

# SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2007 / 06

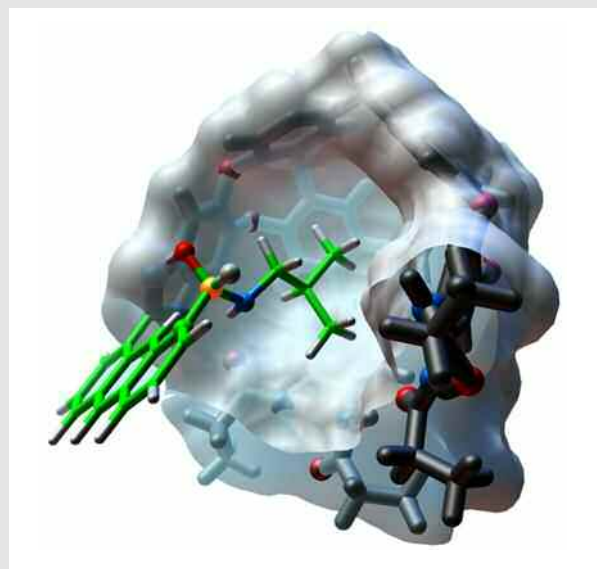
## SYNSTORIES ■ ■ ■ ■

■ New Catalytic Transformations – On the Way to “Dream Reactions”

■ Enantio catalysis in Water

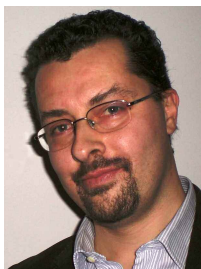
■ Direct Synthesis of Amides (and H<sub>2</sub>) from Alcohols and Amines

■ Snapshot of a Chemical Reaction Intermediate Using a Synthetic Receptor



**CONTACT + + + +**

Your opinion about SYNFORM is welcome, please correspond if you like: [marketing@thieme-chemistry.com](mailto:marketing@thieme-chemistry.com)



Dear readers,

The “41st World Chemistry Congress” of the International Union of Pure and Applied Chemistry (IUPAC) was held on August 5–11, 2007, in Turin (Italy). The congress venue was the former FIAT cars factory “Lingotto

Conference Center” which is a modern and functional structure that hosts concert halls, a theatre, a convention center, shopping arcades and hotels. The “Gianni Agnelli” Auditorium, that can accommodate more than 2000 people, hosted the lectures of three Nobel Awardees and the play “Should’ve” authored by Professor Roald Hoffmann. A rich and multidisciplinary program of lectures and posters was distributed among the many lecture halls of the “Lingotto”. The conference was very well organized and scientifically very stimulating: it’s a pity that the attendance to the lectures has been often rather modest, at least according to my experience. Two remarkable lectures presented at the IUPAC conference are covered and analyzed in this issue of **SYNFORM**: one by Professor Lukas J. Gooßen (University of Kaiserslautern, Germany) and one by Professor Maurizio Benaglia (University of Milan, Italy).

Two **SYNSTORIES** focusing on recent groundbreaking articles from the literature complete this issue: Professor David Milstein from the Weizmann Institute of Science (Rehovot, Israel) with his new synthetic strategies for the synthesis of amide bonds, and Professor Julius Rebek, Jr., from the Scripps Research Institute (USA) with his new strategy for taking snapshots of chemical reactions by using synthetic receptors. Thanks for getting “**SYNFORMed**”!

Matteo Zanda

Editor of **SYNFORM**

CONTACT + + + +

If you have any questions or wish to send feedback, please write to Matteo Zanda at:  
[Synform@chem.polimi.it](mailto:Synform@chem.polimi.it)

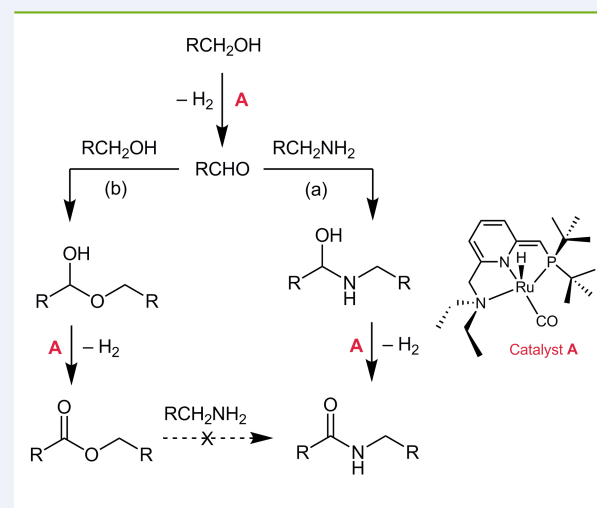
## IN THIS ISSUE

### SYNSTORIES ■ ■ ■ ■

New Catalytic Transformations – On the Way to “Dream Reactions”.....A64

Enantioselective Catalysis in Water.....A66

Direct Synthesis of Amides (and H<sub>2</sub>) from Alcohols and Amines.....A68



Snapshot of a Chemical Reaction Intermediate Using a Synthetic Receptor.....A70

COMING SOON .....A72

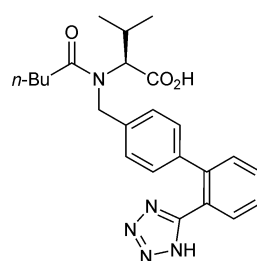
## New Catalytic Transformations – On the Way to “Dream Reactions”

