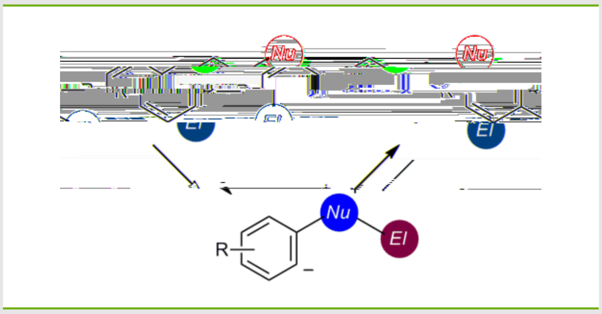
SYNFORM

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: marketing@thieme-chemistry.com

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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 organocatalysts 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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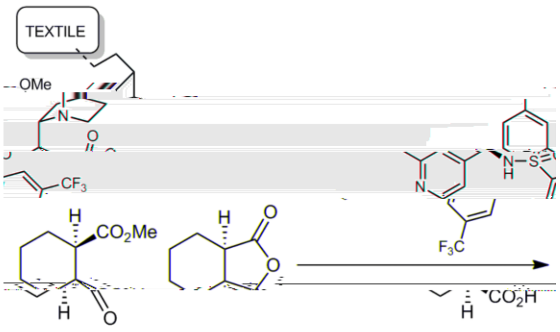

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CONTACT ++++

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

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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 ares by

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tinued Professor Yoshida. “In addition, we have never encountered an example of aryne insertion into an F–Si bond of Me_3SiF, 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 [IZ’c[RsS]tdcd[cIZI’c[R–ScZZ]x/ZXdIZI’c[RSZZZ[S]x/ZXccd[cIZI’c[RiS]x/ZX]eZI’c[Z[l[]x/ZX]bg[dIZI’c[RiS]x/ZX]ebI’c[RoS]x 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 ($Bu_3SnF_2^-$) from Bu_3SnF 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-on rn n l

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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 matex/[illegible]

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."

Matteo Zanda

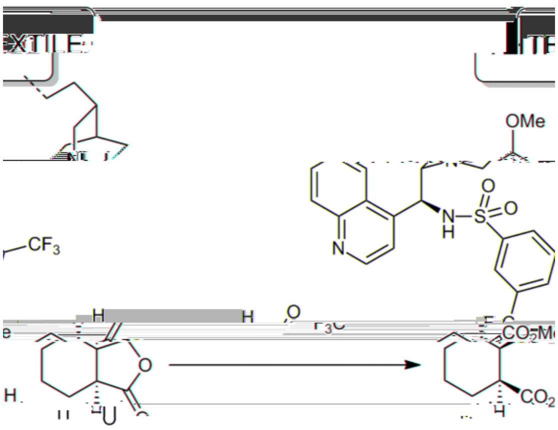

Figure 2 *Enantioselective desymmetrization of cyclic anhydrides with a textile-fixed chinchona-sulfonamide organocatalyst*

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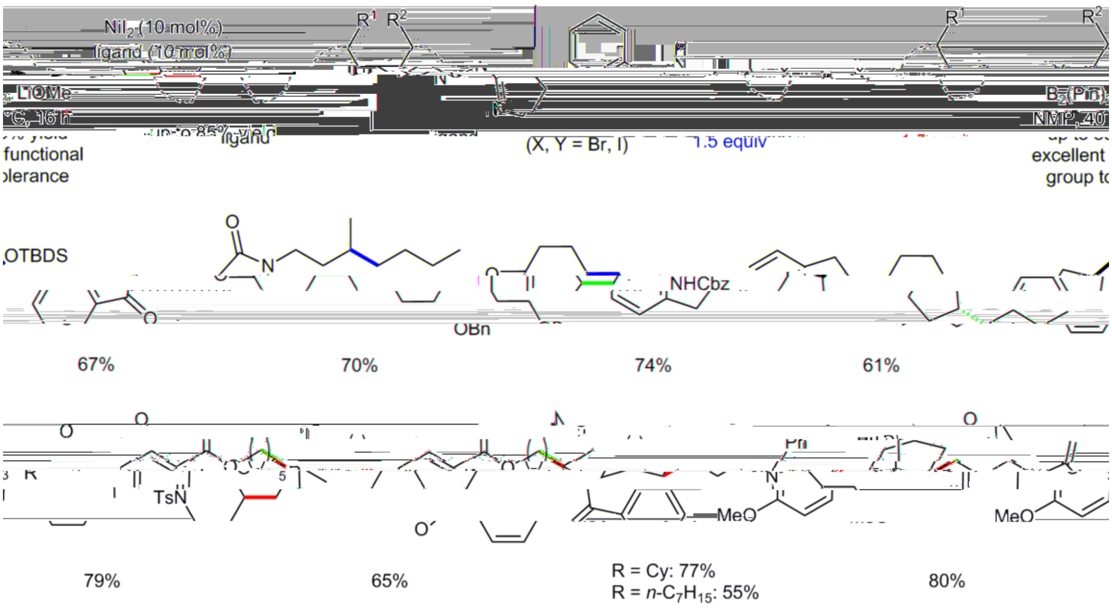
Nickel-Catalyzed Cross-Coupling of Unactivated Alkyl Halides Using Bis(pinacolato)diboron as Reductant

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(sp^3)–C(sp^3) 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(sp^3)–C(sp^3) 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-



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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 [illegible]

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Background and Purpose. SYNFORM will from time to time portrait **SYNTHESIS**/S~~M~~

SYNFORM, 2013/12

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SYNFORM 2014/01

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In the next issues:

SYNSTORIES

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

Efficient Synth [illegible]