Theoretical Studies of Organocatalytic Cycles

Final Report

1. The aim of the project

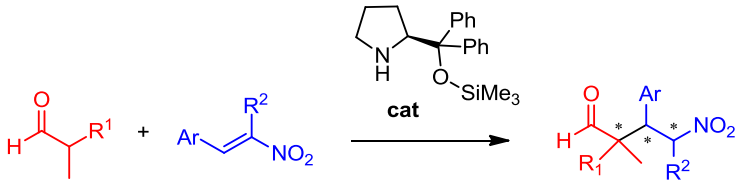
The principal aim of the present project was to gain insight into the mechanistic details of stereoselective organocatalytic transformations of current interest. The ultimate goal of these studies is to identify the rate- and stereoselectivity-determining steps of the catalytic cycles and reveal the origin of stereoselectivity. This knowledge can often be utilized to design and develop new catalysts that provide improved stereoselectivities, or even new type of reactivities. The most successfull strategies along this research line combine experimental and computational methods, and we pursued this approach as well. The majority of our studies were carried out in collaboration with our partners being experts in synthetic and physical organic chemistry. The computational studies described in this report represent our contribution to these joint investigations.

We have defined three major directions in our research program, so the report follows this structure and summarizes the basic achievements. Several additional issues regarding the reactivity and stereoselectivity in organocatalysis were addressed in our collaborations, so some of them are mentioned here as well (section 2.4). The general approach of our theoretical investigations has been decsribed in the research program of the present project, the computational details are provided in the publications referenced for each research topic.

2. Summary of results

2.1. Stereoselectivity of reactions catalyzed by diarylprolinol ethers [1]

Diarylprolinol silyl ether catalyzed Michael additions between aldehydes and nitroalkenes (Scheme 1) have been of particular interest for mechanistic studies. These investigations have revealed interesting new insights, but also have led to conflicting views with regard to the stereochemical control.[1]



Scheme 1: *Michael reactions between aldehydes and nitroolefins catalyzed by a diarylprolinol silyl ethercatalyst.*

The stereocontrol of these reactions was first interpreted via a commonly used simple steric shielding model that emphasizes the role of steric effects in facial differentiation upon the approach of the reacting partners (enamine intermediate and nitroolefin). This model implies that the stereoselectivity is governed by the free energy difference of stereogenic C-C

[1] For reviews highlighting controversial issues, see: (a) Moberg, C. *Angew. Chem., Int. Ed.* **2013**, 52, 2160-2162. (b) Holland, M. C.; Gilmour R. *Angew. Chem., Int. Ed.* **2015**, 54, 3862-3871. (c) Burés, J.; Armstrong, A.; Blackmond, D. G. *Acc. Chem. Res.* **2016**, 49, 214-222.

bond formation transition states (**TS**$_1$ and **TS**$_1$' in Figure 1a). An alternative stereoselectivity model was also introduced, which assumes that the stereoisomeric downstream intermediates (**I** and **I'**) can rapidly interconvert, and the product ratio is actually dictated by the rate-determining step subsequent to C-C bond formation (**TS**$_2$ and **TS**$_2$' in Figure 1b). These two stereoselectivity models are in sharp contrast, therefore, we carried out a detailed computational analysis for C-C bond formation pathways yielding the four stereoisomeric products in the catalytic Michael reaction between propanal and β-nitrostyrene.

