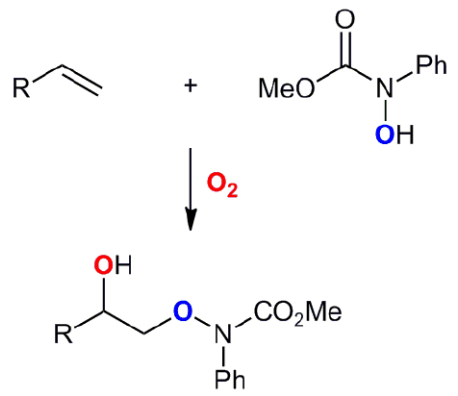
SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2012/01

SYNSTORIES

- **Metal-Free, Aerobic Dioxygenation of Alkenes Using Simple Hydroxamic Acid Derivatives**



- **Copper-Catalyzed Enantioselective Additions to Oxocarbenium Ions**

- **SYNTHESIS/*SYNLETT* Advisory Board Focus: Professor Carsten Bolm (RWTH Aachen University, Germany)**

CONTACT ++++

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Dear readers,

Administration, Teaching and Research: not necessarily in order of preference, but these are the three benchmarks of our academic profession. I am pretty sure that most of us strive to reduce the first in order to maximize the time that can be dedicated to the other two. And some of us, including myself, are lucky enough to have not too much of the second (but please don't tell to the senior management of my college...), and more time for the real fun in our fantastic profession: research! I am not saying that teaching is not rewarding, it definitely is. And I am not saying it is not very useful, not just to the students I mean: it definitely is! But most of you will agree, I am sure, that nothing is as exciting as research! I really believe that one could live one thousand years, or more, and remain in love with research like the very first day. I think you will admit that is not always like that!

And I would bet any money that passion for research was the dominant driving force for the scientists whose work is presented in this issue of ***SYNFORM***. In the first ***SYNSTORY***, Professor M. P. Watson (USA) explains how her group was able to develop an enantioselective copper(I)-catalyzed addition of terminal alkynes to isochroman acetals, which can be used to prepare chiral benzopyrans in high enantioselectivities and yields. The second ***SYNSTORY*** is focused on the work of Professor E. J. Alexanian (USA) and his new methodology for achieving a formal vicinal dioxygenation of terminal alkenes using a strikingly simple metal-free radical process. The issue is completed by an Editorial Advisory Board Profile on Professor C. Bolm (Germany).

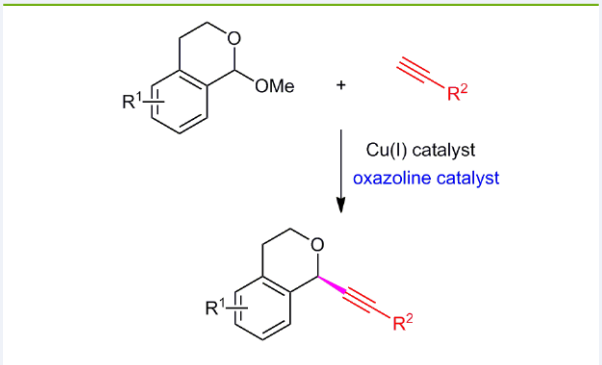
Enjoy your reading!

Matteo Zanda

Editor of ***SYNFORM***

IN THIS ISSUE

SYNSTORIES



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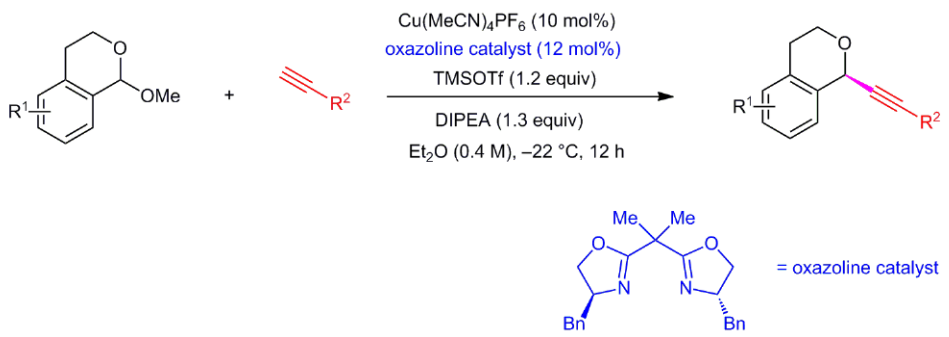
NEWS AND VIEWS NEWS AND VIEWS NEWS AND VIEWS

