*Article*

# A Brønsted Acidic Deep Eutectic Solvent for *N*-Boc Deprotection

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**Abstract:** The tert-butyloxycarbonyl (Boc) group is one of the most widely used amine-protecting groups in multistep reactions in synthetic organic chemistry as well as in peptide synthesis. Traditional methods to remove the Boc group have disadvantages in terms of high acidity, the use of expensive reagents, excessive amounts of catalysts and harmful solvents as well as high temperatures, making them environmentally unsustainable. Therefore, more efforts must be stepwise tightened to make Boc removal practical, clean, and minimize any potential impact. We describe an efficient and sustainable method for *N*-Boc deprotection by means of a choline chloride/*p*-toluenesulfonic acid deep eutectic solvent (DES), which is used as a reaction medium plus catalyst. The adopted conditions allow the deprotection of a wide variety of *N*-Boc derivatives in excellent yields. The strategy has found advantages in greening, simplicity, and short reaction times, resulting in a useful alternative to standard methods.

**Keywords:** Boc protecting group; deprotection; catalytic deep eutectic solvents; *p*-toluenesulfonic acid; amines; amino acids; dipeptides

## 1. Introduction

Over the last few decades, the chemical sector, in line with the European plan that aims to become the first continent in the world with zero climate impact, behind the name of *Green Chemistry*, has faced the concept of "sustainable chemistry", with the aim to eliminate, or at least decrease, the use of potentially dangerous substances, harmful both to the environment and to human health [1]. To this end, 12 guiding principles have been enunciated that accompany the chemists to orient themselves towards a "green" synthetic design [2].

More recently, these principles have also been established in the pharmaceutical industry. In this regard, the ACS Green Chemistry Institute® Pharmaceutical Roundtable (GCIPR) (Washington, DC, USA) [3] has produced a Reagent Guide to inform and guide chemists towards greener reagents for various chemical transformations. In particular, GCIPR has identified among its priority research areas for the pharmaceutical sector the development of general methods for the removal of the Boc protecting group (Figure 1). It is a widely used amino protecting group due to its inertia toward catalytic hydrogenolysis, the induction of favorable solubility characteristics, and resistance to hydrolysis under basic conditions and nucleophilic reagents, making it useful when a condition of orthogonality between protective groups is required [4,5]. Given these advantageous characteristics, several amines, amino acids, and peptide synthons supplied to the pharmaceutical industry are sold BOC-protected [6].
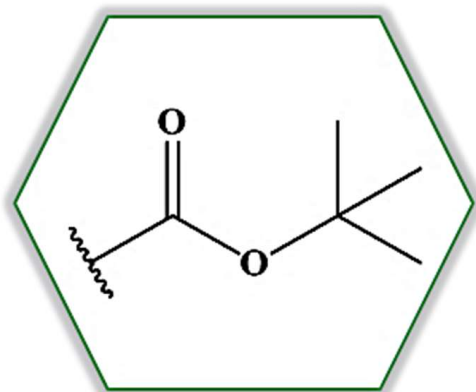
**Figure 1.** Chemical structure of Boc-protecting group.

Various experimental procedures for Boc-deprotection have been developed that generally involve the use of strong acids, such as phosphoric acid [7,8], HCl [9,10], H$_2$SO$_4$ [11], Lewis acids [12–14] or basic conditions [15,16]. These methods present several disadvantages in terms of their high acidity, use of expensive reagents, excessive amounts of catalysts and organic solvents, low chemoselectivity, high temperatures, as well as catalyst recovery problems [17]. Trifluroacetic acid (TFA) still represents the reagent of choice to remove the Boc group; however, even this approach has disadvantages as it is toxic, volatile, corrosive, and not environmentally friendly [18,19]. It is an extremely corrosive compound and relatively expensive, especially when it is used in solid-phase peptide synthesis, which requires large quantities of this material.

Therefore, the main "Green Criteria" requires the replacement of conventional solvents and reagents that present important safety as well as the reduction in hazardous waste to a minimum [20–22]. The development of an environmentally benign, atom-economic, and sustainable method in the Boc-deprotection still remains a contemporary challenge in synthetic chemistry and the chemical industry.

In this regard, G. Wang et al. described the use of supercritical water under pressure as a medium for the *N*-Boc deprotection of both aromatic and aliphatic *N*-Boc amines [23,24]. However, the methodology was characterized by long reaction times and showed incompatibility with the ester functionality. Additionally, an ionic liquid has been proposed as a reaction medium for the *N*-Boc deprotection strategy [25]. Nevertheless, the addition of a water–dioxane mixture to solubilize the substrates, as well as high reaction temperatures, were required. More recently, Mandal et al. reported a FeCl$_3$-mediated Boc-deprotection strategy for peptide synthesis both in the solution and in a solid phase [12–14]. However, the protocol used dichloromethane (DCM) as the medium and presented limitations related to the recovery step of the Boc cleaved product.

In order to reduce the incidence on the environment of chemical applications, deep eutectic solvents (DESs) have emerged as a step ahead in this field, thanks to their green properties over conventional solvents, such as their negligible vapor pressure, recyclability, and modulation of properties [26–29]. In this regard, a recent and very interesting trend is the employment of DESs as actual reactive components. Reactive deep eutectic solvents (RDESs) provide a reaction medium containing one or more reaction reagents or a catalyst, which results in numerous advantages, including minimizing waste formation, improving the atom economy of the process, as well as the efficient separation of the final products by precipitation and enhancing the overall process yield [30–35]. Given the following advantages, the use of neoteoric solvents, such as DESs, in deprotection reactions could gain much importance in sustainable development chemistry.
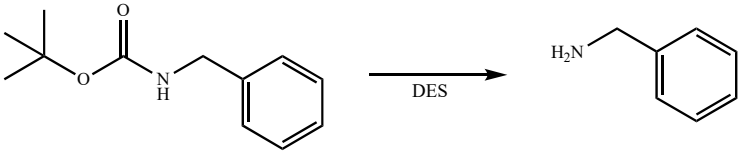
Herein, we demonstrated a very simple method of cleavage by employing a DES composed of *p*-toluenesulfonic acid monohydrate (pTSA) and choline chloride (ChCl), which was used simultaneously as a reaction medium and catalyst.

