SYNSTORIES

- Asymmetric Synthesis of β-Alkynyl Aldehydes by Rhodium-Catalyzed Conjugate Alkynylation
- Development of a Sila-Friedel–Crafts Reaction and Its Application to the Synthesis of Dibenzosilole Derivatives

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

This new issue of SYNFORM is the first of 2010, and I hope you will agree that the three SYNSTORIES featured in this inaugural issue are a very good way to begin the fourth year of life of SYNFORM. Tamio Hayashi and his group (Japan) are protagonists of the first SYNSTORY of the year, which is about the enantioselective rhodium-catalyzed conjugate alkynylation of α,β-unsaturated aldehydes recently developed in Hayashi’s lab. Jeffrey Johnson (USA) in the second SYNSTORY tells us more about his recent stereoselective method to synthesize substituted tetrahydropyrans. Takayuki Kawashima, in the third SYNSTORY, describes the fascinating synthesis of dibenzosilole derivatives through a Sila-Friedel–Crafts reaction. Three pieces of research carrying the hallmark of quality!

Enjoy your reading!

Matteo Zanda
Editor of SYNFORM

IN THIS ISSUE

SYNSTORIES

Asymmetric Synthesis of β-Alkynyl Aldehydes by Rhodium-Catalyzed Conjugate Alkynylation .................................................. A3


Development of a Sila-Friedel–Crafts Reaction and Its Application to the Synthesis of Dibenzosilole Derivatives .................. A8

COMING SOON ................................................................. A10

CONTACT

If you have any questions or wish to send feedback, please write to Matteo Zanda at: Synform@chem.polimi.it
Asymmetric Synthesis of β-Alkynyl Aldehydes by Rhodium-Catalyzed Conjugate Alkynylation


Catalytic asymmetric conjugate addition of terminal alkynes to α,β-unsaturated carbonyl compounds provides a powerful method to construct a stereogenic carbon center at the propargylic position with a high atom efficiency. In 2008, the group of Professor Tamio Hayashi from the Department of Chemistry, Kyoto University (Japan), reported the asymmetric conjugate addition of (triisopropylsilyl)acetylene to α,β-unsaturated ketones catalyzed by a rhodium complex coordinated to a bulky bisphosphine ligand, DTBM-Segphos. The reaction gave high yields of chiral β-alkynyl ketones (J. Am. Chem. Soc. 2008, 130, 1576), thanks to the effective suppression of the dimerization of (triisopropylsilyl)acetylene.

Recently, Professors Hayashi and Nishimura were able to extend the methodology to β-alkynyl aldehydes. This achievement is very important because the β-alkynyl aldehydes produced by this reaction are important chiral building blocks in organic synthesis. “A typical example of the importance of β-alkynyl aldehydes is the synthesis of (+)-8-epi-xanthatin reported by Professor Stephen F. Martin from the University of Texas at Austin (USA), where the key chiral β-alkynyl aldehyde, (S)-3-methyl-5-(triisopropylsilyl)pent-4-ynal, was derived from enantiopure methyl 3-hydroxy-2-methylpropanoate in six steps,” explained Professor Nishimura.

“It looks very easy and straightforward to apply the asymmetric conjugate alkynylation protocol to the synthesis of β-alkynyl aldehydes, but in reality it is not that simple,” continued Professor Nishimura. “Indeed, the reaction of less bulky silylacetylenes in the presence of a less bulky phosphine ligand usually gave the alkyne dimers as major products.

SYNSTORIES

NEWS AND VIEWS

Asymmetric Synthesis of β-Alkynyl Aldehydes by Rhodium-Catalyzed Conjugate Alkynylation


Catalytic asymmetric conjugate addition of terminal alkynes to α,β-unsaturated carbonyl compounds provides a powerful method to construct a stereogenic carbon center at the propargylic position with a high atom efficiency. In 2008, the group of Professor Tamio Hayashi from the Department of Chemistry, Kyoto University (Japan), reported the asymmetric conjugate addition of (triisopropylsilyl)acetylene to α,β-unsaturated ketones catalyzed by a rhodium complex coordinated to a bulky bisphosphine ligand, DTBM-Segphos. The reaction gave high yields of chiral β-alkynyl ketones (J. Am. Chem. Soc. 2008, 130, 1576), thanks to the effective suppression of the dimerization of (triisopropylsilyl)acetylene.

