

# CONFERENCE REPORT

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## Highlights from the 1<sup>st</sup> Firmenich Innovation Through Synthesis (FITS) Symposium, Geneva, Switzerland, 26–27<sup>th</sup> June 2008

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**Abstract:** This conference report highlights the different lectures that took place for Geneva for the first organic synthesis symposium organized by Firmenich.

**Keywords:** Conference report · Firmenich

Over 100 chemists attended the inaugural FITS Symposium held in the Grand Hotel Kempinski overlooking Lake Geneva. Dr. **Roger Snowden** and the organizing committee put together an exciting program of organic synthesis and catalysis. The concept behind this symposium was to have an equal mix of Firmenich and external academic speakers. A selection of chemists from Swiss universities was also invited.

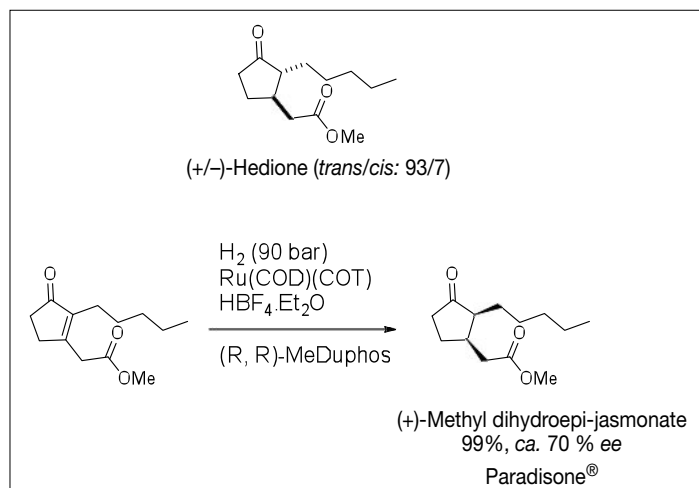
**Patrick Firmenich** (CEO, Firmenich SA, Geneva, Switzerland) in his general introduction pointed out the central role played by organic chemistry in the flavor and fragrance industry and stressed the continual need for more innovation. He finished by emphasizing the increasing importance of making chemistry more sustainable and green.

The scientific part of the program commenced with a presentation by Dr. **Roger Snowden** (Firmenich SA, Geneva, Switzerland) who took us on a journey describing the history and synthesis of two key Firmenich perfumery ingredients: Paradisone<sup>®</sup> and Cetalox<sup>®</sup>.

After the discovery of Hedione<sup>®</sup> by Firmenich in the 1960s, subsequent work showed that only one of the four stereoisomers, Paradisone<sup>®</sup>, was primarily responsible for the excellent quality of the odor. Two synthetic approaches to Paradisone<sup>®</sup>

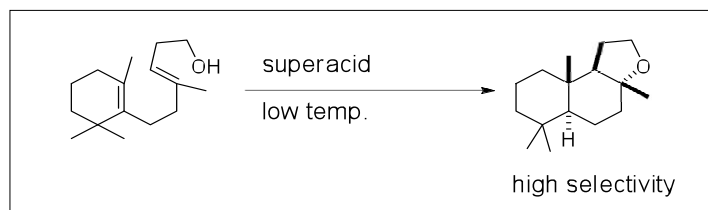
were developed, the more direct one using an unprecedented catalytic asymmetric hydrogenation reaction (Scheme 1).

