

# SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2012/09

## SYNSTORIES ■ ■ ■ ■

■ Focus on the Valencia Fluorine Days: 3rd International Symposium on Organofluorine Compounds in Biomedical, Materials and Agricultural Sciences, May 20–24, 2012, Valencia (Spain)



Valencia Technology Park at night

■ Preparation of Alkylmagnesium Reagents from Alkenes through Hydroboration and Boron–Magnesium Exchange

■ Urea Activation of  $\alpha$ -Nitrodiazoesters: An Organocatalytic Approach to N–H Insertion Reactions

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Dear readers,

I am writing while the 2012 Olympic Games in London are heading towards the end. We are witnessing a fantastic event, although for me it is a bit of a struggle to watch the Games on the BBC, because I am supporting Italy

and 90% of the time is dedicated to the GB team. Fair enough. I wonder whether academic chemists should also compete in some kind of Chemistry Olympic Games every four years or so. I am not talking about the existing Chemistry Olympiads for students; this would be for professional academic chemists, possibly open to chemists in industry, although I suspect they would be too busy to join in. It would be a lot of fun, I think! Who would win the gold medal of Synthetic Organic Chemistry? And what about the Lab-based Organic Chemistry competition? And that for the Best Bioactive Compound? Some of the big names may not even qualify for the semi-finals. I am not sure whether and how this could be actually done, but definitely it would be much more fun than the REF-Assessment or other evaluation platforms meant to measure the quality of our work. Not to mention the thrill of it all! If anybody has an idea, please let me know – we could ask Thieme Chemistry to organize the first Chemistry Olympic Games in Stuttgart. No doubts about the logo: it would be five round-bottomed flasks... It may not be Olympic but this issue of **SYNFORM** is very interesting too! The first **SYNSTORY** is focused on a new methodology developed by Professor B. Breit (Germany) for preparing Grignard Reagents via boron-magnesium exchange. The second article reports on the  $\alpha$ -amination of a phenylglycine synthon prepared from  $\alpha$ -nitrodiazoesters (Prof. A. E. Mattson, USA). Last but not least, this issue is closed with a report on the recent “Valencia Fluorine Days” Symposium, which gathered together a large number of fluorine chemists in the beautiful city in the south-east of Spain.

Enjoy your reading!

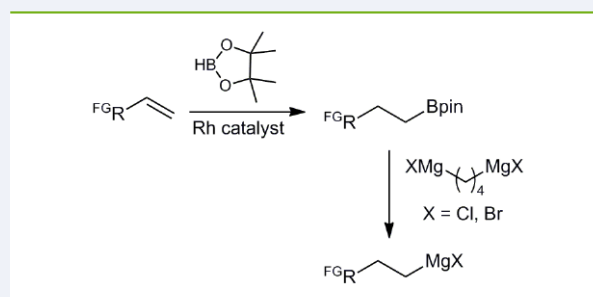
Matteo Zanda

Editor of **SYNFORM**

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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)

## Preparation of Alkylmagnesium Reagents from Alkenes through Hydroboration and Boron–Magnesium Exchange

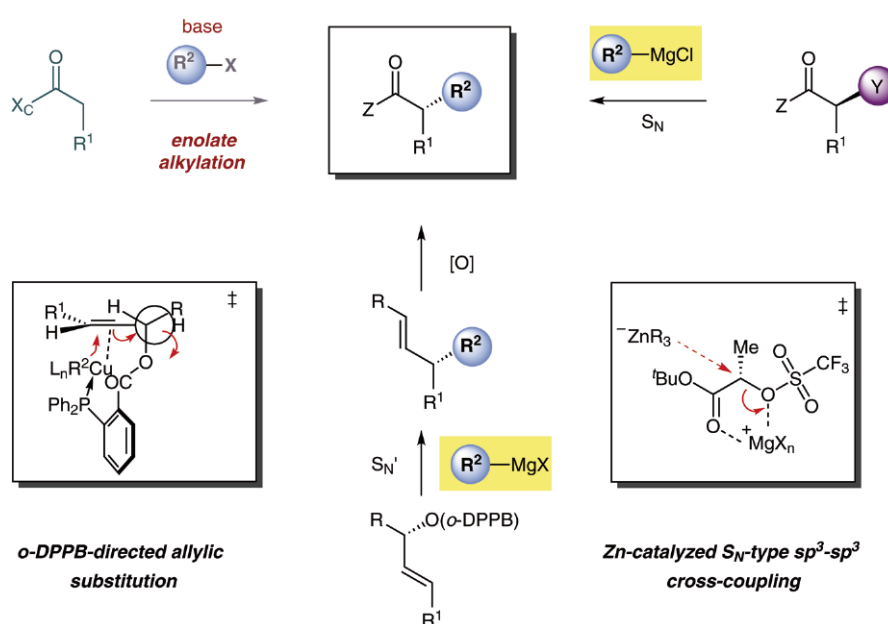
*Angew. Chem. Int. Ed.* **2012**, *51*, 5730–5734; *Angew. Chem.* **2012**, *124*, 5828–5832