Recently, Professors Hayashi and Nishimura were able to extend the methodology to β-alkynyl aldehydes. This achievement is very important because the β-alkynyl aldehydes produced by this reaction are important chiral building blocks in organic synthesis. “A typical example of the importance of β-alkynyl aldehydes is the synthesis of (+)-8-epi-xanthatin reported by Professor Stephen F. Martin from the University of Texas at Austin (USA), where the key chiral β-alkynyl aldehyde, (S)-3-methyl-5-(triisopropylsilyl)pent-4-ynal, was derived from enantiopure methyl 3-hydroxy-2-methylpropanoate in six steps,” explained Professor Nishimura.

“It looks very easy and straightforward to apply the asymmetric conjugate alkynylation protocol to the synthesis of β-alkynyl aldehydes, but in reality it is not that simple,” continued Professor Nishimura. “Indeed, the reaction of less bulky silylacetylenes in the presence of a less bulky phosphine ligand usually gave the alkyne dimers as major products.
enal with (triisopropylsilyl)acetylene under the same reaction conditions as used for ω,ω-unsaturated ketones gave 1,3-bis(alkynyl)butanol as a major product. Professors Hayashi and Nishimura found that changing the solvent from 1,4-dioxane to methanol dramatically improved the selectivity affording the β-alkynyl aldehydes exclusively, without any other side products. “The high efficiency of using methanol as a solvent has been previously reported by Miyaura (J. Org. Chem. 2000, 65, 4450) for the conjugate addition of arylboronic acids to enals,” explained Professor Nishimura.

“The β-alkynyl aldehydes obtained here are highly useful as chiral building blocks for the synthesis of natural products,” said Professor Nishimura. “Deprotection of the silyl group from the alkyn terminus or the modification of the aldehyde functionality is readily performed without loss of enantimetric purity.”

“The rhodium-catalyzed asymmetric conjugate alkynylation still faces major problems like limitation of the substrate scope, low efficiency of the catalyst, and so on. We are approaching the problems to make the asymmetric conjugate alkynylation more general and more practically useful,” concluded Professor Hayashi.

---

**About the authors**

Tamio Hayashi graduated from Kyoto University (Japan) in 1970. He received his PhD in 1975 from Kyoto University under the direction of Professor Makoto Kumada. The title of his thesis was “Catalytic Asymmetric Hydroboration of Olefins and Ketones”. Then, he was appointed as a Research Associate at the Faculty of Engineering, Kyoto University. He spent the year 1976 to 1977 as a Postdoctoral Fellow at Colorado State University (USA) with Professor Louis S. Hegedus. He was promoted to Full Professor in 1989 in the Catalysis Research Center, Hokkaido University (Japan). Since 1994, he has been a Full Professor at the Faculty of Science, Kyoto University. His awards include the Award for Young Chemists of the Society of Synthetic Organic Chemistry (Japan) in 1983, the IBM Japan Prize in 1991, The Chemical Society of Japan Award in 2003, the Thomson Scientific Research Front Award in 2004, the Molecular Chirality Award in 2005, The Ryoji Noyori Prize and the Author C. Cope Scholar Award in 2008. Tamio Hayashi has published more than 300 original papers with a total citation number of around 21000 (h-index 80) by October 2009. He has been interested in the development of new reactions catalyzed by transition-metal complexes, especially in catalytic asymmetric reactions.

---

**Matteo Zanda**

Matteo Zanda

---

SYNFORM, 2010/01

2010 © THIEME STUTTGART · NEW YORK
Takahiro Nishimura was born in Kumamoto (Japan) in 1970. He received his BSc in 1994 and PhD in 2001 from Kyoto University under the supervision of Professor Sakae Uemura. He became an Assistant Professor at Graduate School of Engineering, Kyoto University in 2001. From 2004 to 2005, he was a Postdoctoral Fellow at The University of North Carolina (USA) with Professors Maurice Brookhart and Joseph L. Templeton. In 2005, he was promoted to Lecturer at Graduate School of Science, Kyoto University. He was awarded an Incentive Award in Synthetic Organic Chemistry (Japan) in 2007. His current research interest is the development of new catalytic organic reactions using transition metals.

Takahiro Sawano was born in Shizuoka (Japan) in 1986. He received his BSc degree from Tohoku University (Japan) in 2008 under the supervision of Professor Minoru Ueda. He is currently an MSc course graduate student in the group of Professor Tamio Hayashi. His current research interest is the development of transition-metal-catalyzed organic transformations using terminal alkynes.
Cycloaddition reactions are very useful tools in an organic chemist’s arsenal and have found countless applications in synthesis. Classically, these reactions involve a dipole and a dipolarophile, although several classes of compounds are known to behave as masked dipoles. Among them, appropriately functionalized cyclopropanes are known to be effective substrates in dipolar cycloadditions, whereas the homologous compounds (cyclobutanes) are much less recognized as masked dipoles in spite of their high ring-strain energy. Recently, Professor Jeffrey S. Johnson from the University of North Carolina (USA) described a powerful methodology which makes use of functionalized donor–acceptor cyclobutanes in a formal [4+2] cycloaddition with aldehydes to give substituted tetrahydropyrans.

