SYNSTORIES

- Regioselective Reactions of 3,4-Pyridynes Enabled by the Aryne Distortion Model
- Synthesis of Fluorenones via Quaternary Ammonium Salt Promoted Intramolecular Dehydrogenative Arylation of Aldehydes
- Palladium(0)-Catalyzed Alkynylation of C(sp³)–H Bonds
- Cobalt-Catalyzed C4-Selective Direct Alkylation of Pyridines

CONTACT

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

I am writing this editorial in the bar of a rather posh Hotel in Brussels, while enjoying a very good Belgian beer. What am I doing here? Well... you could easily guess... it’s European Commission stuff. More precisely, EU project evaluations. I can’t say more; it’s confidential, you know. I can easily see what you are thinking now: I am here in this posh Hotel because I am taking advantage of European taxpayers’ money. Well, that’s not true... we get a lump sum from the European Commission, and we can save on that or rather waste it all in a posh Hotel like this one. I like this place, I see it as a reward and I try to make the most of these situations, which don’t happen every day. It’s a perfect situation for thinking and writing. Writing this editorial for example, right now there is classical music in the background – honestly I would prefer Michael Bublé in this situation... but that’s still OK. So, let’s try to remember why I am writing these things... oh yes, of course! It’s SYNFORM! And it’s a great issue of SYNFORM, by the way! The first SYNSTORY is about a new powerful method for achieving alkylation of pyridines on C-4, developed by Professor M. Kanai (Japan). Next, we have the conceptually innovative synthesis of xanthones and fluorenone proposed by Professor F. Glorius (Germany). The third SYNSTORY leads us into the intriguing world of pyridynes (not pyridines!) that was recently explored by Professor N. K. Garg (USA). Finally, we jump into the hot-area of C(sp^3)–H bond functionalizations under the expert guidance of Professor J.-Q. Yu (USA). It’s a heavy load of great chemistry!

Enjoy your reading!

Matteo Zanda

Editor of SYNFORM

PS. And I am still enjoying my Belgian beer ;-)
The nucleophilic addition of organometallic reagents to electrophiles is a fundamental C–C bond-forming reaction in organic synthesis. The generation of nucleophilic organometallic reagents, however, generally requires stoichiometric amounts of strong bases and/or reducing metals, such as Mg and Li, and stoichiometric salt waste is therefore inevitably produced. Thus, the development of atom-economical processes, involving the catalytic generation of nucleophilic organometallic species without any stoichiometric amounts of activating reagents, is highly desirable.

The group of Professor Motomu Kanai at The University of Tokyo (Japan) is trying to develop new methods to catalytically generate nucleophilic active species in situ under first-row transition-metal catalysis (for related recent works in this direction, see also: Angew. Chem. Int. Ed. 2013, 52, 2207 for the generation of nucleophilic aryl-Co species). In the communication covered by this article, Professor Kanai and Dr. Shigeki Matsunaga reported the utility of a low-valent ‘Co-hydride’ species for the generation of nucleophilic alkyl-Co species in the functionalization of pyridines at the C4-position. Although there are many reports on (catalytic) C2-selective pyridine functionalization by using the Lewis basic sp2-nitrogen atom in the pyridine ring as a directing group, examples of direct C4-selective functionalization are quite limited (see the works of Nakao and Hiyama as well as Ong, refs. 10a and 10b in the original paper). Professor Kanai said: “To realize C4-selective functionalization in a different manner from previous reports based on an oxidative addition/insertion/reductive elimination sequence under Ni(0) catalysis, we utilized ‘Co-hydride’ species.” He continued: “Our working hypothesis was as follows (see Scheme 1): Hydrometallation of alkenes with a metal hydride catalyst affords an alkyl-metal species. If the alkyl-metal species has sufficient nucleophilicity, its addition to pyridine would afford a dihydropyridine intermediate. To realize an atom-economical catalytic process, re-aromatization of pyridine without any oxidants and regeneration of the metal-hydride catalyst are the keys for success.”

