

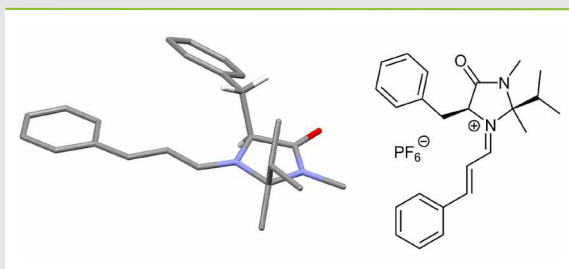
SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2009/05

SYNSTORIES ■ ■ ■ ■

■ Structure of Reactive Intermediates of Organocatalysis



■ A Unique Approach to Aldol Products for the Creation of All-Carbon Quaternary Stereocenters

■ Organocatalytic Asymmetric Alkylation of Aldehydes by S_N1-Type Reaction of Alcohols

CONTACT ++++

Your opinion about SYNFORM is welcome, please correspond if you like:
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Dear readers,

the Thieme Chemistry Editorial Board Meeting 2009 is looming (further information about it will be provided in the next issue of **SYNFORM**); this time we are about to meet in Granada (Spain). While waiting for this impor-

tant event which will set the future goals and the statement of direction for the three Thieme Chemistry journals **SYNLETT**, **SYNTHESIS** and **SYNFACTS**, this issue of **SYNFORM** visits three important research labs, well known for their contributions in the field of organic synthesis.

The first **SYNSTORY** brings you to Switzerland, where Professor D. Seebach and his group give us an insight into their recent discoveries in the field of organocatalysis intermediates. The second **SYNSTORY** reports on a totally new synthetic strategy developed by the group of Professor I. Marek (Israel) to prepare aldol frameworks. Last but not least, the group of Professor P. G. Cozzi (Italy) describes a new organocatalytic strategy for the asymmetric α -alkylation of aldehydes.

Enjoy your reading!!!

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

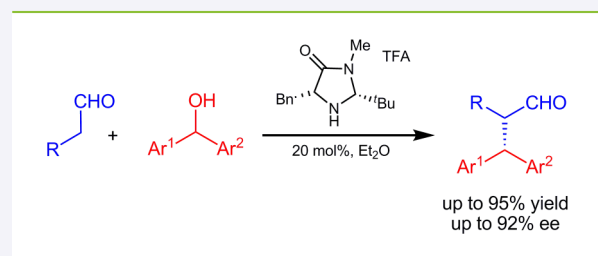
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COMING SOON **A49**

Structure of Reactive Intermediates of Organocatalysis

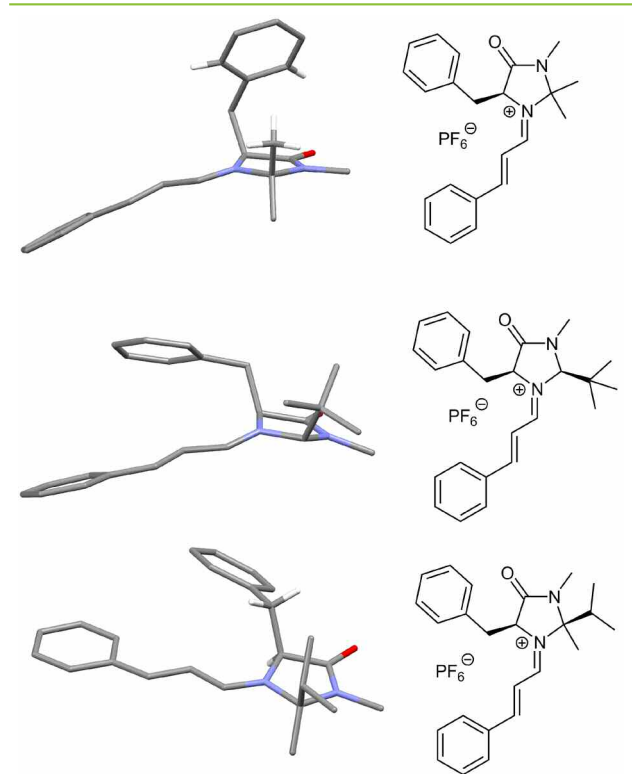
Helv. Chim. Acta **2009**, *92*, 1–13 and *Helv. Chim. Acta* **2008**, *91*, 1999–2034; *Synfacts* **2009**, 323 (*Synfact* of the Month)

