

# SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

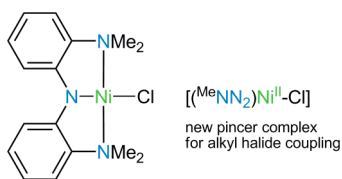
2009/09

## SYNSTORIES ■ ■ ■ ■

■ **Catalytic Enantioselective Intramolecular Redox Reactions: Ring-Fused Tetrahydroisoquinolines**

■ **Functional-Group-Tolerant Kumada–Corriu–Tamao Coupling of Non-Activated Alkyl Halides with Aryl and Heteroaryl Nucleophiles**

■ **Efficient Synthesis of Benzothiophenes by an Unusual Palladium-Catalyzed Vinylic C–S Coupling**



**CONTACT + + + +**

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Dear readers,

this issue of **SYNFORM** features catalysis by metal complexes as the common element of the three **SYNSTORY** articles. Professor D. Seidel (USA) describes his recent methodology for achieving the synthesis of

ring-fused tetrahydroisoquinolines using an intramolecular hydride-shift triggered by a Mg(II)-DBFox ligand. In the second **SYNSTORY** Prof. X. Hu (Switzerland) shows how new Ni(II) pincer complexes can catalyze a functional-group-tolerant Kumada–Corriu–Tamao coupling producing a wide range of aryl- and heteroaryl-alkyl compounds. Last but not least, Professor M. Lautens (Canada) elaborates on his recent synthesis of benzothiophenes using a quite rare Pd-catalyzed vinylation of thiols. Metals rule!

Enjoy your reading!

**Matteo Zanda**

Editor of **SYNFORM**

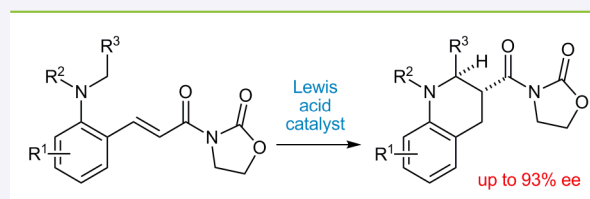
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If you have any questions or wish to send feedback, please write to Matteo Zanda at:  
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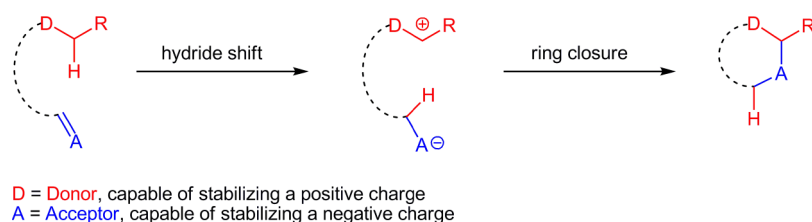
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## Catalytic Enantioselective Intramolecular Redox Reactions: Ring-Fused Tetrahydroisoquinolines

*J. Am. Chem. Soc.* **2009**, *131*, 13226–13227



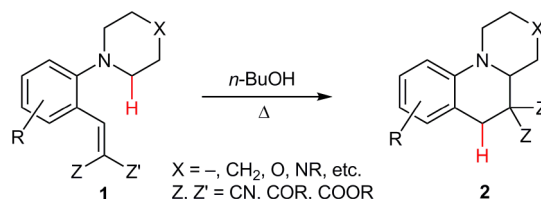
### Scheme 1

According to Professor Daniel Seidel from the Department of Chemistry and Chemical Biology of Rutgers University (New Jersey, USA), there is a major current focus on the development of methods that lead to the direct functionalization of relatively unreactive C–H bonds. “Exciting progress in this highly competitive and intensely active research area has been achieved and many more advances can be anticipated,” said Professor Seidel. A major advancement in this area just came from Seidel’s group, which reported an effective redox methodology to synthesize ring-fused tetrahydroisoquinolines. “Most known C–H bond functionalizations are oxidative in nature and stoichiometric amounts of sometimes expensive oxidants are required,” explained Professor Seidel. Fundamentally different from a mechanistic point of view and comparatively unexplored are reactions that lead to C–H bond functionalization through redox-neutral processes such as the general process outlined in Scheme 1. “In a typical example,” said Professor Seidel, “a hydride shift or sigmatropic rearrangement generates an electrophile/nucleophile pair that recombines in a bond-forming, complexity-enhancing event.”

