The reaction of primary aromatic amines with alkylene carbonates for the selective synthesis of bis-*N*-(2-hydroxy)alkylanilines: the catalytic effect of phosphonium-based ionic liquids†

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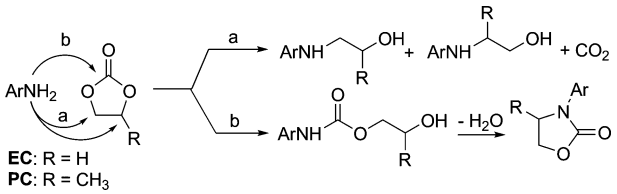
At $T \geq 140$ °C, different primary aromatic amines (pX–$C_6H_4NH_2$; X = H, OCH_3, CH_3, Cl) react with both ethylene- and propylene-carbonates to yield a chemoselective *N*-alkylation process: bis-*N*-(2-hydroxyalkyl)anilines [pX–$C_6H_4N(CH_2CH(R)OH)_2$; R = H, CH_3] are the major products and the competitive formation of carbamates is substantially ruled out. At 140 °C, under solventless conditions, the model reaction of aniline with ethylene carbonate goes to completion by simply mixing stoichiometric amounts of the reagents. However, a class of phosphonium ionic liquids (PILs) such as tetraalkylphosphonium halides and tosylates turn out to be active organocatalysts for both aniline and other primary aromatic amines. A kinetic analysis monitored by ^{13}C NMR spectroscopy, shows that bromide exchanged PILs are the most efficient systems, able to impart a more than 8-fold acceleration to the reaction. The reactions of propylene carbonate take place at a higher temperature than those of ethylene carbonate, and only in the presence of PIL catalysts. A mechanism based on the Lewis acidity of tetraalkylphosphonium cations and the nucleophilicity of halide anions has been proposed to account for both the reaction chemoselectivity and the function of the catalysts.

Introduction

The hydroxyalkylation of primary aromatic amines is extensively used, especially in medicinal chemistry, for the synthesis of aminoalcohols as intermediates.[1] Despite the broad scope, the reaction poses a major concern from both safety and environmental standpoints: conventional *N*-hydroxyalkylation methods are based on ethylene and propylene oxides which are highly toxic and carcinogenic compounds.[2] Moreover, the extreme flammability of these oxides means low reaction temperatures or sealed reactors are necessary.[1,3] Alternative reagents such as ethylene and propylene halohydrins [$X(CH_2)_2OH$, $XCH_2CH(OH)CH_3$; X = Cl, Br] do not reduce the overall impact of the procedure;[1a,4] halohydrins are also very toxic and corrosive products and their use generates stoichiometric amounts of halogenated salts which must be disposed of.[5]

Our long standing interest on green synthetic methodologies promoted by organic carbonates,[6] prompted us to look at alkylene carbonates (ethylene carbonate and propylene carbonate: **EC** and **PC**, respectively) as a valuable option for new hydroxyalkylation protocols of anilines. Although the catalytic insertion of CO_2 on alkylene oxides still represents the most important route for the synthesis of both ethylene and propylene carbonates,[7] nonetheless the latter offers a number of practical benefits over their parent oxides as well as over halohydrins. Among them: i) **EC** and **PC** are classified as irritant but non-toxic products; ii) **EC** is a low-melting solid (35 °C), while **PC** is a liquid, and both products are not flammable; therefore, they can be used as stoichiometric reagents without added solvents; iii) when **EC** or **PC** serve as hydroxyalkylating agents, CO_2 is the only by-product. Thus alkylene carbonates can be safely used even for large scale preparations, as documented by the extensive literature reported over the years.[8] Only few papers however, claim the application of **EC** and **PC** for the hydroxyalkylation of primary aromatic amines (Scheme 1, path a).[9] In the presence of different catalysts, the efficiency of the reaction is limited by the dual electrophilic character of the cyclic carbonates **EC** and **PC** which may cause competitive acylation (possibly followed by cyclization)[6] (Scheme 1, path b).



Scheme 1 Competitive reactions of anilines with alkylene carbonates.

This behaviour is quite general for the reaction of anilines with both linear and cyclic dialkyl carbonates, where mixtures of *N*-alkyl derivatives and carbamates are often obtained.[10] Effective solutions to improve the selectivity toward alkylation have been recently proposed by us through the use of two classes of catalysts: i) zeolites such as alkali metal exchanged faujasites (FAU[11]) and more recently, ii) phosphonium-based ionic liquids (PILs). FAU and PILs however, thanks to their different acid–base properties and steric requisites, promote different reaction outcomes. FAU catalyze the formation of mono-*N*-alkyl amines, while the more active PILs steer the reaction towards the formation of bis-*N*-alkyl derivatives. Scheme 2 describes some relevant examples: in

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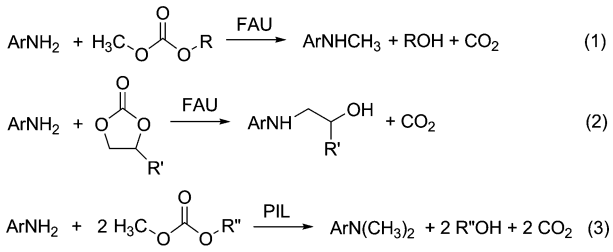
† Electronic supplementary information (ESI) available: ^1H and ^{13}C NMR spectra of PILs **2–13**, compounds **3a–d** and **7a–b**, and a synopsis of major MS signals is reported for all reaction products **2a–d**, **3a–d**, **4a–d**, **5a–d**, **6a–b**, **7a–b**, **8a–b** and **9a–b**. See DOI: 10.1039/c0ob00105h

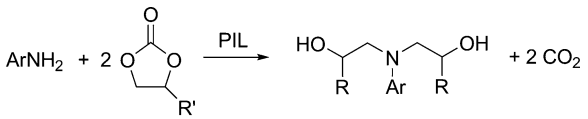


FAU: faujasites of Y- and X-type
PIL: ionic liquids based on phosponium salts
Ar = XC_6H_4-; X = OH, OCH_3, CH_3, H, Cl, $CO_2R"$, NO_2
R= CH_3; $CH_3O(CH_2)_2O(CH_2)_2$;
R' = H; CH_3, CH_2OH
R" = $CH_3O(CH_2)_2O(CH_2)_2O(CH_2)_2$; $CH_3O(CH_2)_2O(CH_2)_2$; $CH_3O(CH_2)_2$

Scheme 2 Selective *N*-alkylation reactions catalysed by FAU and PILs.

the presence of FAU, eqn (1) and (2) show the mono-*N*-alkylation of anilines with dimethyl- and 2-(2-methoxyethoxy)ethylmethyl-carbonates,[10] with **EC** and **PC**,[9a] and with glycerol carbonate;[12] while, eqn (3) refers to the PIL-promoted *N*,*N*-dimethylation of primary aromatic amines with different methylalkyl carbonates.[13] Excellent alkylation selectivities (up to 98%, at complete substrate conversion) are achieved in all cases, although, the reactions show a high activation energy irrespective of the catalyst (FAU or PILs), which usually implies a temperature greater than 140 °C.

A more in-depth analysis of this scenario indicates that the potential of cyclic alkylene carbonates as alkylating agents of anilines is still largely unexplored; in addition, the use of PILs as catalysts for this process, has been hardly investigated. In this paper, we report that at temperatures in the range of 140–170 °C, phosphonium-based ionic liquids catalyze the reaction of different primary aromatic amines ($pX–C_6H_4NH_2$; X = H, OCH_3, CH_3, Cl) with both **EC** and **PC**, towards the formation of the corresponding bis-*N*-hydroxyalkyl derivatives [$pX–C_6H_4N(CH_2CH(R)OH)_2$; R = H, CH_3] with a high selectivity (up to 97%) at complete conversion (Scheme 3).



PIL: 13 different phosponium ionic liquids
Ar = XC_6H_4-; X = *p*-OCH_3, *p*-CH_3, H, *p*-Cl
R= H, CH_3;

Scheme 3 Selective bis-*N*-hydroxyalkylations of anilines by ethylene and propylene carbonates in the presence of PILs catalysts.

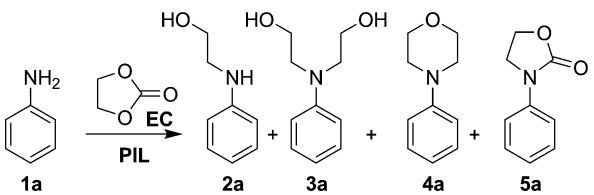
Interestingly, at 140 °C, the model reaction of aniline with ethylene carbonate proceeds to the almost quantitative formation of the bis-*N*-hydroxyethyl derivative, even without the assistance of any catalyst/promoter.

Up to 13 different phosphonium salts have been used. They have been prepared in order to guarantee an accessible synthesis with high purity and high thermal and chemical stability, or selected from commercial sources. In particular, the combination of four cations such as tri-*i*-butyl methylphosphonium [(*i*-Bu)$_3$PMe], tri-*n*-butylmethyl phosphonium [(*n*-Bu)$_3$PMe], tri-*n*-hexylmethylphosphonium [(*n*-Hexyl)$_3$PMe], tri-*n*-octylmethylphosphonium [(*n*-Octyl)$_3$PMe], with bromide (Br), tosylate (TosO), methyl carbonate (OCO_2Me), chloride (Cl) and iodide (I) anions, has been explored. Bromide exchanged PILs have proven to be the most efficient catalysts; while the variation of the cation structure presented a moderate effect, if any. Accurate kinetic profiles have been determined for the reaction of aniline with **EC**, catalysed by PILs: since solventless conditions have been used, the high concentrations of both reagents and products allowed to monitor the process *via* ^{13}C NMR spectroscopy. A mechanistic hypothesis has been formulated to rationalise the performance of the examined catalysts.

Results

The bis-*N*-(2-hydroxy)ethylation of aniline.

