SYNSTORIES

- Featured SynStory: Synthetic Tubulysins as Super-Potent Warheads for Cancer Chemotherapy
- Construction of an All-Carbon Quaternary Stereocenter by the Peptide-Catalyzed Asymmetric Michael Addition of Nitromethane to β-Disubstituted α,β- Unsaturated Aldehydes
- One-Pot, Catalyst-Free Synthesis of β- and γ-Hydroxy Sulfides Using Diaryliodonium Salts and Microwave Irradiation

CONTACT

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

Which aspects of your academic work do you like the most? The last two weeks were quite mixed and intense for me; normally I do not have much teaching (don’t tell it to my College though...) but in the last few days I had to mark a few exams and I dealt with some other teaching-related activity too. Then, I organized a one-day workshop with ca. 50 attendees. I have also been finalizing a grant application, drafting a couple of manuscripts, evaluated several grant applications and a couple of manuscripts, dealt with the usual supervision of my postgraduate students and postdocs. Then, I did quite a lot of ‘administration’ work connected with the fact that I am directing two research centers of my university. And obviously I took care of SYNFORM. Plus some other miscellaneous stuff. Luckily, I did not have to travel. But, unfortunately, I had very little time for keeping myself up-to-date with the literature, which is something that really annoys me. That’s because studying the literature and designing new experiments and projects is by far my favorite activity, I really love browsing journals online and getting inspiration and ideas for new research endeavors. I guess many of you will agree that this is what really makes our work special, together with the excitement of seeing our research plans materialized into exciting experimental results, expected or not (which sometimes is even better!). And I suspect this sentiment is also shared by the researchers whose work is featured in this new issue of SYNFORM, which includes the following SYNSTORIES: the Pd-catalyzed C–H γ-arylation of α-amino acids reported by J. C. Carretero (Spain); a novel stereoselective approach to all-carbon quaternary stereocenters catalyzed by peptides, discovered by K. Kudo (Japan); a novel synthetic approach to β- and γ-hydroxy sulfides developed by J. Leazer (USA); the FEATURED SYNSTORY on the highly potent toxic payloads for targeted chemotherapy developed by P. Lazzari and his company (Italy).

Enjoy your reading!

Matteo Zanda
Editor of SYNFORM
Amino acids are critically important molecules and key building blocks in a vast number of scientific areas spanning molecular sciences and biomedicine. Only 20 ω-amino acids are coded for in the genetic code of humans and many amino acids are rare compounds, neither commercially available nor easily obtained by chemical synthesis. Over the last decade, Pd-catalyzed C(sp3)–H activation reactions have emerged as a powerful and atom-economical synthetic methodology. However, the application to the functionalization of remote C(sp3)–H bonds in organic synthesis is still at its early stages and significant advancements in this field are of much general interest for the chemical community. Particularly, the functionalization of ω-amino acids through a Pd-catalyzed C(sp3)–H activation process is very challenging due to the importance of non-proteinogenic amino acids. However, few examples of functionalization of ω-amino acid derivatives through a Pd-catalyzed C(sp3)–H activation process, especially regarding the remote ω-functionalization process, are known.

The research group of Professor Juan Carlos Carretero at the Universidad Autonoma de Madrid (Spain) has developed an efficient methodology for the Pd-catalyzed ω-CH3 arylation of simple ω-amino acid esters with iodoarenes. Professor Carretero explained: “This process relies strongly on the use of the N-(2-pyridyl)sulfonyl moiety as a crucial activating and directing group. The synthetic utility of this protocol is demonstrated by the ω-arylation of a variety of N-(2-pyridyl)sulphonamide ω-amino acid derivatives (e.g., from valine, threonine or allo-isoleucine), including also ω-quaternary amino acids and β-amino acids (Scheme 1).”

