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

Stephany Zárate-Roldán, M. Concepción Gimeno* and Raquel P. Herrera*

a. Laboratorio de Organocatalysis Asimétrica, Departamento de Química Orgánica. Instituto de Síntesis Química y Catálisis Homogénea (ISQCH), CSIC-Universidad de Zaragoza. C/ Pedro Cerbuna 12, E-50009 Zaragoza, Spain. raquelph@unizar.es

b. Departamento de Química Inorgánica. Instituto de Síntesis Química y Catálisis Homogénea (ISQCH), CSIC-Universidad de Zaragoza. C/ Pedro Cerbuna 12, E-50009 Zaragoza, Spain. gimeno@unizar.es

A novel approach for the allylic alkylation of anilines, hydrazides and indole derivatives by the direct use of allylic alcohols is described under very mild conditions, such as room temperature and using sustainable deep eutectic solvents (DESs). The search of the optimum DES to be used in the reaction reveals that a simple mixture of choline chloride (ChCl) and lactic acid provides excellent results for a wide substrate scope and with high isolated yields. This methodology represents a great improvement compared to other procedures described in literature, for which high temperatures, stronger reaction conditions or metal catalysts are usually required. In some cases, this protocol affords to the first examples of trapping allylic carbocations with indole derivatives. All these features make this procedure an appealing and green alternative in comparison with other examples reported in literature on alkylation of amines by allylic alcohols. Preliminary mechanistic studies using unsymmetrically substituted alcohols support that the reaction should proceed by an S_N1 pathway.

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. In addition to their reactivity, the alkylation of amines is a widely used organic reaction involving an amine and an alkylating reagent having a good leaving group. Hence, some pivotal alkylated amines are also used for drug design in the pharmaceutical industry.

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 amount of leaving groups. In contrast, the N-alkylation of amines via nucleophilic substitution using alcohols is of paramount importance because the only waste of the reaction would be a molecule of water. Depending on the catalytic system, the generation of water could be also 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. A broad variety of metal catalysts have been extensively explored since the first examples of a catalysed alkylation of aniline using an alcohol via the so-called “hydrogen
borrowing”. However, high temperatures are usually required in these metal-catalysed \( N \)-alkylation of amines. Consequently, it is considered a challenge to use lower temperatures and greener catalytic systems from 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 allylamines are also fundamental building blocks and intermediates for the synthesis of some products such as Cinnarizine and Naftifine\(^7\) or Flunarizine\(^8\) (Figure 1).

![Figure 1. Allylamines as important building blocks.](image)

Nowadays, compliance with the principles of green chemistry has become extremely important. Hence, achieving more sustainable processes is of great interest for our society, preferring cheaper processes, with reduced waste production and using renewable sources. Among the improved processes using green solvents or more sustainable conditions especial mention deserves the use of ionic liquids (ILs),\(^9\) water\(^10\) or solvent-free conditions.\(^11\) Even though these approaches manage to avoid the use of organic solvents, they still require metals or high temperatures.

More recently, deep eutectic solvents (DESSs), which are considered a class of ILs, have appeared in the literature as greener alternatives to ILs.\(^12\) DESs are eutectic mixtures of Lewis or Brønsted acids and bases that contain anionic and cationic species.\(^13\) In spite of being considered a new type of ILs, sharing many physical properties with them, the composition and application areas of DES differ significantly. Important advantages over ILs are their lower price, biodegradability, easy preparation and atom economy.\(^14\) In addition, DESs have gained tremendous popularity due to their application in two main research areas as synthetic and catalytic media.\(^15\) These green solvents are obtained from a 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 is in the context of enzymatic catalysis by Gill and co-workers in 1994. There, they showed that DES could provide a better reaction media than conventional organic solvents.\(^16\)

