Novel Chiral Chemistries Japan 2012

The importance of pgms in chiral chemistry

http://dx.doi.org/10.1595/147106712X654853 http://www.platinummetalsreview.com/

Reviewed by David Ager

DSM Innovative Synthesis BV, PMB 150,
9650 Strickland Road, Suite 103, Raleigh, NC 27615, USA
Email: david.ager@dsm.com

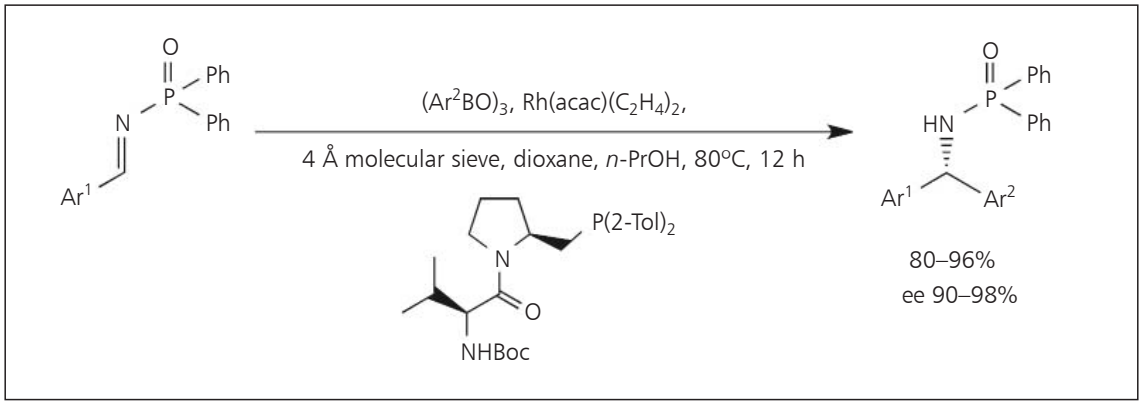
The fourth Novel Chiral Chemistries Japan (NCCJapan) Conference and Exhibition was held in Tokyo, Japan, on 15th and 16th March 2012 (1). The previous meeting had been held in 2009 (2). This meeting had been originally scheduled for April 2011, but the natural disaster just prior led to the meeting being postponed for almost a year. All the meetings in the series have followed a similar format, with keynote addresses and supporting lectures, although this time there were some short company presentations. Professor Takao Ikariya (Tokyo Institute of Technology, Japan) and his team, in particular Kyoko Suzuki, once again did an excellent job to ensure that the conference ran smoothly. There was an exciting mix of speakers from both academia and industry across the world. There were around 100 attendees, with the majority being from Japan. There were also exhibitions from 18 Japanese and multinational companies with products relating to chiral chemistry.

Keynote Presentations

The first keynote was presented by Professor Masahiro Terada (Tohoku University, Japan) on enantioselective carbon–carbon bond forming reactions catalysed by chiral phosphonic acids, mainly derived from 3,3′-disubstituted 2,2′-bisnaphthols. The reactions discussed included hetero-Diels Alder reactions and condensations of vinyl ethers with azlactones to form β-alkoxy α-amido esters.

The first day closed with the second keynote address from Professor Kiyoshi Tomioka (Doshisha Women's College of Liberal Arts, Japan). The first part of the lecture discussed additions of organometallic reagents to imines. Reagents included organolithium, zinc and Grignards. However, high yields and enantioselectivites were observed for the use of arylboroxines with aryl imine in the presence of a chiral ligand and a rhodium precursor to form phosphinic amides (**Scheme I**). The final part of the lecture returned to the additions of lithiated amines to alkenes.