In choosing the best synthetic route for Boc deprotection that meets the criteria required by Green Chemistry, the Pharmaceutical Roundtable of the ACS Green Chemistry Institute has furnished a Guide to Reagents with the aim of guiding the researcher to use more sustainable reagents [36]. The choice of the most suitable reagent was summarized in a Venn Diagram, in which each circle represented a criterion, namely: 'Scalability', 'Greenness,' and 'Wide utility'. The ideal reagent should have all three characteristics, and therefore, should be located in the center, between the intersections of the circles. According to this reagent guide, *p*-toluenesulfonic acid (pTSA) represents the best alternative to TFA for an eco-friendly Boc-deprotection procedure as it is cheap, readily available, and also biodegradable. It is a Brønsted acid catalyst largely investigated for several reactions, given its strong acidity [37–40]. The use of a DES containing pTSA as a component makes the entire procedure more efficient for the cleavage at room temperature of various amines, amino acid methyl esters, and dipeptides in short reaction times [41–43]. In addition, the use of *p*-toluenesulfonic acid in the DES form allows disadvantages to be overcome, such as its deliquescent behavior and difficulty of recovery.

## 2. Results and Discussion

The main goal of our study was to present a simple and cost-effective approach to the deprotection of protected *N*-Boc derivatives that leads to the corresponding deprotected products with high purities and high yields without the need to apply post-reaction purification. Since the selective deprotection of the Boc group is conducted under mildly acidic conditions, we tested the catalytic behavior of different Brønsted acid and Lewis acid-type DESs. In particular, the quaternary ammonium salt choline chloride (ChCl) has been used as HBA since it is an economic, biodegradable, nontoxic, and even edible quaternary salt that can be extracted from biomass or easily synthesized from fossil reserves [44], whereas pTSA, oxalic acid, citric acid, malonic acid, succinic acid, and $FeCl_3$ were chosen as HBDs and catalysts (Table 1).

**Table 1.** Optimization of conditions for the cleavage of *N*-Boc protecting group.



|       |      **1a**       |           |            |      **2a**      |
| ----- | ---------------- | --------- | ---------- | --------------- |

| Entry | DES (1:1 Molar Ratio) | Temp. (°C) | Time [b] (min.) | Yield (%) |
| --- | --- | --- | --- | --- |
| 1 | ChCl: pTSA | 25 | 10 | 98 |
| 2 | ChCl: oxalic acid | 25 | 30 | 58 |
| 3 | ChCl: citric acid | 50 [a] | 30 | 15 |
| 4 | ChCl: malonic acid | 25 | 60 | 26 |
| 5 | ChCl: succinic acid | 25 | 60 | 20 |
| 6 | ChCl: $FeCl_3$ | 25 | 15 | 62 |

[a] Reaction conducted at 50 °C due to the high viscosity of the investigated DES; [b] Times refer to the respective points of maximum conversion of the substrate, according to GC/MS.

All RDESs have been prepared by using a defined protocol based on mixing the components in a defined molar ratio and then heating at 60–80 °C for 2 h, under constant stirring in a round bottom flask, until a stable homogeneous colorless liquid phase was formed [45]. After the preparation, the DESs were cooled to room temperature and kept closed at room temperature. The DESs were confirmed by Infrared Spectrophotometry (FT-IR) and differential scanning calorimetry (DSC) analysis. Our data matched those available from the literature [21,22].

All the prepared RDESs were tested on the deprotection of *N*-Boc-benzylamine (**1a**), selected as a model substrate, and the reaction progress was followed by the TLC and GC/MS analysis of crude reaction mixtures. The results of the development and optimization of the deprotection studies are displayed in Table 1. For a systematic study of the action of the investigated systems, all reactions were conducted at room temperature, except in the case of the DES, which was prepared using citric acid and required a temperature of 50 °C due to its high viscosity that limited the application as a reaction medium. The times shown in the table refer to the respective points of maximum conversion in the substrate, as verified by GC/MS. To our delight, on the treatment of *N*-Boc benzylamine (1 mmol) with 1 mL of ChCl: pTSA (1:1) at room temperature, the deprotection was smoothly accomplished after only 10 min in a 98% yield, and the free amine was detected by GC-MS after aqueous work-up (Table 1, entry 1).

Otherwise, when the model reaction was screened in the other Brønsted acid and Lewis acid type DESs, **2a** was produced in lower yields (**entries 2–6**, Table 1). More specifically, by performing the same procedure in oxalic acid-based DES (**entry 2**, Table 1), the deprotection of the amine was achieved in a 58% yield after 30 min. At the same time, using other DESs based on Brønsted acids (**entries 3–5**, Table 1), a drastic decrease in yield was observed, even when increasing the reaction time. This is probably related to the lower acidic character of the acids used compared to the first mentioned. In the case of the citric acid-based DES, the poor yields observed were probably justified by the highly viscous medium, which did not allow an easy handle of the compound. When the deprotection process was performed in $FeCl_3$ based Lewis acid DES (**entry 6**, Table 1), amine deprotection was obtained in a 62% yield after 15 min, confirming the already present literature data that demonstrate its suitability as a catalyst in this transformation, also because it is economic and sustainable [12–14]. However, as previously reported, the employment of $FeCl_3$ makes the work-up procedure more complicated as a large amount of the deprotected compound went into the water with iron during the work-up. An example of the Boc-deprotection protocol carried out with *p*-toluensulfonic acid was reported by Stone et al. [46]. Nevertheless, *N*-deprotection occurred after 60 min in a mixture of dichloromethane/tetrahydrofuran (DCM/THF), and the purification procedures were very difficult.

