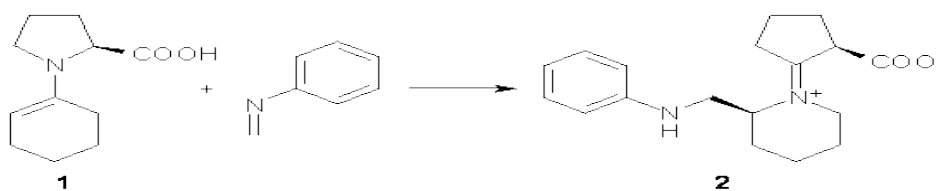


MANNICH REACTION

Houk¹ examined the Mannich reaction of the enamine formed from acetone and *S*-proline with *N*-ethylidene-*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).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.

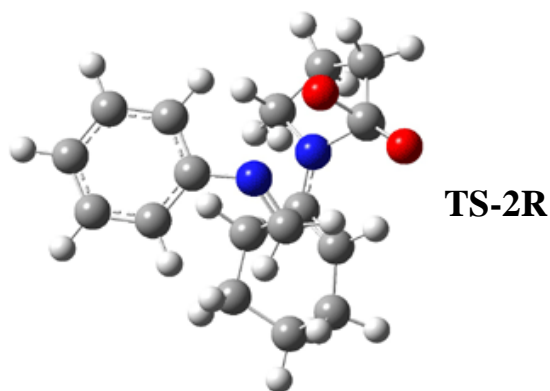


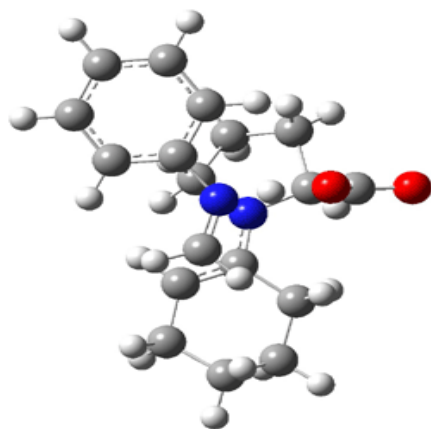
Reaction 1

First, they examined the formation of the enamine **1**, which can be in the *syn* or *anti* conformation. The barrier for formation of the *syn* isomer is 10.2 kcal mol⁻¹. The barrier for the formation of the *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 experiment³ 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.





TS-2S

Figure 1. B3LYP/6-311++G(d,p) optimized transition states leading to **2S** and **2R**.²

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