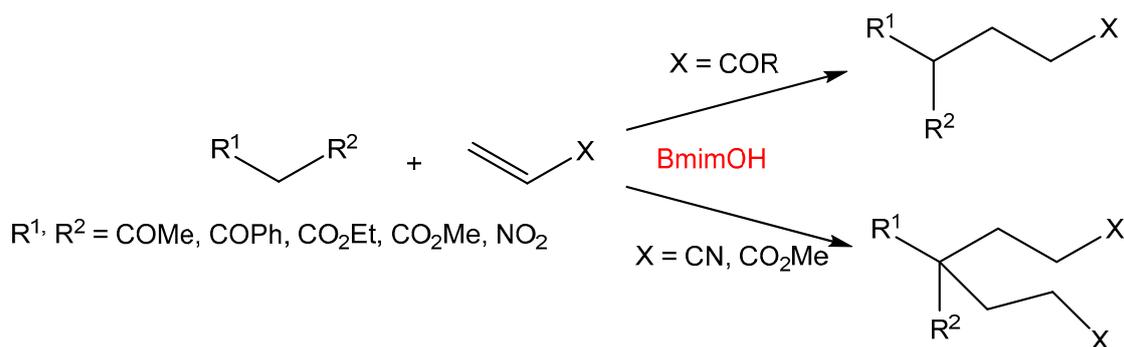
The Michael reaction is a conjugated nucleophilic addition between a nucleophile and an  $\alpha,\beta$ -unsaturated electrophile. The nucleophiles are thiols, anions, or amines, and the electrophiles are alkenes, alkynes in  $\alpha$  and  $\beta$  position of carbonyls, amides, or nitriles. Recently, Yadav et al. reviewed innovative catalysis in Michael addition reactions, including the use of organocatalysts and heterogeneous processes [46]. Gu et al. in 2019 [47] also described the role of functionalized quaternary ammonium salt ionic liquids (FQAILs) as an economical and efficient catalyst for the synthesis of glycerol carbonate from glycerol and dimethyl carbonate.

In 2003, Salunkhe and coll. studied the use of hydrophobic or hydrophilic ionic liquids ([bmim]PF<sub>6</sub>, [bmim]BF<sub>4</sub>, [BuPy]BF<sub>4</sub>) as solvents in the conjugated addition reaction of dimethyl malonate to chalcone in the presence of a quaternary ammonium salt derived from quinine (Scheme 1) [48]. This last compound used as a chiral phase transfer agent led to moderate ee's.



**Scheme 1.** Enantioselective reactions in chiral ionic liquids [48].

The yields were quantitative and the ee up to 56%. Next, in 2005, Ranu and coll. performed the Michael addition of activated methylene compounds on ketones, esters, and conjugated nitriles in the presence of the ionic liquid [Bmim]OH (Scheme 2). This one was used as a solvent and catalyst for the reaction. The reaction products were obtained with good yields; furthermore, the compound issued from the double addition could also be easily obtained in one step, which was surprising when compared to conventional methods [49].



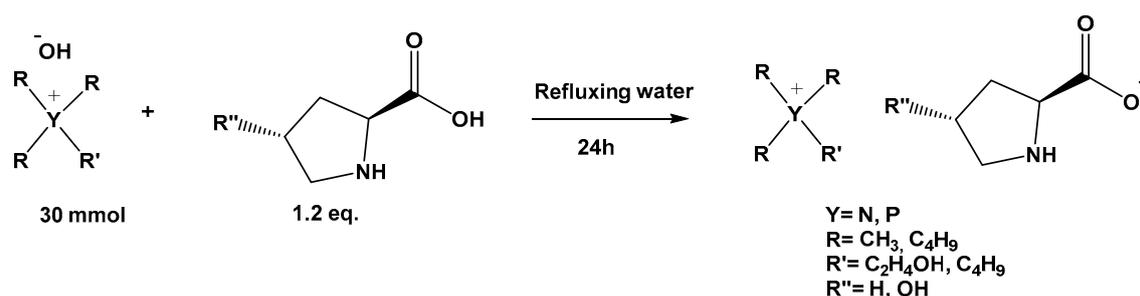
**Scheme 2.** Michael addition of activated methylene compounds in BmimOH [49].

In 2005, Rao and Jothilingam described how microwaves could drastically decrease the reaction time for the Michael addition of active methylene compounds to  $\alpha,\beta$ -unsaturated carbonyl compounds in the presence of a large excess of  $K_2CO_3$  as a base [50]. The reaction took place on the surface of potassium carbonate under microwave irradiation (450 W) and led to good to high yields (50% to 90%) in short times (5–10 min).

As previously mentioned, we prepared some bio-based ionic liquids with natural carboxylates and used these in hydrogenation and Heck couplings [38–45]. Among these ILs, we prepared tetrabutylphosphonium and tetrabutylammonium proline or hydroxyproline. This paper aims to show how these proline-based ionic liquids could be used as solvents and basic catalysts in a Michael model reaction. Furthermore, this study will be extended to cholinium cation, and we will demonstrate that microwaves could generate greener activation conditions for this reaction in ionic liquids.

## 2. Results and Discussion

Biosourced ionic liquids were prepared using an acid-base reaction between the tetrabutyl-ammonium or -phosphonium hydroxides (TBAOH and TBPOH, respectively) or cholinium hydroxide ChOH with natural chiral amino acids (*S*-proline, *R*-proline, and *trans*-4-hydroxy-*S*-proline) (Scheme 3). The synthetic methodology was inspired by Ohno's work [51] in 2005 and previously reported works for some phosphonium or ammonium derivatives [38–45].



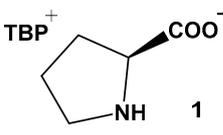
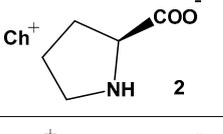
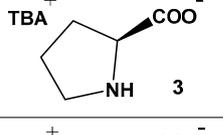
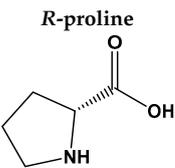
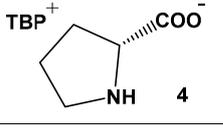
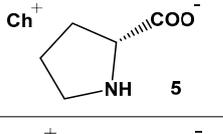
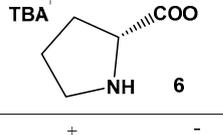
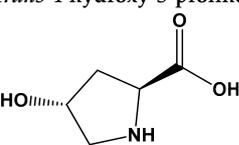
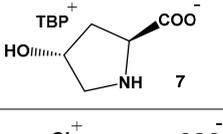
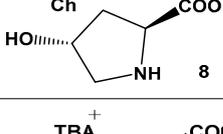
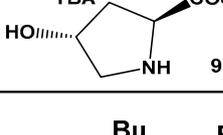
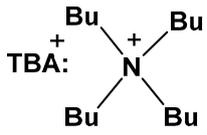
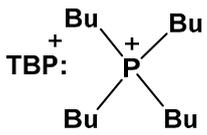
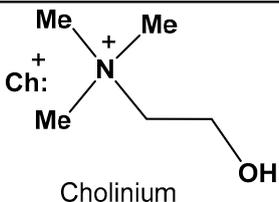
**Scheme 3.** Synthesis of chiral ionic liquids.

