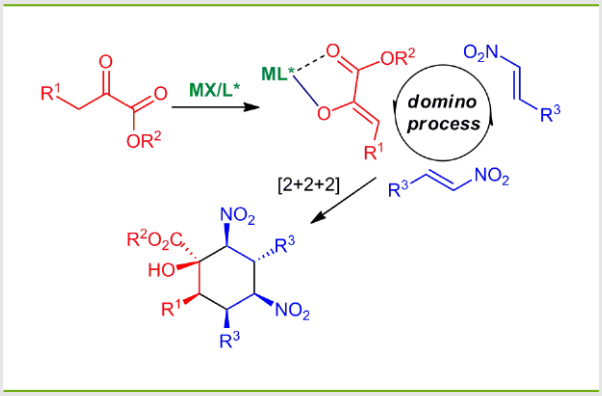
SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2012/05

SYNSTORIES

- **A Highly Diastereo- and Enantioselective Reaction for Constructing Functionalized Cyclohexanes: Six Contiguous Stereocenters in One Step**



- **Radical Addition of Alkyl Halides to Formaldehyde in the Presence of Cyanoborohydride as a Radical Mediator**

- **SYNTHESIS/*SYNLETT* Advisory Board Focus: Professor Keisuke Suzuki (Tokyo Institute of Technology, Japan)**

CONTACT ++++

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Dear readers,

This issue of **SYNFORM** is dominated by Asian chemistry and chemists, which is not at all surprising given the impressive development of countries like P. R. of China, India, Singapore, South Korea and others which are now competing with Japan on the continental scale and synergistically acting with Japan in establishing Asia as the new giant in the global research arena. In the first **SYNSTORY** Professor I. Ryu (Japan) guides us through his recent radical process based on the addition of alkyl halides to an underutilized, at least in radical chemistry, one-carbon building block such as formaldehyde. The second **SYNSTORY** brings us to the P. R. of China where Professor H. Huang has recently established a new world record in the simultaneous formation of six new contiguous stereocenters in one molecule, a highly functionalized cyclohexane, by means of a single synthetic step. Last but not least, the Editorial Advisory Board profile features Professor K. Suzuki (Japan).

Enjoy your reading!

Matteo Zanda

Editor of **SYNFORM**

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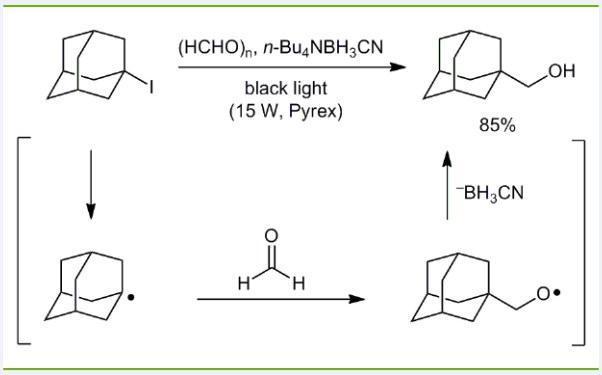

