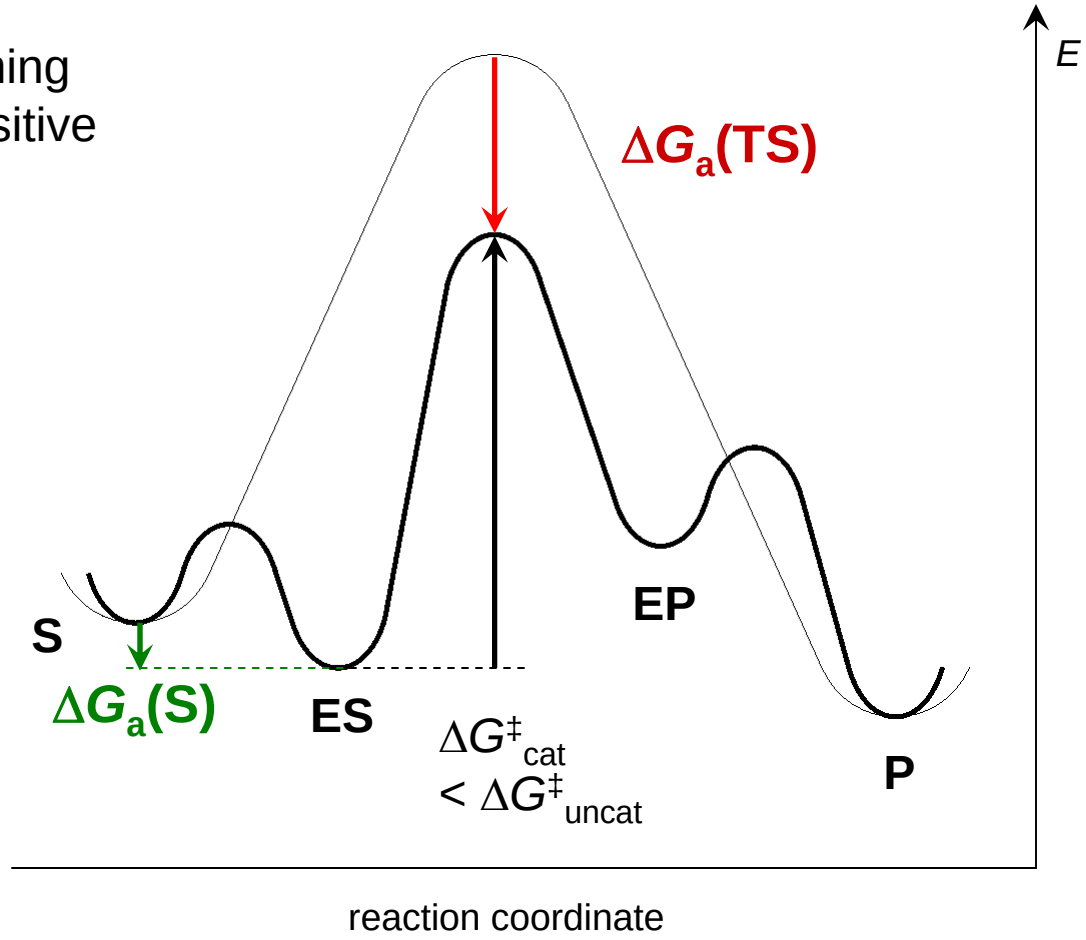
Enthalpic Catalysis: Specific Interactions with Transition States

More common:

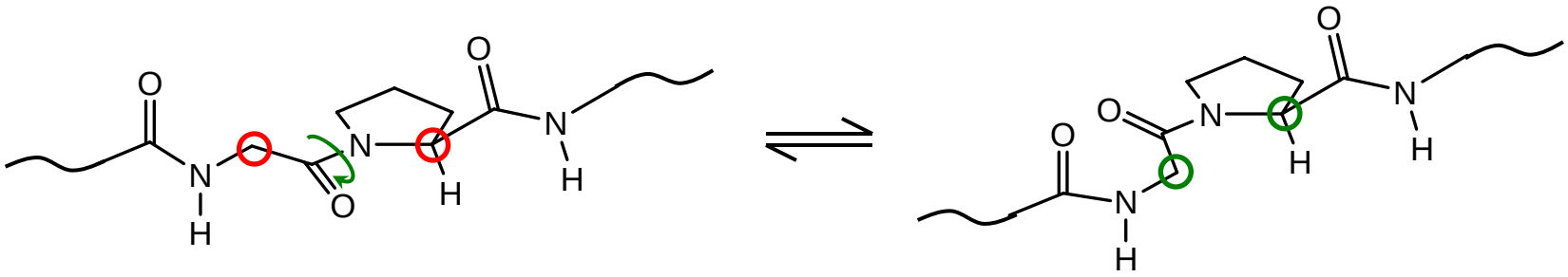
Catalyst stabilizes rate-determining transition state with specific, positive interactions.



