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Practical and sustainable preparation of pyrrolo [2,3-*b*]indoles by Cu/Fe catalyzed intramolecular C(sp²)-H amination†

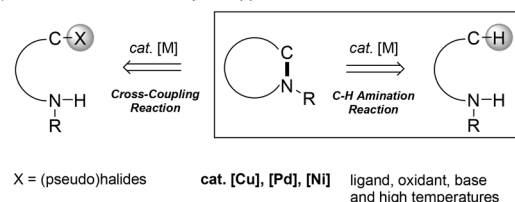
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A practical, robust and chemoselective approach toward the synthesis of pyrrolo[2,3-*b*]indoles via direct intramolecular C–H bond amination of α -indolylhydrazones has been achieved. This base- and oxidant-free chemoselective transformation relies on a Cu/Fe co-catalyst system that operates at 50 °C in air with water as the only reaction medium. The easy product isolation together with the recyclable catalyst aqueous system (reused at least five times, maintaining over 50% of its catalytic activity) can provide an effective environmentally benign approach to fused N-heterocycles of remarkable interest in pharmaceutical and medicinal chemistry. The ability of the hydrazone residue to act as a chelating/directing group as well as an aminating agent guarantees the success of this C–H functionalization.

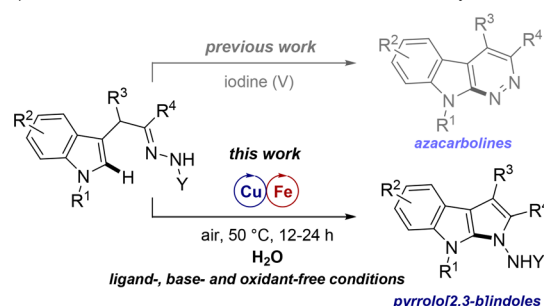
The formation of carbon–nitrogen bonds for the preparation of nitrogen-containing molecules is a manifestly important transformation in organic chemistry. As a result, considerable efforts have focused on the discovery of sustainable, more efficient, and selective methods to access valuable N-heterocyclic frameworks. Until recently, conventional approaches for C–N bond construction, routinely used in academia and industry, focused on variations of metal-catalyzed Buchwald–Hartwig, Ullmann and Chan–Lam cross-coupling between aryl- or heteroaryl (pseudo)halides with amine nucleophiles.^{1–9} Despite the significant progress achieved in the field, including the contributions on the use of bio-based solvents and water,^{10,11} these methodologies are viable only on pre-functionalized substrates, such as aryl- or heteroaryl (pseudo)halides which entails extra steps making them inefficient and unattractive. Conversely, the direct C–H functionalization of non-preactivated substrates undoubtedly constitutes an appealing, cost-effective and atom economical C–N bond connection strategy^{12–18} (Fig. 1a). A number of amination reac-

tions including the intramolecular variants,^{19–33} the first of which reported by pioneering work by Buchwald in 2005,¹⁹ has been successfully realized to date.

a) Intramolecular T.M.-catalyzed approaches to access N-functionalized compounds



b) Intramolecular selective C-H aminations to fused N-Heterocycles



- | | |
|--|---|
| <input checked="" type="checkbox"/> non prefunctionalized substrates | <input checked="" type="checkbox"/> atom economy |
| <input checked="" type="checkbox"/> no added ligand, base and oxidant | <input checked="" type="checkbox"/> high efficiency and selectivity |
| <input checked="" type="checkbox"/> inexpensive/abundant Cu/Fe sources | <input checked="" type="checkbox"/> broad substrate scope |
| <input checked="" type="checkbox"/> air as external oxidant | <input checked="" type="checkbox"/> scalable |
| <input checked="" type="checkbox"/> water as solvent | <input checked="" type="checkbox"/> recyclable catalyst system |

c) Representative examples of bioactive pyrrolo[2,3-*b*]indoles

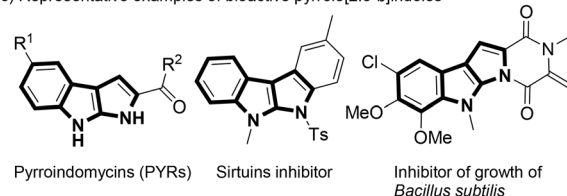


Fig. 1 Approaches of intramolecular C–N cross-coupling: synthesis of fused N-heterocycles.