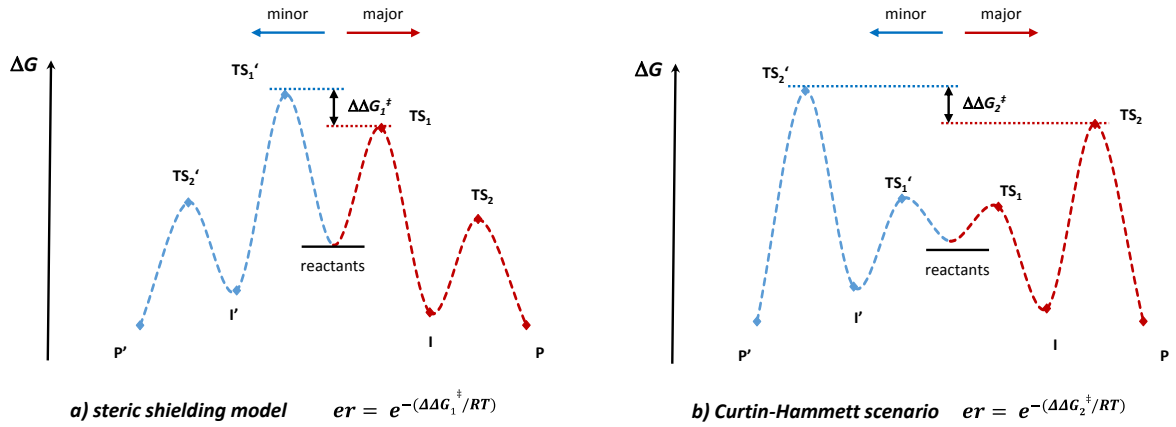


Figure 1: *Stereoselectivity models proposed in the literature as illustrated in terms of qualitative free energy diagrams.* ***TS***$_1$ *and* ***TS***$_2$ *refer to transition states of two key steps of the catalytic cycle (C-C bond formation and protonation). Additional notations:* ***I*** *= OO/CB intermediates,* ***P*** *= product (prime denotes enantiomeric species).*

The free energy profiles computed in our study for the pathways leading to the major enantiomeric products (see Figure 2) indicated that the rate- and stereo-determining steps are not identical as implied by the previous models. We found that the stereoselectivity can be primarily controlled by C-C bond formation even though the reaction rate is dictated by the protonation step.

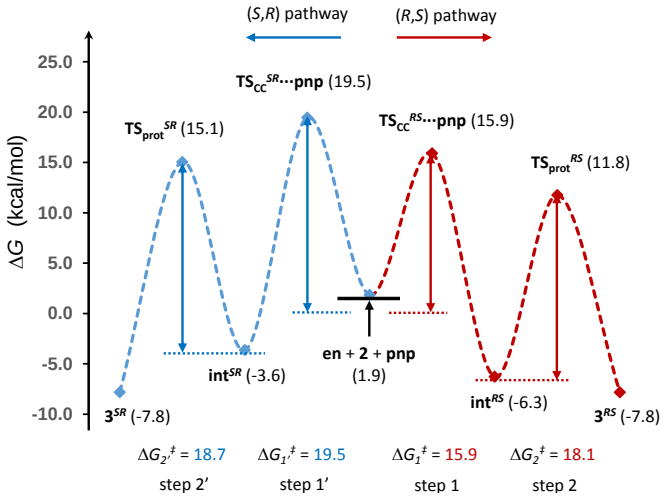
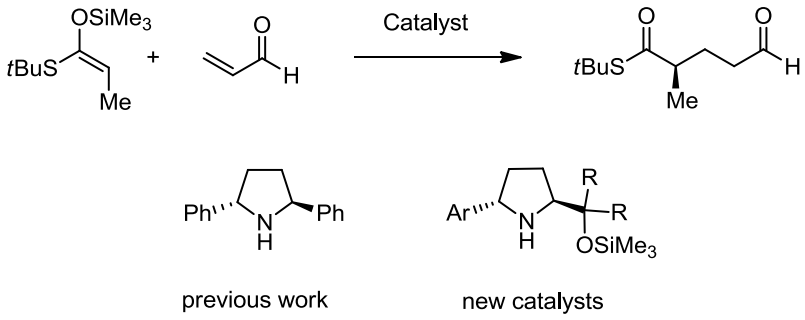


Figure 2: *Free energy profile computed for the (R,S) and (S,R) pathways.*

The kinetic model emerging from the computational results suggested that the enantioselectivity of the retro-Michael process is expected to vary in time along the reaction course and approach the enantioselectivity of the forward reaction. This prediction was actually verified experimentally via mass spectrometric back reaction screening measurements carried out in our institute [1].