■ The exact nature of reactive intermediates in organocatalytic reactions, particularly those involving proline (and derivatives) and chiral imidazolidinones, is still a matter of considerable debate. Considerable progress in the field has been achieved recently by the group of Professor Dieter Seebach from the Department of Chemistry and Applied Biosciences of the ETH Zürich (Switzerland). Professor Seebach and coworkers were able to isolate and characterize a number of reactive organocatalytic intermediates (such as those portrayed below) by means of X-ray diffraction and NMR studies. Many of the structures were then compared with closely related structures previously simulated through computational DFT methods,¹ revealing a remarkable match between the theoretical and the experimental results, and confirming structural effects pre-

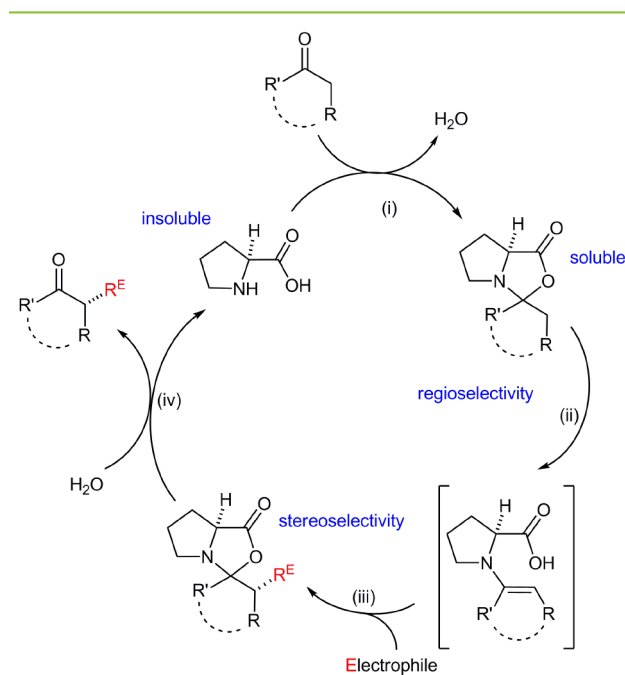
dicted by theory. One of the possible follow-ups of this work is that in the future synthetic chemists might become increasingly aware that computational methods can be successfully exploited to design effective organocatalysts, in synergy with the “hit to lead” experimental optimizations.

“Our group, engaged in the chemistry and biology of β - and α -peptides, was actually lured into the field of organocatalysis by statements in the literature² about the role of oxazolidinones in proline catalysis, which read like this: the *Seebach* oxazolidinones^{3–5} are parasitic, non-productive, dead-end species,” explained Professor Seebach.

A closer look in the ETH laboratories led to the proposal of an alternative mechanism for proline catalysis, with oxazolidinones as key players.⁶ “This was supported by the recent demonstration that such an oxazolidinone (dubbed *SolPro*) is superior to proline as a catalyst,”⁷ confirmed Professor Seebach.



X-ray structures



Proposed alternative oxazolidinone organocatalytic cycle⁶

Further work at ETH provided NMR solution and X-ray crystal structures of numerous reactive intermediates of organocatalysis with diaryl prolinol ethers⁸ and with imidazolidinones.^{8,9} “Especially the structures of the iminium salts formed from 5-benzyl-imidazolidinones and cinnamaldehyde throw new light on the mechanism of organocatalysis with these amino derivatives,⁹ which were first used as catalysts by MacMillan”¹⁰ said Professor Seebach. “Remarkable resemblances *and* differences between the experimental and the DFT-calculated structures are found,” he continued. “Notably, the three most stable conformations around the benzylic ethane bond in 5-benzyl-imidazolidinone iminium salts, as calculated by Houk,¹ are all found in various crystal structures (Figure). Even more spectacular results, such as iminium salts of *Z*-, rather than *E*-configuration, will be published in the near future,” concluded Professor Seebach. ■

Matteo Zanda

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About the authors



Prof. D. Seebach

Dieter Seebach received a Diploma in Chemistry and a PhD (Dr. rer. nat.) from the Universität Karlsruhe (TH) (Germany) under the supervision of R. Criegee. After a postdoctoral stay in Elias J. Corey's group and a Lectureship at Harvard University he returned to the Universität Karlsruhe for a Habilitation; he became a full Professor of Organic Chemistry at the Justus-Liebig-Universität in Gießen (Germany) in 1971. From 1977 to 2003 he was Professor of Chemistry at the Eidgenössische Technische Hochschule (ETH) in Zürich (Switzerland). Since 2003 he is officially retired; as *Professor emeritus and Academic Guest* of ETH he continues doing research with postdoctoral coworkers. His past and present research activities include: development of new synthetic methods (*cf.* Umpolung of reactivity, self-regeneration of chirality centers, the *gem*-diaryl effect in stereoselective synthesis), natural product synthesis, structure determination, chiral dendrimers, the biopolymer PHB, and β -peptides.



