



Transition-metal and organo-catalysis in organic synthesis: Metal-catalyzed reactions

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Abstract

Transition metal catalyzed reactions are fundamental for the synthesis of organic molecules. Homogeneous catalysis offers a very fast approach to new organic compounds, which are then tested for their desired properties, and thus helps to solve current health, environmental, energy storage and other problems. The chemical community has witnessed the fruitful growth of the powerful strategy of transition metal catalysis. Demonstrating the possibility of overcoming any inhibition or quenching by concomitantly merging simple amine catalysts, providing nucleophilic coupled with transition metal activated electrophilic intermediate. Novel strategies adopting the stereodivergent preparation of a wide range of important compounds with multiple stereocenters and with diversified functionalities, which additionally expands the chemical space. We believe this strategy will continue emerging into new innovative reactions allowing the coupling of more challenging components with indefinite chemical transformations.

Keywords: transition metal, organo-catalysis, Homogeneous catalysis, organic synthesis, multiple stereocenters

Introduction

Transition metals are often confused with "d-block" metals in the periodic table. Although transition metals belong to the d-block of the periodic table of the elements, not all d-block metals can be called transition metals. For instance, scandium and zinc are not transition metals, although they are d-block elements^[1]. For a d-block element to be a transition metal, it must possess an incompletely filled d-orbital. Transition metals are any of various metallic elements such as chromium, iron and nickel that have valence electrons in two shells instead of only one. A valence electron refers to a single electron that is responsible for the chemical properties of the atom. Transition metals are good metal catalysts because they easily lend and take electrons from other molecules^[2].

A catalyst is a chemical substance that, when added to a chemical reaction, does not affect the thermodynamics of a reaction but increases the rate of reaction. Transition metal catalyzed cross-coupling reactions to form C-C, C-N, C-O and C-S bonds are among the most powerful organometallic transformations in organic chemistry^[3-4]. In the past few decades, there has been remarkable progress in the cross coupling reactions of organometallic reagents containing various nucleophiles such as B, Mg, Li, Sn, Al, Zn with unsaturated electrophiles containing alkenyl, aryl, allyl, alkynyl groups. Transition metals act by forming complexes with the reagent. If the transition state of the reaction demands electrons, the transition metals in the metal complexes undergo oxidation or reduction reactions to supply electrons.

If there is an excess buildup of electrons, the transition metals can hold the excess electron density, thereby helping the reaction to occur.

The property of transition metals to be good catalysts also depends on the absorption or adsorption properties of the metal and the transition metal complex^[5-6].

Transition Metal Catalyzed Coupling Reactions

Catalytic nucleophilic substitution reactions comprise some of the most commonly used catalytic processes in synthetic organic chemistry.

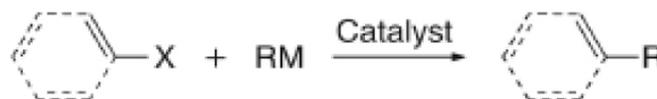
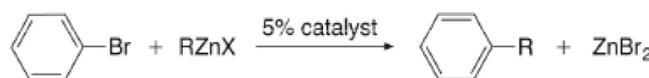


Fig 1

The original cross-coupling reactions formed C-C bonds, however catalytic carbon heteroatom C-X formation has now been developed where X = N, O, S, P, Si, B.

Negishi Coupling

The preparation of unsymmetrical biaryls in good yields via nickel- or palladium-catalyzed coupling of organozinc compounds with various halides (aryl, vinyl, benzyl, or allyl). The Negishi reaction has broad scope, and is not restricted to the formation of biaryls. Pd catalysts tend to be less sensitive to oxygen and are believed to be less toxic than their Ni counterparts. Furthermore they tend to react without the intervention of radical intermediates that can lead to side products (e.g. homocoupling, racemization, Isomerization)^[7-9].



Catalyst = $(\text{PPh}_2)_4\text{Ni}$ from $\text{Ni}(\text{acac})_2/\text{PPh}_3/\text{Bu}^t_2\text{AlH}$
or $(\text{PPh}_3)_2\text{PdCl}_2$ and Bu^t_2AlH

Fig 2

Miyaura Borylation

The coupling of organoboron reagents has become the most commonly used cross-coupling process. Organoboron reagents are less toxic than organotin reagents and tend to undergo coupling reactions in the presence of a variety of functional groups. The Miyaura borylation reaction enables the synthesis of boronates by cross-coupling of bis (pinacolato)diboron with aryl halides and vinyl halides [10-11].

