Research Progress of Suzuki Reaction Catalyst in the Synthesis of Sartan API

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Abstract: It is crucial in the pharmaceutical industry to study and develop a new class of nanocatalysts suitable for Suzuki coupling reactions and capable of being applied to the synthesis of sartans based pharmaceuticals, which are able to improve the synthesis efficiency of sartans based on their ability to resolve current scientific problems in the synthesis process, including the preparation and characterization of nanomaterial supported metal copper salt catalysts, the examination of the performance of metal catalysts in the synthesis of sartans based pharmaceuticals, and so on.

Keywords: Suzuki coupling reaction, Catalyst, Research progress.

1. Introduction

Sartans are prescribed for antihypertensive treatment, and hypertension is a high incidence disease worldwide and one of the chronic conditions with the highest prevalence. Hypertension is ostensibly an independent disease, but if not treated properly it has the potential to initiate a pathology that can trigger a cascade of complications such as cerebral stroke, myocardial infarction, and renal failure. Along with the continuous improvement of the people's quality of life, at the same time, with the continuous change of national dietary structure, hypertension has become an important risk factor for cardio cerebrovascular disease and an important threat point to cause human death. Pharmacotherapy remains the mainstay of treatment of hypertension in the world today, therefore, the study and development of hypertensive drugs is an important topic facing pharmaceutical workers.

Characterized by an entirely new mechanism of antihypertensive action, sartans and valsartan are the most representative with few toxicities, few side effects, good effects, and long duration of action, making them the most potential antihypertensive drugs in development and are listed by the World Health Organization as first-line antihypertensive drugs. Therefore, this project focuses on the synthesis method of sartansine biphenyl, which is an important intermediate required in the synthesis process of sartans, aiming to reduce the synthesis cost and improve the synthesis efficiency of this intermediate.

At present, there are two main synthetic methods for sartansine, one is non catalytic synthesis, the other is transition metal catalyzed synthesis. The latter is mainly adopted in the practical production, the transition metal catalyzed synthesis method, that is, employing halogenated aromatic hydrocarbons as starting materials, under the catalysis of transition metals to react with organometallic reagents, organoboron reagents and so on. Among the above reactions, the transition metal catalyzed reaction of halogenated arenes with organoboron reagents, the Suzuki coupling reaction, is currently the most common synthetic approach (Figure 1). The reaction mechanism of Suzuki coupling reaction is shown in Figure 2. But with the increasing demand for drugs in recent years, the problem also arises. Mainly exist in the following aspects (i.e., problems that business wants to solve at the moment): (1) noble metal palladium is expensive; (2) O-chlorobenzonitrile has low activity and low reaction yield; (3) Phosphine residues are not easily removed; (4) The palladium catalyst is a homogeneous catalyst, consumed in the reaction, and cannot be recycled.

This study proposes novel solutions to the above faced problems, i.e., developing a novel catalyst to replace the original palladium catalyst, achieving cheap production, efficient catalysis and recycling of the catalyst.

To address the problem that catalysts are not easily recyclable, copper salt catalysts attached to materials are discussed below on the basis of literature from several perspectives:

2. Novel Catalyst Advantages Attached to Materials

Currently attachable materials develop rapidly and have a variety of options:

2.1. Graphite Episomes

In 1994, a Suzuki coupling reaction catalyzed using a Pd / C catalyst was first reported by Marck et al. Higher reaction yields were obtained with sodium carbonate as base, bromoarenes, and triflates as substrates with or without the addition of the ligand triphenylphosphine. However, when chloroarenes were used instead of bromoarenes, the results showed that the catalytic activity of the ligand free catalytic system was not high. In 2001, inspired by the study of Marck et al., leblond et al., investigated the Pd / C catalytic system for catalyzing the Suzuki coupling reaction in which chloroarenes participated under the condition of no phosphine ligands, which could obviously improve the selectivity and yield of the reaction by screening suitable reaction solvents. The reaction yields of chloroarenes bearing electron withdrawing groups are all up to 79% using an aqueous solution of dimethylacetamide (DMA) (DMA / H2O = 20 / 1) as solvent and Pd / C as catalyst. Simeone et al found that the addition of multistituted biphenylphosphine ligands to the system could obviously improve the reaction yield of electron donating chloroarenes with phenylboronic acids, especially the addition of two ligands, mephos (2-dicyclohexylphosphino-2' - methylbiphenyl) and xphos (2-dicyclohexylphosphino-2', 4', 6' - triisopropylbiphenyl),
brought the conversion of the reaction up to 91%.