Enthalpic Catalysis: Specific Interactions with Transition States

Catalysts can stabilize existing transition state.

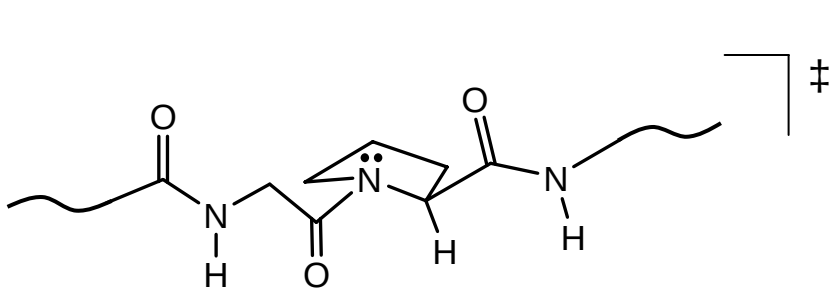
Example: cyclophilin A (a proline isomerase)



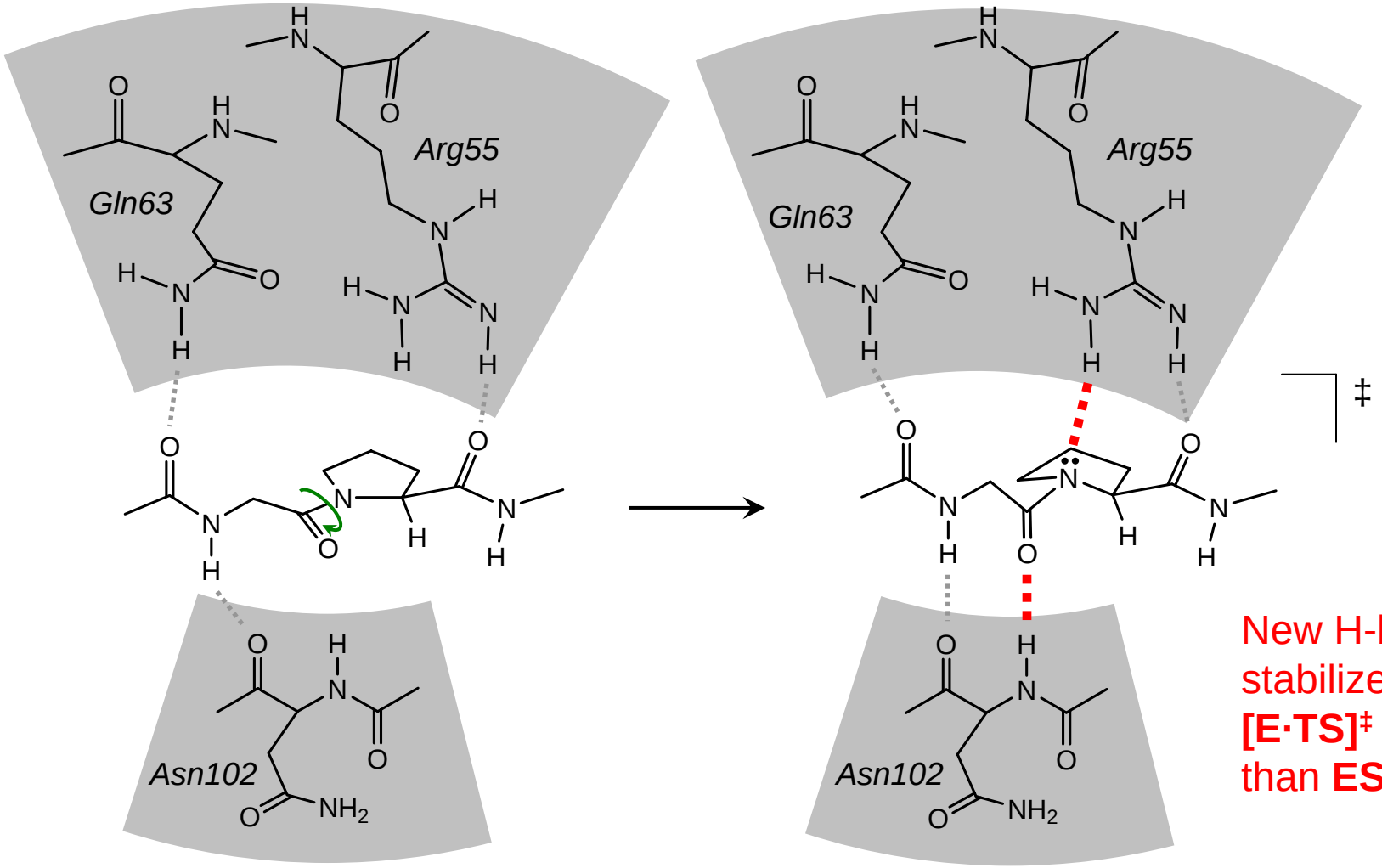
trans-proline
(amino acid in a protein)

