SYNFORM
People, Trends and Views in Synthetic Organic Chemistry

2013/12

SYNSTORIES

- Synchronous Ar–F and Ar–Sn Bond Formation through Fluorostannylation of Arynes

- Nickel-Catalyzed Cross-Coupling of Unactivated Alkyl Halides Using Bis(pinacolato)diboron as Reductant

- Simple Textiles Become Excellent Carriers for Organic Catalysts

- SYNTHESES/SYNLETT Editorial Board Focus: Professor Tomislav Rovis (Colorado State University, Fort Collins, USA)

CONTACT

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

This issue completes the seventh year of SYNFORM, which was first published in June 2007. Since then we have published an awful lot of exciting organic chemistry, often from a rather peculiar perspective, quite different relative to what is published in other journalistic-type publications, and definitely very different from what can be found in the primary literature. We hope you are still finding SYNFORM a useful tool for staying up-to-date with the most recent and exciting research developments in organic chemistry, and hopefully a pleasant and rewarding reading too. From our side, we guarantee that we will definitely continue to strive to publish high quality reports featuring great science from the best chemists worldwide. Dulcis in fundo, this last 2013 issue presents a collection of outstanding pieces of research, starting from the fluorostannylation of arynes developed by Professor Yoshida (Japan). Next, we can learn more about the groundbreaking use of textiles as supports for organo-catalysts developed by Professor List and colleagues (Germany). The third SYNSTORY covers a Ni-catalyzed cross-coupling reaction between alkyl halides recently published by Professor Gong (P. R. of China). The very last article of the year is an Editorial Board Focus on Professor Rovis (USA).

Enjoy your reading and have a fantastic Christmas time!!

Matteo Zanda
Editor of SYNFORM

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CONTACT

If you have any questions or wish to send feedback, please write to Matteo Zanda at: Synform@chem.polimi.it
In view of an increasing demand for convenient and efficient methods for synthesizing fluorinated aromatic compounds, which are found widely in pharmaceuticals, agrochemicals, etc., the development of new Ar–F bond-forming reactions has been an important subject in modern synthetic organic chemistry. Among the diverse aryl fluorides, an effective access to 2-fluoro-biaryl motifs would be of particular importance, since they constitute a valuable class of biologically active compounds that includes drugs such as brequinar, diflunisal, flurbiprofen, ropion and torezolid (Figure 1). Although a wide variety of aryl fluorides are accessible by pyrolysis of arenediazonium tetrafluoroborates (the Balz–Schiemann reaction), nucleophilic aromatic substitution, electrophilic fluorination of aryl Grignard reagents, transition-metal-promoted fluorination and deoxyfluorination of phenols, Ar–F bond-forming reactions utilizing arynes, which have experienced a marked resurgence of interest as synthetic intermediates in the last decade, remain to be exploited.

Professor Hiroto Yoshida’s group in the Department of Applied Chemistry, Graduate School of Engineering, at Hiroshima University (Japan) has been studying aryne insertion reactions into nucleophilic–electrophilic \(\text{Nu–El}^\text{-bonds}\) (Bull. Chem. Soc. Jpn. 2010, 83, 199; Synlett 2012, 23, 1725), which are triggered by nucleophilic attack of the nucleophilic site to arynes (Scheme 1). Professor Yoshida said: “Although a variety of heteroatoms (N, O, P, S, Cl, Se, Br, ...) and even carbon functional groups have been found to serve as the nucleophilic sites, to the best of our knowledge there has been no precedent for the installation of fluorine into aromatic rings by the insertion reaction, probably owing to mismatch between fluorine atoms (hard nucleophile) and arynes (soft electrophile).”

“Actually, we have already observed that an F–C bond of acid fluorides is totally inert toward the insertion reaction of arynes, being in marked contrast to the facility with acid chlorides and bromides (Chem. Commun. 2007, 2405),” con-
continued Professor Yoshida. “In addition, we have never encountered an example of aryne insertion into an F–Si bond of Me₃SiF, generated from 2-(trimethylsilyl)aryl triflate, an aryne precursor, and a fluoride ion.”

