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# Novel Chiral Chemistries Japan 2007

Reviewed by David J. Ager
DSM, PMB 150, 9650 Strickland Road, Suite 103, Raleigh, NC 27615, U.S.A.; E-mail: david.ager@DSM.com

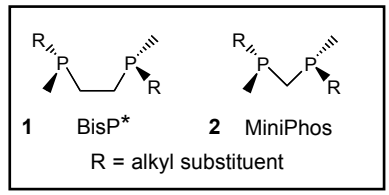
The second Novel Chiral Chemistries Japan (NCCJ) Conference and Exhibition was held in Tokyo from 16th to 17th April, 2007. The first meeting in the series had been held in 2006 and a similar format was followed. There were three keynote addresses with supporting lectures. Professor Takao Ikariya (Tokyo Institute of Technology) did an excellent job as the conference organiser. During the coffee and lunch breaks there was a small exhibition by companies associated with chiral chemistry. The exhibitors ranged from companies that provide biocatalysts, metal catalysts and ligands through to service providers associated with the implementation of methodologies. Some scientific instrumentation was also on display. There were about 100 delegates, most coming from the Japanese fine chemicals industry.

## Keynote Presentations

There were three keynote addresses. The first was by Professor Henri Kagan (University Paris-Sud, France) who described some of the general problems associated with finding a catalyst for a specific purpose when non-linear effects are observed. This was highlighted by examples of asymmetric depletion, when a low degree of asymmetric induction can occur unless the catalyst has an extremely high enantiopurity.

The second keynote address was presented by Professor Gregory Fu (Massachusetts Institute of Technology, U.S.A.). This lecture covered the development of chiral nucleophilic catalysts based on 4-aminopyridines bound to ferrocene derivatives. These catalysts have proved useful for the asymmetric conversion of ketenes to $\alpha$-substituted esters. In the presence of copper, the ferrocene derivatives can be used to prepare $\alpha$-alkoxy esters. This chemistry has led to the development of chiral azaferrocenes for the asymmetric formation of cyclopropanes from diazocompounds.

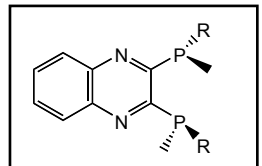
The third and final keynote address was by Professor Tsuneo Imamoto (Chiba University, Japan) who described how his work had progressed from BisP*, **1**, and MiniPhos, **2**, to other ligands based on the concept of *P*-chirality, as originally implemented by Knowles with DIPAMP (1).




**1** BisP* **2** MiniPhos

R = alkyl substituent

The synthesis of both ligand series involves organometallic chemistry, with the phosphorus stabilised as a borane adduct for asymmetric deprotonations with *sec*-butyllithium in the presence of sparteine. The rhodium complexes of these ligands provide high enantioselectivity in the reduction of dehydroamino acid derivatives, enol esters and enamides. Hydrosilylation of ketones provides access to chiral secondary alcohols. The iridium complexes of these ligands can be used to reduce imines to amines, again with high stereoselectivity. This work is now being extended to AlkynylP*, where the methyl group of BisP* has been replaced by alkynyl groups. These ligands have shown high selectivity for the addition of arylboronic acids to enones. This latter reaction can also be performed with QuinoxP*, **3**, which also provides high asymmetric induction in the rhodium-catalysed reduction of enamides and palladium-catalysed addition of dialkylzinc to 7-oxabicyclohepta[2.2.1]dienes.



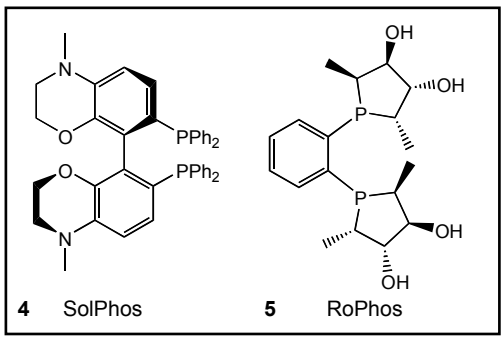

**3** QuinoxP*

R = alkyl substituent

## Asymmetric Catalysis

In addition to these keynote addresses, there were fifteen other presentations. The topics ranged from the use of biocatalysts and chiral auxiliaries through to the design of ligands and applications of both approaches in pharmaceutical case studies. Only the talks relating to the use of platinum group metals (pgms) have been summarised here, in line with the emphasis of this publication.

