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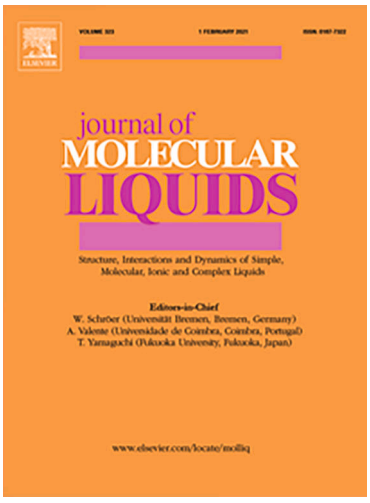

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Imidazolium-urea Low Transition Temperature Mixtures for the UHP-promoted oxidation of boron compounds

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KEYWORDS: Low transition temperature mixtures, imidazolium salts, boron compounds, oxidation reaction, sustainable chemistry

ABSTRACT

Different carboxy-functionalized imidazolium salts have been considered as components of low transition temperature mixtures (LTTMs) in combination with urea. Among them, a novel LTTM based on 1-(methoxycarbonyl)methyl-3-methylimidazolium chloride and urea has been prepared and characterized by differential scanning calorimetry throughout its entire composition range. This LTTM has been employed for the oxidation of boron reagents using urea-hydrogen peroxide adduct (UHP) as the oxidizer, thus avoiding the use of aqueous H_2O_2, which is dangerous to handle. This metal-free protocol affords the corresponding alcohols in good to quantitative yields in up to 5 mmol scale without the need of further purification. The broad composition range of the LTTM allows for the reaction to be carried out up to three consecutive times with a single imidazolium salt loading offering remarkable sustainability with an *E-factor* of 7.9, which can be reduced to 3.2 by the threefold reuse of the system.

1. INTRODUCTION

Throughout the last couple of decades, concerns about the impact of human activities on the environment have grown remarkably, leading to ever-increasing efforts to reduce this human effect in nature. Chemistry has risen to the challenge of sustainability, replacing established classical procedures with more environmentally friendly methodologies. One of the most relevant trends in sustainable chemistry is the development of alternative solvents in which several problems can be addressed at once, such as recyclability, volatility, pollution, and toxicity. Solvents are the major component of reaction mixtures, and their recovery, when possible, requires energy, which in both situations leads to waste generation. Additionally, most organic solvents are volatile, which leads to pollution, and quite a lot of them are toxic making it obvious as to why alternative solvents have gained so much momentum in such a short period of time. Solutions such as the use of water, supercritical fluids, perfluorinated solvents, or biomass-derived compounds have been proposed over the years [1-3]. Nevertheless, dilemmas such as low organic compound solubility, high cost, and low tunability of their properties restrict the use of these alternative media [1,2]. Ionic liquids (ILs) emerged as a highly tunable, recyclable, and, in some cases, catalytically active answer to these problems, but the high cost of production and apprehension about their toxicity led to their disapproval as substitutes for organic solvents [1,4]. At the beginning of the century, low transition temperature mixtures (LTTMs), a new class of solvents, emerged as an improved version of the ILs [5].

LTTMs are a combination of two or more components which interact causing a decrease in the melting point of the mixture relative to that of the pure components [3,6]. Although the concept had already been proposed, it gained prominence following a report by Abbott and coworkers in 2003, in which they described an LTTM based on choline chloride and urea and came up with term deep eutectic solvent (DES) for such mixtures [3,7]. In DESs, one of the components is a hydrogen bond donor (HBD) and another a hydrogen bond acceptor (HBA), in which the melting point depression arises from hydrogen bond interactions between the former [1,3]. In the subsequent years, DES quickly became popular, with more and more combinations being explored as LTTMs gained momentum, including new varieties, such as natural deep eutectic solvents (NADES) [3,5]. The wide variety of available combinations makes LTTMs very attractive as alternative solvents, as they offer very high tunability while being scarcely volatile, made from cheap, non-toxic materials, leading to quantitative atom economy [1,3,6,8]. These advantages have allowed LTTMs to extend their reach beyond conventional organic synthesis, having been applied to asymmetric catalysis [9], CO_2 and SO_2 capture [8], extraction of natural compounds [10], and as electrolytes [11], amongst others. Imidazolium salts have not been widely explored as components of LTTMs, and there are only a few examples in the recent literature [10,12,13], with a probability of this being due to the same reasons that made ILs unfeasible in the first place. However, imidazolium LTTMs

are interesting, as they should still exhibit some, if not all, of the relevant properties of the imidazolium salt, an important part of them being a renewable chemical, and if prepared with a non-alkyl-imidazolium salt, which is usually the most toxic and the least biodegradable [14], the environmental impact of imidazolium salts could be drastically reduced.

Research into alternative catalytic methods is essential to design more sustainable synthetic processes. Conscious of this, our research group is carrying out studies of catalytic systems based on carboxy-functionalized imidazole derivatives, demonstrating their ability to facilitate different transformations with a better environmental viability. Carboxy- and carbamoyl-imidazole derivatives have enabled coupling processes to be carried out by the formation of N-heterocyclic carbene-palladium complexes (NHC-Pd) and/or by the stabilization of palladium nanoparticles (or clusters) in the reaction media [15-17]. Biscarboxy-imidazole derivatives have been used to obtain metal-organic frameworks (MOFs), which have shown remarkable catalytic activity in sustainable synthetic procedures for the preparation of amides and quinolines [18,19]. Whilst in more recent work, it has been observed that these imidazole derivatives catalyze the synthesis of quinolines, acridines, and allylanilines in the absence of solvent [20-22]. In these processes, the presence of favorable interactions between the reagents and the catalytic species (imidazole derivative) is evidenced [22], with such interactions being similar to those described in LTTMs. This led to the speculation that some carboxy-imidazole derivatives will be suitable for forming LTTMs. In this work, we report our findings in the preparation of LTTMs based on carboxy-imidazole derivatives and urea, with a novel LTTM, from 1-(methoxycarbonyl)methyl-3-methylimidazolium chloride [(mcm)mimCl] and urea, being studied by differential scanning calorimetry (DSC). In addition, this LTTM has been applied to the oxidation of boron compounds to alcohols, in particular the synthesis of phenolic compounds, as they bear a broad scope of applications. Phenol derivatives are heavily used in synthetic materials, such as adhesives, gels, and elastomers, as well as being useful building blocks in synthesis [23]. They are present in a variety of food products [24,25] and are well known for their antioxidant properties, which has led to the study of their potential as anticancer agents [25]. This oxidation reaction has been studied extensively [26], with most procedures targeting synthesis under metal-free using aqueous H_2O_2 as oxidizer [27-29], however, there are serious safety concerns regarding the use of this reagent, especially for strongly exothermic reactions. Thus, we explored the possibility of using urea-hydrogen peroxide adduct (UHP), which is much safer to handle [30]. In combination with the imidazolium salt [(mcm)mimCl] it slowly forms a LTTM at room temperature, which would gradually release H_2O_2 into the reaction medium, providing a more regulated and sustainable oxidation procedure.

