SYNSTORIES

- Asymmetric Autocatalysis Triggered by Carbon Isotope (\(^{13}\text{C}/^{12}\text{C}\)) Chirality

- Orthogonal Synthesis of Isoindoles and Isoquinolines via 1,3-Dipolar Cycloaddition and Electrocyclization

- Thieme-Chemistry Journals Editorial Board Meetings 2009

CONTACT

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

I am writing this brief editorial while spending my holidays in Sardinia. Right now, I am on a terrace with a wonderful view of the sea, blue sky, a delightful breeze and an ice-cold cocktail.

But SYNFORM can’t wait; therefore, my laptop had to come out from the bag where it spent one entire week of unusual rest.

But I am sure it’s a worth deal, because also in this issue SYNFORM features very interesting science. In the first SYNSTORY Professor Chiba from Singapore discloses new information about his novel approach to isoindoles and isoquinolines, whereas in another SYNSTORY Professor Soai from Japan explains how he and his co-workers were able to publish the first example of stereoselectivity controlled by stereogenic centers bearing $^{13}C$ or $^{12}C$ carbon isotopes. The issue is closed by a brief report on the Thieme-Chemistry Journals Editorial Board Meetings recently held in Granada (Spain).

Enjoy your reading!!!

Matteo Zanda
Editor of SYNFORM

SYNFORM, 2009/06
Published online: 23.07.2009, DOI: 10.1055/s-0029-1217800

2009 © THIEME STUTTGART · NEW YORK
Nitrogen-containing heterocycles (azaheterocycles) are important and widespread structures, present in numerous natural products, potent pharmaceutical drugs, and various kinds of functional materials. Although a number of diverse synthetic approaches toward azaheterocycles have been developed it is still highly desirable to exploit versatile methodologies to construct such molecules with selective control of substitution patterns using readily accessible building blocks. The group of Professor Shunsuke Chiba from the Nanyang Technological University in Singapore has recently been interested in the chemical reactivity of organic azides to synthesize azaheterocycles via various types of C–N bond formations.

“During the course of our studies,” explained Professor Chiba, “α-azido carbonyl compounds containing a 2-alkenylaryl unit were found to be promising precursors for the synthesis of isoindole and isoquinoline derivatives via 1,3-dipolar cycloaddition of azides onto alkenes and 6π-electrocyclization of $N$–H imine intermediates, respectively.” According to Professor Chiba, this methodology exploits orthogonal modes of chemical reactivity of such organic azides, displayed by slight modification of the reaction conditions as shown in the scheme below.

Isoindoles could be accessed by simple heating of the starting organic azides in toluene, whereupon intramolecular azido–alkene cycloaddition and consecutive elimination of dinitrogen from the resulting triazolines would produce isoindoles. “The appeal of isoindoles prepared by this methodology can be attributed to not only their attractive fluorescent and electroluminescent properties but also their versatility as reaction precursors for the synthesis of oligoacenes,” said Professor Chiba. “By using newly synthesized isoindoles, we are now aiming to prepare new types of oligoacenes with a range of substituents.”

Chiba and Hui discovered the second reactivity pattern of these organic azides – to provide isoquinoline derivatives – serendipitously, when direct conversion of the mesylate into the isoindole was tried using 1.5 equivalents of NaN₃ in DMF at 100 °C via a substitution reaction followed by an azido–alkene 1,3-dipolar cycloaddition (for details, see the original paper). “After understanding that the excess amount of NaN₃ induced the formation of $N$–H imine,” he concluded, “we soon elucidated the optimized reaction conditions to provide isoquinolines selectively.”

---

Matteo Zanda

**Orthogonal Synthesis of Isoindoles and Isoquinolines via 1,3-Dipolar Cycloaddition and Electrocyclization**

About the authors

Shunsuke Chiba was born in Kanagawa (Japan) in 1978. He obtained his B.Eng. degree from Waseda University (Japan) in 2001 and received his Ph.D. degree in 2006 from the University of Tokyo (Japan), the latter under the supervision of Professor Koichi Narasaka. He was appointed as a Research Associate in Professor Narasaka’s group at the University of Tokyo in 2005. In 2007, he moved to the Division of Chemistry & Biological Chemistry, School of Physical & Mathematical Sciences, Nanyang Technological University (Singapore) as an Assistant Professor. His research is focused on the development of organic synthetic methodologies and the synthesis of natural and unnatural products.

