

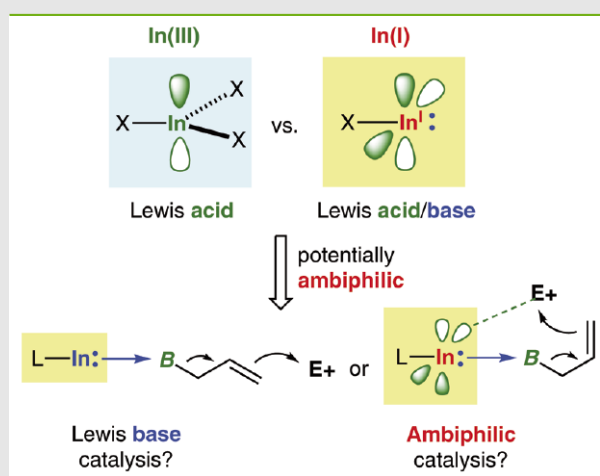
SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2012/02

SYNSTORIES ■ ■ ■ ■

■ **Young Career Focus:**
Dr. Uwe Schneider (University of Edinburgh, UK)



■ **Unclicking the Click: Mechanically Facilitated 1,3-Dipolar Cycloversions**

■ **Tuning Chemoselectivity in Iron-Catalyzed Sonogashira-Type Reactions: Selective Alkynylation of Nonactivated Alkyl Halides**

CONTACT +++++

Your opinion about SYNFORM is welcome, please correspond if you like:
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Dear readers,

Today is the last day of the year. I know this Editorial will be published in the February issue of **SYNFORM**, nevertheless, I can't pretend today is a different day: it's December 31st, 2011 and most of us are ready to celebrate

the looming New Year with family and friends. I found a quote on the web, which reflects pretty well what's going to happen tonight: "An optimist stays up until midnight to see the New Year in. A pessimist stays up to make sure the old year leaves" (Bill Vaughn). I think for most of us this was a mixed year, something was good and something was bad. However, for our beloved art and science of organic chemistry, this was definitely a great year in terms of research achievements and progress, whereas it was less good in terms of funding, at least in Europe, mainly (but not exclusively) because of the globally difficult economic situation. Personally, my commitment for the New Year is to focus the research of my group even more on some of the most important, unmet medical needs, where organic chemistry plays a key role. But certainly organic chemistry will continue to play a pivotal role in many other areas such as preserving our environment, producing and storing energy in more efficient ways, creating smarter materials. I wish to all of You, Dear Readers, a fantastic and productive Year 2012, full of great results and exciting science!

This said; let's have a closer look at the content of this issue. The first **SYNSTORY** reports on a very original and exciting discovery by the group of Professor C. W. Bielawski (USA): the "retro-click" reaction, i.e. how to use mechanical force to achieve an unprecedented 1,2,3-triazole cycloreversion. The second **SYNSTORY** reveals how the group of Professor M. Nakamura (Japan) was able to tune the chemoselectivity in iron-catalyzed Sonogashira-type reactions, achieving a selective alkynylation of non-activated alkyl halides (chlorides, bromides and iodides). The issue is completed by the Young Career Focus on Dr. U. Schneider (UK).

Enjoy your reading ... and a Happy New Year!

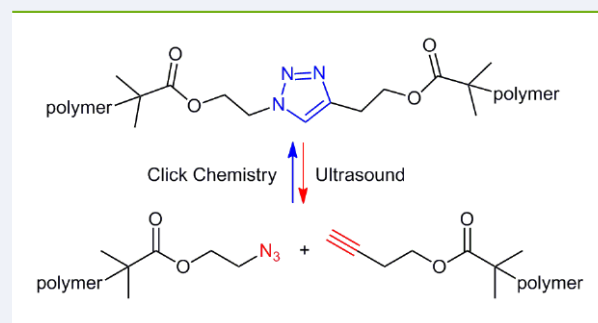
Matteo Zanda

Editor of **SYNFORM**

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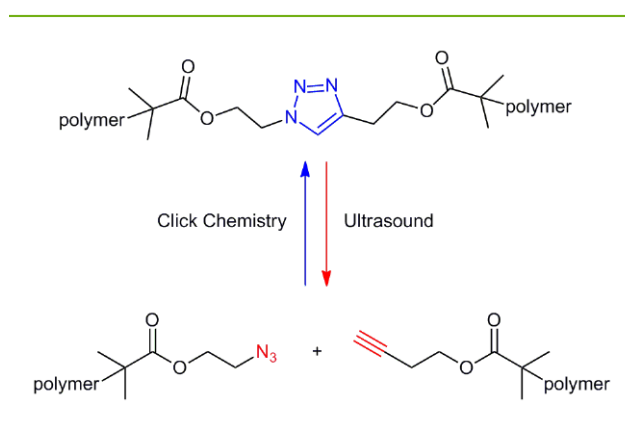
Unclicking the Click: Mechanically Facilitated 1,3-Dipolar Cycloreversions