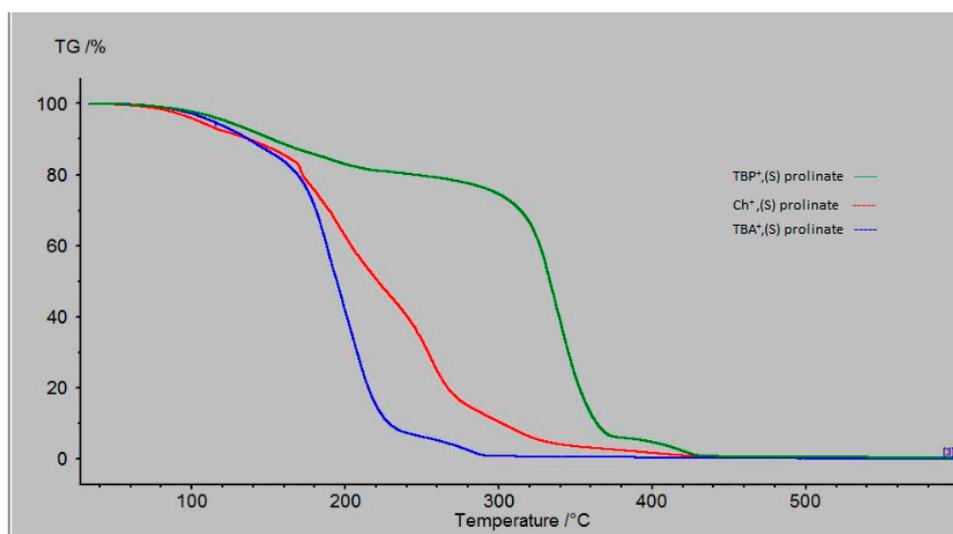
Nine ionic liquids were prepared easily with high yields and purity (Table 1), and the cholinium-based ionic liquids were synthesized following similar procedures previously used with ammonium or phosphonium-based ionic liquids.

The decomposition temperature values obtained by TGA confirmed the good thermal stability of all synthesized ionic liquids ( $T_{dec} \geq 198$  °C). We noticed that the thermal stability of ionic liquids was more dependent on the nature of the cation, particularly with phosphonium cations, as described in the literature [41]. Indeed, the ionic liquid  $TBP^+$  proline was the most stable. However, we could remark that the cholinium based ionic liquids were more stable than the ammonium-based ones when

proline or hydroxyproline were present as a counter anion (Figure 1); this observation is probably due to the formation of hydrogen bonds which could explain this slightly higher thermal stability [52].

**Table 1.** Synthetized ionic liquids.

Acid	Cation	Ionic Liquid	Yield (%)	Dec. Temperature Tdec (°C)	Viscosity (cp) at 60 °C	Ref.
 S-proline	TBP <sup>+</sup>	 1	78	340	75.33	[41]
	Ch <sup>+</sup>	 2	95	230	98.36	This work
	TBA <sup>+</sup>	 3	85	200	68.04	[40,42]
 R-proline	TBP <sup>+</sup>	 4	89	//	76.75	[41]
	Ch <sup>+</sup>	 5	77	//	98.65	This work
	TBA <sup>+</sup>	 6	78	//	68.18	[40,42]
 Trans-4-hydroxy-S-proline	TBP <sup>+</sup>	 7	93	326	245.6	[41]
	Ch <sup>+</sup>	 8	82	222	387.2	This work
	TBA <sup>+</sup>	 9	84	198	188.2	[40,42]
 TBA <sup>+</sup>			 TBP <sup>+</sup>			 Cholinium
Tetrabutylammonium			Tetrabutylphosphonium			Cholinium

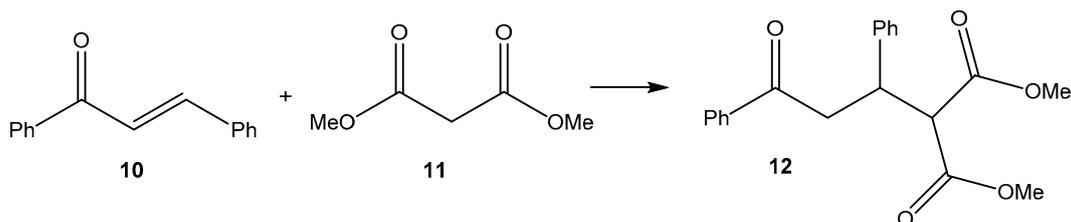


**Figure 1.** Thermal decomposition of ionic liquids 1–3.

The viscosities also show the importance of the anion (Table 1). In fact, with (*R*)-proline or (*S*)-proline as counter-anions, the viscosities at 60 °C are relatively low between 70 and 100 cp. With the same cation, we observed that the viscosity of choline-based ionic liquids was higher, probably due to the OH group present in this cation involved in hydrogen bonds. The same conclusions could be deduced when *trans*-4-hydroxy-*S*-proline was used as anion following much higher viscosity values due, in this case, to the presence of two OH groups (Table 1).

These ionic liquids have been used as a catalyst and solvent in Michael reaction models involving dimethyl malonate and chalcone as starting materials. Preliminary results were obtained with a slight excess of dimethyl malonate towards the chalcone (1.2 eq.) at 50 °C for 24 h (Table 2). DMF was used as a unique solvent or was associated with ionic liquid in a lower amount to reduce the viscosity of the reacting medium.

**Table 2.** Michael reactions under thermic conditions.



Entry	Solvent	Conversion of 10 (%)	Isolated Yield in 12 (%)
1 <sup>a</sup>	DMF	13	8
2 <sup>b</sup>	DMF + ( <i>S</i> ) proline TBP	69	46
3 <sup>b</sup>	DMF + ( <i>S</i> ) proline Ch	49	28
4 <sup>b</sup>	DMF + ( <i>S</i> ) proline TBA	46	33
5 <sup>b</sup>	DMF + ( <i>R</i> ) proline TBP	54	41
6 <sup>b</sup>	DMF + ( <i>R</i> ) proline Ch	58	49
7 <sup>b</sup>	DMF + ( <i>R</i> ) proline TBA	72	64
8 <sup>b</sup>	DMF + <i>trans</i> -4-hydroxy- <i>S</i> -proline TBP	24	13
9 <sup>b</sup>	DMF + <i>trans</i> -4-hydroxy- <i>S</i> -proline Ch	76	68
10 <sup>b</sup>	DMF + <i>trans</i> -4-hydroxy- <i>S</i> -proline TBA	47	29

<sup>a</sup> conditions: 1 eq. chalcone, 1.2 eq dimethylmalonate, DMF (10 mL), K<sub>2</sub>CO<sub>3</sub>(1.5 eq.), 50 °C, 24 h; <sup>b</sup> conditions: 1 eq. chalcone, 1.2 eq dimethylmalonate, DMF (2 mL), 1.2 eq. ionic liquid, 50 °C, 24 h.

