



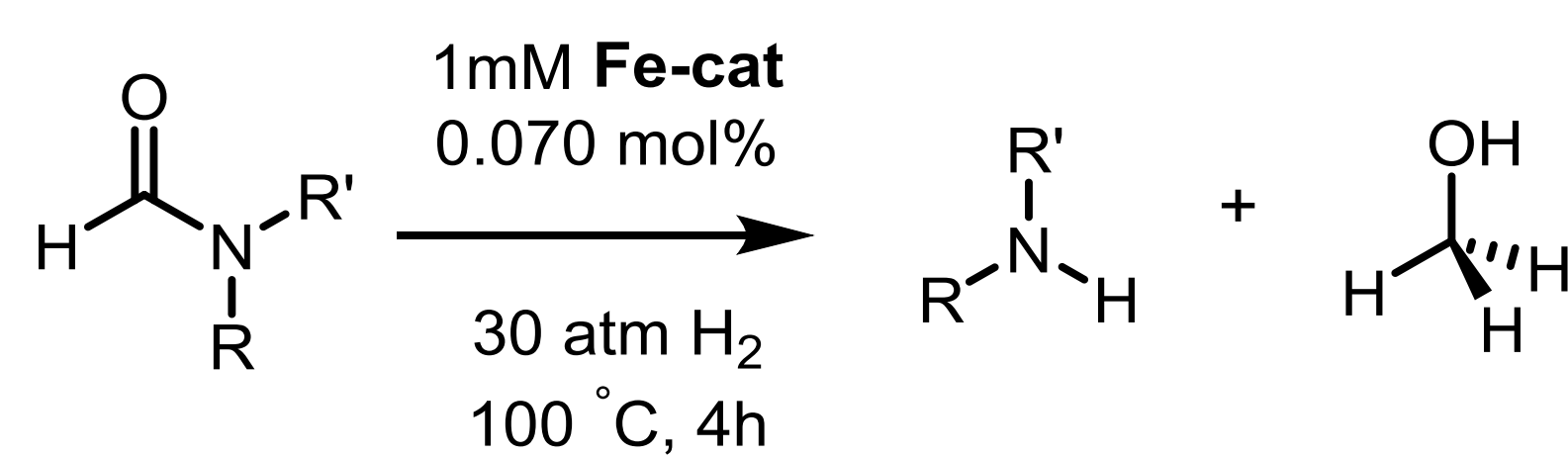
Rational Cocatalyst Design for Amide Hydrogenolysis Based on DFT Calculations

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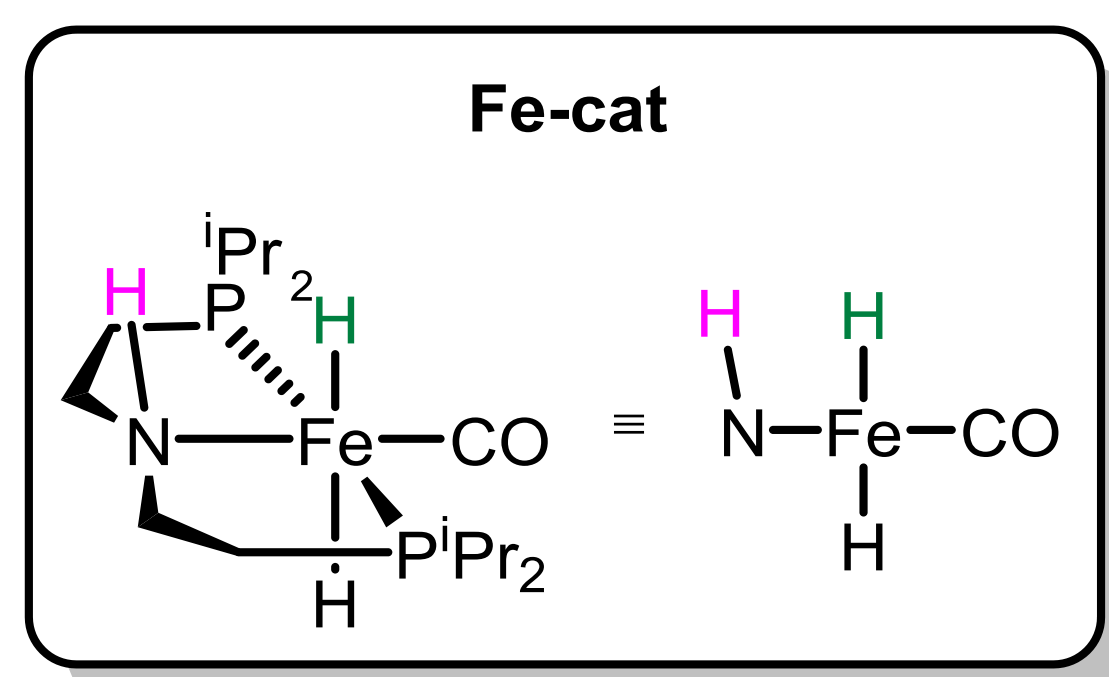


