

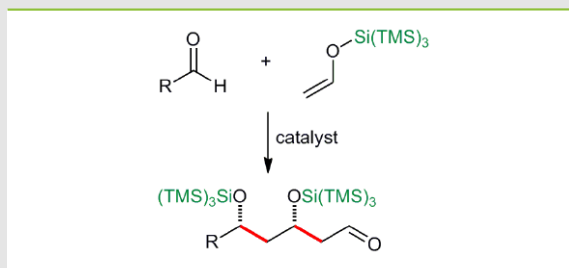
# SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2010/07

## SYNSTORIES ■ ■ ■ ■

■ Aldol Methodologies Utilizing Super Silyl Groups for Polyketide Synthesis



■ Enantioselective Ring Opening of Epoxides by Fluoride Anion

■ SYNTHESIS/SYNLETT  
Advisory Board Focus: Professor Lutz Ackermann (Georg-August-Universität Göttingen, Germany)

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**Dear readers,**

There is little doubt that these are difficult days for scientific research, which is stuck between a rock and a hard place. Indeed, most universities and research institutions are cutting research budgets in an attempt to save

money and limit redundancies, whereas costs of research are increasingly growing. This exercise of remaining competitive with reduced budgets requires remarkable creativity both from scientists and research managers, but every cloud has a silver lining and these hard times might eventually help to streamline and optimize the research output and organization of many research institutions. In terms of creativity, the protagonists of this issue of **SYNFORM** are absolute leaders. Abigail G. Doyle (USA) has developed an intelligent strategy to circumvent the inherently low reactivity and organic solubility of the fluoride anion, using benzoyl fluoride in an enantioselective epoxide ring-opening reaction. Hisashi Yamamoto (USA) has developed a highly 1,3-*syn*-selective aldol reaction methodology exploiting the potential of super-bulky silyl protecting groups. Great creativity, great results! The issue is completed by a brief profile of Lutz Ackermann (Germany), Editorial Advisory Board member of **SYNLETT** and **SYNTHESIS**.

Enjoy your reading!

**Matteo Zanda**

*Editor of SYNFORM*

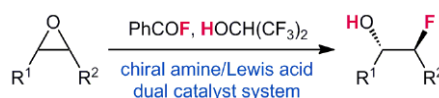
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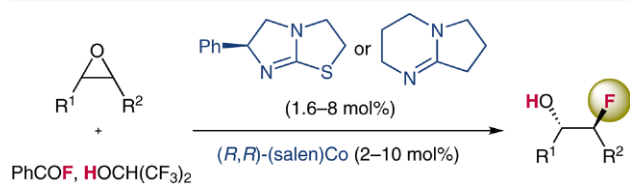
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## NEWS AND VIEWS ■ ■ NEWS AND VIEWS ■ ■ NEWS AND VIEWS ■ ■

## Enantioselective Ring Opening of Epoxides by Fluoride Anion

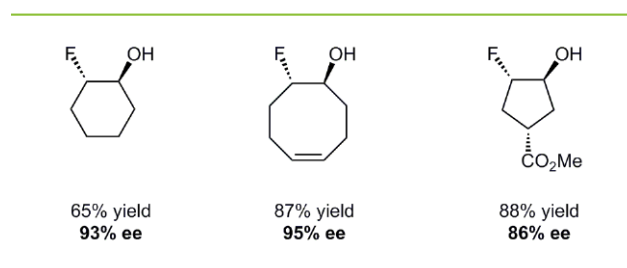
*J. Am. Chem. Soc.* **2010**, *132*, 3268–3269

■ Stereocontrolled incorporation of fluorine into organic molecules remains a challenging endeavor, despite remarkable recent progress in the field. The use of fluoride anion in catalytic C–F bond-forming reactions is particularly attractive, not only for economic and environmental reasons, but also because it could have important applications in emerging fields, such as positron emission tomography. Recently, the group of Professor Abigail G. Doyle from Princeton University (USA) reported an interesting methodology for the ring opening of meso-epoxides by fluoride anion. The reaction is promoted by a dual catalyst system formed by a chiral amine like (–)-tetramisole and a chiral Lewis acid like (salen)Co(II), and affords the target fluorohydrins with very high levels of enantiocontrol.