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CONTACT ++++

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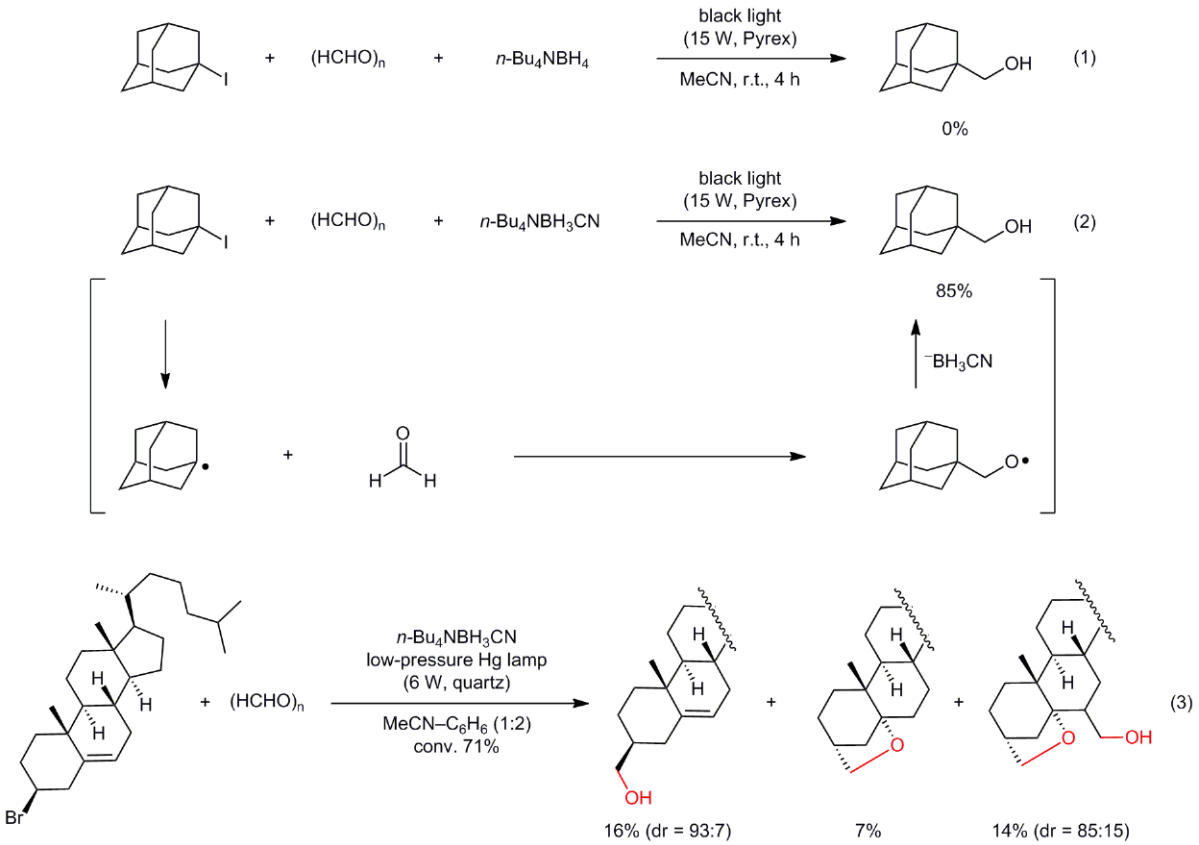
NEWS AND VIEWS NEWS AND VIEWS NEWS AND VIEWS

Radical Addition of Alkyl Halides to Formaldehyde in the Presence of Cyanoborohydride as a Radical Mediator

J. Am. Chem. Soc. **2012**, *134*, 875–877

Whereas carbon monoxide, isonitriles, and substituted oxime ethers have found wide applications in radical-mediated multi-component reactions as viable C1 synthons,[1] the utilization of formaldehyde has been only marginally explored.[2] This is in sharp contrast with the fact that formaldehyde is a quite common reagent in carbanion chemistry, and has been successfully used for one-carbon homologation reactions. Recently, however, the group of Professor Ilhyong Ryu from Osaka Prefecture University (Japan) developed an efficient radical process for the hydroxymethylation of haloalkanes, in which formaldehyde is used as C1 radical synthon. The breakthrough is concerned with the use of tetrabutylammonium cyanoborohydride as a radical mediator.

"It has long been known that radical addition to formaldehyde does occur. We thought that formaldehyde is a cheap and potentially abundant feedstock and it was time to develop synthetically useful radical reactions making use of formaldehyde," said Professor Ryu, who acknowledged that the original work of Fuller and Rust, published in 1958, disclosed that the *tert*-butyl peroxide initiated radical addition of cyclohexane to formaldehyde takes place, affording cyclohexanemethanol.[2a] Another key paper by Brown, Suzuki, and co-workers, pub-



