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

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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 \((\text{^{i}PrPNP})\text{Fe(H)(CO)} \text{^ {i}PrPNP = N[CH}_2\text{CH}_2(P\text{Pr}_2)]}_2\).[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 \((\Delta G^\ddagger_{HT})\) but poisons the catalyst forming an adduct \((\Delta G_{add})\) (Figure 1). In order to improve this reaction, \(\Delta G_{add}\) and \(\Delta G^\ddagger_{HT}\) 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 \(\Delta G_{add}\) and \(\Delta G^\ddagger_{HT}\).

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

References