

Rational co-catalyst design for amide hydrogenolysis based on DFT calculations.

Lluís Artús Suárez, David Balcells and Ainara Nova

Hylleraas Centre for Quantum Molecular Science, Department of Chemistry, University of Oslo, P.O. Box 1033, Blindern, N-0315 Oslo, Norway

l.a.suarez@kjemi.uio.no

The reduction of electron rich carboxylic acid derivatives, such as amides, is still a difficult reaction. In a recently reported method, amide hydrogenolysis was enhanced by the combination of a secondary amide co-catalyst with $(i^{\text{Pr}}\text{PNP})\text{Fe}(\text{H})(\text{CO})$ ($i^{\text{Pr}}\text{PNP} = \text{N}[\text{CH}_2\text{CH}_2(\text{P}^{\text{t}}\text{Pr}_2)]_2$).^[1] The mechanism for this reaction was studied in our group by using DFT methods.^[2] The M06 functional was selected based on a method benchmark using CCSD(T). The mechanistic study showed that the secondary amide co-catalyst acts as a proton shuttle in the rate limiting step ($\Delta G_{\text{HT}}^\ddagger$) but poisons the catalyst forming an adduct (ΔG_{add}) (Figure 1). In order to improve this reaction, ΔG_{add} and $\Delta G_{\text{HT}}^\ddagger$ were calculated using as co-catalysts the molecules shown in Figure 1 and then introduced in a microkinetic model to predict the expected amide conversion.^[3] The most promising candidates were tested in the lab and the experimental results were in good agreement with the computational predictions. Co-catalyst 1 yielded the highest conversion, owing to an optimal balance between ΔG_{add} and $\Delta G_{\text{HT}}^\ddagger$.

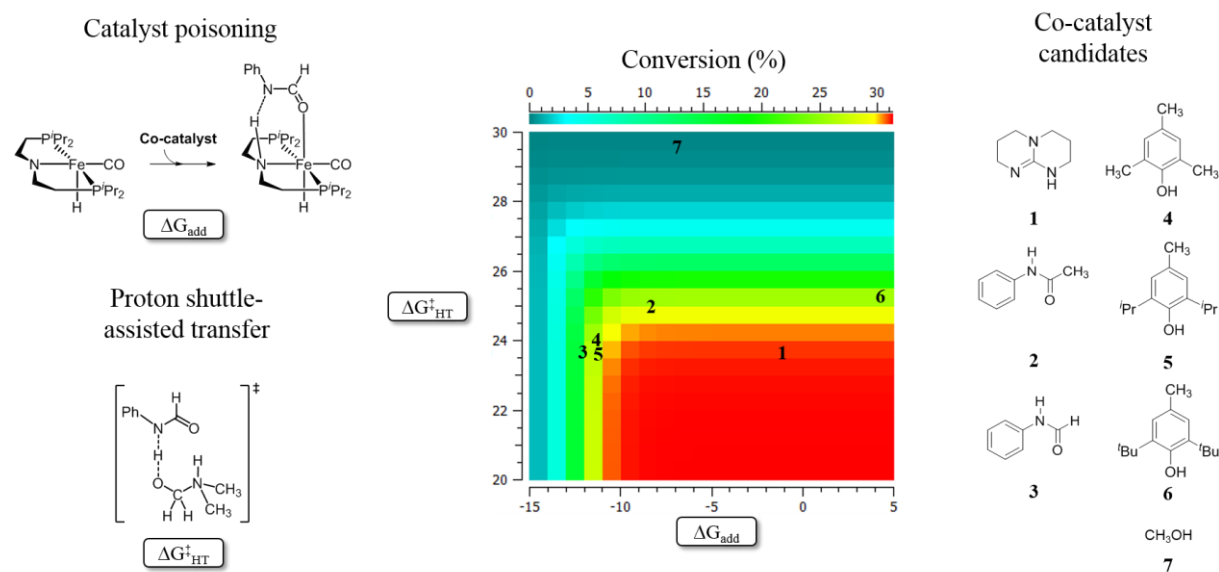


Figure 1: Key reactions in the amide hydrogenolysis co-catalyst design (left); predicted conversion vs ΔG_{add} and $\Delta G_{\text{HT}}^\ddagger$ (middle); co-catalysts tested (right).

References

1. U. Jayarathne, Y. Zhang, N. Hazari and W.H. Bernskoetter, *Organometallics* (2017), **36**, 409
2. L. Artús Suárez, W.H. Bernskoetter, N. Hazari and A. Nova, *ACS Catal.* **8** (2018), 8751
3. L. Artús Suárez, U. Jayarathne, D. Balcells, W.H. Bernskoetter, N. Hazari, M. Jaraiz and A. Nova, *ACS Catal.*, Submitted for publication.