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lished in 1972, demonstrated that in the presence of air, the reaction of tributylborane and formaldehyde gave 1-pentanol.[2b] "After these pioneering efforts, surprisingly this chemistry has been neglected for nearly four decades," pointed out Professor Ryu. "Previously, we demonstrated that tetrabutylammonium hydroborate can be used for Giese-type radical reactions and radical carbonylations as a substitute for tributyltin hydride.[3] We were naturally tempted to apply formaldehyde in combination with borohydride mediators," said Professor Ryu. Next, the Ryu group reported that the hydroxymethylation of iodoalkanes proceeds using CO and tetrabutylammonium borohydride;[4] therefore, this reagent was chosen for the radical reaction of formaldehyde. According to Professor Ryu, the first experiment using tetrabutylammonium borohydride was totally unsuccessful (Scheme, eq. 1). "The key to success was the employment of 'low-reactive' borohydride reagents for the hydride addition to formaldehyde, which Takuji Kawamoto, a PhD student in our group, keenly designed and optimized. Takuji examined a milder reagent, tetrabutylammonium cyanoborohydride, which worked beautifully," said Professor Ryu. Indeed, the reaction of 1-iodoadamantane gave 85% yield of 1-hydroxymethyladamantane (Scheme, eq. 2). "The reaction of cholesteryl bromide gave a set of products via tandem radical reactions, which is a good sign that further applications to cascade reactions would be promising (Scheme, eq. 3)," added Professor Ryu.

"It is interesting to note that, besides borohydride reagents, radical reactions using borane reagents such as NHC-borane are now widely investigated," he continued.[5] "We are quite interested in the reactions of formaldehyde in combination with such newly evolving NHC-borane reagents," said Professor Ryu, who pointed out that executing kinetic studies surrounding alkyl radical addition to formaldehyde and abstraction of hydrogen of the resulting alkoxy radicals from borate anions would be strongly needed in order to accelerate studies focusing on multicomponent reactions. "In the near future, this methodology will be extended to multicomponent reactions that incorporate formaldehyde and other carbon units, such as alkenes and alkynes. Thus, radical chemistry of formaldehyde will open a new chapter," concluded Professor Ryu.

Matteo Zanda

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About the authors

T. Kawamoto

Takuji Kawamoto was born in Sakai, Osaka (Japan). He received his Masters degree from Osaka Prefecture University (Japan) in 2011. He is currently a PhD student at the Osaka Prefecture University (Professor Ryu is the supervisor) and will undertake a JSPS (Japan Society of Promotion of Science) Research Fellowship this April.

Dr. T. Fukuyama

Takahide Fukuyama received his Ph.D. in 1999 from Osaka University (Japan) under the direction of Professor Shinji Murai. He spent the year 1999–2000 as a Postdoctoral Fellow of JSPS at Okayama University of Science (Japan) with Professor Junzo Otera. In 2000, he was appointed as an Assistant Professor in Professor Ryu's group at Osaka Prefecture University. He was promoted to Lecturer in 2007 and to Associate Professor in 2010. He had the experience of working with Max Malacria at the University of Pierre and Marie Curie (France, 2006). He is the recipient of the Dainippon Ink & Chemicals Inc. Award of the Society of Synthetic Organic Chemistry, Japan.

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Prof. I. Ryu

Ilhyong Ryu received his Ph.D. from Osaka University in 1978 under the direction of Professor Noboru Sonoda. After serving as a JSPS Postdoctoral Fellow and a Research Associate at Osaka University, he was appointed Assistant Professor at Osaka University in 1988 and promoted to Associate Professor in 1995. He also had the experience of working with Professor Howard Alper (1991–1992) at the University of Ottawa (Canada). In 2000, he moved to Osaka Prefecture University as a Full Professor. He has been the recipient of many awards, including the Progress Award in Synthetic Organic Chemistry, Japan (1990) and the Chemical Society of Japan Award for Creative Work (2004).

