SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2011/12

SYNSTORIES

- Di-*tert*-butylisobutylsilyl, Another Useful Protecting Group

- Silver-Mediated Trifluoromethoxylation of Aryl Stannanes and Arylboronic Acids

- SYNTHESIS/*SYNLETT* Advisory Board Focus: Professor André B. Charette (Université de Montréal, Canada)

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Dear readers,

I would like to take advantage of this editorial to emphasize the importance of your input to the selection of articles to be published in **SYNFORM**. Normally, top quality articles are selected by me following a thorough screening of the current literature, or (less often) are suggested by the Thieme Chemistry Editorial Board members. However, at **SYNFORM** we believe that You, our Readers, could assume the role of protagonists in the selection process, by suggesting high impact articles from the very recent literature that you would like to see featured in **SYNFORM**, including your own papers of course. This is also true for topics of current great interest that you would like to see covered and discussed in **INSIDE STORIES**, or protagonists of organic chemistry that you would like to see in our Young Career Profiles or in ad hoc **INSIDE STORIES** like the interview to Sir Jack Baldwin that was published in issue 01/2008. We would be delighted to get your suggestions and inputs at synform@chem.polimi.it and we believe that this would make **SYNFORM** even more rich and interesting.

This new issue of **SYNFORM** is in my humble opinion one of the best ever, as it features an outstanding contribution by the group of the Nobel Laureate Professor E. J. Corey (USA) on a novel and highly useful silicon protecting group, and another very exciting piece of research from the group of Professor T. Ritter (USA) about the development of a new methodology for the introduction of the OCF_3 group onto aryl stannanes and boronic acids. The issue is completed by an Advisory Board Focus on Professor A. B. Charette (Canada).

Enjoy your reading!

Matteo Zanda

Editor of **SYNFORM**

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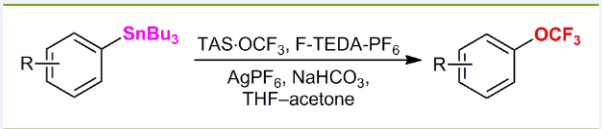

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If you have any questions or wish to send feedback, please write to Matteo Zanda at:
Synform@chem.polimi.it

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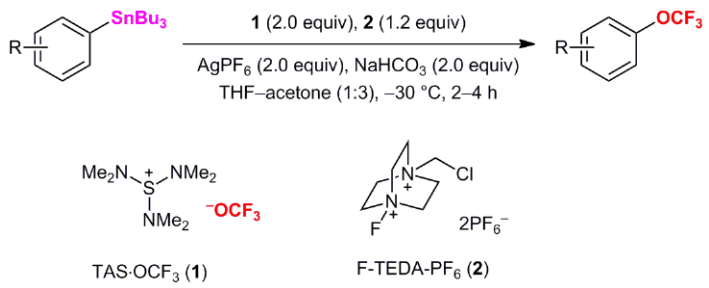
NEWS AND VIEWS NEWS AND VIEWS NEWS AND VIEWS

