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Oxidative C–H/C–H Coupling of Azine and Indole/Pyrrole Nuclei: Palladium Catalysis and Synthesis of Eudistomin U

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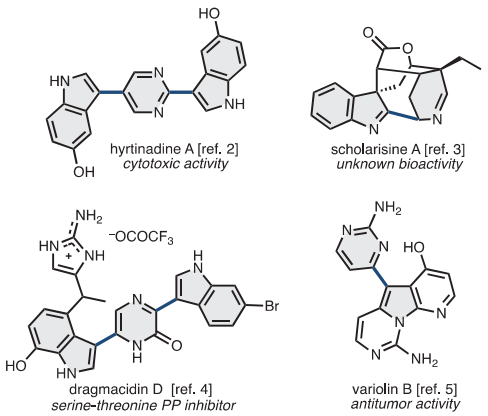
We have developed a palladium-catalyzed C–H/C–H coupling reaction of indoles or pyrroles with azine *N*-oxides. The reaction proceeds selectively at the C3 position of indoles/pyrroles and the C2 position of azine *N*-oxides. Furthermore, we have accomplished the synthesis of marine indole alkaloid eudistomin U by utilizing this newly developed C–H/C–H coupling reaction.

Compounds containing indole–azine and pyrrole–azine moieties are prevalent in natural products and bioactive molecules (Scheme 1).[1–5] Therefore, the development of efficient methods to construct these frameworks has been a topic of considerable interest in organic chemistry. The fields of biochemistry and medicinal chemistry should also benefit from such a synthetic campaign, since these disciplines may see the use of these coupled heterocycles as lead compounds in drug discovery. Currently, the most reliable synthetic method for making indole/pyrrole–azine compounds is by way of palladium-catalyzed cross-coupling reactions of organometallic compounds with haloarenes.[2,4,5] However, each coupling partner must be synthesized from its parent heteroaromatic compound, occasionally requiring several steps. Although the direct C–H bond arylation of heteroarenes[6,7] has emerged as an attractive methodology that can streamline overall synthesis, successful examples of direct C–H bond arylation of electron-deficient nitrogen heterocycles such as azines are rare.[7b,8] Herein, we report our finding of palladium-catalyzed indole–azine and pyrrole–azine C–H/C–H coupling reactions.[9–11]

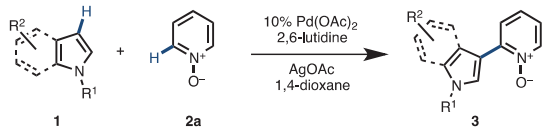
First, we examined the C–H/C–H coupling of an indole derivative and unfunctionalized pyridine. Under palladium catalysis, the coupling product was observed but only in trace amounts. Meanwhile, Fagnou and co-workers reported an indole–benzene C–H/C–H coupling reaction,[9d,9e] and more recently, Chang and co-workers reported the coupling of benzene with pyridine *N*-oxide.[9g] Inspired by these findings, we attempted the coupling of *N*-protected indole with pyridine *N*-oxide[12] as a synthon of pyridine. Employing Fagnou's and Chang's reaction conditions, to a 1,4-dioxane solution of *N*-pivaloylindole (1.0 equiv) were added pyridine *N*-oxide **2a** (4.0 equiv), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (3.0 equiv), and pyridine (1.0 equiv), and the reaction mixture was stirred for 5 h at 105 °C to give the desired coupling product in 39% yield. Despite its low yield, this reaction furnished the C3-substituted indole–azine coupling product selectively. After extensive screening of conditions including Pd sources, oxidants, additives, solvents, and *N*-protecting groups on the indole,[13] the yield of the coupling product was increased to 73%, using MOM-protected indole **1a** as the substrate, 2,6-lutidine[14] and AgOAc[9c,15] as additives (Table 1, Entry 1).

With the optimized conditions for regioselective indole pyridylation in hand, we investigated the scope of direct indole–

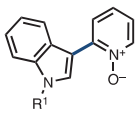
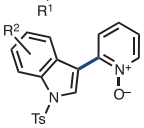
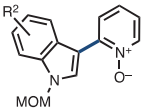
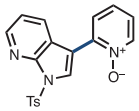
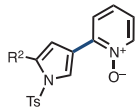


Scheme 1. Natural products containing indole–azine moieties.

