

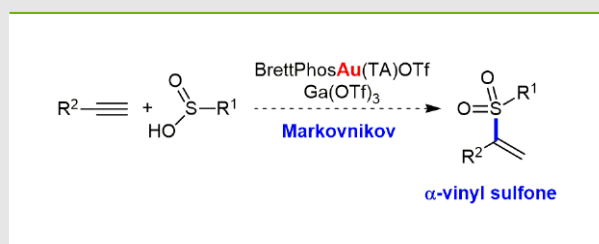
# SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2014/10

## SYNSTORIES ■ ■ ■ ■

■ Gold-Catalyzed Intermolecular C–S Bond Formation: Efficient Synthesis of  $\alpha$ -Substituted Vinyl Sulfones



■ An Insight into Silver-Catalyzed Hydroazidation for a General Synthesis of Vinyl Azides

■ CpRu-Catalyzed Carbene Insertions into Epoxides: 1,4-Dioxene Synthesis via  $\text{S}_{\text{N}}1$ -like Chemistry with Retention of Configuration

■ Young Career Focus:  
Professor David Díaz Díaz  
(University of Regensburg, Germany)

CONTACT ++++

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[marketing@thieme-chemistry.com](mailto:marketing@thieme-chemistry.com)



### Dear Readers,

From the next issue **SYNFORM** will start publishing 'ChemSites', a new exciting editorial feature that will highlight chemistry departments, centers and research institutes all over the world. 'ChemSites' will focus on the cutting-edge research carried out in your departments and institutes, on their structure and organization, on the educational offerings and scientific aims, as well as on staff members. 'ChemSites' is intended to become an essential tool for informing the Thieme Chemistry readership about unique strengths, activities and research & training available at the sites where the most exciting basic and applied organic chemistry is developed. The pilot "ChemSites" article will feature the Institute of Transformative Bio-Molecules (ITbM), Nagoya University (Japan), and I believe it will be an excellent example of how this new type of **SYNSTORY** article can be an extraordinary vehicle for increasing awareness and maximizing the impact of the research activities carried out at Your Institutes and Departments. Self-candidatures are more than welcome; please get in touch with me if you wish to have your site featured by 'ChemSites'!!! There is no 'ChemSites' article in this issue of **SYNFORM**, nonetheless there is plenty of exciting organic chemistry and exclusive information about how the most exciting discoveries were actually made and the scientists who made them. Xihe Bi (P. R. of China) kick-starts the issue with his silver-catalyzed synthesis of vinyl azides from alkynes. Xiaodong Shi follows with the elegant and efficient gold-catalyzed synthesis of  $\beta$ -substituted vinyl sulfones. After silver and gold, instead of bronze we find... ruthenium! In fact, Jérôme Lacour (Switzerland) makes use of a ruthenium for catalyzing carbene insertions into epoxides. Dulcis in fundo, we move into the territory of applied organic chemistry with the Young Career Focus on David Díaz Díaz (Germany).

Enjoy your reading!

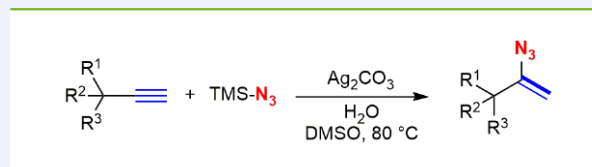
**Matteo Zanda**

Editor of **SYNFORM**

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**CONTACT + + + +**

If you have any questions or wish to send feedback, please write to Matteo Zanda at: [synform@outlook.com](mailto:synform@outlook.com)

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

## An Insight into Silver-Catalyzed Hydroazidation for a General Synthesis of Vinyl Azides

*Angew. Chem. Int. Ed.* **2014**, *53*, 5305–5309 and *Org. Lett.* **2014**, *16*, 3668–3671

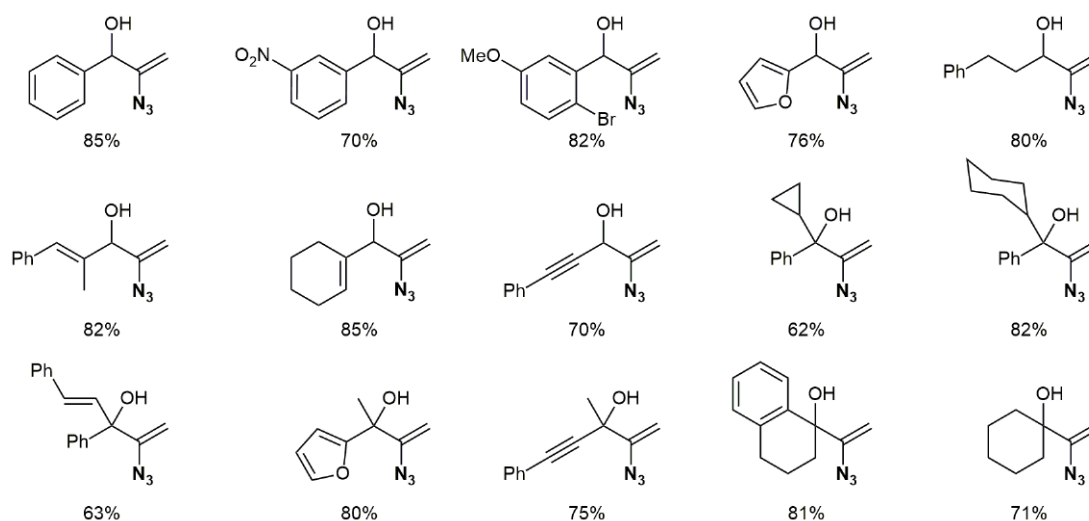
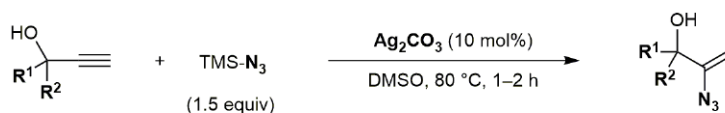
■ Nitrogen-containing heterocycles are ubiquitous in natural products as well as among pharmaceutical substances. Consequently, the development of methods for the introduction of nitrogen in simple organic compounds is an intense focus of modern research. In particular, vinyl azides show unique reactivity in organic synthesis due to the concomitant

presence of the C=C double bond and the azide functionality. In earlier research, much attention was paid to the study of the reactivity of vinyl azides, especially the control of their selectivity and the potential synthetic utilities. However, the synthetic scope of vinyl azides remains largely unexplored because of the intrinsic high reactivity and limited available methods for their preparation. Meanwhile, vinyl azides have drawn much interest for their growing applications in the synthesis of various heterocycles, as well as polysubstituted pyrroles, owing to their remarkably important applications in both medicinal and materials fields. Great efforts have focused on developing simple synthetic approaches for the construction of these privileged structures.