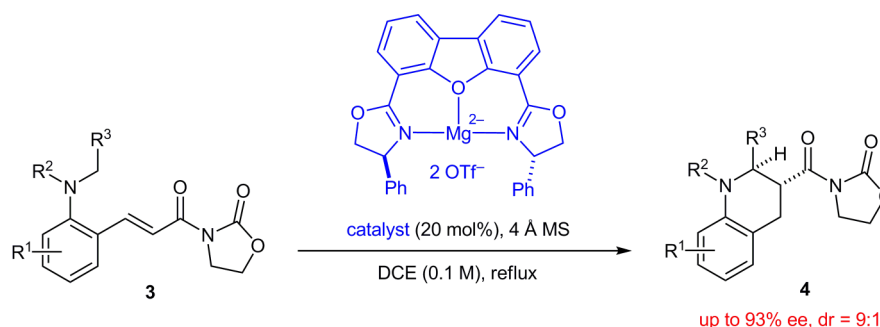
“Reactions of this type are not new by any means,” he continued. “In fact, the first discovery of such a process can be traced back to Pinnow who reported on this in the late 19<sup>th</sup> century (*Ber. Dtsch. Chem. Ges.* **1895**, *28*, 3039).” According to Professor Seidel, the first landmark review of this area was published by Meth-Cohn and Suschitzky who introduced the term *tert*-amino effect to describe these types of reactions (*Adv. Heterocycl. Chem.* **1972**, *14*, 211; more recent developments in this area can be found in *Synthesis* **2006**, 2625).

Professor Seidel explained that prior to their involvement in this field, there were about 50 reports dealing with the transformation shown in Scheme 2. “These previous studies were typically conducted under thermal conditions with only two reported examples that use superstoichiometric amounts of Lewis acids,” he said. “We recently reported a Lewis acid catalyzed version of this reaction ( $Z = Z' = \text{COOMe}$ ) that employs 5 mol% of gadolinium triflate and allows these reactions to be completed within minutes at room temperature in some cases (*Org. Lett.* **2009**, *11*, 129; *Synfacts* **2009**, 367). Unfortunately, attempts to develop a catalytic enantioselective version of this reaction were met with limited success.”

Ultimately, Professor Seidel and his co-workers decided to replace the alkylidene malonate component with an  $\alpha,\beta$ -unsaturated acyl oxazolidinone, a chelating moiety that has been used successfully in a range of catalytic enantioselective transformations. “There was an initial concern as to whether such a substrate would be capable of rearranging,” he explained. “Previous studies by others have concluded that compounds



### Scheme 2



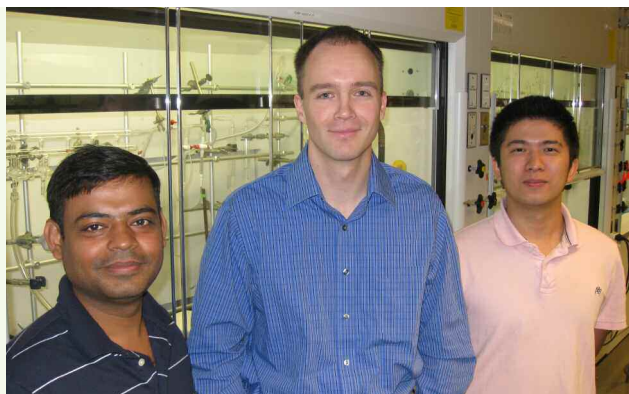
Scheme 3

such as **1** do not rearrange to **2** under thermal conditions in cases where only one activating nitrile, ester or ketone is present. We felt that Lewis acid catalysis should be able to overcome this restriction,” continued Professor Seidel. “Gratifyingly, we were eventually able to develop the process outlined in Scheme 3 which represents the first catalytic enantioselective version of an intramolecular hydride shift/ring closure event. We were particularly pleased with the observed levels of stereoselectivity, given the relatively high reaction tempera-

ture that is required for these reactions to proceed (reflux in dichloroethane, 84 °C).”