Dr. U. Grošelj

Uroš Grošelj was born in 1975 in Kranj, Slovenia. He studied chemistry at the University of Ljubljana (Slovenia) and received his BSc in 2000. He continued his studies under the supervision of Professor J. Svete and received his PhD in 2004. His PhD work focused on the preparation of new camphor-derived heterocycles based on propenoate methodology. Since 2004 he is employed as a researcher in the group of Academician Professor B. Stanovnik at the Faculty of Chemistry and Chemical Technology of the University of Ljubljana. Currently he is a postdoctoral fellow in the group of Professor D. Seebach at the ETH Zürich (Switzerland). His research interests encompass the synthesis of heterocyclic compounds, stereoselective synthesis, chemistry of terpene enamines, cycloadditions, and organocatalysis.



A. K. Beck

Albert Karl Beck was born in 1947 in Karlsruhe (Germany). After completing a chemistry technician's apprenticeship at the Institute for Organic Chemistry of the University of Karlsruhe from 1963 to 1966, followed by 18 months of military service, he joined the Seebach research group at Karlsruhe in 1968. Between 1969 and 1972 he continued his education, obtaining the

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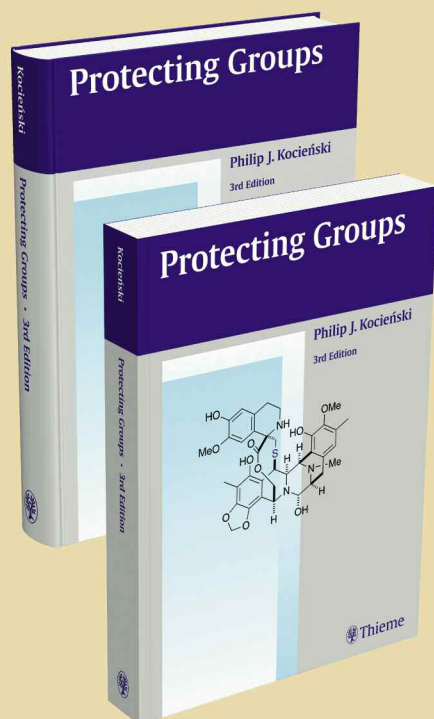
official certification as a chemical technician (Chemotechniker) at the Fachschule für Chemotechnik in Karlsruhe. In 1971 he followed Professor D. Seebach to the Institute for Organic Chemistry at the University of Gießen, and in 1974 he engaged in a six-month research visit to the California Institute of Technology in Pasadena (USA). A. K. Beck has been an active part of the Laboratory for Organic Chemistry at the ETH in Zürich since 1977, the time of Seebach's arrival there. During his long association with the Seebach research group he has participated in essentially all of the group's research themes, as evidenced by his co-authorship of ca. 90 publications.



Dr. B. Schweizer

Bernd Schweizer studied chemistry at the ETH Zürich (Switzerland) and obtained his PhD in chemistry under the supervision of Prof. J. Dunitz in 1977. Responsible for the X-ray analysis and structural databases in the chemistry department of the ETH, he is interested in structural chemistry, applications of structural databases and crystal structure prediction. He teaches chemical crystallography at the ETH and the University of Zürich.

INFORMATION ++++



Do you already have your Protecting Groups?

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A Unique Approach to Aldol Products for the Creation of All-Carbon Quaternary Stereocenters

Nature Chem. **2009**, *1*, 128–132

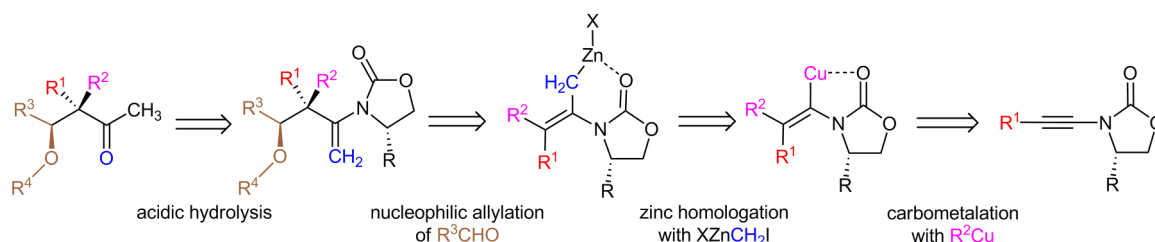
■ Those who think that nothing conceptually new remains to be invented in the realm of synthetic methodology should perhaps give a glance to the recent article published by the group of Professor Ilan Marek from the Technion – Israel Institute of Technology (Haifa, Israel). In this paper, in fact, an aldol framework is disconnected and synthesized according to an original and innovative perspective, without any real sacrifice in terms of synthetic efficiency.