To highlight the synthetic utility of this process in non-proteinogenic amino acid synthesis, the overall three-step sequence for the ω-diarylation of L-valine ester, including the initial introduction and final removal of the directing group, has been achieved (Scheme 2). “From a synthetic point of view, it is important to note that practically no racemization at the Cω center was observed, neither in the Pd-catalyzed arylation process (Scheme 1).”
tion reaction nor in the final cleavage of the sulfonyl moiety (98% ee)," said Professor Carretero.

As a challenging extension of the process, this Pd-catalyzed γ-CH₃ arylation is also effective in the functionalization of dipeptide substrates (Scheme 3). "As far as we are aware," remarked Professor Carretero, "these are the first examples for the remote Pd-catalyzed γ-C(sp³)–H functionalization of dipeptides." He concluded, "We anticipate that the use of the directing 2-(pyridyl)sulfonyl moiety can open new perspectives in the field of metal-catalyzed direct functionalization of remote C(sp³)–H bonds."

**Matteo Zanda**

**About the authors**

Juan Carlos Carretero received his PhD from the Universidad Autónoma de Madrid (UAM, Spain) in 1985 under the supervision of Professor José L. García Ruano. After postdoctoral studies (1985–1988) at the Université Catholique de Louvain (Belgium) with Professor Léon Ghosez, he joined the Department of Organic Chemistry of the UAM, where he became Associate Professor in 1988 and Professor of Organic Chemistry in 2000. In 2010 he received the Janssen-Cilag Award in Organic Chemistry from the Spanish Royal Society of Chemistry. He is currently head of the Department of Organic Chemistry (UAM). His research interests are focused on the development of novel processes in asymmetric catalysis, stereocontrolled metal-catalyzed reactions and C–H activation processes.

M. Ángeles Fernández-Ibáñez received her PhD degree from Universidad Autónoma de Madrid (UAM, Spain) in 2006 under the supervision of Professor José L. García Ruano. During this period, she had a predoctoral stay in Boston College (USA).
with Professor Scott J. Miller. Subsequently, she joined the group of Professor Ben L. Feringa at the University of Groningen (The Netherlands) as a postdoctoral researcher (2006–2009). After one year in the Medicinal Chemistry Institute at CSIC in Madrid (Spain) she moved to the group of Professor Juan C. Carretero at UAM as a research associate. In 2012 she was appointed as an Assistant Professor in the Department of Organic Chemistry at the UAM. Her work focuses on the activation of C–H bonds.

Jose Antonio Romero Revilla was born in Madrid (Spain) in 1985. He studied at the Universidad Complutense de Madrid (Spain) and received his BSc in 2008. Subsequently, he worked at Consejo Superior de Investigaciones Científicas (CSIC, Spain) under the supervision of Dr. Francisco Sánchez until 2010 when he joined the group of Juan C. Carretero at UAM where he is currently doing his PhD.

Nuria Rodríguez was born in 1978 in Valencia (Spain). After completion of her chemistry studies at the University of Valencia (Spain), she gained her doctorate in the group of Professor Gregorio Asensio and Dr. Mercedes Medio-Simón. She worked with Lukas J. Gooßen as a Humboldt postdoctoral fellow starting in 2006. The emphasis of her work was the development of decarboxylative cross-coupling reactions. In 2011, she took up a Ramon y Cajal research position at UAM with Juan C. Carretero. Her current research focuses on the development of catalytic systems for the activation of inert C–H bonds.
Mimicking the synthetic efficiency, specificity, stereoccontrol and environmental sustainability of enzymes is a stimulating challenge for synthetic organic chemists. Recently, the group of Professor Kazuaki Kudo from The University of Tokyo (Japan) developed a process for installing synthetically challenging quaternary carbon centers in a stereocontrolled manner using a peptide-based catalytic system that closely simulates many peculiar aspects of enzymatic catalysis.