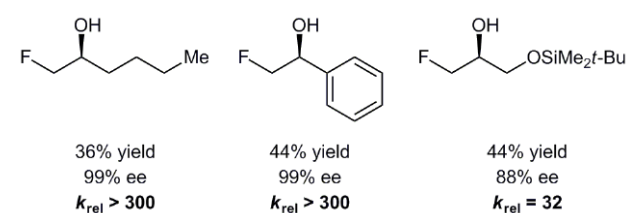
“My laboratory has initiated a program aimed at the development of new catalytic reactions for enantioselective nucleophilic fluorination and trifluoromethylation of organic substrates,” explained Professor Doyle. “Such processes are of fundamental importance for the synthesis and study of existing and novel pharmaceutical agents, agrochemicals, and materials. The incorporation of fluorine into an organic molecule can have a profound effect on its solubility, hydrophobicity, biological activity, and metabolism. Accordingly, approximately 20–25% of drugs in the pharmaceutical pipeline contain at least one fluorine atom. However, our ability to introduce fluorine into organic compounds currently limits the discovery and synthesis of these important targets.”

According to Professor Doyle, the vast majority of existing methods for enantioselective C–F bond formation involve  $\alpha$ -fluorination of carbonyl compounds, where highly enantioselective



Representative scope for enantioselective fluorination of meso-epoxides

lective access to  $\alpha$ -fluoro aldehydes and  $\alpha$ -keto esters has been realized using electrophilic fluorine sources. On the other hand, the development of catalytic enantioselective methods for nucleophilic fluorination has met with limited success despite the availability and low cost of these reagents for synthesis. “Use of nucleophilic fluorine is typically plagued by difficulties with its handling, solubility, and basicity,” said Professor Doyle. “The method that we report in the *JACS* communication is the first to use nucleophilic fluorine for highly enantioselective catalytic C–F bond formation.”



Representative scope for terminal epoxide kinetic resolutions

Julia Kalow, a second-year graduate student in Professor Doyle’s lab, discovered a set of conditions for the enantioselective synthesis of  $\beta$ -fluoro alcohols by catalytic nucleophilic fluorination of epoxides. “High reaction efficiency and selectivity are made possible in this system by the use of benzoyl fluoride as a soluble, latent source of fluoride anion,” explained Professor Doyle. “As a consequence of the use of this

novel fluorinating agent, the reactions that we report can be conducted at room temperature without exclusion of moisture or air.”

One of the unique features of the methodology developed by Professor Doyle's group is that commercial (–)-tetramisole and (*R,R*)-(salen)Co(II) serve as cooperative co-catalysts for desymmetrizations of five- through eight-membered cyclic epoxides, affording products in up to 95% ee. “Reactions with the two chiral catalysts show an unusual pronounced matched/mis-matched effect on the rate and enantioselectivity of the  $\beta$ -fluoro alcohol synthesis,” said Professor Doyle. “Our current efforts are aimed at evaluating the origin of this effect and at identifying the role of the two catalysts in the asymmetric transformation. The opportunity to independently optimize two different chiral catalysts for two different roles in a chemical transformation could be of great utility in further expanding the scope of this reaction,” she continued. “Moreover, we anticipate that a better understanding along these lines will allow us to generalize the approach to previously unexplored asymmetric transformations.”

