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Historical note

# A reminiscence and a future prospect of transition metal-catalyzed cross-coupling processes

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**Abstract**

The discovery of stoichiometric C–C coupling process during our attempt at identifying an active nickel species for propylene dimerization is reviewed and the perspective of the palladium-catalyzed C–C bond formation leading to synthesis of carbonyl-containing compounds under mild conditions is given. © 2002 Published by Elsevier Science B.V.

*Keywords:* Cross-coupling; Reductive elimination; Oxidative addition; Organic halide; Ketone synthesis

## 1. Introduction

> "Keep an eye open for unexpected developments and do not neglect new phenomena as irrelevant to the main project." Karl Ziegler

## 2. Regrettable overlook. No chagrin at first, but later it came

When one is narrow-focused for finding a solution for a specific problem and is not prepared for the occurrence of an unexpected development, a big overlook may happen.

Since the discovery of Ziegler Catalyst in 1953 and the ensuing development of stereospecific polymerization of α-olefins [1,2] the mechanisms of formation of an active catalyst species in mixtures of titanium chlorides and trialkylaluminum and of polymerization of olefins attracted many speculations. In the early sixties, Cossee proposed a simple scheme to account for the formation of the active species as transition metal alkyls produced by exchange of titanium chloride with trialkyl aluminum [3]. He proposed further that polymerization of an olefin takes place by coordination of the olefin leading to the activation of the titanium-alkyl bond followed by insertion of the coordinated olefin into the Ti—alkyl bond. However, because of the paucity of isolated examples of transition metal alkyls [4], the verification of his proposal took a long time. At that time, I was interested in finding the reason why some transition metal alkyls can exist as thermally stable and isolable complexes, whereas in certain cases they are so unstable to defy attempts of isolation. Wilkinson proposed β-hydrogen elimination from transition metal alkyls as the most important decomposition route [5]. Hence by blocking the β-hydrogen elimination route employing a suitable ligand or by using alkyls having no β-hydrogens one should be able to isolate transition metal alkyls as kinetically stable species. His explanation was partly applicable to explain the reasons for instability of certain transition metal alkyls susceptible to β-H elimination, whereas instabilities of transition metal dimethyls and diaryls could not be accounted for by his proposal.

It was at this time that we could fortuitously isolate stable nickel and iron dialkyls having bipyridine ligand(s) as a consequence of a joint work with Yasuzo Uchida's group at Tokyo University. He was interested in the isolation of an active species from catalyst systems for butadiene oligomerization, composed of mixtures containing nickel, cobalt, and iron acetylacetonates and triethylaluminum together with tertiary phosphine or bipyridine ligands. On the occasion of his attending my

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talk at Tokyo Institute of Technology, where I described, what I did at Ziegler's Institute in Mülheim, Germany under the supervision of G. Wilke in isolation of tris(norbornene)nickel complex [6], he saw that I learned a technique of handling unstable air-sensitive complexes in Wilke's group and asked my cooperation. He sent one of his graduate students, Taro Saito, to work with me at Tokyo Institute of Technology and we set out to find out whatever species could be isolated from the reaction mixtures of the late transition metal acetylacetonates and organoaluminum compounds. This joint work proved to be quite successful. In almost the first experiment of examining the reaction of nickel acetylacetonate with $AlEt_2(OEt)$ in the presence of bipyridine (bpy) we obtained dark green, thermally stable crystals, which we first suspected to be an ethylene-coordinated nickel bipyridine complex. At that time there were very few examples of isolated transition metal alkyls in the literature and it was hard for us to believe that an ethylnickel complex can be thermally so stable to be recrystallized from hot benzene or acetone. Our attempts to characterize the complex by elemental analysis and chemical reactions and IR spectroscopy, available at the time, suggested that two ethyl groups are attached to nickel. Later examination with NMR, which was accessible only for the Tokyo University group at the time, unequivocally established that the formulation of the complex as $NiEt_2(bpy)$ (**1**) was correct [7]. We could also isolate the corresponding iron analog, $FeEt_2(bpy)$ (**2**) (Scheme 1) [7a,8].