“I have always been interested in the development of novel and efficient methods for the rapid construction of complex molecular structures,” said Professor Marek. “However, I constantly keep in mind that every new method that we are developing should not only solve the most difficult and challenging problems in synthetic organic chemistry but should also be done in a very elegant way. Chemistry is an art!... (It happens frequently that after reading a paper, I say: *Whoua... really beautiful!* Exactly as if I was in a museum standing in front of a beautiful sculpture!)”

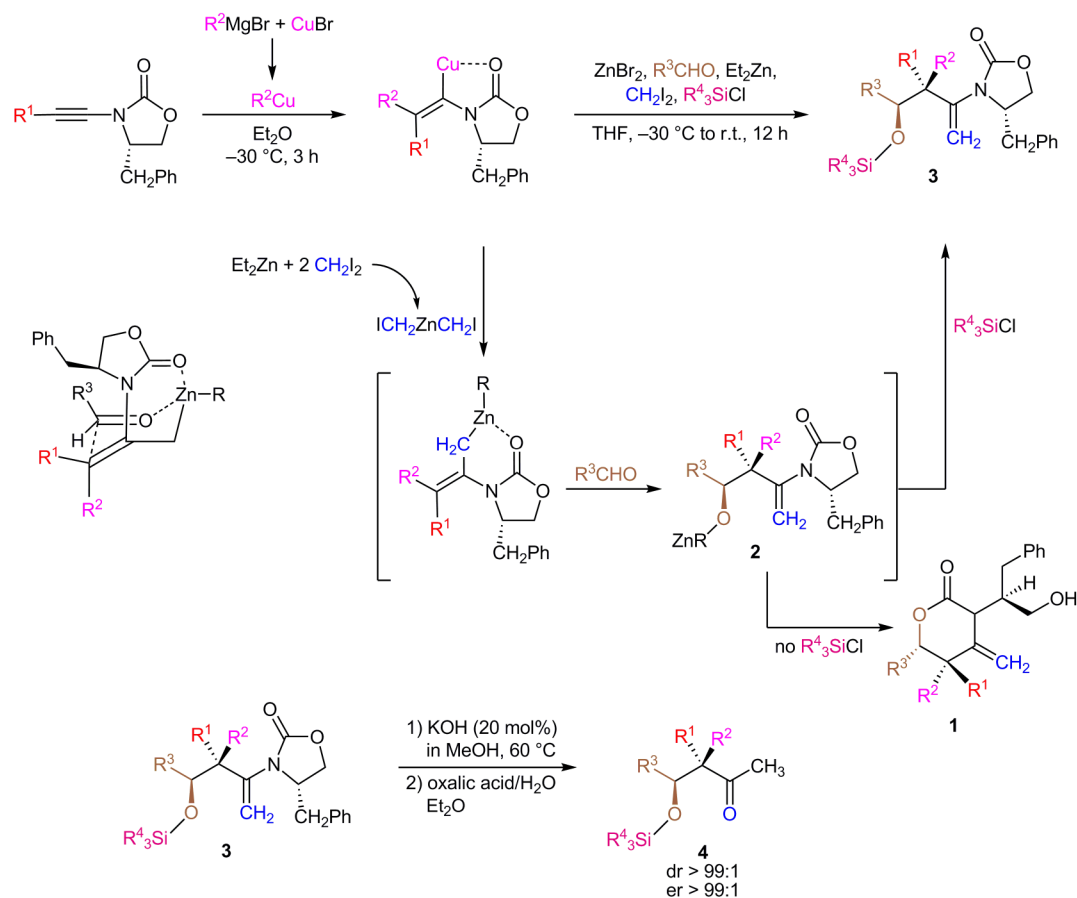
According to Professor Marek, among all the challenging problems that synthetic chemists are facing, the preparation of enantiomerically pure quaternary stereocenters in acyclic systems stands out. “Most of the current methods available for the creation of such quaternary stereocenters are based on asymmetric catalysis, but due to the synthetic challenge a single carbon–carbon bond is usually formed in the process,” he explained. “If one considers the formation of enantiomerically enriched all-carbon quaternary stereocenters in aldol products (*J. Am. Chem. Soc.* **2001**, *123*, 2091), an additional problem originates from the lack of *E/Z*-selectivity in the enolization of α,α -disubstituted carbonyl compounds (*Angew. Chem. Int.*

Ed. **2004**, *43*, 2420). Our approach,” continued Professor Marek, “differs from all the known approaches since we used a heterosubstituted alkyne (ynamide) as starting material and we performed a series of synthetic transformations in a single-pot operation (see retrosynthetic analysis).” It is worth noting that the unique stereochemistry on the double bond comes from a very simple controlled carbometalation reaction. Then, a zinc homologation followed by an allylation reaction as pivotal steps lead to the aldol surrogate that can be hydrolyzed under mild conditions into the expected aldol products. “In such a process,” explained Professor Marek, “three new carbon–carbon bonds were created as well as the expected all-carbon quaternary stereocenters and tertiary alcohols.”

