Recent Advances in Fluorination Technology for Custom Synthesis at Saltigo

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Abstract
Building upon more than 45 years of expertise in the field of fluorine chemistry Saltigo's broad range of fluorination technologies allow for the generation of arrays of advanced pharmaceutical intermediates. In this presentation we will highlight some recent developments in fluorination technologies and discuss these chemistries as key-methods for the synthesis of challenging pharmaceutical intermediates.

We are continuously developing new methods and technologies to ensure timely and cost effective manufacture at scale. In several case studies we will outline the unique role of HF for the synthesis of various pharmaceutical compounds, we will present Saltigo's new phase-transfer catalyst to enable Halex-reaction of non activated substrates and exemplify PBSF as a new fluorinating agent for the selective fluorination of hydroxyl-compounds on multi ton scale.

Access to Poly-Fluorinated Building Blocks via ElectroChemical Fluorination

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Abstract
ElectroChemical Fluorination (ECF) has been one of the technologies most widely used for the production of perfluorinated chemicals, mostly based on chain lenghts of eight carbon atoms. Hystorically, the ECF process converted fully hydrogenated substrates into their corresponding perfluorinated derivatives using anhydrous hydrofluoric acid and electricity as reagents.

$$R_HCOX \xrightarrow[\text{electricity}]{\text{HF}} R_FCOF$$

Due to their environmental burden, C8 and longer chain perfluorinated chemicals are currently under scrutiny. The talk will report a number of strategies, aiming at the replacement of such molecules, based on C3 – C7 chemistry. The ECF technology has successfully produced key intermediates further transformed into a number of poly-fluorinated building blocks carrying useful functional groups.
The prospects for an improved environmental footprint of these substances will be briefly discussed.

"Sulphur - eSSential for life"

Gert de Coster,
Sumitomo Chemical Europe representing Sumitromo Seika
Belgium

Abstract
Our presentation will be about the innovative processes Seika have developed for making high-quality complex sulphur based chemicals on an industrial scale and the application of those chemicals in the manufacture of pharmaceuticals and agrochemicals.

Sulfur Trioxide Amine Complexes: Versatile Reagents in Organic Synthesis

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Abstract
Sulfur is known to form similar compounds as oxygen in organic chemistry, like thiols, thioethers, thio acids and others. However, the organic chemistry of sulfur is dominated by higher oxidation levels of sulfur and here, sulfur trioxide groups and derivatives are often found.

The introduction of sulfur trioxide groups in an organic molecule can be carried out in the simplest way by reacting with sulfur trioxide itself. However, SO_3 shows highly dehydrating properties and hence cannot be used for many reactions with sensitive molecules. Here, various derivatives of sulfur trioxide are applied instead and one specific group are sulfur trioxide amine complexes.

The presented sulfur trioxide amine complexes show different levels of reactivity (and stability) and carry out a wider range of reaction types than only insertion of SO_3. Sulfonation, sulfation and sulfamation are the most prominent reaction types, and here, a higher selectivity can be obtained compared to classical reagents like sulfuric acid, oleum or chlorosulfonic acid.
In addition, other reactions can be carried out with SO_3 amine complexes like a Swern oxidation type reaction, deoxigenation, dehydration as well as carboxamide formation.

The presentation will show typical as well as atypical reaction types of sulfur trioxide amine complexes and special application examples.

Success with Sulfur-based Compounds and Reactions

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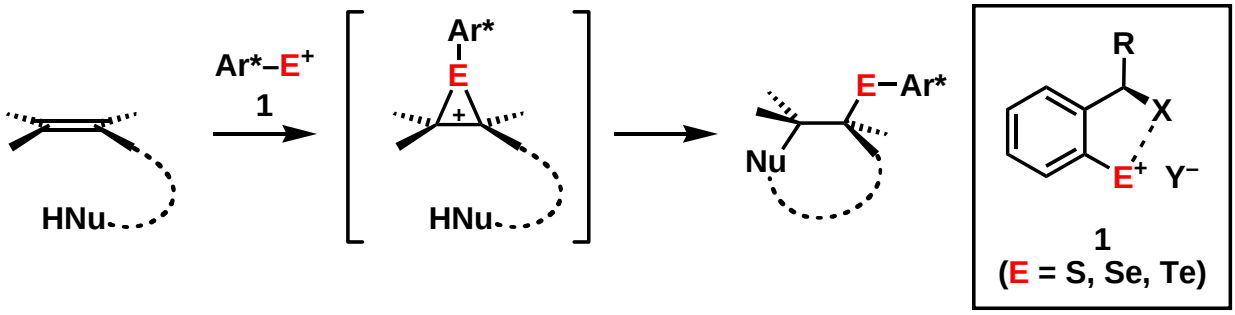
Abstract
Chiral chalcogen electrophiles of type **1** have been used successfully to functionalize inactivated carbon–carbon double bonds.[1] These reagents can also be employed in cyclization reactions for the synthesis of different heterocyclic compounds. For the elaboration of highly functionalized heterocyclic compounds this methodology continues to receive methodological as well as synthetic attention. Different electrophilic reagents and a variety of reaction conditions have been employed and recent reviews have highlighted the scope of this general process.[2]



The use and synthesis of sulfoxides[3] and sulfoximines[4] in these and in other reactions will be discussed as well.

