

## PAPER

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## A sustainable twist on the Ritter reaction: iron-based deep eutectic solvents as a green route to amide synthesis†

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A sustainable and scalable Ritter reaction protocol has been developed for the efficient amidation of diverse secondary and tertiary alcohols with both aliphatic and aromatic nitriles, employing a reusable  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ /glycerol Lewis acidic deep eutectic solvent. The method features mild, aerobic conditions and broad substrate scope, and delivers yields of up to 98% without chromatographic purification. CHEM21 green metrics underscore the significantly reduced environmental footprint of this approach, establishing it as a greener and more efficient alternative to conventional amide synthesis protocols. The practical utility of the method is further demonstrated by the gram-scale synthesis of drug Chlodantane, showcasing its potential for sustainable applications in pharmaceutical manufacturing.

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## Sustainability spotlight

This work presents a scalable Ritter amidation protocol based on a renewable  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ /glycerol Deep Eutectic Solvent, operating under mild, aerobic conditions without the need for chromatographic purification. The method offers markedly improved sustainability metrics – including significantly lower *E*-factor, PMI for the work-up, and renewable intensity – compared to established procedures, while also enhancing safety and enabling reusability of the eutectic medium. By minimizing hazardous reagents and maximizing resource efficiency, this approach aligns well with UN SDG 9 (industry, innovation, and infrastructure), SDG 12 (responsible consumption and production), and SDG 13 (climate action), offering a practical and greener alternative for the synthesis of bioactive molecules in both academic and industrial contexts.

## Introduction

Amides are a fundamental class of compounds in organic chemistry, renowned for their ubiquity in both natural and synthetic systems. Beyond their essential roles as structural components of proteins and enzymes, amides find extensive applications in catalysis, material sciences, and for the preparation of pharmaceuticals, polymers, agrochemicals, and complex, functionalized organic molecules.<sup>1</sup> Moreover, amide-based transformations enable the efficient production of valuable compounds and intermediates, such as ketones, amines, and enaminones, further highlighting their versatility in organic synthesis.<sup>2</sup> Among the various strategies for amide bond formation,<sup>3</sup> the Ritter reaction stands out as a highly versatile and widely employed chemical transformation with broad applicability in synthetic organic chemistry.

First described in 1948 by John Ritter,<sup>4</sup> this reaction involves the interaction of carbocations (or carbocation-like intermediates) with nitriles. In the classical Ritter reaction, carbocations are generated *in situ* via the protonation of alcohols or alkenes under acidic conditions. These reactive intermediates are then trapped by a nitrile, forming a nitrilium ion species which, upon hydrolysis, yields the desired amide. Ritter-type reactions have broadened the scope of the transformation by employing alternative strategies to generate carbocation intermediates, including the activation of carbonyl derivatives, carboxylic acids, ketones, sulfides, cyclopropanes, aromatics, olefins and alkanes – also through photocatalytic and electrosynthetic approaches – thereby expanding both the substrate range and the synthetic utility of the reaction. This versatility has cemented the Ritter reaction and its variants as indispensable tools for constructing amide bonds in both academic research and industrial chemistry.<sup>5</sup> The classical Ritter reaction typically relies on stoichiometric amounts of strong Brønsted acids, such as concentrated sulfuric acid or glacial acetic acid, which are toxic, corrosive, and environmentally harmful.<sup>6</sup> Over the years, significant progress has been made to improve the sustainability of this transformation, including the use of sub-stoichiometric quantities of sulfuric acid in a modified Ritter

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reaction (Scheme 1a),<sup>7a</sup> as well as catalytic amounts of alternative Brønsted acids (e.g., *o*-benzenedisulfonimide, trifluoromethanesulfonic acid, 2,4-dinitrobenzenesulfonic acid, triflic acid).<sup>7b-e</sup> In addition, various Lewis acids have been employed catalytically, including  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ ,  $\text{CoCl}_2$ ,  $\text{Bi}(\text{OTf})_3$ ,  $\text{Ca}(\text{OTf})_2$ ,  $\text{Cu}(\text{OTf})_2$ ,  $\text{In}(\text{OTf})_3$ ,  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ , and  $\text{Fe}(\text{ClO}_4)_3 \cdot \text{H}_2\text{O}$ .<sup>8</sup> Reactive anhydrides, such as propylphosphonic anhydride (T3P®, 50 wt% in ethyl acetate), have also been explored as effective alternatives.<sup>9</sup> Despite these improvements, these methodologies still rely on harsh reaction conditions, such as elevated temperatures (often exceeding 100 °C), prolonged reaction times, and the use of toxic and volatile organic solvents (e.g., cumene, chloroform, dichloroethane, dichloromethane). Moreover, under solvent-free conditions, the nitrile must be in liquid form, as it serves both as a reactant and as the reaction medium, and is typically used in large excess.<sup>5,10</sup> Notably, in 2009, Dughera *et al.* reported that employing equimolar amounts of nitrile and alcohol in the presence of *o*-

benzenedisulfonimide (10–20 mol%) significantly slowed down the reaction, while still required high temperatures up to reflux (Scheme 1b).<sup>7d</sup>

