Recent Advances in Cobalt Catalyzed Carbonyl Reduction using Hydrogen Gas

Reported by Emma Mize November 21st, 2024

Introduction: Asymmetric ketone reduction is a well-represented process in industrial drug synthesis as well as the synthesis of bulk commodity chemicals.[1] This reaction is typically mediated by precious metal catalysts such as derivatives of the famous Noyori hydrogenation catalyst which uses Ruthenium.[2] These precious metals have volatile prices and tend to be expensive.[3] Due to the widespread application of this transformation in drug synthesis, it would be beneficial to develop catalysts using base metals which are consistently cheaper. Recently, there has been much work in discovering catalysts which use cobalt to mediate this process. It's challenging for cobalt to replace the precious metal catalysts which are widely used, as these tend to display millions of turnovers as well as the ability to recycle the catalyst for multiple reactions. Nevertheless, researchers continue to use intuitive ligand design and mechanistic studies to push these cobalt catalysts to the same level as the precious metals. This seminar will cover these recent advancements in cobalt catalyzed ketone reductions.

Early Ligand Design: In 2012 Hason first reported a cobalt catalyst which displayed reactivity in reducing acetophenone.[4] This ligand is classified as a PNP-Type ligand, containing a Phosphine-Amino-Phosphine Backbone (Figure 1). This novel catalyst displayed about 50 turnovers, and gave high yields across all substrates tested (85-100%). Kempe and co-workers attempted to improve upon this initial reactivity with their version of these PNP-type catalysts (Figure 1).[5] With this scaffold modification they were able to increase the turnover numbers to 400, remove the expensive Brookhart's acid, and create a more diversifiable ligand. Overall, these early ligand designs provide a great starting point for this chemistry but are not synthetically useful enough for application in industry due to the low turnover numbers. In the next section with the advent of NHC Ligands some mechanistic limitations can be uncovered about these early systems.

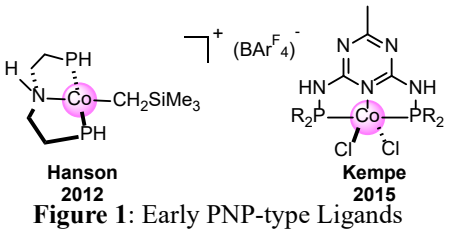

Figure 1: Early PNP-type Ligands

NHC Ligands and Mechanistic Insights: The Liu group in 2019 published a new system to reduce ketones using a cobalt bis-NHC ligand platform (Figure 2a).[6] This ligand design vastly improved the turnover numbers to 2600 and displayed reactivity on more drug-like, late-stage examples. The Qi group soon after asked the question of why this ligand scaffold was so successful and published some crucial insights by studying the mechanism via DFT calculations.[7] They argue that the

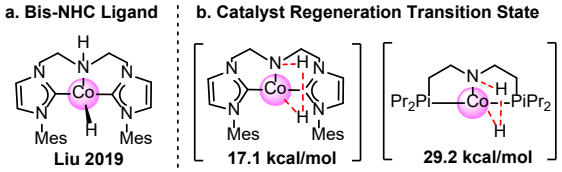

Figure 2: a. Bis-NHC Ligand, b. Catalyst regeneration DFT calculations

key step which differentiates the NHC ligand from the PNP-type ligands is the catalyst turnover step. The energy of the transition state which displays the regeneration of the active catalyst is calculated to be 17.1 kcal/mol with the bis-NHC ligand, but 29.2 kcal/mol with the PNP ligand (Figure 2b). This is proposed to be due to the stabilization of the Cobalt(I) intermediate by the NHC ligand by both sigma donation from the ligand and backbonding from the metal to the ligand. These transition states may explain the drastic increase in turnover the NHC system displayed over the PNP system. The mechanistic insights displayed in this paper are crucial to explaining the reactivity of later systems, and the ability to intuitively design systems which operate via the more successful turnover mechanism.

The transition towards enantioselectivity:

In order to replace the industrially used precious metal catalysts, these base-metal systems need to be rendered asymmetric. The earliest reports of enantioselectivity in cobalt catalyzed carbonyl reductions come from derivatizations of the PNP type ligands published in 2016 and 2021 (Figure 3).[8,9] Due to the previously discussed mechanistic challenges, these ligands were largely unsuccessful, both in terms of turnover and enantioinduction. In 2023 Zhang and coworkers published an asymmetric reduction of alpha-amino ketones (Figure 3).[10] This method was very successful and able to achieve high levels of enantioselectivity and turnover numbers; despite the success of the catalyst this system is not general, as it is only mechanistically feasible for alpha-amino ketones due to the coordination of the amine to the cobalt center. The most recent and successful system was published by Zhang in 2024 (Figure 3).[11] This catalyst was able to achieve turnover numbers of up to 150,000 and high levels of enantioinduction across different classes of substrates. This advancement in turnover may be attributed to the redox non-innocence of the ligand, which helps to stabilize the high energy intermediates.

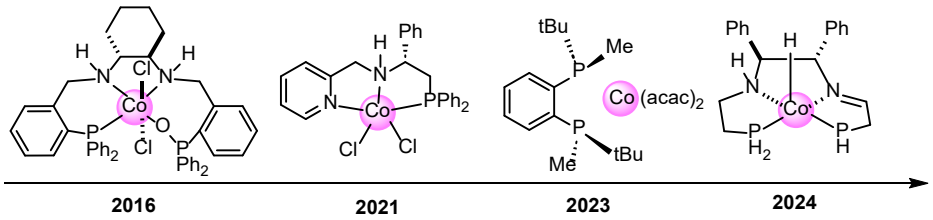

Figure 3: Enantioselectivity Timeline

Outlook

There has been great progress in short amount of time to advance these cobalt based reduction systems. These advancements present an opportunity to replace expensive Ruthenium and Iridium catalysts, which may not be available in the coming years due to the scarcity of material. Although compared to precious metal catalysts, these systems fall short at present, there is continued work in the field to raise the turnover of the base metal catalysts.

References: (1) Noyori, R. (2002), *Asymmetric Catalysis: Science and Opportunities (Nobel Lecture). Angew. Chem. Int. Ed.*, 41: **2008-2022** (2) *Energy Environ. Mater.,* **2019**, 2: 292-312 (3) *Angew. Chem. Int. Ed.,* **2012**, 51: 12102-12106 (4) *J. Am. Chem. Soc.* **2015**, 137, 25, 7998–8001 (5) *Chem* **2019**, 5, 6, 1552 – 1566 (6) *Catal. Sci. Technol.*, **2019**, 9, 5315-5321 (7) *Asian J. Org. Chem.* **2016**, *5*, 1323 (8)*Chinese Chemical Letters* **2021**, 32, 3, 1241-1244 (9) *JACS Au* **2023**, 3, 11, 2981–2986 (10) *J. Am. Chem. Soc.* **2024**, 146, 38, 26416–26426