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Alkylation of amines with allylic alcohols and deep eutectic solvents as metal-free and green promoters†

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A novel approach for the allylic alkylation of anilines, hydrazides, indole derivatives and additional interesting nucleophiles is described, which involves the direct use of a variety of allylic alcohols under very mild conditions, such as room temperature, and the use of sustainable deep eutectic solvents (DESs). The search for the optimum DES to be used in the reaction revealed that a simple mixture of choline chloride (ChCl) and lactic acid provides excellent results for a wide range of substrates with high isolated yields. This methodology represents a significant improvement compared to other procedures described in the literature, for which high temperatures, stronger reaction conditions or metal catalysts are usually required. In some cases, this protocol provides the first examples of trapping allylic carbocations with indole derivatives. In addition, challenging nucleophiles such as amides, carbamates, azides or sulfonamides, among others, have also been successfully used. All these features render this procedure an appealing and green alternative compared to other examples reported in the literature on the alkylation of amines by allylic alcohols. Preliminary mechanistic studies using unsymmetrically substituted alcohols support that the reaction could proceed *via* an S_N1 pathway.

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Introduction

Nitrogen-containing compounds, particularly anilines, indoles, or hydrazides, are important intermediates and building blocks for pharmaceuticals, agrochemicals, polymers, bioactive compounds, and dyes, among others.¹ In addition to their reactivity, the alkylation of amines is a widely used organic reaction that involves an amine and an alkylating reagent with a good leaving group. Hence, some pivotal alkylated amines are also used for drug design in the pharmaceutical industry.²

Although this approach is quite versatile because of the broad scope of alkylating agents, the traditional protocol is not very sustainable, due to the generation of stoichiometric amounts of leaving groups. In contrast, the *N*-alkylation of amines *via* nucleophilic substitution using alcohols is of paramount importance because the only waste generated in the reaction would be a molecule of water. Depending on the cata-

lytic system, the generation of water could also be a problem, but the low price and ease of handling of alcohols used in the alkylation of amines make this approach widely popular in the industry.³ A broad variety of metal catalysts have been extensively explored since the first example of a catalysed alkylation of aniline using an alcohol *via* the so-called “hydrogen borrowing”.⁴ However, this metal-catalysed *N*-alkylation of amines usually requires high temperatures. Consequently, using lower temperatures and developing greener catalytic systems are considered challenges from both an economic and an environmental point of view.⁵

Moreover, the use of allylic alcohols in this procedure is of foremost importance,⁶ since the resulting allyl compounds are also fundamental building blocks and intermediates for the synthesis of some products such as those reported in Fig. 1.

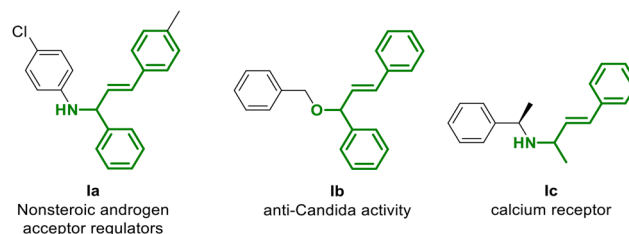


Fig. 1 Allyl derivatives as important building blocks: la,⁷ lb⁸ and lc.⁹

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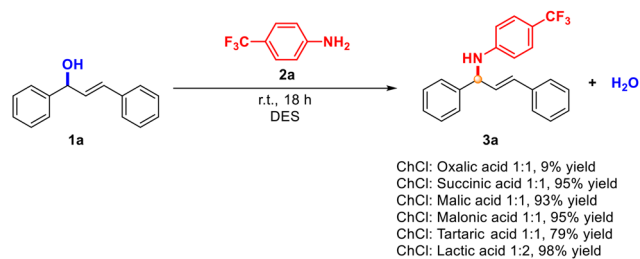
Nowadays, compliance with the principles of green chemistry has become extremely important.¹⁰ Hence, achieving more sustainable processes that are cheaper, produce less waste, and use renewable sources is of great interest to our society. Among the improved processes that employ green solvents or more sustainable conditions, a special mention should be made of the use of ionic liquids (ILs),¹¹ water¹² or solvent-free conditions.¹³ Although these approaches avoid the use of organic solvents, they still require metals or high temperatures.

More recently, deep eutectic solvents (DESs), which are considered a class of ILs, have been proposed as greener alternatives to ILs.¹⁴ DESs are eutectic mixtures of Lewis or Brønsted acids and bases that contain anionic and cationic species.¹⁵ In spite of being considered a new type of IL, sharing many physical properties with them, the composition and application areas of DESs differ significantly. DESs offer several advantages over ILs, including lower cost, biodegradability, ease of preparation, and high atom economy.¹⁶ In addition, DESs have gained tremendous popularity due to their applications in two main research areas as synthetic and catalytic media.¹⁷ These green solvents are obtained from complexation with a hydrogen-bond acceptor (HBA), such as a quaternary salt, and a hydrogen-bond donor (HBD). One of the earliest works in the literature using DESs in the context of enzymatic catalysis was reported by Gill and co-workers in 1994. There, they showed that DESs could provide better reaction media than the conventional organic solvents.¹⁸

To the best of our knowledge, DESs have not been used previously for the *N*-alkylation of amines or their derivatives using allylic alcohols. While only a few examples of allylic amination of alcohols with anilines in the absence of metal systems have been reported,¹⁹ the closest approach for this process is available in the seminal works by Pastor's group.²⁰ In 2018, the authors demonstrated the possibility of achieving a free-metal synthesis of *N*-allylanilines using 1,3-bis(carboxymethyl)imidazolium chloride (bcmim-Cl), an organic salt, as a catalyst. Although this ionic organic solid (IOS) is apparently similar to ionic liquids and despite the advantages of using IOSs in the *N*-alkylation of amines by allylic alcohols, temperatures between 80 °C and 100 °C are required for the success of this process. Hence, in search of an alternative for IOSs, the use of lower temperatures is still interesting from a green and energetic perspective. A pivotal example that also deserves a special mention is the work reported by Alemán's group using photocatalysis to obtain similar compounds.^{21,22}

Results and discussion

Motivated by the necessity of looking for greener conditions to obtain allylamines, in this work, we envisioned the use of an environmentally friendly DES as the medium and as the promoter of the reaction as one of the simplest, greener, and straightforward approaches.²³ First, different DESs were tested as media and as catalysts in the reaction model between (*E*-



Scheme 1 Screening of DESs in the model reaction between alcohol **1a** and aniline **2a**.

1,3-diphenyl-2-propen-1-ol (**1a**) and aniline **2a** in the absence of any additional solvent at room temperature (Scheme 1). Since one of the most frequently used HBA for DESs is (2-hydroxyethyl)trimethylammonium chloride, or choline chloride (ChCl), a member of the vitamin B family, we prepared our medium as a mixture of this component and different hydrogen-bond donors.²⁴

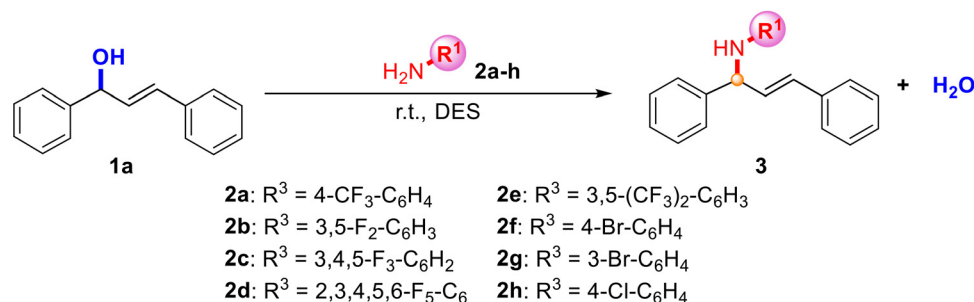
The variety of DESs tested in this reaction were prepared at 60 °C as described in the literature, but then, the medium was cooled down. After the addition of both reagents, the reaction was performed at room temperature for 18 h, to compare the results of the process. We selected these DESs as model media because we hypothesised that the Brønsted acid used, as the HBD component, was also able to promote the formation of the carbocation necessary for the subsequent attack of the aniline. Moreover, we analysed these HBDs to evaluate the possible effect of the high viscosity at room temperature of all these media. This is a crucial effect that must still be considered since the resulting mixture can be difficult to handle when employed.²⁵

Remarkably, in almost all cases, we obtained excellent and almost quantitative yields. It is worth noting that the aniline used is expected to be less nucleophilic than other anilines with electron-donating groups. Even though similar results were achieved in some cases, we proceeded to the next step with the DES formed by ChCl:lactic acid, since the crude product of the reaction was cleaner, and it was easier to work with this medium (for more information about the formation of the DES, see the experimental part). Finally, we also tested the impact of temperature, concluding that room temperature was more appropriate from a sustainable point of view.