Copper-Catalyzed Enantioselective Additions to Oxocarbenium Ions

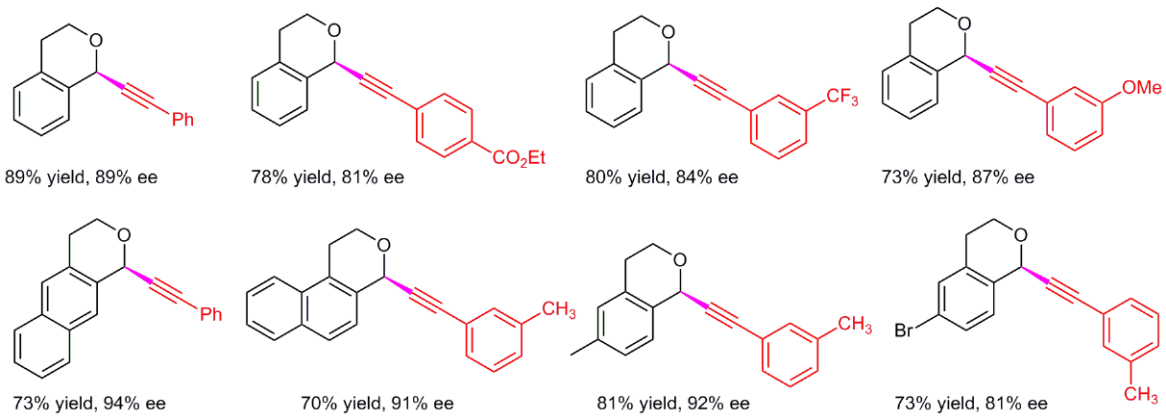
J. Am. Chem. Soc. **2011**, *133*, 17142–17145

The enantioselective addition of terminal alkynes to aldehydes and ketones is a well-established and powerful synthetic methodology that provides an effective entry to chiral propargyl alcohols in high enantiomeric purity (*J. Am. Chem. Soc.* **2011**, *133*, 1286 and references therein). In contrast, the enantioselective alkynylation of oxocarbenium ions is comparatively much less developed and this is particularly true for oxocarbenium ions derived from isochroman acetals, because their alkynylation would produce biologically important scaffolds belonging to the class of chiral substituted benzopyrans. Recently, the group of Professor Mary P. Watson from the University of Delaware (Newark, USA) reported an important breakthrough in the field: an enantioselective TMSOTf-promoted copper(I)-catalyzed addition of terminal alkynes to isochroman acetals, which can be used to prepare chiral benzopyrans in high enantioselectivities and yields. The reaction makes use of chiral oxazoline catalysts and has a significantly broad scope.

"To our knowledge, our method is the first report of a metal-based strategy to control the enantioselectivity of addi-



Some of the products of the new alkynylation reaction:



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tions to prochiral, cyclic oxocarbenium ion intermediates and the first report of enantioselective alkynylation of a racemic acetal substrate," said Professor Watson. "Previously, Eric Jacobsen (*J. Am. Chem. Soc.* **2008**, *130*, 7198) and Scott Schaus (*Angew. Chem. Int. Ed.* **2010**, *49*, 7096) had elegantly shown that chiral thiourea and diol catalysts, respectively, enable enantioselective additions to cyclic oxocarbenium ions. Lewis and Brønsted acid catalysts have also been used for enantioselective Aldol-type additions and intramolecular trans-acetalizations of acyclic oxocarbenium ions (Aldol: *Adv. Synth. Catal.* **2011**, *353*, 1927; *Angew. Chem., Int. Ed.* **2008**, *47*, 4196; *J. Am. Chem. Soc.* **2009**, *131*, 3430; *J. Am. Chem. Soc.* **2005**, *127*, 10506. Trans-acetalization: *J. Am. Chem. Soc.* **2010**, *132*, 8536), as well as Braun's allylation of a cyclic oxocarbenium ion (*Angew. Chem. Int. Ed.* **2004**, *43*, 514)," continued Professor Watson. She added that these methods illustrate that chiral organo- or Lewis acid catalysts can control additions to oxocarbenium ions. "We have now shown that chiral, metal-based catalysts can also control the enantioselectivity in additions of alkynes to oxocarbenium ions via catalytically generated organometallic intermediates," she said. "In our reaction, a chiral copper(I) acetylide is formed and then reacts with the oxocarbenium ion."