Rocco Paciello (BASF, Germany) described how the phosphanylpyridones designed by Professor Bernhard Breit from the University of Freiburg, Germany, can be used in hydroformylation reactions of terminal alkenes in the presence of rhodium, to provide high selectivity for the formation of aldehydes. Asymmetric reactions were illustrated by hydrogenations where phosphonites from the Breit collaboration are available. Catalyst screening was the topic of a number of the presentations, and the BASF approach was illustrated by a synthesis of (*R*)-2-methylpentanol where the successful ligand for the rhodium-catalysed reduction of the allyl alcohol precursor was SolPhos, **4**. For the reduction of itaconic esters, rhodium with RoPhos, **5**, was found to be the successful combination.

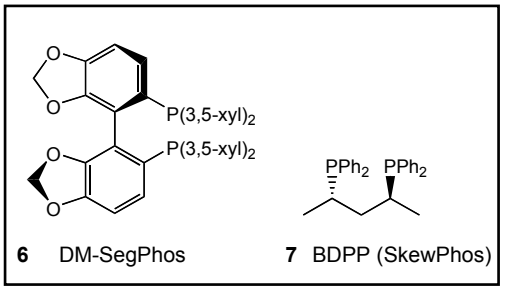



**4** SolPhos **5** RoPhos

For the reduction of ketones, transfer hydrogenation is the preferred method of operation and this is being scaled up using a continuous process. In addition, the presence of a small amount of carbon monoxide has been found to be advantageous.

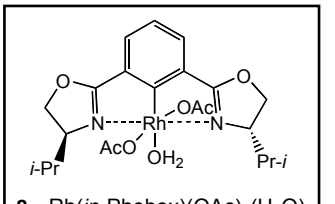
Antonio Zanotti-Gerosa (Johnson Matthey, U.K.) described work that has been done by Johnson Matthey, in collaboration with the Royal Institution and the Universities of Liverpool and Southampton, U.K., on computational investigation into ketone reduction with the ruthenium-BINAP-DPEN system. There seem to be significant differences in performance between the XylBINAP and TolBINAP systems. This could be due to the way in which the substrate docks with the metal catalyst (2).

Hideo Shimizu (Takasago International Corp., Japan) described work on the direct reduction of enamines to $\beta$-amino esters with DM-SegPhos, **6**. The second part of the talk was on new work related to the reduction of aryl ketones by the use of copper catalysts with BDPP, **7**, (also known as SkewPhos) as the chiral ligand.




**6** DM-SegPhos **7** BDPP (SkewPhos)

Professor Hisao Nishiyama (Nagoya University, Japan) described his work with Rh(Phebox), **8**, for the conjugate reductions of $\alpha,\beta$-unsaturated esters, enals and enones. As an enolate is formed in the reaction, the intermediate can be reacted with an electrophile to perform aldol and other reactions. This approach gives a rapid and powerful approach to chiral 3-hydroxy-2-alkyl esters.



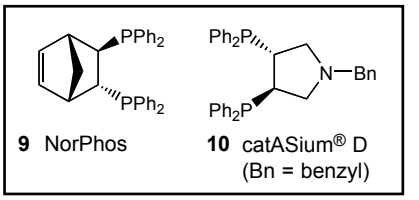

**8** Rh(*ip*-Phebox)$(OAc)_2(H_2O)$

Hans-Jürgen Federsel (AstraZeneca, Sweden) gave a number of examples of different approaches for the preparation of chiral pharmaceutical compounds. For the synthesis of a complex 2-aminotetralin, the nitrogen at the

stereogenic centre was introduced by a reductive amination with phenylethylamine. The Buchwald-Hartwig approach with palladium acetate in the presence of BINAP afforded the piperazine coupled product (Scheme I).

