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Marc Camats, Isabelle Favier, Sonia Mallet-Ladeira, Daniel Pla, Montserrat Gómez. Understanding Cu( ii )-based systems for C(sp<sup>3</sup> )–H bond functionalization: insights into the synthesis of aza-heterocycles. *Organic & Biomolecular Chemistry*, 2021, 20 (1), pp.219-227. 10.1039/D1OB02118D . hal-03806424

**HAL Id: hal-03806424**

**<https://hal.science/hal-03806424>**

Submitted on 7 Oct 2022

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# Understanding Cu(II)-based systems for C(sp<sup>3</sup>)-H bond functionalization: insights on the synthesis of aza-heterocycles

Received 00th January 20xx,  
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Marc Camats,<sup>a</sup> Isabelle Favier,<sup>a</sup> Sonia Mallet-Ladeira,<sup>b</sup> Daniel Pla,<sup>\*a</sup> and Montserrat Gómez<sup>\*a</sup>

*Dedicated to the memory of Prof. David Y. Gin and his contributions in the synthesis of bioactive alkaloids.*

Herein we report the synthesis of imidazo[1,5-*a*]pyridine heterocycles via a Cu(II)-mediated functionalization of α'-C(sp<sup>3</sup>)-H bonds of pyridinylaldimines and subsequent cyclization. This strategy exploits the inherent directing ability of heteroleptic aldimine and pyridine groups in the substrate yielding the C-H functionalization of α'-methylene groups in a regioselective fashion over distant methyl or methylene groups in β or γ positions. The observed correlation between the nature of the anionic ligands (halide vs. carboxylate) bonded to copper and the chemoselectivity of the C(sp<sup>3</sup>)-H activation process points to a concerted metalation-deprotonation pathway prior to cyclization to furnish the corresponding imidazo[1,5-*a*]pyridine derivative. This copper-mediated C(sp<sup>3</sup>)-H bond functionalization reaction works for a variety of substrates incorporating linear alkyl chains (from 3 to 12 carbon atoms), and good functional group tolerance (aryl, ether and ester groups). Cu-catalyzed C(sp<sup>2</sup>)-H cyanation on the imidazole ring can then take place selectively under oxidative conditions.

## Introduction

In contrast to 4d and 5d transition metal catalysts (*e.g.* Pd, Pt, Ru, Rh),<sup>1</sup> first row transition metals have received less attention in direct functionalization methodologies of unactivated C-H bonds.<sup>2</sup> Among them, copper occupies a preferential place due to its abundance, low toxicity and versatility in terms of reactivity as evidenced by the many reports on C(sp<sup>2</sup>)-H activation reactions,<sup>2b, 3</sup> in particular those using bidentate ligands.<sup>4</sup> Since Fujiwara's early reports on the C(sp<sup>3</sup>)-H aminomethylation of alkanes catalyzed by Cu(II) salts,<sup>5</sup> the advent of direct functionalization methodologies for the selective transformation of unactivated C(sp<sup>3</sup>)-H bonds has enabled novel synthetic routes by means of C-C cross-dehydrogenative reactions,<sup>6</sup> carbonylative<sup>7</sup> and

decarboxylative couplings,<sup>6e, 8</sup> aminations,<sup>3b, 9</sup> amidations,<sup>10</sup> alkoxylation,<sup>11</sup> acetoxylation<sup>12</sup> and phosphorothiolations,<sup>13</sup> among the most relevant transformations.<sup>3a, 6f, 14</sup>

The use of bidentate ligands to direct functionalization of C(sp<sup>3</sup>)-H bonds in a regioselective fashion has afforded promising results for the functionalization of such recalcitrant bonds.<sup>3a, 4a, 4c, 15</sup> From a mechanistic point of view, organometallic C-H bond activation, ligand-assisted functionalization and single electron-transfer pathways have been postulated in the process (Figure 2).<sup>16</sup> In particular, the C(sp<sup>3</sup>)-H activation in α position to a nitrogen atom has been described to undergo via the formation of an iminium group arising from a radical cation. This reactivity has thus far been applied in Cu-catalyzed annulation of *N*-heteroaryl aldehydes<sup>17</sup> or ketones<sup>9c, 18</sup> with alkylamines and aminoacids via C(sp<sup>3</sup>)-H amination. The affinity of heterocyclic aldimines for electrophilic Cu(II)-based catalysts represents a straightforward and atom economical manner to accomplish remote C(sp<sup>3</sup>)-H bond activation. Thus, we envisioned that the imidazo[1,5-*a*]pyridine scaffold could be formed via C(sp<sup>3</sup>)-H bond functionalization of aldimines bearing pendant saturated hydrocarbon chains. In this work, we report the direct synthesis of 3-substituted imidazo[1,5-*a*]pyridines via a Cu-mediated C(sp<sup>3</sup>)-H activation/cyclization in excellent yield and regioselectivity, thus providing novel methods which are complementary to established strategies.

<sup>a</sup> Laboratoire Hétérochimie Fondamentale et Appliquée, CNRS UMR 5069, Université Toulouse 3 – Paul Sabatier, 118 route de Narbonne, 31062 Toulouse Cedex 09, France. E-mail: D.P. pla@lhfa.fr; M.G. gomez@chimie.ups-tlse.fr

<sup>b</sup> Institut de Chimie de Toulouse, CNRS UAR 2599, 118 Route de Narbonne, Toulouse 31062 Cedex 09, France

Electronic Supplementary Information (ESI) available:

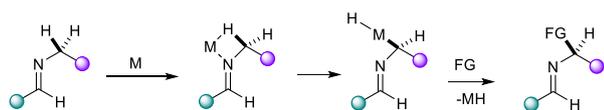
- Instrumentation, materials, experimental procedures, Tables S1-S5, Figures S1-S5, Schemes S1-S4, synthesis and characterization of compounds type-1, type-2, 4 and 6a, NMR spectra of type-1, type-2, 4 and 6a compounds, and single-crystal X-ray diffraction data for CuA, Cu4B, 4 and 6a (Tables S6-S9) (PDF).

- X-ray crystallographic files in CIF format for CuA, Cu4B, 4 and 6a.

