

Hydrogen Bonding Catalysis in Organic Chemistry

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INTRODUCTION

The methods utilized by nature provide inspiration in many scientific disciplines including engineering, physics, biology and chemistry. Nature relies on hydrogen bonds to sustain the intricate architectures and functionality of enzymes, which are biological molecules that catalyze chemical reactions, including those that form carbon-carbon bonds. An emerging strategy in asymmetric synthesis is to harness the power of hydrogen bonds in the design of small

molecule catalysts. Within the last decade, major advances in asymmetric catalysis facilitated by organic Brønsted acids/ hydrogen bond donors have been realized,¹ including, phosphoric acids (**1**),² diols (**2**),³ guanidiniums (**3**),⁴ ureas (**4a**),⁵ and thioureas (**4b**)⁵ (Figure 1). The activation mode by which these catalysts operate involves the donation of hydrogen bonds to carbonyl compounds or imines which lowers the LUMO energy level of the C=O or C=N bond and facilitates nucleophilic attack (Figure 2). Hydrogen bonding catalysis will be discussed with respect to the types of catalysts, and their use in both dual and bifunctional catalyst systems.

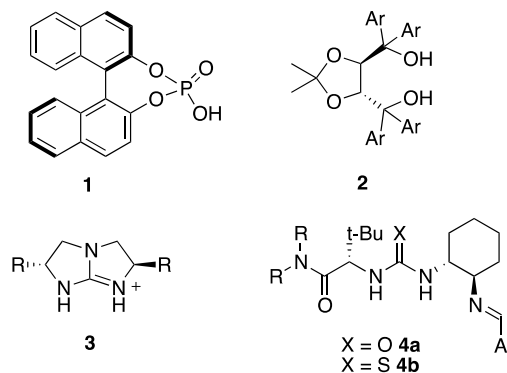


Figure 1. Representative catalysts

lowers the LUMO energy level of the C=O or C=N bond and facilitates nucleophilic attack (Figure 2).

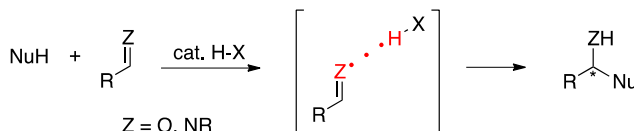


Figure 2. Mode of activation by hydrogen bonding catalysis

HYDROGEN BONDING CATALYSIS

In 2002, Huang and Rawal showed that hetero-Diels-Alder reactions of aldehydes with 1-amino-3-siloxybutadiene were accelerated in protic solvents.⁶ Soon thereafter they reported that chiral diols such as tartrate-derived TADDOL catalysts promoted asymmetric hetero-Diels-Alder reactions to give highly enantioenriched α,β -unsaturated ketones.³ The mode of activation is hypothesized to involve a single hydrogen bond from a hydroxyl group on the TADDOL catalyst **5** to the aldehyde (Figure 3).

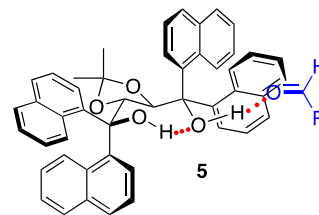
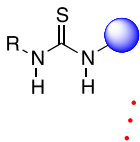


Figure 3. Proposed TADDOL model

The most studied hydrogen bonding catalysts, which were developed by Jacobsen and coworkers, are based on the thiourea template.⁵ These catalysts, and particularly their bifunctional amino thiourea counterparts, have been employed successfully in a plethora of reactions such as aldol,⁷



nitro aldol,⁸ Strecker reactions,⁹ and Claisen rearrangements.¹⁰

A representative example described by Takemoto *et al.* employs the use of bifunctional amino thiourea catalyst in the conjugate addition reaction of malonates to nitroolefins.¹¹ This catalyst system serves a dual function by activating the nitroalkene and organizing the 1,3-dicarbonyl both through hydrogen bonds (Figure 4). This group was able to obtain high enantioselectivities (up to 94%) and yields (up to 93%) for this reaction.

Recently, hydrogen bonding catalysis has spawned the concept of anion binding catalysis,¹² as pioneered by Jacobsen and coworkers. A recent example from the Jacobsen group uses a thiourea catalyst for the enantioselective ring opening of episulfonium ions with indoles.¹³ Based on detailed kinetic and NMR studies, the authors propose that the chiral thiourea catalyst forms a chiral ion pair with the episulfonium ion (Figure 5)

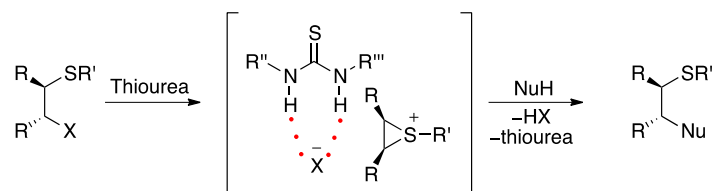


Figure 5. Proposed ring opening via anion binding

CONCLUSION

Biological systems have evolved extremely complex and efficient machinery to facilitate the synthesis of important, life-sustaining molecules. In an attempt to mimic nature, organic chemists have designed chiral catalysts that exploit hydrogen bonds to promote highly enantioselective transformations. The research presented herein describes the current state-of-the-art in hydrogen bonding catalysis, both with respect to catalysis development and to the application of these catalysts in the synthesis of complex molecules.

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