

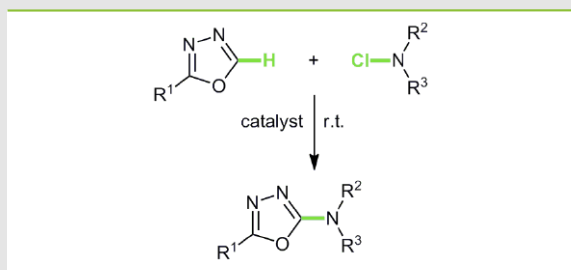
SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2010/08

SYNSTORIES

■ **A New Entry of Amination Reagents for Heteroaromatic C–H Bonds: Copper-Catalyzed Direct Amination of Azoles with Chloroamines at Room Temperature**



■ **Three-Component Domino Reaction Using the Bestmann–Ohira Reagent: A Regioselective Synthesis of Phosphonyl Pyrazole**

■ **Thieme Chemistry Journals Editorial Board Meetings 2010**

CONTACT +++++

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



Dear readers,

It's a real pleasure to write this brief editorial while quietly travelling on a train in the beautiful Italian countryside between Pesaro and Bologna. I had a delightful breakfast this morning with a cappuccino and a hot croissant,

and I feel really peaceful now. To be honest, there is railway strike today and I am not quite sure how I will be able to continue my travel after Milan, but that's part of the pleasures and pains of being in Italy. In the worst case I will just wait for the next train in a restaurant, enjoying a good pizza. Or even two, if the next train will be really late...

Once again, I realize I am writing about food, so let's switch to the real topic: good chemistry, as usual. The first **SYNSTORY** of this issue is about a novel multicomponent reaction leading to phosphonyl pyrazoles, developed by M. Smietana and J.-J. Vasseur (France). The second covers a novel amination reaction of heteroaromatic C–H bonds, as reported by M. Miura (Japan). The issue is closed by a short report on the last Thieme Chemistry Journals Editorial Board Meeting 2010 in Florence (Italy).

Meanwhile I am just arrived at the Central Railway Station of Milan. The departures' big screen is desolately empty. I am afraid I will have to make plans for dinner too...

Enjoy your reading!

Matteo Zanda

Editor of SYNFORM

CONTACT ++++

If you have any questions or wish to send feedback, please write to Matteo Zanda at:
Synform@chem.polimi.it

IN THIS ISSUE

SYNSTORIES ■ ■ ■ ■

Three-Component Domino Reaction Using the Bestmann–Ohira Reagent: A Regioselective Synthesis of Phosphonyl Pyrazole..... **A66**

A New Entry of Amination Reagents for Heteroaromatic C–H Bonds: Copper-Catalyzed Direct Amination of Azoles with Chloroamines at Room Temperature..... **A68**

Thieme Chemistry Journals Editorial Board Meetings 2010..... **A70**

COMING SOON **A71**

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

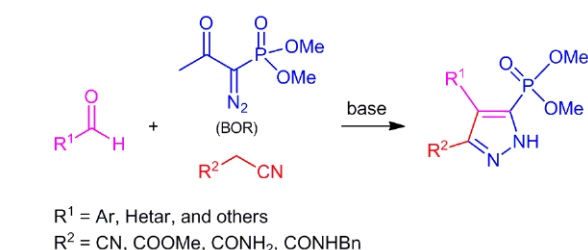
Three-Component Domino Reaction Using the Bestmann–Ohira Reagent: A Regioselective Synthesis of Phosphonyl Pyrazole

