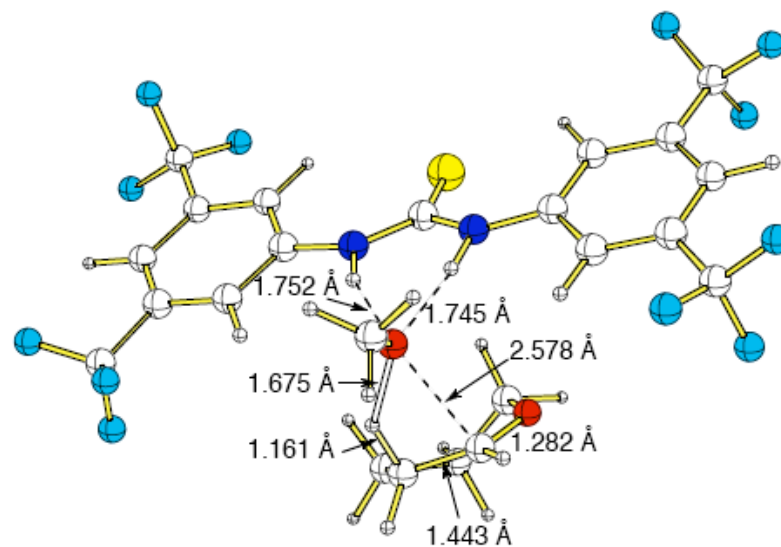


Organocatalytic Tetrahydropyranylation

December 1st., 2006

MIKE KOTKE

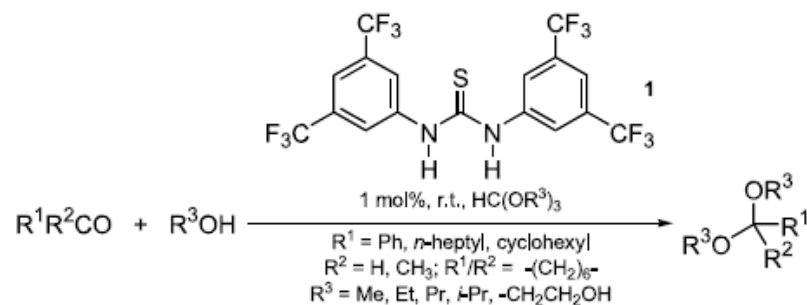
Institut für Organische Chemie, Justus-Liebig-Universität Gießen



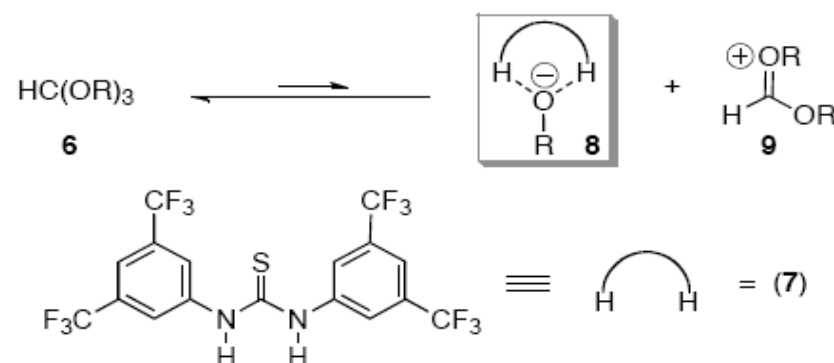
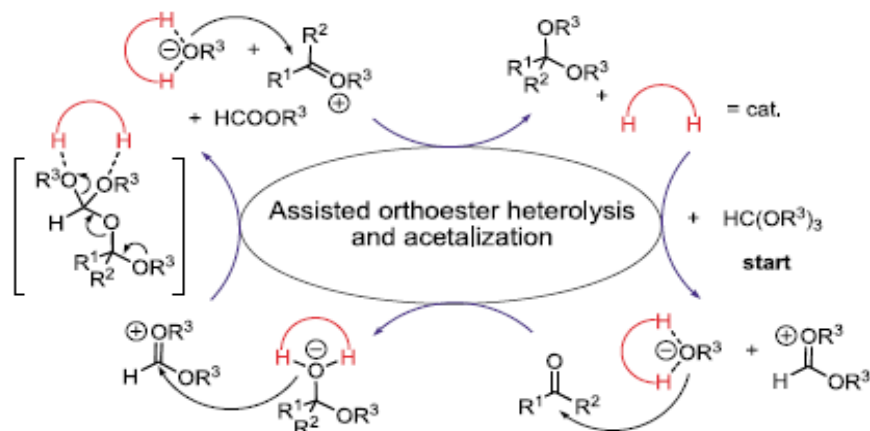
Organocatalysis