Professor Marek’s graduate student Helena Checkik started this project and rapidly found the proper conditions to control the regiochemistry of the carbometalation of ynamides, but when the combined zinc homologation (generated in situ by mixing Et_2Zn and CH_2I_2) and allylation reaction was performed she constantly obtained the aldol surrogate as cyclic products **1**. “She could easily generalize this reaction to many different systems,” confirmed Professor Marek, “but we could never avoid the cyclization reaction.” When Dr. Jaya P. Das joined Marek’s research group, the researchers initially tried to cleave the cyclic aldol surrogate **1** into the aldol product **4**, but they rapidly understood that their approach should be modified from the beginning and a fourth component – R^4_3SiCl – was added to the carbometalated species to trap the zinc alcoholate intermediate **2** in situ. “This addition led to the first preparation of non-cyclic product **3** that could then be easily hydrolyzed into aldol species **4**,” said Professor Marek.



New retrosynthetic analysis



“I still remember the day when Jaya showed me the crude NMR spectrum of his first aldol product... we could only say: *Whoua, it is beautiful!* I was really fortunate to work with these two young scientists,” acknowledged Professor Marek. “They both did an outstanding job and it was extremely rewarding for me to see their constant positive attitudes and to share with them the excitement of solving a scientific problem.”

Professor Marek hopes that this new successful approach will bring many other chemists to view chemistry in a slightly different way and design innovative retrosynthetic plans in order to improve efficiency while answering difficult synthetic questions. “However, the road is still long as the most powerful and beautiful approach would be to combine our method with asymmetric catalysis. We are now extending this chemistry to different important reactions and they are all proceeding beautifully. Chemistry is really an exciting science!”

Matteo Zanda

About the authors



Prof. I. Marek

Ilan Marek was born in Haifa (Israel) in 1963, educated in France, and received his PhD in 1988 from the University Pierre et Marie Curie, Paris (France) under the guidance of Profs. A. Alexakis and J. F. Normant. In 1989, he was a postdoctoral fellow in Louvain-la-Neuve (Belgium) with Professor L. Ghosez and obtained a research position at the CNRS in 1990. After obtaining his Habilitation in Organic Chemistry, he moved to the Technion – Israel Institute of Technology at the end of 1997

where he currently holds a full Professor position. He was awarded the first French Chemical Society–Acros Prize for the best young chemist (1997), the Yigal Allon Fellowship (1998), the Michael Bruno memorial Award from the Rothschild Foundation (2002), Award for excellent Young Chemist from the Israel Chemical Society (2003), the Merck Sharpe and Dohm Lecturer Award (2004), the Bessel Award of the Humboldt Foundation (2005) and recently the Taub Award for Academic Excellence (2009). Since 2005, he is holder of the Sir Michael and Lady Sobell Academic Chair.



Dr. J. P. Das

Jaya Prakash Das was born in Cuttack (India) in 1976. He received his PhD in 2006 from the Indian Institute of Technology, Kharagpur (India) under the guidance of Professor S. Roy. He was awarded the National Scholarship for post-graduate studies from the Ministry of Higher Education for outstanding result in the BSc and the Senior Research Fellowships (2003 and 2006) of the Council of Scientific and

Industrial Research (CSIR). He is currently a postdoctoral fellow in the group of Professor I. Marek and has received the Lady Davis and Schulich postdoctoral fellowships.



Dr. H. Chechik

Helena Chechik was born in Russia in 1977 and immigrated to Israel at the age of 13. She received her PhD in 2007 at the Technion – Israel Institute of Technology under the supervision of Professor I. Marek. She received several times the Award for Excellence in Studies and twice the Award for Excellence in Teaching. In 2006, she received the Gutwirth Special Award for Excellence in Research. After almost two years of experience as Lab Manager at Peptronics Ltd. in the field of organic semiconductors, she started postdoctoral research with Professor E. Keinan at the Technion – Israel Institute of Technology in 2009.

