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Modular Synthesis of γ-Valerolactone-Based Ionic Liquids and Their Application as Alternative Media for Copper-Catalyzed Ullmann-type Coupling Reactions

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Ⓢ Supporting Information

ABSTRACT: A convenient procedure was developed for the manufacturing of partially bio-ionic liquids (ILs) from renewable γ-valerolactone (GVL) and cheap and readily available tetraalkylphosphonium bromides with excellent (>99%) yields. The novel ionic liquids were characterized by their temperature dependent vapor pressure, density, viscosity, and conductivity. We have proven that these ILs can be a useful medium for copper-catalyzed Ullmann-type coupling reactions without the use of any ligand or additive, representing an environmentally benign tool for the synthesis of various amines. Twenty cross-coupling products were isolated with good to excellent yields (50−87%).

KEYWORDS: γ-Valerolactone, Safer media, Ionic liquids, Ullmann-coupling, Green chemistry, Amination
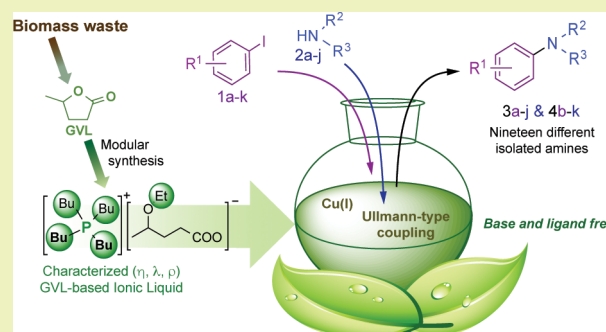
■ INTRODUCTION

The chemical industry uses enormous amount of solvents for many chemical transformations and processes.[1] Since these usually indispensable auxiliary materials could provide one or more liquid phase(s) for reactions, reduce density and viscosity, regulate temperatures, assist separations, etc., a "solvent friendly chemical thinking" has evolved from laboratory to industrial operations. The utilization of common organic solvents usually having high toxicity and flammability with high vapor pressure could raise serious environmental concerns. For example, over 6 million tons of volatile organic compounds including conventional organic solvents was released in the 28 member states of the European Union in 2015.[2] Consequently, the replacement of these usually fossil-based organic solvents with greener alternatives having low vapor pressure even at high temperature, low or no toxicity, and low flammabilityis a crucial part in the development of greener and cleaner chemical technologies.[3] As innovative approaches, several environmentally benign reaction media, e.g. water,[4] supercritical fluids,[5] fluorous solvents,[6] alcohols,[7] and ionic liquids (ILs),[8] were successfully introduced from laboratory to industrial scale in the last few decades. In addition, the introduction of renewable-based solvents, such as glycerol,[9,10] lactic acid,[11] ethyl lactate,[12,13] and γ-valerolactone (GVL)[14−18] in synthetic and/or catalytic chemistry could further control and reduce the environmental impacts.

Due to their extremely low vapor pressure, good solvating properties, reasonable thermal stability, easily tunable chemical (e.g., acidity, basicity, and polarity), and physical properties (e.g., viscosity, melting point, or vapor pressure), ILs have attracted considerable attention as alternative reaction media for a huge variety of chemical transformations.[19−22] However, the synthesis of some ILs can be quite laborious resulting in also some environmental impacts.[23] Therefore, several efforts were devoted to developing partially or fully biomass-based ILs, recently. Horváth and co-workers reported the synthesis of 4-hydroxyvalerate-based ionic liquids prepared by the reaction of nonfossil GVL and corresponding tetraalkylammonium hydroxide ([TAA][OH]).[24] Worthy of note is that cholinium 4-hydroxyvalerate prepared from GVL and cholinium hydroxide is a true bio-ionic liquid. We have recently demonstrated the synthesis of 4-alkoxyvalerate anion containing ILs that can be

68 considered as partially bio-ionic liquids and were successfully
69 utilized for hydrogenation and transfer hydrogenation reactions
70 under mild conditions.[25,26] Nevertheless, the applicability of
71 [TAA]-based ILs is limited by their low thermal stability.[24]
72 Thus, the development of thermally stable biobased ILs with
73 low viscosity for example facilitating proper mixing is highly
74 desired.

75 　　Among useful homogeneous catalytic transformations, the
76 transition metal catalyzed cross-coupling reactions are of
77 utmost importance. Although, several C−C, C−X coupling
78 reactions were successfully performed,[20,27,28] only a few studies
79 have been published on the copper-catalyzed Ullmann-type
80 amination of aryl halides in ILs. The latter reaction represents a
81 powerful tool for the synthesis of various biologically important
82 natural products and pharmaceuticals, and therefore, it has
83 acquired great importance over the past decade.[29] Accordingly,
84 introduction of biomass-based ionic liquids in copper-catalyzed
85 Ullmann-coupling reactions could open a greener way to
86 manufacture several important biologically active compounds
87 the presence or even in the absence of any added base.

