

# SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2009/06

## SYNSTORIES

■ **Asymmetric Autocatalysis  
Triggered by Carbon Isotope  
(<sup>13</sup>C/<sup>12</sup>C) Chirality**



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

■ **Thieme-Chemistry Journals  
Editorial Board Meetings 2009**

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**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  $^{12}\text{C}$  or  $^{13}\text{C}$  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*

**CONTACT ++++**

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

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

*Org. Lett.* **2009**, *11*, 729–732; *Synfacts* **2009**, 479 (*Synfact* of the Month)

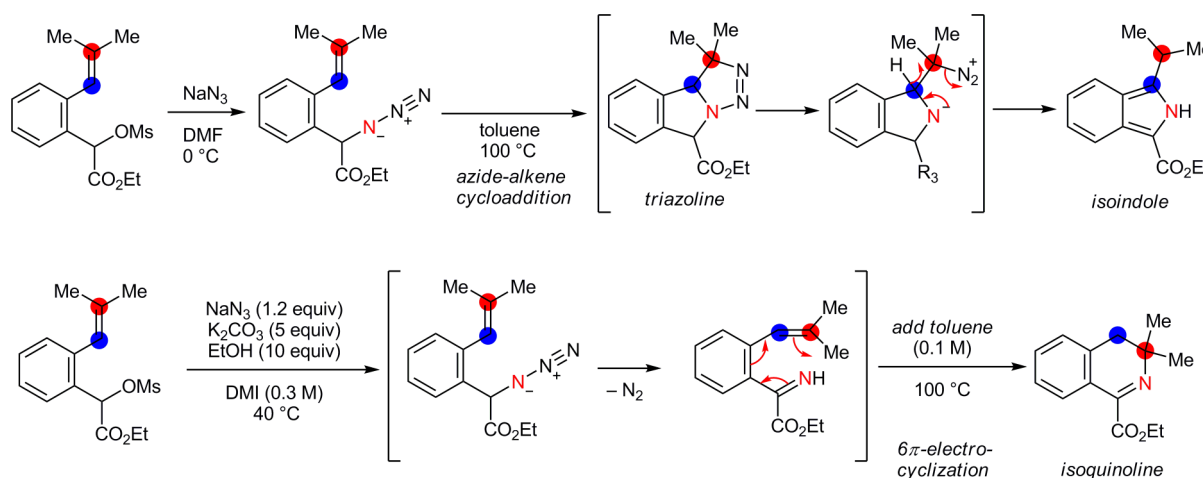
■ Nitrogen-containing heterocycles (azaheterocycles) are important and widespread structures, present in numerous natural products, potent pharmaceutical drugs, and various kinds of functional materials. Although a number of diverse synthetic approaches toward azaheterocycles have been developed it is 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, “ $\alpha$ -azido carbonyl compounds containing a 2-alkenyl-aryl 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  $6\pi$ -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  $\text{NaN}_3$  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  $\text{NaN}_3$  induced the formation of  $N$ -H imine,” he concluded, “we soon elucidated the optimized reaction conditions to provide isoquinolines selectively.” ■

Matteo Zanda



### About the authors



Prof. S. Chiba

**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.



W.-Q. Hui

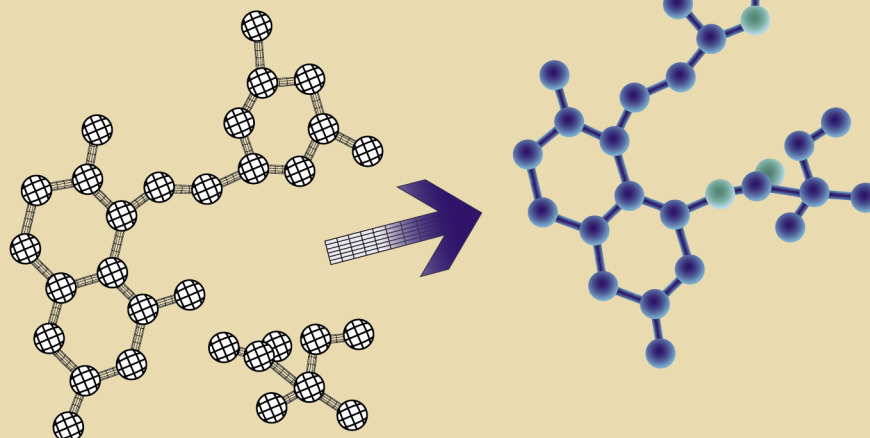
**Benjamin Wei-Qiang Hui** was born in Singapore in 1982 and obtained his bachelor's degree in chemistry from the National University of Singapore (NUS) in 2007. In the same year, he entered the graduate program at Nanyang Technological University (NTU) under the supervision of Professor Shunsuke Chiba.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

