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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 baseand 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 strategy¹²⁻¹⁸ (Fig. 1a). A number of amination reac-

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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.

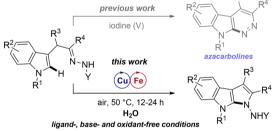
a) Intramolecular T.M.-catalyzed approaches to access N-functionalized compounds

$$\begin{array}{c|c} C + X & \underset{R}{\underbrace{\operatorname{cat} \left[M \right]}} \\ N-H & \underset{Reaction}{\underbrace{\operatorname{coss-Coupling}}} \\ R & \\ \end{array}$$

cat. [Cu], [Pd], [Ni]

and high temp

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



pyrrolo[2,3-b]indoles

- □ non prefunctionalized substrates
 □ no added ligand, base and oxidant
- inexpensive/abundant Cu/Fe sources
- air as external oxidant
- water as solvent

X = (pseudo)halides

- atom economy
- high efficiency and selectivity
- ☐ broad substrate scope
- □ recyclable catalyst system

c) Representative examples of bioactive pyrrolo[2.3-b]indoles

Pyrroindomycins (PYRs) Sirtuins inhibitor

Inhibitor of growth of

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 crosscoupling, 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 hydrazones⁵¹⁻⁵⁶ 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 PhIO2promoted six-membered cycloamination-oxidation 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 group⁶¹⁻⁶³ 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 molecules⁶⁴⁻⁷¹ *via* C-H bond functionalization, we herein report an unprecedented intramolecular C(sp²)-N bond amination strategy that utilizes a combination of more advantageous Cu⁷²⁻⁷⁵/Fe⁷⁶⁻⁷⁸ (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 inibithor 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] $Cu(OAc)_2 \cdot H_2O$ (10 mol%) and $FeCl_3 \cdot 6H_2O$ (5 mol%) in an open flask at room temperature using water as the only reaction

Table 1 Optimization studies

$$\begin{array}{c|c} \text{MeO}_2\text{C} & \text{Cu(OAc)}_2 \cdot \text{H}_2\text{O} \\ \hline \text{N} & \text{NH} & \text{CO}_2\text{Me} \\ \hline \text{1a} & \text{CuoMe} & \text{Cu(OAc)}_2 \cdot \text{H}_2\text{O} \\ \hline \text{Inder air} & \text{NHCO}_2\text{Me} \\ \hline \text{2a} & \text{CO}_2\text{Me} \\ \end{array}$$

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

 a All reaction were performed on 0.2 mmol scale of **1a** in 2 mL of solvent (0.1 M) under air atmospher 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 Fe_2O_3 , $Fe(NO_3)_3$ 9H₂O, $Fe(ClO_4)_3$, $Fe_2(SO_4)_3 \cdot H_2O$ 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 $Cu(OAc)_2 \cdot H_2O$ and $FeCl_3 \cdot 6H_2O$ were essential for this transformation as the omission of one of two catalysts resulted in only a trace amount of $\bf 2a$ (Table 1, entries 9 and 10). To our delight, the product $\bf 2a$ 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 $(R^3 = PO(OMe)_2)$ 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 $(R^5 = NH_2)$ 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 21, a spontaneous conversion to azacarboline

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Table 2 Substrate scope for the intramolecular $C(sp^2)$ -H amination of α -Indolylhydrazones^a

^a Reaction conditions: 1 (0.2 mmol), $Cu(OAc)_2 \cdot H_2O$ (10 mol%) and $FeCl_3 \cdot 6H_2O$ (5 mol%) in H_2O (2.0 mL) at 50 °C, 3–48 h. ^b 3.15 mmol scale reaction (0.933 g). ^c Isolated yields after column chromatography. ^d 50 °C for 36 h then 70 °C for 24 h. ^e A spontaneous conversion to azacarboline 5a (*vide infra*) was observed.

 $5a^{92}$ 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

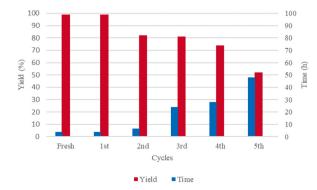


Fig. 2 Recycling of the aqueous catalytic system.

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

DMAD = dimethyl acetylenedicarboxylate DBD = 1,4-diphenyl-1,4-butanedione

Scheme 1 Synthetic transformations of 2.

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Proposed mechanism

Supporting experiments

a)
$$\begin{array}{c} \text{Standard condition} \\ \text{Cu}(OAc)_2 \cdot H_2O \text{ (10 mol\%)} \\ \text{FeCl}_3 \cdot 6H_2O \text{ (5 mol\%)} \\ \text{H}_2O \\ \text{under air, 50 °C} \\ \end{array} \begin{array}{c} \text{2u} \\ \text{not formed; SM recovered} \\ \text{Cu}(OAc)_2 \cdot H_2O \text{ (10 mol\%)} \\ \text{FeCl}_3 \cdot 6H_2O \text{ (5 mol\%)} \\ \text{H}_2O \\ \text{under air, 50 °C} \\ \end{array} \begin{array}{c} \text{Co}_2\text{Me} \\ \text{FeCl}_3 \cdot 6H_2O \text{ (5 mol\%)} \\ \text{H}_2O \\ \text{under air, 50 °C} \\ \end{array} \begin{array}{c} \text{Co}_2\text{Me} \\ \text{NHPh} \\ \text{NHPh} \\ \end{array}$$

Scheme 2 Tentative mechanism and supporting experiments.

hydrazone moiety in 1a to the Cu(OAc)₂ species occurs to form the metallacycle complex I with the release of AcOH. Oxidation of the Cu(II) adduct I to intermediate II by Fe(III) would then facilitate the subsequent electrophilic aromatic substitution. Proton abstraction at the 2-position of indole through a sixmembered 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 Cu(1) specie. The catalytic cycle is completed by the regeneration of the active Cu(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 1a⁵⁷ (not shown) is also supported by an experiment in which the addition of K₂CO₃ as a base resulted in the dramatically 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 C(sp²)-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 Santeusanio: 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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