Organocatalytic acetalization

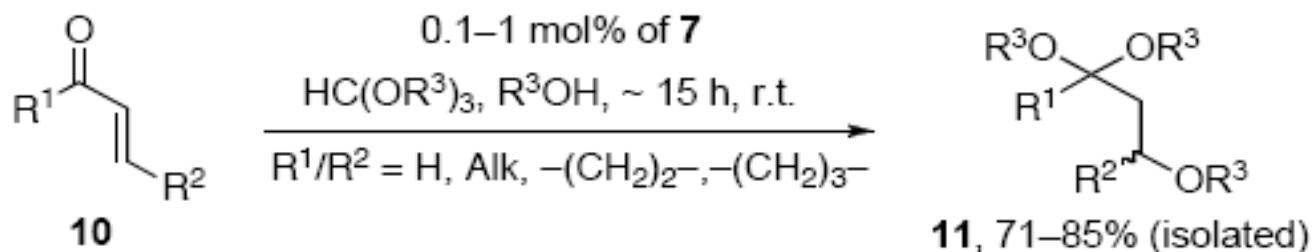


- acid-free protocol
- high-yielding (up to 98%)
- practical reaction times (10-20 h)
- easy work-up
- low catalyst loading (1 – 0,001 mol%)
- TON 632 h⁻¹ (octanal; *p*-chlorobenzaldehyde)





Acetalization of α,β -unsaturated Enals and Enones



Domino Michael addition of alcohols to unsaturated carbonyl compounds followed by acetalization forms 1,1,3-trialkoxo compounds

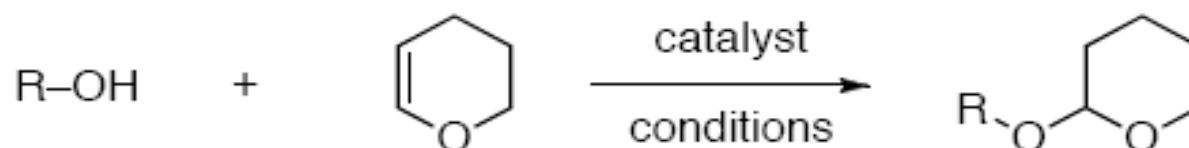
Our hydrogen-bonding thiourea catalyst assists the generation of the free nucleophile (anion stabilization e.g., RO^-)

or

stabilizes the active form of the nucleophile (e.g., a complex).



THP-ether are **mixed acetals** catalytically formed by the reaction of an enol ether with an alcohol.



Working hypothesis:

Alcohols could be used directly since the reactivity is increased organocatalytically through hydrogen-bonding.

Tetrahydropyranylation could be organocatalytically performed utilizing our acetalizing protocol.

Tetrahydropyranylation - known procedures



Previous “acid free” methods with:

- 2.5 mol% $\text{BnP}^+\text{Ph}_3\text{Br}_3^-$ or $\text{Bu}_4\text{N}^+\text{Br}_3^-$ – HBr generated *in situ*, yields 75–97%
Hajibour, A. R.; Pourmousavi, S. A.; Ruoho, A. E. *Synth. Commun.* **2005**, 35, 2889–2804
Naik, S.; Gopinath, R.; Patel, B. K. *Tetrahedron Lett.* **2001**, 42, 7679–7681
- 27 mol% $\text{VO}(\text{OAc})_2$ – yields 75–97%
Choudary, B. M. Neeraja, V.; Kantam, M. L. *J. Mol. Cat. A* **2001**, 175, 169–172
- 500 mol% LiClO_4 or 3 mol% $\text{Fe}(\text{ClO}_4)_3$ – poor yields for tertiary substrates
Babu, B. S.; Balasubramanian, K. K. *Tetrahedron Lett.* **1998**, 39, 9287–9288
Heravi, M. M.; Behbahani, F. K.; Oskooie, H. A.; Shoar, R. H. *Tetrahedron Lett.* **2005**, 46, 2543–2545
- 5 mol% $\text{Bi}(\text{NO}_3)_3 \cdot 5 \text{H}_2\text{O}$ – yields 73–92%
Khan, A. T.; Gosh, S.; Choudhury, L. H. *Eur. J. Org. Chem.* **2005**, 4891–4896