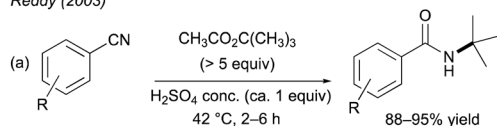
Continued advancements in developing milder and more sustainable reaction conditions – focusing on waste reduction, minimizing hazardous substances, and adopting greener solvents – are essential for promoting environmental stewardship. Such progress is crucial to addressing global challenges, including climate change, pollution, and resource depletion, while fostering more responsible and eco-friendly chemical practices.<sup>11</sup> Deep Eutectic Solvents (DESSs) are increasingly recognized as sustainable reaction media for a wide range of catalytic and stoichiometric chemical applications. Their growing popularity stems from their unique combination of advantageous properties, including high thermal and chemical stability, non-flammability, negligible vapor pressure, low toxicity, customizable properties, straightforward preparation, and excellent potential for recycling and reuse.<sup>12</sup>

As part of our ongoing efforts to develop safer and more sustainable technologies and practices, our group has embarked on a program to explore the potential of DESSs in various chemical transformations to synthesize cornerstone functional groups. These include: (a) the synthesis of aromatic and aliphatic amides *via* Pd-catalyzed aminocarbonylation reactions of aryl iodides<sup>13a</sup> or through reactions between sulfonyl chlorides and amines,<sup>13b</sup> and (b) the production of amines and ethers *via* Goldberg- or Ullmann-type C–N and C–O coupling reactions,<sup>13c-f</sup> as well as the Cu-catalyzed Chan-Evans-Lam amination.<sup>13g</sup> Notably, we recently demonstrated the successful application of iron-based DESSs, which serve a dual role as both solvents and catalysts, in the oxidation of secondary alcohols, and their selective use as monoalkylating reagents for both amides and arylsulfonamide derivatives.<sup>13h</sup> The use of iron-based catalysts for the synthesis of amides from alcohols has been previously documented. In 2009, Cossy *et al.* employed  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  (10 mol%) under sealed-tube conditions at 150 °C, using nitriles as solvents (or diluted in cumene) (Scheme 1c).<sup>8d</sup> Later, in 2018, however, Min Ji *et al.* reported that under solvent-free conditions, alcohols failed to react with nitriles in the presence of  $\text{Fe}(\text{ClO}_4)_3 \cdot \text{H}_2\text{O}$  at 80 °C over 24 h. In that case, the addition of anhydrides such as  $\text{Ac}_2\text{O}$  was necessary to promote the reaction *via* the corresponding ester intermediate (Scheme 1d).<sup>8j</sup>

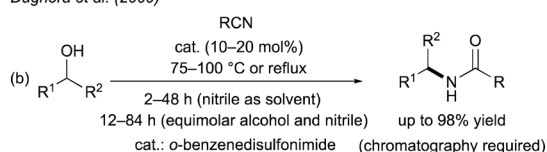
Building on these findings and prior literature,<sup>8</sup> we posited that a Lewis acidic DES (LADES) could serve as an effective medium for promoting the Ritter amidation of alcohols with nitriles, potentially reducing the need for harsh reaction conditions, toxic volatile organic compounds (VOCs), and additional reagents, while expanding the transformation's applicability. Herein, we report that a simple  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ /glycerol (Gly) eutectic mixture (3 : 1 mol mol<sup>-1</sup>) has proven to be highly effective in catalyzing the Ritter reaction of both aliphatic and aromatic secondary and tertiary alcohols with aliphatic and aromatic nitriles. Our approach offers several significant advantages: (i) aerobic and milder conditions, with the reactions proceeding efficiently in most cases at only 40 °C (and only a few requiring 100 °C) within 4 h; (ii) broad substrate

#### Previous work:

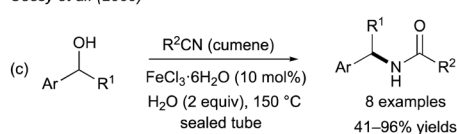
Reddy (2003)



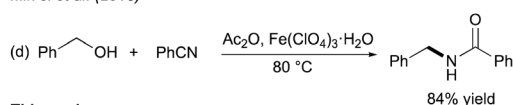
Dughera *et al.* (2009)



Cossy *et al.* (2009)



Min Ji *et al.* (2018)



#### This work:



**Scheme 1** (a) Conversion of aromatic nitriles to the corresponding *N*-*tert*-butyl amides using substoichiometric amounts of  $\text{H}_2\text{SO}_4$  conc.; (b) amidation of benzylic alcohols and nitriles in the presence of catalytic amounts of *o*-benzenedisulfonimide as a Brønsted acid catalyst; (c)  $\text{FeCl}_3 \cdot \text{H}_2\text{O}$ -catalyzed amidation of aromatic secondary alcohols using aliphatic or aromatic nitriles as solvents at 150 °C; (d) solvent-free amidation of benzyl alcohol with benzonitrile in the presence of  $\text{Ac}_2\text{O}$  and  $\text{Fe}(\text{ClO}_4)_3 \cdot \text{H}_2\text{O}$  as a Lewis acid catalyst; (e) Ritter reaction between aromatic/aliphatic secondary or tertiary alcohols and aromatic/aliphatic nitriles in a Fe-based DES at 40 °C, under air (Gly = glycerol).



scope (31 examples), with the corresponding amides being isolated in yields of up to 98% by crystallization, without the need for column chromatography (Scheme 1e).

