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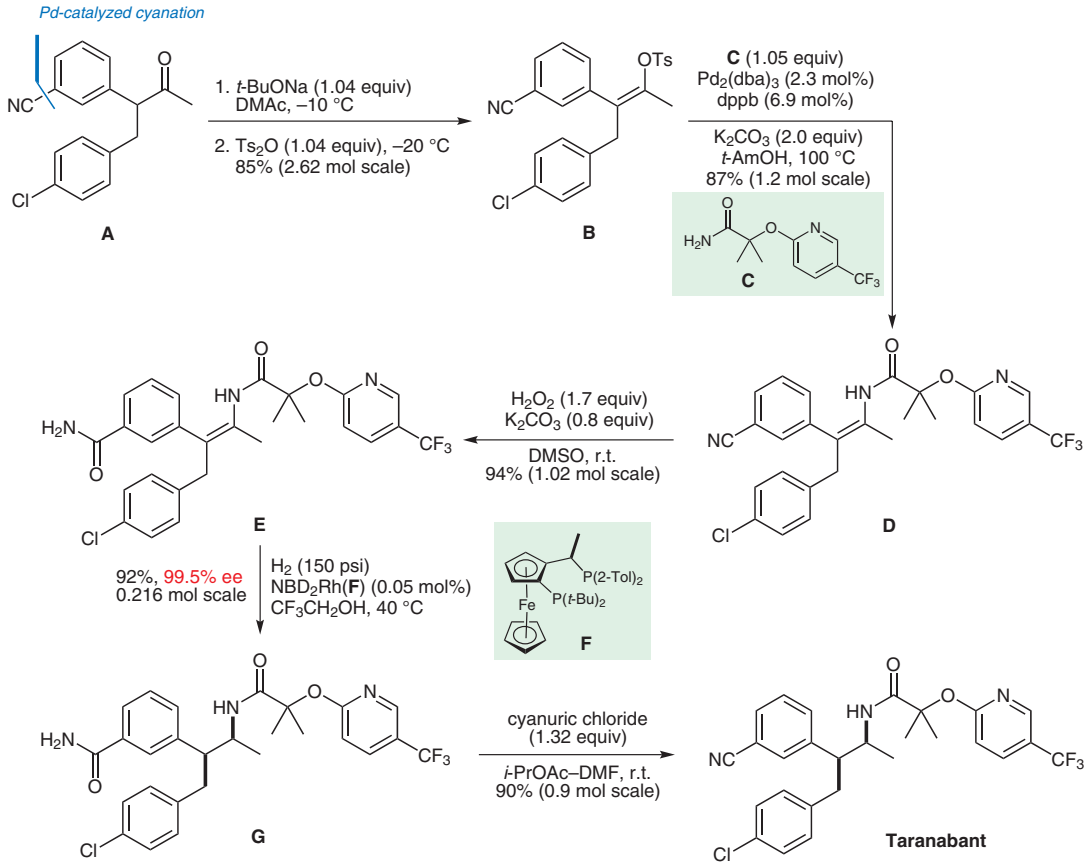
New Efficient Asymmetric Synthesis of Taranabant, a CB1R Inverse Agonist for the Treatment of Obesity
Org. Process Res. Dev. **2009**, *13*, 84-90.

Synthesis of Taranabant



Significance: Taranabant is a potential selective inverse agonist of the cannabinoid-1 receptor which is implicated in the regulation of feeding behaviour. Hence, taranabant is being developed for the treatment of obesity. The synthesis depicted incorporates three key features: (1) a simple highly stereoselective synthesis of the vinyl tosylate (**A** → **B**); (2) an efficient synthesis of a tetrasubstituted enamide by palladium-catalyzed amidation (**B** → **D**); and (3) a highly efficient asymmetric hydrogenation to create two adjacent stereogenic centers in a single step (**E** → **G**).

Comment: An earlier synthesis based on dynamic kinetic resolution (C.-y. Chen et al. *Org. Process Res. Dev.* **2007**, *11*, 616) required the use of sodium azide to introduce the nitrogen atom and suffered from lack of any suitable solid intermediates. In the present synthesis, the direct asymmetric hydrogenation of enamide **D** to taranabant was precluded because the nitrile in **D** coordinated preferentially to the rhodium catalyst. Therefore a two-step detour (nitrile hydrolysis, **D** → **E**) and amide dehydration of **G** was required.

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