Silver-Mediated Trifluoromethoxylation of Aryl Stannanes and Arylboronic Acids

J. Am. Chem. Soc. **2011**, *133*, 13308–13310

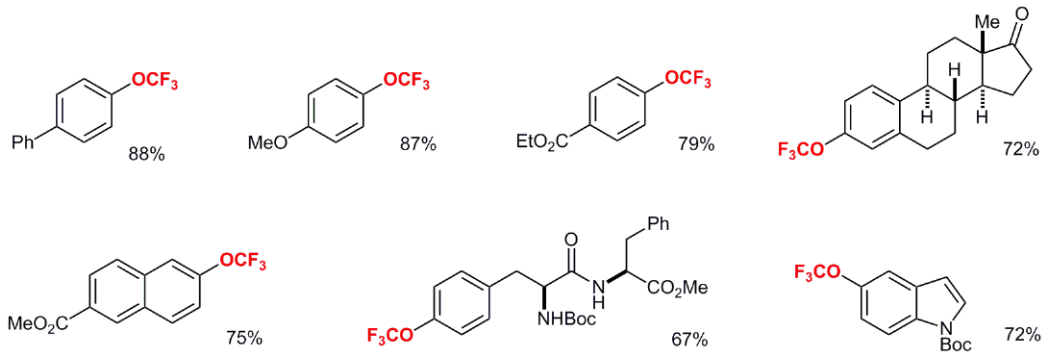


Silver-mediated trifluoromethoxylation of aryl stannanes

The trifluoromethoxy group is commonly encountered as a substituent of aromatic groups in drugs and bioactive molecules, but few synthetic methods are available to incorporate this function in organic molecules. Recently, the group of Professor Tobias Ritter from Harvard University (Cambridge, Massachusetts, USA) reported a new methodology for the synthesis of trifluoromethoxy arenes based on a cross-coupling reaction of both aryl stannanes and arylboronic acids. The reaction leads to the formation of a new C_{aryl}–OCF_3 bond and is mediated by silver.

The new methodology has a wide scope as it can be used to trifluoromethoxylate a range of functionalized aryl stannanes and boronic acids.

"We began by evaluating the established silver-catalyzed fluorination reaction as a platform to develop the C–OCF_3 bond formation," said Professor Ritter. "We knew that C_{aryl}–F bonds could be made at 0 °C and were curious to see if we could use what we believe to be multinuclear silver interactions to allow for the trifluoromethoxide anion, an oxidant, and an aryl nucleophile to be cross-coupled at 0 °C or lower



Some of the products obtained via trifluoromethoxylation of arylstannanes

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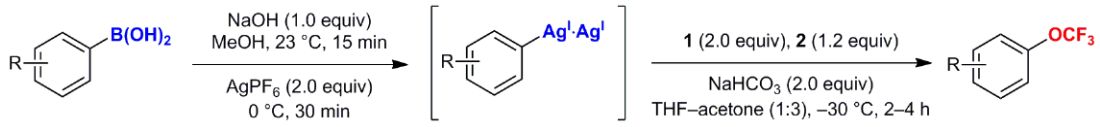

Silver-mediated trifluoromethoxylation of arylboronic acids

temperatures," he continued. "We found that tris(dimethylamino)sulfonium trifluoromethoxide was the most stable compound under our reaction conditions and that the best conditions involved generating the trifluoromethoxide salt in THF while performing the silver-mediated trifluoromethoxylation in acetone." According to Professor Ritter, the use of THF as a co-solvent was critical since trifluoromethoxide salt generation was not successful in acetone. "With boronic acid substrates, one of the challenges was getting the boronic acid to transmetalate onto the silver," he said. "Transmetalation could be accomplished effectively in MeOH, thus, a two-step one-pot procedure was designed for the boronic acid substrates.

"When we designed the project to make C_{aryl}–OCF_3 bonds, cross-coupling seemed an attractive approach," said Professor Ritter. "Many of the challenging C–X bond formations have been accomplished via palladium cross-coupling. However, we recognized that most of these cross-coupling reactions employ strongly basic conditions and often temperatures of 80 °C or higher." At these temperatures, explained Professor Ritter, the cross-coupling partner to form the C_{aryl}–OCF_3 bond, the trifluoromethoxide anion, could decompose to carbonic difluoride before it is able to react with the metal center. "Thus, we wanted to explore the possibility of using multinuclear metal interactions to lower the activation barrier for C_{aryl}–OCF_3 bond formation to temperatures where the trifluoromethoxide salt would be stable during the course of the reaction," he continued. "Previously, we have speculated that bimetallic silver redox catalysis may accomplish challenging C–X bond formations at temperatures lower than those commonly used for other cross-coupling reactions (*J. Am. Chem. Soc.* **2010**, *132*, 12150)."

In the conclusions of the JACS paper, Professor Ritter wrote that "the necessity for toxic aryl stannanes and the two-step procedure from arylboronic acids currently limits the practicality of the presented trifluoromethoxylation reaction." However, he also pointed out that "currently, no other method is available to trifluoromethoxylate aryl nucleophiles via cross-coupling." In spite of these limitations, the new methodology is highly valuable and will undoubtedly facilitate further work in the area of trifluoromethoxy arenes, allowing for a deeper understanding of the true potential of these compounds in drug discovery and materials science.

