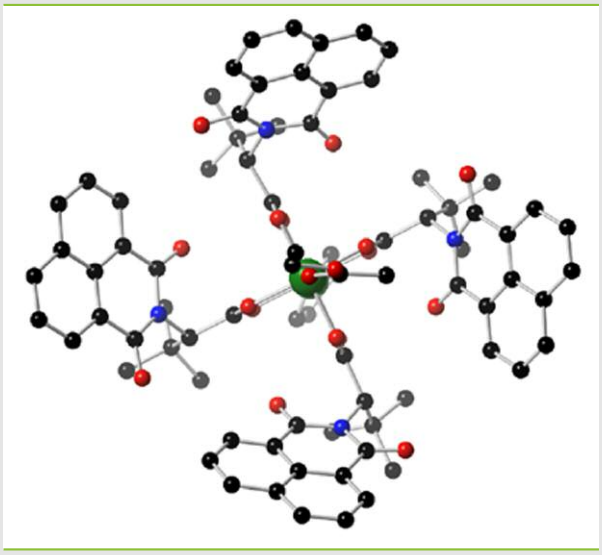
SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2011/05

SYNSTORIES



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Dear readers,

These days Chemistry is changing deeply. On one hand it is becoming progressively more important for a number of exciting new applications at the interface with biomedicine, imaging, materials science, energy and environmental sciences. On the other hand, it is becoming progressively less visible as a single discipline, as demonstrated by the paucity of funding available to support chemistry-focused projects and the fact that many academic chemists are nowadays embedded into non-chemistry departments, giving a key contribution to the development of new and multidisciplinary research areas. Curiously, the current tendency of pharmaceutical companies to outsource large and increasing portions of their research is favoring the opposite effect, namely the growth of Contract Research Organizations (CROs) with a very specific and focused chemistry know-how, for example on the synthesis of small molecules and peptides, bioconjugates and molecular tools for biomedical applications. My feeling is that, albeit in a fluctuating and quickly changing global arena, chemistry will continue to grow in importance and these changes represent a fantastic opportunity for creative chemists rather than a threat for chemistry as a discipline. The increasingly applied and interdisciplinary nature of modern organic chemistry is well demonstrated by the ***SYNSTORIES*** featured in this issue of ***SYNFORM***: a very efficient enantioselective synthetic approach to 2,3-disubstituted indoles, which are privileged structures in medicinal and biological chemistry, developed by Professor J. M. Fox (USA), and an elegant synthesis of 2-amino-2-deoxysugars, which are naturally occurring molecules that have a great importance for biomedical and biochemical applications, developed by Professor N. Sewald (Germany). The issue is completed by an interview with Professor M. Taddei (Italy), Editorial Advisory Board member of ***SYNLETT*** and **SYNTHESIS**.

Enjoy your reading!

Matteo Zanda

Editor of ***SYNFORM***

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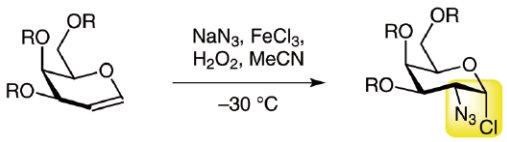
SYNSTORIES



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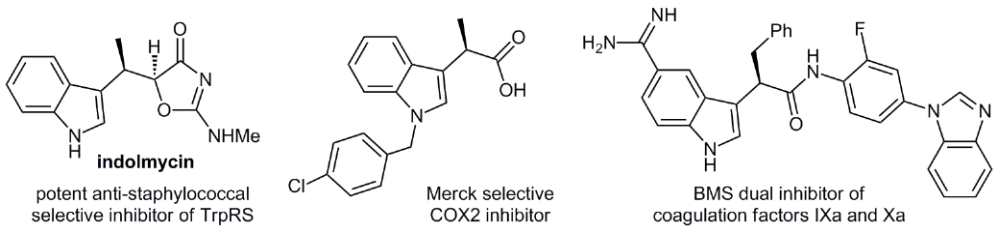
Rhodium(II)-Catalyzed Enantioselective C–H Functionalization of Indoles