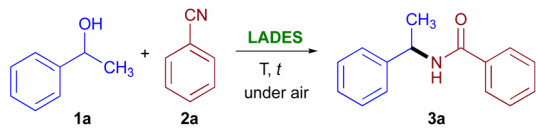
Moreover, the robustness of the methodology was demonstrated through the sustainable, multigram-scale synthesis of the drug chlodantane, with the eutectic mixture effectively reused for up to eight consecutive cycles (*vide infra*). The reduced environmental impact of this newly developed approach was quantitatively validated using the CHEM21 Metrics Toolkit, with metrics applied at both First and Second Pass. These results underscore the potential of LADES to serve as a greener and more efficient platform for industrially relevant transformations.

## Results and discussion

To explore the use of DESs as privileged solvents for the amidation of alcohols—replacing fossil-derived VOCs—with both liquid and solid nitriles, we began investigating the effectiveness of a catalytic amount of a Lewis acid in some prototypical DES mixtures. We chose the reaction between 1-phenyl-1-ethanol (**1a**) and benzonitrile (**2a**) as a model for the Ritter reaction, aiming to synthesize *N*-(1-phenylethyl)benzamide (**3a**). When **1a** (1.5 mmol) was reacted with **2a** (1.65 mmol) in a choline chloride (ChCl)/urea (1 : 2 mol mol<sup>−1</sup>) eutectic mixture (1 g) in the presence of FeCl<sub>3</sub>·6H<sub>2</sub>O (20 mol%), at 40 °C for 4 h, only the starting materials were recovered. The reaction remained unproductive even when ChCl/urea was replaced with ChCl/glycerol (Gly) (1 : 2 mol mol<sup>−1</sup>). Similarly, no improvement was observed upon the addition of various Lewis acids [e.g., AlCl<sub>3</sub>, FeCl<sub>3</sub>, Tf<sub>2</sub>O (triflic anhydride)] or Lewis bases (e.g., Na<sub>2</sub>CO<sub>3</sub>), nor with the inclusion of strong Brønsted acids such as TfOH (triflic acid), even at loadings up to 20 mol% (Table S1, ESI†).

Next, we switched to a LADES as the reaction medium. While the employment of LADESs such as MnCl<sub>2</sub>·4H<sub>2</sub>O/ChCl (2 : 1 mol mol<sup>−1</sup>) or MgCl<sub>2</sub>·6H<sub>2</sub>O/ChCl (1 : 1 or 2 : 1 mol mol<sup>−1</sup>) (40 °C, 4 h) proved to be ineffective, we first observed the formation of **3a** in a FeCl<sub>3</sub>·6H<sub>2</sub>O/urea (2 : 1 mol mol<sup>−1</sup>) in a 31% yield, with the main by-product being bis(1-phenylethyl)urea (69%) (Table 1, entries 1–4). The yield of **3a** could be increased to 40% in a FeCl<sub>3</sub>·6H<sub>2</sub>O/ChCl (2 : 1 mol mol<sup>−1</sup>) mixture, and up to 73% when using a LADES such as FeCl<sub>3</sub>·6H<sub>2</sub>O/Gly (3 : 1 mol mol<sup>−1</sup>) (Table 1, entries 5,6). Conversely, the alternative use of Brønsted acidic DESs (BADESs) such as malic acid/ChCl (1 : 1 mol mol<sup>−1</sup>), L-proline/lactic acid (1 : 2 mol mol<sup>−1</sup>), tartaric acid/ChCl (0.5 : 1 mol mol<sup>−1</sup>), lactic acid/ChCl (2 : 1 mol mol<sup>−1</sup>), oxalic acid/ChCl (1 : 1 mol mol<sup>−1</sup>), malonic acid/ChCl (1 : 2 mol mol<sup>−1</sup>), *p*-toluenesulfonic acid (PTSA)/ChCl (2 : 1 mol mol<sup>−1</sup>), monochloroacetic acid/ChCl (2 : 1 mol mol<sup>−1</sup>), trifluoroacetic acid/ChCl (2 : 1 mol mol<sup>−1</sup>) proved sluggish, with only trace amounts of **3a** detected (up to 13%). The presence of strong Brønsted acids like TfOH in the eutectic composition, either resulted in a complex mixture, as observed with TfOH/ChCl (1 : 1 mol mol<sup>−1</sup>), or led to the recovery of **3a** in 67% yield when using a TfOH/ChCl (3 : 1 mol mol<sup>−1</sup>) mixture. The use of