Selected Presentation from the **41st IUPAC Conference – Turin, August 5–11, 2007**

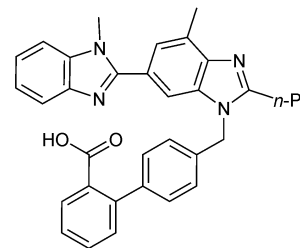
■ Many biologically active and functional molecules contain the biaryl substructure, which is therefore a very important synthetic target. Among the most valuable biaryl-containing molecules, Biphenomycin should be mentioned, as well as several pharmaceuticals having an immense economic value including Valsartan and Telmisartan, agrochemicals such as Boscalid, and liquid crystals for LCD screens.

Classical methods of biaryl (**6**) synthesis in the last decades have been almost completely replaced by the mild and selective Suzuki coupling of arylboronic acids **3** with aryl halides **5**, which is nowadays the method of choice for laboratory and industrial applications. However, the Suzuki reaction still suffers from a fundamental drawback common to almost all catalytic couplings between aryl nucleophiles and electrophiles: it requires the use of stoichiometric amounts of an expensive organometallic compound, in this case a boronic acid, and the syntheses of such carbanion equivalents from sensitive and hazardous aryllithiums, Grignard reagents (**2**), or boranes from aryl bromides **1** involve elaborate anaerobic conditions.

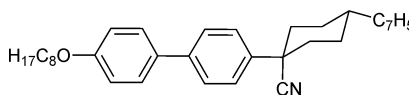
Living organisms, which clearly cannot provide an inert environment, have long before evolved to generate carbanion equivalents in an amazingly straightforward manner: by enzymatic decarboxylation of ubiquitously available carboxylic acid derivatives.



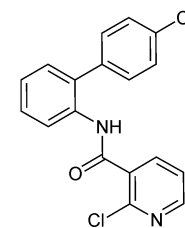
Diovan (Valsartan, Novartis)  
2004 sales: 2.6 billion €



Micardis (Telmisartan, Boehringer)  
2004 sales: 789 million €

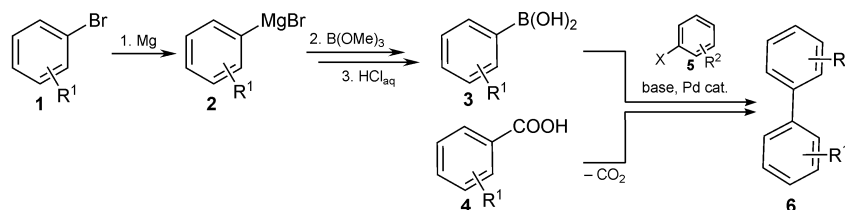


NCB 807 (Liquid crystal, Merck)



Boscalid (BASF)  
est. 1000 t/a, 150 million €/a

Examples of top-selling biaryl products



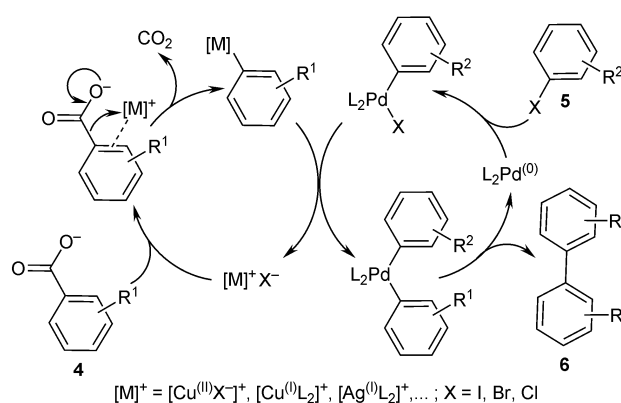
Synthesis of biaryls using the Suzuki (top) and the Gooßen strategy (bottom)

This biochemical route inspired the group of Professor Lukas J. Gooßen from the University of Kaiserslautern (Germany) to adopt a radically different approach to the traditional chemical synthesis of biaryls, using carboxylate salts rather than organometallics as the source of carbon nucleophiles (L. J. Gooßen, G. Deng, L. M. Levy *Science* **2006**, *313*, 662–664). Gooßen and co-workers designed an efficient catalyst system with the dual ability to facilitate the strongly endothermic extrusion of carbon dioxide from aryl carboxylates to form stable aryl–metal compounds, and to mediate the selective cross-coupling of these species with aryl electrophiles. “The main challenge was that, even with the best catalysts, the decarboxylation of aromatic carboxylates still requires high temperatures, and that under such conditions, the intermediate aryl–metal species are very sensitive towards protonolysis by the surrounding medium,” explained Professor Gooßen. Thus, a rigorous exclusion of moisture is required to avoid the unwanted protodecarboxylation.