There is no catalyst /no method that would be applicable to entire spectrum of alcohols.

Organocatalytic method - development



Our goal: Development of an method that is applicable to acid-labile, tertiary, sterically hindered, aliphatic, and phenolic hydroxyl substrates.

First application of our protocol for organocatalytic acetalization: excess alcohol (2.2 eq), r.t. and

2 mmol scales for standard reactions:

Catalytic effect was detected, but not satisfying. Best results with:

2 eq. 3,4-dihydro-2H-pyran (DHP), solvent as well as reagent, r.t. (or 50 °C), 5 mmol standard scale

1 mol% organocatalyst, mixture stirred in an flask, GC-MS control

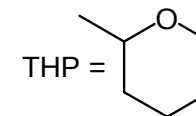


Arrangement for systematic test experiments (~280 performed) at r.t. and 50 °C,

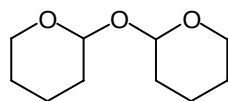
Homogeneous organocatalysis - Tetrahydropyranylation



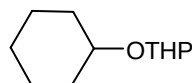
THP-protection of simple *primary* and *secondary hydroxyl substrates*:



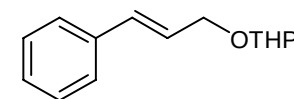
Reactions run at **room temperature**: time (h), preparative yield (%), and catalyst loading are given



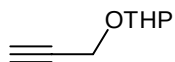
19 / 94 / (1 mol%)



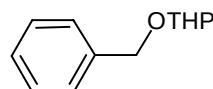
28.5 / 98



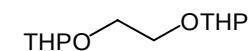
16 / 96 / (1 mol%)



15 / 98 / (1 mol%)



9 / 98 / (1 mol%)
9.5 / 98 (0.1 mol%)
10 / 98 (0.01 mol%)
48 / 98 (0.001 mol%)



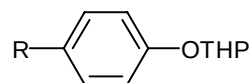
18 / 89 / (1 mol%)

Homogeneous organocatalysis - Tetrahydropyranylation



THP-protection of sterically hindered and phenolic substrates:

Reactions run at **50 °C**: time (h), preparative yield (%), and catalyst loading are given



R = H

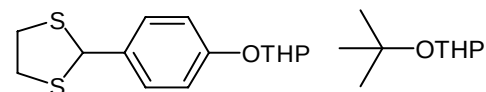
10 / 97 (1 mol%)
10 / 97 (0.1 mol%)
11 / 97 (0.01 mol%)
17 / 97 (0.001 mol%)

R = CH₃

10 / 95 / (1 mol%)

R = CF₃

45 / 86 / (1mol%)



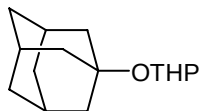
61 / 84 / (1 mol%)

19 / 98 / (1 mol%)

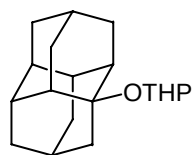
19 / 98 / (0.1 mol%)

26 / 98 / (0.01 mol%)

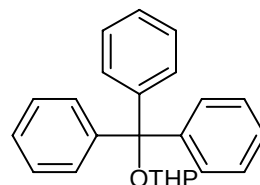
41 / 98 / (0.001 mol%)



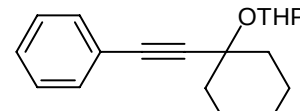
18.5 / 97



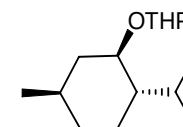
118 / 83



105 / 84



18 / 98 / (1 mol)