Organocatalytic Asymmetric Alkylation of Aldehydes by S_N1 -Type Reaction of Alcohols

Angew. Chem. Int. Ed. **2009**, *48*, 1313–1316; *Synfacts* **2009**, 441 (Synfact of the Month)

Catalysis using chiral secondary amines (asymmetric aminocatalysis) has recently increased opportunities in the domain of stereoselective catalysis through catalytically generated covalent intermediates. These intermediates, formed by unique and peculiar aminocatalytic activation modes, provide new solutions for challenging synthetic problems. “Even reactions considered impossible have become a reality through aminocatalysis!,” confirmed Professor Pier Giorgio Cozzi from the Chemistry Department of the University of Bologna (Italy).

A recent highlight by one outstanding leader in this field, David MacMillan from Princeton University (USA), pointed out the number of new reactivity modes discovered or rediscovered by applying the concept of organocatalysis (*Nature* **2008**, *455*, 304). “Despite this,” said Professor Cozzi, “a simple but enormously important and crucial carbon–carbon bond-forming reaction – the catalytic enantioselective intermolecular α -alkylation of carbonyl derivatives – was still missing from the arsenal of organocatalytic reactions. What is, in fact, as simple as alkylation of aldehydes through an enolate

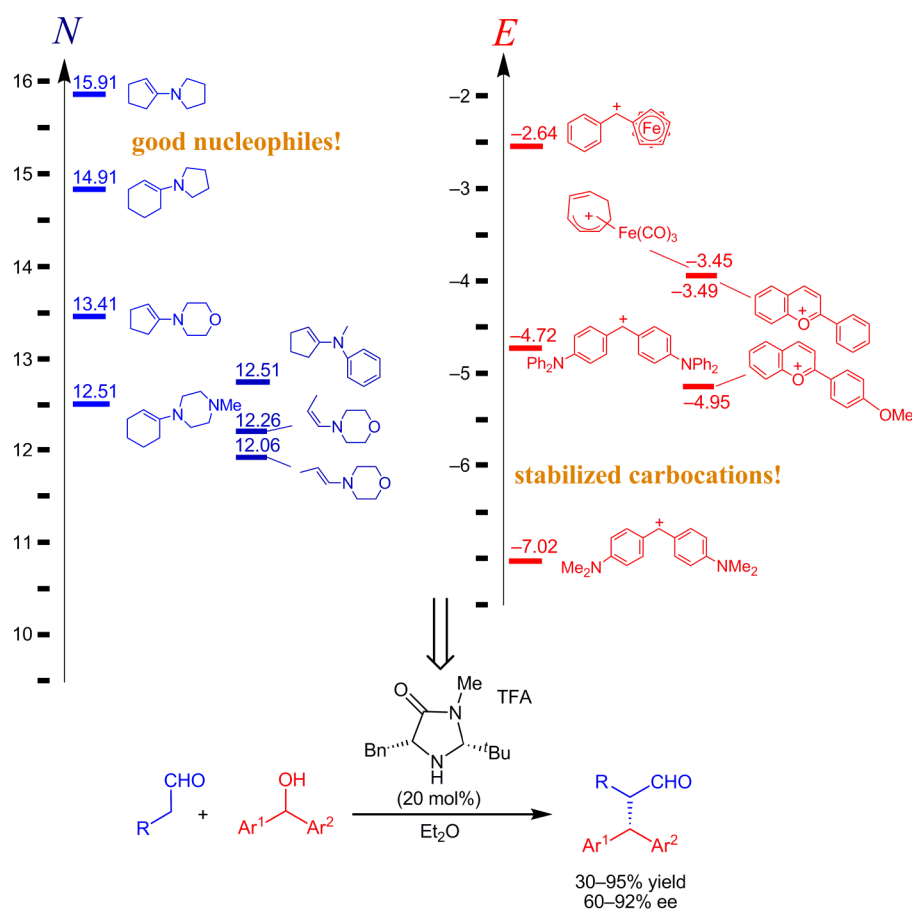


Figure 1 Enamines formed *in situ* by organocatalysts react with stabilized carbocations generated by alcohols.

