Synthesis of Verubecestat

Significance: Verubecestat (MK-8931) is a β-secretase inhibitor that is of interest for the treatment of Alzheimer’s disease. The key step in the µmol-scale synthesis depicted is the construction of the aza-quaternary center in fragment D through a palladium-catalyzed, enantioselective addition of arylboronic acid B to cyclic iminosulfate A. The desired cyclic sulfamate D was obtained in 90% yield and 99% ee.

Comment: The scope of the palladium-catalyzed enantioselective arylation reaction was explored using seven cyclic iminosulfates and eleven arylboronic acids. The reaction tolerates electron-rich, electron-poor, and ortho-substituted arylboronic acids and provides cyclic sulfamidates in high yields with excellent enantioselectivities. This palladium catalyst system significantly expands the scope for the asymmetric arylation of ketimines.