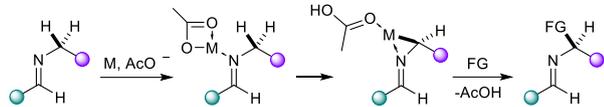
- CCDC-2077016 (CuA), CCDC-2077017 (Cu4B), CCDC-2077019 (4), and CCDC-2077018 (6a), contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

See DOI: 10.1039/x0xx00000x

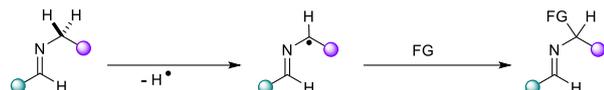
## a) Organometallic C-H bond activation



## b) Ligand-assisted C-H bond functionalization



## c) Single electron-transfer pathways via hydrogen atom abstraction

Figure 2. C(sp<sup>3</sup>)-H bond activation pathways of aldimines.

Diversity-oriented synthesis<sup>19</sup> strategies to explore the chemical space around privileged leads such as purine,<sup>20</sup> imidazo[1,2-*a*]pyridine,<sup>3f</sup> pyrazolo[1,5-*a*]pyrimidine,<sup>21</sup> pyrazolo[1,5-*a*]pyridine<sup>22</sup> and pyrrolo[2,1-*f*][1,2,4]triazine,<sup>23</sup> found in numerous natural products and drug scaffolds (Figure 1) prompted us to explore novel synthetic methodologies for the synthesis of isosteric scaffolds.<sup>24</sup> In particular, imidazopyridine derivatives are garnering increased attention in recent years as tryptophan-2,3-dioxygenase and indoleamine 2,3-dioxygenase inhibitors.<sup>25</sup>

Thus, medicinal chemistry approaches to access variations on such fundamental building blocks in a rapid and efficient manner could provide important breakthroughs in translational science. In this regard, the functionalization of recalcitrant C-H bonds represents a powerful and sustainable transformation in organic synthesis, affording new entries to such valuable motifs of potential biological interest.<sup>26</sup> In this work, we focus on the use of Cu-promoted C-H bond functionalization strategies towards the preparation of new compounds with untapped potential.

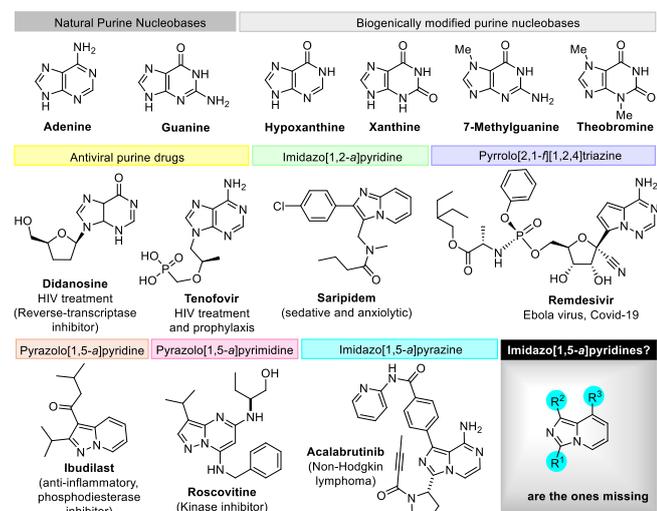
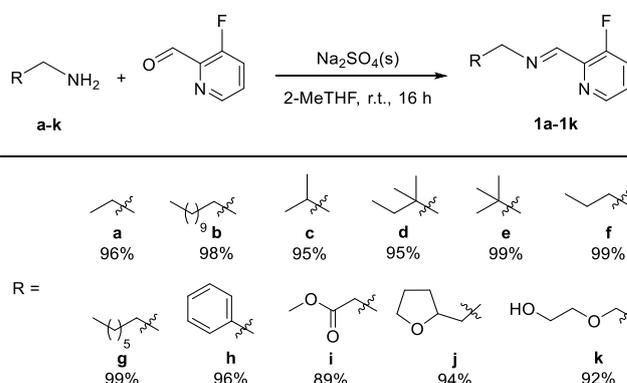


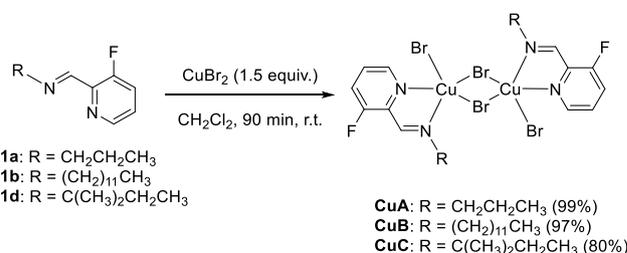
Figure 1. Purine nucleobases and drugs of interest featuring structurally related heterocyclic scaffolds.

## Results and Discussion

We prepared original aldimines by condensation of 3-fluoro-2-pyridinecarboxaldehyde and the corresponding primary amine in 2-methyltetrahydrofuran and in the presence of sodium sulfate, affording the expected products **1a-1k** in high yields (>89%, Scheme 1), together with an ease of analysis by <sup>19</sup>F-NMR.

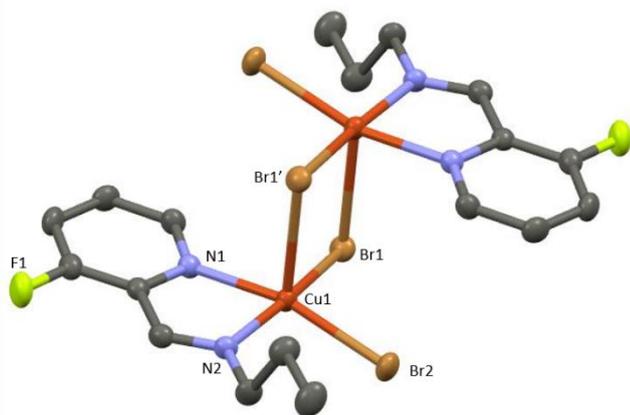
Scheme 1. Synthesis of aldimines **1a-1k**.