In 2004, Professor Yoshida’s group reported on the aryne insertion into an S–Sn bond of stannyl sulfides (thiostannylation), which enabled Ar–S and Ar–Sn bond-forming processes to occur synchronously at neighboring positions of aromatic rings (Chem. Commun. 2004, 1980), and demonstrated that an Sn moiety could act as a good electrophilic site in the insertion process. During their ongoing studies for expanding this aryne stannylation by use of stannyl reagents bearing other nucleophilic sites (Nu–Sn), they unexpectedly found that fluorostannylation of arynes took place to give 2-fluoroarylstannanes. Professor Yoshida remarked: “Since the fluorostannylation products would be produced by the aryne insertion into an F–Sn bond of an in situ generated tin fluoride (from Nu–Sn species and a fluoride ion used as an aryne generator), we naturally examined the reaction of arynes with a tin fluoride, and it worked very well!”

As outlined in Scheme 2, diverse 2-fluoroarylstannanes could be synthesized straightforwardly in high yield by simply mixing 2-(trimethylsilyl)aryl triflates, tributyltin fluoride and a fluoride ion. Perfect regioselectivities were observed in the reaction of 3-methoxybenzyne, 3-bromobenzyne or 3-chlorobenzyne, where fluorine was incorporated into the meta positions of the substituents, showing that the fluoride indeed acts as a nucleophilic site in the fluorostannylation. It should be noted that the TMS moiety of 4-(trimethylsilyl)benzyne remained intact throughout the reaction regardless of the exis-
tence of a fluoride ion, leading to the selective formation of tributyl[2-fluoro-4-(trimethylsilyl)phenyl]stannane.

“In marked contrast to the results above, the reaction of an aryne generated by oxidation of 1-aminobenzotriazole with Pb(OAc)₄ did not give the fluorostannylation product at all, implying that the presence of a fluoride ion is indispensable for the fluorostannylation to proceed,” explained Professor Yoshida. “Hence, we propose a pathway involving the generation of difluorotributylstannate (Bu₃SnF₂⁻) from Bu₃SnF and a fluoride ion (Scheme 3). Subsequent insertion of an aryne into an F–Sn bond via intermediate A, followed by release of a fluoride ion from intermediate B, provides a product.”

This study represented the first aryne insertion reaction into a fluorine-containing σ-bond that produced various 2-fluorarylstannanes, which are versatile synthetic intermediates that can be converted into 2-fluorobiaryls of pharmacological importance by the Migita–Kosugi–Stille reaction. Furthermore, the study demonstrated that the hard/soft mismatch between fluorine atoms and arynes could be overcome by choosing a suitable electrophilic site in σ-bond compounds. The combined use of a tin fluoride and a fluoride ion is also a key to the successful fluorostannylation. Professor Yoshida concluded: “The present findings will undoubtedly trigger further development of new Ar–F bond-forming reactions utilizing arynes, and we are also continuing the research on this topic, of course.”
Organic catalysts represent a relatively new class of catalysts that have a rapidly growing impact on the synthesis of complex and high-value pharmaceuticals and fine chemicals—also due to the fundamental contributions of Professor Benjamin List from the Max-Planck-Institut für Kohlenforschung (MPI Kofo) in Mülheim an der Ruhr (Germany), who has developed basic concepts to chemical synthesis including aminocatalysis, enamine catalysis, and asymmetric-counter-anion-directed catalysis (ACDC, *Angew. Chem. Int. Ed.* 2006, 45, 4193).

The List group has pioneered several new amine- and amino acid-catalyzed asymmetric reactions originating from List’s discovery of the proline-catalyzed direct asymmetric intermolecular aldol reaction in 2000. Shortly thereafter, the group developed the concept of enamine catalysis and introduced the first proline-catalyzed asymmetric Mannich reaction. Subsequently, they pioneered novel Michael reactions, α-aminations, enol-exo-aldolizations, and aldehyde α-alkylations. Furthermore, collaborative efforts involving the List group have provided a clearer mechanistic understanding of enamine catalysis and established the basis for the design of new reactions and catalysts. In particular, the very general ACDC strategy for asymmetric synthesis has recently found widespread use in organocatalysis, transition-metal catalysis, and Lewis acid catalysis.

