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RESEARCH ARTICLE

DES-Type Interactions To Promote Solvent-Free and Metal-Free Reactions between Nitrogen-Containing Heterocycles and Allylic Alcohols

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Abstract: Nitrogen-containing heterocycles are of great interest to organic chemists since they are present in a wide array of bioactive molecules. The use of allylic alcohols to carry out the allylation of heterocycles has been described as a sustainable alternative for this type of functionalization. Among the plethora of methodologies described, the use of metals, solvents, or hazardous reagents is ubiquitous. The protocol described in this work has provided a solventless and metal-free alternative, being mediated by the easy-to-synthesise and reusable 1,3-bis(carboxymethyl)imidazolium chloride. The protocol has resulted compatible with several nitrogen-containing heterocycles (i.e. indole, pyrazole, triazole, tetrazole, carbazole, indazole, and benzotriazole) and allylic alcohols, providing the allylated-heterocycles with up to quantitative yield, being possible to perform the reaction in preparative scale.Based on various green metrics (atom economy, stoichiometric factor, reaction mass efficiency, materials recovery parameter, E-factor, and EcoScale), the overall greenness significance of the methodology has been established.
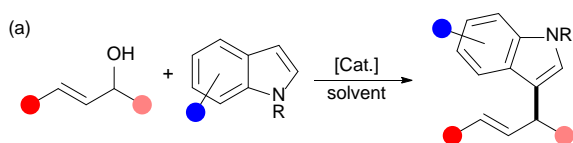
Introduction

The synthesis and functionalization of heterocycles has always been one of the main research topics for organic chemists, as these compounds are ubiquitously present in nature. Nitrogen-containing heterocycles are particularly interesting, as they enjoy overwhelmingly superior numbers over other heterocycles among privileged structures for drug design.[1,2] Indole is one of such scaffolds, present in several biologically relevant molecules, such as the amino acid tryptophan, and its derivatives (e.g. tryptamine, serotonin, melatonin).[2] Regarding functionalization strategies, the allylation of indoles at the C3-position via allylic substitution is a relatively well-known process, albeit one that has not been completely optimized in terms of sustainability. Commonly employed starting materials include allyl halides, acetates, phosphates, or carbonates.[3] While more chemically inert due to the poor leaving ability of hydroxyl groups, allylic alcohols only generate water as a by-product, thus being a more environmentally friendly choice for allylic substitution. In addition, most of the formerly mentioned compounds are prepared from allylic alcohols so their direct use is desirable to avoid

unnecessary reaction steps.[3,4] Over the years, several methodologies have been developed for the allylation of indoles with allylic alcohols (Scheme 1a). Most approaches described in the literature employ metals to promote the reaction, including the Pd-catalysed Tsuji-Trost reaction,[4-7] or salts and complexes of several transition metals (such as gold,[8-10] aluminium,[11] zinc,[12,13] iron,[14-16] ytterbium,[17] ruthenium,[18] iridium,[19] molybdenum,[20] and indium[19,21-23]), and supported catalysts based on copper nanoparticles,[24] or phosphomolybdic acids.[25] Metal-free alternatives have also been reported, employing a variety of Brønsted acidic catalysts, mostly including sulfonic acids[14,26-33] or fluorinated alcohols;[34] although the use of other catalytic systems, such as iodine[35] or frustrated Lewis pairs[36] have been described. A catalyst-free protocol has been explored, employing pressurized high-temperature water.[37]

While these protocols allow for the easy obtention of 3-allylindoles from allylic alcohols, they all suffer from drawbacks; the use of metal catalysts is not desirable from an environmental standpoint, as they tend to be less biodegradable and more expensive, and there are concerns about their toxicity. On the other hand, most of the described metal-free protocols employ sulfonic acids as catalysts, which are extremely acidic, leading to safety concerns and potential issues with sensitive moieties. Fluorinated alcohols (such as hexafluoroisopropanol, HFIP) are not ideal either, as they are corrosive and highly volatile.[38] In addition, most of the reported protocols employ solvents, which can lead to pollution and generate large amounts of waste per mole of the product obtained. Therefore, the development of more sustainable and cost-effective heterocycle functionalization procedures is of paramount importance.

Herein, we demonstrate the potential of employing a simple catalyst to perform a relevant organic transformation (i.e. allylation of indoles) with high atomic economy (only one equivalent of water as by-product), in the absence of solvent (Scheme 1a). In addition, the catalyst is robust, allowing the transformation to be expanded to a wide variety of N-heterocycles (Scheme 1b). The design of the catalytic system facilitates the reaction of the starting materials by forming interactions with the reactants.[39] The 1,3-bis(carboxymethyl)imidazolium chloride (**bcmimCl**), an ionic organic solid (IOS) derived from glycine, plays a key role in the

solvent-free protocol, and allows the possibility of product isolation by simple filtration, which further adds to the already reduced environmental impact of this methodology. Furthermore, we have demonstrated by Differential Scanning Calorimetry (DSC) studies that our IOS is capable of close interaction with the hydroxyl group in the allylic alcohol, providing effective and reliable activation of said moiety.[40] In fact, the possibility to act as hydrogen bond acceptor (HBA) is a remarkable feature of the carboxy-imidazolium halides, leading to the formation of low transition temperature mixtures (LTTMs) in the presence of suitable hydrogen bond donor (HBD) compounds.[41] In our case, this deep eutectic solvent (DES) like interaction provides the environment to carry out the reaction in the absence of any other solvent.[42]
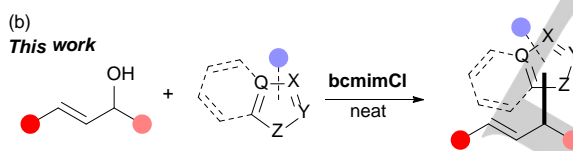

Figure 1. Differential Scanning Calorimetry (DSC) plot: indole (blue-dash line) and mixture of indole and **bcmimCl** (10 mol%) (black line).

