

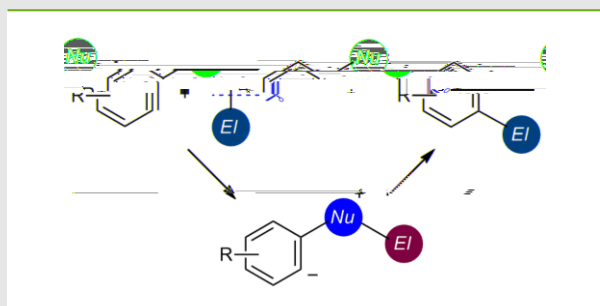
# SYNFORM

*People, Trends and Views in Synthetic Organic Chemistry*

2013/12

## SYNSTORIES ■ ■ ■ ■

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



■ **Simple Textiles Become Excellent Carriers for Organic Catalysts**

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

■ **SYNTHESIS/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:  
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***Dear readers,***

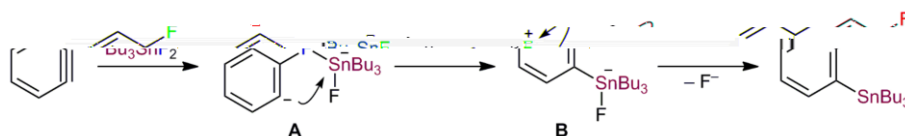
This issue completes the seventh year  
of ***SYNFORM***, w            ve

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  $\sigma$ -bonds (*Nu–El*) ([\*Bull. Chem. Soc. Jpn.\*](#))<sup>1</sup>

tinued Professor Yoshida. “In addition, we have never encountered an example of aryne insertion into an F–Si bond of  $\text{Me}_3\text{SiF}$ , 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 F–Si bond of  $\text{Me}_3\text{SiF}$ , generated from 2-(trimethylsilyl)aryl triflate, an aryne precursor, and a fluoride ion.”



Scheme 3

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  $\text{Pb}(\text{OAc})_4$  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 ( $\text{Bu}_3\text{SnF}_2^-$ ) from  $\text{Bu}_3\text{SnF}$  and a fluoride ion (Scheme 3). Subsequent insertion of an aryne into an  $\text{F}-\text{Sn}$  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  $\sigma$ -bond that produced various 2-fluoroarylstannanes, which are versatile synthetic intermediates that can be converted into 2-fluorobiaryls of pharmaceutical 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  $\sigma$ -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  $\text{Ar}-\text{F}$  bond-forming reactions utilizing arynes, and we are also continuing the research on this topic, of course.”

Matteo Zanda

### About the authors



Prof. H. Yoshida

### Hiroto Yoshida

Dr. Hiroto Yoshida received his B.S. degree from the Faculty of Science, Kyoto University, Japan, in 2004, and his M.S. degree from the Faculty of Science, Kyoto University, Japan, in 2006. He then worked as a research assistant in the Laboratory of Organic Chemistry, Faculty of Science, Kyoto University, Japan, from 2006 to 2008. He received his Ph.D. degree from the Faculty of Science, Kyoto University, Japan, in 2008. He then worked as an assistant professor in the Laboratory of Organic Chemistry, Faculty of Science, Kyoto University, Japan, from 2008 to 2010. He then worked as an associate professor in the Laboratory of Organic Chemistry, Faculty of Science, Kyoto University, Japan, from 2010 to 2012. He received his full professorship in the Laboratory of Organic Chemistry, Faculty of Science, Kyoto University, Japan, in 2012. He is currently working on the synthesis of fluorinated compounds and the development of new fluorostannylation reactions.

