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Asymmetric proton-transfer, cycloaddition, and domino reactions: a unified view involving stabilisation of charge separation with bifunctional organic catalysts

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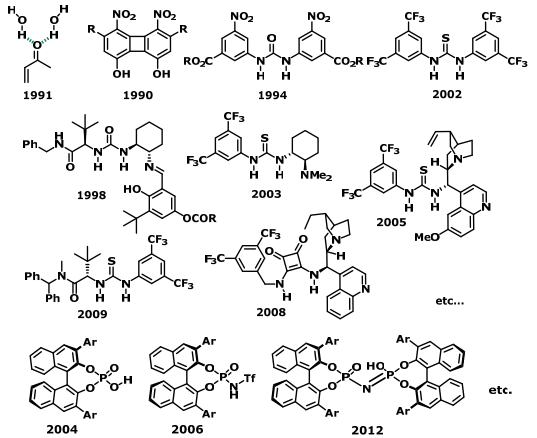
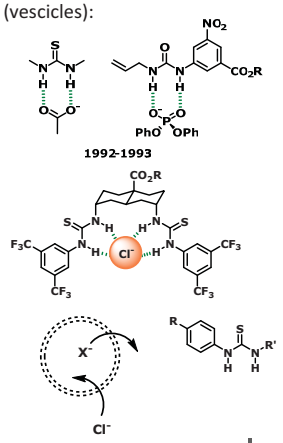
H-bond donors: catalysis, anion binding and transport

-H-bond donor catalysts: Jorgensen model for water acceleration in DA reactions, weak (double) H-bond donors (thioureas, etc), stronger acids (phosphoric acids etc)...

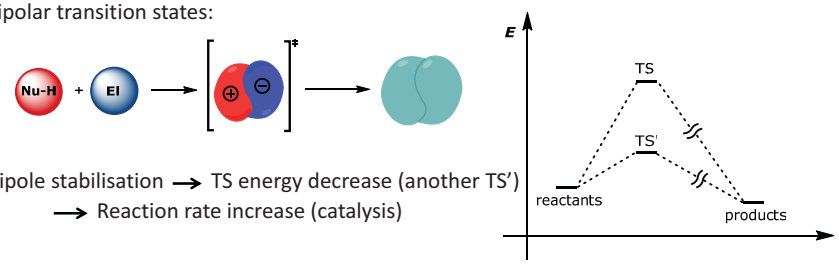


-H-bond donors: strong anion binding and transport through membranes (vescicles):



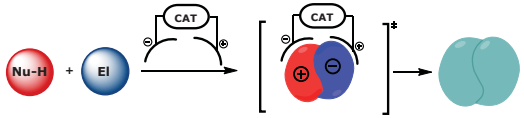
Dipolar transition states and bifunctional catalysis

-Simple additions of neutral nucleophiles to electrophiles proceed through high energy dipolar transition states:



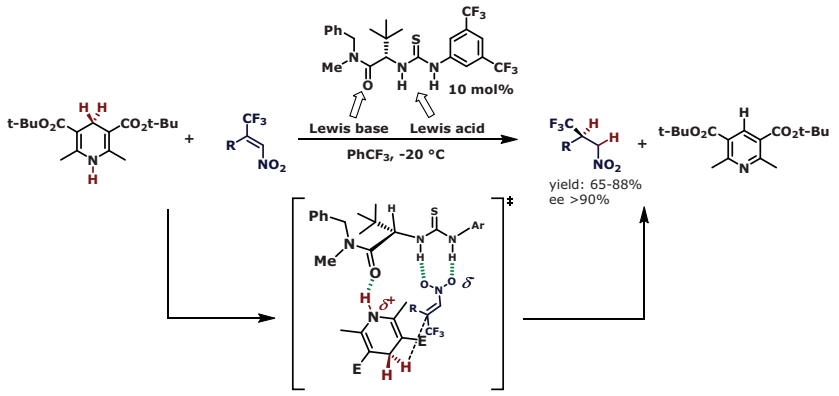
Dipole stabilisation → TS energy decrease (another TS')
→ Reaction rate increase (catalysis)

-To stabilise a dipole (in apolar medium), you need another dipole:

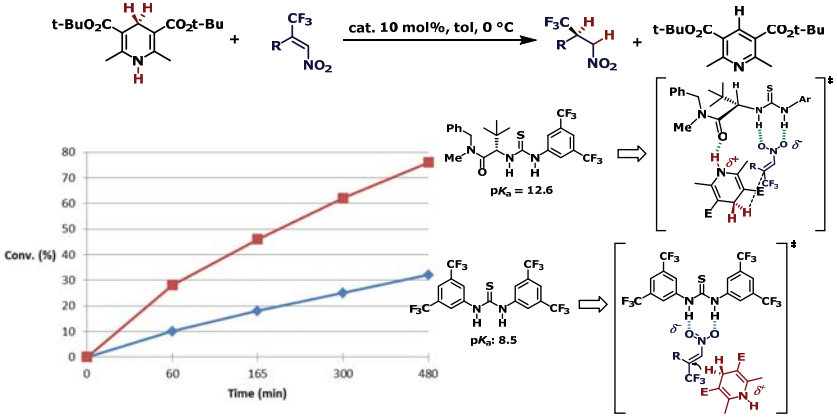


Dipolar transition states and bifunctional catalysis

-Catalytic asymmetric reaction of β-trifluoromethylnitroolefins with Hantzsch esters:



Dipolar transition states and bifunctional catalysis

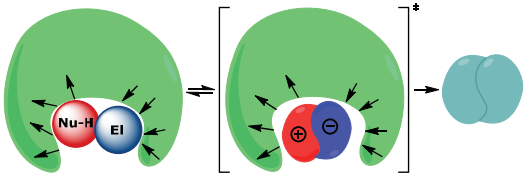


This experiment does not mean that more acidic catalysts are worse, but demonstrates that bifunctional catalysts are better even when a single functionality is worse. pK_a values are in DMSO (Schreiner et al. *Org. Lett.* **2012**, *14*, 1724).

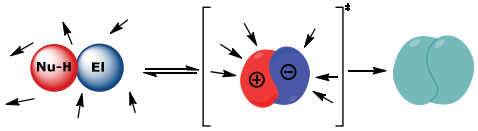
These molecules have been sometimes named as «minimal enzymes» or «enzyme mimics».

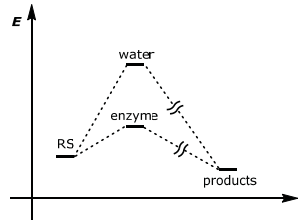
Dipolar transition states and enzymatic catalysis: a very (over)simplified view

-An explanation of enzyme catalysis: there is a pre-organised electrostatic field in the active site, electronically almost matching the TS.



-Compared with a reaction in water (or in a «flexible» environment), wherein the dipoles are not oriented:





The energy difference is the «reorganisation» of the dipoles on going from RS to TS, the energy needed to orientate the dipoles to fit the TS.

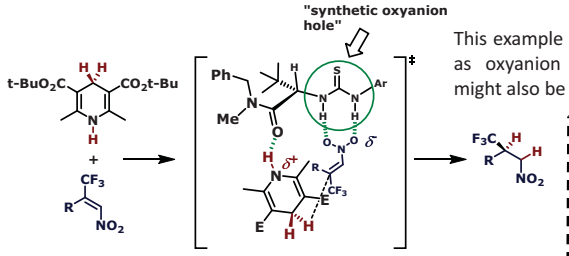
This energy is furnished by the semi-rigid protein structure, which generates the field (and avoid quenching).

Consequence: enzymes catalyse better than water.

See: Warshel et al. *Chem. Rev.* **2006**, *106*, 3210

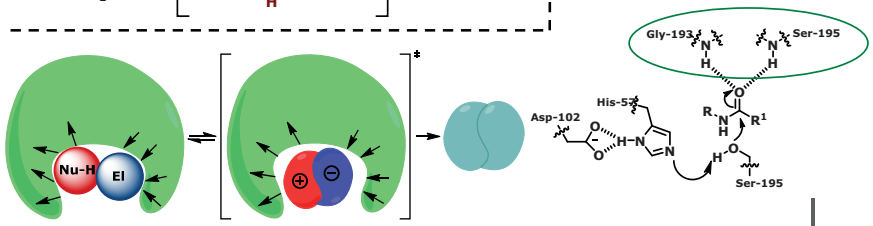
Dipolar transition states, small molecule and enzymatic catalysis

-Catalytic activity is due to coordination («solvation») of a polar TS of the reaction: the bifunctional catalyst has polar groups at the right position (does not need to reorganise too much to match the TS)



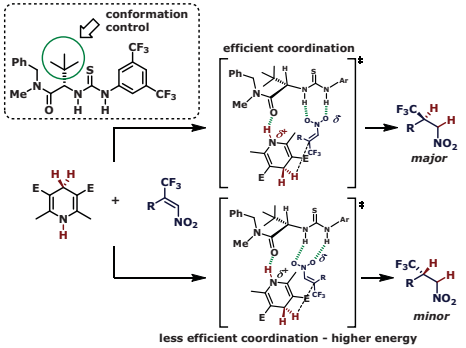
This example involves mainly H-bonds (thioureas as oxyanion holes). Other weak interactions might also be possible.

