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The use of renewable feedstocks and of more environmentally responsible solvents represents one of the strategies in addressing public concerns related to the environmental effects of products during use and as waste, thereby driving the field of synthetic chemistry towards more green practices. The Chan-Evans-Lam amination is an important coupling reaction between a boronic acid and a N–H containing compound, which is still carried out in volatile organic compounds. We propose a scalable Cu-catalysed protocol for the synthesis of secondary amines taking place with a wide substrate scope in *Deep Eutectic Solvents (DESs)* as sustainable and recycling media. This work is aligned with the UN Sustainable Development Goals of: responsible consumption and production (SDG 12) and climate action (SDG 13).



COMMUNICATION

Cu-Catalysed Chan-Evans-Lam Reaction Meets *Deep Eutectic Solvents*: Efficient and selective C–N Bond Formation under Aerobic Conditions at Room TemperatureLuciana Cicco,^a Paola Vitale,^a Filippo Maria Perna,^a Vito Capriati,^{*,a,b} and Joaquín García-Álvarez^{*,c}Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

An unprecedented, simple and general protocol for the selective formation of C–N bonds was developed by using cheap and easily available Cu(OAc)₂ as catalyst for the Cu(II)-catalysed Chan-Evans-Lam reaction in *Deep Eutectic Solvents* (DESs) as sustainable reaction media. The meticulous selection of both components of DES for this transformation (1ChOAc/2Urea) allows C–N coupling reactions under bench-type conditions (room temperature/under air), and in the absence of external ligands. The use of DES also permits to: *i*) recycle the catalytic system for up to four consecutive runs; *ii*) scale-up the C–N coupling reaction (without erosion of the yield); and *iii*) apply this methodology to the synthesis of the anti-inflammatory drug Flufenamic acid (*E*-factor: 10).

Introduction

The use of transition metal catalysts¹ is nowadays considered as one of the cornerstone concepts for the design of more sustainable chemical protocols both at academic and industrial levels.² Moreover, the implementation of transition-metal catalysis in the synthesis of high-value organic compounds usually permits to improve the selectivity of the process under study, which indirectly affects its efficiency, by increasing yields and reducing energy/raw materials consumption,³ in agreement with the Principles of *Green Chemistry*.⁴ However, in most cases, these transition-metal-based catalytic systems are constructed from toxic, non-abundant and expensive metals (e.g., Ir, Rh, Pd, Ru, Au). Thus, the search for new catalytic routes to access fine chemicals and pharmaceuticals using non-precious metals is a “*hot topic*” in modern synthetic organic chemistry.⁵ Among the most commonly used first row, cheap and abundant transition metals in catalysis (e.g., Cr, Mn, Fe, Co, Ni, Zn), copper is one of the best candidates as: *i*) is capable to promote both two-electron or radical bond-formation processes; *ii*) presents a rich and diverse redox chemistry [usually ranging from Cu(0) to Cu(I)/Cu(II), and even to Cu(III) species]; and *iii*) is involved in both σ - or π -interactions with alkenes or alkynes.⁶ Needless to say, the recent Nobel Prize in

Chemistry (2022) has been awarded for research on copper-catalysed azide-alkyne click chemistry.⁷

Together with the choice of a safe, cheap and abundant transition metal as catalyst, another crucial point to take into consideration when designing a more sustainable catalytic chemical process is related to the choice of the solvent employed as the reaction medium. Solvents are, indeed, responsible for the vast majority of the waste generated in chemical synthetic processes, both at academic and industrial levels.⁸ In addition, a large part of the most commonly used organic solvents in organic synthesis, usually denoted as *Volatile Organic Compounds* (VOCs), are toxic (e.g., *n*-hexane, toluene, *N,N*-dimethylformamide, methanol) and/or flammable (e.g., Et₂O, *n*-hexane, toluene, *N,N*-dimethylformamide, methanol, ethyl acetate, ethanol, *t*-butyl methyl ether), and, in some cases, also carcinogenic (e.g., dichloromethane, carbon tetrachloride).⁹