## Simple Textiles Become Excellent Carriers for Organic Catalysts

*Science* **2013**, *341*, 1225–1229

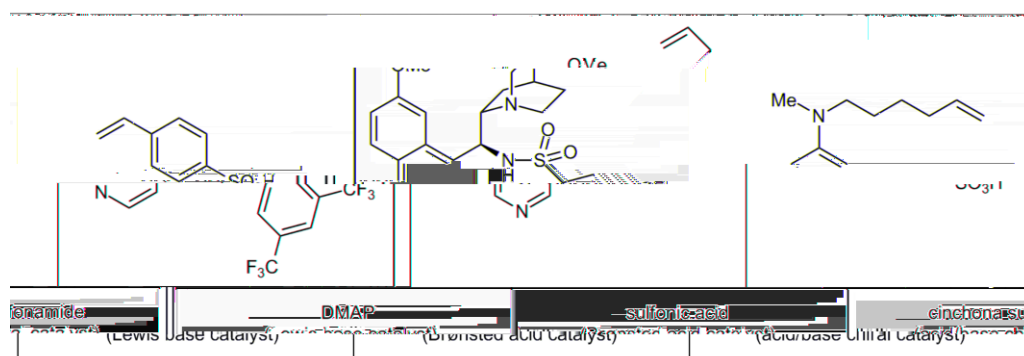
■ Organic catalysts represent a relatively new class of catalysts that have a rapidly growing impact on the synthesis of complex and high-value pharmaceuticals and fine chemicals – also due to the fundamental contributions of Professor Benjamin List from the Max-Planck-Institut für Kohlenforschung (MPI 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,  $\alpha$ -aminations, enol-*exo*-aldolizations, and aldehyde  $\alpha$ -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



**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.

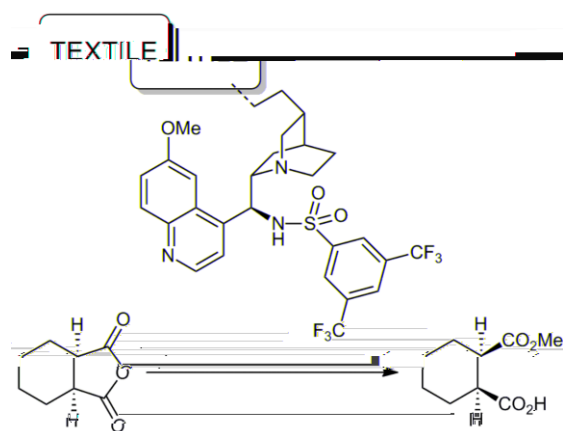
To prove their concept, the DTNW scientists immobilized three organic catalysts provided by Professor List's group: a base (dimethylaminopyridine, DMAP), a sulfonic acid and a catalyst that functions as both an acid and a base (Figure 1).

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-typically 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

### About the authors

#### Ji-Woong Lee

Ji-Woong Lee received his B.S. degree in Chemistry from Seoul National University, Korea, in 2008. He then moved to the Max-Planck Institute for Chemical Physics in Berlin, Germany, where he worked as a postdoctoral fellow under the supervision of Professor Benjamin List. He completed his Ph.D. in 2012. His research interests include the development of new catalytic systems for the synthesis of chiral molecules. He is currently a postdoctoral fellow at the Max-Planck Institute for Chemical Physics in Berlin, Germany.

Synfacts

**Thomas Mayer-Gall***Dr. T. Mayer-Gall***Jochen S. Gutmann***Prof. J. S. Gutmann***Klaus Opwis***Dr. K. Opwis***Benjamin List***Prof. B. List***Choong Eui Song***Prof. C. E. Song*