or enolate equivalent?," he continued. The development of general catalytic enantioselective α -alkylations of carbonyl compounds was, however, extremely challenging. "The reason for that is quite simple," said Professor Cozzi. "Alkylating agents used in excess were also able to alkylate the organocatalyst (a secondary amine) by N-alkylation, hence deactivating it. Only an intramolecular version of the α -alkylation was disclosed by List (*J. Am. Chem. Soc.* **2004**, *126*, 450), but extension to the intermolecular case was not possible, as mentioned before, because of the alkylation of the catalyst. To this perspective, the solution came when we started to consider other alkylating agents or a new activation mode. MacMillan, in fact, introduced new aminocatalytic activation concepts, termed SOMO, and enamine photocatalysis, for solving the problems of α -alkylation of aldehydes (*Science* **2007**, *316*, 582; *Science* **2008**, *322*, 77) in organocatalysis," he continued. "We proposed a simple concept to circumnavigate the alkylation of the catalyst and still be able to use enamines in organocatalytic reactions. The discovery was fueled by our recently published direct substitution of optically active ferrocenyl alcohols and benzylic alcohols with several nucleophiles (*Green Chem.* **2007**, *9*, 1292; *Angew. Chem. Int. Ed.* **2008**, *47*, 4162; *Eur. J. Org. Chem.* **2007**, 2248). Quite important for understanding how these reactions work is to make the right correlation with the stability of the electrophiles in these reactions, namely the carbocations which are generated by alcohols."

According to Professor Cozzi, alcohols are not able to alkylate secondary amines. "When carbocations are generated," he explained, "they react with nucleophiles. Enamines are among the most reactive nucleophiles that an organic chemist can use. A simple inspection of the Mayr list of classified nucleophiles (Figure 1, *N* list) reveals that highly nucleophilic enamines are placed on the top of the list of nucleophiles. Now, as chiral enamines are key intermediates in many organocatalytic methodologies, we decided to use less reactive carbocations generated from alcohols for exploring a direct nucleophilic enantioselective substitution." The elusive α -alkylation of aldehydes was therefore realized in an effective and simple way, using enamine ion catalysis coupled with the generation of stabilized carbocations. "Again," said Professor Cozzi, "the Mayr list of electrophiles (Figure 1, *E* list) explains well the meaning of 'stabilized carbocations'. Sometimes we have the impression that tertiary carbocations are stable, and can be easily generated. They are very reactive indeed. Electrophilic carbocations, reversibly generated from the corresponding alcohols and placed between -2.5 and -7 on the Mayr list, can furnish relatively stable alkylating agents."

Water is necessary for the hydrolysis of the final intermediate (Figure 3), and is produced together with the enamine.

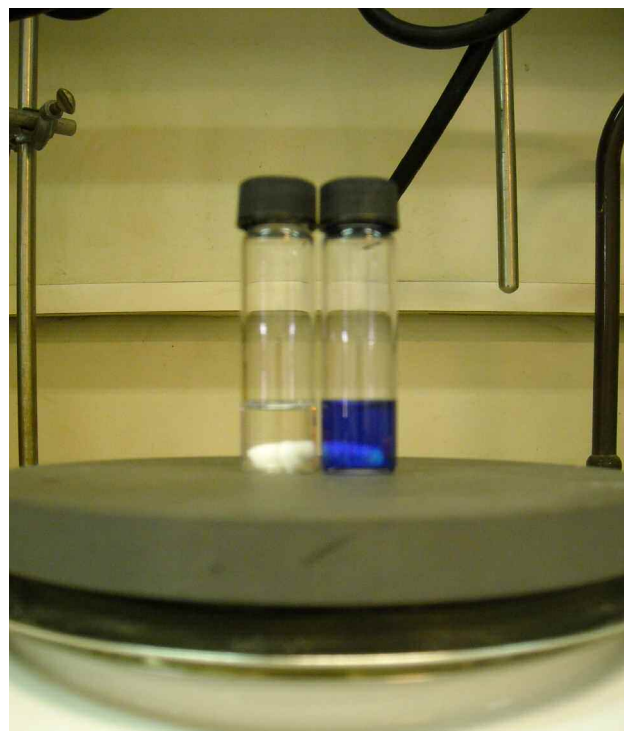


Figure 2 The vial on the left contains 4,4'-bis(dimethylamino)diphenyl carbinol and an aldehyde. After addition of the MacMillan catalyst as trifluoroacetate salt, the developing blue color indicates the formation of the dibenzyl carbocation.