Science **2011**, 333, 1606–1609

■ The copper-catalyzed 1,3-dipolar cycloaddition of azide and alkyne moieties, which allows access to 1,4-disubstituted 1,2,3-triazoles, has found broad applicability over the past decade due to its rapid kinetics under mild conditions, high functional group and solvent tolerance, good atom economy, and the relative chemical inertness and thermal stability of the products. In addition to finding utility in molecular and polymer functionalizations, this motif has been applied to robust, chemically orthogonal ligations for the study of biological systems. Indeed, the triazole products are so stable that no simple chemical or thermal treatment capable of cleanly reverting these moieties into their constituent azides and alkynes was known. Recently, the group of Professor Christopher W. Bielawski from the University of Texas at Austin (USA) envisioned that mechanical force could be used to surmount the otherwise inaccessible barrier to triazole cycloreversion. The researchers found that embedding a 1,2,3-triazole within a poly(methyl acrylate) chain renders it susceptible to a cycloreversion induced by ultrasound.

“Recent advances in mechanochemistry – wherein exogenous forces are directed to mechanophores, or small molecules possessing mechanically labile bonds – have demonstrated that formally disallowed pericyclic reactions and thermally inaccessible isomerizations can be readily induced through site-specific mechanical activation,” explained Professor Bielawski. “Mechanical forces are presumed to promote these otherwise prohibitive reactions through ground-state destabilization of the reactants (as a result of changes in molecular geometry) or the stabilization of reactive intermediates at or near the transition state of the reaction coordinate,” he continued. “Based upon this foundation, we hypothesized that triazoles, while remarkably inert toward chemical and thermal perturbation, could cyclorevert under the strategic application of mechanical force.”

With this in mind, Professor Bielawski wondered if it would be possible to access a dynamic triazole system, where mechanical force was used to afford the reactive azide and alkyne starting materials (a feat that cannot be accomplished by any other stimuli). “While we wished it were possible to



grab onto triazole molecules and simply pull them apart, we knew from previous studies that ultrasound could be used as a source of mechanical force,” he said.

Professor Bielawski explained that while small molecules are largely immune to the mechanical forces generated under ultrasound, polymer chains may be attached to these molecules and effectively function as handles that respond to the forces generated under ultrasonication. “In an acoustic field,” he continued, “solvent cavitation generates small bubbles that rapidly expand and implode.” Solvated polymer chains near these growing cavities essentially are pulled toward the void volume. If this happened to a polymer chain attached to one side of the triazole, for example, but not to the polymer chain attached to the other side of the triazole, tensile forces would be generated in the center of the chain, right where the triazole is located. “It is believed that this mechanical force destabilizes the molecule through bond distortion, which ultimately lowers the energy needed for the cycloreversion to occur,” he added.

Professor Bielawski revealed an anecdote about how the project was actually started in his group. “When I originally proposed this idea to Kelly Wiggins, one of the *Science* paper co-authors, and to a postdoc in our lab in the summer of 2009, they thought it would not work and pursued other mechanical-

ly-activated systems,” he said. “However, when Johnathan Brantley joined our lab, he insisted that we try to apply ultrasound to a triazole centered polymer,” and the research project was eventually kicked off. “As a first-year graduate student, John Brantley was incredibly excited about our work with polymers and mechanical force and took lead on this project, driving it to completion,” said Professor Bielawski. “Kelly Wiggins is a senior graduate student who has worked with many mechanophores in the Bielawski lab and was instrumental in designing control and other important experiments,” he acknowledged.