Introduction

Amides functionalities are among the most widely found groups in biologically active molecules, and their selective catalytic reduction is an important target for new synthetic methods. Recently the deaminative hydrogenation of several amides have been achieved in mild conditions with the Fe-catalyst shown in Figure 1.^[1] Interestingly, secondary amides act as cocatalyst in the hydrogenolysis of tertiary amides and their role in the reaction has been investigated by our group.²

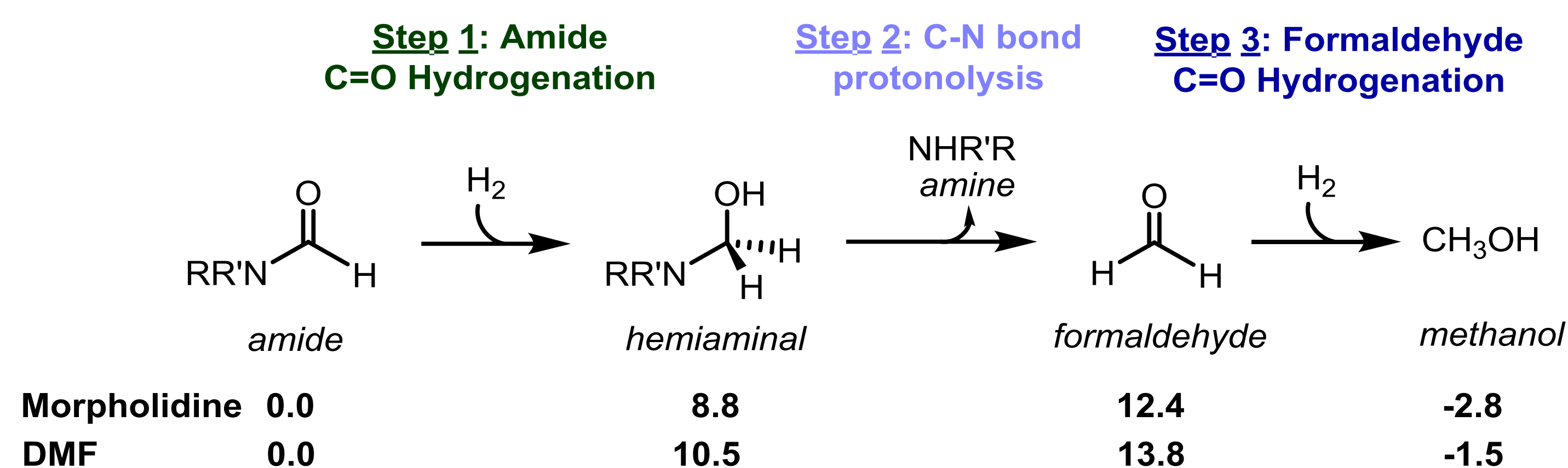


R = H; R' = Ph Conv. = 99.9%
R = R' = Me Conv. = 0 % (13.6%)*



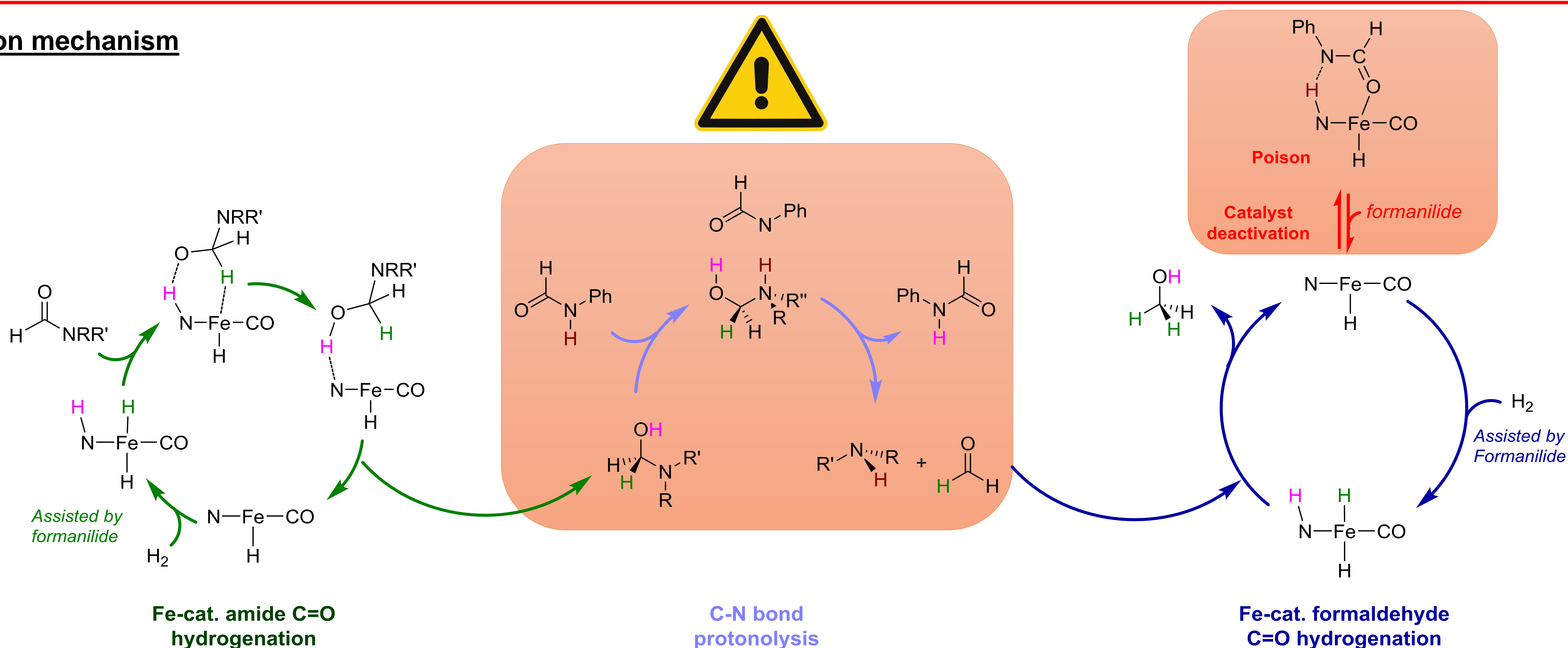
Elementary steps

The amide hydrogenolysis mechanism consists in three steps: amide C=O hydrogenation (catalysed by **Fe-cat**), C-N bond protonolysis (catalysed by a proton shuttle) and formaldehyde C=O hydrogenation (catalysed by **Fe-cat**). The reaction rate is controlled by the C-N bond protonolysis. Organic molecules used as proton shuttles can poison the catalyst and should be chosen wisely.