■ The direct synthesis of organomagnesium reagents by insertion of magnesium metal into the C–X bond of alkyl halides (Grignard reaction) is one of the most popular and used reactions in organic chemistry. However, despite its usefulness, nearly every synthetic chemist has experienced its drawbacks, consisting of a certain degree of capriciousness and the presence of a number of side reactions, particularly with sterically hindered or functionalized compounds.

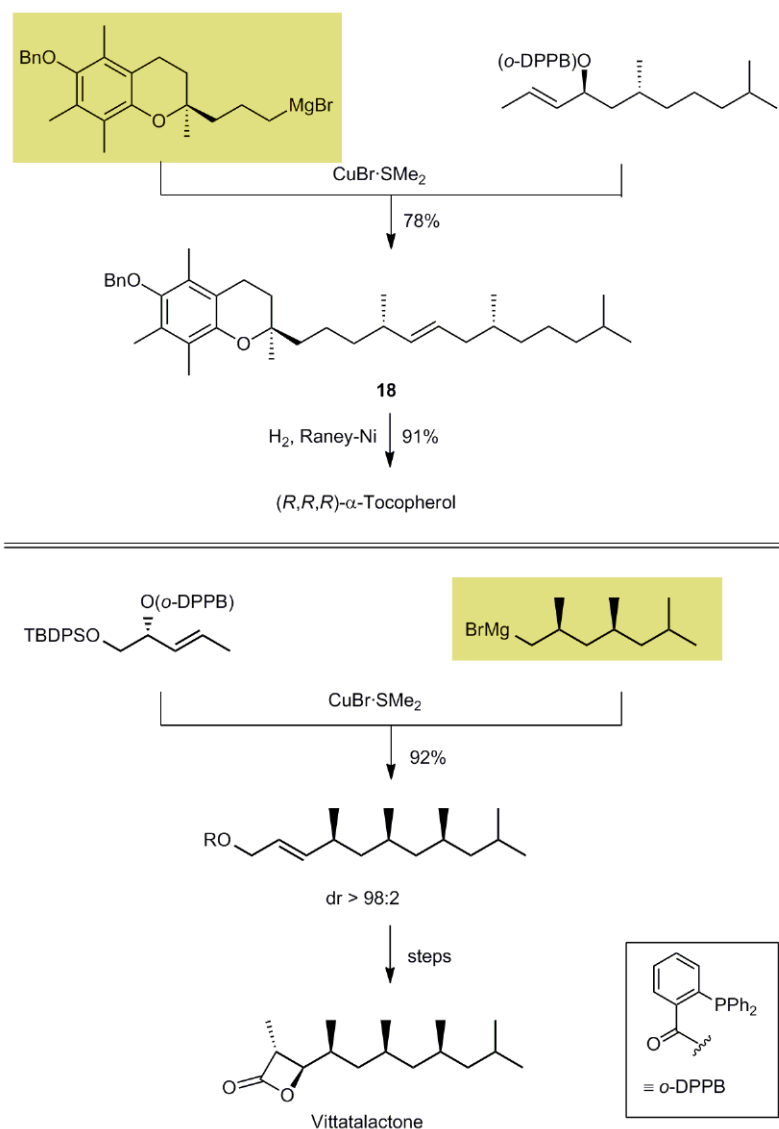
During the last few years, the research group of Bernhard Breit from the Institut für Organische Chemie und Biochemie at the University of Freiburg (Germany) has developed stereospecific  $S_N1'$ - and  $S_N$ -type reactions of organomagnesium compounds catalyzed either by copper or zinc salts (Scheme 1).<sup>1,2</sup> These methods have proved to be valuable synthetic alternatives for enolate alkylation chemistry to access tertiary and quaternary stereogenic carbons in a stereospecific and reliable fashion.

