

CRC International Symposium: Cross Coupling and Organometallics

Reviewed by Thomas Colacot

Johnson Matthey, Catalysis and Chiral Technologies, West Deptford, New Jersey 08066, U.S.A.; E-mail: colactj@jmusa.com

The third CRC International Symposium on Cross Coupling and Organometallics (1) was conducted on 25th September 2007 at the Université de Lyon, ESCPE Lyon, France; the institution where Victor Grignard was a Chemistry Professor. Although it was a one-day gathering, about 250 participants attended from all over the world. Out of the nine speakers, I was the only one from industry. In addition to the talks there were a poster session and vendor booths. The details of the meeting are summarised in this report.

The opening address was given by Professor Tamotsu Takahashi who emphasised that CRC stands for Catalysis Research Center of Hokkaido University, Japan, which is the main sponsor of the Symposium. Professor Takahashi strongly believes that the area of cross-coupling will be recognised by the award of a Nobel Prize in the near future, as no other field of chemistry has grown like this one over the past two decades. He thanked agencies such as the Japan Interaction in Science and Technology Forum (JIST) and various fine chemicals companies for their sponsorship.

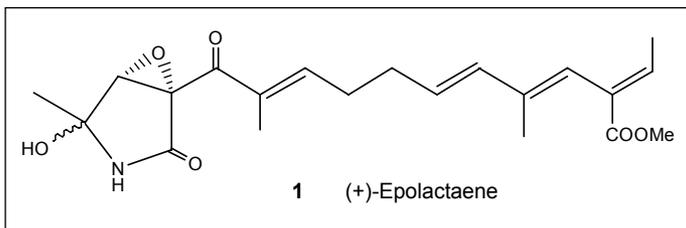
The purpose of this review is to provide a background about the speakers and their original contributions to the area of coupling.

In 1966 Professor E. Negishi joined H. C. Brown's group to work on C–C bond forming reactions using organoboron compounds. From 1976 to 1978 he published about ten papers describing palladium- and nickel-catalysed cross-coupling reactions using magnesium, zinc, boron, aluminium and tin, while he was working at Syracuse University as an Associate Professor. Currently he occupies the chair of the H. C. Brown Distinguished Professor of Chemistry at Purdue University, U.S.A. Negishi is known for his work on coupling using organozinc reagents;

these allow cross-coupling under milder conditions than is the case using organomagnesium reagents.

During his talk Negishi praised Grignard for initiating a new era in organometallic chemistry relevant to organic synthesis. However, "Grignard left a big hole", he said, which Negishi and others are trying to fill currently. The developments in this area are summarised in a recent review (2). Negishi has been very successful in using [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium (dppfPdCl₂), bis(2-diphenylphosphinophenyl)ether dichloropalladium (DPEphosPdCl₂) and bis(tri-*tert*-butylphosphine)-palladium (Pd(*t*-Bu₃P)₂) catalysts for various organozinc-based transformations to make natural products such as xerulin, carotenes, scyphostatin, γ -bisabolenes, 6,7-dehydrostipamide, *O*-methylmyxalamide D, amphotericin B, mycolactone A/B and epolactaene, by simple and efficient ways. He has also successfully completed asymmetric syntheses of various molecules. One of the recent examples from his group is the stereoselective synthesis of (+)-epolactaene, **1**, a microbial metabolite isolated from fungal strain, *Penicillium*.

Professor A. Suzuki spent his entire academic life at Hokkaido University, starting from 1954 as a B.S. student, except for his postdoctoral studies at Purdue with Professor H. C. Brown from 1963 to 1965. He is currently a Professor Emeritus at Hokkaido University. Of the various coupling reactions, Suzuki coupling has received the most attention both in industry and academia, with the greatest number of publications/patents since 1990. Part of the reason for this growth is due to the non-toxicity of readily available boron reagents such as boronic acid, pinacolboronate and potassium salts of trifluoroboronate for



