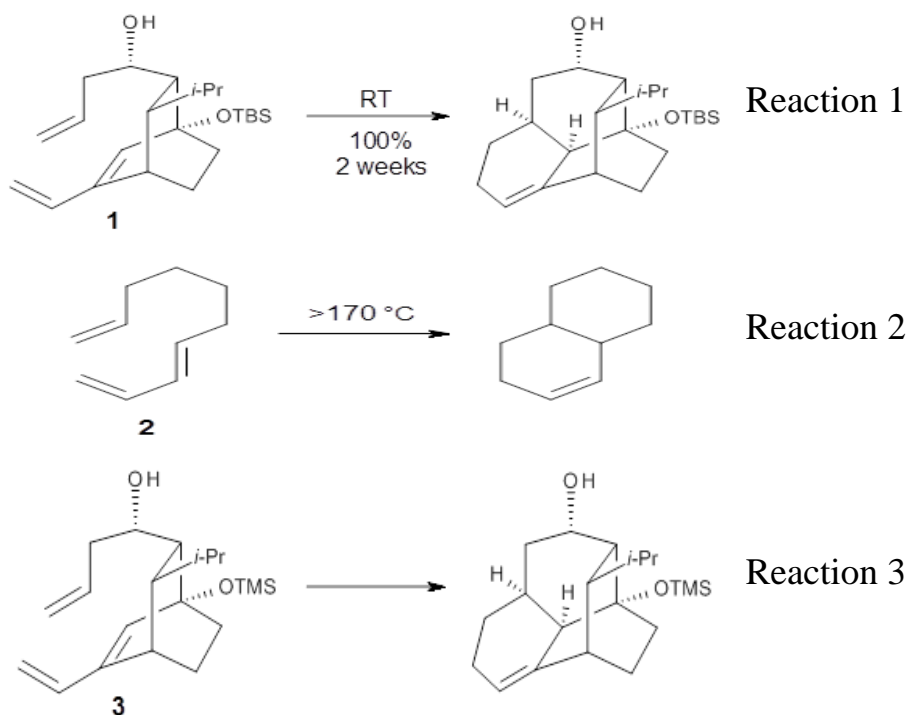


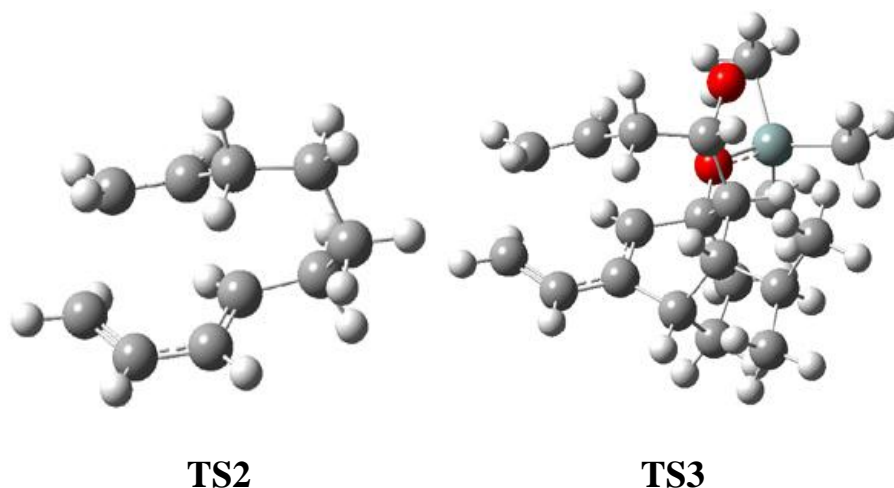
# PROXIMITY-INDUCED DIELS-ALDER REACTION

The intramolecular Diels-Alder reaction of **1** occurs slowly, but quantitatively, at room temperature.<sup>1</sup> This is unusual as most Diels-Alder cyclizations require heating to typically 200 °C. For example, the related cyclization of **2** requires heating to 170 °C.<sup>2</sup> What is the cause for this proximity-induced reaction?



Houk and Baran address this question using a computational approach.<sup>3</sup> The Diels-Alder reaction of **2** and a simplified analogue of **1**, namely **3**, were computed at CPCM/M06-2x/6-311+G(d,p)//B3LYP/6-31G(d). The optimized transition states for the reaction of **2** and **3** are shown in Figure 1.

The free energy of activation of **3** is  $5.4 \text{ kcal mol}^{-1}$  lower in energy than the free energy of activation of **2**. This is consistent with the much faster reaction of **1** than **2** observed in the experiment.



**Figure 1.** B3LYP/6-31G(d) for the transition states of Reactions 2 and 3.

Partitioning **3** into fragments allows Houk and Baran to apply the distortion model. They find that the rigid diene in **3** (and thereby **1**) accelerates the reaction relative to the more flexible diene of **2**. Further, strain relief in going from **3** (and thereby **1**) to **TS3** (and thereby to TS of reaction 1) and the formation of an intramolecular hydrogen bond leads to the lower activation energy of **3**, and therefore of **1**.

Source: <http://comporgchem.com/blog/?p=2342>