

Regioselectivity in an intramolecular Heck-Matsuda reaction: a DFT study

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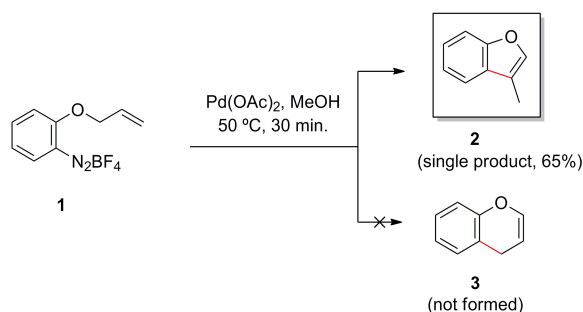
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Introduction

The development of new and more efficient methods for the construction of heterocyclic scaffolds is in continuum demand in organic synthesis and medicinal chemistry. In 2010 Correia's group reported the first examples of intramolecular Heck-Matsuda reactions employing *o*-diazo aryl allyl ethers and amides as substrates, under mild, ligand-free conditions, obtaining benzo-fused heterocycles in moderate to good yields.¹ For the reaction of model substrate **1**, only the benzofuran adduct **2** was formed in the tested conditions (Scheme 1). In this work, we have performed DFT calculations at the M06/6-31+G(d,p) level of theory on the migratory insertion step of this reaction. The energetic barriers associated with the regioisomeric channels were calculated in order to understand the origins of the observed regioselectivity in this model reaction.



Scheme 1: Regioselective intramolecular Heck-Matsuda reaction of **1**

Results and Discussion

The regioisomeric transition states **TS4** and **TS5**, were found and characterized by frequency and IRC calculations. The structures of intermediates, **4-7**, were also found and characterized as local minima. We suppose here that these systems are electronically neutral with acetate anion as a spectator ligand. The energy profiles for both pathways are depicted in Figure 1. In the starting complexes for migratory insertion, the palladium-aryl bond must be either parallel (in **4**) or perpendicular (in **5**) to the carbon-carbon double bond. The starting complex **5** is more stable than **4** by 4.8 kcal.mol⁻¹, this is caused by a stronger back-bonding interaction

in **5**. The order for transition states is reversed, with **TS4** lower in energy than **TS5** by 4.0 kcal.mol⁻¹. In **4** the carbon atom is already close to the aryl moiety, which facilitates carbon-carbon bond formation in **TS4**. On the other hand, In order to **5** adopts the structure of **TS5**, the alkene bond must undergo a twist, which decreases the back-bonding stabilization, leading to a higher energy transition state.

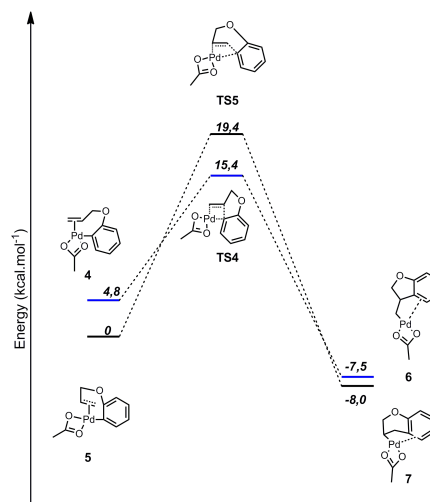


Figure 1: Energy profiles for the regioisomeric migratory insertion pathways (Relative Gibbs energies are in kcal.mol⁻¹)

Conclusions

In this work DFT calculations successfully rationalized the regioselectivity in a model intramolecular Heck-Matsuda reaction. Our results are in close agreement with a recent report in the related intramolecular Heck-Mizoroki reaction.² Further studies regarding the cationic version of the intramolecular Heck-Matsuda reaction and the complete catalytic cycle for these reactions are on going in our laboratories.

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¹ Siqueira, F.A.; Taylor, J.G. e Correia, C.R.D. *Tetrahedron Lett.* **2010**, *51*, 2102

² Gruber, R. Fleurat-Lessard, P. *Organometallics*, **2014**, *33*, 1996