Encouraged by our preliminary results, we next examined the scope and limitations of our method on a variety of aliphatic and aromatic *N*-tert butylcarbamates. The generality of this procedure is shown in Table 2, exhibiting the efficient deprotection of various classes of nitrogen-containing functional groups (primary and secondary amines, anilines, etc.). All substrates display quantitative isolated yields after reaction times varying from 10 to 30 min.

In particular, *N*-Boc-protected 2-phenylethylamine (**1b**) easily undergoes deprotection under the selected reaction conditions to afford the desired amine in an excellent yield (entry 1, Table 2). The removal of the Boc group works well even in the case of *N*-Boc-aniline (**1c**) and its substituted derivatives (entries 2–6, Table 2). More specifically, the deprotection reaction of **1c** proceeded in 10 min, unlike its derivatives like *N*-Boc toluidine (**1d**) and *N*-Boc anisidine (**1e**), which required shorter reaction times (both 8 min), probably for the effect of the electron-donating substituents present in para position to the amino function. *N*-Boc 3-nitroaniline (**1f**) underwent deprotection within 20 min, probably due to the presence of the nitro electron withdrawing group, which reduced the reactivity of the molecule.

**Table 2.** Scope for the deprotection of *N*-Boc amines [a].



| Entry | *N*-Boc-amine | Product | Time (min) | Yield (%) [b] |
|-------|---------------|---------|------------|----------------|
| 1 | 1b | 2b | 10 | >98 |
| 2 | 1c | 2c | 10 | >98 |
| 3 | 1d | 2d | 15 | >98 |
| 4 | 1e | 2e | 15 | >98 |
| 5 | 1f | 2f | 20 | 90 |
| 6 | 1g | 2g | 20 | 86 |
| 7 | 1h | 2h | 15 | >98 |
| 8 | 1i | 2i | 10 | >98 |
| 9 | 1j | 2j | 10 | >98 |

**Table 2.** *Cont.*

| Entry | *N*-Boc-amine | Product | Time (min) | Yield (%) [b] |
|-------|---------------|---------|------------|-----------|
| 10 | **1k** | **2k** | 10 | >98 |
| 11 | **1l** | **2l** | 20 | >98 |
| 12 | **1m** | **2m** | 20 | >98 |
| 13 | **1n** | **2n** | 25 | 70 |
| 14 | **1o** | **2o** | 30 | 56 |

[a] Reaction conditions: all reactions were carried out by using 1 mmol of *N*-Boc amine in 1 mL of ChCl: pTSA at rt for the time reported above. [b] Isolated yields after work-up.

Next, the method was also successfully applied to the deprotection of several *N*-Boc-protected aliphatic amines. As shown in the Table, cyclic and aliphatic primary amines (entries 7–12, Table 2) can be fully deprotected within 10–20 min. At the same time, when the protocol was applied to secondary Boc-protected amines (entries 14–15, Table 2), the free amines were obtained in excellent yields after 30 min.

The secondary heterocyclic amine, such as *N*-Boc piperidine (**2h**), underwent deprotection in 15 min in an almost quantitative yield. The deprotection of *N*-Boc 4pyridin-4-amine (**2f**) required a longer reaction time, about 20 min, and this behavior could be explained by the fact that the nitrogen of the heterocyclic ring was protonated by the DES, also leading to a decrease in the yield. *N*-Boc ethylbenzylamine (**1n**) afforded the unmasked amine in 30 min and with a 70% yield, while the presence of the isopropyl group in the secondary amine *N*-Boc isopropyl benzylamine (**1o**) led to a reduction in the yield (56%), probably due to the steric hindrance that the isopropyl group obtains from the molecule.

An important advantage of the protocol is the simplicity of the recovery of the reaction products. The deprotected substrates can be isolated directly from the reaction mixture as tosylate salts just by washing them with water, followed by recrystallization from ethyl acetate (AcOEt). Free substrates were instead obtained by a simple workup that involved the addition of an aqueous solution of sodium bicarbonate $NaHCO_3$ (5%). The crude material was then extracted with AcOEt (3 × 5 mL). In both cases, no tedious chromatographic purification was required. All the known compounds had spectroscopic data identical to those reported in the literature [21,22].

Considering the great scientific and industrial value of *N*-Boc protection in peptide synthesis, we next investigated the *N*-Boc deprotection of different amino acid derivatives.

For this purpose, some methyl esters of amino acids have been preliminarily protected on the α-amino function with the protecting group Boc. As shown in Table 3, methyl esters of amino acids have aliphatic side chains such as L-Alanine methyl ester and D-Alanine methyl ester, which underwent deprotection in just 10 min and both with yields greater than 98% (entry 1,2, Table 3). Esters are compatible with the reaction conditions (entries 1–5, entry 7, Table 3). In each example, no product resulting from the degradation of methyl esters was observed. The selectivity of deprotection was confirmed in the ^{1}H NMR spectrum by the presence of a methyl ester group signal at about 3.70 ppm. Branched-chain amino acid methyl esters, such as *N*-Boc L-Leucine and *N*-Boc Valine, required longer deprotection times, of about 25 min, with lower yields with respect to amino acids with aliphatic side chains; in particular, leucine was obtained with a yield of 68%, and valine with a yield of 63%, probably both due to the steric hindrance of their side chains (entries 3–4, Table 3).