2.2. Catalyst design for Mukaiyama-Michael reactions [2]

Following our previous work on stereoselective organocatalytic Mukaiyama-Michael reactions between α,β-unsaturated aldehydes and 5-Me-silyloxyfuran,[2] we envisioned that the applied *trans*-2,5-diphenylpyrrolidine catalyst can promote similar degree of enantio-selectivity in reactions with enolsilane nucleophiles as well (Scheme 2). This catalyst turned out to be less effective, however, 2,5-disubstituted pyrrolidines, particularyly those involving Ar and R substituents with electron donating groups, were found to yield the desired enantioselectivities (95:5).



Scheme 2: *Mukaiyama-Michael reaction between α,β-unsaturated aldehydes and enolsilanes catalyzed by chiral amine catalysts.*

DFT calculations for transition states (TS) of the C–C bond formation between the iminium intermediate and the substrate provided insight into the origin of enantioselectivity (Figure 3). The energy difference between the diastereomeric TS structures leading to the major (*R*) and minor (*S*) product could be related to the combined effect of repulsive steric and attractive noncovalent interactions, which varies for the two competing pathways [2].

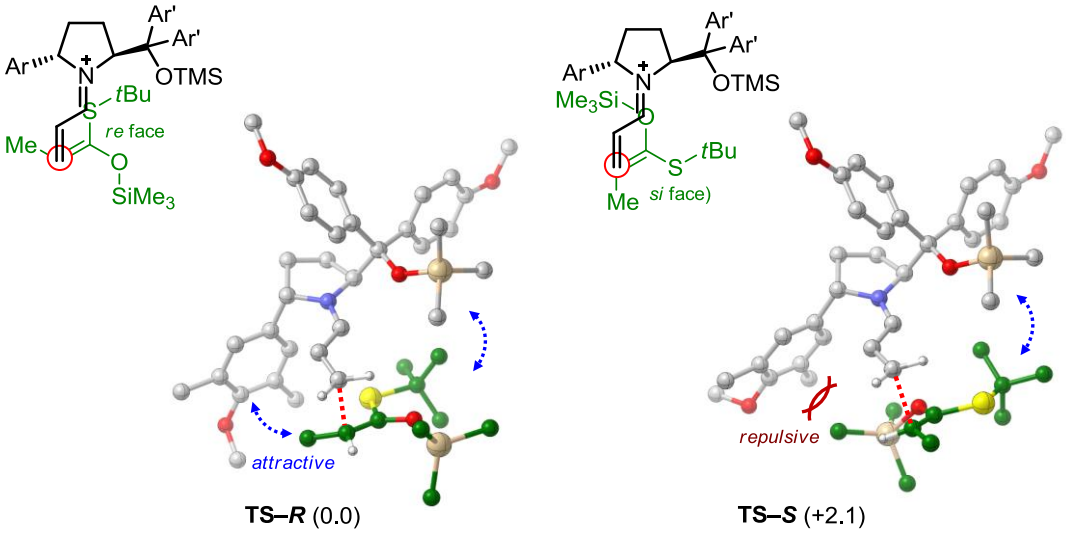
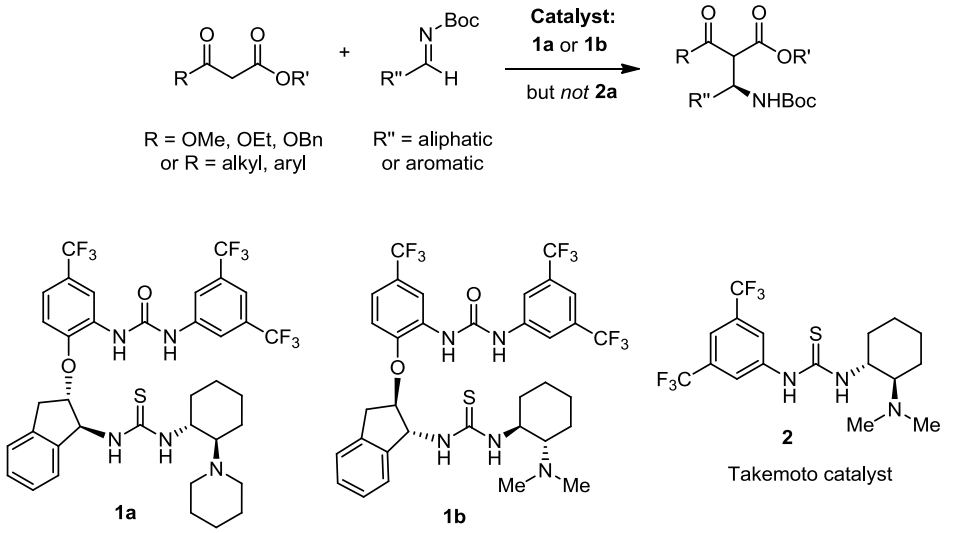