In fact, Professor Kudo and co-worker Dr. Kengo Akagawa have developed resin-immobilized asymmetric peptide catalysts having secondary structures that work under aqueous conditions. Professor Kudo said: “A representative example is Pro-o-Pro-Aib-Trp-Trp-(Leu)$_2$ bound to amphiphilic PEG-PS resin (Aib = 2-aminoisobutyric acid).” He continued: “The pentapeptide at the N-terminus adopts a turn structure whereas the polyleucine part has an α-helical structure. This catalyst was designed to mimic enzymes as follows: 1) enzymes have higher-order structures that are suitable for catalytic functions, and 2) they are amphiphilic molecules with a hydrophobic microenvironment at the reaction center, hence smoothly catalyze reactions in water.” The catalyst was effective for asymmetric hydride-transfer reactions to α,β-unsaturated aldehydes (Org. Lett. 2008, 10, 2035; Tetrahedron: Asymmetry 2009, 20, 461), asymmetric Friedel-Crafts-type reactions to α,β-unsaturated aldehydes (Tetrahedron Lett. 2009, 50, 5602; Adv. Synth. Catal. 2012, 354, 1280), and asymmetric α-oxyamination of aldehydes (Chem. Commun. 2010, 46, 8040; Org. Lett. 2010, 12, 1804; Org. Lett. 2011, 13, 3498).

While exploring the potential of this peptide catalyst, Dr. Akagawa found that asymmetric addition of nitromethane to β-disubstituted α,β-unsaturated aldehydes occurred smoothly. The amine-catalyzed asymmetric addition of nitromethane to β-monosubstituted α,β-unsaturated aldehydes through an iminium-ion activation mechanism is a well-known reaction. However, that with β-disubstituted analogues has not been reported previously. “This might be due to the steric congestion at the β-position which lowers the reactivity for 1,4-addition and allows competing side reactions including 1,2-addition of nitronate anions to occur,” said Professor Kudo, who further remarked: “In fact, the reactions with several known secondary amine catalysts resulted in the formation of a complex mixture in which only a small amount of 1,4-adduct was included. 

![Chemical structure of the reaction](image.png)
After considerable tuning of the reaction conditions and the catalyst, we were able to show the generality of this reaction for a range of substrates.”

Professor Kudo continued: “We think the key to the realization of this reaction might be due to the successful construction of the hydrophobic microenvironment in aqueous solvents with this catalyst. Use of a protic solvent system might also play an important role in lowering the concentration of reactive ionic species that are relevant to side reactions.”

It should be emphasized that the products could be easily transformed to β,β-disubstituted-γ-aminobutyric acids, which should be of interest from a pharmacological point of view due to the structural relationship with GABA, an inhibitory neurotransmitter.

“I feel that we have unveiled only a small part of the rich world of peptide catalysts,” concluded Professor Kudo. “We are now trying to find more ‘enzyme-like’ peptide catalysts that show high regio- or chemoselectivity which cannot be attained by small-molecule catalysts.”

Kazuaki Kudo was born in 1963 in Morioka (Japan). He received his PhD (1993) from The University of Tokyo (Japan) under the direction of Professor Kazuhiko Saigo. He was appointed as a Research Associate at Tokyo Institute of Technology (Japan) in 1993 and moved back to The University of Tokyo as a Lecturer in 1996, where he became an Associate Professor in 1999 and then a Full Professor in 2007. During this period, he joined the group of Barbara Imperiali at Caltech (USA) as a visiting researcher (1997–1998). His current research interests are the development of selective peptide catalysts having specific secondary structures, and also peptide-based functional materials.

