

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.

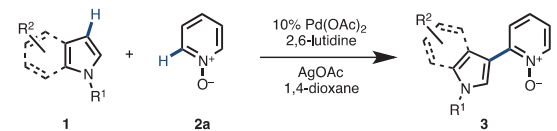
Compounds containing indole–azine and pyrrole–azine moieties are prevalent in natural products and bioactive molecules (Scheme 1).^{1–5} Therefore, the development of efficient methods to construct these frameworks has been a topic of considerable interest in organic chemistry. The fields of biochemistry 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

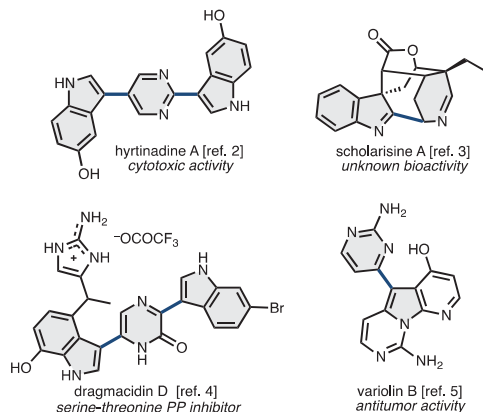
recently, Chang and co-workers reported the coupling of benzene with pyridine *N*-oxide.^{9g} Inspired by these findings, we attempted the coupling of *N*-protected indole with pyridine *N*-oxide¹² as a synthon of pyridine. Employing Fagnou's and Chang's reaction conditions, to a 1,4-dioxane solution of *N*-pivaloylindole (1.0 equiv) were added pyridine *N*-oxide **2a** (4.0 equiv), Pd(OAc)₂ (10 mol %), Ag₂CO₃ (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-lutidine¹⁴ 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–

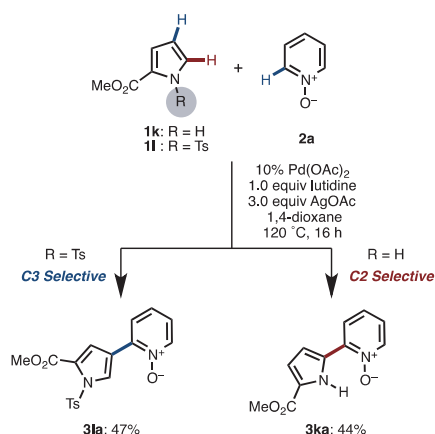
Table 1. Pd-catalyzed C–H/C–H coupling of indoles/pyrroles **1a–1j** with pyridine *N*-oxide (**2a**)^a

			
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 ₂ Me		3ga (55)
9	1h		3ha (46)
10	1i R ² = H		3ia (42)
11	1j R ² = Ac		3ja (47)

^aConditions: **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. ^bIsolated yield. ^c2 mol % of Pd(OAc)₂ was used. The reaction time was 43 h.



Scheme 1. Natural products containing indole–azine moieties.



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

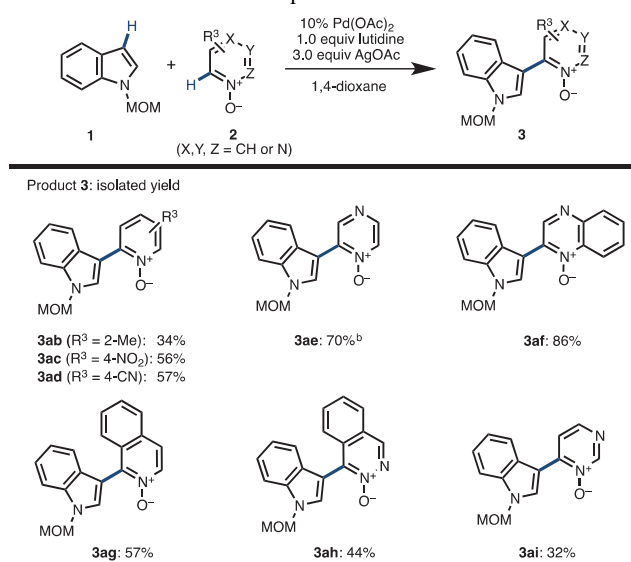
azine *N*-oxide coupling using various indoles and pyridine *N*-oxide (**2a**) (Table 1). A decrease in catalyst loading was found to be possible while maintaining reasonable yield (Entry 2). Although the yield was slightly lower, tosyl-protected indole **1b** also gave a similar result (Entry 3). This 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

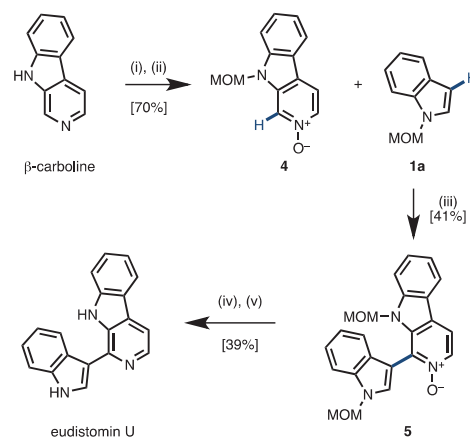
We next examined the scope of the reaction with respect to azine *N*-oxide. Representative results are shown in Table 2. Some modifications on pyridine *N*-oxide such as methyl, nitro, and cyano groups were tolerated and the corresponding coupling products were obtained in moderate yields. When pyrazine *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



^aConditions: **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. ^bAcOH 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) MeReO₃ (3 mol %), H₂O₂ aq (2.0 equiv), rt, CH₂Cl₂, 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) PCl₃ (3.0 equiv), CH₂Cl₂, rt, 11 h (79%). (v) HCO₂H, H₂O, 125 °C, 39 h (49%).

with a MOM protection of commercially available β -carboline followed by MTO (methyltrioxorhenium)-catalyzed pyridine oxidation¹⁹ 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 PCl₃,²⁰ and the follow-up deprotection of MOM groups with HCO₂H 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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