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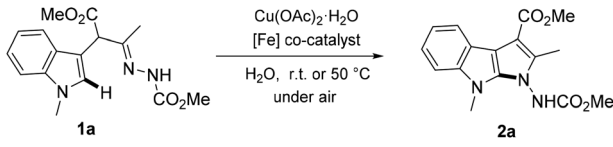


Within this context, noble catalysts (e.g., Pd, Rh, Ir and Ru) along with stoichiometric or excess amount of oxidant (e.g., Cu(OAc)₂, AgOAc, PhI(OAc)₂, CeSO₄, and/or F⁺) and complex/specialized auxiliary ligands and/or additives have been employed predominantly. However, most of the metal catalysts operate at rather high temperature in toxic, polar, aprotic organic solvents (e.g., *N,N*-dimethylformamide (DMF), *N*-methylpyrrolidone (NMP), and *N,N*-dimethylacetamide (DMAc)) which meeting with limited success when used in water. Even with the enormous progress made over the past decade in the most emerging areas of photocatalytic^{34–36}/electrochemical^{37–43}/photoelectrocatalytic⁴⁴ oxidative cross-coupling, however, there is still a necessity for the development of greener alternative and more efficient applicable methods which do not rely on noble metal catalysts^{45–48} (e.g., Cu, Fe, Zn, Mn, Co and Ni), avoid the use of toxic and/or hazardous organic solvents, and circumventing the need for external oxidants.^{49,50} Moreover, despite its conceptual simplicity, the intramolecular C–H bond amination of hydrazones^{51–56} possessing a “privileged” indole ring to afford value-added *N*-fused indoles remains elusive. Just recently, we reported a protocol for the synthesis of azacarbolines *via* PhIO₂-promoted six-membered cycloamination-oxidation of α -indolylhydrazones⁵⁷ (Fig. 1b, previous work). We envisioned that the pendant hydrazone residue in α -indolylhydrazones could be responsible for a five ring-closing C–H amination as result of the potential hydrazone–enamine tautomerization,^{58,59} thus providing a distinct approach for the C(2)–H functionalization of indoles and expedient synthesis of pyrroloindoles⁶⁰ (Fig. 1b, this work). To accomplish this, the hydrazonic residue should serve both as a chelating/directing group^{61–63} and as an intramolecular nitrogen source^{51–57} under the action of the opportune metal.

In designing a complementary and convenient strategy to produce less saturated version of pyrrolo[2,3-*b*]indole molecules^{64–71} *via* C–H bond functionalization, we herein report an unprecedented intramolecular C(sp²)–N bond amination strategy that utilizes a combination of more advantageous Cu^{72–75}/Fe^{76–78} (the most abundant in the Earth's crust) catalyst, at 50 °C in the presence of air as terminal oxidant in aqueous system/medium (Fig. 1b, this work).

Besides remarkable biological activities exemplified by representative compounds such as pyrroindomycins (PYRs) Sirtuins inhibitor, and inhibitor of growth of *Bacillus subtilis* (Fig. 1c), these 1,8-dihydro pyrrolo[2,3-*b*]indoles exhibit a broad spectrum of applications in optoelectronic materials and fluorescent probes.