Oxyanion hole: an array of H-bond donor able to stabilise an oxyanion (intermediate, TS). e.g. protease enzymes:



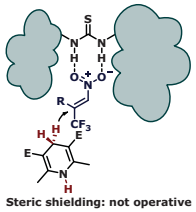
Going 3D: enantioselectivity

The 3D structure of the catalyst is able to coordinate/stabilise only one of the two enantiomeric TS's. Multiple interactions are necessary (3-point reaction model). Stereoselectivity is not due to steric shielding but to difference in stabilisation (same as in enzymes). The *tert*-butyl group of the catalyst does not give steric shielding, but serves to give the catalyst a defined secondary structure, to force it in the appropriate conformation (i.e. amide coming out from the screen).

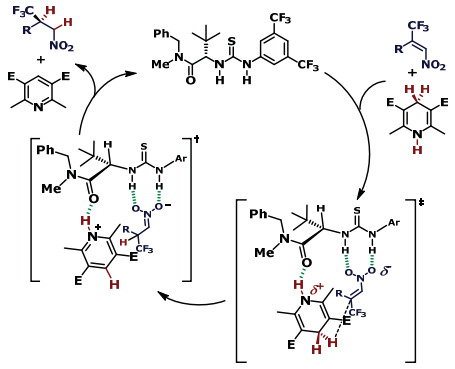


See: Knowles & Jacobsen *PNAS*, **2010**, *107*, 20678

Quite different from most small molecule systems (e.g. enamine catalysis, Lewis acid catalysis, etc.).

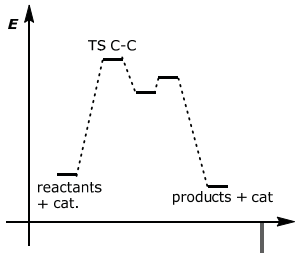


Overall view of the proton transfer reaction: TS, pre-TS, and post-TS



i) Interactions before TS are weak and not defined (Curtin-Hammett control).
ii) Stereoselectivity determined in the C-C TS with multiple H-bond interactions.
iii) After TS, rapid proton-transfer to products.

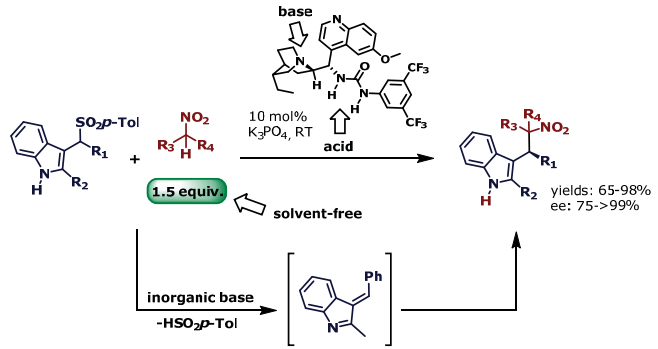
Reaction profile might look (very approximately) like this:



DFT calculations supporting this mechanism in similar systems: Zuend and Jacobsen, *JACS* **2007**, *129*, 15872; *JACS* **2009**, *131*, 15358.

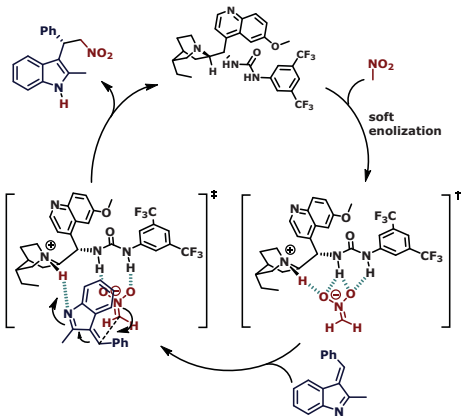
Another H-transfer reaction

-Addition of nitroalkanes to alkylideneindolenines (generated in situ):