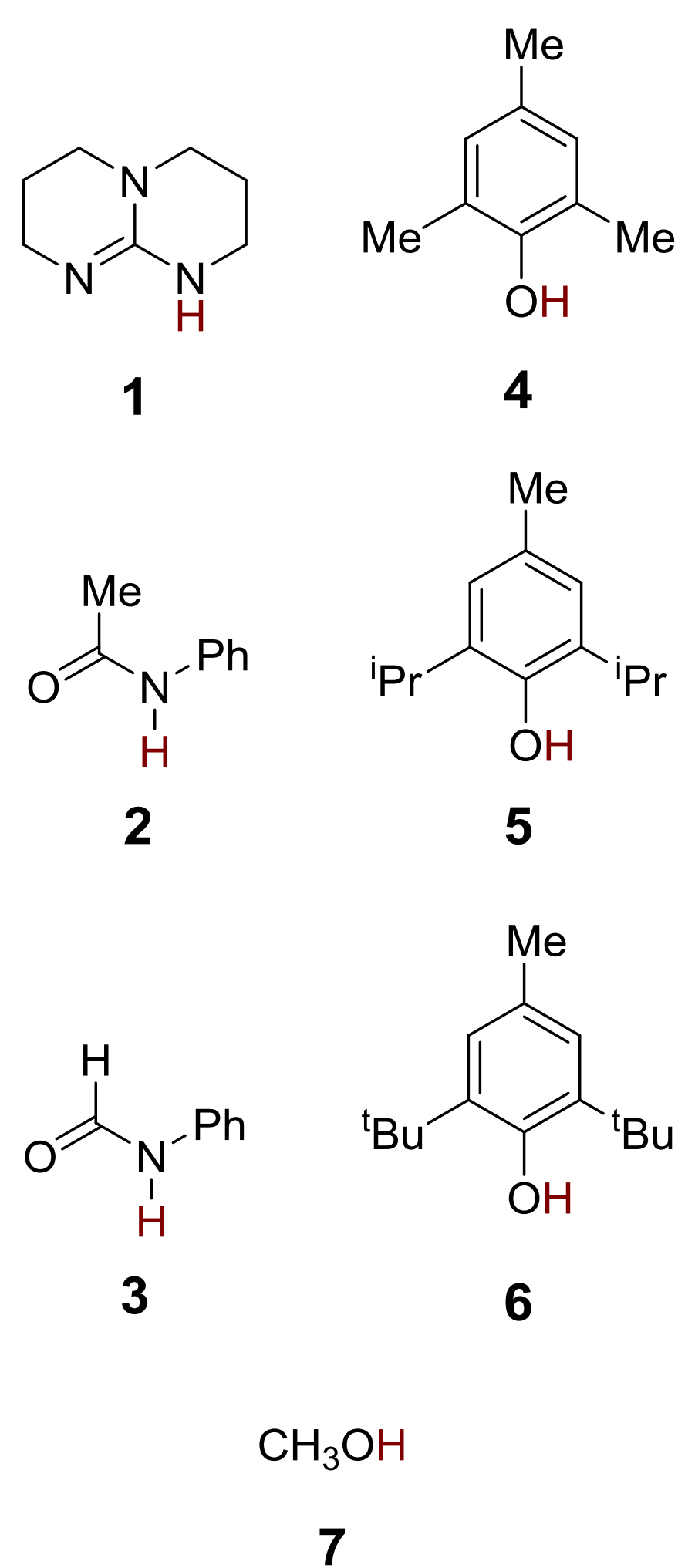
Morpholidine	0.0	8.8	12.4	-2.8
DMF	0.0	10.5	13.8	-1.5