The allylation of 1*H*-indole (**1a**) with (*E*)-1,3-diphenylprop-2-en-1-ol (**2a**) under aerobic neat conditions was selected as model reaction. To keep the experimental conditions as simple as possible, avoiding excess of reagents and any solvent, equimolar amounts of both starting materials (i.e., indole **1a** and alcohol **2a**) and 10 mol% of **bcmimCl** were mixed and analysed by DSC (ramp of 5 °C/min). According to the heat released during the reaction (Figure 2), it can be postulated that the reaction can be performed below 100 °C. Thus, the reaction was set up at 80 °C, observing full conversion after 2 hours. Gladly, the expected product **3** was obtained pure after simple filtration to remove the catalyst, using a small amount of ethyl acetate, a green solvent[43,44] (Scheme 2).

Scheme 1. (a) Previously reported protocols and methodology presented in this work. (b) Allylation of other N-heterocycles by the same protocol.

Figure 2. Differential Scanning Calorimetry (DSC) plot of the reaction mixture: indole (**1a**), alcohol **2a** and **bcmimCl** (10 mol%).

Results and Discussion

The choice of the catalyst for this transformation was determined by several factors. First, **bcmimCl** is a solid with negligible solubility in organic solvents, which greatly facilitates its manipulation, recovery, and reuse. In addition, **bcmimCl** is synthesized from cheap, not environmentally damaging, and readily available materials in two simple and high-yielding steps and without the need of purification.[39] As commented above, **bcmimCl** is able to set up DES-type interactions with different substrates, promoting reactivity. Thus, it was measured the heat flow by DSC of an indole sample in the presence of certain amount (10 mol%) of **bcmimCl** to detect possible interactions. This experiment did not show significant difference in terms of melting temperature (onset lowering from 49.6 °C to 47.8 °C), but the thermal event requires substantially less energy (Figure 1), being a prove of the interactions between both components.
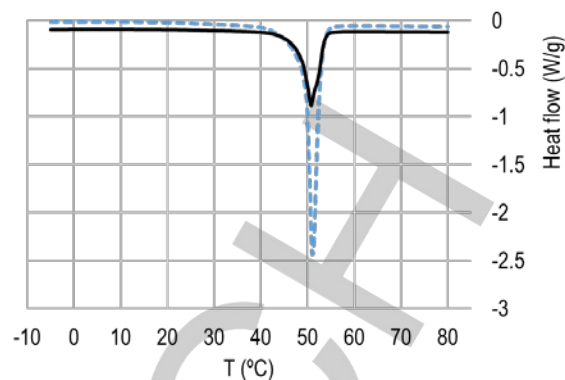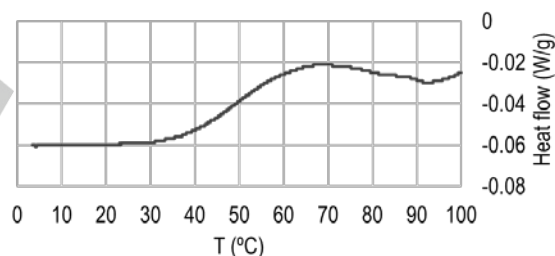
To find the scope of the allylation reaction employing this protocol, several indoles were evaluated (Scheme 2). In general, the reaction proceeded smoothly, obtaining the corresponding 3-allylindoles in good to quantitative yields in relatively short reaction times (2-6 h). The methodology tolerates substitution in the pyrrolic ring of the indole (Scheme 2, compounds **4-6**), with even the sterically challenged 2-phenylindole affording product **6** in 60% yield (Scheme 2). Derivatives of 2-phenylindole are of particular interest, as this scaffold is present in several biologically significant molecules, which further cements the relevance of the procedure described.[2] Next, a variety of indoles bearing substitution on the benzo-condensed ring were submitted to the allylation reaction with alcohol **2a**, providing the expected 3-allylindoles (**7-13**) in almost quantitative yield independently of the electronic properties of the substituent. The position of the substituent seems to influence the rate of the reaction due to steric hindrance since a bromo substituent in the 4-position required a longer reaction time to produce **13**,

although it was isolated in quantitative yield (Scheme 2). Notably, this solventless methodology mediated by **bcmimCl** tolerates

sensitive groups, as evidenced by compound **10** which was obtained in quantitative yield.
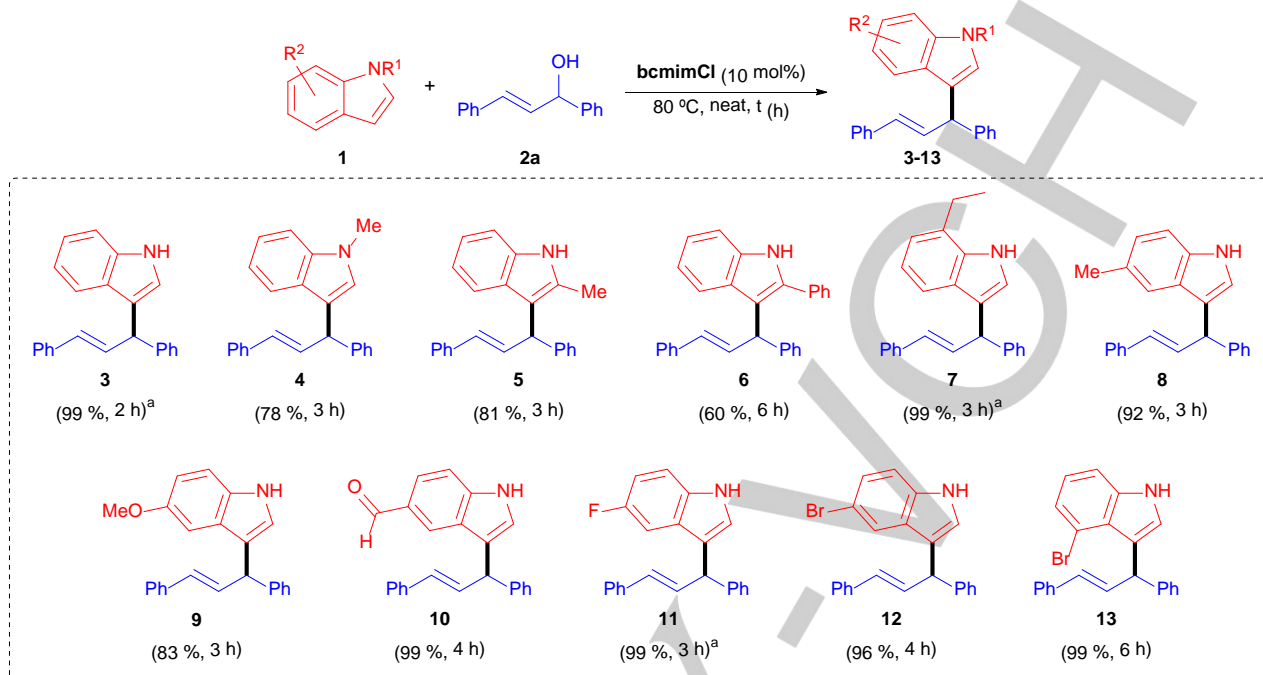
Scheme 2. Evaluation of indoles for the formation of 3-allylindoles using **bcmimCl** as catalyst. Reaction conditions: indole **1** (0.5 mmol), alcohol **2a** (0.5 mmol), **bcmimCl** (10 mol%), 80 ºC, t (h). In brackets: isolated yield of pure product after filtration or column chromatography, and reaction time. [a] Obtained pure after filtration.