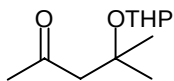


46 / 89 / (1 mol%)

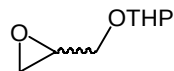
Homogeneous organocatalysis - Tetrahydropyranylation



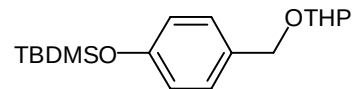
THP-protection of acid-sensitive substrates:



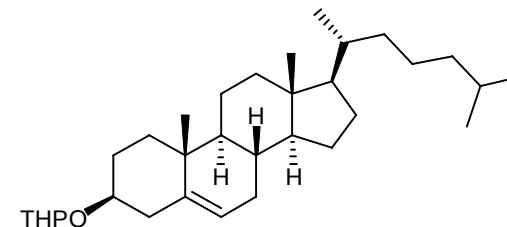
18 / 98 / (1 mol%)
34 / 98 / (0.1 mol%)
35 / 98 / (0.01 mol%)
49 / 98 / (0.001 mol%)



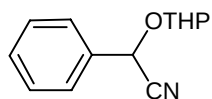
8 / 93 / (1 mol%)



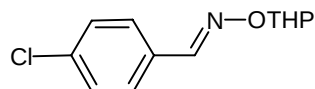
16 / 96 / (1 mol%)



under investigation;
reaction indicated, at 50 °C

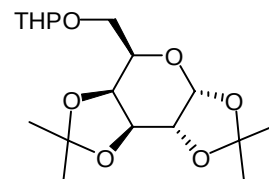


36 / 89 / (1 mol%)

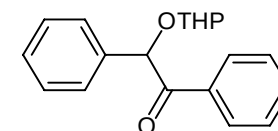


39.5 / 68 / (1 mol%)

at 50 °C



14 / 91 / (1 mol%)



26 / 59 / (1 mol%)

at 50 °C



Protection with alternative enol ether: **2-Methoxypropen (MOP)**
serves as reagent as well as solvent

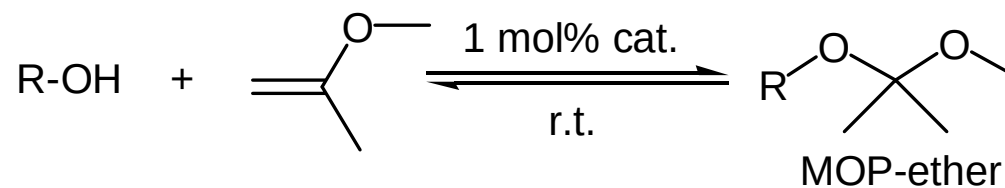
Advantages

- no generation of stereogenic center, no diastereomers (easier interpretation of NMR spectra);
- low boiling point (34 – 36 °C); DHP (86 °C); easy removal of MOP;
- hydrolysis of MOP-ethers furnishes acetone and methanol, easy removal.

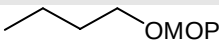
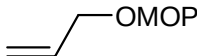
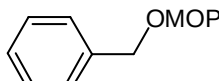
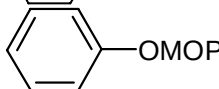
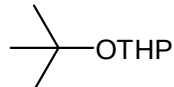
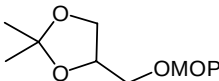
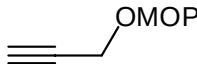
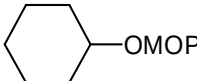
Disadvantages

- tends to polymerization, storage at 5 °C;
 - highly inflammable;
 - MOP-ethers can be hydrolyzed easily;
 - due to low boiling point and the formation of side product reactions should run at max. 25 °C
-

Homogeneous organocatalysis - Methoxypropylation



Results of our MOP test reactions at r.t.:

Product	<i>t</i> / h	Yield / %
	28 (48)	95
	25 (42)	96
	15 (49)	94
	22 (54)	95
	29 (51)	94
	42 (67)	92
	20 (41)	95
	34 (53)	97



