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A Short Asymmetric Synthesis of the Benzopyrano[3,4-*c*]pyrrolidine Core *via* an Organocatalytic Domino Oxa-Michael/Michael Reaction
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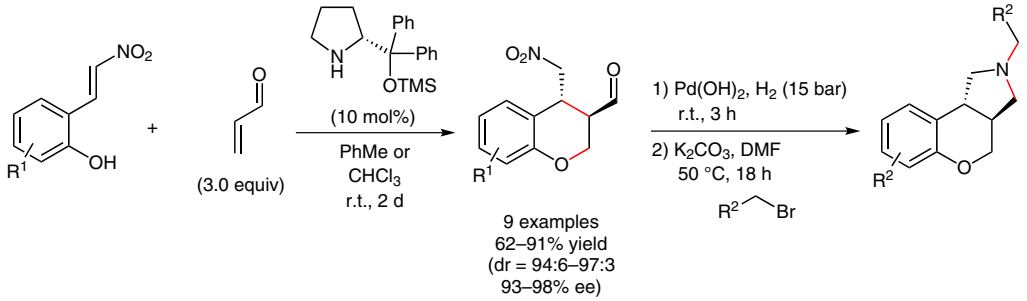
Organocatalytic Synthesis of Chromans and Benzopyrano[3,4-*c*]pyrrolidine



Significance: Reported is the enantioselective synthesis of *trans*-disubstituted chromans through the use of a sequential oxa-Michael–Michael reaction sequence and the subsequent synthesis of benzopyrano[3,4-*c*]pyrrolidine via reductive amination and N-alkylation. *trans*-Disubstituted chromans were obtained in 62–91% isolated yield with diastereomeric ratios ranging from 94:6 to 97:3 and 93–98% ee. The reaction conditions are quite mild and the success of the reaction in either toluene or chloroform allows for a wider solubility range of the phenol starting material. Although the use of many pyrrolidine-containing organocatalysts resulted in product formation, (2*R*)-2-{diphenyl[(trimethylsilyl)oxy]methyl}-pyrrolidine gave the highest product yield. A limitation was the failure of an electron-rich methoxy-substituted phenol to provide the corresponding chroman.

Comment: Benzopyrano[3,4-*c*]pyrrolidines have been investigated in a wide variety of therapeutic areas, including anti-psychotics or anti-depressants (Lavielle et al. EP691243 A1, **1996**), Alzheimer's disease (Asberom et al. WO2007084595 A2, **2007**), obesity, insulin resistance, hypertension (Yao et al. WO2006002349 A1, **2006**), and benign prostatic hyperplasia (A. R. Haight et al. *Org. Process Res. Dev.* **2004**, *8*, 897). Given this variety of therapeutic applications, this new method should garner a fair amount of interest from the drug discovery community. This method appears to be quite suitable for process-scale chemistry, due to its mild conditions and synthetic step reduction when compared to more common techniques, such as the one described by Dubuffet and coworkers (*Bioorg. Med. Chem. Lett.*, **1999**, *9*, 2059). This method also circumvents the use of chiral column chromatography, accelerating the drug discovery process even further.

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Category

Synthesis of Heterocycles

Key words

benzopyrano-[3,4-c]pyrrolidine

oxa-Michael reaction

domino reaction

organocatalysis

chroman