2. EXPERIMENTAL SECTION

2.1. General remarks

All reagents and solvents are commercially available (Alfa Aesar, Apollo Scientific, Honeywell-Fluka, Fluorochem, Sigma-Aldrich, TCI) and were used without further purification. NMR spectra were recorded at the Nuclear Magnetic Resonance Unit from the Technical Services of the University of Alicante (SSTTI-UA). ^{1}HNMR spectra were acquired at 300 or 400 MHz, whereas proton decoupled ^{13}CNMR experiments were carried out at 75 or 100 MHz with Bruker AV300 Oxford or AV400 NMR spectrometers. The solvents used were deuterated chloroform ($CDCl_3$), with tetramethylsilane (TMS) as internal standard, deuterium oxide (D_2O), and deuterated methanol (CD_3OD). Chemical shifts (δ) are given in ppm, while coupling constants (*J*) are reported in Hz. Differential Scanning Calorimetry experiments were carried out at the Porous Solids and Thermal Analysis Unit from the SSTTI-UA with a TA Instruments model Q100 differential scanning calorimeter, using hermetically sealed aluminum crucibles under nitrogen atmosphere. The temperature program was set as follows: from -90 ºC to 150 at a rate of 5 ºC/min. Sample mixtures for the initial screening were prepared by slowly grinding both components on a ceramic mortar. Samples for subsequent analyses were prepared by slow mechanical mixing under an inert atmosphere.

2.2. Procedure for the multigram synthesis of 1,3-bis(carboxymethyl)imidazole (bcmim)

Formaldehyde (37% aq., 25 mmol, 2.2 mL), glyoxal (40% aq., 25 mmol, 4.6 mL), and glycine (50 mmol, 3.8 g) were added to a glass round bottom flask and stirred at 95 ºC for 2 h. After cooling down the reaction, it was filtered through a sintered glass funnel, then washed with 15 mL of water and 15 mL of methanol followed by vacuum drying affording 3.9 g of pure bcmim (87% yield).

2.3. Procedure for the multigram synthesis of 1,3-bis(carboxymethyl)imidazolium chloride (bcmimCl)

Bcmim (21 mmol, 3.9 g), HCl (37% aq., 46 mmol, 4 mL), and water (4 mL) were added to a round bottom flask and refluxed for 30 minutes. After cooling down the reaction, which caused the product to precipitate as a crystalline colorless solid, the reaction was filtered through a sintered glass funnel and washed with two portions of water (15 mL) and methanol (15 mL) followed by vacuum drying affording 3.7 g of pure bcmimCl (80% yield).

2.4. Procedure for the multigram synthesis of 1-(methoxycarbonyl)methyl-3-methylimidazolium chloride [(mcm)mimCl]

1-methylimidazole (40 mmol, 3.2 mL) and methyl chloroacetate (40 mmol, 3.5 mL) were added to a round bottom flask. The reaction vessel was then sonicated for 1 h, after which the product was taken out onto a Petri dish and washed three times with 10 mL portions of Et_2O followed by vacuum drying affording 6.6 g of pure (mcm)mimCl (87% yield).

2.5. Procedure for the multigram synthesis of 1-(carboxymethyl)-3-methylimidazolium chloride [(cm)mimCl]

In a glass round bottom flask, (mcm)mimCl (10 mmol, 1.9 g) was dissolved in HCl (37% aq., 10 mmol, 0.8 mL) and refluxed for 1 h. After cooling down the solution, the resulting precipitate was filtered through a sintered glass funnel and washed twice with acetone (5 mL) and Et_2O (5 mL) followed by vacuum drying yielding 1.5 g of pure (cm)mimCl (84% yield).

2.6. General procedure for the oxidation of boron reagents

(Mcm)mimCl (0,5 mmol, 95 mg) and UHP (1 mmol, 94 mg) were added to a glass tube. The mixture was stirred for 5 minutes, after which a 1 M suspension of organoborane (0.5 mmol) in AcOEt (0.5 mL) was added. The mixture was then stirred at room temperature for an adequate amount of time (30-90 min). After this, the top organic phase was decanted off with a pipette. To ensure full recovery of the product, water (1.5 mL) was added to dissolve the LTTM, and the aqueous phase was then extracted twice with AcOEt (2×1.5 mL). The combined organic phases were concentrated under vacuum, then filtered through a short plug of magnesium sulfate and silica to dry and remove solids in suspension. The solvent was removed under vacuum, yielding the desired alcohol without the need of further purification.

2.7. Procedure for the preparative scale synthesis of 4-phenylphenol

(Mcm)mimCl (5 mmol, 950 mg) and UHP (10 mmol, 940 mg) were added to a 50 mL round bottom flask. The mixture was stirred for 5 minutes, adding then a 1 M suspension of 4-phenylbenzeneboronic acid (98%, 5 mmol, 990 mg) in AcOEt (5 mL). The reaction was stirred at room temperature for 30 minutes. After the reaction is finished, the top organic phase was separated and evaporated under vacuum, yielding 832 mg of 4-phenylphenol (99% yield).

2.8. Procedure for the cumulative synthesis of 4-phenylphenol

(Mcm)mimCl (0.5 mmol, 95 mg) and UHP (1 mmol, 94 mg) were added to a glass tube. The mixture was stirred for 5 minutes, then a 1 M suspension of 4-phenylbenzeneboronic acid (0.5 mmol, 99 mg) in AcOEt was added with the resulting mixture being stirred at room temperature for 30 minutes. The organic phase was removed, and the LTTM was extracted with 1.5 mL de AcOEt to ensure full recovery of the product. After this, more UHP (0.54 mmol, 50 mg) was added to the mixture, which was stirred for 1 minute to ensure full incorporation of the UHP into the LTTM. At this point, the cycle starts over with the addition of more starting material. The reaction was carried out a total of 3 times in which each iteration was treated as an individual reaction and subjected to the processing described in the general procedure.

2.9. Selected spectral data

1-Methoxycarbonylmethyl-3-methylimidazolium chloride [(mcm)mimCl]: White solid; m.p. = 201 ºC [31]; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 10.43 (s, 1H, N-CH-N), 7.72 (s, 1H, N-CH-CH-N), 7.51 (s, 1H, N-CH-CH-N), 5.60 (s, 2H, CH_2), 4.09 (s, 3H, CH_3-N), 3.81 (s, 3H, O-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 166.9, 138.8, 123.6, 53.4, 50.1, 36.8.

Phenol (1): Yellowish oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.26-7.22 (m, 2H, CH_{Ar}), 6.95-6.90 (m, 1H, CH_{Ar}), 6.84-6.81 (m, 2H, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 155.6, 129.8, 120.9, 115.4.

