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Article

1,3-Bis(carboxymethyl)imidazolium chloride as metal-free and recyclable catalyst for the synthesis of N-allylanilines by allylic substitution of alcohols

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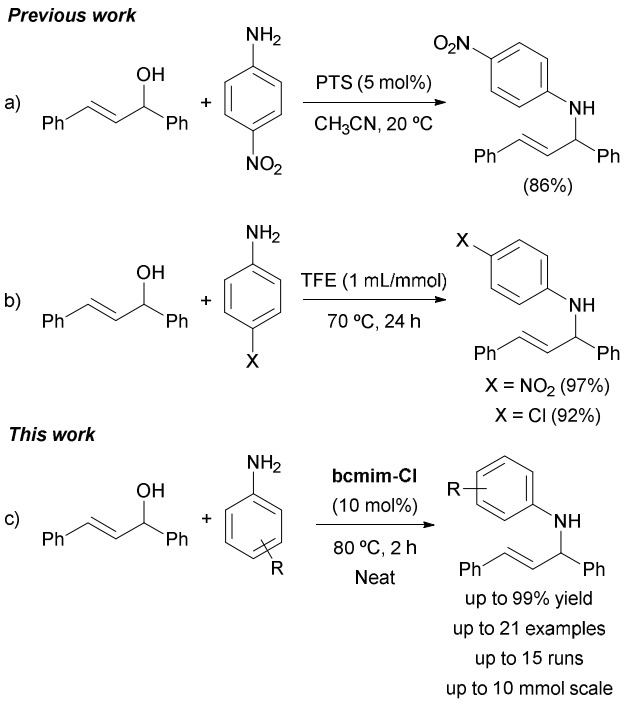
in preparative scale [e.g. 3.30 g of *N*-(1,3-diphenylallyl)-4-nitroaniline]. The catalyst could be reused up to 15 cycles without loss of activity, proving its robustness.

INTRODUCTION

The necessity to develop new strategies for reducing the damage to the environment is currently one of the main concerns of organic chemistry.[1-4] In this sense, the allylic substitution reaction of alcohols is a straightforward and environmentally friendly process to afford a huge variety of allylic derivatives, preventing the derivatisation of the starting material as acetates, phosphates, carbonates or halides, and avoiding the use of coupling agents[5] (for instance, the Mitsunobu[6] reaction). Nevertheless, this strategy has two main inconveniences: the poor ability of the hydroxyl group as leaving group and the formation of stoichiometric amounts of water, which can be detrimental for some catalytic systems.[7] Therefore, the design of new catalytic systems able to overcome these limitations is of interest.[7-13] Among allylic derivatives, allylic amines are present in various biologically active compounds, such as antifungal drugs and calcium channel blockers.[14] The allylic substitution of alcohols with anilines is a simple method to afford this type of compounds. Regarding this reaction, three products are expected depending on the substituents: 2-allylanilines,[15,16] 4-allylanilines[16-24] and *N*-allylanilines,[14-16,19,23,25-45] being this product the predominant regardless of the catalytic system when transition-metal complexes are employed.[19] Nevertheless, only a few examples of the allylic substitution of alcohols with anilines employing metal-free catalytic systems have been described. Both *p*-toluenesulfonic acid monohydrate (PTS) and polymer-bound *p*-toluenesulfonic acid have been used in the allylic substitution of *(E)*-1,3-diphenyl-2-propen-1-ol with 4-nitroaniline to produce the corresponding *N*-arylation product, but other allylic alcohols or anilines have not been tested (Scheme 1a).[26]

Fluorinated alcohols have been proved to be effective in the allylic substitution of *(E)*-1,3-diphenyl-2-propen-1-ol with amines, but only two examples have been reported using anilines, both of them being 4-substituted with an electron-withdrawing group (Scheme 1b).[39] None of the previous catalytic systems was recyclable, and they required the use of solvent. In this work, we have developed a methodology to carry out the substitution of allylic alcohols with different *ortho*-, *meta*- and *para*-substituted anilines by using a recyclable metal-free catalyst, being possible to scale it up to 10 mmol (Scheme 1c).

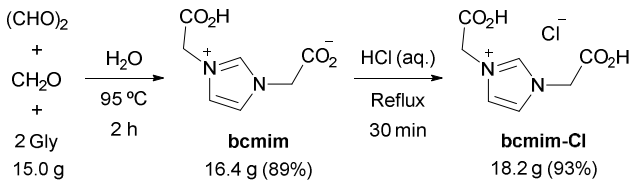


Scheme 1. Previous and present work in the metal-free catalyzed substitution reaction of allylic alcohols with anilines.

Traditionally, heterogeneous catalysts have consisted of metal-based systems. Recently, several types of heterogeneous organocatalysts have been developed to mimic the unique properties of heterogenous metal-based catalytic systems, easily recoverable and recyclable. Until now,

reported metal-free heterogeneous catalysts include carbocatalysts (graphene-type materials)[46,47] and supported organocatalysts, either on organic (covalent organic frameworks)[48] or inorganic (silica-based materials)[49,50] supports. As far as we know, all the heterogeneous organocatalysts found in the literature depend upon a support.

Our research group is aware of the importance of finding sustainable processes. Thus, we consider the search for catalytic systems, both heterogeneous and homogeneous, essential for this aim. In this sense, imidazole derivatives bearing carboxyl moieties can be synthesised by simple methodologies using inexpensive starting materials. From these compounds, it is possible to design a variety of catalytic systems. We employed functionalised imidazolium derivatives as precursors for N-heterocyclic carbene (NHC) ligands for palladium in organic transformations.[51,52] In combination with metal salts, such as iron(III) chloride, imidazolium salts can produce Iron-Based Lewis Acid Ionic Liquids (IBLAILs), which proved to be very versatile catalytic systems.[16] Furthermore, we employed metal-organic frameworks based on imidazolium-dicarboxylate as efficient and robust catalysts for organic transformations.[53,54] Recently, we have envisioned the use of imidazole derivatives bearing carboxylic acids as catalytic systems by themselves. Herein, we report the use of 1,3-bis(carboxymethyl)imidazolium chloride (**bcmim-Cl**), which is an organic salt, as catalyst. Although this Ionic Organic Solid (IOS) is apparently similar to Ionic Liquids (ILs), which have been used as catalysts as well,[55-59] the fact of being solid result in a more facile separation from the reaction mixture by filtration. This behaviour is unprecedented according to our research into the literature. In addition, **bcmim-Cl** is easily prepared from readily accessible starting materials (i.e. formaldehyde, glyoxal, the naturally occurring amino acid glycine and hydrogen chloride) in two simple and efficient steps, being able the preparation in multigram scale (Scheme 2).[53,54]

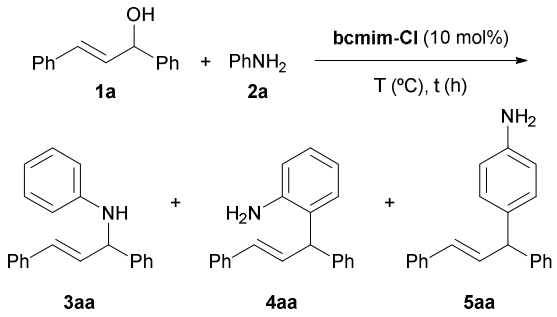


Scheme 2. Synthesis of **bcmim-Cl** in multigram scale.