Reaction mechanism



Microkinetic model

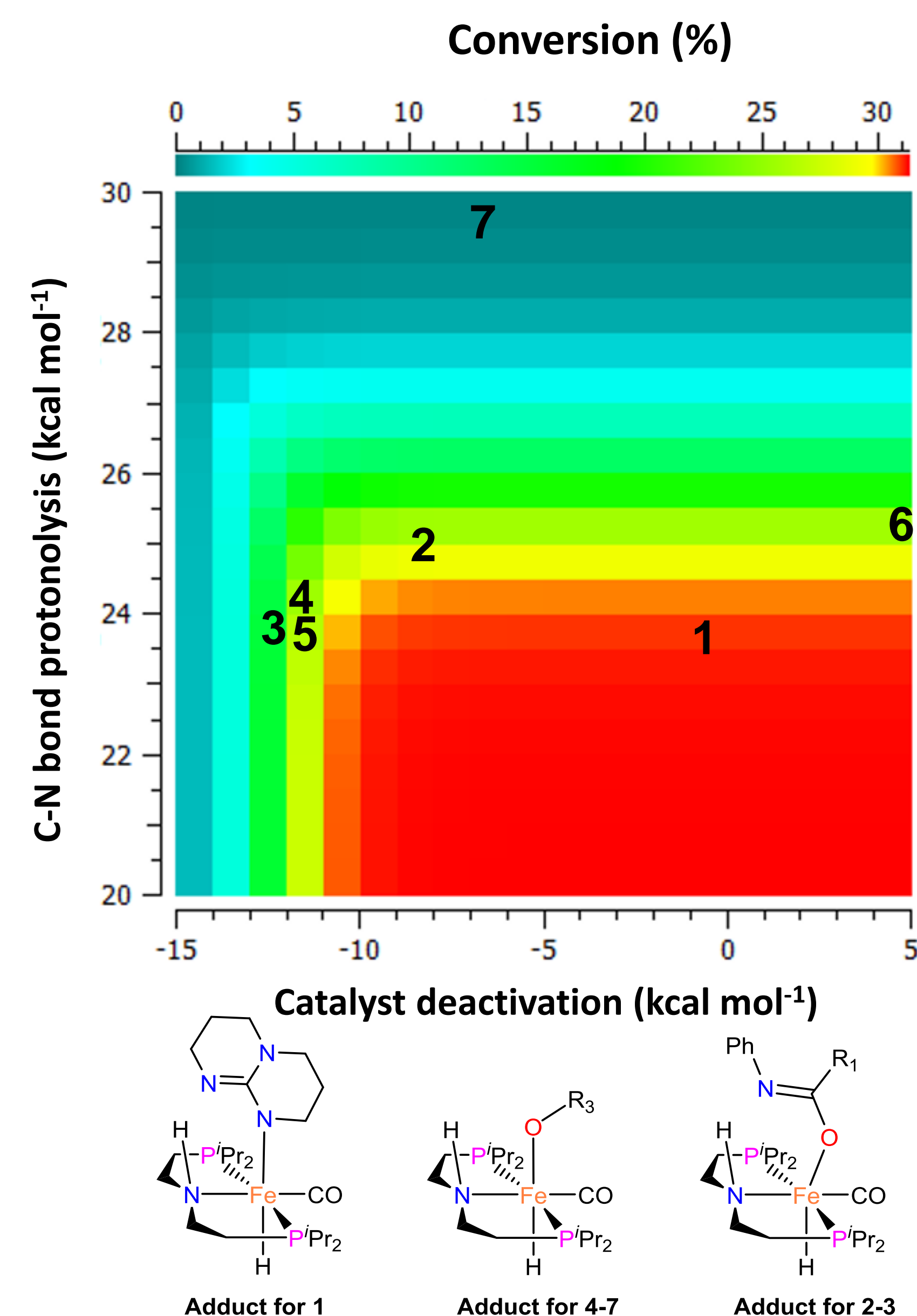
