

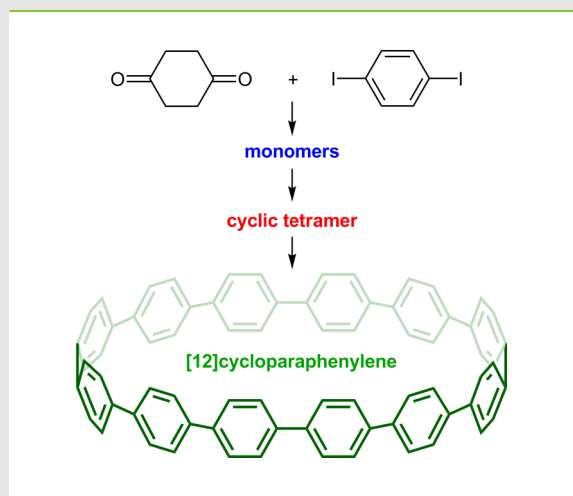
SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2009/07

SYNSTORIES

Selective Synthesis of [12]Cycloparaphenylene



A Route to Primary Amines Using Aqueous Ammonia

Hexaarylanthracenes by Means of $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ -Catalyzed C-H Arylation of Anthraquinone with Arylboronates

CONTACT +++++

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



Dear readers,

I am writing this short Editorial while I am flying over the Atlantic Ocean, back to Aberdeen (Scotland, UK) from Jackson Hole (Wyoming, USA), where I have attended the 19th International Symposium on Fluorine Chemistry

(a special section about this very well organized conference will be featured in the next issue of **SYNFORM**). Here, in this short night, 11 km higher than the huge (and a bit frightening to me...) ocean, I am trying to finalize this issue of **SYNFORM**, as sleep doesn't come even though I am dead tired. Curiously, I am realizing just now that all of the three **SYNSTORIES** cover the work of Japanese scientists; as far as I remember this is the first time that such a total predominance occurs. Well deserved predominance, I would say. In the first **SYNSTORY**, Professor S. Kobayashi (Tokyo) explains how to use simple aqueous ammonia to synthesize primary amines with high yields and selectivity. Then, Professor K. Itami (Nagoya) explains how his group was able to achieve the synthesis of [12]cycloparaphenylene. Last but not least, Professor F. Kakiuchi (Yokohama) tells us more about his recent catalytic synthesis of hexaarylanthracenes.

Kampai!!

Matteo Zanda

Editor of **SYNFORM**

CONTACT ++++

If you have any questions or wish to send feedback, please write to Matteo Zanda at:
Synform@chem.polimi.it