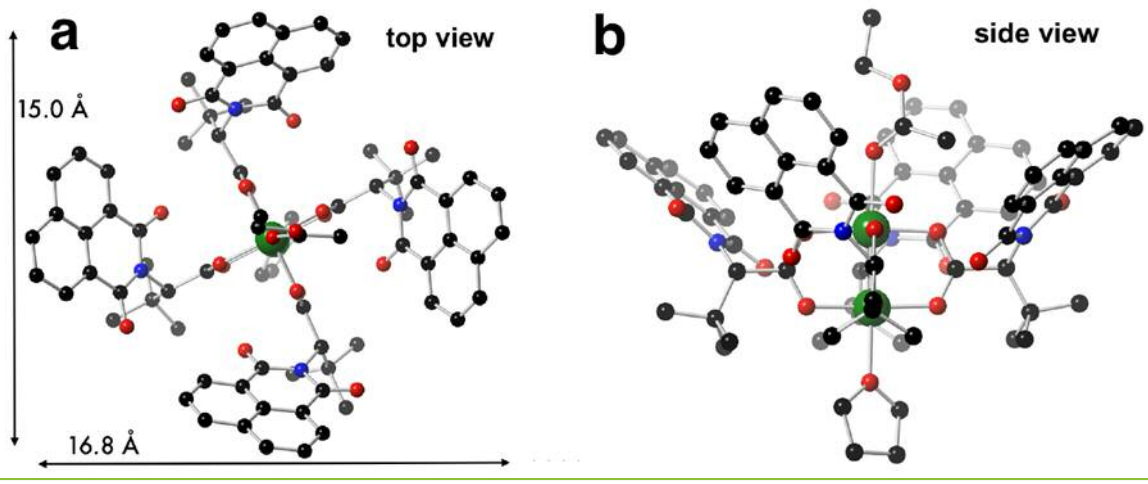
J. Am. Chem. Soc. **2010**, *133*, 1650–1653

Substituted indoles are compounds of great importance in chemical biology and drug discovery. Indeed, a number of naturally occurring bioactive substances and hit molecules obtained from medicinal chemistry campaigns contain this privileged structural framework, which is therefore not surprisingly considered as a hugely attractive synthetic target. Recently, the group of Professor Joseph M. Fox from the University of Delaware (Newark, USA) has developed a novel and very efficient enantioselective synthetic approach to 2,3-disubstituted indoles. The team members who developed the reaction were graduate student Andrew DeAngelis, undergraduate student Valerie Shurtleff, and computational scientist Dr. Olga Dmitrenko.

"During the course of our group's ongoing studies toward the development of intermolecular reactions of alkyl-substituted Rh-carbenes that are selective over β-hydride elimination, we identified the enantioselective functionalization of indoles as an interesting challenge to address," confirmed Professor Fox. "The development of new reactions that allow for the selective functionalization of indoles remains an intense research effort, given the ubiquity of the indole moiety in nature and in pharmaceutically interesting compounds" (see below).

"Furthermore," continued Professor Fox, "we are interested in promoting asymmetric transformations with bimetallic paddlewheel complexes that adopt 'chiral crown' conformations (see crystal structure of Rh_2(S-NTTL)$_4$ below). These combined interests came together in this work."





Examples of indoles with stereocenters α to C-3

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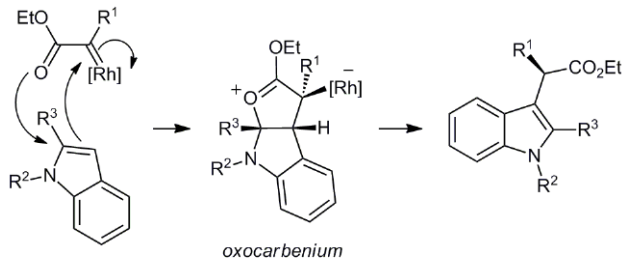
According to Professor Fox, the number of methods for the preparation of indoles with stereocenters α to C-3 is relatively limited. "While the C–H functionalization reaction of indoles by carbenoids was a known reaction, it was unprecedented in the asymmetric sense. Our method represents the first enantioselective Rh-catalyzed C–H functionalization of indoles by carbenoids," he said. Professor Fox explained that with dirhodium(II) tetrakis[*N*-(1,8-naphthaloyl)-(*S*)-*tert*-leucinate [Rh_2(S-NTTL)$_4$], high yields (up to 96%) and enantioselectivities (up to 99%) were obtained with a range of substituted indoles. "The stereocenter being set by our chemistry is a particularly challenging tertiary center as it is highly prone to racemization being adjacent to both an ester and an aromatic group," he continued.

"We were then prompted to probe the mechanism of the reaction, as previous mechanistic proposals included pathways in which it would be difficult to rationalize an asymmetric process (i.e. cyclopropanation/fragmentation)," said Professor Fox. "The results from the mechanistic investigation were interesting, as we found via DFT calculations an ylide intermediate with oxocarbenium character. Although it is not entirely clear how the ylide intermediate progresses to the observed product, we proposed two probable scenarios: the ylide intermediate likely undergoes a dearomatization followed by stereospecific protonation, or undergoes a dynamic kinetic resolution of the rhodium enolate."