Hydroazidation is one of the most suitable and viable methods for the generation of nitrogen-containing reactive



**Scheme 1** Hydroazidation of terminal alkynes toward the synthesis of vinyl azides

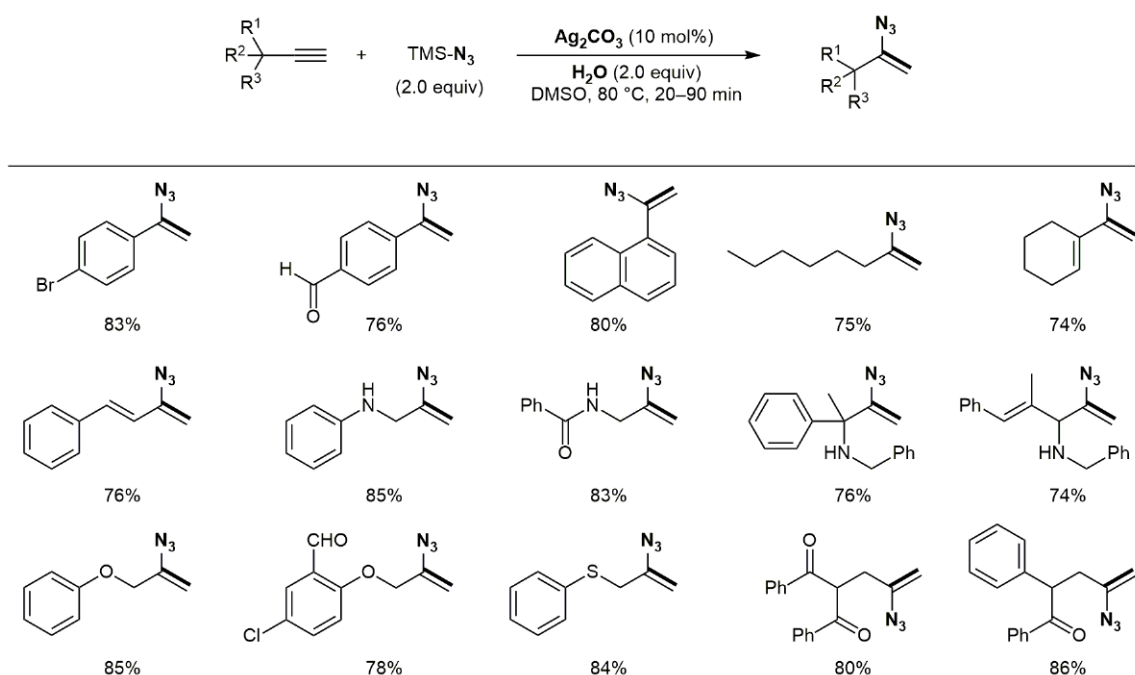


**Scheme 2** Hydroxyl-dependent hydroazidation

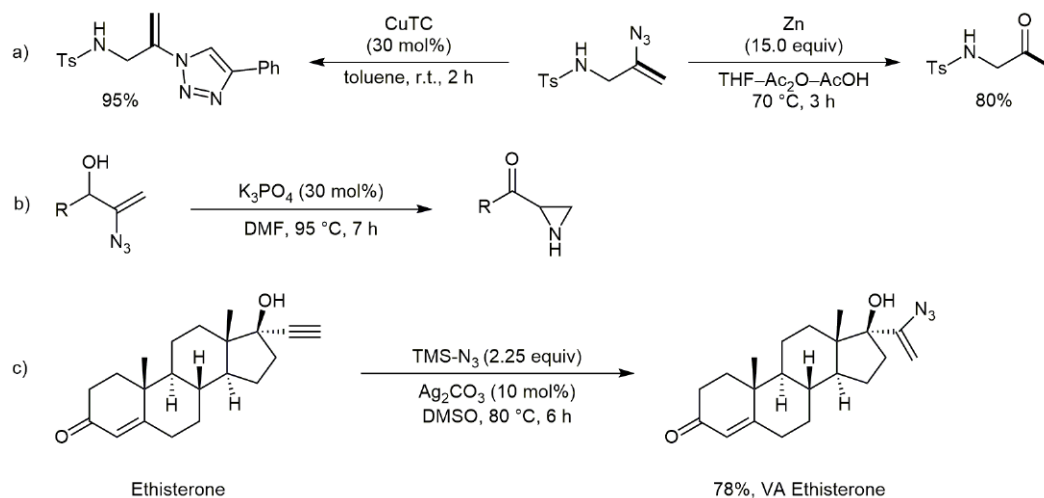
species and useful synthetic intermediates or building blocks. Specifically, hydroazidation of alkynes is an ideal route to obtain vinyl azides (*Angew. Chem. Int. Ed.* **2012**, *51*, 7511) and only a few reports are available for their synthesis. Most recently, Professor Xihe Bi and co-workers at Northeast Normal University (Changchun, P. R. of China) have demonstrated an efficient hydroazidation reaction of unactivated alkynes using silver catalysis and have applied it to the synthesis of structurally diverse vinyl azides from terminal alkynes with trimethylsilyl azide (TMS-N<sub>3</sub>) (Scheme 1). In their continuous efforts to develop novel organic reactions using functionalized alkynes, Professor Bi's group subsequently accomplished a chemo- and regioselective silver-catalyzed hydroazidation of ethynyl carbinols with TMS-N<sub>3</sub>, which afforded diverse 2-azidoallyl alcohols (Scheme 2) (*Angew. Chem. Int. Ed.* **2014**, *53*, 5305). In general, this alkyne hydroazidation reaction, whose success depends on the presence of a vicinal hydroxyl group, can be applied to a wide variety of secondary and tertiary ethynyl carbinols giving corresponding products within 1–2 hours in good to excellent yields. Professor Bi explained that in this reaction the hydroxyl group of ethynyl carbinols played a critical role as the proton source, and it is assumed that a trace amount of water in DMSO was also necessary to alleviate the need for a hydroxyl

