Synthesis of (R)-Sitagliptin

**Significance:** The key step in the synthesis of (R)-sitagliptin depicted is an asymmetric Mannich reaction of dithiomalonate B with bench-stable α-amidosulfone A catalyzed by quinidine-derived squaramide catalyst C (2 mol%). The reaction proceeds at 0 °C under aqueous biphasic conditions to give Mannich adduct D in 72% yield and 95% ee. A single recrystallization affords D in >99% ee. Sixteen examples of the reaction demonstrate its broad scope and utility.

**Comment:** The superior reactivity of dithiomalonate B compared with monothiomalonates and malonates as Mannich donors is attributed to the higher acidity of its α-hydrogen. Under the reaction conditions, the α-amidosulfone undergoes elimination of sodium benzenesulfinate to an N-Boc-protected imine which reacts before tautomerization to the enamine can occur. Sitagliptin (Januvia) is a DPP-4 inhibitor that is prescribed for the treatment of type 2 diabetes.