The final keynote address closed the conference and was delivered by Professor Pher Andersson



Scheme I. Preparation of chiral phosphinic amides by imine addition

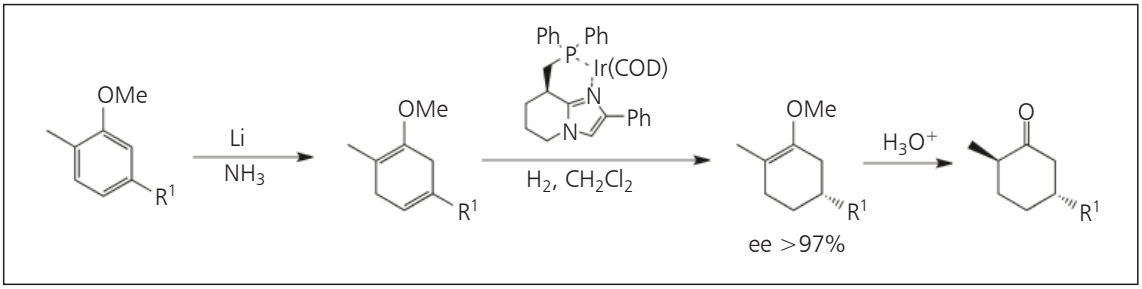
(University of Uppsala, Sweden). Iridium-based catalysts can be used for the asymmetric hydrogenation of unfunctionalised alkenes. The lecture covered the development of new ligand classes and their use in the asymmetric hydrogenation of enol ethers, vinyl trifluoromethyl compounds, vinyl phosphonates, homoallylic sulfones, as well as other classes of substrates. The use of some of the hydrogenation products was illustrated by performing further transformations on them. For example, Birch reduction of a 1,3-disubstituted benzene followed by asymmetric hydrogenation gave good control over the stereochemistry in the 1,3-disubstituted cyclohexane. One of the substituents can also be a functional group, as in methoxy, which can then be converted to a ketone by hydrolysis of the intermediate enol ether (**Scheme II**).

Asymmetric Catalysis

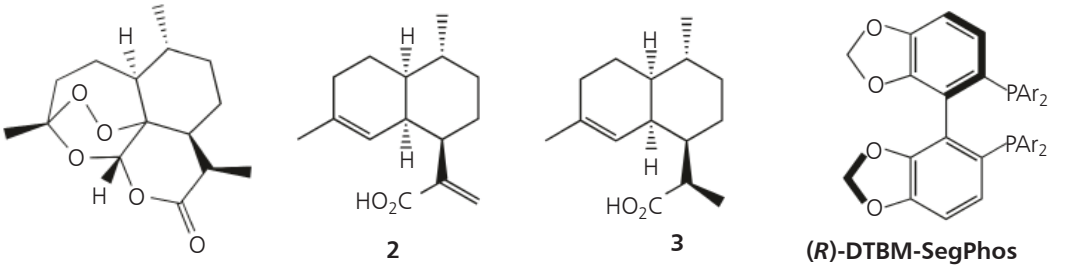
The invited lectures covered a wide range of topics and techniques associated with chiral chemistry. Joël Turconi (Sanofi-Aventis, France) and Tohru Yokozawa (Takasago International Corporation, Japan) gave interrelated talks. The Sanofi project is to make artemisinin, **1**, by a semi-synthetic route with artemisinic acid, **2**, being made by fermentation. The artemisinin will be used to combat malaria in poor countries. The first step in the conversion of **2** to **1** is an asymmetric hydrogenation. The key step is cyclisation of a carbonate by a photochemical reaction, which is a challenge at larger scales. The Takasago contribution was to screen suitable ligands and conditions to maximise the yield of the monoalkene **3**. $RuCl_2[(R)$-DTBM-SEGPHOS$](DMF)_n$ was the catalyst of choice.

Scott Frank (Eli Lilly & Co, USA) described a commercial application of a direct asymmetric reductive amination (DARA) reaction. This reaction was the key step in the synthesis of evacetrapib, **4**, a cholesterol ester transfer protein inhibitor candidate. The use of the ketal **5** allowed for a faster reaction in the imine formation step (**Scheme III**). This also allowed for the imine formation and reduction to be performed concurrently. The catalyst system of choice was Ir with Xyl-BINAP.