Kengo Akagawa was born in Tokyo (Japan) in 1980. He received his PhD from The University of Tokyo in 2009 under the direction of Professor Kazuaki Kudo. During his PhD studies, he joined the group of Professor Albrecht Berkessel at the University of Cologne (Germany) for a three-month internship. He was appointed as a Project Research Associate at The University of Tokyo in 2009, and became a Research Associate in 2011. His current research focuses on the development of novel peptide catalysts and their application to organic synthesis.
Aromatic β- and γ-hydroxy sulfides are valuable organic compounds that have been used in the construction of important biologically active compounds, organolithium complexes, metallophthalocyanines, α,β-unsaturated lactones and organic intermediates, such as aryl vinyl sulfones, to name a few. The C–S cross-coupling reaction is a versatile organic transformation that finds applications in various organic, pharmaceutical and material chemistry synthesis and manipulations. A C–S bond-formation reaction that does not make use of transition metals and expensive ligands would be highly desirable from both the environmental and synthetic viewpoints. With this idea in mind, Dr. Buchi Reddy Vaddula, Dr. Rajender Varma and Dr. John Leazer at the US Environmental Protection Agency (Cincinnati, OH, USA) decided to develop an efficient and simple protocol for the synthesis of hydroxy sulfides. General routes for their preparation usually involve the nucleophilic ring opening of epoxides with thiols. Dr. Vaddula said: “Our ongoing exploratory studies on the application of hypervalent iodine reagents led us to an efficient synthesis of β- and γ-hydroxy sulfides using readily available reagents. This eco-friendly protocol enables the construction of various important organic intermediates and bioactive and natural products from simple and readily accessible starting materials and is amenable to the assembly of a library of β- and γ-hydroxy sulfides.”

Dr. Vaddula continued: “We devised a novel strategy for the one-pot, catalyst-free synthesis of β- and γ-hydroxy sulfides.” This approach to hydroxy sulfide synthesis involves a three-component reaction of diaryliodonium salts, potassium thiocyanate, and 1,2- or 1,3-diols such as ethylene glycol and propane-1,3-diol. “We deem diaryliodonium salts as an efficient substitution for aryl halides in arylation reactions, due to the electrophilic nature of the iodonium salt harnessed by the good leaving ability of one of its arene ligands in the form of iodoarene,” said Dr. Vaddula. “The simplest preparation of diaryliodonium salts, in turn, needs only arenes, elemental iodine, and mild reaction conditions,” he added.

The investigations by the Ohio-based researchers revealed that the three-component reaction progressed via the intermediate formation of an aryl thiocyanate within 10–25 minutes. However, interestingly, an independent reaction of aryl thiocyanate with diol under the same conditions failed to yield the desired product. Another feature is that, in the case of diols containing primary and secondary alcohols, this one-pot reaction acts preferentially on primary alcohols over secondary alcohols. This protocol seems inapplicable for 1,4-diols, leading to speculation that a hydroxyl group in the neighborhood (within a three-carbon distance) helps in assisting the thionation reaction.

“The literature reports the preparation of hydroxy sulfides by heating aryl thiocyanates with ethylene glycol in the presence of triphenylphosphane, which generates its oxide as the byproduct that is detrimental to the environment,” said Dr. Vaddula. “Keeping in mind the importance of these products
in organic and medicinal chemistry and adhering to the tenets of green chemistry, this protocol assumes special significance,” he continued. “We strongly believe that a sustainable method that avoids the deployment of additional reagents and circumvents isolation steps for intermediates is therefore highly desirable and paves the way for further explorations of this newer strategy,” Dr. Vaddula concluded.

**About the authors**

**Buchi Reddy Vaddula** was born in India and received his Bachelors and Masters in Pharmacy from Birla Institute for Technology and Science (BITS, Pilani, India). He received his PhD under the supervision of Professor D. Kumar from the same institution. He has worked on multicomponent reactions in the synthesis of bioactive compounds. Currently, he is working as an ORISE postdoctoral fellow, researching on greener synthetic methods for bioactive compounds and nano catalysis with Professor R. S. Varma and Dr. J. Leazer at US EPA, Cincinnati (OH, USA).