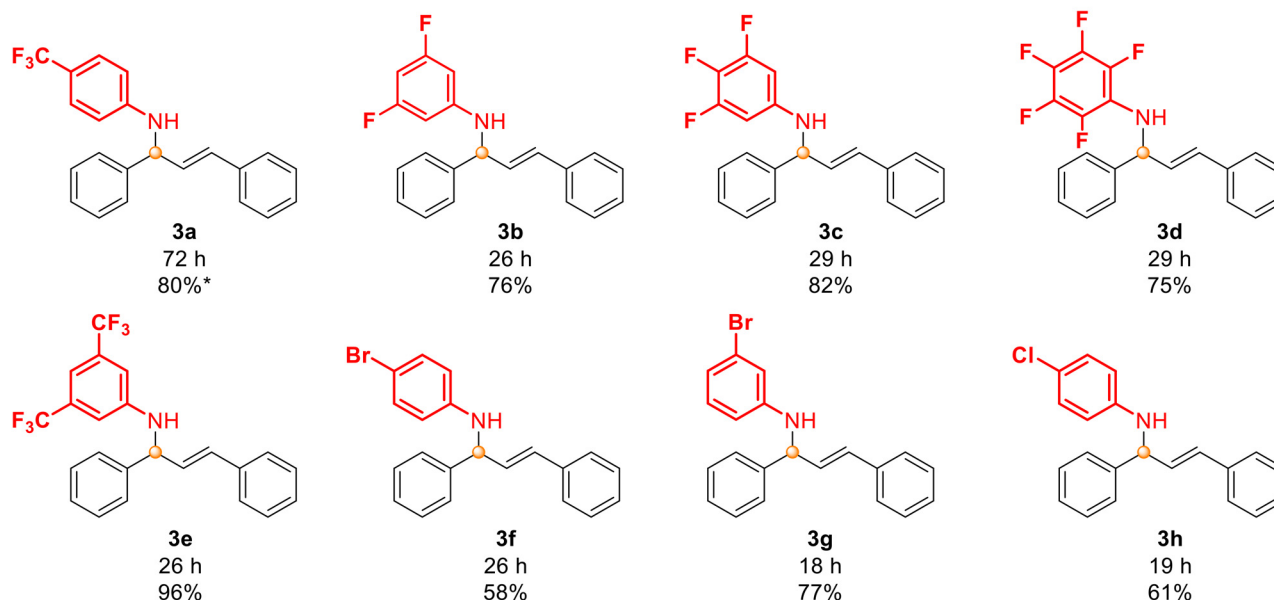
To the best of our knowledge, this is the first example where this reaction has been performed using a DES as both medium and promoter, at room temperature in the absence of another additional catalyst or solvent. With these conditions in hand, the scope and limitations of the substituents and functional group tolerance were evaluated using representative examples of different anilines, allylic alcohols and hydrazides (Schemes 2–4).

As presented in Scheme 2, halogenated anilines smoothly underwent *N*-allylation with excellent isolated yields and selectivity, obtaining in all cases an *E* isomer. Surprisingly, less active anilines (with electron-withdrawing groups)





SCOPE OF HALOGENATED ANILINES



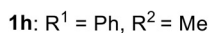
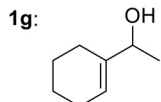
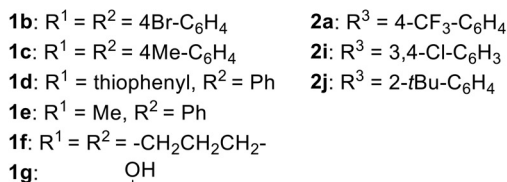
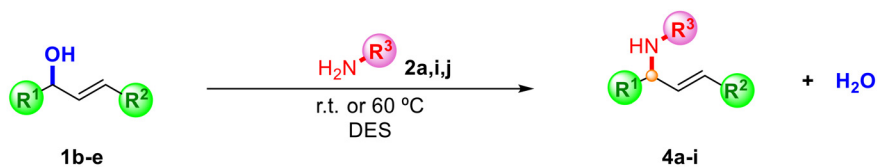
Scheme 2 Scope of the allylic amination employing alcohol **1a** and anilines **2a–h** under the optimised reaction conditions. *Yield for 1 mmol scale.

afforded the best results. Unfortunately, the reaction in the presence of electron-donating groups (4-OMe- or 4-*t*Bu-) in the aniline did not provide the product formation, but an excellent yield was obtained between the hindered aniline **2j** (with a *t*Bu group in the *ortho* position) and alcohol **1b** (Scheme 3). This unexpected behaviour, since anilines with electron-donating groups are expected to be better nucleophiles than those with electron-withdrawing groups, was also observed by Pastor and co-workers,²⁰ and other authors.¹⁹ Based on these findings, the protonation of the alcohol could be inhibited due to the interaction with a more basic aniline (those with electron-donating groups). However, steric hindrance in aniline **2j** prevents such protonation, favouring a nucleophilic attack instead. Moreover, due to the increased nucleophilicity of the monoalkylated product compared to the initial amine, the nitrogen centre could undergo additional alkylation, which may become a drawback in some synthetic approaches. The process was also accomplished at a higher scale with a very good yield of product **3a**, although longer reaction times were required. With the aim of broadening the scope of the reaction

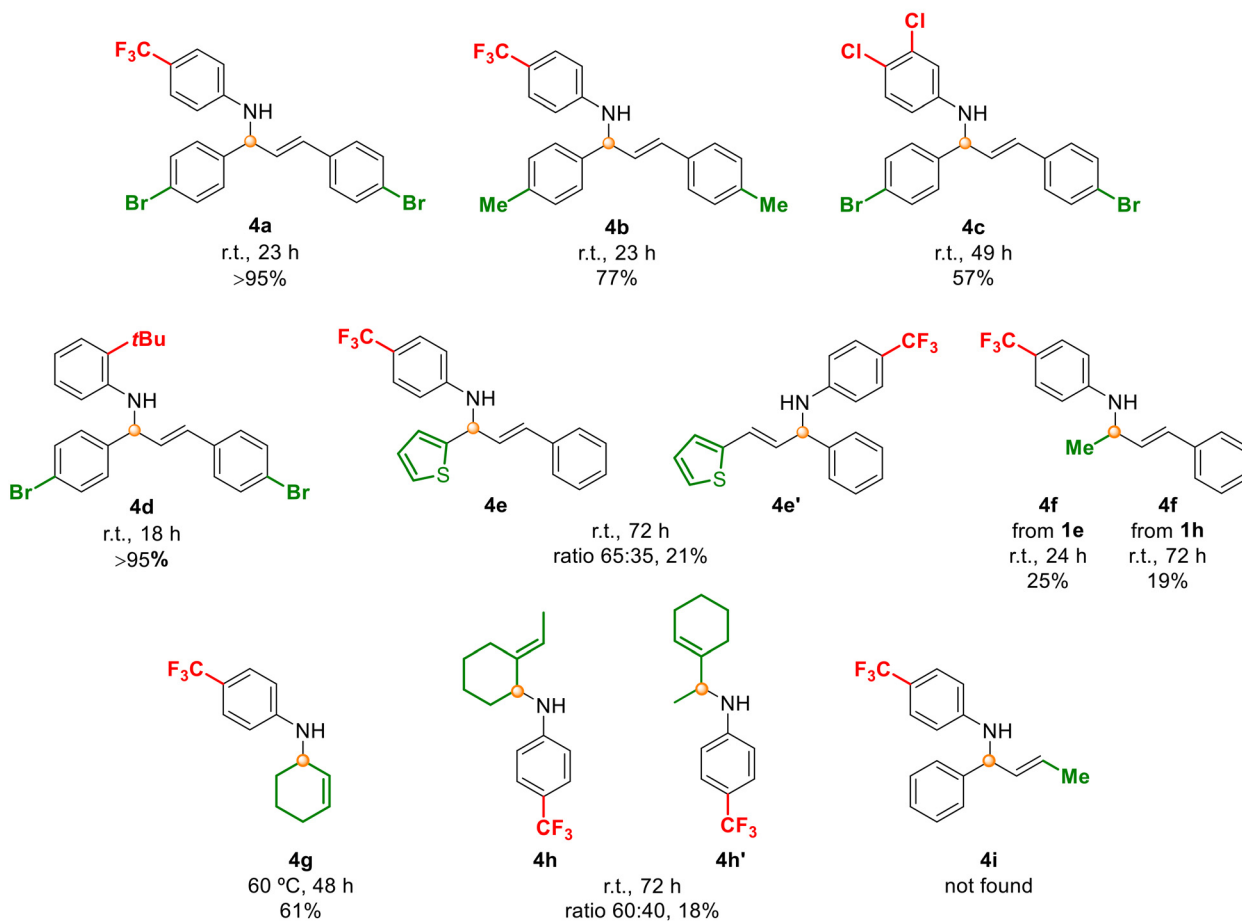
and shedding light on the mechanism involved in this process, different alcohols, including non-symmetric ones, were also explored (Scheme 3).