RESULTS AND DISCUSSION

The imidazolium derivative **bcmim-Cl** was tested as catalyst (using 10 mol%) in the reaction of *(E)*-1,3-diphenyl-2-propen-1-ol (**1a**) and aniline (**2a**) at different temperatures, in the absence of any solvent (Scheme 3). The three expected products (**3aa**, **4aa** and **5aa**) were obtained in different ratios depending on the temperature and the reaction time. At 60 ºC, the major product was **3aa**, either at short and long reaction times, **4aa** and **5aa** being observed as traces (Figure 1a). When the temperature was increased to 80 ºC and 100 ºC, **3aa** was rapidly formed at the beginning, and then it turned into **4aa** and **5aa** at longer reaction times (Figure 1b and c). At 80 ºC, **3aa** continued as the major product after 24 hours (Figure 1b), while at 100 ºC **4aa** became the major product (Figure 1c). At 120 ºC, **4aa** and **5aa** were formed from the beginning and the ratio (38:62 for **4aa**/**5aa**) was maintained after 24 hours (see ESI). These experiments prove that both the *ortho*- and the *para*-substituted products (**4aa** and **5aa**) can be form from the *N*-allylated product **3aa**. Among the conditions in which product **3aa** was selectively formed, 80 ºC and 2 hours were chosen to continue with the study, reaching a trade-off between time and temperature, being the product **3aa** obtained in 82% yield. No further optimisation was necessary since the reaction took place using the starting materials in 1:1 ratio and in the absence of any solvent or additive. At this point, we proved that a higher amount (i.e. 20 mol%) of catalyst

bcmim-Cl produced **3aa** in similar yield (83%), and lowering the amount of catalyst to 1 mol% reduced the yield of **3aa** to 75%.



Scheme 3. Reaction between (*E*)-1,3-diphenyl-2-propen-1-ol (**1a**) and aniline (**2a**): Expected products.

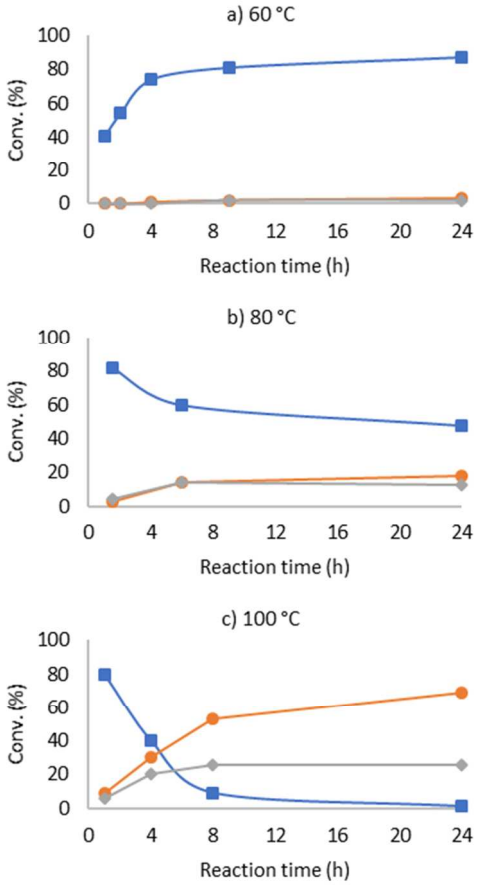


Figure 1. Reaction between (*E*)-1,3-diphenyl-2-propen-1-ol (**1a**) and aniline (**2a**). Reaction profile dependent on the temperature for the three expected products: *N*-allylaniline **3aa** (■), *ortho*-allylaniline **4aa** (●) and *para*-allylaniline **5aa** (♦).

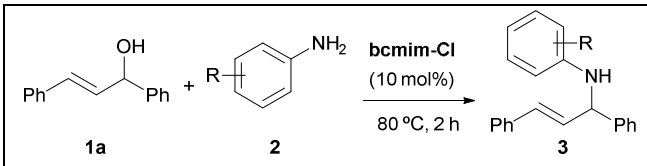
To find the scope of the *N*-allylation reaction using the IOS **bcmim-Cl**, several anilines were evaluated. The *N*-allylation product of the model reaction was isolated in very good yield (Table 1, compound **3aa**, 82%). Anilines bearing electron-withdrawing groups in the *para*-position, such as nitro, chlorine, bromine and carboxy, afforded the corresponding *N*-allylanilines in excellent conversions and very good to excellent yields (Table 1, compounds **3ab**, **3ad**, **3ag** and **3ai**). Likewise, electron-withdrawing groups in the *ortho*-position, such as nitro, chlorine, bromine, cyano, acetyl and benzoyl led to the formation of the corresponding *N*-allylanilines in