Professor Xumu Zhang (Rutgers, The State University of New Jersey, USA) provided some



Scheme II. Preparation of 2,5-disubstituted cyclohexanones from trisubstituted benzenes

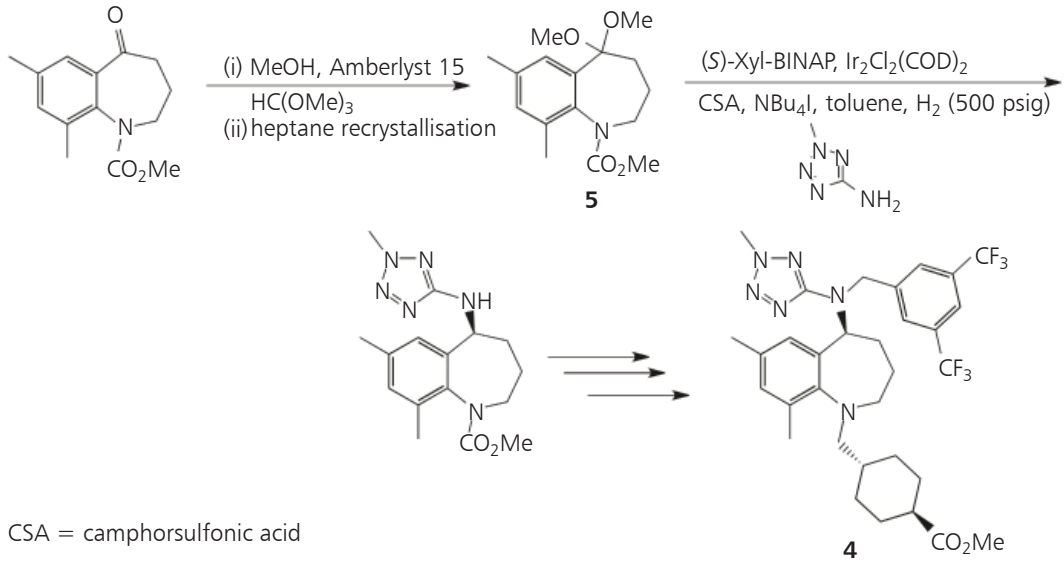


examples where his catalyst systems have been applied to the synthesis of chiral intermediates for use in pharmaceuticals. The illustrations included the use of rhodium-DuanPhos in the manufacture of monomethyl amino alcohol (MMAA) **6**, an intermediate for duloxetine; Rh-TangPhos to prepare the β-amino acid moiety of sitagliptin; and DuanPhos for the manufacture of the α-amino acid intermediate that becomes the bicyclic part of ramipril. As well as C=C hydrogenations, ketone reductions also play a key role in pharmaceutical intermediate syntheses. Examples of this were provided by the use of Ru-C_3-TunePhos for the reduction of methyl acetoacetate and its subsequent incorporation into dorzolamide and the reduction of 3,5-bis(trifluoromethyl) acetophenone with $RuCl_2$[(*S*)-Xyl-C_3*-TunePhos] [(*S*)-DAIPEN] in the synthesis of aprepitant.

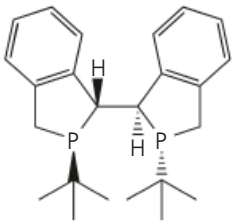
Professor Ilya Gridnev (Tokyo Institute of Technology, Japan) discussed the mechanisms of enantioselective reactions with bifunctional Ru and Ir catalysts, such as **7** and **8**. The reactions discussed included the addition of malonates to enones in a Michael reaction and the addition of aryl cyanomalonates to azodicarboxylates and butynedicarboxylates. The catalysts have to be very active to overcome the background reactions, which lead to racemic products.

Kenichiro Miyazawa (Daicel Corporation, Japan) gave the next presentation on the use of supercritical fluid chromatography (SFC) and how this can be used for preparative separations.