The use of different substituted alcohols **1** also yielded the desired products **4a–d** with very good results. Although compounds **4e–h** were obtained in lower yields, possibly due to the lower stability of the formed carbocation, derivatives of **4e**, **4f** and **4h** have been isolated for the first time in the literature. Additionally, product **4g** had previously only been achieved by hydroamination of 1,3-dienes by using palladium,²⁶ ruthenium²⁷ or zeolite catalysts.²⁸ The reaction with alcohols **1d** and **1g** gave rise to a mixture of both products **4e** and **4e'** and **4h** and **4h'**, respectively, suggesting the presence of an allylic carbocation intermediate. Unfortunately, product **4i** was not found, as the reaction with alcohol **1h** afforded the same final product **4f**, providing proof of a plausible $\text{S}_{\text{N}}1$ mechanism, as previously observed by Nájera and co-workers.²⁹ These findings indicate that the regiochemistry of the process could be related to the stabilisation of the resulting allylic carbocation intermediate, which would afford the most thermodynamically





SCOPE OF ALCOHOLS

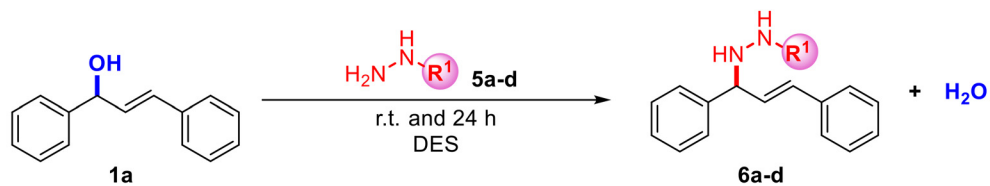


Scheme 3 Scope of the allylic amination employing different allyl alcohols **1b–h** under the optimised reaction conditions.

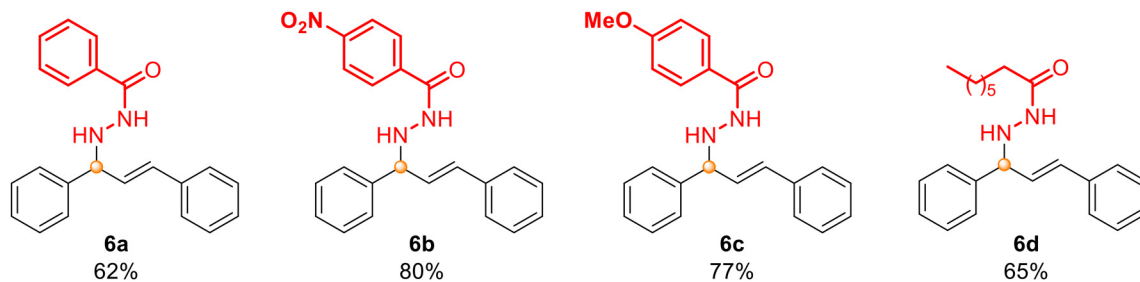
stable intermediate prior to the nucleophilic attack, depending on the substrate. Furthermore, as an additional case of allylic amination, representative hydrazides with electronically and differently substituted aryls and an alkyl derivative also provided the corresponding allylated adducts **6a–d** with excellent isolated yields and selectivity, as depicted in Scheme 4.

In all cases, only the product *E* was cleanly obtained and no mixture of the *Z* isomer was observed (Schemes 2–4). Similar compounds were previously obtained using palladium catalysis,³⁰ which makes our approach as an interesting synthetic alternative. These good results encouraged us to test the utility of our developed protocol with another important structural

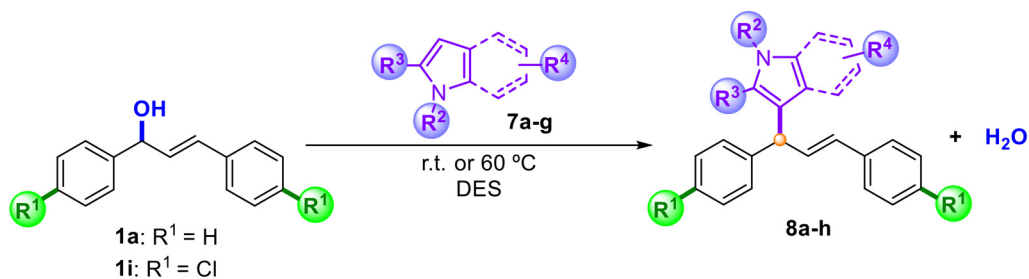




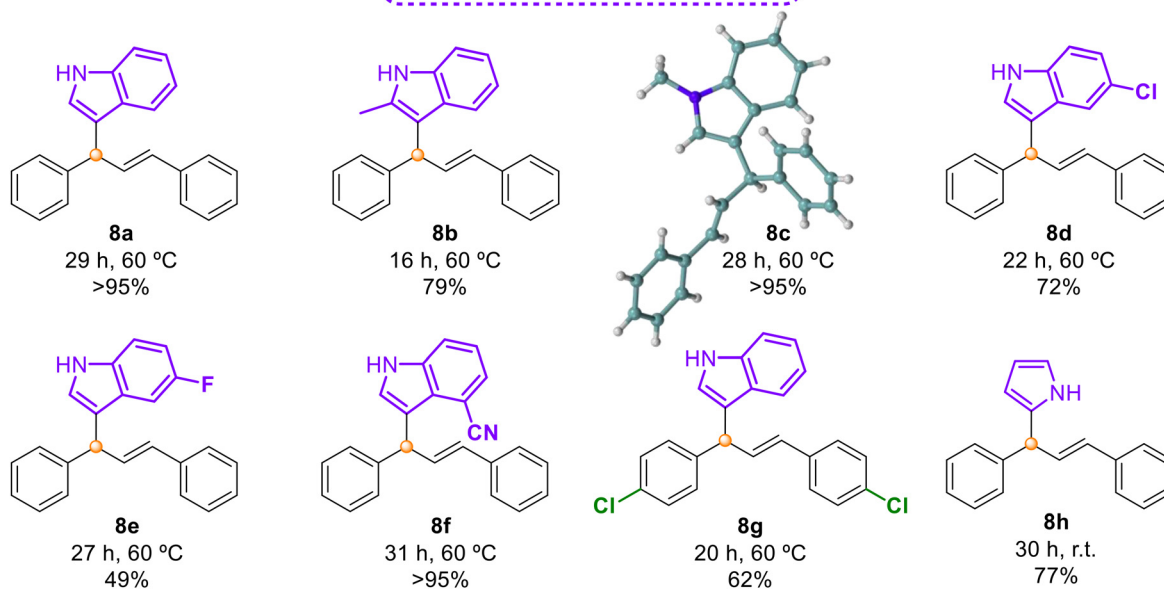
SCOPE OF HYDRAZIDES



Scheme 4 Scope of the allylic amination employing allyl alcohol 1a using hydrazides 5a–d.



SCOPE OF INDOLES AND PYRROLES



Scheme 5 Scope of the allylic alkylation of indoles 7a–g and pyrrole 7h.

