



agence d'évaluation de la recherche
et de l'enseignement supérieur

Section des Unités de recherche

Report from the visiting committee

Research unit :

Laboratoire de Synthèse Sélective Organique et

Produits Naturels (LSSOPN) - UMR 7573

Ecole Nationale Supérieure de
Chimie de Paris



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de recherche

Le Directeur

Jean-Jacques Aubert

February 2008

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The research unit :

Name of the research unit : Laboratoire de Synthèse Sélective Organique et Produits Naturels (LSSOPN)

Requested label : UMR

N° in case of renewal : 7573

Head of the research unit : V. VIDAL (DR2 CNRS)

University or school :

Ecole Nationale Supérieure de Chimie de Paris (ENSCP)

Other institutions and research organization:

CNRS

Date(s) of the visit :

From January 28th to 30th of 2008

Members of the visiting committee



Chairman of the committee :

Pr. Antonio TOGNI, Laboratorium für Anorganische Chemie - ETH Zürich

Other committee members

Dr. Didier BOURISSOU, Université Paul Sabatier - Toulouse

Pr. Claude PIGUET, Department of Inorganic Chemistry, University of Geneva

Pr. Carmen NAJERA, Université d'Alicante

Pr. Reinhard BRUCKNER, Institut für organische Chemie und Biochemie, Albert-Ludwigs-Universität Freiburg

Pr. André CHARRETTE, Université de Montréal

CoNRS représentant representatives :

Pr. Florence DJEDAINI-PILARD (membre du comité national du CNRS), Université d'Amiens

Observers

AERES scientific representative:

Régis REAU, Université de Rennes 1

University or school representative:

A. FUCHS, Director of the ENSCP

Research organization representative (s) :

M-C. LASNE, DSA CNRS

Report from the visiting committee



1 • Short presentation of the research unit

- Numbers of lab members including researchers with teaching duties, full time researchers, ingeneers, PhD, students, technicians and administrative assistants : 30 (9 researchers with teaching duties - 3 PR including 1 PREM and 1 voluntary PR, and 6 MCF), 4 full time researchers (2 DR2, 1 CR1, 1 CR2), 2 ingeneers, 9 PhD, 6 technicians and administrative assistants
- Numbers of HDR and of HDR who are PhD students avisors : 8 / 4
- Numbers of PhD students who have obtained their PhD and average lenght of a PhD during the past 4 years : 11
- Numbers of PhD students currently present in the research unit : 9
- Numbers of PhD students with fellowships : 9
- Numbers of lab members who have been granted a PEDR : 2
- Numbers of "publishing" lab members : 11/11 EC + C ; 2/2 PREM + voluntary PR

2 • Preparation and execution of the visit

The visit took place on January 28-30, 2008. Prior to the visit, a detailed program has been set up by the chairman of the committee in tight collaboration with the representative of the AERES and the directors of the to date existing five UMR's (7611+7071, 7084, 7573 and 7576) constituting the *Institut de Chimie Moléculaire de Paris-Centre, Organique, Inorganique et Biologique* (FR 2769). The program has been sent to the involved parties in the second half of December 2007. Little adjustments had to be made during the following weeks in order to accommodate specific needs. The directors of the single UMR's have provided the committee's members with detailed reports concerning the activities of their respective UMR's during the past four years. Such reports have been available, on paper and/or in electronic form, either just before the end of 2007 or by the beginning of January 2008. These reports, while containing the essential scientific information needed for the evaluation, have not been specifically conceived for the evaluation.

The committee spent three days in Paris visiting the UMR's mentioned above. On the third day, the committee focused his attention on the two UMR's at the ENSCP. The visit started at 8h30 with a short presentation by the director of ENSCP followed by those of the two directors of UMR. The research activities of both UMR's have then been presented in detail by the single team leaders in parallel sessions, interrupted by a common lunch break with a common poster session. The committee also met with representatives of the PhD students, the staff of permanent researchers(chargés and directeurs de recherche, maîtres de conférences and professeurs), as well as technical and administrative personnel.

