Enantioselective Reaction of Tertiary Enamides with Salicylaldehydes

Significance: Tertiary enamides are related to enamines by replacement of an N-alkyl substituent with an electron-withdrawing group. Despite this change, they remain nucleophilic. Taking advantage of this characteristic and of the electrophilicity of the transient iminium, the authors developed a modular titanium(IV)-catalyzed synthesis of 4-chromanol derivatives, by reaction with salicylaldehydes.

Comment: The use of a titanium–(R)-BINOL complex enabled the synthesis of diverse 4-chromanol products with good to excellent enantio- and diastereoselectivity. Water was found to have a marked effect on enantioselectivity: under anhydrous conditions, the ee decreased to 50.8%, whereas it was measured at 96.5% in the presence of 20 mol% water, in the model reaction. The exact mechanism remains to be elucidated.

**Selected examples:**

- Ti(Oi-Pr)₄ (10 mol%) (R)-BINOL (20 mol%) H₂O (20 mol%) o-xylene, 40 °C, 2–168 h

**Mode of reactivity:**

**Product derivatization:**

*Slight loss in ee is explained by the presence of a minor amount of the opposite diastereomer of lower ee in starting material.*