In principle, the ideal synthetic chemical protocol would be the one in which no solvent is used (the so-called *neat conditions*).¹⁰ In real chemical practice, there are very few synthetic protocols that can take place in the absence of an externally-added solvent. Thus, synthetic chemists have focused their attention on finding and using neoteric solvents (as replacement for classical VOCs), which present a reduced environmental impact.¹¹ *Deep Eutectic Solvents* (DESs) are nowadays increasingly utilized as sustainable reaction media for a variety of chemical transformations (ranging from metal-, bio- and organocatalysis to main group chemistry, even including emerging fields related to photosynthesis or crystallization) as they show the following properties: *i*) negligible vapour pressures; *ii*) thermal stability; *iii*) non-flammability; and *iv*) easy recycling.^{12,13} DES concept traces back to 2003 when Abbott and collaborators first described an eutectic mixture with a low melting point (mp, 12 °C) obtained by mixing two solid compounds: choline chloride (*ChCl*, mp = 302 °C) and urea (mp

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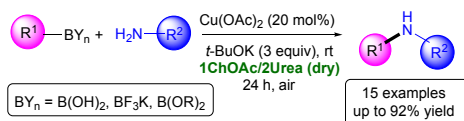
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= 133 °C).^{13a} *DES*s are binary or ternary mixtures comprising at least one hydrogen bond acceptor (*HBA*) and a hydrogen bond donor (*HBD*), which are strongly associated with each other to form a three-dimensional network structured through hydrogen bonds.¹⁴ A wide variety of cheap, non-toxic, renewable and easy accessible *HBA*s [e.g., *ChCl*, choline acetate (*ChOAc*)]¹⁵ and *HBD*s [e.g., naturally occurring amides, alcohols or carboxylic acids (e.g., urea, glycerol (*Gly*), sugars, lactic/citric acid)] are available for the synthesis of *DES*s.¹⁶ In addition, *DES* preparation: *i*) requires no purifications steps; *ii*) takes place with total atom economy and under bench-type reaction conditions; and *iii*) is also accessible through efficient continuous synthesis by a twin-screw extrusion.¹⁷

Some of us have recently demonstrated that the partnership formed between Cu-catalysed organic transformations and *DES*s is an easily accessible, efficient and selective synthetic tool capable of working under mild and bench-type reaction-conditions for: *i*) Goldberg- or Ullmann-type C–N or C–O couplings;¹⁸ *ii*) the synthesis of poly(methyl methacrylate) through ARGET-ATRP polymerization;¹⁹ *iii*) the chemoenzymatic preparation of enantiopure (*R*)- β -hydroxy-1,2,3-triazoles;^{6e} and *iv*) the selective aerobic oxidation of alcohols into carbonyl compounds.²⁰

The Chan-Evans-Lam (*CEL*) amination is a coupling reaction between a boronic acid and a N–H containing compound induced by a stoichiometric or a catalytic amount of a Cu(II) salt. It has been traditionally carried out by using *VOC*s or *VOC*/alcohol/aqueous mixtures in air, with moderate to high heating, and in the presence of additives and/or additional ligands.²¹ To the best of our knowledge, *CEL* coupling has not yet been investigated in *DES*s.^{12c} Thus, we decided to study the C–N bond formation in *DES* between a family of primary amines and different organoboron partners, like aromatic boronic acids, phenylboronic acid pinacole ester, or potassium phenyltrifluoroborate. After screening various conditions, the best conversions were obtained when using the eutectic mixture 1*ChOAc*/2*Urea* as the solvent (Scheme 1). Moreover, the following features are worth mentioning: *i*) *CEL* takes place at room temperature (rt), under aerobic conditions and in the absence of ligands; *ii*) a cheap Cu(OAc)₂ salt is useful to promote the desired C–N coupling; *iii*) the catalytic system could be recycled (up to 4 consecutive runs) and the process scaled-up; and *iv*) the reported methodology has been applied to the synthesis of Flufenamic acid, which is a non-steroidal anti-inflammatory, selective COX-1 inhibitor.²²



Scheme 1. Cu(OAc)₂-catalysed Chan-Evans-Lam C–N coupling of primary amine with different organoboron partners under air, at room temperature, in the absence of ligands, and in the eutectic mixture 1*ChOAc*/2*Urea*.