group in the substrate and provide an alternative proton source. Further, this assumption was confirmed by experimental results.

In general, the hydroazidation reaction of diverse terminal alkynes with TMS-N<sub>3</sub> in the presence of H<sub>2</sub>O has very broad scope and affords the corresponding vinyl azides in excellent yields (Scheme 3) (*Org. Lett.* **2014**, *16*, 3668). Professor Bi said: "Under the optimized reaction conditions, the effect of the stoichiometry of water was investigated at first with a model reaction and we found that in dry DMSO, a mixture of product and starting material was obtained in a ratio of 1:3 (determined by <sup>1</sup>H NMR analysis), whereas two equivalents of water were needed to yield the target vinyl azide as sole product." According to Professor Bi, these findings confirm that an appropriate amount of water is essential to generate HN<sub>3</sub>. The effect of time on the reaction was also investigated and it was noticed that a proportional increase of product and consumption of substrate was observed. "This result proved the clean transformation from substrate to product," said Professor Bi. "Also, it must be mentioned that strict control of the reaction time was necessary in order to avoid the further conversion of vinyl azides into nitriles as previously reported by Jiao (*Angew. Chem. Int. Ed.* **2013**, *52*, 6677)." Under the optimized conditions, a library of vinyl azide derivatives was generated. In general, the substrate scope was quite broad and



**Scheme 3** A general hydroazidation



**Scheme 4** Synthetic utility of vinyl azides

diverse aryl-, alkyl-, and alkenyl-alkynes could be subjected to this silver-catalyzed procedure, thus affording the corresponding vinyl azides chemoselectively and in good to excellent yields within 20–90 min.

Professor Bi remarked: “In addition, the synthetic utility of vinyl azide was further demonstrated by the transformation of various vinyl azides into aziridine, triazole,  $\alpha$ -amino ketone, and by the transformation of ethisterone into vinyl azide (VA) ethisterone without any change in their chiral centers and using known synthetic pathways (Scheme 4).”

Professor Bi concluded: “This novel and practical silver-catalyzed hydroazidation reaction has a broad substrate scope, good functional group tolerance, simple operation, and high reaction efficiency, thus providing an easy access to various functionalized vinyl azides. It opens up new prospects in synthetic and pharmaceutical chemistry for further exploiting the synthetic power of vinyl azides.”

**Matteo Zanda**

### About the authors



Prof. X. Bi

**Xihe Bi** was born in Jilin (P. R. of China) in 1977. He obtained his BSc in 2000 and PhD in 2006 under the guidance of Professor Qun Liu at Northeast Normal University (P. R. of China). He spent two years (2006–2008) as an Alexander von Humboldt postdoctoral fellow with Professor Michael Famulok at Kekulé-Institut für Organische Chemie und Biochemie, University of Bonn (Germany). In 2013, he was promoted to Professor.

His research interests include functionalized alkynes, inert chemical bond transformations, and new organic reagents. He has received several honors and awards, including the Thieme Chemistry Journal Award 2014, the New Century Ex-

cellent Talents in University (2013) from The Ministry of Education of the People's Republic of China, and an Alexander von Humboldt research fellowship (2006) from Alexander von Humboldt-Stiftung.



Z. Liu

**Zhenhua Liu** was born in Shandong (P. R. of China) in 1986. He received his BSc in chemistry from Linyi University (P. R. of China) in 2010, and then joined the Department of Chemistry in the Northeast Normal University as a PhD candidate in 2011, working under the supervision of Professor Xihe Bi. His research interest concerns functionalized alkynes.

# Gold-Catalyzed Intermolecular C–S Bond Formation: Efficient Synthesis of $\alpha$ -Substituted Vinyl Sulfones

*Angew. Chem. Int. Ed.* **2014**, *53*, 4657–4661

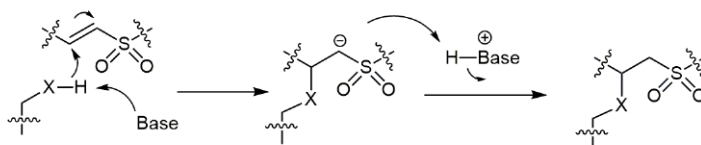
The last decade has witnessed an explosive development of homogeneous gold catalysis. However, a universal drawback of gold as a catalyst is its vulnerability under reaction conditions, especially at high temperatures. In 2009, the laboratory of Professor Xiaodong Shi at the West Virginia University (USA) introduced a new class of gold complexes: 1,2,3-triazole-gold(I) (TA-Au) as catalysts with improved thermal stability. Later it was demonstrated that with 1,2,3-triazole used

as a special ‘X-factor’ [the ligand coordinated to (L-Au)<sup>+</sup>], this class of catalysts possessed unique chemoselectivity in Hashmi phenol synthesis and in a series of transformations related to propargyl ester rearrangements (for a detailed bibliography see Ref. 15 of the original manuscript).