“The application of these methods in total synthesis (Scheme 2) challenged us with the preparation of highly functionalized alkyl Grignard reagents which proved cumbersome in some cases due to side reaction such as homocoupling,” said Professor Breit.<sup>3–5</sup>

“This made us wonder whether there are alternatives for alkyl Grignard generation,” he continued. “We were inspired by the beautiful work of Professor Paul Knochel, who has developed an efficient method for the preparation of dialkylzinc reagents from the corresponding trialkylboranes through a boron–zinc exchange reaction.<sup>6”</sup> Since the corresponding boranes are readily available through anti-Markovnikov hydroboration of alkenes, which occurs with known and reliable regio- and stereoselectivity, this could also be a very valuable synthetic step towards alkylmagnesium reagents, provided that a corresponding boron–magnesium exchange



**Scheme 1** The Breit group developed alternatives to enolate alkylation via stereospecific  $S_N$ - and  $S_N'$ -type reactions employing Grignard reagents

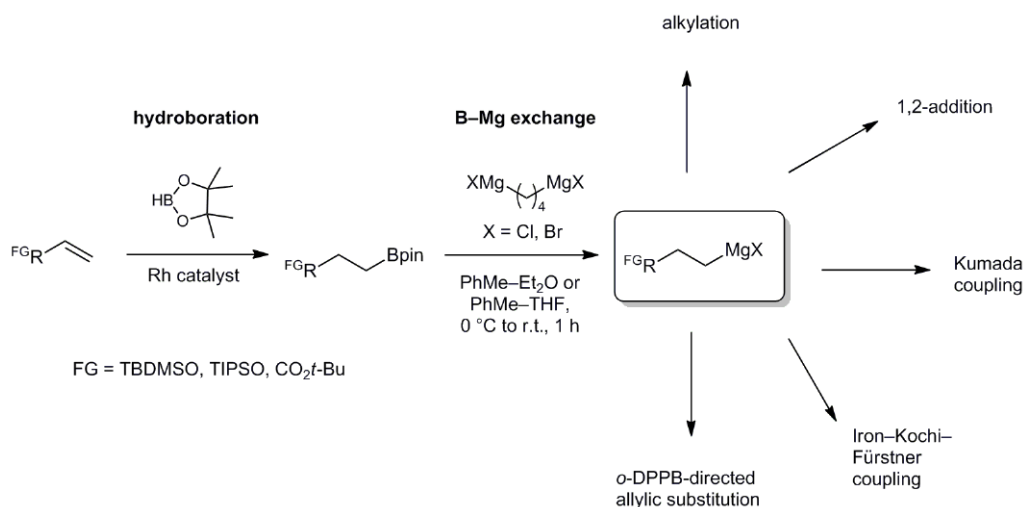


**Scheme 2** Application of functionalized Grignard reagents in total synthesis projects completed by the Breit group

reaction is possible. Professor Breit explained that a former PhD student, Christian Rein (now at BASF), searched the literature for previous work on this matter and found an important early contribution from Murahashi et al.<sup>7</sup> “They explored the use of a C5-diGrignard reagent to effect a boron–magnesium exchange starting from trialkylboranes,” said Professor Breit. “However, the method suffers from three major limitations: First, it is limited to the generation of primary alkyl Grignard reagents starting from mono-substituted alkenes, since steric hindrance inhibits the boron–magnesium exchange reaction. Second, the method is restricted to the use of

trialkylboranes. Third, the use of the more stable alkylboronic esters obtained through rhodium-catalyzed hydroboration would be highly desirable,” he finished.

