Synthesis of (S)-Sitagliptin

Significance: Sitagliptin is a dipeptidyl dipeptidase-4 inhibitor that is prescribed for the treatment of type II diabetes. The small-scale synthesis depicted features a two-step construction of the allylic amine involving an ene reaction using the sulfurdiimide followed by a palladium-catalyzed asymmetric [2,3]-sigmatropic rearrangement of ylid.

Comment: The ylid does not undergo a [2,3]-sigmatropic rearrangement at 4 °C in the absence of the palladium catalyst. A further five 4-arylbut-1-ene substrates with F, CF₃ and OMe substituents gave the allylic amination products in 79–94% yield and 81–94% ee.