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

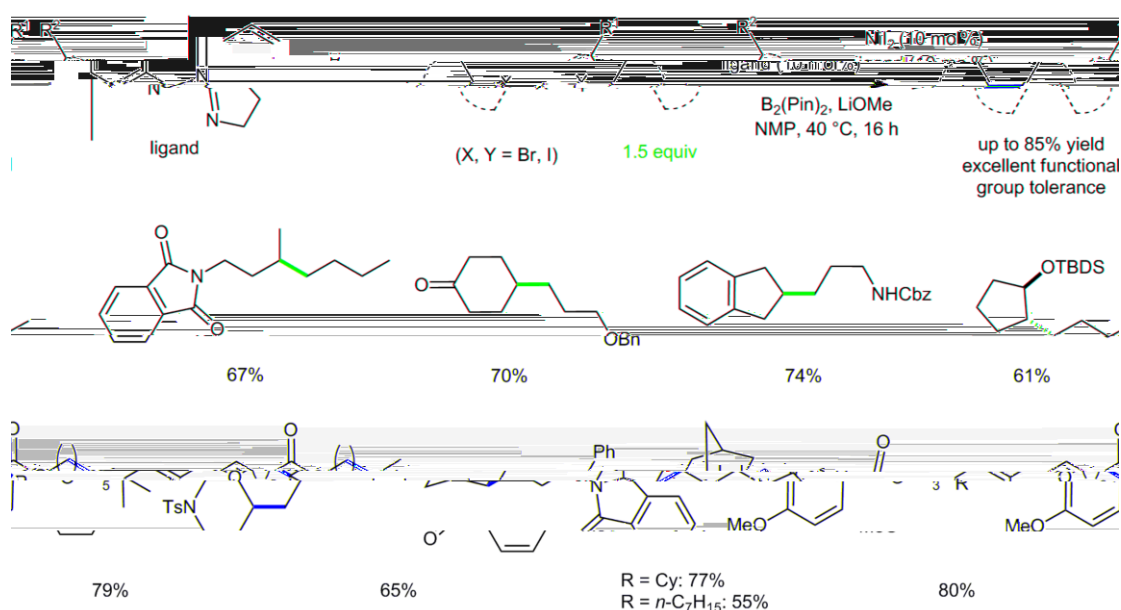
Chem. Sci. 2013, 4, 4022–4029

■ A fundamental issue in organic synthesis is selectivity. Conventional catalytic cross-coupling methods take advantage of reactions between a nucleophile, such as an organo-metallic 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  $C(sp^3)-C(sp^3)$  bond is particularly challenging due to slow oxidative addition and possible  $\beta$ -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  $C(sp^3)-C(sp^3)$  bonds that did not need preparation of organo-metallic 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)<sub>2</sub> 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

Dr. Hegui Gong received his B.S. degree from the Department of Chemistry, Tsinghua University, Beijing, China, in 1998. He then went to the Department of Chemistry, University of California, San Diego, for his M.S. and Ph.D. degrees under the supervision of Professor Robert H. Crabtree. He completed his Ph.D. in 2002 and then worked as a postdoctoral fellow in the Department of Chemistry, University of California, San Diego, from 2002 to 2004. He then joined the Department of Chemistry, Tsinghua University, Beijing, China, as an associate professor. He is currently a full professor and the director of the Institute of Chemistry, Tsinghua University. His research interests are in the development of new catalytic systems for the asymmetric synthesis of chiral molecules.

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Dr. Chenglong Zhao received his B.S. degree from the Department of Chemistry, Tsinghua University, Beijing, China, in 1998. He then went to the Department of Chemistry, University of California, San Diego, for his M.S. and Ph.D. degrees under the supervision of Professor Robert H. Crabtree. He completed his Ph.D. in 2002 and then worked as a postdoctoral fellow in the Department of Chemistry, University of California, San Diego, from 2002 to 2004. He then joined the Department of Chemistry, Tsinghua University, Beijing, China, as an associate professor. He is currently a full professor and the director of the Institute of Chemistry, Tsinghua University. His research interests are in the development of new catalytic systems for the asymmetric synthesis of chiral molecules.

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

■ **Background and Purpose.** *SYNFORM* will from time to time portrait *SYNTHESIS/SYNLETT* 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.

### BIOGRAPHICAL SKETCH



Tomislav Rovis

Prof. T. Rovis

### 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 triazolinyldine 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. ■

Matteo Zanda

COMING SOON      COMING SOON

**SYNFORM 2014/01**

***is available from December 13, 2013***

**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 Tertiary Alkyl Isonitriles**