

# SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2012/07

## SYNSTORIES ■ ■ ■ ■

■ **Young Career Focus: Professor Zoltan Novak (Eötvös University, Budapest, Hungary)**



new benzyne precursor

■ **Benzofurans from Benzophenones and Dimethylacetamide: Copper-Promoted Cascade Formation of Furan O1–C2 and C2–C3 Bonds Under Oxidative Conditions**

■ **Catalytic Asymmetric Hydrogenation of Naphthalenes**

**CONTACT ++++**

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



Dear readers,

I've been travelling recently in the south of Europe, and I was shocked by the impact that the current economic crisis is having on the career of young researchers. I had the chance to speak with many postdocs and postgraduate

students in Spain and Italy, and it was really terrible to hear from them how the lack of opportunities and jobs in research is dashing the hopes and career perspectives of many promising and brilliant researchers, who should represent the next generation of scientists in these countries. The situation is bad everywhere in Europe, but clearly the young researchers living in southern European countries are paying the highest price. I still remember that when I enrolled in the chemistry course as an undergraduate student at the University of Milan, prospects were very exciting for chemists. The situation was already significantly worse by the time of my graduation, and my perception is that the negative trend has continued since then. My message to our young European chemists is: do not hesitate to search for a research job abroad, even far away from home, believe in yourselves, work hard and be creative. There are no guarantees and there is no easy ride for anybody these days, but a job in research is the best job in the world; it's worth some sacrifice and you will get there!

This issue of **SYNFORM** features three exciting articles. The first **SYNSTORY** reports on a new cascade process developed by Professor R. SanMartin and colleagues (Spain) leading to the formation of benzofurans. The second **SYNSTORY** covers the first catalytic asymmetric hydrogenation of naphthalenes, discovered by Professor R. Kuwano (Japan). The third article is a Young Career Profile on Professor Zoltan Novak (Hungary).

I would like to end this Editorial with a warm welcome to Mrs. Alison M. Sage who is joining the **SYNFORM** family as the new Editorial Assistant. This will give me the time to focus on the design and development of new content for **SYNFORM** and, importantly, to go back to the original four-articles-per-issue format that is likely to be restored from January 2013.

Enjoy your reading!

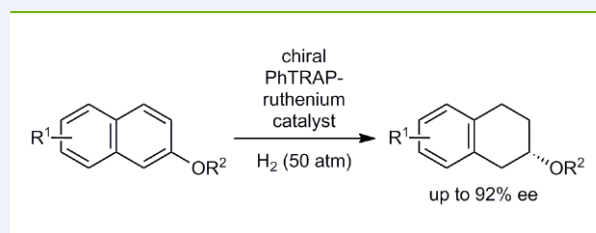
**Matteo Zanda**

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)

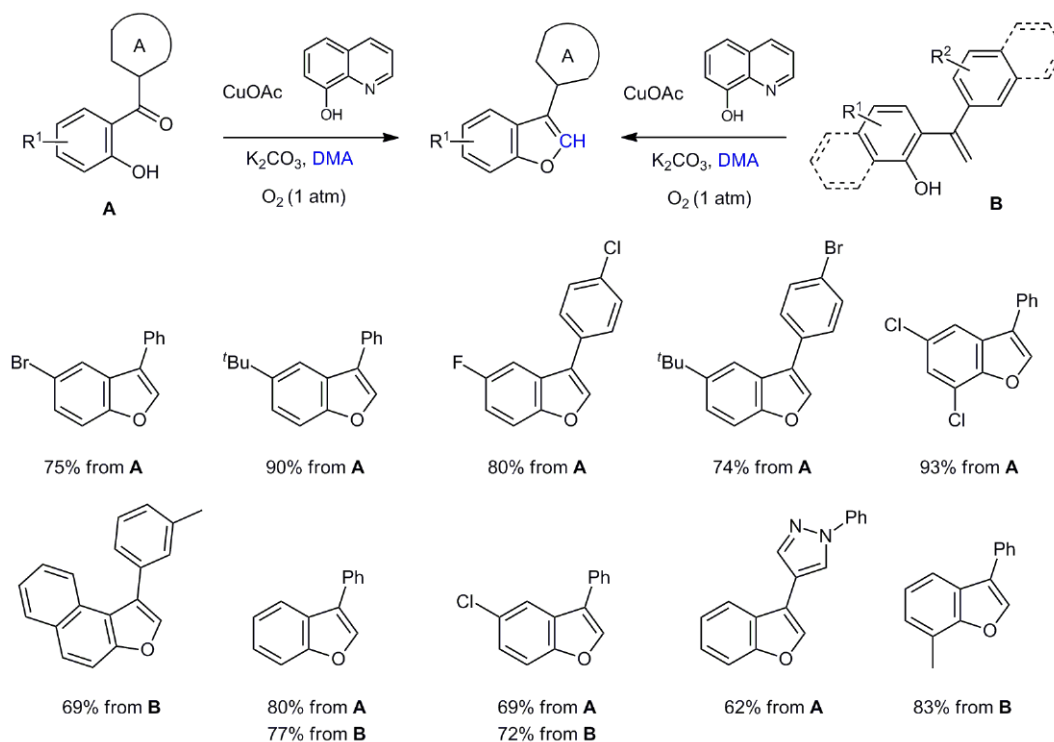
## NEWS AND VIEWS ■ ■ NEWS AND VIEWS ■ ■ NEWS AND VIEWS ■ ■