“We had two motivations in undertaking this project,” explained Professor Johnson. “First, we were simply interested in determining if what we had learned during our studies of cyclopropane/aldehyde annulations would be applicable to a homologous system. At first glance,” continued Professor Johnson, “this would appear to be a relatively trivial modification; however, we were struck by the relative dearth of chemistry associated with donor-acceptor cyclobutanes relative to donor–acceptor cyclopropanes. We believe that this is directly linked to the synthetic availability of the former. No Corey–Chaykovsky reaction exists for cyclobutanes!” According to Professor Johnson, this deficiency prompted the second main question: “Is there a way that we could merge cyclobutane synthesis with the subsequent annulation reaction? Certainly there is no shortage of tetrahydropyran syntheses, but we wished to develop a way where one might ‘snap together’ trivial building blocks in a predictable, advantageous way”, he said.

Prof. Johnson and graduate student Andrew T. Parsons were able to show that these types of annulations are feasible under operationally simple conditions. “Most exciting to us is the discovery that one can make the donor-acceptor cyclo-

**Concept:**

![Concept Diagram]

**Application:**

![Application Diagram]

added via syringe pump over 45 min

62%, dr = 98:2  
48%, dr = 97:3  
63%, dr = 97:3
butane via a catalyzed [2+2] cycloaddition and use the same Lewis acid in the same pot to catalyze the [4+2] annulation,” said Professor Johnson. “The synthesis of arenes and pyridines via [2+2+2] reactions of triple bonds is a well-established reaction, but applying the concept to saturated heterocycles is not a developed concept. We feel this paper provides the experimental blueprint for such annulations,” he concluded.
Silole-based π-electron systems are currently receiving much attention as new organic optical materials because of their low-lying LUMOs. π-Extended silole derivatives show desirable properties, such as high fluorescence quantum yields and high glass-transition temperatures. Various synthetic methodologies for the construction of the silole framework have been developed so far. However, these methodologies have been limited to the synthesis of ladder-type or spiro-type compounds. Recently, the group of Professor Takayuki Kawashima and Dr. Junji Kobayashi from the Department of Chemistry, The University of Tokyo (Japan), reported a further step towards the exploration of silole systems; namely, the synthesis of benzosilole derivatives. “We considered that further extension or modification of the silole framework should explore the silole chemistry, because these new molecules would provide improved properties,” said Professor Kawashima. “We focused our attention to the two-dimensionally π-expanded silole derivatives, not to linearly expanded molecules such as ladder-type compounds. However, these compounds are considered to be difficult to synthesize using conventional methods.” Indeed, according to Professor Kawashima, the development of a new type of synthetic methodology will be a keystone for the further progression to two-dimensionally extended derivatives.

As a promising new method, Professor Kawashima and co-workers proposed the direct silylation of an aromatic ring. “The Friedel–Crafts reaction is a well-known method for the direct substitution of an aromatic ring. On the other hand, the sila-Friedel–Crafts reaction – that is, the Friedel–Crafts-type silylation involving a silicenium ion as an intermediate – is known to occur only with electron-rich aromatic rings such as a ferrocene and a pyrrole,” he explained. However, in the case of a non-activated aromatic ring such as benzene, the conversion of the reaction was reported to decrease markedly.

“Thus,” continued Professor Kawashima, “the sila-Friedel–Crafts reaction has not been used as a versatile synthetic method to date.” Dr. Kobayashi explained that the difficulties of the sila-Friedel–Crafts reaction can be summarized in three points: 1) difficulty of the generation of silicenium ion, 2) arylene–Si+ complex usually favors π-complex rather than σ-complex, and 3) aryl–Si bonds are easily cleaved by acids.

The basic strategy of the sila-Friedel–Crafts reaction developed by Professor Kawashima and co-workers can be summarized as follows:

1) For the generation of a silicenium cation, the authors decided to employ the reaction of a hydrosilane with a trityl cation.
2) By using an intramolecular reaction, the reaction should easily proceed due to an entropy effect.
3) The presence of a base is necessary in this reaction to prevent the occurrence of a reverse reaction. “After the screening of the reaction conditions, the Ph$_3$CB(C$_6$F$_5$)$_4$/2,6-lutidine/CH$_2$Cl$_2$ system gave the best result,” said Dr. Kobayashi. “Our success in the development of the intramolecular sila-Friedel–Crafts reaction indicated that this reaction might be a new candidate for a synthetic methodology toward the silole skeleton.” “Indeed,” continued Professor Kawashima, “our methodology can be applied to the synthesis of the ladder-type silole derivative. These results encouraged us to challenge the synthesis of a more difficult target molecule. We tried to apply our method to the synthesis of trisilasumanene, which is a silicon analogue of sumanene, and succeeded in its first synthesis.” “Now we are going to expand our concept of the intramolecular sila-Friedel–Crafts reaction (electrophilic cyclization) to other main group element analogues such as phosphorus, selenium, and tellurium compounds,” concluded Dr. Kobayashi.