Angew. Chem. Int. Ed. **2010**, *49*, 3196–3199

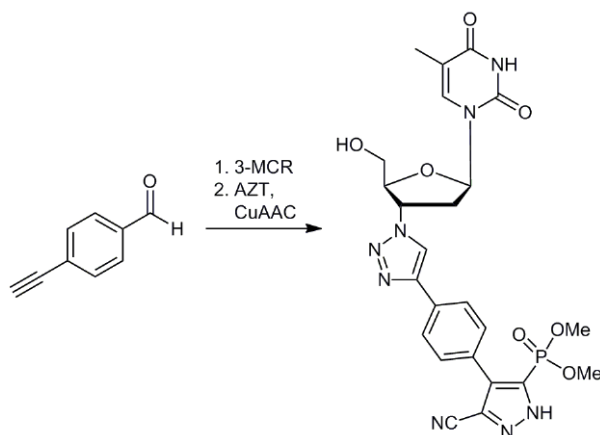
■ No one who has given even a passing glance to the literature of organic chemistry will have failed to note a flourishing development of step-economic reactions that achieve multiple bond formations in one operation. In this context, multicomponent reaction (MCR) processes usually satisfy most criteria (readily available starting reagents, atom-economical, environmentally friendly, etc.) required for ideal organic syntheses. Undoubtedly, such reactions offer an efficient way to generate complex molecular frameworks due to their inherent convergence and complexity-generating ability.

“One of the biggest challenges for synthetic chemists working in the field of MCR is to match the reactivity of the starting materials while at the same time anticipate the compatibility of the intermediates generated in situ,” said Dr. Michael Smietana from the University of Montpellier 2 (France). “Directed towards these objectives, we have developed a new one-pot multicomponent reaction for the synthesis of variously substituted 5-dimethoxyphosphonyl pyrazoles starting from aldehydes, cyanoacid derivatives and the Bestmann–Ohira reagent (BOR). This reagent is a well-known compound commonly used to prepare alkynes from aldehydes under mild reaction conditions,” he explained.

Originally, according to Dr. Smietana, the project started during early work in the group of Dr. Jean-Jacques Vasseur devoted to the development of a one-pot synthesis of 1,2,3-triazoles from aldehydes through a Seyferth–Gilbert homologation/CuAAC reaction sequence (*Synlett* **2007**, 3037). In one experiment performed on an activated substrate, the researchers observed the presence of an unknown and obviously unwanted product. “Dr. Kishor Mohanan, a post-doctoral fellow at that time in our laboratory, carefully examined the reaction and screened various substrates and reaction conditions,” said Dr. Smietana. “From this study, it became obvious that the Bestmann–Ohira reagent could react with activated derivatives to yield phosphonyl pyrazoles.” Searching the literature revealed that Namboothiri’s team from the IIT–Bombay (Mumbai, India) had described the synthesis of phos-



phonylpyrazoles from nitroalkenes and the Bestmann–Ohira reagent (*Org. Lett.* **2007**, *9*, 1125). “Unfortunately, that reaction is restricted to aryl- and heteroaryl nitroalkenes,” explained Dr. Smietana. “We then hypothesized a MCR in the presence of the Bestmann–Ohira reagent involving readily available aldehydes, where Knoevenagel adducts could be generated from aldehydes faster than the homologation reaction. To our great satisfaction, the three-component reaction between Bestmann–Ohira reagent, an aldehyde, and various cyanoacid derivatives afforded the expected phosphonyl pyrazoles in high yield.”



“Our methodology involves a domino Knoevenagel condensation/formal 1,3-dipolar cycloaddition sequence,” said Dr. Smietana. “To the best of our knowledge this represents the first example where the Bestmann–Ohira reagent is used in a multicomponent reaction and in the presence of an aldehyde without leading to the expected homologated alkyne.”

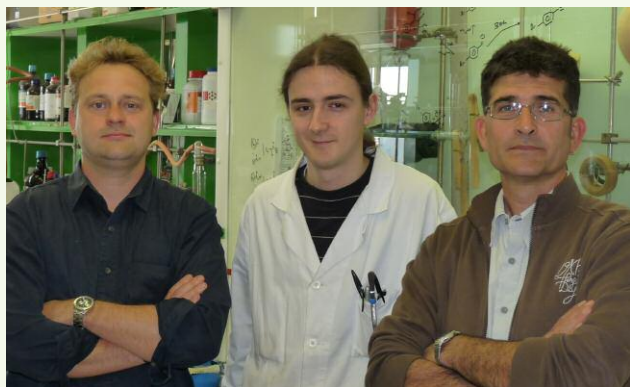
The remarkable feature of this MCR is that trisubstituted phosphonyl pyrazoles can be accessed regioselectively in a one-pot procedure, using one single method for all cases. “Moreover, it has a broad scope as aromatic, heteroaromatic and aliphatic aldehydes can be used,” confirmed Dr. Smietana, who also acknowledged the contribution of Anthony R. Martin.