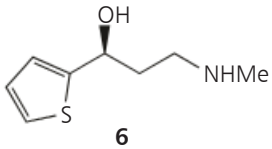
The next presentation was from Rocco Paciello (BASF AG, Germany) and described the new L-menthol process that employs an asymmetric hydrogenation. The starting material is *cis*-citral (**Scheme IV**). The



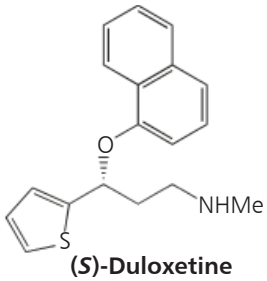
Scheme III. Imine reduction in the synthesis of evacetrapib



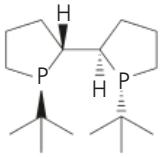
(*S,S′,R,R′*)-DuanPhos



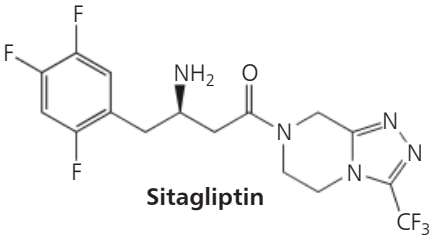
6



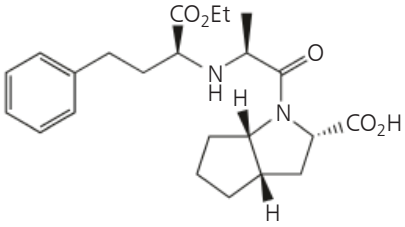
(*S*)-Duloxetine



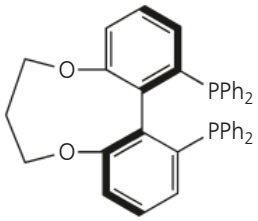
(*S,S′,R,R′*)-TangPhos



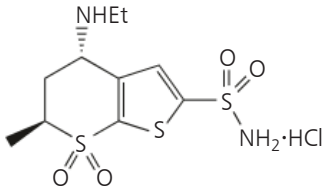
Sitagliptin



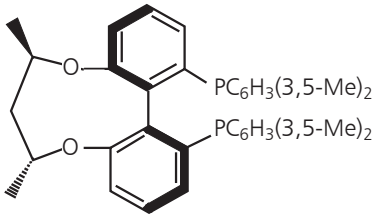
Ramipril



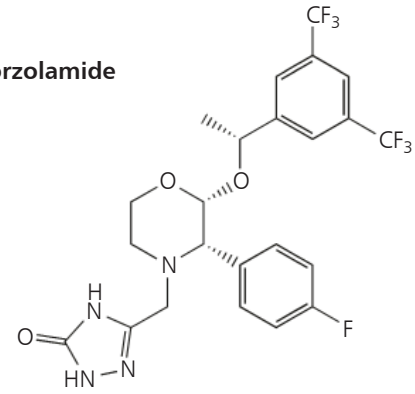
(*R*)-C_3-TunePhos



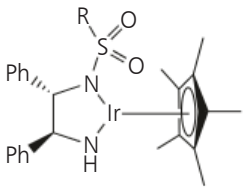
Dorzolamide



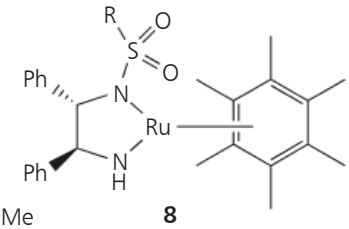
(*S*)-Xyl-C_3*-TunePhos



Aprepitant

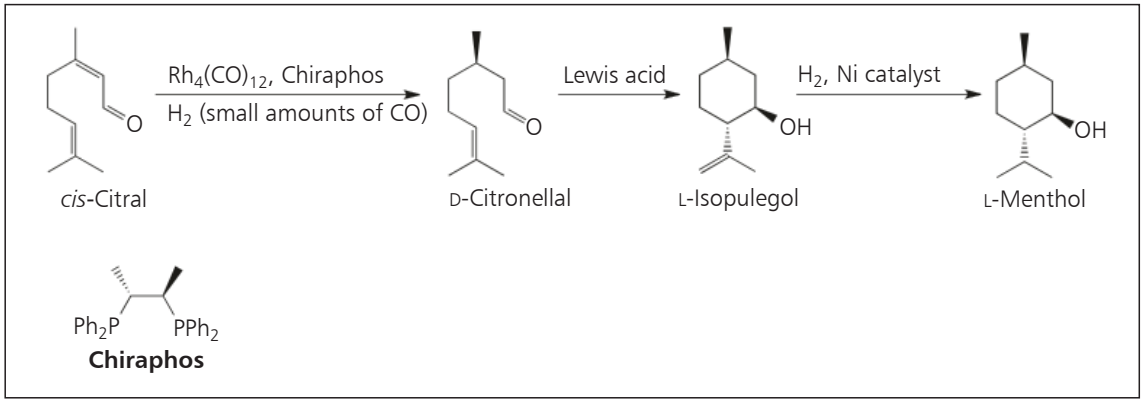


7



8

R = Me
4-MeC_6H_4
(1*R*)-camphor
Me_5C_6

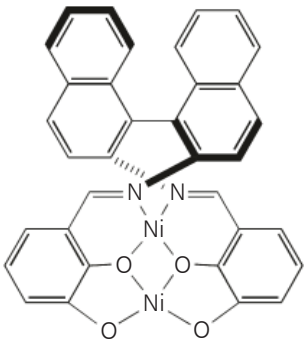


Scheme IV. BASF method for the synthesis of L-menthol

first step is an asymmetric hydrogenation and after screening many catalysis systems, Rh-Chiraphos was found to be the best system if carbon monoxide is added to the hydrogen stream. The method has been adapted to a continuous process. The other steps in the process were not discussed. BASF expects the plant to be online in 2012 (3).