cis-proline
(isomerized)

Moving carbonyl out of plane in TS eliminates resonance with N lone pair, pyramidalizes nitrogen.



Enthalpic Catalysis: Cyclophilin A



New H-bonds stabilize **[E·TS]‡** better than **ES**.

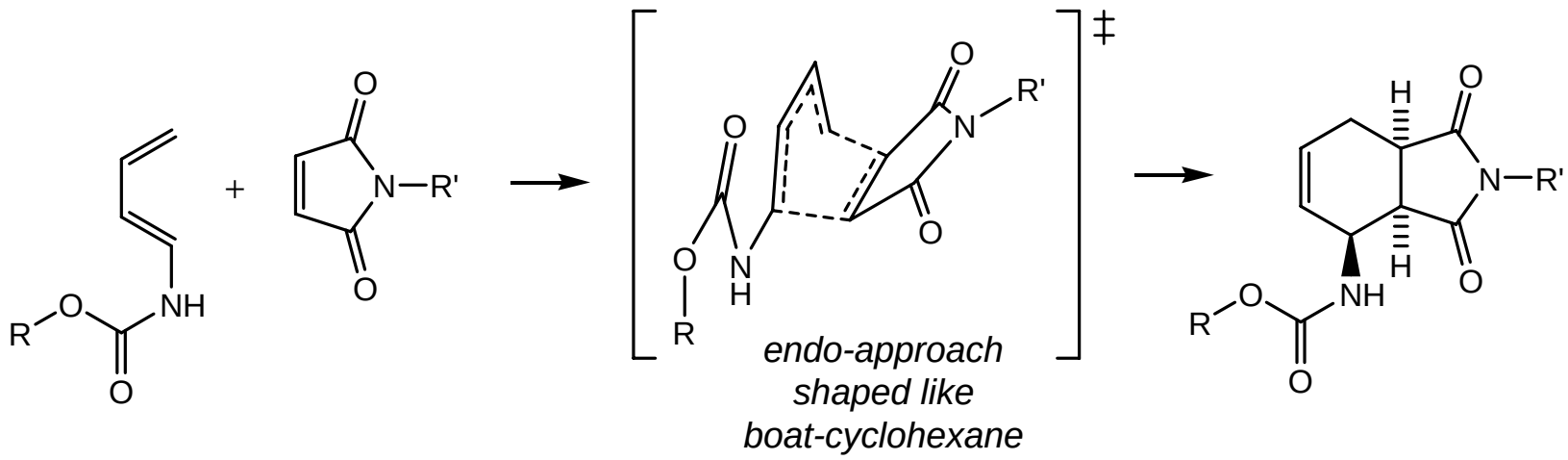
Eisenmesser, E. Z.; Bosco, D. A.; Akke, M.; Kern, D. *Science* **2002**, *295*, 1520-1523.

