

15th IUPAC Symposium on Organometallic Chemistry Directed Towards Organic Synthesis

Latest advances in platinum group metal-mediated synthesis

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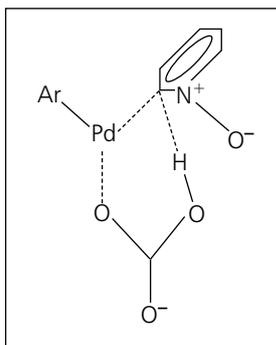
It says much for the enthusiasm of synthetic organic chemists for their subject that in these economically challenged times nearly 500 delegates gathered at the 15th International Union of Pure and Applied Chemistry (IUPAC) Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS 15), held in Glasgow, UK, from 26th to 30th July 2009. The attraction was the opportunity to discuss their common interest in the application of organometallic chemistry to organic synthesis. Twenty-four full lectures and fifteen short oral presentations, supported by nearly 350 posters, provided a varied programme.

Palladium-Catalysed Synthesis

Palladium-catalysed coupling to form carbon–carbon or carbon–heteroatom bonds is now very widely used in organic synthesis (1, 2). Reactions using organozinc reagents were developed in Colorado, USA, in the 1970s and named after Ei-Ichi Negishi (Purdue University, USA) (3, 4). Negishi gave an update on this chemistry concentrating on reactions where other procedures, such as the Sonogashira coupling of alkynes, have been less successful. Other examples included the regioselective synthesis of alkenes. Cross-coupling using boronic acids in the presence of a palladium catalyst such as palladium(II) acetate ($\text{Pd}(\text{OAc})_2$) with tricyclohexylphosphine (PCy_3) or tri(*tert*-butyl)phosphine (P^tBu_3) has proved highly popular for the formation of biaryl units but the boronic acids themselves often present significant synthetic challenges. Gary Molander (University of Pennsylvania, USA) described the use of trifluoroborate reagents as an alternative. As potassium salts, these trifluoroborate reagents are crystalline solids that are readily purified and frequently offer better stability than the corresponding boronic acids. During reaction these trifluoroborates undergo partial hydrolysis yielding aryl difluoroborates ($\text{ArBF}_2(\text{OH})$) and it is believed that the hydroxyl function is important for

the initial interaction of the boron derivative with the palladium(0) catalyst.

Avoiding the formation of the organometallic reagent entirely through carbon–hydrogen bond activation of the parent arene (direct arylation) has been the focus of much recent research. In the OMCOS Award lecture, Keith Fagnou (University of Ottawa, Canada) discussed the mechanism of direct arylation using Pd(OAc)₂ as a catalyst. His studies have suggested formation of the arene intermediate *via* concerted metallation/deprotonation (CMD) rather than by the oxidative addition mechanism that is known for aryl halides. Studies of the interaction of palladium complexes with pyridine-*N*-oxide were helpful in highlighting the role of the carbonate base in deprotonation (Scheme 1) (5).



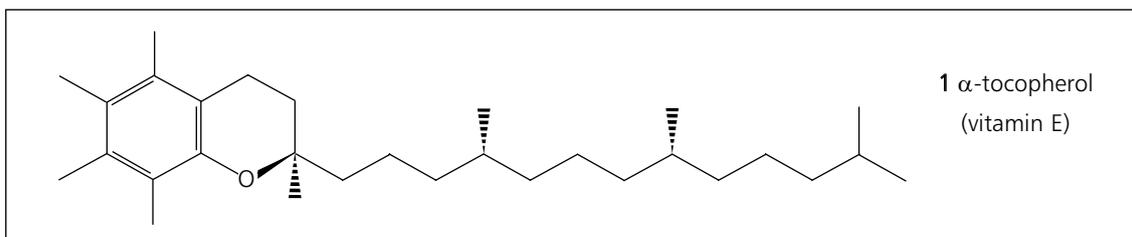
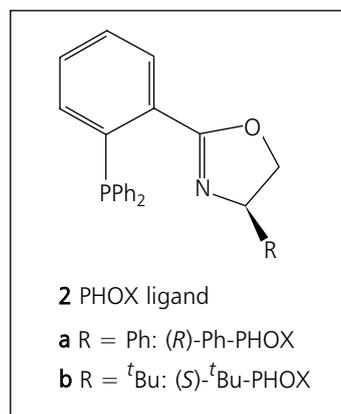
Scheme 1. Arene intermediate formed between the palladium complex and pyridine-*N*-oxide, showing the role of the base in deprotonation during palladium-catalysed direct arylation reactions (5)

