SYNSTORIES

■ Catalytic Intermolecular Tail-to-Tail Hydroalkenylation of Styrenes with α-Olefins

■ Chiral Brønsted Acid Catalyzed Enantioselective α-Aminooxylolation of Enecarbamates

■ Highly Enantioselective Hydroxy-carbonylation and Alkoxy carbonylation of Alkenes Using Dipalladium Complexes as Precatalysts

CONTACT

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

This issue of SYNFORM features three SYNSTORIES, one from Europe and two from Asia. The first one comes from Scotland, where Dr. Matthew L. Clarke and his group envisaged a very interesting method for producing carboxylic acids in enantiocontrolled manner directly from olefins through a hydroxycarbonylation process. The second SYNSTORY comes from Singapore, where Professor Guofu Zhong and coworkers developed a novel organocatalytic α-aminoxylation of enecarbamates, eventually resulting in the production of stereodefined N-alkoxycarbonyl β-amino-alcohols. The third SYNSTORY comes from China, and more specifically from Hong Kong, where the group of Professor Chun-Yu Ho discovered an extremely interesting tail-to-tail hydroalkenylation of styrenes with α-olefins leading to the corresponding elongated alkenes. Great science for a great issue!

Enjoy your reading!

Matteo Zanda
Editor of SYNFORM
A number of biologically and pharmaceutically interesting compounds contain a stereodefined α-hydroxy-carbonyl framework, which is therefore a target of great interest for synthetic chemists. The stereocontrolled introduction of the hydroxy group through α-aminoxylation reactions is an attractive methodology, but the protocol is difficult to apply to linear ketones, which normally feature lower reactivity and stereoselectivity. Recently, the group of Professor Guofu Zhong from the Nanyang Technological University (NTU, Singapore) has developed a novel strategy which holds promise in alleviating this problem.

“Our research group has a long-standing interest in the organocatalytic α-aminoxylation reactions using nitroso compounds as terminal oxidants,” said Professor Zhong. “In 2003, we first reported the facile process converting unmodified aldehydes into enantiopure 1,2-diols via α-aminoxylation catalyzed by L-proline, demonstrating the debut of organocatalysis in this chemistry (Angew. Chem. Int. Ed. 2003, 42, 4247).” Professor Zhong explained that the contracted term ‘aminoxylation’ is new and was first applied in his Angewandte paper above (a VIP paper), and is, according to Professor Zhong, easier to use and write than the traditional term ‘aminoxylation’. “Now, most people accept this term in their publications,” he said. In subsequent years, exciting advancements have been made with the aminoxylation reaction. “With extremely high and predictable enantioselectivity, operational simplicity, and catalyst availability in both enantiomeric forms holding a touch of ‘green’ aspect, the proline-catalyzed α-aminoxylation of carbonyl compounds and its tandem protocols quickly moved up the ranks to a well-established tool for constructing complex chiral molecules,” said Professor Zhong. “However, certain limitations that come along with L-proline and its derivatives persist with respect to the low catalyst turnover numbers and limited substrate scope, which prompted us to design new alternative activation modes.”

Professor Zhong and co-workers envisioned that by the judicious choice of Brønsted acids, selective protonation of the basic nitrogen of nitroso compounds will facilitate the subsequent nucleophilic attack at the oxygen atom through electrophilic activation. “In light of this blueprint, we identified the first BINOL–phosphoric acid catalyzed α-aminoxylation of β-dicarbonyl compounds with concomitant N/O bond heterolysis (J. Am. Chem. Soc. 2009, 131, 4562). This finding sets up a novel platform with tremendous opportunities in α-aminoxylation chemistry,” said Professor Zhong.
Next, the Singapore researchers set out to address the most challenging substrates in the field of α-aminoxylation, namely, aromatic ketones. “Steric hindrance accompanying extended conjugation made this type of compound extremely reluctant to succumb to the reign of proline,” explained Professor Zhong. “However, by implementing an enecarbamate moiety as activation group with an ideal H-bond handle, the long-desired α-aminoxylation finally took place with excellent enantiocntrol and can be finished in a couple of minutes,” he said. The usefulness of the transformation was demonstrated through facile access to biologically important building blocks such as α-hydroxy ketones, orthogonally protected vicinal amino alcohols, and cis-oxazolidinones. “The fact that $E$- and $Z$-isomers of enecarbamates lead to different regioselective products provided further insights into the origin of O/N selectivity,” concluded Professor Zhong.

**About the authors**

**Guofu Zhong** is a faculty member at the Division of Chemistry & Biological Chemistry (CBC), School of Physical & Mathematical Sciences (SPMS), Nanyang Technological University (NTU), Singapore. He obtained his PhD from The Scripps Research Institute (USA) in 1998 under the direction of Professors R. A. Lerner and C. F. Barbas III. He started his academic career at Scripps as Assistant Professor (1999–2004), accepted the Changjiang Professorship (granted by the Chinese Ministry of Education) in the Department of Chemistry at Fudan University, Shanghai (P. R. of China) (2005–2006) and Outstanding PI in the Institutes of Biomedical Sciences (IBS) at the same university (2005–2006), and then moved to NTU in Singapore as Associate Professor in 2006. His research fields cover synthetic methodologies, asymmetric catalysis, and medicinal and bio-organic chemistry.