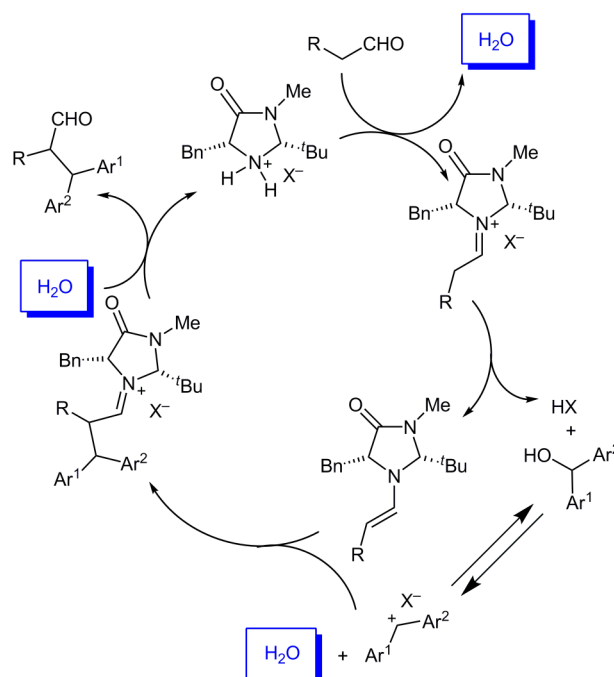


Figure 3 General scheme for the transformation

“We are fighting against the water that is acting as a nucleophile, and so re-forming the starting alcohol,” said Professor Cozzi. “Therefore, the stability of the carbocations is crucial. More reactive carbocations are more difficult to generate. To find a way to generate and use quite reactive (unstable) carbocations placed on the top of the Mayr list is our current task,” he concluded.

According to Professor Benjamin List, a leading expert in organocatalysis from the Max Planck Institute in Mülheim (Germany), “The development of catalytic asymmetric inter-

molecular α -alkylation reactions of aldehydes and ketones is an enormous challenge for organocatalysis. The work of Cozzi et al. therefore constitutes an important step forward – especially since alcohols can be used as electrophiles. While the reaction is limited to certain benzhydryl electrophiles, the paper is clearly a tribute to two powerful concepts: enamine catalysis and Mayr’s electrophilicity scales.”

Matteo Zanda



From left: Dr. F. Benfatti, Prof. P. G. Cozzi, L. Zoli

About the authors

Pier Giorgio Cozzi was born in Legnano in the North of Italy. He received his Laurea degree in chemistry (1989) at the University of Milan (Italy). After four years in Switzerland working with Professor C. Floriani in inorganic and organometallic chemistry, he was appointed Assistant Professor (1994), and then Associate Professor (2000) at the University of Bologna (Italy). He has visited many laboratories in Europe and outside Europe, among them those of Professors C. Bolm, A. Pfaltz, and K. A. Jørgensen. His predominant interest is the development of new

catalytic enantioselective processes. In 2007 he received the C.I.N.M.P.I.S. Award from the Italian Chemical Society for the development of the catalytic enantioselective Reformatsky reaction. He was involved in two European projects in the FP6 framework (LigBANK and IBAAC). He currently coordinates the project CATAFLU.OR and he is involved in the project BioChem Lig, both part of the FP7 European framework.

Fides Benfatti was born in Mantova (Italy) in 1980. She received her master’s degree in 2004 and her PhD in organic chemistry in 2008 from the University of Bologna (Italy), both under the supervision of Professor G. Cardillo. In the same year she joined Professor Cozzi’s group, where she is presently a postdoctoral associate. She has published 20 papers in bio-organic, organometallic, medicinal organic chemistry and catalysis. Her current research focuses on the development of new protocols for organocatalytic asymmetric α -alkylation, and CH-activation reactions.

Luca Zoli was born in Ravenna (Italy) in 1982. He received his master’s degree from the University of Bologna in 2006. In 2007 he joined Professor Cozzi’s research group. He is currently a PhD student at Department “G. Ciamician” in the same university. His current research interests are the supramolecular functionalization of carbon nanotubes, C–H bond activation, and organocatalysis.

COMING SOON ► ► COMING SOON ► ►

SYNFORM 2009/06

is available from
July 23, 2009

In the next issues:

SYNSTORIES ■ ■ ■ ■ ■

■ Synthesis of Isoindoles and Isoquinolines via 1,3-Dipolar Cycloaddition and Electrocyclization

(Focus on an article from the current literature)

■ Asymmetric Autocatalysis Triggered by Carbon Isotope (¹³C/¹²C) Chirality

(Focus on an article from the current literature)

■ Palladium-Catalyzed Allylic Amination Using Aqueous Ammonia for the Synthesis of Primary Amines

(Focus on an article from the current literature)

FURTHER HIGHLIGHTS + + + +

SYNTHESIS

Review on: Direct Methods for Stereoselective Polypropionate Synthesis: A Survey

(by D. Menche)

SYNLETT

Account on: En Route to New Chiral Ferrocene Derivatives: Dead-ends, Detours, and Avenues

(by A. Moyano)

SYNFACTS

Synfact of the Month in category "Synthesis of Natural Products and Potential Drugs": [Synthesis of Zaragozaic Acid C](#)

CONTACT + + + +

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