To further study the versatility of this protocol, the reaction was carried out with other allylic alcohols, forming the products with good to quantitative yields (Table 1). (*E*)-1,3-Bis(4-chlorophenyl)prop-2-en-1-ol (**2b**) was reacted with indole giving compound **14** in 95% yield by simple filtration (Table 1, entry 1). The reaction of indole with non-symmetrically substituted allylic alcohols, such as (*E*)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-ol (**2c**), (*E*)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-ol (**2d**), (*E*)-1-(4-chlorophenyl)-3-phenylprop-2-en-1-ol (**2e**) and (*E*)-4-phenylbut-3-en-2-ol (**2f**), produced a mixture of regioisomers in about 1:1 ratio (Table 1, entries 2-5). The reactions with 1,3-diaryl substituted allylic alcohols were quantitative regardless of the nature of the substituent, albeit a substrate with an electron-donating group required a slightly longer reaction time (Table 1, compare entry 2 with entries 3 and 4). Moreover, alcohol **2d** and its isomer **2e** gave the mixture of isomers **16a** and **16b** in the same ratio, confirming that the reaction takes place via the formation of an allylic carbocation.[45] The methodology also works with non-diaryl allylic alcohols, such as **2f** (Table 1, entry 5). This alcohol was reacted with indole giving the mixture (ca. 1:1) of regioisomers **17a** and **17b**, which could be separated by column chromatography.

After exploring the scope of the allylation of indoles, the model reaction between **1a** and **2a** was scaled up (5 mmol) to prove the applicability of the methodology. The expected compound **3** was exclusively obtained in 99% yield (1.54 g) from the reaction after removing the catalyst by filtration using ethyl acetate (Scheme 3). Due to the ease of operation and high performance of the protocol, even on a larger scale, we postulate that the efficiency of its environmental impact should be excellent. In this

sense, the EcoScale is a semiquantitative scale which considers the yield, cost of the materials, safety reaction conditions, and ease of work-up/purification to evaluate an organic synthesis, with a maximum value of 100 points.[46] The evaluation of the protocol described with the EcoScale classifies it as an excellent synthesis, obtaining a score of 87 (Table 2). To further study this aspect, different metrics, such as atom economy (AE), stoichiometric factor (SF), reaction mass efficiency (RME), materials recovery parameter (MRP), reaction yield (RY), and environmental factor profile (E-factor referring to kernel, excess, solvent, catalyst, work-up, and purification), have been analysed (Table 2).[47] The E-factor of the whole process is 6.0, which is close to the values for Bulk Chemical production in the industry.[48] The detailed analysis of the environmental factor profile shows that the main source of waste in this process comes from the purification step (Table 2), i.e. the ethyl acetate used to obtain the final product and separate it from the catalyst. Apart from the quantitative yield (>99%), the reaction has excellent values for other parameters, such as AE (95%), the SF (1), and the RME (60%). Besides, after the reaction in gram scale, the catalyst was recovered by filtration (almost completely), and the ethyl acetate employed was recovered by distillation (90% of the solvent mass). Thus, the reaction presents a 64% of MRP (Table 2). The radial-pentagon diagram with these material efficiency parameters (RY, AE, 1/SF, MRP, and RME) gives a visual evaluation of the protocol for one-step synthesis (Figure 3). In addition, the overall material efficiency determined by these five parameters (i.e., RY, AE, 1/SF, RME, and MRP), which measure the greenness condition (ranging 0-1), can be combined in a vector magnitude ratio (VMR) to

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provide unbiased quantification of the overall degree of greenness. The vector magnitude ratio (VMR) is calculated according to the Equation 1,[47] and it has a value of 0.853 for the preparation of compound **3** by means of the **bcmimCl**-catalysed reaction (Figure 4). In summary, the VMR and EcoScale values

are sufficiently high to consider, as assumed, that this protocol is excellent from an environmental point of view. However, it is important to compare with other methodologies described to get a better picture of the results.

Table 1. Scope of the reaction: allylic alcohols.[a]

Entry	Allylic alcohol	Product	t (h)	Yield (%)
1	**2b** R¹ = 4-ClC₆H₄ R² = 4-ClC₆H₄		2	95[b]
2	**2c** R¹ = Ph R² = 4-ClC₆H₄		2	99[b,c] [49:51]
3	**2d** R¹ = Ph R² = 4-(MeO)C₆H₄		3	99[b,c] [52:48]
4	**2e** R¹ = 4-(MeO)C₆H₄ R² = Ph	**16a / 16b**	3	99[b,c] [51:49]
5	**2f** R¹ = Me R² = Ph		4	26 / 39[d] [53:47][e]

[a] Reaction conditions: indole **1a** (0.5 mmol), alcohol **2** (0.5 mmol), **bcmimCl** (10 mol%), 80 °C, t (h). [b] Obtained pure after filtration. [c] Inseparable mixture of compounds; ratio [in square brackets] determined by NMR or GC-MS of the reaction mixture. [d] Isolated yields of each isomer (**17a** and **17b**) after column chromatography. [e] Ratio of the isomers in the reaction mixture.