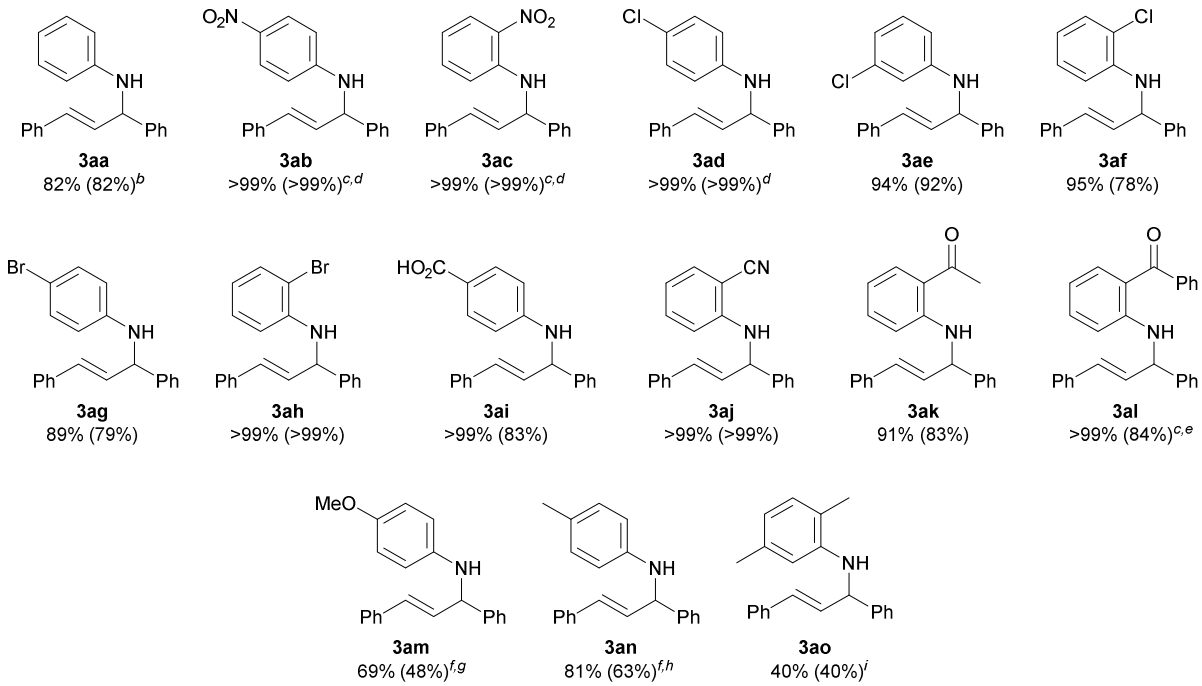
very good to excellent yields (Table 1, compounds **3ac**, **3af**, **3ah**, **3aj**, **3ak** and **3al**). Furthermore, we proved that *meta*-substituted anilines, such as 3-chloroaniline, led to the formation of the corresponding product in excellent yield (Table 1, compound **3ae**). These results demonstrate the robustness of the methodology with electron-poor aromatic systems regardless of the position of the substituent. Furthermore, excellent conversions were obtained in all the cases and decreases in the yield were due to the isolation process. Regarding electron-donating groups, both 4-methylaniline and 4-methoxyaniline, gave the corresponding products in moderate yields, even when the time was extended to 24 hours (Table 1, compounds **3am** and **3an**). Finally, we tested 2,5-dimethylaniline as nucleophile and the expected product was formed in moderate yield (Table 1, compound **3ao**), albeit in this case the formation of other by-products was observed. Additionally, we tried a non-aromatic amine, such as benzylamine, without observing the formation of the substitution product. It should be pointed out that several products could be obtained with >95% purity (determined by ^{1}H NMR) by simple filtration (Table 1, compounds **3ab**, **3ac** and **3ad**), which shows the usefulness of this procedure for synthetic purposes. Moreover, this proves that the catalyst can be completely recovered from the reaction mixture by simple filtration, since no traces appear in the filtrate.

To further explore the versatility of this catalytic system, the reaction was performed with other allylic alcohols. Thus, *(E)*-1,3-bis(4-chlorophenyl)-2-propen-1-ol (**1b**) was reacted with anilines **2b** and **2d**, obtaining full conversion and quantitative isolated yield in both cases by simple filtration (Table 2, compounds **3bb** and **3bd**). Non-symmetrically substituted alcohols, such as *(E)*-3-(4-chlorophenyl)-1-phenyl-2-propen-1-ol (**1c**) and *(E)*-3-(4-methoxyphenyl)-1-phenyl-2-propen-1-ol (**1d**) led to the formation of two regioisomers in a ratio *ca.* 1:1 when they were reacted with different anilines (Table 2, compounds **3cb**, **3cj**, **3dh**, **3dl** and regioisomers). These

experiments proved that the reaction takes place via allylic carbocation. The conversions and yields were excellent regardless of the nature of the substituent. Compounds **3dh** and **3dl** (together with their regioisomers) could be obtained by simple filtration.

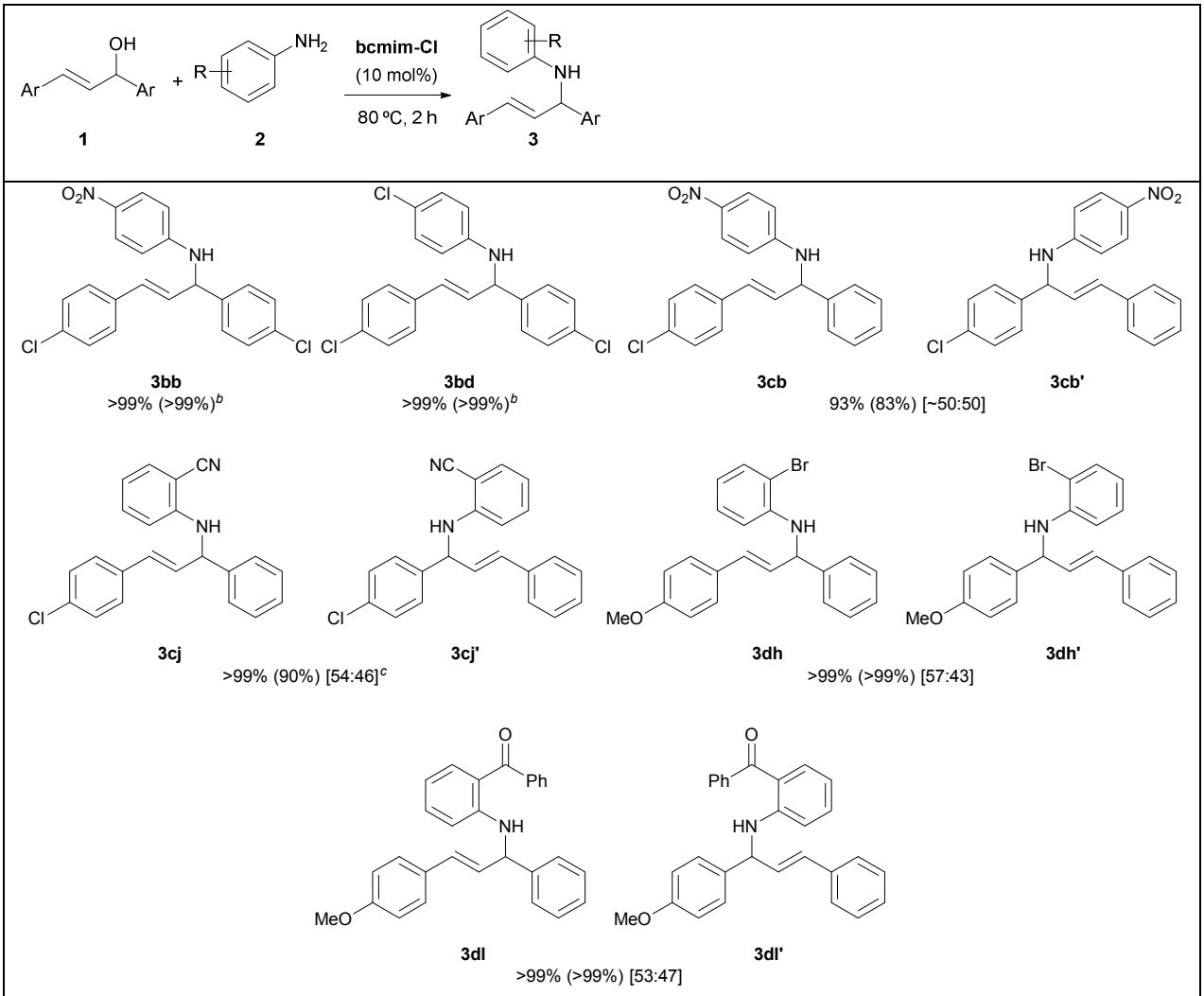
Table 1. Scope of the reaction: Anilines[a]