Professor Doyle acknowledged that Julia also found that the co-catalytic protocol is effective for kinetic resolutions of racemic terminal epoxides, which proceed with *k*<sub>rel</sub> values as high as 300. “High regioselectivity for fluoride addition to the terminal position of the epoxides is observed in all cases,” she

said. “These reactions are characterized by remarkably mild conditions in comparison with known stoichiometric reactions for fluoride ring opening, allowing for broad substrate scope and functional group tolerance. Indeed, even a TBS glycidyl ether undergoes reaction with high selectivity and minimal silyl deprotection under the fluorination conditions,” concluded Professor Doyle. ■

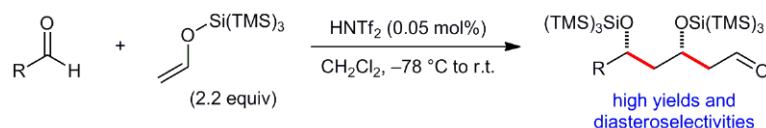
Matteo Zanda



From left: J. A. Kalow, Prof. A. G. Doyle

## Aldol Methodologies Utilizing Super Silyl Groups for Polyketide Synthesis

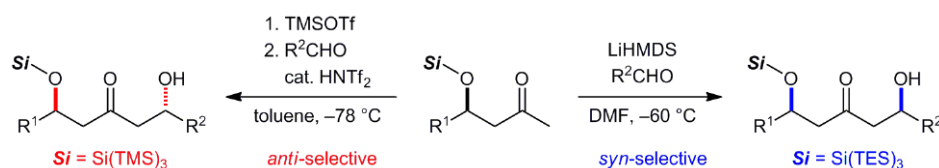
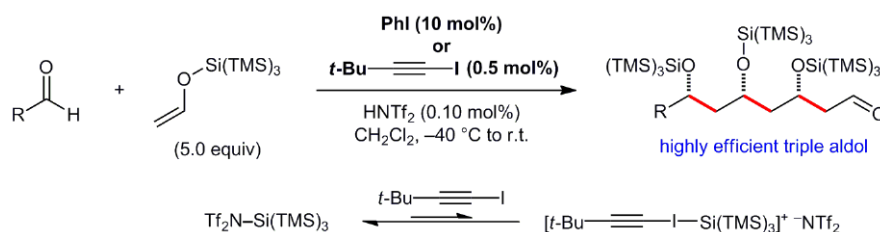
*Angew. Chem. Int. Ed.* **2010**, *49*, 2747–2749; *J. Am. Chem. Soc.* **2010**, *132*, 5354–5356

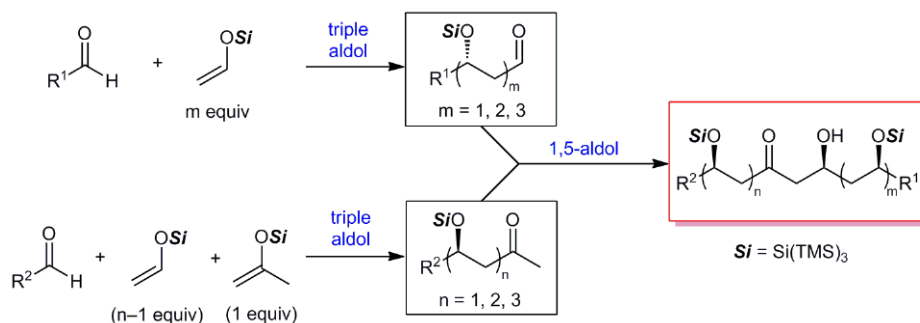


The aldol reaction is undoubtedly one of the most important and investigated reactions in chemistry. The group of Professor Hisashi Yamamoto, a *Synlett* and *Synfacts* Editorial Board Member from The University of Chicago (USA), is actively involved in this area, and has recently reported remarkable advances in aldol-reaction methodology. “We feel that there is still significant room for improvement in this field,” said Professor Yamamoto, who pointed out that the unique reactivity and steric bulk of the tris(trimethylsilyl)silyl group went unnoticed by organic chemists for decades. “However, now we hope that we are creating new paradigms for polyketide synthesis. We recently discovered the unique properties of the tris(trimethylsilyl)silyl group in the Mukaiyama aldol reaction (*J. Am. Chem. Soc.* **2006**, *128*, 48; *J. Am. Chem. Soc.* **2007**, *129*, 2762)” he explained. “The high yields and *syn*-selectivities were a consequence of the extreme steric bulk and electronic nature of the tris(trimethylsilyl)silyl group.” According to Professor Yamamoto some

major advantages of this reaction are: (1) that the direct products are aldehydes which can be further manipulated in the same reaction vessel, (2) low catalyst loading, and (3) high 1,3-*syn*-selectivity which, to date, has been elusive.