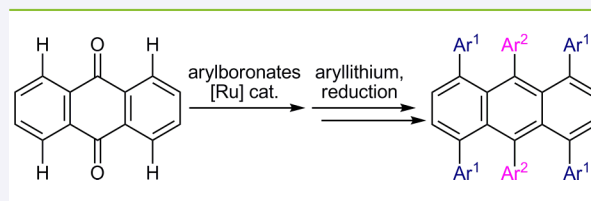
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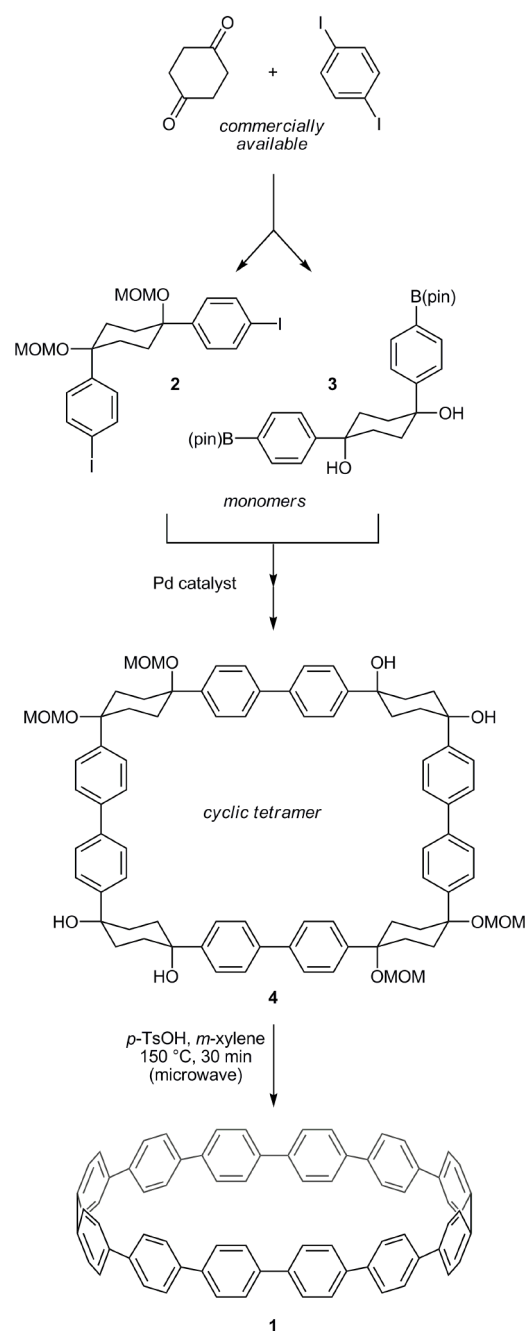
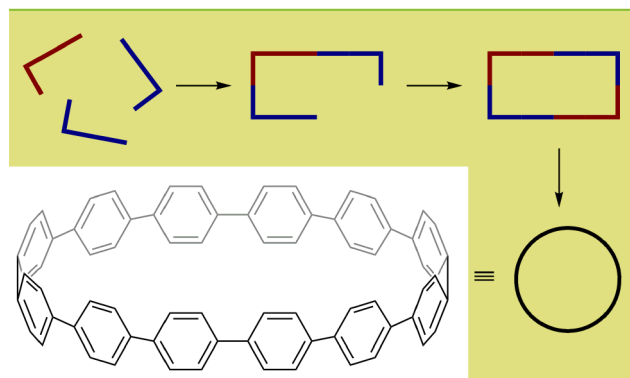
Selective Synthesis of [12]Cycloparaphenylene

Angew. Chem. Int. Ed. **2009**, *48*, 6112–6116

■ “Can you imagine how embarrassing it is for chemists to accept that there exist many aesthetically appealing molecules that can be easily assembled with molecular models by kids, but not in the flask by us?,” asked Professor Kenichiro Itami from the Nagoya University, Japan. “Cycloparaphenylene, a simple string of benzene, is such a molecule and had eluded the challenge of synthetic chemists for more than 70 years (one of the earliest attempts in literature: *J. Indian Chem. Soc.* **1934**, *11*, 95),” he continued. “My son and daughter made this in a minute, but it took us nearly four years completing the synthesis.”

In 2005, the group of Professor Itami initiated a synthetic study of aromatic belts/rings ultimately aimed at contributing to a bottom-up organic synthesis of structurally uniform single-walled carbon nanotubes. “We selected cycloparaphenylene (the shortest segment of a carbon nanotube) as a first target in view of a comparatively straightforward approach to their synthesis through aryl–aryl bond formation,” he explained. “Despite its structural simplicity, however, no successful synthesis had been reported at the inception of our work. After a four-years campaign, we finally accomplished a selective synthesis of [12]cycloparaphenylene (**1**) through stepwise Pd-catalyzed coupling reactions (six steps from commercially available reagents).”

The synthesis of Professor Itami capitalizes on the ability of *cis*-1,4-dihydroxycyclohexane-1,4-diyl to attenuate the build-up of strain energy during the macrocyclization as well



as its benzene-convertible nature. Through the stepwise Suzuki–Miyaura-type cross-coupling annulation connecting four 1,4-diphenylcyclohexane monomers (**2** and **3**), cyclic tetramer **4** was synthesized in reasonable overall yield. Finally, the transformation of **4** to **1** was accomplished by treatment of **4** with a stoichiometric amount of *p*-TsOH in *m*-xylene under microwave irradiation.