“We anticipate that our work will stimulate the development of a variety of other catalytic enantioselective processes that involve hydride shift triggered reaction cascades,” concluded Professor Seidel. “These potentially powerful methods might find use in the synthesis of natural products and other biologically active materials.”

*Matteo Zanda*



From left to right: Dr. I. Deb, Prof. D. Seidel, C. Zhang

### About the authors

**Daniel Seidel** was born in Mühlhausen, Thüringen (Germany) in 1972 and studied chemistry at the Friedrich-Schiller-Universität Jena (1993–1998). His Ph.D. research at the University of Texas at Austin (USA) (1998–2002) under the supervision of Professor Jonathan L. Sessler involved the development of new methods for the synthesis of expanded porphyrin analogues. From 2002 to 2005, Daniel was an Ernst Schering Postdoctoral Fellow in the group of Professor David A. Evans at Harvard University (USA), focusing on the design of new metal catalysts

for catalytic enantioselective transformations. He started his independent career at Rutgers University in August of 2005. Research in his group is focused on new concepts for asymmetric catalysis and methods development.

**Indubhusan Deb** was born in West Bengal (India). He obtained his B.Sc. (Honors in Chemistry) degree from the University of Calcutta (India) and his M.Sc. degree in Organic Chemistry from Banaras Hindu University (India) in 2002. In 2008 he received his Ph.D. degree under the supervision of Professor I. N. N. Namboothiri at the Indian Institute of Technology Bombay (India). He is currently a Postdoctoral Fellow in the Seidel group.

**Chen Zhang** was born in Fuzhou (P. R. of China) in 1982. He received his B.Sc. degree from University of Science and Technology of China in Hefei (P. R. of China) in 2005. In September of 2005, he joined the Seidel group as a Ph.D. student. His research is focused on the development of redox-neutral reaction cascades.

**Sandip Murarka** (not pictured) was born in West Bengal (India). He obtained his B.Sc. (Honors in Chemistry) degree from Vidyasagar University (India) (1st rank) in 2005 and his M.Sc. in Chemistry from IIT Bombay (India) in 2007. He was a member of the Seidel group from 2007 to 2009.

# Functional-Group-Tolerant Kumada–Corriu–Tamao Coupling of Non-Activated Alkyl Halides with Aryl and Heteroaryl Nucleophiles

*J. Am. Chem. Soc.* **2009**, *131*, 9756–9766; *Synfacts* **2009**, 1139 (Synfact of the Month)

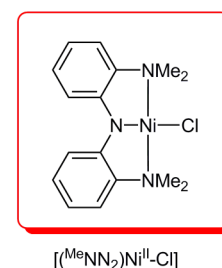
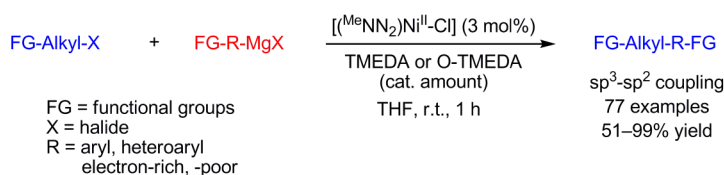
■  $C_{sp^2}$ – $C_{sp^3}$  coupling reaction of aryl or heteroaryl organo-magnesium reagents with non-activated primary and secondary alkyl halides is an attractive method for the synthesis of the corresponding aryl- or heteroaryl-alkyl derivatives, but the presence of sensitive functional groups can make the reaction difficult. Recently, the group of Professor Xile Hu from the École Polytechnique Fédérale de Lausanne (EPFL) in Switzerland reported a valuable methodology to perform a functional-group-tolerant Kumada–Corriu–Tamao (KCT) coupling which proceeds under mild reaction conditions and leads to short reaction times.

“Some excellent recent work, especially that by the groups of Knochel, Fu, Kambe, and their co-workers, provides a number of efficient methods for the coupling of non-activated and  $\beta$ -H-containing alkyl halides which had been challenging substrates for C–C cross-coupling,” explained Professor Hu. “To achieve high functional-group tolerance, mild nucleophiles such as boron or zinc reagents are often used. Grignard reagents are less employed due to their high reactivity which leads to poor compatibility with functional groups.” However, according to Professor Hu, Grignard reagents are desirable coupling partners under many circumstances. “They are relatively economical and easy to prepare, and many of them are commercially available,” he confirmed. “Furthermore, no prior transmetalation is required for their synthesis. Improvement of group tolerance in the Grignard (KCT) coupling will certainly make this atom-economic technology more popular in synthesis.”