Results and discussion

We started our investigations by employing the archetypical *DES* formed by *ChCl* and urea (1*ChCl*/2*Urea*), taking as a model reaction

the Cu(OAc)₂-catalysed *CEL* C–N coupling between phenylboronic acid (**1a**) and 4-methoxyaniline (anisidine, **2a**) (Table 1). We selected as catalyst Cu(OAc)₂ as good efficiency and selectivity have been reported with this Cu(II)-source in the presence of different ligands and in polar solvents like water,^{23a,b} MeOH^{23c} or DMF.^{23d} After 24 h, working at rt, under air and using *t*-BuOK as a base, the desired secondary amine **3a** formed in poor yield (10%; entry 1, Table 1). We screened the nature of the *HBD* to include: *i*) natural polyols [e.g., glycerol (*Gly*) forming the eutectic mixture 1*ChCl*/2*Gly*] (entry 2, Table 1); *ii*) biorenewable carboxylic acids [e.g., lactic acid (*LA*), forming the eutectic mixture 1*ChCl*/2*LA*] (entry 3, Table 1); or *iii*) water, forming the eutectic mixture 1*ChCl*/2*H₂O* (entry 4, Table 1). However, in all cases, a complete shutdown of the *CEL* C–N coupling took place. We envisaged that a possible *in-situ* scramble of anions between the acetate (AcO[−]) and the Cl[−] of the *ChCl*-based eutectic mixtures could convert the starting Cu(OAc)₂ into CuCl₂, the latter being previously described as a barely non-active catalyst for this transformation.^{23a}

Thus, next experiments fulfilled the following requirements: *i*) absence of chlorinated *HBA*s; and *ii*) the presence of urea as *HBD* (compare entries 1–3, Table 1). Based on this premise, the eutectic mixture 1*ChOAc*/2*Urea* was selected and used, under the previously reaction conditions, with a considerable increase of the yield of **3a** up to 70% (entry 5, Table 1).^{18c}

Table 1. Cu-catalysed Chan-Evans-Lam C–N coupling between phenylboronic acid (**1a**) and 4-methoxyaniline (**2a**) in different solvents^a

