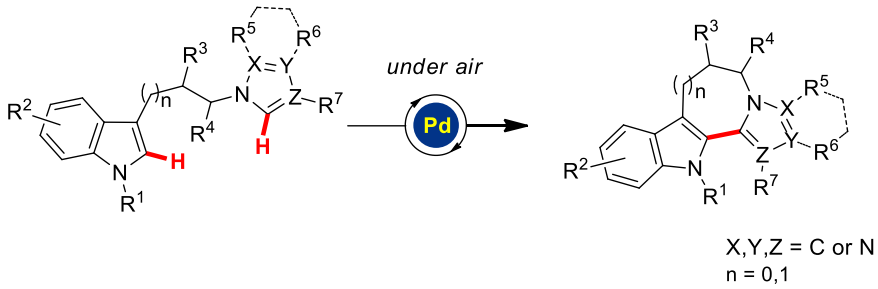
Palladium(II)-Catalyzed Intramolecular Oxidative C−H/C−H Cross-Coupling Reaction of C3,N-linked Biheterocycles: Rapid Access to Polycyclic Nitrogen Heterocycles

Serena Mantenuto,[†,§] Cecilia Ciccolini,[†,§] Simone Lucarini,[‡] Giovanni Piersanti,[‡] Gianfranco Favi*[,†] and Fabio Mantellini[†]

†Department of Biomolecular Sciences, Section of Organic Chemistry and Organic Natural Compounds, University of Urbino "Carlo Bo", Via I Maggetti 24, 61029 Urbino, Italy

‡Department of Biomolecular Sciences, Section of Chemistry, University of Urbino "Carlo Bo", Piazza Rinascimento 6, 61029 Urbino, Italy

Supporting Information Placeholder



ABSTRACT: A Pd(II)-catalyzed intramolecular oxidative C−H/C−H cross-coupling has been developed for the direct construction of valuable polycyclic heteroarene scaffolds. From a retrosynthetic point of view, the strategic formation of a C-C bond *via* C(sp^2)-H/C(sp^2)-H dehydrogenative coupling across C3,N-linked biheterocyclic precursors may be useful in *de novo* syntheses of indole-derived natural products and pharmaceuticals. The reaction exhibited good functional group/heterocycle tolerance, and a proposed mechanism involving an azoylpalladium complex is also supported.

The construction of polyheterocylic compounds represents a major entry to complex naturally occurring molecules, pharmaceuticals, and functional materials. Despite the significant advancements made to develop atom- and step-economic strategies toward complex frameworks, especially those involving privileged moieties, rapid, alternative and versatile approaches to assemble fused azaheterocycles are still needed. Recently, the transition metal-catalyzed Cross-Dehydrogenative Coupling (CDC) reactions[1] have emerged as an ideal method for the selective formation of carbon-carbon bonds because no pre-functionalization of substrates is required. Although impressive intermolecular[2] dehydrogenative cross-coupling has been developed to date, the intramolecular variant[3] remains underdeveloped. In 2011, Greaney and coworkers reported an elegant Pd(II)-catalyzed intramolecular oxidative C-H coupling reaction of indole *N*-linked arene/heteroarene compounds for the fabrication of medium sized rings.[4] Although synthetically very attractive, this protocol suffers from the disadvantages of a limited substrate/heterocycle scope and generality. The presence of an electron-withdrawing group (EWG = CHO, CN, NO_2) in the C3-position of the indole ring was essential to ensure the success of the reaction, which mainly focused on the formation of seven- and eight-membered rings. With the same philosophy a

copper- promoted intramolecular C-H coupling reaction using 1,10-phenanthroline as ligand between indole and imidazole moieties has been also developed for polycyclic heteroarene synthesis.[5]