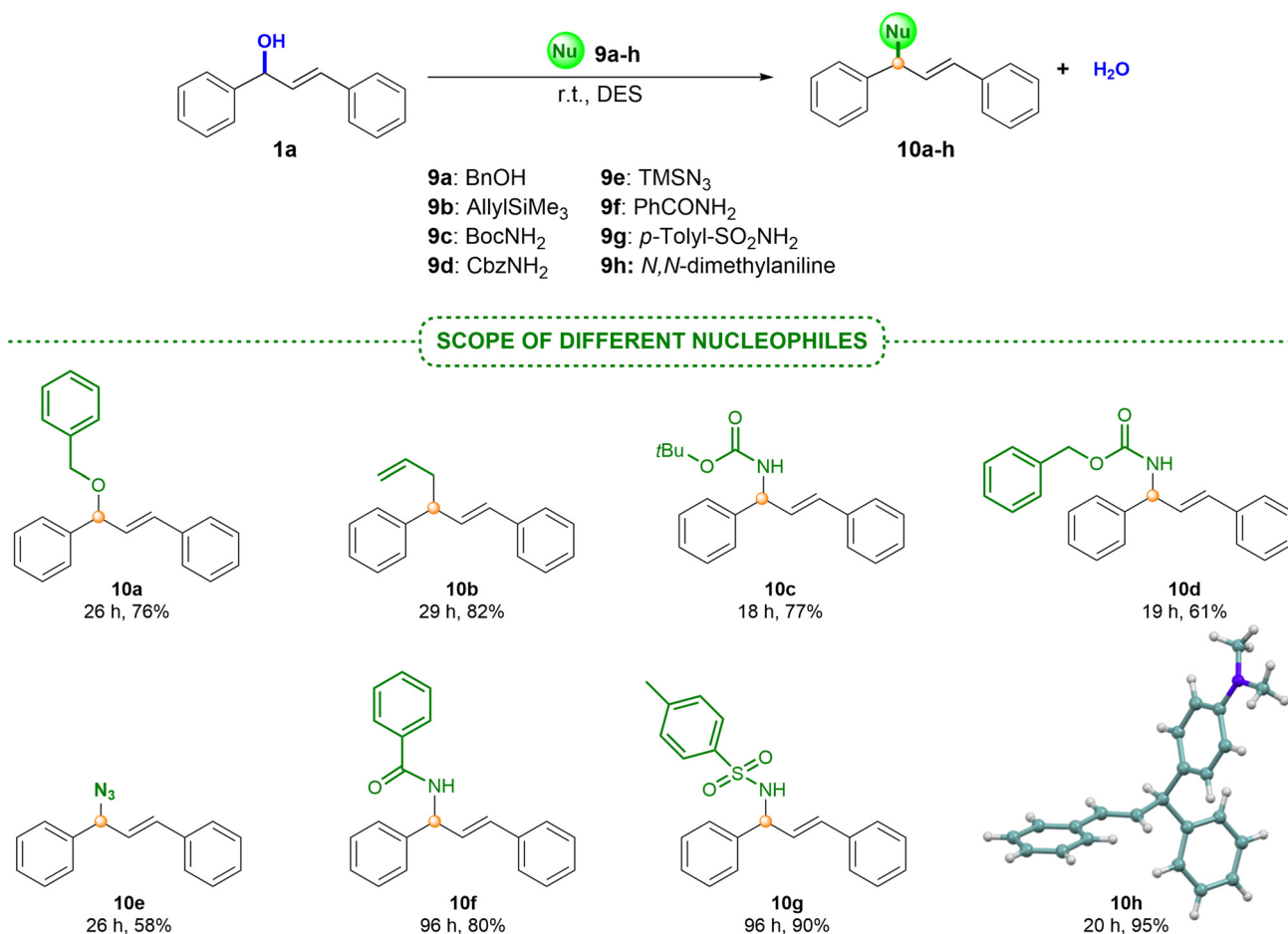


core, the indole, as a representative example of a pivotal structure. We have extensive experience in the field of the Friedel–Crafts alkylation reaction using nitroalkenes, aldehydes and β,γ -unsaturated- α -ketoesters,³¹ since indole is considered a key structural core present in many biologically active compounds.³² Therefore, we tried to trap the *in situ* generated allylic carbocation with different indole derivatives as reported in Scheme 5.

It is worth noting that this protocol has been overlooked in the literature so far for the preparation of these products.⁴ Therefore, our methodology represents the first example for trapping allylic carbocation intermediates with these model molecules. In all cases, high isolated yields with indoles bearing electron-donating or electron-withdrawing groups **7a–f** and pyrrole **7g** were obtained (Scheme 5). The crude products of these reactions were clean and, in some cases, the final products were achieved after a simple extraction from the DES medium (75% for **8a**). The structure of the final derivative **8c** has also been confirmed by X-ray diffraction.³³ Finally, in order to define the scope and limitations of this methodology, we turned our attention to nucleophiles of different nature (Scheme 6). For this purpose, alcohol **9a**, carbamates **9b** and **9c**, trimethylsilylated nucleophile **9d**, azide **9e**, amide **9f**, sulfo-

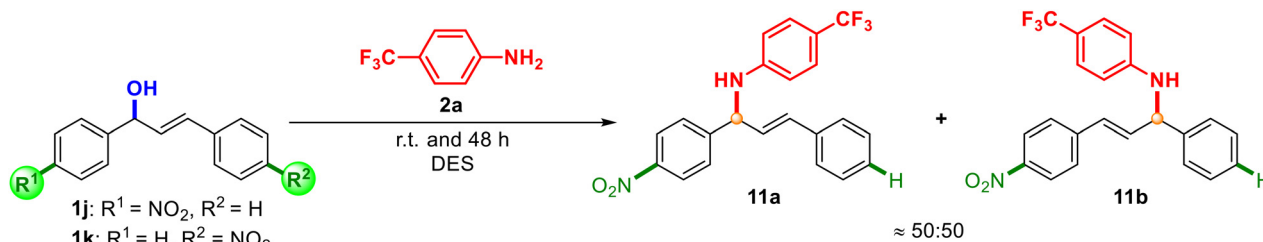
namide **9g** and *N,N*-dimethylaniline **9h** were successfully evaluated. In all cases, the final products **10a–h** were isolated in high yields. Challenging nucleophiles, such as allyltrimethylsilane **9d**, or sulfonamide **9g** gave rise to the corresponding diene **10d** or derivative **10g**, respectively, in excellent yields. Moreover, **9h** also led to the corresponding product of a Friedel–Crafts alkylation reaction with remarkable results after a simple extraction.³³ Interestingly, we also tested the possibility of recycling the same DES medium in successive runs for the reaction between alcohol **1a** and aniline **9h** (ratio 1 : 1). After 10 runs, the same excellent results were obtained with a simple extraction using hexane (>90% of product **10h**). These findings suggest that this process could continue with more rounds without impairing the reactivity of the process. These examples support the utility of this procedure as a simple and straightforward protocol that enables the use of diverse nucleophiles under very mild reaction conditions, resulting in the corresponding allylic adducts in high yields. This provides an alternative greener option to those previously reported.

To shed light on the reaction mechanism, beyond the above-mentioned observations, we also synthesised unsymmetrically substituted alcohols **1j** and **1k** and we analysed the results of their reaction with aniline **2a** (Scheme 7).



Scheme 6 Scope of the methodology employing allyl alcohol **1a** and nucleophiles **9a–h**.





Scheme 7 Mechanistic assays using alcohols **1j** and **1k**.

In both cases, a mixture of products **11a** : **11b** was observed in a ratio around 50 : 50, which supported the generation of an allylic carbocation intermediate in the medium and a S_N1 -type mechanism.^{34,35} Different reactivity was observed, since starting from alcohol **1j**, 36% of the final mixture was obtained, while starting from **1k**, a 66% yield was achieved. However, it is worth noting that with alcohol **1e** (Scheme 3), with the possibility of isomerisation of the carbocation affording two different products, only one product (**4f**) was detected, which suggested that the reaction with the carbocation was faster than the isomerisation of the carbocation. Based on the experimental results, a plausible reaction mechanism is depicted in Scheme 8. In this proposal, the hydroxyl group could be activated with the assistance of ChCl and lactic acid as a source of proton $[\text{H}^+]$, which would act as a Brønsted acid catalyst (**A**). The release of a molecule of H_2O would generate allylic carbocation **B**. Finally, the attack of the corresponding amine or nucleophile would trap the formed carbocation, giving rise to a protonated intermediate **C**. Final deprotonation of the product would recover the initial source of $[\text{H}^+]$ to initiate the cycle again. Besides, the effect of the stability of the carbocations is supported when comparing alcohol **1a** with **1e-g**, having obtained better results with **1a** (benzylic and allylic carbocations) against **1e-g**, which are only allylic carbocations (Schemes 2 and 3). As previously mentioned in this work, the stabilisation of the resulting allylic carbocation intermediate, prior to the nucleophilic attack, can influence the regio-

chemistry of the reaction with other non-symmetric alcohols such as **1d**, **1g**, and **1h**.

