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Regioselective C–H alkenylation of imidazoles and its application to the synthesis of unsymmetrically substituted benzimidazoles†

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A palladium-catalyzed C–H alkenylation of imidazoles has been developed. High C5 selectivity was achieved for C2-unsubstituted and C2-substituted imidazoles using oxygen and copper(II) acetate, respectively, as oxidants. The obtained products were applied to benzannulation through a sequence involving transposition of *N*-alkyl groups to give C4-alkenyl imidazoles, alkenylation, thermal 6 π -electrocyclization, and oxidation, affording unsymmetrically substituted benzimidazoles.

Imidazoles and their benzannulated forms, benzimidazoles, are an important class of heterocycles, which are found in a number of commercial drugs, biologically active compounds, *N*-heterocyclic carbene ligands, and ionic liquids.¹ Thus, selective syntheses of (benz)imidazoles have been essential to provide a wide range of derivatives containing a chosen functional group at a desired position. Particularly, parent (NH)-(benz)imidazoles are in tautomeric equilibrium, being formally symmetric, and approaches to access unsymmetrically substituted (benz)imidazoles have been of great interest in organic synthesis. However, most of the available methods rely on the formation of C–N bonds, which presents difficulties in the preparation of more sterically hindered regioisomers (Fig. 1A).^{2,3} The synthesis of unsymmetrically substituted benzimidazoles also depends on C–N bond forming processes, such as the installation of primary amines onto multi-substituted aromatic rings and subsequent ring closure, making it challenging to increase structural diversity in the aromatic ring (Fig. 1B).⁴ Alternatively, the regioselective formation of C–C bonds *via* direct C–H functionalization of *N*-substituted imidazoles could provide a systematic access to functionalized (benz)imidazoles.⁵ In fact, notable progress has been made in the installation of aryl groups to afford C5-arylated imidazoles.^{6,7} However, C–H alkenylation, also known as the Fujiwara–Moritani

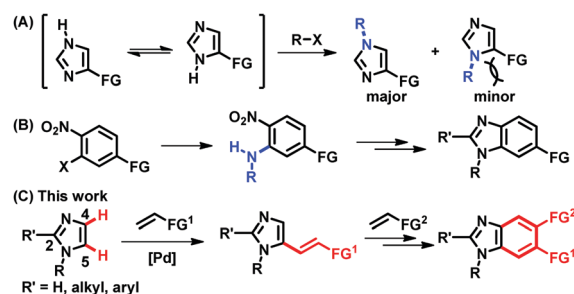


Fig. 1 (A) (NH)-Imidazoles in tautomeric equilibrium leading to regioisomeric mixtures of *N*-substituted products. (B) Synthesis of benzimidazoles from multi-substituted arenes *via* C–N bond formation. (C) Synthesis of C5-alkenyl imidazoles and functionalized benzimidazoles *via* regioselective C–C bond forming reactions.

reaction, has been much less successful than arylation.^{8–10} Despite the importance of alkenyl imidazoles in drug discovery and natural product synthesis, either as chemical motifs or as latent functional groups, the regioselective C5-alkenylation of *N*-alkylimidazoles using readily available olefins has not been reported to the best of our knowledge.¹¹ Furthermore, the installed alkenyl groups offer a great opportunity to build unsymmetrically substituted benzimidazoles; however, this possibility has been underexplored.¹²

The underdevelopment of imidazole C–H alkenylation is attributed to the unique reactivity of this heterocyclic core. Compared to the other two-nitrogen-containing five-membered heterocycle, pyrazole, imidazole is significantly basic, undergoing protonation at the nitrogen atom in the presence of acids and outcompeting nitrogen-based ligands that are frequently used in aerobic oxidation reactions.^{13,14} Instead of searching for ligands that could compete with imidazoles, we envisioned that an imidazole substrate itself could be a competent ligand to facilitate dehydrogenative alkenylation of imidazoles.¹⁵ More specifically, we hypothesized that imidazole-ligated Pd(II) carboxylate complexes should enable palladation at the more nucleophilic C5 position in preference to the C2 position of imidazoles, which requires strong bases and/or Lewis acidic metal additives.^{16,17}