“It should be emphasized that during our investigation, in the very last step (two months before completion),” said Professor Itami, “we realized that the group of Bertozzi had accomplished the elegant first synthesis of [9]-, [12]-, and [18]cycloparaphenylenes (*J. Am. Chem. Soc.* **2008**, *130*, 17646).

Although we missed the first synthesis of cycloparaphenylenes, we very much enjoyed the beautiful spectra of [12]cycloparaphenylene,” said Professor Itami. “We won’t

forget the moment when we observed the dramatic transition from the very complicated NMR spectra of precursor **4** to the very simple ones of final compound **1** (one peak in ¹H NMR and two peaks in ¹³C NMR).”

Although in this paper Professor Itami and co-workers focused on the selective synthesis of one specific cycloparaphenylene, they believe that the strategy of stepwise assembly would provide a synthetic platform for other [*n*]cycloparaphenylenes. “By carefully selecting monomers with variable numbers of linear (arene) and bent (cyclohexane) units in the cross-coupling annulation steps, a range of cycloparaphenylenes of discrete ring size could be accessible,” he concluded. ■

Matteo Zanda

About the authors



Prof. K. Itami

Kenichiro Itami was born in Pittsburgh, USA (1971) and raised in Tokyo. Educated in chemistry at Kyoto University (Japan) under the guidance of Professor Yoshihiko Ito, he received his Ph.D. in 1998. From 1997–1998, he was a post-doctoral researcher in the group of Professor Jan-Erling Bäckvall at Uppsala University (Sweden). In the fall of 1998, he began his academic career at Kyoto University as an Assistant Professor (with Professor Jun-ichi Yoshida). He moved to Nagoya University to become an Associate Professor (with Professor Ryoji Noyori) in 2005, and was promoted to Full Professor in 2008. Representative awards include the Merck-Banyu Lectureship Award (2008), the Minister Award for Distinguished Young Scientists (2006), the Mitsui Chemicals Catalysis Science Award of Encouragement (2005), the Chemical Society of Japan Award for Young Chemists (2005), and the Thieme Chemistry Journals Award (2004). The main emphasis of his research is on the development of new synthetic methods, strategies, and concepts to solve challenging synthetic problems for realizing ideal chemical synthesis and for generating as yet unexplored molecules of significant interest. Representative projects include (1) new reactions and catalysts for C–H bond transformation, (2) programmed chemical synthesis, (3) biologically active molecules and natural products, (4) optoelectronic materials, and (5) nano-carbon materials.



From left to right: H. Takaba, Y. Yamamoto, H. Omachi

Hiroko Takaba was born in Obu, Aichi (Japan). She received her M.Sc. degree from Nagoya University (Japan) in 2009 under the supervision of Professor Kenichiro Itami. She is currently a researcher in a chemical company.

Haruka Omachi was born in Gamagori, Aichi (Japan). He received his B.Sc. degree from Nagoya University (Japan) in 2008 under the supervision of Professor Kenichiro Itami. He is currently an M.Sc. course graduate student in the group of Professor Itami.

Yosuke Yamamoto was born in Fukuroi, Shizuoka (Japan). He received his B.Sc. degree from Nagoya University (Japan) in 2006 under the supervision of Professor Kenichiro Itami. He is currently working in a city hall.