88 　　Herein, we report the modular synthesis of tetraalkyl-
89 phosphonium 4-hydroxy- and 4-alkoxyvalerate type ionic
90 liquids and demonstrate their practical application in ligand-
91 and base-free Ullmann-type carbon−nitrogen coupling reac-
92 tions under mild conditions.

93 ■ RESULTS AND DISCUSSION

94 　　**Synthesis of GVL-Based Ionic Liquids.** The application
95 of tetraalkylammonium cations in transition metal catalyzed
96 reactions is limited above 90−100 °C, depending on the alkyl
97 chain length, due to decomposition. Phosphonium-based ILs
98 have generally significantly higher thermal stability compared to
99 the ammonium analogues.[30] Thus, the reaction of GVL or alkyl
100 4-alkoxyvalerate with tetraalkylphosphonium hydroxide
101 ([TAP][OH]) could result in the formation of an IL with
102 similar structure, albeit a higher thermal stability. Obviously,
103 one of the best approaches for preparation of [TAP][OH] is
104 the use of an efficient ion exchange method performed with a
105 commercially available and cheap tetraalkylphosphonium
106 bromide ([TAP][Br]) salt. Because tetrabutylammonium ILs
107 have already been systematically characterized and proven as an
108 appropriate media for catalysis,[25,26] initially tetrabutyl-
109 phosphonium bromide as a starting material was selected.
110 When 5 wt % of an aqueous solution of tetrabutylphosphonium
111 bromide [TBP][Br] (5.9 mmol) was stirred in the presence of
112 the hydroxide form of Amberlite NR-410 anion exchange resin
113 (32 mL), the removal of Br⁻ from the solution was completed
114 within 40 min at room temperature. It was demonstrated that
115 GVL can react with [TAA][OH] under aqueous conditions to
116 form tetraalkylammonium valerates.[24] By analogy, to obtain a
117 P-based IL, 5 g GVL (50 mmol) was reacted with a 40%
118 aqueous solution of 13.82 g (50 mmol) [TBP][OH] (40%
119 solution in H₂O, prepared by ion exchange). After 1 h, the
120 water was removed by vacuum (0.5 mmHg (ca. 67 Pa)) at 80
121 °C and tetrabutylphosphonium 4-hydroxyvalerate [TBP]-
122 [4HV] was isolated as a colorless viscous liquid at room
123 temperature with a yield >99%. The residual water content was
124 determined to be below 0.5 wt % by Karl Fischer titration.
125 Similarly, tetraphenylphosphonium hydroxide [TPP][OH] was
126 prepared from tetraphenylphosphonium bromide by ion
127 exchange and subsequently reacted with GVL for 1 h. After
128 removal of water (0.5 mmHg, 80 °C) a white solid was formed
129 indicating that the tetraphenylphosphonium salt is not an IL at

130 room temperature (RT-IL). Furthermore, in order to
131 synthesize tetraalkylphosphonium 4-alkoxyvalerate type ILs,
132 methyl 4-methoxyvalerate (50 mmol) and ethyl 4-ethoxy-
133 valerate (50 mmol) were reacted with 40 wt % aqueous
134 solutions of 50 mmol of [TBP][OH] resulting in the formation
135 of tetrabutylphosphonium 4-methoxyvalerate [TBP][4MeOV]
136 and tetrabutylphosphonium 4-ethoxyvalerate [TBP][4EtOV],
137 respectively. After removal of solvent (0.5 mmHg, 80 °C),
138 products were isolated as pale yellow liquids at room
139 temperature with yields >99% and water content <0.5 wt %.
140 The modular synthesis of ILs is summarized in Scheme 1.