After growing polymer chains from a bifunctional triazole initiator, the Texas researchers subjected the material to ultrasound. “Upon isolation, the polymeric material showed a reduction in molecular weight consistent with what we would expect if the retro-cycloaddition were occurring,” recalled Professor Bielawski. “Further examination by infrared spectroscopy indicated that the desired azide and alkyne products had formed. To confirm, we used selective conjugation reactions to label the liberated azides and alkynes with chromophores that were easily detectable by UV-Vis spectroscopy,” he continued. “These labeling reactions were compelling evidence that we were forming the azides and alkynes under ultrasound. Furthermore, after mechanically ‘un-clicking’ the triazoles we were able to re-couple the polymer chains using classic click chemistry conditions.”

According to Professor Bielawski, a number of specifically designed control experiments showed that the cycloreversion of the triazole under ultrasound was a mechanically induced process. “For example, thermal experiments (where we heated

the triazole-centered polymer to elevated temperatures) showed no reduction in molecular weight and no evidence of azide or alkyne formation,” he said.

This research has very exciting potential applications and future perspectives. “The cycloreversion may find use as a molecular force sensor for applications in biological assays or in mapping points of stress in plastics, where the locations of the cycloreversion reactions show the areas where the material is under the most duress,” confirmed Professor Bielawski, who added that triazoles are used extensively throughout materials chemistry in polymer synthesis because of their robustness. “Our results suggest that, in conjunction with other internal and environmental factors, triazole cycloreversion under stress could be a process that contributes to the overall failure of load-bearing materials into which this moiety has been incorporated,” he continued. Additionally, click chemistry is often used in bioconjugation studies because the resulting triazoles are biologically orthogonal moieties. “An interesting potential application of our work could be the development of systems or sensors that use mechanical forces to reversibly label biomolecules (e.g., proteins) with a variety of small molecules,” pointed out Professor Bielawski. “We are currently undertaking a theoretical study to understand the role that mechanical forces play in the reactivity we have observed. We are also exploring new areas, such as the application of mechanical forces in a biological context, and we intend to continue exploring the development of mechanically responsive materials,” he concluded. ■

Matteo Zanda

About the authors



Prof. C. W. Bielawski



J. N. Brantley



K. M. Wiggins

Tuning Chemoselectivity in Iron-Catalyzed Sonogashira-Type Reactions: Selective Alkynylation of Nonactivated Alkyl Halides

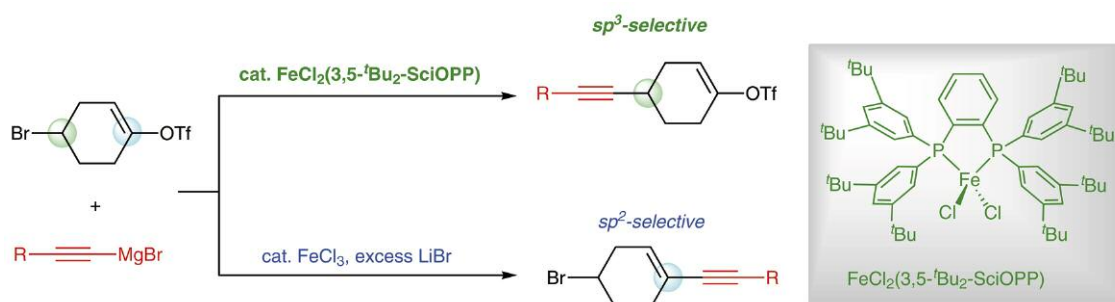
Angew. Chem. Int. Ed. **2011**, *50*, 10973–10976

The formation of novel carbon–carbon bonds through catalytic reactions involving non-activated substrates represents a very hot area of research, undergoing rapid evolution. The use of rather inert alkyl halides as substrates in metal-catalyzed C–C bond-forming reactions is particularly attractive. Recently, the group of Professor Masaharu Nakamura from Kyoto University (Japan) reported a new process catalyzed by a bisphosphine–iron(II) complex which leads to the formation of a new $C_{sp}-C_{sp^3}$ bond between non-activated alkyl halides (chlorides, bromides and iodides) and terminal alkynes. The reaction is remarkably efficient and takes place both with primary and secondary alkyl halides.