[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), **bcmim-Cl** (10 mol%), 80 ºC, 2 h. Conversion determined by GC analysis (in brackets, isolated yield after preparative TLC). [b] Reaction time: 1.5 h. [c] Conversion determined by ^{1}H NMR. [d] Obtained pure after filtration. [e] Isolated by column chromatography. [f] Reaction time: 24 h. [g] (*E*)-2-(1,3-Diphenylallyl)-4-methoxyaniline was observed (21% conversion) along with **3am**. [h] (*E*)-2-(1,3-Diphenylallyl)-4-methylaniline was observed (19% conversion) along with **3an**. [i] (*E*)-2-(1,3-Diphenylallyl)-3,6-dimethylaniline was observed (22% conversion) along with **3ao**.

Table 2. Scope of the reaction: Alcohols[a]



[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), **bcmim-Cl** (10 mol%), 80 ºC, 2 h. Conversion determined by ^{1}H NMR (in brackets, isolated yield after preparative TLC) [in square brackets, ratio of the regioisomers determined by ^{1}H NMR]. [b] Obtained pure after filtration. [c] Conversion and ratio of the regioisomers determined by GC analysis.

At that point, we tried to recycle the catalyst in the reaction between alcohol **1a** and aniline **2d**. As the catalyst remained solid after the reaction, it was recovered by centrifugation using ethyl acetate to remove the product. Then, the reaction was set again by only adding the starting materials and we were glad to observe that the desired product was obtained in full conversion.

The efficiency and ease to recover and reuse the catalyst allowed us to prove its robustness, being used up to 15 cycles without loss of activity (Figure 2, cumulative TON: 150). To prove the purity with which the reaction took place, the product from the last run was purified, isolating **3ad** in 97% yield. It is worth mentioning that the catalyst was completely recovered after each cycle, as it is insoluble in the work-up solvent, with no loss of catalyst mas being observed after the different cycles. In addition, as previously mentioned, no traces of catalyst were detected in the product obtained (^{1}H NMR) in the filtrate. However, we cannot rule out the possibility that during the reaction the catalyst can be partially solubilized when it interacts with the reactants, being recovered as solid after the reaction is completed.

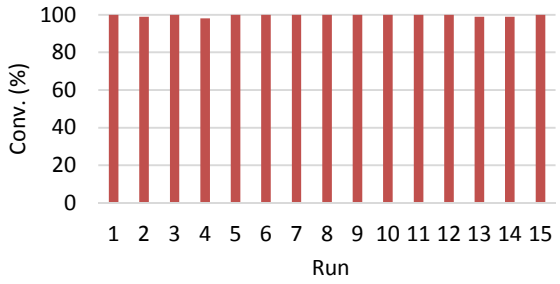
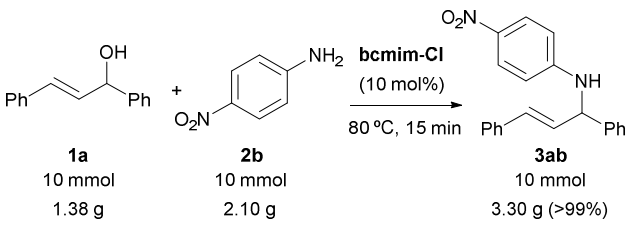


Figure 2. Recycling of the catalyst.

The reaction between **1a** and **2b** was scaled up to 10 mmol, obtaining the expected product in 99% yield (3.3 g) after removing the catalyst by filtration using ethyl acetate (Scheme 4). It should be pointed out that the reaction time could be reduced to 15 minutes. The *E-factor* was calculated to measure the environmental impact of the process. Taking into account that only 10 mL of ethyl acetate were necessary to separate the product from the catalyst, an *E-factor* of 2.8 was obtained, which is within the numbers of production of bulk chemicals in the industry.[4]

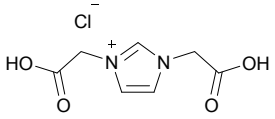
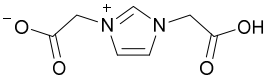
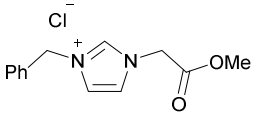
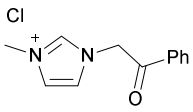


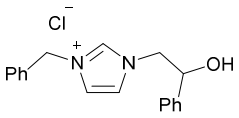
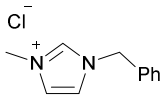
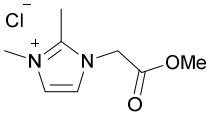
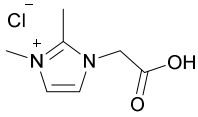
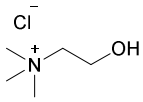
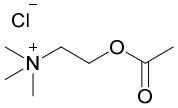
Scheme 4. Reaction between **1a** and **2b** in multigram scale.

To discern the significance of the moieties of the IOS **bcmim-Cl** during the catalysis, the reaction between **1a** and **2d** was carried out using similar imidazole derivatives under the standard conditions (Table 3). With the zwitterion **bcmim**, the reaction did not proceed at all, even at longer reaction times (Table 3, entry 2). Using 1-benzyl-3-(methoxycarbonylmethyl)imidazolium chloride (**Im1**), an imidazolium salt bearing an ester group, gave rise to full conversion to the product **3ad**, similar than **bcmim-Cl** (Table 3, entry 3). The presence of other oxygen-containing functional groups in the catalyst led to a drop in the conversion to the expected product. Indeed, an imidazolium chloride bearing a ketone [i.e. 1-methyl-3-(2-oxo-2-phenylethyl)imidazolium chloride, **Im2**] as catalyst gave only a conversion of 43%, and an imidazolium chloride bearing a hydroxy group [i.e. 1-benzyl-3-(2-hydroxy-2-phenylethyl)imidazolium chloride, **Im3**] provided similar conversion (40%, Table 3, entries 4 and 5). Finally, the use of 1-benzyl-3-methylimidazolium chloride (**Im4**), under the same conditions, resulted in a conversion of 36% (Table 3, entry 6). From these results, we could conclude that (a) the presence of the hydrogen (OH) is not sufficient for the activation to be effective and (b) the chloride, the carbonyl and the alkoxy (or hydroxy) moieties have a key role in the mechanism, being they complementary. Consequently, the presence of only one of them led to the formation of the desired product in lower yield than when the three of them were present in the catalyst (compare with Table 3, entry 1). Besides, the presence of an acid moiety is