Scheme 1. Synthesis of GVL-Based ILs[a]
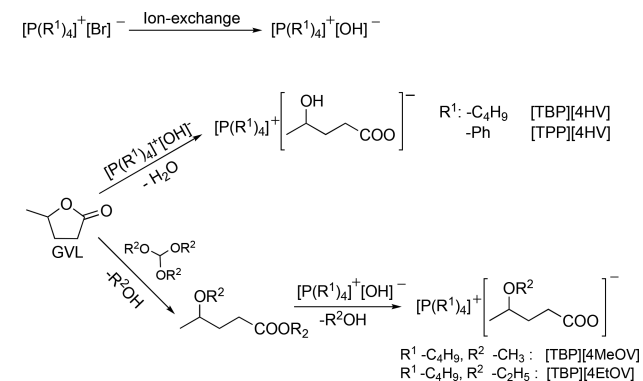
[a][TBP][4HV] tetrabutylphosphonium 4-hydroxyvalerate, [TPP]-
[4HV] tetraphenylphosphonium 4-hydroxyvalerate, [TBP][4MeOV]
tetrabutylphosphonium 4-methoxyvalerate, [TBP][4EtOV] tetrabutyl-
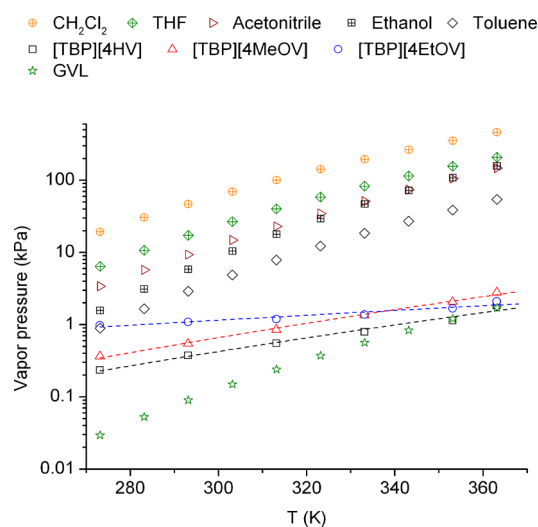phosphonium 4-ethoxyvalerate.

141 　　The temperature dependence of the vapor pressure of a
142 designed solvent is a key property pointing out their
143 applicability as an environmentally benign medium. Thus, the
144 novel ILs, which were already liquids at room temperature,
145 were characterized first by their vapor pressure. Negligible
146 volatilities were determined compared to other commonly used
147 organic solvents for example toluene, THF, acetonitrile,
148 methylene chloride, and ethanol, just to name a few (Figure 1).

149 　　As true ILs their vapor pressure remained relatively constant
150 compared to GVL and selected conventional solvents at a
151 broad temperature range. It should be noted that the moisture
152 content of the ILs could result in comparable vapor pressures
153 with GVL at lower temperatures. The constants of Antoine's eq
154 (eq 1) of ionic liquids were determined by minimizing of an
155 objective function (eq 2, N number of measured points) and
156 presented in Table 1.

$$\log(p_{IL}^{0}/kPa) = A - \frac{B}{C + T/K} \tag{1}$$

$$\Delta p\% = \frac{100}{N} \sum_{i=1}^{N} \frac{|p_i^{meas} - p_i^{calc}|}{p_i^{meas}} \tag{2}$$
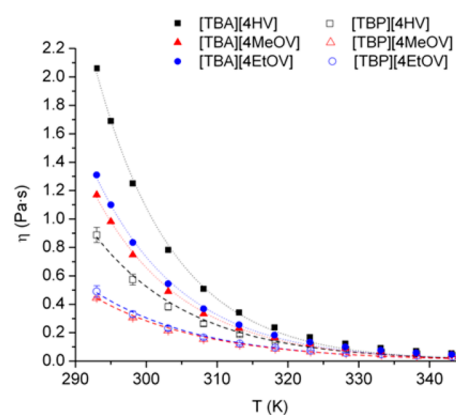
159 　　Viscosity (η) of a solvent is a crucial factor for stirring,
160 diffusion, mass transfer, etc., and could have a significant
161 influence on the reaction's performance. Accordingly, we
162 measured the temperature dependence of viscosities of ILs,
163 which decreased exponentially when temperature was in-
164 creased. The change of viscosity (η; Pas) with temperature
165 can be expressed by Arrhenius-type eq (eq 3), where A_η is a
166 pre-exponential constant, $E_{a,\eta}$ is the activation energy of viscous
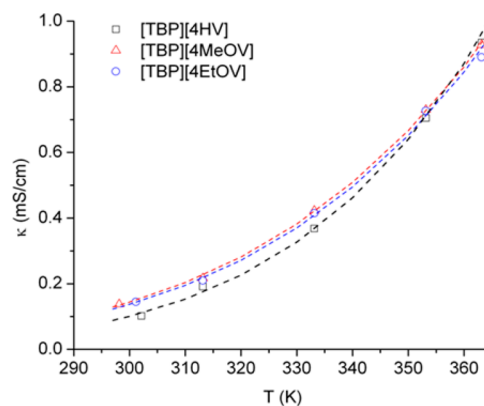
Figure 1. Temperature dependence of vapor pressures of tetrabutyl-phosphonium-based ionic liquids and selected conventional solvents. [TBP][4HV] tetrabutylphosphonium 4-hydroxyvalerate, [TBP]-[4MeOV] tetrabutylphosphonium 4-methoxyvalerate, [TBP][4EtOV] tetrabutylphosphonium 4-ethoxyvalerate. Vapor pressure data were obtained as follows: GVL from ref 31; dichloromethane, tetrahydrofuran (THF), acetonitrile, ethanol, and toluene from ref 32.

