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 \( \text{[Ph}_4\text{Rh}\text{C}_4\text{CO}]\text{Ru(CO)}_3 \) 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.

**Chemical Equations:**

1. Et(\( \text{Me} \))NCOCl (2.0 equiv)  
   NaH (2.0 equiv)  
   CH\(_2\text{Cl}_2\), r.t., 4 h  
   85%

2. NaBH\(_4\) (1.0 equiv)  
   MeOH, 0 °C  
   96% (er > 99:1)

3. K\(_2\text{CO}_3\) (1.0 equiv)  
   MeOH–H\(_2\text{O}\), r.t., 2 h  
   92%

4. MsCl (1.3 equiv)  
   Et\(_3\text{N}\) (3.0 equiv)  
   CH\(_2\text{Cl}_2\), 0 °C, 30 min  
   77%

5. Me\(_2\text{NH}\) (4.0 equiv)  
   THF, r.t., 2 d  
   77%

6. Novozyme 435 (30 mg/mmol)  
   K\(_2\text{CO}_3\) (1.0 equiv)  
   PhMe (0.3 M), r.t., 1 d  
   96% (er > 99:1)