## Benzofurans from Benzophenones and Dimethylacetamide: Copper-Promoted Cascade Formation of Furan O1–C2 and C2–C3 Bonds under Oxidative Conditions

*Angew. Chem. Int. Ed.* **2012**, *51*, 3220–3224

■ The synthesis of the benzofuran core is an important goal in organic chemistry, as an increasing number of bioactive compounds and materials contain this ubiquitous ring system. Of particular relevance are synthetic methods that involve one-pot formation of two furan bonds, because this is associated with increased efficiency and versatility of the process. Recently, Professors Esther Domínguez and Raul SanMartin together with postgraduate student Maria Jesús Moure from the University of the Basque Country (Spain) reported a new strategy for the synthesis of benzofurans involving the simultaneous formation of two bonds (O1–C2 and C2–C3) of the heterocycle as a result of a reaction pathway that, according to

the authors, has never been reported before. “Our paper describes an unprecedented approach to benzofurans by a cascade formation of the O1–C2 and C2–C3 bonds of the furan ring. The reaction involves a key participation of DMA (dimethylacetamide) which was used not just as a solvent or reaction medium but also as a one-carbon building-block unit,” said Professor SanMartin. “We found that copper catalysis and an environmentally friendly oxidant, oxygen, are required for the ‘activation’ of DMA and its insertion as the C2 carbon of the heterocycle.” The reaction has broad scope and is remarkably efficient, as shown in Scheme 1.



**Scheme 1** Representative examples of copper-catalyzed construction of 3-arylbenzofurans

“We found that the combination of CuOAc, 8-hydroxyquinoline,  $K_2CO_3$ , DMA and an atmosphere of  $O_2$  promoted the transformation from benzophenones or diaryl ketones to 3-arylbenzofurans in good yields,” explained Professor SanMartin. “Obviously, we were initially puzzled by the latter result and its mechanistic implications, but a serious study led us to the mechanistic conclusions summarized in Scheme 2,” he continued.

In order to shed light on the reaction pathway, the Spanish researchers employed isotopically enriched ( $^2H$ ,  $^{13}C$ ) DMA in the preparation of some of the intermediates proposed in the mechanistic pathway leading to benzofurans, and such intermediates were subjected to the above reaction conditions to provide the target heterocycles. “Our efforts proved fruitful, as in addition to substantial evidence in support of the proposed mechanism (Scheme 2), another general approach to the benzofuran core, this time from 2-hydroxy- $\alpha$ -arylstyrenes, was also discovered (Scheme 1),” said Professor SanMartin. “Moreover, in both approaches a proposed key step (alternative/complementary to the copper-catalyzed epoxidation of the aforementioned styrenes) would involve the first example of a copper-catalyzed Wacker cyclization,” he continued. “Palladium has monopolized this reaction since its discovery and copper sources have been employed just as re-oxidants in the catalytic cycle. This fact provides an additional interest to this intriguing mechanism,” reckoned Professor SanMartin. “More research is now under way to expand the scope of the reported protocols to other ketones and alkenes and to discover other advantageous copper-catalyzed oxidative processes,” he concluded. ■