Improvement of practicability through application of heterogeneous catalysis

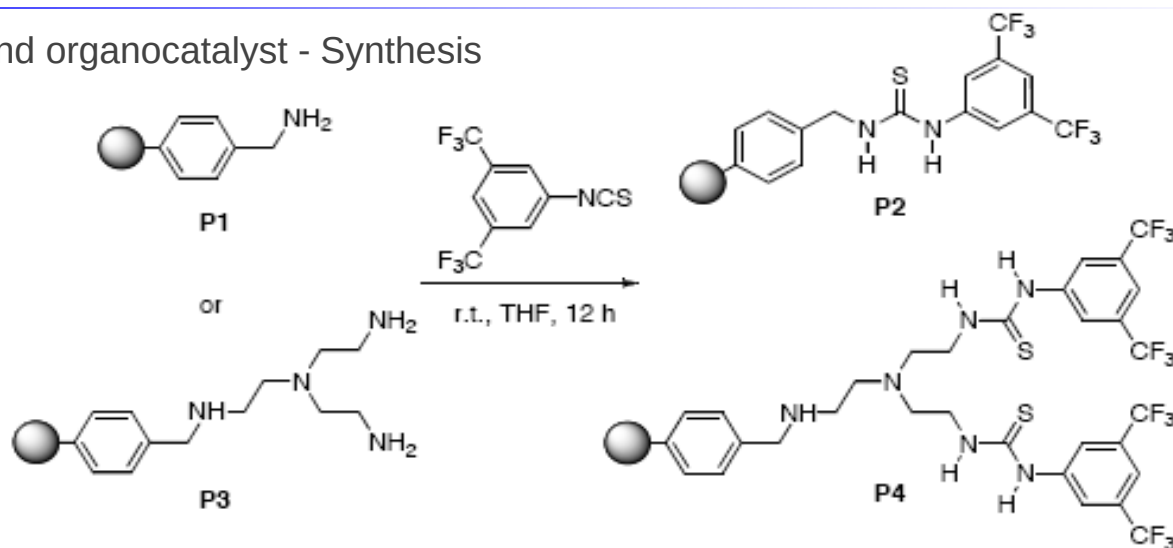
Heterogeneous catalysts are

- easily to handle
 - easily to separate (e.g., simple filtration) from product
 - recoverable, recycable, and reusable
 - often less effective and larger quantities are necessary
-

Heterogeneous organocatalysis - tetrahydropyranylation



Polystyrene-bound organocatalyst - Synthesis



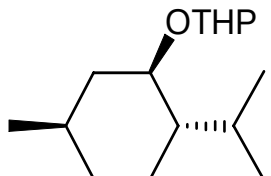
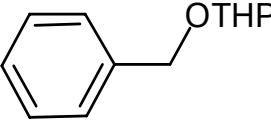
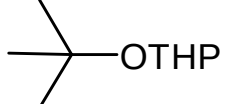
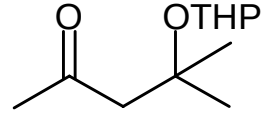
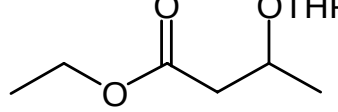
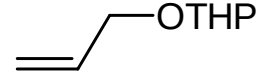
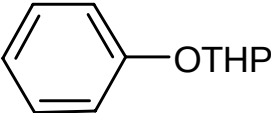
Amino-functionalized polystyrene **P1**: pale, amorphous, lumped (left);
polystyrene-bound catalyst **P2**: yellowish, crystalline, free flowing particles (right)



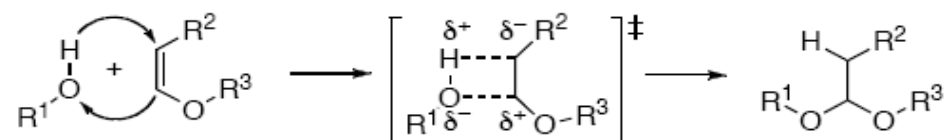
- To the best of our knowledge our polystyrene-bound thiourea **P2** catalyst is the first organocatalyst utilized for heterogeneous catalysis.
 - **P2** reveals all typical advantageous of heterogeneous catalysis.
 - **P2** (loading 4 mmol/g) was utilized in 2 mmol scale experiments, 50 mg (~ 10 mol%) were weighted directly into reaction flask;
 - longer reaction times, but easy recovery by filtration and subsequent washing with dry DCM, reusability checked in 4 catalytic cycles without loss of activity.
-