Professor Jaiwook Park (Pohang University of Science and Technology, South Korea) described his work on the dynamic kinetic resolution of amines through the use of enzymes to stereospecifically prepare an amide from racemic amine. A metal catalyst provides the ability for an *in situ* recycling of the amine enantiomer that is not a substrate for the enzyme. The metal catalyst is based on palladium nanoparticles entrapped in aluminium hydroxide, prepared by heating aluminium tri-*sec*-butoxide and tetrakis(triphenylphosphine)palladium in butanol in air.

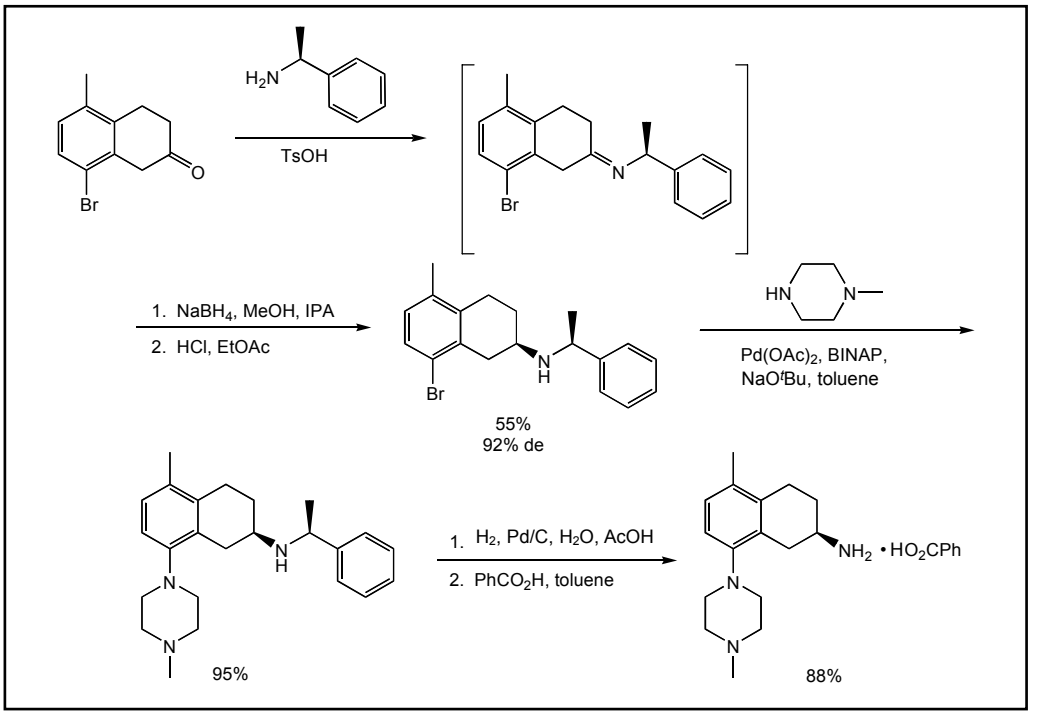
The theme of a dynamic kinetic resolution was continued by Renat Kadyrov (Degussa Homogeneous Catalysts, Germany), who described how the use of Rh(Norphos), **9**, could be employed for the reduction of racemic *N*,*O*-acetals, aminols, to prepare chiral amines, as 1,2-amino alcohols. Other reductive approaches to chiral amines include the use of catASium® D, **10**, to prepare $\alpha$-amino acids from $\alpha$-keto acids and a transfer hydrogen method with ruthenium TolBINAP for ketones.