### About the authors



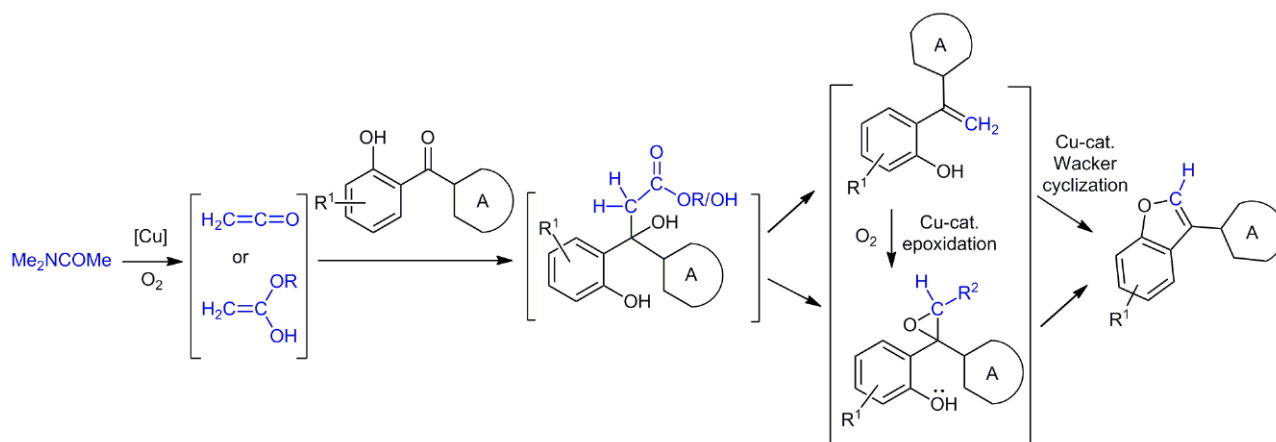
From left: Prof. E. Domínguez, M. J. Moure, Prof. R. SanMartin

**Esther Domínguez**, after a postdoctoral stay at the London University College (UK) working in the group of Professor P. J. Garratt, occupied several academic positions at the University of the Basque Country until her appointment as Full Professor in 1989. She has been Head of the Department of Organic Chemistry and Vice-President of the Organic Chemistry group of the Spanish Royal Society of Chemistry, and presently is the Dean of the Faculty of Science and Technology (UPV/EHU). Her research interests are heterocyclic and natural products chemistry.

**Raul SanMartin** is a Professor with tenure at the University of the Basque Country. After a short predoctoral stay at Boston College (USA) under the supervision of Professor

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Matteo Zanda

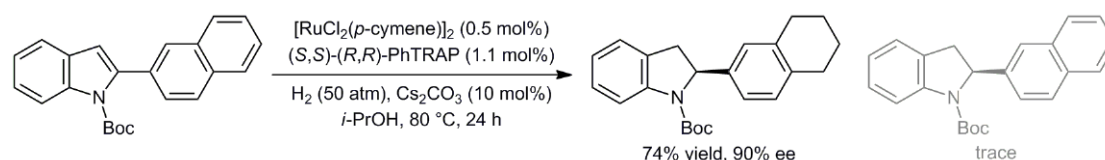


**Scheme 2** Mechanistic proposal for the formation of 3-arylbenzofurans: An overview

T. Ross Kelly, he finished his PhD in 1997. Then, granted a Doctorate Extraordinary Award, he joined Professor Timothy C. Gallagher's group at the University of Bristol (UK) as a post-doctoral researcher, working on selective O- and C-glycosylations of 2-galactosamine, and was appointed Associate Professor at the University of the Basque Country in 2000. His research interests deal mainly with the development of new catalytic systems for arylation and heteroarylation reactions applying sustainability criteria.