Professor Hu explained that with very active catalysts, like those based on Fe developed by Fürstner, Cahiez, Nakamura, and their co-workers, the KCT coupling of alkyl halides with simple aryl Grignard reagents can be carried out under very mild conditions and with a broad substrate scope. “However, the same coupling with functionalized aryl and heteroaryl Grignards (of the Knochel type) is not reported yet,” said Professor Hu. “In general, coupling using functionalized Grignard reagents is only reported in several recent studies by Knochel and Buchwald.”

“Our group at EPFL has developed a new nickel pincer complex,  $[(Me_2NN_2)Ni^I-Cl]$ , for the coupling of alkyl halides,” continued Professor Hu. “We found earlier that Ni alkyl complexes of this pincer ligand resist  $\beta$ -H elimination, thus making the Ni system efficient for the transformation of alkyl groups (*J. Am. Chem. Soc.* **2008**, *130*, 8156; *Angew. Chem. Int. Ed.* **2009**, *48*, 2937). In this paper, we have shown that by using a small loading of this preformed, well-defined, and easy-to-handle catalyst a wide range of primary and secondary alkyl halides could be coupled to aryl and heteroaryl Grignard reagents.”

Professor Hu explained that the key component is an amine additive such as TMEDA (tetramethylethylenediamine) or O-TMEDA {bis[2-(*N,N*-dimethylaminoethyl)]ether}, which suppresses the homo-coupling of the Grignard nucleophile. “The coupling is rapid and reaches completion within a couple of hours at room temperature,” he said. “The catalysis has a high group tolerance for both coupling partners, and allows



for the selective coupling in the presence of many valuable functionalities, such as ester, amide, alcohol, acetal, nitrile, thioether, heterocycle, etc. (see Figure).”

According to Professor Hu, this appears to be the first general protocol for the coupling of functionalized aryl and heteroaryl Grignard reagents to non-activated alkyl halides. “We hope that this straightforward coupling method can be used for the synthesis or derivatization of natural products,

bioactive molecules, ligands, organic materials, etc. Currently, we are working on coupling reactions using other nucleophiles, especially those derived from C–H bonds. For instance, we just reported the first Ni-catalyzed Sonogashira coupling of alkyl halides (*J. Am. Chem. Soc.* **2009**, *131*, 12078),” he concluded. ■