Entry	Catalyst	Solvent	Base	Yield (%) ^b
1	Cu(OAc) ₂	1 <i>ChCl</i> /2 <i>Urea</i>	<i>t</i> -BuOK	10 ^c
2	Cu(OAc) ₂	1 <i>ChCl</i> /2 <i>Gly</i>	<i>t</i> -BuOK	-
3	Cu(OAc) ₂	1 <i>ChCl</i> /2 <i>LA</i>	<i>t</i> -BuOK	-
4	Cu(OAc) ₂	1 <i>ChCl</i> /2 <i>H₂O</i>	<i>t</i> -BuOK	<5 ^c
5	Cu(OAc) ₂	1 <i>ChOAc</i> /2 <i>Urea</i>	<i>t</i> -BuOK	70
6	Cu(OAc) ₂	1 <i>ChOAc</i> /2 <i>Urea</i>	<i>t</i> -BuOK	8 ^{c,d}
7	Cu(OAc) ₂	1 <i>ChOAc</i> /2 <i>Gly</i>	<i>t</i> -BuOK	-
8	Cu(OAc) ₂	<i>Gly</i>	<i>t</i> -BuOK	-
9	Cu(OAc) ₂	<i>EG</i>	<i>t</i> -BuOK	-
10	Cu(OAc) ₂	1 <i>Lys</i> /4.5 <i>Gly</i>	<i>t</i> -BuOK	36
11	Cu(OAc) ₂	1 <i>Bet</i> /3 <i>Gly</i>	<i>t</i> -BuOK	5 ^c
12	Cu(OAc) ₂	1 <i>Arg</i> /4.5 <i>Gly</i>	<i>t</i> -BuOK	16 ^c
13	Cu(OAc) ₂	1 <i>Prol</i> /3 <i>Gly</i>	<i>t</i> -BuOK	-
14	Cu(OAc) ₂	1 <i>ChOAc</i> /2 <i>Urea</i>	-	-
15	-	1 <i>ChOAc</i> /2 <i>Urea</i>	<i>t</i> -BuOK	-
16	Cu(OAc) ₂	1 <i>ChOAc</i> /2 <i>Urea</i>	K ₂ CO ₃	12 ^c
17	Cu(OAc) ₂	1 <i>ChOAc</i> /2 <i>Urea</i>	KOH	5 ^c
18	Cu(OAc) ₂	1 <i>ChOAc</i> /2 <i>Urea</i>	Cs ₂ CO ₃	10 ^c
19	Cu(OAc) ₂	1 <i>ChOAc</i> /2 <i>Urea</i>	HCOOK	2 ^c
20	Cu(OAc) ₂	1 <i>ChOAc</i> /2 <i>Urea</i>	CH ₃ CO ₂ K	-
21	Cu(NO ₃) ₂	1 <i>ChOAc</i> /2 <i>Urea</i>	<i>t</i> -BuOK	20
22	Cu(SO ₄)	1 <i>ChOAc</i> /2 <i>Urea</i>	<i>t</i> -BuOK	11 ^c
23	CuCl ₂	1 <i>ChOAc</i> /2 <i>Urea</i>	<i>t</i> -BuOK	7 ^c
24	Cu(OAc) ₂ ·H ₂ O	1 <i>ChOAc</i> /2 <i>Urea</i>	<i>t</i> -BuOK	30
25	Cu(OAc) ₂	1 <i>ChOAc</i> /2 <i>Urea</i> (dry)	<i>t</i> -BuOK	92 (97) ^e
26	CuI	1 <i>ChOAc</i> /2 <i>Urea</i>	<i>t</i> -BuOK	-

^a General conditions: reactions performed under air, at room temperature (rt) using 0.50 mmol of **1a** and 0.25 mmol of **2a** in 1 g of solvent. ^b Isolated yield. ^c Yield determined by ¹H NMR analysis of the crude reaction mixture in the presence of the internal standard CH₂Br₂. ^d Reaction run under argon. ^e Conversion: 97%, by GC analysis.



On the other hand, upon running the reaction under Ar, formation of **3a** was suppressed dramatically (8%) (entry 6, Table 1). This result is also in agreement with previous studies in this field,²³ and with the proposed mechanism for this reaction.²¹

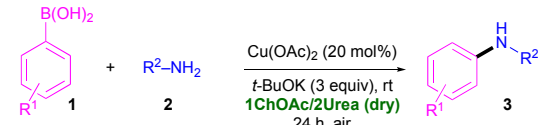
Either the replacement of urea with *Gly* as *HBD* in the above eutectic mixture, or with pure *Gly* or ethylene glycol (*EG*), was found to erode completely the catalytic activity of $\text{Cu}(\text{OAc})_2$ (entries 7–9, Table 1). Next, we tested the $\text{Cu}(\text{OAc})_2$ -catalysed *CEL* C–N coupling protocol in the following eutectic mixtures, which are not based on *ChCl*: *i*) 1*Lys*/4.5*Gly* (*Lys* = *L*-lysine; entry 10, Table 1); *ii*) 1*Bet*/3*Gly* (*Bet* = betaine; entry 11, Table 1); *iii*) 1*Arg*/4.5*Gly* (*Arg* = arginine; entry 12, Table 1); and *iv*) 1*Prol*/3*Gly* (*Prol* = *L*-proline; entry 13, Table 1). However, previous results obtained with 1*ChOAc*/2*Urea* could not be improved (yields up to 36%). Thus, the proper selection of both components of the eutectic mixture is important for designing an effective transition-metal-catalysed protocol. As control experiments, we found that the reaction did not take place in the absence of the base (entry 14, Table 1) or the $\text{Cu}(\text{II})$ -catalyst (entry 15, Table 1). At this point, we decided to deepen the effect of different bases on the outcome of this catalytic reaction.