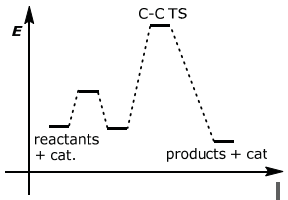
Adv. Synth. Catal. **2012**, *354*, 1373 (with Prof. Marino Petrini) [*Synfacts* **2012**, *8*, 875]

Overall view: soft enolisation, C-C bond formation, H-transfer



i) A basic catalyst (tertiary amine) is needed to reach the C-C bond forming step.
ii) Multicoordinated intermediate (soft-enolisation). H-bonds reinforced by electrostatics.
iii) Enantioselectivity in C-C bond derived from the same principles as before.
iv) Proton-relay from TS to products.

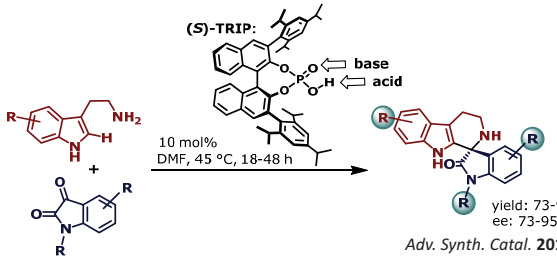
Reaction profile looks (very approximately) like this:



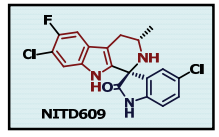
DFT calculations in similar systems: Soós, Papai et al. *JACS* **2006**, *128*, 13151; Himo et al. *Adv. Synth. Catal.* **2007**, *349*, 2537; Soós, Papai et al. *Chem. Eur. J.* **2014**, *20*, 5631.

…and another H-transfer reaction

-Pictet-Spengler reaction of isatins: asymmetric synthesis of «spiroindolones»:

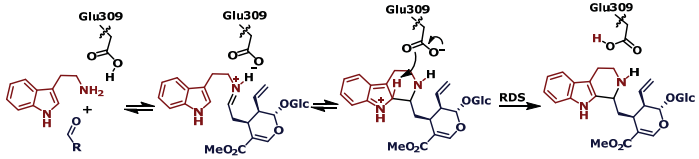


Spiroindolones are powerful antimalarial agents:
[M. Rottmann et al., Science **2010**, *329*, 1175.

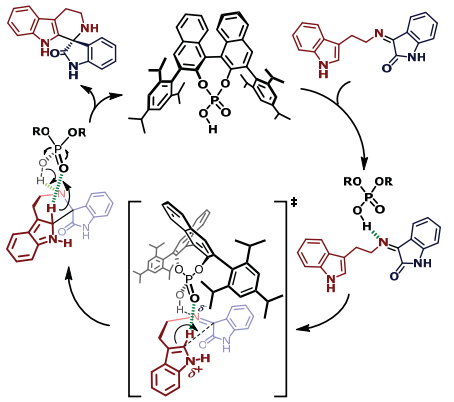


Adv. Synth. Catal. **2011**, *353*, 860 (with Dr. Giorgio Bencivenni).

-Mechanism of strictosidine synthase, catalyzing tryptamine + secologanin:
[Stöckigt, Peters, O'Connor, J. Am. Chem. Soc. **2008**, *130*, 710]



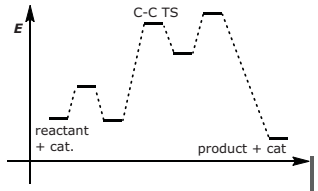
Overall view: imine coordination, C-C bond formation, H-transfer



First DFT-evidences for Nu-H coordination by P=O in TS: Marcelli, Hammar, Himo, *Chem. Eur. J.* **2008**, *14*, 8562; Simón and Goodman, *J. Am. Chem. Soc.* **2008**, *130*, 8741.