Density functional theory (DFT) calculations showed this pathway to be much lower in energy than oxidative addition (with a difference of ~50 cal mol⁻¹ (~209 kJ mol⁻¹)). DFT calculations also showed good correlation with the regioselectivity of further reaction on the aryl ring. The role of a directing group in initiating carbon–hydrogen and carbon–silicon bond activation, and the intermediacy of palladacyclic structures, were described by John Brown (University of Oxford, UK). Lutz Ackermann (University of Göttingen, Germany) reported on his studies of direct arylation using palladium and ruthenium complexes of secondary phosphine oxides.

Reactions with a variety of electrophilic substrates such as aryl and alkenyl chlorides or tosylates and mesylates were described. Carbon–hydrogen bond activation through the use of a chelating directing group with catalysts such as Pd(OAc)₂ or triruthenium dodecacarbonyl (Ru₃(CO)₁₂) (6) was described by Naoto Chatani (University of Osaka, Japan). He also discussed methods of breaking C–CN bonds for the removal of a nitrile function introduced to direct *ortho*-substitution, using a (1,5-cyclooctadiene)rhodium(I) chloride dimer ([RhCl(cod)]₂) catalyst (7).

Another way to increase the efficiency of synthesis is to conduct sequential reactions, avoiding the need for isolation of an intermediate. Even better improvements can be obtained by ‘domino sequences’, where the reaction forms a functionality that then reacts further under the same conditions. Work in this area using palladium-catalysed cross-coupling reactions was described by Lutz Tietze (University of Göttingen, Germany), reporting the synthesis of steroids (8) and α -tocopherol, vitamin E (1) (9).

Using natural product synthesis as a focus for developing new reactions was discussed by Brian Stoltz (California Institute of Technology (Caltech), USA). Palladium catalysts bearing phosphinoxazoline (PHOX) ligands, **2**, were shown to be effective for



enantioselective allylation of enol carbonates (Tsuji allylation, **Scheme II**) (10).

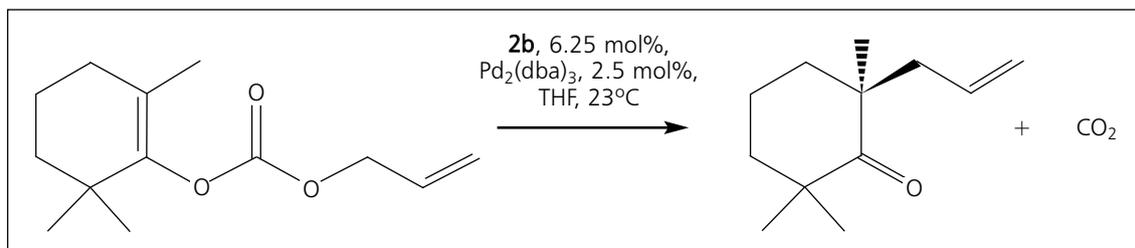
Ruthenium-Catalysed Synthesis

Ruthenium, through its range of coordination complexes of differing oxidation states, has the versatility to catalyse a wide variety of reactions. This was illustrated by a number of talks. Robert Grubbs (Caltech, USA) described recent progress in developing ruthenium alkylidene complexes for metathesis. Significant progress was made by changing from bis(tricyclohexylphosphine) complexes (first generation Grubbs catalysts) to those containing *N*-heterocyclic carbene ligands (second generation Grubbs catalysts). Further optimisation in this series has now allowed the catalysts to be used at lower loadings (typically 50 ppm to 1000 ppm). This is important both for controlling catalyst costs and for reducing ruthenium residues in the products, which is especially important for pharmaceutical intermediates. One means of increasing turnover numbers has been to minimise the degradation of the catalyst, which occurs, for example, through carbon–hydrogen bond activation reactions. For tricyclohexylphosphine-containing methylene complexes this leads to formation of methyltricyclohexylphosphonium salts. This can be avoided by using catalysts of the Grubbs-Hoveyda type, **3**.