3 • Overall appreciation of the activity of the research unit, of its links with local, national and international partners

This research unit is internationally well known for the contributions made over the past years mainly, but not only, in the area of asymmetric hydrogenation. In this field the unit has a sufficiently large critical mass and has also shown a high degree of creativity and innovation. The unit is engaged in several significant collaborations with industry. Within ENSCP (Département Friedel) the collaboration with UMR 8151 should be mentioned.



The overall scientific production over the last 4 years in terms of publications (85) and presentations at conferences and at universities (131) is high. The unit has been involved in the training of 10 PhD students, which can be considered as satisfactory.

The unit is newly directed by a Directeur de Recherche who has been a co-director from 2004 to 2006. This has allowed for a smooth transition to the new situation.

4 • Specific appreciation team by team and/or project by project

1) Team: "Catalyse, Synthèse totale, Chimie du phosphore"

The team "Catalysis, Total Synthesis and Chemistry of Phosphorus" includes one Directeur de Recherche, one Maître de Conférence and one "Attaché Temporaire d'Enseignement et de Recherche". In addition and during the 2004-2007 period, 4 master and 5 Ph.D students and 2 post-doctorants completed the team.

The central theme of the research program of the team revolves around the discovery of two very effective, world-class bis(phosphine) ligands in the early 2000's (SYNPHOS and DIFLUOROPHOS). These were so effective that scale up syntheses and commercialization were undertaken by Synkem S.A.S.. In the past 4 years, most of the efforts were directed towards examining the scope of hydrogenation reactions using these ligands. Furthermore, superb fundamental work was undertaken to try to explain the electronic and binding properties of these ligands relative to others and to learn how to fine-tune them to maximize enantioselectivities. A second very important aspect of the program is the application of the asymmetric hydrogenation reaction in total synthesis. This area is not highly original, however, it is necessary to illustrate the full scope of the hydrogenation in "real life" systems. The team wants to build upon the ligand synthesis foundation to develop new chiral ligands that will be tested in Lewis acid catalyzed processes as well as in iridium catalyzed reactions. Given the past success of the team in this area, one must assume that they will make ground-breaking discoveries even though this is a highly competitive area. Although the quality of the publications is excellent, one must stress that the team should make a special effort in publishing their work in the journals with the highest impact factors to make sure that the team and the team leader gets the appropriate world-wide recognition.

Given the size of the team, the productivity in the 2004-2007 period is good with seventeen publications in good journals. Although the training component seems modest since only 2 students have graduated at the PhD level, this number will likely be on the rise since there are currently 5 PhD students and 2 postdoctoral fellows. The visibility of the team leader is quite good with 35 invited lectures in 4 years in several countries.

The published work is very important especially in the context of the enantioselective synthesis of small chiral synthons. Because of the economical nature of the hydrogenation, this reaction is one of the most important industrially. The team has shown over the years that the reaction can be applied to a variety of systems including in total synthesis. In addition, fundamental studies to increase their understanding of the subtle electronic effects of the ligands will allow them to develop even more effective ligands. Their position as leaders in the area of the asymmetric hydrogenation has led to a large number of collaborations not only with other academic groups but also with industry.

- **Strong points** : Good scientific productivity and visibility in terms of publication, clear identity as expert team in the area of asymmetric hydrogenation
- **What needs to be improved**: Although the overall quality of the work is excellent, the screening of new ligands in reactions that already proceed with high enantiocontrol is not highly original. Furthermore, the applications to total syntheses usually only feature the key asymmetric transformation developed in the group.
- **Recommendations** : This team has produced high quality work over the years in the hydrogenation area. It is clear that the proposed future work lies on a solid foundation and it is recommended to further concentrate on this "core business". Furthermore, it is recommended that a lot of efforts be placed on the reactions that do not have general solutions rather than reinvestigating reactions that are already proceeding very well with common commercially available chiral ligands (such as BINAP).



2) Team: "Chimie dans l'eau, Catalyse"

The team "Chimie dans l'eau et catalyse" is one of the components of the main research axis "Synthèse et catalyse". It includes two permanent positions (1 Directeur de Recherche, 1 Maître de Conférence). Over the last 4 years, 1 Attaché Temporaire d'Enseignement et de Recherche, 3 post-doctoral fellows, 4 PhD students and 5 undergraduate students have been involved.