## INFORMATION ++++

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- Contains 24 860 review articles (from journals and books)
- Covers literature from 1970 to the end of 2008 and is updated annually
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## Asymmetric Autocatalysis Triggered by Carbon Isotope ( $^{13}\text{C}/^{12}\text{C}$ ) Chirality

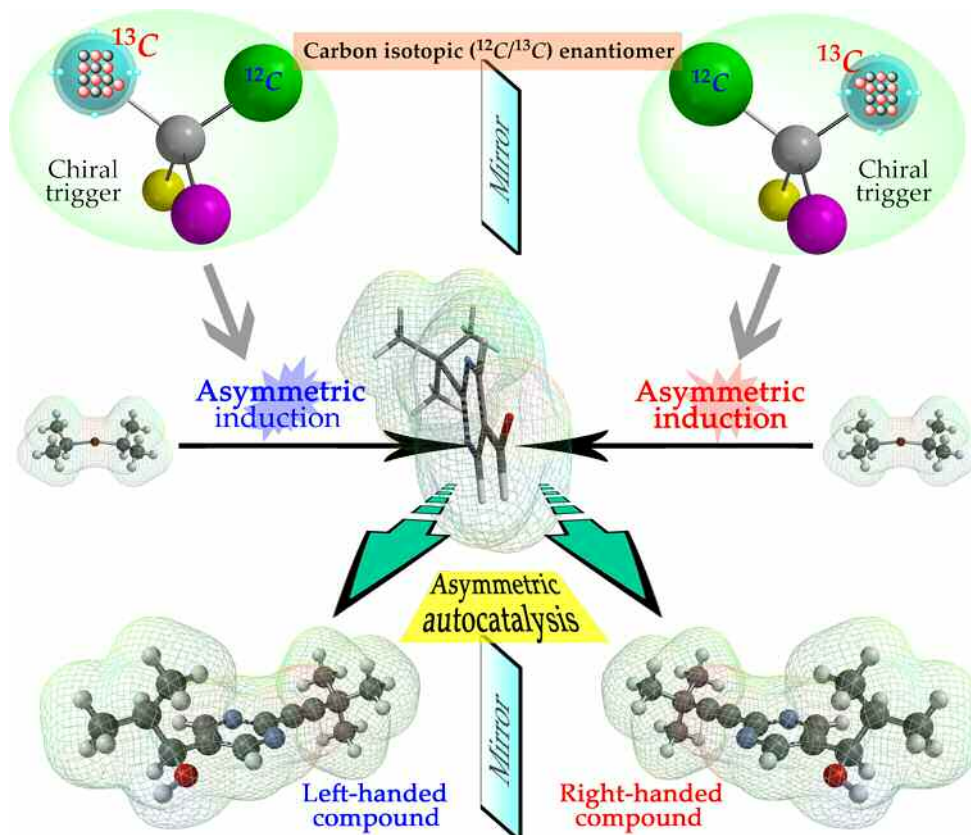
*Science* **2009**, *324*, 492–495

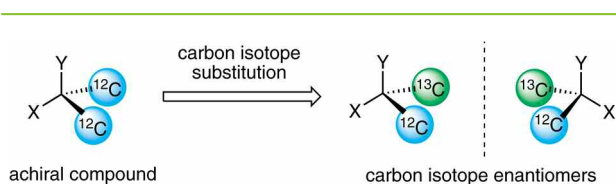
■ The origin of homochirality of biomolecules such as L-amino acids and D-sugars has attracted significant interest of many researchers. Many apparently achiral molecules may be chiral because of random substitution of the 1.1% naturally abundant  $^{13}\text{C}$  for  $^{12}\text{C}$ .<sup>1</sup> Hydrogen isotope chirality (H/D) in a polymer has been shown to cooperatively control macromolecular helical handedness.<sup>2</sup>

