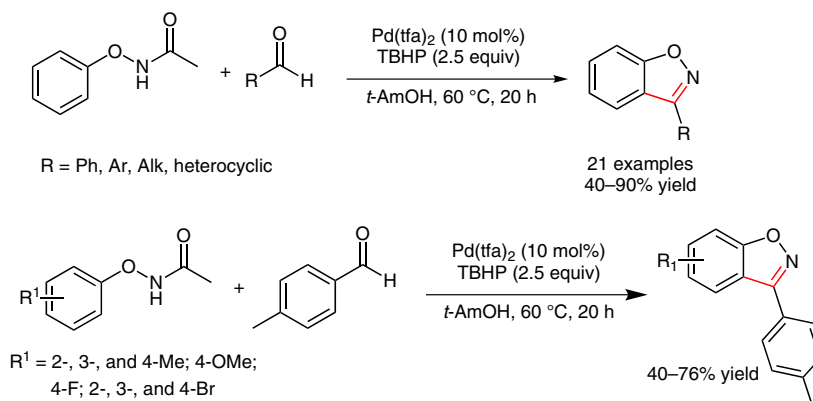


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P. DUAN,* Y. YANG, R. BEN, Y. YAN, L. DAI, M. HONG, Y.-D. WU, D. WANG, X. ZHANG,*
J. ZHAO* (SHENZHEN GRADUATE SCHOOL OF PEKING UNIVERSITY AND NANJING
UNIVERSITY, P. R. OF CHINA)
Palladium-Catalyzed Benzo[*d*]isoxazole Synthesis by C–H Activation/[4+1] Annulation
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Synthesis of 1,2-Benzisoxazoles by Palladium-Catalyzed [4+1] Annulation



Significance: The benzisoxazole skeleton is present in many natural products and pharmaceuticals, for example in the antipsychotic risperidone and its analogues. Previous methods for the preparation of the 1,2-benzisoxazoles include the N–O bond formation of 2-azidobenzophenones (B. J. Stokes et al. *Org. Lett.* **2010**, *12*, 2884) or 2-hydroxyaryl N–H ketimines (C.-y. Chen et al. *Org. Lett.* **2011**, *13*, 6300). Reported is a Pd(tfa)₂-catalyzed reaction between *N*-phenoxyacetamides and aldehydes to synthesize 1,2-benzisoxazole derivatives. The present method is the first example of a palladium-catalyzed C–H activation and C–C/C=N bond-forming process for the synthesis of 1,2-benzisoxazoles.

Comment: The present method is an additional route for the construction of 1,2-benzisoxazoles which shows the considerable scope of 21 aldehydes and 9 *N*-phenoxyacetamides. Yields range from moderate (40%) to excellent (90%). Phenoxyacetamides with electron-donating and -withdrawing groups participated well in the reaction. However, a decrease in the yields of products by a steric effect was noted for *ortho*-substituted substrates. Observation of a kinetic isotope effect ($K_H/K_D = 3.2$) and a DFT calculation led to the conclusion that a Pd(II)–Pd(IV)–Pd(II) catalytic cycle is involved, which makes the presence of an oxidizing agent necessary. The study additionally showed the role of the solvent to be important, as *t*-BuOH afforded in optimization studies a 46% yield whereas *t*-AmOH afforded a 75% yield under otherwise identical conditions.

SYNFACTS Contributors: Victor Snieckus, Keller G. Guimarães
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