The second half of the lecture was directed towards Cetalox<sup>®</sup>. Within Firmenich, ambergris-type compounds have a long history starting with the discovery of Ambrox<sup>®</sup> in 1950. Due to price fluctuations in the natural products (*e.g.* sclareol) leading to Ambrox<sup>®</sup>, attention turned towards the possibility of finding an industrial synthesis of the unknown racemate, Cetalox<sup>®</sup>. After many years of effort, this

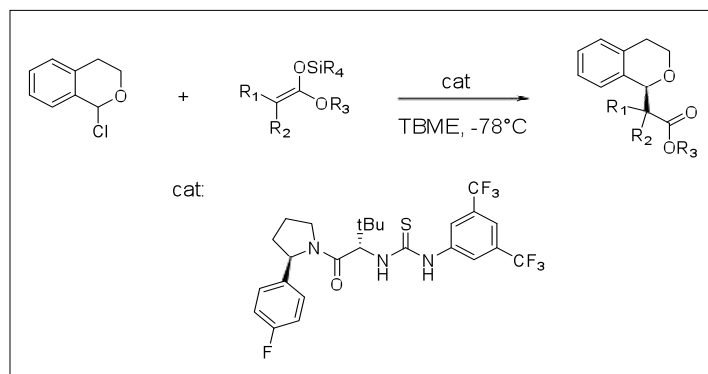


Scheme 1.

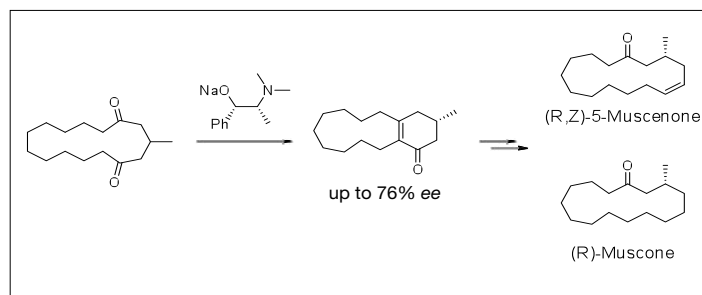
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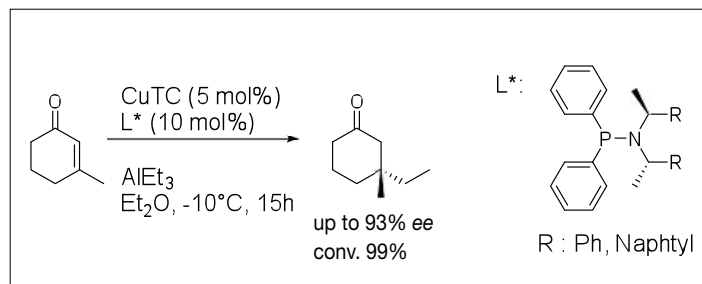
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

goal was successfully attained (Scheme 2).

The Thursday afternoon session was continued by Prof. **Eric Jacobsen** (Harvard University, Cambridge, USA) who focused on asymmetric catalysis either with a metal or by organo-catalysis. He contradicted a common belief that in asymmetric catalysis a large bulky ligand is needed in order to obtain good selectivity. He showed how 'privileged ligands' can have a broad scope and allow the development of new reactions. A special emphasis was placed on small-molecule chiral hydrogen-bond donors and their wide applicability in current organic chemistry (Scheme 3).

The subject of the next presentation was a new approach to the synthesis of musk odorants (*R*)-muscone (3-Me-cyclopentadecene) and (*R,Z*)-5-musconone) by Dr. **Oliver Knopff** (Firmenich SA, Geneva, Switzerland). Musk odorants are essential molecules in the perfumers' palette and since the discovery of nitromusks in 1891 several new classes of musk compounds have subsequently been discovered. Amongst them macrocyclic musks have always owned a special place. (*R*)-muscone, the most famous representative, was isolated in the beginning of the 20<sup>th</sup> century. The use of an efficient intramolecular aldol addition/asymmetric dehydration reaction as the key step provided an industrial synthesis of enantio-enriched (*R*)-muscone and (*R,Z*)-5-musconone (Scheme 4).