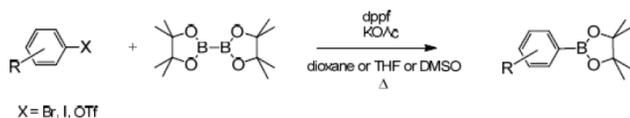


Fig 3

Suzuki Coupling

The coupling of organoboron reagents has become the most commonly used cross-coupling process. Organoboron reagents are less toxic than organotin reagents and tend to undergo coupling reactions in the presence of a variety of functional groups. Like neutral organosilicon groups (Denmark rxn), however, neutral organoboron reagents do not undergo metal-catalyzed cross-coupling without an additive. Suzuki showed that addition of a hard base, e.g. OH⁻ or F⁻, causes the organoboron reagent to undergo cross-coupling by generating a four-coordinate anionic organoboron reagent that transfers the organic group from boron to the metal catalyst [12].

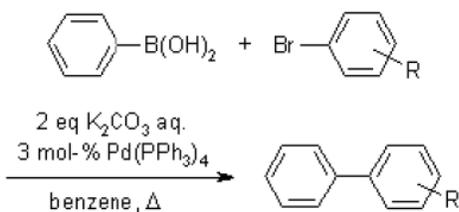


Fig 4

Organocatalysis

Organocatalysis uses small organic molecules predominantly composed of C, H, O, N, S and P to accelerate chemical reactions. The advantages of organocatalysts include their lack of sensitivity to moisture and oxygen, their ready availability, low cost, and low toxicity, which confers a huge direct benefit in the production of pharmaceutical intermediates when compared with (transition) metal catalysts. Organocatalysts for asymmetric synthesis can be grouped in several classes:

- Biomolecules: proline, phenylalanine. Secondary amines in general. The cinchona alkaloids, certain oligopeptides.
- Synthetic catalysts derived from biomolecules.
- Hydrogen bonding catalysts, including TADDOLS, derivatives of BINOL such as NOBIN, and organocatalysts based on thioureas.
- Triazolium salts as next-generation Stetter reaction catalysts [14-16].

Shi epoxidation

The Shi epoxidation is a chemical reaction described as the asymmetric epoxidation of alkenes with oxone (potassium peroxymonosulfate) and a fructose-derived catalyst. This

reaction is thought to proceed via a dioxirane intermediate, generated from the catalyst ketone by oxone (potassium peroxymonosulfate) [17].

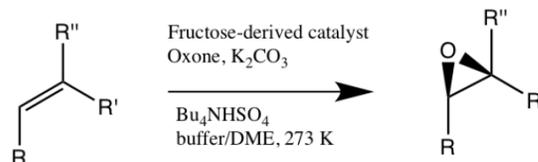
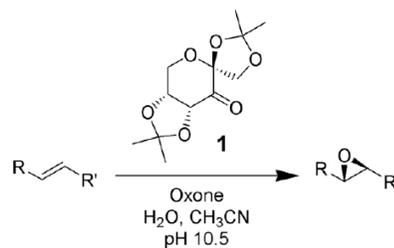


Fig 5

Asymmetric Michael reaction

The scope of asymmetric Michael additions is the most common methods involve chiral phase transfer catalysis, such as asymmetric quaternary ammonium salts derived from the Cinchona alkaloids; or organocatalysis, which uses enamine or iminium activation with chiral secondary amines, usually derived from proline. In the reaction between cyclohexanone and β-nitrostyrene sketched below, the base proline is derivatized and works in conjunction with a protic acid such as p-toluenesulfonic acid:

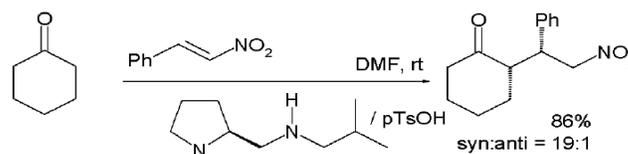


Fig 6

The synthesis of warfarin from 4-hydroxycoumarin and benzylideneacetone

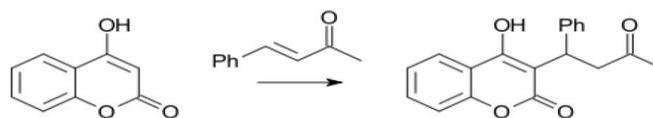


Fig 7

The **Stetter reaction** is a reaction used in organic chemistry to form carbon-carbon bonds through a 1,4-addition reaction utilizing a nucleophilic catalyst [18].