According to Professor Gooßen “Dr. Guojun Deng performed close to 2000 test runs for the model reaction of 4-bromochlorobenzene with 2-nitrobenzoic acid to form 4-chloro-2-nitrobiphenyl – a key intermediate in the production of Boscalid – before he observed the desired product in more than trace quantities. A few weeks later, he had achieved nearly quantitative yields in the presence of a catalyst system generated in situ from 1 mol% CuI, 0.5 mol% Pd(acac)<sub>2</sub> and 3 mol% 1,10-phenanthroline using simple potassium carbonate as the base.” Since then, the reaction has been steadily improved by a growing number of students in the Gooßen group, especially Dr. Nuria Rodríguez, Christophe Linder, Bettina Melzer, Thomas Knauber, Paul Lange and Dr. Laura Levy. “The reaction is rather generally applicable to a wide range of aryl bromides, iodides and even activated aryl chlorides,” said Professor Gooßen, “and its scope with regard to the carboxylic acid coupling partner has been extended from *o*-nitrobenzoic acid first to carboxylic acids with other strongly coordinating groups in the *ortho* position that significantly increase the copper-ligating quality of the carboxylate substrate (2-acyl, 2-formyl), then to carboxylic acids with weakly coordinating *ortho* substituents (2-fluorobenzoic, 2-cyanobenzoic acid), and finally to vinylic or heterocyclic derivatives (cinnamic, thiophenecarboxylic acid).”

“The proposed reaction mechanism of this transformation initially follows the established pathway for protodecarboxylation reactions,” explained Professor Gooßen, “wherein the copper derivative is believed to coordinate to the carboxylate oxygen, then shift to the aryl  $\pi$ -system and insert into the C–C(O) bond with extrusion of CO<sub>2</sub> to form a stable aryl–copper intermediate.” In parallel, the aryl halide adds oxidative-

ly to the palladium catalyst to form an aryl palladium(II) complex. In a transmetalation step, the aryl group is transferred from copper to palladium with liberation of copper halide, and in a reductive elimination the desired biaryl is released from the palladium, regenerating the initial Pd(0) species and resuming the catalytic cycle for the palladium. The reaction of the copper halide with fresh alkali metal carboxylates through salt exchange closes the catalytic cycle for the copper. “This last step proved to be more troublesome than expected as it was unfavorable for non-*ortho*-substituted carboxylic acids so that with the first-generation catalysts,” said Professor Gooßen, “stoichiometric copper loadings were required for their conversion.”



Proposed mechanism for the decarboxylative biaryl synthesis

In his lecture at the IUPAC conference, Professor Gooßen showed that this remaining limitation might soon be overcome. “The successful reaction of *m*-nitrobenzoic acid with *p*-tolyl triflate in the presence of only catalytic amounts of both palladium and copper suggests that in halide-free systems, a coordinating *ortho* substituent is not required even with the first-generation decarboxylation catalysts,” he said. He also expressed his confidence that with new ligand generations designed to induce a stronger preference of the copper(I) center for carboxylate ions over halides, the extension of the double catalytic protocol to the entire range of aromatic, vinylic, and heteroaromatic acids may soon become possible even for aryl halides.

The methodology has been applied recently by the Gooßen group for the synthesis of Valsartan (L. J. Gooßen, B. Melzer



Part of the Gooßen group (Prof. L. Gooßen is third from the right)

*J. Org. Chem.* **2007**, *72*, 7473–7476), and a broad array of structurally diverse biaryls, some of which are of substantial industrial relevance (L. J. Gooßen, N. Rodríguez, B. Melzer,

C. Linder, G. Deng, L. M. Levy *J. Am. Chem. Soc.* **2007**, *129*, 4824–4833). ■

Matteo Zanda

## Enantio catalysis in Water

Selected Presentation from the **41st IUPAC Conference – Turin, August 5–11, 2007**

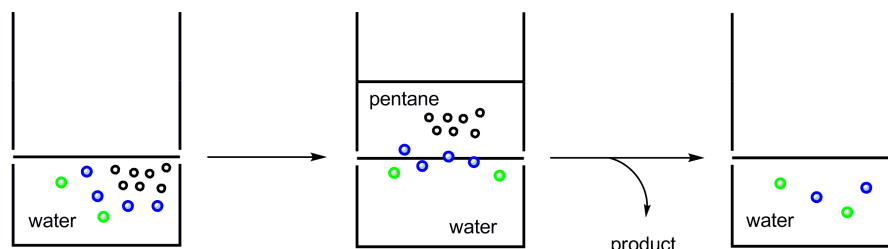
■ Organocatalysis holds great promise with the view of developing environmentally benign chemical processes and water is by definition “the green solvent”. Therefore, the combination of organocatalysis and water is apparently a win-win situation in terms of eco-sustainability. However, the challenges connected with the development of truly effective organocatalytic processes in water appear to be daunting and solutions are unlikely to be just around the corner. Many research groups are actively working to address these challenges; one of them is the group of Professor Maurizio Benaglia from the University of Milano, Italy. “Our group became interested in studying enantio catalysis in water a few years ago already (see M. Benaglia et al. *Org. Biomol. Chem.* **2004**, *3401–3407*),” confirmed Professor Benaglia. “In this field, our work follows two different approaches. In one case the idea is to mobilize the catalyst in the aqueous phase by connecting it to a water-soluble compound, such as a

poly(ethylene)glycol (PEG) chain.”