Figure 3: *Diastereomeric transition states computed for the investigated Mukaiyama-Michael reaction. Relative energies, in kcal/mol, are shown in parenthesis.*

[2] Kemppainen, E. K; Sahoo, G.; Piisola, A.; Hamza, A.; Pápai, I.; Pihko, P. M., *Chem. Eur. J.*, **2014**, 20, 5983-5993.

2.3. Transition state stabilization with bifunctional amine catalysts [3-6]

Bifunctional amine catalysts bearing hydrogen-bond donor (HBD) functionalities such as thiourea or squaramide represent one of the most successfully applied organocatalysts. We have previously demonstrated that the catalytic efficiency of these type of catalysts can be further improved by cooperative effects induced via intramolecular H-bonding interactions.[3] These so-called foldamer catalysts were shown to promote highly enantioselective Mannich reactions of malonates and β-keto esters with both aromatic and aliphatic imines (Scheme 3). In contrast, the prototype small molecule bifunctional catalyst, the Takemoto catalyst, is efficient only for aromatic imines.



Scheme 3: *Bifunctional amine-HBD catalysts and their contrasting reactivity for Mannich reactions.*

Our computational analysis suggests that the improved catalytic performance of foldamer catalysts in Mannich reactions with aliphatic imines cannot be explained solely by the cooperative effects of intramolecular H-bonding interactions between urea and thiourea, because computations revealed enhanced binding of the aliphatic substrates by dispersion interactions, which are largely absent with a simpler catalyst (green regions in Figure 4) [3].

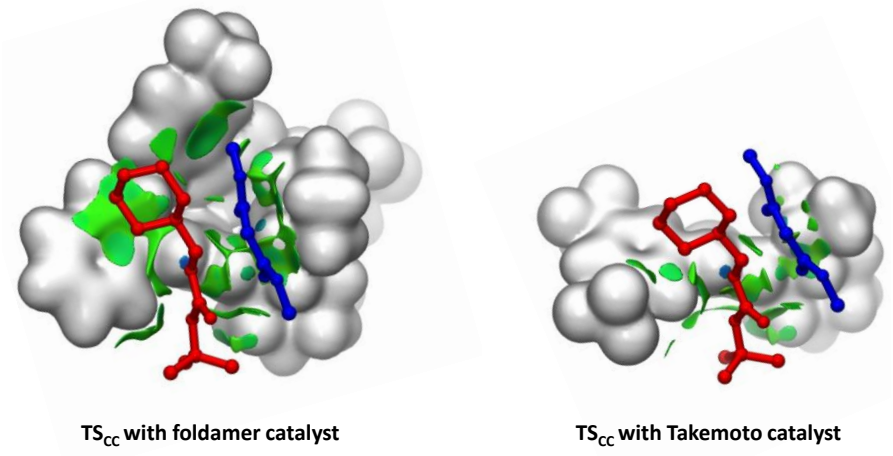
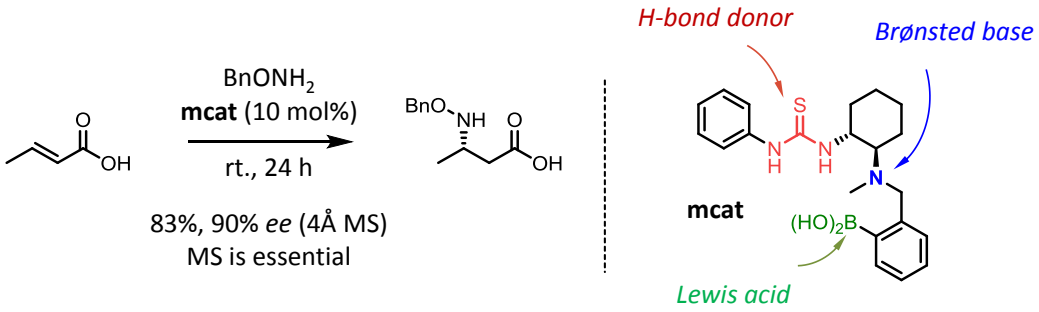


