Pd(0)-CATALYZED DIRECT INTER- AND INTRAMOLECULAR C_2 OR C_5-H FUNCTIONALIZATION OF 4-CARBOXYIMIDAZOLES

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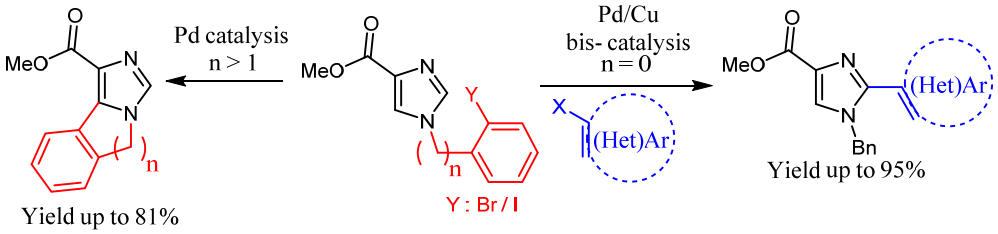
The transition metal-catalyzed direct C–H bond arylation of heterocycles is considered to be one of the key methods for the construction of valuable bis-(hetero)aromatic systems, frequent in both natural products and pharmaceuticals. Over the past ten years, efforts have been made to develop methodologies to improve the chemoselectivity of C–H arylation reactions of heterocycles, functionalized with various functions such as halogen, amine, nitro, ester, cyano…

Imidazole represents an important class of naturally occurring heterocycle. In pharmaceutical applications, this scaffold is a very attractive target for the design of peptidomimetics. From this perspective, the use of C–H arylation may give new classes of chemical compounds.

In this context, an efficient palladium-catalyzed direct hetero-arylation or alkenylation of methyl imidazole-4-carboxylate with various (hetero)aryl and alkenyl halides. Intermolecular direct C-H arylation was carried out with Cu/Pd bis-catalysis using 1,4-dioxane as a low-polarity solvent[1] allowing the synthesis of **C_2**-(hetero)aryl- or alkenylimidazoles in good to high yields.

Further, the regioselectivity was explored thanks to Pd-catalyzed intramolecular arylations. As expected, the **C_5**-arylated compound was mainly obtained with a good regioselectivity without copper. This reaction provide 4-carboxyimidazole tricyclic heterocycles with 5-,6- and 7-membered rings, starting from various methyl *N*-alkylated imidazole-4-carboxylates.[2]



Scheme 1 : Pd catalyzed C-H functionalization inter- and intermolecular of methylimidazole-4-carboxylate

[1] Jérémy Thireau et al, *Eur. J. Org. Chem.* **2017**, 2491–2494.

[2] Steven Frippiat et al, …. This work is under publication