First, two previously reported protocols, which employ metal catalysts, have been considered. The protocol employing iron(III)-based catalyst[15] in water has lower metric parameters, except for the AE, than our methodology (Figure 3a), due to the use of an excess of indole, the use of solvent (water), and the purification process. The zinc(II)-catalysed[13] protocol has similar values of RY, AE and 1/SF, since the reaction is performed without solvent and with equimolar amounts of reagents, but the purification process results in worse values for

other parameters (Figure 3a). For the latter protocol, a high-speed vibration mill was employed, which restricted the scale of the reaction (0.1 mmol). The comparison of VMR and EcoScale values show that **bcmimCl**-catalysed reaction is significantly better than other metal-catalysed ones (Figure 4). Next, two non-metal catalysed methodologies have been considered: *p*-toluenesulfonic acid (PTSA) catalysed allylation in dichloromethane (DCM),[27] and the use of hexafluoroisopropanol (HFIP) as catalyst and reaction

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medium.[34] These protocols were found to have worse greenness metrics than the methodology reported in this work (Figures 3b and 4). In overall, the scores for VMR and EcoScale are 11-14% lower (Figure 4), although, some material efficiency parameters (such as AE, RY and SF) are as high as the observed for **bcmimCl**-catalysis (Figure 3b). Finally, it is noteworthy that any of the catalytic processes considered in this comparison generates more waste, with environmental factors between 16 and 27 times higher (Figure 5). The waste, in these cases, comes from the use of a solvent, an excess of a reagent, and a work-up and/or a purification step.
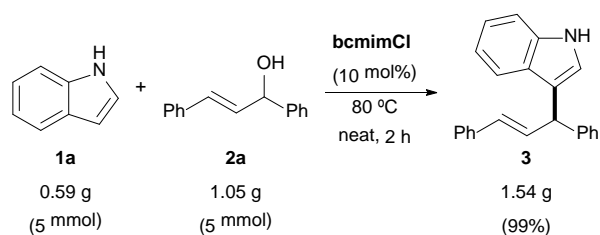
Scheme 3. Reaction between **1a** and **2a** in preparative scale.

$$VMR = \frac{1}{\sqrt{5}} \left[\sqrt{(RY)^2 + (AE)^2 + \left(\frac{1}{SF}\right)^2 + (MRP)^2 + (RME)^2} \right]$$

Equation 1. Vector magnitude ratio based on five parameters: reaction yield (RY), atom economy (AE), stoichiometric factor (SF), materials recovery parameter (MRP), and reaction mass efficiency (RME).

Table 2. Green metrics for the allylation reaction of indole catalysed by **bcmimCl**.

Parameter		Value	(%)[a,b]
EcoScale		87	87
Reaction yield (RY)		0.988	99
Atom economy (AE)		0.945	95
Stoichiometric factor (SF)		1.001	
1/SF		0.999	100
Reaction mass efficiency (RME)		0.599	60
Materials recovery parameter (MRP)		0.642	64
E-factor	Total	6.0	
	Kernel	0.071	
	Excess	0.0	
	Catalyst	0.071	
	Solvent	0.0	
	Work-up	0.0	
	Purification	5.86	

[a] Some parameters can be expressed as a percentage (%). [b] The value has been rounded off to the nearest whole number value.
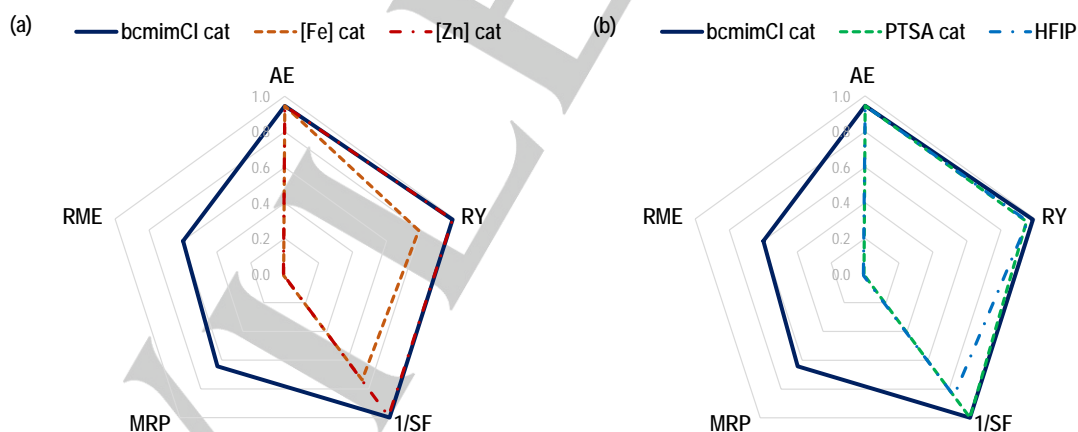

Figure 3. Radial-pentagon diagram of metrics: reaction yield (RY), atom economy (AE), inverse of stoichiometric factor (1/SF), material recovery parameter (MRP), and reaction mass efficiency (RME). Comparison for the preparation of compound **3** of the protocol in this work (**bcmimCl** cat) with (a) metal catalysed methodologies [iron(III) (ref. 15), zinc(II) (ref. 13)], and (b) non-metal catalysed methodologies [PTSA (ref. 27), HFIP (ref. 34)].