Professor Yamamoto’s research group has recently published two major contributions on this topic. “In *Angew. Chem. Int. Ed.* **2010**, *49*, 2747,” he explained, “we reported a triple aldol cascade of simple aldehydes and acetaldehyde tris(trimethylsilyl)silyl enol ether that was made possible by the addition of organoiodides, such as iodoarenes or iodoacetylenes. This is the only general and high-yielding method for a triple aldol reaction which, in principle, could save chemists many reaction steps. Moreover,” he continued, “this reaction was made possible by the addition of organoiodides to generate a more reactive catalyst, a discovery that we found quite interesting, albeit not fully understood, and a strategy that we feel will be broadly applicable to silicon and metal chemistry.”



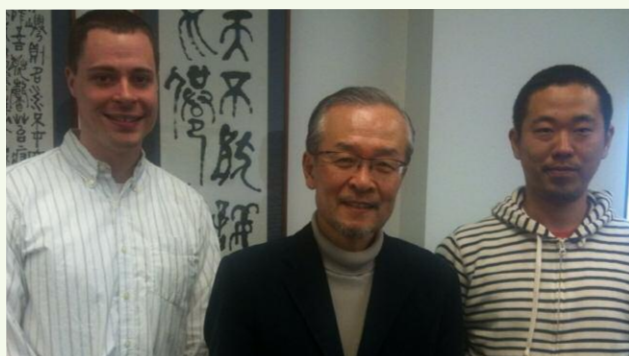


“Furthermore, in *J. Am. Chem. Soc.* **2010**, *132*, 5354 we reported 1,5-asymmetric aldol reactions of  $\beta$ -siloxy methyl ketones and simple aldehydes,” said Professor Yamamoto. “Excellent *anti*- and *syn*-selectivities were achieved by using the extremely bulky tris(triethylsilyl)silyl and tris(trimethylsilyl)silyl protecting groups, respectively, on the ketone.” This reaction proved to be quite general in scope and is the only current method available for high 1,5-*syn*-selectivity that only relies on substrate control. “This should nicely complement the high *anti*-selectivity obtained using the boron enolates of  $\beta$ -alkoxy ketones and add to the utility of linchpin synthesis.”

Professor Yamamoto and his co-workers are currently utilizing both of these strategies in the construction of complex polyketides, which can be performed with unprecedented ease using their polyaldol and acetone linchpin methods. “We anticipate that natural product chemists will be utilizing our methods in the near future for synthetic applications such as the preparation of long-chain polyketides or spiroketals. We hope to discover an enantioselective method for the iterative acetaldehyde and propionaldehyde aldol reactions,” concluded Professor Yamamoto. ■

Matteo Zanda

### About the authors



From left: Dr. B. J. Albert, Prof. H. Yamamoto, Dr. Y. Yamaoka

**Hisashi Yamamoto** received his B.S. degree from Kyoto University (Japan) and his Ph.D. from Harvard University (USA) under the mentorship of Professors Hitoshi Nozaki and E. J. Corey, respectively. His first academic position was as an Assistant Professor and Lecturer at Kyoto University and, in 1977, he was appointed Associate Professor of Chemistry at the University of Hawaii (USA). In 1980, he returned to Japan to Nagoya University where he became Professor in 1983.