The reaction of aniline (**1a**) with **EC** was selected as a model to begin the investigation. Our previously reported results[13] suggested the use of tri-isobutylmethylphosphonium tosylate [(*i*-Bu)$_3$PMe]Tos (**PIL1**) as a catalyst for a preliminary screening: this salt had a structure similar to PILs active for the *N*-methylation of primary aromatic amines with dialkyl carbonates (Scheme 2, eqn 3), it was stable at a high temperature, commercially available (in high-purity) and inexpensive. Two sets (a and b) of experiments were carried out by varying the loading of both the catalyst and ethylene carbonate, as well as the reaction temperature. In the first set (a), a mixture of aniline (**1a**, 0.80 g, 8.6 mmol), and ethylene carbonate (**EC**, in a two molar excess over aniline), was set to react at 150 °C, in the presence of different amounts of **PIL1** (the molar ratio Q = **PIL1** : **1a** was varied between 0.05 and 0.75). All reactions were stopped after 2 h and analysed by GC-MS. In the second set (b), a mixture of aniline (0.8 g, 8.6 mmol), and **PIL1** (0.1 molar equiv. with respect to aniline, Q = 0.1), was set to react with increasing amounts of ethylene carbonate (the molar ratio **EC** : **1a** was 2, 2.2, and 4), at two different temperatures of 150 and 170 °C. The reactions were monitored by GC-MS at time intervals of 2, 6, and 8 h. For both sets (a) and (b), the major products were the mono- and the bis-*N*-(hydroxy)ethyl derivatives of aniline (Scheme 4: compounds **2a** and **3a**, respectively). Traces (~1%) of *N*-phenylmorpholine (**4a**) and 3-phenyloxazolidin-2-one (**5a**) along with other unidentified by-products (total amount 1–5%) were also detected. Compound **3a** was isolated and fully characterised by ^1H and ^{13}C NMR, while the structures of **2a** and **4a** and **5a** were assigned from their MS spectra and by comparison to authentic commercial samples. An experiment was also conducted in the absence of the salt **PIL1**. The results of sets (a) and (b) are reported in Fig. 1 and Table 1, respectively. In the figure, the light gray profile refers to the overall *N*-alkyl selectivity ($S_{N\text{-alk}}$) expressed as: $S_{N\text{-alk}}$ = [(**2a**+**3a**)/Conversion]×100 (left ordinate), while the dark gray profile is the ratio of bis- to mono-*N*-alkyl products, *i.e.* (**3a**/**2a**) (right ordinate).



Scheme 4 Products observed in the reaction of aniline with ethylene carbonate catalysed by **PIL1**.

Table 1 The reaction of aniline (**1a**) with EC (**EC**) in the presence of [MeP(*i*-Bu)$_3$]Tos[a]

#	EC : **1a** (mol : mol)[b]	*T*/°C	t/h	Conversion (%, by GC)[c]	Products (%)[c]					
					2a	**3a**	**4a**	**5a**	Others[d]	Yield (**3a**,%)
1	2	150	2	74	67	5			2	
2			6	95	51	38		1	5	
3	4	150	2	72	64	6			2	
4			6	97	50	45	1		1	
5	2	170	2	97	49	46	1	1		
6			6	99	23	74			2	
7	2.2	170	2	97	46	48		1	2	
8			6	98	17	79		1	1	
9			8	98	9	86	2	1		74
10	4	170	2	96	52	41	2			
11			6	99	15	81	1		2	
12			9	98		95	2	1		61

[a] All reactions were carried out using a mixture of aniline (**1a**, 0.8 g) and compound **PIL-1** in a 1 : 0.1 molar ratio. [b] The molar ratio ethylene carbonate : aniline. [c] The reaction conversion and the amounts of products were determined by GC-MS analyses (columns 5 and 6, respectively). The conversion was referred to aniline (the limiting reagent). [d] Total amounts of unidentified by-products.

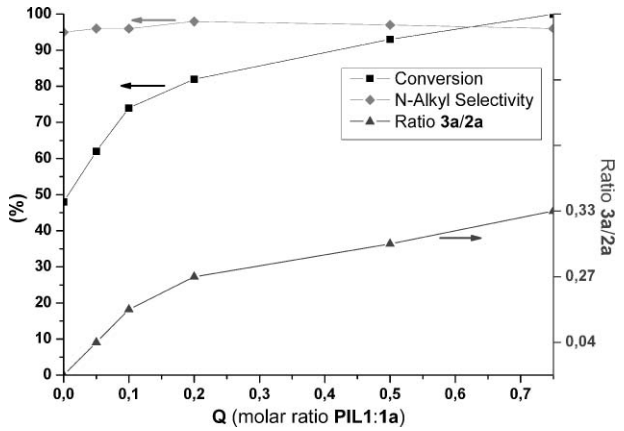


Fig. 1 The reaction of aniline with ethylene carbonate (150 °C, 2h): effects of the amount of **PIL1**.

Set (a) (Fig. 1). At 150 °C, the reaction proceeded even without catalyst (Q = 0): the conversion of aniline was of 48% and the mono-*N*-alkyl derivative **2a** was formed almost quantitatively (46%).[14] However, the reaction outcome was improved by the ionic liquid: the conversion was significantly larger (up to 73%) with the addition of even small quantities of **PIL1** (Q = 0.05–0.1) and, by further increasing the Q ratio from 0.1 to 0.75, the conversion finally rose up to a quantitative value. With respect to the uncatalysed process, the presence of the ionic liquid promoted the formation of both the mono- and the bis-*N*-alkyl derivatives of aniline (compounds **2a** and **3a**). Although the overall *N*-alkyl selectivity was very high ($S_{N\text{-alk}}$ = [(**2a**+**3a**)/conversion]×100 = 96–98%), mixtures of products **2a** and **3a** were always obtained. At Q ≥ 0.1, the (**3a**/**2a**) ratios were in the range of 0.2–0.33 (dark gray profile, right ordinate).

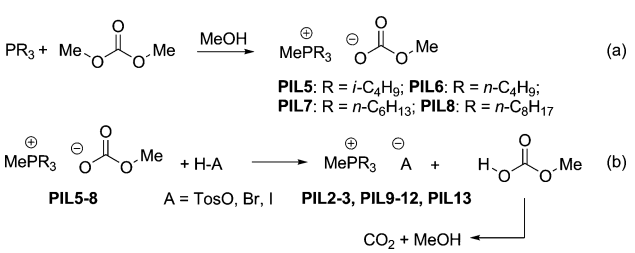
Set (b), Table 1. Experiments were continued at a constant Q ratio (**PIL1** : **1a**) of 0.1,[15] by varying the temperature and **EC**:**1a** ratio. At 150 °C, going from 2 to 6 h reaction times, a substantially quantitative conversion (95–97%) was observed with an excellent *N*-alkyl selectivity ($S_{N\text{-alk}}$: 95–98%; entries 1–2 and 3–4). The ratio of bis-*N*- to mono-*N*-alkyl compounds (**3a**/**2a**) also increased significantly, but it was still in favour of the product **2a** (50–51%; entries 2 and 4).

The reaction outcome was greatly improved at 170 °C. Aniline was detected in trace amounts (3–4%) after only 2 h (entries 5, 7 and 10), and, as the reaction proceeded further, compound **2a** was efficiently transformed in the bis-*N*-alkyl product **3a** with yields of 86–95% (by GC, entries 9 and 12).

At both 150 °C and 170 °C, the increase of the **EC** : **1a** molar ratio (from 2 to 4) moderately favoured the conversion of **2a** to the desired final product **3a** (compare entries 1–2 to 3–4, and entries 5–6 to 7–8 and 10–11). Nonetheless, when the reaction mixtures were purified by FCC (gradient elution: MeOH–diethyl ether/petroleum ether; from 0 : 1 : 4 to 1 : 7.5 : 1.5 v/v, total of 650 mL), **EC** was partly co-eluted with compound **3a**; hence, the higher the amount of ethylene carbonate, the lower the final isolated yields (entries 9 and 12: yields of 74% and 61%, respectively).[16]

The synthesis of phosphonium based ionic liquids (PILs)

PILs were prepared according to a new green protocol recently reported by us.[17] Four alkylphosphines (R_3P; R = *n*-octyl, *n*-hexyl, *i*-butyl, and *n*-butyl) were set to react with dimethyl carbonate ($MeOCO_2Me$) as a green methylating agent, to obtain methyltrialkylphosphonium methylcarbonate salts **PIL5–8** [Scheme 5, (a)]. These compounds were anion-exchanged by reaction with Brønsted acids (H–A, A = TsO, Br, and I) [(Scheme 5, (b)] to yield the corresponding tosylate, bromide, and iodide salts (**PIL2–4**, **PIL9–12**, and **PIL13**, respectively) along with methyl hydrogen



Scheme 5 The synthesis of PILs.

Table 2 List of ionic liquids synthesized in this work

Cation	Anion [TosO]	[OCO_2Me]	[Br]	[I]
[*i*-Bu_3PMe]	[a]	**PIL5**	**PIL9**	
[*n*-Bu_3PMe]	**PIL2**	**PIL6**	**PIL10**	
[*n*-Hex_3PMe]	**PIL3**	**PIL7**	**PIL11**	
[*n*-Oct_3PMe]	**PIL4**	**PIL8**	**PIL12**	**PIL13**

[a] [*i*-Bu_3PMe][TosO] was commercially available (Aldrich).

carbonate (*i.e.*, the half-ester of carbonic acid). The latter was unstable above −36 °C[18] and immediately decomposed to form methanol and CO_2, thus providing its built-in removal.

Overall, the two-step procedure allowed to synthesize 13 different PILs whose structures are summarized in Table 2. These products were obtained on a 2–3 g scale. They were fully characterized by ^1H and ^{13}C NMR in their natural state, not dissolved in any solvent, at the lowest monitoring temperature that kept them as liquids (see experimental for further details).

The bis-*N*-(2-hydroxy)ethylation of aniline in the presence of different ionic liquids

The reaction of aniline with ethylene carbonate was investigated in the presence of the different PILs of Table 2. Preliminary experiments carried out with strongly basic IL such as [*i*-Bu_3PMe][OCO_2Me] and [*n*-Oct_3PMe] [OCO_2Me] (**PIL5** and **PIL8**),[17] gave complex mixtures of products. For this reason, the use of the methylcarbonate exchanged PILs (**PIL5–8**) was not further examined.