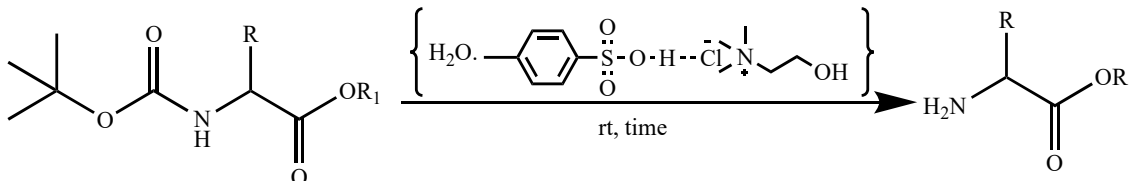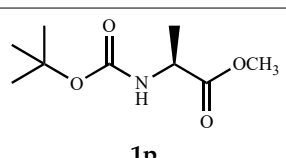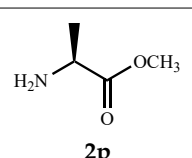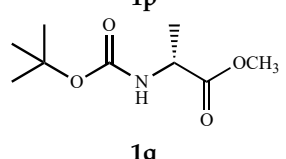**Table 3.** DES-catalyzed deprotection of *N*-Boc amino acid derivatives and *N*-Boc dipeptide [a].
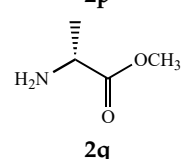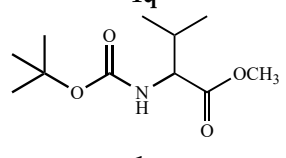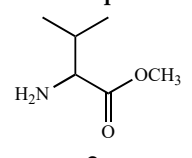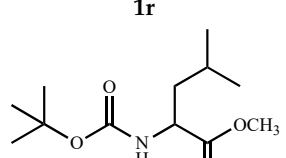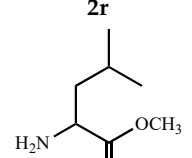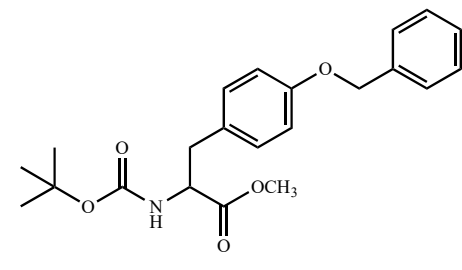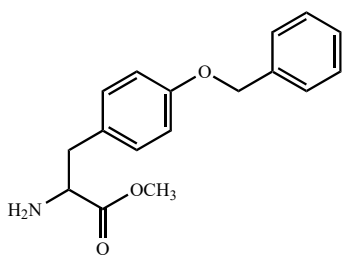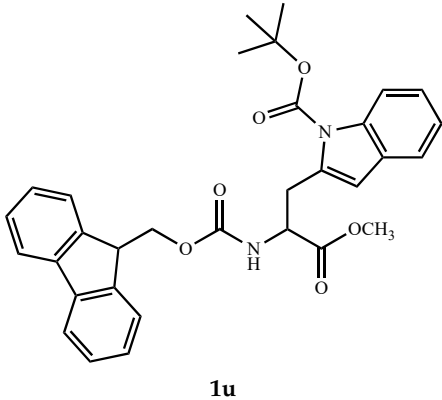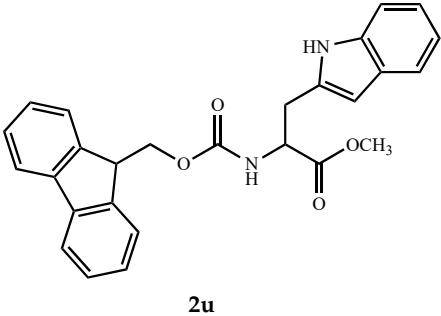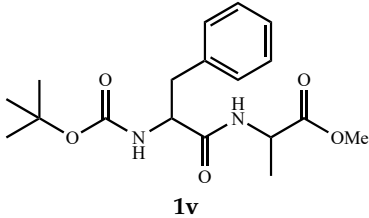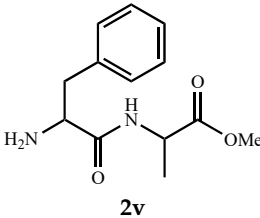


| Entry | *N*-Boc-amino Acid | Product [c] | Time (min.) | Yield (%) [b] |
|-------|--------------------|-------------|-------------|---------------|
| 1 | **1p** | **2p** | 10 | >98 [d] |
| 2 | **1q** | **2q** | 10 | >98 [d] |
| 3 | **1r** | **2r** | 20 | 63 |
| 4 | **1s** | **2s** | 15 | 68 |
| 5 | **1t** | **2t** | 35 | >98 |

**Table 3.** *Cont.*

| Entry | *N*-Boc-amino Acid | Product [c] | Time (min.) | Yield (%) [b] |
|---|---|---|---|---|
| 6 | **1u** | **2u** | 40 | 90 |
| 7 | **1v** | **2v** | 15 | >98 |

[a] Reaction conditions: all reactions were carried out using 1 mmol of Boc-amine in 1 mL of ChCl: the pTSA at rt for the time reported above. [b] Isolated yields after work-up. [c] MS and NMR were used to verify the exact mass and structure of the prepared product. [d] To verify enantiomeric purity, chiral HPLC was performed and compared with the commercially available racemic mixture. A single peak was observed at the corresponding retention time, while the racemic mixture provided two.

It was important, at this point, to verify whether the reaction conditions adopted could make the strategy orthogonal, that is, without affecting other protecting groups present in the side chains of the amino acids. Substrates bearing acid-labile protecting groups, such as benzyl ether, remained stable under our conditions. In this regard, we have chosen as substrate the *O*-Benzyl-L-tyrosine methyl ester since the Boc/Bn strategy, where the Boc group was used as a temporary protecting group of the amino function and Bn (benzyl) of the side chains of the amino acids, is one of the most widely used protection strategies in peptide synthesis [47].

In particular, the α-amino function of the *O*-benzyl-tyrosine methyl ester was protected with the Boc protecting group, and subsequently, its deprotection was carried out in DES ChCl:pTSA (entry 5, Table 3). In this case, the Boc-group was removed selectively without affecting the O-benzyl ether protection, as proven by the GC/MS and NMR analysis (see Supplementary Information).