1-Naphthol (2): Colorless needles; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.18-8.15 (m, 1H, CH_{Ar}), 7.81-7.77 (m, 1H, CH_{Ar}), 7.50-7.41 (m, 3H, CH_{Ar}), 7.34-7.21 (m, 1H, CH_{Ar}), 6.77 (dd, J = 7.4, 0.9 Hz, 1H, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 151.5, 134.9, 127.8, 126.6, 125.9, 125.4, 124.5, 121.7, 120.8, 108.8.

2,6-Dimethylphenol (3): Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 6.96-6.94 (m, 2H, CH_{Ar}), 6.77-6.73 (m, 1H, CH_{Ar}), 4.25 (br s, 1H, OH), 2.24 (s, 6H, 2xCH_3); ^{13}C NMR (100 MHz, MeOD-d_4) δ_C = 152.3, 128.7, 123.1, 120.3, 15.9.

2-Methoxyphenol (4): Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 6.97-6.94 (m, 1H, CH_{Ar}), 6.91-6.86 (m, 3H, CH_{Ar}), 5.71 (br s, 1H, OH), 3.89 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 146.7, 145.8, 121.6, 120.3, 114.7, 110.9, 55.9.

2-Hydroxyphenol (5): Grey needles; ^{1}H NMR (400 MHz, MeOD-d_4) δ_H = 6.79-6.75 (m, 2H, CH_{Ar}), 6.68-6.64 (m, 2H, CH_{Ar}), 5.00 (br s, 2H, 2xOH); ^{13}C NMR (100 MHz, MeOD-d_4) δ_C = 146.12 120.9, 116.4.

2-Fluorophenol (6): Faint yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.09-7.04 (m, 1H, CH_{Ar}), 7.03-6.97 (m, 2H, CH_{Ar}), 6.87-6.82 (m, 1H, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 151.3 (d, J = 237.0 Hz), 143.7 (d, J = 14.1 Hz), 125.0 (d, J = 3.7 Hz), 120.9 (d, J = 6.5 Hz), 117.4 (d, J = 1.4 Hz), 115.6 (d, J = 18.0 Hz).

2-Chlorophenol (7): Faint yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H =7.30 (dd, J = 8.0, 1.5 Hz, 1H, CH_{Ar}), 7.17 (ddd, J = 8.2, 7.4, 1.6 Hz, 1H, CH_{Ar}), 7.01 (dd, J = 8.2, 1.5 Hz, 1H, CH_{Ar}), 6.86 (ddd, J = 8.0, 7.4, 1.5 Hz, 1H, CH_{Ar}), 5.57 (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 151.5, 129.1, 121.5, 116.4.

2-Bromophenol (8): Faint yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.46 (dd, J = 8.0, 1.5 Hz, 1H, CH_{Ar}), 7.22 (ddd, J = 8.2, 7.3, 1.5 Hz, 1H, CH_{Ar}), 7.02 (dd, J = 8.2, 1.5 Hz, 1H, CH_{Ar}), 6.80 (ddd, J = 8.0, 7.4, 1.6 Hz, 1H, CH_{Ar}), 5.53 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 152.4, 132.2, 129.3, 121.9, 116.3, 110.4.

3-Methylphenol (9): Faint yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.12 (t, *J* = 7.9 Hz, 1H, CH_{Ar}), 6.75 (br d, *J* = 7.5 Hz, 1H, CH_{Ar}), 6.65-6.62 (m, 2H, CH_{Ar}), 4.41 (br s, 1H, OH), 2.30 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 155.6, 139.9, 129.6, 121.7, 116.2, 112.4, 21.5.

3-Methoxyphenol (10): Orange oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.11 (t, *J* = 8.1 Hz, 1H, CH_{Ar}), 6.49-6.42 (m, 3H, CH_{Ar}), 5.07 (br s, 1H, OH), 3.75 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 156.9, 130.3, 108.0, 106.6, 101.7, 55.4.

3-Nitrophenol (11): Yellow crystals; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.81 (ddd, *J* = 8.2, 2.1, 0.8 Hz, 1H, CH_{Ar}), 7.71 (t, *J* = 2.3 Hz, 1H, CH_{Ar}), 7.41 (t, *J* = 8.2 Hz, 1H, CH_{Ar}), 7.20 (ddd, *J* = 8.2, 2.5, 0.9 Hz, 1H, CH_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 156.5, 149.2, 130.4, 122.2, 115.9, 110.7.

3-Fluorophenol (12): Faint yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.20-7.14 (m, 1H, CH_{Ar}), 6.68-6.55 (m, 3H, CH_{Ar}), 4.46 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 163.6 (d, *J* = 245.4 Hz), 156.8 (d, *J* = 11.3 Hz), 130.5 (d, *J* = 10.0 Hz), 111.2 (d, *J* = 2.8 Hz), 107.7 (d, *J* = 21.3 Hz), 103.2 (d, *J* = 24.6 Hz).

4-Phenylphenol (13): Colorless needles; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.54 (br d, *J* = 7.4 Hz, 2H, CH_{Ar}), 7.48 (br d, *J* = 8.5 Hz, 2H, CH_{Ar}), 7.41 (br t, *J* = 7.5 Hz, 2H, CH_{Ar}), 7.30 (m, 1H, CH_{Ar}) 6.90 (br d, *J* = 8.5 Hz, 2H, CH_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 155.2, 140.9, 134.2, 128.9, 128.5, 126.9, 115.8.

4-Methoxyphenol (14): Yellowish crystals; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 6.80-6.75 (m, 4H, CH_{Ar}), 4.85, (br s, 1H, OH), 3.76 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 153.7, 149.6, 116.2, 115.0, 55.9.

4-Fluorophenol (15): Faint yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 6.94-6.90 (m, 2H, CH_{Ar}), 6.78-6.75 (m, 2H, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 157.4 (d, *J* = 237.9 Hz), 151.2 (d, *J* = 1.8 Hz), 116.4 (d, *J* = 8.0 Hz), 116.1 (d, *J* = 23.3 Hz).

4-Chlorophenol (16): Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.22-7.17 (m, 2H, CH_{Ar}), 6.80-6.74 (m, 2H, CH_{Ar}), 3.37 (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 154.3, 129.7, 125.8, 116.8.

4-Bromophenol (17): Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.35-7.30 (m, 2H, CH_{Ar}), 6.75-6.70 (m, 2H, CH_{Ar}), 4.45 (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 154.6, 132.5, 117.2, 112.9.

4-Trifluoromethylphenol (18): Faint yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.50 (d, *J* = 8.4 Hz, 2H, CH_{Ar}), 6.90 (d, *J* = 8.4 Hz, 2H, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 158.3, 127.3 (q, *J* = 3.8 Hz), 124.5 (q, *J* = 271.1 Hz), 123.4 (q, *J* = 32.6 Hz), 115.6.

2-Methylphenol (19): Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.12 (d, *J* = 7.4 Hz, 1H, CH_{Ar}), 7.09 (td, *J* = 7.5, 1.1 Hz, 1H, CH_{Ar}), 6.86 (td, *J* = 7.4, 1.0 Hz, 1H, CH_{Ar}), 6.76 (dd, *J* = 8.0, 0.6 Hz, 1H, CH_{Ar}) 2.24 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 153.9, 131.2, 127.2, 123.9, 120.8, 115.0, 15.8.