This team carries out a research of high quality. Its contribution in homogeneous catalysis is well-recognized, and the emerging projects are promising. Its productivity over the last 4 years is very good (21 publications), and the team leader has already a good visibility (19 invited lectures).

This team is active in three main areas. One concerns *new hydrosoluble phosphines for transition-metal catalysis*. Thus, the tris(meta-carboxylate) version of triphenylphosphine has been prepared and its behaviour was compared with that of its sulfonated counterpart. The new ligand appears to be particularly effective for the Rh-catalyzed addition of arylboronic acids to alkynes under biphasic conditions. Ongoing research focuses on hydrosoluble versions of the MeO-BIPHEP diphosphine, in collaboration with an industrial partner.

Another major topic deals with *Ir, Pd, Pt and Au-catalyzed cycloisomerization of enynes*. An original alkoxylation process allowing for the tandem formation of C-C and C-O bonds has been developed. The reaction is atom economic, highly diastereoselective and applicable to a broad range of substrates. Interesting results were obtained in its asymmetric variant using the BINEPINE/PtCl₂/AgSbF₆ system. In addition, the nature of the nucleophilic partner could be varied further with the PPh₃/AuCl₃/AgSbF₆ system (to deactivated amines, activated aromatic systems and carboxylic acids), thereby extending the scope of the reaction considerably. Future research in this area will seek to develop efficient asymmetric versions of the reactions. In parallel, the preparation of *Pd, Au and Ni nanoparticles* and their application in such catalytic transformations is an emerging and ambitious project. This work is carried out in collaboration with a research group that has gained expertise in the preparation of nanoparticles, and is supported by an ANR grant for young researchers.

A third research topic concerns the synthesis of *fluorescent architectures* combining π -extended systems and phosphorus(V) moieties (phosphine oxides and sulfides) and their application to the sensing of heavy metals. This project is developed in collaboration with a group specialized in photophysics and has been supported by an ACI grant for young researchers.

- **Strong points** : The team has a good scientific productivity and is able to make original and innovative contribution to the field of transition-metal catalyzed reactions.
- **What needs to be improved**: Mid-term objectives and strategy are poorly defined. Most of the projects appear as developments of ongoing research.
- **Recommendations** : the relatively small size of the team the committee recommends to carefully equilibrate the human resources and research efforts between the new emerging projects, and those specific areas where the team had first important contributions.

3) Team: "Dérivés du bore en catalyse, Activation catalytique de liaisons C-H"

At present, this research team comprises 1 researcher (Maître de Conférence), who has teaching duties (192 h/year) and acts as a PhD student advisor, 1 ATER. 1 PhD student from this group obtained his degree after 3 years of research (2004-2007). In addition, 2 PhD students graduated (in 2004 and 2006) from joint research projects of the research team leader and the leader of another research teams within the same UMR. Moreover, 1 postdoc worked in this team and 3 students earned their Master degrees there. Currently, the team consists of 2 doctoral students. Each of the 6 PhD or master graduates from this group obtained publications to their credit; it is noteworthy that their authorships are unshared with any other experimentalist or shared with a single other experimentalist.

This team has established itself internationally by having found a number of quite remarkable transition-metal catalyzed C-C bond forming reactions starting from alkyl, alkenyl, or aryl trifluoroborates. They include the following important findings:

a) In Rh-catalyzed 1,4-additions to α,β -unsaturated ketones or esters (including anhydroaminoesters) the mentioned trifluoroborates are distinctly superior in terms of reactivity with respect to ate-complexes generated in situ from boronic acids or their esters. Hence, stoichiometric amounts of the trifluoroborates suffice for obtaining the same yields as resulting from using several equivalents of the analogous boronic acids or boronic esters.



b) The mentioned trifluoroborates add to aromatic aldehydes in the presence of Rh-catalysts. This makes genuine organometallic reagents in such an alcohol synthesis obsolete.