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 per-

form 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-





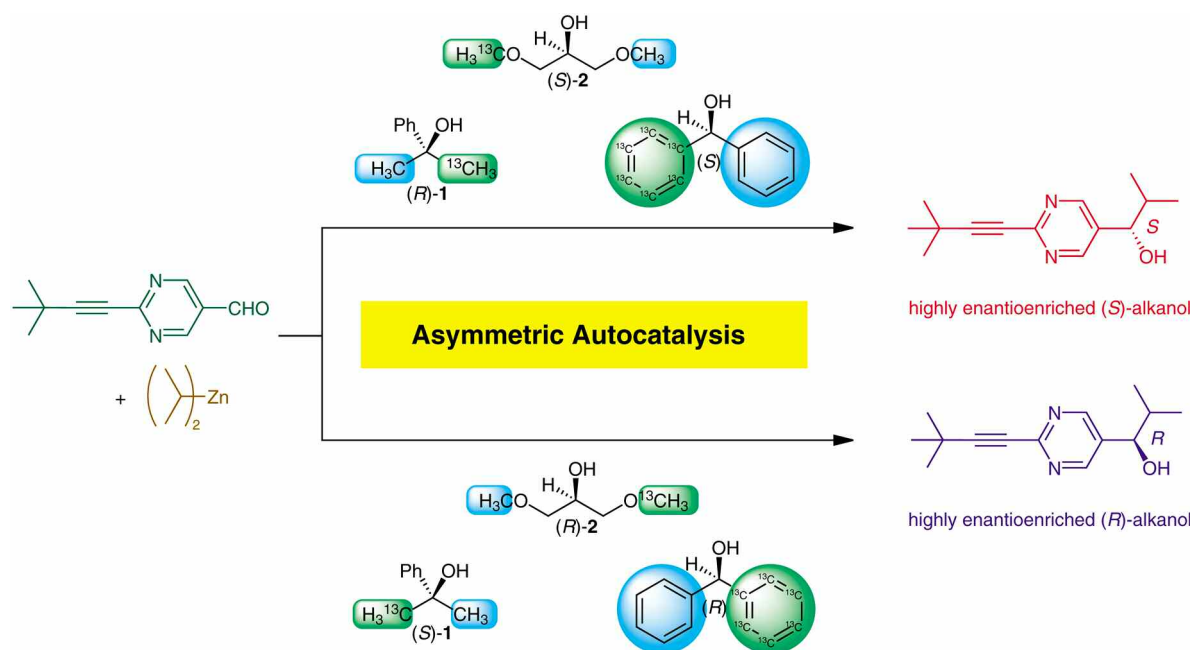
dine-5-carbaldehyde and diisopropylzinc exhibits significant amplification of chirality, that is, starting from an asymmetric autocatalyst with extremely low enantiomeric excess (ee), three consecutive asymmetric autocatalyses afford almost enantiopure (>99.5% ee) pyrimidyl alkanol with significant multiplication of the amount.<sup>3</sup> 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.”<sup>4</sup>

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 <sup>13</sup>C and <sup>12</sup>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 <sup>13</sup>C/<sup>12</sup>C isotope chirality. “For example,” said Professor Soai, “we prepared both enantiomers of dimethylphenylmethanol <sup>13</sup>C/<sup>12</sup>C isotopes by independent methods. By using the same enantiomer of chiral catalyst, the enantioselective additions of (A) <sup>13</sup>C-labelled dimethylzinc [(<sup>13</sup>CH<sub>3</sub>)<sub>2</sub>Zn] to acetophenone and (B) (CH<sub>3</sub>)<sub>2</sub>Zn to <sup>13</sup>C-labelled acetophenone (C<sub>6</sub>H<sub>5</sub>CO<sup>13</sup>CH<sub>3</sub>) gave the opposite enantiomers of which one of the methyl groups is <sup>13</sup>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, <sup>13</sup>C/<sup>12</sup>C chirality induced an enantioenrichment in the asymmetric reaction.