“He studied the scope and limitations of the reaction and combined the MCR with a copper-catalyzed azide–alkyne 1,3-dipolar cycloaddition (CuAAC) to generate two heterocycles and five new bonds in a sequential one-pot procedure,” said Dr. Smietana.

“We anticipate that this method will be useful to medicinal or agrochemical chemists, who need access to phosphonyl pyrazole based scaffolds. In the meantime,” he concluded, “the extension of this methodology is in progress.”

Matteo Zanda

About the authors



From left: Dr. M. Smietana, A. R. Martin, Dr. J.-J. Vasseur

Michael Smietana was born in Créhange (France) in 1973. He studied at the École Normale Supérieure (ENS Ulm) in Paris from 1996 to 1999. After undergraduate studies at the ENS in the laboratory of Dr. Christian Rolando, he received his Ph.D. in 2001 under the guidance of the late Professor Charles Mioskowski at the University of Strasbourg (France). Afterwards, he worked as a postdoctoral fellow for two years in the group of the Professor Eric Kool at Stanford University (USA). In 2004, he moved to the University of Montpellier 2 (France), where he was appointed as Assistant Professor at the Max Mousseron Institute of Biomolecules (IBMM) in the group of Dr. J.-J. Vasseur. His current research interests focus on the development of new synthetic methodologies for the preparation of novel bioactive molecules such as DNA and RNA analogues.

Jean-Jacques Vasseur was born in Oran (Algeria) in 1958. He joined the CNRS in 1984 and received his Ph.D. (1988) from the University of Montpellier under the mentorship of Professor Jean-Louis Imbach and Dr. Bernard Rayner. From 1990 to 1992 he was a visiting scientist at Isis Pharmaceuticals in Carlsbad (USA) where he developed oligonucleotide analogues as anti-sense therapeutic agents. In 1993, he returned to Montpellier

where he was appointed Research Director at the CNRS in 1998. He is currently co-director of IBMM and team leader of the “Modified Oligonucleotides” group of the institute. He is also a board member of the International Society of Nucleosides, Nucleotides and Nucleic Acids. His research interests include various aspects of nucleic acid chemistry focusing on the design of chemically modified DNAs and RNAs and their conjugates for therapeutic and diagnostic applications.

Anthony R. Martin was born in Sète (France) in 1984. He graduated from the University of Montpellier 2 in 2008 with a Master’s degree in organic and biomolecular chemistry. He is currently pursuing his Ph.D. at the University of Montpellier 2 under the supervision of Drs. J.-J. Vasseur and M. Smietana.



Dr. K. Mohanan

Kishor Mohanan was born in 1979 and raised in Thodupuzha, Kerala State (India). He received his Ph.D. degree in 2007 under the guidance of Dr. G. Vijay Nair at the National Institute for Interdisciplinary Science and Technology, CSIR Trivandrum (India). After two years of postdoctoral work in Professor B.-J. Uang’s laboratory at the National Tsing Hua University (Taiwan), he went on to pursue postdoctoral research under the guidance of Drs. M. Smietana and J.-J. Vasseur in Montpellier. Currently he is a postdoctoral associate with Professor J. Rodriguez at the Paul Cezanne University, Aix-Marseille III (France).

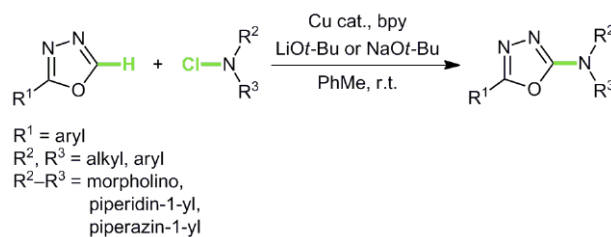
Loïc Toupet was born in Rennes (France) in 1949. He obtained his Ph.D. in molecular sciences at the University of Rennes in 1976 (under the supervision of Professor R. Carrié). He is currently a crystallographic specialist and a project leader (phase transition, pulse laser and LIESST) in the group of Professor E. Collet at the Institute of Physics in Rennes.