Matteo Zanda

About the authors

Prof. T. Ritter

Tobias Ritter was born in 1975 in Lübeck (Germany). He received his undergraduate education in Braunschweig (Germany), Bordeaux (France), Lausanne (Switzerland), and Stanford (USA), and received a Master of Science from Braunschweig University in 1999. He has done undergraduate research with Professor Barry M. Trost at Stanford, obtained his PhD working with Prof. Erick M. Carreira at ETH Zürich (Switzerland) in 2004, and was a postdoctoral fellow with Professor Robert H. Grubbs at Caltech (USA). In 2006, Tobias was appointed as Assistant Professor in the Department of Chemistry and Chemical Biology at Harvard University and promoted to Associate Professor in 2010. His research program is based on synthetic organic and organometallic chemistry. The Ritter lab currently focuses on fluorination chemistry for late-stage functionalization of complex natural and unnatural products and bimetallic transition-metal redox catalysis.

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Di-*tert*-butylisobutylsilyl, Another Useful Protecting Group

Org. Lett. **2011**, *13*, 4120–4123

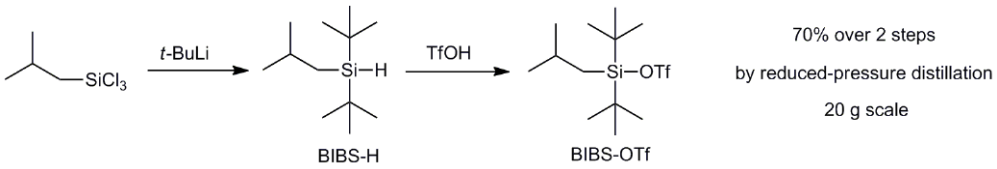
Protecting groups are key elements in synthetic organic chemistry and although there are many good reasons for limiting their use (atom economy, environmental factors, cost of reagents, just to mention a few) they will likely continue to be essential items in the toolbox of organic chemists for the next decades at least. For this reason, the development of new protecting groups having improved chemoselectivity, orthogonality and an optimized profile in terms of stability/reactivity (i.e., deprotection) continues to represent an important and very active area of research. Recently, Professor E. J. Corey and Dr. Huan Liang, an NSERC postdoctoral fellow, from the Department of Chemistry and Chemical Biology, Harvard University (USA), reported a novel highly versatile and selective silicon-based protecting group, the di-*tert*-butylisobutylsilyl or BIBS.

"Silicon is well known for its utility in coupling reactions, as a blocking agent, and for its pharmaceutical properties. In this regard, we initiated a project to explore some bulky silicon groups and their applications in chemical reactions," said Dr. Liang. "We aimed to create a general method to prepare and utilize these silyl groups in the total synthesis of natural products, preparation of drug candidates, green chemistry, and other related areas." Significant progress was achieved by developing the first synthesis of di-*tert*-butylisobutylsilyl triflate (BIBS-OTf). "We have developed a very efficient synthesis of this particular compound in two steps from inexpensive, commercially available starting materials," confirmed Dr. Liang (Scheme 1). In this process, isobutyltrichlorosilane was condensed with 3.5 equivalents of *t*-BuLi at high temperature to give di-*tert*-butyl isobutylsilane, which was then reacted with triflic acid to give the corresponding triflate in ~70% yield on large scale (10–20 grams). "Among the different leaving groups, triflate is the most effective in terms of enhancing the electrophilicity of the silicon center, and offsets its low reactivity imparted by the steric bulk of the alkyl groups," he explained.

Dr. Liang and Professor Corey explained that lack of commercial availability sometimes limits the extensive use of a reagent. "In order to solve this problem, we initiated a collaboration with Gelest, Inc., the world's largest silicon R&D company, and successfully commercialized this useful reagent (Figure 1)," said Dr. Liang.