Matteo Zanda

Selective coupling products and isolated yields

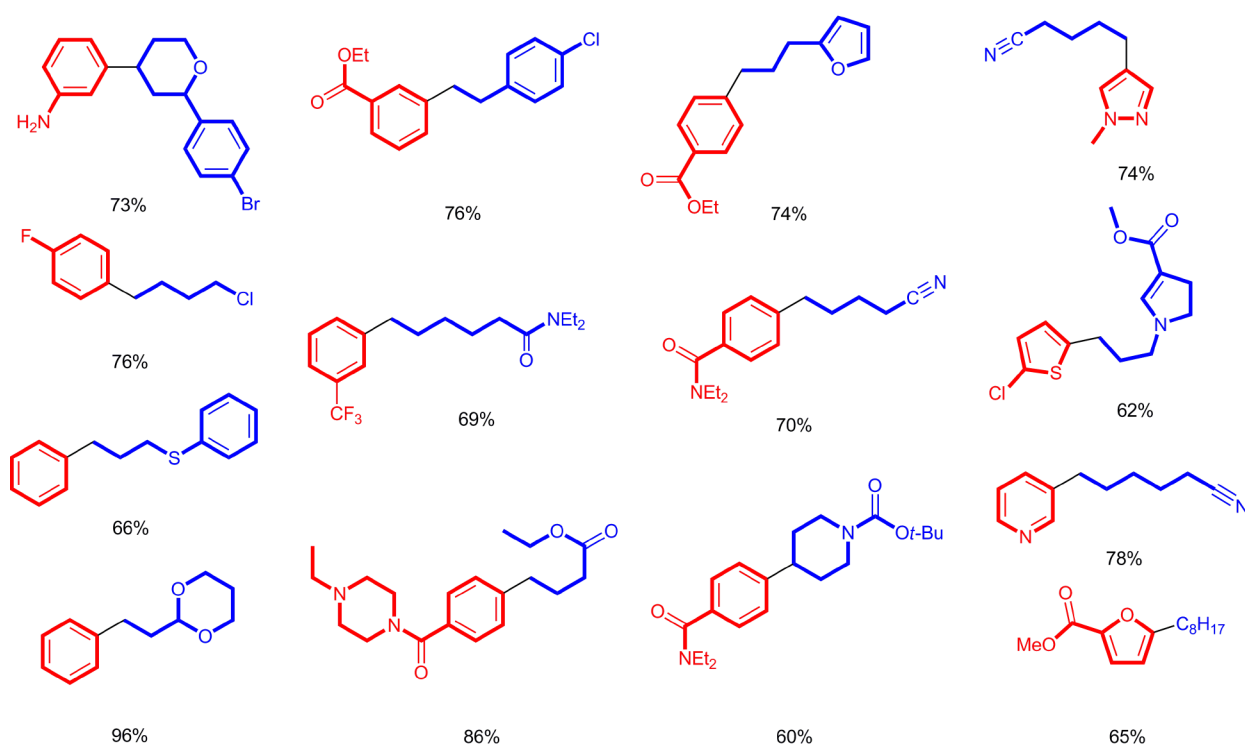
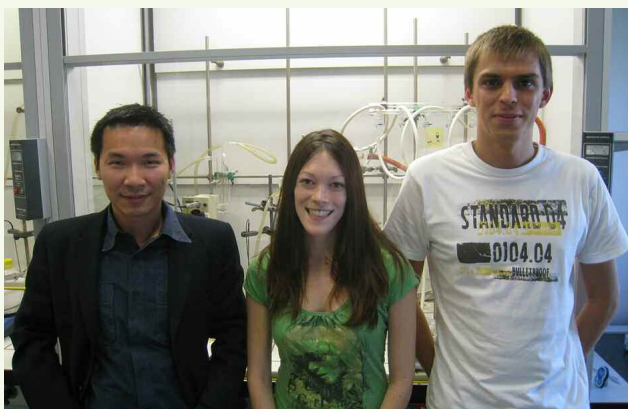


Figure Ni-catalyzed cross-coupling of alkyl halides with aryl and heteroaryl Grignard reagents

About the authors >>



From left to right: Prof. X. Hu, V. Proust, O. Vechorkin

### About the authors

**Xile Hu** was born in 1978 in Fujian (P. R. of China). He studied chemistry at Peking University (P. R. of China) and received his B.S. degree in 2000. Shortly thereafter, he moved to the USA and began his doctoral studies under the guidance of Professor Karsten Meyer at the University of California, San Diego (USA). In December 2004, after having defended his dissertation on "Metal Complexes of Tripodal N-Heterocyclic Carbene Ligands: Synthesis, Structure, Bonding, and Reactivity", he was awarded a Ph.D. in inorganic chemistry. He became a Postdoctoral Scholar in the group of Professor Jonas C. Peters at Caltech (USA) in February 2005 where he worked on electrocatalytic hydrogen production, in collaboration with Professor Nathan S. Lewis and Dr. Bruce S. Brunschwig. In 2007, he was appointed as a tenure-track Assistant Professor of Chemistry at the EPFL in Switzerland where he directs the Laboratory of Inorganic Synthesis and Catalysis. He is interested in developing molecular catalysts based on earth-abundant elements for applications in synthesis and in energy and sustainability.

**Oleg Vechorkin** was born in the Ukraine. He obtained a diploma in chemistry (magna cum laude) from the Kharkov National University and is currently a Ph.D. student in the Hu group at EPFL. He won a Silver Medal in the 34<sup>th</sup> International Chemistry Olympiad (2002) and recently obtained a travel award from the Swiss National Academy of Sciences.