The final speaker for day one was Prof. **Alexandre Alexakis** (University of Geneva, Switzerland). The focus of this lecture was the development of new ligands for Michael

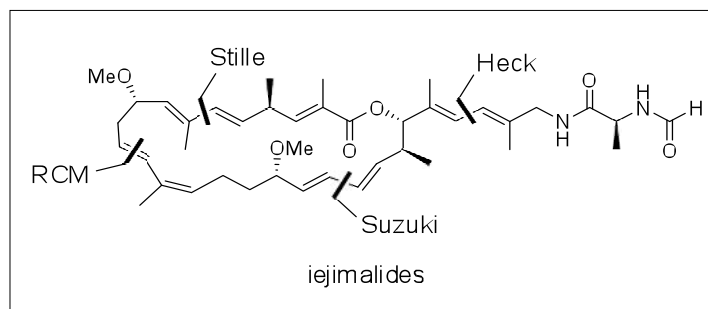
additions. New phosphorus ligands, *e.g.* SimplePhos, integrating central chirality and atropoisomerism have been developed. To tackle the long-standing problem of conjugate addition to a trisubstituted double bond, giving rise to all-carbon chiral quaternary centers, new *N*-heterocyclic carbenes have been successfully synthesised. The lecture ended with the copper-catalyzed S<sub>N</sub>2' allylic substitution reactions, showing how high degrees of selectivities could be obtained (Scheme 5).

This last lecture did not mark the end of the day for the audience, as a special buffet based on 'cuisine moléculaire', using as its

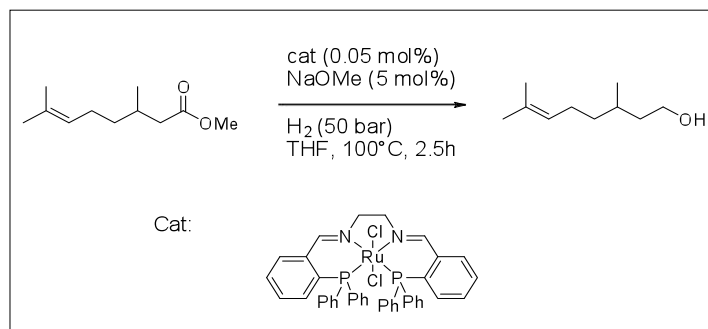
theme perfumery ingredients and laboratory equipment, was waiting for guests and speakers and gave a beautiful finish to the day.

The second day of the meeting started with Prof. **Alois Fürstner** (Max-Planck Institute, Mülheim an der Ruhr, Germany) who provided a very entertaining lecture on natural product synthesis with special emphasis on how catalysis of ring-closing metathesis and coupling reactions has brought new ways of thinking about synthetic organic chemistry. A maelstrom of reactions, combining bitter disappointments with

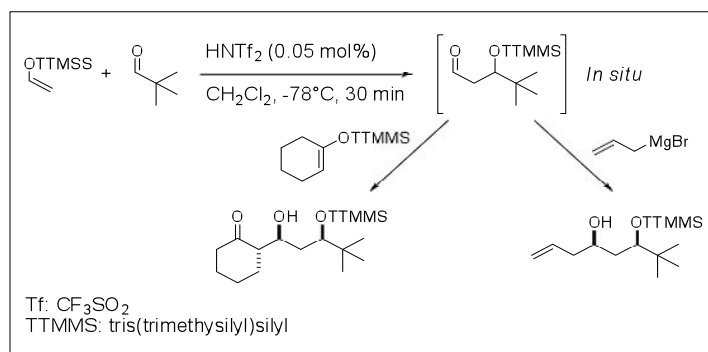




Scheme 6.



Scheme 7.



Scheme 8.