c) The transformations summarized in paragraphs (a) and (b) were modified entirely when run in the presence of acetone. Acting as an oxidant, this additive turns what used to be the additions to the C=X bond (X = C or O) into a substitution of an H atom attached to the C=X bond. The resulting transformations are very unusual as they give access to chain-elongated α,β -unsaturated ketones or esters from vinyl ketones or acrylates, respectively. Furthermore, they enable the synthesis of aromatic ketones from aromatic aldehydes (!) and organotrifluoroborates.

d) Another line of research of this team has been Rh-catalyzed aromatic and aliphatic C^{sp^2} -H-activation. In the latter case, the final position of the C=C bond is often not yet controlled. However, it is remarkable that this kind of reaction works at all.

- **Strong points** : Oxidative additions of alkyl, alkenyl, or aryl trifluoroborates to acceptor-substituted olefins or aromatic aldehydes (or nucleophilic substitutions of hydride in these substrates, as they might equally be called) are unique transformations. Accordingly, the publication record of this team is very good.
- **What needs to be improved**: Despite the novelty of the trifluoroborate-based methodology introduced and actively explored by the team, the risk of a too narrow focus in future projects should not be underestimated.
- **Recommendations** : It would be very useful and undoubtedly widely recognized if, in the future, the research team were able to expand the scope of their oxidative additions to more highly substituted starting materials in these reactions.

4) Team: "Synthèse asymétrique, Synthèse de biomolécules"

The researchers involved in this team over the past 4 years are one Maître de Conférence (new team leader), one professor (the former director of the UMR), one Chargé de recherche, 1 PhD students. The scientific production amounts to 11 publications and 6 invited talks.

The research activity of this team is concerned with the total synthesis of natural products. The choice of targets very often is dictated by the opportunity to apply asymmetric catalytic processes, in particular, but not only, asymmetric hydrogenation. Thus, for example in the total synthesis of sulfobacine A, a compound with antithrombotic activity, the installation of the three stereogenic centers has occurred via Ru-catalyzed hydrogenation processes. Similar considerations apply to the macrocyclic lactone dolabelide A, a compound of interest because of its cytotoxic activity. Other natural products that have been the object of synthetic work in the team are the paraconic acids, discodermolide, stevasteline B, isovenaciolide, pseudodistomine D.

- **Strong points** : This team has the advantage of exploiting highly efficient in-house catalytic hydrogenation methods.
- **What needs to be improved**: Besides the application of asymmetric hydrogenation in the synthesis of natural product, there are no significant, original methodological contributions to the field of total synthesis.
- **Recommendations** : This team is deemed too small to be able to produce high impact work in total synthesis. However, there are sufficient meaningful and close opportunities for collaborations in the area of total synthesis, in view of an appropriate choice of target molecules, both within this UMR and e.g. with the "Laboratoire de Chimie Organique de l'ESPCI" where partly very similar natural products are being targeted. A re-orientation of the team in this perspective is highly recommended.

5) Team: " Biochimie des micro-organismes: enzymologie, métabolisme et antibiotiques"

The total number of researchers and teaching-researchers with permanent position was 5 for the past four years (3 PU, 1CR-CNRS and 1 MCU) and will remain the same for the following four years (2PU, 1CR-CNRS and 2 MCU). However, the team had to cope with important changes: The director of the team as well as a PU and a CR-CNRS have left since 2006. Furthermore, a new team leader has taken over since October 2007 and a MCU and a CR-CNRS have joined this team in January 2008.



Because of these profound changes, there has been a decrease in productivity (publications, invited lecture and number of PhD theses) and of the coherence of the research. Nevertheless, the research related to the Laccase studies has led to the conception of a bio-battery and the creation of a national network with a good productivity. The antibacterial screening project exploiting a French National Library of compounds seems also to be a very useful initiative.

Based on these considerations, it is important this team is viewed as an emerging research unit directed by a young and promising leader. For the following four years, the already described projects will be maintained and two other projects (the study of cyanotoxines and the inhibitors of specific amino transferases) are also proposed. The long-term viability of this team needs also a real and strong support of the whole UMR and the interactions between the main research lines must be emphasized. In this context and as an illustration, the cyanotoxines project implies the synthesis of interesting molecules such as microcystine or the anatoxines analogues. Those molecules can be considered as targets for the “synthèse de biomolécules” team and a starting-point for productive interactions between the teams.