“The development of iron catalysts featuring state-of-the-art selectivity has been, at least for us, a labor-intensive research for a long time,” said Professor Nakamura, who revealed that he started a research project aiming to control the reactivity of iron catalysts under nucleophilic/organometallic reaction conditions when he was a Ph.D. student in Professor Eiichi Nakamura’s group at The University of Tokyo (Japan). “It took me two years to find the first iron-catalyzed enantioselective olefin carbometallation reaction by using catalytic amounts of an iron salt and a chiral bisphosphine BINAP in the presence of an excess amount of a diamine ligand, TMEDA,” said Professor Nakamura.¹ “Since then, bisphosphines and diamines have been the prime candidates for my research group in order to develop iron-catalyzed selective organic/organometallic transformations,” he continued. “TMEDA, thus, has turned out to be an effective addi-

tive in iron-catalyzed cross-coupling and related reactions,” said Professor Nakamura.² “However, the iron catalyst appeared to be an unruly horse: it goes well only when it likes to go!” Professor Nakamura recalled that, at the beginning of this project, aryl Grignard reagents were the only choice for the iron-catalyzed cross-coupling reaction. “The situation took a turn for the better after finding a way to control the iron catalyst by means of catalytic bisphosphines,” he said.³

Based on a mechanistic study on the reaction of a paramagnetic diaryliron–TMEDA complex and an alkyl halide,⁴ Professor Nakamura and his co-workers developed new bisphosphine ligands, which were dubbed *SciOPPs*,⁵ as they were named after Professor Nakamura’s design concept of spin control of the metal center (SciOPP is thus an abbreviation of Spin-control-intended Ortho-PhenylenebisPhosphine). “Having the *SciOPPs* in hand,” he said, “we succeeded in developing iron-catalyzed Kumada–Tamao–Corriu,⁵ Negishi,⁶ Suzuki–Miyaura⁷ coupling reactions and also the Sonogashira-type cross-coupling being featured in this *Angewandte* paper.” Professor Nakamura revealed that there are two tips to effectively performing this iron-catalyzed Sonogashira-type coupling. “First of all, the alkynyl Grignard reagents should be added to a mixture of $FeCl_2(SciOPP)$, the catalyst precursor, and alkyl halide substrates at the appropriate temperatures and addition rates. Secondly, the introduction of a bulky substituent at the alkynyl terminus of the Grignard reagents is also helpful for achieving high selectivity and yield.” Under these conditions, the researchers from Kyoto University could gene-



rate a neutral diorganoiron species coordinated by a SciOPP as the catalytically active species. “Of course, the peripheral steric hindrance of the ligand helps the formation of the diorganoiron species by avoiding further alkynylation of the iron center to prevent undesirable ferrate formation,” said Professor Nakamura, who pointed out that the reaction is highly selective for the C_{sp^3} –halogen bond and almost no reaction takes place with alkenyl triflates and aryl bromides. “Recently, Hu and co-workers reported a similar Sonogashira-type cross-coupling of non-activated alkyl halides with alkynyl Grignard reagents, where a divalent nickel–amine catalyst and an amino ether additive effect the coupling reaction,” acknowledged Professor Nakamura.⁸ “This reaction works well with primary alkyl halides and sterically unhindered alkynyl groups, hence is complementary to our iron-catalyzed Sonogashira-type reaction,” he said. “We are expecting that continuing and widespread research efforts to utilize abundant alkyl halide substrates in selective cross-coupling will become mainstream in alkylation technology, not only in alkyne synthesis but also in any type of alkylative C–C bond formations,” concluded Professor Nakamura. ■

Matteo Zanda

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About the authors



From left: Prof. M. Nakamura, T. Hatakeyama, Y. Okada, Y. Yoshimoto

Young Career Focus: Dr. Uwe Schneider (University of Edinburgh, UK)

■ **Background and Purpose.** *SYNFORM* will from time to time meet young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This *SYNSTORY* with a **Young Career Focus** presents Dr. Uwe Schneider, University of Edinburgh, UK.

BIOGRAPHICAL SKETCH



Dr. U. Schneider

Uwe Schneider is a Lecturer in the EaStCHEM School of Chemistry at the University of Edinburgh, UK. He was born and raised in Würzburg (Germany), and studied chemistry in Würzburg and Marburg (Germany), and in Lille and Lyon (France). Supported by Kekulé and ATER fellowships, he obtained his PhD degree working with Professor Xavier Pannecoucke and Professor Jean-Charles

Quirion at IRCOF in Rouen (France) in 2003. He then moved in 2004 to the University of Tokyo (Japan) to join the group of Professor Shū Kobayashi as a Postdoctoral Research Associate (JST Fellow). Subsequently, he was appointed as an ERATO Group Leader (2006–2007) and an Assistant Professor (2007–2011), before taking up his present position in September 2011.