In 2002, he moved to The University of Chicago as Arthur Holly Compton Distinguished Professor. His honors include: the Prelog Medal (1993), The Chemical Society of Japan (1995), the Max-Tishler Prize (1998), Le Grand Prix de la Fondation Maison de la Chimie (2002), National Prize of Purple Medal (Japan, 2002), Yamada Prize (2004), Tetrahedron Prize (2006), The Karl-Ziegler Professorship (2006), The Japan Academy Prize (2007), Honorary Member of the Chemical Society of Japan (2008), ACS Award for Creative Work in Synthetic Organic Chemistry (2009).

**Brian J. Albert** graduated from the University of Illinois at Urbana-Champaign (USA) in 2002. Subsequently, he undertook graduate studies at the University of Pittsburgh (USA) in the laboratory of Professor Kazunori Koide. In 2007 he began post-doctoral research with Professor Yamamoto.

**Yousuke Yamaoka** received his B.S. (2003), M.S. (2005), and Ph.D. (2008) degrees from Kyoto University under the guidance of Professor Yoshiji Takemoto. Currently he is a postdoctoral fellow in the laboratory of Professor Yamamoto.

## SYNTHESIS/SYNLETT Advisory Board Focus: Professor Lutz Ackermann (Georg-August-Universität Göttingen, Germany)

■ **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 Lutz Ackermann from the Georg-August-Universität Göttingen in Germany.

### BIOGRAPHICAL SKETCH



Prof. L. Ackermann

**Lutz Ackermann** was born in 1972 and obtained his Chemistry Diploma from the Christian-Albrechts-Universität zu Kiel (Germany) in 1998. He then joined the group of A. Fürstner at the Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr (Germany) where he obtained his PhD in 2001. From 2001 to 2003 he carried out postdoctoral work at the University of California at Berkeley (USA) with R. G. Bergman before moving back to Germany to start his independent research career at the Ludwig-Maximilians-Universität München. He was appointed Full Professor of Chemistry in 2007 at the Georg-August-Universität Göttingen (Germany) where his current research interest is the development of efficient catalytic transformations based on environmentally benign processes under consideration of economical aspects. Topics include, among others, C–H functionalizations, transition-metal catalysis, and the catalytic coupling of unactivated halogen arenes. Lutz Ackermann is a member of the advisory board of *SYNTHESIS* and *SYNLETT*. He has received several awards and fellowships, including an “Emmy Noether Fellowship” in 2003, the Thieme Chemistry Journal Award in 2004, the Award of the Dr. Otto-Röhm-Gedächtnisstiftung in 2006, the ADUC Prize in 2007, and the Japan Society for the Promotion of Science (JSPS) Fellowship in 2009.

### INTERVIEW

**SYNFORM** | Professor Ackermann, which are your main current research interests?

**L. Ackermann** | C–H bond functionalization, transition-metal catalysis, ligand design, challenging catalytic cross-couplings, atom-economical addition reactions.

**SYNFORM** | Do you have hobbies, besides chemistry?

**L. Ackermann** | Sports and reading.

**SYNFORM** | What is the main goal in your scientific career?

**L. Ackermann** | The development of efficient catalytic processes for sustainable organic synthesis. ■

Matteo Zanda

COMING SOON ► ► COMING SOON ► ►

## SYNFORM 2010/08 is available from July 22, 2010

In the next issues:

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■ **Three-Component Domino Reaction Using the Bestmann–Ohira Reagent: A Regioselective Synthesis of Phosphonyl Pyrazole**  
(Focus on an article from the current literature)

■ **Meeting Report**  
(Focus on the Thieme-Chemistry Journals Editorial Board Meeting 2010, Florence, Italy, May 21–22, 2010)

### FURTHER HIGHLIGHTS + + + +

#### SYNTHESIS

**Review on: Methods for Vinyl Ether Synthesis**  
(by C. A. Merlic)

#### SYNLETT

**Account on: Homogeneous Multiphase Catalysis. Common Procedures and Recent Applications**  
(by M. Lombardo)

#### SYNFACTS

**Synfact of the Month in category “Metal-Mediated Synthesis”:  
[Palladium-Catalyzed Oxidative Arylation of o-Phenylcarbamates with Arenes](#)**

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