This was the starting point of the diploma work and finally PhD thesis of Markus Reichle. “Markus started by looking at the corresponding C4-diGrignard reagent,” explained Professor Breit. “We speculated that formation of the five-membered spiroboronates would be faster, hence accelerating the boron–magnesium exchange reaction.” This indeed proved to be the case. Furthermore, he was then able to apply, for the first time, the more stable alkylboronic esters derived from



**Scheme 3** Alkyl-Grignard reagents from alkenes through hydroboration and B-Mg-exchange reaction

metal-catalyzed hydroboration of alkenes with pinacolborane to generate both primary alkyl and secondary alkyl organomagnesium reagents (Scheme 3).<sup>8</sup>

“The boron–magnesium exchange was monitored by <sup>11</sup>B NMR and in all cases high yields of the corresponding Grignard reagents were obtained,” remarked Professor Breit. Functional groups such as silyl ethers and *tert*-butyl esters were tolerated. Professor Breit concluded, “The resulting Grignard reagents could be applied in a wide range of alkylations, 1,2-additions as well as iron-, copper- and palladium-catalyzed cross-coupling reactions. Now, the method is under exploration in total synthesis projects going on in my group.” ■

Matteo Zanda

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*About the authors*

From left: Prof. B. Breit, Dr. M. Reichle

**Bernhard Breit** studied chemistry at the University of Kaiserslautern (Germany) where he obtained his doctorate in 1993 with Professor Manfred Regitz. After postdoctoral training with Professor Barry Trost at Stanford University (USA), he worked in Marburg (Germany) with Professor R. W. Hoffmann to obtain his habilitation in 1998. In 1999 he was appointed as an Associate Professor at the University of Heidelberg (Germany). Since 2001 he has been a Full Professor of Organic Chemistry at the Albert-Ludwigs-Universität Freiburg i. Brsg. His current research interests focus on the development of new concepts and methodology for organic synthesis, including organometallic reagents and homogeneous catalysis.

**Markus Reichle** was born in Weingarten (Germany) in 1982. He studied chemistry in Freiburg (Germany) and at Stanford University (USA), where he gained his first experience in research by working on palladium-catalyzed asymmetric allylic alkylation in the group of Professor Barry Trost. He then obtained his diploma at the Albert-Ludwigs-Universität Freiburg in 2008 in the group of Professor Bernhard Breit, where he continued his research on developing the boron-magnesium exchange to obtain his PhD in 2012.



# Urea Activation of $\alpha$ -Nitrodiazo Esters: An Organocatalytic Approach to N–H Insertion Reactions

*J. Am. Chem. Soc.* **2012**, *134*, 8798–8801

■  $\alpha$ -Aryl-glycine derivatives are important  $\alpha$ -amino acids present in a number of natural and biologically active molecules. Recently, the group of Professor Anita E. Mattson from The Ohio State University (Columbus, Ohio, USA) devised a new synthetic strategy for accessing  $\alpha$ -aryl-glycines, based on the use of  $\alpha$ -nitrodiazo esters as building blocks. Despite limited accounts on the chemistry of  $\alpha$ -nitrodiazo compounds, these nitrocarbene precursors have interesting reactivity and have been shown to undergo cyclopropanation reactions as well as O–H insertion reactions under transition-metal catalysis. “To the best of our knowledge, non-covalent organocatalysts have not been previously explored to activate  $\alpha$ -nitrodiazo esters,” said Professor Mattson. “Our desire to develop complementary reactions to those typically catalyzed by metals led us to the use of hydrogen bond donor ureas and thioureas in N–H insertion chemistry,” she continued.

Professor Mattson explained that Sonia So, a third-year graduate student, began initial studies with the synthesis of  $\alpha$ -nitrodiazo ester **1**, which was easily accessed following a literature procedure. “The nitrodiazo esters were stable, easy to work with, and synthesized on a 10 gram scale, although any diazo compound should be handled with care,” Professor Mattson explained.