A first screening on the behaviour of the other PILs as catalysts was carried out, based on the results of Table 1. In particular, tosylate and bromide-exchanged salts (**PIL2–4** and **PIL9–12**, respectively), were used. The complete combination of four cations (from C4 to C8: [*i*-Bu_3PMe], [*n*-Bu_3PMe], [*n*-Hex_3PMe], and [*n*-Oct_3PMe] was available for these anions (TosO and Br, Table 2). A mixture of aniline (**1a**, 0.8 g, 8.6 mmol), ethylene carbonate (**EC**) and a **PIL** (the molar ratio **1a** : **EC** : **PIL** was 1 : 2 : 0.1, respectively) was set to react at 170 °C and the progress of the reaction was monitored by GC-MS at time intervals in the range of 2–4 h. Analogous to the commercial **PIL1**, the major products were the desired mono- and the bis-*N*-(hydroxy)ethyl derivatives of aniline (compounds **2a** and **3a** of Scheme 4). *N*-phenylmorpholine (**4a**) and 3-phenyloxazolidin-2-one (**5a**) were also detected along with other unidentified by-products (total amount 3–12%). The results are reported in Table 3 which, for a more complete comparison, includes also the data related to compound **PIL1** (entries 5–6 of Table 1).

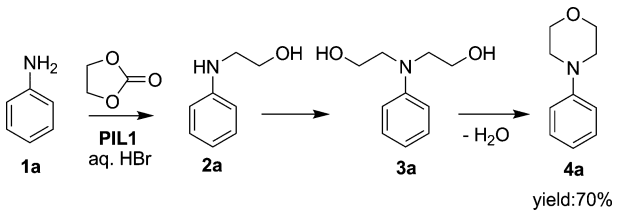
At 170 °C, after 2 h, the comparison of our model PILs showed that: i) high aniline conversions (80–100%) were reached in all cases; ii) bromide salts (**PIL9–12**) were by far, more efficient than tosylate ones (**3**) for the transformation of the mono-*N*-alkyl derivative **2a** into the final desired bis-*N*-alkyl product **3a**. The ratio **3a**/**2a** was 4–6.5 for bromides **PIL9–12**, (entries 9–12), while it ranged between 0.3 and 1 for tosylates **PIL1–4** (entries 1, 3, 5, and 7). Overall, the bromide-catalysed processes were substantially over after 2 h, while the tosylate-catalysed reactions were far from complete even after 4 h (entries 2, 4, 6, and 8). In the case of **PIL9**

Table 3 The reaction of aniline with ethylene carbonate at 170 °C, in the presence of different PILs[a]

#	PIL	t/h	Conversion (%)[b]	Products (%)[b] **2a**	**3a**	**4a**	**5a**	Others
1	**PIL1** MeP(*i*-Bu)$_3$ TosO	2	97	49	46	1	1	
2		4	99	25	68	1		5
3	**PIL2** MeP(*n*-Bu)$_3$ TosO	2	80	57	17		1	5
4		4	96	42	41	3	1	8
5	**PIL3** MeP(*n*-Hex)$_3$ TosO	2	85	56	18	4		7
6		4	91	45	34	2	1	9
7	**PIL4** MeP(*n*-Oct)$_3$ TosO	2	97	48	51			
8		4	100	36	58	1		5
9	**PIL9** MeP(*i*-Bu)$_3$ Br	2	98	13	64	9	4	7
10	**PIL10** MeP(*n*-Bu)$_3$ Br	2	98	9	61	12	3	12
11	**PIL11** MeP(*n*-Hex)$_3$ Br	2	100	12	80	5		3
12	**PIL12** MeP(*n*-Oct)$_3$ Br	2	100	18	77	4	1	

[a] All reactions were carried out at 170 °C, using a mixture of aniline (**1a**, 0.8 g), ethylene carbonate, and PIL in a 1 : 2 : 0.1 molar ratio, respectively. [b] The reaction conversion and the amounts of products were determined by GC-MS analyses. Others were unidentified by-products.

and **PIL10**, an apparent drop of the *N*-alkyl selectivity ($S_{N\text{-alk}}$) was observed (entries 9–10). This was mainly due to the formation of *N*-phenylmorpholine **4a** (9–12%). Two additional experiments explained this result: under the conditions of entry 1 (Table 3), aniline was set to react with ethylene carbonate in the presence of water or of aq. HBr (both H_2O and HBr were used in 10% mol with respect to aniline). While the addition of water had no appreciable effects on the reaction outcome, a catalytic amount of aq. HBr prompted the transformation of compound **3a** into **4a** in 70% GC yield, after 18 h (Scheme 6).[19]

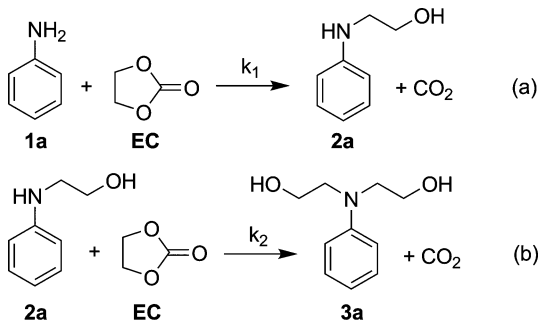


Scheme 6 The reaction of aniline and ethylene carbonate with added water or aq. HBr.

Traces of residual acidity (HBr) from the synthesis of ionic liquids (Scheme 5), reasonably accounted for the presence of the by-product **4a** in Table 3. However, any attempt to purify **PIL9** and **10** to improve their performance, was not successful.

The kinetic characterization of the reaction of aniline with EC

In the presence of small aliquots of PILs, mixtures of aniline and **EC** were perfectly homogenous and retained their liquid state even at room temperature. Hence, the alkylation of aniline with ethylene carbonate (Scheme 7) could be adequately followed by ^1H decoupled ^{13}C NMR spectroscopy, in a measuring tube equipped with a sealed capillary of [D_6]DMSO, for locking and homogeneity purposes. In order to slow down the reaction and to make its kinetic analysis easier, the experiments were performed at 140 °C, by placing a mixture of **1a**, **EC**, and a **PIL** (in a 1 : 2 : 0.05 molar ratio, respectively), in a NMR tube. The tube was dipped into a



Scheme 7 Consecutive reactions for the formation of compounds **2a** and **3a**.

thermostatted silicon oil bath. The highest possible concentrations assured the swift acquisition of the signals, that were also well separated. The modalities for the correct translation of the signal intensities into molar concentrations were detailed elsewhere.[20]

The concentrations at $t = 0$ were corrected by a measured factor of 1.10 due to the thermal expansion of the fluid. In addition, at 140 °C, the release of CO_2 caused a significant volume shrinking (Scheme 7). For example, a volume reduction by a factor of 0.71 was measured for the uncatalysed process after 8 h. Both chemical and physical features evolved during the reaction time. As detailed elsewhere,[20] the chemical evolution was described by the kinetic constants k_1 and k_2, the physical evolution by the time dependent activity coefficients α(t).

Fig. 2 exemplifies the behavior of the reaction of aniline and **EC** catalysed by **PIL11** [MeP(*n*-Hex)$_3$Br]: the disappearance of reactants, the transient formation of **2a** and the final conversion into **3a** are quantitatively displayed.

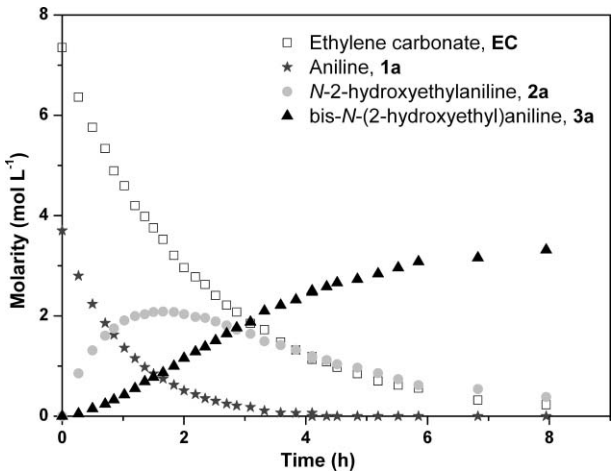


Fig. 2 The reaction at 140 °C of aniline **1a** and ethylene carbonate **EC** (3.70 and 7.35 mol L^{-1}, respectively), in the presence of **PIL11** ([MeP(*n*-Hex)$_3$Br], 0.19 mol L^{-1}). Time dependence of the molarities of **EC**, **1a**, *N*-2-hydroxyethylaniline **2a**, and bis-*N*-(2-hydroxyethyl)aniline **3a**.

In analogy to Fig. 2, the same kinetic analysis was carried out for reactions catalyzed by **PIL1**, **PIL3–4**, **PIL9**, **PIL12–13** as well as for the uncatalysed process. The kinetic constants k_1 and k_2 and the time dependent activity coefficients α(t) were necessary parameters for an acceptable fitting of the experimental concentrations into the system of differential equations describing the reactions of Scheme 7.

$$d[\mathbf{EC}]/dt = -k_1[\mathbf{EC}][\mathbf{1a}] - k_2[\mathbf{EC}][\mathbf{2a}]$$

$$d[\mathbf{1a}]/dt = -k_1[\mathbf{EC}][\mathbf{1a}]$$

$$d[\mathbf{2a}]/dt = k_1[\mathbf{EC}][\mathbf{1a}] - k_2[\mathbf{EC}][\mathbf{2a}]$$

$$d[\mathbf{3a}]/dt = k_2[\mathbf{EC}][\mathbf{2a}]$$

No analytically integrated form of this system was available. Therefore we resorted to the Runge–Kutta numerical integration and to the simplex fitting thereof.[20] For all the investigated reactions, it emerged that: i) without the introduction of the activity coefficients α(t), the routine was unable to reach a correct fit, but ii) only one α(t) function was sufficient, holding for all involved concentrations; iii) the optimized parameters k_1, k_2 and α(t) were biased by high co-variance, and could not be utilized for coherent comparisons within the examined panel of reactions.