Improved stability certainly costs in terms of reactivity. For this reason, recent efforts by Professor Shi’s group were aimed at developing a novel catalytic system with restored

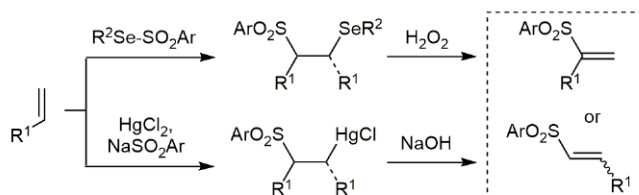
1) Vinyl sulfone in biological research: covalent trapping of nucleophiles

X = O, NR, S



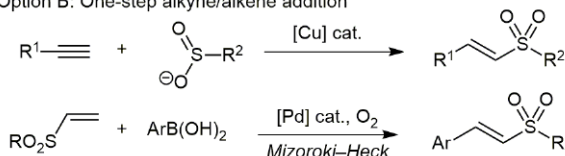
2) Current strategies for vinyl sulfone synthesis

Option A: Two-step alkene addition–elimination



**Drawbacks:**  
toxic materials  
stoichiometric reagents  
less atom-economy  
regioselectivity

Option B: One-step alkyne/alkene addition



**Stereochemical outcome:**  
anti-Markovnikov

3) **This work:** first Markovnikov addition to alkynes with triazole-gold catalyst



**$\alpha$ -vinyl sulfone**  
more reactive Michael acceptor with  
less hindered  $\beta$ -carbon

Scheme 1 General design

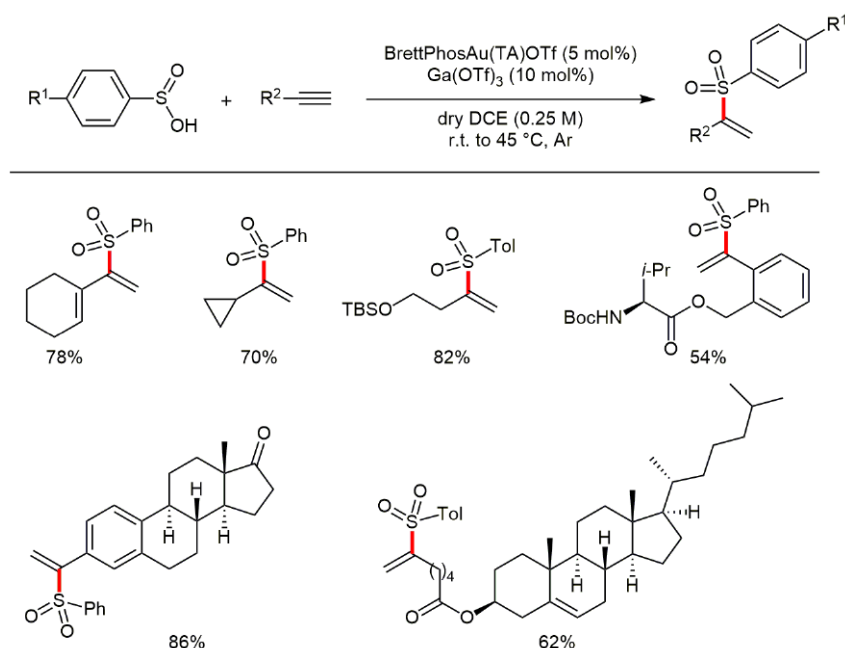
catalytic efficiency while maintaining a reasonable level of stability. Professor Shi said: “Lewis acid was devised as the activator for the TA-Au catalyst to reversibly remove the triazole off the gold center, which is a thermodynamically and kinetically favored process. Gallium triflate turned out to be a good candidate.”

Professor Shi continued: “Vinyl sulfone, a valuable building block in synthesis and a functional unit in biology, has been an interesting target. Typical sulfinic acid addition to an alkyne gives the anti-Markovnikov products through radical processes. It is envisioned that the gold catalyst will preferentially promote Markovnikov addition to alkynes and using sulfinic acid would yield  $\alpha$ -substituted vinyl sulfones, which typical methods cannot easily access. Even more importantly, in principle,  $\alpha$ -substituted vinyl sulfones, with a much less hindered  $\beta$ -carbon atom, should react faster in Michael additions and should therefore be more suitable substrates. Replacing the  $\beta$ -substituted vinyl sulfone units with  $\alpha$ -substituted vinyl sulfones should lead to significant improvements in terms of Michael reactivity.”

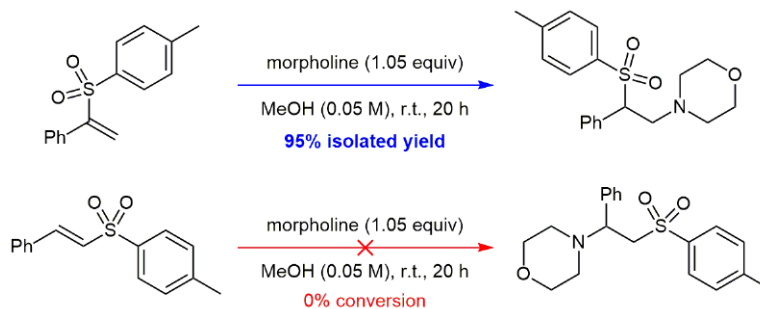
In order to achieve high yield and efficiency, various gold catalysts were screened by Professor Shi’s co-workers. It was found that the ligand used had a strong influence on the reaction performance. Remarkably, the combination of 5 mol% BrettPhosAu(TA)OTf and 10 mol% Ga(OTf)<sub>3</sub> gave the best

result (91% yield) while the Au/Ag system generally performed worse (highest yield obtained with 5 mol% BrettPhosAuCl and 5 mol% AgSbF<sub>6</sub>, 76%). Employing only 5 mol% BrettPhosAu(TA)OTf or 10 mol% Ga(OTf)<sub>3</sub> alone resulted in a slower reaction, or no reaction at all. The optimized reaction was then applied to various terminal alkynes for the synthesis of the corresponding  $\alpha$ -substituted vinyl sulfones. Professor Shi remarked: “Generally, the yields were good with both aromatic and aliphatic alkynes. More importantly, this method could also be applied to complex molecules, such as amino acids, estrone and cholesterol derivatives.”