Given our interest in heterocyclic chemistry, especially in tryptamine derivatives, we propose a distinct approach to the synthesis of polycyclic fused indoles via palladium catalyzed oxidative C−H/C−H cross-coupling from indole-based alkyl-linked biheterocycles (indole-imidazoles, indole-pyrroles and indole-triazoles).[6] To access the polycyclic indole framework **II** (Figure 1), we intend to apply the intramolecular cross-dehydrogenative coupling reaction between indole and azole units that are connected through *C3,N* linkage, respectively. Consequently, varying the heterocycle linked to the indole and the type of junction between two heteroarene rings, diversified polycyclic heteroarenes are obtained via dual C(sp^2)−H functionalization process. To the best of our knowledge, the preparation of such attractive indole-fused polycyclic systems through palladium-catalyzed CDC reaction from tryptamine-derived biheterocycles have yet to be described.

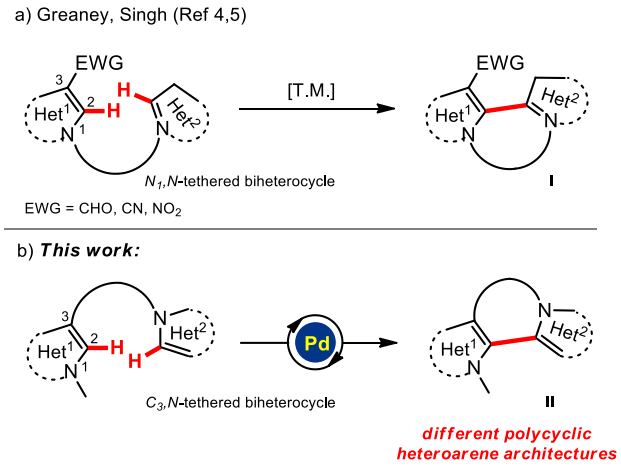


Figure 1. Approaches of heterocyclic CDC reactions: synthesis of different fused polycyclic heteroarene architectures.

For this study, the tryptamine (and homologue)-derived biheterocyles has been considered in light of its occurrence in a wide range of biologically active molecules, pharmaceuticals, and naturally occurring compounds[7] such as norketoyobyrine, rutaecarpine, cladoniamide G, isogranulatimide A and B, homofascaplisin B and C, vincamine and yohimbine (Figure 2).