The Fluorenylmethyloxycarbonyl (Fmoc) and Boc protecting groups are widely used in peptide synthesis, and therefore, it is of great importance to developing conditions that successfully remove the Boc protecting group while leaving the Fmoc protection unchanged [48–52]. To this aim, the stability of the Fmoc group present in the tryptophan side chain was evaluated (entry 6, Table 3), and it was shown that Fmoc was well tolerated under the reaction conditions adopted. Finally, the preparation of the dipeptide *N*-Boc-L-Phenylalanyl-L-Alanine methyl ester allowed us to explore the possible extension of the protocol for the deprotection of the amino function of a dipeptide. The dipeptide under consideration underwent the deprotection reaction in Bronsted acidic DES ChCl:pTSA within 15 min (entry 8, Table 3). The removal of the Boc protecting group was monitored by TLC and GC/MS (see Supplementary Materials) analysis from which it was shown that cleavage occurred in the yields demonstrating the high advantage of the DES in this protocol.

Even in the case of deprotection reactions carried out on amino acid systems and the dipeptide, the final products were recovered by a simple work-up operation without the need for any chromatographic purification. To obtain the amino acid or dipeptide not charged and neutralized, a saturated aqueous solution of $NaHCO_3$ was added and extracted with ethyl acetate and was subsequently washed with brine. The combined organic layers were dried on magnesium sulphate ($MgSO_4$), filtered, and vacuum-evaporated to provide the raw product in quantitative yield. All the compounds obtained have been characterized by GC/MS and NMR and show spectroscopic data comparable to those reported in the literature [21,22,51].

Based on the previously reported literature [53,54], a plausible mechanistic pathway for Boc-cleavage has been hyphotized (Scheme 1). At first, the Bronsted acidic site of the CHCl:pTSA DES activated the carbamate oxygen by protonation, therefore, weakening and breaking the C=O bond causing the loss of the *t*-butyl carbocation. The reversible hydrogen bonding between the DES and the substrate made it so that the resultant carbamic acid underwent proton transfer followed by decarboxylation to provide the deprotected amine salt. The final basic workup affords the free amine.
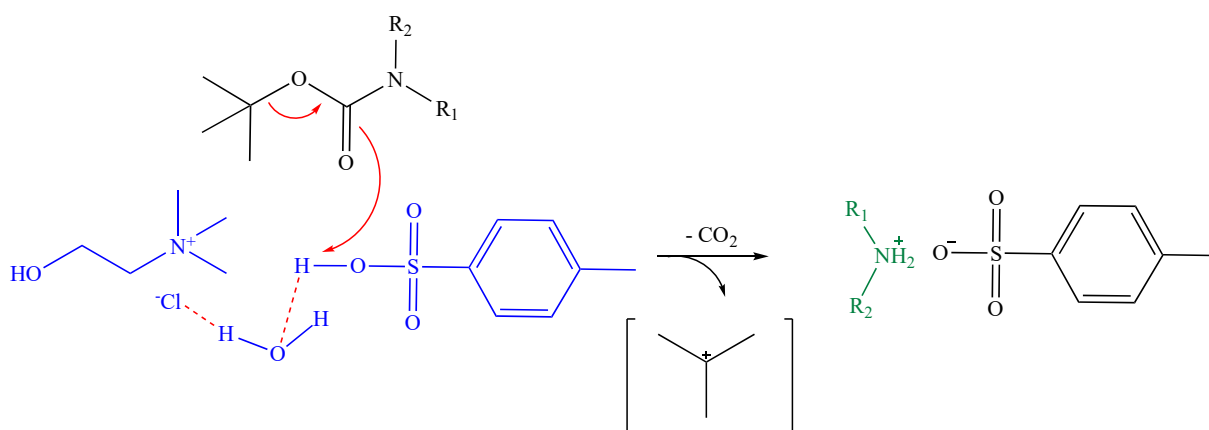


**Scheme 1.** Proposed mechanism for Boc-deprotection in RDES.

Finally, the feasibility of the developed method was evaluated for a somewhat scaled-up (on the gram scale) experiment with the model substrate *N*-Boc benzylamine. Even in this case, the reaction proceeded smoothly, affording the desired free amine in 94% of yields, almost similar in all respects to the 1 mmol scale entry (Table 1, entry 1). These results highlighted the efficiency of the RDES for large-scale production as well.

To understand the efficiency of our protocol with respect to conventional methods already reported in the literature for the deprotection of the Boc group, we calculated the process mass intensity (PMI) and complete environmental factor (E-factor). These two metrics are key mass-based metrices useful for the evaluation of the *greenness* of a synthetic process. [55–57]: The E-Factor takes into account waste byproducts, solvent losses, and anything else that can be regarded as a waste; PMI, instead, takes into account the mass of all the material used in a synthetic process relative to the amount of the final product. Table 4 shows the two metrics calculated for our procedure and compares them with those of other reported methodologies.

The PMI and E-factor for our procedure were calculated as 68 and 67, respectively, whereas those for the other procedures were found to be higher (see supporting information for calculation). Nevertheless, the ideal E factor is 0, and higher E factors are relatively less amenable. However, it matters what kind of wastes are produced because, in our protocol, choline chloride and *p*-toluensulfonic acid may be of little concern compared to toxic organic volatile solvents and corrosive acids. Therefore, these data indicate the feasibility, greenness, and sustainability of our process.

