The Bombay Technologist

ARTICLE

Nobel Prize Winning Transition-Metal Mediated Processes

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Transition-metal mediated processes have revolutionized synthetic organic chemistry with the introduction of several Nobel Prize winning reactions which have been highlighted in this review.

Introduction

Organic chemistry has undergone a tremendous change in the past several decades with the introduction of a large number of ‘Named reactions’ providing easy access to molecules of synthetic relevance. Although, general C-C bond formation processes have had an amazing impact on the way synthesis has been carried out, these processes most commonly suffer from a wide variety of problems ranging from lower yields, exceedingly high reaction temperature, longer reaction times and poor selectivity.[1] To address this issue, researchers have developed efficient metal-mediated catalytic alternatives that have expedited these synthetic processes to a larger extent. Transition-metal mediated processes are one of the most powerful C-C bond forming technologies that have found applications in academia as well as industries for the synthesis of simple to complex molecules[2] having useful biological applications. The advent of transition-metal catalyzed reactions, however, dates back to the early 1900s and since then has only undergone rapid development[3].

Fundamentally, the ability of the transition metals to catalyze reactions has been attributed to the electronic configuration of these metals, which are also characterized by the presence of the d electrons capable of exhibiting variable oxidation states essential for the enhanced catalytic activity[4]. The best catalysts or catalytic activity has been observed for the metals present in the first 3 transition series. This series of transition metals are versatile and have given researchers solutions to synthetic problems on academic as well as industrial scales contributing immensely towards the development of several important industrial processes[5]. The founders of these processes who recognized the potential of employing transition metals as the rate-accelerating catalysts have won laurels from world over. Culmination of these achievements allowed the scientists to be recognized with the most prestigious award in science – Nobel Prize in Chemistry – with the first one awarded as early as 1909 and the most recent was in 2010[6].

The current review is a compilation of some of these contributions which have found excellent industrial applications with examples provided to highlight the commercial relevance of these processes.

Early years of Transition-Metal mediated processes

The idea of utilizing transition metals as reagents or catalysts comes from the fundamental understanding of a broader area of research called Organometallic Chemistry[7]. The presence of a metal-carbon bond signifies the formation of an organometallic reagent which in early years of scientific development was restricted to the alkali and alkaline earth metals. One of the most illustrious examples of organometallic compound finding instant recognition is the Grignard reagent named after Victor Grignard[8]. Within 13 years of the introduction of the Grignard reagent in 1899, Victor Grignard was recognized with the Nobel prize in 1912[9]. Although, the real contribution of organometallic chemistry towards the development of Transition-metal mediated processes was recognized by William Christopher Ziese in 1831 by the synthesis of what we now know as Ziese’s salt[10]. A platinum-ethylene complex that was prepared for understanding the reaction of $PtCl_2$ with boiling ethanol laid the foundation for the application of transition metals in synthetic organic chemistry. Several other contributions during the late 1800s and early 1900s accelerated the development further[11].

1. Nitric acid synthesis from ammonia (Wilhelm Ostwald, 1909)

The earliest example for the application of a transition metal in catalysis was provided by Wilhelm Ostwald who was born on September 2, 1853 in Latvia. After his early education in Latvia, Ostwald moved to Leipzig University, Germany as a full professor of physical chemistry[12]. Besides giving the research fraternity with an industrial scale synthesis of nitric acid from ammonia using platinum and/or rhodium catalyst, he is also credited with the meteoric rise of physical chemistry alongside scientific geniuses such as Svante August Arrhenius (Nobel prize, 1903), Walther Hermann Nernst (Nobel prize, 1920), Jacobus Henricus van’t Hoff (Nobel prize, 1901) [13].

The development of the Ostwald process for nitric acid synthesis is an excellent example for an academic exploration initiated by Charles Frederic Kuhlmann in 1838 to be taken to the commercial level. Such an adventure would have also been a failure due to the lack of commercial ammonia production possibility[14]. However, with the advent of Haber-Bosch ammonia synthesis process, Ostwald was able to realize his dream of preparing nitric acid using platinum/rhodium catalyst on large scales eventually promoting fertilizer and explosives production.

2. Hydrogenation of organic compounds (Paul Sabatier, 1912)

Paul Sabatier who was born on November 5, 1854 in Southern France, completed his education and moved to University of Toulouse where he went on to develop his concept of catalysis (heterogeneous catalysis) and applied these investigations towards the area of hydrogenation of organic compounds[15]. The concept of finely divided transition metal catalysts (mainly nickel) to be employed as hydrogenation catalysts was put forth by Sabatier for the first time. In the subsequent years, Raney nickel was developed as a highly active heterogeneous catalyst for hydrogenation (Murray Raney, 1926) [16].

The work done by Sabatier has greater significance as it was able to deliver two important concepts in terms of catalysis and hydrogenation of organic compounds; both being non-existent during the 1900s[17]. These results proved to be basis of the commercial production of margarine, oil hydrogenation and many more processes including synthetic methanol industries. Sabatier's work on catalysis is recognized as the most fundamental and providing extensive insights into the concept of catalytic intermediates which was far ahead of the time and still stands a concept referred by those working in the area of catalysis[18].