The results obtained proved the positive impact of the use of ionic liquids for this Michael reaction while higher conversions of chalcone were observed (Table 2, entries 2–7, 9 and 10 vs. entry 1). Nevertheless, the conversions were not complete, and further experiments were conducted using an excess of dimethylmalonate. Indeed, with 3 or 4 equivalents of dimethylmalonate, the conversions obtained are much higher; furthermore, the reaction time could also be reduced to 4 h (Table 3, entry 4).

**Table 3.** Michael addition with an excess of dimethylmalonate (conditions: 1 eq. chalcone, 1.2 eq. (S) proline TBP<sup>+</sup>, 2 mL DMF, 50 °C).

Entry	Equivalent of 11	Time (h)	Conversion of 10 (%)
1	1.2	24	69
2	3	24	89
3	4	24	84
4	4	4	97

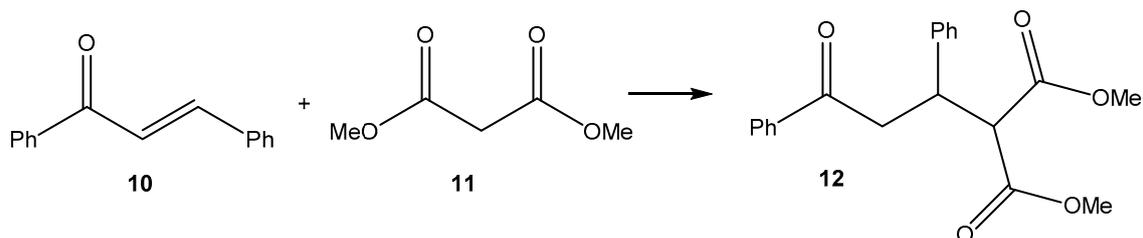
Based on these results, Michael's reaction was carried out using the various synthesized ILs as solvents (without the addition of DMF) under microwaves activation.

The conditions were adjusted after several experiments; at the beginning, the reactions were carried out with a power of 220 W leading to significant temperature variations depending on the ionic liquid. This aspect was unfavorable to the stability of the reactants or products. In addition, we observed that the presence of water in the ILs could also influence the conversion of the chalcone. Indeed, according to the results obtained in GC, the conversion rate of chalcone was low, and this was probably due to the low solubility of chalcone in water. Therefore, it was important to work with ionic liquids containing as little water as possible. Michael reactions were performed under microwaves during 45 min with a power limited to 100 W, and the ionic liquids were dried under vacuum for 4 h before use.

The reaction conducted under microwaves in DMF with the addition of K<sub>2</sub>CO<sub>3</sub> as a base led to a high conversion of chalcone over 45 min (Table 4, entry 1). Next, the DMF and the base could be substituted by the ionic liquid, which played further roles (Table 4, entries 2–10). Good to very good conversions of chalcone (60 to 85%) were obtained again in 45 min, proving that the microwaves could decrease the activation energy [53,54]. According to the literature concerning the Michael addition [55], we proposed a mechanism that is described in Scheme 4.

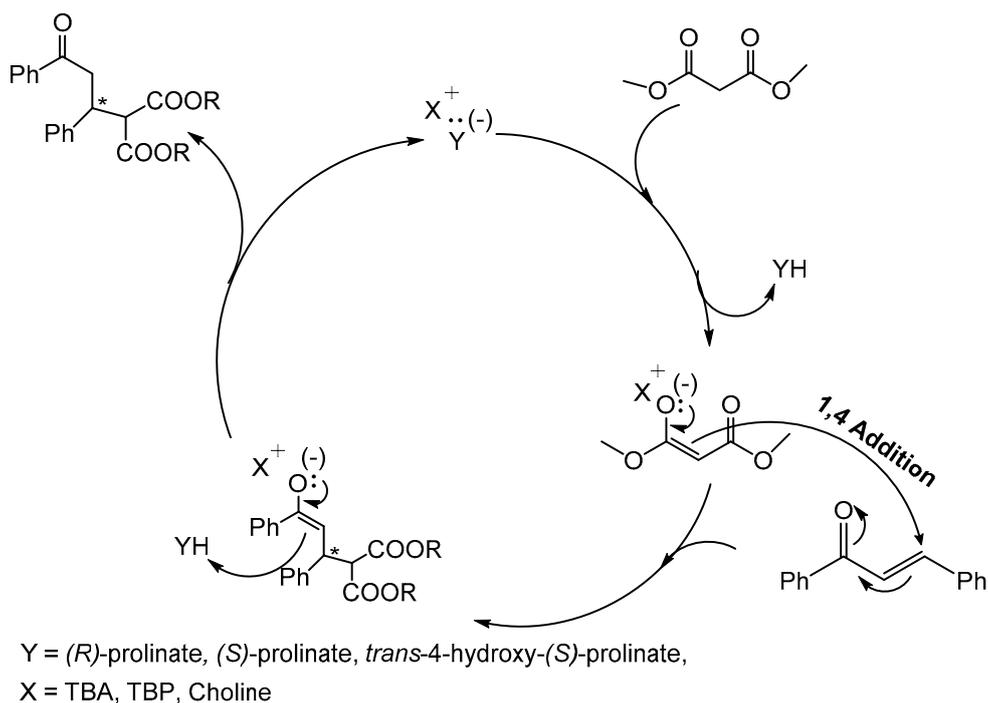
The anion plays the role of the base towards the dimethyl malonate, the Michael's donor, which subsequently reacts with the chalcone (the Michael's acceptor) to produce a stabilized enolate. The latter will recover the proton and regenerate the anion from the ionic liquid to produce the coupling adduct. The pK<sub>a</sub> of proline (10.64) and the hydroxyproline (9.65) led to suitable basic media when ionic liquids 1–9 were used. The anions of the ionic liquids played the role of the base. The whole ionic liquids played the crucial role of phase transfer agents as explained by Ceccarelli and et al. in 2006 [56].