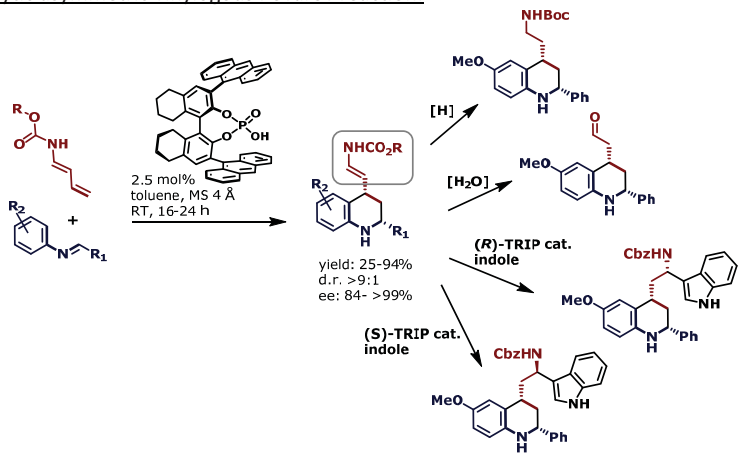
i) An acidic catalyst (stabilising better the charge at N in the TS) is needed for the reaction. Consequence: formation of an imine-coordinated intermediate.
ii) Enantioselectivity in C-C bond formation: two H-bonds, bifunctional catalysis, but also steric interactions.
iii) Proton-relay from intermediate to product restoring the catalyst proton.

Reaction profile might look (very approximately and without considering imine formation) like this:



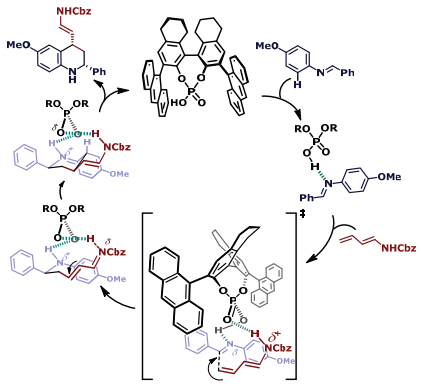
Cycloaddition/domino reaction

-Catalytic asymmetric vinylogous Povarov reaction:



Chem. Commun. **2013**, *49*, 880

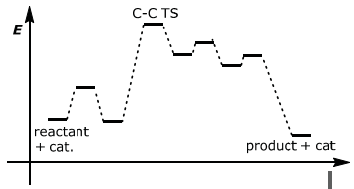
Overall view: imine coordination, C-C bond formation, intramolecular cycloaddition



2 equiv. of phosphoric acids "protonate" quantitatively an N-PMP imine in $CDCl_3$: [Dagousset, Zhu, Masson, *J. Am. Chem. Soc.* **2011**, *133*, 14804]

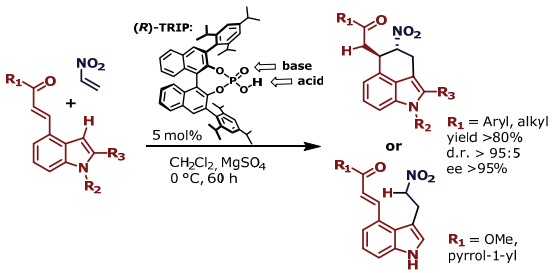
i) Similar to the previous reaction (acidic catalyst, imine coordination, sterics guiding enantioselectivity).
ii) Instead of by proton-transfer, the intermediate relaxes by an intramolecular nucleophilic attack.
iii) Then, rapid proton-transfer to restore the aromatic ring and the catalyst. The H-transfer is «inside» the electrophile.

Reaction profile might look (very approximately) like this:

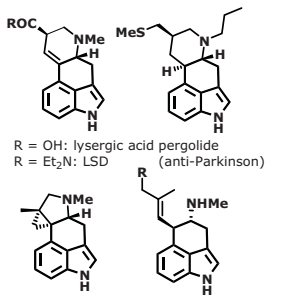


Cycloaddition/domino reaction

-Cycloaddition/domino vs simple H-transfer:



Ergot alkaloids:

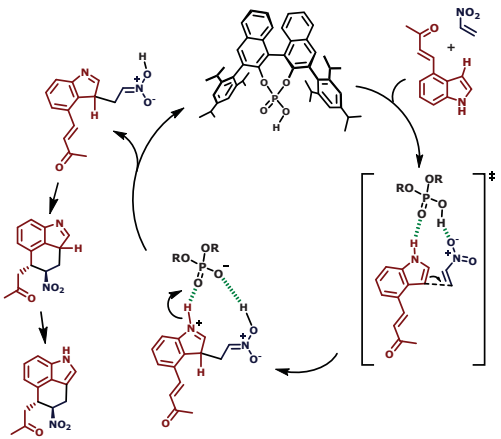


R = OH: lysergic acid
R = Et_2N: LSD
pergolide (anti-Parkinson)

cycloclavine
R = H: 6,7-secoagroclavine
R = OH: chanoclavine I

Use of these indoles in another domino reaction: *Chem. Commun.* **2014**, *50*, 445 [*Synfacts* **2014**, *10*, 206]