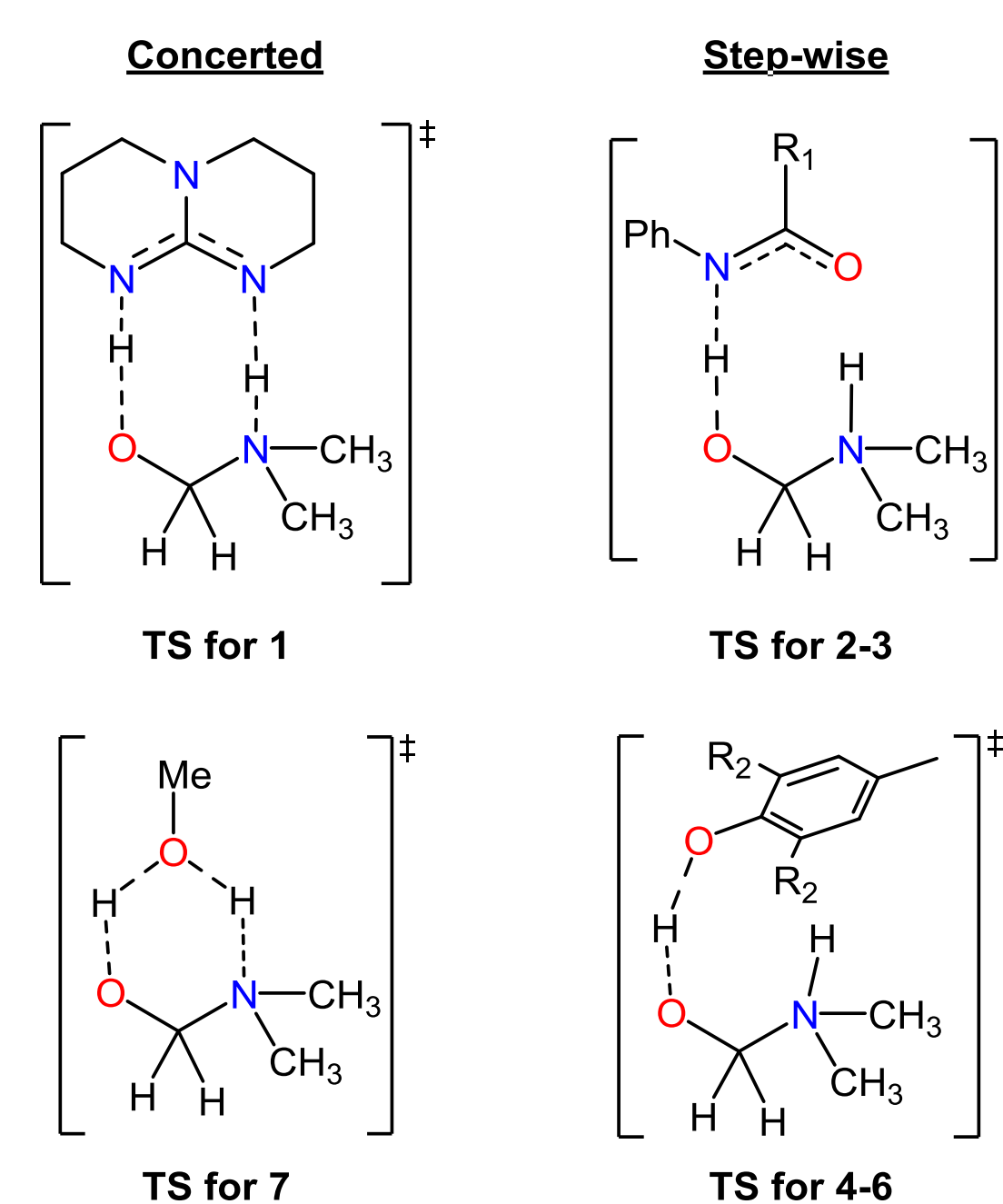
Cocatalysts



