Houk\textsuperscript{1} examined the Mannich reaction of the enamine formed from acetone and S-proline with \(N\)-ethyldiene-\(N\)-phenylamine (see Chapter 5.3.3 in my book). Parasuk and Parasuk now extend this to the reaction of the enamine of cyclohexanone and S-proline with \(N\)-phenylmethanimine (Reaction 1).\textsuperscript{2} Geometries were optimized at B3LYP/6-31++G(d,p) and single-point energies computed with PCM (for the solvent DMSO) at both B3LYP and MP2.

![Reaction 1](image)

First, they examined the formation of the enamine 1, which can be in the \textit{syn} or \textit{anti} conformation. The barrier for formation of the \textit{syn} isomer is 10.2 kcal mol\(^{-1}\). The barrier for the formation of the \textit{anti} conformer is much higher, 17.9 kcal mol\(^{-1}\), and this is with a single water molecule used to assist the proton migration. However, the rotational barrier between the two conformers is only 4.2 kcal mol\(^{-1}\).
So, they conclude that the syn isomer is the only conformer directly formed by the reaction of cyclohexanone and S-proline, and then rotation can produce the anti conformer.

The located the transition state for the reaction of either syn-1 or anti-1 with phenylmethanimine. The two transition states are shown in Figure 1. The barrier for the reaction of syn-1 is 8.5 kcal mol$^{-1}$, leading to the S product. The other barrier is higher, 13.0 kcal mol$^{-1}$, and the R product 2R is 6.8 kcal mol$^{-1}$ higher in energy than the S product 2S. Thus, the reaction to give the S product is both kinetically and thermodynamically favored. This is consistent with experiment$^3$ which gives the S product with 99%ee. Inclusion of solvent makes the S product even more thermodynamically and kinetically favored over the R isomer.
Figure 1. B3LYP/6-311++G(d,p) optimized transition states leading to 2S and 2R.²

Source: http://comporgchem.com/blog/?p=165