To the best of our knowledge, DESs have not been used before for the \( N \)-alkylation of amine or derivatives by allylic alcohols. Despite only a scarce example of allylic amination of alcohols with anilines in absence of metal systems have been reported,\(^17\) the closest approach for this process is
In 2018, the authors showed the possibility to achieve a free-metal synthesis of \(N\)-allylanilines using 1,3-bis(carboxymethyl)imidazolium chloride (bcmim-Cl), an organic salt, as 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 the process. Hence, looking for an alternative for IOS, the use of lower temperatures is still interesting from a green and energetic perspective. A pivotal example that also deserves especial mention is the work reported by Alemán’s group using photocatalysis to obtain similar compounds.\(^{19,20}\)

**Results and discussion**

Motivated by the necessity of looking for greener conditions to obtain allylamines, in this work we envisioned the use of environmentally friendly DES as the medium and as promoter of the reaction as one of the simplest, greener, and straightforward approaches.\(^{21}\) First, different DESs were tested as medium and as catalysts in the reaction model between \((E)\)-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 prepare our media as a mixture of this component and different hydrogen-bond donors.\(^{22}\)

![Scheme 1](image)

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

The variety of DESs tested in this reaction were prepared at 60 °C as described in the literature, but then, the medium was cold 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 Bronsted acid used as the HBD component was able also 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 be still considered since the resulting mixture can be hard to handle when employed.\textsuperscript{23} Remarkably, in almost all cases we obtained excellent and almost quantitative yields. It is remarkable that the aniline used is expected to be less nucleophilic than other anilines with electron-donating groups. Even though in some cases similar results were achieved, we continued to the next step with the DES formed by ChCl:lactic acid (for more information about the formation of the DES see supporting information), since the crude of the reaction were cleaner, and it was easier to work with this medium. 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 as catalyst and at room temperature in absence of another additional catalysts 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 and hydrazides (Scheme 2 and Scheme 3).
Scheme 2. Scope of the allylic amination employing allyl alcohols 1a-e under the optimized reaction conditions using anilines 2a-j.
As presented in Scheme 2, halogenated anilines smoothly underwent N-allylation with excellent isolated yields and selectivity, obtaining in all cases the E isomer. Surprisingly, less active anilines (with electron-withdrawing groups) afforded the best results. Unfortunately, the reaction in the presence of electron-donating groups (OMe- or Me- ) in the aniline did not provide the product formation, but excellent yield was obtained between hindered aniline 2j and alcohol 1b. 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.\(^{18}\) The use of different substituted alcohols 1b-e also yielded the desired products 4a-f with very good results. More interesting was the obtention of products 4e and 4f, which until now had only been achieved by hydroamination of 1,3-dienes by using palladium,\(^{24}\) ruthenium\(^{25}\) or zeolite catalysts.\(^{26}\) Furthermore, representative hydrazides with electronically and differently substituted aryls and an alkyl derivate also provided the corresponding allylated adducts 6a-d with excellent isolated yields and selectivity, as depicted in Scheme 3.

Scheme 3. Scope of the allylic amination employing allyl alcohol 1a using hydrazides 5a-d.

In all cases, only the products E are cleanly obtained and no mixture of the Z isomer is observed (Schemes 2 and 3). Similar compounds were previously obtained using palladium catalysis,\(^{27}\) which makes our approach as an interesting synthetic alternative. These good results encouraged us to test the utility of our developed protocol with another structural core, the indole, as a representative example of pivotal structure. We have a large experience in the field of the Friedel-Crafts alkylation reaction using nitroalkenes, aldehydes and \(\beta,\gamma\)-unsaturated-\(\alpha\)-ketoesters,\(^{28}\) since the indole is considered a key structural core present in many biologically active compounds.\(^{29}\) Therefore, we tried to trap the in situ generated allylic carbocation with different indole derivatives as reported in Scheme 4.
Scheme 4. Scope of the allylic alkylation of indoles and pyrrole 7a-g.