Benzyl alcohol (20): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.38-7.25 (m, 5H, CH_{Ar}), 4.64 (s, 2H, CH_2), 2.39 (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 140.9, 128.6, 127.7, 127.1, 65.3.

2-Phenylethanol (21): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.32-7.28 (m, 2H, CH_{Ar}), 7.23-7.20 (m, 2H, CH_{Ar}), 3.82 (t, *J* = 6.6 Hz, 2H, O-CH_2), 2.84 (t, *J* = 6.6 Hz, 2H, Ar-CH_2), 1.92 (br s, 1H,OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 138.6, 129.1, 128.6, 126.5, 63.7, 39.2.

*2.10. Preparation of 4-phenylphenol (**13**): E-factor*

The reaction used (mcm)mimCl (0.5 mmol, 9.53×10^{-5} kg), UHP (1 mmol, 9.41×10^{-5} kg), 4-phenylbenzeneboronic acid (0.5 mmol, 9.9×10^{-5} kg), and AcOEt (0.5 mL, 4.51×10^{-4} kg), so the mass (kg) of reagents was 7.38×10^{-4} kg. The amount of product **13** obtained was 8.26×10^{-5} kg. The E-factor is defined as the amount (kg) of waste (mass of reagents – mass of product = 7.38×10^{-4} – 8.26×10^{-5}) per kg of product (8.26×10^{-5} kg). This ratio is (6.56×10^{-4} kg)/(8.26×10^{-5} kg) = 7.9.

3. RESULTS AND DISCUSSION

Several imidazolium salts were tested as components of LTTMs with urea as the HBD. The selection of imidazole derivative candidates was based on our previous experience using carboxy-functionalized imidazole derivatives as components of catalytic systems [20-22], where 1,3-bis(carboxymethyl)imidazolium halides evidenced (DSC) LTTM behavior when combined with allylic alcohols [22]. Aside from this, we set some criteria regarding convenience and environmental consciousness: the salts used had to be easy to synthesize, with readily available and inexpensive starting materials, simple protocols and no purification and they had to be reasonably nontoxic. Thus, the four imidazolium salts in Figure 1 were selected. They all are prepared by one-pot protocols in excellent yields, without the need of further purification after the reaction. In addition, these imidazolium salts are relatively innocuous. 1,3-Bis(carboxmethyl)imidazole (bcmim), for instance, has been identified as a byproduct of the Maillard reaction of saccharides [32], whereas (mcm)mimCl has proven to be non-inhibitory for several ATCC strains of yeasts and fungi [33]. For the initial screening, the imidazolium salts were mixed with urea in 1:1 molar proportion (Scheme 1) and analyzed by DSC (see Supporting Information). To our delight, all four combinations seemed to form LTTMs, exhibiting some

degree of melting point depression, especially (cm)mimCl and (mcm)mimCl, whose mixtures partially or completely melted upon mixing (Table 1).

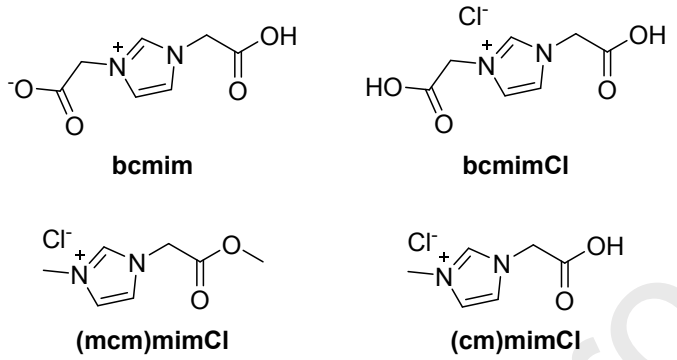
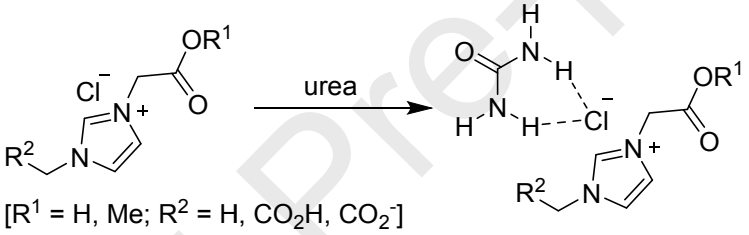


Figure 1. Imidazolium salts selected for LTTM assays with urea



Scheme 1. General reaction in the formation of LTTM between imidazolium salts and urea

Table 1. Melting points of imidazolium-urea mixtures.[a]

Entry	Mixture	Melting point (ºC)
1	bcmim:urea (1:1)	122.6
2	bcmimCl:urea (1:1)	116.5
3	(cm)mimCl:urea (1:1)	N/D[b]
4	(mcm)mimCl:urea (1:1)	N/D[b]

[a]Melting point determined by DSC analysis. [b]Not determined: LTTM is formed upon mixing, thus m.p. < 45 ºC.

With these results in hand, it was decided to focus efforts on the (mcm)mimCl:urea LTTM, as it gave the most promising results. To study the compositional behavior of the mixture, several

combinations ranging from 100% imidazolium salt to 100% urea were prepared and analyzed by DSC, putting particular care into sample preparation and handling to avoid as much premature melting or sample hydration as possible. The results are compiled in Table 2 and Figure 2. The lowest melting point (35.2 ºC) was measured for a mixture 2:1 ratio (mcm)mimCl-urea (Table 2, Entry 5), albeit for a wide range of compositions the said temperature is well below 100 ºC without staying too much above this minimum value (Figure 3). Composition-wise, the DSC graphs present one endothermic thermal event, which becomes increasingly broad and jagged as the molar fraction of (mcm)mimCl increases (Figure 2). This is probably due to the differences in molar weight and density concerning the two components of the mixture. The sheer difference in bulk hinders the initial interaction, resulting in slower melting with a broadening of the DSC peaks, as the drop in melting point is a consequence of charge delocalization due to the network of hydrogen bonds formed between the components [34].

Table 2. Melting points and enthalpies of LTTM formation for the (mcm)mimCl:urea system.[a]

Entry	Mixture [(mcm)mimCl:urea]	$\chi_{(mcm)mimCl}$[b]	Melting point (ºC)	Enthalpy of fusion (kJ/mol)
1	Pure urea	0	135.7	10.20
2	1:3	0.25	79.2	6.95
3	1:2	0.33	45.5	7.47
4	1:1	0.5	40.4	9.15
5	2:1	0.66	35.2	9.05
6	3:1	0.75	51.8	8.27
7	Pure (mcm)mimCl	1	201.4	26.73

[a]Data obtained by DSC analysis. [b]Fraction amount (χ) of the imidazolium salt in the mixture calculated as [moles of (mcm)mimCl]/[moles of (mcm)mimCl + moles of urea].