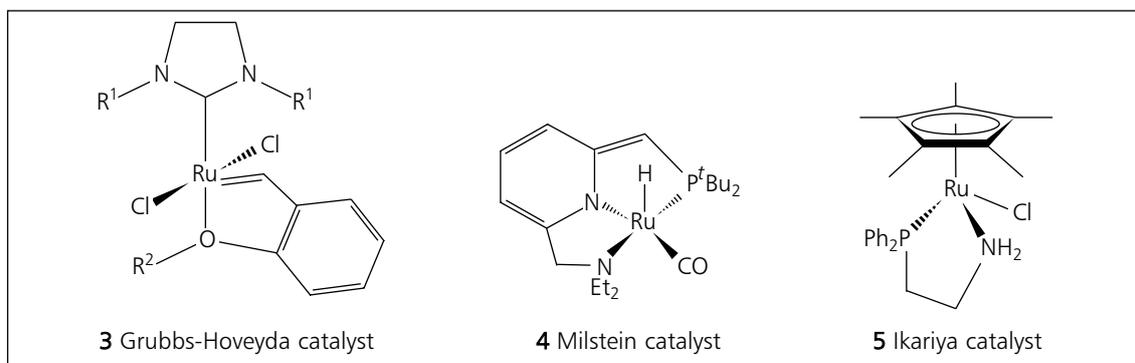
Ruthenium catalysts have proved particularly useful for ring-closing metathesis (RCM) for creating ring sizes of more than eight atoms, but the alternative strategy of ring-expansion metathesis was also described. An example of RCM for the formation of lactone rings was described by Janine Cossy (École Supérieure de Physique et de Chimie Industrielles de la Ville de Paris (ESPCI), France).

Pincer complexes have been known for some years to offer interesting properties for the activation of small molecules. David Milstein (Weizmann Institute of Science, Israel) discussed a number of hydrogenation and dehydrogenation reactions carried out with a pyridine-centred pincer ruthenium complex, **4**. These included the hydrogenation of esters to alcohols under mild conditions and the reverse dehydrogenative formation of esters, the coupling of amines and alcohols to form amides, and the direct synthesis of primary amines from alcohols and ammonia.

Transfer of a hydrogen atom from the metal to the ligand facilitates these reactions. In a similar way, cooperation between the ligand and ruthenium achieves heterolytic cleavage of hydrogen allowing very effective catalysis for the chiral reduction of ketones by complexes of the type shown, **5**, and reported by Takao Ikariya (Tokyo Institute of Technology, Japan). Use of such catalysts for both enantioselective



Scheme II. Palladium-catalysed Tsuji allylation for the enantioselective allylation of enol carbonates. dba = dibenzylideneacetone (10)



oxidation and reduction reactions was described. Similar oxidation reactions can be carried out using vanadyl complexes as described by Chien-Tien Chen (National Taiwan Normal University, Taiwan).

Other Developments

Hydrogenations are one of the largest classes of reactions in catalytic asymmetric synthesis. Improvements in both enantioselectivity and turnover, which will in turn allow the catalyst loading to be reduced, are needed to extend the industrial applicability of the method. Xumu Zhang (Rutgers University, USA) described work in his group on developing new chiral ligands aimed at achieving these objectives with rhodium or palladium catalysts. Notable examples of new ligands are the TunePhos series (C_n -TunePhos) and those with a chiral backbone (C_n^* -TunePhos), for example C_3^* -TunePhos (**6**). The formation of chiral amines by hydrogenation of imines is a desirable reaction in pharmaceutical synthesis and the use of palladium catalysis in conjunction with TangPhos, **7**, has proved successful.