Therefore we had to look for an independent method for retrieving the correct values of k_1 and k_2. According to the initial rate method:

$$d[\mathbf{EC}]/dt = d[\mathbf{1a}]/dt = -k_1[\mathbf{EC}]_0[\mathbf{1a}]_0$$

However, the rates could not be derived from the first concentrations of **EC** and **1a**, because of the action of the physical evolution as represented by α(t), but rather from the first order coefficient of the polynomial fittings (8th degree) of the whole sets of these same concentrations. The first order coefficients of these polynomials were the zero order coefficients of the derivatives, and were the only surviving coefficients at zero time. They are reported in Table 4. Their degree of similarity is a test for the procedure. The k_1 values are derived from their average. The k_2 values are measured at the time when the concentration of **2a** reaches the highest value. Here $d[\mathbf{2a}]/dt = 0$ and, because of the uniqueness of α(t), $k_2/k_1 = [\mathbf{1a}]/[\mathbf{2a}]$.[20]

The kinetic analysis qualitatively agreed with the general behaviour of the PIL catalysts reported in Fig. 1 and Table 1 and 3. Moreover, the quantitative evaluation of k_1 and k_2 kinetic constants helped to highlight some features of the process and some differences among the PIL catalysts. In particular: i) experiments confirmed that the reaction proceeded up to complete conversion of aniline to the bis-*N*-alkyl derivative **3a**, even in the absence of PILs (entry 1). However, with respect to the non catalysed process, the rate constant k_1 was almost doubled by the presence of tosylate salts (**PIL1–4**; entries 2–4); ii) the reaction rate was considerably improved by bromide salts (**PIL9–12**) which allowed an up to 8-fold increase of k_1 (entries 4–8); iii) the k_2/k_1 ratio was between 0.25 and 0.37 (far right column), essentially similar for all processes, either in the presence or in the absence of the catalyst, meaning that the bis-*N*-alkylation of aniline was always slower than the formation of the mono-derivative **2a**, but the relative rates of the two alkylation steps were not affected by the nature of the catalysts (nor changed in their absence). In addition, the k_2/k_1 ratio also suggested that the catalyst was operating on the only specie present in both processes of Scheme 7, **EC**; iv) within each set of tosylate and bromide salts, the cations had poor, if any, effects: no appreciable variation of the reaction rate was observed as the size of the alkyl P-substituents was increased (compare entries 2–4 and 4–7); v) the iodide exchanged **PIL13** (entry 8) offered an intermediate behaviour between **PIL1** and

Table 4 Kinetic analysis for the reaction of aniline **1a** with **EC**, carried out both with and without PILs as catalyst.[a]

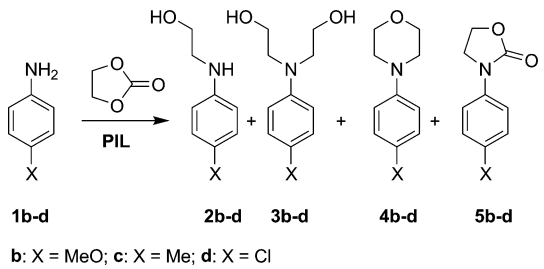
PIL	[EC]	Initial concentration/mol L^{-1}			Initial rate/mol L^{-1} h^{-1}		k_1 ($\times 10^2$)/L mol^{-1} h^{-1}	k_2 ($\times 10^2$)/L mol^{-1} h^{-1}	k_2/k_1
		[1a]	[PIL] ($\times 10$)	-d[EC]/dt	-d[1a]/dt				
	None	8.29	4.15		0.58	0.61	1.71	0.43	0.25
PIL1	*i*-Bu_3PMe TosO	7.32	3.70	1.82	0.84	0.81	3.05	0.76	0.25
PIL3	*n*-Hex_3PMe TosO	7.19	3.58	1.82	0.82	0.86	3.26	0.81	0.25
PIL4	*n*-Oct_3PMe TosO	7.01	3.53	1.76	0.72	0.78	3.03	0.79	0.26
PIL9	*i*-Bu_3PMe Br	7.53	3.78	1.88	3.78	3.59	12.9	4.47	0.37
PIL11	*n*-Hex_3PMe Br	7.35	3.70	1.86	3.54	3.45	12.9	4.63	0.36
PIL12	*n*-Oct_3PMe Br	7.19	3.61	1.82	2.53	2.44	9.57	3.26	0.34
PIL13	*n*-Oct_3PMe I	7.10	3.56	1.78	1.12	1.10	4.39	1.32	0.30

[a] All reactions were carried out at 140 °C, in a NMR tube charged with a mixture of **1a**, **EC**, and a **PIL** (in a 1 : 2 : 0.05 molar ratio, respectively).

PIL9 which were less and more active catalysts than **PIL13**, respectively. This further substantiated the role of the anion for the reaction outcome.

The reaction of different anilines with ethylene carbonate

PIL1 and **PIL12** [MeP(*i*-Bu)$_3$TosO and MeP(*n*-Oct)$_3$Br), respectively] were chosen as catalysts for the reaction of primary aromatic amines (*p*-anisidine, *p*-toluidine, and *p*-chloroaniline: compounds **1b–d**, respectively) with ethylene carbonate (**EC**). A mixture of the primary amine (8.6 mmol), ethylene carbonate, and a PIL in a 1 : 2.2 : 0.1 molar ratio, respectively, was set to react at temperatures in the range of 150–170 °C. All reactions were followed by GC-MS at different time intervals. Major products were the mono- and the bis-*N*-(2-hydroxy)ethyl derivatives of the reactant amines (Scheme 8: compounds **2** and **3**, respectively).



Scheme 8 The products observed in the reaction of different anilines with ethylene carbonate catalysed by **PIL1** and **PIL12**.

N-[(*p*-substituted)phenyl]morpholines (**4**: 1–4%) and *N*-[(*p*-substituted)phenyl]-oxazolidin-2-ones (**5**: 2–4%) along with other unidentified by-products (total amount 2–8%) were also detected. Compounds **3b–d** were isolated and fully characterised by ^{1}H and ^{13}C NMR, while the structures of **2b–d**, **4b–d** and **5b–d**, were assigned from their MS spectra. The results are reported in Table 5 where, for a more complete comparison, also the data related to aniline (Tables 1 and 2) are included.

Three main considerations emerged: i) the bromide exchanged PIL was more active than the tosylate salt. At 150 °C for example, both *p*-anisidine and *p*-toluidine were completely converted in 4–7 h and in 15–18 h, using **PIL12** [MeP(*n*-Oct)$_3$Br] and **PIL1** [MeP(*i*-Bu)$_3$TosO], respectively (entries 8–9 and 4–5). ii) The reaction was of a general scope for different amines. On average, *p*-anisidine (entries 3–4, and 8) was more reactive than *p*-toluidine (entries 5 and 9), aniline (entries 1–2 and 7), and *p*-chloroaniline (entry 6). iii) as for the case of aniline, the FCC-purification of bis-*N*-alkyl derivatives **3b–d** was rather difficult: these compounds however, were isolated in reasonably good yields (62–74%; entries 4–6).

The reaction of primary aromatic amines with propylene carbonate

Three different PILs, namely tri-*i*-butylmethylphosphonium tosylate and bromide [**PIL1** and **PIL9**: MeP(*i*-Bu)$_3$TosO and MeP(*i*-Bu)$_3$Br), respectively] and tri-*n*-octylphosphonium bromide [**PIL12**: MeP(*n*-Oct)$_3$Br)], were selected as catalysts for the

Table 5 The reaction of different anilines with ethylene carbonate catalysed by **PIL1** and **PIL12** [a]

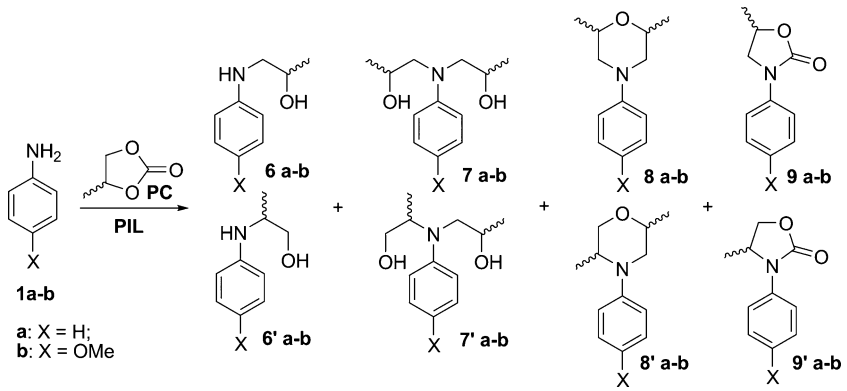
#	$XC_6H_4NH_2$	Catalyst	*T*/°C	t/h	Conversion (%)[b]	Products (%) [b]					**3** (Yield, %) [c]
						2	**3**	**4**	**5**	Others	
1	**1a** X = H	**PIL1** [MeP(*i*-Bu)$_3$] Tos	170	6	99	23	74			2	
2	**1a** X = H	**PIL1**	150	6	95	51	38		1	5	
3	**1b** X = *p*-MeO	**PIL1**	170	4	100	21	72	1	2	4	
4	**1b** X = *p*-MeO	**PIL1**	150	15	100	3	86	1	4	6	74
5	**1c** X = *p*-CH_3	**PIL1**	150	18	100	9	87		2	2	70
6	**1d** X = *p*-Cl	**PIL1**	170	14	100	17	72	4	3	4	62
7	**1a** X = H	**PIL12** [MeP(*n*-Oct)$_3$] Br	170	2	100	18	77	4	1		
8	**1b** X = *p*-MeO	**PIL12**	150	4	99	16	71	2	2	8	
9	**1c** X = *p*-CH_3	**PIL12**	150	7	99	13	74	4	1	7	

[a] All reactions were carried out using a mixture of the primary amine (8.6 mmol), ethylene carbonate, and a **PIL** in a 1 : 2.2 : 0.1 molar ratio, respectively. [b] The reaction conversion was referred to the primary amine. Both the conversion and the amounts of products were determined by GC-MS analyses. Others: total amounts of unidentified by-products. [c] Isolated yields of bis-*N*-alkyl derivatives **3b-d**.