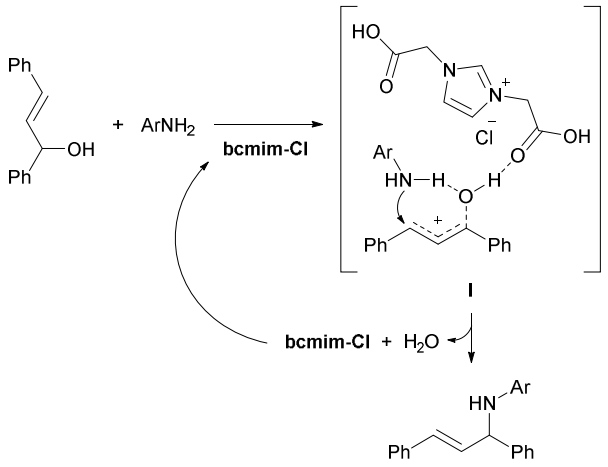
not strictly necessary, since the use of an ester moiety instead of gave similar results as proved with **Im1** and also comparing **Im5** and **Im6** (Table 3, entries 7 and 8). Based on these results and others from the literature,[7,16] we speculate that **bcmim-Cl** assists in the formation of the allylic carbocation via hydrogen bonding of the alcohol with the carbonyl and the chlorine (Scheme 5, intermediate **I**). The fact of the ester and the acid being more effective than the ketone could be due to the enhanced electron-donor capacity of these species on account of the alkoxy or hydroxy moieties. As a consequence of the formation of an allylic carbocation, two regioisomers can be obtained from non-symmetric carbocations. Finally, we have considered other ammonium chlorides bearing oxygenated functional groups, such as choline chloride (ChCl) and acetylcholine chloride (AcChCl), as catalysts, observing low conversions to the corresponding product **3ad** (Table 3, entries 9 and 10). Thus, the imidazolium core can help in the activation due to its structure or additional interactions, although we cannot confirm that is necessary.

Table 3. Reaction between **1a** and **2d** with different imidazole derivatives[a]

Entry	Imidazole derivative		Conversion to **3ad** (%)
1	**bcmim-Cl**[b]		>99
2	**bcmim**		0
3	**Im1**		>99
4	**Im2**		43

5	**Im3**		40
6	**Im4**		36
7	**Im5**		92
8	**Im6**		89
9	**ChCl**		8
10	**AcChCl**		11

[a] Reaction conditions: **1a** (0.5 mmol), **2d** (0.5 mmol), the corresponding imidazole (10 mol%), 80 °C, 2 h. Conversion determined by GC analysis. [b] The surface area is 0.398 m^2/g (N_2 isotherm at 77 K). Thus, 11 mg (10 mol%) of **bcmim-Cl** represent 0.0044 m^2 of catalyst area.



Scheme 5. Proposed mechanism for the formation of *N*-allylanilines by allylic substitution of alcohols with anilines.

CONCLUSIONS

The use of IOS **bcmim-Cl** in the allylic substitution of alcohols with anilines meet most of the criteria established in the 12 principles of Green Chemistry by Anastas.[1a] The only waste generated in the reaction is water, which is a non-harmful substance (Principle 1: Prevention). From the starting materials (alcohol and amine in 1:1: ratio), only water is released (Principle 2: Atom economy). Allylic alcohols and anilines do not have a high level of toxicity (Principle 3: Less hazardous chemical synthesis). Neither solvents nor auxiliaries are used during the reaction, and only ethyl acetate, an environmentally friendly solvent,[60] is employed to separate the catalyst from the crude (Principle 5: Safer solvents and auxiliaries). The reaction is carried out at atmospheric pressure and 80 °C (Principle 6: Design for Energy Efficiency). The catalyst is formed from renewable materials (Principle 7: Use of renewable feedstocks). No derivatisation is needed (Principle 8: Reduce derivatives). A catalyst is used to accelerate the reaction, which, additionally, is recyclable (Principle 9: Catalysis). All the substances used in the reaction are solids or liquids with high boiling points, and the only gas which can be released is water (Principle 12: Inherently safer chemistry for accident prevention).

To conclude, we have developed a robust, simple and effective process to obtaine allylic anilines making use of a metal-free and easily recyclable catalyst, which is synthesised from commercially available materials, being possible to scale up the process to multigram scale, and with an *E-factor* of 2.8. This methodology constitutes a sustainable process since only a small amount of ethyl acetate is required to separate the product from the catalyst and the only waste is water. Thus, the described protocol is appealing to be used in preparative scale, being above other previously described methods. Moreover, a variety of anilines in the presence of this

catalyst reacted selectively as a nitrogen-nucleophile, independently of the substituents, giving exclusively the corresponding *N*-allylanilines.

EXPERIMENTAL SECTION

Reagents and instruments. All commercially available reagents and solvents were purchased (Acros, Aldrich, Fluka) and used without further purification. Melting points were determined using a Gallenkamp capillary melting point apparatus (model MPD 350 BM 2.5) and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at the technical service of the University of Alicante (SSTTI–UA), employing a Bruker AC-300 or a Bruker Advance-400. Chemical shifts (δ) are given in ppm and the coupling constants (*J*) in Hz. The conversion of the reactions and purity of the products were determined by GC analysis using an Agilent 7820A apparatus, equipped with a flame ionization detector and a Phenomenex ZB-5MS column (5% PH-ME siloxane): 30 m (length), 0.25 mm (inner diameter) and 0.25 μm (film). Low-resolution mass spectra (EI) were obtained at 70 eV with an Agilent 5973 Network spectrometer, with fragment ions m/z reported with relative intensities (%) in parentheses. Low-resolution HPLC with electrospray ionization (HPLC-ESI) mass spectra were recorded at the technical service of the University of Alicante (SSTTI–UA), employing an Agilent 1100 series apparatus with the possibility of MS/MS. High resolution mass spectra (IE) were recorded at the technical service of the University of Alicante (SSTTI–UA) with an Agilent 7200 Network spectrometer (Q-TOF). Infrared spectra were recorded with an FT-IR 4100 LE (JASCO, Pike Miracle ATR) spectrometer. Spectra were recorded from neat samples and results are given in cm^{-1}. Analytical TLC was performed on Merck aluminium sheets with silica gel 60 F254, 0.2 mm thick. Silica gel 60 (0.04-0.06 mm) was employed for column chromatography. P/UV_{254} silica gel with $CaSO_4$

supported on glass plates was employed for preparative TLC. Centrifugation was carried out with a Nahita Model 2610 apparatus (4000 rpm).

Synthesis of 1,3-bis(carboxymethyl)imidazole (bcmim).[54] A mixture of glycine (100 mmol, 7.5 g), glyoxal (40% in water, 50 mmol, 5.7 mL) and formaldehyde (36% in water, 100 mmol, 3.9 mL) was stirred at 95 °C for 2 hours. The mixture was allowed to cool down to room temperature and the resulting brown solid was filtered, washed with cold water and dried at room temperature to afford the corresponding product as a white solid in 89% yield.