A New Entry of Amination Reagents for Heteroaromatic C–H Bonds: Copper-Catalyzed Direct Amination of Azoles with Chloroamines at Room Temperature

J. Am. Chem. Soc. **2010**, *132*, 6900–6901

Over the last decade, transition-metal-mediated or -catalyzed reactions involving a C–H bond cleavage have received much attention and the area has grown rapidly because of the possibility of transforming ubiquitous C–H bonds into versatile functions in just one synthetic step. In 1997, Professor Masahiro Miura and co-workers from Osaka University (Japan) reported the palladium-catalyzed direct arylation of phenolic compounds with aryl halides (*Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740), which is one of the pioneering works in the field of C–H bond activation chemistry. Subsequently, they demonstrated that the reaction conditions were effective for the direct arylation of heteroaromatic azole compounds too (*Bull. Chem. Soc. Jpn.* **1998**, *71*, 467). Since then, the group of Professor Miura has contributed greatly to the development of this research area. In the course of their studies, the Japanese scientists found that a copper co-catalyst dramatically enhanced the efficiency of the direct C–H arylation of certain azoles and affected the regioselectivity of the reaction. “The cost-efficient first transition elements including copper would provide new opportunities for C–H bond functionalization,” said Professor Miura. Indeed, the group recently succeeded in the direct C–C bond-forming reactions of the heteroarenes by nickel (*Org. Lett.* **2009**, *11*, 1737; *Org. Lett.* **2009**, *11*, 4156; *Angew. Chem. Int. Ed.* **2010**, *49*, 2202) as well as copper catalysis (*Org. Lett.* **2009**, *11*, 3072; *J. Org. Chem.* **2010**, *75*, 1764; *Org. Lett.* **2010**, *12*, 2358). The relevant reactions using first transition metal catalysts have also been developed concurrently by other groups (for a leading review, see: *Synthesis* **2009**, 4087).

“Around the same time, Lei and Jarvo investigated and developed the synthetic potential of chloroamines and -amides as an electrophilic nitrogen source in, respectively, the copper- (*Angew. Chem. Int. Ed.* **2008**, *47*, 6414) and nickel-catalyzed (*J. Am. Chem. Soc.* **2009**, *131*, 15598) reactions with organometallic compounds,” explained Professor Miura. “These leading examples encouraged us to explore the catalytic direct C–H amination with chloroamines. Thus, it was conceived that an appropriate copper or nickel catalyst would allow chloroamine to serve as an effective amination reagent for aromatic C–H bonds,” he continued.



“Our methodology has several advantages compared to the precedent C–H amination reactions: (1) the *intermolecular* direct C–H amination is possible even at room temperature, (2) the use of chloroamines enables the *external-oxidant-free* conditions, and (3) aminoazoles, which are of great importance in biological and pharmaceutical sciences, are now readily accessible. Further elucidation of the reaction mechanism would help in expanding the scope of arenes and chloroamines that have great potential in C–H amination chemistry,” explained Professor Miura.

“A combination of further development of new catalyst systems and introduction of a new type of reagent opens the door to truly useful and practical synthetic transformations based on C–H activation chemistry,” he concluded.

Matteo Zanda

About the authors



Prof. M. Miura

Masahiro Miura is Professor at the Graduate School of Engineering, Osaka University (Japan). He studied chemistry at Osaka University and received his Ph.D. in 1983 under the guidance of Professors S. Kusabayashi and M. Nojima. After working in the chemical industry for one and a half years, he started his academic career as Research Associate at Osaka University. He was promoted to Associate Professor in 1994 and to

Full Professor in 2005. He also worked as a Humboldt fellow with Professor K. Griesbaum at Karlsruhe University (Germany) from 1990 to 1991. His current research interests include transition-metal catalysis and the synthesis of functional molecules, especially new π -conjugated aromatic substances.