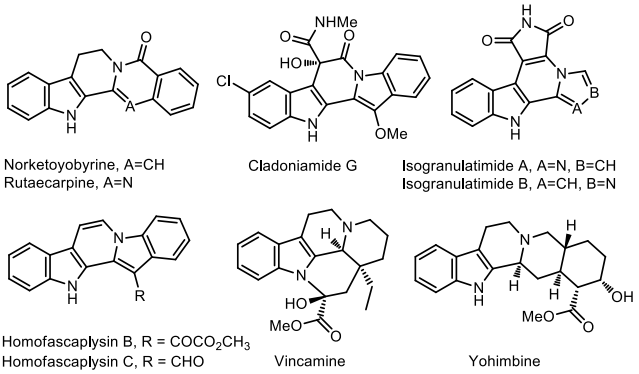


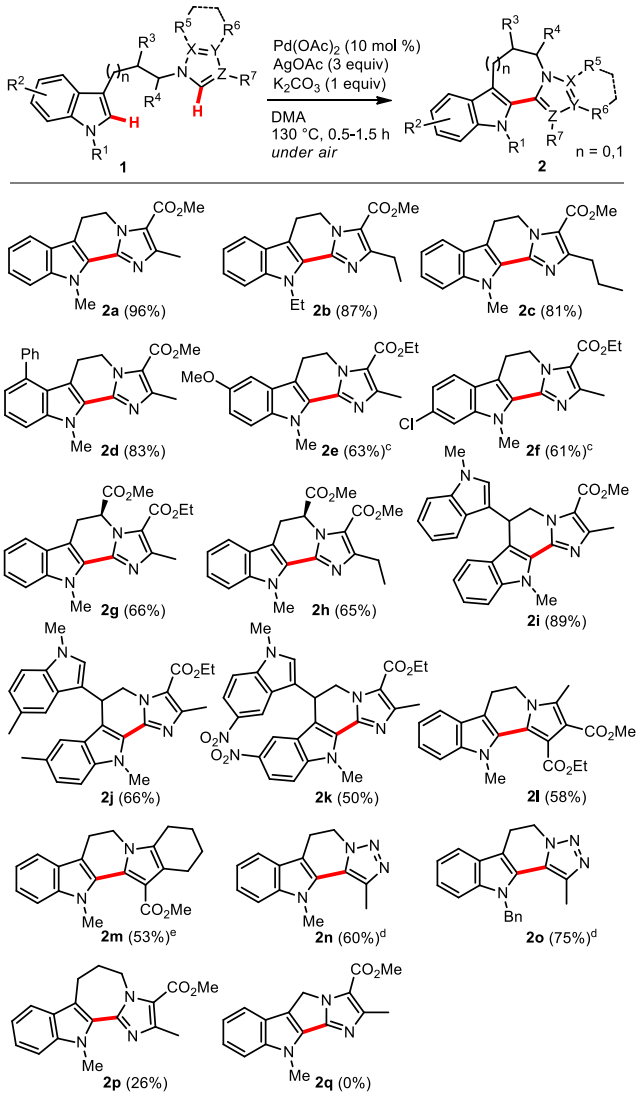
Figure 2. Selected naturally occurring compounds containing polycyclic fused indoles.

We initiated our investigations with **1a** as the model substrate to optimize various reaction parameters (Table S1, Supporting Information). At the outset, we probed with $Pd(OAc)_2$ as catalyst and Ag_2CO_3 as oxidant in DMF at 140 °C for 9 h, affording the relative product **2a** in 47% along with overoxidized cross-coupling byproduct **2a'**[8] in 23% yield. A screen of different oxidants [such as $Cu(OAc)_2•H_2O$, $Cu(OAc)_2$, Ag_2CO_3, AgOAc, $AgNO_3$, $K_2S_2O_8$, BQ, I_2, $PhI(OAc)_2$, Ag_2O], revealed AgOAc to be better in term of yield and selectivity. Thus, reaction conditions including $Pd(OAc)_2$ (10 mol %), AgOAc (3.0 equiv), and K_2CO_3 (1.0 equiv) in DMA at 130 °C under air atmosphere became beneficial, giving exclusively desired product **2a** in 96% isolated yield. No further improvement was observed by changing the palladium source. Instead, the reaction did not work in the absence of any palladium catalyst[9] highlighting the crucial role of palladium in this reaction. Subsequent investigation showed positive effects of K_2CO_3, since elimination of such base decreased both efficiency and selectivity. In addition, lowering the temperature from 130 to 110 °C and 90 °C led to 88% and 60% yield of **2a**, respectively. Also the presence of catalytic amount of PivOH[10] exhibited formation of not negligible overoxidized cross-coupling product **2a'**[8] due to the susceptibility of benzylic type position of indole to oxidation with consequent aromatization. Again, control experiment performed in the absence of oxidant revealed that, whilst Pd(II) was fundamental for this transformation, coupling product **2a** was also produced in the presence of stoichiometric amount of PivOH, albeit with lower efficiency and selectivity over the oxidized derivative **2a'**.[8] Notably, no oxidative dimerizations at acidic CH bonds of both heterocycles were observed; the reactions occurred smoothly to furnish the sole intramolecular coupling products. With the optimized reaction conditions in hand, the generality of the present Pd(II)-catalyzed intramolecular cross-dehydrogenative coupling reaction was investigated. A wide range of indole-based tethered biheterocycles incorporating manifold points of diversity (R^1 to R^8) performed consistently well in the reaction, giving structurally different polyheterocycle systems (Scheme 1). In particular, branched and nonbranched tryptamine-derived indole-imidazoles with both electron-donating and –withdrawing substituents such as methyl, phenyl, methoxy, chloro, nitro on the benzo ring furnished the corresponding embedded six-membered ring systems (**2a–f**) in good to excellent yields. Most importantly, the reaction worked well to de-