Dr. J. Bouffard

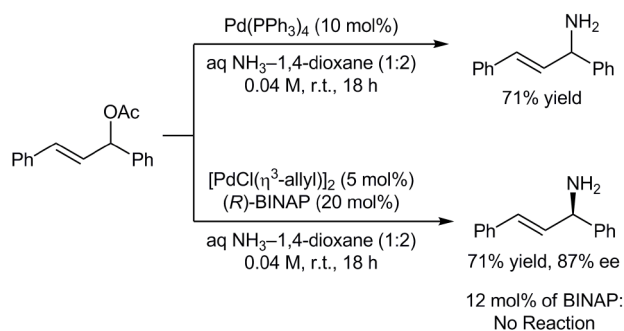
Jean Bouffard was born in Québec (Canada). He received his Ph.D. degree from Massachusetts Institute of Technology (USA) in 2007 under the supervision of Professor Timothy M. Swager. He is currently a JSPS postdoctoral researcher in the group of Professor Itami.

A Route to Primary Amines Using Aqueous Ammonia

J. Am. Chem. Soc. **2009**, *131*, 4200–4201; *Synfacts* **2009**, 668

Ammonia is one of the most attractive nitrogen sources from a cost and atom-economical point of view, and increasing attention has recently been paid to the direct use of ammonia as a nitrogen source for organic synthesis. Now, according to Professor Shū Kobayashi from The Department of Chemistry, University of Tokyo (Japan), it is possible to use aqueous ammonia for palladium-catalyzed allylic amination to prepare primary allylic amines. In general, the difficulty in the use of ammonia for metal-catalyzed processes seems to originate from the facts that (i) many kinds of transition metals are deactivated by ammonia to give stable amine complexes, and (ii) when a reaction forms a primary amine, this product is more reactive than ammonia and causes problematic overreactions. Thus, (i) choice of metal and (ii) how to suppress overreaction are both important for developing new reaction systems using ammonia. “In fact, in the course of our study on using aqueous ammonia for primary amine synthesis, we have conducted many trials without success,” said Professor Kobayashi. “One day, we tried the reaction of allyl acetate with aqueous ammonia in the presence of a catalytic amount of Pd(PPh₃)₄ without expectations because all the textbooks and review articles mention that ammonia cannot be used for palladium-catalyzed allylic substitution reactions,” said Dr. Takashi Nagano, a co-worker of Professor Kobayashi. According to Dr. Nagano, Professor Kobayashi often says “Textbooks are sometimes incorrect. See the results with your eyes and believe them even though textbooks say: it’s impossible” to his students. “Kobayashi’s faith is really true!” acknowledged Dr. Nagano. The NMR spectra Professor Kobayashi and co-workers obtained clearly showed full conversion of the starting allyl acetate and the formation of the desired primary amine along with the corresponding secondary amine. “Palladium-catalyzed allylic amination using ammonia proceeded contrary to the common knowledge!” said Dr. Nagano.

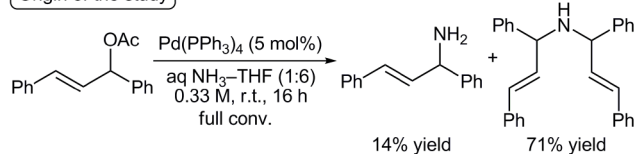
This finding prompted the authors to carry out further investigations, leading to the development of acceptable primary amine selectivity by using high-dilution conditions in aqueous NH₃-1,4-dioxane. The authors also reported a preliminary study for an asymmetric variant of this reaction. Simple BINAP can work even in the presence of an excess amount of ammonia. “The result clearly shows the robustness of BINAP against ligand replacement by NH₃,” said Professor Kobayashi, “and is the first example of catalytic asymmetric synthesis using aqueous ammonia as a nitrogen source.”



One drawback to be overcome is that a relatively large amount of chiral ligand (20 mol%) is needed. As to this point, Professor Kobayashi indicated: “We are now trying to reduce the catalyst loading. The excess chiral ligand, which is required to suppress catalyst deactivation in the current system, will be replaced by an appropriate inexpensive achiral ligand. We have already found a good candidate for this purpose.”

“In our report, the chemistry itself is not so new. One could claim that we just replaced an amine with ammonia as a nucleophile, but such insistence is to be called *Egg of Columbus*. We believe that this paper will be a foundation for further application,” the authors concluded.