**Maria Jesús Moure** was born in Santiago do Compostela (Spain) and did her undergraduate studies at the University of the Basque Country. She received her B.Sc. in 2007 and her M.Sc. from the same university in 2008. She is currently pursuing a Ph.D. in organic chemistry under the guidance of Professors Domínguez and SanMartin.

## Catalytic Asymmetric Hydrogenation of Naphthalenes

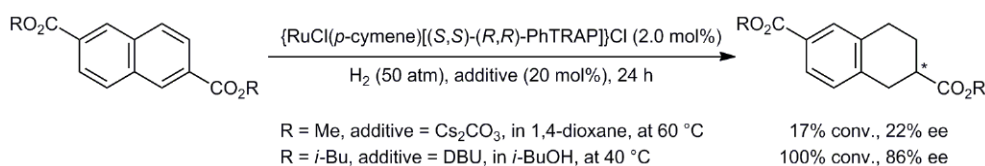
*Angew. Chem. Int. Ed.* **2012**, *51*, 4136–4139

Scheme 1

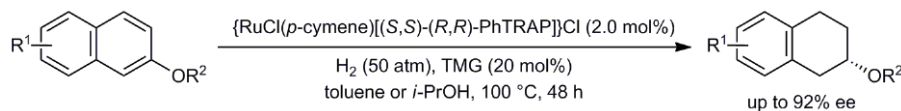
■ The catalytic asymmetric hydrogenation of aromatic hydrocarbons, i.e., aromatic molecules containing no heteroatoms, has remained largely elusive and no successful examples of such a transformation have been reported in the literature until very recently, when the group led by Professor Ryoichi Kuwano, from the Kyushu University (Japan), reported the first stereoselective hydrogenation of naphthalenes using a chiral ruthenium complex.

The same group had previously developed the catalytic asymmetric hydrogenation of indoles in 2005–2006 (*Org. Lett.* **2006**, *8*, 2653). “During the course of the study, Mr. Manabu Kashiwabara attempted the hydrogenation of *N*-Boc-2-(2-naphthyl)indole with the PhTRAP–ruthenium catalyst (Scheme 1),” said Professor Kuwano. “Contrary to our expectations, no 2-(2-naphthyl)indoline was observed in the experiment. The addition of hydrogen took place at the naphthyl group as well as the nitrogen-containing five-membered ring.” According to the Japanese researchers, this observation suggested that the chiral catalyst possesses the catalytic activity for the hydrogenation of carbocyclic arenes, and inspired them to develop the enantioselective hydrogenation of naphthalenes.

“However,” recalled Professor Kuwano, “our initial attempts on the catalytic asymmetric hydrogenation of naphthalenes failed. We chose various 2-substituted naphthalenes as the substrates, because they are relatively easily obtained. However, the naphthalene compound was reduced at its non-substituted carbocycle in preference to another ring, and we failed to obtain the desired chiral tetralins,” he said. “Then, we attempted the hydrogenation of dimethyl 2,6-naphthalenedicarboxylates under various reaction conditions (Scheme 2). In most cases, however, the naphthalene substrate did not react with hydrogen at all, because it is not soluble in any organic solvent,” continued Professor Kuwano. The desired chiral tetralin was obtained only when the reaction was conducted in 1,4-dioxane, but the hydrogenation proceeded very sluggishly and the yield of the product was very low. Furthermore, chiral HPLC analysis of the product indicated that the stereoselectivity was very disappointing. “We therefore gave up on developing the catalytic asymmetric hydrogenation of naphthalenes temporarily,” said Professor Kuwano. “Mr. Kashiwabara started to study the asymmetric hydrogenation of pyrroles instead (*J. Am. Chem. Soc.* **2008**, *130*, 808).”