We have simulated the conversion of DMF co-catalysed by formanilide by using a microkinetic model build with DFT energies and the experimental initial concentration of reactants, pressure and temperature. Results showed a clear dependence of the conversion on the energy barrier for the C-N bond protonolysis and the catalyst deactivation.

This information was used to predict the conversion of different cocatalyst candidates (1-7), by computing the TS for the C-N bond protonolysis (TS) and catalyst deactivation (Adduct) with these systems, and including these energies in the microkinetic model of the overall DMF hydrogenolysis reaction.³

The best cocatalyst was found to be TBD (1), which does not block the catalyst active site, and has a low energy barriers for C-N bond protonolysis.



Computational details: The hybrid meta-GGA M06 functional was selected on the basis of geometry and energy benchmarks, using X-Ray crystal structures and CCSD(T) energies computed with cc-pVTZ basis set as references. Geometry optimizations were performed with LANL2DZ (for Fe) and 6-31+G** (on all other elements) basis set. Gibbs energies were refined with triple-z basis set analogs. Calculations were performed taking into account the experimental conditions: 30 atm of H₂, 100 °C, and THF solvent (SMD model). The software used were Gaussian09 (for energy calculations) and COPASI (for the microkinetic modelling).

1. U. Jayarathne, Y. Zhang, N. Hazari, W. Bernskoetter. Organometallics 2017, 35, 409
2. L. Artús Suárez, Z. Culakova, D. Balcells, W. H. Bernskoetter, O. Eisenstein, K. I. Goldberg, N. Hazari, M. Tilset, A. Nova. ACS Catal. 2018, 8, 8751

3. L. Artús Suárez, U. Jayarathne, D. Balcells, W. H. Bernskoetter, N. Hazari, M. Jaraiz, A. Nova, submitted