These nickel and iron ethyl complexes as well as a related cobalt complex were found to act as active catalysts for butadiene oligomerization. We also examined the reactions of these transition metal alkyls with olefins since these metal alkyls were thought to provide the touchstone for the validity of the Cossee's proposal. The diethyl(bipyridine)nickel complex **1** reacted with acrylonitrile at low temperature to give an acrylonitrile adduct and gave a polymer at higher temperatures. When the reaction of acrylonitrile with **1** was carried out at −78 °C, we obtained an orange, thermally unstable complex as a 1:1 adduct of acrylonitrile and **1**. On warming to room temperature the two ethyl groups combined with each other forming butane and giving an acrylonitrile-coordinated Ni(0) complex. Other olefins such as methyl methacrylate also reacted with **1** to form adducts, which on warming were led to Ni(0)–olefin complexes with coupling of the two ethyl groups. Thus the diethylnickel complex provided a model of a transition metal alkyl to interact with an olefin with activation of the transition metal alkyl bonds to cause the C–C bond coupling by a process now termed as reductive elimination (Scheme 2) [9,10].

$$Ni(acac)_2 + AlEt_2(OEt) + bpy \longrightarrow \underset{(\mathbf{1})}{NiEt_2(bpy)}$$

$$Fe(acac)_3 + AlEt_2(OEt) + bpy \longrightarrow \underset{(\mathbf{2})}{FeEt_2(bpy)_2}$$

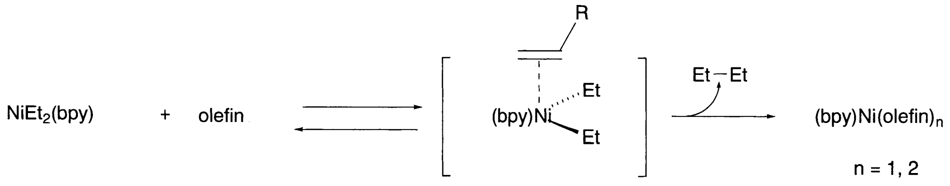
Scheme 1.

Much later, it was revealed that palladium and nickel alkyl complexes having diimine type ligands related with bipyridine showed the catalytic activity for ethylene polymerization by Brookhart and others [11].

On the other hand, the isolated iron ethyl complex **2** proved to serve as active polymerization catalyst of polar vinyl monomers, providing a closer model for the Cossee mechanism [12]. Again later, an iron chloride complex having a related diimine ligand was found to develop a catalytic activity for ethylene polymerization on treatment with methylalumoxane [13,14].

Having found that the isolated late transition alkyls served as models in polymerization of olefins, we started examining the reactions of the nickel ethyl complex with propylene. Although complex **1** proved to be a catalyst for butadiene oligomerization to give cyclododecatriene, it was not active for propylene polymerization in the absence of added ethylaluminum dichloride. Our coworker Masahiro Uchino, who just returned from the University of Paris obtaining the degree under the supervision of Chauvin, was involved with propylene oligomerization in France using a catalyst system of nickel compounds with diethylaluminum monochloride in chlorobenzene [15,16]. Upon our isolation of the nickel ethyl complex, we set out to examine the catalytic activity of the ethylnickel complex **1** with propylene in cholorobenzene [17,18]. The study revealed that the dimerization activity was remarkably enhanced when **1** was treated with ethylaluminum dichloride in chlorobenzene. In retrospect, the reaction of **1** with added ethylaluminum dichloride may be related with enhancement of the catalytic activity for olefin polymerization of diimine-ligated transition metal alkyl catalyst. In relation with the activating effect of methylalumoxane co-catalyst, it is now established that activity of transition metal alkyls is enhanced by addition of a Lewis acid catalyst, which abstracts an alkyl group to generate a cationic organometallic species as a catalyst of enhanced activity. However, at that time when we could isolate the diethylnickel complex from the mixed catalyst system, it did not seem attractive for me to go back to the mixed catalyst system again and make the chemistry less clear cut. Thus we decided to examine first the remarkable enhancement effect of chlorobenzene for the catalytic dimerization activity by investigating the reaction of **1** with chlorobenzene in the absence of added organoaluminum compounds.

On addition of chlorobenzene to the solution containing **1** at room temperature or on slight warming, the dark green color of **1** changed to red accompanied by evolution of butane. From the brownish red solution an orange-colored complex having the formula of



Scheme 2.

Ni(Ph)Cl(bpy)(1/2PhCl) (**3**) was isolated as reddish brown fine crystals after recrystallization from chlorobenzene. The result suggested the occurrence of the following reaction with cleavage of the two Ni-ethyl bonds in **1** on its treatment with chlorobenzene (Scheme 3) [17].

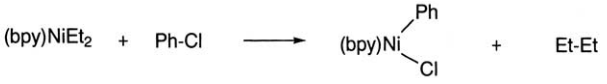
The identity of the phenyl nickel complex was also established by treatment of **3** with a dilute nitric acid yielding stoichiometric amounts of benzene and chlorobenzene.