Professor Corey and Dr. Liang pointed out that to be qualified as an ideal protecting group, the NMR spectrum of the resulting compound must have an easily recognizable pattern, namely its chemical shifts must be distinguishable from the core molecule's functional groups. "Di-*tert*-butylisobutylsilyl

Figure 1 *BIBS-H and BIBS-OTf from Gelest, Inc. (first batch)*



Scheme 1

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triflate (BIBS-OTf) meets this criterion (Figure 2)," said Dr. Liang. "In a ^{1}H NMR spectrum, the two *tert*-butyl groups show at 1–1.1 ppm as a singlet (with integration of 18 H, peak c) and the geminal methyl groups show at 0.9–1 ppm as a doublet (6 H, peak b); the methylene group (CH_2) shows at 0.6–0.9 ppm as a doublet (2 H, peak d); and the only CH shows at ~2.0 ppm as a septet (1 H, peak a)," he explained.

Professor Corey explained that this unique reagent (BIBS-OTf) finds application in several aspects of chemical synthesis. "For example, BIBS triflate reacts with alcohols, carboxylic acids and phenols to afford the corresponding silyl ethers and esters in good to excellent yields (Scheme 2)," continued Dr. Liang. "In general, protection of amines with silyl-based reagents is not very useful in chemical synthesis because of the instability of the N–Si bond to hydrolysis. BIBS provides a solution to this long-standing problem and demonstrates itself as a new nitrogen-protecting group which survives under various basic and reducing conditions," he said. "Due to its large steric size, a BIBS group also achieves extremely high selectivity when preparing kinetic BIBS enol ethers from ketone precursors."

Another key feature of a good protecting group is chemoselectivity. "BIBS-OTf reacts chemoselectively with primary amines or carboxylic acids in the presence of alcohols or phenols in a very efficient manner," said Dr. Liang. "This unusual reactivity is unprecedented in the traditional silyl groups, such as TBS, TIPS and TBDPS (Figure 3)."

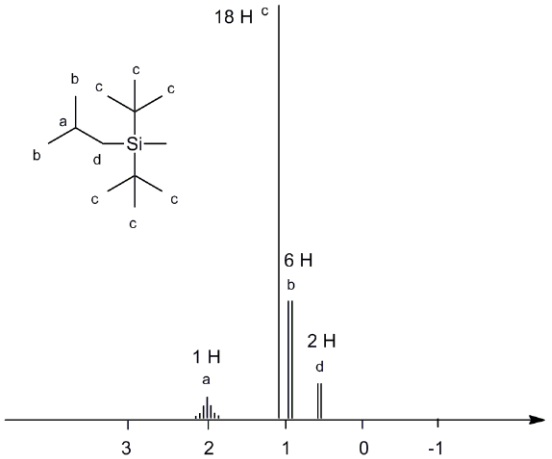
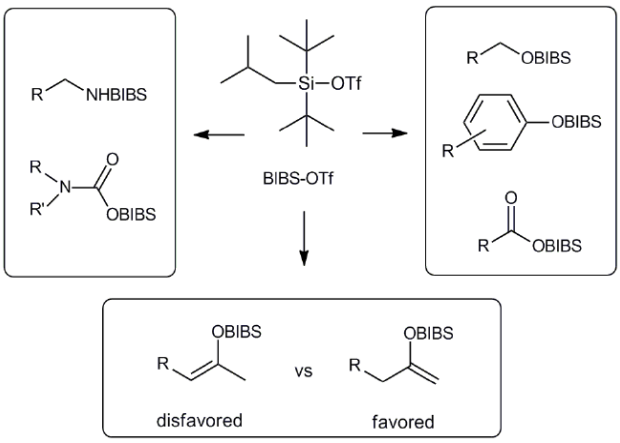