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Table 3 C–H alkenylation of 1,2-substituted imidazoles



Reaction conditions: imidazole (0.50 mmol), alkene (1.5 mmol), Pd(OAc)₂ (0.050 mmol), Cu(OAc)₂ (1.0 mmol), 1,4-dioxane (1.5 mL), 100 °C, 15 h.

of C4-alkenylation of C5-alkenylated imidazoles remained modest (<40%). Thus, an alternative strategy based on the SEM-group switch, which had previously been demonstrated for the preparation of C4,5-diarylated imidazoles, was adopted.^{2b,16} Heating the C5-alkenyl imidazoles in the presence of a catalytic amount of 2-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl) afforded the corresponding C4-alkenyl imidazoles in good-to-high yields (Table 4, step a). For imidazoles bearing a substituent at the C2 position, the alkenylation at the C5 position using Pd(OAc)₂ and Cu(OAc)₂ was applied to smoothly generate the corresponding dialkenylated products (**11b**, **12b**, and **13b**; step b). For the subsequent ring closure, the oxidative conditions developed by Langer's group gave a mixture of products, resulting from undesired pathways, including SEM-switch, removal of the SEM group, and most significantly, incomplete oxidation.¹² Other oxidizing reagents that could enable thermal 6π-electrocyclization and oxidation were tested; the desired benzimidazoles were ultimately formed employing catalytic amounts of DDQ and

Table 4 Sequential alkenylation and cyclization for the synthesis of substituted benzimidazoles



Step a: imidazole (1.0 equiv.), SEM-Cl (0.050 equiv.), CH₃CN (0.10 M), 100 °C, 24 h. Step b: imidazole (1.0 equiv.), alkene (3.0 equiv.), Pd(OAc)₂ (0.10 equiv.), Cu(OAc)₂ (2.0 equiv.), 1,4-dioxane (0.33 M), 100 °C, 15 h. Step c: DDQ (0.10 equiv.), NaNO₂ (0.10 equiv.), Ph₂O (0.10 M), 180 °C, 36 h; 3 N HCl, 80 °C.



Scheme 1 Benzannulation of a C2-unsubstituted imidazole using N-methylation.

NaNO₂ under an oxygen atmosphere (step c).¹⁹ However, high temperatures (200 °C) were required and thus, the scrambling of the SEM group could not be eliminated. Hence, SEM deprotection was performed to obtain the final (NH)-free benzimidazoles (**11c**, **12c**, and **13c**).

This strategy using sequential alkenylation, switch of the N-substituent, and cyclization was useful for the regioselective formation of N-methylbenzimidazoles. For example, the alkenylation product **5b** was subjected to trimethyloxonium tetrafluoroborate, and the obtained product was subsequently treated with TFA at ambient temperature, giving 1-methyl-4-alkenyl imidazole **14a** (Scheme 1). Remarkably, the next alkenylation of imidazole **14a** bearing an electron-withdrawing group at the C4 position took place preferentially at the C5 position, giving **14b**. Ring closure led to the formation of benzimidazole **14c**, which has different substituents at the C5 and C6 positions and fixed regiochemistry at the N1 position.

In conclusion, we have demonstrated Pd-catalyzed C–H alkenylation reactions of imidazoles at the C5 position. Imidazole substrates served as effective ligands in the palladium-catalyzed system, allowing the oxidative coupling to olefins. A variety of alkenylated imidazoles were easily prepared from readily available simple imidazoles and olefins in a single step. Furthermore, the resulting imidazoles were converted to unsymmetrically substituted benzimidazoles in a systematic way. In addition to the importance in the synthesis of imidazole and benzimidazole derivatives, these results suggest the potential role of imidazoles as ligands in dehydrogenative C–C bond forming reactions, which are currently being investigated in our laboratory and will be reported in due course.

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Conflicts of interest

There are no conflicts to declare.

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