The second day started with a presentation by Professor Shigeki Matsunaga (University of Tokyo, Japan) on dinuclear Schiff base complexes as bifunctional catalysts. A wide variety of transformations were discussed but the common theme was additions to imines and aziridines with catalysts containing two metals, and the use of nickel, as in **9**, circumventing the need for a rare earth metal.

David Ager (DSM Innovative Synthesis BV, USA) gave a number of examples for the asymmetric synthesis of amines with screening for appropriate catalysts being a key contribution. For the reduction of the enamine **10**, the phosphite **11** was found to be superior to the usual phosphoramidites used by DSM. The use of the ligand class **12** with Ir gave good asymmetric induction with the imine **13**. The final example was for a greener route to the amino acid **14**, where the aryl–nitrogen bond is formed by a copper-catalysed reaction with the stereogenic centre being introduced by an enzymatic reaction prior to the cyclisation step.

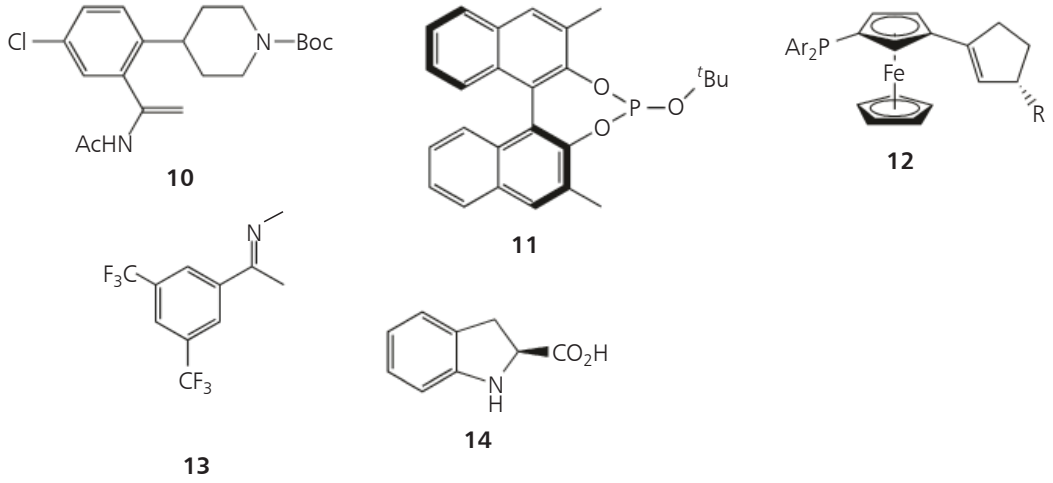


9

Yongkui Sun (Merck & Co, Inc, USA) described how collaborations might lead to useful solutions to problems. The first example was the reduction of keto imines without the need for *N*-protection, where for aryl alkyl examples Ir-(*f*-binaphane) was found to be the best catalyst. For diarylimines, Ir was also the metal of choice with the MonoPhos ligand **15** being the choice in the case of the imine **16**. The last example was for a reductive intramolecular cyclisation with Ru(TsDPEN)-based catalysts where the carbon dioxide formed was found to play a significant role in the reaction kinetics.

