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 \( \alpha \)-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 \( \alpha \)-hydrogen. Under the reaction conditions, the \( \alpha \)-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.