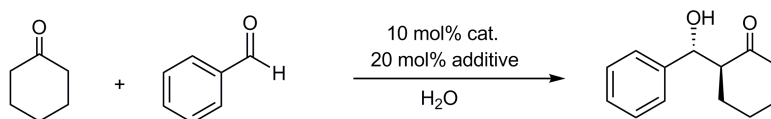
The recycling of the supported catalyst is possible by simple extraction of the product with an organic solvent and addition of new reagents to the aqueous phase, containing the catalyst, in a kind of ‘in continuo’ process that does not require the isolation and recovery of the immobilized catalyst.

“In principle, this procedure could be very attractive also to industries, in view of possible large-scale productions, with positive features from economical, environmental, and safety points of view. Of course the chemical and stereochemical efficiency of the methodology needs to be improved,” admitted Professor Benaglia.

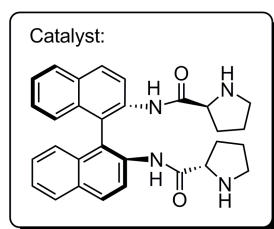
“Following another approach,” he continued, “we have shown that organic catalysts may be used to promote enantioselective reaction ‘on water’, or, as we have written in our paper *Org. Lett.* **2007**, *9*, 1247–1250, «in the presence of a



○ = product   ● = catalyst   ● = additive



1st run: 80% yield, 99:1 dr, 93% ee



without addition of stearic acid

with addition of stearic acid

2nd run: 45% yield, 98:2 dr, 93%

2nd run: 73% yield, 99:1 dr, 93% ee

3rd run: 69% yield, 99:1 dr, 93% ee

massive amount of water». There is a big discussion today about what may be considered a truly aqueous version of a reaction (for a very interesting discussion of enantioselective organocatalysis ‘in water’ or ‘in the presence of water’ see A. P. Brogan, T. J. Dickerson, K. D. Janda *Angew. Chem. Int. Ed.* **2006**, *45*, 8100–8102 and Y. Hayashi *Angew. Chem. Int. Ed.* **2006**, *45*, 8103–8104). Here, I just want to point out that several papers were published in the last two years claiming enantioselective organocatalysis in aqueous systems; however, they all suffer from some drawbacks. Some of them work in mixed aqueous organic solvent or require the use of surfactants. Often a large excess of ketone is employed and the catalyst performs in what really is, even if it is defined an aqueous medium, a wet organic system. Currently only two organocatalytic systems, developed by Hayashi and Barbas, really work in the presence of large amounts of water.”

The catalytic system proposed by the group of Professor Benaglia works in the presence of large amounts of water, but it is not completely soluble. “In our case,” he explained, “water is not really the reaction solvent but simply the reaction medium that increases the chemical and stereochemical efficiency of the whole system by keeping all the hydropho-

bic components close to each other. That is why our reaction is not ‘in water’ but ‘on water’.”

However, there are some other relevant issues. “Professor Blackmond, in a recent essay (*Angew. Chem. Int. Ed.* **2007**, *46*, 3798–3800), has correctly pointed out that just combining the words water and organocatalyst does not automatically make a reaction environmentally friendly,” said Professor Benaglia. “Water is truly a green solvent if not only the reaction, but also the work-up, does not add further chemical waste. If you need, for example, an organic solvent to extract the product from water, the whole process may not be so ‘green’ and appealing as it might seem. In our case the product is extracted with pentane, so we need to work on this aspect of the process; but in principle, if the product is water-insoluble, you do not really need an organic solvent, since the product can be easily separated from water by precipitation or phase separation. If the reaction is run on large scale, it should be feasible.”

“The recycling of the catalytic system is also a very interesting issue,” he concluded. “The organocatalyst is recyclable, once again without the need to isolate it, but we need to improve the efficiency of the process.”





Prof. M. Benaglia

*About the author.* Maurizio Benaglia was born on June 29, 1966, in Bergamo, Italy. He received both his ‘Laurea’ degree in 1991 and his PhD in Chemistry in 1994 at the University of Milano (Advisor Professor M. Cinquini). He then worked as a postdoctoral research fellow at the Department of Chemistry and Biochemistry of the University of California, San Diego, with Professor Jay S. Siegel from 1995–1997 with a CNR-NATO fellowship. He was an Assistant Professor at the Department of Organic Chemistry, University of Milano, from 2000–2006, and was then promoted to Associate Professor. He is author of over 90 articles in professional journals and a few chapters in books. He is the recipient of the ‘G. Ciamician’ Medal awarded by the Italian Chemical Society (Trieste, Italy, 2001).

Matteo Zanda

## Direct Synthesis of Amides (and H<sub>2</sub>) from Alcohols and Amines

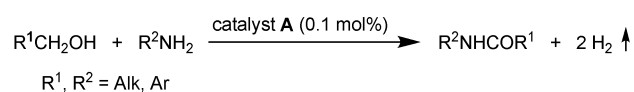
*Science* **2007**, *317*, 790–792

Amides have wide utility, both as synthetic intermediates and as end products in a variety of industrial applications. Current use includes plasticizers, detergents, lubricants, and foamers. The synthetic fibers Nylon and Aramide (Kevlar, Twaron) are polyamides. In biology, peptides and proteins are based on the amide linkage.