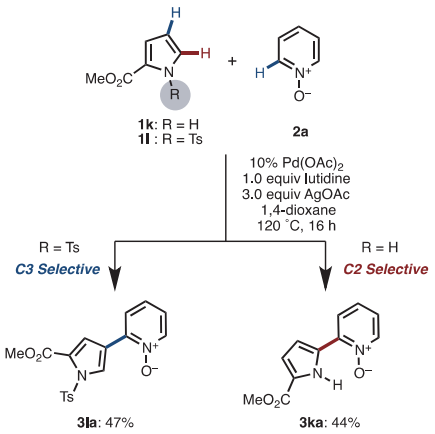
Table 1. Pd-catalyzed C–H/C–H coupling of indoles/pyrroles **1a**–**1j** with pyridine *N*-oxide (**2a**)[a]



1 2a 3

Entry	1	Product	3 (Yield/%)[b]
1	**1a** R^1 = MOM		**3aa** (73)
2	**1a** R^1 = MOM		**3aa** (54)[c]
3	**1b** R^1 = Ts		**3ba** (67)
4	**1c** R^2 = 5-CN		**3ca** (52)
5	**1d** R^2 = 6-OMe		**3da** (38)
6	**1e** R^2 = 5-NO_2		**3ea** (56)
7	**1f** R^2 = 6-NO_2		**3fa** (49)
8	**1g** R^2 = 6-CO_2Me		**3ga** (55)
9	**1h**		**3ha** (46)
10	**1i** R^2 = H		**3ia** (42)
11	**1j** R^2 = Ac		**3ja** (47)

[a]Conditions: **1a**–**1j** (0.4 mmol), **2a** (1.6 mmol), $Pd(OAc)_2$ (0.04 mmol), 2,6-lutidine (0.4 mmol), AgOAc (1.2 mmol), 1,4-dioxane (1.2 mL), 120 °C, 16 h. [b]Isolated yield. [c]2 mol % of $Pd(OAc)_2$ was used. The reaction time was 43 h.



Scheme 2. Regioselectivity switch in C–H arylation of pyrroles.

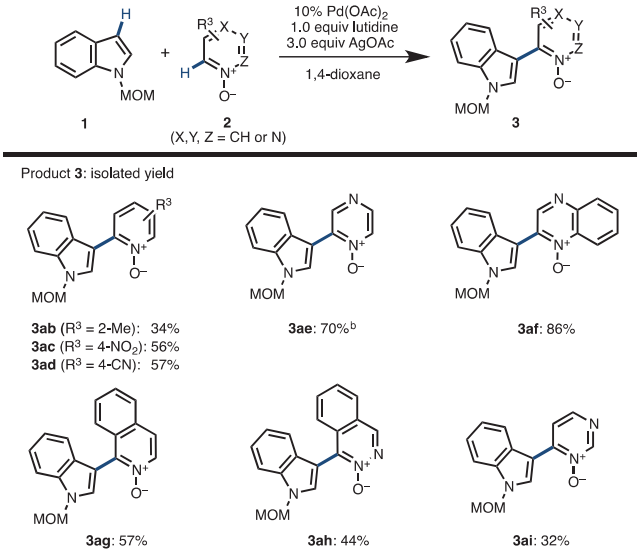
azine *N*-oxide coupling using various indoles and pyridine *N*-oxide (**2a**) (Table 1). A decrease in catalyst loading was found to be possible while maintaining reasonable yield (Entry 2). Although the yield was slightly lower, tosyl-protected indole **1b** also gave a similar result (Entry 3). This reaction tolerated substitutions on indole ring such as cyano (Entry 4), methoxy (Entry 5), nitro (Entries 6 and 7), and ester (Entry 8) groups. This coupling reaction even proceeded when using azaindole (Entry 9), which is more electron-deficient. Furthermore, we found that the C–H/C–H coupling of pyrroles with **2a** also proceeded, albeit in a lower yield (Entries 10 and 11). Interestingly, it was revealed that the reaction selectively afforded the 3-pyridinated pyrrole product (the same selectivity observed with indoles), adding to the small but growing repertoire of β-selective arylations of five-membered heteroarenes.[7i–7k]