liver fused tetracyclic products (**2g,h**) when tryptophan-derived indole-imidazoles were employed. To our delight, no five-membered ring formation from C−H coupling reaction between both indole-2 moieties of bisindoles **1i−k** were observed. Thus, the 2,2'-cross-coupled products were obtained as single regioisomers with C−H activation occurring exclusively at the C-2 position of both the indole and azole units. It is worth noting that a desymmetrization of bisindole moieties take places to give intriguing heteroarene architectures (**2i−k**). Also, alkyl and ester substituents can be accommodate on the imidazole portion. Notably, the reaction of indole derivatives with methyl, ethyl and benzyl *N*-protecting groups were well tolerated under the standard conditions. Unfortunately, dehydrogenative coupling with free *N*-H indole biheterocycle provided unsatisfactory yields, generating only scarce amount of overoxidized coupling compound (27% yield) while no reaction occurred with deactivated *N*-Ac indole.

The range of coupling partner amenable to indoles was not limited to imidazole derivatives. Sensitive indole-pyrrole **1l,m** and indole-triazole **1n,o** substrates were efficiently subjected to CDC in good yields. In particular, we achieved the synthesis of pentacyclic indole-fused indolizine derivative **2m**, which is structurally related to that of the marine alkaloids such as fascaplysin and homofascaplysin C.[11] Although these latter polycyclic heterocycles occupy an important place in medicinal chemistry and life science, their construction often requires multistep approaches, harsh reaction conditions and suffers from disadvantages of a limited substrate scope.[12,13] To the best of our knowledge, our findings represent also the first examples of intramolecular C-H/C-H cross-coupling of indoles with pyrrole and 1,2,3-triazole partners.

Again, when homotriptamine-derived indole-imidazole **1p** was subjected to palladium catalyzed oxidative C−H/C−H cross-coupling, an annulated seven-memered ring product (**2p**) with an unprecedented molecular architecture was obtained in 26% yield. On the other hand, gramine-derived indole-imidazole **1q** did not furnish the desired tetracyclic product (**2q**).[14]

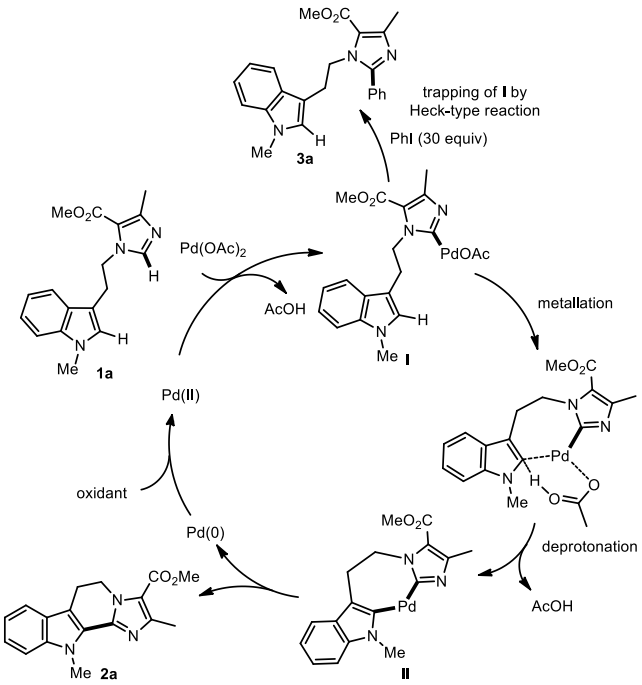


Scheme 1. Substrate Scope for the Intramolecular Oxidative Coupling of Indole-based Tethered Biheterocycles[a,b]

[a]Reaction conditions: **1** (0.2 mmol, 1 equiv), $Pd(OAc)_2$ (10 mol %), AgOAc (3.0 equiv), base (1.0 equiv) in DMA (2.0 mL) at 130 °C; DMA = dimethylacetamide. [b]Isolated yields. [c]Traces of oxidized product was observed. [d]PivOH (30 mol %) was used as additive. [e]Based on recovered starting material.