Origin of the study



Matteo Zanda

About the authors



Prof. S. Kobayashi

Shū Kobayashi was born in 1959 in Tokyo (Japan). He studied chemistry at the University of Tokyo, receiving his Ph.D. in 1988 working under the direction of Professor T. Mukaiyama. Following an initial period as Assistant Professor, he was promoted to Lecturer and then Associate Professor at the Science University of Tokyo. In 1998 he moved to the Graduate School of Pharmaceutical Sciences, University of Tokyo, as Full Professor.

In April 2007, he was appointed to his current position as Professor of Organic Chemistry in the Department of Chemistry within the Faculty of Science of the University of Tokyo. He has held various visiting professorships, including the Université Louis Pasteur, Strasbourg, France (1993), Kyoto University, Japan (1995), Nijmegen University, The Netherlands (1996) and Philipps-University of Marburg, Germany (1997).

Professor Kobayashi has wide-ranging research interests that include the development of new synthetic methods and novel catalysts, organic reactions in water, solid-phase synthesis, total synthesis of biologically interesting compounds, and organometallic chemistry. He has held numerous named lectureships and is a recipient of many prestigious awards, including the Chemical Society of Japan Award for Young Chemists (1991), Teijin Award in Synthetic Organic Chemistry (1992),

Ciba-Geigy Research Foundation Award (1994), Springer Award in Organometallic Chemistry (1997), IBM Science Award (2001), Mitsui Chemical Catalysis Science Award (2005), JSPS Prize (2005), the Arthur C. Cope Scholar Award from the American Chemical Society (2006), and C. S. Hamilton Award (2006).



Dr. T. Nagano

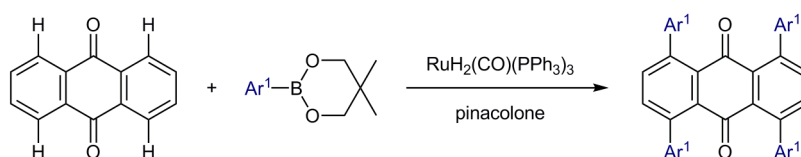
Takashi Nagano was born in Kochi (Japan) in 1977. He received his B.Sc. degree from Kochi University (Japan) under the direction of Professors Shun-ichi Kiyooka and Yuichi Kaneko in 2000, and his M.Sc. and Ph.D. degrees from Kyoto University (Japan) in 2002 and 2005, respectively, under the direction of Professors Tamio Hayashi and Masamichi Ogasawara. From 2005–2007 he worked as a Postdoctoral Fellow with Professor

Alois Fürstner at the Max-Planck-Institut für Kohlenforschung in Mülheim/Ruhr (Germany), where he carried out total synthesis of natural products, especially from the ipomoeassin family. He then joined to ERATO Kobayashi Highly Functionalized Reaction Environment Project (JST, The University of Tokyo) as a group leader in 2007. During this period, he focused on the development of metal-catalyzed reactions in water. He is currently Specific Researcher at Kyoto University and also Visiting Scholar at Sun Yat-sen University in Guangzhou (P. R. of China). His current research interest is the development of truly practical metal-catalyzed organic syntheses.

Hexaarylanthracenes by Means of $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ -Catalyzed C–H Arylation of Anthraquinone with Arylboronates

Org. Lett. **2009**, *11*, 1951–1954; *Synfacts* **2009**, 856 (*Synfact* of the Month)