Table 1 LADES-catalyzed Ritter reaction of **1a** with **2a**<sup>a</sup>



Entry	LADES	T (°C)	t (h)	<b>3a</b> Yield (%)
1	MnCl <sub>2</sub> ·4H <sub>2</sub> O/ChCl (2 : 1)	40	4	NR <sup>b</sup>
2	MgCl <sub>2</sub> ·6H <sub>2</sub> O/ChCl (1 : 1)	40	4	NR <sup>b</sup>
3	MgCl <sub>2</sub> ·6H <sub>2</sub> O/ChCl (2 : 1)	40	4	NR <sup>b</sup>
4	FeCl <sub>3</sub> ·6H <sub>2</sub> O/urea (2 : 1)	40	4	31 <sup>c,d</sup>
5	FeCl <sub>3</sub> ·6H <sub>2</sub> O/ChCl (2 : 1)	40	4	40 <sup>c</sup>
6	<b>FeCl<sub>3</sub>·6H<sub>2</sub>O/Gly (3 : 1)</b>	<b>40</b>	<b>4</b>	<b>73<sup>e</sup></b>
7	FeCl <sub>3</sub> ·6H <sub>2</sub> O/Gly (3 : 1) <sup>f</sup>	40	4	32 <sup>c</sup>
8	FeCl <sub>3</sub> ·6H <sub>2</sub> O/Gly (3 : 1)	40	1	35 <sup>c</sup>
9	FeCl <sub>3</sub> ·6H <sub>2</sub> O/Gly (3 : 1)	40	12	52 <sup>c</sup>
10	FeCl <sub>3</sub> ·6H <sub>2</sub> O/Gly (3 : 1)	25	12	68 <sup>c</sup>
11	FeCl <sub>3</sub> ·6H <sub>2</sub> O/Gly (3 : 1)	60	4	36 <sup>c,g</sup>
12	FeCl <sub>3</sub> ·6H <sub>2</sub> O/Gly (3 : 1)	40	4	14 <sup>c,h</sup>
13	FeCl <sub>3</sub> ·6H <sub>2</sub> O/Gly (3 : 1)	40	4	48 <sup>c,i</sup>
14	— <sup>j</sup>	40	4	— <sup>k</sup>
15	— <sup>l</sup>	40	4	NR <sup>b</sup>

<sup>a</sup> Reaction conditions: 1 g LADES per 1.5 mmol of **1a** and 1.65 mmol of **2a**. <sup>b</sup> NR = no reaction. <sup>c</sup> Calculated by <sup>1</sup>H NMR analysis of the crude reaction mixture using an internal standard technique (NMR internal standard: CH<sub>2</sub>Br<sub>2</sub>). <sup>d</sup> The main by-product isolated was bis(1-phenylethyl)urea. <sup>e</sup> Isolated yield. <sup>f</sup> Molar ratio **1a** : **2a** = 1 : 1 (1.5 mmol). <sup>g</sup> A complex mixture formed at temperatures above 80 °C. <sup>h</sup> 0.5 g LADES per 1.5 mmol of **1a** and 1.65 mmol of **2a**. <sup>i</sup> 2 g LADES per 1.5 mmol of **1a** and 1.65 mmol of **2a**. <sup>j</sup> With FeCl<sub>3</sub>·6H<sub>2</sub>O, under neat conditions. <sup>k</sup> Bis(α-phenylethyl)ether was obtained as the sole product (>98% yield, <sup>1</sup>H NMR and GC-MS analysis). <sup>l</sup> Without FeCl<sub>3</sub>·6H<sub>2</sub>O, under neat conditions.

hydrophobic DESs, such as decanoic acid/menthol (1 : 1 mol mol<sup>−1</sup>), was also ineffective (Table S2, ESI†).

To further enhance the yield of **3a** when using the FeCl<sub>3</sub>·6H<sub>2</sub>O/Gly (3 : 1 mol mol<sup>−1</sup>) eutectic mixture (Table 1, entry 6), we explored several modifications. The addition of Brønsted acids (up to 20 mol%), such as TfOH, malic acid, or PTSA·H<sub>2</sub>O, resulted in the recovery of **3a** in 45–68% yield (Table S3, ESI†). Adjusting the molar ratio of **1a** to **2a** to 1 : 1 ratio (each 1.5 mol), as well as varying reaction times (1 h or 12 h) at 40 °C, led to **3a** yields ranging from 32 to 52% (Table 1, entries 7–9). When the reaction was performed at room temperature (25 °C) for 12 h, **3a** was isolated in 68% yield (Table 1, entry 10). However, increasing the temperature up to 60 °C caused a significant decrease in the yield of **3a**, down to 36%, and resulted in complex mixtures at temperatures above 80 °C (Table 1, entry 11). We also investigated the concentration of the substrates in DES: the yield of **3a** decreased when the amount of DES was reduced to 0.5 g or increased to 2 g per 1.5 mmol **1a**, yielding to 14% and 48%, respectively (Table 1, entries 12, 13). Finally, to evaluate the role of the DES medium, we performed the following control experiments: (a) with FeCl<sub>3</sub>·6H<sub>2</sub>O (5 mol%) under neat conditions (40 °C, 4 h): bis(α-phenylethyl)ether was obtained as the sole product (>98% yield, as determined by <sup>1</sup>H NMR and GC-MS analysis), resulting from the intermolecular