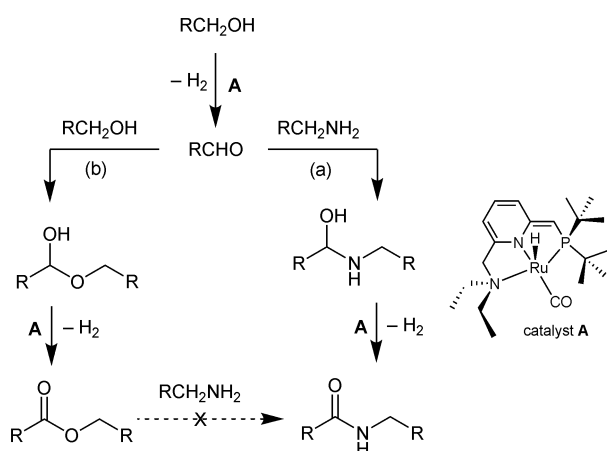
“Commercially, amides are prepared by condensation reactions of amines and carboxylic acid derivatives (such as the corrosive acid chlorides),” explained Professor David Milstein from the Department of Organic Chemistry, Weizmann Institute of Science, Rehovot (Israel). “These reactions produce waste, which results in environmental and economic concerns. The preparation of the carboxylic acid derivatives frequently involves toxic reagents (such as thionyl chloride). In addition, in many cases, carboxylic acids are prepared by oxidation of the corresponding alcohols.” Now, Professor Milstein, his postdoctoral fellow Chidambaram Gunanathan and his technician Yehoshoa Ben-David have reported a novel methodology for preparing amides through an environmental-

ly friendly process.

“In our method,” said Professor Milstein, “alcohols are coupled directly with amines to form amides and molecular hydrogen. The liberated hydrogen gas drives the reaction. The process is clean and selective (producing no secondary amines or imines) and proceeds under neutral conditions. No additives are required.” The reaction is selective to the primary amine functionality; compounds containing both primary and secondary amine groups react only at the primary amine, requiring no protection of the secondary amine. Moreover, the reaction is efficient, requiring very low catalyst loading and in many cases resulting in high yields.



The novel ruthenium catalyst **A** was rationally designed. “It is based on a ‘pincer’-type dearomatized PNN ligand, in which the phosphine ‘arm’ is tightly bound, while the amine arm is capable of de-coordination,” explained Professor Milstein. “It operates in a unique way, involving cooperation between the metal and the ligand: the catalytic cycle includes reversible aromatization of the pyridine backbone and reversible opening of the amine ‘arm’. We have reported before that this complex is an excellent catalyst for the coupling of alcohols to make esters and molecular hydrogen (*J. Am. Chem. Soc.* **2005**, *127*, 10840–10841; see also the highlight in *Science* **2005**, *309*, 853).” In this process (which was developed by postdoctoral fellow Jing Zhang in Milstein’s group), an intermediate hemiacetal (formed from alcohol and intermediate aldehyde) is involved, which undergoes dehydrogenation to form the product esters. “This led us to think that amide formation might be possible if an amine was added to the alcohol,” said Professor Milstein, “since in this case the formation of a hemiaminal is expected to be more favorable than that of a hemiacetal, as a consequence of the fact that an amine is more nucleophilic than an alcohol.”



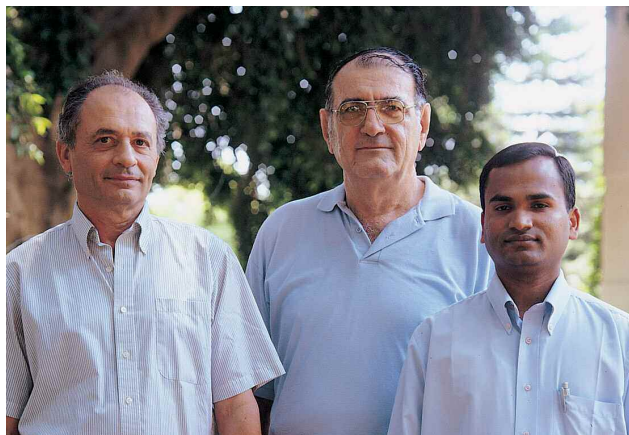
Remarkably, the same complex is also an excellent catalyst for the hydrogenation of esters to alcohols under mild (5 atm) hydrogen pressure (in industry, high pressures and temperatures are required for ester hydrogenation), generating no waste, as opposed to the reduction of esters with hydride reagents, which generates stoichiometric amounts of waste (see: *Angew. Chem. Int. Ed.* **2006**, *45*, 1113–1115). “We plan to explore the scope of the amidation chemistry and apply it to specific synthetic problems,” concluded Professor Milstein. “In parallel, we are also planning to continue our stu-

dies on metal–ligand cooperation (such as reversible ligand aromatization) in bond activation and catalysis.”