Figure 4: *Noncovalent contacts in C–C bond formation transition states for catalysts* ***1a*** *and* **2**.

[3] Probst, N.; Madarász, Á.; Valkonen, A.; Pápai, I.; Rissanen, K.; Neuvonen, A.; Pihko, P. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 8495–8499.

The folding patterns of these foldamer-type catalysts have recently been characterized in solution and solid states. Related DFT calculations have greatly assisted the analysis of NMR spectra. We found that the foldamer catalysts do not uniformly adopt the *anti-anti* conformation of the thiourea unit desired for efficient catalysis, but the less-reactive *syn-anti* thiourea conformers are also present in solution [4].

The implementation of boronic acid moieties into the bifunctional amine-HBD framework represents another successful strategy in catalyst design for challenging reactions. This multifunctional approach has been implemented by the Takemoto group to achieve aza-Michael additions to α,β-unsaturated carboxylic acids (Scheme 4) [5].



Scheme 4: *Aza-Michael reaction between crotonic acid and O-benzylhydroxylamine catalyzed by a multifunctional organocatalyst.*

Our DFT calculations revealed that the C-N addition and the proton transfer processes in this reaction take place via a concerted asynchronous mechanism (transition states in Figure 5). N-H...O type H-bonding interactions between the substrate amine and the catalyst could be identified as a key factor in the induction of enantioselectivity. Transition state stabilization can occur only on the pathway resulting in the major product [5].

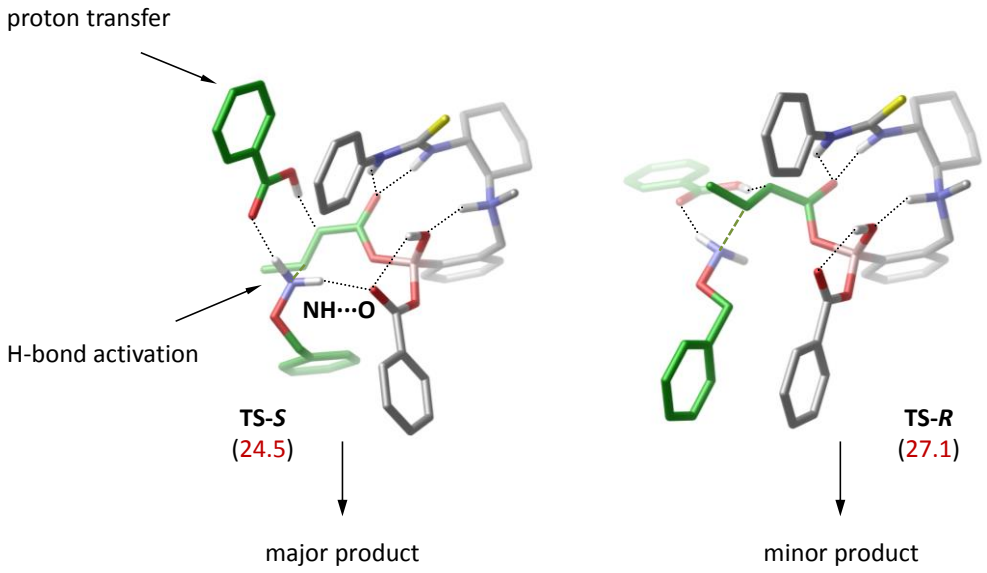
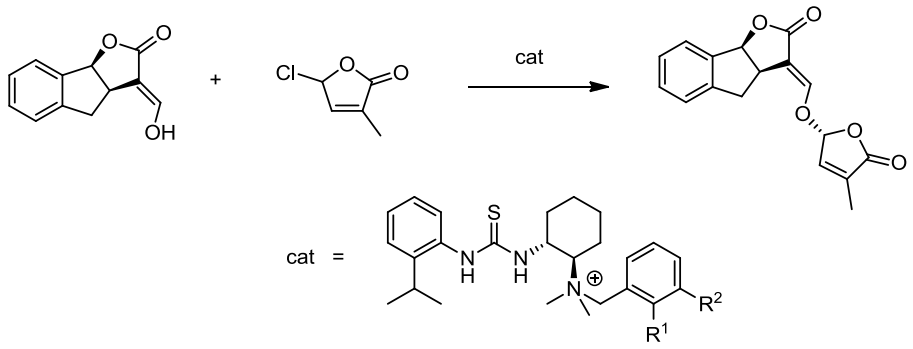