Table 6 The reaction of different anilines with propylene carbonate in the presence of PIL catalysts[a]

#	$XC_6H_4NH_2$	Catalyst	T/°C	t/h	Conversion (%)[b]	Products (%)[b]					
						6	**7**	**8**	**9**	Others	**7** (Yield %)[c]
1	X = H	None	170	16	1					1	
2			190	10	3					3	
3		**PIL1** MeP(*i*-Bu)$_3$ TosO	190	54	98	41	36	10	1	11	
4		**PIL9** MeP(*i*-Bu)$_3$ Br	170	35	96	9	63	11		13	58
5		**PIL12** MeP(*n*-Oct)$_3$ Br	170	40	99	6	65	15	4	9	
6	X = *p*-MeO	**PIL1** MeP(*i*-Bu)$_3$ TosO	170	21	89	48	18	4	1	18	
7		**PIL9** MeP(*i*-Bu)$_3$ Br	150	29	100	6	60	3	6	25	55
8		**PIL12** MeP(*n*-Oct)$_3$ Br	150	24	100	6	58	6	7	23	

[a] All reactions were carried out using a mixture of the primary amine (8.6 mmol), propylene carbonate, and a **PIL** in a 1 2.2 : 0.1 molar ratio, respectively. [b] The reaction conversion was referred to the primary amine. Both the conversion and the amounts of products were determined by GC-MS analyses. Others: unidentified by-products were constituted by two isomers (m/z = 193). [c] Isolated yields of bis-*N*-alkyl derivatives **7a–b**



Scheme 9 The products observed in the reaction of different anilines with propylene carbonate catalysed by **PIL1**, **PIL9**, and **PIL12**.

reaction of primary aromatic amines (aniline and *p*-anisidine) with propylene carbonate (**PC**). A mixture of the primary amine (8.6 mmol), racemic propylene carbonate, and the chosen PIL in a 1 : 2.2 : 0.1 molar ratio, respectively, were set to react at temperatures in the range of 150–190 °C. An additional experiment was carried out also in the absence of PILs. All reactions were followed by GC-MS. The asymmetry of **PC** implied the formation of a number of products whose structures are outlined in Scheme 9. Major products derived from the *N*-alkylation of the reactant amines. The double nucleophilic attack of the amine at the C in position 5 of **PC** gave rise to bis-*N*-(2-hydroxy)propyl derivatives (compounds **7a–b**) as a pair of diastereoisomers in a 1 : 1 ratio. A non-negligible amount of other bis-*N*-alkylated compounds originated also from the reaction of the amine at the highly hindered C in position 4 of **PC** (compounds **7′a–b**): the ratio **7a–b**/**7′a–b** was ~ 4–5.[21] Two isomeric morpholines, *i.e.* 2,6-dimethyl- and 2,5-dimethyl-*N*-[(*p*-substituted)phenyl] morpholines (compounds **8a–b** and **8′a–b**, respectively; total of 3–11%), as well as two isomeric oxazolidin-2-ones, *i.e.* 5-methyl- and 4-methyl-*N*-[(*p*-substituted)phenyl]-oxazolidin-2-ones (compounds **9a–b** and **9′a–b**, respectively; total of 1–7%) were also detected.

Finally, pairs of isomeric unidentified by-products were observed (m/z = 193 in the reaction of aniline; m/z = 223 in the reaction of *p*-anisidine) in 11–25% yields. The isomeric ensemble **7a–b**/**7′a–b** were isolated and fully characterised by ^{1}H and ^{13}C NMR, while the structures of **6**, **8** and **9** were assigned from their MS spectra.

The results are reported in Table 6.

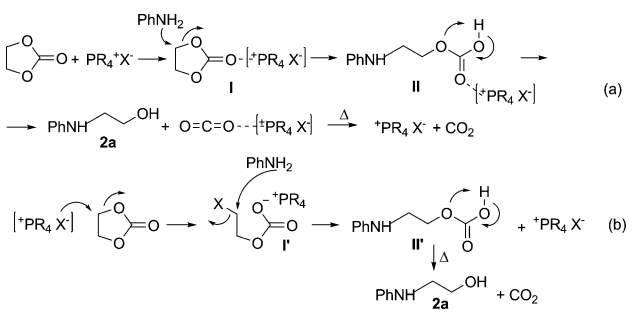
In the absence of PILs, the conversion of aniline was negligible even at high temperature (190 °C, entry 2). This remarkable difference with respect to ethylene carbonate, was likely to be due to the weaker electrophilic character of **PC**. However, the use of a catalytic amount of PILs allowed the reaction of aniline with propylene carbonate to proceed up to completion. Bromide exchanged salts (**PIL9** and **12**) were also able to promote the transformation of mono-*N*-alkyl products **6** to bis-*N*-alkyl derivatives **7** (entries 4–5 and 7–8). This process instead, was rather sluggish in the presence of the tosylated **PIL1**: for example, in the reaction of aniline, the ratio **6a**/**7a** was in favor of the mono-alkyl compound (**6a**) even after 54 h at 190 °C (entry 3). A similar situation held true for *p*-anisidine (entry 6).

In any case, the poorer reactivity of **PC** implied long reaction times (>20 h). This increased the formation of by-products at the point that the overall *N*-alkyl selectivity ($S_{N\text{-alk}}$ = [(**6**+**7**)/Conversion]×100) could not exceed 75%. A value, by far, lower than that achieved with ethylene carbonate (up to 97%, Table 5). However, to the best of our knowledge, this was the first ever reported reaction in which organocatalysts, particularly PILs, were able to activate **PC** as an alkylating agent of primary aromatic amines. Bis-*N*-alkyl derivatives **7** were purified by FCC and the corresponding isolated yields were in agreement to their GC amounts (entries 4 and 7).

Discussion

The reaction of aniline with alkylene carbonates: the effects of PILs

A first significant feature of the reaction of aniline with ethylene carbonate comes from the analysis of Fig. 1 and Table 4. At 140–150 °C, the process not only proceeds in the absence of catalysts but, under such conditions, it yields selectively the bis-*N*-(2-hydroxy)ethyl derivatives of the amine with no concurrent formation of carbamates. This behaviour is rather unexpected, especially if compared to the literature data discussed in the introduction (Scheme 1).[9,10,14] Aniline is perfectly capable, as a nucleophile, of discriminating between the two electrophilic centres of ethylene carbonate (the alkyl and the carbonyl carbons, respectively), with a preference for the β carbon. This preference is not altered by the action of the PIL catalysts. The cyclic structure of **EC** offers two plausible reasons for this result: i) on one hand, the *N*-alkylation selectivity would be favoured by the rigid 5-membered ring of **EC** which hinders access to the carbonyl carbon; ii) on the other hand, the relief of some ring strain consequent to the alkylation of aniline with **EC**, would allow even the non-catalytic reaction to proceed. It should be noted that this last effect is often offered to explain the higher reactivity of ethylene carbonate with respect to linear dialkyl carbonates.[22] Fig. 1 and Tables 3 and 4 however, leave few doubts about the catalytic action of PILs. In general, the alkylation rate of aniline with **EC** is doubled by the use of tosylate salts (**PIL1–4**), while the reaction is up to eight-fold accelerated by the more efficient bromide exchanged PILs (**PIL9–12**). This effect is even more pronounced when propylene carbonate is the alkylating agent (Table 6): *N*-(2-hydroxy)propyl derivatives of aniline (**6a** and **7a**) form only in the presence of catalytic amounts of PILs, otherwise no reaction takes place at all. Also in this case, bromide salts (**PIL9** and **12**) offer a better performance than the tosylated **PIL1**. Table 4 however, indicates that the relative rates (the ratio k_2/k_1) of mono- and bis-*N*-alkylation steps of aniline is not substantially affected by the nature of the catalysts. This suggesting that the catalyst should be active on the only species present in both processes: **EC**. Hence, a convenient reaction mechanism should consider the action of both the cationic and the anionic parts of the PILs. Scheme 10 illustrates two plausible hypotheses (for simplicity, only the mono-*N*-(2-hydroxy)ethylation of aniline is shown).



Scheme 10 Mechanistic hypothesis for the mono-*N*-(2-hydroxy)-ethylation of aniline with **EC**.

The hypothesis (a) stands on the weak Lewis acidity of phosponium cations,[23] and the great affinity between phosphorous and oxygen atoms.[24] An initial coordination of the P center of the catalyst to the carboxylic oxygen of **EC**, produces the acid–base adduct (**I**); a similar structure, with pentavalent phosphorus, has been described in the literature.[25]

Although the carboxylic carbon of the complex (**I**) undergoes electrophilic activation, no reaction occurs at this position because of the rigid structure of **EC** (see above), and of the steric crowding imposed by the bulky phosphonium cation.[26] Aniline directs its nucleophilic attack to the β-alkyl carbons (in positions 3 and 4) of **EC**: both these atoms are rather accessible, and they experience an activating inductive effect caused by the strong polarisation of the C═O bond in the complex (**I**). An amino carbonic acid (**II**) forms. This unstable compound[27] quickly releases CO_2 to give the final product **2a**.

Path a) hardly explains why halide salts, more specifically bromides, are remarkably more active than tosylate PILs. The size, the polarisability, and the stability of anions alter the strength of ionic pairs in PILs and therefore, the Lewis acidity of the corresponding cations is also modified. However, a crucial role is plausibly played by the nucleophilic properties of bromides and tosylates. Path b) accounts for this last aspect in analogy to a mechanism previously proposed for the reaction of **EC** with carboxylic acids in the presence of tetraalkylammonium halides ($[NR_4^+X^-]$) as catalysts.[3] The following steps are considered: i) the aperture of the ethylene carbonate ring takes place through the attack of an halide anion (X^-) to one β alkyl carbon, and **I′** is formed; ii) then, aniline displaces the X-group and the amino carbonic acid **II′** is obtained; iii) finally, the evolution of CO_2 from **II′** brings to the final derivative **2a**. The greater nucleophilic strength of bromide or iodide anions with respect to the tosylate anions, makes path b) especially valid for PILs **9–12** and **13**, but not for the poor nucleophilic tosylate catalysts (PIL **1–4**).[28] This may account for the activity displayed by the two types of PILs: paths (a) and (b) may simultaneously operate with halides, while only path (a) is active for tosylates.