**Table 4.** Calculated green metrics percentage yield, PMI, and E-factor for our Boc deprotection procedure and for already reported methods.

| Entry | Solvents and Reagents | Yield (%) | PMI | E-Factor | Ref. |
|---|---|---|---|---|---|
| 1 | THF, aqueous $H_3PO_4$ | 94 | 91 | 90 | [7] |
| 2 | DCM, aqueous $H_3PO_4$ | 91 | 96 | 95 | [8] |
| 3 | DCM, $H_2SO_4$ | 93 | 383 | 382 | [11] |
| 4 | DCM, TFA | 98 | 92 | 91 | [18,19] |
| 5 | ChCl:pTSA | 98 | 68 | 67 | Our work |

## 3. Materials and Methods

### 3.1. General Informations

Commercially available reagents were purchased from Sigma-Aldrich Chemical Co. (Milano, Italy) and used as supplied unless stated otherwise. All syntheses were carried out in atmospheric conditions. The $^1$H NMR and $^{13}$C NMR spectra were recorded at 300 MHz. Spectral analysis was performed at 293 K on the diluted solutions of each compound by using $CDCl_3$ as the solvent. Chemical shifts ($\delta$) are reported in ppm and referenced to $CDCl_3$ (7.25 ppm for $^1$H and 77.0 ppm for $^{13}$C spectra). Coupling constants ($J$) are reported in hertz (Hz). Reaction mixtures were monitored by thin layer chromatography (TLC) using Merck Silica gel 60-F254 precoated glass plates or 0.2% ninhydrin in ethanol. GC-MS analyses were carried out using a 30 m HP-35MS capillary column with a 0.25 mm internal diameter and a 0.25 μm film thickness. The mass detector was operated in the electron impact ionization mode (EI-MS) at an electron energy of 70 eV. He was used as the carrier gas. The injection port was heated to 250 °C. The oven temperature program was initially set at 50 °C and held for 2 min, then was ramped to 280 °C at a rate of 14 °C/min and maintained at 280 °C for a further 10 min.

### 3.2. Preparation of DESs

DESs were prepared following the heating method [58]. First, choline chloride was dried in a high vacuum pump at 50 °C for 1 day, while the hydrogen bond donors (pTSA, oxalic acid, citric acid, malonic acid, succinic acid, and $FeCl_3$) were used without any further purification (Table 5). The hydrogen bond acceptor (HBA) and hydrogen bond donors (HBDs) at a proper molar ratio (1:1) were placed in a glass screw cap vial and were heated to 60–70 °C under a constant stirring speed of 100 rpm by using a heating plate (Bibby Scientific Limited, Beacon Road, Stone, Staffordshire, UK) until a homogeneous clear liquid was formed.

**Table 5.** Deep eutectic solvents investigated in the present work.

| Entry | HBA | HBD | HBA/HBD Molar Ratio | mp HBD (°C) | Tm (°C) | Ref. |
|---|---|---|---|---|---|---|
| 1 | ChCl | Monohydrated pTSA | 1:1 | 103 | 37 | [42] |
| 2 | ChCl | Oxalic acid | 1:1 | 101 | 34 | [58] |
| 3 | ChCl | Citric acid | 1:1 | 153 | 69 | [58] |
| 4 | ChCl | Malonic acid | 1:1 | 136 | 10 | [59,60] |
| 5 | ChCl | Succinic acid | 1:1 | 184 | 71 | [59,60] |
| 6 | ChCl | $FeCl_3$ | 1:1 | 306 | 65 | [58] |

### 3.3. General Procedure for the N-Boc Deprotection of Amines and Amino Acid Derivatives

In a 10 mL round-bottomed flask, 1 mL of DES (ChCl:pTSA) was maintained under stirring, and an *N*-Boc-protected amine or *N*-Boc-protected amino acid derivative (1 mmol) was added. The mixture was allowed to stir at room temperature. TLC and GC/MS were used to monitor the reaction. Upon completion of the reaction, an aqueous solution of sodium bicarbonate $NaHCO_3$ (5%) was added. The crude material was then extracted with AcOEt (3 x 5 mL). The organic layer was dried over anhydrous $Na_2SO_4$, filtered, and finally concentrated under a low vacuum using a rotary evaporator to yield the pure

deprotected amine. Spectroscopic data (GC-MS, $^1$H-NMR e $^{13}$C-NMR) were compared to those of the pure products. The obtained spectroscopic data are in agreement with the literature data [21,22,51].

### 3.3.1. Benzylamine (**2a**)

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.40–7.20 (m, 5H, ArH), 3.86 (s, 2H), 1.53 (2, 2H, NH$_2$). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 143.3, 129.1, 127.7, 126.9, 46.5. GC/MS (EI): $m/z$ (%) 107 (M$^+$) (59), 106 (100), 91 (14), 79 (43), 77 (25), 65 (7), 51 (17).

### 3.3.2. 2-Phenylethylamine (**2b**)

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.32–7.18 (m, 5H, ArH), 2.94 (t, 2H, J = 6.7 Hz, CH2), 2.72 (t, 2H, J = 6.7 Hz, CH2), 1.24 (s, 2H, NH2) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) δ 139.9, 128.8, 128.0, 126.2, 42.8, 39.4. GC/MS (EI): $m/z$ (%) 121 (M$^+$) (23), 117 (5), 103 (9), 91 (100), 77 (18), 65 (48), 51 (25), 41 (7).

### 3.3.3. Aniline (**2c**)

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.24–7.12 (m, 3H), 6.77–6.65 (m, 2H), 3.61 (br s, 2H, NH2) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) δ 132.8, 130.2, 128.2, 123.5. GC/MS (EI): $m/z$ (%) 93 (M$^+$) (100), 92 (13), 66 (42), 65 (23), 52 (5).

### 3.3.4. *p*-Toluidine (**2d**)

$^1$H NMR (300 MHz, CDCl$_3$) δ 6.94 (d, 2H, *J* = 8.4 Hz, ArH), 6.60 (d, 2H, *J* = 8.4, ArH), 3.32 (br s, 2H, NH$_2$), 2.23 (s, 3H, CH$_3$) ppm. GC/MS (EI): $m/z$ (%) 107 (M$^+$) (68), 106(100), 91 (4), 77 (18), 63 (4), 52 (9), 41 (4).