Figure 2



Scheme 2

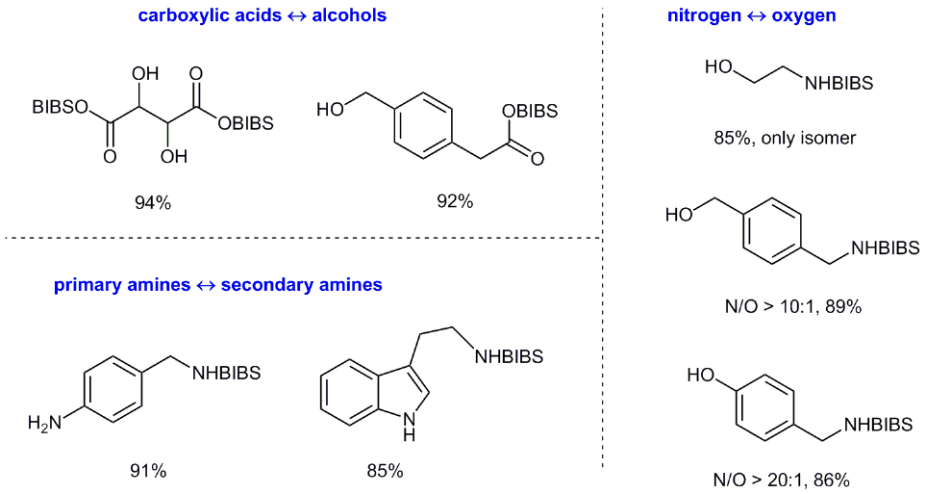


Figure 3

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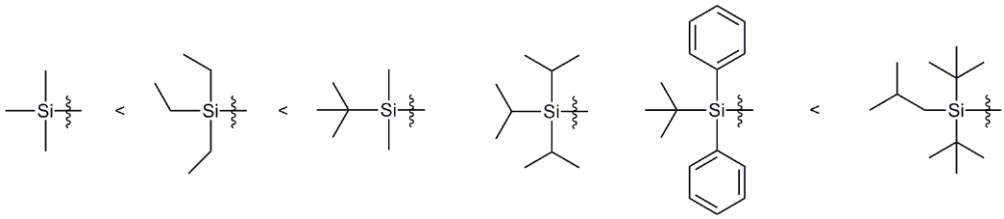


acidic conditions: TMS < TES < TBS < TIPS < TBDPS < BIBS

basic conditions: TMS < TES < TBS, TBDPS < TIPS < BIBS

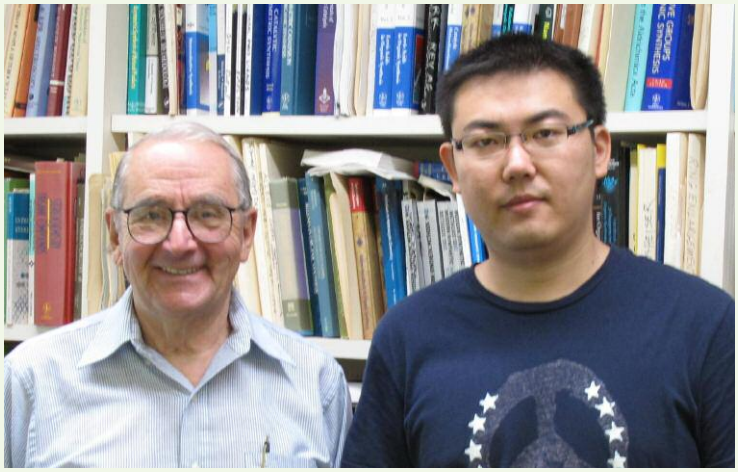
Figure 4

Also in terms of stability, the BIBS group showed very interesting and peculiar properties. "Due to steric hindrance, BIBS ethers showed the highest stability towards deprotection conditions, such as TBAF, HF in pyridine, and hydrolysis, when compared to commonly used silyl ethers (Figure 4)."

"We are confident that our results will be of great assistance to other researchers operating in the area of synthetic organic chemistry. As pointed out by one of the manuscript's referees, we hope that *This new silyl protecting group will find many applications in our everyday laboratory operations dealing with polyfunctional molecules. It will especially complement the TBDPS/TIPS groups and also extend the repertoire of chemoselective protecting groups*," concluded Dr. Liang.

Matteo Zanda

About the authors



From left: Prof. E. J. Corey, Dr. H. Liang

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SYNTHESIS/*SYNLETT* Advisory Board Focus: Professor André B. Charette (Université de Montréal, Canada)

Background and Purpose. ***SYNFORM*** will from time to time portrait **SYNTHESIS/*SYNLETT*** 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 André B. Charette, Université de Montréal (Canada).