The replacement of either *t*-BuOK with various organic or inorganic bases (K_2CO_3 , KOH, Cs_2CO_3 , HCOOK, $\text{CH}_3\text{CO}_2\text{K}$) (entries 16–20, Table 1) or the acetate in $\text{Cu}(\text{OAc})_2$ with other anions (nitrate, sulphate, chloride) (entries 21–23, Table 1), as well as the use of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (entry 24, Table 1), all resulted in a dramatic decrease in **3a** yield. A careful analysis of the crude reaction mixtures by GC-MS, where yields of **3a** were low or null (Table 1), revealed the formation of phenol and diphenyl ether as the main side products. According to Evans and co-workers,²⁴ these products can originate from O-arylation of water (adventitious or deliberate addition), and the subsequent Cu-promoted arylation of phenol with the starting arylboronic acid, the latter process taking place competitively with the desired C–N cross-coupling reaction. Based on these and previous results related to the direct use of hygroscopic eutectic mixtures,^{18c,25} we run a new experiment in which the dry *DES* 1*ChOAc*/2*Urea* was used as the reaction medium. Satisfactorily, under these new conditions, the yield of the secondary amine **3a** increased up to 92% (entry 25, Table 1). Finally, we confirmed that an anhydrous $\text{Cu}(\text{II})$ salt is crucial for the success of the reaction as a $\text{Cu}(\text{I})$ precursor (CuI) was ineffective (entry 26, Table 1). This result is in good agreement with previous reported examples in the field of Cu-catalysed *CEL* couplings in polar solvents.²³ It is worth noting that, in order to catalytically generate the new C–N bond under copper catalysis, compound **3a** has been alternatively isolated in 89% yield by reacting aniline (0.2 mmol) with the corresponding aryl boronic acid (2 equiv) in MeOH, in the presence of K_2CO_3 (1 equiv) and a tetradentate copper(II) *N*-heterocyclic carbene complex (8 mol%).²⁶

With these satisfactory conditions in place, we explored the scope of this reaction with a series of anilines (**2a–e**, Table 2). The presence of electron-donating groups in the aromatic ring of the starting anilines [e.g., MeO (**2a,b**; entries 1,2, Table 2)] afforded the secondary aromatic amines **3a,b** in good to almost quantitative yields (79–92%) when using $\text{Ph-B}(\text{OH})_2$ (**1a**) as the coupling partner. The presence of electron-withdrawing substituents in the aromatic ring of the starting aniline [e.g., Cl (**2c**), $\text{C}\equiv\text{N}$ (**2d**), CF_3 (**2e**)] produced similar or lower yields of the corresponding secondary anilines **3c–e**

(52–81%; entries 3–5, Table 2). Aniline **2f** proved to be a competent reaction partner as well, yielding the corresponding diphenylamine (**3f**) in a good yield (80%, entry 6, Table 2). The employed catalytic system also tolerates the use of other aromatic/aliphatic primary amines like: *i*) benzylamine (**2g**; entry 7, Table 2); *ii*) 2-phenylethan-1-amine (**2h**; entry 8, Table 2); or *iii*) aliphatic cyclohexylamine (**2i**; entry 9, Table 2), providing moderate to good yields of secondary amines **3g–i** (40–70%). Aromatic boronic acids containing either electron-donating [e.g., Me (**1b**, entry 10, Table 2), Et (**1c**, entry 11, Table 2)] or electron-withdrawing groups [e.g., $\text{C}\equiv\text{N}$ (**1d**, entry 12, Table 2), CF_3 (**1e**, entry 13, Table 2)] are also well tolerated, furnishing the anticipated non-symmetric secondary amines **3j–m** in reasonable yields (52–67%).