So far, the industrial use of organic catalysts has been hindered by the lack of effective and inexpensive techniques for the immobilization on certain carrier materials to use them repeatedly or even continuously without complicated, expensive separation and recovery processes. Now, the high-impact journal *Science* has published parts of an ongoing German research project funded by resources from the Federal Ministry of Economics suggesting a simple but groundbreaking solution.

An international team working with chemists from the Deutsches Textilforschungszentrum Nord-West (DTNW) in Krefeld (Germany), the Max-Planck-Institut für Kohlenforschung (MPI Kofo) in Mülheim an der Ruhr (Germany) and Sungkyunkwan University in Suwon (Korea) has developed an innovative process for the durable fixation of organic catalysts on a simple nylon fabric typically known from ladies tights. With the help of monochromatic ultraviolet light (222 nm), the catalysts can be easily grafted onto the fiber’s surface. The fabric thereby acts as a support for the substances on which a chemical reaction occurs.

The textile experts from DTNW, Thomas Mayer-Gall and Klaus Opwis, explain that up until now, science has focused more on the macroscopic functionality of textiles, for example clothing. “In contrast to this, our method can give simple textiles microscopic functionalities,” added the Korean chemist.

![Chemical structures of immobilized organic catalysts](image1.png)

*Figure 1 Chemical structures of immobilized organic catalysts*
Ji-Woong Lee, who recently completed his Ph.D. at the MPI Kofo under the supervision of Professor Benjamin List.

To prove their concept, the DTNW scientists immobilized three organic catalysts provided by Professor List’s group: a base (dimethylaminopyridine, DMAP), a sulfonic acid and a catalyst that functions as both an acid and a base (Figure 1).

Afterwards, Ji-Woong Lee carried out several hundred test runs for various enantioselective reactions. All three catalysts converted around 90 percent of the source materials into the desired products. In particular, the textile-fixed acid/base chiral catalyst shows an amazing performance with regard to catalytic activity, enantioselectivity and recyclability. For example, the enantioselective desymmetrization of cyclic anhydrides runs for more than 250 cycles, without any significant loss of its catalytic activity, while providing an impressive enantiomeric ratio of 96.5:3.5 (Figure 2). “This is a remarkably high number and far better than what we expected at the beginning of our work,” project leader Klaus Opwis from DTNW explains, “especially with regard to the negligible low price of the textile compared to conventional carrier materials for catalysts, the simple processing and the inherent advantages of fibrous materials such as flexibility, mechanical strength and high surface area!”

“We are pretty confident that this new organotextile catalysis is able to open the door for manifold new applications in pharmaceuticals, fine chemicals, biochemistry and materials science,” Professor List added. “In the future, it will be much easier to produce some active pharmaceutical substances and chemical compounds than was the case to date.” The catalyst-loaded textiles can be used for various syntheses of industrial relevance. For instance, one of the immobilized catalysts that the researchers used in this way plays an important role in the synthesis of valuable precursors of statin derivatives, which could only be used previously in dissolved form, making the production process very complicated and expensive. Immobilizing this catalyst on fabric simplifies production considerably.

Moreover, this process may be expected to yield similar advantages for other chemical processes or even non-traditionally chemical applications such as the treatment of water in locations where people are cut off from the water supply. “Our textile carrier nylon is flexible and very inexpensive. Dry textiles loaded with catalysts are easy to transport, which means that it is simpler to meet the requirements for some chemical processes where it is practically impossible to set up sophisticated chemical systems. In addition, the photochemical method enables the low-cost production of long-term functionalized textiles without causing any pollution,” the research team summarizes. “Our future work foresees the extension of our smart approach to other catalytic systems not explicitly limited to applications in chemical syntheses.”