Table 1. Antoine's Constants of Tetrabutylphosphonium-Based Ionic Liquids

ionic liquid	A	B	C	R^2
[TBP][4HV]	7.1919	5918.1749	482.5366	0.982
[TBP][4MeOV]	7.6178	5962.6536	464.7164	0.995
[TBP][4EtOV]	4.5463	5754.2928	983.2076	0.924

flow. Its constants and activation energies of viscous flow[33] are given in Table 2, and the linearized formula of the function are

Table 2. Activation Energies and Pre-exponential Constants of Ionic Liquids for Viscous Flow

entry	ionic liquid	$\ln A_\eta$	$E_{a,\eta}$ (kJ/mol)	R^2
1	[TBP][4HV]	−21.12	50.8	0.997
2	[TBP][4MeOV]	−19.40	45.24	0.995
3	[TBP][4EtOV]	−19.31	44.83	0.995

presented in the Supporting Information (Figure S1). Advantageously, the viscosity values are slightly less than those measured for similar ILs[34] or even for tetraalkyl-ammonium-GVL-based ILs having significant (2–5 wt %) water content (Figure 2). The lower viscosity data of P-containing ILs compared with N-based is in correspondence with literature data.[35] However, the difference in viscosity practically diminishes above 50 °C (Figure 2).

$$\ln \eta = \ln A_\eta + \frac{E_{a,\eta}}{RT} \tag{3}$$

Conductivities were also determined in the temperature range of 25–90 °C (Figure 3) showing exponentially increasing tendency (with a correlation factor >0.99), when temperature was increased. Hardly any differences can be seen between each other. The measured values are 1 order of magnitude less with those reported for imidazolium-based ILs for example butyl-methyl-imidazolium tetrafluoroborate [BMIM][BF$_4$] or hexa-

Figure 2. Temperature dependence of viscosity of valerate-based ionic liquids.

Figure 3. Temperature dependence of conductivity of valerate-based ionic liquids.

fluorophosphate [BMIM][PF$_6$].[36,37] The activation energies by Arrhenius-type eq (eq 4) were calculated, as well (Table 3).

Table 3. Activation Energies and Pre-exponential Constants of Ionic Liquids for Conductivity

ionic liquid	$\ln A_\kappa$	$E_{a,\kappa}$ (kJ/mol)	R^2
[TBP][4HV]	10.64	32.28	0.998
[TBP][4MeOV]	8.79	26.7	0.996
[TBP][4EtOV]	8.91	27.19	0.996

Density of [TBP][4HV], [TBP][4MeOV], and [TBP]-[4EtOV] decreased linearly by increased temperature with correlation factor higher than 0.99 (Figure 4). The measured values are in accordance with literature data reported for room temperature ILs.[38,39]

$$\ln \kappa = \ln A_\kappa + \frac{E_{a,\kappa}}{RT} \tag{4}$$

The thermal stability is of utmost importance for catalytic reactions performed at higher temperature. Therefore, to investigate their stability, 0.5 mL of [TBP][4HV], [TBP]-[4MeOV], and [TBP][4EtOV] were heated at 150 °C for 24 h. Samples taken afterward for ^{1}H-, ^{31}P-, and ^{13}C NMR measurements showed no decomposition of ILs. To monitor the thermal stability of novel ILs, they were investigated by thermogravimetric analysis (TGA) up to 600 °C. The onset temperatures were as follows: [TBP][4HV] 207 °C, [TBP]-
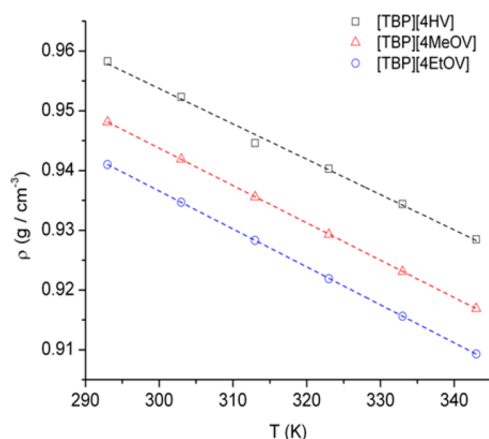
Figure 4. Temperature dependence of density of valerate-based ionic liquids.