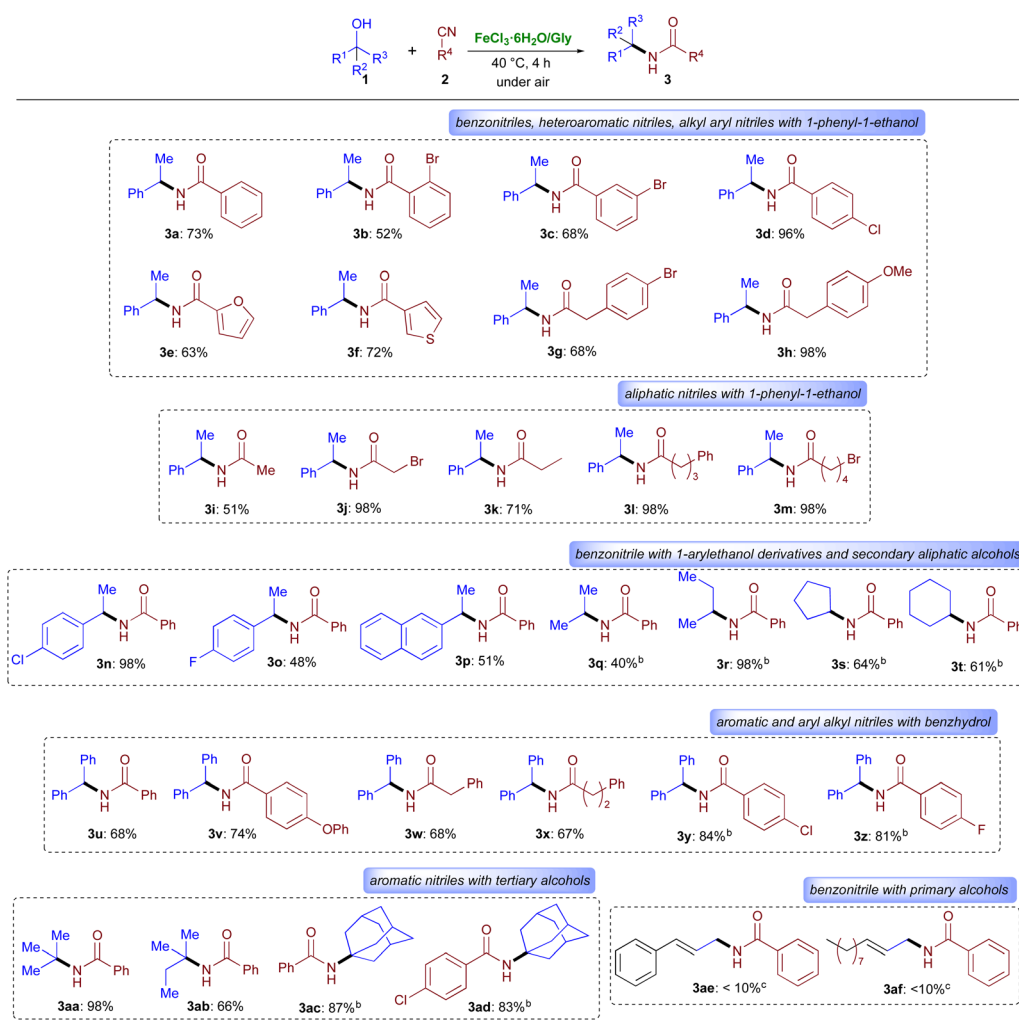
dehydration of the alcohol (Table 1, entry 14); (b) without  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  (5 mol%) under neat conditions (40 °C, 4 h): no reaction occurred (Table 1, entry 15). These findings unambiguously demonstrate that the DES medium plays a pivotal role – not merely as a non-inhibitory environment, but as an essential component in activating the nitrile and selectively promoting amidation over competing etherification pathways. Accordingly, performing a reaction under neat conditions does not inherently translate into a greener process. Beyond the intrinsic limitation of requiring both substrates to be liquids, neither the reaction outcome nor selectivity can be reliably ensured.

With the optimal conditions established (Table 1, entry 6), we next set out to explore the scope of this transformation by reacting various alcohols bearing different substituents with both aromatic and aliphatic nitriles. We began by examining the reactivity of secondary alcohols. Benzonitrile derivatives featuring electron-withdrawing substituents (Br, Cl) at the *ortho*- (2b), *meta*- (2c), or *para*-position (2d), as well as electron-rich

heteroaromatic nitriles such as furan-2-carbonitrile (2e) and thiophene-3-carbonitrile (2f), smoothly underwent the Ritter reaction with 1a, furnishing the corresponding (hetero)aromatic amides 3b–f in yields ranging from 52 to 96% (Table 2). In addition, aryl alkyl nitriles such as 2-(4-bromophenyl)acetonitrile (2g) and 2-(4-methoxyphenyl)acetonitrile (2h), along with aliphatic nitriles including acetonitrile (2i), 2-bromoacetonitrile (2j), propionitrile (2k), and longer-chain derivatives like 4-phenylbutanenitrile (2l) and 5-bromopentanenitrile (2m), also proved to be effective reaction partners, affording the desired amides 3g–m in good to excellent yields (51–98%, Table 2). However, when 1a was treated with benzonitrile derivatives bearing a strong electron-withdrawing group such as  $\text{NO}_2$  (e.g., 3-nitro and 4-nitrobenzonitrile), no traces of the corresponding amides were detected, most likely due to the complete suppression of the nucleophilic character of the nitrile.

Furthermore, benzonitrile (2a) demonstrated its versatility as a suitable coupling partner for 1-arylethanol derivatives such

Table 2 LADES-catalyzed Ritter reaction of alcohols 1 with nitriles 2 to give amides 3<sup>a</sup>



<sup>a</sup> Reaction conditions: 1 g LADES per 1.5 mmol of 1a and 1.65 mmol of 2a. Yields of isolated compounds. <sup>b</sup> Reactions carried out at 100 °C. <sup>c</sup> Not isolated.