Figure 5: *Acid-assisted C-N bond formation transition states leading to (S) and (R) product enantiomers in the investigated aza-Michael reaction. Relative stabilities are given in kcal/mol with respect ground state reactants.*

The collaboration with the Takemoto group has recently been extended to other reactions, for instance, to stereoselective enol etheration of racemic butenolides as well. These reactions are found to be catalyzed by a cationic thiourea-amonium catalyst (Scheme 5).



Scheme 5: *Stereoselective enol etheration of racemic γ-chlorobutenolide.*

Related DFT calculations reproduce the observed stereoselectivity, and they point to the importance of electrostatic stabilization as a main source of selective transition state stabilization (Figure 6). The publication of these results is in progress [6].

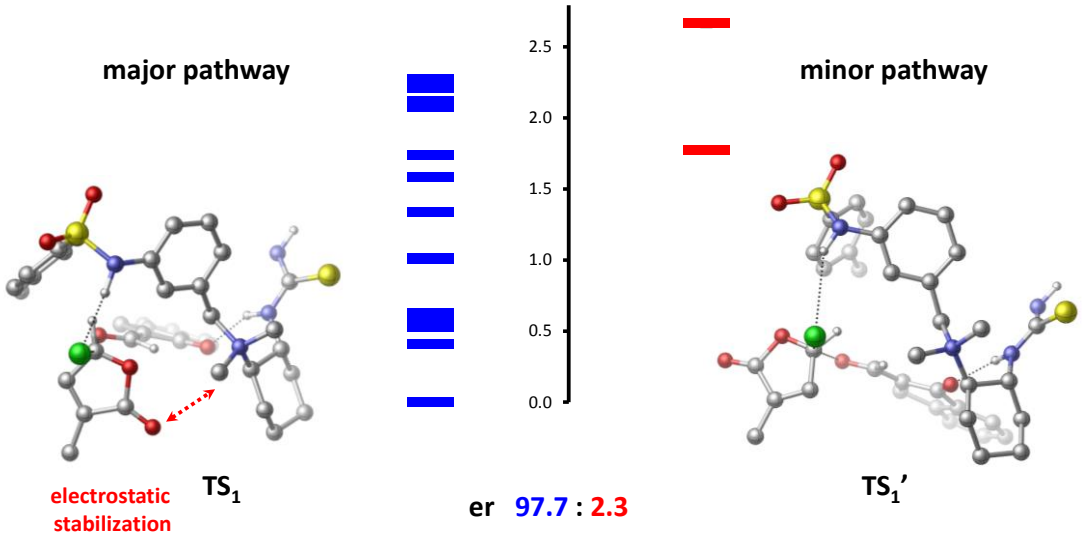
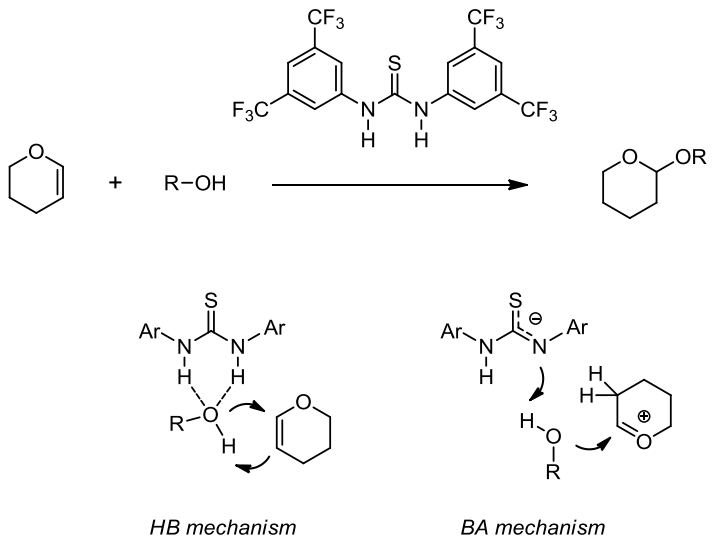