We began our studies by testing the conversion of α -indolylhydrazone **1a** to 1-amino pyrrolo[2,3-*b*]indole **2a** using simple copper/iron salts (Table 1). After preliminary screening of a variety of conditions including nature of copper source, (co)catalyst loading, solvent, additive and temperature (see Table S1 of the ESI† for more details), we found that a combination^{79–87} of catalytic [commercially accessible] Cu(OAc)₂·H₂O (10 mol%) and FeCl₃·6H₂O (5 mol%) in an open flask at room temperature using water as the only reaction

Table 1 Optimization studies^a


Entry	Catalyst [mol%]	Co-catalyst [mol%]	T [°C]	t [h]	Yield [%] ^b
1	Cu(OAc) ₂ ·H ₂ O (10)	FeCl ₃ ·6H ₂ O (5)	r.t.	24	99 ^d
2	Cu(OAc) ₂ ·H ₂ O (10)	Fe ₂ O ₃ (5)	r.t.	20	98 ^d
3	Cu(OAc) ₂ ·H ₂ O (10)	Fe(NO ₃) ₃ ·9H ₂ O (5)	r.t.	10	32
4	Cu(OAc) ₂ ·H ₂ O (10)	Fe(ClO ₄) ₃ (5)	r.t.	48	73
5	Cu(OAc) ₂ ·H ₂ O (10)	Fe ₂ (SO ₄) ₃ ·H ₂ O (5)	r.t.	48	Trace ^c
6	Cu(OAc) ₂ ·H ₂ O (10)	Fe(acac) ₃ (5)	r.t.	40	99
7	Cu(OAc) ₂ ·H ₂ O (5)	FeCl ₃ ·6H ₂ O (2.5)	r.t.	40	99 ^d
8	Cu(OAc) ₂ ·H ₂ O (10)	FeCl ₃ ·6H ₂ O (5)	50	3	99 ^d
9	Cu(OAc) ₂ ·H ₂ O (10)	—	r.t.	48	Trace ^c
10	—	FeCl ₃ ·6H ₂ O (10)	r.t.	48	Trace ^c

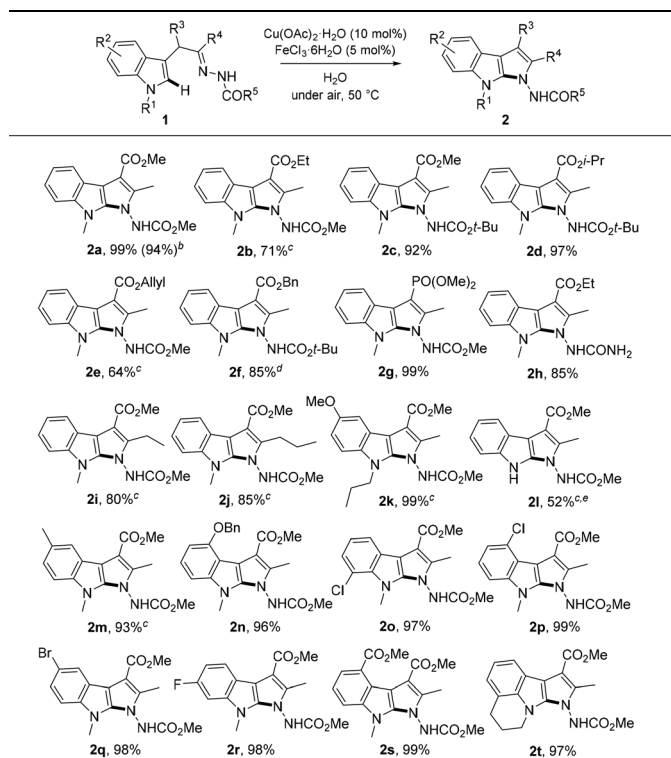
^a All reaction were performed on 0.2 mmol scale of **1a** in 2 mL of solvent (0.1 M) under air atmosphere for the indicate time. ^b Unless noted, yields are referred to the isolated product after column chromatography. ^c The unreacted starting material was recovered. ^d Without column chromatography.

medium,^{88–91} was beneficial for this transformation, with the compound **2a** being formed in 99% yield (entry 1). Reactions that employed other iron cocatalysts such as Fe₂O₃, Fe(NO₃)₃·9H₂O, Fe(ClO₄)₃, Fe₂(SO₄)₃·H₂O or Fe(acac)₃ led to inferior results in term of reactivity/efficiency (entries 2–6). Reducing the amount of catalyst/co-catalyst did not affect the yield albeit an extended reaction time was required for complete consumption of **1a** (entry 7). On the other hand, we found that a mild heating (50 °C) significantly accelerated the reaction, and **1a** was produced in almost quantitative yield within 3 h (entry 8).