Catalytic Antibodies

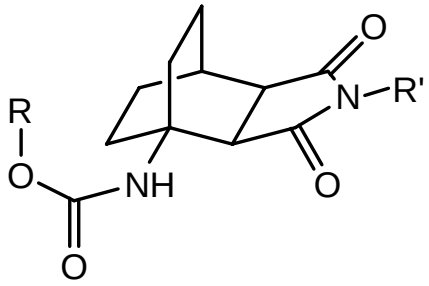
- In principle, anything that binds a transition state extremely well might be a good catalyst.
- But…we don't know exactly what transition states look like, so it's difficult to design catalysts.
- ***An alternative:*** Synthesize molecules that look like transition states, and find things that bind them well. These should be good catalysts.
- Antibodies bind antigens (foreign substances) really well.
- ***Strategy:*** Inoculate organisms* with transition-state analogs. When one shows immune response, isolate antibodies that bind analog. These antibodies should be great catalysts.

*or, more commonly, hybridomas

Catalytic Antibodies

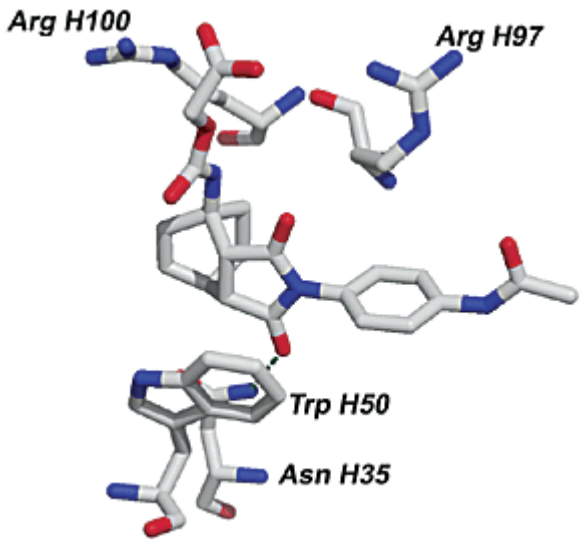


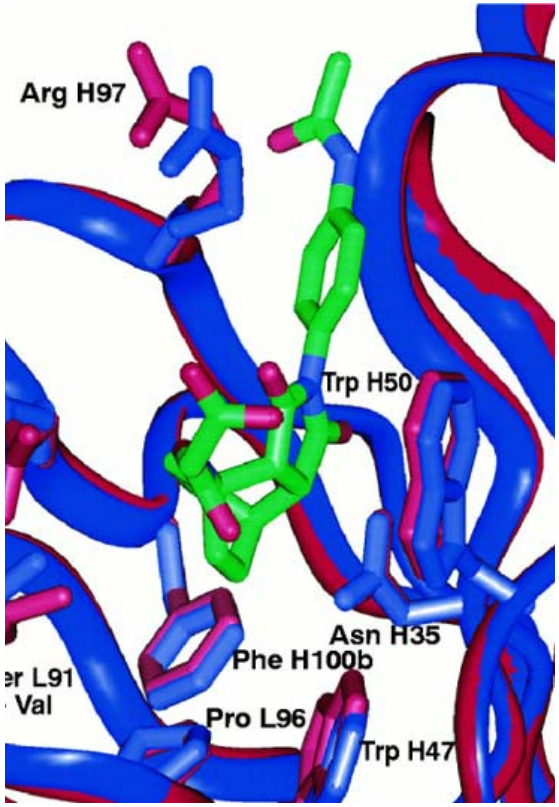
Transition-state analog:

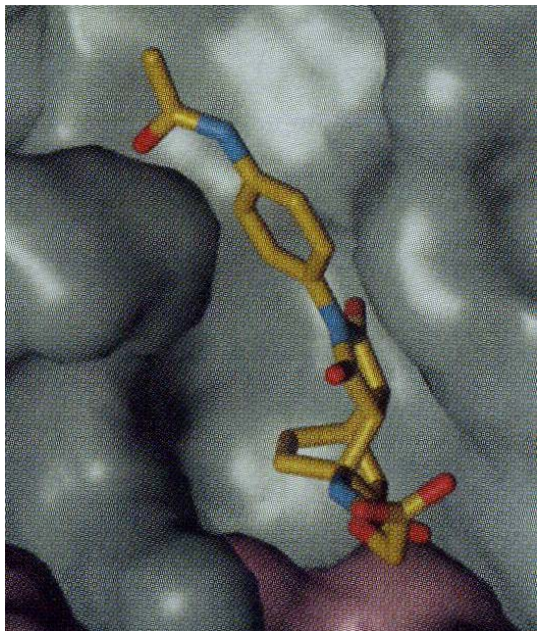


Hypothesis: Antibodies that bind this molecule should be good catalysts.