After intensive screening and optimization studies to fulfill the above-mentioned requirements, the Japanese researchers found that the Co salt in combination with LiEt3BH was quite effective. The catalyst was suitable for both styrene derivatives and aliphatic alkenes. “Styrene derivatives gave branched adducts in >20:1 selectivity, while aliphatic alkenes predominantly afforded linear adducts (1:20),” explained Professor Kanai. In almost all cases, high C4-selectivity was observed (Scheme 2). A high catalyst turnover number (TON = 3.4 x 10^3) based on the Co salt was observed as demonstrated in the gram-scale reaction with low catalyst loading (s/c=4000).

“Further mechanistic studies are essential for the precise understanding of the reaction mechanism, as well as for clarifying the reason for high C4-selectivity,” said Dr. Matsunaga, “but we believe the present communication clearly demonstrated the utility of first-row transition-metal catalysis for generating nucleophilic active species in situ. The process is ideal in terms of both atom- and step-economy. Further studies to expand the scope of heterocycles are actively ongoing in our group, and new results will be published in due course.”

For the future, the group wishes to see the application of their Co catalysis for the late-stage functionalization of complex biologically active compounds bearing heteroaromatic rings, such as pyridines and quinolines, but the limited functional group compatibility of the present catalyst system remains problematic for addressing the late-stage functional-
Because LiEt₃BH is utilized in the current system, applicable functional groups are limited at the moment. Professor Kanai concluded: “We are currently working hard to develop alternative procedure(s) to generate ‘Co-hydride’ species without using LiEt₃BH.”

Matteo Zanda

About the authors

Motomu Kanai was born in 1967 in Tokyo (Japan) and received his BSc from The University of Tokyo (UT, Japan) in 1989 under the direction of the late Professor Kenji Koga. In the middle of his PhD course at UT (in 1992), he obtained an Assistant Professor position at Osaka University (Japan) under the direction of Professor Kyoshi Tomioka. He obtained his PhD from Osaka University in 1995. Then, he moved to the University of Wisconsin (USA) for postdoctoral studies with Professor Laura L. Kiessling. In 1997 he returned to Japan and joined Professor Masakatsu Shibasaki’s group at UT as an Assistant Professor. After some time as a Lecturer (2000–2003) and Associate Professor (2003–2010), he became a Full Professor at UT. He is also the PI of ERATO Kanai Life Science Catalysis Project (since 2011). He has received The Pharmaceutical Society of Japan Award for Young Scientists (2001), the Thiem Chemisty Journals Award (2003), the Merck-Banyu Lectureship Award (2005), the Asian Core Program Lectureship Award and the Novartis Lecturer in Organic Chemistry (2011). His research interests entail design and synthesis of functional molecules.

Shigeki Matsunaga is an Associate Professor at the University of Tokyo (Japan) in Professor Kanai’s group. He was born in 1975 in Kyoto, and received his PhD from The University of
Tokyo under the direction of Professor Masakatsu Shibasaki. He started his academic career in 2001 as an Assistant Professor in Professor Shibasaki's lab at UT. He was promoted to a Senior Lecturer in 2008, and to his current position in 2011. He is the recipient of the Chemical Society of Japan Award for Young Chemists (2006), the Thieme Chemistry Journals Award (2008), the Mitsui Chemicals Catalysis Award of Encouragement (2009), the Merck-Banyu Lectureship Award (2010), and others. His research interests are in homogeneous catalysis for C–H activation, asymmetric C–C bond formation, and in the synthesis of biologically active compounds.
Fluorenones and xanthones are core motifs of many natural and biologically active compounds, as well as organic light-emitting materials. Existing synthetic routes to these compounds, such as Friedel–Crafts-type ring closures or the oxidation of fluorenes, are usually limited to electron-rich arenes or require multiple-step synthesis.