Concerning the enantioselectivity of the reaction, all coupling compounds were racemic. The chiral anion of the ionic liquids seemed not to influence the protonation of the enolate species. The presence of residual water in the ILs could also explain the lack of enantioselectivity. The size of our anions was also relatively small contrary to the PCT agents used by Mahajan and al., leading to good enantiomeric excesses in similar Michael's additions [57].

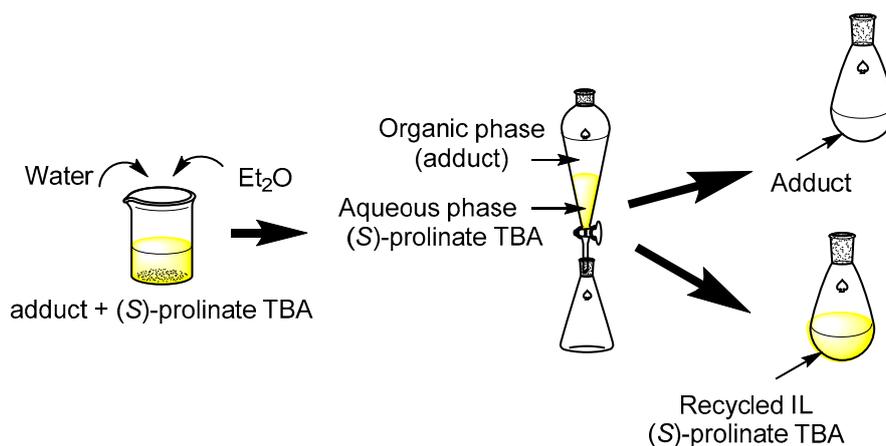
**Table 4.** Michael's reaction under microwaves.

Entry	Solvent	Conversion of 10 (%)	Isolated Yield in 12 (%)
1 <sup>a</sup>	Dimethylformamide (DMF)	95	79
2 <sup>b</sup>	( <i>S</i> ) proline TBP	69	48
3 <sup>b</sup>	( <i>S</i> ) proline Ch	74	62
4 <sup>b</sup>	( <i>S</i> ) proline TBA	90	72
5 <sup>b</sup>	( <i>R</i> ) proline TBP	71	59
6 <sup>b</sup>	( <i>R</i> ) proline Ch	88	65
7 <sup>b</sup>	( <i>R</i> ) proline TBA	80	61
8 <sup>b</sup>	<i>trans</i> -4-hydroxy- <i>S</i> -proline TBP	74	50
9 <sup>b</sup>	<i>trans</i> -4-hydroxy- <i>S</i> -proline Ch	60	47
10 <sup>b</sup>	<i>trans</i> -4-hydroxy- <i>S</i> -proline TBA	95	81

<sup>a</sup> conditions: 1 eq. chalcone, 4 eq. dimethylmalonate, DMF (10 mL), K<sub>2</sub>CO<sub>3</sub>(1.5 eq.), 100W, 45 min; <sup>b</sup> conditions: 1 eq. chalcone, 4 eq dimethylmalonate, 1.2 eq. ionic liquid, 100W, 45 min.

**Scheme 4.** A plausible mechanism for Michael's addition in ionic liquids.

The final work was to prove the possibility of recycling our ILs in the studied Michael's addition. One of the advantages of ionic liquids is the possibility to recycle them. We studied this possibility with the (*S*)-proline TBA. We chose this ionic liquid and not the *trans*-4-hydroxy-*S*-proline TBA, which furnished the best conversions because the yields of the first run were high (90%), and secondly, the price of the counter anion (*S*-proline) was lower than the *trans*-4-hydroxy-*S*-proline one. The procedure is described in Scheme 5.



**Scheme 5.** Recycling procedure for the Michael addition in (S)-proline TBA.

The chalcone conversions for the three first cycles were good (81 to 94%). Then, we observed a loss of activity of the reacting medium, probably due to the loss of the anion, which plays a basic role in the Michael's reaction mechanism and led to the amino acid by protonation. This hypothesis has been confirmed by NMR spectrum of the regenerated IL where a slight modification of its structure has been observed (See Table 5).

**Table 5.** Chalcone conversion during 5 runs.

Entry	Run	Chalcone Conversion (%)
1	1	94
2	2	90
3	3	81
4	4	66
5	5	61

conditions: 1 eq. chalcone, 4 eq. dimethylmalonate, 1.2 eq. (S)-proline TBA, 100 W, 45 min.

### 3. Experimental

All reagents were commercially available and used as received. Solvents were dried and distilled under argon before use ( $\text{CH}_2\text{Cl}_2$  over  $\text{CaCl}_2$  and THF over sodium/benzophenone) and stored over molecular sieves.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on an AC 250 Bruker in  $\text{CD}_3\text{OD}$  for  $^1\text{H}$  and  $^{13}\text{C}$  spectra. The infrared spectra were recorded with a Spectrafile IR<sup>TM</sup> Plus MIDAC. Chromatography was carried out on an SDS Silica 60 (40–63  $\mu\text{m}$ ), Art 2050044 (flash-chromatography), or silica 60 F<sub>254</sub> (TLC plates).

The GC analyses were recorded on a Hewlett Packard 6890 Series. The conditions used are specified in this Table 6.

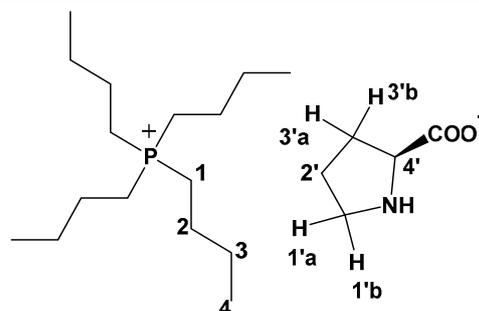
**Table 6.** The microwaves oven is a monomode CEM DISCOVERS-CLASS.

Conditions	Columns	
	B-DM (Chiral)	TR-1
Initial Temperature ( $^{\circ}\text{C}$ )	60	60
Initial time (min)	5	5
Gradient ( $^{\circ}\text{C}/\text{min}$ )	10	10
Final Temperature ( $^{\circ}\text{C}$ )	220	220
Final time (min)	20	20

### 3.1. Synthesis of Phosphonium Based Ionic Liquids-General Procedure [21d]

In a 100 mL two-neck round-bottom flask, one equivalent of a 40% wt aqueous solution of tetrabutylphosphonium hydroxide  $\text{TBP}^+\text{OH}^-$  (30 mmol, 21 mL) and 1.2 equivalents of (*R*), (*S*)-proline or *trans*-4-hydroxy-*S*-proline (36 mmol) previously dissolved in 40 mL distilled water were stirred at 100 °C during 24 h. After cooling, the solvent was evaporated, and the resulting mixture was washed with ethyl acetate ( $4 \times 80$  mL) to remove the small excess of amine. Finally, the aqueous phase was evaporated.