A similar reaction of **1** with bromobenzene and iodobenzene as well as halotoluenes also gave arylnickel halide complexes having the bipyridine ligand [18]. We found further that the propylene dimerization activity with the diethylnickel complex in combination with a Lewis acid such as $AlEtCl_2$, and $AlEt_2Cl$ could be manifested only in the haloarene solvents, but the isolated arylnickel halide complexes were found to exhibit high catalytic activities in non-chlorinated solvents as well.

Again in retrospect, the development of the catalytic activity for propylene dimerization may be related with possible formation of a cationic organonickel complex which presumably has a higher catalytic activity for the propylene dimerization vis-a-vis the neutral organonickel complex.

Being satisfied with establishment of the identity of the diethylnickel complex by chemical means (at that time the NMR instrument was not readily accessible to us), and further with isolation of another type of novel arylnickel complexes from **1**, we published the result in a communication form in J. Organometal. Chem. [17]. We did not realize at all of the potential application of the finding to organic synthesis nor were aware of the significance of the finding as important concepts of reductive elimination and oxidative addition in organometallic chemistry.

The applicability of the result was not overlooked by keen observers who recognized the importance of the carbon–carbon coupling process. Tamao and Kumada of Kyoto University [19] and Corriu in Montpellier [20] independently devised catalytic systems to bring about the cross-coupling of aryl halides and alkylmagnesium halides, or of vinyl halides with aryl Grignard reagents, in the presence of nickel complexes. At the time we did not feel so much chagrin since we did not fully realize the significance of the process. But the process soon attracted intense attention, because, of its obvious significance (now I can see) in organic synthesis. The nickel-catalyzed process was followed by discovery of efficient and more versatile palladium catalysts. Further succeeding discoveries of cross-coupling reactions using organozinc, tin, lithium, aluminum, boron, and zirconium [21] have been made by various research groups, interestingly by many Japanese for some reasons or another. The transition metal-catalyzed cross-coupling processes have now become one of the most important tools in organic synthesis, as featured in the present issue.

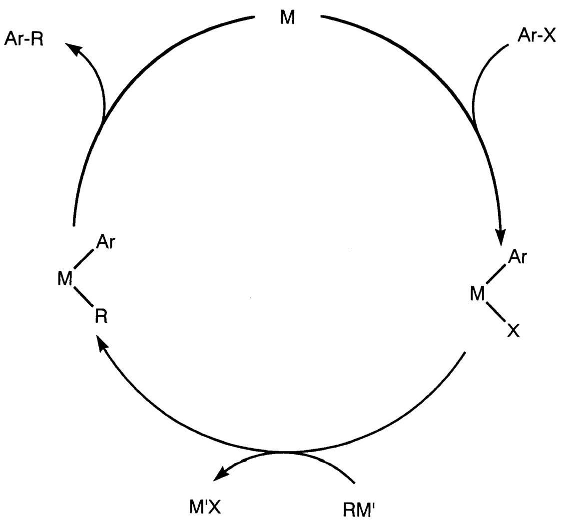


Scheme 3.

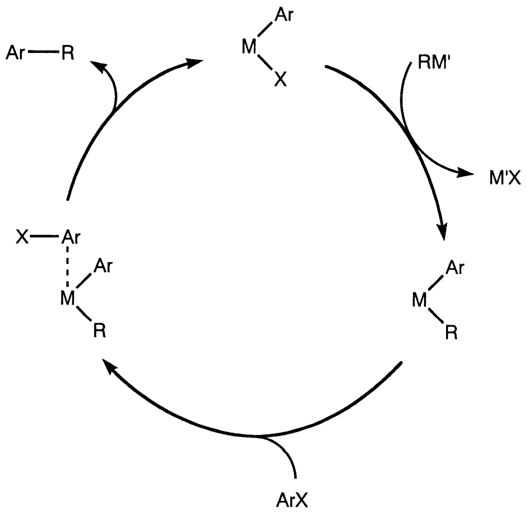
The discovery of the C–C cross-coupling process provided the important concepts in organometallic chemistry directed toward organic synthesis (OMCOS), namely a catalytic cycle can be constructed on the basis of elementary processes. Presently the catalytic cycle is usually understood by a mechanism as shown in Schemes 1–4, where the ligand is omitted for clarity. It is composed of elementary processes involving (a) oxidative addition involving cleavage of a carbon–halogen bond to produce an aryltransition metal halide intermediate, (b) transmetallation with another organometallic compounds such as alkylmagnesium reagent to give a diorganotransition metal intermediate, and (c) reductive elimination causing the C–C bond formation with regeneration of a transition metal(0) species that carries the catalytic cycle.