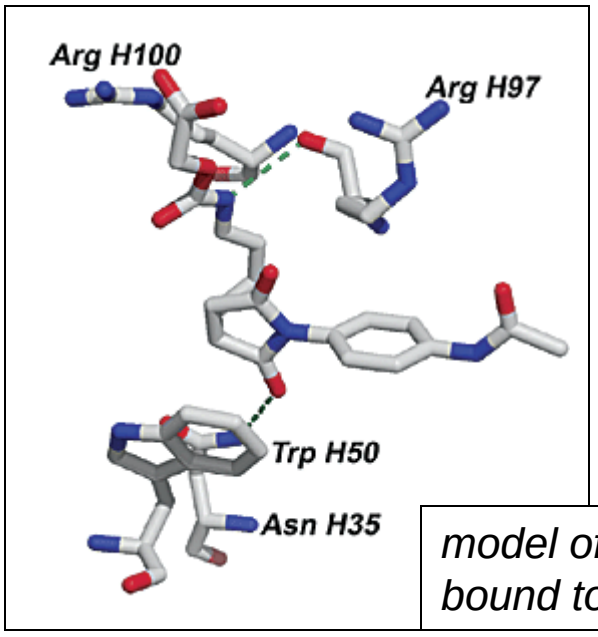
Catalytic Antibodies







X-ray structures of transition-state analog bound to antibody 39A11

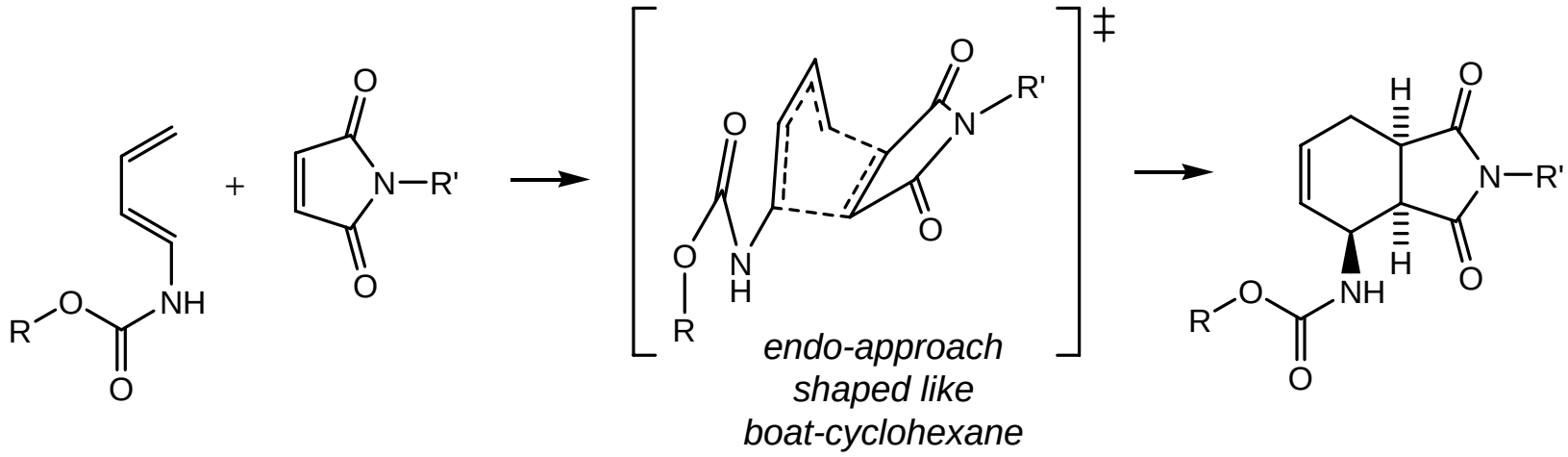


model of starting materials bound to active site

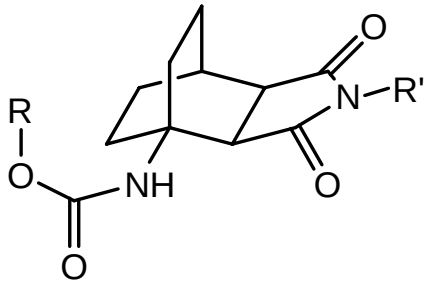
$$\frac{k_{cat}}{k_{uncat}} = \mathbf{1000\ M}$$

