SYNFACTS

Highlights in Current
Synthetic Organic
Chemistry

REPRINT

Thieme

Category

Synthesis of Heterocycles

Key words

palladium catalysis

spirooxindoles

C(sp^3)–H activation

quinolinones

Heck reaction

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Activation of a C(sp^3)–H Bond by a Transient σ-Alkylpalladium(II) Complex: Synthesis of Spirooxindoles Through a Palladium-Catalyzed Domino Carbopalladation/C(sp^3)–C(sp^3) Bond-Forming Process

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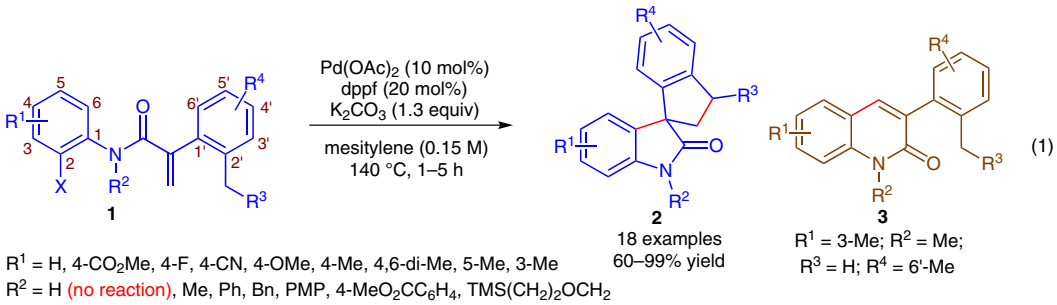
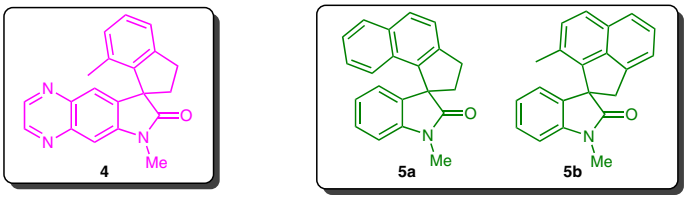
Pd-Catalyzed Synthesis of Spirooxindoles



R^1 = H, 4-CO_2Me, 4-F, 4-CN, 4-OMe, 4-Me, 4,6-di-Me, 5-Me, 3-Me
R^2 = H (no reaction), Me, Ph, Bn, PMP, 4-$MeO_2CC_6H_4$, TMS$(CH_2)_2OCH_2$
R^3 = H, Me
R^4 = H (no reaction), 6'-Me, 6'-Et, 3',5',6'-tri-Me, 4'-OMe-6'-Me, 4'-*t*-Bu-6'-Me
X = Br, I (1 example), Cl (no reaction)

Also,



Significance: Reported is the synthesis of spirooxindoles **2** from **1** via a Pd-catalyzed sequential intramolecular carbopalladation/C–C bond formation. Compounds **1** were synthesized from ethyl pyruvate in five steps. The optimized conditions favoring the formation of **2** (5-*exo*-trig cyclization) over **3** (6-*endo*-trig cyclization) were achieved by variation of bases, additives and ligands. Attempts to obtain optically active **2** through the use of chiral bidentate ligands were unsuccessful. The iodo- and bromoanilides (**1**, X = I, Br) afforded **2** in good yields while chloroanilides failed to undergo the spirocyclization reaction. The reaction also failed for R^2 or R^4 = H. EWGs, EDGs, heterocyles (**4**) and *meta* and *para* X-substituents were tolerated. However, presence of an *ortho* X-substituent resulted in the formation of **3**. Compounds **5a**,**b** were obtained in a ratio of 1:3, indicating that activation of the C(sp^2)–H bond is favored over C(sp^3)–H bonds.

Comment: Spirooxindoles have gained attention in the last decade due to their biological activities, such as antimalarial, antituberculosis, and growth hormone secretagogue (see Reviews below). They are generally synthesized via nucleophilic addition and spirocyclization on indole-2,3-dione or 3-alkylidine oxindole. A conceptually similar work involving Heck reaction and C(sp^2)–H bond activation has been reported (R. T. Ruck et al. *Angew. Chem. Int. Ed.* **2008**, *47*, 4711). The current method is a rare example of a C(sp^2)–H bond activation/C(sp^3)–C(sp^3) bond formation for the synthesis of spirooxindoles. The yields are generally good and the substrate scope is broad. Development of an enantioselective version of this reaction will be awaited by organic and medicinal chemists.

Reviews: J. J. Badillo, N. V. Hanhan, A. K. Franz *Curr. Opin. Drug Discovery Dev.* **2010**, *13*, 758–776; N. R. Ball-Jones, J. J. Badillo, A. K. Franz *Org. Biomol. Chem*. **2012**, *10*, 5165–5181.

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