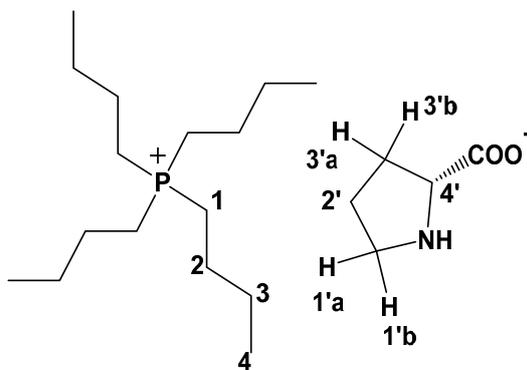
tetrabutylphosphonium (*S*)-prolinate



#### 3.1.1. General Procedure with 4.14 *S*-proline (36 mmol). Yield: 78%

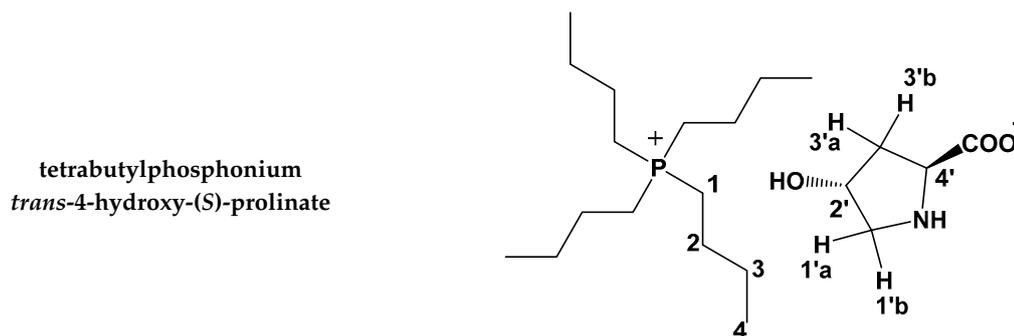
$\delta_{\text{H}}$  (250.1 MHz;  $\text{D}_2\text{O}$ ) ppm: 0.89 (t,  $J = 7.3$  Hz, 12H,  $\text{H}_4$ ); 1.31 (m, 16H,  $\text{H}_2$  and  $\text{H}_3$ ); 1.6 (m, 3H,  $\text{H}_2'$  and  $\text{H}_{3'a}$ ); 2 (m, 1H,  $\text{H}_{3'b}$ ); 2.48 (m, 8H,  $\text{H}_1$ ); 2.7 (m, 1H,  $\text{H}_{1'a}$ ); 2.95 (m, 1H,  $\text{H}_{1'b}$ ); 3.4 (m, 1H,  $\text{H}_{4'}$ ).  $\delta_{\text{C}}$  (62.5 MHz;  $\text{D}_2\text{O}$ ) ppm: 13.4 ( $\text{C}_4$ ); 18.4 ( $\text{C}_1$ ); 23.6 ( $\text{C}_2$ ); 23.9 ( $\text{C}_1$ ); 25.5 ( $\text{C}_2'$ ); 30.9 ( $\text{C}_3'$ ); 46.7 ( $\text{C}_1'$ ); 62 ( $\text{C}_4'$ ); 177.9 (C=O). IR:  $\nu$  ( $\text{cm}^{-1}$ ) 1746 (C=O). Analysis: calculated for  $\text{C}_{21}\text{H}_{44}\text{NO}_2\text{P}$ : C 67.52; H 11.87; N 3.75%. Found: C 66.98; H 11.38; N 3.42%.

tetrabutylphosphonium (*R*)-prolinate



#### 3.1.2. General Procedure with 4.14 g (*R*)-proline (36 mmol). Yield: 89%

$\delta_{\text{H}}$  (250.1 MHz;  $\text{D}_2\text{O}$ ) ppm: 0.89 (t,  $J = 7.3$  Hz, 12H,  $\text{H}_4$ ); 1.32 (m, 16H,  $\text{H}_2$  and  $\text{H}_3$ ); 1.6 (m, 3H,  $\text{H}_2'$  and  $\text{H}_{3'a}$ ); 2 (m, 1H,  $\text{H}_{3'b}$ ); 2.48 (m, 8H,  $\text{H}_1$ ); 2.7 (m, 1H,  $\text{H}_{1'a}$ ); 2.95 (m, 1H,  $\text{H}_{1'b}$ ); 3.4 (m, 1H,  $\text{H}_{4'}$ ).  $\delta_{\text{C}}$  (62.5 MHz;  $\text{D}_2\text{O}$ ) ppm: 13.4 ( $\text{C}_4$ ); 18.4 ( $\text{C}_1$ ); 23.6 ( $\text{C}_2$ ); 23.9 ( $\text{C}_1$ ); 25.5 ( $\text{C}_2'$ ); 30.9 ( $\text{C}_3'$ ); 46.7 ( $\text{C}_1'$ ); 62 ( $\text{C}_4'$ ); 177.9 (C=O). IR:  $\nu$  ( $\text{cm}^{-1}$ ) 1746 (C=O). Analysis: calculated for  $\text{C}_{21}\text{H}_{44}\text{NO}_2\text{P}$ : C 67.52; H 11.87; N 3.75%. Found: C 67.0; H 11.48; N 3.52%.