As a result, this protocol is complementary to those previously reported and an interesting alternative to the use of metal catalysts for the activation of these types of substrates.

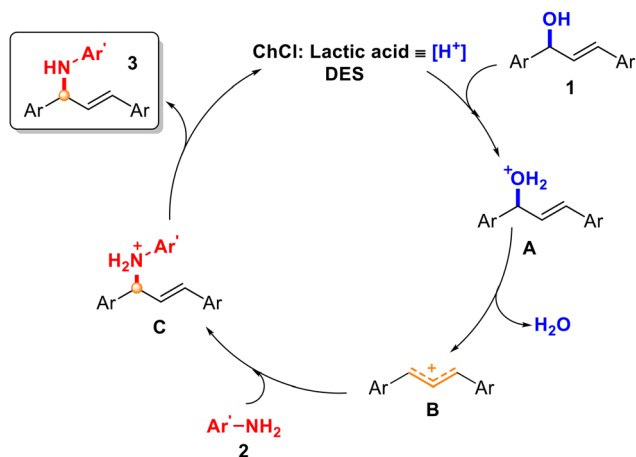
Conclusions

In this work, we have shown that the allylation of anilines, hydrazides, indole derivatives and several interesting nucleophiles can be performed using a new approach under very mild conditions, including room temperature and a green medium. This means a great improvement in comparison with most of the examples described in the literature so far, where high temperatures or stronger reaction conditions are usually necessary. In addition, we show that a simple mixture of ChCl and lactic acid provides the best results for a wide substrate scope with moderate to quantitative isolated yields. These features make our approach an attractive green and interesting alternative compared with other examples reported in the literature on alkylation of amines by allylic alcohols. Moreover, preliminary mechanistic experiments support that the reaction should proceed *via* an S_N1 pathway. This novel methodology can not only be considered as an alternative to the conventional metal or Brønsted acid-catalysed allylic substitution reactions, but also as a complementary method, as it enables the successful use of certain nucleophiles that frequently fail in previously reported procedures.

Experimental

General experimental methods and instrumentation

Analytical thin-layer chromatography was performed on 0.25 mm silica gel 60-F plates. ESI and a micrOTOF-Q mass analyser were used for HRMS measurements. NMR spectroscopy was conducted using a Bruker AVANCE-II spectrometer. ^1H NMR spectra were recorded at 300 and 400 MHz; ^{13}C $\{^1\text{H}\}$ -APT NMR spectra were recorded at 75 and 101 MHz; CD_3CN or CD_3COCD_3 were used as the deuterated solvents. Chemical shifts were reported in the δ scale relative to the residual CH_3CN (1.94 ppm) and CH_3COCH_3 (2.05 ppm) for ^1H -NMR and the central line of CD_3CN (1.32 ppm) and CD_3COCD_3 (29.84 ppm) for $^{13}\text{C}\{^1\text{H}\}$ -APT NMR.



Scheme 8 Plausible catalytic cycle.



All commercially available solvents and reagents were used as received. Spectral data for many of the synthesised compounds were consistent with the values previously reported in the literature: **3a**,³⁶ **3e**,³⁷ **3f**,^{20a} **3h**,^{19b} **4g**,^{26a} **6a**,³⁸ **8a**,³⁹ **8b**,³⁹ **8c**,³⁹ **8d**,⁴⁰ **8e**,⁴¹ **8g**,⁴¹ **8h**,⁴² **10a**,⁴³ **10b**,⁴⁴ **10c**,^{19b} **10d**,^{19b} **10e**,^{19b} **10f**,^{19b} **10g**,^{19b} and **10h**.⁴⁵ For all known products, we have also provided the ¹H NMR spectra. The synthesis of alcohols **1b–d** and **1g–k** was performed following the described procedures in the literature.⁴⁶

General procedure for the preparation of DES mixtures

Choline chloride (1 equiv., 83.3 mg) and lactic acid (2 equiv., 162.2 μL) were mixed in a 5 mL vial. The mixture was stirred and heated for 5 min at 60 °C until a clear homogeneous solution appeared. Then, the DES was cooled down in some cases prior to setting up the reaction.

General procedure for the synthesis of allylic anilines **3a–h** and **4a–i**

In a vial with a magnetic stirring bar and a cap, a DES (250 mg) was prepared in advance. Then, alcohols **1a–h** (0.1 mmol) and anilines **2a–j** (0.2 mmol) were added to the vessel at room temperature. When the reaction was over, neutralisation was done with a microspatula of potassium carbonate. Then, 5 mL of water was added to the crude reaction mixture and it was extracted with ethyl acetate (3 × 5 mL). The organic layer was dried over MgSO₄, the crude mixture was filtered, and the organic phase was evaporated under vacuum. The final product was purified by short flash column chromatography (silica gel and toluene), and if the crude product was clean, a Pasteur pipette could also be used for fast purification.⁴⁷

(*E*)-*N*-(1,3-Diphenylallyl)-4-(trifluoromethyl)aniline (**3a**)

Following the general procedure, compound **3a** was obtained as a yellow solid in 98% yield (34.6 mg).

(*E*)-*N*-(1,3-Diphenylallyl)-3,5-difluoroaniline (**3b**). Following the general procedure, compound **3b** was obtained as a colourless oil in 76% yield (24.4 mg). ¹H NMR (ppm) (300 MHz, CD₃CN): δ = 7.50–7.19 (m, 10H), 6.61 (dd, *J* = 15.9, 1.2 Hz, 1H), 6.41 (dd, *J* = 15.9, 6.5 Hz, 1H), 6.28–6.08 (m, 3H), 5.53 (br d, *J* = 6.7 Hz, 1H), 5.16 (t, *J* = 6.6 Hz, 1H). ¹³C{¹H} APT NMR (ppm) (75 MHz, CD₃CN): δ = 165.0 (d, *J* = 179.2 Hz, 1C), 164.8 (d, *J* = 180.0 Hz, 1C), 151.2 (t, *J* = 13.7 Hz, 1C), 142.8 (s, 1C), 137.7 (s, 1C), 131.7 (s, 1C), 131.3 (s, 1C), 129.8 (s, 2C), 129.7 (s, 2C), 128.8 (s, 1C), 128.6 (s, 1C), 128.1 (s, 2C), 127.4 (s, 2C), 96.9 (d, *J* = 28.7 Hz, 1C), 92.4 (t, *J* = 26.6 Hz, 2C), 60.6 (s, 1C). ¹⁹F{¹H} NMR (ppm) (282 MHz, CD₃CN): δ = -112.3. HRMS (ESI+ μ-TOF): *m/z* (%) = [M - H]⁺ calcd for [C₂₁H₁₆F₂N]⁺ 320.1256, found 320.1263.

(*E*)-*N*-(1,3-Diphenylallyl)-3,4,5-trifluoroaniline (**3c**)

Following the general procedure, compound **3c** was obtained as a colourless oil in 82% yield (27.8 mg). ¹H NMR (ppm) (300 MHz, CD₃CN): δ = 7.52–7.19 (m, 10H), 6.61 (dd, *J* = 15.9, 1.2 Hz, 1H), 6.45–6.26 (m, 3H), 5.33 (br d, *J* = 6.7 Hz, 1H), 5.09 (t, *J* = 9.0 Hz, 1H). ¹³C{¹H} APT NMR (ppm) (75 MHz, CD₃CN): δ = 152.6 (dd, *J* = 180.7, 4.5 Hz, 1C), 152.5 (dd, *J* = 180.7, 4.5

Hz, 1C), 145.1 (td, *J* = 11.8, 2.4 Hz, 1C), 142.6 (s, 1C), 137.6 (s, 1C), 132.6 (td, *J* = 176.2, 12 Hz, 1C), 131.8 (s, 1C), 131.2 (s, 1C), 129.8 (s, 2C), 129.7 (s, 2C), 128.8 (s, 1C), 128.6 (s, 1C), 128.1 (s, 2C), 127.4 (s, 2C), 98.0–97.5 (m, 2C), 60.8 (s, 1C). ¹⁹F{¹H} NMR (ppm) (282 MHz, CD₃CN): δ = -137.5 (d, *J* = 21.1 Hz, 2F), 179.2 (t, *J* = 21.1 Hz, 1F). HRMS (ESI+ μ-TOF): *m/z* (%) = [M - H]⁺ calcd for [C₂₁H₁₅F₃N]⁺ 338.1162, found 338.1167.

