Development of Atom-economical Catalytic Asymmetric Reactions and Their Application to Practical Synthesis of Therapeutics

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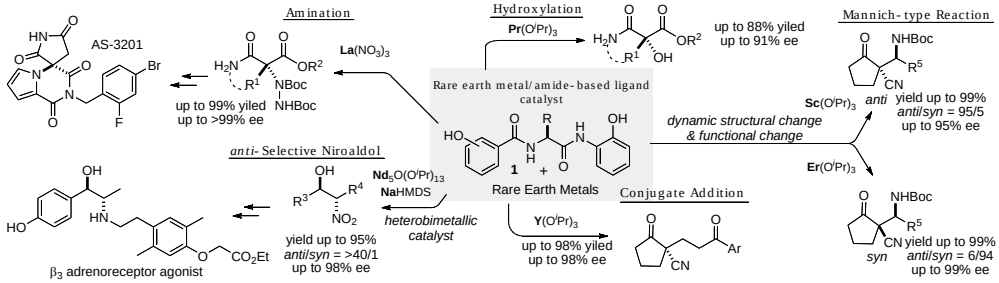
Recent advances in modern organic synthesis enabled an efficient access to a broad range of complex molecules in a highly stereocontrolled manner. The methodologies, however, usually require the stoichiometric use of activating reagents to achieve high reactivity and chemo/stereoselectivity, thereby co-producing the unwanted wastes. In this context, we envisioned the development of atom-economical catalytic asymmetric reactions, where chiral centers are produced via a proton-transfer between unactivated substrates, leading to environmentally benign synthesis of optically active therapeutics.

1. The development of rare earth metal (RE)/amide-based ligand 1 catalysts and their application to efficient synthesis of therapeutics: We disclosed that the combination of RE and **1** constituted an intriguing catalytic system. **1** is characterized by its rigidity (amide plane) and flexibility (α-carbon). On the other hand, RE exhibits high coordination number and multiple coordination modes depending on the chemical environment. Complexation of RE and **1** afforded asymmetric catalysts providing multiple asymmetric environment with a small set of ligand variation and exerting multiple functions based on in-situ dynamic structural change.



2. Chemoselective activation of Lewis basic pronucleophiles via proton-transfer with a soft Lewis acid/hard Brønsted base catalyst: Catalytic asymmetric addition to ketoimines and ketones mostly rely on the stoichiometric use of activated reagents to compensate for the low reactivity of these substrates. We focused on the a) Lewis basicity; and b) minimal steric bias of allylic cyanides, which can be chemoselectively activated by a soft Lewis acid/hard Brønsted base catalyst to generate active nucleophile. The methodology was successfully expanded to thioamide pronucleophile to achieve catalytic asymmetric direct Mannich-type and aldol reactions.