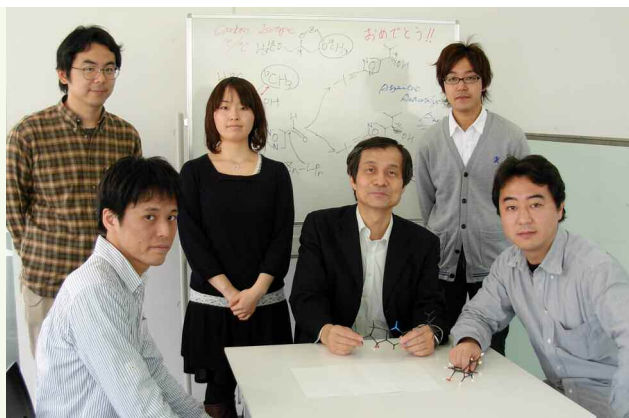
“Because the asymmetric autocatalysis has now been shown to be capable of discriminating the <sup>13</sup>C/<sup>12</sup>C chirality,” concluded Professor Soai, “the concept of the origin of chirality may have expanded significantly.”

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  $^{13}\text{C}$  incorporation is able to exert sufficient influence on the early stages of Soai's highly tuned *i*-Pr<sub>2</sub>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. ■

Matteo Zanda



From left to right: K. Suzuki, T. Tsutsumi, Y. Matsumura, Prof. K. Soai, M. Ito, Dr. T. Kawasaki

### About the authors

**Kenta Suzuki** obtained his B.Sc. and M.Sc. degrees from Tokyo University of Science (Japan). He is currently a Ph.D. course graduate student in Professor Soai's group.

**Takashi Tsutsumi** received his B.Sc. and M.Sc. degrees with Professor Soai and joined a chemical company in 2007.

**Yukari Matsumura** obtained her B.Sc. and M.Sc. degrees under the supervision of Professor Soai. She joined a chemical company in 2009.

**Kenso Soai** graduated from University of Tokyo (Japan) (B.Sc.) and obtained his Ph.D. degree (1979) with Professor T. Mukai - yama. He was a fellow of the Japan Society for the Promotion of Science (JSPS). He joined the group of Professor E. L. Eliel

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- (4) T. Kawasaki, H. Tanaka, T. Tsutsumi, T. Kasahara, I. Sato, K. Soai *J. Am. Chem. Soc.* **2006**, *128*, 6032.

as a Postdoctoral Fellow at the University of North Carolina at Chapel Hill (USA) in 1979. He was appointed as Lecturer at Tokyo University of Science in 1981 and established his research group. He was promoted to Associate Professor in 1986 and to Full Professor in 1991. His awards include: Progress Award in Synthetic Organic Chemistry, Japan (1988), Chisso Award in Synthetic Organic Chemistry (1990), The Chemical Society of Japan Award for Creative Work for 1999, Inoue Prize for Science (2000), Molecular Chirality Award (2002), Merit of Tokyo Metropolitan for Science and Technology (2002), Synthetic Organic Chemistry Award (2003), Medal of The National Academy of Science, Letters and Art, Modena (2003), Chirality Medal (2005), Special Award for Excellent Researcher of Tokyo University of Science (2006), Tetrahedron: Asymmetry, Most Cited Paper 2003-2006 Award (2006), Prize for Science and Technology (2007) of the Minister of Education, Culture, Sports, Science and Technology.

**Masateru Ito** obtained his B.Sc. and M.Sc. degrees with Professor Soai. He joined a chemical company in 2009.

**Tsuneomi Kawasaki** studied chemistry at the University of Tokyo and received his B.Sc. (1999) and Ph.D. (2004) degrees under the supervision of Professor Takeshi Kitahara. As a Research Associate, he moved to the Department of Applied Chemistry, Tokyo University of Science in the group of Professor Soai in 2004 where he currently is a Junior Assistant Professor. He received the Nissan Chemical Industry Award in Synthetic Organic Chemistry, Japan in 2005, the Royal Society of Chemistry: Organic & Biomolecular Chemistry Poster Award in Chirality at the Nanoscale 2007 and the Lectureship Award of Young Generation Special Forum from the Chemical Society of Japan in 2009.

## Thieme-Chemistry Journals Editorial Board Meetings 2009

■ The 2009 Editorial Boards Meeting of the Thieme Chemistry journals *SYNLETT*, *SYNTHESIS* and *SYNFACTS*, including the supplement *SYNFORM*, was held on June 5<sup>th</sup> and 6<sup>th</sup> 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 40<sup>th</sup> anniversary of *SYNTHESIS* and the 20<sup>th</sup> 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). ■



Matteo Zanda





COMING SOON ► ► 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](#)

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