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[1] *Top. Curr. Chem.* (Ed. T. Wirth), Springer, Berlin, **2000**, vol. 208. b) T. Wirth, *Angew. Chem.* **2000**, *112*, 3890 – 3900, *Angew. Chem. Int. Ed.* **2000**, *39*, 3742 – 3751. c) D. M. Browne, T. Wirth, *Curr. Org. Chem.* **2006**, *10*, 1893 – 1903. d) D. M. Freudendahl, S. A. Shahzad, T. Wirth, *Eur. J. Org. Chem.* **2009**, 1649 – 1664.

[2] a) S. A. Shahzad, C. Vivant, T. Wirth, *Org. Lett.* **2010**, *12*, 1364 – 1367. b) S. A. Shahzad, C. Venin, T. Wirth, *Eur. J. Org. Chem.* **2010**, in press.

[3] D. M. Freudendahl, M. Iwaoka, T. Wirth, *Eur. J. Org. Chem.* **2010**, in press.

[4] S. Schäfer, T. Wirth, *Angew. Chem. Int. Ed.* **2010**, *49*, 2786 – 2789; *Angew. Chem.* **2010**, *122*, 2846 – 2850.

Lithium + Boron: Two Elements of Success in High-Performance Fine Chemicals Production

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Abstract
An overview on the latest developments in the field of industrial organometallic chemistry is given with the focus on lithium and boron compounds. This includes technologies for the economic production of the lithium compounds via tailored protocols. Many examples for the selective conversion of the lithium intermediates to "tricky" boronic acids are given, including heterocyclic materials, products with sensitive functional groups or otherwise tricky materials like cyclopropylboronic acid.
Additionally, a new synthesis of previously difficult to make 4-trifluoromethylpyridines is presented, which is based on a cyclisation of precursors accessible via lithium chemistry.

Tools for Organic Synthesis - New Reagents for Lithium Assisted Deprotonation and Addition Reactions

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Abstract
Directed ortho metalation reactions using organolithium bases are frequently used tools in organic synthesis. A major drawback of this methodology is its limited tolerance against functional groups in the substrate molecules. Recently developed complexes of Mg- and Zn-amides with LiCl exhibit a high kinetic basicity in ortho metalation reactions of aromatic and heteroaromatic substrates, nevertheless the resulting organometallics show a high tolerance against functional groups. Zincation even tolerates sensitive groups like aldehydes.

The synthesis of tert-alcohols by the addition of Grignard reagents to ketones is often complicated by side reactions like enolization and reduction. These side reactions can be reduced by Lewis acid activation of the ketone. The well known Imamoto method using $CeCl_3$ can be considerably improved by changing to the THF-soluble $LaCl_3$ x 2 LiCl complexes.

All reactions described are not limited to laboratory scale, the reagents mentioned are already available in pilot or industrial quantities allowing easy scale-up of highly selective deprotonation and 1,2-addition reactions.

Cryogenic Lithiation Reactions for the Production of Starting Materials for Transition Metal Catalyzed Reactions

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Abstract
The synthesis of boronic acids and other compounds will be presented. These compounds were synthesized via cryogenic lithiation reaction either by Li/Halogen exchange or Li/H exchange. The formation and consumption of the lithiated intermediates were controlled by online IR measurement.
The application of the products for transition metal catalyzed reactions like Suzuki reactions and carbonylation will be discussed in the second part of the talk.

Lithiation from Lab to Commercial Scale – in the Field of Hazardous Chemistry

Urs Brändli
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Abstract
DOTTIKON EXCLUSIVE SYNTHESIS AG is well known as a producer of advanced intermediates and APIs, specializing in hazardous chemical reactions. At first sight lithiation reactions at low temperature have few common topics with hazardous chemistry but the synergies regarding the know-how of reactions, development and scaling up the processes with the resulting benefits are obvious.

A case study of a recently performed cryogenic lithiation process is presented from first familiarization work to the proof of concept. Critical reaction parameters which are responsible to achieve the needed selectivity are described and discussed. In addition factors like short minimum hold time for intermediates and efficient heat exchange play an important role regarding the scale-up of this process. As a consequence in addition to the batch reaction mode also the continuous reaction mode was developed and tested. The test results are shown and the advantages and disadvantages of each are discussed. Due to selectivity reasons the continuous mode proved to be beneficial compared to the batch process. With the achieved improved selectivity of the reaction the process results in increased product purity and in a higher total yield and has advantages in the scale-up.

Further the valuable combination of low temperature chemistry with hazardous chemistry is presented. This combination results in new building blocks for the chemical and pharmaceutical industry.

Boronic Acids Manufacture at Industrial Scale

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Abstract

Boronic acids and derivatives are now common tools in the toolbox of the organic chemists. Many are available at industrial scale. However, their manufacture is not always straightforward, and quality of the final product can be difficult to guarantee.
During this speech, we will briefly review the syntheses and uses of boronic acids and derivatives. Then, we will focus on boronic acids manufacture at industrial scale, with emphasis on process issues, analytical issues and quality issues. Finally, we will expand the scope to derivatives of boronic acids, which are being developed by Minakem and can be used as an alternative to free boronic acids in some cases.