Synthesis of (–)-Nutlin-3

Significance: Nutlin-3 inhibits the interaction between proteins p53 and MDM2. It is of interest as an investigative tool in cancer biology. The key step in the decagram-scale synthesis depicted is an enantioselective aza-Henry reaction catalyzed by the novel bis(amidine) C that provides high enantioselectivity at higher temperatures and lower catalyst loadings than previously possible (T. A. Davis, J. Johnston Chem. Sci. 2011, 2, 1076).

Comment: The optimized conditions of the aza-Henry reaction include the following: 0.5 mol% catalyst loading, slow addition of imine (ca. 0.06 equiv aliquots over 8 h), essentially stoichiometric amounts of the two partners A and B, a relatively high reaction concentration (0.4 M in PhMe), and exclusive precipitation of the desired diastereoisomer. A 90% yield of product D was produced after filtration in 91% ee and a dr > 200:1.