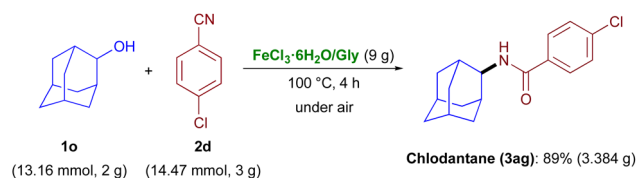


as 1-(4-chlorophenyl)ethanol (**1b**), 1-(4-fluorophenyl)ethanol (**1c**), and 1-(2-naphthyl)ethanol (**1d**), leading to the formation of amides **3n–p** in 48–98% yield (Table 2). Limitations were observed when using 1-arylethanol derivatives bearing electron-donating groups (Me, MeO) at the *para* position, as no amide formation was detected, even at a higher temperature (100 °C). This is likely due to the increased delocalization of the positive charge on the carbocation intermediate, which renders it less susceptible to nucleophilic attack by **2a**. Secondary aliphatic alcohols, including isopropanol (**1e**), 2-butanol (**1f**), cyclopentanol (**1g**), and cyclohexanol (**1h**) were found to be unreactive under the standard conditions at 40 °C, but underwent efficient amidation when the temperature was raised to 100 °C, affording the corresponding secondary amides **3q–t**, in moderate to excellent yields (40–98%, Table 2).

Next, we focused on the preparation of diarylmethylamide derivatives, which represent either reliable *N*-protected forms of diarylmethylamines – compounds known for their antihistaminic, antiarrhythmic, diuretic, antidepressant, anesthetic and anticholinergic properties<sup>14a,b</sup> or valuable intermediates in pharmaceutical synthesis, for example, in the preparation of medicinal agents acting as melatonin-concentrating hormone receptor antagonists.<sup>14c</sup> To explore the feasibility of obtaining such functionalized amides, an array of substituted nitriles was employed as substrates in the reaction with benzhydrol (**1i**). Aromatic nitriles like **2a** and 2-phenoxybenzonitrile (**2n**), as well as aryl alkyl nitriles like phenylacetone nitrile (**2o**) and 3-phenylpropane nitrile (**2p**), all proved to be suitable substrates for this Fe-promoted amidation with **1i**, affording the corresponding amides **3u–x** in good yields (67–74%). Higher yields were achieved in the reaction of nitriles **2d** and *p*-fluorobenzonitrile (**2r**) with **1i**, giving amides **3y** and **3z** in 81–84% yield at 100 °C (Table 2). In contrast, when these reactions were performed at 40 °C, the yields dropped significantly, reaching no more than 32%. Once again, the presence of electron-withdrawing substituents on the benzonitrile aromatic ring (e.g., 3-nitro, 4-nitro, 4-formyl, 4-acetyl) markedly hampered the formation of the corresponding amides, regardless of whether the reaction was carried out at 40 or 100 °C.

Tertiary alcohols such as *t*-BuOH (**1j**), 2-methyl-2-butanol (**1k**), and 1-adamantanol (**1l**), were also evaluated in the reaction with benzonitriles **2a** and **2d**, affording the desired amides **3aa–3ad** in good to excellent yields (66–98%) (Table 2). Conversely, more sterically hindered alcohols, such as triphenylmethanol and 1-phenyl-1-cyclohexanol, proved unreactive under the same reaction conditions. Finally, we investigated the reactivity of challenging allylic primary alcohols. The reaction of (*E*)-3-phenyl-2-propen-1-ol (**1m**) and (*E*)-2-undecen-1-ol (**1n**) with **2a** at 100 °C furnished the corresponding amides **3ae** and **3af**, respectively, only in traces (<10%). In contrast, ethanol and 1-pentanol proved completely unreactive, further confirming the limited applicability of this methodology to less activated aliphatic alcohols. Moreover, diols and triols, such as ethylene glycol and glycerol, also failed to react with **2a** under the same conditions.

The robustness and the synthetic practicality of the protocol were further highlighted by its successful application on a gram



Scheme 2 Gram-scale synthesis of actoprotector chlodantane (ADK-919) (**3ag**) from 2-adamantanol (**1o**) and *p*-chlorobenzonitrile (**2d**).

scale for the preparation of the actoprotector Chlodantane (ADK-919) (**3ag**).<sup>15</sup> Notably, the reaction between 2-adamantanol (**1o**) (13.16 mmol, 2 g) and nitrile **2d** (14.47 mmol, 3 g) efficiently delivered the target amide **3ag** in an excellent 89% isolated yield (3.384 g) after 4 h at 100 °C in a  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}/\text{Gly}$  (3 : 1) (9 g) eutectic mixture (Scheme 2).

Reuse studies of the  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}/\text{Gly}$  LADES were carried out in the synthesis of amide **3ag**. Alcohol **1o** (5 mmol, 760 mg) and nitrile **2d** (5.5 mmol, 754 mg) were added to 3.5 g of  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}/\text{glycerol}$  (3 : 1 mol mol<sup>−1</sup>) in a vial and stirred vigorously under air for 4 h at 100 °C. Upon completion (monitored by TLC), the solid product **3ag** was separated carefully decanting the liquid phase (*i.e.*, the DES) into a second vial. The solid was then washed with 5 mL of cyclopentyl methyl ether (CPME) and dried under vacuum. The CPME washings were evaporated under reduced pressure to recover any trace amounts of DES, which were subsequently added back to the main DES phase. Fresh substrates (**1o** and **2d**, in the same amounts) were then charged to the recovered DES, and the reaction was repeated under the same conditions (air, 100 °C, 4 h). This cycle was repeated eight times consecutively, consistently affording product **3ag** as a solid with 98% purity (as determined by <sup>1</sup>H NMR), and with only a minimal decrease in yield: from 96% in the first run to 75% in the eighth (Fig. 1, ESI†).