Overall view: C-C bond formation, and then?



i) Substrate weakly basic, weak coordination before TS.
ii) Bifunctional coordination at TS

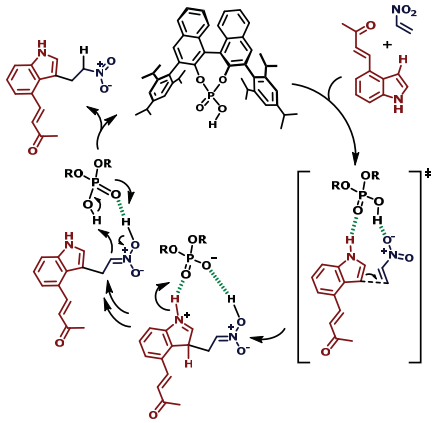
What happens next?

First hypothesis: cyclisation with «memory» of chirality.
But….

Slower reaction with **96% ee**

DFT evidence for N-H indole coordination to P=O: Hirata & Yamanaka, *Chem. Asian J.* **2011**, *6*, 510; Zheng, Sheng, Li, You, *Tetrahedron* **2010**, *66*, 2875

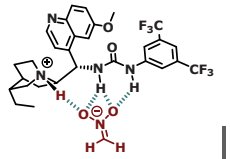
Overall view: C-C bond formation, and then?



i) Substrate weakly basic, weak coordination before TS.
ii) Bifunctional coordination at TS

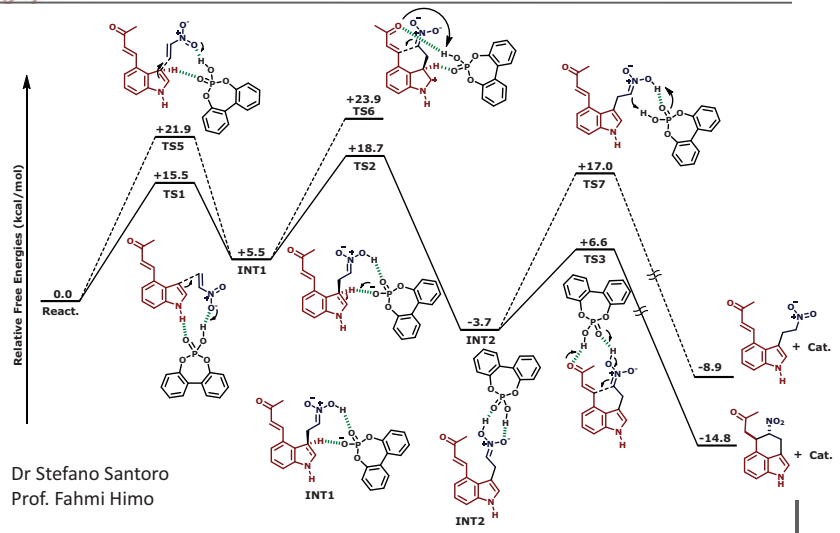
What happens next?

Second hypothesis: phosphoric acid abstracts NH, still coordinating the nitronic acid.
But….nitronate «quench» appears facile. Most previuosly reported «nitronate» based domino reaction involve basic catalysts (able to stabilise a nitronate). No examples with phosphoric acids.



DFT evidence for N-H indole coordination to P=O: Hirata & Yamanaka, *Chem. Asian J.* **2011**, *6*, 510; Zheng, Sheng, Li, You, *Tetrahedron* **2010**, *66*, 2875

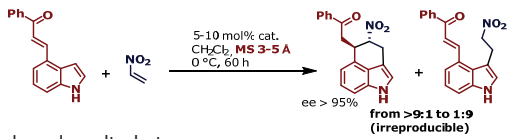
Overall view by DFT (B3LYP-D) calculations



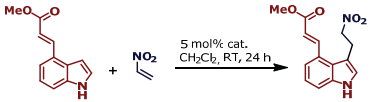
Dr Stefano Santoro
Prof. Fahmi Himo

Molecular sieves: dehydrating agents or more than that?