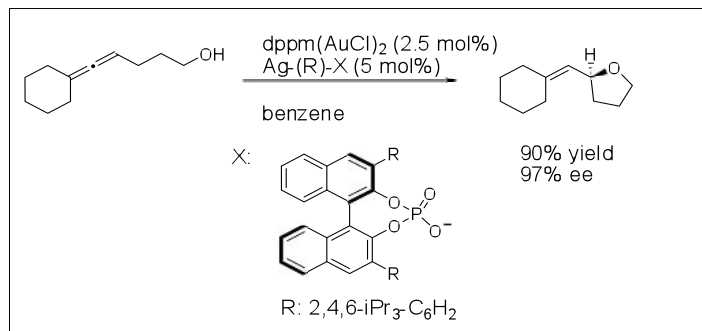
huge successes took the audience from dicydodendrin A-E to iejimalide (Scheme 6).

The morning session was continued by Dr. **Lionel Saudan** (Firmenich SA, Geneva, Switzerland). The reduction of an ester to a primary alcohol is a widely employed transformation in chemistry, classically achieved by using stoichiometric amounts of a hydride reducing agent. The search for a new catalytic hydrogenation of esters using mild conditions (low pressure and low temperature) has now led to the development of a novel ruthenium based catalytic process. The scope of the reaction is broad. Aliphatic and aromatic esters as well as lactones are reduced. Di and tri-substituted double bonds are also tolerated, although terminal or conjugated olefins are hydrogenated under the reaction conditions (Scheme 7).

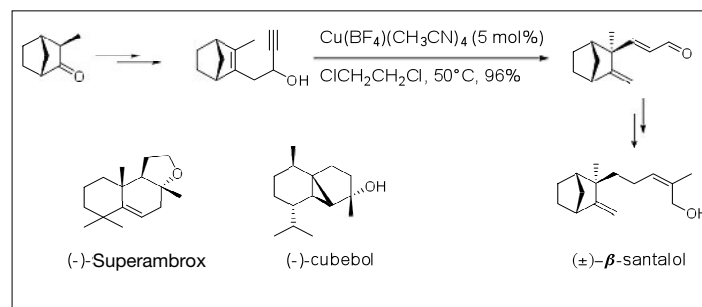
Prof. **Hisashi Yamamoto** (University of Chicago, IL, USA) gave a stunning lecture on the design of organic catalysts. We all

embarked on a tour from classical aluminum and boron based Lewis acids to super Brønsted acids. Professor Yamamoto's group has developed new powerful carbon Brønsted acids based on a combination of the trifluoromethanesulfonyl and pentafluorophenyl groups. A polystyrene-bound catalyst was also disclosed. The unique behavior of this class of compounds combined with the use of the tris(trimethylsilyl)silyl enoethers unveiled new reactivity (Scheme 8).

Prof. **Dean Toste** (University of California, Berkeley, CA, USA) gave a stimulating account on gold catalysis in the past couple of years. His laboratory has been very active and has outlined a number of unique reactivities. New gold catalyzed reactions encompassing cycloisomerization, rearrangement, ring expansion and addition reactions have been developed. A natural extension of this chemistry towards enantioselective catalysis was also discussed. Besides the



Scheme 9.



Scheme 10.

classical use of chiral bisphosphine ligands, a more powerful and poorly studied chiral counterion strategy was used with very good results. Both methods combined gave rise to asymmetric reactions that could not have been achieved with a single strategy (Scheme 9).

To close the scientific part of the symposium Dr. **Charles Fehr** (Firmenich SA, Geneva, Switzerland) beautifully demonstrated how projects starting from a well-defined target namely (-)-Superambrox could, according to new results, lead to further applications for two important flavor and fragrance ingredients. A cycloisomerization step catalyzed by platinum, gold or copper was applied to the syntheses of (-)-cubebol, a flavor ingredient possessing an interesting cooling effect, and β-santalol, the key odorant principle of East Indian Sandalwood oil. This gave a truly spectacular finish to the FITS symposium (Scheme 10).

In closing, Dr. **Antoine Gautier** (Firmenich SA, Geneva, Switzerland) and Dr. Roger Snowden (Firmenich SA, Geneva, Switzerland) again reinforced the pivotal role of research and chemistry in the present and future success and of Firmenich.

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