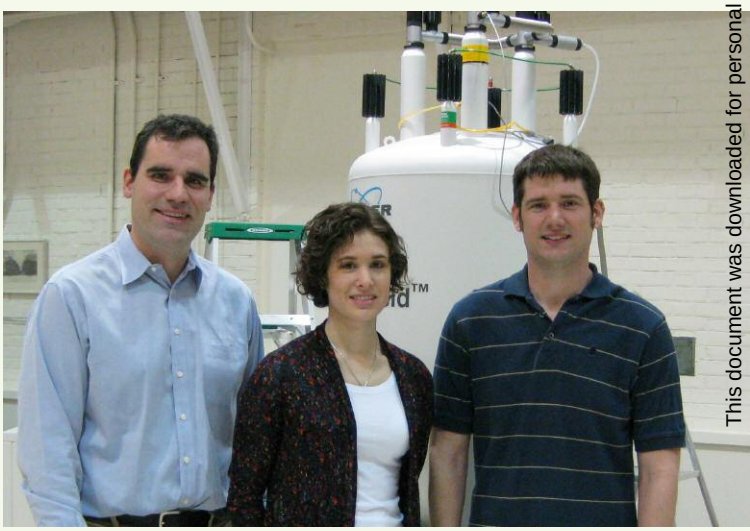


oxocarbenium intermediate

"We believe that this method could have an immediate industrial impact as functionalized indoles are important pharmaceutical scaffolds, and accessing them in enantioenriched form can be challenging. Efforts in our laboratory are ongoing to develop new asymmetric transformations of indoles as well as explore new modes of reactivity for bimetallic complexes that adopt 'chiral crown' conformations," concluded Professor Fox.

Matteo Zanda

About the authors



From left: Prof. J. M. Fox, V. Shurtleff, A. DeAngelis

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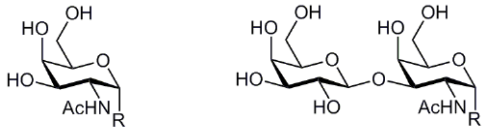
One-Pot Azidochlorination of Glycals

Org. Lett. **2011**, *13*, 545–547

2-Amino-2-deoxysugars are naturally occurring molecules which play a key role in a number of biological and physiological events, such as molecular and immuno-recognition, as well as cell adhesion and differentiation. However, the chemical synthesis of these amino sugars, and particularly of oligosaccharides incorporating them, is still very challenging. Recently, the group of Professor Norbert Sewald from Bielefeld University (Germany) has developed a novel synthetic methodology for the one-pot azidochlorination of glycals, which is expected to give a significant contribution to the advancement of the field.

"Some years ago we embarked on a project aiming at the synthesis and structural modification of antifreeze glycoproteins (AFGP), natural cryoprotectants found in arctic and antarctic fish," explained Professor Sewald. "Interestingly, the glycosyl residue found in these compounds, β-D-galactosyl-(1→3)-α-D-*N*-acetylgalactosamine, glycosidically linked to the hydroxy group of the threonine side chain, is also found in mammals and is known as a tumor-associated carbohydrate antigen (T-antigen)."



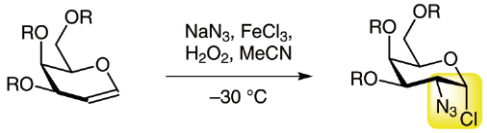
T_N-antigen T-antigen

Professor Sewald said that Carolin Plattner was the first PhD student to start on that project. Different literature-known strategies were evaluated and special emphasis was placed on scaling up the reactions while maintaining reproducible yields and diastereoselectivities. "For protection of the carbohydrate moiety we chose the acetyl group, while Fmoc was employed as temporary amine-protecting group for threonine," said Professor Sewald.

"Carolin followed different routes for the synthesis of T-antigen-modified Fmoc-threonine as building block for peptide synthesis, among them the derivatization of 2-nitroglycals, as well as the azidonitration, and the azidochlorination of glycals. Although different approaches had been published, crucial bottlenecks were identified for most of the multistep syntheses."

For example, according to Professor Sewald, the azidonitration developed by Lemieux and Ratcliffe in the 1960s oxidizes glycals while installing an azido group in position 2 together with a glycosyl nitrate in position 1. "At least in our hands, the isolated yields of the azidonitration varied between 7 and 84%," he said, "but normally amounted between 20 and 35%. This reproducibility problem is known, but is usually not discussed in journals. Moreover, the yields significantly decreased if more than 50 mmol of starting material were used."