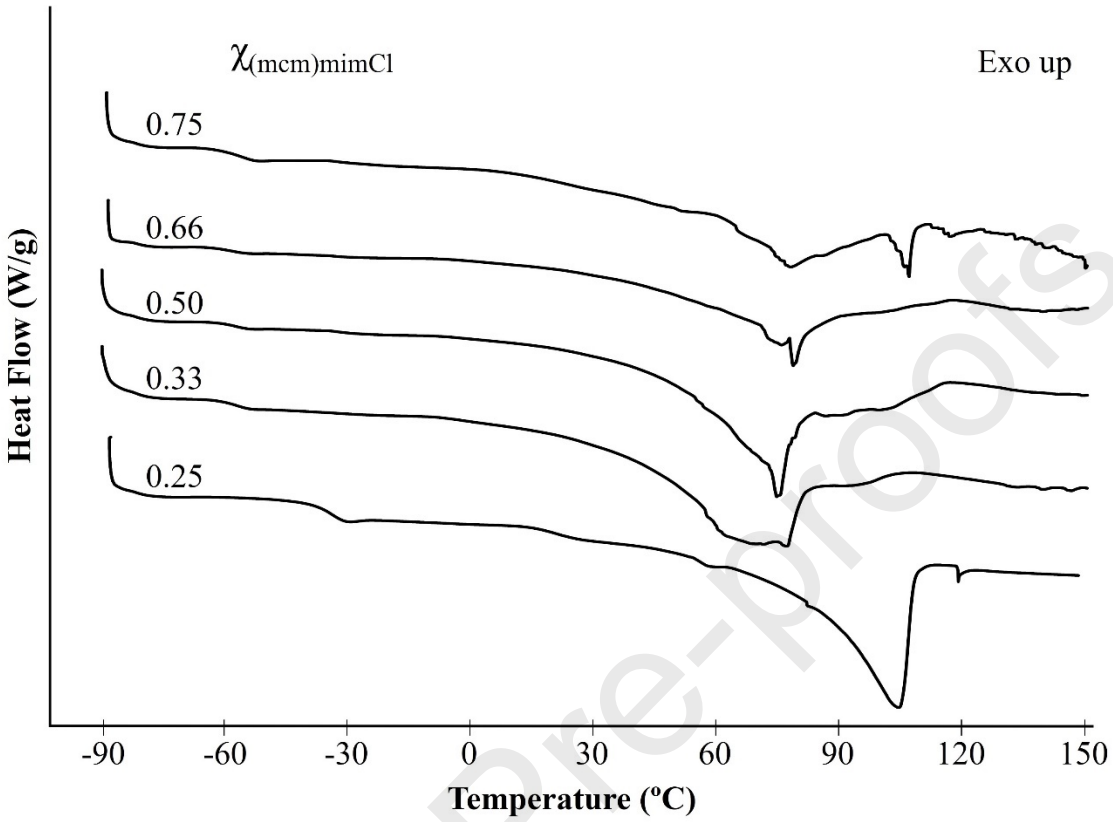


Figure 2. DSC curves for different (mcm)mimCl:urea molar ratios. Heat flow with no-scale.

The DSC graph for the 3:1 ratio mixture of (mcm)mimCl:urea (χ = 0.75, Figure 2) shows a small secondary peak, after the main thermal event. This first thermal event is possibly due to the melting of the mixture (limit composition), being the latter peak the melting of the imidazolium excess in the presence of the already formed LTTM. As it has been reported for other eutectic mixtures, different stoichiometries can result in the formation of systems with phases showing a more complex set of transitions [35]. In addition, the formation enthalpies for the LTTMs resulted in lower values (Table 2, Figure 3B) than the observed for urea [36] and the imidazolium salt (Table 2). This difference in required energy suggested favorable interactions imidazolium-urea. A more detailed analysis of the data reveals that over a wide range of mole fractions of the imidazolium salt (0.20 to 0.80) the system has a melting point low enough to be employed as a dispersion medium in synthetic processes. This wide range of ratios with low melting point enhances the robustness of the system.

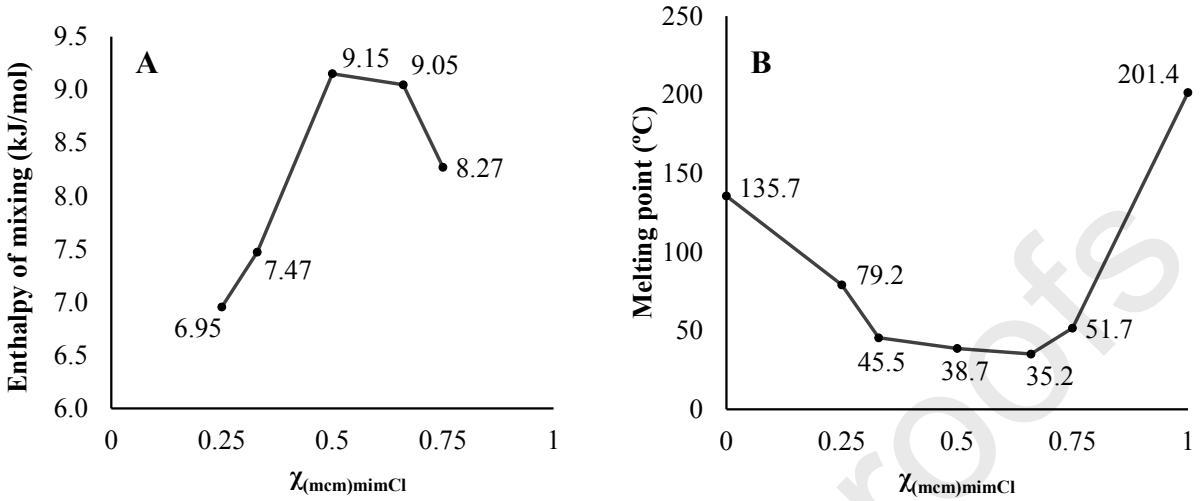
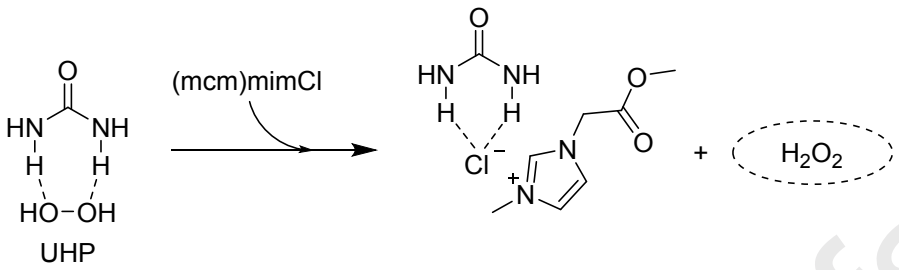


Figure 3. Melting point (A) and enthalpy-composition (B) diagrams for the (mcm)mimCl:urea system.