Based on our data (*vide infra*) and literature precedent, palladium-catalyzed CDC reaction under oxidative conditions could proceed through a Pd^0/Pd^{II} cycle (Scheme 2).

Scheme 2. Proposed mechanism of the CDC reaction.



First, regioselective palladation at the C2 position of the imidazole forms complex **I**, an intermediate that could be successfully trapped with iodobenzene in a Heck-type process to give intermolecular cross coupling product **3a**. Afterward, an intramolecular C-H cleavage via a Concerted Metalation-Deprotonation (CMD) pathway may be followed to generate intermediate **II**. Thus, the abstraction of more acidic hydrogen from imidazole nucleus should be favored process,[15] thereby rendering a base-assisted palladation likely to be operative. Finally, reductive elimination would produce the product **2a** and regenerate the catalyst. In line with the mechanism proposed, the prior palladation of the imidazole nucleus well justifies the exclusive formation of six-membered ring (cf Scheme 2, products **2i–k**) such that 2,2'-cross-coupled indole-indole five-membered products were not detected when bisindoles **1i–k** were employed.

In conclusion, we have reported the successful application of $Pd(OAc)_2$ to the intramolecular cross-dehydrogenative coupling of different C3,N-linked biheterocycles leading coupled products. Importantly, these reactions show high efficiency, practicality (all the reactions are performed under an air atmosphere), generality and selectivity. We believe that this operationally simple protocol could provide a new access to industrially and medicinally relevant polycyclic fused molecules. Further studies and applications of this method are currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental details, procedures, and characterization of all compounds (PDF).

AUTHOR INFORMATION

Corresponding Author

* E-mail: gianfranco.favi@uniurb.it

Author Contributions

§ S.M. and C.C. contributed equally.

Notes

The authors declare no competing financial interest.

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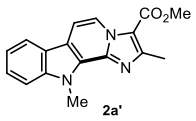
(8) Overoxidized cross-coupling byproduct **2a'**, structure of which is shown below, was generated under the reaction con-

ditions in an inseparable mixture with compound **2a** (see Supporting Information for details).



2a'

(9) Attempts at intramolecular cross coupling using a Cu promoter based on a previously reported method (ref 5) were fruitless. Metal-free oxidative intramolecular cross-coupling mediated by Brønsted acids like PTSA or TFA alone or in combination with DDQ as the oxidant analogous to a previously reported methods (Gribble, G. W.; Pelcman, B. *J. Org. Chem.*, **1992**, *57*, 3637; Sun, S.; Yang, J.; Li, F.; Lv, Z.; Li, W.; Lou, H.; Liu, L. *Tetrahedron Lett.* **2014**, *55*, 6899) were unsuccessfully. Also, the irradiation with a halogen lamp in the presence of cyclohexene as sacrificial hydrogen acceptor in acetonitrile according to the method described by Terpin and coworkers for the synthesis of isogranulatimide analogues (Terpin, A.; Winklhofer, C.; Schumann, S.; Steglich, W. *Tetrahedron* **1998**, *54*, 1745) was ineffective.

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(14) As an unexpected result, only the formation of 3-formylindole was observed in the presence of AcOH under standard conditions (For an example of C−H formylation of 3-aminomethylindole derivative, see: Wang, Y.-F.; Zhang, F.-L.; Chiba, S. *Synthesis* **2012**, 1526).

(15) This fact is in accordance with the heteroarene's pK_a values. For details, see: Shen, K.; Fu, Y.; Li, J.-N., Liu, L.; Guo, Q.-X. *Tetrahedron*, **2007**, *63*, 1568.