Uwe Schneider has diverse research interests, including green chemistry, asymmetric catalysis, elements in their peculiar low-oxidation and low-valence states, unusual Lewis bases and Lewis acids, and innovative strong bond activation in small molecules. Recently, he has been the recipient of two Global COE Overseas Lectureship Awards (2008 and 2010), a Global COE Chemistry Innovation Grant to Young Principal Investigators (2009–2010), a Thieme Chemistry Journal Award (2011), and a Marie Curie Career Integration Grant (2012–2016).

INTERVIEW

SYNFORM | *Dr. Schneider, what is the focus of your current research activity?*

Dr. Schneider | My current research activity lies in the area of synthetic organic chemistry, with a particular focus on the invention of new catalytic asymmetric methodologies. My group aims to contribute to today's challenges with an innovative program directed toward the design and development of novel catalysts, with the ultimate goal of streamlining organic synthesis via previously underexplored or unrecognized catalysis. We are also interested in performing organic reactions in green media – including water – and in activating strong bonds in small molecules.

SYNFORM | *When did you get interested in synthesis?*

Dr. Schneider | Simply during my undergraduate studies! I definitely felt most attracted toward the *Modern Organic Chemistry* and *Synthetic Methods* classes and tutorials delivered by Professor Reinhard Hoffmann and Professor Paul Knochel. In addition, my very first research project in organic chemistry – within the group of Professor Waldemar Adam – proved to be both very stimulating and pretty successful.

SYNFORM | *What do you think about the modern role and perspectives of organic synthesis?*

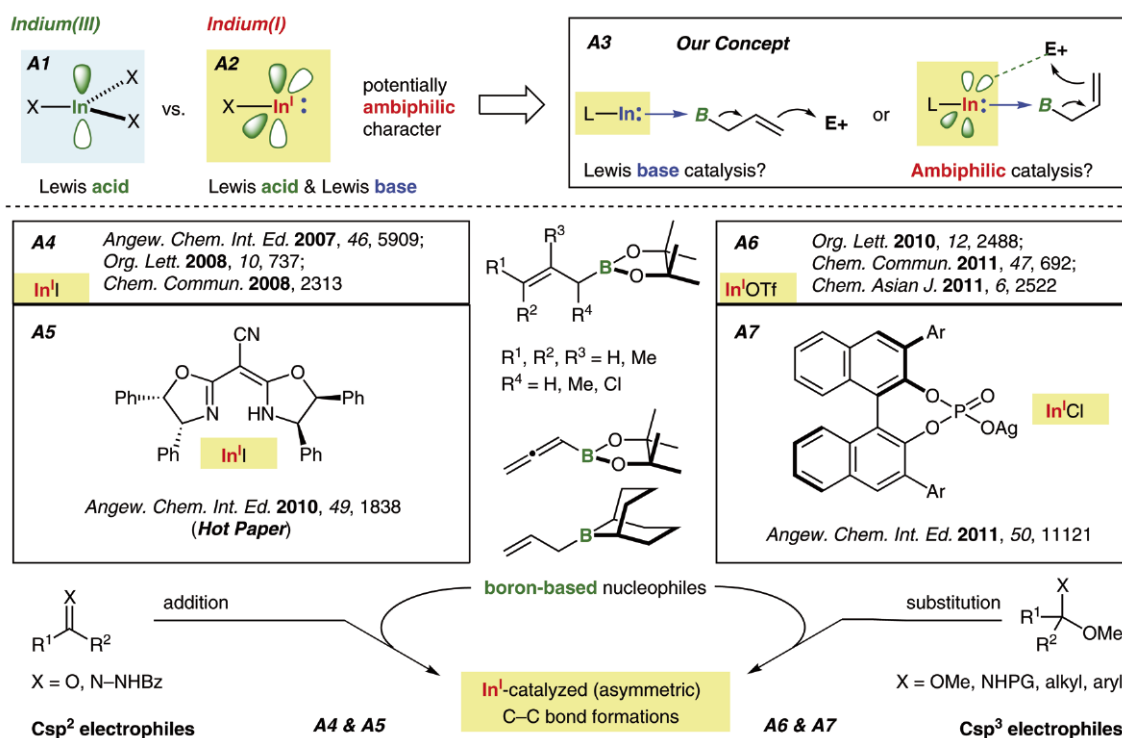
Dr. Schneider | Although some funding agencies may have a very different opinion, I believe that organic synthesis – and catalysis in particular – is among the most important green key technologies in the 21st century: catalysis is concerned with environment, health, and safety – and thus our society in general. In my opinion, the most crucial point to further advance catalysis will be the discovery of innovative catalysts, the invention of novel modes for catalytic activation of strong bonds, and the careful elucidation of reaction intermediates and mechanisms involved. I trust that fundamental studies toward these goals are worthwhile, because unprecedented reactivity and unique selectivity may be uncovered, ultimately leading to new concepts and perspectives in chemistry.