Benjamin Wei-Qiang Hui was born in Singapore in 1982 and obtained his bachelor’s degree in chemistry from the National University of Singapore (NUS) in 2007. In the same year, he entered the graduate program at Nanyang Technological University (NTU) under the supervision of Professor Shunsuke Chiba. His research focuses on the development of new synthetic methods to access azaheterocyclic compounds.

INFORMATION

Synthesis Reviews

Your free database of review articles in synthetic organic chemistry!

- Contains 24,860 review articles (from journals and books)
- Covers literature from 1970 to the end of 2008 and is updated annually
- Is hosted by SYNTHESIS & SYNLETT
The origin of homochirality of biomolecules such as L-amino acids and D-sugars has attracted significant interest of many researchers. Many apparently achiral molecules may be chiral because of random substitution of the 1.1% naturally abundant $^{13}$C for $^{12}$C. Hydrogen isotope chirality (H/D) in a polymer has been shown to cooperatively control macromolecular helical handedness.

However, because the effect of carbon isotopic chirality is far smaller than hydrogen isotopic chirality, it has been a question whether carbon-isotopically chiral compounds can perform asymmetric induction in organic reactions. A brilliant answer to this intriguing question came recently from Professor Kenso Soai and his group from the Tokyo University of Science (Japan), who demonstrated that carbon isotope chirality can actually trigger asymmetric autocatalysis, at least in appropriately designed systems.

“We have been studying asymmetric autocatalysis reactions in which a chiral product acts as a chiral catalyst for its own production,” said Professor Soai. “Our asymmetric autocatalysis of pyrimidyl alkanol in the reaction between pyrimi-

---

**Asymmetric Autocatalysis Triggered by Carbon Isotope ($^{13}$C/$^{12}$C) Chirality**

*Science 2009, 324, 492–495*
Dine-5-carbaldehyde and diisopropylzinc exhibits significant amplification of chirality, that is, starting from an asymmetric autocatalyst with extremely low enantiomeric excess (ee), three consecutive asymmetric autocatalyses afford almost enantiopure (> 99.5% ee) pyrimidyl alkanol with significant multiplication of the amount. Moreover,” he continued, “when the asymmetric autocatalysis is initiated in the presence of a chiral initiator with tiny enantiomeric imbalance, the highly enantioenriched product with the absolute configuration correlated with that of the chiral initiator is formed. So far, we have used cryptochiral compounds, including a saturated quaternary hydrocarbon, as chiral initiators.”

The use of such compounds – chiral only because of the carbon isotope chirality – as the chiral initiators of asymmetric autocatalysis was a challenge for the Soai group because of the small difference in atomic weight (only 8%) between $^{13}$C and $^{12}$C. “To the best of our knowledge,” confirmed Professor Soai, “there has been no report on asymmetric induction using carbon isotope chirality.” In the course of the research, Professor Soai and his coworkers paid the utmost attention to exclude the effect of chiral materials other than those featuring the $^{13}$C/$^{12}$C isotope chirality. “For example,” said Professor Soai, “we prepared both enantiomers of dimethylphenylmethanol $^{13}$C/$^{12}$C isotopes by independent methods. By using the same enantiomer of chiral catalyst, the enantioselective additions of (A) $^{13}$C-labelled dimethylzinc [($^{13}$CH$_3$)$_2$Zn] to acetophenone and (B) (CH$_3$)$_2$Zn to $^{13}$C-labelled acetophenone (C$_6$H$_5$CO$^{13}$CH$_3$) gave the opposite enantiomers of which one of the methyl groups is $^{13}$C-labelled. Thus,” continued Professor Soai, “even if any contaminant derived from the chiral catalyst were present in the enantiomeric dimethylphenylmethanol, it would have the same chirality and would effect the reaction in the same sense of chirality.” The experimental results clearly revealed that, as anticipated by the authors, the absolute configuration of the carbon-isotopically chiral compound controlled the absolute configuration of the product; that is, $^{13}$C/$^{12}$C chirality induced an enantioenrichment in the asymmetric reaction.