Our attempts towards the functionalization of pyridinylaldimine substrate **1a** began with the use of superstoichiometric amounts of CuBr<sub>2</sub> (1.5 equiv.) in CHCl<sub>3</sub> or CH<sub>3</sub>CN at 100 °C under microwave irradiation, resulting in the formation of Cu(II) coordination complexes (no C-H bond activation was observed). Thus, the bimetallic **CuA** was isolated and further crystallized by reaction of CuBr<sub>2</sub> with **1a** in CH<sub>2</sub>Cl<sub>2</sub> at room temperature. Similar results were obtained with **1b** and **1c** (Scheme 2).

Scheme 2. Synthesis of complexes **CuA**, **CuB** and **CuC** from aldimines **1a**, **1b** and **1d**, respectively.

**CuA** X-ray crystal structure shows the formation of a centrosymmetric bimetallic complex with two bromide anions bridging both metals, in agreement with other related structures containing *N,N*-bidentate ligands: pyridyl-benzimidazole,<sup>27</sup> pyridyl-oxime,<sup>28</sup> and pyridyl-pyrazole.<sup>29</sup> The asymmetric unit consists of a five-membered metalocycle featuring a bidentate *N,N*-coordination of the 1-(3-fluoropyridin-2-yl)-*N*-propylmethanimine ligand (bite angle N1Cu1N2 = 80.11(8)°) and two bromide anions in a slightly distorted square planar arrangement around the metal center (the distance between the N1N2Br1Br2 plane and Cu is 0.21 Å). Each Cu(II) center is pentacoordinated exhibiting a distorted square pyramidal arrangement constituted of a N1N2Br1Br2

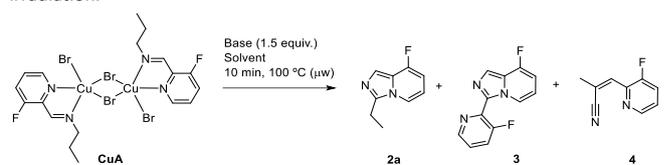
plane and an apical bromide anion (Cu-Br(apical) distance = 2.781(1) Å); no metal-metal interaction is observed (Cu-Cu distance = 3.601(1) Å) (Figure 3 and Figure S1 in the ESI).



**Figure 3.** Molecular view of **CuA**. Hydrogen atoms have been omitted for clarity purposes (ellipsoids representing 50% probability). Selected distances (Å) and angles (°) [symmetry code (i): 1-x, 2-y, 1-z]: Cu1-Br1' = 2.781(1), Cu1-Br1 = 2.425(1), Cu1-Br2 = 2.386(1), Cu1-N1 = 2.065(2), Cu1-N2 = 2.039(2); N1-Cu1-N2 = 80.11(8); Br1-Cu1-Br2 = 91.24(1); N1-Cu1-Br1 = 92.33(6); N2-Cu1-Br2 = 94.48(6).

Reactivity studies of **CuA** in the absence of base were carried out in  $\text{CHCl}_3$  and  $\text{CH}_3\text{CN}$ , but no conversion was detected, pointing that this complex is not involved in the C-H bond activation, probably due to the formation of unsaturated reactive copper species (see Table S1 in the ESI). When  $\text{Ac}_2\text{O}$  was used as solvent, only by-products coming from imine hydrolysis were observed. Even though the use of a solvent mixture of  $\text{AcOH}:\text{CHCl}_3$  (1:4) rendered a very low conversion (5%), a new 3-alkyl-8-fluoroimidazo[1,5-*a*]pyridine product (**2a**) was identified albeit in low yield. Finding the right balance in terms of stability and reactivity of the Cu-based intermediates seems crucial to enable a selective transformation overriding hydrolysis pathways. To facilitate the  $\text{C}(\text{sp}^3)\text{-H}$  amination,  $\text{NH}_4\text{OAc}$  (1.5 equiv.) was used to perform the transformation under buffered conditions in a solvent mixture of  $\text{AcOH}:\text{CHCl}_3$  (1:4), but only 8-fluoro-3-(3-fluoropyridin-2-yl)imidazo[1,5-*a*]pyridine (**3**) and (2*Z*)-3-(3-fluoropyridin-2-yl)-2-methylprop-2-enitrile (**4**; see the ESI for single-crystal XRD structure) by-products were obtained (Table 1, entries 1 and 2) arising from deleterious hydrolytic pathways. The formation of **3** can be justified by imine transimination with ammonia followed by condensation with a second aldehyde in the absence of copper(II) species as described in the literature (Table 1, entry 2).<sup>30</sup> This secondary reaction was also favored in glycerol (69% conversion, Table 1, entry 3). Concerning the formation of **4**, a rational is proposed in the mechanistic discussion (see below). Transformation of the dimer **CuA** into the heterocycle **2a** occurred in  $\text{CH}_3\text{CN}$  the presence of  $\text{NH}_4\text{OAc}$ , albeit in low yield (23%, Table 1, entry 4), whereas only traces of the product could be detected in  $\text{CHCl}_3$  (4% Table 1, entry 5).

**Table 1.** Reactivity of **CuA** in different solvents and bases under microwave irradiation.<sup>[a]</sup>



Entry	Solvent	Base	Conversion (%) <sup>[b]</sup>	Yield (%) <sup>[b]</sup>		
				<b>2a</b>	<b>3</b>	<b>4</b>
1	$\text{AcOH}:\text{CHCl}_3$ (1:4)	$\text{NH}_4\text{OAc}$	76	<1	49	15
2 <sup>[c]</sup>	$\text{AcOH}:\text{CHCl}_3$ (1:4)	$\text{NH}_4\text{OAc}$	90 <sup>[d]</sup>	0	34	0
3	Glycerol	$\text{NH}_4\text{OAc}$	69 <sup>[e]</sup>	5	54	4
4	$\text{CH}_3\text{CN}$	$\text{NH}_4\text{OAc}$	32	23	0	0
5	$\text{CHCl}_3$	$\text{NH}_4\text{OAc}$	6	4	0	0
6	$\text{CH}_3\text{CN}$	$\text{NBu}_4\text{OAc}$	72	64	n.d. <sup>[f]</sup>	n.d. <sup>[f]</sup>
7	$\text{CH}_3\text{CN}$	KOPiv	87	84	n.d. <sup>[f]</sup>	n.d. <sup>[f]</sup>

[a] Reaction conditions: **CuA** (0.15 mmol, 117.0 mg), 0.45 mmol of base, 4 mL of the corresponding solvent, at 100 °C for 10 min under microwave irradiation (max. 200 W). [b] Conversions and yields were determined by  $^{19}\text{F}$  NMR with 4-fluorotoluene as standard. [c] **1a** was used as starting material instead of **CuA**. [d] Complex mixture of degradation by-products. [e] Complex mixture composed of acetals and by-products. [f] n.d. for not detected.