SYNFORM | Your research group is active at the interface of organic synthesis and green chemistry. Could you tell us more about your research and its aims?

Dr. Schneider | The overall theme of our research program is to explore chemical elements in their unusually low-oxidation or low-valence states, because these molecules potentially display intriguing properties readily exploitable in catalysis. These features include ‘hidden’ Lewis basicity or acidity and unique Lewis ambiphilicity (= switchable acid–base character at a single element center in view of unprecedented dual catalytic activation modes). The candidates we examine comprise specific low-toxicity metals and non-metals. This innovative concept requires critical ligand and counter-ion design and control for expression and exploitation: (i) in catalysis, (ii) for small-molecule activation, and (iii) in green organic media. We aim at increasing the efficiency of existing reactions, find interesting reactivity and selectivity, enable challenging bond formations, and invent fundamentally new reactions.

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

Dr. Schneider | My most important scientific achievement to date deals with the development of various (asymmetric) bond transformations based on the catalytic use of (chiral) low-oxidation/low-valent indium species. Indium is a low-toxic main group metal, and organoindium compounds are typically water-compatible, remarkably functional-group-tolerant, and very selective. Indium(III) species are commonly used as ‘classical’ Lewis acid catalysts (vacant orbitals; **A1**, Scheme). In contrast, indium(I) may display Lewis acidic (vacant orbitals) and basic (one lone pair of electrons) behavior (**A2**, Scheme); this ‘switchable’ feature may be called Lewis amphiphilicity, previously unexplored in catalysis. Based on our unique concept for indium(I) catalysis (**A3**, Scheme), we achieved the first catalytic use of indium(I) for selective C–C bond formations between various boron-based pro-nucleophiles and C_{sp}² electrophiles (ketones, imines; **A4**, Scheme). Our concept proved to be applicable to the first



asymmetric indium(I) catalysis through the use of a chiral ligand (**A5**, Scheme). In parallel, we also developed indium(I)-catalyzed, selective reactions with C_{sp³} electrophiles (carbohydrates, *O,O*-acetals, *N,O*-aminals, ethers; **A6**, Scheme). Importantly, we achieved the first asymmetric indium(I) catalysis directed by a chiral counter-anion (**A7**, Scheme). These indium(I) studies – in organic solvents – also set the stage for another discovery: the first catalytic

use of metallic indium [indium(0)] for C–C bond formation, which proceeds regio- and stereoselectively and which requires water as a solvent (*J. Am. Chem. Soc.* **2008**, *130*, 13824). Two forthcoming papers in *Acc. Chem. Res.* and *Pure Appl. Chem.* will summarize the crucial points of these catalyses. ■

Matteo Zanda



COMING SOON ► ► COMING SOON ► ►

SYNFORM 2012/03

is available from
February 20, 2012

In the next issues:

SYNSTORIES ■ ■ ■ ■ ■

■ Gold-Catalyzed Oxidative Acyloxylation of Arenes

(Focus on an article from the current literature)

■ Enantioselective Preparation and Chemoselective Cross-Coupling of 1,1-Diboron Compounds

(Focus on an article from the current literature)

FURTHER HIGHLIGHTS + + + + +

SYNTHESIS

Review on: Transition Metal-Catalyzed Enantioselective Propargylic Substitution Reactions of Propargylic Alcohol Derivatives with Nucleophiles

(by Y. Nishibayashi)

SYNLETT

Account on: The Wieland–Miescher Ketone: A Journey from Organocatalysis to Natural Product Synthesis

(by B. Bradshaw, J. Bonjoch)

SYNFACTS

Synfact of the Month in category "Metal-Mediated Synthesis":

Fe-Catalyzed Cross-Coupling of Alkyl Halides with Alkynyl Grignard Reagents

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