Figure 6: *Set of transition states identified along the major and minor nucleophilic substitution pathways in the organocatalytic etheration reaction.*

2.4. Additional reactivity and stereoselectivity studies [7-9]

The symmetric thiourea compound *N*,*N*'-bis[3,5-bis(CF_3)phenyl]thiourea introduced by Schreiner is considered as a prototype for H-bond-assisted organocatalysis. The results of our combined computational-experimental mechanistic studies carried for catalytic tetrahydropyranylation of alcohols (Scheme 6) challenge the common mechanistic view that the catalytic effect is related to stabilizing double hydrogen-bonding interactions between the thiourea and the alcohol (HB mechanism). Computations indicate that thiourea can acts as a Brønsted acid, protonating DHP to form an oxacarbenium ion, which then reacts with the

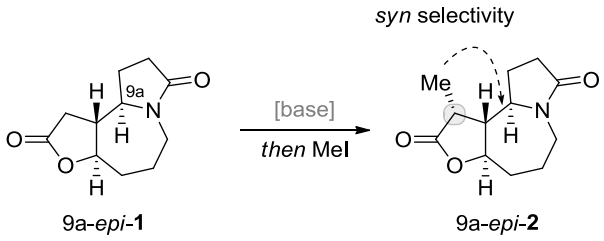
alcohol (BA mechanism). We find clear preference of transition states associated with the BA mechanism [7].



Scheme 6: *Catalytic tetrahydropyranylation of alcohols and two mechanistic alternatives*

The proposed BA mechanism predicts similar catalytic activity for *N*-methylated thiourea and thiouracil, which was confirmed experimentally [7]. These results have practical implications since different strategy is needed for synthetic developments utilizing hydrogen-bond or Brønsted-acid catalysis.

In a recent stereodivergent total synthesis approach used in the Pihko group, a quite unexpected *syn* selectivity was observed for the methylation of 9a-*epi*-norstemoamide (9a-*epi*-**1**) (Scheme 7).



Scheme 7: *Counterintuitive syn selectivity observed for methylation of 9a-epi-norstemoamide.*

Computations predict the *syn* attack of MeI to be clearly favoured, and the structural analysis suggests that the *syn* facial selectivity of methylation could be associated with the nonplanar structure of the ground state enolate (Figure 7). Additional computational analysis carried out for a series of *trans*-fused bicyclic butyrolactones demonstrates that the observed selectivity arises from the strained 5-membered cyclic enolate structure resulting in a nonplanar conformation, which is locked via the ring fusion. This simple qualitative model can account for all related synthetic examples reported in the literature.