### 3.3.5. *p*-Anisidine (**2e**)

$^1$H NMR (300 MHz, CDCl$_3$) δ 6.77 (d, 2H, *J* = 8.4 Hz, ArH), 6.66 (d, 2H, *J* = 8.4 Hz, ArH), 3.78 (s, 3H, OMe), 3.41 (s, 2H, NH$_2$) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) δ 152.8, 140.0, 116.0, 114.8, 55.6. GC/MS (EI): $m/z$ (%) 123 (M$^+$) (62), 108 (100), 95 (4), 80 (48), 65 (8), 53 (19), 41 (4).

### 3.3.6. Pyridin-4-amine (**2f**)

$^1$H NMR (300 MHz, CDCl$_3$) δ 8.29 (d, 2H, *J* = 5.1 Hz, ArH), 7.02 (d, 2H, *J* = 5.1 Hz, ArH), 3.68 (s, 2H, CH$_2$), 1.37 (s, 2H, NH2) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) δ 151.8, 129.4, 121.8, 44.7. GC/MS (EI): $m/z$ (%) 108 (M$^+$) (24), 107 (25), 92 (4), 80 (100), 79 (26), 65 (6), 51 (17), 40 (3).

### 3.3.7. 3-Nitroaniline (**2g**)

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.60 (d, 1H, *J* = 8.1 Hz, ArH), 7.45 (s, 1H, ArH), 7.29 (m, 1H, ArH), 6.96 (d, 1H, *J* = 7.8 Hz, ArH), 4.00 (br s, NH$_2$) ppm. GC/MS (EI): $m/z$ (%) 138 (M$^+$) (75), 122 (4), 108 (5), 92 (85), 80 (10), 65 (100), 52 (12), 39 (25).

### 3.3.8. Piperidine (**2h**)

$^1$H NMR (300 MHz, CDCl$_3$) δ 2.80–2.77 (M, 4H, NHCH$_2$, NHCH$_2$), 2.12 (S, 1H, NH), 1.53–1.50 (M, 6H, (CH$_2$)$_3$) ppm. GC/MS (EI): $m/z$ (%) 85 (M$^+$) (50), 84 (100), 70 (11), 57 (30), 56 (49).

### 3.3.9. Allylamine (**2i**)

$^1$H NMR (300 MHz, CDCl$_3$) δ 5.78–5.65 (m, 1H, CH), 4.90 (m, 1H, CH$_2$), 4.79 (m, 1H, CH$_2$), 3.06 (d, 2H, *J* = 5.4 Hz, CH$_2$), 1.02 (s, 2H, NH$_2$) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) δ 139.6, 113.2, 44.5.

### 3.3.10. Cyclopentylamine (**2j**)

$^1$H NMR (300 MHz, CDCl$_3$) δ 3.31 (m, 1H, CH), 1.80–1.68 (m, 4H, CH$_2$, CH$_2$), 1.60–1.59 (m, 2H, CH$_2$), 1.57–1.51 (m, 2H, CH$_2$), 1.32–1.21 (m, 2H, NH$_2$) ppm. GC/MS (EI): *m/z* (%) 85 (M$^+$) (12), 67 (4), 56 (100), 43 (12).

### 3.3.11. Pentylamine (**2k**)

$^1$H NMR (300 MHz, CDCl$_3$) δ 2.61 (t, 2H, *J* = 6.9 Hz, CH$_2$), 2.16 (s, 2H, NH$_2$), 1.43–1.34 (m, 2H, CH$_2$), 1.32–1.24 (m, 4H, CH$_2$), 0.85 (t, 3H, *J* = 6.7 Hz, CH$_3$) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) δ 41.9, 33.1, 28.9, 22.4, 13.9. δ GC/MS (EI): *m/z* (%) 87 (M$^+$) (98), 69 (10), 58 (5), 55 (23), 51 (5), 45 (70), 41 (91), 30 (100).

### 3.3.12. (*R*)-1-Phenylethylamine (**2l**)

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.51–7.22 (m, 5H, ArH), 4.10 (q, 1H, *J* = 13.4 and *J* = 6.6 Hz, CH), 2.15 (s, 2H, NH2), 1.57 (d, 3H, *J* = 6.6 Hz, CH3) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 147.6, 129.4, 126.9, 125.9, 51.4, 25.5. GC/MS (EI): *m/z* (%) 121 (M$^+$) (1), 120 (6), 106 (100), 103 (4), 79 (30), 77 (24), 51 (10).

### 3.3.13. (*S*)-1-Phenylethylamine (**2m**)

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.31–7.22 (m, 5H, ArH), 4.10 (q, 1H, *J* = 13.2 *J* = 6.6 Hz, CH), 2.05 (s, 2H, NH$_2$), 1.57 (d, 3H, *J* = 6.6 Hz, CH3) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) δ 174.6, 129.4, 126.9, 125.8, 51.4, 25.4. GC/MS (EI): *m/z* (%) 121 (M$^+$) (1), 120 (6), 106 (100), 103 (4), 79 (30), 77 (25), 51 (10).

### 3.3.14. Ethyl Benzylamine (**2n**)

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.40–7.25 (m, 5H, ArH), 3.79 (s, 2H, CH$_2$Ph), 2.74–2.67 (q, 2H, *J* = 7.1 Hz, CH$_2$CH$_3$), 1.54 (s, 1H, NH), 1.16 (t, 3H, *J* = 7.2 Hz) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 140.5, 128.3, 127.2, 126.8, 53.7, 43.6, 15.2. GC/MS (EI): *m/z* (%) 135 (M$^+$) (13), 134 (15), 120 (32), 92 (6), 91 (100), 79 (6), 65 (13), 58 (15), 51 (5).