“Because the asymmetric autocatalysis has now been shown to be capable of discriminating the $^{13}$C/$^{12}$C chirality,” concluded Professor Soai, “the concept of the origin of chirality may have expanded significantly.”

In a comment on this work, Professor Guy C. Lloyd-Jones from the University of Bristol (UK) and Editorial Advisory Board member of the Thieme-Chemistry journals, said: “This is a beguiling piece of work: elegant in design and packed full...”
of painstaking experimentation. A heavy-isotope effect (of as-yet undetermined mechanism) in highly enantioenriched alcohols that are chiral solely by virtue of $^{13}$C incorporation is able to exert sufficient influence on the early stages of Soai’s highly tuned i-Pr$_2$Zn/pyrimidine aldehyde reaction to trigger asymmetric autocatalysis. There is a highly reproducible sense of enantiomer induction, and the control experiments, for example using the same enantiomer of ligand to make both enantiomers of alcohol 1, and the stereoinversion to synthesize the enantiomer of alcohol 2, are impressive. One is left with the feeling that the effect is genuine and significant. Soai reports on a challenging, erudite and fascinating study that will undoubtedly stimulate the search for other manifestations of this subtle chirality,” concluded Professor Lloyd-Jones.

REFERENCES

The 2009 Editorial Boards Meeting of the Thieme Chemistry journals *SYNLETT*, *SYNTHESIS* and *SYNFACTS*, including the supplement *SYNFORM*, was held on June 5th and 6th in the city of Granada (Spain). The Editorial Boards of the three journals and the staff of the Thieme Chemistry editorial office met at the Alhambra Palace Hotel. A manuscript submission system and initiatives to further increase the quality of the journals were among the most relevant issues which were discussed in a friendly and relaxed atmosphere.

The 40th anniversary of *SYNTHESIS* and the 20th anniversary of *SYNLETT* were also duly celebrated (see picture on the right), first with a toast to the two Editors-in-chief, Professor Dieter Enders and Professor K. Peter C. Vollhardt, respectively, followed by a general toast involving all of the Editorial Board members and accompanying persons. Among the main attractions of the night was the performance of the well-known folk song “La Cucaracha”, brilliantly directed by Professor Erick M. Carreira, one of the *SYNTHESIS* Editors.

The program included a guided tour of the Alhambra (where the group picture was taken), the citadel-palace and fortress on a hill overlooking Granada. The Alhambra hosts royal residential quarters, court complexes flanked by official chambers, a mosque and beautiful gardens, which was started in the thirteenth century by Ibn al-Ahmar, founder of the Nasrid dynasty, and was continued by his successors in the fourteenth century.

The appointment for the next Editorial Board Meeting is in 2010 in Florence (Italy).
COMING SOON

SYNFORM 2009/07
is available from September 22, 2009

In the next issues:

SYNSTORIES

- Palladium-Catalyzed Allylic Amination Using Aqueous Ammonia for the Synthesis of Primary Amines
  (Focus on an article from the current literature)

FURTHER HIGHLIGHTS

SYNTHESIS
Special Issue on “Total Synthesis” in issue 17/2009

SYNLETT
Account on: Developing Continuous-Flow Microreactors as Tools for Synthetic Chemists
(by P. H. Seeberger)

SYNFACTS
Synfact of the Month in category “Synthesis of Heterocycles“: Synthesis of 5-Alkoxy Pyrimidines via Enamides

CONTACT

Matteo Zanda,
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, 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
Assistant 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 779
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/SYNFACTS, 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 9 times in 2009 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
Americas: Thieme New York, 333 Seventh Avenue, New York, NY 10001, USA. To order: customerservice@thieme.com or use the Web site facilities at www.thieme.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.

All other countries: Thieme Publishers, Rüdigerstraße 14, 70469 Stuttgart, Germany. To order: customerservice@thieme.de or use the Web site facilities at www.thieme.com.
For further inquiries please contact Mrs. Birgid Härtel: 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 SYNFACTS are available through Thieme-connect (www.thieme-connect.com/journals), 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.
Americas: esales@thieme.com, phone: +1 212 584 4695
All other countries: 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.