**Valérie Proust** is a Swiss native. She is currently an apprentice in the Hu group at EPFL.

## Efficient Synthesis of Benzothiophenes by an Unusual Palladium-Catalyzed Vinylic C–S Coupling

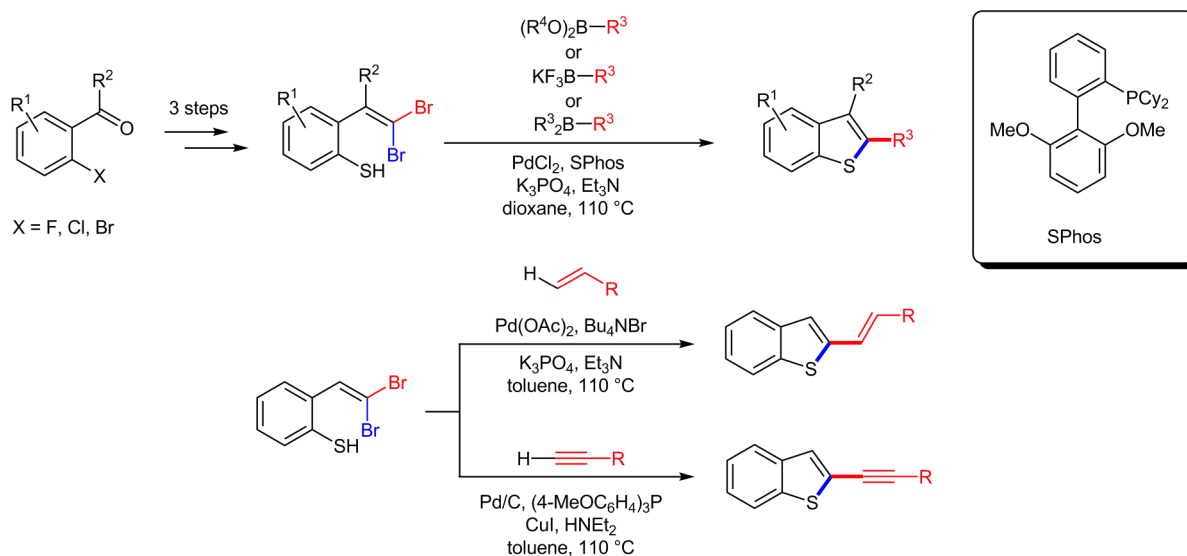
*Angew. Chem. Int. Ed.* **2009**, *48*, 7064–7068

■ The efficient synthesis of sulfur-containing heterocycles remains a rather challenging endeavor, particularly when using catalytic methods based on metal catalysts, despite the importance of thiophenes and related structures in drug discovery and materials science. Recently, the group of Mark Lautens, a Professor of Organic Synthesis from the University of Toronto (Ontario, Canada) and an Editorial Board Member of *Synthesis* and *Synfacts*, reported a novel palladium-catalyzed process which conveniently produces functionalized benzothiophenes.

“Palladium-catalyzed carbon–heteroatom bond formation has revolutionized the way chemists think about synthesizing small molecules,” said Professor Lautens. “Combining these transformations with orthogonal catalytic steps in a tandem process creates an especially powerful reaction wherein a diverse array of targets can be synthesized rapidly and with minimal environmental impact. We have previously used this strategy in the synthesis of a range of indole derivatives (*J. Org. Chem.* **2008**, *73*, 538),” he continued, “and we were intrigued as to whether a similar tactic could be applied to benzothiophene synthesis, where an aryl thiol would be used as a coupling partner.” According to Professor Lautens, palla-

dium-catalyzed vinylation of thiols is extremely rare – especially when compared to the analogous transformation of amines as developed by Buchwald and Hartwig – largely due to sulfur’s long-standing reputation as a catalyst poison. Although efficient catalytic systems have been developed recently, there are no previous examples of a reaction combining catalytic thiol coupling with a second catalytic process.

Professor Lautens and co-workers devised a reaction wherein the intramolecular S-vinylation of a *gem*-dibromolefin was paired with a Suzuki coupling, and found high functional-group tolerance. “The intermolecular process is selective for the Suzuki product, even when the boronic acid also contains moieties such as alcohols, amines or Heck acceptors, which might be expected to undergo alternative Pd-catalyzed processes,” said Professor Lautens. “With slight modifications to the conditions, a number of different types of boron-coupling partners could be used. The intramolecular S-vinylation could also be paired with intermolecular Heck or Sonogashira couplings; however, these reactions each required a separate set of re-optimized conditions. In the case of the Heck coupling, use of the quaternary ammonium salt was necessary to prevent the formation of the Michael addition





product. Notably, for the Sonogashira reaction, Pd/C can be used as a precatalyst, which offers economic advantages over ligated palladium complexes.