According to Dr. Andy Whiting, an expert in this field from the Department of Chemistry of the University of Durham (UK), “The cleanest and greenest possible amide formation is the direct reaction of an amine with a carboxylic acid, a process known and used since the 1800s;<sup>1,2</sup> however, there are limitations in that the lowest temperature they can be run at is around 85 °C and they are highly substrate-selective at lower temperatures.<sup>2</sup> Boron-based catalysts, though, help to solve many of these problems,”<sup>2–4</sup> continued Dr. Whiting, “though, again, ambient (<85 °C) reactions have yet to be developed. These new results by Milstein et al. do not provide an immediate solution, but they do provide a potentially important new lead since, with suitable tuning of the ruthenium catalyst system, they may well be applicable under milder conditions than currently available by direct amide formation or boron-based catalysis, and catalyst loadings are low compared to boron-based systems.<sup>2–4</sup> These new ruthenium catalysts offer the prospect of a useful new tool in the box for clean amide formation; however, there needs to be clear evidence that they don’t simply act as oxidizing agents for the alcohols to carboxylic acids, followed by direct thermal amide formation.” In a reply to Dr. Whiting’s comment, Professor Milstein points out that “the direct thermal coupling of carboxylic acids with amines, generating amides and water, has found little application since its discovery many years ago, while reactions based on acid derivatives (such as acid chlorides) became the methods of choice. The recent work with boronic acid based catalysts represents an interesting advance, although not without its limitations (the reaction at 85 °C requires 10 mol% catalyst, fluorobenzene solvent and a water scavenger<sup>2</sup>). It should be stressed,” concluded Professor Milstein, “that our reaction is *fundamentally* different from all carboxylic acid based approaches. It generates *hydrogen gas* and *not water* (or salt), hence it definitely does not involve alcohol oxidation to carboxylic acid, followed by its reaction with the amine. No additives or scavengers are required, as the evolved hydrogen gas (itself valuable) drives the reaction. The reaction is highly atom-economical, proceeds under neutral conditions and uses a low catalyst loading (0.1 mol%).”

*About the authors.* **David Milstein** is the Israel Matz Professor at the Department of Organic Chemistry at the Weizmann Institute of Science (since 1987). He is also the Director of the Kimmel Center for Molecular Design at the same institute. From 1979–1986 he was Group Leader at the DuPont Company in the USA. Recent awards include the I. M. Kolthoff Prize (2002), The Israel Chemical Society Prize





From left: Prof. D. Milstein, Y. Ben-David, Dr. C. Gunanathan

(2006), and the American Chemical Society National Award in Organometallic Chemistry (2007). In 2006 he was elected to the German Academy of Sciences – Leopoldina. His research emphasizes bond activation by transition-metal complexes and the rational design of new catalytic reactions. **Chidambaram Gunanathan** received his PhD in 2005 with Professor S. Muthusamy at the Central Salt and Marine Chemicals Research Institute, India. He joined the groups of Professor David Milstein and Professor Hadassa Degani at Weizmann Institute of Science for his postdoctoral research in

2005. His current research interest is the chemistry of transition-metal pincer complexes and their catalytic applications. In addition to the invention of new organic reactions for achieving high atom-economy and selectivity, he is also interested in the design and synthesis of novel lanthanide complexes for MRI and EPR applications. **Yehoshua Ben-David** obtained his BSc degree from the Faculty of Science of the University of Khartoum, Sudan, in 1967. Thereafter he immigrated to Israel and joined the Department of Organic Chemistry of the Weizmann Institute of Science. He has worked with several synthetic organic chemists. In 1987 he joined the group of Professor David Milstein and has been engaged mainly in the synthesis of various organic ligands.

## REFERENCES

- (1) A. W. Hofmann *Ber.* **1882**, *15*, 977–978 and references therein.
- (2) K. Arnold, B. Davies, R. L. Giles, C. Grosjean, G. E. Smith, A. Whiting *Adv. Synth. Catal.* **2006**, *348*, 813–820.
- (3) T. Maki, K. Ishihara, H. Yamamoto *Org. Lett.* **2006**, *8*, 1431–1434 and references therein.
- (4) P. Tang *Org. Synth.* **2005**, *81*, 262–272.

Matteo Zanda

## Snapshot of a Chemical Reaction Intermediate Using a Synthetic Receptor

*Science* **2007**, *317*, 493–496

■ The biological solution to the problem of highly selective and efficient catalysis involves macromolecules that use weak binding forces to stabilize reactive intermediates and transition states. Enzymes both isolate intermediates from the reactive outer medium and provide them with hydrogen-bonding and other non-covalent forces to lower their barriers to undergo reactions. This concept is well precedented, but most of the evidence comes from indirect analysis methods, because the high activity of natural enzymes means that inter-

mediates are very rapidly converted into products. Direct detection of labile intermediates is rare, and generally occurs at cryogenic temperatures (e.g., A. Heine et al. *Science* **2001**, *294*, 369–374).

Under most reaction conditions, formation of imines proceeds via steady state kinetics, and the intermediate hemiaminals are present at vanishingly small concentrations, far too low to be observed by conventional NMR spectroscopy. The advantage of using synthetic receptors to mimic natural