Scheme 2



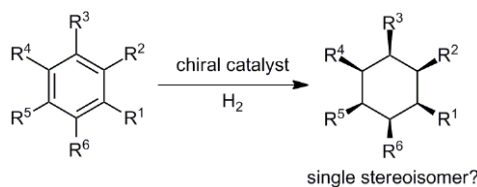
Scheme 3

Professor Kuwano recalled that several years later, Mr. Ryuichi Morioka joined his group and restarted the project on the hydrogenation of naphthalenes. “To solve the above solubility problem, we changed the ester substituents of the naphthalenedicarboxylate,” he said. “Mr. Morioka found that the isobutyl ester is highly soluble in various organic solvents; the reaction conditions could be optimized in detail. We were successful in fully converting the naphthalene substrate into the chiral tetralin with good enantiomeric excess (Scheme 2),” said Professor Kuwano, who continued recalling that he then investigated the substrate scope of the catalytic asymmetric hydrogenation. “Mr. Morioka attempted the PhTRAP–ruthenium-catalyzed hydrogenation with various symmetrically substituted naphthalenes, including dihydroxynaphthalenes and diamionaphthalenes. The chiral ruthenium catalyst failed to reduce most of the naphthalene substrates, but only dialkoxynaphthalenes could be converted into the tetralins (Scheme 3),” he said. “Although the chiral alkoxytetralins were obtained with sufficient enantiomeric excesses, the reaction rate was very low. Therefore, he made huge efforts to achieve full conversion of each substrate within 48 hours. Furthermore, he challenged the hydrogenation of unsymmetrically substituted naphthalenes.”

Professor Kuwano recalled that after Mr. Morioka graduated from the master’s course, Ms. Nao Kameyama joined his group. “She also tried, unsuccessfully, to expand the scope of the naphthalene substrate. However, she did contribute to understanding the reaction pathway of the hydrogenation of naphthalenes and recently developed the asymmetric hydrogenation of oxazoles (*J. Am. Chem. Soc.* **2011**, *133*, 7312),” he acknowledged.

“At this stage, it will be difficult to apply the catalytic asymmetric hydrogenation of naphthalenes to the production of useful compounds, because applicable substrates are very limited,” admitted Professor Kuwano. “However, the asymmetric catalysis may be useful as a key reaction for the synthesis of steroids, if the limited substrate scope can be improved.”

According to Professor Kuwano, one of the ultimate goals in asymmetric catalysis is the catalytic asymmetric hydrogenation of benzene rings. “This reaction will be a powerful tool for the synthesis of various chiral cyclohexanes,” he said. “Furthermore, the asymmetric reaction may allow the creation of six chiral centers in a single process if the catalyst can hydrogenate hexasubstituted benzenes (Scheme 4). To solve the ultimate goal, we will continue the research on the asymmetric hydrogenation of aromatic compounds,” concluded Professor Kuwano. ■



Scheme 4

Matteo Zanda

*About the authors**Prof. R. Kuwano*

**Ryoichi Kuwano** was born in Nagoya (Japan). He received his Master's degree in 1994 and Ph.D. in 1998 from Kyoto University (Japan) under the direction of Professor Yoshihiko Ito. He was appointed as an Assistant Professor in Professor Ito's group at Kyoto University in 1995. In 2001–2002, he joined the research group of Professor John F. Hartwig at Yale University (USA) as a researcher. He then moved to Kyushu University (Japan) as an Associate Professor in 2002, and was promoted to Full Professor in 2009. He has received the Mitsui Chemicals Catalysis Science Award of Encouragement (2005), the Incentive Award in Synthetic Organic Chemistry, Japan (2005), the Commendation for Science and Technology by MEXT, and The Young Scientists' Prize (2008).

**Manabu Kashiwabara** was born in Fukuoka (Japan). He received his Master's degree in 2007 under the direction of Professor Ryoichi Kuwano from Kyushu University.

**Ryuichi Morioka** was born in Ehime (Japan). He received his Master's degree in 2009 under the direction of Professor Ryoichi Kuwano from Kyushu University. He is currently a researcher at Bridgestone.

**Nao Kameyama** was born in Fukuoka (Japan). She received her Master's degree in 2012 under the direction of Professor Ryoichi Kuwano from Kyushu University. She is currently a researcher at JNC.



## Young Career Focus: Professor Zoltan Novak (Eötvös University, Budapest, Hungary)

■ **Background and Purpose.** *SYNFORM* will from time to time meet young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This *SYNSTORY* with a **Young Career Focus** presents Professor Zoltan Novak, Eötvös University, Budapest, Hungary.