The two PIL partners (cation and anion) only act on **EC**, and therefore mechanisms (a) and (b) are valid for the attack of both primary and secondary amines, **1a** and **2a**, to **EC**. This explains why the ratios k_2/k_1 are similar for all PILs. Within these ratios, $k_2 < k_1$: the steric features of the secondary aniline **2a** seem to be preeminent with regard to the enhanced nucleophilicity.

It should be noticed that species **I–II** and **I′II′**are intrinsically short-lived compounds, especially under the conditions (140–170 °C) explored here. This is plausibly the reason why the structures of these intermediates were never detected during the NMR investigation of the reaction of aniline with **EC** catalysed by PILs.

The reaction of different anilines with EC and PC

Tables 5 and 6 show that both activated and scantly nucleophilic amines react with alkylene carbonates to yield mainly the corresponding bis-*N*-alkyl derivatives. Three major observations emerge: i) on average, the reactivity of different aromatic amines agrees with the electron-donating properties of their ring substituents, *i.e.* p-OCH_3 > *p*-CH_3> H ≫ Cl; ii) **PC** is by far, less reactive than **EC**. As reported by different authors and by us,[7a,21,29] the steric hindrance of the methyl group in **PC**, likely accounts for its poor electrophilicity with respect to **EC**; iii) the higher activity of bromide exchanged salts (**PIL9** and **12**) over the

tosylate (**PIL1**) in the alkylation of *p*-anisidine and *p*-toluidine with both **EC** and **PC**, suggests that the mechanism of Scheme 10 discussed for aniline, holds for *p*-substituted anilines as well.

Conclusions

The reaction of primary aromatic amines with alkylene carbonates is a rather unexplored transformation. This investigation describes an advantageous methodology to carry out the bis-*N*-hydroxyalkylation of anilines with **EC** and **PC**. Although the methodology is rather energy intensive, several advantages can be recognized from both synthetic and environmental standpoints: i) the reaction is of a general scope for different anilines and for **PC** and **EC**; ii) non toxic alkylene carbonates replace very harmful hydroxyalkylating agents such as alkylene oxides or halohydrins; iii) the reactions are chemoselective, occurring almost exclusively at the β carbons of **EC** and **PC**. The competitive formation of carbamate products is ruled out; iv) the reaction setup is very simple and it allows truly catalytic processes using robust systems based on phosphonium salts (PILs). In particular, bromide exchanged PILs have proven to be the most efficient organocatalysts; v) a catalyst is not always required for the reaction: the quantitative formation of *N*,*N*-bis(2-hydroxy) ethylaniline is achieved at a reasonable temperature by merely mixing stoichiometric amounts of aniline and **EC**; vi) no additional solvents are required.

Two mechanistic hypothesis are proposed to account for the efficiency of the PILs organocatalysts: the Lewis acidic phosphonium cations may electrophilically activate the alkyl carbons of alkylene carbonates, while nucleophilic halide anions (but not tosylates) assist the aperture of the carbonate ring through a direct attack at the alkyl positions.

Propylene carbonate is a weaker electrophile than ethylene carbonate: primary aromatic amines react with **PC** only in the presence of catalytic amounts of bromide or tosylate onium salts.

Experimental

Anilines **1a–d** (*p*-$XC_6H_4NH_2$: **1a**: X = H; **1b**: X = OMe; **1c**: X = Me; **1d**: X = Cl), ethylene carbonate (**EC**), propylene carbonate (**PC**) and tri-isobutylmethylphosphonim tosylate (**PIL1**) were ACS grade and were employed without further purification. **PIL2–13** were prepared accordingly to a method recently reported by us.[17] GC-MS (EI, 70 eV) analysis were run using a HP5/MS capillary column (30 m). ^{1}H NMR were recorded at 400 MHz, ^{13}C NMR spectra at 100 MHz, ^{31}P NMR spectra were recorded at 200 MHz. Chemical shifts were reported in δ values downfield from TMS; $CDCl_3$ or CD_3OD were used as solvents. ^{31}P chemical shifts were reported with respect to 85% orthophosphoric acid (as external standard). IR spectra were recorded at room temperature on KBr disks.

Reaction procedure

The bis-*N*-(2-hydroxy)ethylation of aniline in the presence of different ionic liquids (Table 3). A glass reactor (7 mL) shaped as a test tube and equipped with a side screw-capped neck for the withdrawal of samples and a condenser, was charged with aniline (**1a**, 0.80 g, 8.6 mmol), ethylene carbonate (**EC**, 1.51 g, 17.2 mmol, molar ratio **EC** : **1a** was 2), and a PIL (0.86 mmol, molar ratio PIL : **1a** was 0.1). The chosen catalysts were PILs **1–4** and **9–12**. The reactor was then immersed in an oil bath thermostated at the desired temperature (170 °C) and the mixture was kept under magnetic stirring throughout the reaction. At intervals, samples of the reaction mixture were withdrawn and analysed by GC-MS. The procedure was used to run an experiment also in the absence of PILs. The above described procedure was adapted for the following experiments [(i)–(v)].

(*i*) *Reactions with different catalyst loadings* (Fig. 1) being all other conditions unaltered, the molar ratio Q = **PIL1** : **1a** was set to 0.05, 0.1, 0.2, 0.5 and 0.75, and the reaction temperature was set to 150 °C; (*ii*) *reactions with different ethylene carbonate loadings* (Table 1): being all other conditions unaltered, the molar ratio **EC** : **1a** was set to 2.2 and 4, and the reaction temperature was set to 150 or to 170 °C; (*iii*) *reactions with added water or aq. HBr* (Scheme 6): being all other conditions unaltered, water (0.015 g, 0.86 mmol, molar ratio H_2O:**1a** was 0.1) or an aqueous solution of HBr [48%] (0.1 mL, HBr 0.88 mmol, molar ratio HBr : **1a** was 0.1) were added. The reaction temperature was set to 170 °C; (*iv*) *reactions of different anilines with ethylene carbonate* (Table 5): the glass reactor was charged with the amine (**1b–d**, 8.6 mmol; **1b**: 1.06 g, **1c**: 0.92 g, **1d**: 1.09 g), ethylene carbonate (**EC**, 1.66 g, 18.9 mmol, molar ratio **EC**:**1** was 2.2), and a PIL (0.86 mmol, molar ratio PIL : **1** was 0.1). The chosen catalysts were **PIL1** and **PIL12**. The reactor was then immersed in an oil bath thermostated at the desired temperature (150–170 °C); (*v*) *reactions of different amines with propylene carbonate* (Table 6): the glass reactor was charged with the amine (**1a–b**, 8.6 mmol; **1a**: 0.8 g, **1b**: 1.06 g), propylene carbonate (**PC**, 1.93 g, 18.9 mmol, molar ratio **PC** : **1** was 2.2), and a PIL (0.86 mmol, molar ratio **PIL** : **1** was 0.1). The chosen catalysts were **PIL1**, **PIL9**, and **PIL12**. The reactor was then immersed in an oil bath thermostated at the desired temperature (150–190 °C).

Kinetic profiles *via* $^{13}C\{^1H\}$ NMR spectra (Fig. 2 and Table 4)

A solution (~1 mL) of aniline, ethylene carbonate and a PIL (molar ratio **1a** : **EC** : PIL were 1 : 2 : 0.05) was placed in a screw-cap NMR tube equipped with a coaxial calibrated glass capillary filled with pure [D_6]DMSO for locking and homogeneity purposes. The chosen catalysts were tosylate and halide salts (PILs **1**, **3–4** and **9**, **11–13**). The tube was dipped in an oil bath at 140 °C. At intervals, the tube was taken out from the thermostat, cooled at room temperature, and finally, inserted in the NMR spectrometer. All spectra were recorded at 25 °C. For each measure, it was assumed that the heating and the cooling times of the mixture were comparable and that a negligible reaction advancement occurred at room temperature. The $^{13}C\{^1H\}$NMR signals were used to obtain a plot of concentration *vs.* time for all the reactants and the products involved in the reaction. Fig. 2 exemplifies the process carried out in the presence of **PIL11**. Analogous plots were obtained for each of the catalysts used. The numerical integration of these profiles was performed through a method recently developed by us:[20] accordingly, the kinetic constants of Table 4 were determined.

Synthesis of PILs (Table 2)

Synthesis of methyltrialkylphosphonium methylcarbonate salts. PIL5–8: a sealed 200 mL steel autoclave fitted with a pressure

gauge and a thermocouple for temperature control was charged with a trialkylphosphine (R_3P, 56 mmol; R = *i*-butyl, 15 mL, 12.2 g; R = *n*-butyl, 15 mL, 12.2 g; R = *n*-hexyl, 20 mL, 16.2 g; R = *n*-octyl, 25 mL, 20.8 g), dimethyl carbonate (30 mL, 32.1 g, 356 mmol) and methanol (30 mL). Three freeze–pump–thaw cycles were carried out to ensure complete degassing of the mixture and air removal. The empty volume was then filled with nitrogen. The autoclave was heated for 24 h at the desired temperature (140 °C: R = *n*-octyl, *n*-hexyl, *n*-butyl; 170 °C: R = *i*-butyl) with magnetic stirring. Then, the reactor was cooled to room temperature and vented. Methanol and the residual DMC were removed from the mixture by rotary evaporation. A small amount (<1 equiv.) of methanol could remain incorporated in the sample even after a prolonged high vacuum was applied. Isolated yields were: **PIL6** (17.4 g) 96%; **PIL7** (21.5 g) 94%; **PIL8** (27.5 g) 100%. These salts were fully characterized as such, by ^{1}H and ^{13}C NMR, and used without further purifications. **PIL5** (15.8 g, 87%) was washed with *n*-hexane (3 × 15 mL) to remove some unreacted phosphine; then, it was characterized and used.