The rapid access to  $\alpha$ -substituted vinyl sulfones enabled by this methodology provides an opportunity for further derivatization, as demonstrated by the Diels–Alder reaction of *N*-maleic anhydride with 1,3-dienyl sulfone. Professor Shi said: “Furthermore, this method may also find potentially wide applications in biology for the synthesis of covalent enzymatic inhibitors, as highlighted by the strikingly different reactivity of Michael additions involving either  $\alpha$ - or  $\beta$ -substituted vinyl sulfones using the secondary amine morpholine as nucleophile. In fact, the  $\alpha$ -substituted vinyl sulfone gave the Michael adduct in almost quantitative yield at room temperature, while the  $\beta$ -substituted vinyl sulfone gave no conversion at all under the same set of conditions. Considering the mild



Scheme 2 Reaction scope

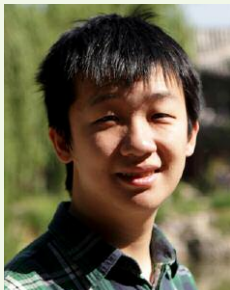


**Scheme 3** Improved Michael receptor

conditions and high efficiency, one may envision the potential application of this method to vinyl sulfone introduction through addition to alkyne-containing biologically interesting targets.” Overall, the combination of a TA-Au catalyst and  $\text{Ga}(\text{OTf})_3$  enables a general synthesis of  $\alpha$ -substituted vinyl sulfones from simple terminal alkynes and sulfinic acids. “This success opens up intriguing opportunities to perform other challenging transformations with this novel system,” said Professor Shi, who concluded: “Furthermore, a comparison of the reactivity of  $\alpha$ - and  $\beta$ -substituted vinyl sulfones towards Michael addition highlights the potential application of the former compounds in biological and pharmaceutical sciences.” ■

Matteo Zanda



*About the authors*

Y. Xi

**Yumeng Xi** was born in Wuhan (P. R. of China) in 1990. He received his BS degree in chemistry from Peking University (P. R. of China) working in Professor Zhen Yang's laboratory. He recently obtained a Master's degree in Professor Xiaodong Michael Shi's group at the West Virginia University and will move to the University of California, Berkeley (USA) as a PhD student.



Prof. X. M. Shi

**Xiaodong Michael Shi** was born in Tianjing (P. R. of China). He went to Nankai University (P. R. of China) in 1990 and received his BS and MS degrees in 1994 and 1997, respectively. He then moved to the USA and earned his PhD in 2002 from University of Maryland, College Park, under the guidance of Professor Jeffery T. Davis, with research focused on self-assembled nucleosides. After finishing graduate school, Dr. Shi moved to the

Chemistry Department at the University of California Berkeley and joined Professor Paul A. Bartlett's group as a postdoctoral research associate. In July 2003, he joined Professor F. Dean Toste's group and studied transition-metal catalysis. Professor Shi started his independent research in the fall of 2005 at the Chemistry Department of West Virginia University and was promoted to Associate Professor in 2011.

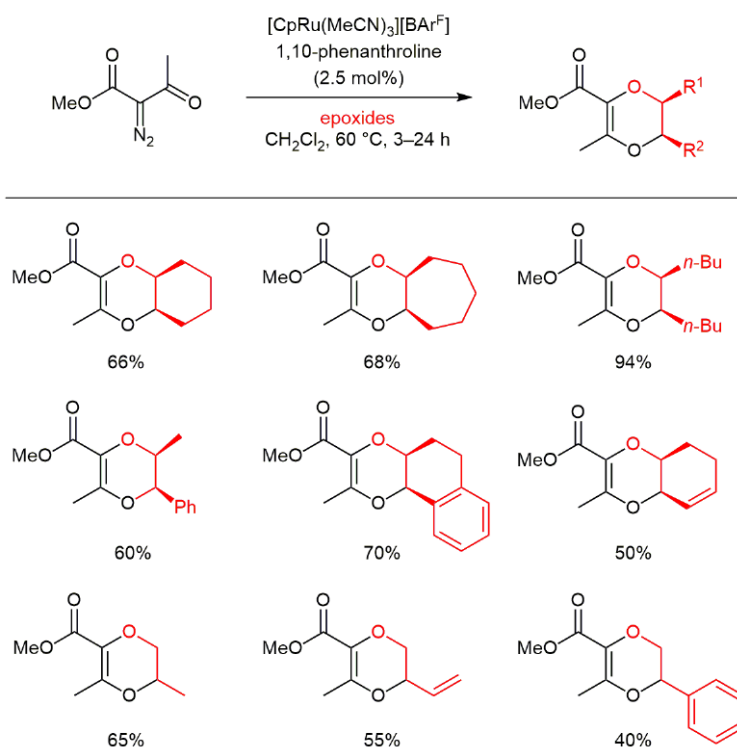
# CpRu-Catalyzed Carbene Insertions into Epoxides: 1,4-Dioxene Synthesis via S<sub>N</sub>1-like Chemistry with Retention of Configuration

*Angew. Chem. Int. Ed.* **2014**, *53*, 6140–6144

The group of Professor Jérôme Lacour at the University of Geneva (Switzerland) has recently reported a series of original transformations, using cyclic ethers as substrates,  $\alpha$ -diazo- $\beta$ -keto esters as reagents and rhodium/ruthenium catalysts for the diazo decomposition, that are best rationalized by the successive formation of metal carbenes and oxonium ylide intermediates. Professor Lacour explained that, interestingly, under the same reaction conditions, very different results are usually obtained under Rh(II) and Ru(II) catalysis. For instance, with THF, 16-membered macrocycles are obtained with Rh<sub>2</sub>(OAc)<sub>4</sub> (*Angew. Chem. Int. Ed.* **2010**, *49*, 7253) while products of 1,3-C–H insertions result from combina-

tions of CpRu complexes and diimine ligands (*Angew. Chem. Int. Ed.* **2012**, *51*, 5847).