Synthesis of 1,3-bis(carboxymethyl)imidazolium chloride (bcmim-Cl).[54] A mixture of **bcmim** (89 mmol, 16.4 g) and concentrated aqueous HCl (196 mmol, 16.2 mL) was stirred and refluxed for 30 minutes. Then, HCl was removed under reduced pressure and the resultant solid was filtered and washed with acetone and diethyl ether to afford a white solid in 93% yield.

General procedure for the synthesis of *N*-allylanilines (3). The corresponding allylic alcohol (**1**, 0.5 mmol), the corresponding aniline (**2**, 0.5 mmol) and **bcmim-Cl** (10 mol%, 11.0 mg, pK_a = 1.33)[61] were placed in a tube provided with a stirring bar. The mixture was stirred at 80 °C for 2 hours. Then, ethyl acetate was added and the mixture was filtered to separate the catalyst, which is insoluble in ethyl acetate. After evaporating the solvent under vacuum, the corresponding crude was purified by preparative TLC or column chromatography using mixtures of hexane/ethyl acetate. In some cases, the product was obtained pure after evaporation of the solvent. In the recycling experiments, the catalyst was separated by centrifugation. After separation, the catalyst was washed twice with ethyl acetate and once with diethyl ether. Then, the catalyst was dried at 50 °C for 2 hours or at room temperature overnight before the next run.

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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REFERENCES

1. Anastas, P. T.; Warner, J. C., *Green Chemistry: Theory and Practice*. Oxford University Press: New York, 1998.

2. Sheldon, R. A., *Green Chemistry and Catalysis*. Wiley-VCH: Weinheim, 2007.

3. Anastas, P. T.; Eghbali, N., Green Chemistry: Principles and Practice. *Chem. Soc. Rev.* **2010,** *39* (1), 301-312. DOI 10.1039/B918763B

4. Sheldon, R. A., Fundamentals of green chemistry: efficiency in reaction design. *Chem. Soc. Rev.* **2012,** *41* (4), 1437-1451. DOI 10.1039/C1CS15219J

5. Johannsen, M.; Jørgensen, K. A., Allylic Amination. *Chem. Rev.* **1998,** *98* (4), 1689-1708. DOI 10.1021/cr970343o

6. Mitsunobu, O., The Use of Diethyl Azodicarboxylate and Triphenylphosphine in Synthesis and Transformation of Natural Products. *Synthesis* **1981,** *1981* (01), 1-28. DOI 10.1055/s-1981-29317

7. Baeza, A.; Nájera, C., Recent Advances in the Direct Nucleophilic Substitution of Allylic Alcohols through S_N1-Type Reactions. *Synthesis* **2014,** *46* (01), 25-34. DOI 10.1055/s-0033-1340316

8. Bandini, M., Allylic Alcohols: Sustainable Sources for Catalytic Enantioselective Alkylation Reactions. *Angew. Chem. Int. Ed.* **2011,** *50* (5), 994-995. DOI 10.1002/anie.201006522

9. Bandini, M.; Tragni, M., π-Activated alcohols: an emerging class of alkylating agents for catalytic Friedel-Crafts reactions. *Org. Biomol. Chem.* **2009,** *7* (8), 1501-1507. DOI 10.1039/b823217b

10. Biannic, B.; Aponick, A., Gold-Catalyzed Dehydrative Transformations of Unsaturated Alcohols. *Eur. J. Org. Chem.* **2011,** (33), 6605-6617. DOI 10.1002/ejoc.201100858

11. Butt, N. A.; Zhang, W., Transition metal-catalyzed allylic substitution reactions with unactivated allylic substrates. *Chem. Soc. Rev.* **2015,** *44* (22), 7929-7967. DOI 10.1039/C5CS00144G

12. Emer, E.; Sinisi, R.; Capdevila, M. G.; Petruzziello, D.; De Vincentiis, F.; Cozzi, P. G., Direct Nucleophilic S_N1-Type Reactions of Alcohols. *Eur. J. Org. Chem.* **2011,** (4), 647-666. DOI 10.1002/ejoc.201001474

13. Muzart, J., Procedures for and possible mechanisms of Pd-catalyzed allylations of primary and secondary amines with allylic alcohols. *Eur. J. Org. Chem.* **2007,** (19), 3077-3089. DOI 10.1002/ejoc.200601050

14. Ohshima, T.; Miyamoto, Y.; Ipposhi, J.; Nakahara, Y.; Utsunomiya, M.; Mashima, K., Platinum-Catalyzed Direct Amination of Allylic Alcohols under Mild Conditions: Ligand and Microwave Effects, Substrate Scope, and Mechanistic Study. *J. Am. Chem. Soc.* **2009,** *131* (40), 14317-14328. DOI 10.1021/ja9046075

15. Chen, K.; Li, Y.; Pullarkat, S. A.; Leung, P.-H., Palladacycle-catalyzed tandem allylic amination/allylation protocol for one-pot synthesis of 2-allylanilines from allylic alcohols. *Adv. Synth. Catal.* **2012,** *354* (1), 83-87. DOI 10.1002/adsc.201100424

16. Trillo, P.; Pastor, I. M., Iron-Based Imidazolium Salts as Versatile Catalysts for the Synthesis of Quinolines and 2- and 4-Allylanilines by Allylic Substitution of Alcohols. *Adv. Synth. Catal.* **2016,** *358* (18), 2929-2939. DOI 10.1002/adsc.201600315

17. Liu, Y.-L.; Liu, L.; Wang, Y.-L.; Han, Y.-C.; Wang, D.; Chen, Y.-J., Calix[n]arene sulfonic acids bearing pendant aliphatic chains as recyclable surfactant-type Bronsted acid

catalysts for allylic alkylation with allyl alcohols in water. *Green Chem.* **2008,** *10* (6), 635-640. DOI 10.1039/b719278a

18. Tao, Y.; Wang, B.; Zhao, J.; Song, Y.; Qu, L.; Qu, J., Friedel-Crafts-Type Allylation of Nitrogen-Containing Aromatic Compounds with Allylic Alcohols Catalyzed by a [$Mo_3S_4Pd(\eta^3$-allyl)] Cluster. *J. Org. Chem.* **2012,** *77* (6), 2942-2946. DOI 10.1021/jo2024812

19. Chen, K.; Chen, H. J.; Wong, J.; Yang, J.; Pullarkat, S. A., Copper(II) Triflate Catalyzed Allylic Arylation of Allylic Alcohols: Direct and Selective Access to C-Allylanilines. *ChemCatChem* **2013,** *5* (12), 3882-3888. DOI 10.1002/cctc.201300408