**Rajender S. Varma** was born in India and obtained his PhD in 1976. After postdoctoral research at the Robert Robinson Laboratories, Liverpool (UK), he was a faculty member at Baylor College of Medicine and Sam Houston State University (USA) prior to joining the Sustainable Technology Division at US EPA in 1999. He has over 40 years of research experience in management of multi-disciplinary technical programs ranging from natural products chemistry to therapeutics and development of environmentally friendlier alternatives for synthetic methods, using microwaves, ultrasound, etc. Lately, he has focused on greener approaches to assembly of nano materials and sustainable applications of magnetically retrievable nano catalysts in benign media. He has published over 350 scientific papers and has been awarded 12 US patents.

**John Leazer** obtained his BSc from Davidson College (NC, USA), his MSc in synthetic organic chemistry from the North Carolina State University (USA) and his PhD in synthetic organic chemistry from the University of Pennsylvania (USA). After completing his graduate studies, John joined Merck, where he worked as a process chemist for 22 years. He is the Director of the Sustainable Technology Division in the US EPA’s Office of Research and Development and has responsibility for the division’s research portfolio and sustainability advances.
Featured SynStory: Synthetic Tubulysins as Super-Potent Warheads for Cancer Chemotherapy

**Background and Purpose.** *FEATURED SYNSTORIES* report non-peer-reviewed scientific information about research activities conducted by a private company. Other potential authors from the private sector are welcome to get in touch with *SYNFORM* for writing similar articles. Contributions of this type clearly focus on scientific content and have no advertisement character.

Tubulysins are a family of natural tetrapeptides produced in small quantities (<4 mg·L⁻¹ culture broth) by two different species of *Myxobacteria*.

Tubulysins are extremely toxic to mammalian cells, with IC₅₀ values in the range of 0.01–10 nM. The cytotoxic activity of the tubulysins is due to their ability to bind tubulin and disintegrate microtubules of dividing cells, thus inducing apoptosis. Owing to their remarkable interest and great potential as potent anticancer agents, several total syntheses of natural or modified tubulysins have been published.

Structurally, tubulysins are linear tetrapeptides incorporating l-isoleucine and three unnatural amino acids. At the N-terminus, all the family members have N-methyl piperolic acid (Mep) and isoleucine (Ile). The unusual amino acid tubuvaline (Tuv) containing a thiazole heterocycle occupies the central position. At the C-terminus there is either tubuphenylalanine (Tup, present in tubulysin D and others) or tubutyrosine (Tut, present in tubulysins A and others), which are γ-amino acid homologues of phenylalanine and tyrosine, respectively. Additionally, the N-terminal moiety of Tuv may be further functionalized with an unusual N,O-acetal substituent having different ester functionalities, which is of paramount impor-

<table>
<thead>
<tr>
<th>Compound</th>
<th>MESO (48 h)</th>
<th>STO (48 h)</th>
<th>LoVo (72 h)</th>
<th>LoVo/Dx (72 h)</th>
<th>MCF7 (72 h)</th>
<th>MCF7/Dx (72 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEMTUB010</td>
<td>0.5</td>
<td>0.525</td>
<td>5.4</td>
<td>4.5</td>
<td>0.325</td>
<td>1.45</td>
</tr>
<tr>
<td>TUBULYSIN A</td>
<td>5.120</td>
<td>7.780</td>
<td>54.9</td>
<td>68.8</td>
<td>15.8</td>
<td>35.0</td>
</tr>
<tr>
<td>PACLITAXEL</td>
<td>26</td>
<td>27</td>
<td>1000</td>
<td>3500</td>
<td>30.0</td>
<td>530</td>
</tr>
<tr>
<td>VINCBLASTIN</td>
<td>21.5</td>
<td>5.6</td>
<td>375</td>
<td>1740</td>
<td>4.3</td>
<td>77.7</td>
</tr>
<tr>
<td>DOXORUBICIN</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50.0</td>
<td>507</td>
</tr>
</tbody>
</table>

**Table** Cell Cytotoxicity of One of KemoTech’s Tubulysins (KEMTUB010), Compared to Other Tubulin-Targeting Antimitotic Compounds

Meso = Malignant peritoneal mesothelioma cell line; STO = Mouse embryonic fibroblast cell line; LoVo = Human colon carcinoma cell line; LoVo/Dx = Doxorubicin-resistant Human colon carcinoma cell line; MCF7 = Breast cancer cell line; MCF7/Dx = Doxorubicin-resistant Breast cancer cell line.
ance for imparting the high potency typical of most cytotoxic natural tubulysins, such as A and D.