3. Coordination chemistry of transition metals (Alfred Werner, 1913)

Although the work done by Alfred Werner is not directly related to transition metal-catalyzed reactions, the fundamental understanding of the coordination chemistry of transition metals which forms the basis of their catalysis applications is of great scientific importance. Alfred Werner was born on December 12, 1866 and after completing education took up an independent research career in the University of Zurich as a full professor at a young age of 29 years[19].

Werner's work involving the synthesis of coordination compounds of cobalt as the transition metal is still regarded as classics of organometallic chemistry. His most memorable contribution to coordination chemistry comes from an example of a cobalt complex which was resolved after 1000 recrystallizations and was shown to have an extraordinarily high specific rotation of 36,000°.

4. Haber ammonia synthesis (Fritz Haber, 1918)

Fritz Haber has been credited with the commercial scale synthesis of ammonia during the early 1900s[20], a common feedstock for the synthesis of urea as fertilizer and various nitrates as explosives as well as nitric acid (Ostwald process) [21]. Born in a merchant family on December 9, 1868 in Breslau, Germany, Fritz Haber studied chemistry under some of the illustrious names in science of those times namely, Bunsen, Hoffmann and Liebermann. He later was appointed as a Professor and director of Institute of Kalsruhe.

His initial work on the production of ammonia by the fixation of nitrogen from air was performed at relatively higher temperature of 1000ºC between N_2 and H_2 (source: natural gas or methane) in the presence of Fe as a catalyst. However, poor yields prompted Haber to screen a range of metal catalysts (Fe, Os and Ru) [22] for the improvement of the catalytic conditions. Eventually, it was found that in the presence of osmium or iron catalyst the production of ammonia could be carried out at pressures of 150-200 atmospheres and 500 ºC reaction temperature. Further modification of Haber process also allowed the synthesis of ammonium sulfate as a fertilizer.

5. Period of 1925 to 1958

The period between the 1920s till the late 1950s was dominated heavily by the organic chemists such as Robert Robinson (Bio-active molecule synthesis, 1947) [23], Otto Diels and Kurt Alder (Diels Alder reaction, 1950)[24] and Linus Pauling (Chemical bond, 1954)[25]. Besides these contributions, researchers contributing in the area of radioactivity were also recognized by the Nobel committee. During this period the only significant contribution involving the transition metals was provided by Richard Adolf Zsigmondy (Nobel prize in 1925) demonstrating the heterogeneous nature of colloid solutions (primarily gold) and fundamentals related to colloidal chemistry. Similarly, two other contributions during this period provides an insight into the usefulness of transition metals not just in synthesis but also in biology, Hans Fischer (Haemin synthesis which contains Fe, 1930) and Frederic Sanger (Insulin containing Zn, 1958).

6. Ziegler-Natta Polymerization (Karl Ziegler and Guillo Natta, 1963)

The early 1900s saw Europe in a major political turmoil because of the conflicts between different countries. One of the major requirements for maintaining the health of the population was sanitation and cleanliness. Production of soap and detergents in the post-war era increased dramatically and to meet the demands of the growing European population, newer methods of synthesis of soaps (long chain fatty acid sodium salts) was needed. Karl Ziegler who was born on November 26, 1898 in Helsa, Germany first introduced aluminium based compounds (Et_3Al or triethylaluminium) for the oligomerization of ethylene under high temperature and pressure conditions providing access to long chain fatty alcohols as precursors for soaps and detergents[26]. Ziegler was the director of the Max-Planck-Institut für Kohlenforschung where he developed the aluminium chemistry.

Karl Ziegler is also credited to be one of the founding fathers of an area of insertion polymerization which was discovered by him as a continuation of the work on the aluminium-based oligomerization of ethylene[27]. An exploration into the possibility of lowering the reaction temperature as well as pressure of the oligomerization process, Ziegler discovered that an organometallic mixed catalyst obtained by the combination of diethyl aluminium chloride and a transition metal namely, titanium tetrachloride[28], proved to be most effective in providing high-density polyethylene for the first time at ambient temperature and pressure. This discovery by Ziegler has proved to be groundbreaking as it paved the way for the rapid growth of the polymer industry worldwide. In 1955, Ziegler discovered another interesting aspect about insertion polymerization while working with propylene as the feed instead of ethylene. For the first time, it was observed that the organometallic mixed catalyst provided a well-defined polymeric material (isotactic polypropylene - consisting of methyl groups in the same plane) exhibiting excellent mechanical properties. This unique selectivity obtained in case of the Ziegler catalytic system was explained many years later by the Cossee-Ariman mechanism put forth by E. Ariman and P. J. Cossee[29].