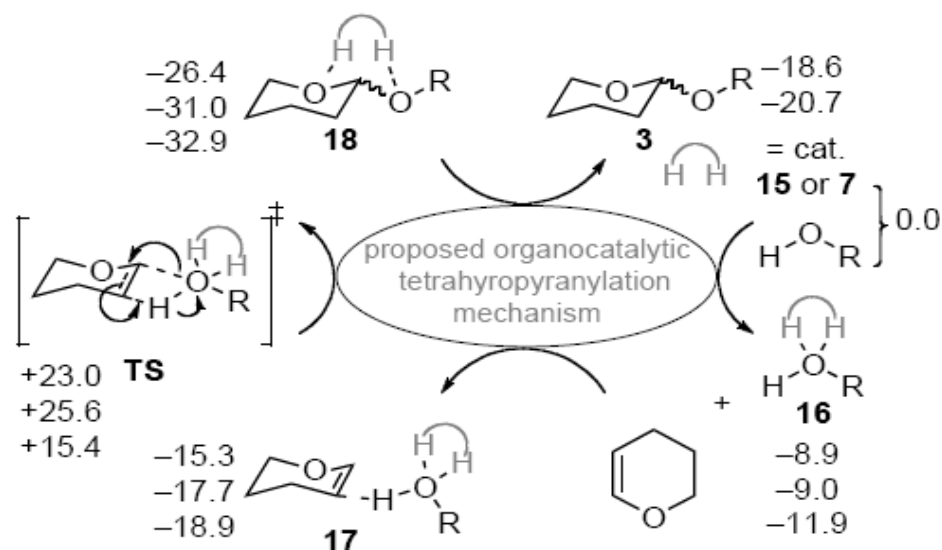
Results of our test reactions utilizing **P2** at 50 °C:

Product	<i>t</i> / h	Yield / %
	53	92
	21	97
	29	98
	36	95
	38	95
	21	97
	25	96

Approach to potential mechanism



Scheme 5 Generalized mechanism for the uncatalyzed formally forbidden [2+2] cycloaddition of an alcohol to an enol ether, and importance of strong polarization in the transition structure.



Scheme 6 Proposed thiourea-catalyzed tetrahydropyranylation cycle. First entry: ΔH_0 at B3LYP/6-31G(d,p) for MeOH and thiourea as models; second entry: ΔH_0 at CCSD(T)/cc-pVDZ//B3LYP/6-31G(d,p) + ZPVE for MeOH and thiourea (15) as models; third entry: ΔH_0 at B3LYP/6-31G(d,p) for MeOH and our thiourea catalyst 7 (all entries in kcal mol⁻¹).