Recently, Professor Frank Glorius and Dr. Zhuangzhi Shi of the Organic Chemistry Institute at the Universität Münster (Germany) developed a novel and efficient route for the synthesis of fluorenones via direct intramolecular dehydrogenative arylation of aldehydes. The Glorius group has focused its research activity on the catalytic selective functionalization of aldehyde C–H bonds to construct ketones via transition-metal complexes and N-heterocyclic carbene catalysts. Professor Glorius said: “Our initial intention in this project was to develop a Pd(OAc)₂-catalyzed direct acylation of 2-phenylbenzaldehyde (1a) to form fluoronone (2a); the desired acylation product 2a was observed in 48% yield in the presence of 10 mol% Pd(OAc)₂ as the catalyst, 2.0 equivalents of K₂S₂O₈ as the oxidant and 2.0 equivalents of TBAB (tetrabutylammonium bromide) as the additive at 80 °C in DCE.” He continued: “We hypothesized that 2-phenylbenzaldehyde (1a), which incorporates an aldehyde group, might analogously function as a directing group to coordinate with palladium (II) followed by C–H bond activation/insertion and reductive elimination leading to fluorenones (Scheme 2).”

However, the researchers were surprised by the outcome of the control reactions, in which the desired cyclization product 2a was observed in a similar yield even in the absence of any additional palladium catalyst. A further investigation of the cation identified that 10 mol% TEAB (tetraethylammonium bromide) was the optimum catalyst, affording 2a in 68% yield. Dr. Zhuangzhi Shi suggested: “This direct acylation reaction might proceed via a free-radical pathway. This is actually more attractive than our originally proposed palladium-catalyzed process because it proceeds without the aid of any transition metals, acids or bases, and uses a catalytic amount of a quaternary ammonium salt in the presence of a persulfate oxidant.”

Dr. Shi continued: “A key step in this transformation involves TEAB, which may act as a special initiator for generating sulfate radical anions through an unexplored type of catalytic process. This radical could react with the aldehyde 1 through a hydrogen-abstraction process providing an acyl radical A and a bisulfate anion. The resulting acyl radical
would then readily add to the arene to form radical intermediate B. Single-electron oxidation of B by another sulfate radical gives cation C, which is deprotonated by the formed sulfate dianion to give the annulation product and another bisulfate anion (Scheme 3).

With the developed protocol in hand, the fluorenone synthesis could be readily scaled up to gram quantities without difficulty (Scheme 4, eq. 1). The researchers also expanded the scope of this method to the synthesis of xanthones in moderate yield (Scheme 4, eq. 2). Interestingly, for the reaction of substrate 5, they isolated bianthronyl 6, which may derive from the desired anthrone intermediate via homocoupling (Scheme 4, eq. 3).

Professor Glorius concluded: “This reaction proceeds with an inexpensive system (i.e., catalytic TEAB + K2S2O8) and displays a broad scope with respect to the substituents. We anticipate this transformation can complement Friedel–Crafts approaches in the synthesis of fluorenones and xanthones.”
About the authors

Zhuangzhi Shi was born in Nantong, Jiangsu Province (P. R. of China), in 1983. He received his BSc in chemistry and MSc in organic chemistry from Yangzhou University (P. R. of China) in 2005 and 2008, and obtained his PhD (2011) at Peking University (Beijing, P. R. of China), under the supervision of Professor Ning Jiao. He is currently an Alexander von Humboldt Postdoctoral Fellow in the laboratory of Professor Frank Glorius at the Westfälische Wilhelms-Universität Münster (Germany). His research interests include aerobic oxidations and C–H activation chemistry.

Frank Glorius was educated in chemistry at the Universität Hannover (Germany), at Stanford University (USA) with Professor Paul A. Wender, at the Max-Planck-Institut für Kohlenforschung (Mülheim/Ruhr, Germany) and the Universität Basel (Switzerland) with Professor Andreas Pfaltz, and at Harvard University (USA) with Professor David A. Evans. In 2001, he began his independent research career at the Max-Planck-Institut für Kohlenforschung and in 2004 was promoted to Associate Professor for Organic Chemistry at the Philipps-Universität Marburg (Germany). Since 2007, he has been Full Professor at the Westfälische Wilhelms-Universität Münster. His research focuses on the development of new concepts for catalysis and their implementation in organic synthesis.
Regioselective Reactions of 3,4-Pyridynes Enabled by the Aryne Distortion Model

_Nature Chem._ **2013**, *5*, 54–60

Arynes are fascinating, yet synthetically useful and highly reactive intermediates, which occupy a pivotal role in organic synthesis. Although benzyn is probably the best known and most used aryne intermediate, a number of heterocyclic arynes have been described and successfully used in a wide range of synthetic methods. The first aryne proposed (over 100 years ago) in fact was a heterocyclic aryne, which was obtained from 3-bromobenzofuran ([B]er. Dtsch. Chem. Ges. **1902**, *35*, 1633). However, arguably the synthetic potential of such compounds has not been unlocked until recently.