Table 4. Coupling Reaction of Iodobenzene and Benzylamine in Different Ionic Liquids[a]

1a	**2a**	**3a**

entry	solvent	yield of 3a (%)[b]
1	[BMIM][Cl]	56
2	[BMIM][OctS]	30
3	[BMIM][PF$_6$]	0
4	[BMIM][BF$_4$]	57
5	[EMIM][BF$_4$]	47
6	[EMIM][TfO]	0
7	[TEA][4HV]	63
8	[TEA][4MeOV]	66
9	[TEA][4EtOV]	68
10	[TBA][4HV]	72
11	[TBA][4MeOV]	76
12	[TBA][4EtOV]	79
13	[TBP][4HV]	79
14	[TBP][4MeOV]	82
15	[TBP][4EtOV]	85

[a]Reaction conditions: 1 mmol iodobenzene, 1.2 mmol benzylamine, 0.05 mmol of copper(I)-iodide, 2 mmol ethylene glycol, 2 mmol sodium-acetate, 1 mL IL. T = 80 °C, t = 18 h. [b]Isolated yield.

[4MeOV] 216 °C, and [TBP][4EtOV] 226 °C. TGA analysis confirmed our NMR measurements as well as revealed that these ILs could be considered as thermally stable reaction media up to 200 °C (Supporting Information (SI) Figures S11−S13) proving their applicability for a wide range of transition metal-catalyzed reactions.

The modular synthesis of tetraalkylphosphonium 4-alkoxy-valerate- or 4-hydroxyvalerate-based ionic liquids were demonstrated followed by determination of their basic physical properties. It was revealed that these ILs exhibit lower viscosity and density values as well as higher thermal stability than that of corresponding tetraalkylammonium-based ones. It is important to emphasize that the properties of ILs can easily be tuned to the claimed values by the variation of R^1 and R^2 groups (Scheme 1).

Catalytic C−N Coupling Reactions. We propose that tetraalkylphosphonium-based ionic liquids could be an ideal reaction media for Cu-catalyzed C−N coupling reactions that can easily be performed by an excellent protocol published by Buchwald and co-workers in the presence of cheap Cu(I) salt, a ligand, and a base.[40] Since these GVL-based ILs have a negligible vapor pressures compared to volatile conventional organic solvents, such as FDA Class 1 benzene or FDA Class 2 toluene applied for cross-coupling reactions, the combination of benefits of a bioderived ILs with Cu-catalyzed reaction could result in an environmentally benign alternative method for preparation of various synthetically important amines.

Initially, the Cu(I)-catalyzed conversion of iodobenzene (1a) and benzylamine (2a) to N-benzylaniline (3a) was repeated as a model reaction.[40] When Cs$_2$CO$_3$ as a base was used in iPrOH, 65% isolated yield was obtained. By the replacement of toxic Cs$_2$CO$_3$ (LD$_{50(rat, oral)}$ = 1000 mg/kg)[41] with anhydrous sodium-acetate, no reaction was detected in iPrOH. Similarly, when GVL was used as a solvent no conversion was observed. Hereafter, we compared the conventional imidazolium-type ILs on the Cu(I)-catalyzed Ullmann-type reaction of 1a (1 mmol) and 2a (1.2 mmol) in the presence of 2.0 equiv ethylene glycol as a ligand proposed by Buchwald and 2 mmol NaOAc (LD$_{50(rat, oral)}$ = 3530 mg/kg)[42] as a less toxic base (Table 4). Similar yields were obtained by the use of [BMIM][Cl] (56%) and [BMIM][BF$_4$] (57%). When [BMIM][octylsulfate] was applied, slightly lower activity was detected, and no transformation occurred in case of [BMIM][PF$_6$]. Although the water content of the latter is below 1 wt %, the hydrolysis of

[PF$_6$]$^−$ cannot be excluded (Table 4 entries 1−4).[43,44] The introduction of 1-ethyl-3-methylimidazolium [EMIM] based ILs could not enhance the catalytic performance, as in fact no reaction was detected at all with [EMIM][CF$_3$SO$_3$] (Table 4, entries 5 and 6). By replacing the solvent with tetraalkyl-ammonium containing GVL-based ILs, slightly higher activities were observed (Table 4, entries 7−9). Both alkoxyvalerate- and hydroxyvalerate-derived ILs proved to be superior to ILs used previously, resulting in 66−68% isolated yields, respectively. It was shown that higher catalytic activities were detected by using tetrabutylammonium-based media for hydrogenation reactions.[26] Hence both hydroxyvalerate and alkoxyvalerate anion-based tetrabutylammonium type ILs were investigated under identical conditions (Table 4, entries 10−12) resulting in better performance, indeed. When phosphonium-based ILs having lower viscosity were used (Table 4, entries 13−15), 79−85% isolated yields were obtained. Consequently, further experiments were performed in [TBP][4EtOV].