In  $\text{CH}_3\text{CN}$ , other bases were tested (Table 1, entries 6-7 and Table S2 in the ESI). Notably,  $\text{NBu}_4\text{OAc}$  furnished up to 72% conversion and good selectivity towards **2a** (64% yield, Table 1, entry 6) and KOPiv, 87% conversion (84% yield, Table 1, entry 7).  $\text{CsOAc}$  or  $\text{KOAc}$  showed low conversions (8 and 26%, respectively, Table S2 in the ESI) albeit in excellent selectivity for the latter. Other salts were tested as bases, namely,  $\text{KOH}$  and  $\text{KO}^t\text{Bu}$ ;  $\text{KOH}$  did not trigger any transformation and more basic  $\text{KO}^t\text{Bu}$  directed a nucleophilic attack to the imine moieties of the binuclear complex (see Table S2 in the ESI). These results point to a plausible anion exchange on the complex (bromide by carboxylate; encompassing an instantaneous color change from deep red to green) that enables the C-H bond functionalization. Once the reactivity of the binuclear copper complex was optimized, we studied the in-situ reaction of imines type-1 with  $\text{CuBr}_2$  (1.5 equiv.) in the presence of  $\text{NBu}_4\text{OAc}$  (1.5 equiv.). Gratifyingly, under these conditions, the  $\text{C}(\text{sp}^3)\text{-H}$  amination and cyclization furnished the desired imidazo[1,5-*a*]pyridine product (**2a**) in comparable yield and selectivity to the reaction carried out from the preformed complex **CuA** (52% vs 64% yield, Table S3, entry 1 vs Table 1, entry 6, respectively).<sup>31</sup>

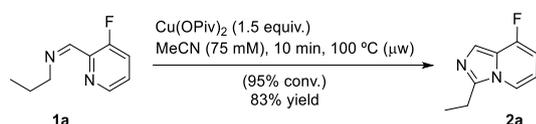
This result prompted us to examine the use of  $\text{Cu}(\text{OAc})_2$  towards the C-H functionalization of the aldimine **1a** (reaction conditions: 100 °C under microwave irradiation for 10 min in different solvents: EtOH, glycerol, AcOH,  $\text{CF}_3\text{COOH}$ ,  $\text{CHCl}_3$ , EtOAc,  $\text{CH}_3\text{CN}$ ; see Table S4 in the ESI). Full decomposition was observed with superstoichiometric amounts of  $\text{Cu}(\text{OAc})_2$  in both  $\text{CF}_3\text{COOH}$  and EtOAc as solvents; moreover, major substrate hydrolysis to propylamine and 6-fluoropyridine-2-carboxaldehyde precursors was obtained for many of the tested conditions using protic solvents. When  $\text{CH}_3\text{CN}$  and  $\text{CHCl}_3$  were

used as solvents, **2a** was obtained in low to moderate yields (48 and 17%, respectively, see Table S4 in the ESI, entries 6–7). Interestingly, a cubane tetranuclear copper(II) complex (**Cu4B**) with the composition  $[\text{Cu}_4\text{OCl}_6(\mathbf{2b})_4]$  was obtained by crystallization of the crude reaction mixture in  $\text{CHCl}_3$ . Its single-crystal X-ray analysis showed a central oxygen atom coordinated to four copper atoms in a tetrahedral geometry (Cu–O–Cu angles are  $110.57(5)^\circ$  and  $108.92(2)^\circ$ ), each of which connected to the three other Cu atoms via bridging chlorine atoms (placed at the tetrahedron edges), analogously to related structures already reported in the literature.<sup>32</sup> Each copper center shows a distorted trigonal bipyramid geometry with chlorine atoms occupying the three equatorial positions and the central oxygen atom and imine nitrogen of the heterocycle **2b** in axial positions (Figure 4).

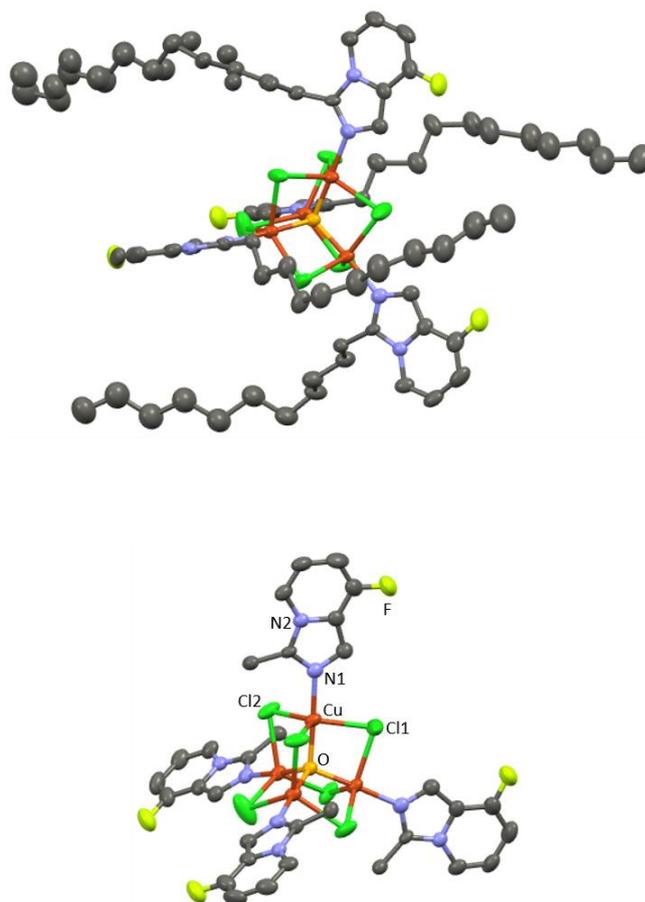
The isolation of this copper cluster encouraged us to assess its role in the reaction. Thus, its plausible precursor  $[\text{Cu}_4\text{OCl}_6(\text{CH}_3\text{CN})_4]$  (**5**) was prepared.<sup>33</sup> However, the reaction of **5** with aldimine **1b**, aiming at the in situ generation of **Cu4B** via the displacement of the  $\text{CH}_3\text{CN}$  ligands by **1b**, did not furnish any traces of the desired product **2b** under our reaction conditions, suggesting that the copper cluster **5** is inactive towards  $\text{C}(\text{sp}^3)\text{--H}$  activation (see Scheme S1 in the ESI).