**Figure 2** Enantioselective desymmetrization of cyclic anhydrides with a textile-fixed chinchona-sulfonamide organocatalyst

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**About the authors**

**Ji-Woong Lee** received his M.Sc. in chemistry from Sungkyunkwan University (Korea) in 2009 under the guidance of Professor Choong Eui Song. Afterwards, he moved to Max-Planck-Institut für Kohlenforschung (Mülheim an der Ruhr, Germany), where he recently finished his Ph.D. in organic chemistry (Magna cum laude) in the group of Professor Benjamin List. Today, he is a postdoctoral fellow at Sungkyunkwan University. His main interests are in the field of unconventional asymmetric heterogeneous and homogeneous organocatalysis. He has received many awards, honors and scholarships, including a Brain Korea 21 Scholarship (Sungkyunkwan University, Graduate School), a Best Publication Award (Center for Intelligent NanoBio-Materials, Ihwa Womans University, Department of Chemistry) and a Promotionsstipendium of the Max-Planck-Institut für Kohlenforschung. In addition, he was a contributor to Synfacts (Ed. B. List) in 2009.
Thomas Mayer-Gall graduated in organometallic chemistry at the University of Bochum (Germany). At present, he is a member of the scientific staff of the Deutsches Textilforschungszentrum Nord-West (DTNW) located in Krefeld (Germany) and of the working group of Professor Jochen S. Gutmann at the University of Duisburg-Essen (Germany). His main interests are in the field of new functional adsorbing textiles and catalytic active surfaces/textiles. Together with Klaus Opwis he developed the first textile-fixed organometallic catalyst in 2007. Recently, he started working on metal-adsorbing textile surfaces for the recovery of noble metals and on new heterogeneous asymmetric catalysts.

Klaus Opwis received his diploma in chemistry from Duisburg University (Germany) in 1996. Afterwards, he moved to Deutsches Textilforschungszentrum Nord-West. In his Ph.D. thesis (University Duisburg-Essen, 2003) he described the concept for the immobilization of catalysts on textile materials for the first time. Since 2007 he is the head of the working group “Biotechnology & Catalysis” at DTNW. Besides textile-fixed catalysts, his research interests include enzymatic processes in textile finishing, biopolymers, modifications in supercritical carbon dioxide and ionic liquids, flexible textile-based solar cells, photochemical surface modifications of synthetic polymers, conductive textiles and flame-retardant finishing of textiles.

Choong Eui Song, born in 1955, has been a full Professor at Sungkyunkwan University (Korea) since 2004. He received his B.Sc. in 1980 from Chungang University (Korea) and obtained a Diploma (1985) and a Ph.D. (1988) at RWTH Aachen (Germany). After completing his Ph.D. he worked as a Principal Research Scientist at the Korea Institute of Science and Technology (KIST). In 2001, he was appointed as Head of the National Research Laboratory for Green Chirotechnology in Korea. In 2004, he moved to his current position and in 2006 he was appointed as a Director at the Research Institute of Advanced Nanomaterials and Institute of Basic Sciences at Sungkyunkwan University. His research interests focus on asymmetric catalysis, ionic-liquid chemistry and nanochemistry. He received the Scientist of the Month Award from the Ministry of Science and Technology in Korea (2001).

Jochen S. Gutmann studied chemistry at the Technische Hochschule Darmstadt (Germany) and the University of Bristol (UK). He received his Ph.D. from the University of Mainz (Germany) and worked as a postdoctoral fellow at the IFP Dresden (Germany) and Cornell University (USA). In 2002, he joined the MPI for Polymer Research and was appointed as a Professor for Physical Chemistry at the University Mainz in 2005. Since 2010 he is a Professor for Physical Chemistry at the University of Duisburg-Essen (Germany) and the Managing Director of the DTNW in Krefeld. His research focuses on the characterization of multicomponent polymer materials and chemistry at interfaces.

