A green synthesis method-nitrile hydration to synthesize amide

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Abstract: Amide compounds which are closely related to people’s clothing, food, shelter, and transportation play an important role in people’s daily production and life. Therefore, exploring and improving the synthesis of amide compounds is one of the topics that researchers have focused on in recent years. The hydration of nitriles to amides is an environmental-friendly and 100% atom economic method. Among the reported nitrile hydration catalytic systems, metal complexes have attracted considerable attention due to their high catalytic activity, excellent selectivity, mild reaction conditions, and tunability of catalytic performance at a molecular level. In this paper, we summarize the recent progress in the synthesis of metal complex catalysts and understanding of the catalytic mechanism, which provides a basis for the industrialization of metal complex catalysts.

1. Introduction

As a common raw material, amide compounds are widely used in the synthesis of polymers[1] and pharmaceutical molecules. At present, the preparation methods of amides mainly include: carbodiimide condensation method, mixed acid anhydride method, acid halide method, transesterification method, and nitrile hydration method. However, the first several types of synthetic methods have some shortcomings in their applications. For example, the carbodiimide condensation method requires the addition of a co-catalyst, the raw materials in the acid halide method are corrosive and unstable, and the products generated in the transesterification method are not easy to separate[2-4]. In contrast, the nitrile hydration method (Figure 1) not only has 100% atomic economy, but also is an environmentally friendly synthetic method that conforms to the development concept of green chemistry, so it is widely used by scientific researchers.

![Figure 1. The synthesis of amides by nitrile hydration](image)

The traditional nitrile hydration to prepare amides usually requires the participation of strong acids or strong bases. In the presence of strong bases, cyano groups are easily overly hydrolyzed into acids, and the amide product further reacts with the base to form salts, causing difficulty in product separation. Although strong acid can control the hydrolysis in the amide stage, the temperature and the stoichiometric ratio of nitrile to water need to be strictly controlled during the reaction. In order to overcome the disadvantages of traditional inorganic strong acid/strong base catalysis, researchers have developed a variety of new homogeneous[5] or heterogeneous[6-12] catalytic systems for nitrile hydration.
reactions, including nitriles hydrating enzymes\textsuperscript{[13]}, polymetallic oxygen clusters\textsuperscript{[11]}, metal nanoparticles\textsuperscript{[14]}, metal oxides\textsuperscript{[15, 16]}, metal complexes\textsuperscript{[5]}. As a class of molecular catalysts, metal complexes can be controlled by adjusting the structure and quantity of organic ligands. Metal complex catalysts are widely used in nitrile hydration due to the design and controllability of the catalyst. Therefore, this article classifies and summarizes the recent reports of metal-organic complexes catalyzed by the hydration of nitriles to prepare amides. This review mainly focuses on two aspects: the types of metal atoms and the structure of organic ligands.

2. Ruthenium metal complex catalyst

Ruthenium metal complex is a kind of highly efficient catalyst to catalyze the hydration of nitrile. The central metal ruthenium which has a rich oxidation state (from -2 to +8) exhibits a variety of coordination geometric configurations and can form stable complexes with a variety of ligands. In addition, compared with precious metals such as palladium, platinum, rhodium and iridium, the price of ruthenium is relatively cheap. Therefore, ruthenium metal complexes have a huge advantage in catalyzing the hydration reaction of nitrile. In fact, the latest breakthrough in this field is achieved by using metal ruthenium complexes.

![Figure 2. The structure of representative metal complexes](image)

In 2015, Frost found that \textdollar{(η^6-toluene)RuCl_2(κ^1-PTA-P^Pr_2)} (complex 1, in Figure 2) is an efficient catalyst\textsuperscript{[17]}. In the process of nitrile hydration, the catalyst dissociates a chloride ion and turns into \textdollar{(η^6-toluene)RuCl(PTA-P^Pr_2)(NCPh)(H_2O)}^+. The exposed metal center is coordinated with the N atom in the cyano group, and the entire catalytic process is confirmed by mass spectrometry monitoring. Mukhopadhyay\textsuperscript{[18]} synthesized three ruthenium complexes 2-2b (Figure 2) to investigate the effect of
the type and quantity of organophosphine ligands on the activity of ruthenium catalysts. It is found that the catalytic activity of complex 2 is better than that of complex 2a and complex 2b. On the one hand, complex 2 contains two coordinated chloride ions, and the leaving of chloride ions during the catalytic process allows the catalytic active sites to be fully exposed. On the other hand, due to the large steric hindrance of the ligands in 2a and 2b, it is difficult for the nitrile substrates to coordinate with Ru. Therefore, the design of the ligand to easily expose the active sites of metal ruthenium is the key to improving the efficiency of nitrile hydration catalyst. Complex 3[19] is a nitrile hydration catalyst with a half-sandwich structure (Figure 2), and the oxygen and nitrogen atoms in the ligand are involved in the coordination[20-22]. In the presence of strong bases, NaOH deprives the proton of isopropanol, and the chloride ion in complex 3 leaves to form a ruthenium complex coordinated by isopropanol. Subsequently, the alcoholic hydroxyl group undergoes α-β elimination, and the Ru-H active substance is produced. The catalytic mechanism is shown in Figure 3, the cyano group of benzonitrile replaces the nitrogen atom in the oxazoline to coordinate with the metal ruthenium, and then the water molecules in the solution attack the C≡N bond to obtain the amide product.