General anion exchange reaction procedure. a 50-mL round-bottomed flask was charged with an equimolar mixture of methyltrialkylphosphonium methylcarbonate (**PIL5–8**; 6 mmol, 1.75–2.76 g) and of a Brønsted acid (H–A: *A* = TsO, Br, or I), and methanol (5 mL) as a co-solvent. $TsOH{\cdot}H_2O$ (1.14 g) was used as a solid, while both HBr (0.68 mL) and HI (0.79 mL) were used in aqueous commercial solutions (48% and 57%, respectively). The mixture was kept under magnetic stirring for 1 h at 40 °C. Then, water and methanol were removed by rotary evaporation. The desired **PIL2–4** and **PIL9–13** were obtained in quantitative yields and fully characterized as such, by ^{1}H and ^{13}C NMR. They were used without further purification.

PIL2 (viscous clear colourless liquid) [(*n*-Bu)$_3$MeP][TosO]: ^{1}H NMR ($CDCl_3$, 25 °C, 400 MHz): δ (ppm): 7.61 (d, *J* = 8 Hz, 2H), 7.00 (d, *J* = 8 Hz, 2H), 2.21 (s, 3H; –CH_3), 2.10–2.02 (m, 6H; P–CH_2), 1.72 (d, *J*(P,H) = 14 Hz, 3H; P–CH_3), 1.30–1.25 (m, 12H), 0.77 (brt, 9H); ^{13}C NMR ($CDCl_3$, 25 °C, 100 MHz): δ (ppm): 144.1 (1C), 138.9 (1C), 128.4 (2C), 125.8 (2C), 23.7 (d, *J*(P,H) = 16 Hz, 3C), 23.4(d, *J*(P,H) = 5 Hz, 3C), 21.2 (1C), 19.6 (d, *J*(P,H) = 49, 3C), 13.4 (3C), 4.0 (d, *J*(P,H) = 52 Hz, 1C). ^{31}P NMR ($CDCl_3$, 25 °C, 200 MHz): δ (ppm): 31.8.

PIL3 (viscous clear colourless liquid) [(*n*-Hex)$_3$MeP][TosO]: ^{1}H NMR ($CDCl_3$, 25 °C, 400 MHz): δ (ppm): 7.73 (d, *J* = 8 Hz, 2H), 7.09 (d, *J* = 8 Hz, 2H), 2.31 (s, 3H; –CH_3), 2.26–2.18 (m, 6H; P–CH_2), 1.93 (d, *J*(P,H) = 14, 3H, P–CH_3), 1.47–1.34 (m, 12H), 1.28–1.22 (m, 12H), 0.85 (brt, 9H); ^{13}C NMR ($CDCl_3$, 25 °C, 100 MHz): δ (ppm): 144.5 (1C), 138.6 (1C), 128.3 (2C), 125.8 (2C), 31.0 (3C), 30.1(d, *J*(P,C) = 15 Hz, 3C), 22.2 (3C), 21.4 (d, *J*(P,C) = 5 Hz, 3C), 21.1 (1C), 19.8 (d, *J*(P,C) = 49 Hz, 3C, P–*C*H_2), 13.8 (3C), 3.9 (d, *J*(P,H) = 52 Hz, 1C). ^{31}P NMR ($CDCl_3$, 25 °C, 200 MHz): δ (ppm): 31.6.

PIL4 (white solid) [(*n*-Oct)$_3$MeP][TosO]: ^{1}H NMR ($CDCl_3$, 25 °C, 400 MHz): δ (ppm): 7.70 (d, *J* = 8 Hz, 2H), 7.06 (d, *J* = 8 Hz, 2H), 2.28 (s, 3H; –CH_3), 2.21–2.15 (m, 6H; P–CH_2), 1.88 (d, *J*(P,H) = 14, 3H, P–CH_3), 1.41–1.33 (m, 12H), 1.20 (brs, 24H), 0.83 (t, 9H); ^{13}C NMR ($CDCl_3$, 25 °C, 100 MHz): δ (ppm): 144.0 (1C), 138.7 (1C), 128.3 (2C), 125.8 (2C), 31.6 (3C), 30.5(d, *J*(P,C) = 15 Hz, 3C), 28.9 (3C), 28.8 (3C), 22.5 (3C), 21.6 (d, *J*(P,C) = 5 Hz, 3C), 21.1 (1C), 19.9 (d, *J*(P,C) = 48 Hz, 3C, P–*C*H_2), 13.9 (3C), 4.1 (d, *J*(P,H) = 52 Hz, 1C; P–*C*H_3). ^{31}P NMR ($CDCl_3$, 25 °C, 200 MHz): δ (ppm): 31.7.

PIL5 (viscous pale yellow liquid) [(*i*-Bu)$_3$MeP][OCO_2CH_3]: ^{1}H NMR ($CDCl_3$, 25 °C, 400 MHz): δ (ppm): 3.13 (s, 3H; CH_3OCOO), 1.97 (dd, *J*(P,H) = 13 Hz, *J*(H,H) = 7 Hz, 6H; P–CH_2), 1.78–1.68 (m, 3H; P–CH_2–C*H*(CH_3)$_2$), 1.72 (d, *J*(P,H) = 13 Hz, 3H; P–CH_3), 0.76 (d, *J*(H,H) = 7 Hz, 18H; P–CH_2–CH(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 25 °C, 100 MHz): δ (ppm): 157.8 (1C; C═O), 51.2 (1C; CH_3O), 29.5 (d, *J*(P,C) = 46 Hz, 3C; P–*C*H_2–CH(CH_3)$_2$), 23.7 (d, *J*(P,C) = 9 Hz, 6C; P–CH_2–CH(*C*H_3)$_2$), 22.9 (d, *J*(P,C) = 5 Hz, 3C; P–CH_2–*C*H(CH_3)$_2$), 6.2 (d, *J*(P,C) = 50 Hz, 1C; P–*C*H_3). ^{31}P NMR ($CDCl_3$, 25 °C, 200 MHz): δ (ppm): 29.0.

PIL6 (viscous pale yellow liquid) [(*n*-Bu)$_3$MeP][OCO_2CH_3]: ^{1}H NMR ($CDCl_3$, 25 °C, 400 MHz): δ (ppm): 3.00 (s, 3H; CH_3OCOO), 1.92–1.80 (m, 6H; P–CH_2), 1.52 (d, *J*(P,H) = 14 Hz, 3H; P–CH_3), 1.06 (brs, 12H), 0.50 (brt, 9H); ^{13}C NMR ($CDCl_3$, 25 °C, 100 MHz): δ (ppm): 156.8 (1C; C═O)), 50.7 (1C; CH_3O), 22.5 (d, *J*(P,H) = 15 Hz, 3C), 22.3(d, *J*(P,H) = 4 Hz, 3C), 18.6 (d, *J*(P,H) = 49, 3C; P–*C*H2), 12.1 (3C), 2.8 (d, *J*(P,H) = 53 Hz, 1C; P–*C*H_3). ^{31}P NMR ($CDCl_3$, 25 °C, 200 MHz): δ (ppm): 31.6.

PIL7 (viscous pale yellow liquid) [(*n*-Hex)$_3$MeP][OCO_2CH_3]: ^{1}H NMR ($CDCl_3$, 25 °C, 400 MHz): δ (ppm): 3.44 (s, 3H; CH_3OCOO), 2.26–2.18 (m, 6H; P–CH_2), 1.92 (d, *J*(P,H) = 14, 3H, P–CH_3), 1.46–1.38 (m, 12H), 1.26–1.21 (m, 12H), 0.82 (brt, 9H); ^{13}C NMR ($CDCl_3$, 25 °C, 100 MHz): δ (ppm): 157.7 (1C; C═O)), 51.5 (1C; CH_3O), 30.4 (3C), 29.6 (d, *J*(P,C) = 15 Hz, 3C), 21.7 (3C), 20.9 (d, *J*(P,C) = 4 Hz, 3C), 19.3 (d, *J*(P,C) = 49 Hz, 3C, P–*C*H_2), 13.3 (3C), 3.5 (d, *J*(P,H) = 52 Hz, 1C; P–*C*H_3). ^{31}P NMR ($CDCl_3$, 25 °C, 200 MHz): δ (ppm): 31.8.

PIL8: a complete NMR characterization is given in reference 17 ^{31}P NMR ($CDCl_3$, 25 °C, 200 MHz): δ (ppm): 31.7.

PIL9 (white hygroscopic solid) [(*i*-Bu)$_3$MeP][Br]: ^{1}H NMR ($CDCl_3$, 25 °C, 400 MHz): δ (ppm): 2.17 (dd, *J*(P,H) = 13 Hz, *J*(H,H) = 7 Hz, 6H; P–CH_2), 1.88 (d, *J*(P,H) = 13 Hz, 3H; P–CH_3), 1.92–1.82 (m, 3H; P–CH_2–C*H*(CH_3)$_2$), 0.84 (d, *J*(H,H) = 7 Hz, 18H; P–CH_2–CH(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 25 °C, 100 MHz): δ (ppm): 29.9 (d, *J*(P,C) = 46 Hz, 3C), 23.9 (d, *J*(P,C) = 9 Hz, 6C), 23.0 (d, *J*(P,C) = 5 Hz, 3C), 7.5 (d, *J*(P,C) = 50 Hz, 1C). ^{31}P NMR ($CDCl_3$, 25 °C, 200 MHz): δ (ppm): 29.2.

PIL10 (viscous clear colourless liquid) [(*n*-Bu)$_3$MeP][Br]: ^{1}H NMR ($CDCl_3$, 25 °C, 400 MHz): δ (ppm): 2.03–1.96 (m, 6H; P–CH_2), 1.62 (d, *J*(P,H) = 13, 3H, P–CH_3), 1.14–1.03 (m, 12H), 0.50 (brt, 9H); ^{13}C NMR ($CDCl_3$, 25 °C, 100 MHz): δ (ppm): 22.6 (d, *J*(P,C) = 16 Hz, 3C), 22.5 (d, *J*(P,H) = 4 Hz, 3C), 19.3 (d, *J*(P,H) = 49, 3C), 12.3 (3C), 4.1 (d, *J*(P,H) = 52 Hz, 1C). ^{31}P NMR ($CDCl_3$, 25 °C, 200 MHz): δ (ppm): 31.6.