Benjamin List is currently the Managing Director of the Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr. He has been a Director there since 2005. He obtained his Ph.D. in 1997 at the Johann-Wolfgang-Goethe-University in Frankfurt am Main (Germany). From 1997 until 1998 he conducted postdoctoral research at The Scripps Research Institute in La Jolla (USA) and became an Assistant Professor there in January 1999. In 2003, he joined the Max-Planck-Institut für Kohlenforschung in Mülheim. He has been an honorary professor at the University of Cologne (Germany) since 2004. Professor List’s research focuses on organic synthesis and catalysis. He has contributed fundamental concepts to chemical synthesis including aminocatalysis, enamine catalysis, and asymmetric-counter-anion-directed catalysis (ACDC). His latest work deals with chiral anions in asymmetric catalysis. He has received many honors and awards, including the 2003 Carl Duisberg Memorial Award, the 2004 Degussa Prize for Chiral Chemistry, the 2004 Lieseberg Prize of the University of Heidelberg, the 2005 Novartis Young Investigator Award, the 2007 AstraZeneca Research Award in Organic Chemistry, and the 2012 Otto Bayer Award. Very recently, he obtained the 2013 Mukaiyama Award.
Nickel-Catalyzed Cross-Coupling of Unactivated Alkyl Halides Using Bis(pinacolato)diboron as Reductant

Chem. Sci. 2013, 4, 4022–4029

A fundamental issue in organic synthesis is selectivity. Conventional catalytic cross-coupling methods take advantage of reactions between a nucleophile, such as an organometallic species, and an electrophile, for example an alkyl halide or a Michael acceptor, in the presence of a transition-metal catalyst. However, coupling of two structurally and electronically similar electrophiles, such as two alkyl halides, suffers a severe selectivity issue. For instance, the Ullman reaction, discovered in 1901, is generally limited to homo-couplings. The coupling of alkyl halides to form a new C(sp³)–C(sp³) bond is particularly challenging due to slow oxidative addition and possible β-elimination problems.

Professor Hegui Gong from the Department of Chemistry, Shanghai University (P. R. of China) remarked: “When I started my independent career in late 2008, I was fascinated with developing a convenient approach to the construction of C(sp³)–C(sp³) bonds that did not need preparation of organometallic reagents such as Grignards and organozincs. We believed this could significantly reduce the laborious operations involved in this process, and might lead to new reaction mechanisms that differ from the conventional coupling reactions.” Inspired by the Ni-catalyzed Negishi coupling of alkylzincs with alkyl halides, pioneered by Knochel and Fu, Professor Gong’s group initiated their first attempt by mixing two different alkyl halides in the presence of zinc powder and catalytic amounts of a Ni/pybox ligand. This strategy efficiently provided alkyl–alkyl compounds in moderate to good yields with excellent functional group tolerance; however, one of the coupling halides was required in excess (3 equiv). The highly competitive homo-coupling side reaction was problematic, suggesting that the Ni/Zn reductive conditions could not effectively bias the two alkyl coupling partners (Org. Lett. 2011, 13, 2138).

“In order to promote the chemoselectivity of the Ni-catalytic conditions, we turned our attention to boron reductants,” said Professor Gong. “We anticipated that a possible Ni–B complex might differentiate the two alkyl halides’ oxidative coupling stage by taking advantage of subtle electronic and steric differences in the two alkyl partners. After tremendous effort, my co-worker Hailiang Xu eventually dis-
covered that (Bpin)_2 serves this purpose.” The reaction requires only 1.5 equivalents of the second alkyl halides, which works quite well for the coupling of secondary as well as hindered primary halides with primary bromides. In most cases, the results were good in comparison to the conventional Ni-catalyzed Suzuki reactions. “To the best of our knowledge, this work should represent the first efficient coupling of unactivated alkyl halides using boron as the terminal reductant,” remarked Professor Gong. Preliminary mechanistic studies suggest that an in situ organoboron/Suzuki process is not possible. Professor Gong concluded: “Although the details of the mechanism are still not clear, we believe double oxidative additions of alkyl halides to Ni are operative.”

About the authors

Hegui Gong was born in 1974. He received a bachelor’s degree in 1995 from Zhengzhou University of Light Industry and a Master’s degree from Tsinghua University in 1998 (both P. R. of China). In 2005 he obtained his Ph.D. degree from the University of Texas at Austin (USA) under the supervision of Professor Michael Krische. After postdoctoral research at the University of North Carolina at Chapel Hill in Professor Michel Gagné’s laboratories, he was appointed as a Full Professor at Shanghai University (P. R. of China) in 2008. His research focuses on two general areas of organic chemistry: supramolecular chemistry and organic synthesis.