(*E*)-*N*-(1,3-Diphenylallyl)-2,3,4,5,6-pentafluoroaniline (**3d**)

Following the general procedure, compound **3d** was obtained as a colourless oil in 75% yield (28.2 mg). ¹H NMR (ppm) (300 MHz, CD₃CN): δ = 7.50–7.18 (m, 10H), 6.60 (d, *J* = 15.9 Hz, 1H), 6.49 (dd, *J* = 15.8, 7.0 Hz, 1H), 5.41–5.30 (m, 1H), 4.73 (br d, *J* = 9.7 Hz, 1H). ¹³C{¹H} APT NMR (ppm) (75 MHz, CD₃CN): δ = 142.9 (s, 1C), 141.3–137.7 (m, 2C), 137.6 (s, 1C), 136.5–133.7 (m, 2C), 132.4 (s, 1C), 131.3 (s, 1C), 129.7 (s, 2C), 129.7 (s, 2C), 128.9 (s, 1C), 128.7 (s, 1C), 127.8 (s, 2C), 127.4 (s, 2C), 124.3–123.8 (m, 1C), 63.2 (t, *J* = 4.1 Hz, 1C). ¹⁹F{¹H} NMR (ppm) (282 MHz, CD₃CN): δ = -157.3–(-157.4) (m, 2F), -166.6 (tdd, *J* = 21.2, 4.8, 2.5 Hz, 2F), -172.3 (tt, *J* = 21.2, 5.6 Hz, 1F). HRMS (ESI+ μ-TOF): *m/z* (%) = [M - H]⁺ calcd for [C₂₁H₁₃F₅N]⁺ 374.0974, found 374.0983.

(*E*)-*N*-(1,3-Diphenylallyl)-3,5-bis(trifluoromethyl)aniline (**3e**)

Following the general procedure, compound **3e** was obtained as a yellow solid in 96% yield (40.5 mg).

(*E*)-4-Bromo-*N*-(1,3-diphenylallyl)aniline (**3f**). Following the general procedure, compound **3e** was obtained as an orange oil in 58% yield (21.1 mg).

(*E*)-3-Bromo-*N*-(1,3-diphenylallyl)aniline (**3g**). Following the general procedure, compound **3g** was obtained as an orange oil in 77% yield (28.1 mg). ¹H NMR (ppm) (400 MHz, CD₃CN): δ = 7.49–7.19 (m, 10H), 6.98 (t, *J* = 8.0 Hz, 1H), 6.79 (t, *J* = 2.1 Hz, 1H), 6.74 (ddd, *J* = 7.8, 1.9, 0.9 Hz, 1H), 6.66–6.56 (m, 2H), 6.42 (dd, *J* = 15.9, 6.5 Hz, 1H), 5.21 (d, *J* = 6.8 Hz, 1H), 5.16 (td, *J* = 6.6, 1.2 Hz, 1H). ¹³C{¹H} APT NMR (ppm) (101 MHz, CD₃CN): δ = 150.1 (s, 1C), 143.1 (s, 1C), 137.7 (s, 1C), 131.7 (s, 1C), 131.6 (s, 2C), 129.7 (s, 2C), 129.7 (s, 2C), 128.7 (s, 1C), 128.4 (s, 1C), 128.1 (s, 2C), 127.3 (s, 2C), 123.4 (s, 1C), 120.5 (s, 1C), 116.7 (s, 1C), 113.4 (s, 1C), 60.5 (s, 1C). HRMS (ESI+ μ-TOF): *m/z* (%) = [M - H]⁺ calcd for [C₂₁H₁₇BrN]⁺ 362.0539, found 362.0535.

(*E*)-4-Chloro-*N*-(1,3-diphenylallyl)aniline (**3h**). Following the general procedure, compound **3h** was obtained as a yellow solid in 61% yield (28.1 mg).

(*E*)-*N*-(1,3-Bis(4-bromophenyl)allyl)-4-(trifluoromethyl)aniline (**4a**). Following the general procedure, compound **4a** was obtained as a yellow viscous oil in >95% yield (49.6 mg). ¹H NMR (ppm) (300 MHz, CD₃CN): δ = 7.52 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.40–7.32 (m, 4H), 7.34–7.24 (m, 2H), 6.73–6.67 (m, 2H), 6.56 (dd, *J* = 15.9, 1.2 Hz, 1H), 6.43 (dd, *J* = 15.9, 6.5 Hz, 1H), 5.55 (br d, *J* = 6.7 Hz, 1H), 5.21 (t, *J* = 6.5 Hz, 1H). ¹³C{¹H} APT NMR (ppm) (75 MHz, CD₃CN): δ = 151.1 (s, 1C), 142.0 (s, 1C), 136.8 (s, 1C), 132.7 (s, 2C), 132.7 (s, 2C), 131.8 (s, 1C), 130.9 (s, 1C), 130.2 (s, 2C), 129.2 (s, 2C), 127.2 (q, *J* = 3.9 Hz, 2C), 125.9 (q, *J* = 200.2 Hz, 1C), 122.0 (s, 1C), 121.7 (s, 1C), 118.7 (q, *J* = 24.0 Hz, 1C), 113.8 (s, 2C), 59.7 (s, 1C). ¹⁹F{¹H} NMR (ppm) (282 MHz, CD₃CN): δ = -115.5. HRMS (ESI+



μ -TOF): m/z (%) = $[M - H]^+$ calcd for $[C_{22}H_{15}Br_2F_3N]^+$ 507.9529, found 507.9506.

(E)-N-(1,3-Di-*p*-tolylallyl)-4-(trifluoromethyl)aniline (4b).

Following the general procedure, compound **4b** was obtained as a yellow solid in 77% yield (29.4 mg). M.p. 115–116 °C. 1H NMR (ppm) (300 MHz, CD_3CN): δ = 7.40–7.22 (m, 6H), 7.23–7.04 (m, 4H), 6.71 (d, J = 8.6 Hz, 2H), 6.56 (dd, J = 15.9, 1.1 Hz, 1H), 6.36 (dd, J = 15.9, 6.5 Hz, 1H), 5.49 (br d, J = 6.5 Hz, 1H), 5.17 (t, J = 6.6 Hz, 1H), 2.31 (s, 3H), 2.29 (s, 3H). ^{13}C $\{^1H\}$ APT NMR (ppm) (75 MHz, CD_3CN): δ = 151.5 (s, 1C), 140.0 (s, 1C), 138.7 (s, 1C), 138.2 (s, 1C), 135.0 (s, 1C), 131.5 (s, 1C), 130.5 (s, 1C), 130.4 (s, 2C), 130.3 (s, 2C), 128.0 (s, 2C), 127.3 (s, 2C), 127.2 (q, J = 3.9 Hz, 2C), 126.6 (q, J = 241.5 Hz, 1C), 113.7 (s, 2C), 60.1 (s, 1C), 21.2 (s, 1C), 21.1 (s, 1C). $^{19}F\{^1H\}$ NMR (ppm) (282 MHz, CD_3CN): δ = –61.3. HRMS (ESI– μ -TOF): m/z (%) = $[M - H]^+$ calcd for $[C_{22}H_{21}F_3N]^+$ 380.1632, found 380.1636.

(E)-N-(1,3-Bis(4-bromophenyl)allyl)-3,4-dichloroaniline (4c).