For some time, the research laboratory of Professor Neil Garg at the University of California, Los Angeles (UCLA, USA) has been interested in the chemistry of heterocyclic arynes. Professor Garg said: “In earlier efforts, we studied ‘indolynes’ as a means to prepare substituted indole derivatives. This work led to the synthesis of alkaloids, such as indolactam V and several welwitsdinone natural products.” Importantly, collaborative studies with Professor Ken Houk at UCLA also led to the establishment of the aryne distortion model. This model allows one to make reliable predictions about regioselectivity in reactions of unsymmetrical arynes, including hetarynes. Professor Garg continued: “The predictive powers of this model are best showcased by the computational predictions we made on > 150 of heterocyclic arynes ([An]gew. Chem. Int. Ed. **2012**, *51*, 2758) and studies where indolyn regioselectivities could be controlled by a neighboring halide substituent ([J. Am. Chem. Soc. **2011**, *133*, 3832]).”

“Given the importance of pyridines in drug discovery,” said Professor Garg, “we hoped to further develop the chemistry of ‘pyridynes’ to enable their widespread use in synthesis. The 3,4-pyridyne seemed like a natural system for our studies because of its rich history.” The compound has been shown to react with little or no regioselective preference in a variety of trapping agents over the past 50 years. However, a small set of examples, by Snieckus, Caubère, and Guitián, demonstrated that substituted 3,4-pyridynes could react with some regioselectivity. “We were therefore very excited by the possibility of controlling the reactivity of this intermediate to give highly substituted pyridines in a predictable and synthetically useful fashion,” said Professor Garg, adding: “I would like to emphasize that a stellar graduate student named Adam Goetz (first author of this paper) did all of the computational and experimental work from this manuscript single-handedly.”

He continued: “We first carried out a series of simple computational experiments to evaluate substituted 3,4-pyridynes using the aryne distortion model. This allowed us to make predictions regarding pyridyne regioselectivities that would guide future experimentation.” Taking the most promising results, while considering synthetic access to potential pyridyne precursors, they opted to synthesize three pyridyne precursors (precursors to the three pyridynes shown below). “Synthesizing the pyridyne precursors turned out to be a bigger challenge than we had anticipated,” explained Professor Garg. “Nonetheless, we developed syntheses that provided gram quantities of each of the corresponding silyltriflate precursors.” Although silyltriflate precursors to arynes are sometimes criticized because of the challenge in their preparation, it should be noted that they can be used in a tremendous variety of aryne-trapping experiments, using mild fluoride-based reaction conditions, and are therefore very attractive.

Professor Garg said: “With access to the pyridyne precursors, it was exciting to find that pyridynes could be generated

---

**SYNFORM** 2013/06
Published online: 16.05.2013, DOI: 10.1055/s-0033-1338711
2013 © THIEME STUTTGART · NEW YORK
and trapped in nucleophilic addition and cycloaddition experiments. Moreover, the regioselectivity we observed experimentally was consistent with the predictions made by the aryne distortion model.”

One of the most useful aspects of this chemistry is the potential to further manipulate the products obtained from pyridine-trapping experiments, by virtue of the bromo or sulfonyl substituents. “To test this notion, we chose the products resulting from pyridyne trapping with dimethylurea because they are obtained as single regioisomers and are structurally reminiscent of benzodiazepines,” explained Professor Garg. Using Pd or Ni catalysis, the bromide or sulfamate, respectively, could be readily manipulated in C–C, C–N, or C–H bond-forming events.