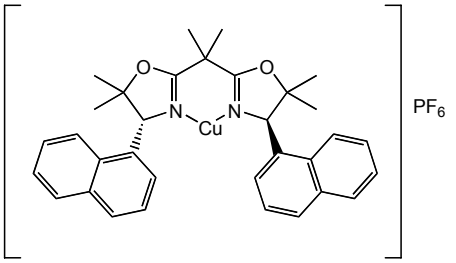

**9** NorPhos **10** catASium® D (Bn = benzyl)

Makoto Itagaki (Sumitomo Chemical Co., Ltd., Japan) described the development of catalysts for the asymmetric synthesis of cyclopropanes. In addition to control of enantioselectivity, the *cis*:*trans* ratio has to be controlled. The products are used in the agricultural industry and may be applied as a mixture, but there is still a need to produce the active isomer in the most cost-efficient manner available. The development of catalysts for the addition of the diazoesters to alkene has led to the copper-pybox analogue **11**.

David Ager (DSM, U.S.A.) described the methods employed to find the best catalyst for an

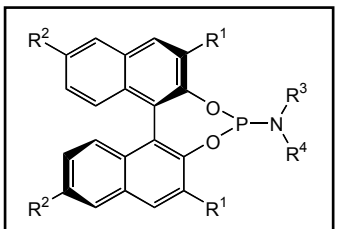



*Scheme I Synthesis of a complex 2-aminotetralin (de = diastereomeric excess)*



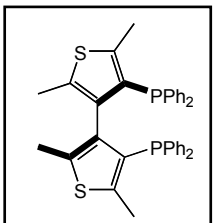

**11** Cu-pybox analogue

asymmetric transformation. The ligand system is a monodentate phosphoramidite and those based on BINOL are known as the MonoPhos™, **12**, family. These ligands can provide excellent asymmetric induction for the reduction in the presence of rhodium of a wide range of carbon–carbon double bonds (3). The ligands are now proving useful in the rhodium-catalysed additions of arylboronic acids to aldehydes and imines.




**12** MonoPhos™ family

Yongkui Sun (Merck & Co., U.S.A.) described how screening is a powerful tool to find asymmetric catalysts in the pharmaceutical industry. Three case studies were presented. The first involved a dynamic kinetic resolution approach for the reduction of a ketone to alcohol with control of the $\alpha$-stereocentre to produce the desired isomer. The method used a Noyori approach. The synthesis also involved the conversion of an aryl bromide to nitrile with Pd(*o*-Tol)$_4$ and zinc cyanide. In the second example, the target molecule was the same, but Rh(TMBTP), **13**, was used to reduce an enamide. For this approach, the enamide was prepared by a palladium-catalysed coupling of a vinyl tosylate with an amide. The third example was for the synthesis of sitagliptin, where a Ru(BINAP) reduction of an unsaturated acid provides the desired isomer as isomerisation of the substrate occurs under the conditions employed for the reduction.




**13** TMBTP

## Concluding Remarks

As with the first meeting, NCCJ 2007 was held in the same week as CPhI Japan (4). The meeting allows interactions between Japanese companies and academics with their counterparts from Europe and the U.S. In addition to new methodologies, application of methods and the problems associated with implementation in industrial settings provide a background emphasising the need to develop both more efficient catalysts and the means to identify them.

The wide variety of topics and applications discussed demonstrates that use of the pgms continues to provide new and useful methodologies to prepare molecules on an industrial scale. I hope this excellent series continues to grow and prosper.

### References

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2 S. A. French, *Platinum Metals Rev.*, 2007, **51**, (2), 54

3 D. J. Ager, A. H. M. de Vries and J. G. de Vries, *Platinum Metals Rev.*, 2006, **50**, (2), 54

4 CPhI Japan: http://www.cphijapan.com/eng/

**The Reviewer**

David Ager has a Ph.D. (University of Cambridge), and was a post-doctoral worker at the University of Southampton. He worked at Liverpool and Toledo (U.S.A.) universities; NutraSweet Company's research and development group (as a Monsanto Fellow), NSC Technologies, and Great Lakes Fine Chemicals (as a Fellow) responsible for developing new synthetic methodology. David was then a consultant on chiral and process chemistry. In 2002 he joined DSM as the Competence Manager for homogeneous catalysis. In January 2006 he became a Principal Scientist.