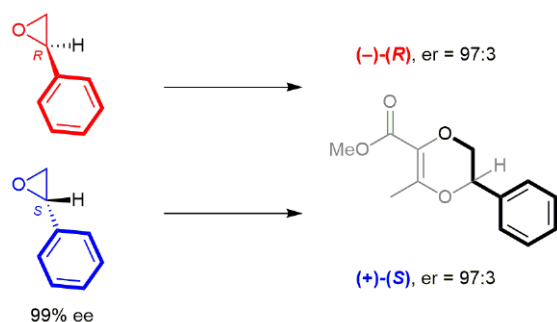
“As part of this program, it was then interesting to study the reactivity of  $\alpha$ -diazo- $\beta$ -keto ester reagents with the smallest cyclic ethers, the epoxides (oxiranes),” said Professor Lacour. “However, it was not clear whether remarkable results would occur this time.” Professor Lacour continued: “Epoxides are highly useful synthetic building blocks owing to their availability in well-defined stereochemical forms and their reactivity with a wide array of nucleophiles and acids leading to ring-opening reactions with often excellent levels of regioselectivity and/or stereoselectivity. Yet, as a rule,



Scheme 1

epoxides do not react with metal carbenes to afford synthetically useful oxonium ylide intermediates but undergo instead (less interesting) deoxygenation processes that transform them into alkenes.” Professor Lacour revealed that it was a surprise when Dr. Thierry Achard and graduate student Cecilia Tortoreto observed that the treatment the *cis*-stilbene oxide with methyl diazoacetylacetate in the presence of 1,10-phenanthroline and  $[\text{CpRu}(\text{MeCN})_3][\text{BAR}_F]$  (2.5 mol% respectively) led to the clean formation of an original product of condensation of 1,4-dioxene type (Scheme 1). This first result was rapidly confirmed by a series of experiments with cyclic and acyclic symmetrical *cis*-epoxides. Satisfyingly, in all examples, 1,4-dioxene adducts were again obtained as single stereoisomers. Professor Lacour remarked: “All these experiments led to another surprise as, upon  $^1\text{H}$  NMR and then later X-ray diffraction analyses, it became clear that the products were all of *cis*-configuration themselves. *syn*-Stereoselective openings of epoxides are known but they remain rare. It was thus a pleasure to have found another example.”

Furthermore, while working towards expanding the scope of the reaction to unsymmetrical *cis*-disubstituted and mono-substituted epoxides, it was found that ring-opening products were always obtained as single regioisomers as well, with the substitution reactions occurring at the activated carbon centers (benzylic, allylic or more substituted). Professor Lacour said: “The example with 2-vinylloxirane was particularly sweet as only the product of direct ring opening was obtained with no evidence of byproducts of [2,3]-sigmatropic reactions. Still, more globally and quite surprisingly, these latest experiments were advocating for a pathway occurring through an  $\text{S}_{\text{N}}1$ -like mechanism; this preference being at first glance in contradiction with the highly stereoselective nature of transformation.”



Scheme 2

To shed some light on the process, a few unsymmetrical epoxides were used in enantiopure form by the researchers. For instance (Scheme 2), both (*R*)- and (*S*)-styrene oxides were tested and the corresponding products were obtained with an astonishing 97:3 enantiomeric ratio! Care was taken to determine the absolute configurations by X-ray diffraction analysis with the help of Dr. Laure Guénée and also by vibrational circular dichroism (VCD): both methods indicated *R*- and *S*-configurations for the corresponding 1,4-dioxenes and hence a retention of configuration! Professor Lacour mentioned: “It was important to perform the VCD study with a renowned expert, Prof. Thomas Bürgi, to ascertain the result of the solid-state analysis which had been performed without a heavy atom. VCD is a well-established spectroscopic method for the determination of absolute configurations. It is unfortunate that it is not used more often by synthetic chemists.”

Finally, thanks to computational studies, a mechanistic rationale coherent with the experimental information could be proposed. Professor Lacour continued: “Dr. Amalia Poblador-Bahamonde was able to define the ruthenium carbene species. She then showed that a nucleophilic attack of the epoxide occurs and a metal-bound oxonium ylide intermediate is formed. From there, promoted by strain and by the electrophilic activation, a carbocationic intermediate is produced which is very rapidly trapped by the keto group at proximity to form the cyclic 1,4-dioxene skeleton – and this with retention of the original configuration of the reacting carbon center.”

Professor Lacour concluded: “We have found a new reactivity for metal carbenes with epoxides owing to the combination of 1,10-phenanthroline and  $[\text{CpRu}(\text{MeCN})_3][\text{BAR}_F]$  as catalyst. The protocol allows the formation of unprecedented 1,4-dioxene motifs as single regio- and stereoisomers. It relies on a strict *syn*-stereochemistry (retention of configuration, er up to 97:3) for the ring opening that behaves otherwise like an  $\text{S}_{\text{N}}1$ -like transformation! Such unusual reactions are strokes of luck and those are the transformations that ‘make my day’!”

Matteo Zanda

### About the authors



Dr. A. I. Poblador-Bahamonde

**Thierry Achard** studied at the University of Aix-Marseille, Faculté de St. Jérôme (France) and obtained his Master's degree in 1999. He received his PhD from both King's College London and Newcastle-upon-Tyne University (UK) in 2006. Then, he joined groups in Barcelona (Spain; Institute for Research in Biomedecine, 2006–2008), in Marseille (France; Ism2, 2009–2010) and in Geneva (Switzerland; 2011–2014) as a postdoctoral fellow. Since 2014, he is Chargé de Recherche (CNRS) at the Institut de Physique et Chimie des Matériaux de Strasbourg (UMR7504, équipe DMO) (France).