It is worth noting, that this protocol has been overlooked in the literature so far for the preparation of these products. Therefore, our methodology represents the first example for trapping this allylic carbocation with these model molecules. In all cases, quantitative isolated yields with indoles bearing electron-donating or electron-withdrawing groups 7a-f and pyrrole 7g are obtained. The crudes of these reactions were clean and, in some cases, the final products were achieved after a simple extraction from the DES medium. The structure of final derivative 8c has been also confirmed by X-ray diffraction. To elucidate the reaction mechanism, we also synthesised unsymmetrically substituted alcohols 1h and 1i and we analysed the results of their reaction with aniline 2a (Scheme 5).

Scheme 5. Mechanistic assay.
As expected, in both cases a mixture of products 9a:9b is observed in a ratio around 50:50, which supports the generation of a carbocation in the medium and a S_N1-type mechanism.\textsuperscript{31,32} Although different reactivity is observed, since starting from alcohol 1h a 36% of final mixture is obtained, while starting from 1i a 66% yield is achieved. However, it is worth noted that with alcohol 1d, with possibility of isomerization of the carbocation affording to two different products, only one product (4e) is detected, which suggests that the reaction with the carbocation is faster than the isomerisation of the carbocation. Therefore, we believe that the hydroxyl group is activated with the assistance of ChCl and lactic acid, which would act as Lewis acid catalyst. Moreover, the effect of the stability of the carbocations is supported when comparing alcohol 1a with 1d and 1e, getting better results with 1a (benzylic and allylic carbocation) against 1d and 1e which are only an allylic carbocations (Scheme 1 and Scheme 2).

As a result, this protocol is complementary and an interesting alternative to the use of metal catalysts for the activation of this kind of substrates. Likewise, since the DES acts as both catalyst and solvent, the use of organic solvents is not necessary either.

**Conclusions**

In this work we have shown that the allylation of anilines, hydrazides and indole derivatives 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 to most of the examples described in literature so far, where high temperatures or stronger reaction conditions are usually necessary. In addition, we pioneer that 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 literature on alkylation of amines by allylic alcohols. Moreover, preliminary mechanistic experiments support that the reaction should proceed by an S_N1 pathway.

**Experimental**

**General experimental methods and instrumentation**

Analytical thin-layer chromatography was performed on 0.25 mm silica gel 60-F plates. ESI and MicroTof-Q mass analyser were used for HRMS measurements. NMR spectroscopy was conducted using a Bruker AVANCE–II spectrometer. \textsuperscript{1}H NMR spectra were recorded at 300 and 400 MHz; \textsuperscript{13}C\{\textsuperscript{1}H\}-APT NMR spectra were recorded at 75 and 101 MHz; CD\textsubscript{3}CN or CD\textsubscript{3}COCD\textsubscript{3} were used as the deuterated solvents. Chemical shifts were reported in the \(\delta\) scale relative to residual CH\textsubscript{3}CN (1.94 ppm) and CH\textsubscript{3}COCH\textsubscript{3} (2.05 ppm) for 1H-NMR and the central line of CD\textsubscript{3}CN (1.32 pp) and CD\textsubscript{3}COCD\textsubscript{3} (29.84 ppm) for \textsuperscript{13}C\{\textsuperscript{1}H\}-APT NMR.
All commercially available solvents and reagents were used as received. Spectral data for many of the synthesized compounds are consistent with values previously reported in the literature: 3a, 3b, 3c, 3d, 3e, 4a, 4b, 4c, 4d, 4e, 4f, 4g, 4h, 4i, 4j, 4k, 4l, 4m, 4n, 4o. The synthesis of alcohols 1b-i was performed following the described procedures in the literature. For all known products we also provide the $^1$H NMR.

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 appears. Then, the DES is cooled down in some cases before to set up the reaction.