Following the general procedure, compound **4c** was obtained as a yellow oil in 57% yield (29.2 mg). 1H NMR (ppm) (400 MHz, CD_3CN): δ = 7.52 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.8 Hz, 1H), 6.72 (d, J = 2.7 Hz, 2H), 6.59–6.51 (m, 1H), 6.39 (dd, J = 15.9, 6.4 Hz, 1H), 5.31 (br d, J = 6.7 Hz, 1H), 5.12 (t, J = 6.3 Hz, 1H). $^{13}C\{^1H\}$ APT NMR (ppm) (101 MHz, CD_3CN): δ = 148.2 (s, 1C), 141.9 (s, 1C), 136.8 (s, 1C), 132.9 (s, 1C), 132.7 (s, 2C), 132.7 (s, 2C), 131.8 (s, 1C), 131.5 (s, 1C), 130.9 (s, 1C), 130.2 (s, 2C), 129.2 (s, 2C), 122.0 (s, 1C), 121.8 (s, 1C), 119.8 (s, 1C), 115.3 (s, 1C), 114.6 (s, 1C), 59.9 (s, 1C). HRMS (ESI+ μ -TOF): m/z (%) = $[M - H]^+$ calcd for $[C_{21}H_{14}Br_2Cl_2N]^+$ 507.8864, found 507.8855.

(E)-N-(1,3-Bis(4-bromophenyl)allyl)-2-(*tert*-butyl)aniline (4d).

Following the general procedure, compound **4d** was obtained as a yellow oil in >95% yield (47.9 mg). 1H NMR (ppm) (400 MHz, CD_3CN): δ = 7.56–7.50 (m, 2H), 7.49–7.43 (m, 2H), 7.41–7.37 (m, 2H), 7.35–7.28 (m, 2H), 7.24 (dd, J = 7.8, 1.6 Hz, 1H), 6.98–6.92 (m, 1H), 6.66–6.47 (m, 4H), 5.21 (t, J = 5.8 Hz, 1H), 4.48 (br s, J = 5.2 Hz, 1H), 1.44 (s, 9H). $^{13}C\{^1H\}$ APT NMR (ppm) (101 MHz, CD_3CN): δ = 145.6 (s, 1C), 143.1 (s, 1C), 136.9 (s, 1C), 134.7 (s, 1C), 132.8 (s, 2C), 132.7 (s, 1C), 132.6 (s, 2C), 131.0 (s, 1C), 130.1 (s, 2C), 129.3 (s, 2C), 127.8 (s, 1C), 127.3 (s, 1C), 122.0 (s, 1C), 121.6 (s, 1C), 118.5 (s, 1C), 114.1 (s, 1C), 61.0 (s, 1C), 34.8 (s, 1C), 30.3 (s, 3C). HRMS (ESI+ μ -TOF): m/z (%) = $[M]^+$ calcd for $[C_{25}H_{24}Br_2N]^+$ 496.0270, found 496.0267.

(E)-N-(4-Phenylbut-3-en-2-yl)-4-(trifluoromethyl)aniline (4f).

Following the general procedure, compound **4f** was obtained as a pale-yellow oil in 25% yield (5.5 mg). 1H NMR (ppm) (300 MHz, CD_3COCD_3): δ = 7.51–7.15 (m, 7H), 6.79 (d, J = 9.0 Hz, 2H), 6.64 (d, J = 15.0 Hz, 1H), 6.29 (dd, J = 16.0, 6.1 Hz, 1H), 5.73 (br d, J = 6.0 Hz, 1H), 4.27 (sext, J = 6.5 Hz, 1H), 1.42 (d, J = 6.7 Hz, 3H). ^{13}C $\{^1H\}$ APT NMR (ppm) (101 MHz, CD_3CN): δ 151.9 (s, 1C), 138.2 (s, 1C), 133.6 (s, 1C), 130.2 (s, 1C), 129.6 (s, 4C), 128.4 (s, 1C), 127.2 (q, J = 4.0 Hz, 1C), 127.2 (s, 2C), 113.4 (s, 2C), 51.3 (s, 1C), 21.8 (s, 1C). $^{19}F\{^1H\}$ NMR (ppm) (282 MHz, CD_3COCD_3): δ = –61.2 (CF_3). HRMS (ESI+ μ -TOF): m/z (%) = $[M - H]^+$ calcd for $[C_{17}H_{15}F_3N]^+$ 290.1151, found 290.1162.

N-(Cyclohex-2-en-1-yl)-4-(trifluoromethyl)aniline (4g).

Following the general procedure, compound **4g** was obtained as a colourless oil in 61% yield (14.7 mg).

(E)-N-(2-Ethylidenecyclohexyl)-4-(trifluoromethyl)aniline (4h).

Following the general procedure, a mixture of compounds **4h** and **4h'** was obtained as a pale-yellow oil in 18% yield (4.5 mg). 1H NMR (ppm) (300 MHz, CD_3CN): δ = 7.35 (d, J = 8.7 Hz, 2H), 6.62 (d, J = 8.8 Hz, 2H), 5.69–5.62 (m, 0.65H), 5.26 (q, J = 6.8 Hz, 0.35H), 5.08–4.89 (m, 1H), 3.82 (quint, J = 6.9 Hz, 0.65H), 3.78–3.69 (m, 0.35H), 2.06–1.82 (m, 3H), 1.70–1.43 (m, 5H), 1.27 (d, J = 6.8 Hz, 3H). $^{19}F\{^1H\}$ NMR (ppm) (282 MHz, CD_3CN): δ = –61.1 (CF_3). HRMS (ESI+ μ -TOF): m/z (%) = $[M - H]^+$ calcd for $[C_{15}H_{17}F_3N]^+$ 268.1308, found 268.1301.

General procedure for the synthesis of allylic hydrazides 6a–d

In a vial with a magnetic stirring bar and a cap, the DES (250 mg) was prepared in advance. Alcohol **1a** (0.1 mmol) and hydrazides **5a–d** (0.2 mmol) were added to the vessel at 60 °C. When the reaction was over, neutralisation was done with a microspatula of potassium carbonate. Then, 5 mL of water was added to the crude reaction mixture and it was extracted with ethyl acetate (3 \times 5 mL). The organic layer was dried over $MgSO_4$, the crude mixture was filtered, and the organic phase was evaporated under vacuum. The final product was purified by short flash column chromatography (silica gel and heptane : AcOEt), and if the crude product was clean, a Pasteur pipette could also be used for fast purification.⁴⁷

(E)-N'-(1,3-Diphenylallyl)benzohydrazide (6a). Following the general procedure, compound **8d** was obtained as a pale-yellow solid in 62% yield (20.4 mg).

(E)-N'-(1,3-Diphenylallyl)-4-nitrobenzohydrazide (6b).

Following the general procedure, compound **6b** was obtained as a white solid in 80% yield (29.9 mg). M.p. 152–153 °C. 1H NMR (ppm) (300 MHz, CD_3CN): δ = 8.70 (br d, J = 6.4 Hz, 1H), 8.23 (d, J = 8.9 Hz, 2H), 7.86 (d, J = 9.0 Hz, 2H), 7.60–7.18 (m, 10H), 6.70 (d, J = 15.9 Hz, 1H), 6.44 (dd, J = 15.9, 8.0 Hz, 1H), 5.19 (br dd, J = 6.5, 3.3 Hz, 1H), 4.82 (dd, J = 8.0, 3.1 Hz, 1H). $^{13}C\{^1H\}$ APT NMR (ppm) (75 MHz, CD_3CN): δ = 166.2 (s, 1C), 152.2 (s, 1C), 141.9 (s, 1C), 139.8 (s, 1C), 137.9 (s, 1C), 132.9 (s, 1C), 131.2 (s, 1C), 129.6 (s, 4C), 129.4 (s, 2C), 128.8 (s, 2C), 128.8 (s, 1C), 128.7 (s, 1C), 127.4 (s, 2C), 124.6 (s, 2C), 67.9 (s, 1C). HRMS (ESI+ μ -TOF): m/z (%) = $[M + Na]^+$ calcd for $[C_{22}H_{19}N_3NaO_3]^+$ 396.1319, found 369.1296.

(E)-N'-(1,3-Diphenylallyl)-4-methoxybenzohydrazide (6c).

Following the general procedure, compound **6c** was obtained as a pale-grey solid in 77% yield (27.6 mg). M.p. 135–136 °C. 1H NMR (ppm) (300 MHz, CD_3CN): δ = 8.42 (br s, 1H), 7.66 (d, J = 8.9 Hz, 2H), 7.54–7.18 (m, 10H), 6.92 (d, J = 8.9 Hz, 2H), 6.66 (d, J = 15.9 Hz, 1H), 6.43 (dd, J = 15.9, 8.0 Hz, 1H), 5.15 (br s, 1H), 4.78 (d, J = 8.0 Hz, 1H), 3.80 (s, 3H). $^{13}C\{^1H\}$ APT NMR (ppm) (75 MHz, CD_3CN): δ = 167.5 (s, 1C), 163.3 (s, 1C), 142.2 (s, 1C), 138.0 (s, 1C), 132.6 (s, 1C), 131.6 (s, 1C), 129.8 (s, 1C), 129.6 (s, 2C), 129.6 (s, 2C), 128.8 (s, 2C), 128.6 (s, 2C), 128.7 (s, 1C), 127.4 (s, 2C), 126.4 (s, 1C), 114.6 (s, 2C), 68.0 (s, 1C), 56.1 (s, 1C). HRMS (ESI+ μ -TOF): m/z (%) = $[M + Na]^+$ calcd for $[C_{23}H_{22}N_2NaO_2]^+$ 318.1573, found 318.1568.