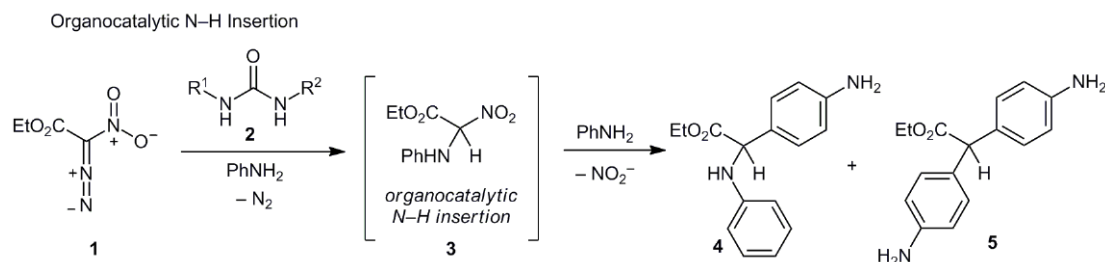
“With the nitrodiazo compound in hand, our initial experiments began by heating the reaction mixtures with aniline to 80 °C,” she continued. “We proposed that N–H insertion into aniline could lead to nitro ester **3**.” Professor Mattson explained how the consumption of the starting diazo compound had been observed by  $^1\text{H}$  NMR spectroscopy, but they had difficulty isolating the product. “We found that some of the products were slightly unstable to silica, so a short silica gel or

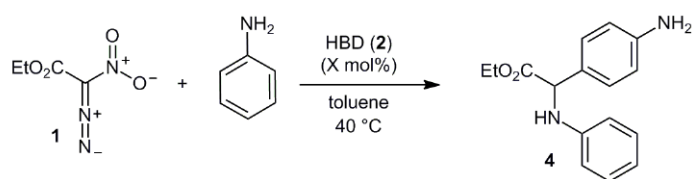
basic alumina column helped in isolating the products in good yield,” she said. “We were finally able to isolate compound **4** along with compound **5** and determined the structure following NMR and mass spectrometry studies. We deduced that initial N–H insertion into aniline formed ester **3**; however, extrusion of  $\text{NO}_2^-$  then allowed for a second molecule of aniline to add forming  $\alpha$ -amino- $\alpha$ -aryl ester **4**.” She went on to explain how, under optimized reaction conditions, they were able to minimize the formation of compound **5**. Extension of this chemistry to include three-component coupling reactions allowed for selective insertion into 4-fluoroaniline in the presence of aniline.

“A short catalyst screen determined that boronate urea **2a** was the most active catalyst while boronate urea **2b**, containing pinacol ligands, was much less active, perhaps due to issues of solubility,” said Professor Mattson. Thiourea **2c**, a catalyst generally more active than urea **2d**, was found to give poorer yields of the desired product, most likely due to decomposition of the catalyst.

“The elusive nitrocarbene intermediate has yet to be observed and we are currently investigating the possibility of the formation of a hydrogen bond donor stabilized nitrocarbene,” continued Professor Mattson.

“This initial report introduces a new area of hydrogen bond donor catalyzed reactions, breaking from traditional activation of carbonyls or nitroalkenes. Chiral catalysts are currently being investigated to afford three-component coupling products in an enantioselective fashion. Further extension of this chemistry could include dipolar cycloadditions as well as C–H activation reactions,” she concluded. ■



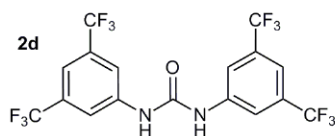
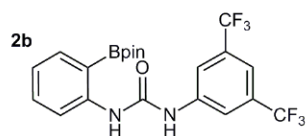
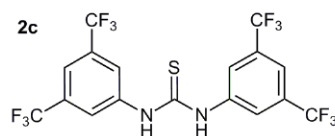
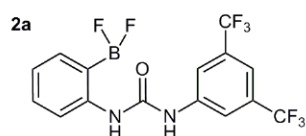


Entry	<b>2</b> (20 mol%)	Time (h)	Yield (%) <sup>a</sup>	$k_{\text{obs}}$ ( $\times 10^{-5} \text{ s}^{-1}$ ) <sup>b</sup>	
1	<b>2a</b>	24	83	9.19	
2	<b>2b</b>	24	61	0.77	catalyst structure study
3	<b>2c</b>	24	27	1.10	
4	<b>2d</b>	24	58	1.38	

Reactions performed using 10 equiv of aniline at a concentration of 1 M (for experimental details see Supporting Information of the original publication).