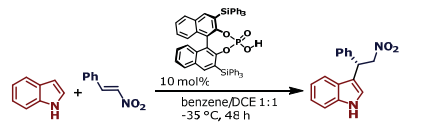
Applying MS as dehydrating agents (to avoid catalyst inhibition by water) led to non-reproducible results, and surprisingly shifted the reaction pathway towards the open-chain product.



$MgSO_4$ gave instead good results, but:



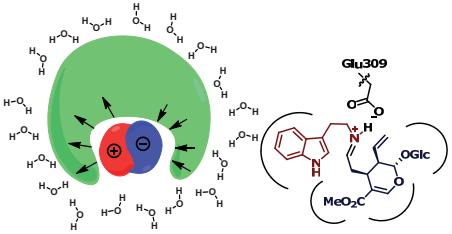
From the literature:



Itoh, Fuchibe, Akiyama, *Angew. Chem. Int. Ed.* **2008**, *47*, 4016

Some speculation on enzymatic and small molecule catalysis

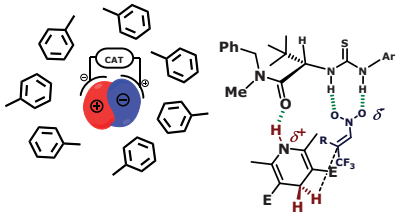
Enzymatic reaction:



Very high affinity for TS due to many interactions, active site isolated from the aqueous environment
Operative in a complex environment

-Formation of a Michaelis-Menten complex
-Catalysis is highly efficient
-Aqueous conditions
-Very diluted conditions
-Narrow reaction scope
-Regulation (allosteric, reversible covalent etc)

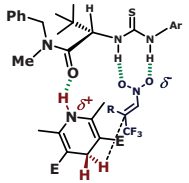
Small molecule catalysis:



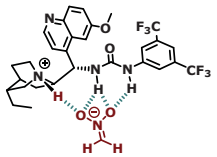
TS coordination given by few interactions, coordinated complex exposed to the environment

-Weak interactions prior to TS
-Catalysis is not very efficient
-Apolar aprotic solvents not disrupting interactions
-Concentrated conditions (vs self-aggregation)
-Broad reaction scope

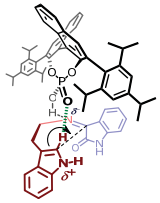
Few more words about reaction environment



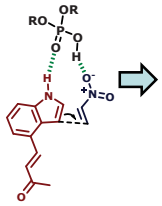
Few interactions prior to TS: necessary to use an apolar aprotic solvent (otherwise the solvent will coordinate the catalyst). Concentration is very good for the rate but cannot be too high due to catalyst self-aggregation.



Stabilised intermediate, prevents self-aggregation: solvent-free, highly concentrated reaction is possible



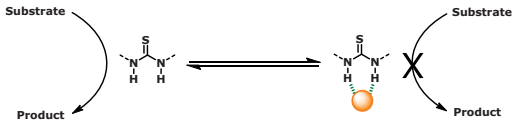
Strong interactions prior to TS, and then intra-molecular reaction: a polar medium (DMF) can be used

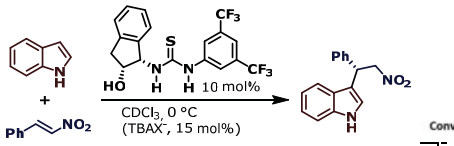


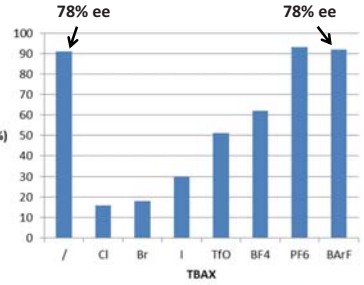
Weak interactions prior to TS, an apolar, aprotic medium must be used (in THF the reaction does not work)

Reversible control of the activity of small molecule catalysis: a simple approach

-Thiourea catalysts coordinating weakly the neutral substrates can be inhibited by anions (strongly coordinating). This inhibition depends on the size of the anion (small anions, strong interaction, large anions, loose interaction, catalyst is active).







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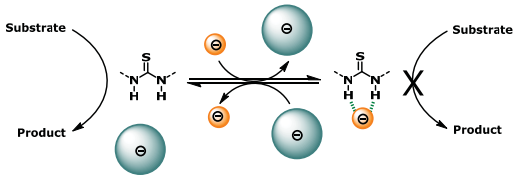
-Inhibition is reversible if the small anion can be removed and exchanged with a large one.



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