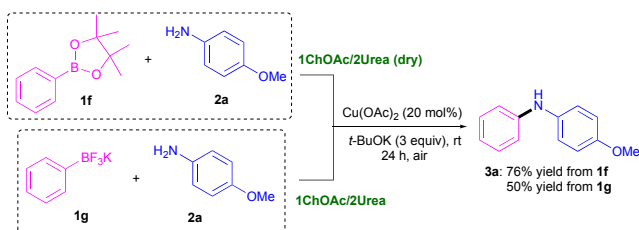
Table 2. $\text{Cu}(\text{OAc})_2$ -catalysed Chan-Evans-Lam C–N coupling between boronic acids **1a–e** and different primary amines **2a–k** in the eutectic mixture 1*ChOAc*/2*Urea*.^a



Entry	R ¹ (1a–d)	R ² (2a–k)	Product 3	Yield (%) ^b
1	H (1a)	4-MeOC ₆ H ₄ (2a)	3a	92
2	H (1a)	2-MeOC ₆ H ₄ (2b)	3b	79
3	H (1a)	4-ClC ₆ H ₄ (2c)	3c	81
4	H (1a)	3-CN-4-Tolyl (2d)	3d	62
5	H (1a)	3-CF ₃ C ₆ H ₄ (2e)	3e	52
6	H (1a)	Ph (2f)	3f	80
7	H (1a)	Benzyl (2g)	3g	67
8	H (1a)	Ph(CH ₂) ₂ (2h)	3h	70
9	H (1a)	Cy (2i)	3i	40
10	2-Me (1b)	4-FC ₆ H ₄ (2j)	3j	60
11	4-Et (1c)	4-MeOC ₆ H ₄ (2a)	3k	67
12	2-CN (1d)	3-CF ₃ C ₆ H ₄ (2k)	3l	52
13	4-CF ₃ (1e)	4-MeOC ₆ H ₄ (2a)	3m	62

^a General conditions: reactions performed under air, at room temperature using 0.50 mmol of **1a–e** and 0.25 mmol of **2a–k** in 1 g of dry eutectic mixture 1*ChOAc*/2*Urea*. ^b Isolated yield. Cy = cyclohexyl.

The described methodology could also be successfully applied to other boron-containing organometallic coupling partners, like acid pinacole ester (**1f**) or potassium phenyltrifluoroborate (**1g**),²⁷ jointly with **2a**, (Scheme 2), giving rise to the secondary aromatic amine **3a** in moderate to good yields (50–76%).

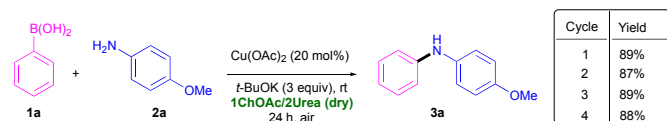


Scheme 2. $\text{Cu}(\text{OAc})_2$ -catalysed *CEL* C–N coupling of 4-methoxyaniline (**2a**) with organoboron partners **1f,g**, working under air, at room temperature, in the absence of ligands, in the eutectic mixture 1*ChOAc*/2*Urea*.

In order to prove the robustness of our approach, we scaled-up this protocol up to 1 g of **1a** (8.2 mmol) in 10 g of 1*ChOAc*/2*Urea*, (Scheme 3). Under these conditions, secondary amine **3a** was isolated in similar yield (89%) after 24 h reaction time. One of the advantages associated with the use of biorenewable eutectic mixtures as solvents in transition-metal-catalysed organic transformations is the possibility to recycle the catalytic