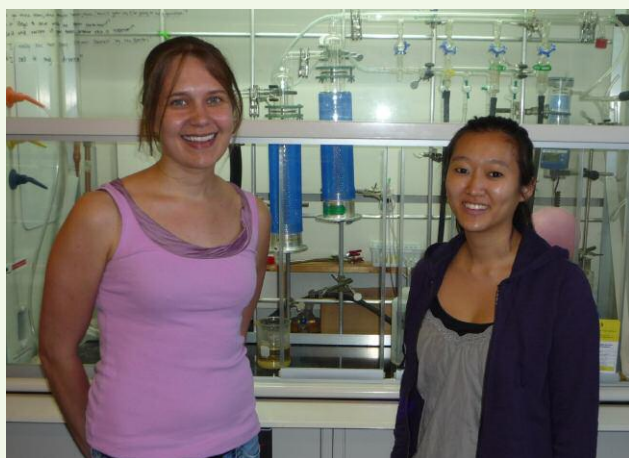
<sup>a</sup> Isolated yield.

<sup>b</sup> An average of  $k_{\text{obs}}$  determined at multiple catalyst loadings (see Supporting Information of the original publication).



Matteo Zanda

### About the authors



From left: Prof. A. E. Mattson, S. S. So



## Focus on the Valencia Fluorine Days: 3rd International Symposium on Organofluorine Compounds in Biomedical, Materials and Agricultural Sciences, May 20–24, 2012, Valencia (Spain)



Night view of the Valencia Technology Park



More than 145 scientists from 15 countries contributed to the recent “Valencia Fluorine Days” symposium, held in sunny Valencia (Spain) on from May 20–24, 2012, with nine plenary lectures, 41 invited lectures and 56 posters reflecting the progress in different fields and topics of organofluorine chemistry.

The aim of the symposium was to provide an overview of current directions in all research areas of fluorine chemistry and it actually provided a unique opportunity to contribute to discussions on the most recent developments in fluorine chemistry, including biomedical applications, materials and nano science, agrochemistry, PET imaging and more. The meeting saw significant participation by companies, such as Syngenta, Ely Lilly, Janssen and many more.

“**Valencia Fluorine Days**” forms part of an initiative by Professor Manfred Schlosser and Professor Renzo Ruzziconi, who first considered the idea and then organized the first ‘Fluorine Days’ symposium, held in Perugia in 2001,” explained the chief organizer, Professor Santos Fustero from the University of Valencia. “Taking the ‘Perugia Fluorine Days’ as

a model, Professor Schlosser, together with Professors K.-H. Altmann, P. Maienfisch, and K. Müller organized the ‘Fluorine in the Life Sciences’ symposium in Bürgenstock (July 6–9) in 2003. In July 2010, R. Ruzziconi and M. Schlosser organized the second ‘Perugia Fluorine Days’ (July 11–15), which I attended as a participant. Both prompted me to organize ‘Valencia Fluorine Days’ and finally I accepted.”