"Our use of a catalytically generated chiral metal acetylide was inspired by the enantioselective zinc-catalyzed alkynylation of aldehydes, pioneered by Erick Carreira," acknowledged Professor Watson. "Although enantioselective alkynylations of both aldehydes and ketones are known, our report is the first example of enantioselective alkynylation of an acetal substrate," she continued. Professor Watson explained that an important application of this method is that it enables the synthesis of 1-alkynyl isochromans from readily available isochroman acetals, and the alkynyl products can be easily reduced to prepare 1-alkyl-substituted isochromans, which comprise a number of important molecular targets, including natural and bioactive compounds. "Perhaps more importantly," she pointed out, "it suggests that a strategy based on metal catalysis may provide a general solution for controlling enantioselectivity in additions to oxocarbenium ion intermediates. Within my group, we are currently working to determine how general this strategy is."

Professor Watson acknowledged that her co-workers, postdoctoral fellow Dr. Prantik Maity and graduate student Harathi D. Srinivas ("Hari"), played a key role in the successful development of this project. "This project stemmed from our previous work using nickel(0) catalysts with iminium ions, generated in situ from *N*,*O*-acetals," said Professor Watson. "We were excited about using transition-metal catalysts to control reactions of electrophilic intermediates and imagined that such an approach could enable new, potentially enantioselective reactions to oxocarbenium ion intermediates. With this 'big-picture' idea in mind, Prantik began to consider that the conditions for enantioselective zinc(II)- or copper(I)-catalyzed alkynylation of aldehydes may translate to oxocarbenium ion intermediates," she recalled. "In particular, he recognized that Professor Wade Downey had shown that TMSOTf, often used to form oxocarbenium ions from acetals in situ, was compatible with zinc-catalyzed alkynylations of aldehydes (*J. Org. Chem.* **2008**, *73*, 3299). Based on this precedent," continued Professor Watson, "he quickly found conditions for the alkynylation of isochroman acetals and proceeded to optimize them and examine the scope of the enantioselective alkynylation of this substrate class. Working with Prantik, Hari performed some of the initial ligand screens that suggested that bis(oxazoline) ligands may give useful enantioselectivity in these types of transformations," she said. "Then Hari began to investigate the enantioselective alkynylation of chromene acetals, which have proven to be a more challenging substrate class in the enantioselective alkynylation. He has recently made progress toward a highly enantioselective variant, and we are optimistic that we are close to a solution for this substrate class." According to Professor Watson, Prantik has been instrumental not only in establishing the group's research in enantioselective additions to oxocarbenium ions, but also in mentoring graduate and undergraduate students. "He is a very creative chemist, always designing new reactions," she added. Professor Watson also recognized that the second co-worker, Hari, "is exceptionally hard-working and patient, two qualities that have served him well in developing the challenging enantioselective alkynylation of chromene acetals."

Professor Watson is convinced that there are exciting future perspectives and potential developments for this type of chemistry. "As we show in the paper, we are investigating copper-catalyzed alkynylations of other cyclic acetals. Hari has made substantial progress toward the development of a highly enantioselective alkynylation of chromene acetals," she revealed. "Ultimately, we hope to show that this strategy of using metal-based catalysts will enable a variety of enantioselective transformations of prochiral oxocarbenium ion intermediates," Professor Watson concluded.

Matteo Zanda

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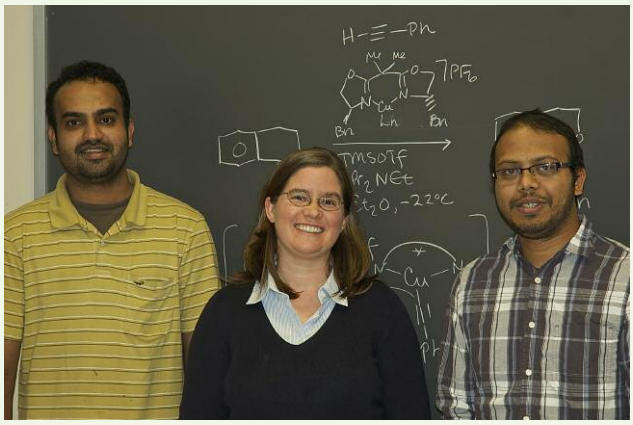

