Computational Investigation of the Regioselective γ-Insertion of Alkynyl Carbenes into O–H Bonds: Mechanistic Insights and Selectivity Control

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This study investigates the high regioselectivity of alkynyl carbene insertion into O-H bonds, utilizing DFT calculations [1] for geometry optimizations and frequency analyses using the ωB97X-D/6-31+G(d,p) method, and single-point energy corrections at the B2PLYP/6-31+G(d,p) method to enhance accuracy. Solvent effects were modeled using the SMD solvation model in DCM. Computational results reveal that using TFE as a substrate leads to both γ- and α-products form, with γ being the major product. The high selectivity with TFE is attributed to its strong H-bonding ability and electronic effects, which stabilize key transition states and lower the activation energy barrier for γ-product formation. This selectivity follows the Curtin-Hammett principle [2], where the product distribution is governed by the activation energy barriers. In addition, when using ethanol as the substrate leads solely to the α-product, highlighting the role of substituent electronic effects in determining selectivity.

This study reports the first O-H insertion reaction of alkynyl diazo compounds, achieving remarkable regioselectivity. A regioselectivity ratio of 20:1 for the γ-product underscores the precise control over product distribution enabled by the strategic choice of reactants and reaction conditions.

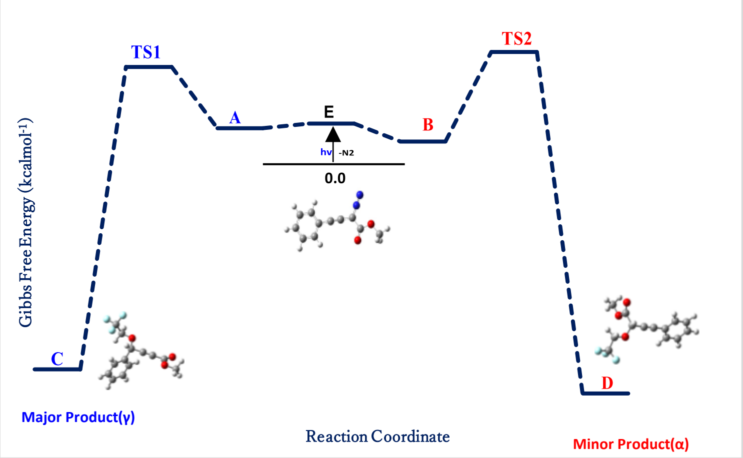

Fig: Energy Diagram for γ- vs. α-Selective O–H Insertion.

References

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2. Filby, P. S.; Rayat, S. *J. Org. Chem.*, **2018**, 83(4), 1790-1796.