Professor Garg concluded: “We hope that others will now view pyridynes as a productive means to access highly substituted pyridines, especially those that represent new classes of compounds that might be difficult to access by other methods. We are working now with suppliers to make our pyridyne and indolyne precursors commercially accessible. We are also eager to synthesize other heterocyclic arynes as synthetic building blocks and as a means to further test predictions made by the aryne distortion model.”

About the authors

Adam E. Goetz was born in Dayton, OH (USA) in 1985. He received his B.A. in Chemistry from Carleton College in Northfield, MN (USA) and conducted summer research with Professor Robert Kempton at Northern Kentucky University (USA). After graduating, he spent a year as a research assistant for Segetis, Inc. in Minneapolis, MN (USA). He is currently a fourth-year graduate student in Professor Neil Garg’s laboratory at UCLA, where his graduate studies are focused on understanding and controlling selectivity in the reactions of heterocyclic arynes.

Neil K. Garg is an Associate Professor of Chemistry at UCLA. Professor Garg received a B.S. degree in Chemistry from New York University (USA) where he carried out undergraduate research with Professor Marc Walters. During his undergraduate years, he spent several months in Strasbourg (France) conducting research with Professor Wais Hosseini at the...
Université Louis Pasteur as an NSF REU Fellow. Subsequently, he obtained his Ph.D. degree in 2005 from the California Institute of Technology (Pasadena, CA, USA) under the direction of Professor Brian Stoltz. He then spent two years in Professor Larry Overman’s research laboratory at the University of California, Irvine (USA) as an NIH Postdoctoral Scholar. Professor Garg started his independent career at UCLA in 2007, where his laboratory develops novel synthetic strategies and methodologies to enable the total synthesis of complex bioactive molecules.
alpha-Propargyl carboxylic acids and their derivatives are extremely important and valuable molecules having a number of applications as drugs, key building blocks for the synthesis of complex natural and bioactive compounds, tools for biomedical research, and innovative bio-materials. In fact, the propargyl function imparts increased reactivity and offers the possibility of introducing further bespoke functionalities for the fine-tuning of their biological activity, as well as acting as a bioconjugation site. An attractive strategy for the synthesis of alpha-propargyl carboxylic acid derivatives would be the conversion of a C–H bond positioned beta to a carboxamide function into an alkyne by formation of a new C–C bond with an activated alkyne derivative. Unfortunately, this potentially versatile methodology has remained elusive owing to the apparent lack of reactivity of such an inactivated C–H bond and the absence of suitable catalytic systems. Recently, the group of Professor Jin-Quan Yu from the Scripps Research Institute (La Jolla, CA, USA) developed a methodology for achieving such a striking transformation, based on the use of Pd(0) catalysts with N-heterocyclic carbene (NHC) or phosphine (PR3) ligands. Key to the success of the methodology was also the use of an electron-deficient amide derived from commercially available carboxylic acids and (4-CF3)C6F4–NH2 as substrates for the beta-alkynylation with alkynyl bromides.

The new synthetic method was thoroughly optimized and a number of catalysts, ligands, and conditions were carefully screened in order to identify the best reaction conditions.

“Despite the long history of using Pd(0)/PR3 and Pd(0)/NHC catalysts to functionalize aryl C–H bonds using aryl halides as coupling partners, intermolecular activation of C(sp3)–H bonds using this system has only been reported in a single example of arylation (see the first example from our group: J. Am. Chem. Soc. 2009, 131, 9886),” said Professor Yu.

“This work uses alkynyl halides as coupling partners and converts C(sp3)–H bonds into synthetically versatile alkylnyl groups. Mechanistically, this demonstrates for the first time that [L–Pd(II)–alkynyl] complexes can cleave and alkylnylate C(sp3)–H bonds in an intermolecular fashion,” he continued.