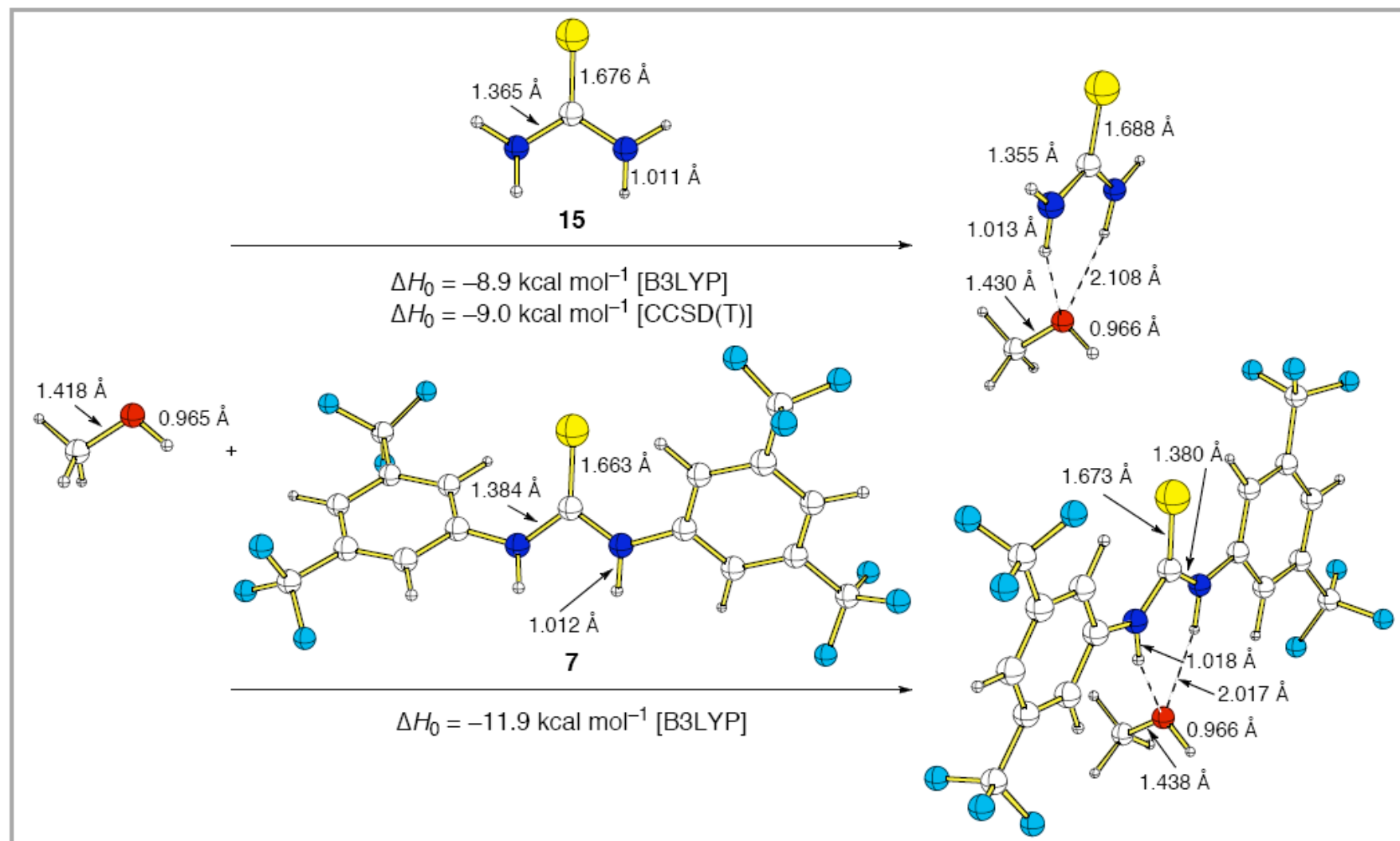


Figure 1 Computed structures (at B3LYP/6-31G(d,p) and CCSD(T)/-cc-pVDZ + ZPVE(B3LYP/6-31G(d,p)) and dissociation energies of the complexes of methanol as a model alcohol with thiourea and 7.