### 3.3.15. *N*-Isopropylbenzylamine (**2o**)

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.36–7.27 (m, 5 H, ArH), 3.81 (s, 2H, CH$_2$), 2.89 (q, 1H, *J* = 6.2 Hz, CH), 1.33 (s, 1H, NH), 1.29 (d, 6H, *J* = 6.3 Hz, CH(CH$_3$)$_2$) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 140.8, 128.5, 127.5, 127.4, 50.6, 48.1, 23.5. GC/MS (EI): *m/z* (%) 149 (M$^+$) (4), 134 (42), 106 (4), 92 (5), 91 (100), 77 (5), 65 (11), 51 (5).

### 3.3.16. ʟ-Alanine Methyl Ester (**2p**)

$^1$H NMR (300 MHz, CDCl$_3$) δ 8.70–8.61 (m, 2H, NH$_2$), 4.30 (m, 1H, -CH), 3.81 (s, 3H, OMe), 1.74 (d, 3H, *J* = 7.2 Hz, CH$_3$) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 170.6, 52.9, 49.5, 16.0. GC/MS (EI): *m/z* (%) 103 (M$^+$) (3), 88 (5), 59 (3), 44 (100), 40 (5), 32 (22).

### 3.3.17. ᴅ-Alanine Methyl Ester (**2q**)

$^1$H NMR (300 MHz, CDCl$_3$) δ 8.70–8.61 (m, 2H, NH$_2$), 4.30 (m, 1H, α-CH), 3.81 (s, 3H, OMe), 1.74 (d, 3H, *J* = 7.2 Hz, CH$_3$) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 170.6, 52.9, 49.5, 16.0. GC/MS (EI): *m/z* (%) 103 (M$^+$) (2), 88 (5), 59 (3), 44 (100), 40 (5). GC/MS (EI): *m/z* (%) 103 (M$^+$) (2), 88 (5), 59 (3), 44 (100), 40 (5).

### 3.3.18. ʟ-Valine Methyl Ester (**2r**)

$^1$H NMR (300 MHz, CDCl$_3$) δ 8.82 (m, 2H, NH$_2$), 3.97 (m, 1H, -CH), 3.81 (s, 3H, OMe), 2.49 (m, 1H, CH), 1.17–1.14 (m, 6H, (CH$_3$)$_2$) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 168.8, 58.6, 52.7, 29.9, 18.3. GC/MS (EI): *m/z* (%) 131 (M$^+$) (3), 88 (32), 72 (100), 55 (36), 41 (10).

### 3.3.19. L-Leucine Methyl Ester (**2s**)

$^1$H NMR (300 MHz, CDCl$_3$) δ 8.90–8.75 (br s, 2H, NH$_2$), 4.12 (m, 1H, α-CH), 3.81 (s, 3H, OCH$_3$), 2.10–1.82 (m, 3H, CH$_2$ and CH(CH$_3$), 1.03 (d, 6H, CH(CH$_3$)$_2$) ppm. GC/MS (EI): *m/z* (%) 145 (M$^+$) (2), 130 (3), 86 (100), 70 (3), 44 (56).

### 3.3.20. *O*-Benzyl-L-Tyrosine Methyl Ester (**2t**)

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.89 (brs, 2H, NH$_2$), 7.46–7.21 (m, 5H, ArH), 7.10–6.99 (m, 2H, ArH), 6.95–6.82 (m, 2H, ArH), 5.08 (s, 2H, OCH$_2$), 3.79 (m, 1H, a-CH), 3.61 (s, 3H, OMe), 2.72 (m, 2H, CH$_2$Ph) ppm. GC/MS (EI): *m/z* (%) 285 (M$^+$) (4), 226 (7), 197 (30), 135 (2), 107 (7), 91 (100), 77 (4), 65 (8), 51 (2).

### 3.3.21. Nα-Fmoc-Tryptophane (**2u**)

$^1$H NMR (300 MHz, DMSO-d$_6$) δ 8.08 (d, 1H, *J* = 7.5 Hz, NH), 7.73–7.71 (m, 3H, ArH), 7.56–7.16 (m, 10 H), 5.33 (m, 1H, α-CH), 4.43–4.18 (m, 3H, CH, CH$_2$-Fmoc), 3.83 (m, 2H, CH$_2$-Trp) ppm.

### 3.3.22. L-Phenylalanyl-L-Alanine Methyl Ester (**2v**)

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.23–7.15 (m, 5H, ArH), 6.70 (br s, 1H, OCONH), 5.14 (d, 1H, *J* = 8.2 Hz, NHCHCH3), 4.47 (m, 1H, α–CHAla); 4.38 (m, 1H, α–CHPhe), 3.66 (s, 3H, OMe), 3.09–2.92 (m, 2H, CH2Ph), 1.15 (d, 3H, *J* = 7.2 Hz, CHCH3) ppm. GC/MS (EI): *m/z* (%) 191 (M$^{+.}$ –59), 159 (14), 127 (4), 120 (100), 99 (16), 91 (14), 77 (7), 65 (5), 51 (3).

## 4. Conclusions

In summary, we have reported a highly efficient protocol for the deprotection of Boc protecting groups by using PTSA-based RDES as both a medium and catalyst. This sets the stage for the selective deprotection of a wide variety of *N*-Boc derivatives in high yields with excellent purities by a simple workup. The developed strategy displays a broad substrate scope in the case of structurally different amines, amino acids, and dipeptides. Mild reaction conditions, operational simplicity, as well as the absence of tedious purification procedures, and clean reaction profiles represent advantages that underline the possibility of using this procedure as a cost-effective and environmentally friendly alternative to classical strategies.

**Supplementary Materials:** The following are available online at https://www.mdpi.com/article/10 .3390/catal12111480/s1, The IR spectra of ChCl; pTSA; DES (ChCl:pTSA); General procedures; and $^1$H-NMR spectra of some representative synthesized compounds.

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