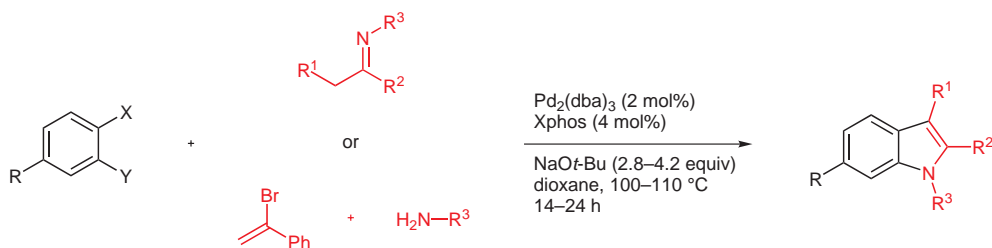


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The Azaallylic Anion as a Synthone for Pd-Catalyzed Synthesis of Heterocycles: Domino Two- and Three-Component Synthesis of Indoles

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Synthesis of Indoles by Domino C/N-Arylation of Azaallylic Anions



X = Cl, Br; Y = Cl, Br, I

R = H, OBn

R¹ = H, Me, *n*-Bu

R² = Me, *n*-Pent, Ph, 4-MeOC₆H₄

R³ = *t*-Bu, Bn, Ph, 4-MeOC₆H₄, 2-ClC₆H₄

R¹-R² = (CH₂)₃, (CH₂)₄, (CH₂)₅

19 examples
56–86%

Significance: A new reasonably efficient method for the synthesis of indoles utilizing an azaallylic anion equivalent, generated by imine deprotonation that undergoes chemoselective C-arylation followed by intramolecular N-arylation, is reported. Extraordinarily, the overall process may be carried out as a three-component reaction via generation of imine from an in situ C–N coupling of styryl bromide with a primary amine. Bulky and electron-rich monophosphines function best as ligands and regioselectivity based on the expected rates of oxidative addition is observed using simple and commercially available dihaloarenes. Unsymmetrical dialkyl imines give regioisomeric products with modest selectivities (favoring C-arylation with the less-substituted available azaallylic anion prior to C–N coupling), a direct contrast in terms of the regiochemistry which is observed in the Fischer indole synthesis under standard conditions (D. Zhao, D. L. Huges, D. R. Bender, A. M. DeMarco, P. J. Reider *J. Org. Chem.* **1991**, *56*, 3001-3006).

Comment: This chemistry is a continuing theme in the Barluenga group for the regioselective preparation of substituted indoles (J. Barluenga, M. A. Fernández, F. Aznar, C. Valdéz *Chem. Eur. J.* **2005**, *11*, 2276-2283) and is an important contribution to a recently blooming field of Pd-catalyzed cascade processes (A. Fayol, Y.-Q. Fang, M. Lautens *Org. Lett.* **2006**, *8*, 4203-4206) for the regioselective synthesis of privileged indole heterocycles.

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Category

Synthesis of Heterocycles

Key words

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cascade arylation
domino reaction
indoles

SYNFACT
of the month