As commented before, the catalyst is easily separated from the reaction mixture due to its insolubility in organic solvents, so its reuse was considered. After running the model reaction, the resulting mixture was dissolved in ethyl acetate, which was

decanted off, and the catalyst was washed to be reused in a new reaction. As depicted in Figure 6, the catalyst was employed in five consecutive cycles giving full conversion to the

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expected product. The absence of activity loss demonstrates the robustness of the catalyst in the allylation of indoles.
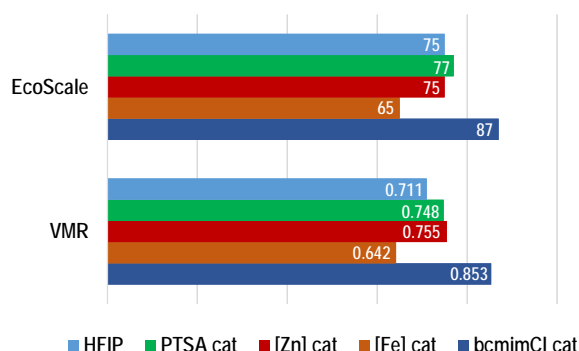

Figure 4. Values of EcoScale score, and of vector magnitude ratio (VRM). Comparison for the preparation of compound **3** of the protocol in this work (**bcmimCl** cat) with metal catalysed methodologies [iron(III) (ref. 15), zinc(II) (ref. 13)], and non-metal catalysed methodologies [PTSA (ref. 27), HFIP (ref. 34)].
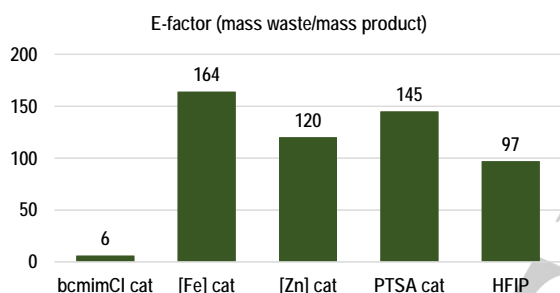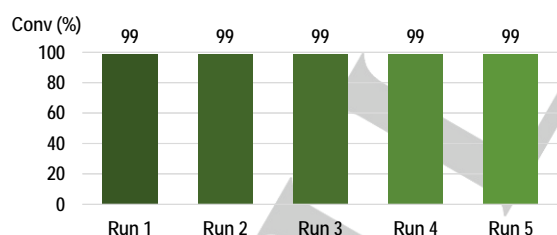

Figure 5. Values of E-factor (total) [mass units of waste per mass unit of product]. Comparison for the preparation of compound **3** of the protocol in this work (**bcmimCl** cat) with metal catalysed methodologies [iron(III) (ref. 15), zinc(II) (ref. 13)], and non-metal catalysed methodologies [PTSA (ref. 27), HFIP (ref. 34)].

Figure 6. Recycling of the catalyst.

Encouraged by the excellent results obtained and considering the simplicity, effectiveness, and low environmental impact of the methodology, it was considered to expand the scope of the allylation reaction beyond indoles. Thus, an equimolar mixture of (*E*)-1,3-diphenylprop-2-en-1-ol (**2a**) and a variety of nitrogen containing heterocycles, such as pyrazoles, triazoles, tetrazoles, benzopyrazole, benzotriazole, and carbazole, was heated in the presence of **bcmimCl** (Scheme 4). Delightfully, the methodology proved to be perfectly suitable for the allylation of heterocycles, obtaining selectively the N-allyl-substituted heterocycles in moderate to quantitative yields, not requiring any additional purification in many cases (Scheme 4). Pyrazoles gave

quantitative conversions, such as compounds **18** and **20** (Scheme 4), which can be separated from the reaction mixture by simple filtration. 3(5)-Methylpyrazole reacted also efficiently giving full conversion, although as a mixture of the two regioisomers **19a** and **19b** in 2:1 ratio. The mixture could be separated, isolating **19a** with 54% yield and **19b** with 22% yield (Scheme 4). The methyl substituent in 3(5)-position does not have a great influence on the tautomer equilibrium of the starting 3(5)-methylpyrazole (ca. 1:1 isomers mixture),[49,50] but it seems to influence in the environment in which the substitution occurs.[50,51] The presence of **bcmimCl** without any solvent may facilitate the proton (H-N) abstraction promoting the nucleophilic addition of pyrazole to the incipient allylic carbocation, wherein steric constraints imposed by the substituent is the factor favouring the regioselectivity to **19a**. This is in concordance with the fact that 3,5-dimethylpyrazole needed a longer reaction time (6 h) to quantitatively yield compound **20** (Scheme 4). The use of 1,2,4-triazole produced compound **21**, which was isolated by filtration with 99% yield, with the allylation occurring exclusively in the N1-position (Scheme 4).[52] Tetrazole and 5-phenyltetrazole were reacted successfully with alcohol **2a** to get full conversion towards the mixture of isomers **22** and compound **23** respectively (Scheme 4). Interestingly, compound **23** was isolated as the exclusive regioisomer after filtration of the reaction mixture. On the contrary tetrazole gave both regioisomers (ca. 1:1 ratio), which were successfully separated (isomer **22a**, 41% yield, and isomer **22b**, 36% yield). The formation of hydrogen bonds and ionic pairs between the reagents and the catalyst (**bcmimCl**) can be postulated, highlighting the steric hindrance of the C5-substituent.[53,54] Carbazole was also found to be compatible with the protocol, affording the expected compound **24** (62% yield, Scheme 4). Finally, benzo-fused nitrogen-containing heterocycles, such as indazole and benzotriazole, were tested. Alkylation of the indazole and benzotriazole results in the formation of a mixture of the two regioisomers with selectivity influenced by the reaction conditions.[55-57] The reaction mediated with **bcmimCl** gave full conversion in the allylation of both heterocyclic systems, forming the two regioisomers with preference to the thermodynamic isomer (Scheme 4). Interestingly, in both cases the different isomers were isolated. From indazole, compounds **25a** and **25b** were obtained in a 3:2 ratio, being isolated with 60% and 38% yield respectively (Scheme 4). From benzotriazole, higher regioselectivity was observed (ca. 9:1 ratio) favouring the 1-substituted isomer; and compound **26a** was isolated with 85% yield and compound **26b** with 10% yield (Scheme 4).