**Cecilia Tortoreto** studied at the University of Perugia (Italy) and received her MSc degree in 2009. Then, she moved to the chemical development department of GlaxoSmithKline research center in Verona (Italy) for a master graduate fellowship. She has been a PhD student at the University of Geneva since 2010.



Dr. A. I. Poblador-Bahamonde

**Amalia I. Poblador-Bahamonde** received her PhD (2009) from Heriot-Watt University (UK). In 2010, she moved to Montpellier (France) as a postdoctoral fellow. In January 2013, she joined the Organic Chemistry Department of the University of Geneva as a lecturer. Her research interests lie in the use of computational chemistry to understand the structures and reactivity of transition-metal systems, particularly in organo-metallic chemistry.

**Laure Guénée** studied at the University of Paris XI, Orsay (France) and then obtained her PhD in crystallography from the University of Geneva (Switzerland) in 2002. After a postdoctoral stay at the Institut des Matériaux Jean Rouxel, Nantes (France), she returned to the University of Geneva in 2005. She is now collaboratrice scientifique in the Laboratoire de cristallographie.

**Thomas Bürgi** studied chemistry and obtained his PhD (1995) at the University of Berne (Switzerland). After a postdoctoral stay at MIT (USA), he did his habilitation at ETH Zürich (Switzerland). He became Assistant Professor at the University of Neuchâtel (Switzerland) in 2005 and Full Professor at the University of Heidelberg (Germany) in 2008. In 2010, he moved to the University of Geneva, where he is Professor of physical chemistry. His research focuses on chiral nanoparticles, plasmon-based metamaterials and in situ vibrational spectroscopy.

**Jérôme Lacour** was educated at the École Normale Supérieure (Ulm, Paris, France) and obtained in 1993 his PhD in chemistry at the University of Texas, Austin (USA). After postdoctoral studies at Harvard University (USA) in 1993–1994, he joined the Organic Chemistry Department of the University of Geneva in 1995. In 2001, he received the Sandoz Family Foundation professorship. Since 2004, he holds a Full Professor position in the department. Currently, his primary research interests are in asymmetric synthesis and catalysis using organic, physical organic, organometallic and coordination chemistry tools.

## Young Career Focus: Professor David Díaz Díaz (University of Regensburg, Germany)

■ **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 David Díaz Díaz (University of Regensburg, Germany).

### BIOGRAPHICAL SKETCH



Prof. D. Díaz Díaz

**David Díaz Díaz** was born in Tenerife (Spain) in 1974. He obtained his B.Sc. in chemistry at the University of La Laguna (ULL), Tenerife, in 1997. He then continued his studies at the University Institute for Bio-Organic Chemistry 'Antonio González' (IUBO, ULL), conducting his Ph.D. under the supervision of Professor Víctor Martín García, where he worked on the use of acetylene complexes

with  $\text{Co}_2(\text{CO})_8$  in the development of new methodologies for the stereocontrolled synthesis of natural products. After completing his Ph.D. in 2002, he joined Professor M. G. Finn's research group at The Scripps Research Institute (San Diego, USA) for a postdoctoral stay, where he also worked with Professors K. Barry Sharpless and V. V. Fokin. The focus of his work was on the chemistry of amidines and on the application of click chemistry to materials synthesis. In 2006, he was appointed as a 'Ramón y Cajal' researcher at the Autonomous University of Madrid (Spain). One year later, he joined The Dow Chemical Company (Switzerland) and in 2009 he was appointed as a Tenured Scientist of The Spanish National Research Council (CSIC). In 2010, he received the Alexander von Humboldt Fellowship for Experienced Researchers and established a research group at the University of Regensburg (Germany). In 2013, he became a permanent Scientist of the Institute of Advanced Chemistry of Catalonia (IQAC-CSIC, Barcelona, Spain) and was awarded with the prestigious DFG Heisenberg Professorship in Germany. Among different awards, he was finalist of the European Young Chemist Award in 2008, and he is also the Editor of the Journal of Physical and Chemicals Gels. He is currently W2 Professor at the University of Regensburg (Germany) and carries out his teaching and research activities through a bilateral agreement between IQAC-CSIC and this university.

### INTERVIEW

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

**Prof. David Díaz Díaz** | My research focuses on the development and studies of soft functional materials for biomedical, catalysis, sensing, coatings and energy applications. In terms of the type of materials, my major interests are in chemical and physical (supramolecular) gels, adhesives, biopolymer-based materials, and organic–inorganic hybrids. The research in all these areas is highly interdisciplinary and involves a great deal of synthesis, characterization and isolation of organic compounds, as well as a deep knowledge of the core of materials science.

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

**Prof. David Díaz Díaz** | I have been interested in organic synthesis ever since my first course in chemistry as an undergraduate student. I have always been captivated by the association between any process occurring in nature and different chemical reactions, but even more by the fact that a chemist could learn how to make molecular connections and access a large number of new structures. Organic synthesis would give me the opportunity to understand the mechanisms behind molecular connectivity, and therefore chemical properties. During my Ph.D. studies, I worked with a plethora of synthetic methods, reaction conditions, and retro-synthetic analyses that gave me the training and a valuable perspective that I needed later to pursue a fascinating journey from organic synthesis to materials science.

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

**Prof. David Díaz Díaz** | In my opinion, the need for more sustainable and orthogonal chemical processes will continue to drive the evolution of modern organic synthesis with the aim of transforming substances to enhance the quality of life. Despite the major advances in catalysis and high-throughput experimentation, organic synthesis still has vast areas to be optimized (e.g., flow chemistry, 'green' aspects,

automation). Nowadays, organic synthesis is a powerful tool for the development of multifunctional and multiresponsive materials for numerous high-tech applications. Thus, I envision the development of new synthetic methods to fulfil the requirements defined by sustainable and large-scale industrial productions. In other words, process research will establish the major criteria for the selection of appropriate synthetic methods or for the development of new ones.