Romesberg, F. E. et al. *Science* **1998**, *279*, 1929.
Braisted, A. C.; Schultz, P. G. *J. Am. Chem. Soc.* **1990**, *112*, 7430.

Catalytic Antibodies



Transition-state analog:



Antibody 39A11:

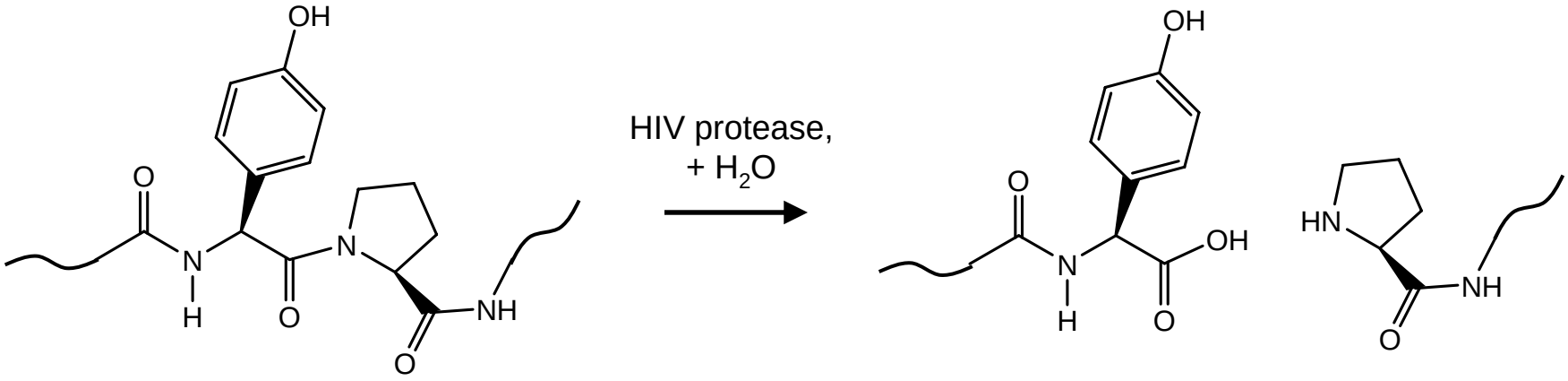
$$\frac{k_{cat}}{k_{uncat}} = \mathbf{1000\ M}$$

Conclusion: Antibodies that bind transition-state analogs are (sometimes) good catalysts.