To further assess the eco-sustainability of our method employing LADES  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}/\text{Gly}$  as the solvent, we selected the synthesis of amide **3a** as a representative model transformation. Using the First Pass CHEM21 Metrics Toolkit developed by Clark *et al.*,<sup>16</sup> we calculated key sustainability parameters including atom economy (AE), reaction mass efficiency (RME), optimum efficiency (OE), effective mass yield

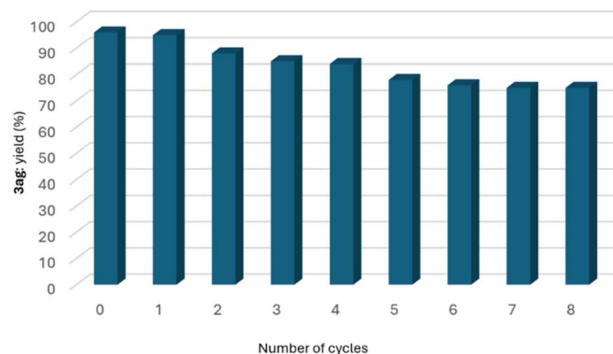


Fig. 1 Reusing of  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}/\text{Gly}$  LADES in the synthesis of Chlodantane (**3ag**) from 2-adamantanol (**1o**) and *p*-chlorobenzonitrile (**2d**).



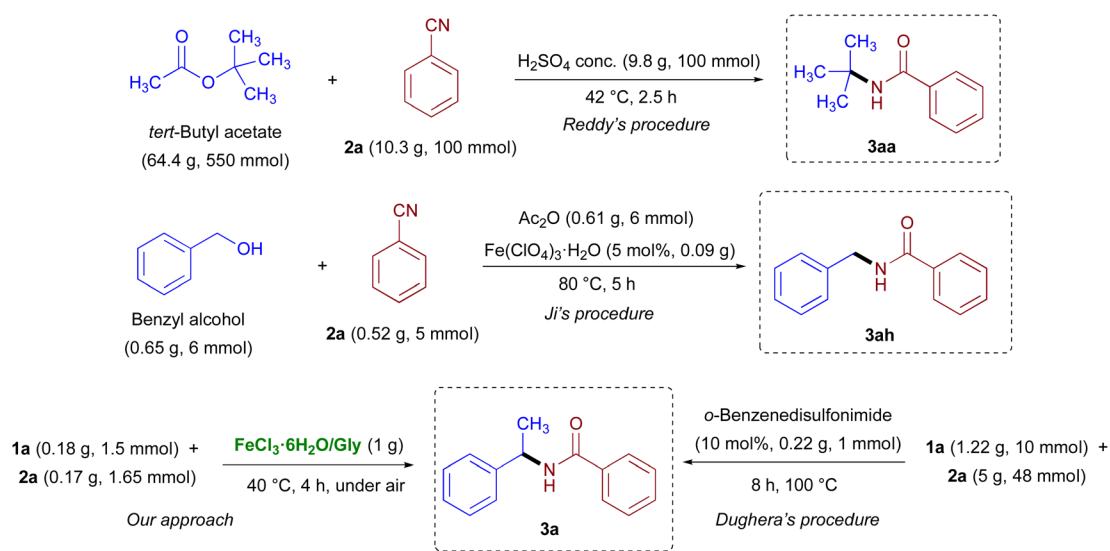
(EM), and process mass intensity (PMI) metrics. Notably, PMI was determined both for the whole process ( $\text{PMI}_{\text{RXN}}$ ), which accounts for all reactants, reagents, and solvents, and for the work-up procedure alone ( $\text{PMI}_{\text{WU}}$ ), which encompasses the solvents and reagents used during purification. Additionally, we computed further metrics from the Second Pass CHEM21 Metrics Toolkit – namely, renewable intensity ( $R_i$ ) and renewable percentage ( $R_p$ ) – to provide a comprehensive analysis of the method's green credentials (Table 3).

These values were then compared with those obtained for representative literature procedures reported by Reddy, Ji, and Dughera, which were carried out under neat conditions for the synthesis of amides **3aa**,<sup>7a</sup> **3ah**,<sup>8j</sup> and **3a**,<sup>7d</sup> respectively. In particular: (i) Reddy's method employs substoichiometric amounts of concentrated, corrosive  $\text{H}_2\text{SO}_4$ ; (ii) Ji's protocol uses  $\text{Ac}_2\text{O}$  and  $\text{Fe}(\text{ClO}_4)_3 \cdot \text{H}_2\text{O}$  (5 mol%) as a Lewis acid catalyst at 80 °C; (iii) Dughera's approach utilizes *o*-benzenedisulfonimide (10 mol%) as a Brønsted acid catalyst at 100 °C.