20. Srinivas, H. D.; Zhou, Q.; Watson, M. P., Enantiospecific, Nickel-Catalyzed Cross-Couplings of Allylic Pivalates and Arylboroxines. *Org. Lett.* **2014,** *16* (13), 3596-3599. DOI 10.1021/ol5016724

21. Tao, J.-L.; Yang, B.; Wang, Z.-X., Pincer-Nickel-Catalyzed Allyl-Aryl Coupling between Allyl Methyl Ethers and Arylzinc Chlorides. *J. Org. Chem.* **2015,** *80* (24), 12627-12634. DOI 10.1021/acs.joc.5b02151

22. Gómez-Martínez, M.; Baeza, A.; Alonso, D. A., Pinacol rearrangement and direct nucleophilic substitution of allylic alcohols promoted by graphene oxide and graphene oxide CO_2H. *ChemCatChem* **2017,** *9* (6), 1032-1039. DOI 10.1002/cctc.201601362

23. Hikawa, H.; Ijichi, Y.; Kikkawa, S.; Azumaya, I., Cobalt(II)/TPPMS-Catalyzed Dehydrative Nucleophilic Substitution of Alcohols in Water. *Eur. J. Org. Chem.* **2017,** (3), 465-468. DOI 10.1002/ejoc.201601501

24. Yang, B.; Wang, Z.-X., Nickel-Catalyzed Cross-Coupling of Allyl Alcohols with Aryl- or Alkenylzinc Reagents. *J. Org. Chem.* **2017,** *82* (9), 4542-4549. DOI 10.1021/acs.joc.6b02564

25. Ozawa, F.; Okamoto, H.; Kawagishi, S.; Yamamoto, S.; Minami, T.; Yoshifuji, M., (π-Allyl)palladium Complexes Bearing Diphosphinidenecyclobutene Ligands (DPCB): Highly Active Catalysts for Direct Conversion of Allylic Alcohols. *J. Am. Chem. Soc.* **2002,** *124* (37), 10968-10969. DOI 10.1021/ja0274406

26. Sanz, R.; Martínez, A.; Miguel, D.; Alvarez-Gutierrez, J. M.; Rodriguez, F., Bronsted acid-catalyzed nucleophilic substitution of alcohols. *Adv. Synth. Catal.* **2006,** *348* (14), 1841-1845. DOI 10.1002/adsc.200606183

27. Yang, S.-C.; Hsu, Y.-C.; Gan, K.-H., Direct palladium/carboxylic acid-catalyzed allylation of anilines with allylic alcohols in water. *Tetrahedron* **2006,** *62* (17), 3949-3958. DOI 10.1016/j.tet.2006.02.035

28. Guo, S.; Song, F.; Liu, Y., Gold-catalyzed direct amination of allylic alcohols. *Synlett* **2007,** (6), 964-968. DOI 10.1055/s-2007-973865

29. Huang, W.; Shen, Q.-S.; Wang, J.-L.; Zhou, X.-G., Direct substitution of the hydroxy group at the allylic propargylic position with carbon- and heteroatom-centered nucleophiles catalyzed by $Yb(OTf)_3$. *Chin. J. Chem.* **2008,** *26* (4), 729-735. DOI 10.1002/cjoc.200890136

30. Wang, G.-W.; Shen, Y.-B.; Wu, X.-L., Phosphotungstic acid catalyzed amidation of alcohols. *Eur. J. Org. Chem.* **2008,** (25), 4367-4371. DOI 10.1002/ejoc.200800413

31. Yang, H.; Fang, L.; Zhang, M.; Zhu, C., An efficient molybdenum(VI)-catalyzed direct substitution of allylic alcohols with nitrogen, oxygen, and carbon nucleophiles. *Eur. J. Org. Chem.* **2009,** (5), 666-672. DOI 10.1002/ejoc.200800976

32. Giner, X.; Trillo, P.; Nájera, C., Gold versus silver-catalyzed amination of allylic alcohols. *J. Organomet. Chem.* **2010,** *696* (1), 357-361. DOI 10.1016/j.jorganchem.2010.09.072

33. Haubenreisser, S.; Niggemann, M., Calcium-Catalyzed Direct Amination of π-Activated Alcohols. *Adv. Synth. Catal.* **2011,** *353* (2+3), 469-474. DOI 10.1002/adsc.201000768

34. Ohshima, T.; Nakahara, Y.; Ipposhi, J.; Miyamoto, Y.; Mashima, K., Direct substitution of the hydroxy group with highly functionalized nitrogen nucleophiles catalyzed by Au(III). *Chem. Commun.* **2011,** *47* (29), 8322-8324. DOI 10.1039/c1cc12760h

35. Wang, Y.; Vaismaa, M. J. P.; Haemaelaeinen, A. M.; Tois, J. E.; Franzen, R., Utilization of IndPHOX-ligands in palladium-catalysed asymmetric allylic aminations. *Tetrahedron: Asymmetry* **2011,** *22* (5), 524-529. DOI 10.1016/j.tetasy.2011.03.004

36. Zhao, Y.; Foo, S. W.; Saito, S., Iron/Amino Acid Catalyzed Direct *N*-Alkylation of Amines with Alcohols. *Angew. Chem. Int. Ed.* **2011,** *50* (13), 3006-3009. DOI 10.1002/anie.201006660

37. Das, B. G.; Nallagonda, R.; Ghorai, P., Direct Substitution of Hydroxy Group of π-Activated Alcohols with Electron-Deficient Amines Using Re_2O_7 Catalyst. *J. Org. Chem.* **2012,** *77* (13), 5577-5583. DOI 10.1021/jo300706b

38. Ohshima, T.; Ipposhi, J.; Nakahara, Y.; Shibuya, R.; Mashima, K., Aluminum Triflate as a Powerful Catalyst for Direct Amination of Alcohols, Including Electron-Withdrawing Group-Substituted Benzhydrols. *Adv. Synth. Catal.* **2012,** *354* (13), 2447-2452. DOI 10.1002/adsc.201200536

39. Trillo, P.; Baeza, A.; Nájera, C., Fluorinated Alcohols As Promoters for the Metal-Free Direct Substitution Reaction of Allylic Alcohols with Nitrogenated, Silylated, and Carbon Nucleophiles. *J. Org. Chem.* **2012,** *77* (17), 7344-7354. DOI 10.1021/jo301049w

40. Trillo, P.; Baeza, A.; Nájera, C., $FeCl_3 \cdot 6H_2O$ and TfOH as Catalysts for Allylic Amination Reaction: A Comparative Study. *Eur. J. Org. Chem.* **2012,** (15), 2929-2934. DOI 10.1002/ejoc.201101844

41. Fan, G.-P.; Liu, Z.; Wang, G.-W., Efficient $ZnBr_2$-catalyzed reactions of allylic alcohols with indoles, sulfamides and anilines under high-speed vibration milling conditions. *Green Chem.* **2013,** *15* (6), 1659-1664. DOI 10.1039/c3gc40262b