To further investigate the interesting C3-regioselectivity of pyrroles, the coupling reaction of various pyrroles with pyridine *N*-oxide (**2a**) was carried out. As a result, we found that the C2/C3 regioselectivity can be controlled by merely manipulating protecting group on the nitrogen atom (Scheme 2). For example, when using methyl pyrrole-2-carboxylate (**1k**) as the substrate, the reaction proceeded at the C2 position of the pyrrole to give **3ka** in 44% yield, whereas the use of tosyl-protected pyrrole **1l** gave C3-substituted pyrrole **3la** in 47% yield.[16]

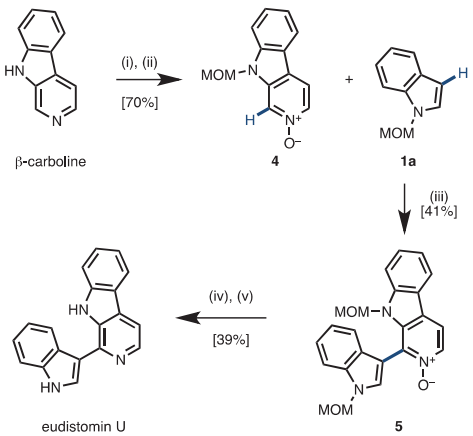
We next examined the scope of the reaction with respect to azine *N*-oxide. Representative results are shown in Table 2. Some modifications on pyridine *N*-oxide such as methyl, nitro, and cyano groups were tolerated and the corresponding coupling products were obtained in moderate yields. When pyrazine *N*-oxide was used, the reaction proceeded smoothly in the presence of acetic acid.[17] Notably, the use of quinoxaline *N*-oxide gave rise to coupling product **3af** in even higher yield than the parent indole–pyridine *N*-oxide coupling reaction. Furthermore, we also obtained the corresponding coupling products with isoquinoline, phthalazine, and pyrimidine *N*-oxides and their regioselective outcomes were consistent with the parent coupling reaction.

Finally, we applied our C–H/C–H coupling to the synthesis of marine indole alkaloid eudistomin U,[18] which possesses DNA-binding activity (Scheme 3). This short synthesis begins

Table 2. Scope of azine *N*-oxides[a]



[a]Conditions: **1a** (0.4 mmol), **2a**–**2i** (1.6 mmol), $Pd(OAc)_2$ (0.04 mmol), 2,6-lutidine (0.4 mmol), AgOAc (1.2 mmol), 1,4-dioxane (1.2 mL), 120 °C, 16 h. [b]AcOH was used instead of 2,6-lutidine.



Scheme 3. Synthesis of eudistomin U through C–H/C–H coupling. (i) MOMCl (1.1 equiv), NaH (1.3 equiv), DMF, rt, 8 h (89%). (ii) $MeReO_3$ (3 mol %), H_2O_2 aq (2.0 equiv), rt, CH_2Cl_2, 14 h, (79%). (iii) **1a** (1.0 equiv), **6** (4.0 equiv), $Pd(OAc)_2$ (10 mol %), 2,6-lutidine (1.0 equiv), AgOAc (3.0 equiv), 1,4-dioxane, 120 °C, 23 h (41%). (iv) PCl_3 (3.0 equiv), CH_2Cl_2, rt, 11 h (79%). (v) HCO_2H, H_2O, 125 °C, 39 h (49%).

with a MOM protection of commercially available β-carboline followed by MTO (methyltrioxorhenium)-catalyzed pyridine oxidation[19] to afford the corresponding *N*-oxide **4** in 70% yield over two steps. Subsequent C–H/C–H coupling of indole **1a** and **4** under the key palladium catalysis delivered the desired framework of eudistomin U in 41% yield. Although the yield of coupling product **5** was not high, this coupling reaction proceeded at the C3 position of indole and the C1 position of β-carboline regioselectively. After reduction of the *N*-oxide by PCl_3,[20] and the follow-up deprotection of MOM groups with HCO_2H in water completed the synthesis of eudistomin U.

In summary, we have developed a palladium-catalyzed C–H/C–H coupling reaction of indoles/pyrroles and azine *N*-oxides, proceeding selectively at the C3 position of indoles/pyrroles and the C2 position of azine *N*-oxides. Furthermore, we have accomplished the synthesis of eudistomin U, utilizing the newly developed C–H/C–H coupling reaction. Total syntheses of more complex natural products based on this oxidative C–H/C–H coupling as well as mechanistic studies are ongoing in our laboratory.

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