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Cu-catalysed Chan–Evans–Lam reaction meets deep eutectic solvents: efficient and selective C–N bond formation under aerobic conditions at room temperature†‡

Luciana Cicco,^{ID}^a Paola Vitale,^{ID}^a Filippo Maria Perna,^{ID}^a Vito Capriati^{ID}^{*ab}
and Joaquín García-Álvarez^{ID}^{*c}

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

Sustainability spotlight

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 as sustainable and recyclable media. This work is aligned with the UN sustainable development goals of: responsible consumption and production (SDG 12) and climate action (SDG 13).

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,

^aDipartimento di Farmacia–Scienze del Farmaco, Università di Bari “Aldo Moro”, Consorzio C.I.N.M.P.I.S., Via E. Orabona 4, I-70125 Bari, Italy. E-mail: vito.capriati@uniba.it

^bIstituto di Chimica dei Composti Organometallici (CNR-ICCOM), Via Madonna del Piano 10, Sesto Fiorentino, 50019, Italy

^cLaboratorio de Química Sintética Sostenible (QuimSinSos), Departamento de Química Orgánica e Inorgánica, (IUQOEM), Centro de Innovación en Química Avanzada (ORFEO-CINQA), Facultad de Química, Universidad de Oviedo, E-33071 Oviedo, Spain. E-mail: garciajoaquin@uniovi.es

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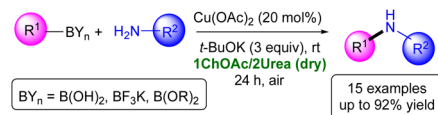


toluene, *N,N*-dimethylformamide, methanol) and/or flammable (*e.g.*, Et₂O, *n*-hexane, toluene, *N,N*-dimethylformamide, methanol, ethyl acetate, ethanol, *t*-butyl methyl ether), and, in some cases, also carcinogenic (*e.g.*, dichloromethane, carbon tetrachloride).⁹

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 = 133 °C).^{13a} DESs 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 HBAs [*e.g.*, ChCl, choline acetate (ChOAc)]¹⁵ and HBDs [*e.g.*, naturally occurring amides, alcohols or carboxylic acids (*e.g.*, urea, glycerol (Gly), sugars, lactic/citric acid)] are available for the synthesis of DESs.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 DESs 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 VOCs 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 DESs.^{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



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

ester, or potassium phenyltrifluoroborate. After screening various conditions, the best conversions were obtained when using the eutectic mixture 1ChOAc/2Urea 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

Results and discussion

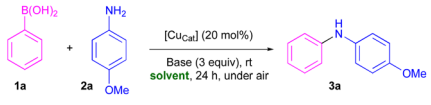
We started our investigations by employing the archetypical DES formed by ChCl and urea (1ChCl/2Urea), taking as a model reaction the Cu(OAc)₂-catalysed CEL C–N coupling between phenylboronic acid (**1a**) and 4-methoxyaniline (anisidine, **2a**) (Table 1). We selected as catalyst Cu(OAc)₂ as good efficiency 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 1ChCl/2Gly] (entry 2, Table 1); (ii) biorenewable carboxylic acids [*e.g.*, lactic acid (LA), forming the eutectic mixture 1ChCl/2LA] (entry 3, Table 1); or (iii) water, forming the eutectic mixture 1ChCl/2H₂O (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 HBAs; and (ii) the presence of urea as HBD (compare entries 1–3, Table 1). Based on this premise, the eutectic mixture 1ChOAc/2Urea 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}