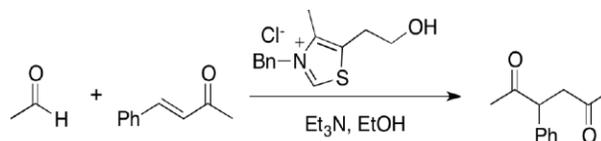


Fig 8

Asymmetric Mannich reactions

The asymmetric Mannich reaction with an unmodified aldehyde was carried with (S)-proline as a naturally occurring chiral catalyst.

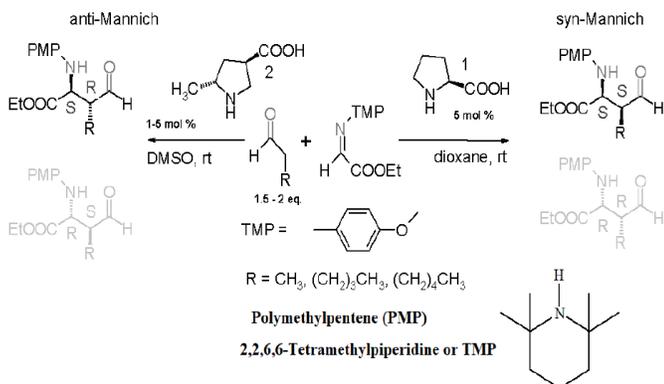


Fig 9

Kumada Coupling

Kumada coupling involves coupling of a Grignard reagent with alkyl, vinyl or aryl halides in the presence of a Ni transition metal catalyst providing an economic transformation [19].

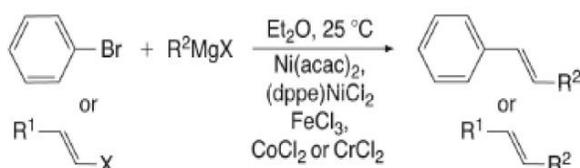


Fig 10

Cross-Coupling Reactions

Cross-coupling reactions are those in which two different starting materials, each of which is usually endowed with an activating group, are reacted together with the aid of a metal catalyst. The result is the loss of the two activating groups and the formation of a new covalent bond between the remaining fragments. In these reactions, carbon-carbon bond forming reactions can be performed by the combination of electrophilic carbon species of aryl/vinyl halides and organometallic agents of Grignard reagents and organoboron compounds. Also, the use of nucleophilic hetero atoms such as phenols and amines is efficient to form carbon-hetero atom bonds. By the development of these synthetic methods, substitution reactions to sp² carbon and sp carbon are easily accomplished while it had been difficult to perform these transformations by classical synthetic reactions without using metal catalysts [20-21].

Two types of coupling reactions are recognized

Heterocouplings couple two different partners, for example the Heck reaction of an Alkene (RC=CH) and an Alkyl halide (R'-X) to give a substituted Alkene (RC=CR').

Homocouplings couple two identical partners, for example, the Glaser coupling of two Acetylide (RC≡CH) to form a dialkyne (RC≡C-C≡CR).

- The Heck reaction (also called the Mizoroki-Heck reaction)

It is the chemical reaction of an unsaturated halide (or triflate) with an alkene in the presence of a base and a palladium catalyst (or palladium nanomaterial-based catalyst) to form a substituted alkene.

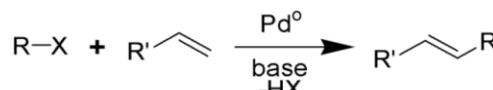


Fig 11

▪ The Glaser coupling

It is a type of coupling reaction. It is by far the oldest acetylenic coupling and is based on cuprous salts like copper (I) chloride or copper (I) bromide and an additional oxidant like oxygen. The base in its original scope is ammonia. The solvent is water or an alcohol [22-23].

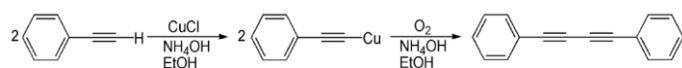


Fig 12

Conclusion

The use of enzymes, organo-catalysts or transition metal catalysts, as opposed to the employment of stoichiometric quantities of other traditional promoters of different organic synthetic processes (like, inorganic/organic bases, Brønsted acids, radicals, etc.) has allowed the discovery of a great number of new synthetic protocols within the toolbox of organic chemists. Moreover, the employment of the aforementioned catalysts in organic synthesis permits the diminution of the global energy demand and production cost, the enhancement of both the chemo selectivity and stereo selectivity of the global process and the reduction of metal-, organo- or bio-catalyst consumption, thanks to the possible recycling of the catalysts; all these being synthetic concepts closely related with the principles of so-called green Chemistry.

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