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A Highly Diastereo- and Enantioselective Reaction for Constructing Functionalized Cyclohexanes: Six Contiguous Stereocenters in One Step

Angew. Chem. Int. Ed. **2012**, *51*, 1248–1251

The stereoselective installation of contiguous multiple stereocenters through catalytic reactions from simple starting materials represents one of the most important subjects in synthetic organic chemistry, since structural frameworks featuring multiple contiguous stereocenters are widespread in natural and unnatural products that exhibit potent biological activity. The number of possible stereoisomers increases exponentially with the number of stereocenters; therefore, the highly stereoselective synthesis of chiral molecules with contiguous multiple stereocenters from simple starting materials in one step represents a challenging endeavor. Asymmetric domino processes that generate more than one chemical bond concomitantly with the creation of multiple stereocenters in a one-pot fashion has emerged as a promising way to synthesize these structural units. Recently, the group of Professor Hanmin Huang from the Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences (P. R. of China) reported a new methodology for the generation of highly functionalized cyclohexane carboxylates with six stereogenic centers (up to 98% ee, dr > 20:1) via transition-metal-catalyzed asymmetric formal [2+2+2] annulation between α-keto esters and nitroalkenes (Figure 1).

"Our group is actively involved in the development of new and efficient asymmetric tandem reactions for the synthesis of functionalized chiral compounds with multiple stereocenters," said Professor Huang. "One year ago, we developed efficient asymmetric tandem reactions for the construction of three contiguous stereogenic centers in acyclic open-chain systems with high diastereo- and enantioselectivity based on the careful control of the geometry of acyclic enolates produced in situ (*Angew. Chem. Int. Ed.* **2010**, *49*, 2728; *Org. Lett.* **2011**, *13*, 5596). Based on these results, we decided to develop some

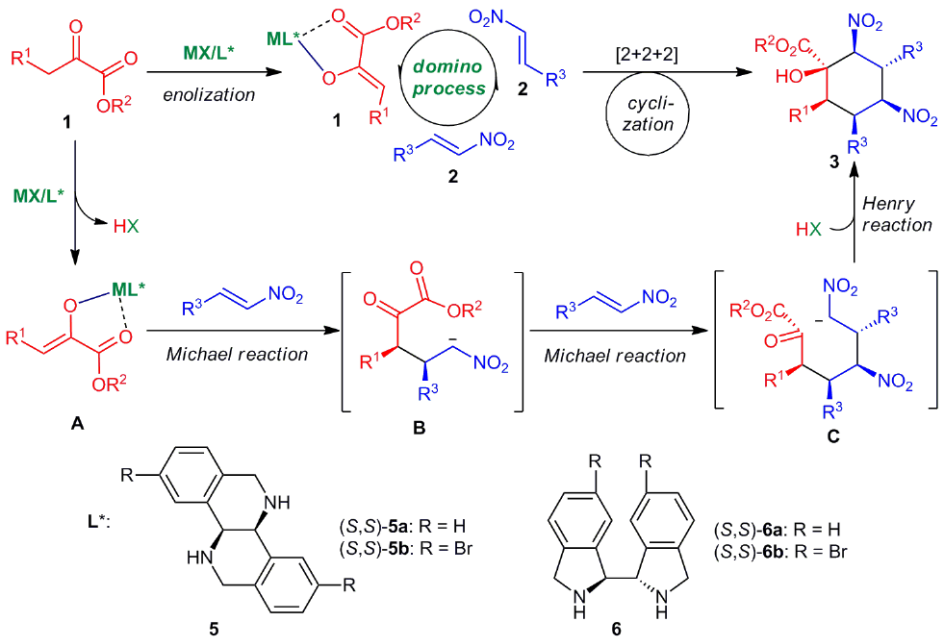

Figure 1

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domino processes that could generate many more stereocenters in one step," he continued. "Chiral functionalized cyclohexanes with contiguous multiple stereocenters are a highly desirable structural motif found in natural and synthetic bioactive compounds. Previously, the highest number of contiguous stereocenters generated in one single step in functionalized cyclohexanes was five, as reported by Karl Anker Jørgensen (*Angew. Chem. Int. Ed.* **2007**, *46*, 9202) and Bor-Cherng Hong (*Org. Lett.* **2011**, *13*, 1278). A cyclohexane with six contiguous stereocenters was reported as a byproduct by Mikiko Sodeoka and colleagues (*J. Am. Chem. Soc.* **2010**, *132*, 4036; *Tetrahedron: Asymmetry*, **2010**, *21*, 1682) in their Ni-catalyzed conjugate addition reaction, while Jean Rodriguez and co-workers also synthesized only one cyclohexane compound with six chiral centers in lower yield using an organocatalytic method (*Org. Lett.* **2010**, *12*, 5246)." With the background above, Professor Huang and his co-workers designed a cascade process (Figure 1) which was triggered by an active enolate species generated from the α-keto ester. "The principal challenge for establishing such a domino catalytic asymmetric process was to identify a good catalyst for facilitating the formation of the metal-enolate active species **A** and constructing a well-oriented chiral environment around the enolate intermediate (Figure 1)," he explained.