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



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

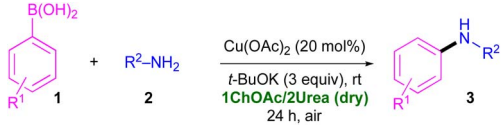
Either the replacement of urea with Gly as HBD in the above eutectic mixture, or with pure Gly or ethylene glycol (EG), was found to erode completely the catalytic activity of Cu(OAc)₂ (entries 7–9, Table 1). Next, we tested the Cu(OAc)₂-catalysed CEL C–N coupling protocol in the following eutectic mixtures, which are not based on ChCl: (i) 1Lys/4.5Gly (Lys = *L*-lysine; entry 10, Table 1); (ii) 1Bet/3Gly (Bet = betaine; entry 11, Table 1); (iii) 1Arg/4.5Gly (Arg = arginine; entry 12, Table 1); and (iv) 1Prol/3Gly (Prol = *L*-proline; entry 13, Table 1). However, previous results obtained with 1ChOAc/2Urea 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 Cu(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 (K₂CO₃, KOH, Cs₂CO₃, HCOOK, CH₃CO₂K)

(entries 16–20, Table 1) or the acetate in Cu(OAc)₂ with other anions (nitrate, sulphate, chloride) (entries 21–23, Table 1), as well as the use of Cu(OAc)·H₂O (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 1ChOAc/2Urea 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 Cu(II) salt is crucial for the success of the reaction as a Cu(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 K₂CO₃ (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

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



| Entry | R ¹ (1a–e) | 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 |

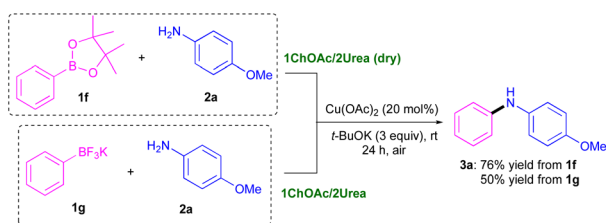
^a General conditions: reactions performed under air, at room temperature using 0.50 mmol of **1a–e** and 0.25 mmol of **2a–k** in 1 g of dry eutectic mixture 1ChOAc/2Urea. ^b Isolated yield. Cy = cyclohexyl.



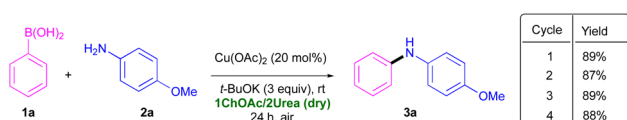
of the starting anilines [e.g., MeO (**2a,b**; entries 1, 2, Table 2)] afforded the secondary aromatic amines **3a,b** in good to almost quantitative yields (79–92%) when using Ph-B(OH)₂ (**1a**) as the coupling partner. The presence of electron-withdrawing substituents in the aromatic ring of the starting aniline [e.g., Cl– (**2c**), C≡N (**2d**), CF₃ (**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 cyclohexanamine (**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., C≡N (**1d**, entry 12, Table 2), CF₃ (**1e**, entry 13, Table 2)] are also well tolerated, furnishing the anticipated non-symmetric secondary amines **3j–m** in reasonable yields (52–67%).

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%).

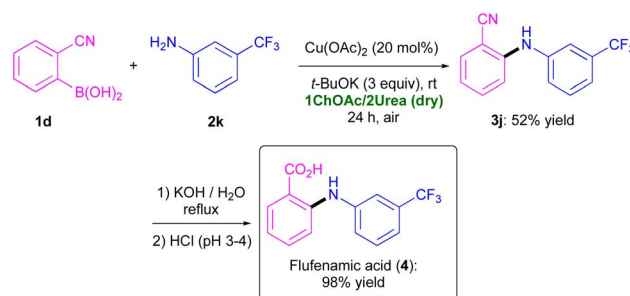
In order to prove the robustness of our approach, we scaled-up this protocol up to 1 g of **1a** (8.2 mmol) in 10 g of 1ChOAc/2Urea, (Scheme 3). Under these conditions, secondary amine **3a** was isolated in similar yield (89%) after 24 h reaction time. One of the advantages associated with the use of 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



Scheme 2 Cu(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 1ChOAc/2Urea.



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



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 1ChOAc/2Urea, followed by hydrolysis.

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 1ChOAc/2Urea, 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 1ChOAc/2Urea 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

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%.

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 1ChOAc/2Urea 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.

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