General procedure for the synthesis of allylic anilines 3a-h and 4a-f
In a vial with a magnetic stirring bar and a cap, the DES (250 µL) is previously prepared. Then, alcohol 1a-e (0.1 mmol) and anilines 2a-j (0.2 mmol) were added to the vessel at room temperature. When the reaction is over, a neutralization was done with a micro spatula of potassium carbonate. Then, 5 mL of water is added to the reaction crude and it is extracted with ethyl acetate (3 x 5 mL). The organic layer was dried over MgSO$_4$, the crude was filtered, and the organic phase was evaporated under vacuum. The final product is purified by column chromatography (silica gel and toluene).

(E)-N-(1,3-diphenylallyl)-3,5-difluoroaniline (3b). $^1$H NMR (ppm) (300 MHz, CD$_3$CN): $\delta = 7.50-7.19$ (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). $^{13}$C($^1$H) APT NMR (ppm) (75 MHz, CD$_3$CN): $\delta = 165.0$ (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). $^{19}$F($^1$H) NMR (ppm) (282 MHz, CD$_3$CN): $\delta = -112.3$. HRMS (ESI+ µ-TOF): m/z (%) = [M-H]$^+$ Calcd for [C$_{21}$H$_{13}$F$_2$N]$^+$ 320.1256, found 320.1263.

(E)-N-(1,3-diphenylallyl)-3,4,5-trifluoroaniline (3c). $^1$H NMR (ppm) (300 MHz, CD$_3$CN): $\delta = 7.52-7.19$ (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). $^{13}$C($^1$H) APT NMR (ppm) (75 MHz, CD$_3$CN): $\delta = 152.6$ (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). $^{19}$F($^1$H) NMR (ppm) (282 MHz, CD$_3$CN): $\delta = -137.5$ (d, $J = 21.1$ Hz, 2F), 179.2 (t, $J = 21.1$ Hz, 1F). HRMS (ESI+ µ-TOF): m/z (%) = [M-H]$^+$ Calcd for [C$_{21}$H$_{15}$F$_3$N]$^+$ 338.1162, found 338.1167.

(E)-N-(1,3-diphenylallyl)-2,3,4,5,6-pentafluoroaniline (3d). $^1$H NMR (ppm) (300 MHz, CD$_3$CN): $\delta = 7.50-7.18$ (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). $^{13}$C($^1$H) APT NMR (ppm) (75 MHz, CD$_3$CN): $\delta = 142.9$ (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, 2C), 127.8 (s, 2C), 127.4
(E)-3-bromo-N-(1,3-diphenylallyl)aniline (3g). 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 [C₂₁H₁₃F₃N]⁺ 374.0974, found 374.0983.

(E)-N-(1,3-bis(4-bromophenyl)allyl)-(trifluoromethyl)aniline (4a). 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), 128.7 (s, 1C), 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 [C₂₂H₁₂BrF₂N]⁺ 507.9529, found 507.9506.

(E)-N-(1,3-di-p-tolyllallyl)-(trifluoromethyl)aniline (4b). ¹H NMR (ppm) (300 MHz, CD₃CN): 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). ¹³C(¹H) APT NMR (ppm) (75 MHz, CD₃CN): 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). ¹⁹F(¹H) NMR (ppm) (282 MHz, CD₃CN): δ = -61.3. HRMS (ESI- µ-TOF): m/z (%) = [M-H]^+ Calcd for [C₂₂H₁₂Br₂F₂N⁺ 380.1632, found 380.1636.

(E)-N-(1,3-bis(4-bromophenyl)allyl)-3,4-dichloroaniline (4c). ¹H NMR (ppm) (400 MHz, CD₃CN): δ = 7.52 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 8.5 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). ¹³C(¹H) APT NMR (ppm) (101 MHz, CD₃CN): 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 [C₂₁H₁₂Br₂Cl₂N]⁺ 507.8864, found 507.8855.