Hypothesizing that the conformationally rigid structure would have good chiral induction abilities, Professor Huang and his co-workers designed and synthesized a series of rigid chiral diamines (*Org. Lett.* **2009**, *11*, 4536) with an intriguing structural motif. "The design of these chiral diamines is based on the structure of DPEN," he said. "Although DPEN has already been proven to be a good ligand for asymmetric reactions, the free rotation of the phenyl group on the backbone renders it conformationally flexible. We reasoned that the conformational mobility can be restricted by introducing two additional methylene groups on its scaffold to bridge the phenyl and amino groups. Thus, the chiral amines **5** and **6** were designed (Figure 2)," said Professor Huang, who pointed out that these chiral diamines have subsequently been developed into excellent catalysts for the asymmetric hydrogenation of ketones (*Chem. Eur. J.* **2011**, *17*, 7760).

"Inspired by these results, Dengjian Shi, a third-year graduate student in our group, had the idea to try to prepare a series of Lewis acid catalysts with these chiral diamines for promotion of the above-described enolate-triggered tandem reaction," acknowledged Professor Huang. "First of all, the catalyst should be highly chemoselective for overcoming the major side reaction that leads to the undesired linear conjugate addition byproduct. Secondly, the catalyst should be highly stereoselective for enantioselectively producing only one enantiomer out of 64 (2^6) possible stereoisomers, since six stereocenters are generated in this cascade asymmetric reaction," he said. After extensive screening of a number of experimental factors, the Chinese researchers finally found that the catalyst composed of $Cu(OAc)_2 \cdot H_2O$ and chiral diamine **5a** was able to afford the target cyclohexane carboxylates with excellent enantioselectivity and complete diastereoselectivity under mild and environmentally friendly reaction conditions. "The reaction could be performed with 0.1 mol% of Cu catalyst on a gram-scale of substrate to afford the desired product with high yield and excellent selectivity," he added. "From a practical point of view, we believe that our method represents a record for the synthesis of the highest number of contiguous stereocenters in a molecule made in just one highly selective step," Professor Huang pointed out. "Although a method for generating chiral compounds with eight contiguous stereocenters has been reported previously, two steps were needed to

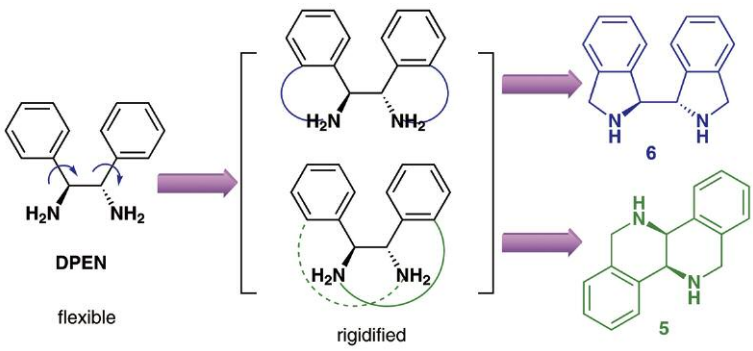

Figure 2

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perform it (*Angew. Chem. Int. Ed.* **2007**, *46*, 467)," he said. "This research has advanced the state-of-the-art of asymmetric catalytic tandem reactions and, furthermore, confirms that the asymmetric tandem reaction is a powerful and efficient tool in synthetic organic chemistry. It is our opinion that continuing and extensive research efforts to merge different reaction modes into one domino process will become mainstream in asymmetric synthesis," concluded Professor Huang.