**Min Lu** was born in Suzhou (P. R. of China) in 1983. He obtained his BSc in 2006 from Fudan University. He has been studying for his PhD at NTU since April 2007 under the guidance of Professor Guofu Zhong. Due to the excellence of his research at NTU, he was awarded the prestigious Chinese Government Outstanding Student Award for overseas Chinese students in May 2010.
Simple alkenes represent an important chemical feedstock in industry, where they are used as primary starting materials for the large-scale preparation of important classes of compounds at a relatively low cost. While olefin cross-metathesis and hydrovinylation with ethylene have proven to be particularly important to construct internal and monosubstituted olefins in modern chemical industry, the selective construction of various asymmetric gem-disubstituted olefins from the feedstock remains challenging. Recently the group of Professor Chun-Yu Ho from the Chinese University of Hong Kong (P. R. of China) described a novel process for the efficient tail-to-tail hydroalkenylation of styrenes with α-olefins mediated by a nickel–N-heterocyclic carbene (Ni–NHC) complex.

“α-olefins can be very useful building blocks for the construction of value-added molecules by making use of a large variety of alkene functionalization technologies, which are well documented in the literature,” said Professor Ho. “Unfortunately, they are of limited availability; therefore, we recently started a research program to develop new catalytic methodology to synthesize them. This was mainly based on the very important nickel chemistry reported by several research groups, namely those of Professors RajanBabu, Cavell, Sigman, Montgomery and Jamison,” acknowledged Professor Ho, “and was partly initiated by our related finding in the Ni–NHC-mediated cyclization reaction (Chem. Commun. 2010, 46, 466).” Professor Ho explained that he felt that one of the major implications in the cyclization was that the IPr-Ni(II) combination may have a positive effect by attenuating the facile β-H elimination at a certain point and provide enough time for a new C–C bond formation to take place, complementary to other approaches using bi/tridentate ligands. “After that work, I thought that another area for testing the potential of the IPr-Ni(II) combination was that represented by processes of intermolecular C–C bond formation directed by benzylic stabilization, for example revisiting the hydrovinylation reaction by joining the advantages of NHC ligand effects with the aforementioned elegant Ni-H and Ni(0) chemistry.”

Professor Ho explained that besides the concerns of isomerization and regio- and chemoselectivity, the major question in his mind before the testing was whether the steric bulk offered by the first insertion product was strong enough to stop oligomerization. “Pleasingly, the cross-hydroalkenylation between simple styrene and a long-chain α-olefin worked at the first trial,” he said. “Later, Lisi He, who is a first-year M.Phil student in my group, took on the challenge related to process optimization and scope expansion. She did well by picking up everything rapidly; notably, she had received no organometallic chemistry training prior to that,” said Professor Ho. “Once the process becomes more efficient, the hurdles of accessing the subsequent chemical products will be lowered accordingly,” said Professor Ho. The researchers are now working towards that goal. Meanwhile they are also exploring the potential applications of the products and exploring the NHC-Ni effect on other transformations.
“We hope that our research can stimulate further developments in the field of Ni-NHC chemistry and related insertion processes. Finally, I would like to give my most sincere thanks to Professor Tim Jamison for providing me with a research opportunity in his group,” concluded Professor Ho.

About the authors

Chun-Yu Ho was born in Hong Kong and received his BSc from The University of Hong Kong (P. R. of China). His interest in alkene research stems from his undergraduate projects on organocatalytic asymmetric epoxidation in 1999. He received his PhD in 2005 from the same institution under the supervision of Professor Dan Yang. After pursuing postdoctoral research at MIT with Professor Timothy F. Jamison (2005–2007), he joined the Center of Novel Functional Molecules, The Chinese University of Hong Kong (CUHK) as an independent Research Assistant Professor. He is the recipient of The Croucher Foundation Fellowship and Asian Core Program Lectureship Award. His current research interests include the applications of NHC in catalytic asymmetric synthesis, and the development of phosphorylation and cyanation methods for the synthesis of biologically important molecules.

Lisi He was born in China in 1986. She obtained her BSc from Sun Yat Sen University (P. R. of China) in 2009 and started her graduate study as an M.Phil student under Professor Chun-Yu Ho’s supervision at CUHK.
A stereoselective synthesis of carboxylic acids by direct enantiocontrolled installation of the carboxylic group (hydroxy carbonylation) on an olefin substrate is potentially a very powerful approach, but until recently no truly practical and user-friendly methods were available for standard laboratory applications. A breakthrough was recently achieved by the group of Dr. Matthew L. Clarke from the University of St. Andrews (UK), who developed a highly efficient methodology for both hydroxy- and alkoxy-carbonylation of alkenes based on the use of dipalladium complexes as precatalysts.