While Dughera's and Ji's procedures achieve the highest isolated yield (94%) and EM (73), respectively, they fall short in several key green metrics compared to our DES-based process. In particular, our method delivers a substantially higher RME of 71%, outperforming Dughera (34%), Ji (50), and Reddy (19). This

underscores a more efficient use of starting materials and lower waste formation. Notably, the  $\text{PMI}_{\text{WU}}$  of our process is only  $20.2 \text{ g g}^{-1}$ , markedly lower than that of Dughera ( $121.3 \text{ g g}^{-1}$ ) and Ji ( $141.5 \text{ g g}^{-1}$ ), highlighting a dramatic reduction in solvent and reagent consumption during purification. In terms of overall waste generation, our approach yields the lowest *E*-factor (15.2) compared to Ji (61.9) and Dughera (96.6), clearly demonstrating the waste-minimizing benefits of the LADES system. From a renewables perspective, our approach offers a significantly lower renewable intensity ( $R_i = 8.0$ ) and a higher renewable percentage ( $R_p = 39.6\%$ ) compared to Dughera ( $R_i = 23.7$ ,  $R_p = 19.5$ ), and a markedly lower  $R_i$  than Ji ( $R_i = 78.7$ ). This is largely attributable to the use of glycerol as a renewable hydrogen bond donor, and the complete absence of VOCs or corrosive mineral acids. Finally, the EcoScale score for our method is 82.5, notably higher than that of Dughera's procedure (71), further highlighting its superior environmental compatibility, enhanced safety profile, and operational simplicity. Collectively, these advantages demonstrate that our DES-based approach not only meets but exceeds the green performance of established procedures, offering a more sustainable and industrially viable alternative for amide synthesis, especially where environmental impact is a critical concern.

**Table 3** Quantitative metrics calculated for the procedures reported by Reddy, Ji, and Dughera, as well as the present DES-based approach, for the synthesis of amides **3aa**, **3ah**, and **3a**, respectively



Reaction	Solvent	Yield (%)	AE (%)	RME (%)	OE (%)	EM (%)	$\text{PMI}_{\text{RXN}}^a$ ( $\text{g g}^{-1}$ )	$\text{PMI}_{\text{WU}}^b$ ( $\text{g g}^{-1}$ )	$R_i^c$	$R_p$ (%)	<i>E</i> -factor <sup>d</sup>	EcoScale
Reddy's procedure	Neat, $\text{H}_2\text{SO}_4$	<b>3aa</b> : 91	56	19	34	19.2	23.8	—	—	—	7.3	—
Ji's procedure	Neat, $\text{Fe}(\text{ClO}_4)_3 \cdot \text{H}_2\text{O}$	<b>3ah</b> : 84	67	50	75	73	2.1	141.5	78.7	55.6	61.9	—
Dughera's procedure	Neat, catalyst <sup>e</sup>	<b>3a</b> : 94	100	34	34	40.4	3.1	121.3	23.7	19.5	96.6	71
Our approach	DES <sup>f</sup>	<b>3a</b> : 73	100	71	71	23.6	5.4	20.2	8.0	39.6	15.2	82.5

<sup>a</sup> Process mass intensity ( $\text{PMI}_{\text{RXN}}$ ): chemicals and reaction solvents. <sup>b</sup> Process mass intensity ( $\text{PMI}_{\text{WU}}$ ): chemicals and reaction solvents, solvents, and reagents in workup. <sup>c</sup> Renewable sources: water, 1-phenylethanol. <sup>d</sup> This value does not consider the amount of water solution used for work-up. <sup>e</sup> Catalyst: *o*-benzenedisulfonimide (10 mol%, 0.22g, 1 mmol). <sup>f</sup> DES:  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}/\text{Gly}$  (3 : 1 mol mol<sup>-1</sup>).



## Conclusions

In conclusion, this study presents a robust and sustainable protocol for the Ritter amidation of both aliphatic and aromatic secondary and tertiary alcohols with a wide range of aliphatic and aromatic nitriles, including solid substrates—enabled by the use of a  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ /glycerol (3:1) Lewis acidic deep eutectic solvent. The excellent combination of mild, aerobic conditions, broad functional group compatibility, and yields up to 98%—achieved without chromatographic purification—strongly underscores the practical efficiency and operational simplicity of the methodology. The comprehensive CHEM21 green metrics analysis further validates the significantly reduced environmental impact of this approach compared to conventional procedures, highlighting its relevance for sustainable amide synthesis. Importantly, the demonstrated reusability of the eutectic mixture, the scalability of the process, and its successful application to the preparation of bioactive molecules collectively reinforce its strong potential for industrial implementation. Overall, this work not only establishes a greener and more efficient route to amide bond formation, but also showcases the broader potential of Lewis acidic DESs as enabling media for environmentally responsible synthetic chemistry.

## Data availability

The data supporting this article have been included as part of the ESI.†

## Author contributions

L. C. and A. Y.: methodology, investigation, data curation, validation, visualization, writing – review & editing; P. V.: methodology, formal analysis, resources, writing – review & editing; F. M. P.: conceptualization, methodology, formal analysis, resources, supervision, writing – review & editing; V. C.: conceptualization, methodology, resources, funding acquisition, supervision, project administration, writing – original draft, writing – review & editing.

## Conflicts of interest

There are no conflicts to declare.

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