Intramolecular Palladium-catalyzed C-H activation reactions: Synthesis of substituted quinolones

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In the last years, the Palladium-catalyzed direct alkenylation of Csp2-H bonds, an oxidative variant of the Heck reaction known as Fujiwara-Moritani reaction, has emerged as an efficient, atom-economical, and environmentally friendly synthetic tool for the preparation of highly functionalized aromatic molecules. In connection with our work in catalytic C-H activation chemistry,¹ we decided to apply this procedure to the synthesis of polysubstituted quinolone scaffolds, an important structural motif embedded in a wide variety of bioactive natural products and pharmaceuticals. An efficient approach to the synthesis of biologically active 3-alkenyl-4-substituted quinolin-2(1H)-ones that involves two sequential C-H alkenylation reactions has been developed. First, a Pd(II) catalyzed selective 6-endo intramolecular C-H alkenylation of N-phenylacrylamides has allowed the construction of the quinolone core, which could be further functionalized in C-3 through a second intermolecular C-H alkenylation reaction. This method is a significant advance over the existing procedures that require preactivated reaction partners. Furthermore, these reactions can also be carried out in aqueous media at room temperature, using a 2% aqueous solution of PTS, or even in water, in good yields. Details of these transformations will be given.

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