PIL11 (viscous pale yellow liquid) [(*n*-Hex)$_3$MeP][Br]: ^{1}H NMR ($CDCl_3$, 25 °C, 400 MHz): δ (ppm): 2.29–2.23 (m, 6H; P–CH_2), 1.91 (d, *J*(P,H) = 13, 3H, P–CH_3), 1.42–1.28 (m, 12H), 1.15–1.12 (m, 12H), 0.71 (brt, 9H); ^{13}C NMR ($CDCl_3$, 25 °C, 100 MHz): δ = 30.6 (3C), 29.9 (d, *J*(P,C) = 15 Hz, 3C), 21.9 (3C), 21.3 (d, *J*(P,C) = 4 Hz, 3C), 20.3 (d, *J*(P,C) = 49 Hz, 3C), 13.5 (3C), 4.9 (d, *J*(P,H) = 53 Hz, 1C). ^{31}P NMR ($CDCl_3$, 25 °C, 200 MHz): δ (ppm): 31.7.

PIL12 (white hygroscopic solid) [(*n*-Oct)$_3$MeP][Br]: ^{1}H NMR ($CDCl_3$, 25 °C, 400 MHz): δ (ppm): 2.42–2.36 (m, 6H; P–CH_2), 2.06 (d, *J*(P,H) = 13, 3H, P–CH_3), 1.52–1.38 (m, 12H), 1.26–1.20 (m, 24H), 0.82 (brt, 9H); ^{13}C NMR ($CDCl_3$, 25 °C, 100 MHz): δ (ppm): 31.4 (3C), 30.4 (d, *J*(P,C) = 15 Hz, 3C), 28.9 (3C), 28.8 (3C),

22.5 (3C), 21.6 (d, J(P,C) = 5 Hz, 3C), 21.1 (1C), 19.9 (d, J(P,C) = 48 Hz, 3C), 13.9 (3C), 4.1 (d, J(P,H) = 52 Hz, 1C; P–CH_3). ^{31}P NMR ($CDCl_3$, 25 °C, 200 MHz): δ (ppm): 31.6.

PIL13 (viscous yellow liquid) [(n-Oct)$_3$MeP][I]: ^{1}H NMR ($CDCl_3$, 25 °C, 400 MHz): δ (ppm): 2.45–2.38 (m, 6H; P–CH_2), 2.09 (d, J(P,H) = 13, 3H, P–CH_3), 1.56–1.41 (m, 12H), 1.30–1.1.23 (m, 24H), 0.84 (brt, 9H); ^{13}C NMR ($CDCl_3$, 25 °C, 100 MHz): δ (ppm): 31.5 (3C), 30.4 (d, J(P,C) = 15 Hz, 3C), 28.7 (3C), 28.8 (3C), 22.4 (3C), 21.6 (d, J(P,C) = 5 Hz, 3C), 20.7 (d, J(P,C) = 48 Hz, 3C, P–CH_2), 13.8 (3C), 5.6 (d, J(P,H) = 52 Hz, 1C). ^{31}P NMR ($CDCl_3$, 25 °C, 200 MHz): δ (ppm): 31.7.

Isolation and characterization of the products

All the reaction products **2a–d**, **3a–d**, **4a–d**, **5a–d**, **6a–b**, **7a–b**, **8a–b** and **9a–b** were characterized by GC-MS (see ESI†). Compounds **3a–d** and **7a–b** were isolated and fully characterized by ^{1}H and ^{13}C NMR (see ESI†).

Bis-*N*-(2-hydroxy)ethyl aniline, 3a[1d,30]. The product was isolated from the reactions carried out under the conditions of entries 9 and 12 of Table 1. The final mixtures were purified by flash column chromatography (FCC) on silica gel, using a gradient elution with methanol–diethyl ether/petroleum ether (PE) solutions (initial MeOH–Et_2O : PE = 0 : 1 : 4 v/v, final MeOH–Et_2O:PE = 1 : 7.5 : 1.5 v/v). Compound **3a** was a dark yellow oil (74 and 61% respectively, Table 1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.27–7.20 (m, 2H), 6.81–6.60 (m, 3H), 3.84 (t, J = 4.9 Hz, 4H), 3.57 (t, J = 4.9 Hz, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 147.7 (1C), 129.1 (2C), 116.7 (1C), 112.4 (2C), 60.5 (2C), 55.1 (2C). IR (KBr): ν = 3368, 2881, 1597, 1504, 1384, 1033.

Bis-*N*-(2-hydroxy)ethyl *p*-anisidine, 3b[30b,31]. The product was isolated from the reaction carried out under the conditions of entry 4 of Table 5. The final mixture was purified by flash column chromatography (FCC) on silica gel, using a ethyl acetate (EA)/petroleum ether (PE) solution (EA:PE = 3 : 1 v/v). Compound **3b** was isolated as brown solid (74%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.83 (d, J = 9.2 Hz, 2H), 6.76 (d, J = 9.2 Hz, 2H), 3.79 (t, J = 5.0 Hz, 4H), 3.76 (s, 3H), 3.46 (t, J = 5.0 Hz, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 152.4 (1C), 142.6 (1C), 115.7 (2C), 114.8 (2C), 60.5 (2C), 55.9 (2C), 55.7 (1C). IR (KBr): ν = 3305, 2950, 1651, 1511, 1250, 1036.

Bis-*N*-(2-hydroxy)ethyl *p*-toluidine, 3c[31]. The product was isolated from the reaction carried out under the conditions of entry 5 of Table 5. The final mixture was purified by flash column chromatography (FCC) on silica gel, using a gradient elution with EA/PE solutions (initial EA:PE = 1 : 1 v/v, final EA:PE = 3 : 1 v/v). Compound **3c** was a dark brown solid (70%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.04 (d, J = 8,7 Hz, 2H), 6.63 (d, J = 8,7 Hz, 2H), 3.81 (t, J = 4.9 Hz, 4H), 3.52 (t, J = 4.9 Hz, 4H), 2.25 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 145.7 (1C), 129.7 (2C), 126.2 (1C), 113.0 (2C), 60.5 (2C), 55.3 (2C), 20.0 (1C). IR (KBr): ν = 3391, 2934, 1618, 1520, 1382, 1082.

Bis-*N*-(2-hydroxy)ethyl *p*-chloroaniline, 3d[31]. The product was isolated from the reaction carried out under the conditions of entry 6 of Table 5. The final mixture was purified by flash column chromatography (FCC) on silica gel, using a EA/PE solution (EA:PE = 1 : 1 v/v). Compound **3d** was a pale brown solid (62%). ^{1}H NMR (CD_3OD, 400 MHz) δ (ppm): 7.05 (d, J = 9,2 Hz, 2H), 6.64 (d, J = 9.2 Hz, 2H), 3.64 (t, J = 6.0 Hz, 4H), 3.45 (t, J = 6.0 Hz, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 146.5 (1C), 129.0 (2C), 121.8 (1C), 113.8 (2C), 60.5 (2C), 55.2 (2C). IR (KBr): ν = 3314, 2866, 1618, 1865, 1593, 1500, 1383, 1062, 1037, 1014.

Bis-*N*-(2-hydroxy)propyl aniline, 7a. The product was isolated from the reaction carried out under the conditions of entry 4 of Table 6. The final mixture was purified by flash column chromatography (FCC) on silica gel, using a gradient elution with EA/PE solutions (initial EA : PE = 7 : 3 v/v, final EA : PE = 3 : 7 v/v). Compound **7a** (sum of diastereoisomers) was isolated as a pale yellow oil (58%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.26–7.20 (m, 4H), 6.82–6.78 (m, 2H), 6.78 6.71 (m, 2H), 6.59–6.57 (m, 2H), 4.24–4.16 (m, 2H), 4.16–4.08 (m, 2H), 3.65 (dd, J_1 = 15 Hz, J_2 = 2 Hz, 2H), 3.40 (dd, J_1 = 15 Hz, J_2 = 3 Hz, 2H), 3.18 (dd, J_1 = 15 Hz, J_2 = 9 Hz, 2H), 3.02 (dd, J_1 = 15 Hz, J_2 = 10 Hz, 2H), 1.22 (d, J = 6 Hz, 6H), 1.20 (d, J = 6 Hz, 6H). ^{13}C NMR ($CDCl_3$, 25 °C, 100 MHz): δ (ppm): 149.2 (1C), 148.0 (1C), 129.2 (2C), 129.0 (2C), 117.4 (1C), 116.6 (1C), 114.0 (2C), 112.2 (2C), 65.9 (2C), 64.9 (2C), 62.4 (2C), 60.0 (2C), 20.2 (4C). IR (KBr): ν = 3339, 2988, 1598, 1503, 1500, 1384, 1129, 1059, 1024.

Bis-*N*-(2-hydroxy)propyl *p*-anisidine, 7b[32]. The product was isolated from the reaction carried out under the conditions of entry 6 of Table 6. The final mixture was purified by flash column chromatography (FCC) on silica gel, using a gradient elution with EA/PE solutions (initial EA : PE = 7 : 3 v/v, final EA : PE = 3 : 7 v/v). Compound **7b** was a brown oil (55%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.86–6.78 (m, 6H), 6.61–6.58 (d, J = 9 Hz, 2H), 4.12–4.03 (m, 2H), 4.03–3.94 (m, 2H), 3.75 (s, 6H), 3.51 (dd, J_1 = 15 Hz, J_2 = 2 Hz, 2H), 3.26 (dd, J_1 = 14 Hz, J_2 = 2 Hz, 2H), 3.02–2.92 (m, 4H), 1.17 (d, J = 6 Hz, 6H), 1.16 (d, J = 6 Hz, 6H). ^{13}C NMR ($CDCl_3$, 25 °C, 100 MHz): δ (ppm): 152.8 (1C), 151.8 (1C), 143.8 (1C), 142.7 (1C), 117.4 (2C), 114.8 (2C), 114.5 (2C), 114.4 (2C), 65.8 (2C), 64.7 (2C), 63.0 (2C), 61.2 (2C), 55.7 (1C), 55.5 (1C), 20.1 (4C). IR (KBr): ν = 3392, 2941, 1511, 1384, 1241, 1047.

Acknowledgements

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15 Although the increase of the amount of **PIL1** (Fig. 1), favoured the reaction rate, the Q ratio was set 0.1 for practical reasons: the separation of the IL from the reaction products was easier and interferences in the GC-MS analyses were greatly limited.

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