Although Scheme 4 represents a useful concept in accounting for the catalytic C–C coupling cycle, the actual catalytic cycle may proceed through a somewhat different route.

The phenyl–chlorine bond strength is strong and the oxidative addition of chlorobenzene to a palladium(0) complex proceeds much less easily than with aryl bromide and iodide. For example, the reaction of phenyl iodide with $Pd(PPh_3)_4$ is known to take place readily at room temperature and the reaction with phenyl bromide at 80 °C, whereas chlorobenzene does not react even at 135 °C with the same complex [22]. Recently much effort has been devoted to realize a palladium-catalyzed coupling process utilizing aryl chlorides, which are much less expensive than bromides and iodides [23]. It is interesting to note that in the first catalytic synthesis



Scheme 4.



Scheme 5.

found by Tamao a nickel complex was used in combination with aryl chlorides using tertiary phosphine ligands. There may be some reasons why the aryl–Cl bond cleavage takes place easily on reaction with nickel complexes.

A recent work by my former coworker, T. Yamamoto, showed that interaction of an aromatic ring in an aryl halide with diethylnickel complex **1** promotes the cleavage of the carbon–halogen bond concomitant with C–C bond formation [24]. It is interesting to note that even the C–F bond in hexafluorobenzene can be readily cleaved on interaction with **1** to give a pentafluorophenyl–nickel complex. These results suggest that in the actual metal-catalyzed cross-coupling reactions, a mechanism involving interaction of an arene ring in aryl halide with diorganotransition metal complex may be involved. A possible mechanism taking these possibilities into account is shown in Scheme 5.

## 3. Application of the concept of transition metal-catalyzed cross-coupling to difunctional substrates

Although we failed to apply the finding we encountered in the nickel-induced C–C coupling to the development of the useful cross-coupling process, because of our lack of OMCOS mind, we could later make some contribution to polymer synthesis by using the concept of the cross-coupling process. T. Yamamoto and myself were familiar with polymer chemistry and he envisioned the application of the process to dihaloarenes as well as alkane dihalides for making polymers by polycondensation processes. As shown below we could prepare various polymers by simply applying the concept with organic monohalides into organic dihalides (Scheme 6) [25].

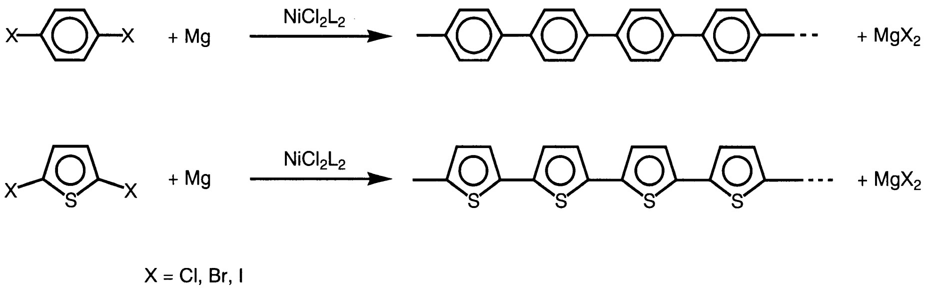
After our successful preparation of polyphenylenes the same polycondensation principle was applied to polythiophene synthesis. These polythiophenes were later found to become conducting polymers on doping with iodine in a similar way to the enhancement of conductivity of polyacetylene by doping it with iodine reported by Shirakawa, another colleague in our group at Tokyo Institute of Technology [26]. The polycondensation method using dihaloarenes has been recognized as important means in preparation of polyarenes by cleanly connecting the arene–arene entities [27].

## 4. Development of ketone synthesis

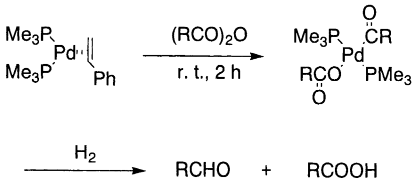
The cross-coupling process has been extensively utilized in organic synthesis as simple and efficient method of causing aryl–alkyl, and alkenyl–alkyl couplings. One disadvantage of the process is that the process uses aryl or alkenyl halide and organometallic reagents that are prepared from aryl halides. The halide, however, has to be removed eventually for preparing products without the halide. Thus there remains a room to improve the process to make it more atom efficient and environmentally benign.