Professor Lautens pointed out that in all cases, due to pre-functionalization of the starting materials, the products are formed regiospecifically. "This is an improvement over traditional methods of benzothiophene synthesis, where the benzenoid ring acts as a nucleophile and a mixture of regioisomers may be obtained, depending on the functionality pre-

sent," he said. "We have detected 2-bromobenzothiophene as an intermediate, indicating that it is the intramolecular step which occurs first. This is contrary to what would be expected on steric grounds (*Tetrahedron Lett.* **1988**, *29*, 3541), and indicates that the sulfur atom may be directing oxidative addition to the (Z)-bromide. We are currently studying the nature and potential applications of this selectivity," he concluded. ■

Matteo Zanda

### About the authors



Prof. M. Lautens

**Mark Lautens** was born in Hamilton (Ontario, Canada) in 1959. He obtained his undergraduate degree in chemistry at the University of Guelph (Canada) in 1981 and his Ph.D. in 1985 from the University of Wisconsin – Madison (USA), under the supervision of Barry M. Trost. He was an NSERC Postdoctoral Fellow in the group of David A. Evans at Harvard University (USA) from

1985–1987, and then joined the Faculty at the University of Toronto. Promoted to Full Professor in 1995, he is currently the AstraZeneca Chair in Organic Synthesis and the NSERC/Merck Frosst Industrial Research Chair. He has received numerous awards including an Eli Lilly Granteeship, an A. P. Sloan Fellowship, an E. W. R. Steacie Fellowship, the Rutherford Medal in Chemistry from the Royal Society of Canada, the Alfred Bader Award, and the R. W. Lemieux Award from the Canadian Society for Chemistry. In 2001, he was elected as a Fellow of the Royal Society of Canada, and in 2006 selected as an A. C. Cope Scholar from the American Chemical Society. Most recently he received the Humboldt Senior Scientist Award. Throughout his career he has been interested in metal-catalyzed transformations that make carbon–carbon and carbon–heteroatom bonds as well as asymmetric catalysis. His work has appeared in over 200 publications, reviews, and book chapters. He was the editor for Volume 1 of *Science of Synthesis* and is an Editorial Board Member of *Synthesis* and *Synfacts*.



C. S. Bryan

**Christopher S. Bryan** was born in Winnipeg (Canada) in 1982. He received his B.Sc. degree with distinction in 2005 from the University of Victoria (Canada), where he worked in the laboratory of Professor Scott McIndoe. While an undergraduate, he worked as a Co-op student in the medicinal chemistry department at Boehringer-Ingelheim Pharmaceuticals in Laval (Québec, Canada). He is currently

pursuing his Ph.D. at the University of Toronto under the supervision of Professor Mark Lautens. His research is focused on the synthesis of heterocycles via metal-catalyzed tandem processes.



J. A. Braunger

**Julia A. Braunger** was born in Biberach (Germany) in 1984. She obtained her diploma degree in 2009 from the University of Göttingen (Germany) where she studied the interaction of ezrin, a membrane cytoskeleton linker, with solid-supported lipid membranes using quartz crystal microbalance under the direction of Professor Claudia Steinem. She is currently pursuing Ph.D. studies in the same group. She worked as a visiting student in the group of Professor Mark Lautens in the summer of 2008.

COMING SOON ►► COMING SOON ►►

## SYNFORM 2010/01 is available from December 21, 2009

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(Focus on an article from the current literature)

■ **Development of a Sila-Friedel–Crafts Reaction and Its Application to the Synthesis of Dibenzosilole Derivatives**  
(Focus on an article from the current literature)

■ **Formal [4+2] Cycloaddition of Donor–Acceptor Cyclobutanes and Aldehydes: Stereoselective Access to Substituted Tetrahydropyrans**  
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### FURTHER HIGHLIGHTS + + + +

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#### SYNFACTS

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