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Preparation of (–)-Nutlin-3 Using Enantioselective Organocatalysis at Decagram Scale
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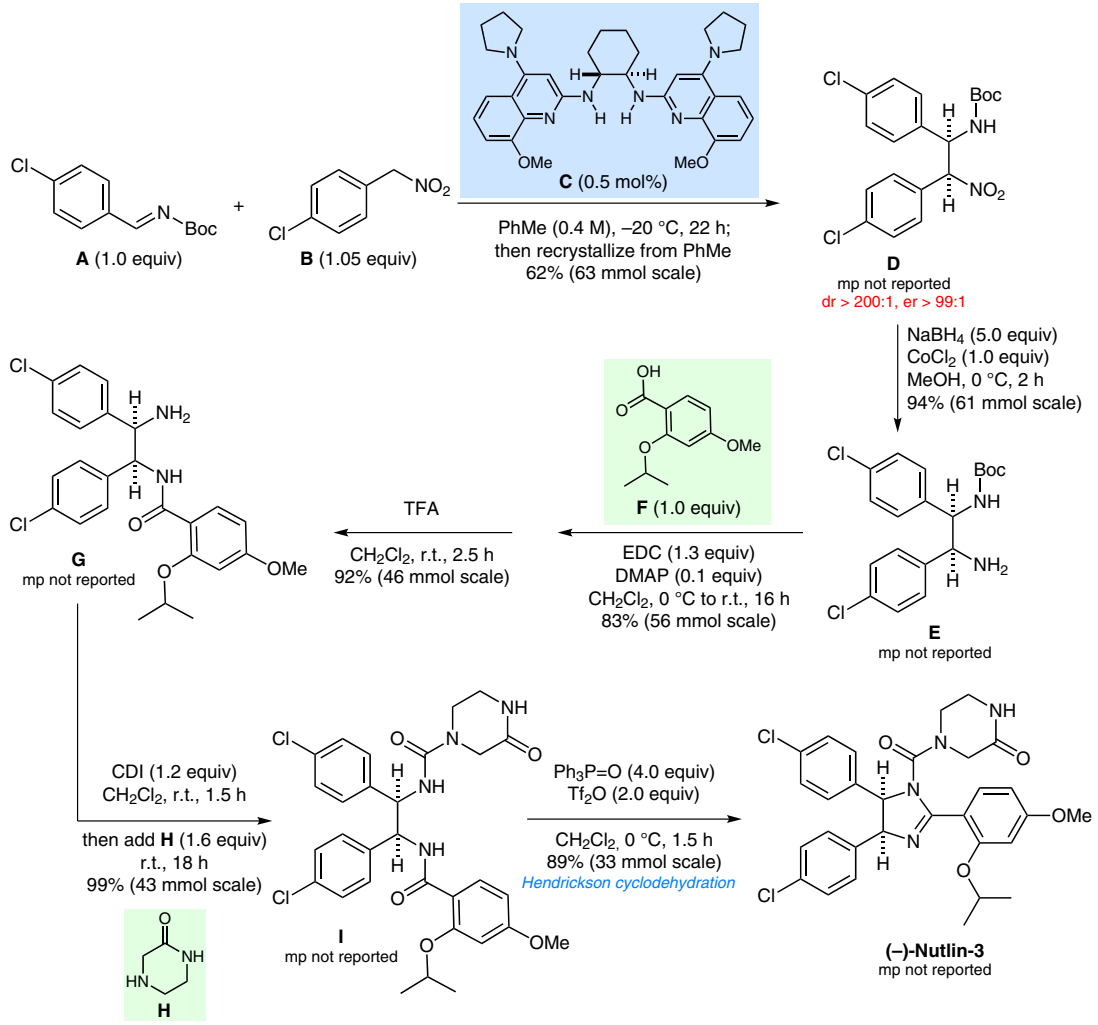
Synthesis of (–)-Nutlin-3



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.

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Category
Synthesis of Natural Products and Potential Drugs

Key words
nutlin-3
cis-imidazolines
organocatalysis
chiral bis(amidine) catalysts
asymmetric aza-Henry reaction