2.2. Metal Oxide Support

In 1999, kabalka et al applied a ligand free, Pd (0) - doped KF / Al2O3 catalytic system to a solvent-free Suzuki coupling reaction and showed that iodoarenes all achieved good reaction yields with bromoarenes, whereas the catalytic effect on chloroarenes was not significant. Based on this research, vilemin and kabalka et al., both tried microwave heating method to catalyze the solvent-free iodoarene involved Suzuki coupling reaction using PD doped KF / Al2O3 catalyst, and found that it took only a few minutes for the experiment to complete the reaction and obviously increased the reaction rate. In 2005, Gao et al grafted azacyclic carbene palladium complexes onto thin polymer shells with iron oxide nanoparticles as cores to produce supported catalyst L1, which was applied to catalyze the Suzuki coupling reaction involving bromoarenes and iodoarenes, and found that the catalyst exhibited excellent stability and high activity (yields ranged from 70% to 89%) with only 0.015 mol% catalyst used to recover the catalyst using a magnet. Repeated 5 times and found that the activity of the catalyst did not decrease.

2.3. Aluminosilicate Microporous Zeolite

2.3.1. Negative Support

Garci et al used alkaline zeolite as a support to load Pd onto the support to prepare an alkaline zeolite supported palladium catalyst and applied the catalyst in Suzuki coupling reaction for the first time, because the zeolite framework oxygen itself can act as an effective base site, so the catalyst does not need to add the base again during use, and the solvent toluene can avoid the loss of metal. Also, we compared the reusability of the catalysts and found that the catalysts washed with a mixed solution of water, ethanol, and ethanol / water could also be reused, except for a slight decrease in the activity of the catalysts, which was more obvious after washing with water. Subsequently, Bulut and artok et al.25 prepared nay type zeolite zeolite zeolite supported Pd (0) and Pd (II) catalysts, respectively, and applied them in Suzuki coupling reactions. In the absence of ligand addition, this type of supported palladium catalyst catalyzed the Suzuki coupling of bromoarenes and iodoarenes, and higher yields were obtained, however, the catalytic activity of this type of supported catalyst for chloroarenes was not very good. In addition, they made an important conclusion: the catalytic reaction is carried out on the outer surface of the catalyst, which can also be reused after it has been regenerated.

2.4. Silica Mesoporous Material Loadings

2.4.1. High Molecular Weight Loadings

At present, the research on silica mesoporous materials mainly includes: M41S, sba-n, FSM-16, msa-n, fdu-n, HMS, etc. Among them, MCM-41 is a two-dimensional hexagonal structure, the pores are regular and ordered, and the presence of bare silicon hydroxyl groups on the surface facilitates modification, so it has been applied to many research efforts in catalysis, and has been favored by many scientific workers. In 2004, Kim et al used PD (PPh3) 4, tetrapolyethylene glycol, methyl orthosilicate, etc., to synthesize a silica supported palladium catalyst via a one pot procedure and to catalyze the Suzuki coupling involving bromoarenes and iodoarenes, which showed high activity with greater than 86% reaction yield, but the catalytic effect on chloroarenes was not as good (less than 5% reaction yield). In 2008, domestic researcher Tao Zhang et al synthesized mesoporous molecular sieves SBA-15 modified on the inner and outer surfaces by using 3-Mercaptopropyltrimethoxysilane and trimethoxyxysilane as the inner and outer surface modifiers, respectively, to produce a palladium supported catalyst, and applied it to the Suzuki coupling reaction of p-bromonitrobenzene and phenylboronic acid involved, which showed tetrabutylammonium base as a base in supercritical carbon dioxide medium Reaction at 90 ° C for 48 h afforded the coupled product in 71% yield, and the catalyst was stable without black palladium evolution, exhibiting good catalytic activity. In the last two years, bhunia et al prepared mesoporous silica material MCM-41 supported Pd (II) catalyst with 0.3 wt% of palladium in the catalyst. Application of this protocol to the Suzuki coupling involving chlorobenzene, bromobenzene, and iodobenzene revealed that both iodobenzene and bromobenzene can be converted in 100% yield within 2-3 h, and the yields are also all as high as 99%, whereas the catalytic effect of chlorobenzene is not significant.