Direct tetraarylation of C–H bonds



In late 1993, a new synthetic procedure using carbon–hydrogen bonds as a functional group was reported by Murai and co-workers (*Nature* **1993**, 366, 529). This reaction enabled efficient and selective introduction of alkyl groups onto aromatic rings via regioselective carbon–hydrogen bond cleavage and opened a new research area in organic synthesis. Following this seminal discovery, a variety of catalytic carbon–carbon and carbon–heteroatom bond formations via direct carbon–hydrogen bond cleavage have been developed (*Synthesis* **2008**, 3013; *Adv. Synth. Catal.* **2003**, 345, 1077). “The next step we must take is the application of these reactions in practical and efficient syntheses of valuable organic compounds such as natural products, bio-active compounds, pharmaceuticals, and organoelectronic devices,” said Professor Fumitoshi Kakiuchi from the Keio University, Yokohama (Japan). “I started the project concerning catalytic functionalizations of carbon–hydrogen bonds with Professor Murai at Osaka University,” he explained. In 2005, Professor Kakiuchi moved to Keio University and continued his studies in this field with his co-workers. “To date, our group has developed several types of catalytic carbon–carbon bond-formation reactions of aromatic ketones,” said Professor Kakiuchi, “for example, alkylations using olefins, alkenylations using alkynes, alkenylboronates, or alkenyl acetates, and arylation using arylboronates.” According to Professor Kakiuchi, the important merits of the use of ketones as substrates are that the carbonyl groups can be used not only as a directing functionality for regioselective carbon–hydrogen bond cleavage, but also as a functional group for further transformations. “At the initial stage of this project with Professor Murai, I focused on this synthetic potential of the ketone carbonyl group,” continued Professor Kakiuchi, “and designed a convenient syn-

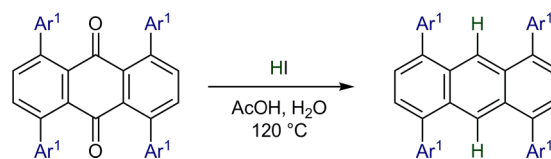
thesis of multisubstituted acenes such as anthracenes and pentacenes, which are important, promising compounds in organoelectronic materials. In particular, we applied our *ortho*-selective arylation of aromatic ketones to the convenient synthesis of multisubstituted anthracenes from anthraquinone.”

The reaction of anthraquinone with arylboronates, bearing an electron-donating or -withdrawing group, carried out in the presence of $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ catalyst under pinacolone reflux conditions afforded the target tetraarylated anthraquinones selectively in high yields.

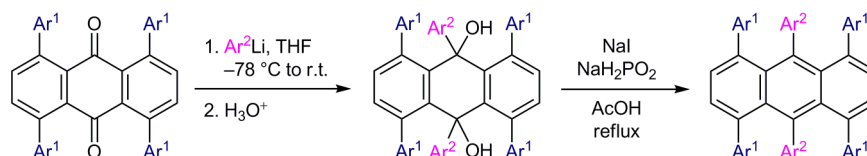
These compounds were further elaborated to a variety of functionalized arylanthracenes. Direct reductive arylation of the tetraarylated anthraquinones using HI led to 1,4,5,8-tetraarylanthracenes in high yields. Arylation of the carbonyl groups in the tetraarylanthraquinones with aryllithium gave the corresponding hexaaryldiols. Reductive aromatization of the diols using $\text{NaI}/\text{NaH}_2\text{PO}_2$ afforded hexaarylanthracenes in high yields. “Our protocol enabled the short-step synthesis of multiarylated anthracenes (2 or 3 steps) from anthraquinone,” confirmed Professor Kakiuchi.

“Over the last 15 years, a large number of new reactions involving carbon–hydrogen bond cleavage have been developed,” said Professor Kakiuchi. “Now, there are many synthe-

Conversion into tetraarylanthracene



Conversion into hexaarylanthracene

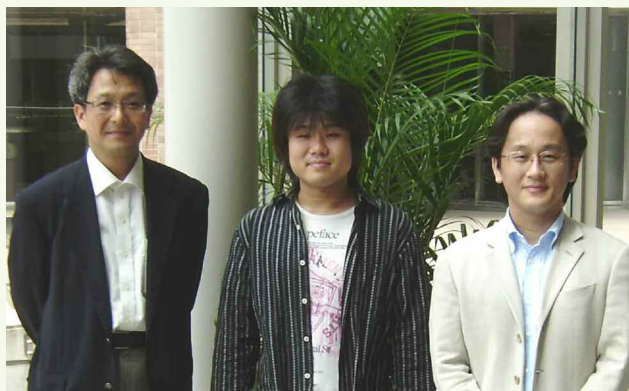


tic tools for making a variety of carbon–carbon and carbon–heteroatom bonds using carbon–hydrogen bonds. In the next decade, the practical synthesis of various valuable organic compounds via carbon–hydrogen bond cleavage will become a highly important research subject in organic and materials chemistry. Indeed, a few promising results have already been