### BIOGRAPHICAL SKETCH



Prof. Z. Novak

**Zoltan Novak** was born in 1974 in Budapest, Hungary. After completing his MSc studies at Eötvös University, Budapest with Professor András Kotschy in 1999, he performed doctoral studies in the same research group and received his PhD in 2004. His research focused on the utilization of palladium catalysts in the synthesis and functionalization of heterocycles. From 2004 to 2005

he joined the group of Professor Brian M. Stoltz at the California Institute of Technology, Pasadena (USA) as a postdoctoral researcher. After returning to Hungary he continued his research at Eötvös University, again in Professor Kotschy's group. In September 2007 he started his independent research career at the Department of Organic Chemistry, Institute of Chemistry at Eötvös University as an Assistant Professor.

### INTERVIEW

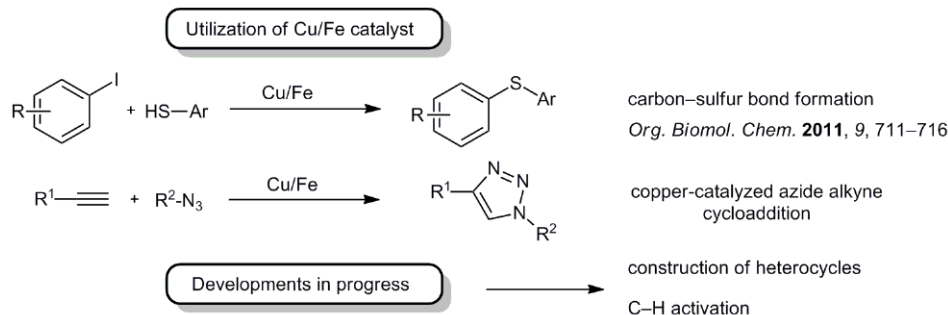
**SYNFORM** | *What is the focus of your current research activity?*

**Professor Novak** | There are several research topics running in our laboratory. Our research mainly focuses on the examination of catalytic transformations based on C–H activation and cross-coupling reactions using different approaches. We apply different homogeneous and heterogeneous transition-metal catalysts for the construction of new carbon–carbon and carbon–heteroatom bonds, and other activation modes (e.g., visible light induced activation) are also a focus. Currently, we are performing in situ spectroscopic studies to examine and understand the mechanisms and elementary steps of transition-metal-catalyzed C–H activation reactions.

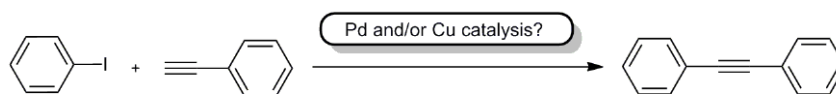
**SYNFORM** | *When did you get interested in synthesis?*

**Professor Novak** | The decision was made when I was a 4<sup>th</sup> year student at Eötvös University. The view, perspective and possibilities of organic synthesis given by my supervisor, Professor András Kotschy, made the decision so easy for me. There was no doubt in choosing this branch of chemistry after tasting the beauty and challenges of synthesis.

**SYNFORM** | *What do you think about the modern role and prospects of organic synthesis?*



Scheme 1



ppb levels of palladium impurities have dramatic effect on the Sonogashira reaction