Conclusion

The vector of improvement of organic synthetic processes must seek advances that make these more effective, efficient, and in better concordance with the environment. In this way, the synthetic procedure presented has high atom economy (AE), since only water is formed as waste during the reaction, combined with high reaction yield (RY, quantitative in most of the cases). Reactants (allylic alcohols and nitrogen-containing heterocycles), which are nonharmful substances, have been employed in stoichiometric amounts, conducting the reaction without the need of any derivatization or auxiliary under solvent-

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free conditions. Only ethyl acetate, a recommended solvent,[58] has been employed to separate the catalyst from the reaction mixture. The catalyst is based on carboxy-functionalized imidazole derivative, being its structural motifs essential to mediate favourable interactions of the reactants. This has

allowed the reaction to proceed under mild conditions (80 °C, open atmosphere). Moreover, the catalyst, which is effectively prepared in a straightforward manner, and from renewable sources, can be recycled.
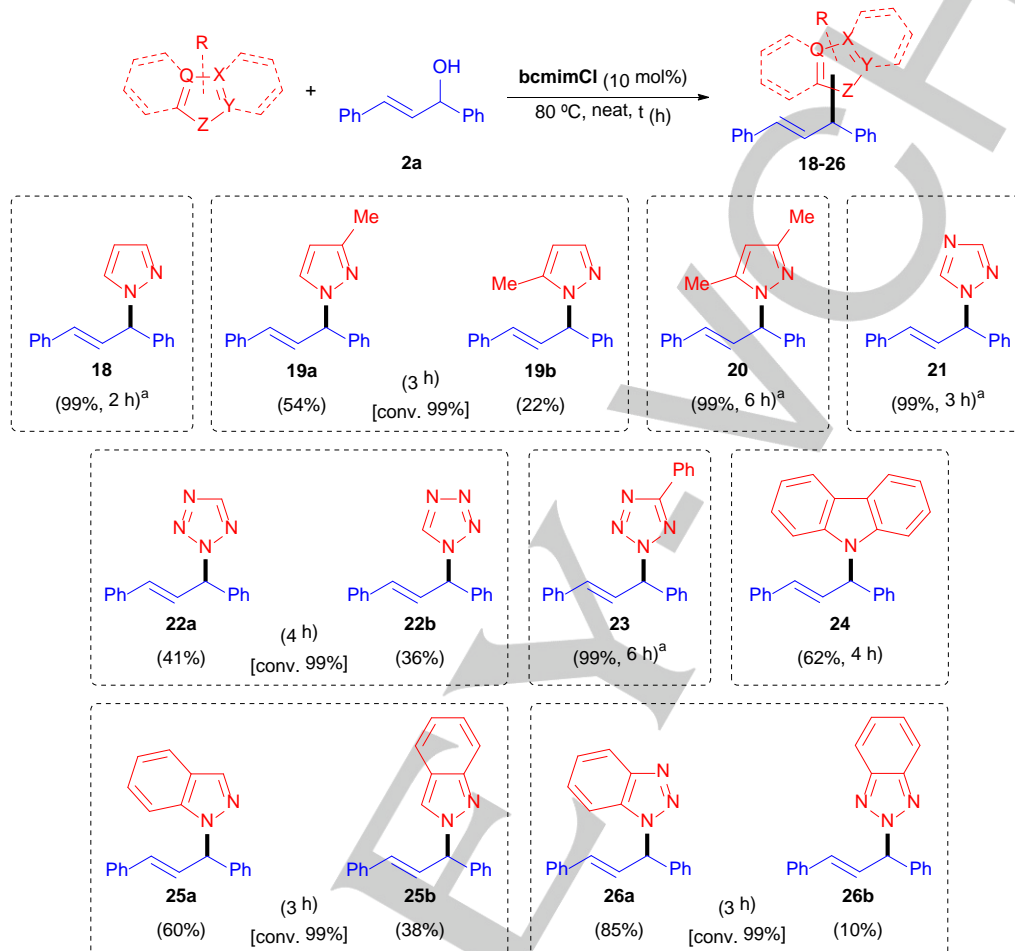
Scheme 4. Evaluation of the allylation reaction of nitrogen containing heterocycles using **bcmimCl** as catalyst. Reaction conditions: nitrogen-heterocycle (0.5 mmol), alcohol **2a** (0.5 mmol), **bcmimCl** (10 mol%), 80 °C, t (h). In brackets: isolated yield of pure product. [a] Obtained pure product by simple filtration.

To summarise, a metal-free, robust, simple, and efficient catalytic protocol has allowed the preparation of allyl-functionalized nitrogen-containing heterocycles (i.e. indoles, pyrazoles, 1,2,4-triazole, tetrazoles, carbazole, indazole, and benzotriazole), which are of interest due to its potential bioactivity. For the model reaction, it has been proved the possibility of carrying out the reaction in preparative scale (gram scale). Based on different metrics (AE, RY, SF, MRP, RME, EcoScale, VMR, and E-factor), it has been demonstrated that the **bcmimCl**-protocol is above other previously reported methodologies, both metal- and non-metal catalysed. The model reaction has an E-factor (total) of 6.0, mainly due to the solvent employed to separate the catalyst, with an E-factor (kernel) of 0.07. Moreover, the EcoScale and VMR (based on AE, RY, 1/SF, MRP, and RME) have been used for the unbiased comparison of the overall greenness against representative reported methodologies, with the **bcmimCl**-protocol providing significantly better results.

Experimental Section

General remarks. Full general statements were described elsewhere.[41]

Procedure for the multigram synthesis of 1,3-bis(carboxymethyl)imidazolium chloride (bcmimCl). In a round bottom flask, glyoxal (40% w/w in water, 5.7 mL, 50 mmol), formaldehyde (37% w/w in water, 3.7 mL, 50 mmol) and glycine (7.5 g, 100 mmol) were added. The mixture was stirred at 95 °C for 2 h, after which it was allowed to cool down back to room temperature, causing a crystalline precipitate to appear. After vacuum filtering and washing with cold water (10 mL) and diethyl ether (2x10 mL), the resulting brownish crystalline solid was added into another round bottom flask along with hydrochloric acid (37%, 9 mL, 110 mmol). The mixture was refluxed for 30 minutes, then allowed to cool down to room temperature. After vacuum filtering and washing with acetone (10 mL) and diethyl ether (10 mL), 8.9 g of pure **bcmimCl** were obtained (81% yield).