2.5. High Molecular Weight Loadings

2.5.1. Natural high molecular weight supported catalysts

Natural polymers have been selected as supports for catalysts and have gradually attracted the interest and attention of a wide range of researchers due to their advantages such as low price, abundant reserves, and biodegradable. Natural polymeric compounds mainly include the following: starch, cellulose, protein, chitosan and lignin, etc. A modified chitosan supported palladium catalyst was applied in the Suzuki coupling reaction, and the study showed that the lower yield of 8 from the reaction may be due to decomposition of the catalyst by the nitrogen containing substrate. In 2005, Gronow et al applied a expanded starch Schiff base supported palladium catalyst to the Suzuki coupling of bromobenzene with phenylboronic acid and found that the catalyst had poor reusability, with a reaction yield of only 17% after 3 reuses.

2.5.2. Synthesis of High Molecular Weight Supported Catalysts

Synthetic polymer compounds mainly include: polyethylene, polyvinyl chloride, polystyrene, plastic, synthetic rubber, etc., at present, there are also many reports on the synthesis of high molecular weight supported palladium catalysts. According to different requirements, various designs and combinations are performed to prepare
synthetic polymeric carriers that meet the requirements.

3. Nano Copper Catalyst Advantages

Compared with the general catalysts, nano catalysts can exhibit more excellent catalytic activity and selectivity because of various special effects such as large specific surface area, high surface energy, short diffusion channels within crystals, strong adsorption capacity, and many catalytic active sites on the surface, which make it possible to not only reduce the catalyst dosage, control the reaction rate, and improve the reaction efficiency, but even make the otherwise impossible reactions possible.

3.1. Hollow Microspheres

Hollow microspheres are a kind of special core-shell nanomaterials whose core is air or solution, which have a wide application prospect in catalysis because of their unique hollow structure. Hollow copper microsphere catalysts were prepared by using ZSM-5 molecular sieves as templates. Cu\(^{2+}\) was first adsorbed on the surface of molecular sieves, followed by nanoparticles that were reduced into copper, which acted as seeds and self catalysts, a large amount of copper was continually reduced, gradually aggregated into copper shells, and finally removed the molecular sieves by hydrofluoric acid to prepare hollow copper microspheres.

Hollow copper microspheres have good catalytic activity for the Suzuki coupling reaction, and the hollow structure increases the surface area of the catalyst, making more contact in the reaction, and the coupling yield also grows obviously in a certain range with the increasing amount of catalyst. Through the experiment, the cycle was used 3 times, and the activity of the catalyst had no obvious decline.

3.2. Flower Like Nanomaterials

Flower like nanomaterials are a kind of nanomaterials consisting of some nanorods and nanosheets jointly connected by the center of the particles, with a three-dimensional structure. Flower like nanostructures were used as the support to prepare supported copper catalysts. First, the molecular sieves type 5A were soaked using hydrofluoric acid to obtain flower like nanostructures. Flower like nanostructures were then electroless coated with copper to prepare supported copper catalysts.

Experimentally, it is thought that in heterogeneous catalytic systems the whole process of catalysis is completed at the surface of the solid catalyst, which, within a fixed time frame, has a greater chance of contacting the reactant in the solvent as the catalyst amount increases. However, more catalyst dosage did not substantially contribute to the improvement in coupling yield. The coupling reaction yield was still above 30% after 3 times of catalyst cyclic use.

4. Conclusion

With advances in modern medicinal chemistry and organic chemistry, Suzuki reaction catalysis will usher in a new height in the future.

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