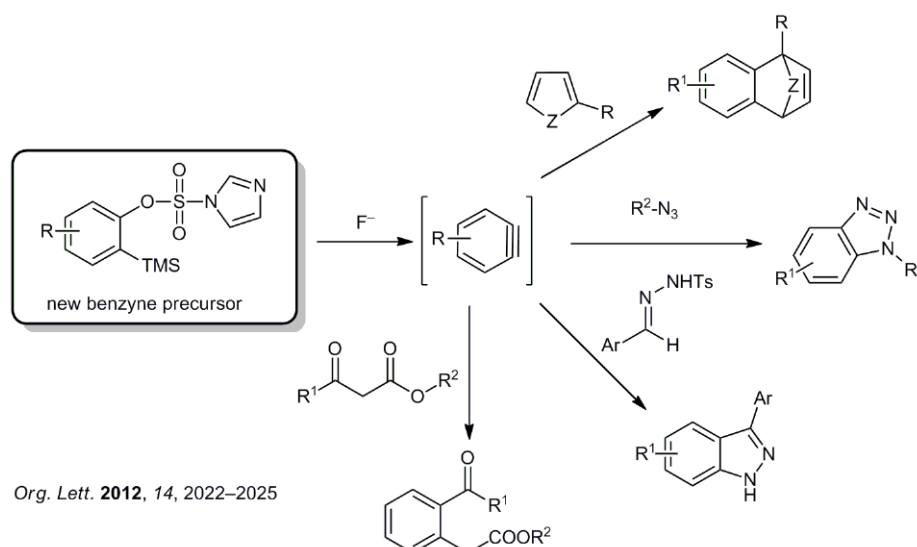
*Chem. Eur. J.* **2010**, *16*, 11822–11826

### Scheme 2

**Professor Novak** | Organic synthesis had, has, and will have an important role in science and everyday life. It is enough to think of polymers and any kind of materials around us, medicines, agrochemicals, etc. Development of transformations in which we can build up organic compounds efficiently, together with the discovery of new catalytic processes will also be within the realm of future research in the field of organic synthesis. Until the day when we can't cut particular bond(s) specifically, and/or make new one(s) as we imagine, organic syntheses will have relevance.

**SYNFORM** | Your research group is active at the frontier of organic synthesis and catalysis. Could you tell us more about your research and its aims?

**Professor Novak** | Currently, we are studying copper- and iron-catalyzed transformations to construct new carbon–carbon and carbon–heteroatom bonds. Design and application of copper/iron bimetallic catalytic systems in several transformations are also a focus (Scheme 1). The major goal of this research is the straightforward preparation of supported copper nanoparticles and its application in organic synthesis. Utilization of these catalysts in C–H activation is a challenging but very interesting field. There is also the prospect of looking at palladium-catalyzed C–H activation reactions under aqueous conditions for the construction of new C–C bonds. I feel that the appropriate choice of the reaction conditions will enable C–H activation under mild conditions. From the materials point of view, we are extensively studying the reaction and functionalization of acetylene derivatives using transition-metal catalysts.



*Org. Lett.* **2012**, *14*, 2022–2025

### Scheme 3

**SYNFORM** | *What is your most important scientific achievement to date and why?*

**Professor Novak** | I like all the results published recently, but if I had to choose a favorite, I'd pick the demonstration of the effect of palladium impurities on the "copper-catalyzed" Sonogashira reaction (Scheme 2), because the whole study required special circumstances and all the experiments were challenging to ensure extra-clean conditions. From the outcome point of view, this finding directs attention to the

possible effect of metal impurities in some transition-metal-catalyzed transformations. Another favorite is the design and application of a new, imidazolate-based benzyne precursor for organic synthesis (Scheme 3). This benzyne source may replace the popular and widely used trimethylsilyl triflate analogue in the near future. ■

**Matteo Zanda**



COMING SOON ►► COMING SOON ►►

**SYNFORM 2012/08***is available from  
July 19, 2012***In the next issues:****SYNSTORIES** ■ ■ ■ ■ ■■ **Programmable Enantioselective One-Pot Synthesis of Molecules with Eight Stereocenters***(Focus on an article from the current literature)*■ **Catalytic Asymmetric Mono-Fluorination of  $\alpha$ -Keto Esters***(Focus on an article from the current literature)***FURTHER HIGHLIGHTS** ++++**SYNTHESIS****Review on: NHCs in Asymmetric Organocatalysis: Recent Advances in Azolium Enolate Generation and Reactivity***(by A. D. Smith et al.)***SYNLETT****Account on: Inter- and Intramolecular Carbon–Carbon Bond-Forming Radical Reactions***(by H. Miyabe)***SYNFACTS****Synfact of the Month in category “Synthesis of Heterocycles”:****Ruthenium-Catalyzed Dehydrative Benzofuran Synthesis via C–H Activation****CONTACT** ++++**Matteo Zanda,  
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