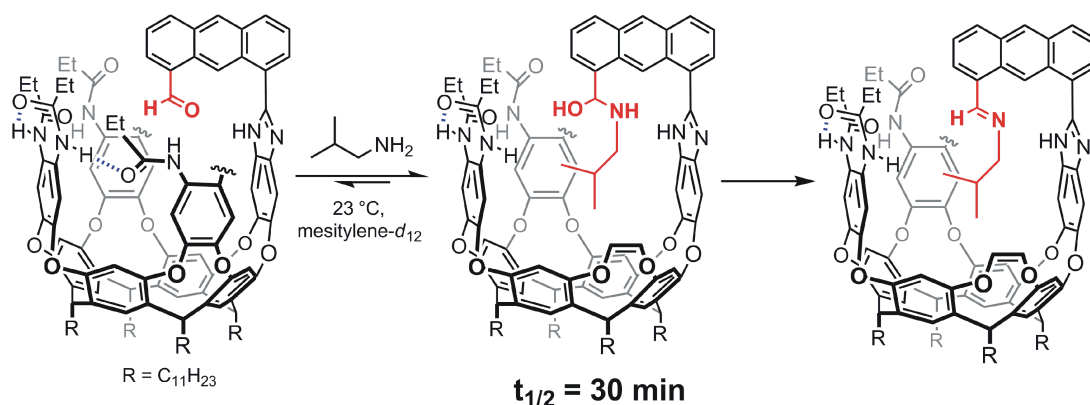
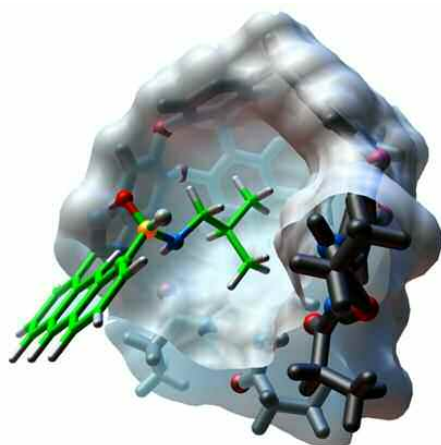


Illustration of the imine-forming process



Minimized structure (AM1 forcefield) of the stabilized hemiaminal bound inside the cavity

systems is that the structures are much simpler; they are under the experimenters' control, and allow more analysis techniques to come into play. Recently, Professor Julius Rebek, Jr. and co-workers at The Scripps Research Institute (USA) reported the stabilization of tetrahedral intermediates from the addition of small aliphatic amines to an aldehyde inside the binding pocket of a deep cavitand. "The bound hemiaminal intermediates are stable for many minutes at ambient temperature, allowing for observation and analysis by standard  $^1\text{H}$  NMR techniques," explained Professor Rebek. "The cavitand provides the bound amine with an inwardly directed, covalently bound aldehyde group." While common in natural systems, this arrangement of functional groups is rarely possible in supramolecular chemistry, owing to the synthetic difficulty in functionalizing concave surfaces. According to Professor Rebek "the nature of the stabilization is a combination of hydrogen bonding to an organized peptide-like framework

at the cavitand rim and mechanical isolation from reactive species (e.g., excess starting amine) of the bulk medium. Previous examples have illustrated this effect in single-step reactions such as the Menschutkin reaction (e.g., B. W. Purse et al. *J. Am. Chem. Soc.* **2003**, *125*, 14682–14683), but this is the first multistep process to be altered in this way." This result provides direct evidence of reactive intermediate stabilization in synthetic recognition systems that applies to biomolecules as well.

*About the corresponding author.* **Julius Rebek, Jr.** was born in Hungary in 1944. He received his undergraduate education at the University of Kansas in 1966, and obtained his PhD from the Massachusetts Institute of Technology (1970) for studies in peptide chemistry with Professor D. S. Kemp. After professorships at the University of California at Los Angeles and the University of Pittsburgh, he became the Camille Dreyfus Professor of Chemistry at the Massachusetts Institute of Technology, and devised synthetic, self-replicating molecules. In July 1996, he moved with his research group to The Scripps Research Institute to become the Director of The Skaggs Institute for Chemical Biology, where he continues to work on molecular recognition and self-assembling systems. ■



Prof. J. Rebek



Dr. R. Hooley



Dr. T. Iwasawa

**Matteo Zanda**

COMING SOON ► ► COMING SOON ► ►

## SYNFORM 2007/07 IS AVAILABLE FROM November 22, 2007

In the next issues:

### SYNSTORIES ■ ■ ■ ■ ■

#### ■ Oxidative Hydration of Alkynes: A Modular Connection Tool

(Focus on a presentation at the 234th ACS Conference - Boston, USA, August 19–23, 2007)

#### ■ New Palladium(II)-Catalyzed Aerobic Oxidative Carbocyclizations

(Focus on a presentation at the 234th ACS Conference - Boston, USA, August 19–23, 2007)

#### ■ “Cycloaddition Fluorination” Strategy for the Synthesis of Monofluorinated Carbocycles

(Focus on an article from the current literature)

#### ■ A General Synthesis of *syn*-Deoxypolypropionates by Rhodium-Catalyzed Enantioselective Desymmetrization of *meso*-3,5-Dimethyl Glutaric Anhydride

(Focus on an article from the current literature)

### FURTHER HIGHLIGHTS ++++

#### SYNTHESIS

Special Topic on “Small-Ring Chemistry” in issue 22/2007

#### SYNLETT

Account on: Progress in Coenzyme NADH Model Compounds and Asymmetric Reduction of Benzoylformate

(by N.-X. Wang)

#### SYNFACTS

Synfact of the Month in category “Organo- and Biocatalysis”:  
Arylpropionic Alcohols via Enzyme – Mediated Dynamic Kinetic Resolution

### CONTACT ++++

Matteo Zanda,  
C.N.R. – Istituto di Chimica del Riconoscimento Molecolare,  
Via Mancinelli, 7, 20131 Milano, Italy,  
e-mail: [Synform@chem.polimi.it](mailto:Synform@chem.polimi.it), fax: +39 02 23993080