We have been long interested in the development of synthetic methods without using organic halides and have studied the cleavage processes of oxygen-containing compounds with low valent transition metal complexes [28]. Interaction of a palladium(0) complex with a carboxylic anhydride causes the oxidative addition of the anhydride involving the C–O bond cleavage to give an acyl(carboxylato)palladium complex, which reacts with hydrogen to liberate aldehyde and carboxylic acid (Scheme 7).

The finding led us to the construction of a catalytic cycle to produce aldehydes catalytically from carboxylic



Scheme 6.



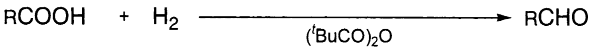
Scheme 7.

anhydrides under $H_2$ [29]. By further combining the results with the information on relative reactivities of carboxylic anhydrides with Pd(0) complexes we could develop a method of directly hydrogenating various carboxylic acids into aldehydes at the cost of less reactive carboxylic anhydrides such as pivalic anhydride (2,2-dimethylpropionic anhydride) (Scheme 8) [30].

The concept of generation of a reactive acylpalladium species by the C–O bond cleavage in carboxylic anhydrides on reaction with Pd(0) species further prompted us to examine the applicability of the C–O bond cleavage to ketone synthesis. It was reasoned that by combining the oxidative addition of carboxylic anhydride with transmetallation and reductive elimination one might achieve ketone synthesis as represented by Schemes 9 and 10 by modification of the concept of Suzuki–Miyaura process [31].

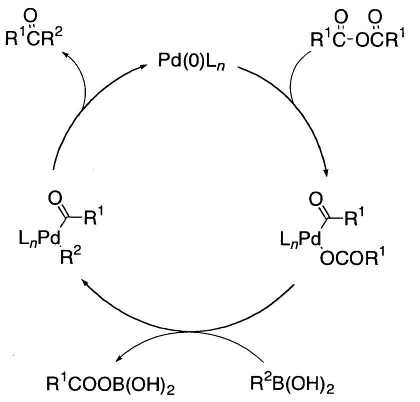
In fact, by treatment of carboxylic anhydride with organoboron compounds in the presence of a palladium catalyst we could realize the catalytic synthesis of ketones from carboxylic anhydride. We have also found that electronegative esters such as phenyl trifluoroacetate can be catalytically converted into trifluoroketones by utilizing the oxidative addition of the ester to a Pd(0) complex [32].

By further combining the catalytic cycle involving carboxylic anhydrides with an auxiliary cycle to prepare a mixed anhydride with carboxylic acids, on treatments with an additive such as dimethyl dicarbonate or pivalic anhydride, a novel and general catalytic method for preparation of various ketones has been realized [31].

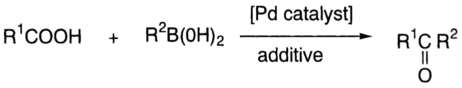


$$\mathrm{RCOOH} + \mathrm{H_2} \xrightarrow[(^t\mathrm{BuCO})_2\mathrm{O}]{\mathrm{Pd(OAc)_2} + \mathrm{P}(p\text{-tol})_3} \mathrm{RCHO}$$

Scheme 8.



Scheme 9.



$$\mathrm{R^1COOH} + \mathrm{R^2B(OH)_2} \xrightarrow[\text{additive}]{\text{[Pd catalyst]}} \mathrm{R^1\underset{\underset{O}{\|}}{C}R^2}$$

Scheme 10.

An advantage of the process is that no base is required as in the Suzuki–Miyaura coupling. No organic halides are used except for the preparation of certain organoboron compounds. Thus the process approaches toward the goal of realizing more environmentally benign and atom efficient processes.

## 5. Conclusion

Through studies of fundamental processes in organotransition metal complexes one can sometimes come across an interesting observation. If you are OMCOS minded, you may not overlook the opportunities of application to organic synthesis. The previous failure described in the reminiscence part in this article taught me a lesson and has made me prepare to look for the possibilities of application. It has been always rewarding to work with reactive organotransition metal complexes that provide exciting possibilities of application.

## Acknowledgements

Of course the work described here could not be accomplished without the assistance of able coworkers. I would like to express my sincere thanks to the coworkers whose names are cited in the references. My sincere thanks are due to the Nippon Zeon Company who created a chair for me at Waseda University after my retirement from Tokyo Institute of Technology and to the Ministry of Education, Science, Sports, and Culture for the financial support.

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