(E)-N'-(1,3-Diphenylallyl)octanehydrazide (6d). Following the general procedure, compound **6d** was obtained as a colourless oil in 65% yield (19.1 mg). ^1H NMR (ppm) (300 MHz, CD_3CN): δ = 7.89 (br s, 1H), 7.50–7.17 (m, 10H), 6.62 (d, J = 15.9 Hz, 2H), 6.34 (dd, J = 15.9, 8.0 Hz, 1H), 4.91 (br s, 1H), 4.66 (d, J = 8.0 Hz, 1H), 2.04–1.96 (m, 3H), 1.57–1.42 (m, 2H), 1.35–1.14 (m, 8H), 0.86 (t, J = 6.0 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ APT NMR (ppm) (75 MHz, CD_3CN): δ = 173.5 (s, 1C), 142.2 (s, 1C), 138.0 (s, 1C), 132.5 (s, 1C), 131.5 (s, 1C), 129.6 (s, 2C), 129.6 (s, 2C), 128.7 (s, 2C), 128.6 (s, 1C), 128.6 (s, 1C), 127.4 (s, 2C), 67.8 (s, 1C), 34.9 (s, 1C), 32.5 (s, 1C), 29.5 (s, 1C), 29.7 (s, 1C), 26.5 (s, 1C), 23.4 (s, 1C), 14.4 (s, 1C). HRMS (ESI+ μ -TOF): m/z (%) = $[\text{M} + \text{Na}]^+$ calcd for $[\text{C}_{23}\text{H}_{22}\text{N}_2\text{NaO}_2]^+$ 373.2250, found 373.2253.

General procedure for the allylic alkylation of indoles 7a–f and pyrrole (7g)

In a vial with a magnetic stirring bar and a cap, the DES (250 mg) was prepared in advance. Alcohols **1a** and **1g** (0.1 mmol), indoles **7a–f** (0.1 mmol) and pyrrole (**7g**) (0.1 mmol) were added to the vessel at 60 °C and at room temperature, respectively. When the reaction was over, neutralisation was done with a microspatula of potassium carbonate. Then, 5 mL of water was added to the crude reaction mixture, and it was extracted with ethyl acetate (3 \times 5 mL). The organic layer was dried over MgSO_4 , the crude mixture was filtered, and the organic phase was evaporated under vacuum. The final product was purified by short flash column chromatography (silica gel and toluene), and if the crude product was clean, a Pasteur pipette could also be used for fast purification.⁴⁷

(E)-3-(1,3-Diphenylallyl)-1H-indole (8a). Following the general procedure, compound **8a** was obtained as a red solid in >95% yield (29.7 mg).

(E)-3-(1,3-Diphenylallyl)-2-methyl-1H-indole (8b). Following the general procedure, compound **8b** was obtained as an orange solid in 79% yield (25.6 mg).

(E)-3-(1,3-Diphenylallyl)-1-methyl-1H-indole (8c). Following the general procedure, compound **8c** was obtained as a red solid in >95% yield (31.4 mg).

(E)-5-Chloro-3-(1,3-diphenylallyl)-1H-indole (8d). Following the general procedure, compound **8d** was obtained as a yellow oil in 72% yield (24.8 mg).

(E)-3-(1,3-Diphenylallyl)-5-fluoro-1H-indole (8e). Following the general procedure, compound **8d** was obtained as a yellow oil in 49% yield (16.0 mg).

(E)-3-(1,3-Diphenylallyl)-1H-indole-4-carbonitrile (8f). Following the general procedure, compound **8f** was obtained as a brown solid in >95% yield (33.6 mg). M.p. 116–117 °C. ^1H NMR (ppm) (300 MHz, CD_3CN): δ = 9.64 (br s, 1H), 7.67 (dd, J = 8.2, 1.0 Hz, 1H), 7.36 (dd, J = 7.4, 1.0 Hz, 1H), 7.34–7.04 (m, 12H), 6.74 (dd, J = 15.8, 7.3 Hz, 1H), 6.28 (d, J = 16.0 Hz, 1H), 5.54 (d, J = 7.2 Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ APT NMR (ppm) (75 MHz, CD_3CN): δ = 144.6 (s, 1C), 138.4 (s, 1C), 137.9 (s, 1C), 134.1 (s, 1C), 131.2 (s, 1C), 129.6 (s, 2C), 129.5 (s, 2C), 129.4 (s, 2C), 128.3 (s, 1C), 128.0 (s, 1C), 127.4 (s, 1C), 127.3 (s, 1C), 127.2 (s, 2C), 126.4 (s, 1C), 122.4 (s, 1C), 120.3 (s, 1C), 117.9 (s, 1C),

102.4 (s, 1C), 45.5 (s, 1C). HRMS (ESI+ μ -TOF): m/z (%) = $[\text{M} + \text{Na}]^+$ calcd for $[\text{C}_{24}\text{H}_{18}\text{N}_2\text{Na}]^+$ 357.1362, found 357.1348.

(E)-3-(1,3-Bis(4-chlorophenyl)allyl)-1H-indole (8g). Following the general procedure, compound **8f** was obtained as a red viscous oil in 62% yield (23.5 mg).

(E)-2-(1,3-Diphenylallyl)-1H-pyrrole (8h). Following the general procedure, compound **8h** was obtained as a red solid in 77% yield (20.0 mg).

General procedure for the synthesis of allylic derivatives 10a–h

In a vial with a magnetic stirring bar and a cap, the DES (250 mg) was prepared in advance. Alcohol **1a** (0.1 mmol) and nucleophiles **9a–h** (0.5 mmol) were added to the vessel at room temperature. When the reaction was over, neutralisation was done with a microspatula of potassium carbonate. Then, 5 mL of water was added to the crude reaction mixture and it was extracted with ethyl acetate (3 \times 5 mL). The organic layer was dried over MgSO_4 , the crude mixture was filtered, and the organic phase was evaporated under vacuum. The final product was purified by short flash column chromatography (silica gel and heptane : AcOEt), and if the crude product was clean, a Pasteur pipette could also be used for fast purification.

(E)-(3-(Benzyloxy)prop-1-ene-1,3-diyl)dibenzene (10a). Following the general procedure, compound **10a** was obtained as a colourless oil in 76% yield (22.8 mg).

(E)-Hexa-1,5-diene-1,3-diyl dibenzene (10b). Following the general procedure, compound **10b** was obtained as a colourless oil in 82% yield (19.2 mg).

tert-Butyl (E)-(1,3-diphenylallyl)carbamate (10c). Following the general procedure, compound **10b** was obtained as a white solid in 77% yield (23.8 mg).

Benzyl (E)-(1,3-diphenylallyl)carbamate (10d). Following the general procedure, compound **10b** was obtained as a white solid in 61% yield (20.9 mg).

(E)-(3-Azidoprop-1-ene-1,3-diyl)dibenzene (10e). Following the general procedure, compound **10b** was obtained as a colourless oil in 58% yield (13.6 mg).

(E)-N-(1,3-Diphenylallyl)benzamide (10f). Following the general procedure, compound **10f** was obtained as a white solid in 80% yield (25.1 mg).

(E)-N-(1,3-Diphenylallyl)-4-methylbenzenesulfonamide (10g). Following the general procedure, compound **10g** was obtained as a white solid in 90% yield (32.7 mg).

(E)-4-(1,3-Diphenylallyl)-N,N-dimethylaniline (10h). Following the general procedure, compound **10h** was obtained as a red oil in 95% yield (29.8 mg).

Author contributions

M. C. G. and R. P. H. conceptualised the idea and supervised the project. S. Z.-R. performed the experiments. All the authors discussed the results, wrote, and revised the manuscript.



Conflicts of interest

There are no conflicts to declare.

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