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General procedure for the allylation of heterocycles. In a round bottom flask, precisely weighed allyl alcohol (1 eq.), heterocycle (1 eq.) and **bcmimCl** (10 mol%) were added. The mixture was stirred at 80 ºC for an adequate amount of time. After completion (monitored by TLC or GC-MS), the reaction mixture was diluted with ethyl acetate and filtered to remove the catalyst. Then, the solvent was removed under reduced pressure to afford the corresponding allyl heterocycle, which was purified by column chromatography/preparative TLC when required.

Procedure for the gram scale synthesis of 1. In round bottom flask, (*E*)-1,3-diphenyl-2-propen-1-ol (1.05 g, 5 mmol), indole (0.59 g, 5 mmol) and **bcmimCl** (110 mg, 10 mol%) were added. The mixture was stirred at 80 ºC for 2 h, after which the reaction mixture was diluted with ethyl acetate (5 mL) and filtered to remove the catalyst, eluting with an additional 5 mL of ethyl acetate The solvent was then removed under reduced pressure, affording 1.53 g of pure compound **1** (99% yield).

Procedure for the recycling of bcmimCl. In a round bottom flask, (*E*)-1,3-diphenyl-2-propen-1-ol (53 mg, 0.25 mmol), indole (29 mg, 0.25 mmol) and **bcmimCl** (5.5 mg, 10 mol%) were added. The mixture was stirred at 80 ºC for 2 h, after which it was diluted with ethyl acetate (2 mL). The organic phase was decanted off and the catalyst was washed with ethyl acetate (2x2 mL). After vacuum drying the catalyst, fresh reagents were added for the next cycle.

Acknowledgements

Keywords: Allylation • Catalysis • DES-type interaction • Nitrogen heterocycles • Sustainable chemistry
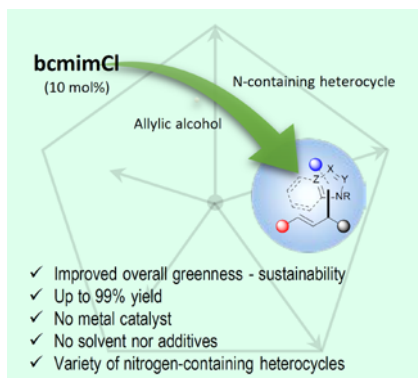
[1] M. E. Welsch, S. A. Snyder, B. R. Stockwell, *Curr. Opin. Chem. Biol.* **2010**, *14*, 347–361.

[2] N. K. Kaushik, N. Kaushik, P. Attri, N. Kumar, C. H. Kim, A. K. Verma, E. H. Choi, *Molecules* **2013**, *18*, 6620–6662.

[3] A. Baeza, C. Nájera, *Synthesis* **2014**, *46*, 25–34.

[4] S. Akkarasamiyo, S. Sawadjoon, A. Orthaber, J. S. M. Samec, *Chem. Eur. J.* **2018**, *24*, 3488–3498.

[5] C. C. Roberts, D. M. Matías, M. J. Goldfogel, S. J. Meek, *J. Am. Chem. Soc.* **2015**, *137*, 6488–6491.

[6] C. Xu, V. K. Murugan, S. A. Pullarkat, *Org. Biomol. Chem.* **2012**, *10*, 3875–3881.

[7] D. Das, S. Pratihar, U. K. Roy, D. Mal, S. Roy, *Org. Biomol. Chem.* **2012**, *10*, 4537–4542.

[8] W. Rao, P. W. H. Chan, *Org. Biomol. Chem.* **2008**, *6*, 2426–2433.

[9] K. Huang, H. Wang, L. Liu, W. Chang, J. Li, *Chem. Eur. J.* **2016**, *22*, 6458–6465.

[10] Y. Lu, X. Du, X. Jia, Y. Liu, *Adv. Synth. Catal.* **2009**, *351*, 1517–1522.

[11] A. Cullen, A. J. Muller, D. B. G. Williams, *RSC Adv.* **2017**, *7*, 42168–42171.

[12] G. Bertuzzi, L. Lenti, D. Giorgiana Bisag, M. Fochi, M. Petrini, L. Bernardi, *Adv. Synth. Catal.* **2018**, *360*, 1296–1302.

[13] G.-P. Fan, Z. Liu, G.-W. Wang, *Green Chem.* **2013**, *15*, 1659–1664.

[14] P. Trillo, A. Baeza, C. Nájera, *Eur. J. Org. Chem.* **2012**, *2012*, 2929–2934.

[15] P. Trillo, A. Baeza, C. Nájera, *ChemCatChem* **2013**, *5*, 1538–1542.

[16] U. Jana, S. Maiti, S. Biswas, *Tetrahedron Lett.* **2007**, *48*, 7160–7163.

[17] W. Huang, Q.-S. Shen, J.-L. Wang, X.-G. Zhou, *Chin. J. Chem.* **2008**, *26*, 729–735.

[18] S. Gruber, A. B. Zaitsev, M. Wörle, P. S. Pregosin, L. F. Veiros, *Organometallics* **2008**, *27*, 3796–3805.

[19] P. N. Chatterjee, S. Roy, *Tetrahedron* **2012**, *68*, 3776–3785.

[20] H. Yang, L. Fang, M. Zhang, C. Zhu, *Eur. J. Org. Chem.* **2009**, *2009*, 666–672.

[21] M. Yasuda, T. Somyo, A. Baba, *Angew. Chem. Int. Ed.* **2006**, *45*, 793–796.

[22] J. S. Yadav, B. V. S. Reddy, S. Aravind, G. G. K. S. N. Kumar, A. S. Reddy, *Tetrahedron Lett.* **2007**, *48*, 6117–6120.