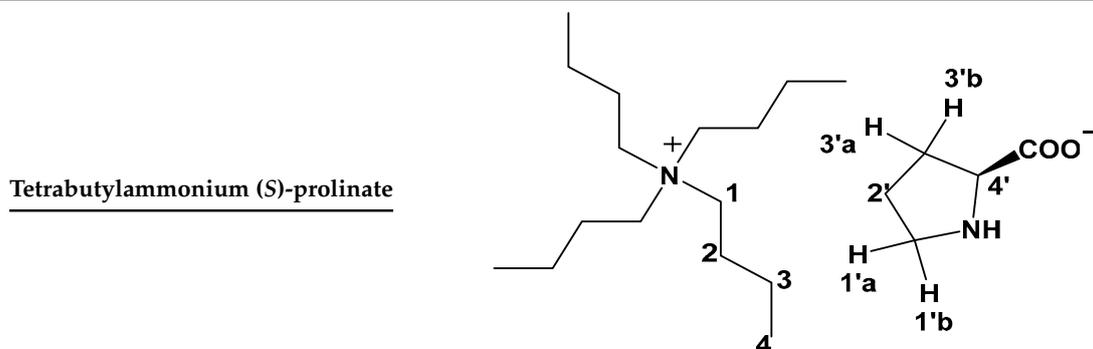


3.1.3. General Procedure with 4.72 g *Trans*-4-hydroxy-(S)-prolinate (36 mmol). Yield: 93%

$\delta_{\text{H}}$  (250.1 MHz;  $\text{D}_2\text{O}$ ) ppm: 0.89 (t,  $J = 7.3$  Hz, 12H,  $\text{H}_4$ ); 1.31 ppm (m, 16H,  $\text{H}_2$  and  $\text{H}_3$ ); 1.50 (m, 1H,  $\text{H}_{3'_{\text{b}}}$ ); 1.71 (m, 1H,  $\text{H}_{3'_{\text{a}}}$ ); 2.4 (m, 1H,  $\text{H}_{1'_{\text{a}}}$ ); 2.92 (dd,  $J = 12.3$ ; 5.1 Hz,  $\text{H}_{1'_{\text{b}}}$ ); 3.21 (m, 8H,  $\text{H}_1$ ); 3.41 (m, 1H,  $\text{H}_{2'}$ ); 4.00 (m, 1H,  $\text{H}_{4'}$ ).  $\delta_{\text{C}}$  (62.5 MHz;  $\text{D}_2\text{O}$ ) ppm: 13.4 ( $\text{C}_4$ ); 19.5 ( $\text{C}_3$ ); 24.4 ( $\text{C}_2$ ); 41.3 ( $\text{C}_3'$ ); 55.4 ( $\text{C}_1'$ ); 58.7 ( $\text{C}_1$ ); 61.9 ( $\text{C}_4'$ ); 72.2 ( $\text{C}_2'$ ); 177.7 ( $\text{C}=\text{O}$ ). IR:  $\nu$  ( $\text{cm}^{-1}$ ) 1746 ( $\text{C}=\text{O}$ ). Analysis: calculated for:  $\text{C}_{21}\text{H}_{44}\text{NO}_3\text{P}$ : C 64.75; H 11.38; N 3.60%. Found: C 64.39; H 10.98; N 3.32%.

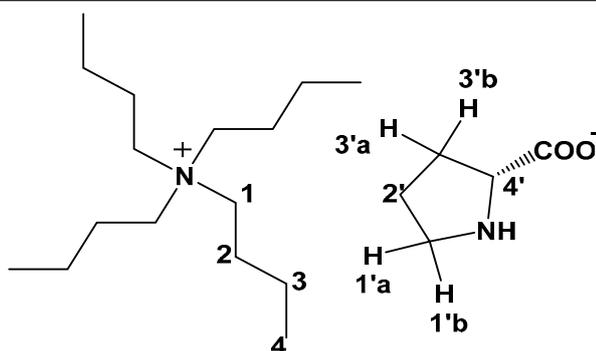
### 3.2. Synthesis of Ammonium Based Ionic Liquids-General Procedure [21c,e]

In a 100 mL two-neck round-bottom flask, one equivalent of a 40% wt aqueous solution of tetrabutylammonium hydroxide  $\text{TBA}^+\text{OH}^-$  (30 mmol, 19.6 mL) and 1.2 equivalents of (*R*), (*S*)-proline or *trans*-4-hydroxy-*S*-proline (36 mmol) previously dissolved in 40 mL distilled water were stirred at 100 °C during 24 h. After cooling, the solvent was evaporated, and the resulting mixture was washed with ethyl acetate ( $4 \times 80$  mL) to remove the small excess of amine. Finally, the aqueous phase was evaporated.



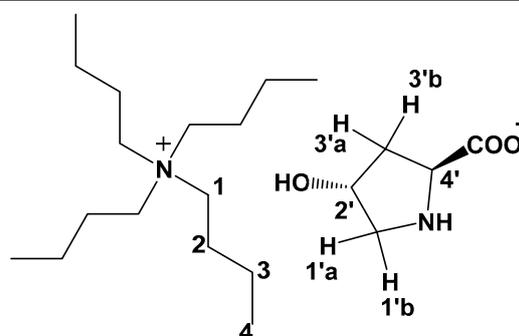
3.2.1. General Procedure with 4.14 *S*-proline (36 mmol). Yield: 85%

$\delta_{\text{H}}$  (250.1 MHz;  $\text{D}_2\text{O}$ ) ppm: 0.89 (t,  $J = 7.3$  Hz, 12H,  $\text{H}_4$ ); 1.32 (m, 8H,  $\text{H}_3$ ); 1.55 (m, 8H,  $\text{H}_2$ ); 1.60 (m, 3H,  $\text{H}_{2'}$  and  $\text{H}_{3'_{\text{b}}}$ ); 2.00 (m, 1H,  $\text{H}_{3'_{\text{a}}}$ ); 2.70 (m, 1H,  $\text{H}_{1'_{\text{a}}}$ ); 2.9 (m, 9H,  $\text{H}_1$  and  $\text{H}_{1'_{\text{b}}}$ ); 3.40 (m, 1H,  $\text{H}_{4'}$ ).  $\delta_{\text{C}}$  (62.5 MHz;  $\text{D}_2\text{O}$ ) ppm: 14.1 ( $\text{C}_4$ ); 20.6 ( $\text{C}_3$ ); 24.7 ( $\text{C}_2$ ); 26.7 ( $\text{C}_2'$ ); 32.2 ( $\text{C}_3'$ ); 47.6 ( $\text{C}_1'$ ); 59.4 ( $\text{C}_1$ ); 63.04 ( $\text{C}_4'$ ); 180.9 ( $\text{C}=\text{O}$ ). IR:  $\nu$  ( $\text{cm}^{-1}$ ) 1743 ( $\text{C}=\text{O}$ ). Analysis: calculated for:  $\text{C}_{21}\text{H}_{44}\text{N}_2\text{O}_2$ : C 70.73; H 12.44; N 7.86%. Found: C 70.29; H 11.98; N 7.37%.

**Tetrabutylammonium (*R*)-prolinate**

3.2.2. General Procedure with 4.14 *R*-proline (36 mmol). Yield: 78%

$\delta_H$  (250.1 MHz;  $D_2O$ ) ppm: 0.89 (t,  $J = 7.3$  Hz, 12H,  $H_4$ ); 1.32 (m, 8H,  $H_3$ ); 1.55 (m, 8H,  $H_2$ ); 1.60 (m, 3H,  $H_{2'}$  and  $H_{3'b}$ ); 2.00 (m, 1H,  $H_{3'a}$ ); 2.70 (m, 1H,  $H_{1'a}$ ); 2.9 (m, 9H,  $H_1$  and  $H_{1'b}$ ); 3.40 (m, 1H,  $H_{4'}$ ).