The direct azidochlorination according to a patent required large amounts of inorganic reagents and the yield of the 2-azido glycosyl chloride was only moderate (21%). "Carolin became interested in the question whether the massive amounts of different reagents were really required for a successful synthesis," continued Professor Sewald. "She systematically varied the reagents also with respect to stoichiometry and found that significantly reduced amounts of the azide, a redox-active metal (iron), a chloride source and hydrogen peroxide as the oxidant resulted in complete conversion of the triacetyl galactal with 70–80% yield. This approach nicely complements the previously known methodology and can be applied without problems to 15 or more grams of starting material."



Professor Sewald explained that this simple preparation of a nitrogen-containing Koenigs-Knorr donor does not require anhydrous reaction conditions. "The crude product consists of the α-anomeric glycosyl chloride as the major product (85–90%)," he said. "The crude product should be employed directly in glycosylation reactions, as it decomposes during column chromatography. In the frame of his bachelor thesis, Michael Höfener together with Carolin investigated the application of the azidochlorination protocol to disaccharide-based glycals with different protecting groups. They found that T-antigen precursors can be obtained efficiently along this route."

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Professor Sewald disclosed that the referees of the manuscript submitted to *Org. Lett.* stated that the paper "presents an elegant solution for a long-standing problem in carbohydrate chemistry. The classical synthesis of 2-azido donors via azidonitration is tedious and quite unreliable. By use of a simple and robust chemistry employing cheap reagents the authors provide a long-sought substantial improvement for the conversion of mono- and disaccharide glycals." The target compounds have "importance in chemical biology and it is of enormous value to have available reliable and efficient methods..." Undoubtedly, organic chemists have a new powerful tool in their arsenal of reactions for the synthesis of this important class of sugars.

Matteo Zanda

About the authors

Prof. N. Sewald

Norbert Sewald was born in 1961 in Munich (Germany). He obtained his PhD in Organic Chemistry at the Technical University of Munich. After a postdoctoral fellowship with Professor J. E. Baldwin at the Dyson Perrins Laboratory, University of Oxford (UK), he started independent research at the Technical University of Munich and later at the University of Leipzig (Germany). In 1998 he finished his habilitation and was appointed to full Professor of Organic and Bioorganic Chemistry at Bielefeld University in 1999. His research interests comprise organic chemistry at the interfaces with biology and medical sciences. Special focus is placed on the development of synthetic methods, the isolation, structure elucidation, and total synthesis of bioactive natural products, studies regarding the interaction of peptides with proteins or DNA, analysis of the solution structure of peptides using NMR, and the development of novel molecular tools for biochemical research.

Dr. C. Plattner

Carolin Plattner (née Heggemann) studied Chemistry at Bielefeld University and the University of Michigan, Ann Arbor (USA) and obtained her PhD degree on synthetic antifreeze glycopeptides in 2009. She now works for ChemCon GmbH in Freiburg (Germany).

M. Höfener

Michael Höfener studied Biochemistry at Bielefeld University and obtained his MSc degree in 2010. He is currently preparing his PhD thesis in the Sewald group on molecular tools for functional proteomics.

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SYNTHESIS/*SYNLETT* Advisory Board Focus: Professor Maurizio Taddei (University of Siena, Italy)

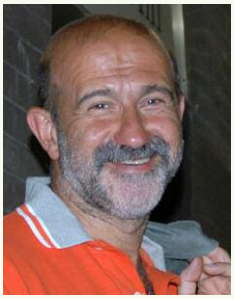
Background and Purpose. ***SYNFORM*** will from time to time portrait **SYNTHESIS/*SYNLETT*** Advisory Board members who answer several questions regarding their research interests and revealing their impressions and views on the developments in organic chemistry as a general research field. In this issue, we present Professor Maurizio Taddei, University of Siena (Italy).

INTERVIEW

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

M. Taddei | Organic synthesis. For me, the possibility to synthesize (create) something new that never existed before is a priceless pleasure. Of course, the synthesis must be applied to useful molecules and must be carried out as much as possible in a sustainable way. Therefore, I am currently working on the synthesis of new anti-cancer compounds and on the application of catalytic (microwave-assisted) transformations to organic synthesis. Hydroformylation, carbonylation and C–H activation are the targets but always with one eye directed to the overall synthetic process more than on the single step.