Mechanistic studies on the reaction were conducted, showing that substrates incorporating a deuterium atom alpha to the carboxamide moiety fully retain deuterium, thus suggesting that a beta-hydride elimination pathway, as previously observed in conceptually related reactions by Baudoin et al. (Angew. Chem. Int. Ed. 2010, 49, 7261), is unlikely. This and other experimental evidence led the authors to hypothesise the possible intermediate shown in Scheme 1. The new methodology has remarkably broad scope and allows for the synthesis of a number of structurally diverse propargyl carboxamides in good yields. “Practically, this reaction does not need any external oxidant compared to the Pd(II)-catalyzed C–H activation reactions. Most importantly, the use of optically enriched phosphine and carbene ligands in these transformations could lead to the development of enantioselective C(sp3)–H activation reactions,” concluded Professor Yu.

Scheme 1
About the authors

Jin-Quan Yu received his B.Sc. in Chemistry from East China Normal University (Shanghai, P. R. of China; undergraduate thesis study with Professor L.-X. Dai and B.-Q. Wu at the Shanghai Institute of Organic Chemistry, P. R. of China). He obtained his M.Sc. from the Guangzhou Institute of Chemistry (P. R. of China) with Professor X.-D. Xiao, and his Ph.D. from the University of Cambridge (UK) with Professor J. B. Spencer. Following time as a Junior Research Fellow at Cambridge, he joined the laboratory of Professor E. J. Corey at Harvard University (USA) as a postdoctoral fellow. He then began his independent career at Cambridge (2003–2004), before moving to Brandeis University (Waltham, MA, USA) from 2004–2007, and finally to The Scripps Research Institute (USA), where he is currently Frank and Bertha Hupp Professor of Chemistry.

Jian He obtained his first degree from Zhejiang University (Hangzhou, P. R. of China) in 2011, where he worked with Shengming Ma, and is now a second-year student in the Yu group at Scripps.

Prof. J.-Q. Yu

J. He
In the next issues:

SYNSTORIES

- Efficient and Stereoselective Nitration of Mono- and Disubstituted Olefins with AgNO₃ and TEMPO (Focus on an article from the current literature)
- Highly Efficient Cu(I)-Catalyzed Oxidation of Alcohols to Ketones and Aldehydes with Diaziridinone (Focus on an article from the current literature)
- N-Chlorosuccinimide, an Efficient Reagent for On-Resin Disulfide Formation in Solid-Phase Peptide Synthesis (Focus on an article from the current literature)

FURTHER HIGHLIGHTS

SYNTHESIS
Review on: Enantioselective Organocatalyzed Domino Synthesis of Six-Membered Carboxycles (by D. Bonne, J. Rodriguez et al.)

SYNLETT
Account on: N-Alkyl Sulfonamides as Useful Carbon Electrophiles (by Y. Gu, S.-K. Tian)

SYNFACS
Synfact of the Month in category “Synthesis of Natural Products and Potential Drugs”: Synthesis of Tatanans A–C and Reinvestigation of their Glucokinase-Activating Properties

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

Editorial Assistant: Alison M. Sage
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
Assistant Scientific Editor: Michael Binanzer, michael.binanzer@thieme.de, phone: +49 711 8931 768
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 Editor: Thorsten Schin, thorsten.schin@thieme.de, phone: +49 711 8931 781
Editorial Assistant: Sabine Heller, sabine.heller@thieme.de, phone: +49 711 8931 744
Marketing Manager: Julia Stötzner, julia.stoetzner@thieme.de, phone: +49 711 8931 771
Postal Address: SYNTHESIS/SYNLETT/SYNFACS, Editorial Office, Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany,
Homepage: www.thieme-chemistry.com

Publication Information
SYNFORM will be published 12 times in 2013 by Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, and is an additional online service for SYNTHESIS, SYNLETT and SYNFACS.

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 SYNFACS
The Americas: Thieme Publishers New York, Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. To order: customerservice@thieme.de 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 Expediters 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
The online versions of SYNFORM as well as SYNTHESIS, SYNLETT and SYNFACS are available through Thieme-connect (www.thieme-connect.com/electronic) 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: products@thieme.de, phone: +49 711 8931 407
India: eproducts@thieme.in, phone: +91 120 45 56 600
Japan: bhoseya@poplar.ocn.ne.jp, phone: +81 3 3358 0692

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.