At this point, we turned our attention to the application of this new LTTM [(mcm)mimCl-urea] in an organic transformation, such as the oxidation of boron reagents to form the corresponding alcohols. He and coworkers had previously reported the oxidation of boronic acids in water with H_2O_2 (30% aq.) in the presence of a substoichiometric amount (10 mol%) of the choline chloride/urea (ChCl/U) mixture [27]. Even though choline chloride and/or urea seemed to promote the reaction under metal-free conditions, the reaction takes place in an aqueous solution rather than in the LTTM, since both components (ChCl and urea) are solvated by water due to the big excess used relative to them (>125 mmol of water per 0.1 mmol of ChCl/U) [27]. Nevertheless, this methodology represented a step up on other described procedures, which rely on transition metal catalysis [26], costly [37] or unwieldy [38] reagents, and stoichiometric amounts of additives [39-43]. What is more, these procedures use a large excess of aqueous H_2O_2, which tends to slowly decompose over time spoiling the reagent [44]. No attempt has been made, in this reaction, to use the urea-hydroperoxide (UHP), which is a more stable and safer to handle oxidant. Thermal decomposition of UHP releases H_2O_2 above 75 ºC [30], although it has been proved to occur at lower temperatures (45 ºC) by activation with fluorinated solvents [45]. We envisioned the possibility of triggering such release through forming a (mcm)mimCl:urea LTTM, as the required interaction between both components should force the liberation of H_2O_2 from the adduct (Scheme 2) [22]. Additionally, the presence of (mcm)mimCl, which is substantially acidic [31], may promote the reaction further, activating the H_2O_2 via hydrogen bonding [45]. This approach may allow the reaction to be carried out in the absence of another solvent, with the so-formed LTTM acting both as a dispersion medium and as an activating agent for the reagents.

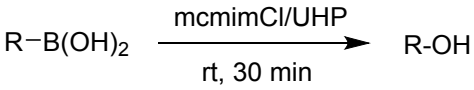


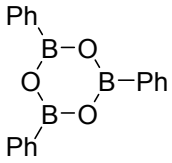
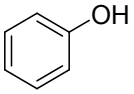
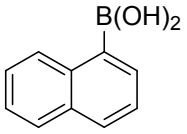
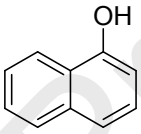
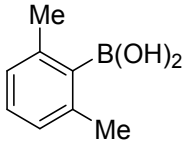
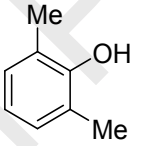
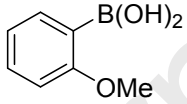
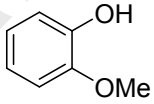
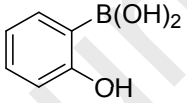
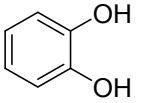
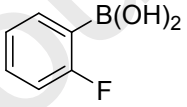
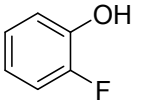
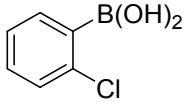
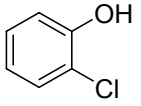
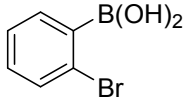
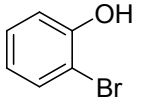
Scheme 2. Plausible interaction between UHP and (mcm)mimCl for LTTM formation and H_2O_2 release.

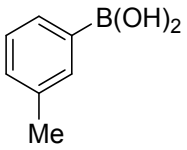
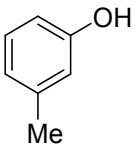
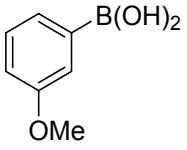
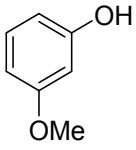
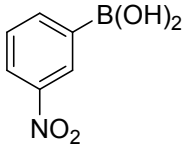
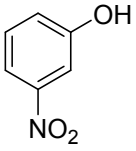
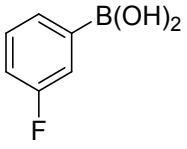
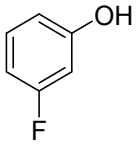
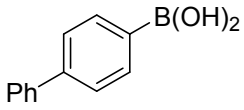
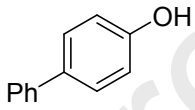
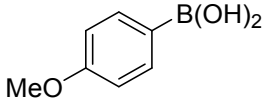
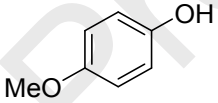
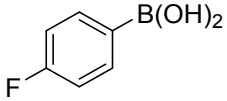
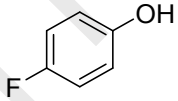
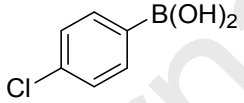
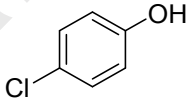
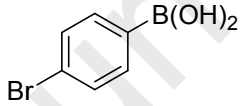
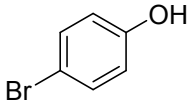
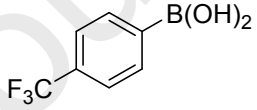
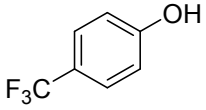
The oxidation of 4-phenylbenzeneboronic acid was selected as the model reaction, being the formed product (4-phenylphenol) non-volatile facilitating its isolation. From the LTTM formation studies, it was considered that a mixture of 1:2 ratio (mcm)mimCl-UHP provides enough dispersion media, while slowly melting at room temperature ensures a steady supply of the oxidizer. This would minimize oxidant decomposition, so two equivalents of UHP adduct were deemed enough to successfully carry out the reaction while avoiding the overoxidation. After 30 minutes at room temperature [27], 4-phenylphenol was the exclusive product to be formed in ca. 60% yield. After an analysis of the result, the reaction had failed to complete under these conditions due to an accumulation of solid product preventing further formation of the LTTM, and by extension, halting the reaction. The work-up of the reaction requires the extraction of the product in a proper solvent from the reaction mixture. Thus, performing the extraction as the product is formed may help to ensure full conversion of the starting material, preventing solid buildup in the LTTM. At the end of the reaction, the upper phase containing the product would simply be separated. Ethyl acetate was the solvent of choice for extraction since (a) it is considered a "green solvent", with low environmental impact [46], and recommended (or preferred) solvent for the pharmaceutical industry [47], (b) it is completely immiscible with the LTTM prepared, and (c) it is widely available and affordable. Also, the reaction is very exothermic due to the high oxophilicity of the boron with the heat released speeding up the formation of the LTTM and increasing the release of H_2O_2. This positive feedback loop can result in the heat output of the reaction spiraling out of control after an induction period. The presence of ethyl acetate would help to control the interaction of the reagent with the LTTM to maintain the reaction temperature under control, eliminating the need of cooling baths. It is noteworthy that the solubility of most boronic acids (and potassium trifluoroborates) in ethyl acetate is relatively low, while the solubility of the corresponding phenols and alcohols is high. Thus, the reaction takes place within the LTTM, and the product is extracted as soon as it is formed. To validate the protocol, the oxidation of 4-phenylbenzeneboronic acid was set up, as described, in the presence of ethyl acetate (1 mL/mmol boronic acid). Delightfully, the reaction proceeded as expected, giving after 30 minutes, the 4-phenylphenol in 97% yield as a pure white solid by simply taking the (upper) organic phase, filtering it through a thin plug of silica and evaporating the solvent. The product was found to be adequately pure by NMR analysis. In

comparison, this type of oxidation with aqueous H_2O_2 needs at least 5 equivalents, so the procedure employing LTTM is more sustainable in terms of atomic economy and waste generation. It is also worth noting that, under these reaction conditions, over-oxidation of the phenol derivative was not detected, as has been described using fluorinated solvents using a significant excess (7.5 equivalents) of oxidant (UHP) [45]. The use of the (cm)mimCl salt in combination with UHP to carry out the model reaction proved to be less active forming of the product in 61% yield.