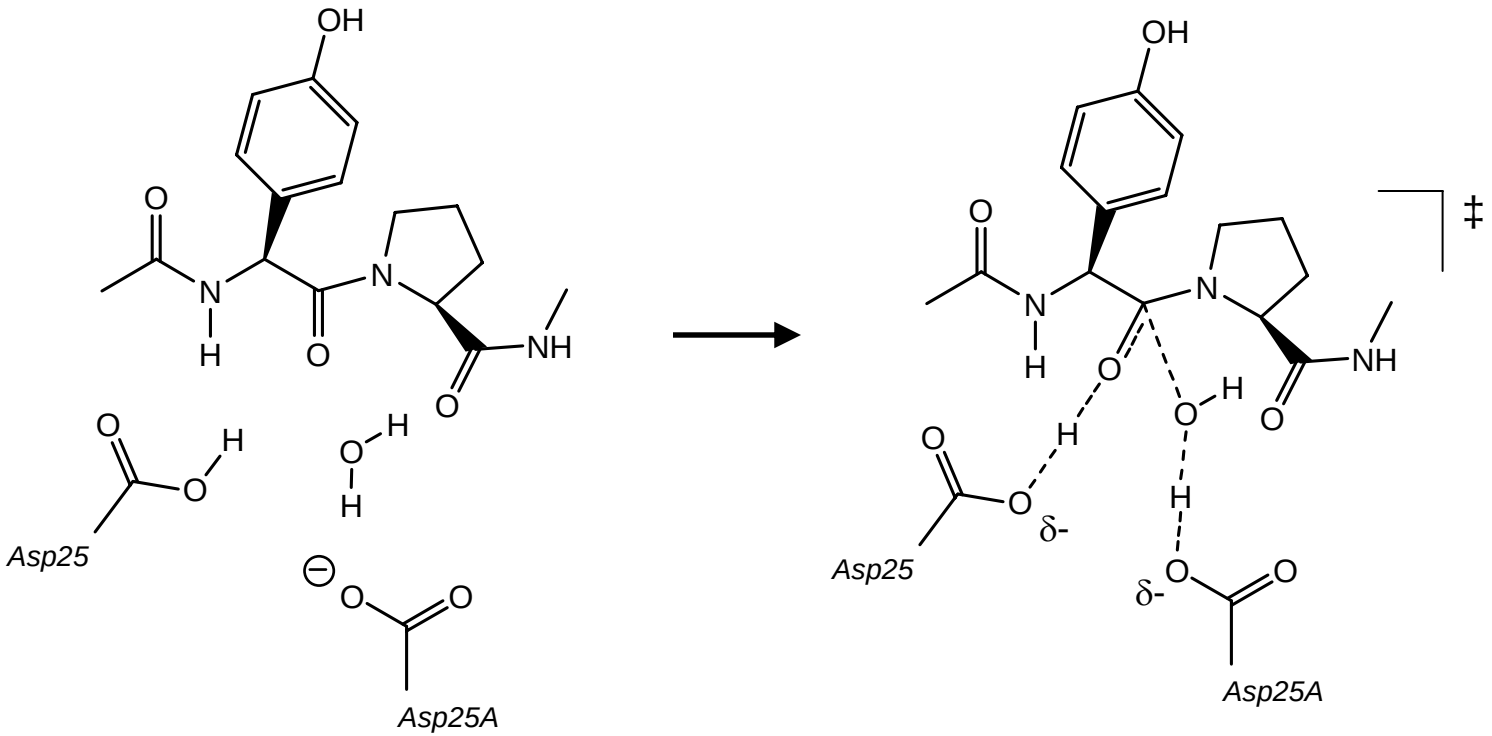
Transition-State Analogs as Enzyme Inhibitors

If catalysts (enzymes) have evolved to bind to a transition state, the best binders should be molecules that look like that transition state.

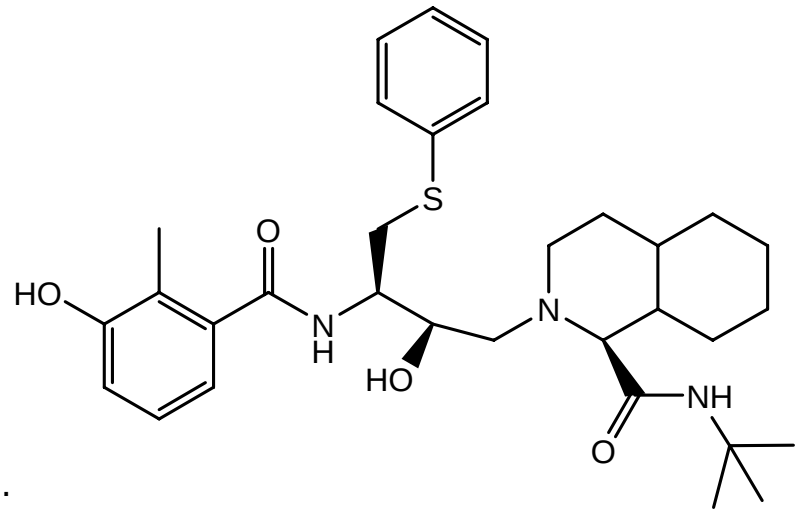
<u>Example:</u> HIV protease inhibitors.