Ethylene glycol has an LD$_{50(rat,oral)}$ value of 4700 mg/kg.[45] By elimination of this ligand the C−N coupling reaction could be more environmentally benign. Because the role of ionic liquids as coordination ligands for transition metal species was demonstrated,[20,46,47] and copper carboxylates complexes are well-known compounds,[48] we subsequently attempted the coupling reaction by elimination of the ligand. It can be proposed that carboxylate group of the 4-ethoxyvalerate anion could stabilize the catalytically active species. In addition, the carboxylate functionality could act as a base in the reaction mixture allowing elimination of NaOAc, as well. Indeed, when 0.5 mmol iodobenzene and 0.6 mmol of N-benzylamine was reacted in the presence of 1 mmol NaOAc in 0.5 mL [TBP][4EtOV] at 80 °C for 18 h, 81% isolated yield was obtained. By repeating the reaction in the absence of a base no change of the isolated yield (80%, Table 5, entry 1) was detected. By comparison, van Koten reported ligand-free N-

Table 5. Copper(I)-Catalyzed Amination of Iodobenzene with Different Amines[a]

#	N-substrate	Product	Yield (%)[b]
1	**2a** H₂N–CH₂Ph	**3a**	85
2	**2b** H₂N–cyclohexyl	**3b**	87
3	**2c** H₂N–C₇H₁₅	**3c**	84
4	**2d** HN piperidine	**3d**	81
5	**2e** HN morpholine (O)	**3e**	78
6	**2f** HN piperidine-COOEt	**3f**	70
7	**2g** H₂N–CH₂-pyridin-2-yl	**3g**	50
8	**2h** H₂N–CH₂-pyridin-3-yl	**3h**	55
9	**2i** H₂N–CH₂-pyridin-4-yl	**3i**	52
10	**2j** HN imidazole	**3j**	81
11[c]	**2k** H₂N–Ph	**3k**	0

[a]Reaction conditions: 1 mmol iodobenzene, 1.2 mmol amine, 0.5 mL [TBP][4EtOV], 5 mol % CuI, T = 80 °C, t = 18 h. [b]Isolated yield. [c]No conversion was detected.

and O-arylations in N-methylpyrrolidone; however, K_2CO_3 (1.1 equiv) as a base and higher temperature (160 °C) were applied. In addition, significantly lower product yields were observed for the amination of iodobenzene.[49]

By screening of the catalytic activity of different Cu(I) salts; CuCl, CuBr, CuI, and CuOAc were all found to be effective precatalysts. Isolated yields were obtained between 76 and 81% (SI Table S1). It is in accordance with an observation that initial copper source is not very important for the outcome of the reaction, because the redox processes always lead to Cu(I) at some stage of the reaction sequence.[50]

Water content of the reaction media could be a crucial parameter affecting the efficiency of a metal-catalyzed reaction. Since these ILs were prepared under aqueous conditions, the investigation of the influence of moisture content on the coupling reaction was essential. That the method is hardly sensitive to a significant water content was demonstrated by observation that no decreases in yields occurred when water content of the reaction mixture was varied between 0.5 and 7.5 wt % (SI Table S2). Consequently, no special pretreatment or handling to exclude small amount of water from the reaction mixture is necessary.

Henceforward, air-stable and cheap CuI were applied in the absence of any ligand and base to facilitate C−N bond couplings involving various amines and functionalized aryl iodides in [TBP][4EtOV]. Generally, the catalytic system was found to be applicable for several amines and no dramatic influence was observed on the reactivity of the substrates by the electronic parameters of the substituents. Aliphatic amines

including cyclic secondary aliphatic types, i.e., morpholine and piperidines, gave comparable isolated yields (Table 5, entries 1−6). Under identical conditions, pyridine derivatives could also easily be converted to the corresponding amine; however, these compounds could be isolated with slightly lower yields (Table 5, entries 7−9). Imidazole gave also comparable yield (Table 5, entry 10). In accordance with Buchwald's observation, no conversion was detected for aniline.[40] Subsequently, a series of iodoaromatic compounds, which can readily be dissolved in [TBP][4EtOV] were subjected to the amination reaction under identical conditions. It was shown that both electron donating (methyl, methoxy, and *tert*-butyl) and electron withdrawing (bromo, chloro, fluoro, and nitro) groups were tolerated on the aryl iodide species (Table 6). The

Table 6. Copper(I)-Catalyzed Amination of Various Iodoaromatic Compounds with Benzyl-Amine[a]

