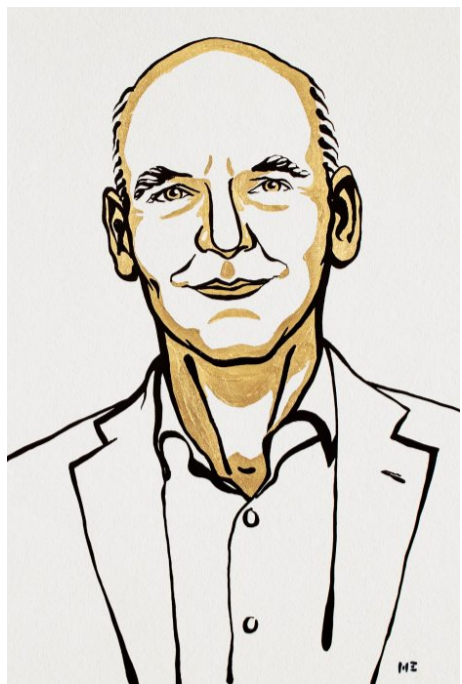


Nobel Prize for Chemistry 2021 for ORGANOCATALYSIS



Benjamin List



David W.C. MacMillan

Connections

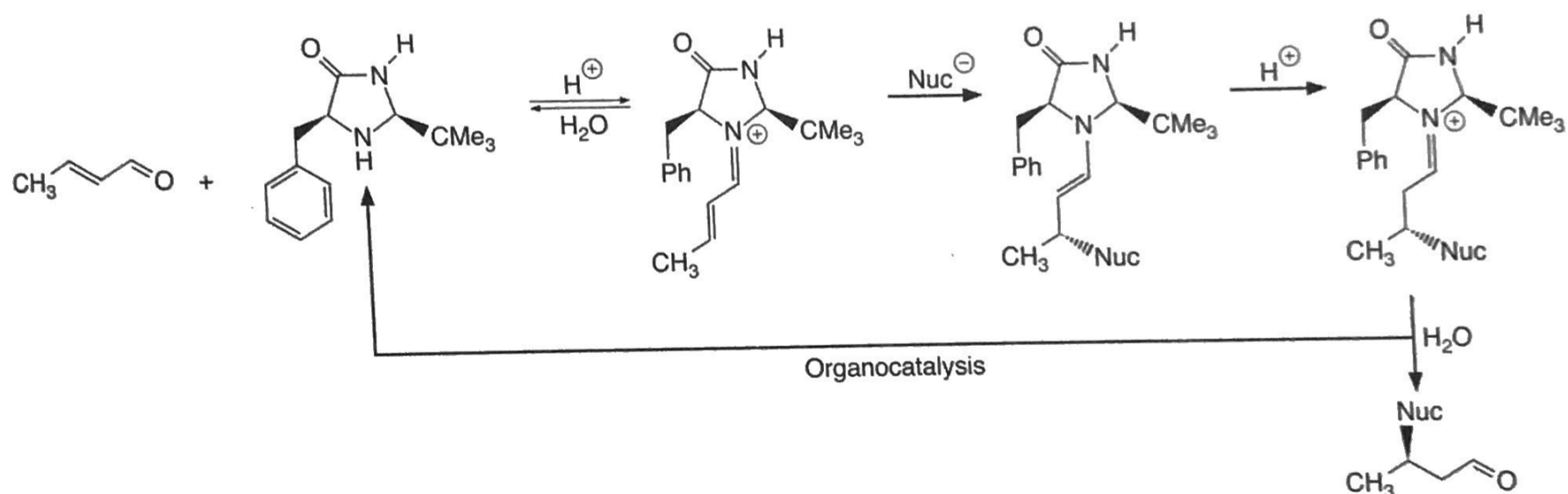
Organocatalysis

In organic synthesis we usually think of catalysts as being based on transition metals, main group elements, and other elements besides C, H, N, and O. Recently, however, there have been significant advances in **organocatalysis**, the development of all organic systems that have desirable catalytic behaviors. Part of the motivation for such efforts is the air and water instability often associated with metal-based systems, the environmental benefit of avoiding toxic metals, and the ready availability of a large number of enantiomerically pure organic substances for developing chiral catalysts.