Control experiments revealed that both Cu(OAc)₂·H₂O and FeCl₃·6H₂O were essential for this transformation as the omission of one of two catalysts resulted in only a trace amount of **2a** (Table 1, entries 9 and 10). To our delight, the product **2a** was purified simply by extraction with EtOAc, filtration through a plug of silica gel, concentration, and precipitation without the tedious column chromatography.

With these conditions in hand, the generality and scope of this novel intramolecular C–H amination process was explored (Table 2). First, the effect of different O-alkyl groups on the ester moiety of α -indolylhydrazone **1** was investigated. It was found that, in addition to methyl, ethyl, isopropyl, allyl or benzyl substituted substrates also worked well under the standard conditions, producing the desired products **2a–f** in good to excellent yields. Incorporation of a phosphonate residue (R³ = PO(OMe)₂) into the product (**2g**) was tolerated. Notably, the cyclization could also proceed successfully to deliver product **2h** when a substrate with an amide N-protective group (R⁵ = NH₂) was used. Compounds **2i,j**, which vary in the substitution pattern at the R⁴, resulted in good yields. An evaluation of the substituents on indolic nitrogen revealed that *N*–H indole is most sensitive for this transformation. Specifically, for compound **2l**, a spontaneous conversion to azacarboline

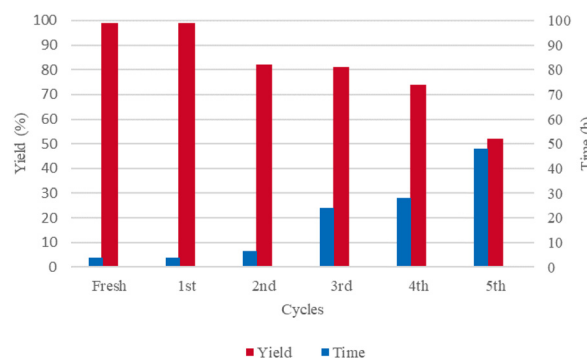


Table 2 Substrate scope for the intramolecular C(sp²)-H amination of α -indolylhydrazones^a

5a⁹² was registered. This observation imply that the substituent attached to the nitrogen of the indole nucleus is crucial in precluding ring expansion.

Then, we examined the substituent (R²) effect on the indole ring. Delightedly, the reaction well tolerated either EDG or EWG groups at 4-, 5-, 6-, or 7-positions of the indole rings affording the corresponding products **2m–s** in excellent yields. Finally, pyrrolo[2,3-*b*]indole **2t** incorporating a ring system between the N and C7 atoms of the indole ring was successfully generated.

For the majority of the reactions, purification of products by column chromatography can be avoided. Also, the recovery and reutilization of the aqueous solution containing the Cu/Fe co-catalyst system was tested using the formation of compound **2a** as model reaction (see (Fig. 2) and Table S2 of the ESI†). Thus, after the isolation of the latter compound, the recovered aqueous solution was used again to accomplish the same transformation up to five times. As shown in (Fig. 2), it is possible to use the water solution two times with no variation in both the yields and times of conversion of **1a** to **2a**. However, for the second recycling run, a clear decrease in the yield was observed. Comparable yield with a remarkable increase of the time of conversion resulted for the third run. While modest variations are observed for the fourth run, a more sensible