Professor Katsuhiko Tomooka (Kyushu University, Japan) discussed his work on planar chiral heterocycles where the ring conformation is the source of the asymmetry. Karen Holt-Tiffin (Chirotech Technology Ltd, Dr Reddy's, Custom Pharmaceutical Services, UK) described a coupled enzymatic approach to α-amino acids.

Noboru Sayo (Takasago International Corporation, Japan) started by describing the conversion of a β-keto ester to a β-amino aster by a reductive amination with Ru(DM-SegPhos). The main emphasis of the presentation was on the use of Ru-MACHO for the reduction of esters to alcohols. RUCY is a family of Ru catalysts based on BINAP, which are superior for the asymmetric reduction of acetophenone derivatives. The final example was with DENEB as an oxo-tethered Ru(II) complex,

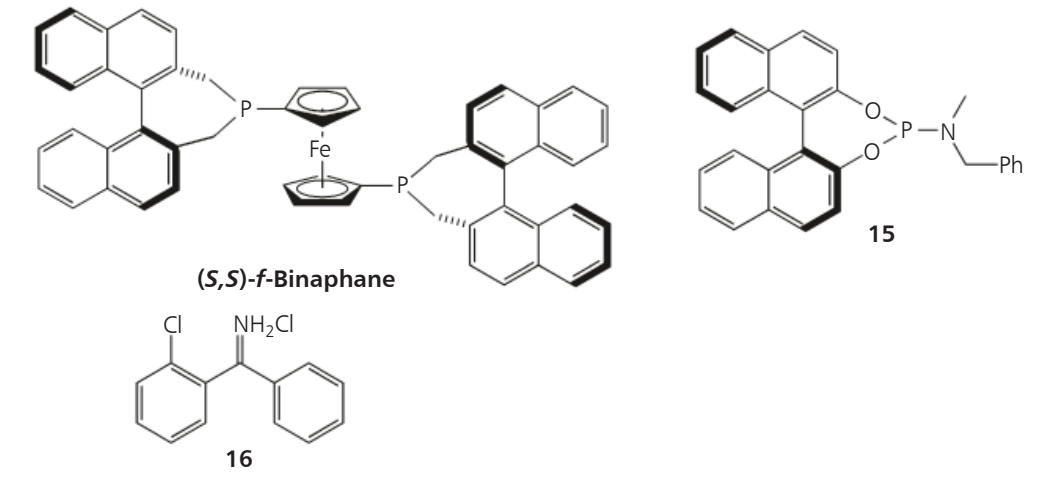


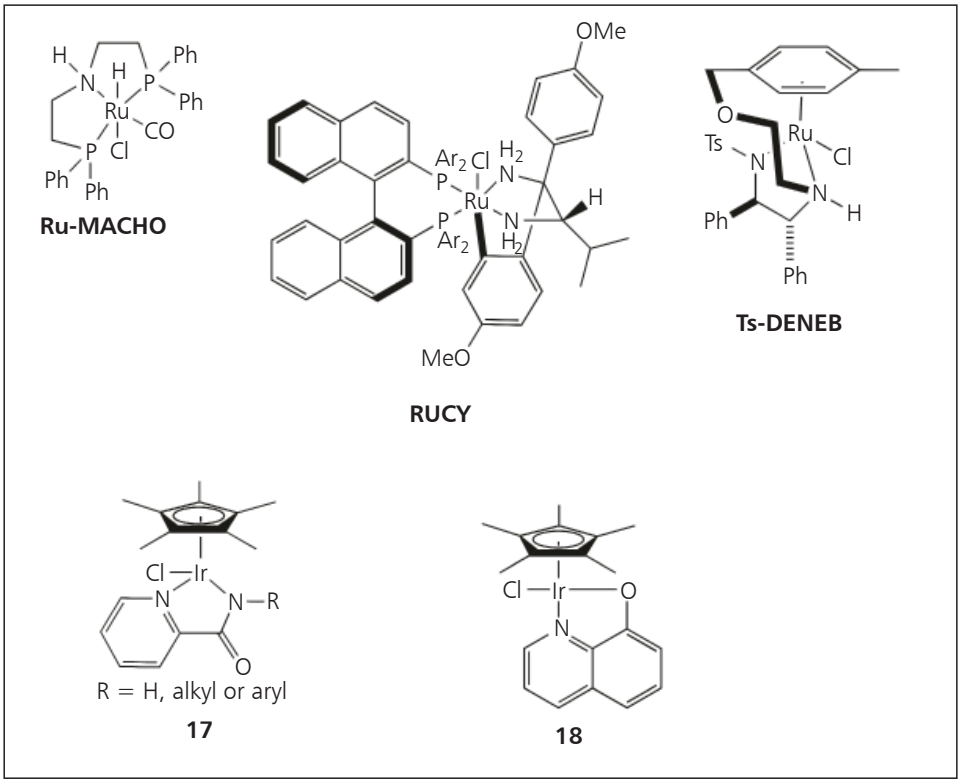
which performs the same transformation but under transfer hydrogenation conditions; the reactivity is at a maximum when the tether length is four atoms.