“We started work on this goal about six years ago,” said Dr. Clarke. “I am quite odd for a synthetic chemist, in that I am attracted to reactions that don’t work!” According to the Scottish researchers, asymmetric hydroxycarbonylation had been known about for about 30 years, but the only ee values that seemed to be reproducible were about 11% for a BINAP system, and an example with about 40% ee. “There had been some good ee values for alkoxy carbonylation, but in both reactions there were issues with the yield, the amount of co-catalyst, temperature and, for styrene derivatives, regioselectivities,” said Dr. Clarke. “If it were not for all these problems, it would be one of the most useful reactions for research and industry alike; carboxylic acid derivatives are everywhere, and making them this way uses the most economic precursors, alkenes, carbon monoxide and a nucleophile, and all of the atoms in these substrates go into the products.”

“We did some work that helped in sorting out regioselectivities for making racemic products (Chem. Eur. J. 2009, 15, 10504; J. Mol. Catal. 2010, 330, 18) and by 2006, we had our own 40% ee,” he continued. “However, most of the ligands failed to give any ee. I like to think we deserved a bit of luck, when we came across the dimetallics. Tina, the PhD student who did most of the work, did the right thing by not ignoring a mystery side product when making the monometallic complexes of Pye and Rossen’s planar-chiral Phanepon ligand. She decided to make this and found out it was the dipalladium species,” (see X-ray crystal structure).
“However, I was not too optimistic they would do much in asymmetric carbylonylations,” said Dr. Clarke; “bridging diphosphines are not the way to do asymmetric catalysis, right? If they re-arranged to chelates, you would expect them to be a bit worse than the mono-metallic catalysts. Anyway, I was wrong, and we got some very promising enantioselectivity in both hydroxycarbonylation (up to 85% ee) and alkoxy-carbonylation (up to 95% ee).” Dr. Clarke argued that it may be important that they were able to work at much lower temperatures and lower acid co-catalyst concentration than other studies. “We think this is the first big hurdle overcome towards making this long-desired process a reality, and it is probably the only project I have worked on where the results were much better than I dreamed of! A colleague in industry suggested we file a patent, which we did in 2009, and they are now supporting a student to tune these up for possible industrial application,” said Dr. Clarke. “We still have some work to do, for sure. Either the activity has to go up a bit more or we have to be able to recycle in a convenient way and we are working on both approaches.” The authors pointed out that this article mainly deals with styrene, since that was the benchmark substrate, and from a synthesis point of view, the regioselectivities make it useless for that aryl-propanoic acid. “However, since the paper was written, we have now fixed the regioselectivity to get only the chiral regioisomer, while keeping the same sort of level of ee, and this important modification will be one of the first papers we will write next year,” said Dr. Clarke. “In any case, quite a few substrates of interest to industry don’t present this problem (norbornene is the only one of these noted in the paper). Anyway, we are very excited about these catalysts and about the relatively untapped potential of alkene carbylonylations in organic synthesis in general. I hope some readers have a go at using them; both asymmetric hydroformylations (also one of our favorite reactions to apply in synthesis) and palladium carbylonylations are not only appealing for large scale, they are a piece of cake to do in a research lab,” he said. “Finally, there is this tantalizing possibility regarding the pre-catalyst structure; we are dead keen to piece together the mechanism of this reaction. Maybe there will be lots of other catalytic reactions where a bridging diphosphine does the business when chelates do not?” concluded Dr. Clarke.
COMING SOON

SYNFORM 2011/03
is available from
February 16, 2011

In the next issues:

SYNSTORIES

- Ni-Catalyzed Reduction of Inert C–O Bonds
  (Focus on an article from the current literature)

- Pd(II)-Catalyzed Carbonylation of C(sp³)–H Bonds
  (Focus on an article from the current literature)

- An Efficient Organocatalytic Method for Constructing Biaryls through Aromatic C–H Activation
  (Focus on an article from the current literature)

FURTHER HIGHLIGHTS

SYNTHESIS

Review on: α-Functionalization of Carbonyl Compounds Using Hypervalent Iodine Reagents
(by E. A. Merritt, B. Olofsson)

SYNLETT

Account on: Synthesis and Application of Redox-Active Hybrid Catalytic Systems Consisting of Polyanilines and Transition Metals
(by T. Amaya, T. Hirao)

SYNFACTS

Synfact of the Month in category “Metal-Mediated Synthesis”:
Palladium(II)-Catalyzed Decarboxylative Addition of Benzoic Acids to Nitriles

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 Schönh, thorsten.schoen@thieme.de, phone: +49 711 8931 781
Editorial Assistant: Sabine Heller, sabine.heller@thieme.de, phone: +49 711 8931 744
Marketing: Julia Stötzer, julia.stoetzer@thieme.de, phone: +49 711 8931 771
Postal Address: SYNTHESIS/SYNLETT/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 12 times in 2011 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., 337 Seventh Avenue, New York, NY 10001, USA.
To order: customerservice@thieme.com or use the Web site facilities at www.thieme-chemistry.com.
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 via Thieme-connect
The online versions of SYNFORM as well SYNTHESIS, SYNLETT and SYNFACTS are available through Thieme-connect (www.thieme-connect.com/courantla) 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 Roswood Drive, Danvers, MA 01923, USA, 0341-0501/02

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