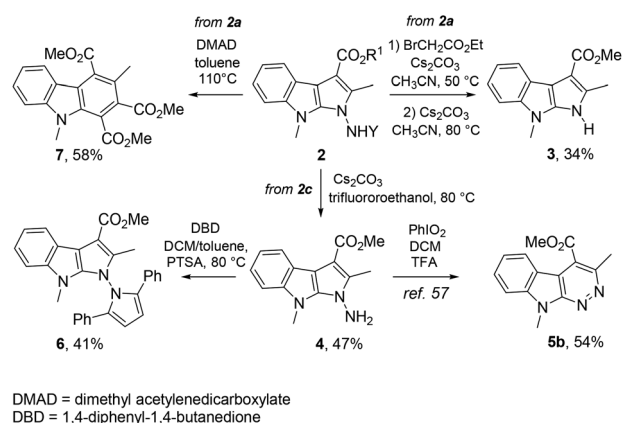
**Fig. 2** Recycling of the aqueous catalytic system.

change of both the yield and process time was registered for the subsequent run with the aqueous catalytic system that retains over 50% of its activity after five cycling runs. Interestingly, recycling involves not only the catalytic system but also the aqueous reaction medium itself, differently from most of the methods reported in the literature in which the metal species has to be prior separated from the reaction medium and often reactivated before its reuse.

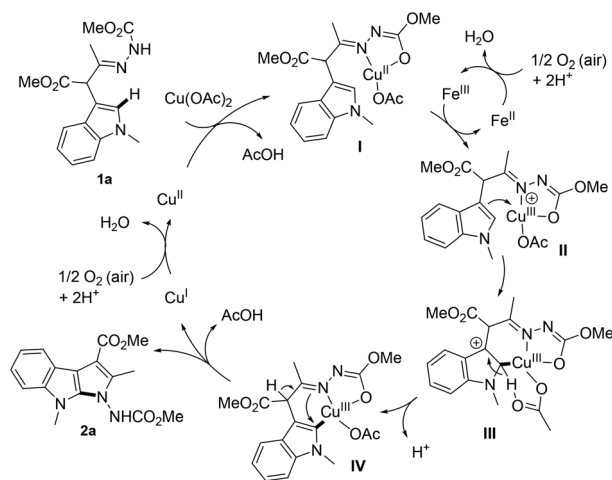
In addition, this intramolecular C(sp²)-H amination was found to be scalable delivering product **2a** in 94% yield (0.933 g) on 3.15 mmol scale.

To further explore the synthetic potential of the developed method, transformations of the thus formed pyrrolo[2,3-*b*]indoles were conducted (Scheme 1). Pyrroloindoles **3** and **4** can be easily obtained by N-N bond reductive cleavage (Magnus's protocol⁹³) and removal of *N*-Boc protecting group, respectively. Also, azacarboline **5b** can be prepared from compound **4** following our previously reported oxidation procedure.⁵⁷ Alternatively, a Paal-Knorr pyrrole synthesis from **4** generated the N-N indole-pyrrole scaffold **6**.⁹⁴ The acetylenic dienophile DMAD also reacted in Diels-Alder reaction with **2** to give 9*H*-carbazole **7**, after *N*-aminonitrene extrusion.⁹⁵

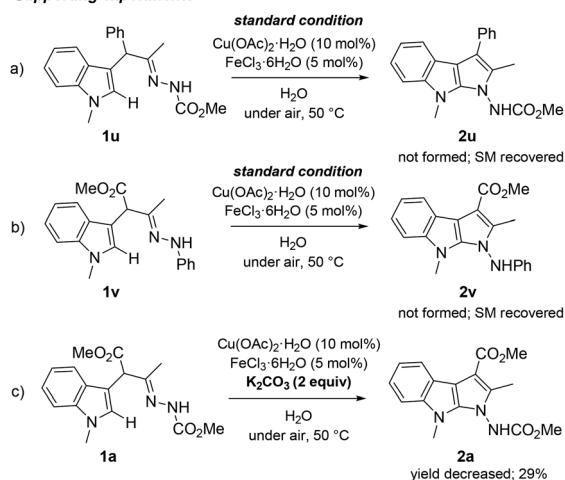
On the basis of literature information and our findings, a tentative mechanism for the transformation of **1a** to **2a** is illustrated in (Scheme 2). Initial *N,O*-bidentate coordination of the