Hailiang Xu was born in 1986 in Hebei province (P. R. of China). He was awarded a bachelor’s degree from Huazhong Agricultural University in 2010 and a Master’s degree from Shanghai University in 2013 (both P. R. of China) under the guidance of Professor Hegui Gong, where he worked on the Ni-catalyzed reductive cross-coupling of unactivated alkyl halides. He is currently a research assistant at City University of Hong Kong (P. R. of China) with Professor Peggy Lo.

Chenglong Zhao was born in 1988 in Xian, Shanxi province (P. R. of China). He received a bachelor’s degree in Chemistry from Northwest A & F University (P. R. of China) in 2011. Presently, he is enrolled in the chemistry Master’s program at Shanghai University under the supervision of Professor Hegui Gong. His thesis research involves the reductive coupling of alkyl halides with acids.
SYNFORM Editorial and 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 Tomislav Rovis from Colorado State University in Fort Collins, USA.

### INTERVIEW

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

**Prof. T. Rovis** | We continue to be enamored with the possibilities that N-heterocyclic carbenes (NHCs) afford for novel bond disconnections. We are also actively engaged in Rh-catalyzed C–H activations, particularly as a route to nitrogen heterocycles. Last, and most recent, in collaboration with Tom Ward at Basel we are pursuing the development of artificial metalloenzymes for organic synthesis.

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

**Prof. T. Rovis** | If one limits that question to achievements done some time ago, so that the achievement can be analyzed in the context of some history, it would have to be the introduction and development of aminoindanol-derived chiral triazolinylidene carbenes. These catalysts and the umpolung reactivity they enable have caught people’s imagination. We were lucky to be there early on.

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

**Prof. T. Rovis** | Skiing, basketball, golf, wine.

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

**Prof. T. Rovis** | The training of the next generation of scientists, to think clearly, deeply and critically about the world around them. Of course, science would not move forward if this were the only thing we did. It is also important to educate the community about a new way to think about a given problem. That’s also a major goal.

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**BIOGRAPHICAL SKETCH**

**Tomislav Rovis** was born in Zagreb in former Yugoslavia but was largely raised in southern Ontario, Canada. Following his undergraduate studies at the University of Toronto (Canada), he earned his Ph.D. degree at the same institution in 1998 under the direction of Professor Mark Lautens. From 1998–2000, he was an NSEC Postdoctoral Fellow at Harvard University (USA) with Professor David A. Evans. In 2000, he began his independent career at Colorado State University and was promoted in 2005 to Associate Professor and in 2008 to Professor. His group’s accomplishments have been recognized by a number of awards including an Arthur C. Cope Scholar and an NSF CAREER Award. He has been named a GlaxoSmithKline Scholar, Amgen Young Investigator, Eli Lilly Grantee, Alfred P. Sloan Fellow, a Monfort Professor at Colorado State University, Roche Excellence in Chemistry Awardee, a Fellow of the American Association for the Advancement of Science and a Katritzky Young Investigator in Heterocyclic Chemistry. He currently holds the John K. Stille Chair in Chemistry.

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**Matteo Zanda**
In the next issues:

**SYNSTORIES**

- Stereoinversion of Tertiary Alcohols to Tertiary-Alkyl Isonitriles and Amines
  *(Focus on an article from the current literature)*

- Efficient Synthesis of Functionalized Unsymmetrical Dialkyl Trisulfanes
  *(Focus on an article from the current literature)*

**FURTHER HIGHLIGHTS**

**SYNTHESIS**

Review on: Direct Carboxylative Reactions for the Transformation of Carbon Dioxide into Carboxylic Acids and Derivatives
*(by X. Cai and B. Xie)*

**SYNLETT**

Account on: Site-Selective Heterofunctionalization of Cyclodextrins: Discovery, Development, and Use in Catalysis
*(by M. Sollogoub)*

**SYNFACTS**

Synfact of the Month in category “Metal-Mediated Synthesis”: Florination of Aryl Trifluoroborates

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