Inhibition of HIV Protease



Saquinavir (Roche)



Elements of TS in inhibitor:

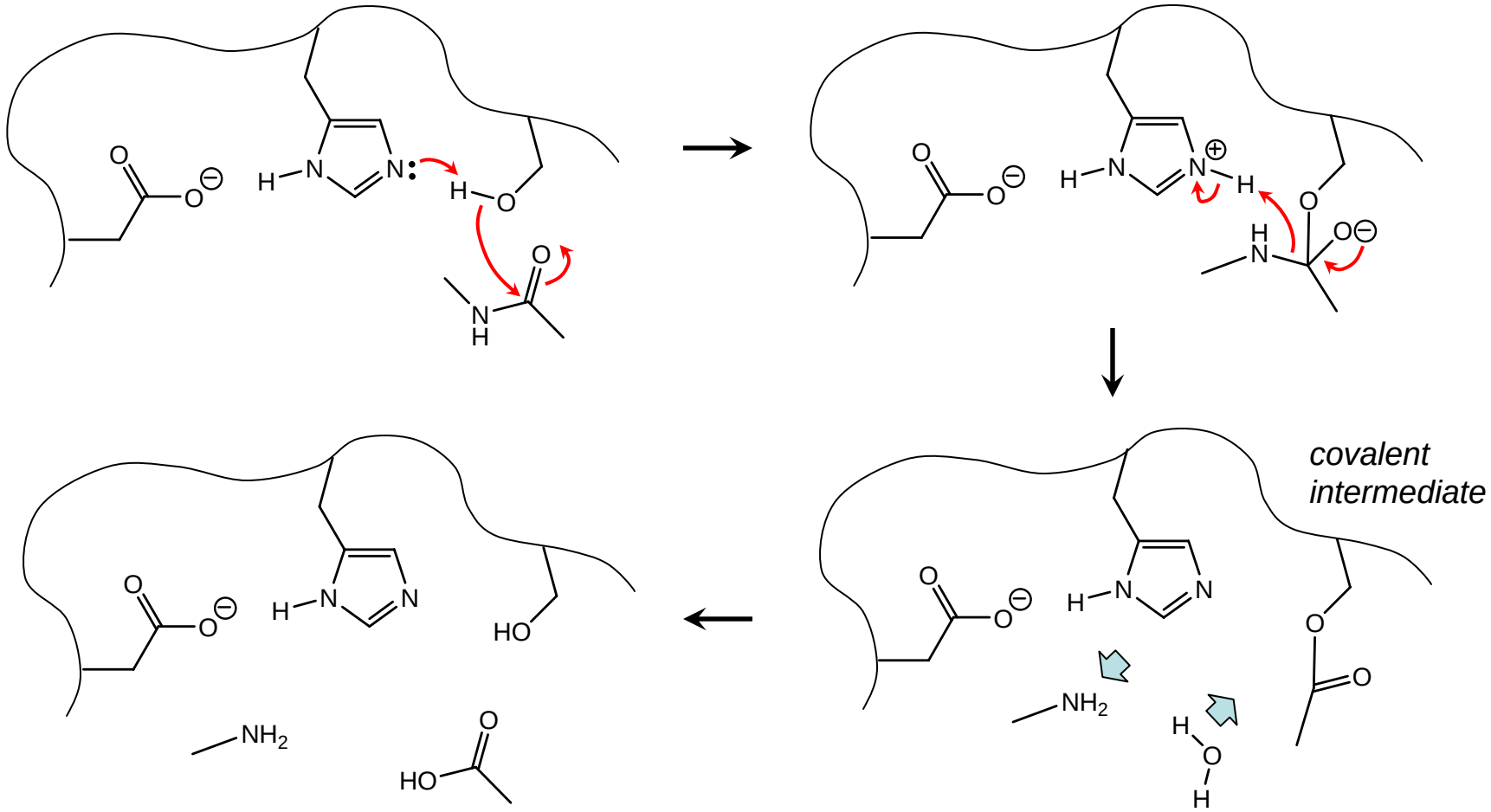
- Tetrahedral carbon
- Unconjugated amine
- Replicates basic structure

Review: Brik, A.; Wong, C.-H. *Org. Biomol. Chem.* **2003**, *1*, 5.

Covalent Catalysis

More frequently, catalysts accelerate reactions by changing their mechanism.

Example: Serine proteases. (Digestive enzymes)



Why covalent catalysis predominates: Zhang, X.; Houk, K. N. *Acc. Chem. Res.* **2005**, *38*, 379.