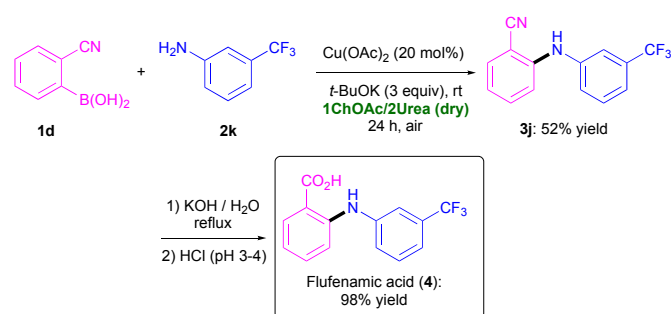


system/DES.^{12,13} To this end, both the study of the lifetime of a catalytic system and its level of reusability are crucial.²⁸ The recyclability of Cu(OAc)₂, the eutectic mixture and the base was assessed in the CEL C–N coupling between **1a** and **2a** in 1*ChOAc*/2*Urea*, when using *t*-BuOK as base, and working under aerobic conditions at rt (Scheme 3). Extraction of the reaction crude with cyclopentyl methyl ether (CPME),²⁹ followed by the addition of new fresh reagents (**1a** and **2a**), allowed the recycle of the catalyst, the 1*ChOAc*/2*Urea* mixture and the base for three consecutive runs with no reduction of the catalytic activity (Scheme 3). After 4 cycles, DES mass loss was within 5%. To better quantify the green credentials of the synthetic process developed, we calculated the Sheldon's environmental factor (*E*-factor; total mass of waste/mass of product),³⁰ finding a value of 10,³¹ which is in good agreement with that suggested for fine chemicals (between 5 and 50).³⁰



Scheme 3. Cu(OAc)₂-catalysed CEL C–N coupling between phenylboronic acid (**1a**) and 4-methoxyaniline (**2a**) in the eutectic mixture 1*ChOAc*/2*Urea* for the scaled-up synthesis of **3a**, and recycling studies.

Finally, we targeted the synthesis of Flufenamic acid (**4**), which is known to be a COX-1 inhibitor.²² This drug could be smoothly synthesized after hydrolysis of the nitrile moiety present in adduct **3j** (98% yield), the latter in turn being obtained via a CEL C–N coupling between **1d** and **2k** (entry 12, Table 2) (Scheme 4). Flufenamic acid (**4**) was isolated with an overall yield of 51%.



Scheme 4. Synthesis of COX-1 inhibitor Flufenamic acid (**4**) through a Cu(OAc)₂-catalysed CEL C–N coupling between **1d** and **2k** in the eutectic mixture 1*ChOAc*/2*Urea*, followed by hydrolysis.

Conclusions

In summary, we have reported the first example of Cu(II)-catalysed Chan-Evans-Lam C–N coupling between a family of organoboron reagents and different primary amines in *Deep Eutectic Solvents (DESs)* as sustainable reaction media. The screening of the eutectic mixture's components identified 1*ChOAc*/2*Urea* as the best *DES* for carrying out the above coupling reaction, which took place: *i*) under bench-type reaction conditions (rt/under air); *ii*) in the absence of external ligands; and *iii*) with high chemoselectivity, with electron-withdrawing and electron-donating groups being well tolerated.

Additional benefits include: *i*) the possibility to scale-up the process; *ii*) the effective recycling of the catalytic system and *DES* (up to four consecutive runs), without erosion of the catalytic activity; *iii*) a low *E*-factor value (up to 10); and *iv*) the successful synthesis of Flufenamic acid, a COX-1 inhibitor. Overall, this methodology represents a reliable, sustainable, affordable and chemoselective synthetic tool for the formation of C–N bonds, which is considered one of the most important transformations in transition-metal-catalysed organic transformations.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

L.C. and J.G.A. thank MCIN/AEI/10.13039/501100011033 (Projects number RED2018-102387-T and PID2020-113473GB-I00) for financial support. This work was carried out within the framework of the PRIN project "Unlocking Sustainable Technologies Through Nature-Inspired Solvents" (NATUREChem) (Grant No. 2017A5HXFC_002) financially supported by the Ministero dell'Università e della Ricerca (MUR-PRIN), the Interuniversity Consortium C.I.N.M.P.I.S., and the University of Bari Aldo Moro. L.C. also thanks the Erasmus+ Staff Mobility for a Training (SST) Programme 2020-2021.

Notes and references

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View Article Online
DOI: 10.1039/D3SU00093A