**tetrabutylammonium *trans*-4-hydroxy-(*S*)-prolinate**

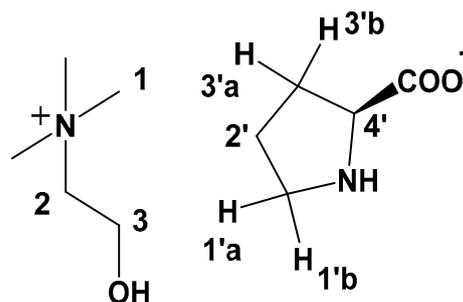
3.2.3. General Procedure with 4.72 *Trans*-4-hydroxy-(*S*)-prolinate (36 mmol). Yield: 85%

$\delta_H$  (250.1 MHz;  $D_2O$ ) ppm: 0.89 (t,  $J = 7.3$  Hz, 12H,  $H_4$ ); 1.31 ppm (m, 16H,  $H_2$  and  $H_3$ ); 1.5 (m, 1H,  $H_{3'b}$ ); 1.7 (m, 1H,  $H_{3'a}$ ); 2.4 (m, 1H,  $H_{1'a}$ ); 2.9 (dd,  $J = 12.2; 5.1$  Hz,  $H_{1'b}$ ); 3.20 (m, 8H,  $H_1$ ); 3.41 (m, 1H,  $H_{2'}$ ); 4.00 (m, 1H,  $H_{4'}$ ).  $\delta_C$  (62.5 MHz;  $D_2O$ ) ppm: 13.5 ( $C_4$ ); 19.9 ( $C_3$ ); 24.0 ( $C_2$ ); 41.3 ( $C_3'$ ); 55.4 ( $C_1'$ ); 58.7 ( $C_1$ ); 61.9 ( $C_4'$ ); 72.2 ( $C_2'$ ); 177.7 ( $C=O$ ). IR:  $\nu$  ( $cm^{-1}$ ) 1741 ( $C=O$ ). Analysis: calculated for:  $C_{21}H_{44}N_2O_3$ : C 67.70; H 11.90; N 7.52%. Found: C 67.31; H 11.48; N 7.23%.

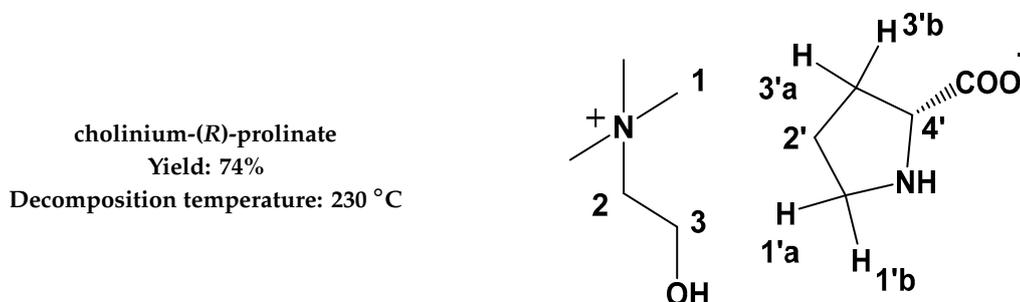
### 3.3. Synthesis of Cholinium Based Ionic Liquid

In a 100 mL Bicol, a mixture of 46% wt aqueous solution of cholinium hydroxide (1 eq. 30 mmol, 7.37 mL) and proline (1.2 eq., 36 mmol, 14 g) previously dissolved in 40 mL distilled water was stirred under reflux for 24 h at 100 °C. After cooling, the mixture was evaporated, washed (4 × 80 mL) with ethyl acetate, and finally, the aqueous phase was evaporated.

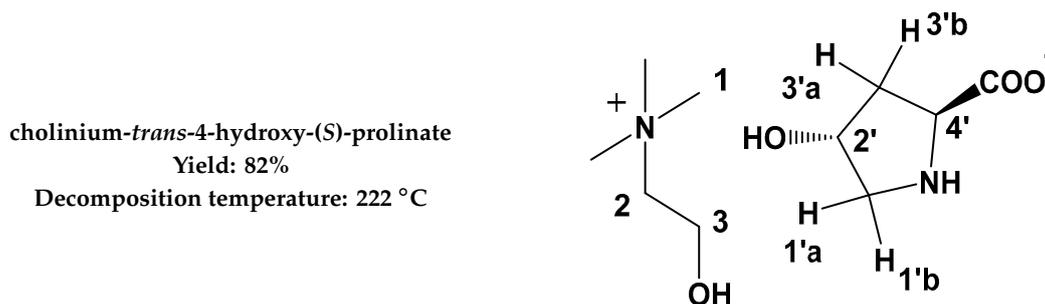
**cholinium-(*S*)-prolinate**  
Yield: 93%  
Decomposition temperature: 230 °C



$\delta_{\text{H}}$  (250.1 MHz; D<sub>2</sub>O) ppm: 1.60 (m, 3H, H<sub>2'</sub> and H<sub>3'a</sub>); 2.00 (m, 1H, H<sub>3'b</sub>); 2.70 (m, 1H, H<sub>1'a</sub>); 2.80 (m, 1H, H<sub>1'b</sub>); 3.11 (s, 9H, H<sub>1</sub>); 3.30 (t, 2H, H<sub>2</sub>); 3.45 (t, 1H, H<sub>4'</sub>); 3.80 (t, 2H, H<sub>3</sub>).  $\delta_{\text{C}}$  (62.5 MHz; D<sub>2</sub>O) ppm: (62.5 MHz; D<sub>2</sub>O): 22.8 (C<sub>2'</sub>); 32.3 (C<sub>3'</sub>); 46.5 (C<sub>1'</sub>); 55.7 (C<sub>1</sub>); 64.2 (C<sub>3</sub>); 67.5 (C<sub>4'</sub>); 70.2 (C<sub>2</sub>); 180.4 (C=O). IR:  $\nu$  (cm<sup>-1</sup>) 1741 (C = O). Analysis: calculated for: C<sub>10</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>: C 55.02; H 10.16; N 12.83%. Found: C 54.78; H 9.78; N 12.47%.



$\delta_{\text{H}}$  (250.1 MHz; D<sub>2</sub>O) ppm: 1, 60 (m, 3H, H<sub>2'</sub> and H<sub>3'b</sub>); 2.00 (m, 1H, H<sub>3'b</sub>); 2, 70 ppm (m, 1H, H<sub>1'a</sub>); 2.80 (m, 1H, H<sub>1'b</sub>); 3.10 (s, 9H, H<sub>1</sub>); 3.30 (t, 2H, H<sub>2</sub>); 3.45 (s, 1H, H<sub>4'</sub>); 3.80 ppm (t, 2H, H<sub>3</sub>).  $\delta_{\text{C}}$  (62.5 MHz; D<sub>2</sub>O) ppm: 22.6 (C<sub>2'</sub>); 32.3 (C<sub>3'</sub>); 46.7 (C<sub>1'</sub>); 55.4 (C<sub>1</sub>); 64.9 (C<sub>3</sub>); 67.3 (C<sub>4'</sub>); 70.7 (C<sub>2</sub>); 180.3 (C=O). Analysis: calculated for: C<sub>10</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>: C 55.02; H 10.16; N 12.83%. Found: C 54.89; H 9.78; N 12.36%.