Around the same time as Ziegler's discovery of isotacticity in the polymerization of propylene, Guillo Natta from Institute of Technology, Milan, Italy reported another intriguing result obtained by the replacement of $TiCl_4$ in the organometallic mixed catalyst with VCl_4 (vanadium tetrachloride). The result of this change provided an exclusive syndiotactic polypropylene (methyl groups place alternately above and below the plane)[30]. Natta for this result shared the Nobel prize with Ziegler as both these pioneering technologies have found applications in day to day life.

7. Sandwich compounds (Ernst Otto Fischer and Geoffrey Wilkinson, 1973)

Organometallic chemistry was further advanced by the synthesis of sandwich compounds of Fe and Ni (Ferrocene and Nickelocene) by Ernst Otto Fischer and Geoffrey Wilkinson in the mid-1900s[31]. The name sandwich compound comes from the idea to sandwich a transition metal ion between molecules such as cyclopentadienes, benzene etc. Although the catalytic application for these molecules wasn't explored by Fischer and Wilkinson, recent literature suggests the employment of ferrocene-based phosphine[32] containing ligands namely, diphenylphosphino ferrocene (dppf) as activating ligand in transition metal-catalyzed processes[33].

8. Enantioselective Synthesis (William Knowles, Ryoji Noyori and Barry Sharpless, 2001)

Synthesis of chiral compounds have wide-reaching applications in the field of natural product synthesis, bio-active drug synthesis and many more. Achieving enantioselectivity in synthesis is a challenge that many of the researchers have taken up in the past several decades. Three such scientists who through their extraordinary work on enantioselective synthesis demonstrated the possibility of achieving excellent selectivity[34]. Several industrially relevant processes have been initiated based on the work done by them. William Knowles has been credited with the development of Rhodium-catalyzed asymmetric hydrogenation reactions and went onto share the Nobel prize with Ryoji Noyori whose Rh-based Noyori catalyst has revolutionized industrial scale synthesis[35]. Some of the industrially relevant molecules synthesized using asymmetric hydrogenation are as follows: L-DOPA – a direct precursor of dopamine[36] (Knowles), Candoxatril – a natriuretic factor potentiator (Chirotech company), Tipranavir – HIV protease inhibitor (Chirotech), Pregabalin – anticonvulsant (Chirotech).

On a slightly different note, Barry Sharpless was also presented with a share of the Nobel prize for the excellent work done on the asymmetric titanium-catalyzed epoxidation and enantioselective osmium-catalyzed dihydroxylation[37].

9. Palladium-Catalyzed Cross-Coupling Reactions

One of the most powerful C-C bond formation technologies using palladium as the metal of choice was introduced in the form of a series of catalytic processes in the last few decades[38]. Together these processes are termed as cross-coupling reactions and involve the coupling between electrophiles and an organometallic reagent in the presence of a palladium catalyst. Accordingly, palladium-catalyzed cross-coupling reactions have been developed based on the type of organometallic reagent employed, and the in the order of date of discovery, they are as follows: Kumada-Corriu coupling (Organomagnesium, 1972)[39], Heck reaction (Alkenes, 1972)[40], Sonogashira coupling (Alkynes, 1975)[41], Negishi coupling (Organozinc, 1977)[42], Stille coupling (Organotin, 1978)[43], Suzuki-Miyaura coupling (Organoboron, 1979)[44], Hiyama-Denmark coupling (Organosilicon, 1988)[45], Buchwald-Hartwig amination (Amines, 1994)[46]. Tremendous amount of research has been undertaken since the discovery of all these technologies.

With the advent of highly electron-rich ligands such as phosphines and N-heterocyclic carbenes[47], palladium-catalyzed cross-coupling reactions have benefitted immensely with applications ranging from simple biaryls to highly complex natural products, drugs[48] as well as agrochemicals. Although, most of these processes have exhibited usefulness due to the mild nature of the catalytic process, three amongst these namely, Heck reaction, Negishi coupling and Suzuki-Miyaura cross-coupling reactions were awarded Nobel prize for the significant contributions in academic and industrial domains. Richard Heck, Akira Suzuki and Eichi Negishi demonstrated the utility of the respective catalytic processes in a variety of fields including bio-active molecule synthesis, material science, agrochemicals and many more[49]. Some of the commercially successful applications[50] of the above mentioned cross-coupling reactions could be summarized as below: Naproxen – non steroidal anti-inflammatory drug (Heck reaction)[51], Telmisartan – an antihypertension drug (Suzuki-Miyaura coupling)[52], Boscalid – a fungicide (Suzuki-Miyaura coupling)[53], PDE 472 – a phosphodiesterase type 4D inhibitor for asthma treatment

(Negishi coupling)[54], Octylmethoxycinnamate – sunscreen component (Heck reaction)[55].

Conclusion

In conclusion, there is a lot of potential in transition-metal catalyzed processes and development of novel methods for synthesis every day as we speak. A few current areas of interest to scientists and industries include C-H bond functionalisation, Heterometallic catalysis, Metal-Organic-Frameworks (MOFs) etc.

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