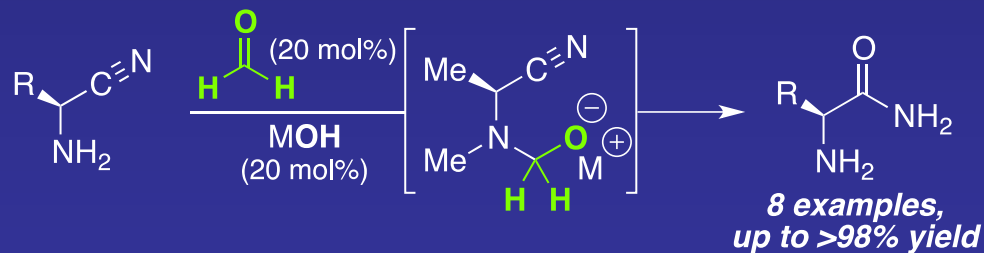
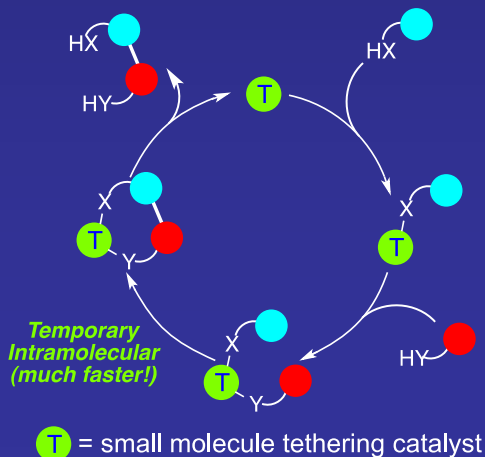


Catalysis Via Temporary Intramolecularity: Aldehydes as Organocatalysts

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Catalysis of intermolecular reactions is at the basis of chemical reactivity. Enzymes are remarkably efficient at catalyzing intermolecular reactions: rate accelerations as high as 10^{17} can be achieved, with the selective formation of one product when several are possible. To achieve high activity and control, enzymes pre-organize reagents and consequently induce a "temporary intramolecularity" that minimizes the entropic penalty associated with intermolecular reactions. It is accepted that rate accelerations of 10^4 - 10^8 for 1 M reactants can be obtained for room temperature reactions via temporary intramolecularity. Not surprisingly, multiple transformations building on preassociation have been developed, and several families of bifunctional catalysts have emerged. In contrast, the catalysis of transformations only through temporary intramolecularity has received little attention from the synthetic community. Indeed, simple catalysts operating only through this pathway are rare, perform relatively simple reactions and highly efficient asymmetric catalysts have not been reported.

How simple can a catalyst operating via temporary intramolecularity be? Can tethering catalysis be used for the reactions relying on temporary tethers (which are typically formed, used and cleaved in separate steps)? Building on excellent recent results obtained for intermolecular alkene hydroamination (including asymmetric variants), we are exploring the use of *destabilized* aldehydes as tethering catalysts. Current results include the discovery that formaldehyde is a highly active catalyst, and that fast, mild hydrolyses are possible for both α - and β -aminoacid derivatives (see example below). The development of more complex reactions and asymmetric variants is underway.



- Typical conditions: 5 min to 2 h, at 22 °C, in **water**
- *Destabilized carbonyls are active catalysts (favorable preassociation)*
- Results demonstrate that tandem concurrent catalysis is possible
- Preliminary results with β -amino-nitriles and -amides (new reactivity)