With the aim of obtaining Cu(II) carboxylate complexes, we carried out a number of attempts to prepare the corresponding **1a** and **1b** aldimine complexes with  $\text{Cu}(\text{OPiv})_2$  (due to its better reactivity; see below); unfortunately, no suitable monocrystals for XRD analyses were obtained. However, MS analyses revealed the complexation of **1a** affording bis-pivalate  $[\text{Cu}(\text{OPiv})_2(\mathbf{1a})]$  species ( $[\text{M}+\text{H}]$ ,  $m/z$  432.1), together with the presence of the mono-pivalate peak,  $[\text{Cu}(\text{OPiv})(\mathbf{1a})]^+$  ( $m/z$  330.1; see Figure S2 in the ESI).

To assess the determinant role of copper carboxylates in facilitating the C–H amination, several copper salts (namely formate, acetate, benzoate and pivalate) were tested (see Table S3 in the ESI, entries 3–5). Despite the poor results obtained for both copper formate and copper benzoate (**2a** obtained in 55 and 14% yields, respectively), these results point to the key assistance of carboxylate groups in the C–H activation event. Among the copper(II) carboxylates used,  $\text{Cu}(\text{OPiv})_2$  exhibited the best conversion and selectivity (95% conversion and 83% yield; Scheme 3 and see Table S3 in the ESI, entry 5).



**Scheme 3.** Optimized reaction conditions for the synthesis of imidazo[1,5-*a*]pyridines type-2 with stoichiometric  $\text{Cu}(\text{OPiv})_2$ .

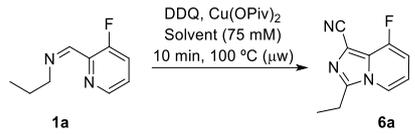


**Figure 4.** TOP: Molecular view of a cubane tetranuclear copper(II) complex **Cu4B** with the composition  $\text{Cu}_4\text{OCl}_6(\mathbf{2b})_4$  (ellipsoids representing 50% probability) where hydrogen atoms have been omitted for clarity purposes and only the major position of the disordered alkyl chain is shown (for atom labelling see bottom view). BOTTOM: **Cu4B** molecular view where hydrogen and carbon atoms of the alkyl chains have been omitted for clarity purposes. Selected distances (Å) and angles ( $^\circ$ ): Cu–N1 = 1.967(6); Cu–Cl = 2.374(2), 2.407(3) and 2.424(2); Cu–O = 1.909(1); Cl–Cu–Cl = 114.04(6), 119.85(4) and 123.60(6); Cl–Cu–N1 = 93.26(16), 94.50(15) and 97.99(18); Cl–Cu–O = 84.03(6), 84.36(5) and 85.75(5); N1–Cu–O = 177.36(17).

In order to translate the stoichiometric reaction into its catalytic version, several oxidizing reagents were studied under microwave irradiation (10–20 mol% catalyst loadings of  $\text{Cu}(\text{OPiv})_2$  in  $\text{CH}_3\text{CN}$  at  $100^\circ\text{C}$ ; see Table 2 and Table S5 in the ESI). Among the oxidizing agents tested, only stoichiometric amounts (related to copper salt) of the desired product were obtained in the presence of pivalic anhydride (1.5 equiv.), benzoquinone (1.5 equiv.) and a mixture of  $\text{K}_3[\text{Fe}(\text{CN})_6]$  (1.5 equiv.) and dibenzo-18-crown-6 (for further details, see Table S5 in the ESI). It is noteworthy to mention that a new 8-fluoroimidazo[1,5-*a*]pyridine-1-carbonitrile product (**6a**) was obtained when 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was used (Table 2, entry 1; see the ESI for single-crystal XRD of **6a**). Taking into account literature reports on the role of  $\text{CH}_3\text{CN}$  as a cyanating reagent with copper catalysts,<sup>34</sup> we reasoned that the nitrile group could come from the solvent. However, this hypothesis was discarded as the reaction in CpOMe did also provide **6a** together with by-products (Table 2, entry 2), whereas the reaction in the absence of DDQ did not

provide any traces of **6a** (Table 2, entry 3). These results indicate that DDQ acts as cyanating agent, in agreement with copper-catalyzed cyanation of arylboronic acids described by Cheng and co-workers.<sup>35</sup> Optimization of the reaction was carried out (Table 2, entries 4–6), finding the following optimal conditions: Cu(OPiv)<sub>2</sub> (20 mol%), DDQ (1 equiv.) in CH<sub>3</sub>CN at 100 °C for 10 min under microwave irradiation (Table 2, entry 4). This new copper-mediated C–H cyanation reaction brings a new entry to non-hazardous cyanide sources.<sup>36</sup>

**Table 2.** Optimization of the reaction conditions for the Cu(II)-catalyzed synthesis of **6a** under microwave irradiation.