$\delta_{\text{H}}$  (250.1 MHz; D<sub>2</sub>O) ppm: 1.50 (m, 1H, H<sub>3'b</sub>); 1.70 (m, 1H, H<sub>3'b</sub>); 2,40 ppm (m, 1H, H<sub>1'a</sub>); 2.90 (dd, J = 12.2 Hz, 5.1 Hz, 1H, H<sub>1'b</sub>); 3.10 (s, 9H, H<sub>1</sub>); 3.40 (m, 3H, H<sub>2'</sub>); 3.45 (s, 2H, H<sub>3</sub>); 3.80 ppm (t, J = 3.43 Hz, 2H, H<sub>2</sub>), 4 (m, 1H, H<sub>4'</sub>).  $\delta_{\text{C}}$  (62.5 MHz; D<sub>2</sub>O) ppm: 41.3 (C<sub>3'</sub>); 54.6 (C<sub>1'</sub>); 55.4 (C<sub>1</sub>); 61.9 (C<sub>4'</sub>); 64.9 (C<sub>3</sub>); 70.2 (C<sub>2</sub>); 72.2 (C<sub>2'</sub>); 177.7 (C=O). IR:  $\nu$  (cm<sup>-1</sup>) 1738 (C = O). Analysis: calculated for: C<sub>10</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>: C 51.26; H 9.46; N 11.96%. Found: C 51.49; H 9.58; N 11.66%.

### 3.4. Michael Addition Procedures

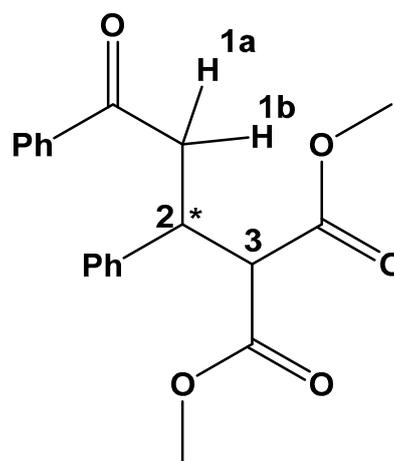
#### 3.4.1. General Procedure without Ionic Liquids

In a Schlenk tube, the chalcone (1 eq., 2 mmol, 0.42 g), the dimethyl malonate (1.2 eq or 4 eq.) and K<sub>2</sub>CO<sub>3</sub> (1.2 eq.) were mixed in DMF (10 mL). The reaction mixture was stirred for 24 h at 50 °C. The reaction was stopped by adding 15 mL of ice water with the formation of a white precipitate that corresponds to the coupling product. This precipitate was dissolved in diethyl ether. Extractions with diethyl ether were carried out (3 × 60 mL). The organic phases were then dried over sodium sulfate and then evaporated. The resulting compound was purified by chromatography (silica and eluent: Petroleum ether/Ethyl acetate (7/3)).

### 3.4.2. General Procedure in Ionic Liquids

In a Schlenk tube, 1.2 eq. of ionic liquid (2.4 mmol) was introduced and placed under vacuum for 10 min. Then at atmospheric pressure, 1 eq. of chalcone (2 mmol, 0.42 g) and an excess of dimethyl malonate (4 eq.) were dissolved in DMF (2 mL) in order to fluidify the mixture. The reaction mixture was stirred for 24 h at 50 °C and in the presence of argon. The reaction was stopped by adding 15 mL of ice water. We observed the formation of a white precipitate that corresponded to our product. The latter was dissolved by adding diethyl ether. Extractions with diethyl ether were carried out (3 × 60 mL). The organic phases were then dried over sodium sulfate and then evaporated. The resulting compound was purified by chromatography (silica and eluent: Petroleum ether / Ethyl acetate (7/3)). Finally, the aqueous phase was also evaporated to recover the ionic liquid.

2-(3-oxo-1,3-diphenylpropyl)  
dimethylmalonate [58]  
C<sub>20</sub>H<sub>20</sub>O<sub>5</sub>  
White Powder



$\delta_{\text{H}}$  (500 MHz; CDCl<sub>3</sub>) ppm: 3.50 (m, 4H, H<sub>1b</sub> and OMe); 3.55 (dd, 1H, H<sub>1a</sub>); 3.75 (s, 3H, OMe); 3.85 (d, 1H, H<sub>3</sub>); 4.25 (m, 1H, H<sub>2</sub>); 7.15 (m, 1H, H<sub>arom</sub>); 7.25 (m, 4H, H<sub>arom</sub>); 7.43 (t, 2H, H<sub>arom</sub>); 7.50 (m, 1H, H<sub>arom</sub>); 7.85 (m, 2H, H<sub>arom</sub>). IR:  $\nu$  (cm<sup>-1</sup>) 1735 (C = O<sub>Ester</sub>), 1715 (C = O<sub>Ketone</sub>).

### 3.4.3. General Procedure in Ionic Liquids under Microwaves

In a balloon, 1.2 eq. of ionic liquid (2.4 mmol) was introduced and placed under vacuum for 10 min. 1 eq. of chalcone (2 mmol, 0.42 g) and an excess of dimethyl malonate (4 eq.) was added, and the mixture was stirred for 45 min under 100 W. The extraction of the Michael's adduct and the recycling of the ILs was as previously described for the reaction under thermic conditions.

## 4. Conclusions

Nine proline-based ionic liquids were synthesized in water with high yields and at the best sustainable chemistry processes. Michael reactions were performed using these synthesized ionic liquids as both solvent and base with improved yields by increasing the amount of dimethylmalonate. Furthermore, the use of microwaves activation reduced the reaction time drastically. Therefore, the combined use of recyclable biosourced ionic liquids and microwaves represents an alternative to achieve greener synthesis processes than commonly used methods. Eco- and cyto-toxicological analyses are in progress to support the use of such biosourced ionic solvents, and the Michael addition will be tested with more sterically enhanced compounds in order to induce good ee values.

**Author Contributions:** K.B. and K.A. have realized the experimental work (synthesis and analysis). J.-P.M. and S.B. have supervised this work and J.-P.M. realized also some preliminary and crucial works on the synthesis of ILs. All authors have read and agreed to the published version of the manuscript.

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

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