**Scheme 1** Synthetic transformations of **2**.

Proposed mechanism



Supporting experiments



Scheme 2 Tentative mechanism and supporting experiments.

hydrazone moiety in **1a** to the $\text{Cu}(\text{OAc})_2$ species occurs to form the metallacycle complex **I** with the release of AcOH . Oxidation of the $\text{Cu}(\text{II})$ adduct **I** to intermediate **II** by $\text{Fe}(\text{III})$ would then facilitate the subsequent electrophilic aromatic substitution. Proton abstraction at the 2-position of indole through a six-membered transition state **III** (or *via* acetate ligand-assisted concerted C–H activation pathway) may be followed to give *endo*-metallacycle⁹⁶ intermediate **IV**. Finally, reductive elimination promoted by CH/NH tautomerization generates product **2a** along with the $\text{Cu}(\text{I})$ specie. The catalytic cycle is completed by the regeneration of the active $\text{Cu}(\text{II})$ catalyst by air oxidation.

Some control experiments to support this mechanistic scenario were carried out. Under the reaction conditions, α -indolylhydrazone **1u** bearing a phenyl substitution failed to produce **2u** (Scheme 2a), which implies that the electron-withdrawing group (EWG) at the α -position of the hydrazone substrate results indispensable for the reaction to occur. Furthermore, no cycloamination was detected in the case of *N*-phenyl **1v** because the copper complex *via* a bidentate

coordination could not formed during the catalytic cycle, indicating the crucial role of *N*-carboxyalkyl moiety in directing/assisting the cyclization at 2-position of the indole ring. A pathway in which a hydrogen abstraction promotes the reductive elimination of metallacycle intermediate **IV** instead of a preliminary CH/NH tautomerization on **1a**⁵⁷ (not shown) is also supported by an experiment in which the addition of K_2CO_3 as a base resulted in the dramatic decrease of the product yield of **2a** (29% yield).

Our new method is clearly distinguished from reported copper-catalyzed aerobic annulation of (hetero)aromatic hydrazones. With respect to Xiao and Xu protocol,⁵⁶ this method furnishes 1,8-dihydro pyrrolo[2,3-*b*]indoles (instead of cinnolines) with excellent control of the chemoselectivity and the obvious benefit of providing more sustainable solution with water under mild reaction conditions.

Conclusions

In conclusion, we herein described the first biocompatible Cu/Fe -catalyzed chemoselective intramolecular C–H bond amination of α -indolylhydrazones. Under a cooperative action of iron(III) and copper(II) salts in the absence of an external oxidant or any other additive a variety of substituted pyrrolo [2,3-*b*]indoles (relevant bioactive pharmacophoric core) has been prepared in excellent yields. Easy products isolation, recyclability of the catalyst system, mild and clean conditions, use of aqueous medium are the main features that demonstrate the potential of this transformation for industrial application. Further new synthetic applications of this green and low-cost $\text{C}(\text{sp}^2)\text{--H}$ amination are currently underway in our laboratory.

Author contributions

Matteo Corrieri: conceptualization, investigation, methodology, data curation, formal analysis; Lucia De Crescentini: data curation, formal analysis; Fabio Mantellini: data curation, resources, supervision; Giacomo Mari: investigation, methodology, and validation; Stefania Santeusano: data curation, formal analysis; Gianfranco Favi: conceptualization, funding acquisition, supervision, project administration, writing – original draft and writing – review & editing.

Conflicts of interest

There are no conflicts to declare.

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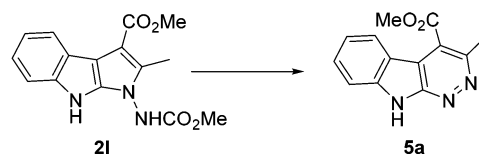


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