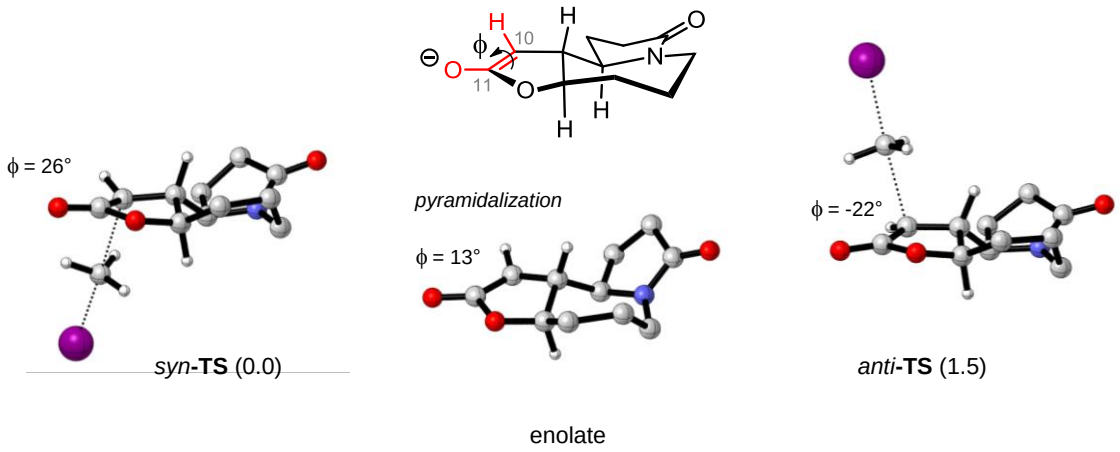


Figure 7: *Transition states computed for the methylation of enolates derived from 9a-epi-**1**. The deviation from the planar structure of the enolates (pyramidalization of the carbon atom) is measured via the $O_{11}C_{11}C_{10}H_{10}$ dihedral angle (denoted as ϕ). Relative Gibbs free energies are given in kcal/mol (in parenthesis)*

Two manuscripts are being finalized on this subject [8,9], and we intend to submit them to Organic Letters as back-to-back papers.

Publication following the order of citations

[1] T. Földes, Á. Madarász, Á. Révész, Z. Dobi, Sz. Varga, A. Hamza, P. R. Nagy, P. M. Pihko and I. Pápai: *Stereocontrol in Diphenylprolinol Silyl Ether Catalyzed Michael Additions: Steric Shielding or Curtin-Hammett Scenario?*, **J. Am. Chem. Soc.**, 139, 17052 (2017).

[2] A. Claraz, G. Sahoo, D. Berta, Á. Madarász, I. Pápai and P. M. Pihko: *A catalyst designed for the enantioselective construction of methyl- and alkyl-substituted tertiary stereocentres*, **Angew. Chem. Int. Ed.**, 55, 669, (2016).

[3] A. J. Neuvonen, T. Földes, Á. Madarász, I. Pápai and P. M. Pihko: *Organocatalysts Fold To Generate an Active Site Pocket for the Mannich Reaction*, **ACS Catal.** 7, 3284, (2017).

[4] A. J. Neuvonen, D. Noutsias, F. Topić, K. Rissanen, T. Földes, I. Pápai and P. M. Pihko: *Dynamic Refolding of Ion-Pair Catalysts in Response to Different Anions*, **J. Org. Chem.**, Just Accepted (2019).

[5] N, Hayama, R, Kuramoto, T, Földes, K, Nishibayashi, Y, Kobayashi, I, Pápai and Y, Takemoto: *Mechanistic Insight into Asymmetric Hetero-Michael Addition of α,β-Unsaturated Carboxylic Acids Catalyzed by Multifunctional Thioureas*, **J. Am. Chem. Soc.**, 140, 12216, (2018).

[6] M. Yasui, C. Tsukano, A. Yamada, A. Hamza, I. Pápai, and Y. Takemoto: *Stereoselective enol etheration of racemic butenolide for synthesis of strigolactones*, manuscript in preparation.

[7] Á. Madarász, Z. Dósa, S. Varga, T. Soós and I. Pápai: *Thiourea Derivatives as Bronsted Acid Organocatalysts*, **ACS Catal.** 6, 4379 (2016).

[8] J. H. Siitonen, D. Csókás, I. Pápai and P. M. Pihko: *Stereodivergent Total Synthesis of Stemoamide, 9a-epi-Stemoamide and 9a,10-epi-Stemoamide*, to be submitted (**Org. Lett.**).

[9] D. Csókás, J. H. Siitonen, P. M. Pihko and I. Pápai: *Conformational Locking Explains the Counterintuitive Methylation Stereochemistry of trans-Fused Bicyclic Lactones*, to be submitted (**Org. Lett.**).