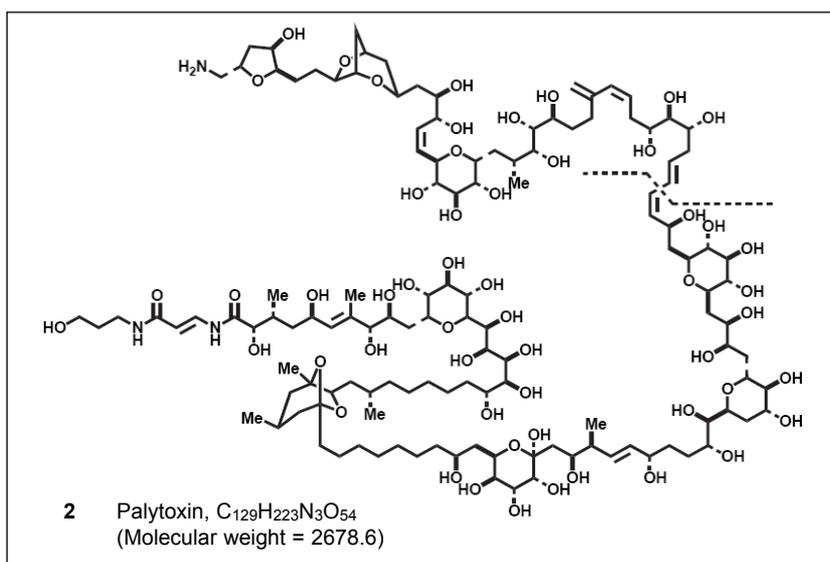
coupling reactions with both alkenyl- and aryl-based electrophiles. These reactions can be carried out under both homogeneous and heterogeneous conditions in the presence or absence of water. The conditions are typically milder. Because of the wider applications of his work in industry, Suzuki should be the first name to be considered for a Nobel Prize in the area of cross-coupling.

In his talk, Suzuki highlighted the developments in this area from 1979 onwards. Some of the important generations of catalysts which were mentioned in his talks were tetrakis-(triphenylphosphine)palladium ($\text{Pd}(\text{Ph}_3\text{P})_4$), dppfPdCl_2 , $\text{Pd}(\text{Bu}_3\text{P})_2$ and Buchwald ligands in conjunction with Pd. The electron-rich and bulky ligand-based catalysts were responsible for coupling aryl chlorides (3) and hindered substrates (4). Suzuki also touched upon recent progress on alkyl halide coupling, a very challenging area due to the propensity of alkyl substrates to undergo β -hydrogen elimination. Interestingly, Professor Suzuki

had published a paper in 1992 (5) on the coupling of *n*-hexyl iodide with *n*-octyl 9-borabicyclo[3.3.1]nonane (*n*-octyl-9-BBN) to produce tetradecane in 64% yield using the catalyst $\text{Pd}(\text{Ph}_3\text{P})_4$. Fu's reinvestigation of the reaction using *n*-dodecyl bromide yielded 93% product when the catalyst system was changed to palladium acetate/tricyclohexylphosphine ($\text{Pd}(\text{OAc})_2/\text{C}_y_3\text{P}$) (6). Suzuki's talk also pointed towards the Suzuki coupling step in Kishi's synthesis of palytoxin, 2, an incredibly complex marine natural product containing 71 stereochemical elements (7). This is still considered by many to be the greatest synthetic accomplishment ever, due to its structural complexity.

Professor K. Tamao has been the Director of RIKEN's Advanced Science Institute since 2005. Earlier, he spent most of his career at Kyoto University. His lecture was dedicated to M. Kumada who died on 28th June 2007.

Tamao started his lecture by stating that



Ni-catalysed cross-coupling was reported independently by Corriu (8) from France and Kumada (9) from Japan in 1972. Applications of Ni chemistry were different from those of Pd chemistry even in the 1970s, in the sense that some Ni catalysts were useful for aryl chloride and aryl fluoride coupling. Although his lecture gave a brief account of what has happened in the area of Ni- and Pd-catalysed Kumada type coupling since 1972, Tamao's major focus was on communicating some characteristic features of Ni-catalysed coupling, in addition to providing insights into the mechanistic understanding of Ni-catalysed coupling *vs.* Pd-catalysed coupling. Tamao also emphasised the common role of Lewis acids in activating aryl-fluoride and aryl-nitrogen bonds in cross-coupling reactions (10).