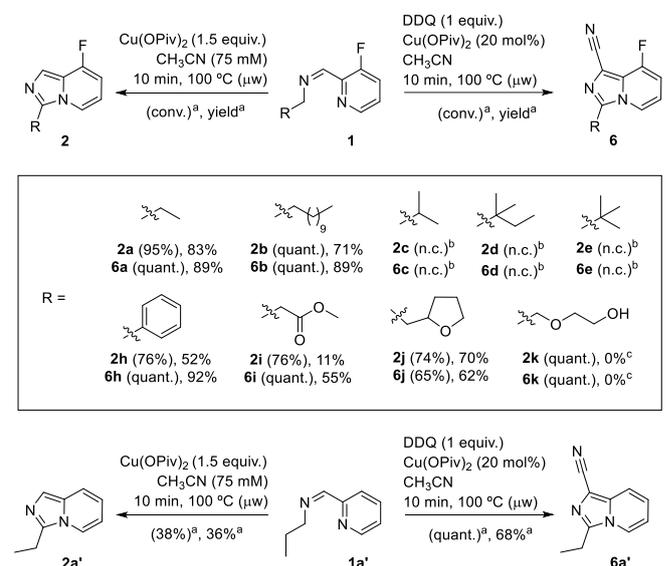
Entry	Catalyst loading (mol%)	DDQ (equiv.)	Solvent	Conversion (%) <sup>[a]</sup>	<b>6a</b> (%) <sup>[a]</sup>
1	20	1.5	CH <sub>3</sub> CN	100	87
2	20	1.5	CpOMe	100	25 <sup>[b]</sup>
3	20	0	CH <sub>3</sub> CN	18	0 <sup>[c]</sup>
4	20	1	CH <sub>3</sub> CN	100	89
5	10	1	CH <sub>3</sub> CN	100	68 <sup>[d]</sup>
6	0	1	CH <sub>3</sub> CN	100	0 <sup>[b]</sup>

[a] Conversions and yields were determined by <sup>19</sup>F NMR with 4-fluorotoluene as standard. [b] Complex mixture of 6-fluoropyridine-2-carboxaldehyde and by-products. [c] **2a** was obtained in the absence of DDQ. [d] Two non-identified by-products were obtained (in 15% each), m/z 218 and 230.

With the optimized reaction conditions both in stoichiometric and catalytic versions in hand, we next investigated the substrate scope. A variety of aldimines gave the corresponding 3-substituted 8-fluoroimidazo[1,5-*a*]pyridines and 8-fluoroimidazo[1,5-*a*]pyridine-1-carbonitrile derivatives in good to excellent yields (Scheme 4). Substrates **1a** and **1b** including linear alkyl chains (C<sub>*n*</sub>, *n* = 3, 12; Scheme 4) showed excellent regioselectivity for the geminal C(sp<sup>3</sup>)–H functionalization α' to the aldimine, providing **2a–b** and **6a–b** in good yields. To test the feasibility of remote functionalization in β' or γ' positions, α'-branched substrates (isopropyl **1c**, neopentyl **1d** and tert-butyl **1e**) were tested without success. Gratifyingly, when an aldimine substrate bearing a benzyl group was employed, the desired heterocycles arylated in position 3 were obtained (**2h** in 52%, and **6h** 92% yield) in high regioselectivity, precluding C(sp<sup>2</sup>)–H activation on the aryl ring. The ester group is a well-tolerated functionality and gives the desired products **2i** and **6i** in 76 and 55% yields, respectively.

In the search of applying this methodology to other substrates incorporating heterocyclic units, we found that the placement of a tetrahydrofurfuryl moiety provides the C–H cyclization products **2j** and **6j** in good yields (70% and 62%, respectively, Scheme 4), despite the fact that free alcohol functional groups were not compatible with these reaction conditions (only decomposition by-products were obtained from **1k**).

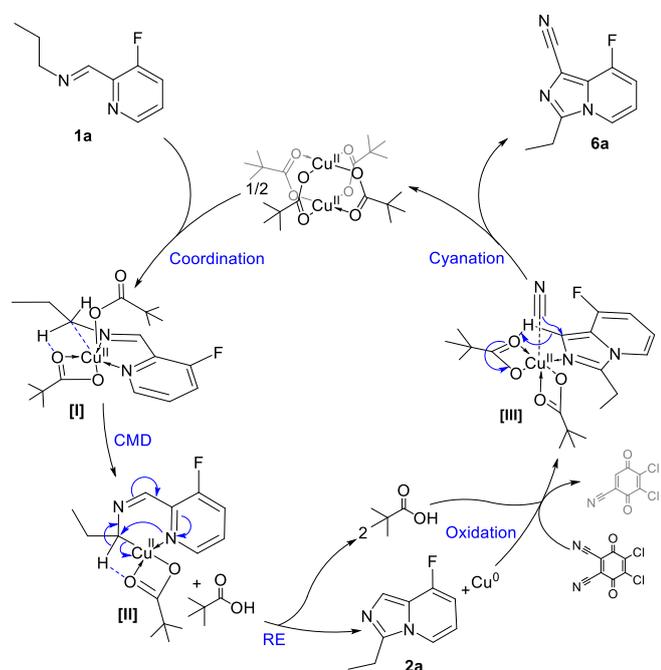
The generality of both methods has been assessed with a non-fluorinated substrate **1a'**, exhibiting good selectivities towards **2a'** (38% conv., 36% yield) and **6a'** (quant. conv., 68% yield), respectively (Scheme 4). Notably, the bidentate *N,N'*-coordination of the substrate poises **1a'** to selectively undergo C(sp<sup>3</sup>)–H activation and cyclization (no C(sp<sup>2</sup>)–H functionalization by-products on the pyridine ring were detected).



**Scheme 4.** TOP: Reaction scope for the synthesis of imidazo[1,5-*a*]pyridines type-2 and type-6 in both stoichiometric and catalytic versions. BOTTOM: Reactivity of **1a'** towards **2a'** and **6a'**. [a] Conversions and yields were determined by <sup>19</sup>F NMR with 4-fluorotoluene as internal standard.