#### Editor

Matteo Zanda, C.N.R. – Istituto di Chimica del Riconoscimento Molecolare  
Via Mancinelli, 7, 20131 Milano, Italy  
[Synform@chem.polimi.it](mailto:Synform@chem.polimi.it)  
Fax: +39 02 23993080

#### Editorial Office

- Managing Editor: Susanne Haak,  
[susanne.haak@thieme.de](mailto:susanne.haak@thieme.de), phone: +49 711 8931 786
- Scientific Editor: Selena Boothroyd,  
[selena.boothroyd@thieme.de](mailto:selena.boothroyd@thieme.de), phone: +49 711 8931 776
- Assistant Scientific Editor: Christiane Holst,  
[christiane.holst@thieme.de](mailto:christiane.holst@thieme.de), phone: +49 711 8931 768
- Production Editors:  
Herbert Krieg,  
[herbert.krieg@thieme.de](mailto:herbert.krieg@thieme.de), phone: +49 711 8931 781  
Thomas Loop,  
[thomas.loop@thieme.de](mailto:thomas.loop@thieme.de), phone: +49 711 8931 778
- Production Assistant: Helene Deufel,  
[helene.deufel@thieme.de](mailto:helene.deufel@thieme.de), phone: +49 711 8931 929
- Editorial Assistant: Sabine Heller,  
[sabine.heller@thieme.de](mailto:sabine.heller@thieme.de), phone: +49 711 8931 744
- Marketing: Thomas Krimmer,  
[thomas.krimmer@thieme.de](mailto:thomas.krimmer@thieme.de), phone: +49 711 8931 772
- Postal Address: SYNTHESIS/SYNLETT/SYNFACTS, Editorial Office,  
Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany,  
phone: +49 711 8931 744, fax: +49 711 8931 777
- Homepage: [www.thieme-chemistry.com](http://www.thieme-chemistry.com)

#### Publication Information

SYNFORM will be published 7 times in 2007 by Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, and is an additional online service for SYNTHESIS, SYNLETT and SYNFACTS.

#### Publication Policy

Product names which are in fact registered trademarks may not have been specifically designated as such in every case. Thus, in those cases where a product has been referred to by its registered trademark it cannot be concluded that the name used is public domain. The same applies as regards patents or registered designs.

#### Ordering Information for Print Subscriptions to SYNTHESIS, SYNLETT and SYNFACTS

Americas: Thieme New York, 333 Seventh Avenue, New York, NY 10001, USA. To order: [customerservice@thieme.com](mailto:customerservice@thieme.com) or use the Web site facilities at [www.thieme.com](http://www.thieme.com), phone: +1 212 760 0888  
Order toll-free within the USA: +1 800 782 3488  
Fax: +1 212 947 1112

Airfreight and mailing in the USA by Publications Expeditors Inc., 200 Meacham Ave., Elmont NY 11003. Periodicals postage paid at Jamaica NY 11431.

All other countries: Thieme Publishers, Rüdigerstraße 14, 70469 Stuttgart, Germany. To order: [custserv@thieme.de](mailto:custserv@thieme.de) or use the Web site facilities at [www.thieme.com](http://www.thieme.com).

For further inquiries please contact Mrs. Birgid Härtel:  
Phone: +49 711 8931 421; Fax: +49 711 8931 410

Current list prices are available through [www.thieme-chemistry.com](http://www.thieme-chemistry.com).

#### Online Access via Thieme-connect

The online versions of SYNFORM as well SYNTHESIS, SYNLETT and SYNFACTS are available through Thieme-connect ([www.thieme-connect.com/ejournals](http://www.thieme-connect.com/ejournals)) where you may also register for free trial accounts. For information on multi-site licenses and pricing for corporate customers as well as backfiles please contact our regional offices:

Americas: [esales@thieme.com](mailto:esales@thieme.com), phone: +1 212 584 4695

All other countries: [eproducts@thieme.de](mailto:eproducts@thieme.de), phone: +49 711 8931 407

#### Manuscript Submission to SYNTHESIS and SYNLETT

Please consult the Instructions for Authors before compiling a new manuscript. The current version and the Word template for manuscript preparation are available for download at [www.thieme-chemistry.com](http://www.thieme-chemistry.com). Use of the Word template helps to speed up the refereeing and production process.

#### Copyright

This publication, including all individual contributions and illustrations published therein, is legally protected by copyright for the duration of the copyright period. Any use, exploitation or commercialization outside the narrow limits set by copyright legislation, without the publisher's consent, is illegal and liable to criminal prosecution. This applies to translating, copying and reproduction in printed or electronic media forms (databases, online network systems, Internet, broadcasting, telecasting, CD-ROM, hard disk storage, microcopy edition, photomechanical and other reproduction methods) as well as making the material accessible to users of such media (e.g., as online or offline backfiles).

#### Copyright Permission for Users in the USA

Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by Georg Thieme Verlag Stuttgart · New York for libraries and other users registered with the Copyright Clearance Center (CCC) Transactional Reporting Service, provided that the base fee of US\$ 25.00 per copy of each article is paid directly to CCC, 22 Rosewood Drive, Danvers, MA 01923, USA, 0341-0501/02.