Professor G. Fu is currently a full professor at the Massachusetts Institute of Technology (MIT), U.S.A. He worked with Professor Evans (Harvard University, U.S.A.) and Professor Grubbs (California Institute of Technology (Caltech), U.S.A.) for his Ph.D. and postdoctoral studies, respectively. Fu's contributions are very significant in revitalising the area of coupling by establishing the importance of bulky electron ligands (such as $t\text{Bu}_3\text{P}$) in aryl chloride coupling, although Koei from Japan has also earlier worked on the bulky $t\text{Bu}_3\text{P}$.

In his lecture Fu described his latest work in one of the yet challenging areas in coupling namely, coupling reactions between two sp^3 -hybridised carbon centres (Csp^3-Csp^3 coupling). His recent contributions in developing Ni- and Pd-based methodologies for coupling unactivated primary and secondary alkyl electrophiles that bear β -hydrogen were discussed in detail. In his lecture he also suggested that Kochi's radical mechanism might be more suited to explaining the Ni-catalysed coupling in comparison to the oxidative addition, transmetallation and reductive elimination steps in the Pd-catalysed coupling. His work on asymmetric Negishi coupling was also discussed in some detail.

Professor T. Hiyama has been a full professor at Kyoto University since 1997. Prior to this he held various academic and industrial positions in Japan.

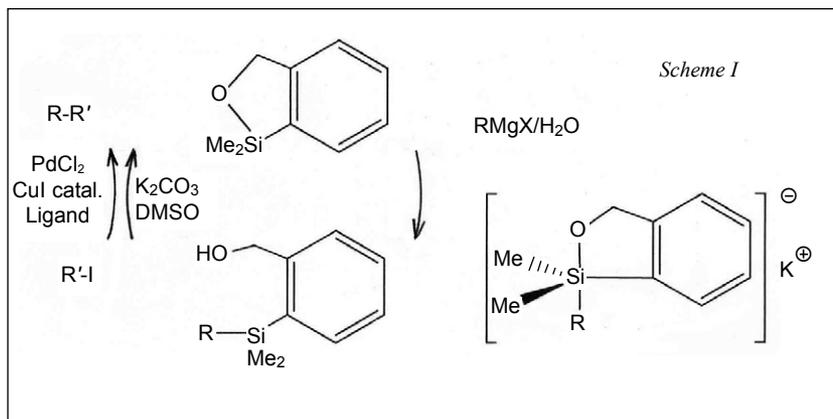
The Hiyama coupling involves the coupling of aryl, alkenyl or alkyl halides or pseudohalides with organosilanes. To drive silicon-based cross-coupling, formation of a pentacoordinated silicate intermediate is required in the catalytic cycle. Therefore this reaction requires an activating agent such as a base or fluoride ions, for example tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) or tetra-*n*-butylammonium fluoride (TBAF). The reaction rate is typically increased by using silanes containing R groups such as fluoro or alkoxy instead of alkyl. In his talk Hiyama discussed stable and easy-to-handle tetraorganosilicon reagents with 2-hydroxymethylphenyl groups on Si as reagents to deliver organic groups to palladium, copper and rhodium during catalysis, Scheme I.

In general, organosilanes are stable and easily prepared compounds, with lower toxicity than their Sn analogs. Hiyama's talk also focused on some of his recent published results; see References (11–13).

Professor P. Dixneuf is a Professor of Chemistry at the Université de Rennes, France. He has published over 350 papers in international journals including several reviews; also book chapters and patents.

Unlike conventional cross-coupling processes, Dixneuf's focused on making C–C bonds using ruthenium-based organometallics. The use of Ru(II) complexes such as cyclopentadienyl 1,5-cyclooctadienyl ruthenium chloride ($\text{Cp}^*\text{Ru}(\text{COD})\text{Cl}$) in regio- and stereoselective oxidation was highlighted with several examples. His approach is to develop novel greener pathways to organic molecules in an atom economic way. The details of the work are already published; see References (14–16).