reported (*Science* **2006**, *312*, 67; *Bull. Chem. Soc. Jpn.* **2008**, *81*, 548). Important advantages of these protocols are that they can shorten synthetic steps and reduce chemical waste during the reactions,” he concluded. ■

Matteo Zanda

About the authors



From left to right: Prof. F. Kakiuchi, K. Kitazawa, Dr. T. Kochi

Fumitoshi Kakiuchi was born in Hyogo (Japan) in 1965 and received his B.Sc. in 1988 and Ph.D. in 1993 from Osaka University under the guidance of Professor Shinji Murai. He was appointed as an Assistant Professor at Osaka University in 1993. He did his postdoctoral work with Professor E. N. Jacobsen at Harvard University (USA) from 1996–1997. In 2000, he was promoted to Associate Professor at Osaka University. In 2005, he moved to Keio University as a Full Professor. His research interests include the development of new transition-metal-catalyzed reactions.

Takuya Kochi was born in Tokyo (Japan) in 1975. He received his undergraduate and master's degrees from the University of Tokyo, working with Professors Masanobu Hidai and Youichi Ishii, and his Ph.D. in chemistry from the University of California at Berkeley (USA), under the guidance of Professor Jonathan A. Ellman. After carrying out postdoctoral research with Professor Kyoko Nozaki at the University of Tokyo, he joined the group of Professor Kakiuchi at Keio University as an Assistant Professor in 2007. His research interests include the development of new reactions and their application to the synthesis of a wide range of organic molecules.

Kentaroh Kitazawa was born in Nagano (Japan) in 1983 and received his B.Sc. (2006) and M.Sc. (2008) degrees from Keio University, working with Professor Kakiuchi. He is currently a Ph.D. student in Professor Kakiuchi's group at Keio University. His research interest is catalytic C–H functionalization.



Dr. M. Sato

Mitsuo Sato was born in Tokyo (Japan) in 1977. He received his B.Sc. (2000), M.Sc. (2002), and Ph.D. (2005) degrees from Keio University under the guidance of Professor Tohru Yamada. He joined the group of Professor Kakiuchi at Keio University as an Assistant Professor in 2005. In 2007, he moved to Fine Electronic Materials Research Laboratories in JSR Corporation.

COMING SOON ► ► COMING SOON ► ►

SYNFORM 2009/08 is available from October 22, 2009

In the next issues:

SYNSTORIES ■ ■ ■ ■ ■

■ **Biomedical Applications of Semifluorinated Block Copolymers**
(Focus on the 19th International Symposium on Fluorine Chemistry, Jackson Hole, WY, USA, August 23–28, 2009)

■ **Efficient Synthesis of Benzothiophenes by an Unusual Palladium-Catalyzed Vinylic C–S Coupling**
(Focus on an article from the current literature)

FURTHER HIGHLIGHTS + + + +

SYNTHESIS

Special Topic on “C–H Activation” in issue 20/2009

SYNLETT

Account on: Organometallic Strategies for the Synthesis of Conjugated Oligomers

(by F. Naso)

SYNFACTS

Synfact of the Month in category “Polymer-Supported Synthesis”: [Hydration of Nitriles to Amides with Supported Silver Nanoparticles](#)

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, 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
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- Senior Production Editor: Thomas Loop,
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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/SYNLETT/SYNFACTS, Editorial Office,
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