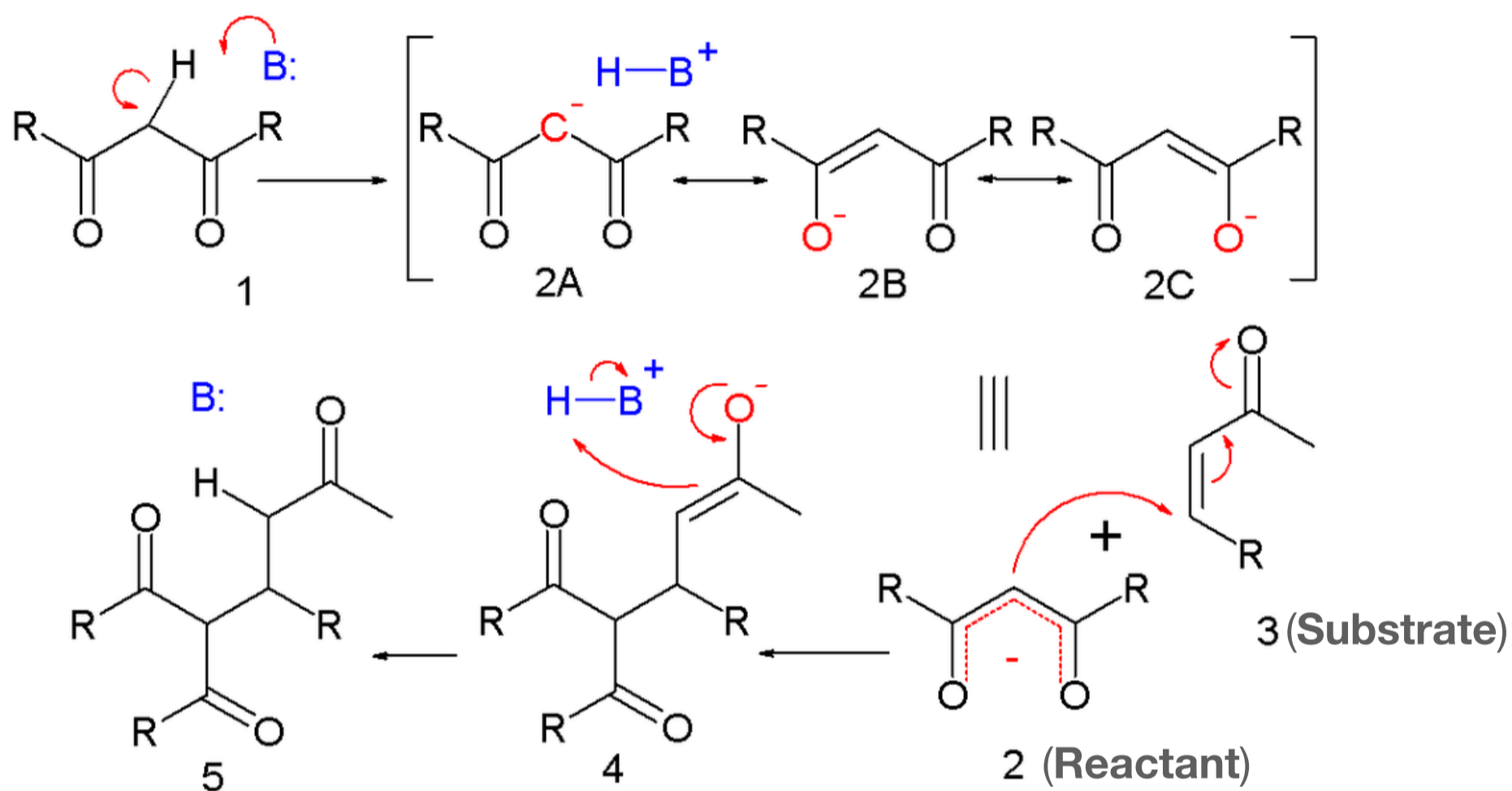
One especially successful example of organocatalysis is the chiral amine catalyst shown developed by MacMillan and co-workers. The key feature of such systems is that forming the iminium ion creates a much lower-lying LUMO relative to that found in the starting enone. This makes the structure much more susceptible to nucleo-

philic attack, ensuring that all reaction occurs via the iminium ion. The well-defined geometry of the system produces very high stereoselectivities. Turnover is achieved by hydrolysis of the product iminium ion, and often the water produced in the first step is sufficient for this purpose. While the turnover numbers generally seen with such organocatalysts are typically nowhere near those seen with organometallic catalysts, the benefits of inexpensive catalysts and the ability to run the reaction in the open air with wet solvents often more than compensates. Using this approach, a variety of reactions have succumbed to organocatalysis, including Diels–Alder reactions, Friedel–Crafts reactions, direct alkylations of heterocycles such as furan and indole, and a variety of Michael additions.

Austin, J. F., and MacMillan, D. W. C. "Enantioselective Organocatalytic Indole Alkylations. Design of a New and Highly Effective Chiral Amine for Iminium Catalysis." *J. Am. Chem. Soc.*, **124**, 1172 (2002).



General scheme of the Michael addition (condensation) reactions



A well-known Michael reaction is the synthesis of [warfarin](#) (anticoagulant) from [4-hydroxycoumarin](#) and [benzylideneacetone](#) first reported by Link in 1944:^[17]

