Theoretical Study – Assisted Tandem Pd Catalysis Enables Regiodivergent Heck Arylation of Transiently-Generated Substituted Enol Ethers

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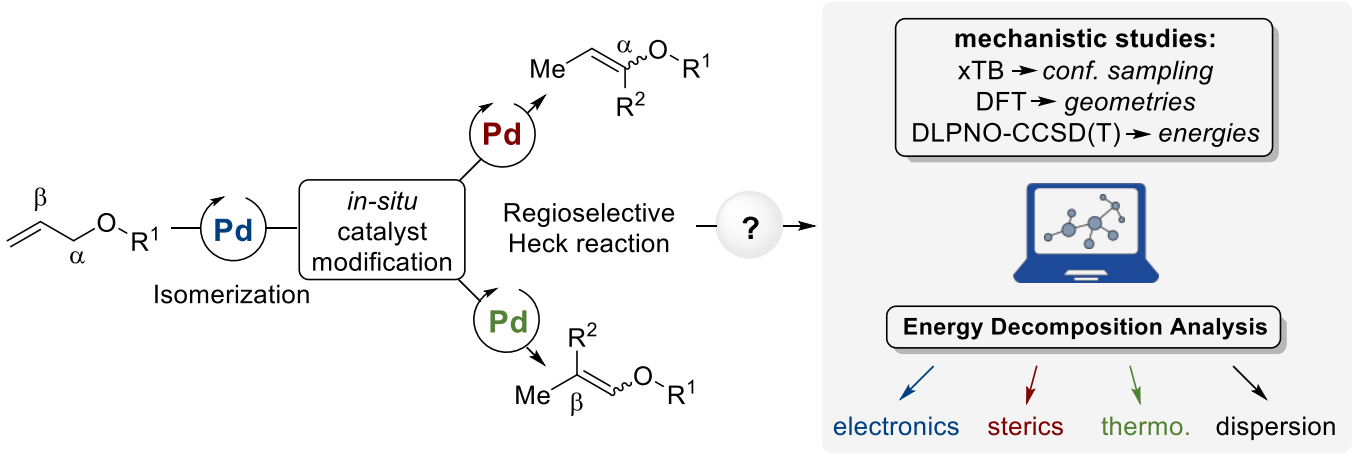
Over the last decades, extensive efforts have focused on accessing substituted vinyl ethers by Heck reactions.[1] In most cases, less hindered and more accessible terminal vinyl ethers were employed. Polysubstituted vinyl ethers were only used sporadically, with limited success.



Part of our research program consists in the design of multicatalytic processes in which transition metal catalysts are engaged in sequential olefin migration/cross-coupling reactions.[2] In this work, we have developed two complementary and regiodivergent Pd-catalyzed assisted tandem reactions. In both cases, the isomerization is conducted with [Pd(P*t*Bu$_3$)$_2$(H)(Cl)] as precatalyst. Subsequent catalyst modification by addition of a chelating bisphosphine ligand (dppp) in the presence of a base and NaOAc affords preferentially the α-arylation pathway in the reaction with aryl triflates. The β-arylation pathway is accessible instead when the catalyst is simply modified by an excess of base (NEt$_3$) after isomerization and reaction with aryl halides. The regioselectivity in the latter case is strongly dependent on the electronic nature of the aryl halides.
In-depth computational investigations helped determine the origin of the regioselectivity in both cases, notably by means of Energy Decomposition Analysis (EDA) of the migratory insertion transition-states.[3]

[1] Selected examples: a) Arai, I.; Doyle Daves, G. *J. Org. Chem.* **1979**, *44*, 21. b) Cabri, W.; Candiani, I.; Bedeschi, A.; Penco, S. *J. Org. Chem.* **1992**, *57*, 1481. c) Nilson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2001**, *123*, 8217-8225. d) Domzalska-Pieczykolan, A.; Funes-Ardoiz, I.; Furman, B.; Bolm, C. *Angew. Chem. Int. Ed.* **2022**, *61*, e202109801
[2] a) Fiorito, D.; Scaringi, S.; Mazet, C. *Chem. Soc. Rev.* **2021**, *50*, 1391. b) Romano, C.; Mazet, C. *J. Am. Chem. Soc*. **2018**, *140*, 4743. c) Romano, C.; Fiorito, D.; Mazet, C. *J. Am. Chem. Soc*. **2019**, *141*, 16983.
[3] a) Schneider, W. B.; Bistoni, G.; Sparta, M.; Saitow, M.; Riplinger, C.; Auer, A. A.; Neese, F. *J. Chem. Theory Comput.* **2016**, *12*, 4778. b) Altun, A.; Neese, F.; Bistoni, G. *Beilstein J. Org. Chem.* **2018**, *14*, 919.