Table 3. Scope of the reaction (isolated yields): boronic acids.



Entry	Boron reagent	Product	**No.**	Yield (%)
1			**1**	93
2			**2**	98
3			**3**	72[a]
4			**4**	93
5			**5**	99
6			**6**	93
7			**7**	89
8			**8**	90

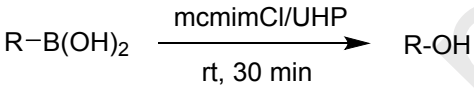
9			**9**	94
10			**10**	87
11			**11**	99
12			**12**	90
13			**13**	99[b]
14			**14**	88
15			**15**	99
16			**16**	96
17			**17**	94
18			**18**	99

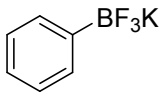
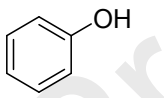
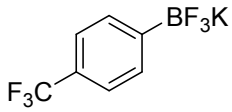
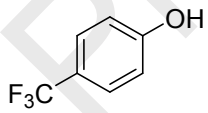
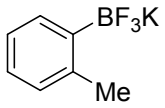
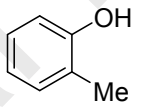
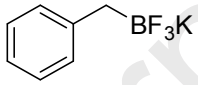
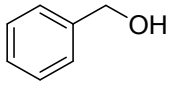
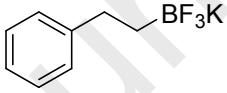
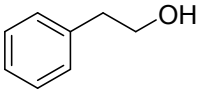
[a] Reaction time: 90 min. [b] Reaction performed in 5 mmol scale.

To prove the relevance of this simple protocol, a variety of boronic acids were considered to explore the scope of the oxidation with the results summarized in Table 3. Generally, the reactions proceeded smoothly, obtaining good to quantitative yields across the board without further purification being required for any of the products obtained. Judging by these results, the electronic nature of the aryl-substituents does not seem to affect the outcome of the reaction in any significant manner. Moreover, almost negligible differences in the yields of different 2-, 3- and 4-substituted-

phenols proved that the substitution pattern of the starting organoboron does not influence the reaction. The procedure was extended to other aromatic systems, such as 1-naphthylboronic acid, which gave compound **2** in 98% yield. Likewise, boronic acid anhydrides are also active in this transformation, with triphenylboroxin being transformed in **1** in 93% yield. More congested boron reagents, such as 2,6-dimethylbenzeneboronic acid, resulted in a slower reaction, giving the phenol **3** in 51% isolated yield after 30 minutes. The result can be improved by extending the reaction time, obtaining the product in 72% yield after 90 minutes (Table 3). Yet, the excellent results obtained for *ortho*-monosubstituted arylboronic acids and 1-naphthylboronic acid prove that only truly congested centers exhibit reduced reactivity under these conditions. Thus, this different behavior could be utilized for the selective oxidation of non-hindered boron moieties.

Table 4. Scope of the reaction: potassium trifluoroborates.



Entry	Boron reagent	Product	**No.**	Yield (%)
1			**1**	80
2			**18**	99
3			**19**	80
4			**20**	95
5			**21**	99

Having obtained excellent results with boronic acids, attention was turned to less reactive boron reagents, i.e. trifluoroborate salts and boronic esters [48]. As expected, the reaction time needed to be extended (90 min.) to achieve better results. The protocol was effective for the pinacol phenylboronate, giving product **1** in 79% conversion but with the need of a purification step. Similarly, aryltrifluoroborates, which are stable and easy to obtain compounds [48], resulted to be suitable substrates for this oxidation (Table 4). As proof of that, compounds **1**, **18**, and **19** were obtained in appropriate yield from the corresponding organotrifluoroborates (80-99%, Table 4). Remarkably, this oxidation methodology seems to perfectly tolerate aliphatic substrates, as compounds **20** and **21** were obtained in almost quantitative yield (Table 4). The oxidation reaction

starting from potassium organotrifluoroborates allowed the isolation from the reaction media of the corresponding alcohols without the need of further purification. The good results obtained with the wide variety of compounds assayed prove our protocol to be both versatile and robust, with a very effective activation of the reagents by the LTTM components. To extend the utility and convenience of the methodology presented, the model reaction was performed at preparative scale. Thus, 0.99 g (5 mmol) of 4-phenylbenzeneboronic acid were subjected to the reaction conditions, resulting in 99% yield of phenol **13**. Regarding the sustainability of the protocol, this reaction presented an *E-factor* of 7.9, being at the lower level of the reported range for Fine Chemical production in the industry [49]. The reusability of catalysts is a topic that is explored in almost every study nowadays, but in this case however, there is not a cost-effective and environmentally friendly way of separating the imidazolium salt from the reaction media. Still, as we demonstrated, the composition range of the (mcm)mimCl-urea mixture with low temperature is quite broad, so the possibility of performing successive reactions by simply reloading the LTTM with more product and UHP was considered. Therefore, the model reaction was set up again. After each iteration, the organic phase was removed and, after washing with an equal volume of AcOEt, additional UHP and boronic acid suspension were added. As the volume of the dispersion media was not a constricting factor, only 1.1 equivalents of UHP were used from the second reaction on. We managed to successfully perform the reaction 3 consecutive times without any loss of performance, isolating phenol **13** in 94, 99 and 97% yields, respectively, with a total cumulative yield of 98%. This demonstrates the robustness of our protocol, with a cumulative effectiveness of the imidazolium salt along the three runs (cumulative TON = 2.9). Although the mole fraction of (mcm)mimCl in the mixture decreases (from 0.33 to 0.19) by the addition of more UHP in each run, it still maintains the same activity in the H_2O_2 release and the formation of favorable interaction with the boronic acid, facilitating the reaction (cumulative TOF = 1.9 h^{-1}, being comparable to each run), therefore, this set of three consecutive reactions resulted in an *E-factor* of 3.2, halving the mass of waste generated per mass of product (Figure 4). This number of *E-factor* is in the range of Bulk Chemical production in the industry [49]. This improvement in sustainability is mainly due to the reuse of the imidazolium salt and the use of half-amount of the UHP in the second and third run, compared to the standard procedure.