With the aim of studying a plausible surface reactivity, preformed zero-valent copper nanoparticles (CuNPs) were used as catalyst for the synthesis of **2a** and **6a**; the reactivity observed was similar to that using Cu(OPiv)<sub>2</sub> (see Figures S3 and S4 in the ESI). Considering that only copper agglomerates were detected after reaction (TEM analysis), it can be assumed that the C–H functionalization is merely promoted by molecular species, due to copper leaching from CuNPs.<sup>37</sup> Taking into account that imidazo[1,5-*a*]pyridines are only formed in the presence of copper(II) carboxylates together with the coordination ability of aldimines to give five-coordinated Cu(II) complexes (**[I]**, Figure 5), a concerted metalation-deprotonation mechanism can be proposed for the α'-C(sp<sup>3</sup>)–H activation via the formation of a six-membered cupracycle **[II]**, analogously to what has been proposed for Pd-promoted C–H activation.<sup>38,39</sup> A reductive elimination then delivers **2a** and Cu(0), both observed for the stoichiometric reaction [Cu(0) evidenced by powder X-ray diffraction; see Figure S5 in the ESI]. To gain an insight on the metal intermediates, monitoring studies by cyclic voltammetry of the stoichiometric reaction [Cu(OPiv)<sub>2</sub> and **1a** in CH<sub>3</sub>CN] revealed the exclusive presence of Cu(II) species in solution, together with a peak intensity decrease over time, due to the formation of insoluble Cu(0) (see Figure S6 in the ESI). Under catalytic conditions, DDQ acts both as oxidant and cyanating agent, taking advantage of the fairly acidic proton in

the imidazole ring and leading to the formation of **6a** through a plausible intermediate **[III]**. According to control experiments, Copper(II) cyanide species were detected by FTIR when DDQ was reacted with Cu(0) in the presence of potassium pivalate (C≡N stretching bands at *ca.* 2160 cm<sup>-1</sup>; see Figure S7 in the ESI). The cyanation step was demonstrated by the addition of DDQ (1 equiv.) to **2a**, furnishing **6a** (62% yield; see Scheme S2 in the ESI).



**Figure 5.** A plausible reaction mechanism for the synthesis of imidazo[1,5-*a*]pyridines via Cu(II) C–H bond functionalization reactions. For simplicity purposes, **1a** was used as substrate.

Reaction manifolds involving single electron transfer processes and Cu(I) species could be ruled out (see Scheme S3 in the ESI). Thus, the presence of the radical scavenger 2,6-di-*tert*-butyl-4-methylphenol (1 equiv.) did not inhibit the catalytic transformation (53% yield of **2a**). The reaction of **1a** with CuI (1.5 equiv.) and potassium pivalate (1.5 equiv.) only resulted in traces of **2a** (9% yield).<sup>40</sup> These experiments evidence the crucial role of both electrophilic Cu(II) species and carboxylates to promote aldimine  $\alpha'$ -C(sp<sup>3</sup>)–H functionalization. Furthermore, the isolation of an acrylonitrile derivative (**4**) under harsher reaction conditions, indicates that successive C–H deprotonation events may be feasible (see Scheme S4 in the ESI).

## Conclusion

This work focuses on the study of *N,N'*-bidentate substrates that act as directing groups towards multiple C–H bond functionalization reactions via coordination to Cu(II) carboxylate salts. We have developed a Cu(II)-mediated C(sp<sup>3</sup>)–H amination/cyclization of 1-(2-pyridinyl)methanimines to afford imidazo[1,5-*a*]pyridine heterocycles via a Cu(II)/Cu(0) mechanism, under microwave irradiation. In addition, a

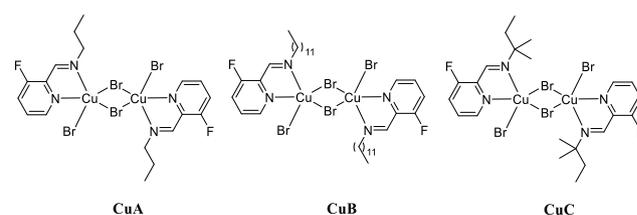
telescoped Cu-catalyzed C(sp<sup>3</sup>)–H amination/cyclization followed by C(sp<sup>2</sup>)–H cyanation process could be optimized towards the synthesis of imidazo[1,5-*a*]pyridine-1-carbonitrile derivatives through a Cu(II)/Cu(0) mechanism. Notably, the *N,N'*-bidentate coordination renders this process selective towards C(sp<sup>3</sup>)–H functionalization, precluding side C(sp<sup>2</sup>)–H activation reactions on the pyridine ring. This synthetic platform offers great potential for the straightforward syntheses of bioisosteres of purine alkaloids and analogues thereof, providing novel means to explore the vast chemical space of non-natural alkaloids. Transition-metal promoted C–H functionalization strategies confer powerful and versatile tools towards late stage molecular edition via the installation of functional groups in a selective manner. Thus, orthogonal methods for the synthesis of imidazo[1,5-*a*]pyridine and imidazo[1,5-*a*]pyridine-1-carbonitrile derivatives were successfully achieved.

These methods highlight the emerging value of unactivated C(sp<sup>3</sup>)–H bonds as functional groups in organic synthesis. A fine tuning of the carboxylate basicity resulted a determinant factor, suggesting a concerted metalation–deprotonation mechanism. Moreover, this contribution enables the development of sustainable processes based on simple copper salts.

## Experimental Section

**1. General procedure for the synthesis of aldimines 1a–1l.** Amine **a**–**l** (8.00 mmol) was added to a suspension of 3-fluoro-2-pyridinecarboxaldehyde (1.00 g, 8.00 mmol) and sodium sulfate (6.81 g, 47.99 mmol, 6 equiv.) in 2-methyltetrahydrofuran (40 mL), and the resulting mixture was stirred at r.t. for 16 h. The solid was then filtered out and the filtrate was evaporated under reduced pressure to furnish aldimine **1a–1l** (yields 89 to 99%, see the ESI for characterization details).

**2. General procedure for the preparation of CuBr<sub>2</sub>-aldimine complexes CuA, CuB and CuC.**



CuBr<sub>2</sub> (402 mg, 1.80 mmol) was added in one solid portion to a solution of aldimine **1a** (200 mg, 1.20 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL). The initial green solution was stirred for 90 min at rt, turning rapidly to a dark red color. The reaction mixture was then filtered through a 0.2  $\mu$ m PTFE filter and the solvent was removed under reduced pressure, furnishing the desired complex **CuA** (459 mg, 99%) as a dark solid that was used without further purification. Suitable monocrystals for XRD analysis of **CuA** were obtained by vapor diffusion crystallization of pentane in a CH<sub>2</sub>Cl<sub>2</sub> solution.