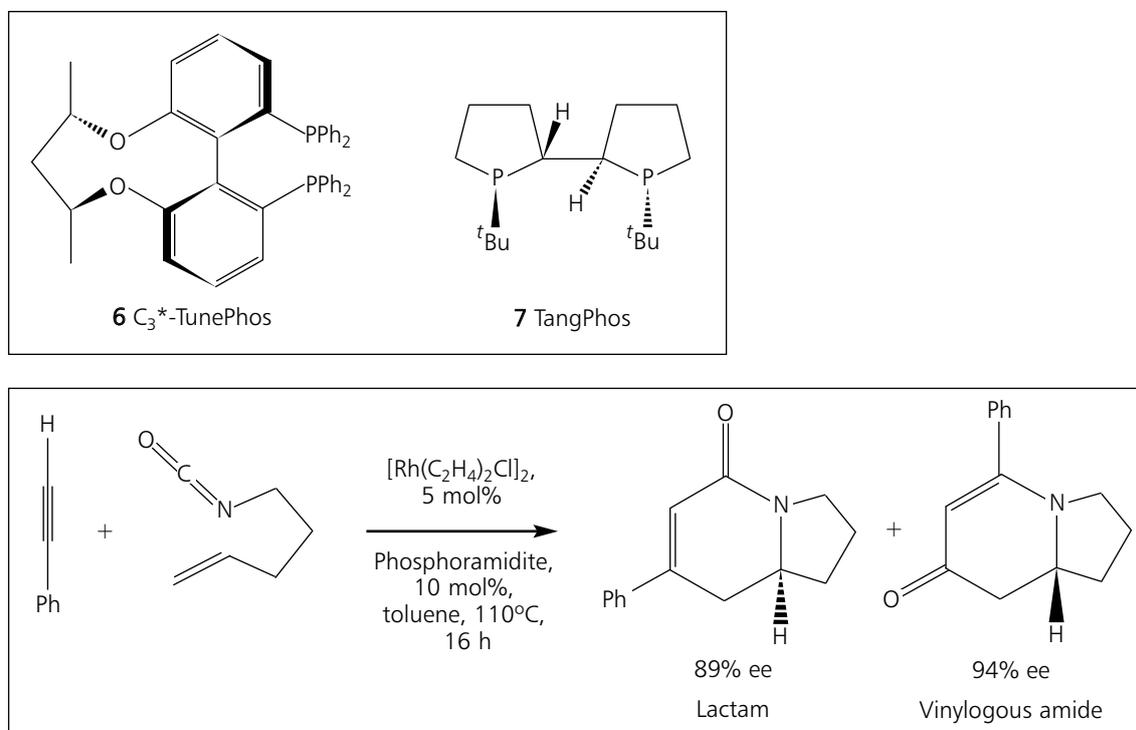
Tomislav Rovis (Colorado State University, USA) described the formation of heterocyclic products *via* metallacycles. For rhodium catalysis, formation of the

metallacycle occurs through interaction of the metal with unsaturated bonds (carbon–nitrogen and carbon–carbon) in the substrate. Depending on the nature of the catalyst and the substituents of the substrate some control may be achieved over the different regioisomers that are formed (**Scheme III**) (11). The formation of different ring sizes presents a number of challenges and this aspect was addressed by P. Andrew Evans (University of Liverpool, UK). Using rhodium-catalysed carbocyclisation reactions, he contrasted the ready formation of six- and eight-membered rings with the often more difficult formation of five- and seven-membered rings.

Concluding Remarks

Overall the conference demonstrated the power of pgm-catalysed reactions in promoting the formation of carbon bonds and emphasised the considerable progress being made with control of the regio- and enantioselectivity required for efficiently synthesising complex natural products. The many posters on display also provided a variety of examples of progress in these areas.

Abstracts for the OMCOS series of conferences will be available through the IUPAC website (12).



Scheme III. Regioselective synthesis of heterocyclic products via a rhodium metallacycle (11)

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The Reviewer



Chris Barnard is a Scientific Consultant in the Liquid Phase Catalysis Group at the Johnson Matthey Technology Centre, Sonning Common, UK, with interests in homogeneous catalysis employing the platinum group metals. He is also interested in the application of platinum compounds as cancer therapy.

Professor Keith Fagnou

We sadly report that on 11th November 2009 Professor Keith Fagnou died of complications after contracting the H1N1 (swine flu) virus. He will be much missed by his family and friends, but also by the wider chemistry community. Keith studied for his MSc at the University of Toronto, Canada, between 1998 and 2000 and then completed a PhD at Toronto working with Professor Mark Lautens. On completion of those studies in 2002 he transferred to the University of Ottawa, Canada, as an Assistant Professor. In 2007 he was made an Associate Professor and awarded a Research Chair in the Development of Novel Catalytic Transformations. In recent years, his work on coupling reactions involving carbon-hydrogen bond activation was highly regarded and the OMCOS Award was only the most recent of a large number of research awards he received during his time at Ottawa.