Figure 3. Catalytic cycle of complex 3

During the hydration process of nitriles, the ligand not only affects the exposure of the metal active center, but also provides the intramolecular addition of hydroxyl to the substrate, reducing the activation energy of the reaction. Lopez[23] designed ruthenium metal complexes (4 and 4a, in Figure 2). Compared with complex 4, the catalytic activity of complex 4a is significantly reduced. This is because when the phenyl group replaces p-cymene, the change in the electron donating ability of the ligand leads to an increase in the Gibbs free energy barrier for the intramolecular addition of the hydroxyl group in the complex to the substrate.

The hydration process of nitrile usually requires the coordination of the cyano group with the metal center, and the electron deficiency of the metal reduces the activation energy of the cyano group hydration. In recent years, studies on the hydration of nitriles by ruthenium metal complexes have found that the design and regulation of ligands can change the catalytic activity of the catalyst to achieve a more ideal catalytic effect.
3. Non-ruthenium metal complex catalyst

3.1 Precious metal complex catalyst
In addition to ruthenium metal complexes, there are many noble metal complexes used to catalyze the hydration of nitriles. Osmium, as a group metal of ruthenium, also has good catalytic properties. In 2018, Cadierno synthesized a half-sandwich Os(II) complex\cite{24} containing different amino phosphine ligands [OsCl$_2$(η$^6$-p-cymene)PPh$_3$$_n$(NR$_2$)$_n$] (n = 1-3). Taking complex 5 as an example (n = 1) (Figure 2), this complex can quickly and selectively convert a variety of nitrile substrates into target amide compounds in pure water. The catalytic system not only has higher activity, but also does not need to add any acidic or basic additives. The mechanism investigation found that the ligand in 5 will be hydrolyzed in solvent water, and the PN single bond will be broken to form a P-OH bond. At this time, 5 will be converted to 5a ([OsCl$_2$(η$^6$-p-cymene)(PPh$_2$OH)]) (Figure 2). The hydroxyl group of the phosphine ligand and the substrate nitrile undergo intramolecular addition, thereby generating a metal five-membered ring transition state, and the nucleophilic attack of water causes the five-membered ring to open to form a product.

In recent years, in the periodic table, rhodium adjacent to ruthenium is also often used to catalyze the hydration of nitriles. In 2020, Czégéni\cite{25} mixed 1,3-diarylimidazole or 1,3-diarylimidazole salt, RhCl(cod)$_2$ and K$_2$CO$_3$ in toluene solution, and stirred at 70°C to react to form complex 6 ([RhCl(cod)(NHC)) (cod = η$^4$-1,5-cyclooctadiene, NHC = nitrogen heterocyclic carbene) (Figure 2). Complex 6 can catalyze the hydration of aromatic nitriles in the mixed solvent of water and 2-propanol. With benzonitrile as the substrate, the TOF of the reaction can reach 93 h$^{-1}$, but the reaction needs to add a basic cocatalyst (NaOH, KOH, K$_2$CO$_3$).

3.2 3d metal complex catalyst
Most nitrile hydration catalysts contain precious metals. Although the efficiency of the hydration reaction is improved, the catalyst is expensive and the production cost is high. In order to solve this problem, researchers have begun to explore cheap 3d metal complexes to catalyze the hydration of nitriles. As 3d metals, manganese and nickel which are cheaper than precious metals have industrial application prospects. In 2018, Anderson\cite{26} synthesized the first Mn complex for hydration of nitriles, but this catalyst will over-hydrolyze nitriles into acids. In addition, Ni$^{II}$ catalysts containing nitrogen-containing heterocyclic carbene ligands\cite{27} (Complex 11, in Figure 2) is reported to be used to catalyze the hydration reaction of nitrile, showing good catalytic activity.

4. Conclusion and Perspective
At present, noble metal complexes play an important role in the catalysis of nitrile hydration, especially ruthenium metal complexes are favored by scientific researchers for their excellent chemical properties. Although the development of non-precious metal catalysts is not yet mature, it has great development potential in industrial applications because of its low price. As a type of molecular catalyst, the catalytic performance of metal complex can be designed and adjusted, and the mechanism of nitrile hydration catalysis can be understood at the atomic/molecular scale, providing a theoretical basis for the design of high-efficiency catalysts.

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