Paolo Lazzari and co-workers at KemoTech (www.kemotech.it) have recently developed a scalable synthesis (up to one gram) of super-potent synthetic analogues of the natural tubulysins.1 KemoTech’s proprietary synthetic tubulysins have distinctive features, such as (1) increased potency and cytotoxicity on a number of cancer cell lines, including multidrug-resistant cell lines (see Table) and (2) increased metabolic and chemical stability relative to the natural tubulysins, such as tubulysins A and D. In fact, KemoTech’s proprietary tubulysins feature a highly stable alkylaryl, alkylcycloalkyl, alkylheteroaryl, etc. group R2 replacing the labile and synthetically challenging alkoxy carbonylalkyl N-Tuv fragment which characterizes the natural tubulysins.

Owing to their impressive cytotoxicity, synthetic tubulysins appear to be ideal candidates for targeted chemotherapy. Therefore these compounds have been successfully functionalized with different chemical handles for allowing the attachment to targeting vectors, such as antibody formats,1 peptides, polymers and nanoparticles. However, synthetic tubulysins also have a remarkable potential as ‘classical’ anticancer drugs, as demonstrated by very encouraging preliminary preclinical results showing an interesting therapeutic window despite the extremely high potency featured by these tubulysin derivatives.

In summary, synthetic tubulysins are highly promising candidate drugs for oncology that may find important applications both as highly toxic payloads in targeted chemotherapy and as cytotoxic anti-cancer drugs, especially if a suitable therapeutic window can be identified.

**REFERENCES**

In the next issues:

SYNSTORIES

Copper/Titanium Catalysis Forms Fully Substituted Carbon Centers from the Direct Coupling of Acyclic Ketones, Amines, and Alkynes (Focus on an article from the current literature)

Phosphine-Based Redox Catalysis in the Direct Traceless Staudinger Ligation of Carboxylic Acids and Azides (Focus on an article from the current literature)

Taming of Fluoroform: Direct Nucleophilic Trifluoromethylation of Si, B, S, and C Centers (Focus on an article from the current literature)

FURTHER HIGHLIGHTS

SYNTHESIS
Review on: Guanidine Organocatalysis (by P. Selig)

SYNLETT
Account on: Recent Progress in Chemistry of Mucohalic Acids: Versatile Building Blocks in Organic Synthesis (by J. Zhang et al.)

SYNFACTS
Synfact of the Month in category “Synthesis of Heterocycles”: Synthesis of 3-Nitroindoles via an Intramolecular α-Selective Heck Reaction

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 Biannizer, michael.biannizer@thieme.de, phone: +49 711 8931 769
Senior Production Editor: Thomas Loos, thomas.loos@thieme.de, phone: +49 711 8931 778
Production Editor: Helene Deufel, helene.deufel@thieme.de, phone: +49 711 8931 929
Production Editor: Thorsten Schöm, thorsten.schoem@thieme.de, phone: +49 711 8931 781
Editorial Assistant: Sabine Heller, sabine.heller@thieme.de, phone: +49 711 8931 744
Marketing Manager: Julia Stöttner, julia.stoetzner@thieme.de, phone: +49 711 8931 771
Postal Address: SYNTHESIS/SYNLETT/SYNFACTS, 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 SYNFACTS.

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 SYNFACTS
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
Airmail 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 SYNTHESIS, SYNLETT and SYNFACTS are available through The online services (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: products@thieme.de, phone: +49 711 8931 407
India: subscriptions@thieme.in, phone: +91 120 45 56 600
Japan: behessey@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.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.