Novel Synthesis of Rasagiline via a Chemoenzymatic Dynamic Kinetic Resolution


Significance: Rasagiline mesylate (Azilect®) is a selective monoamine oxidase B inhibitor that is administered as initial monotherapy in early Parkinson’s disease and as adjunct therapy to levodopa in moderate-to-advanced disease. The key step in the synthesis depicted is the dynamic kinetic resolution of racemic 1-aminoindan A catalyzed by immobilized Candida antarctica lipase B (CALB) together with a palladium racemization catalyst – a process that could be conducted in a concentration of up to 200 g/L.

Comment: The palladium nanocatalyst Pd/Al(OH) racemizes the amine via an imine intermediate (hydrogen borrowing). Racemization was complete in four hours using only 0.5 mol% of palladium in toluene at 70 °C. The catalyst was prepared as palladium nanoparticles entrapped in aluminum hydroxide according to the procedure of Y. Kim et al. (Tetrahedron Lett. 2010, 51, 5581). The chemoenzymatic catalyst system could be recycled 5–6 times.

Preparation of the racemization catalyst:

\[(\d-BuO)\text{Al} + H_2O \rightarrow \text{Al(OH)} \rightarrow \text{Pd(OAc)} \rightarrow \text{Pd/Al(OH)} \]

The reaction scheme shows the synthesis of (R)-Rasagiline via dynamic kinetic resolution.