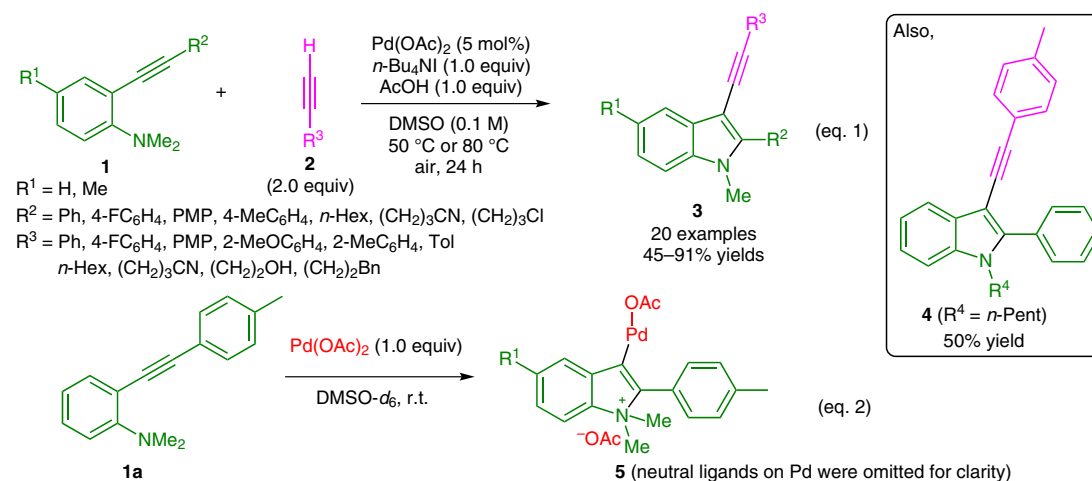


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Palladium-Catalyzed Coupling of *ortho*-Alkynylanilines with Terminal Alkynes Under Aerobic Conditions: Efficient Synthesis of 2,3-Disubstituted 3-Alkynyloindoles
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Palladium-Catalyzed Synthesis of 3-Alkynyloindoles



Significance: Reported is the synthesis of 2,3-di-substituted 3-alkynyloindoles **3** via a palladium(II)-catalyzed coupling of *N,N*-dimethyl-*ortho*-alkynylanilines **1** with terminal alkynes **2** under mild aerobic conditions (eq. 1). The required *o*-alkynylanilines **1** were synthesized by a Sonogashira coupling of the corresponding *N,N*-dimethyl-2-iodoaniline with the terminal alkynes. The optimum reaction conditions shown were applicable to aliphatic as well as aromatic alkynes bearing a variety of functionalities such as benzyloxy and cyano groups or chloro substituents (R², R³). The reaction of *N*-methyl-*N*-pentyl-*ortho*-(1-phenylethynyl)aniline with 4-ethynyltoluene afforded **4**, while no reaction occurred when the *N*-methyl-*N*-phenyl derivative was used. The *N,N*-dibenzyl derivative gave the corresponding indole product in only 11% yield. The reaction was suggested to proceed via the aminopalladation of **1** leading to σ -indolylpalladium(II) intermediate **5** which was characterized spectroscopically (eq. 2).

Comment: The synthesis of substituted indoles has been a major area of focus for organic chemists due to their pharmaceutical applications (see Book below). 2- and 3-Alkynyloindoles are generally synthesized via functionalization of the indole ring or, in recent developments, by the palladium(0)-catalyzed alkylation–heteroannulation of *ortho*-alkynylanilines. The current method allows the use of terminal alkynes instead of 1-haloalkynes and therefore is an advancement over previously reported methods. Broad substrate scope, good functional group tolerance, and easily available starting materials are some of the strengths of this chemistry.

Book: *Heterocyclic Scaffolds II: Reactions and Applications of Indoles*, G. W. Gribble (Ed.); In *Topics in Heterocyclic Chemistry*, B. U. W. Maes (Series Ed.); Springer Link: New York, **2010**; Vol. 26.

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