Prof. T. Satoh

Tetsuya Satoh is Associate Professor at the Graduate School of Engineering, Osaka University. He received his Ph.D. in 1998 from Osaka University under the supervision of Professors M. Nomura and M. Miura. He was appointed as Assistant Professor at Osaka University in 1995. He did his postdoctoral work with Prof. W. D. Jones at University of Rochester (USA) from 2000 to 2001. In 2005, he was appointed as Associate Professor at

Osaka University. His current research interests are in the areas of organometallic chemistry and catalysis.



Prof. K. Hirano

Koji Hirano was born in Aichi (Japan) in 1980. He received his B.S. degree and Ph.D. from Kyoto University (Japan) in 2003 and 2008 under the supervision of Professor Koichiro Oshima. He served as a JSPS post-doctoral fellow, working with Professor Tamio Hayashi at Kyoto University from April to September of 2008. He has been an Assistant Professor at Osaka University since October 2008. His current research interests are

organic synthesis and organometallic chemistry, especially the development of new synthetic reactions catalyzed by transition-metal catalysts.



T. Kawano

Tsuyoshi Kawano was born in Osaka (Japan) in 1985. He earned his B.S. in 2008 at Wakayama University (Japan) under the guidance of Professor Waro Nakanishi. In 2008, he joined Professor Masahiro Miura's research group and obtained his M.S. degree at Osaka University in 2010. He is currently a researcher at SDS Biotech K.K.

Thieme Chemistry Journals Editorial Board Meetings 2010

■ The 2010 Editorial Boards Meeting of the Thieme Chemistry journals **SYNLETT**, **SYNTHESIS** and **SYNFACTS**, including the supplement **SYNFORM**, took place on 21st and 22nd of May 2010 in the city of Florence (Italy). The Editorial Boards of the three journals and the staff of the Thieme Chemistry editorial office met at the Grand Hotel Villa Medici. A great deal of attention was devoted to the current difficult global financial and economic situation that, not surprisingly, is also having an impact on the world of scientific publishing. However, this is not expected to have a significant effect on the high standards featured by the Thieme Chemistry journals, which will continue to offer the usual high quality at affordable prices to the organic chemistry community.

In Florence, the Editorial Board members were keen to take full advantage of the vibrant local artistic and cultural atmosphere, with a short tour in the “Galleria degli Uffizi” museum and visits to remarkable restaurants and “trattorie”, enjoying the fantastic local food and wine. Everybody returned home with an unforgettable cultural experience, and perhaps also a couple of extra kilograms... ■

Matteo Zanda



COMING SOON ►► COMING SOON ►►

SYNFORM 2010/09 is available from August 23, 2010

In the next issues:

SYNSTORIES ■ ■ ■ ■ ■

■ Quaternary Ammonium (Hypo)iodite Catalysis for Enantioselective Oxidative Cycloetherification

(Focus on an article from the current literature)

■ In vivo Chemistry for Pretargeted Tumor Imaging in Live Mice

(Focus on an article from the current literature)

FURTHER HIGHLIGHTS + + + +

SYNTHESIS

Review on: Piperazine Scaffolds via Isocyanide-Based Multicomponent Reactions

(by A. Dömling)

SYNLETT

Account on: Sustainability in Catalysis – Concept or Contradiction?

(by B. Plietker)

SYNFACTS

Synfact of the Month in category “Metal-Catalyzed Asymmetric Synthesis and Stereoselective Reactions”: [Regiocontrol in the Nickel-Catalyzed Aldehyde-Alkyne Reductive Coupling](#)

CONTACT + + + +

Matteo Zanda,
NRP Chair in Medical Technologies
Institute of Medical Sciences
University of Aberdeen
Foresterhill, Aberdeen, AB25 2ZD, UK
and
C.N.R. – Istituto di Chimica del Riconoscimento Molecolare,
Via Mancinelli, 7, 20131 Milano, Italy,
e-mail: Synform@chem.polimi.it, fax: +39 02 23993080

Editor

Matteo Zanda, NRP Chair in Medical Technologies, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, AB25 2ZD, UK and
C.N.R. – Istituto di Chimica del Riconoscimento Molecolare
Via Mancinelli, 7, 20131 Milano, Italy
Synform@chem.polimi.it
Fax: +39 02 23993080