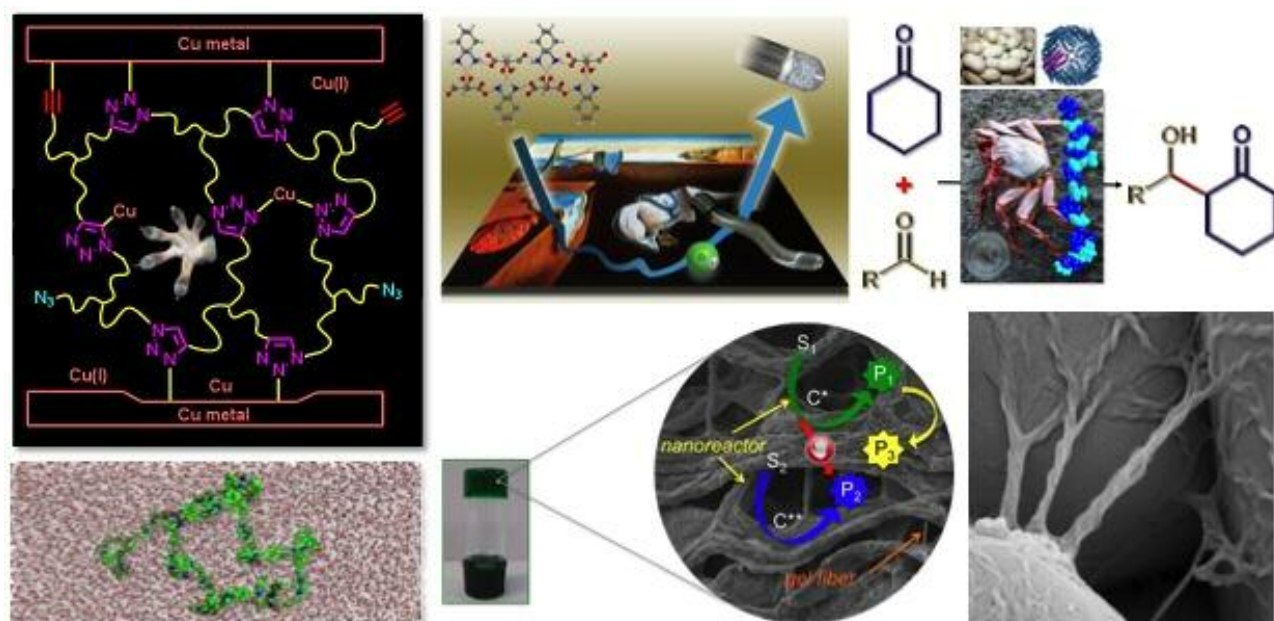
**SYNFORM** | *Your research group is active in the area of organic chemistry, catalysis and materials science. Could you tell us more about your research and its aims?*

**Prof. David Díaz Díaz** | Among my research goals, I seek to better understand the gelation phenomenon (which involves the elusive equilibrium between gelation and crystallization) and chemical reactivities inside polymer and gel networks; to evaluate the intrinsic catalytic activity of bio-polymer- and protein-based materials in different physical states; to develop conductive and sustainable adhesive polymers; and to develop new strategies for improving the stability and functionality of hybrid organic–inorganic materials. One of the aims of my research is to develop gel-based nano- and microreactors that could enhance the selectivity of chemical transformations and/or activate new reaction pathways. Moreover, I also have a particular interest in the preparation of gel-based materials with autonomous self-healing

and load-bearing properties, as well as on the use of natural polymers and proteins for the better understanding of their role in evolution and for the development of ‘greener’ catalysts. In general, I am convinced that the discovery of new versatile and functional materials with a solid prospect for practical applications is intimately associated with inexpensive, simple, sustainable and scalable processes. Thus, I am always looking for the selection of the most practical chemical approaches in order to synthesize new materials, fine-tuning specific properties, and creating new functions. In this sense, and inspired by Kelly Johnson, I would like to coin and spread the ‘KISSu’ principle (**K**ee**P** **I**t **S**imple and **S**ustainable) in modern materials synthesis.

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

**Prof. David Díaz Díaz** | During my scientific trajectory I have been immersed in different research fields, trying to understand some of the most important channels that interconnect different disciplines. In this sense, some of the most relevant contributions that I have achieved with my co-workers are the result of this career path that I decided to follow. For instance, the discovery of the 1,3-chirality transfer during the Nicholas reaction, which permitted the development of a robust methodology to access to trialkyl-substituted stereogenic carbons, or the first practical and modular



synthesis of highly versatile formamidine ureas, represent important achievements in the field of organic synthesis. On the other hand, the pioneering application of click chemistry for the synthesis of superior gel networks and metal adhesive polymers constitute seminal contributions for the use of this chemistry in the field of materials synthesis. More recently, the isolation of transient gel phases, the preparation of supramolecular self-healing metallogel networks, the development of a synergistic computational–experimental approach to improve the gelation ability of ionenes, and the demonstration of the link between physical state and catalytic activity of biopolymers and proteins, represent major achievements in the interface of different research areas. ■

*Matteo Zanda*



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## ■ A Biocompatible Alkene Hydrogenation Merges Organic Synthesis with Microbial Metabolism

*(Focus on an article from the current literature)*■ The Synthesis of  $\alpha$ -Azidoesters and Geminal Triazides*(Focus on an article from the current literature)*

## ■ Iron-Catalyzed Intermolecular Hydroamination of Styrenes

*(Focus on an article from the current literature)*

## FURTHER HIGHLIGHTS + + + +

## SYNTHESIS

## Review on: Synthesis of Aryl(di)azinylmethanes and Bis(di)azinylmethanes via Transition Metal-Catalyzed Cross-Coupling Reactions

*(by J. De Houwer, B. U. W. Maes)*

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## SYNFACTS

Synfact of the Month in category "Synthesis of Heterocycles": [Manganese-Mediated Coupling Approach to Fused Lactone-Pyrrolidinones](#)

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