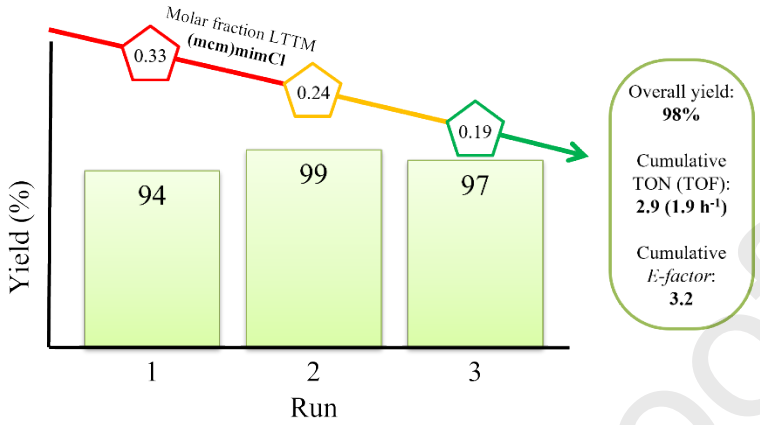
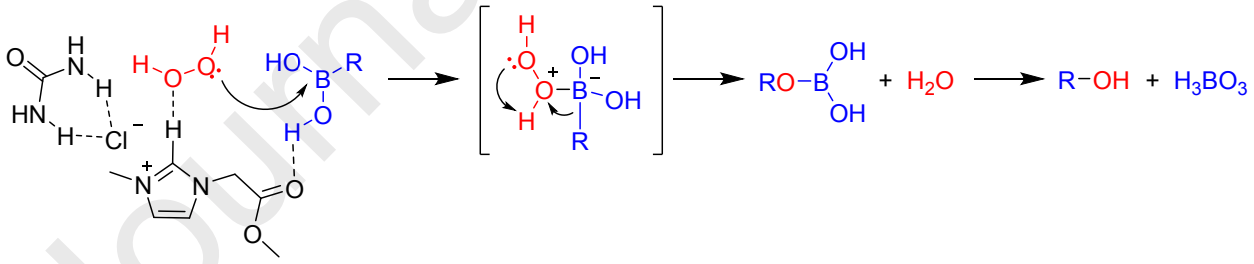


Figure 4. Cumulative synthesis of **13** in 3 consecutive cycles maintaining the catalytic system activity and reducing the environmental impact of the synthesis.

The reaction is performed in the presence of the LTTM formed by (mcm)mimCl and urea, being the amount of (mcm)mimCl equimolecular with the organoboron reagent and the urea a two-fold molecular amount. As before mentioned in Scheme 2, the (mcm)mimCl interacts with the UHP in the formation of the LTTM, releasing the H_2O_2. The presence of a carboxy-functionalized imidazolium unit may be crucial for establishing favorable interactions with the boron reagent while keeping the released oxidant molecule in close proximity, due to its possibility of acting both as hydrogen bond donor and hydrogen bond acceptor [22]. These interactions would assist the reaction between the H_2O_2 and the boron atom. Then, a rearrangement takes place leaving a boronate which can be promptly hydrolyzed to yield the corresponding alcohol (Scheme 3).



Scheme 3. Proposed interaction between the (mcm)mimCl, UHP and the boronic acid during the oxidation reaction.

4. CONCLUSSIONS

To conclude, different carboxy-functionalized imidazole derivatives have been combined with urea to form low transition temperature mixtures (LTTMs). One carboxy substituent resulted in

mixtures with lower melting temperatures compared to these of biscarboxy-functionalized imidazoles. These carboxy-imidazolium salts form low melting point mixtures over a wide range of mole fractions, setting robust dispersion media for synthetic procedures. To prove this, the metal-free oxidation of boron compounds has been successfully accomplished employing urea-hydroperoxide adduct in combination with (mcm)mimCl. The interaction of the imidazolium chloride with the urea in the UHP forms the LTTM and releases the H_2O_2 providing an active reaction medium. A variety of arylboronic acids, as well as aryl and alkyltrifluoroborates, have been effectively converted to the corresponding alcohols, with the desired products being isolated by simple extraction from the reaction media without the need for further purification. This oxidation of organoboron reagents represents a significant improvement compared to the previously reported ones, with the possibility of performing the reaction in preparative scale (5 mmol) with identical results. Noteworthy, the reaction has an *E-factor* of 7.9 due to the small molecular amounts of the LTTM components [1:1:2 mol-ratio of organoboron/(mcm)mimCl/UHP], resulting in a very competitive process in terms of sustainability. In addition, it is possible to reuse the mixture three consecutive times without loss of activity by only adding extra oxidant (UHP) and substrate. This reuse reduces the environmental impact of the chemical process (*E-factor*: 3.2).

ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures, complete characterization data, control experiments and ^{1}H NMR and ^{13}C NMR spectra are available.

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Notes

The authors declare no conflict of interest.

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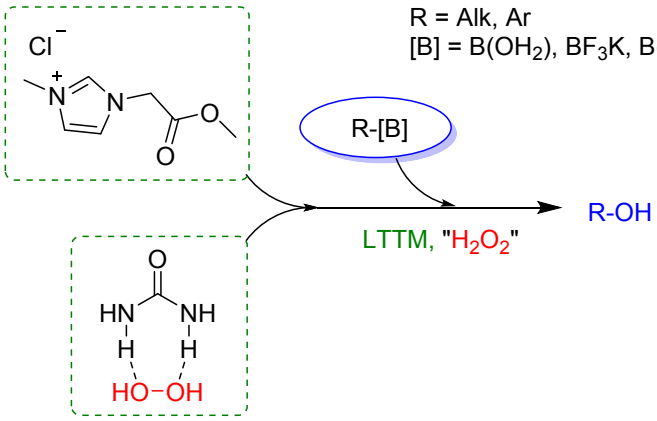
Graphical Abstract



- 25 examples
- Up to 99% yield
- Up to 5 mmol scale
- Mild and metal-free conditions
- Safe-to-handle oxidizer
- No chromatographic purification
- Up to 3 reactions with a single Im loading

Mario Martos: Methodology, Validation, Formal analysis, Investigation, Writing (original and revision), Visualization

Isidro M. Pastor: Conceptualization, Methodology, Validation, Formal analysis, Writing (original and revision), Supervision, Project administration

- 1-Methoxycarbonylmethyl-3-methylimidazolium chloride and urea form a LTTM over a wide range of mole-ratios.
- The combination (mcm)mimCl and UHP is excellent to oxidize boron reagents under safe and mild conditions.
- The oxidations employing the LTTM [(mcm)mimCl-urea] need lower amounts of oxidant compared to other similar procedures.
- The sustainability of this oxidation lies in effective activation of the reagents and the reuse of the imidazolium salt.
- The structure of the mixture plays a key role during the catalytic process, increasing the activity and robustness.