#		Iodoaromatic compounds	Product	Yield (%)[b]
1	**1b**	2-methyl-iodobenzene (CH₃)	**4b**	80
2	**1c**	3-methyl-iodobenzene (H₃C)	**4c**	77
3	**1d**	4-methyl-iodobenzene (H₃C)	**4d**	73
4	**1e**	4-methoxy-iodobenzene (H₃CO)	**4e**	78
5	**1f**	4-tBu-iodobenzene (tBu)	**4f**	79
6	**1g**	3-nitro-iodobenzene (O₂N)	**4g**	65
7	**1h**	3-bromo-iodobenzene (Br)	**4h**	50
8	**1i**	4-fluoro-iodobenzene (F)	**4i**	70
9	**1j**	4-chloro-iodobenzene (Cl)	**4j**	79
10	**1k**	3-chloro-iodobenzene (Cl)	**4k**	85

[a]Reaction conditions: 1 mmol iodoaromatic substrate, 1.2 mmol benzylamine, 0.5 mL [TBP][4EtOV], 5 mol % CuI, T = 80 °C, t = 18 h. [b]Isolated yields.

nitro (entries 6, **1g**) and bromoaryl (**1h**) functionalities did not react under reaction conditions used, so further functionalization of the corresponding amines in these positions could be carried out. By varying electronic and steric properties of iodoaromatic substrates at all *ortho*-, *meta*-, and *para*- positions, no significant change in the product yields were achieved as well as a large variety of functional groups were tolerated similarly to the series of amines presented in Table 5.

■ EXPERIMENTAL SECTION

The sources of chemicals are listed in the SI. Alkyl 4-alkoxyvalerates and tetraalkylammonium-based ILs were prepared by published methods[26] with details presented in the SI. The NMR spectra were

recorded on a BrukerAvance 250 spectrometer. Water contents of the ionic liquids were determined by Karl Fischer titration performed by HANNA Instruments 904. Viscosity values were determined by using Anton Paar Physica MCR 301 instrument (cone−plate geometry, oscillation at an angular frequency of 10 1/s and a strain of 5%, heating rate 1 °C/min). Densities were determined by the use of Anton Paar DMA 4500 M equipment. Vapor pressures were determined by a published method.[26]

Tetrabutylphosphonium hydroxide [TBP][OH] was prepared by treatment of 5 wt % of an aqueous solution of tetrabutylphosphonium bromide [TBP][Br] (5.9 mmol in 48 g H_2O) by hydroxide form of Amberlite NR-410 anion exchange resin (32 mL) at room temperature. The removal of Br^- from the solution was checked by acidic solution of $AgNO_3$. After 40 min, the ion exchange was completed. To concentrate the solution ca. 40 mL of water was evaporated under reduced pressure (10 mmHg (*ca.* 1330 Pa)) at 45 °C. The colorless solution of [TBP][OH] was used as obtained.

General Procedure for the Preparation of Tetrabutyl-phosphonium-Based Ionic Liquids. In a round-bottomed flask, equimolar amounts of aqueous solution of [TBP][OH] and GVL or corresponding alkyl 4-alkoxyvalerate were mixed and stirred at 60 °C for 2 h. The colorless homogeneous liquid was concentrated under reduced pressure (ca. 10 mmHg) at 50 °C. The residual amount of water and corresponding alcohol was removed by addition/ evaporation of 5 × 5 mL *n*-hexane. The product was further dried under reduced pressure (0.5 mmHg) at 80 °C.

Tetrabutylphosphonium 4-Hydroxyvalerate [TBP][4HV]. With 5 g (50 mmol) of GVL in an aqueous solution of 50 mmol [TBP][OH], the product was isolated as a colorless viscous liquid. Yield: 18.6 g (99%). Water content: 0.1%. ^{1}H NMR (250 MHz, CDCl₃): δ (ppm) 0.92 (t, 12H), 1.09 (d, 3H), 1.38−1.54 (m, 16H), 1.56−1.68 (m, 2H), 2.21−2.54 (m, 10H), 3.77 (sx, 1H) (SI Figure S2). ^{13}C NMR (62.8 MHz, CDCl₃): δ (ppm) 13.3, 18.4 (d), 23.6 (d), 24.8, 30.8, 34.8, 36.8, 68.6, 179.8 (SI Figure S3) ^{31}P NMR (101 MHz, CDCl₃): δ (ppm) 33.02. (SI Figure S4)

Tetrabutylphosphonium 4-Ethoxyvalerate [TBP][4MeOV]. With 7.3 g (50 mmol) methyl 4-methoxyvalerate in an aqueous solution of 50 mmol [TBP][OH], yield was 19.3 g (99%). Water content: 0.2%. ^{1}H NMR (250 MHz, CDCl₃): δ (ppm) 0.94 (t, 12H), 1.10 (d, 3H), 1.40−1.58 (m, 16H), 1.63−1.76 (m, 1H), 1.81−1.99 (m, 1H), 2.16 (t, 2H), 2.30−2.49 (m, 8H), 3.28 (s, 3H), 3.30−3.39 (m, 1H) (SI Figure S5). ^{13}C NMR (62.8 MHz, CDCl₃): δ (ppm) 13.3, 18.4 (d), 19.1, 23.7, 23.8 (d), 33.4, 35.0, 56.6, 77.1, 178.2 (SI Figure S6). ^{31}P NMR (101 MHz, CDCl₃): δ (ppm) 33.07. (SI Figure S7).