From left: H. D. Srinivas ("Hari"), Prof. M. P. Watson, Dr. P. Maity

Professor Mary P. Watson grew up in Tampa, Florida (USA), and earned her A.B. from Harvard University, working with Professor David Evans. Mary earned her Ph.D. (2006) under the direction of Professor Larry Overman at the University of California, Irvine (USA), where she studied the enantioselective palladium-catalyzed allylic imidate rearrangement. For part of this work, Mary and Professor Overman collaborated with Professor Bob Bergman at the University of California, Berkeley (USA), where she conducted kinetic and computational studies of the rearrangement. As a National Institutes of Health NRSA postdoctoral fellow in Professor Eric Jacobsen's group at Harvard University (USA), she developed an enantioselective nickel-catalyzed olefin arylcyanation via activation of C–CN bonds. She began her independent career at the University of Delaware in July 2009. Mary's research is focused on the development of new catalytic reactions, particularly enantioselective transformations.

Dr. Prantik Maity is a postdoctoral fellow in Professor Watson's group. Originally from West Bengal (India), he earned his B.Sc. from the University of Calcutta and his M.Sc. from the Indian Institute of Technology in Madras. His Ph.D. research was conducted at the University of Regensburg (Germany) and was focused on the development of new chiral heterocyclic peptide mimics with Professor Burkhard König. He did his first postdoctoral fellowship with Professor Bernhard Breit at the University of Freiburg (Germany), working on self-assembled asymmetric catalysts. Prantik joined Watson's group in October 2009, just a few months after she started at the University of Delaware.

Harathi D. Srinivas ("Hari") is one of the first graduate students in Professor Watson's group; he joined the research group on the very first day (June 2009). He is originally from Hyderabad (India) and earned his B.Sc. and his M.Sc. at Osmania University in Hyderabad. He then worked in custom synthesis at Dr. Reddy's Laboratories, Ltd. (India), before starting his Ph.D. studies at the University of Delaware in early 2009.

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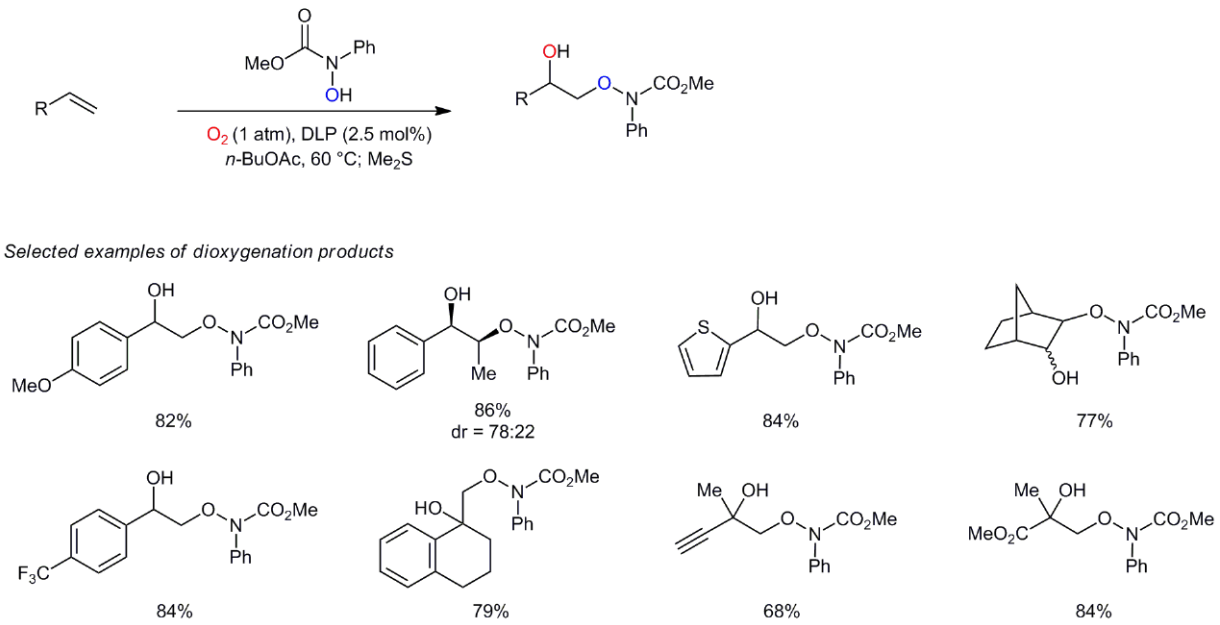
Metal-Free, Aerobic Dioxygenation of Alkenes Using Simple Hydroxamic Acid Derivatives