(E)-N-(1,3-bis(4-bromophenyl)allyl)-2-(tert-butyl)aniline (4d). ¹H NMR (ppm) (400 MHz, CD₃CN): 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). ¹³C(¹H) APT NMR (ppm) (101 MHz, CD₃CN): 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), 7.37 (m, 2H), 7.29 (d, J = 8.8 Hz, 1H), 6.73 (dd, J = 15.9, 6.5 Hz, 1H).
General procedure for the synthesis of allylic hydrazides 6a-d

In a vial with a magnetic stirring bar and a cap, the DES (250 µL) is previously prepared. Alcohol 1a (0.1 mmol) and hydrazides 5a-d (0.2 mmol) were added to the vessel at 60 °C. When the reaction is over, a neutralization was done with a micro spatula of potassium carbonate. Then, 5 mL of water is added to the reaction crude and it is extracted with ethyl acetate (3 x 5 mL). The organic layer was dried over MgSO₄, and the crude was filtered, and the organic phase was evaporated under vacuum. The final product is purified by column chromatography (silica gel and toluene).

\((E)-N'-(1,3\text{-diphenylallyl})-4\text{-nitrobenzohydrazide (6b)}\). \(^1\)H NMR (ppm) (300 MHz, CD₃CN): \(\delta = 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\{\(^1\)H\} APT NMR (ppm) (75 MHz, CD₃CN): \(\delta = 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 [C₂₂H₂₂N₂NaO₃]⁺ 396.1319, found 396.1296.

\((E)-N'-(1,3\text{-diphenylallyl})-4\text{-methoxybenzohydrazide (6c)}\). \(^1\)H NMR (ppm) (300 MHz, CD₃CN): \(\delta = 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\{\(^1\)H\} APT NMR (ppm) (75 MHz, CD₃CN): \(\delta = 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 [C₂₃H₂₂N₂NaO₂]⁺ 318.1573, found 318.1568.

\((E)-N'-(1,3\text{-diphenylallyl})\text{-octanehydrazide (6d)}\). \(^1\)H NMR (ppm) (300 MHz, CD₃CN): \(\delta = 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). \(^{13}\)C\{\(^1\)H\} APT NMR (ppm) (75 MHz, CD₃CN): \(\delta = 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 (%) = [M+Na]⁺ Calcd for [C₂₃H₂₂N₂NaO₂]⁺ 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 µL) is previously prepared. Alcohol 1a,g (0.1 mmol) and 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 is over, a neutralization was done with a micro spatula of 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 [C₂₅H₂₄Br₂N]⁺ 496.0270, found 496.0267.
potassium carbonate. Then, 5 mL of water is added to the reaction crude and it is extracted with ethyl acetate (3 x 5 mL). The organic layer was dried over MgSO₄, and the crude was filtered, and the organic phase was evaporated under vacuum. The final product is purified by column chromatography (silica gel and toluene).

**Synthesis of (E)-3-(1,3-diphenylallyl)-1H-indole-4-carbonitrile (8f).** ^1^H NMR (ppm) (300 MHz, CD₃CN): 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). ^1^C[^1^H] APT NMR (ppm) (75 MHz, CD₃CN): 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, 2C), 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 (%) = [M+Na]^+ Calcd for [C₂₄H₂₈N₂Na]^+ 357.1362, found 357.1348.

**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.

**Acknowledgements**

This research was funded by Agencia Estatal de Investigación (AEI), project PID2019-104379RB-C21 and PID2020-117455GB-I00/AEI/10.13039/501100011033; and Gobierno de Aragón-Fondo Social Europeo (Research Group E07_20R). S.Z.-R. thanks Consejo Nacional de Ciencia y Tecnología (CONACYT, Mexico) for a predoctoral fellowship.

**Notes and references**


30 CCDC 2218009 (8c) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk.


32 Other authors have also proposed a plausible S_N1 mechanism to explain this reactivity. Among them, authors of ref. 19, supporting with computational calculations their example.