42. Trillo, P.; Baeza, A.; Nájera, C., Direct nucleophilic substitution of free allylic alcohols in water catalyzed by $FeCl_3 \cdot 6\ H_2O$: which is the real catalyst? *ChemCatChem* **2013,** *5* (6), 1538-1542. DOI 10.1002/cctc.201200650

43. Banerjee, D.; Junge, K.; Beller, M., Cooperative Catalysis by Palladium and a Chiral Phosphoric Acid: Enantioselective Amination of Racemic Allylic Alcohols. *Angew. Chem. Int. Ed.* **2014,** *53* (48), 13049-13053. DOI 10.1002/anie.201405511

44. Huang, K.; Wang, H.; Liu, L.; Chang, W.; Li, J., Mutual Cooperation in the Formal Allyl Alcohol Nucleophilic Substitution and Hydration of Alkynes for the Construction of γ-Substituted Ketones. *Chem. Eur. J.* **2016,** *22* (19), 6458-6465. DOI 10.1002/chem.201600248

45. Kwon, Y.; Jung, J.; Kim, J. H.; Kim, W.-J.; Kim, S., Amide Acetal in Palladium-Catalyzed Allylation with Allylic Alcohols under Neutral Conditions. *Asian J. Org. Chem.* **2017,** *6* (5), 520-526. DOI 10.1002/ajoc.201600578

46. Mohammadi, O.; Golestanzadeh, M.; Abdouss, M., Recent advances in organic reactions catalyzed by graphene oxide and sulfonated graphene as heterogeneous nanocatalysts: a review. *New J. Chem.* **2017**, *41*, 11471-11497. DOI 10.1039/c7nj02515g

47. Sengupta, D.; Ghosh, S.; Basu, B., Advances and Prospects of Graphene Oxide (GO) as Heterogeneous 'Carbocatalyst'. *Curr. Org. Chem.* **2017,** *21* (9), 834-854. DOI 10.2174/1385272820666161021102757

48. Xu, H.; Gao, J.; Jiang, D., Stable, crystalline, porous, covalent organic frameworks as a platform for chiral organocatalysts. *Nat. Chem.* **2015,** *7* (11), 905-912. DOI 10.1038/nchem.2352

49. Corma, A.; García, H., Silica-Bound Homogenous Catalysts as Recoverable and Reusable Catalysts in Organic Synthesis. *Adv. Synth. Catal.* **2006,** *348* (12-13), 1391-1412. DOI 10.1002/adsc.200606192

50. Ferre, M.; Pleixats, R.; Wong Chi Man, M.; Cattoen, X., Recyclable organocatalysts based on hybrid silicas. *Green Chem.* **2016,** *18* (4), 881-922. DOI 10.1039/C5GC02579F

51. Allegue, A.; Albert-Soriano, M.; Pastor, I. M., A comparative study of hydroxyl- and carboxylate-functionalized imidazolium and benzimidazolium salts as precursors for N-heterocyclic carbene ligands. *Appl. Organomet. Chem.* **2015,** *29* (9), 624-632. DOI 10.1002/aoc.3343

52. Gisbert, P.; Trillo, P.; Pastor, I. M., Comparative Study of Catalytic Systems Formed by Palladium and Acyl-Substituted Imidazolium Salts. *ChemistrySelect* **2018,** *3* (3), 887-893. DOI 10.1002/slct.201702818

53. Albert-Soriano, M.; Pastor, I. M., Metal–Organic Framework Based on Copper and Carboxylate-Imidazole as Robust and Effective Catalyst in the Oxidative Amidation of Carboxylic Acids and Formamides. *Eur. J. Org. Chem.* **2016,** (30), 5180-5188. DOI 10.1002/ejoc.201600991

54. Albert-Soriano, M.; Trillo, P.; Soler, T.; Pastor, I. M., Versatile Barium and Calcium Imidazolium-Dicarboxylate Heterogeneous Catalysts in Quinoline Synthesis. *Eur. J. Org. Chem.* **2017,** (43), 6375-6381. DOI 10.1002/ejoc.201700990

55. Chowdhury, S.; Mohan, R. S.; Scott, J. L., Reactivity of ionic liquids. *Tetrahedron* **2007,** *63* (11), 2363-2389. DOI 10.1016/j.tet.2006.11.001

56. Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Zanatta, N.; Bonacorso, H. G., Ionic Liquids in Heterocyclic Synthesis. *Chem. Rev.* **2008,** *108* (6), 2015-2050. DOI 10.1021/cr078399y

57. Olivier-Bourbigou, H.; Magna, L., Ionic liquids: perspectives for organic and catalytic reactions. *J. Mol. Catal. A: Chem.* **2002,** *182* (Supplement C), 419-437. DOI 10.1016/S1381-1169(01)00465-4

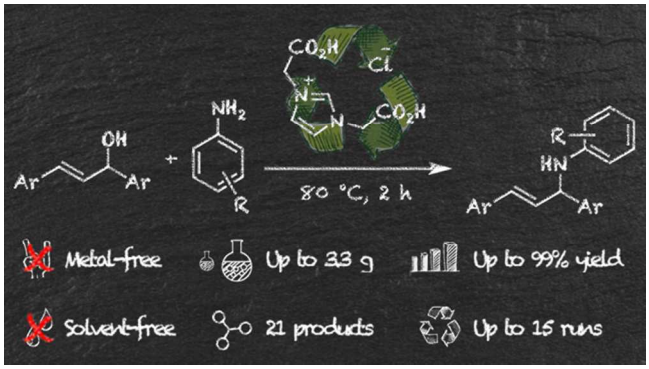
58. Sheldon, R., Catalytic reactions in ionic liquids. *Chem. Comm.* **2001,** (23), 2399-2407. DOI 10.1039/B107270F

59. Wilkes, J. S., Properties of ionic liquid solvents for catalysis. *J. Mol. Catal. A: Chem.* **2004,** *214* (1), 11-17. DOI 10.1016/j.molcata.2003.11.029

60. Prat, D.; Wells, A.; Hayler, J.; Sneddon, H.; McElroy, C. R.; Abou-Shehada, S.; Dunn, P. J., CHEM21 selection guide of classical- and less classical-solvents. *Green Chem.* **2016,** *18* (1), 288-296. DOI 10.1039/C5GC01008J

61. Fei. Z.; Zhao, D.; Geldbach, T. J.; Scopelliti, R.; Dyson, P. J., Brønsted acidic ionic liquids and their zwitterions: Synthesis, characterization and pK_a determination. *Chem. Eur. J.* **2004**, *10*, 4886-4893. DOI 10.1002/chem.200400145

TOC



1,3-Bis(carboxymethyl)imidazolium chloride is employed as efficient and recyclable catalyst in the synthesis of N-allylanilines from allylic alcohols and anilines