J. Am. Chem. Soc. **2011**, *133*, 13320–13322

Alkene difunctionalizations are an important class of reactions that incorporate vicinal heteroatomic functionality in simple alkene substrates. However, current methods for alkene difunctionalization rely on the use of highly toxic and/or expensive transition-metal catalysts (e.g., osmium), which is a major drawback to the use of these methods in organic synthesis. Recently, the group of Professor Erik J. Alexanian from the University of North Carolina at Chapel Hill (USA) reported a new methodology for achieving a formal vicinal dioxygenation of terminal alkenes using a strikingly simple metal-free radical process relying on the use of oxygen as an oxidant, dilauroyl peroxide as initiator, and simple hydroxamic acid derivatives as reagents.

"Our group seeks to develop new, general approaches to the synthesis of functionalized organic compounds through the metal-free difunctionalization of alkenes using hydroxamic acids," said Professor Alexanian. "Our initial work developed alkene dioxygenations and oxyaminations using unsaturated hydroxamic acids (*Angew. Chem. Int. Ed.* **2010**, *49*, 4491; *J. Am. Chem. Soc.* **2011**, *133*, 11402). In the next phase of this project, we asked ourselves: could the alkene dioxygenation take place via an intermolecular addition process?" he continued. Professor Alexanian revealed that he and the two co-authors of the paper, Ben C. Giglio and Valerie A. Schmidt, were concerned for two main reasons: 1) there were no general synthetic methods involving the intermolecular addition of oxygen-centered radicals to alkenes, and 2) the activation entropy of such a process was greater than in their previous intramolecular work. Indeed, their initial efforts utilizing simple acylated *N*-phenylhydroxylamine derivatives were met with limited success, as yields were low and several by-products were observed.

"Ben Giglio, now a third-year in the group, had the idea to try a related hydroxamic acid derivative formed from the condensation of methyl chloroformate and *N*-phenylhydroxylamine," recalled Professor Alexanian. "This proved to be crucial to obtaining the desired reactivity." According to Professor Alexanian, one major side-reaction this particular hydroxamate eliminates is the undesired *N*-to-*O* acyl migration of the hydroxamic acid prior to amidoxyl radical alkene



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addition. "We had observed this side-reaction in a number of our initial experiments," he said. "This simple reagent proved to be an excellent source of the amidoxyl radical for the metal-free, aerobic dioxygenation of a wide variety of unsaturated hydrocarbons. We view the amidoxyl radical as a useful, general source of oxygen-centered radicals for chemical synthesis," said Professor Alexanian. "Our current efforts are focused on applying this approach to additional difunctionalization processes, as well as developing asymmetric variants," he concluded.

Matteo Zanda

About the authors

From left: B. C. Giglio, V. A. Schmidt, Prof. E. J. Alexanian

Ben C. Giglio was born in Richmond, VA (USA). He received his B.S. degree in chemistry from the University of Richmond in 2009 before beginning a Ph.D. at UNC Chapel Hill.

Valerie A. Schmidt was born in western Maryland in 1985. She received her B.S. degree in chemistry from Towson University, MD (USA) in 2007. Valerie is currently a Burroughs-Wellcome Fellow working under the supervision of Professor Erik J. Alexanian at UNC Chapel Hill.

Erik J. Alexanian was born and raised in Boston, MA (USA). He received his A.B. degree in chemistry from Harvard University (USA) in 2001. Erik went on to earn his Ph.D. in 2006 from Princeton University (USA) under the supervision of Professor Erik J. Sorensen where he contributed to the total synthesis of the furanosteroid viridin and developed new metal-catalyzed alkene difunctionalizations. Following a postdoctoral stay with Professor John F. Hartwig at the University of Illinois at Urbana-Champaign (USA), Erik joined the faculty at UNC Chapel Hill where he is currently an Assistant Professor.