Professor John Blacker (University of Leeds, UK) discussed how the formation of CO can affect the reaction kinetics of a cyclic imine with RhClCp*[(*R,R*)-TsDPEN] as catalyst. The use of IrCp*TsDPEN showed a loss of enantioselectivity as the reaction was left, due to racemisation of the product under the reaction conditions. This led to the development of the SCRAM catalyst $[Cp^*IrI_2]_2$ for the racemisation of amines, which can be useful when coupled with resolution methods such as an enzymatic transformation or crystallisation. The SCRAM catalyst can also be used for the alkylation of amines with alcohols in water. The alcohol is converted to the aldehyde and then the intermediate imine is reduced with the 'borrowed' hydrogen. Amines can also be used as the alkyl group donors.

In the company presentations, which were distributed amongst the main programme, Masahito Watanabe (Kanto Chemical Co, Inc, Japan) described the use of the Ir complexes **17** and **18** for reductive aminations. For primary amines, ammonium formate can be used as the nitrogen and hydrogen source, while for the preparation of secondary and tertiary amines, the corresponding amine is used to prepare an intermediate imine and formic acid is used as the hydrogen source.

Takeshi Inoue (Tokyo Chemical Industry Co, Ltd, Japan) described a new chiral separation high-performance liquid chromatography (HPLC) column based on polymaleimide. Yukio Dobashi





(Nippon Shokubai Co, Ltd, Japan) described how mandelic acid is made from benzaldehyde using hydroxynitrilase.

Concluding Remarks

As with the other meetings in this series, NCCJapan 2012 was held just before CPhI Japan, allowing participants to attend both. This latter meeting had also been postponed from 2011 due to the earthquake. The participants of NCCJapan 2012 were given an experience of this with two earthquakes occurring over the days when the meeting was held.

There was sufficient time between lectures and at the banquet to allow for interaction between the participants, exhibitors and speakers. As noted above, a wide variety of methodology was covered, but there was a strong emphasis on the use of transition metal catalysis, and in particular the use of platinum group metal-based systems with phosphine ligands. We look forward to the fifth conference in this series.

References

1 Novel Chiral Chemistries Japan 2012 (NCCJapan) Conference Programme: http://www.apc.titech.ac.jp/~tikariya/NCCJ/2012NCCJ.pdf (Accessed on 9th August 2012)

2 D. J. Ager, *Platinum Metals Rev.*, 2009, **53**, (4), 203

3 BASF adds L-menthol to product range, Aroma Ingredients BASF: http://aromachemicals.basf.com/About_us/AboutLmenthol.aspx (Accessed on 9th August 2012)

The Reviewer

David Ager has a PhD (University of Cambridge, UK), and was a post-doctoral worker at the University of Southampton. He worked at Liverpool and Toledo (USA) universities; then as a Fellow in NutraSweet Company's research and development group, NSC Technologies, and Great Lakes Fine Chemicals 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.