Tetrabutylphosphonium 4-Ethoxyvalerate [TBP][4EtOV]. With 8.7 g (50 mmol) ethyl 4-ethoxyvalerate in an aqueous solution of 50 mmol [TBP][OH], yield was 20.1 g (99%). Water content: 0.07%. ^{1}H NMR (250 MHz, CDCl₃): δ (ppm) 0.92 (t, 12H), 1.09 (d, 3H), 1.11 (t, 3H), 1.35−1.58 (m, 16H), 1.63−1.75 (m, 1H), 1.78−1.94 (m, 1H), 2.16 (t, 2H), 2.28−2.49 (m, 8H), 3.32−3.50 (m, 3H) (SI Figure S8). ^{13}C NMR (62.8 MHz, CDCl₃): δ (ppm) 13.2, 15.5, 18.4 (d), 19.8, 23.6, 23.8 (d), 33.6, 35.2, 63.1, 75.4, 178.3 (SI Figure S9). ^{31}P NMR (101 MHz, CDCl₃): δ (ppm) 33.07 (SI Figure S10).

General Procedure for Ullmann-type Coupling Reactions. In a 4 mL screw-cap vial, 0.5 mmol of iodobenzene or its corresponding derivative, 1.2 equiv of corresponding amine, 0.05 equiv Cu(I)-iodide, and 0.5 mL of ionic liquid were mixed and stirred at 80 °C overnight. After cooling, the mixture was partitioned between 5 mL of water and 5 mL of *n*-pentane. The aqueous phase was extracted subsequently with 2 × 5 mL of *n*-pentane. The combined organic phase was washed with brine, dried over MgSO₄, filtered, and the solvent was evaporated under reduced pressure (ca. 10 mmHg). The oily residue was purified by chromatography on silica gel (Merck Silicagel 60 (0.063−0.200 mm) for column chromatography (70−230 mesh ASTM)) eluted with *n*-pentane:EtOAc.

Thermogravimetric analysis of the [TBP][4MeOV], [TBP]-[4EtOV], and [TBP][4HV] samples were carried out with a PerkinElmer Simultaneous Thermal Analyzer. Samples of about 10 mg were heated from 30 to 600 °C at a scanning rate of 10 °C/min under a nitrogen atmosphere.

CONCLUSIONS

A convenient procedure was developed for the manufacturing of partially bio-ionic liquids from renewable γ-valerolactone and cheap and readily available tetraalkylphosphonium bromides. The novel ILs were fully characterized. By replacement of tetraalkylammonium cation with tetraalkylphosphonium ones resulted in comparable densities and lower viscosities even in the presence of lower water content and higher thermal stability.

It was demonstrated that these ionic liquids can be utilized as alternative reaction media for copper-catalyzed coupling reaction of aryl iodides and primary or secondary amines under mild conditions. We pointed out that both ligands and bases could be eliminated from the reaction mixture without significant decrease in activity of the catalyst system. The isolated yields of the reactions were good to excellent, and no significant influence of the electronic effect of the amine substituents was detected. The base and ligand free reactions can be carried out under air and are also highly tolerant to moisture.

ASSOCIATED CONTENT

S **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acssusche-meng.7b04775.

Source of chemicals, experimental details, and NMR spectra (PDF)

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DEDICATION

This paper is dedicated to Professor István T. Horváth on the occasion of his 65th birthday.

ABBREVIATIONS

[4EtOV], 4-ethoxyvalerate anion; [4HV], 4-hydroxyvalerate anion; [4MeOV], 4-methoxyvalerate anion; [BMIM], 1-butyl-3-methylimidazolium cation; [EMIM], 1-ethyl-3-methyl-imidazolium cation; [OctS], octylsulfate anion; [TAA], tetra-alkylammonium cation; [TAP], tetraalkylphosphonium cation; [TBA], tetrabutylammonium cation; [TBP], tetrabutyl-phosphonium cation; [TEA], tetraethylammonium cation;

[TfO], trifluoromethanesulfonate anion; [TPP], tetraphenyl-phosphonium cation; GVL, γ-valerolactone

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