About the authors

Shunsuke Furukawa obtained his BSc degree from Hosei University (Japan) and MSc degree from the University of Tokyo. He is currently a PhD course graduate student in Professor Kawashima’s group.

Junji Kobayashi is a Research Associate of the University of Tokyo. He was born in Toyama, Japan in 1973 and received his BSc (1996) and MSc (1998) degrees from the University of Tokyo under the supervision of Professor Renji Okazaki. He became a Research Associate in the research group of Professor Takayuki Kawashima in 2001 and received his PhD from the University of Tokyo in 2001 under his supervision. He was Postdoctoral Researcher at University of Pennsylvania and Iowa State University (USA) from 2003 to 2005. His research interests are focused on organoheteroatom chemistry, especially on the chemistry of fluorescent compounds bearing main group elements as well as the chemistry of hyper-coordinate compounds with a rigid tetradeinate ligand.

Takayuki Kawashima was born in Kanagawa-ken, Japan in 1946 and received his BSc (1969), MSc (1971), and PhD (1974) from the University of Tokyo under the supervision of Professor Naoki Inamoto. He was Research Associate, Lecturer, and Associate Professor in the Department of Chemistry, Faculty of Science, The University of Tokyo from 1974 to 1998 and became a Professor of the Department of Chemistry, Graduate School of Science, The University of Tokyo, in 1998. From 1976 to 1978 he pursued postdoctoral research at Iowa State University and University of Utah (USA). His research interest is centered on organoheteroatom chemistry with an emphasis on the chemistry of small-ring compounds containing a high-coordinate main group element.
Asymmetric Histidine-Catalyzed Cross-Aldol Reactions of Enolizable Aldehydes

(Focus on an article from the current literature)

SYNFORM 2010/02 is available from January 22, 2010

In the next issues:

SYNSTORIES

■ Formation of N-Alkylpyrroles via Intermolecular Redox Amination
  (Focus on an article from the current literature)

■ Asymmetric Histidine-Catalyzed Cross-Aldol Reactions of Enolizable Aldehydes
  (Focus on an article from the current literature)

SYNTHESIS

Review on: Catalytic Asymmetric Michael Additions of α-Cyano Acetates
(by S. Jautze, R. Peters)

SYNLETT

Account on: Strategies for Heterocyclic Synthesis via Cascade Reactions Based on Ketenimines
(by P. Lu, Y. Wang)

SYNFACS

Synfact of the Month in category “Metal-Mediated Synthesis”:
Pd-Catalyzed Conversion of Aryl Triflates to Aryl Fluorides

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 768
Scientific Editor: Selena Boothroyd, selena.boothroyd@thieme.de
Assistant Scientific Editor: Stefanie Baumann, stefanie.baumann@thieme.de, phone: +49 711 8931 776
Assistant Scientific Editor: Christiane Kemper, christiane.kemper@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 729
Production Assistant: Theksten Schön, theksten.schoen@thieme.de, phone: +49 711 8931 744
Editorial Assistant: Sabine Heller, sabine.heller@thieme.de, phone: +49 711 8931 744
Marketing: Thomas Krinner, thomas.krinner@thieme.de, phone: +49 711 8931 772
Postal Address: SYNTHESISTH/ SYNFLACTS, Editorial Office, Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, phone: +49 711 8931 744, fax: +49 711 8931 777
Homepage: www.thieme-chemistry.com

Publication Information
SYNFORM will be published 12 times in 2010 by Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, and is an additional online service for SYNTHESIS, SYNLETT and 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 New York, 333 Seventh Avenue, New York, NY 10001, USA. To order: customerservices@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.
Europe, Africa, Asia, and Australia: Thieme Publishers, Rüdigerstraße 14, 70469 Stuttgart, Germany. To order: customerservices@thieme.de or use the Web site facilities at www.thieme.com.
For further inquiries please contact Mrs. Birgild 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 SYNFACS as well SYNTHESIS, SYNLETT and SYNFACS are available through Thieme-connect (www.thieme-connect.com/couriers) 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

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.