Professor G. Balme has been a Research Director first class (DR1) at the Centre National de la Recherche Scientifique (CNRS), Université Claude Bernard Lyon 1, France, since 2005. Her talk was centred on 'cyclo-functionalising' unactivated C–C multiple bonds using Pd catalysts. Her work has practical applications such as one-pot synthesis of substituted furans,



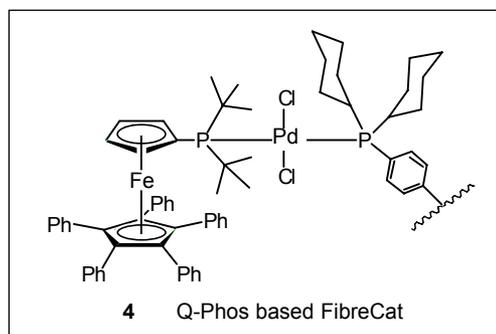
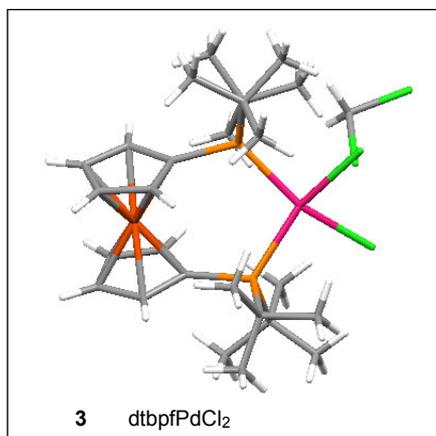
lactone lignans and cyclopropanes. Professor Balme has published several articles in this area.

Professor O. Baudoin has been an Associate Professor of Chemistry at the Université Claude Bernard Lyon 1 and ESCPE Lyon, France, since 2006. In his talk Professor Baudoin discussed the Pd-catalysed C–H activation, also called direct arylation. This area has received much attention recently as it is one step ahead of the conventional C–C cross coupling chemistry such as that of Suzuki, Miyama and Negishi. The other significant players in this area are Fagnou, Samford, Sames and Lautens. Some of the important publications in this area are References (17–19).

Thomas J. Colacot has been working as a Research and Development Manager in Homogeneous Catalysis at Johnson Matthey Catalysis and Chiral Technologies (CCT) with

global responsibilities since 2004, in addition to a part-time assignment as a visiting graduate professor at Rutgers, the State University of New Jersey, U.S.A.

The work is mainly aimed at developing and commercialising Pd-based catalysts, as well as providing practical catalytic solutions to challenging coupling reactions in the fine chemicals and pharmaceuticals arena. In addition to developing new catalysts, research involves understanding the roles of the catalyst, substrate and reaction conditions. One of the air-stable, highly active and versatile catalysts that has been developed recently is [1,1'-bis(di-*tert*-butylphosphino)-ferrocene]dichloropalladium ($dtbpfPdCl_2$), **3**. An example of a supported Pd catalyst is structure **4**. A few typical publications in this are given in References (20–23).



Conclusion

Although work on coupling dates back to the 1970s, the last two decades have seen major breakthroughs in the area. These have been driven by applications in the fine chemical and

pharmaceutical industries for the construction of complex organic molecules. This area will grow continuously. Remaining challenges include Csp^3-Csp^3 coupling, asymmetric coupling and metal residues in the product.

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The Reviewer



Thomas Colacot is a Research and Development Manager in the Catalysis and Chiral Technologies Division at Johnson Matthey, West Deptford, U.S.A. with global reports and responsibilities. He holds a Ph.D. in Chemistry and an MBA in Strategic Management. He is involved in the development of new organometallic compounds for catalysis, process development, supported homogeneous catalysts and high throughput screening of catalysts for organic reactions, such as C–C couplings and C–heteroatom couplings. He is also a visiting faculty member of Rutgers University in the Graduate School of Chemistry, where he teaches an applied organometallic chemistry course relevant to the fine chemicals and pharmaceutical industries. He has published over fifty papers, in addition to giving numerous lectures all over the world.