BIOGRAPHICAL SKETCH



Prof. M. Taddei

Maurizio Taddei was born in Florence (Italy) in 1955 and obtained his doctoral degree in chemistry in 1979 from the University of Florence at the Department of Organic Chemistry under the supervision of Professor Alfredo Ricci.

After a postdoctoral period at the University Chemical Laboratories in Cambridge (UK) with Professor Ian Fleming, he started his academic career at the University of Florence where he became Research Assistant in 1984 at the Faculty of Science and where he was promoted to Associate Professor at the Faculty of Agronomy in 1992. In 1994 he became Professor of Organic Chemistry at the Faculty of Science at the University of Sassari and moved to Sardinia where he carried out his research activities until 2001. Then he moved to the University of Siena where he is now Professor of Organic Chemistry at the Faculty of Pharmacy. In 1990 he was awarded the G. Ciamician Silver Medal of the Organic Chemistry Division of the Italian Chemical Society. He is author of more than 170 papers in scientific journals, ten patents and several reviews and book chapters in the fields of organic synthesis, bioorganic chemistry and medicinal chemistry. In addition, he has promoted strong interactions with different pharmaceutical, biotech and chemical companies (e.g., GSK, Sigma-tau, Nikem, Sienabiotech, Dipharma, Chemo) focusing on the development of new synthetic approaches to molecules having biological activities. He is also Director of a Master in Drug Design and Synthesis at the University of Siena.

Born as an “organosilicon” chemist, his interest has moved over the years towards bioorganic and applied chemistry, always maintaining the distinctive feature of a synthetic chemist. This partial metamorphosis was possible also thanks to a 25-year collaboration and friendship with Dr. André Mann at the CNRS in Strasbourg (France).

Maurizio Taddei developed methodologies in combinatorial chemistry, solid-phase organic synthesis and asymmetric synthesis. In 1998 he started to be interested in the application of microwaves to organic transformations, which remains one of his major interests today. Finally, as a member of the Faculty of Pharmacy, he is now working on medicinal chemistry targets in the field of anti-cancer compounds. In this area he has recently synthesized compounds with remarkable activity against HDAC (Histone Deacetylase), HSP-90 (Heat Shock Protein 90) and Hh (Hedgehog Signalling Pathway).

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

M. Taddei | The application of microwaves to hydroformylation. I believe that hydroformylation is a powerful reaction with a high potential to simplify complex organic synthesis, but it has been scarcely utilized due to problems of using autoclaves and syngas (CO/H_2). As we have now demonstrated that it is possible to carry out this reaction in a (simple) microwave oven without autoclave and syngas, I hope that this reaction will find more and more applications among organic chemists.

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

M. Taddei | As a consequence of my previous answer, catalysis in organic synthesis. It is amazing as nowadays it is possible to make a new C–C bond without assistance of a particular functional group, without strong bases or acids and all thanks to (metal) catalysis. I think that we are close to the possibility to selectively prepare hydrocarbon chains without losing atoms of functional groups and this will have an enormous impact in the real world where tons of molecules must be prepared in a sustainable way for Nature and humans.

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

M. Taddei | I have the privilege to live in the Chianti area, in a house in the middle of the countryside. I grow vegetables, tomatoes, zucchini, cabbages, and so on. It is a pleasure to have your "compounds" directly on your table.

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

M. Taddei | As I am in the university, I do science with my group to produce chemists (possibly) at the top level. When my students finish a PhD, find positions in industry or academia and grow in their personal achievements, I consider to have reached one goal of my scientific career. Another goal (not yet reached) is to see one of my molecules get really used for doing something – a drug on the market or a product that may help people to live better. I am trying hard, maybe we will meet again in some years.

Matteo Zanda

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COMING SOON ►► COMING SOON ►►

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In the next issues:

SYNSTORIES

Palladium-Mediated Intracellular Chemistry
(Focus on an article from the current literature)

Three-Component Synthesis of Ynediones by a Glyoxylation/Stephens–Castro Coupling Sequence
(Focus on an article from the current literature)

FURTHER HIGHLIGHTS

SYNTHESIS

Review on: Recent Developments in Asymmetric Catalysis in the Presence of Chiral Gold Complexes
(by V. Michelet)

SYNLETT

Account on: Development of New N,N-Ligands for the Enantioselective Copper(II)-Catalyzed Henry Reaction
(by G. Blay, J. R. Pedro)

SYNFACTS

Synfact of the Month in category "Metal-Catalyzed Asymmetric Synthesis and Stereoselective Reactions":
Pd/V Contemporaneous Dual Catalysis

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