BIOGRAPHICAL SKETCH

Prof. A. B. Charette

André B. Charette was born in 1961 in Montréal in the province of Québec, Canada. Shortly after obtaining his B.Sc. from Université de Montréal in 1983, he moved south of the border to pursue his graduate studies at the University of Rochester in the state of New York. Under the supervision of Robert Boeckman Jr., he completed the total synthesis of the ionophore calcimycin, which earned him the degrees of M.Sc. (1985) and Ph.D. (1987) in organic chemistry. Following a two-year NSERC postdoctoral fellowship at Harvard University (Cambridge, USA) with D. A. Evans, he began his academic career at Université Laval (Québec City, Canada) in 1989. In 1992, he returned to his alma mater at Université de Montréal as Assistant Professor, where he quickly rose through the ranks to Full Professor, a position he has held since 1998. Today, he is also the holder of a Canada Research Chair in Stereoselective Synthesis of Bioactive Molecules. With a record of over 175 publications and numerous invited lectures throughout the world, Professor Charette has achieved worldwide recognition in his field. His research lies primarily in the development of new methods for the stereoselective synthesis of organic compounds and natural products. He has devised conceptually novel approaches to catalyst and reaction design with important applications in the synthesis of chiral cyclopropanes, amines and heterocyclic derivatives. Among his recent honors are the R. U. Lemieux (2006) and Alfred Bader (2009) awards from the Canadian Society for Chemistry, the Urgel Archambault Award (2006), the ACS Cope Scholar Award (2007) and the Prix Marie-Victorin (2008) from the Government of Québec. His scientific and leadership abilities have also been rewarded by the establishment of the NSERC/Merck Frosst/Boehringer Ingelheim Industrial Chair in Stereoselective Drug Synthesis from 2000 to 2010.

INTERVIEW

SYNFORM | *Professor Charette, what are your main current research interests?*

A. B. Charette | My main current research interests are in the area of stereoselective synthesis of cyclopropane derivatives, heterocycle synthesis and functionalization as well as simple chemoselective transformations using amides. We are also involved in using phosphonium salts as solubility control groups for reagents, scavengers and solution-phase parallel synthesis.

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

A. B. Charette | One of the most important scientific achievements to date is in the area of the enantioselective cyclopropanation of allylic alcohols to generate either 1,2- or 1,2,3-substituted cyclopropanes using zinc carbenoids. This transformation is quite important, since it is one of the most effective ways to make this class of compounds. It is also good to see that this chemistry is used industrially.

SYNFORM | *Can you mention a recent discovery in the area of organic chemistry, which you consider to be particularly important?*

A. B. Charette | Most of the chemistry involving direct C–H functionalization reactions is quite impressive. We are now able to do things that we could not have imagined doing before. I also like flow chemistry a lot, but this is considered to be more a new technique than a fundamental discovery.

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

A. B. Charette | My main goal is really to continue having fun doing chemistry. I believe that when you enjoy what you do and are passionate about doing research and teaching, good things happen naturally. One of the greatest satisfactions I get from work is to witness how my students evolve as chemists over the years and to see what career path they

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end up choosing after they leave my group. It's always nice to hear from them and to know that they are successful in the career they are pursuing and that they too enjoy it. I always feel like I must have played some role in their education.

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

A. B. Charette | I do a lot of cardiovascular activities (cycling, running, swimming,). This allows me to have enough energy to deal with chemistry and family-related activities.

Matteo Zanda

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In the next issues:

SYNSTORIES

Copper-Catalyzed Enantioselective Additions to Oxocarbenium Ions
(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: Supported Synthesis of Halogenated Organic Compounds
(by V. Gouverneur et al.)

SYNLETT
Account on: 'Pseudo-halide' Derivatives of Grubbs- and Schrock-Type Catalysts for Olefin Metathesis
(by E. B. Anderson, M. R. Buchmeiser)

SYNFACTS
Synfact of the Month in category "Synthesis of Materials and Unnatural Products": An All-Organic Porphyrin and its Properties

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