[23] J. S. Yadav, B. V. S. Reddy, K. V. R. Rao, G. G. K. S. N. Kumar, *Synthesis* **2007**, 3205–3210.

[24] S. Mallick, P. Mukhi, P. Kumari, K. R. Mahato, S. K. Verma, D. Das, *Catal. Lett.* **2019**, *149*, 3501–3507.

[25] J. S. Yadav, B. V. S. Reddy, A. S. Reddy, *J. Mol. Catal. A Chem.* **2008**, *280*, 219–223.

[26] S. Shirakawa, S. Kobayashi, *Org. Lett.* **2007**, *9*, 311–314.

[27] J. Le Bras, J. Muzart, *Tetrahedron* **2007**, *63*, 7942–7948.

[28] S. Sayin, M. Yilmaz, *Tetrahedron* **2014**, *70*, 6669–6676.

[29] Y.-L. Liu, L. Liu, Y.-L. Wang, Y.-C. Han, D. Wang, Y.-J. Chen, *Green Chem.* **2008**, *10*, 635–640.

[30] S. Sayin, M. Yilmaz, *Tetrahedron* **2016**, *72*, 6528–6535.

[31] R. Sanz, A. Martínez, D. Miguel, J. M. Álvarez-Gutiérrez, F. Rodríguez, *Adv. Synth. Catal.* **2006**, *348*, 1841–1845.

[32] A. Suárez, M. Gohain, M. A. Fernández-Rodríguez, R. Sanz, *J. Org. Chem.* **2015**, *80*, 10421–10430.

[33] S. Shirakawa, S. Shimizu, *Synlett* **2008**, 1539–1542.

[34] P. Trillo, A. Baeza, C. Nájera, *J. Org. Chem.* **2012**, *77*, 7344–7354.

[35] Z. Liu, L. Liu, Z. Shafiq, Y.-C. Wu, D. Wang, Y.-J. Chen, *Tetrahedron Lett.* **2007**, *48*, 3963–3967.

[36] H. Zhang, X.-Y. Zhan, Y. Dong, J. Yang, S. He, Z.-C. Shi, X.-M. Zhang, J.-Y. Wang, *RSC Adv.* **2020**, *10*, 16942–16948.

[37] T. Hirashita, S. Kuwahara, S. Okochi, M. Tsuji, S. Araki, *Tetrahedron Lett.* **2010**, *51*, 1847–1851.

[38] O. Hartman, C. Zhang, E. L. Adams, M. C. Farach-Carson, N. J. Petrelli, B. D. Chase, J. F. Rabolt, *Biomaterials* **2010**, *31*, 5700–5718.

[39] M. Albert-Soriano, L. Hernández-Martínez, I. M. Pastor, *ACS Sustain. Chem. Eng.* **2018**, *6*, 14063–14070.

[40] M. Albert-Soriano, I. M. Pastor, *Adv. Synth. Catal.* **2020**, *362*, 2494–2502.

[41] M. Martos, I. M. Pastor, *J. Mol. Liq.* **2022**, *347*, 118349.

[42] D. A. Alonso, A. Baeza, R. Chinchilla, G. Guillena, I. M. Pastor, D. J. Ramón, *Eur. J. Org. Chem.* **2016**, *2016*, 612–632.

[43] P. G. Jessop, *Green Chem.* **2011**, *13*, 1391–1398.

[44] D. Prat, J. Hayler, A. Wells, *Green Chem.* **2014**, *16*, 4546–4551.

[45] P. Trillo, I. M. Pastor, *Adv. Synth. Catal.* **2016**, *358*, 2929–2939.

[46] K. Van Aken, L. Strekowski, L. Patiny, *Beilstein J. Org. Chem.* **2006**, *2*, 3.

[47] J. Andraos, *Reaction Green Metrics-Problems, Exercises, and Solutions*, CRC Press (Taylor & Francis Group), Boca Raton (FL, USA), **2019**.

[48] R. A. Sheldon, *Chem. Soc. Rev.* **2012**, *41*, 1437–1451.

[49] J. Catalán, M. Sánchez-Cabezudo, J. L. G. De Paz, J. Elguero, R. W. Taft, F. Anvia, *J. Comput. Chem.* **1989**, *10*, 426–433.

[50] A. Secrieru, P. M. O'Neill, M. L. Cristiano, *Molecules* **2020**, *25*, 42.

[51] H. Zhuang, N. Lu, N. Ji, F. Han, C. Miao, *Adv. Synth. Catal.* **2021**, *363*, 5461–5472.

[52] C. Ainsworth, R. G. Jones, *J. Am. Chem. Soc.* **1955**, *77*, 621–624.

[53] J. Roh, K. Vávrová, A. Hrabálek, *Eur. J. Org. Chem.* **2012**, *2012*, 6101–6118.

[54] S. A. Egorov, M. A. Ishchenko, Y. V. Prokopovich, V. I. Ivanova, *Russ. J. Org. Chem.* **2020**, *56*, 1196–1203.

[55] K. W. Hunt, D. A. Moreno, N. Suiter, C. T. Clark, G. Kim, *Org. Lett.* **2009**, *11*, 5054–5057.

[56] M.-H. Lin, H.-J. Liu, W.-C. Lin, C.-K. Kuo, T.-H. Chuang, *Org. Biomol. Chem.* **2015**, *13*, 11376–11381.

[57] A. R. Katritzky, B. Yang, *J. Heterocycl. Chem.* **1996**, *33*, 607–610.

[58]   C. R. McElroy, A. Constantinou, L. C. Jones, L. Summerton, J. H. Clark,
       Green Chem. **2015**, *17*, 3111–3121.

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Entry for the Table of Contents

- ✓ Improved overall greenness - sustainability
- ✓ Up to 99% yield
- ✓ No metal catalyst
- ✓ No solvent nor additives
- ✓ Variety of nitrogen-containing heterocycles

The catalyst [1,3-bis(carboxymethyl)imidazolium chloride] under neat conditions interacts with the reagents in a DES-like manner, providing both substrate activation and reaction media, representing a significant improvement on the way to a lower environmental impact.

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