Matteo Zanda

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SYNTHESIS/*SYNLETT* Advisory Board Focus: Professor Keisuke Suzuki (Tokyo Institute of Technology, Japan)

Background and Purpose. ***SYNFORM*** will from time to time portrait **SYNTHESIS/*SYNLETT*** Advisory Board members who answer several questions regarding their research interests and revealing their impressions and views on the developments in organic chemistry as a general research field. In this issue, we present Professor Keisuke Suzuki, Tokyo Institute of Technology (Japan).

BIOGRAPHICAL SKETCH

Prof. K. Suzuki

Keisuke Suzuki was born in 1954 in Chigasaki (Japan). He obtained a Doctor of Science Degree in 1983 at The University of Tokyo (Japan) under the guidance of Professor Teruaki Mukaiyama. He was appointed Research Associate to the late Professor Gen-ichi Tsuchihashi in the Department of Chemistry, Keio University (Japan, 1983), and promoted to Lecturer (1987), Associate Professor (1989), and Professor (1994) at Keio University. He enjoyed a year as a Visiting Professor at ETH Zürich (Switzerland, 1990–1991) with Professor Dieter Seebach. In 1996, he moved to the Department of Chemistry, Tokyo Institute of Technology, where he remains today. The awards he has received include The Chemical Society of Japan (CSJ) Award for Young Chemists in 1986, the Takasago Award of the Synthetic Organic Chemical Society, Japan (SOCSJ) in 1994, the Japan IBM Award in 1994, the Teshima Award in 1997, the Nagoya Silver Medal in 1999, the SOCSJ Award in 2003, Prizes for Science and Technology, Ministry of Education, Culture, Sport, Science and Technology, Japan in 2006, The CSJ Award in 2008, the Humboldt Research Prize in 2009, and the Medal with Purple Ribbon in 2010.

INTERVIEW

SYNFORM | *What are your main current research interests?*

K. Suzuki | Organic synthesis, focusing the attention to new strategies and tactics in natural/unnatural product synthesis. In spite of the great advances in organic synthesis, certain classes of compounds still remain difficult to access. An example is the densely functionalized polycyclic compounds derived from the type-II polyketide biosynthesis. The synthesis becomes even more challenging when the structure is hybridized with other biosynthetic products, for example, sugars or terpenoids, which we call *hybrid natural products* (Review: K. Suzuki, Lessons from Total Synthesis of Hybrid Natural Products, *Chem. Rec.* **2010**, *10*, 291). Other current targets include the catechin-class polyphenols and their oligomers and the pluramycin-class bis-*C*-glycoside antibiotics.

SYNFORM | *What is your most important scientific achievement to date and why?*

K. Suzuki | The total synthesis of mycinamicin IV, a macrolide antibiotic (T. Matsumoto, H. Maeta, K. Suzuki, G. Tsuchihashi, First Total Synthesis of Mycinamicin IV and VII. Successful Application of New Glycosidation Reaction, *Tetrahedron Lett.* **1988**, *29*, 3575). It was my early contribution to the area of natural product synthesis which was completed by using original tactics, including acyclic stereocontrol via stereospecific 1,2-shift for assembling the aglycon and the hafnocene-based *O*-glycoside synthesis. It was also important in my research career because it was through the struggle that I came to notice the importance and synthetic challenge posed by *hybrid natural products*.

SYNFORM | *Do you have hobbies besides chemistry?*

K. Suzuki | Soccer. I used to play in much earlier days, but nowadays I'm just watching games, of course.

Matteo Zanda

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SYNSTORIES

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(Focus on an article from the current literature)

Diastereoselective Rhodium-Catalyzed Ene-Cycloisomerization Reactions of Alkenylidenecyclopropanes: Total Synthesis of (–)-α-Kainic Acid
(Focus on an article from the current literature)

FURTHER HIGHLIGHTS

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SYNLETT

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SYNFACTS

Synfact of the Month in category "Metal-Catalyzed Asymmetric Synthesis and Stereoselective Reactions": Asymmetric Synthesis of Indolines by Pd-Catalyzed C(sp^3)–H Activation

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