Editorial Office

- Managing Editor: Susanne Haak,
susanne.haak@thieme.de, phone: +49 711 8931 786
- Scientific Editor: Selena Boothroyd,
selena.boothroyd@thieme.de
- Scientific Editor: Stefanie Baumann,
stefanie.baumann@thieme.de, phone: +49 711 8931 776
- Senior Production Editor: Thomas Loop,
thomas.loop@thieme.de, phone: +49 711 8931 778
- Production Editor: Helene Deufel,
helene.deufel@thieme.de, phone: +49 711 8931 929
- Production Assistant: Thorsten Schön,
thorsten.schoen@thieme.de, phone: +49 711 8931 781
- Editorial Assistant: Sabine Heller,
sabine.heller@thieme.de, phone: +49 711 8931 744
- Marketing: Thomas Krimmer,
thomas.krimmer@thieme.de, phone: +49 711 8931 772
- Postal Address: SYNTHESIS/SYNLETT/SYNEFACTS, Editorial Office,
Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany,
phone: +49 711 8931 744, fax: +49 711 8931 777
- Homepage: www.thieme-chemistry.com

Publication Information

SYNFORM will be published 12 times in 2010 by Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, and is an additional online service for SYNTHESIS, SYNLETT and SYNEFACTS.

Publication Policy

Product names which are in fact registered trademarks may not have been specifically designated as such in every case. Thus, in those cases where a product has been referred to by its registered trademark it cannot be concluded that the name used is public domain. The same applies as regards patents or registered designs.

Ordering Information for Print Subscriptions to SYNTHESIS, SYNLETT and SYNEFACTS

The Americas: Thieme Publishers New York, Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA.

To order: customerservice@thieme.com or use the Web site facilities at www.thieme-chemistry.com, phone: +1 212 760 0888

Order toll-free within the USA: +1 800 782 3488

Fax: +1 212 947 1112

Airfreight and mailing in the USA by Publications Expeditors Inc., 200 Meacham Ave., Elmont NY 11003. Periodicals postage paid at Jamaica NY 11431.

Europe, Africa, Asia, and Australia: Thieme Publishers Stuttgart, Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany.

To order: customerservice@thieme.de or use the Web site facilities at www.thieme-chemistry.com.

Phone: +49 711 8931 421; Fax: +49 711 8931 410

Current list prices are available through www.thieme-chemistry.com.

Online Access via Thieme-connect

The online versions of SYNFORM as well SYNTHESIS, SYNLETT and SYNEFACTS are available through Thieme-connect (www.thieme-connect.com/ejournals) where you may also register for free trial accounts. For information on multi-site licenses and pricing for corporate customers as well as backfiles please contact our regional offices:

The Americas: esales@thieme.com, phone: +1 212 584 4695

Europe, Africa, Asia, and Australia: eproducts@thieme.de, phone: +49 711 8931 407

Manuscript Submission to SYNTHESIS and SYNLETT

Please consult the Instructions for Authors before compiling a new manuscript. The current version and the Word template for manuscript preparation are available for download at www.thieme-chemistry.com. Use of the Word template helps to speed up the refereeing and production process.

Copyright

This publication, including all individual contributions and illustrations published therein, is legally protected by copyright for the duration of the copyright period. Any use, exploitation or commercialization outside the narrow limits set by copyright legislation, without the publisher's consent, is illegal and liable to criminal prosecution. This applies translating, copying and reproduction in printed or electronic media forms (databases, online network systems, Internet, broadcasting, telecasting, CD-ROM, hard disk storage, microcopy edition, photomechanical and other reproduction methods) as well as making the material accessible to users of such media (e.g., as online or offline backfiles).

Copyright Permission for Users in the USA

Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by Georg Thieme Verlag KG Stuttgart · New York for libraries and other users registered with the Copyright Clearance Center (CCC) Transactional Reporting Service, provided that the base fee of US\$ 25.00 per copy of each article is paid directly to CCC, 22 Rosewood Drive, Danvers, MA 01923, USA, 0341-0501/02.