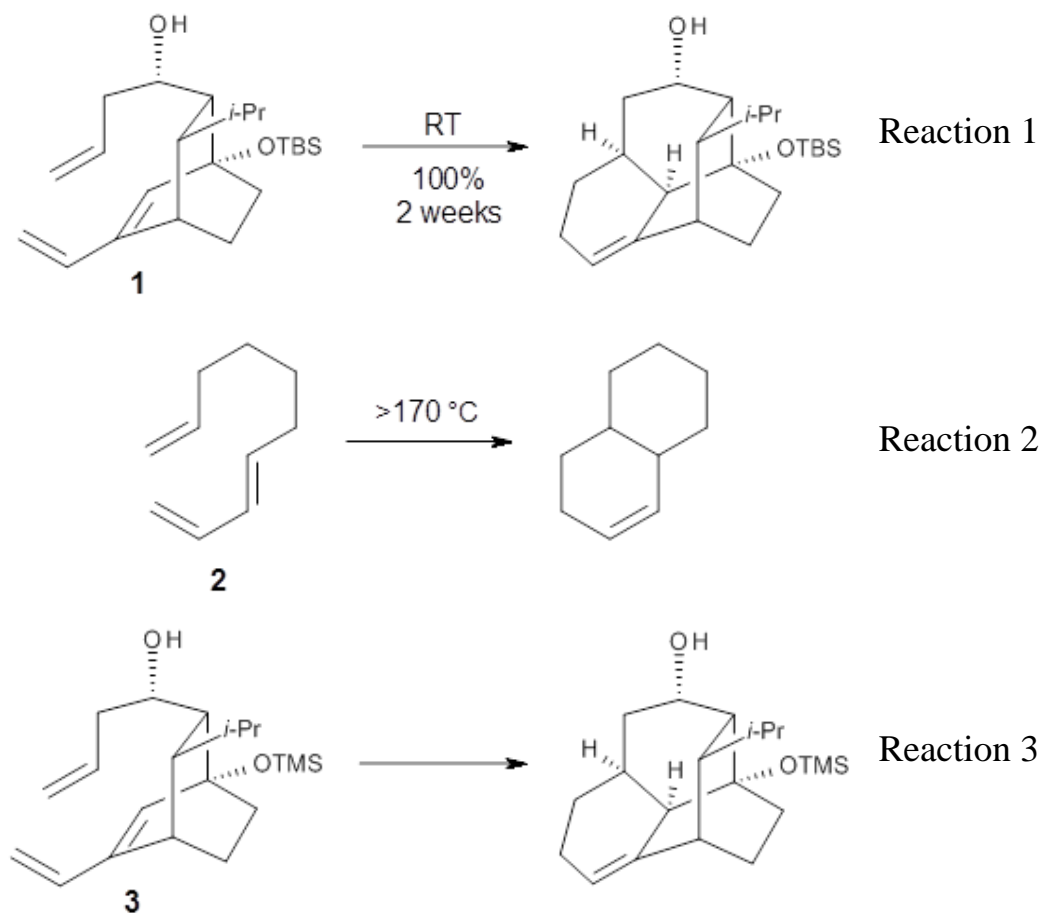


WHY A PROXIMITY-INDUCED DIELS–ALDER REACTION IS SO FAST

The intramolecular Diels-Alder reaction of **1** occurs slowly, but quantitatively, at room temperature.¹ 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.² What is the cause for this proximity-induced reaction?



Houk and Baran address this question using a computational approach.³ 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.

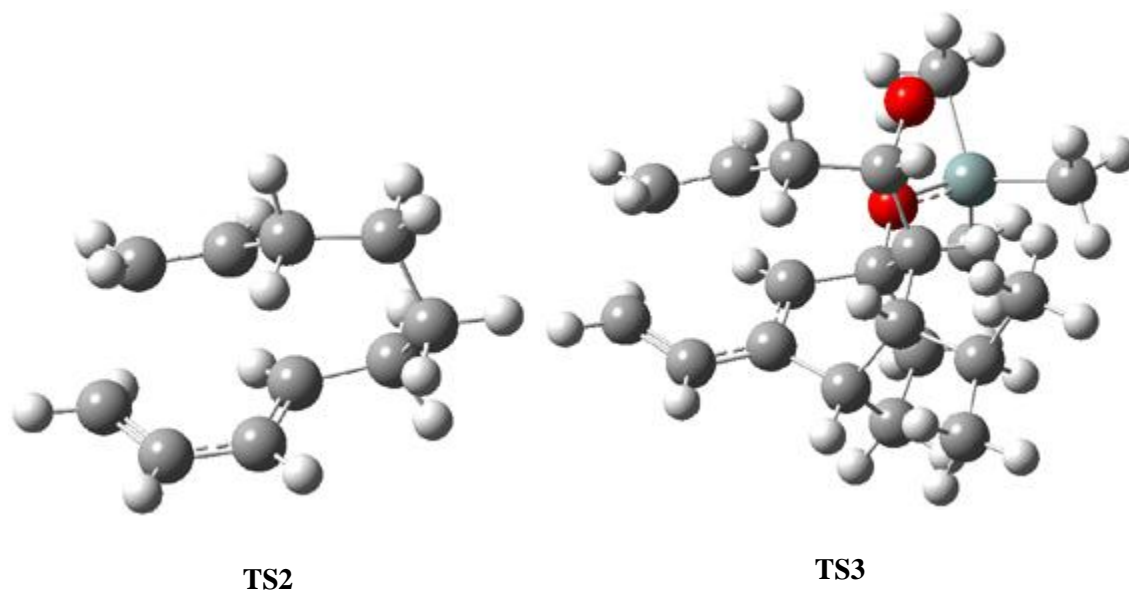


Figure 1. B3LYP/6-31G(d) for the transition states of Reactions 2 and 3.

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://www.compchemhighlights.org/2012/10/why-proximity-induced-dielsalder.html>