Computations

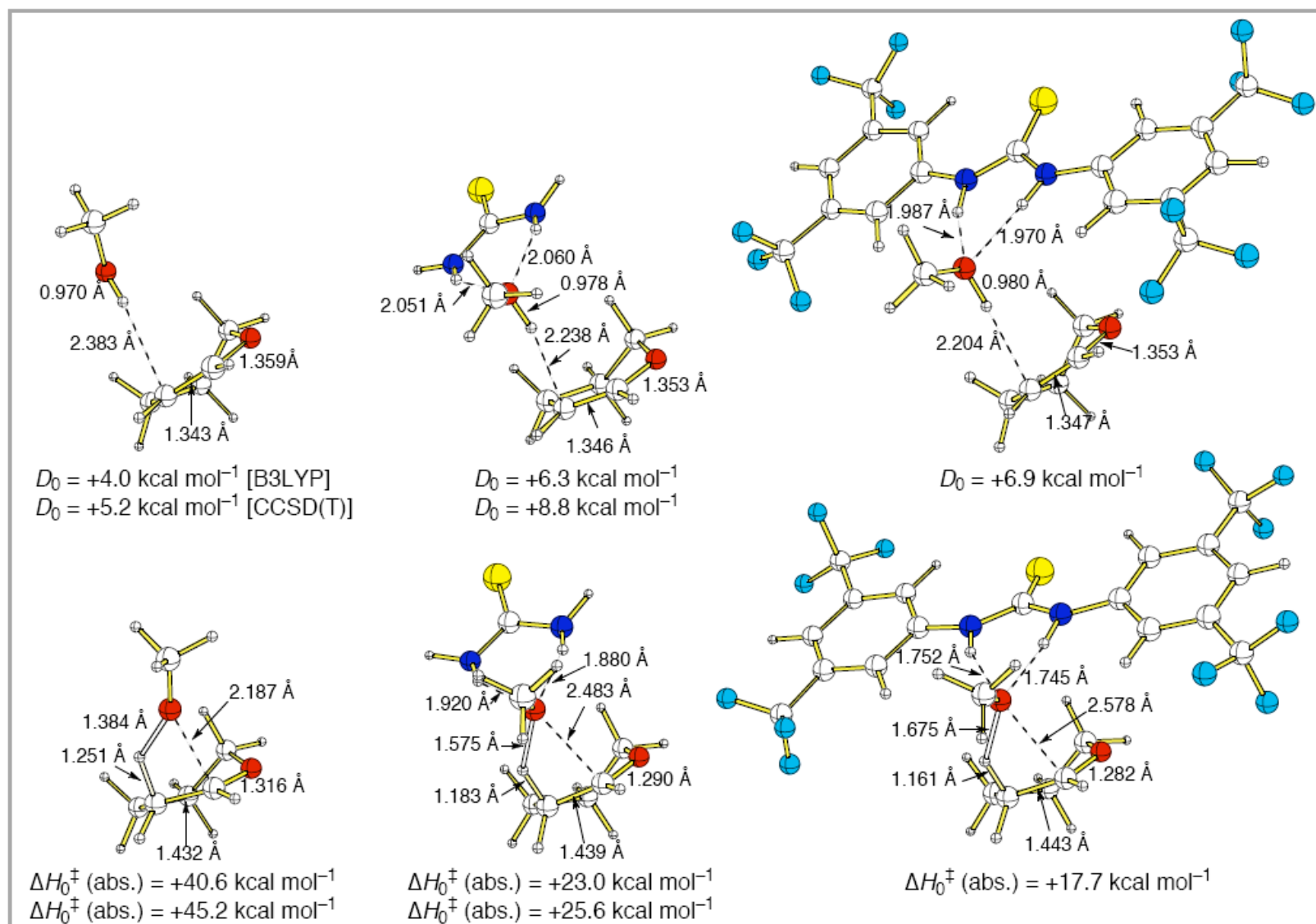


Figure 2 Optimized complexes (top) between methanol and DHP without and with thiourea (**15**) as well as catalyst **7**; transition structures (bottom) for the addition of methanol to DHP without and with thiourea as well as with **7** as catalyst. Level of theory for optimization: first entry = B3LYP/6-31G(d,p), energy evaluations: second entry = CCSD(T)/cc-pVDZ, including ZPVE corrections at B3LYP/6-31G(d,p).



- We developed a protocol for organocatalytic tetrahydropyranylation and methoxypropylation.
- Our method is highly efficient (TOFs up to 5700 h⁻¹).
- Our protocol is straightforward, high-yielding, applicable to a broad spectrum of labile substrates, and works under mild reaction conditions.
- We prepared the first heterogeneous polymer-bound thiourea organocatalyst.
- Our mechanistic proposal is supported by the first computations on an addition reaction of ROH to enol derivatives.



Typical picture looking out of our lab window in late summer.
Green color means hope...

Meanwhile our results on organocatalytic tetrahydropyranylation
are published:

FEATURE ARTICLE

Generally Applicable Organocatalytic Tetrahydropyranylation of Hydroxy Functionalities with Very Low Catalyst Loading

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and

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