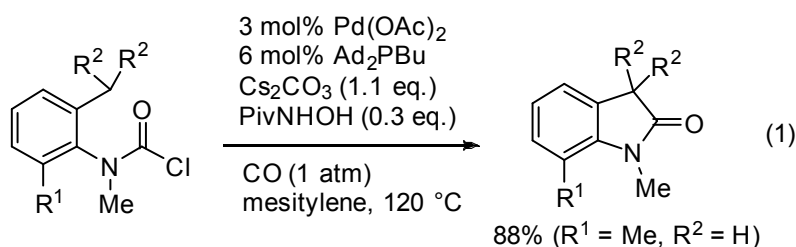


Palladium-Catalyzed Amidation by Chemoselective C(sp³)-H functionalization: Concise Route to Oxindoles and its application

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The oxindole moiety is a core structure in many complex natural products; such natural products often possess interesting biological activities. This structure has also drawn the attention of medicinal chemists because of its potential as an important pharmacophore. In the course of the synthetic studies of spirooxindole skeleton, we focused on the utilities of carbamoyl chloride, which undergo oxidative addition to palladium catalyst. If C(sp³)-H bond activation is occurred after the oxidative addition, oxindoles would be accessed concisely. When we started the project, several groups reported the related cyclization using palladium catalyst via C(sp³)-H bond activation of a methyl group and the following reductive elimination. Thus we examined the formation of oxindoles from carbamoyl chloride bearing an alkyl group in proper position.



The cyclization of carbamoyl chloride (R¹ = Me, R² = H), which was prepared 2,6-dimethylaniline, proceeded smoothly under the conditions of palladium acetate (3 mol%), di(1-adamantyl)-*n*-butylphosphine (6 mol%), Cs₂CO₃ and *N*-hydroxypivalamide in mesitylene at 120 °C to give oxindole in 88% yield (eq. 1). These conditions could be applied to several substrates having chloro, methoxy groups and so on. Further studies to disclose the reaction scope and apply to the synthesis of natural products are currently underway and will be reported.