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) 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.

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