In an analogous manner and starting from **1b** (351 mg, 1.20 mmol) or **1d** (233.1 mg, 1.20 mmol), **CuB** and **CuC** complexes

were obtained [548 mg, 89% (**CuB**), and 401 mg, 80% (**CuC**)], respectively (see the ESI for characterization details).

### 3. Stoichiometric C–H bond functionalization reactions

**3.1. General procedure with Cu(OPiv)<sub>2</sub>.** A solution of aldimine **1** (0.30 mmol) and Cu(OPiv)<sub>2</sub> (119.6 mg, 0.45 mmol) in CH<sub>3</sub>CN (4 mL) was heated to 100 °C for 10 min under microwave irradiation (max. 200 W). The reaction crude was diluted with 2-methyltetrahydrofuran (15 mL) and washed with tetrasodium ethylenediaminetetraacetate (3 × 15 mL, 0.4 M solution, pH 10–11). The combined organic extracts were dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and solvents evaporated under reduced pressure. The residue was then purified by column chromatography on neutral alumina to give compound **2a–2b**,<sup>41</sup> **2j** (yields 69–87%).

**3.2. General procedure with CuA.** A base (0.45 mmol) was added to a solution of the CuBr<sub>2</sub>-aldimine complex **CuA** (0.15 mmol, 117.0 mg) in the specified solvent (4 mL). The reaction mixture was heated to 100 °C for 10 min under microwave irradiation (max. 200 W). Work-up A: Na<sub>2</sub>S (50.0 mg, 0.65 mmol) was then added and the crude reaction mixture was stirred for 20 min with intermittent ultrasonic irradiation. The crude was then filtered through a 0.45 μm PTFE filter and solids were rinsed with 2-methyltetrahydrofuran (5 × 5 mL) and the solvent was removed under reduced pressure. Work-up B: The reaction crude was diluted with 2-methyltetrahydrofuran (15 mL) and washed with tetrasodium ethylenediaminetetraacetate (3 × 15 mL, 0.4 M solution, pH 10–11). The combined organic extracts were dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and solvents evaporated under reduced pressure. Conversion and yields were determined by <sup>19</sup>F NMR with 4-fluorotoluene as standard.

**4. General procedure for the catalytic C–H bond functionalization reaction: synthesis of 6a–k.** 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (0.30 mmol, 68.1 mg) was added in one solid portion to a solution of aldimine **1a–k** (0.30 mmol) and of Cu(OPiv)<sub>2</sub> (16 mg, 0.06 mmol, 20 mol%) in CH<sub>3</sub>CN (4 mL). The reaction mixture was heated to 100 °C for 10 min under microwave irradiation (max. 200 W). Na<sub>2</sub>S (14 mg, 0.18 mmol) was then added and the crude reaction mixture was stirred for 20 min under ultrasonic irradiation. The crude was then filtered through a 0.20 μm PTFE filter and solids were rinsed with 2-methyltetrahydrofuran (5 × 5 mL) and the solvent was removed under reduced pressure. The reaction residue was then purified by column chromatography on silica gel to give the title compound **6a–k** (yields 55–81%).

### Author Contributions

M. C. prepared the substrates, optimized the C–H bond functionalization reactions, studied the scope and mechanistic studies. I. F. carried out the cyclic voltammetry experiments and proofread the experimental part and main article. S. M-L. carried out the X-ray crystallographic studies and the refinement of the structures. D. P. identified the heterocycle via C–H bond functionalization, revised the experimental part, designed a research plan and co-wrote the manuscript. M. G. supervised the work, co-wrote the manuscript and coordinated the overall project.

### Conflicts of interest

There are no conflicts to declare.

### Acknowledgements

The Centre National de la Recherche Scientifique (CNRS) and the Université Toulouse 3 – Paul Sabatier are gratefully acknowledged for their financial support. M. C. thanks the Ministère de l'Enseignement Supérieur et de la Recherche of the French government for a PhD scholarship. Dr. Gyorgy Szaloki is acknowledged for his valuable help in the cyclic voltammetry studies. The authors thank Dr. Nathalie Saffon-Merceron of the X-ray diffraction service of the Institut de Chimie de Toulouse ICT-UAR 2599 (www.ict.ups-tlse.fr) for her valuable help in single crystal analysis.

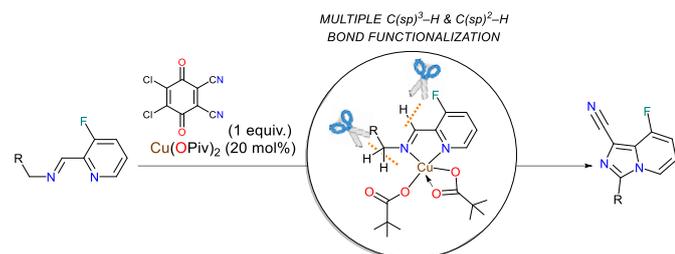
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39. Given that the cleavage of the  $\alpha'$ -C(sp<sup>3</sup>)-H via the direct formation of copper hydride species has not been detected (Table S1 in the ESI, entries 1-2), and the fact that the selectively formation of **2a** can only be achieved by addition of carboxylate salts (Table 1), both experimental results point to the assistance of the carboxylate anion in triggering C(sp<sup>3</sup>)-H bond functionalization through a concerted metalation-deprotonation pathway.
40. A partial oxidation of copper(I) salts by air can be feasible as microwave reactions are carried out under aerobic conditions.
41. The instability of **2a** and **2b** upon purification precluded their isolation in pure form (see Figure S7 in the ESI for **2b**).

## Table of Contents graphic



Carboxylate-assisted Cu(II)-catalyzed relay towards the synthesis of imidazo[1,5-*a*]pyridines encompassing C(sp<sup>3</sup>)-H amination and cyclization of aldimines followed by C(sp<sup>2</sup>)-H cyanation, is reported.

Keywords: Cu(II) complexes • aldimines • C(sp<sup>3</sup>)-H bond functionalization • imidazo[1,5-*a*]pyridines • catalysis