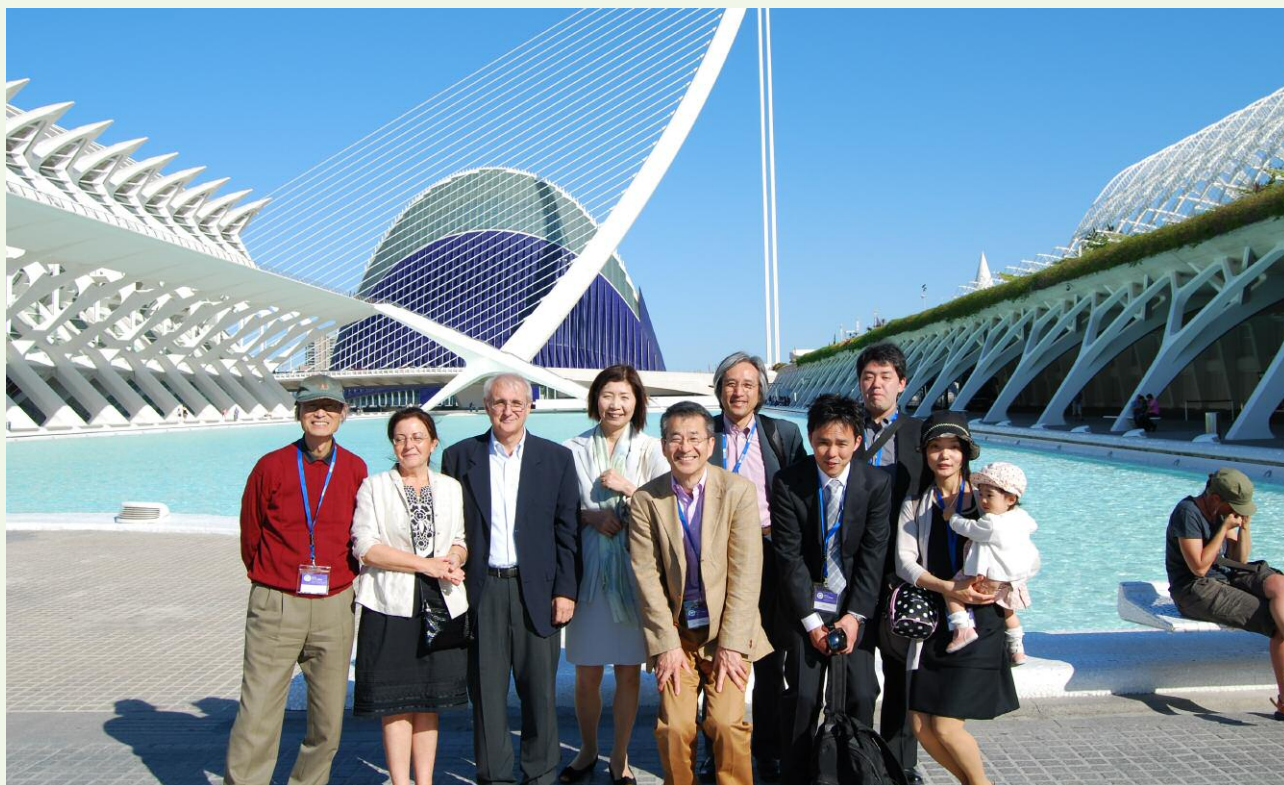
The final result was spectacular and the ‘Fluorine Days’ meeting, which was superbly organized in Valencia, holds promise to become a classic event in fluorine chemistry. “Professor Tamejiro Hiyama and Professor Koichi Mikami took up the idea, and they have announced the first Fluorine Days symposium ‘TokyoTech Fluorine Days’ to be held for the first time in a non-European country in April 2013,” said Professor Fustero. The next European ‘Fluorine Days’ will be organized in Bordeaux (France) in 2014. ■

Matteo Zanda

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Group picture with Professor S. Fustero (third from left) and Professor K. Mikami (center)

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# SYNFORM 2012/10

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In the next issues:

## SYNSTORIES ■ ■ ■ ■ ■

■ **Chiral Monodentate Phosphines and Carboxylic Acids: Cooperative Effects in Palladium-Catalyzed Enantioselective C(sp<sup>3</sup>)-H Functionalization**

P137, Poster Presented at the ISACS-7 Conference, Edinburgh (UK), June 12–15, 2012

(Focus on a poster presented at an international conference)

■ **B(OCH<sub>2</sub>CF<sub>3</sub>)-Mediated Amidation and Transamidation Reactions**

P48, Poster Presented at the ISACS-7 Conference, Edinburgh (UK), June 12–15, 2012

(Focus on a poster presented at an international conference)

## FURTHER HIGHLIGHTS + + + +

## SYNTHESIS

Special Topic on "Aziridines and Azetidines/Small Rings" in issue 18/2012

## SYNLETT

Account on: The Application of Bis(trifluoroacetoxy)iodo]benzene (PIFA) in the Synthesis of Nitrogen-Containing Heterocycles

(by E. Domínguez, I. Tellitu)

## SYNFACTS

Synfact of the Month in category "Synthesis of Natural Products and Potential Drugs": [Synthesis of \(-\)-Teuvidin](#)

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