- **Strong points** : The new team is tackling new projects and makes a highly motivated impression; in this respects it deserves to be trusted
- **What needs to be improved**: The fit between the project and the size of the team should be improved.
- **Recommendations** : The committee recommends to increase the number of PhD students and postdoctoral co-workers and to actively seek for UMR-internal collaborations.

5 • Appreciation of resources and of the life of the research unit

This research unit, while well-equipped in terms of laboratory facilities and instruments, experiences a partly outdated laboratory infrastructure (as pointed out to the committee by several co-workers). Although the committee could not get more than a glance of the laboratories, it is clear that the situation is not as severe as for UMR 7611.

6 • Recommendations and advice

– Strong points :

This research unit has a high international reputation in the area of ligand and catalyst development, in particular for asymmetric hydrogenation reactions. To a large extent, this reputation is the reputation of the former director. Industry collaborations are also very important and there is a good balance between fundamental and applied research. Recent contributions in the area of organotrifluoroborate and their use in catalytic reactions are also very significant, besides excellent results obtained in the area of cycloisomerizations.

– What needs to be improved:

The efforts in the area of total synthesis are often not as original and novel as the fundamental contributions to asymmetric catalysis.

– Recommendations :

The main catalysis axis of this UMR is very strong and future work should concentrate on keeping the very good international position in this area. The promising new biochemistry team should be given enough time to develop new projects, while trying to better integrate its activities into those of the larger organic chemical section by stablishing internal collaborations.



CENTRE NATIONAL
DE LA RECHERCHE
SCIENTIFIQUE

Département Chimie
La directrice scientifique

Paris, le

20 MARS 2008

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Monsieur Jean-Jacques AUBERT
Directeur de la section des unités
Agence d'Evaluation de la Recherche
et de l'Enseignement Supérieur
20 rue Vivienne
75002 PARIS

Monsieur le Directeur,

J'ai bien reçu le rapport d'évaluation de l'unité de recherche UMR7573 que nous acceptons dans sa forme et je vous en remercie.

Conformément à votre demande de transmission par voie hiérarchique, je vous adresserai la réponse du Directeur d'Unité dès qu'elle me sera parvenue.

L'avis définitif de l'AERES sera un élément important pour les décisions que nous aurons à prendre lors de la contractualisation de cette unité.

Je vous prie d'agréer, Monsieur le Directeur, l'expression de ma haute considération.


Gilberte CHAMBAUD



Réponse au rapport AERES de l'Unité UMR 7573 ENSCP-CNRS (V.Vidal)

Regarding the comments made on Team « Catalyse, Synthèse totale, Chimie du phosphore », it is important to emphasize that its work has been published in journals such as *Angew. Chem. Int. Ed*, *Proc. Natl. Acad. Sci*, *Chem. Commun*, *Adv. Synth. Catal*. All these journals are recognized as journals with good impact factors.

As far as comments on Team « Synthèse asymétrique, synthèse de biomolécules » are concerned, certain important elements ought to be clarified and further explained. Concerning the total synthesis of biologically active natural and non-natural products in order to access to these compounds, multistep synthesis is required. For all the synthetic approach, among all the reactions used, at least one reaction developed by our group has been introduced successfully as the key step. This strategy is used by all synthesizing teams who are involved in multistep synthesis of biologically active compounds. It should be mentioned that all the reactions of a multistep total synthesis cannot be expected to originate from a single laboratory. Moreover, it is important to have versatile and efficient methods in order to generate analogues. The scientific teams of pharmaceutical companies, with whom we are collaborating, have acknowledged the asymmetric hydrogenation as an efficient tool for the syntheses of fine chemicals. The adequately and effectively combination of both our synthetic methods and those developed by other research groups, should bring about efficient and original route to obtain the target product as well as a variety of analogues (see UMR 7084).

Transmis par A. Fuchs, Directeur de l'ENSCP