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SYNTHESIS/*SYNLETT* Advisory Board Focus: Professor Carsten Bolm (RWTH Aachen University, Germany)

Background and Purpose. ***SYNFORM*** will from time to time portrait **SYNTHESIS/*SYNLETT*** Advisory Board members who answer several questions regarding their research interests and revealing their impressions and views on the developments in organic chemistry as a general research field. In this issue, we present Professor Carsten Bolm, RWTH Aachen University (Germany).

BIOGRAPHICAL SKETCH

Prof. C. Bolm

Carsten Bolm was born and raised in Braunschweig (Germany). He studied chemistry at the Technical University of Braunschweig and at the University of Wisconsin in Madison (USA). In 1987 he finished his doctoral work with Professor Reetz in Marburg (Germany). After postdoctoral studies at MIT, Cambridge (USA), with Professor Sharpless, he began to work on his habilitation at the University of Basel (Switzerland) in the group of Professor Giese. In 1993 he became Professor of Organic Chemistry at the University of Marburg (Germany), and since 1996 he is Full Professor for Organic Chemistry at the RWTH Aachen University (Germany). Over the past 20 years Carsten Bolm has held visiting professorships at several universities in Europe, Japan and the USA.

The list of awards he has received include the Heinz-Maier-Leibnitz Prize, the ADUC-Jahrespreis for Habilitands, the Annual Prize for Chemistry of the Akademie der Wissenschaften zu Göttingen, the Otto-Klung Prize, the Otto-Bayer Award, a Fellowship of the Japan Society for the Promotion of Science, the Prix Franco-Allemand by the Société Francaise de Chimie and the Boehringer Ingelheim Lectureship (Canada).

Besides being on the **SYNTHESIS/*SYNLETT*** Advisory Board, Carsten Bolm is also an Associate Editor for the *Journal of Organic Chemistry* and member of several Editorial Advisory Boards of international chemistry journals.

INTERVIEW

SYNFORM | *Professor Bolm, what are your main current research interests?*

C. Bolm | My current interests are in the area of asymmetric metal catalysis/organocatalysis, in the synthesis and study of novel sulfur compounds (in catalysis and bio-directed chemistry), as well as in the search for reactivity with and without metals.

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

C. Bolm | I think there are several important contributions from my group: the first asymmetric metal-catalyzed Baeyer–Villiger reaction (*Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1848), the discovery of a highly enantioselective vanadium catalyst for asymmetric sulfide-to-sulfoxide oxidations (*Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2640), the development of highly enantioselective anhydride openings and aryl transfer reactions (*J. Org. Chem.* **2000**, *65*, 6984; *J. Am. Chem. Soc.* **2002**, *124*, 14850), and the introduction of novel sulfur compounds as chiral ligands and bioactive agents (*J. Am. Chem. Soc.* **2001**, *123*, 3830; *Angew. Chem. Int. Ed.* **2008**, *47*, 8920; *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4888).

SYNFORM | *Can you mention a recent discovery in the area of organic chemistry, which you consider to be particularly important?*

C. Bolm | Definitely, the C–H functionalizations of unreactive substrates.

SYNFORM | *What is the main goal in your scientific career?*

C. Bolm | To help mankind.

SYNFORM | *Do you have hobbies, besides chemistry?*

C. Bolm | My hobbies are my family and sports in general.

Matteo Zanda

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COMING SOON ▶▶ COMING SOON ▶▶

SYNFORM 2012/02 is available from January 19, 2012

In the next issues:

SYNSTORIES

Tuning Chemoselectivity in Iron-Catalyzed Sonogashira-Type Reactions
(Focus on an article from the current literature)

Enantioselective Preparation and Chemoselective Cross-Coupling of 1,1-Diboron Compounds
(Focus on an article from the current literature)

FURTHER HIGHLIGHTS

SYNTHESIS
Review on: Synthesis of Carbo- and Heterocycles via Coupling–Isomerization Reactions
(by T. J. J. Müller)

SYNLETT
Account on: SmI_2-Mediated Carbonyl–Alkene Couplings for the Synthesis of Small Carbocyclic Rings
(by H. Y. Harb, D. J. Procter)

SYNFACTS
Synfact of the Month in category "Synthesis of Natural Products and Potential Drugs": Synthesis of Pyripyropene A

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