Synthesis of (S)-Rivastigmine

**Significance:** Rivastigmine (Exelon®) is an acetylcholinesterase inhibitor that is prescribed for the treatment of mild to moderate dementia in patients with Alzheimer’s disease and Parkinson’s disease. The key step in the synthesis depicted is a dynamic kinetic resolution of the benzylic secondary alcohol B involving a lipase (Novozyme 435) coupled with a polymer-bound racemization catalyst (C).

**Comment:** The polymer-bound racemization catalyst C was prepared by heating a polymer-bound benzoyl chloride with [Ph₄][η⁵−C₅CO]Ru(CO)₃ in toluene for one day. The catalyst can be recycled several times. The enzymatic resolution was performed on a 1 mmol scale. For an alternative chemoenzymatic synthesis of rivastigmine, see: J. Mangas-Sánchez et al. *J. Org. Chem.* 2009, 74, 5304.

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**Chemical Structures**

1. Et(Me)NCOCl (2.0 equiv) NaH (2.0 equiv) CH₂Cl₂, r.t., 4 h
2. NaBH₄ (1.0 equiv) MeOH, 0 °C 85%

B → Novozyme 435 (30 mg/mmol) isopropenyl acetate (1.5 equiv) K₂CO₃ (1.0 equiv) PhMe (0.3 M), r.t., 1 d 96% (er > 99:1)

D → K₂CO₃ (1.0 equiv) MeOH-H₂O, r.t., 2 h 92%

(S)-Rivastigmine

1. MsCl (1.3 equiv) Et₃N (3.0 equiv) CH₂Cl₂, 0 °C, 30 min
2. Me₂NH (4.0 equiv) THF, r.t., 2 d 77%