SYNSTORIES

- Young Career Focus: Dr. Tanja Gaich (Leibniz University of Hannover, Germany)

- \(\text{sp}^3\) C–H Bond Activation with Ruthenium(II) Catalysts and C(3)-Alkylation of Cyclic Amines

- Highly Diastereoselective and Enantioselective Synthesis of \(\alpha\)-Hydroxy \(\beta\)-Amino Acid Derivatives: Lewis Base Catalyzed Hydrosilylation of \(\alpha\)-Acetoxy \(\beta\)-Enamino Esters

CONTACT

Your opinion about SYNFORM is welcome, please correspond if you like: marketing@thieme-chemistry.com
Dear readers,

The recent decision of one of the UK Research Councils, the EPSRC, to significantly reduce funding for synthetic organic chemistry has generated a vast international debate. This event is in line with a general trend of decreasing support for synthetic organic chemistry; as an example the European Commission axed the funding for organic chemistry, which essentially disappeared from the list of fundable research areas, at the time of Framework Programme 5. So, is organic synthesis truly becoming less important relative to other areas of chemistry, which in turn has already witnessed a significant and generalized drop of funding in the past ten years or so relative to other disciplines? As a synthetic organic chemist, am I still allowed to pursue a purely curiosity-driven research project, for example exploring new reactivity patterns, or a new reaction mechanism, or the synthesis of an intriguing natural compound? Or, as a synthetic organic chemist, I am increasingly expected to provide a “service” to other researchers working in more funded scientific areas in order to deserve a slice of the funding cake? I am well aware that we, scientists, are largely relying on tax-payers’ money to cover the cost of our expensive research, but are we absolutely sure that trimming down the funding for synthetic organic chemistry won’t ultimately have a terribly detrimental effect on drug discovery, biomedical research, materials science, energy and all of the areas of research that heavily rely on organic synthesis and have a direct impact on the quality of tax-payers’ life? My answer is easy to guess, because there is a massive amount of unsolved and urgent issues in modern organic synthesis which are very difficult to address in the current funding climate. Forcing organic chemists to abandon blue sky research is a shortsighted strategy, which will eventually have a detrimental effect on our capacity of treating diseases, using safe and versatile materials, preserving the environment, and making rational use of energy. Organic synthesis needs more focused and clever investments, not cuts.

Switching to more rewarding arguments, this issue of SYNFORM features two very elegant pieces of research in the area of organic synthesis. Dr. C. Bruneau (France) guides us through his recently published Ru(II)-catalyzed reaction for the C(3)-alkylation of cyclic amines. The second article deals with a novel method developed by Prof. X. Zhang (P. R. of China) to synthesizing α-hydroxy β-amino acids in totally stereocontrolled manner. The issue is completed by a “Young Career Focus” on Dr. T. Gaich and her research at the interface of organic and biomimetic total synthesis.

Matteo Zanda
Editor of SYNFORM
C–H bond functionalization remains a very hot area in organic chemistry and a number of research groups are actively involved in the development of increasingly mild, efficient and operatively simple methodologies to achieve what was once considered the Holy Grail of synthetic chemistry. Recently, the group of Dr. Christian Bruneau from the CNRS and University of Rennes (France) reported an extremely interesting and amazingly efficient reaction that allows for the formation of a new C–C bond by β-amino C–H bond activation of cyclic amines with aldehydes. The reaction has a remarkably broad scope and can be used to produce rather complex and functionalized cyclic amines.

“In this paper we describe a one-pot transformation of cyclic amines, which implies sequential catalytic steps, all of them catalyzed by ruthenium species,” explained Dr. Bruneau. “The first one is a formal oxidation of saturated cyclic amine into enamine without oxidant but using a hydrogen-transfer process. The second step consists of the reaction of the intermediate enamine with the electrophilic aldehyde followed by dehydration and hydrogenation via hydrogen auto-transfer,” he continued. “Two equivalents of amines are necessary for the whole transformation, but the addition of an external hydrogen donor, namely formic acid, helps for the final hydrogenation step.”

“Dehydrogenation of amines into enamines had previously been reported by A. S. Goldman with iridium catalysts (Chem. Commun. 2003, 2060) and M. Brookhart (J. Am. Chem. Soc. 2007, 129, 14544) with cobalt complexes,” acknowledged Dr. Bruneau, “but no further sequential reaction was investigated. The only example of C(3)-functionalization of cyclic...
amine was performed upon oxidation in the presence of oxygen and platinum catalyst, followed by Michael addition leading to C(3)-substituted enamines, but with no additional hydrogenation (J. Org. Chem. 2010, 75, 2893).

Dr. Bruneau explained that the present work results from an evaluation of new (arene)ruthenium catalysts featuring a bidentate phosphinesulfonate ligand in the hydrogen-transfer reaction and was preceded by another unprecedented cascade reaction leading to the same type of C(3)-functionalized cyclic amines but starting from alcohols and unprotected cyclic amines (Adv. Synth. Catal. 2010, 352, 3141). “One of my former group members, Zhou Tang, who is currently a PhD student at the University of Amsterdam (The Netherlands), is not a coauthor of this paper but made a key contribution to the development of this chemistry,” acknowledged Dr. Bruneau. “Our ruthenium(II)-catalyzed cascade transformation is a very interesting new C–H bond functionalization process,” said Dr. Bruneau. “While functionalization of amines in the α-position is relatively common, we have succeeded in developing a rare example of amine β-functionalization from unreactive aliphatic amines. This work, which is an important achievement, will undoubtedly inspire further development in this exciting area, especially its asymmetric version,” he concluded.

About the authors

From left: Dr. C. Bruneau, Dr. M. Achard, Dr. G. V. M. Sharma, B. Sundararaju, Z. Tang
Owing to the significance of paclitaxel and its analogues, chiral α-hydroxy β-amino acid moieties have attracted much attention. Indeed, these compounds are key constituents of a number of biologically active and natural compounds; therefore, it is not surprising that numerous methodologies targeted at their synthesis have been developed. Recently, the group of Professor Xiaomei Zhang from the Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences (P. R. of China) added a new powerful synthetic tool to the arsenal of organic chemists interested in the synthesis of non-racemic α-hydroxy β-amino acids. The method relies on an elegant enantioselective hydrosilylation of α-acetoxy β-enamino esters mediated by a Lewis base organocatalyst.

“The α-hydroxy β-amino acid unit is a highly functionalized structural framework,” said Professor Zhang; “therefore we asked ourselves how to introduce the vicinal amino group and the hydroxy group in their exact positions? Different methods have different strategies,” he continued. “Based on our previous research of chiral Lewis base organocatalyzed asymmetric hydrosilylation of C=N bond compounds, our strategy is to arrange the two groups in the enamine substrates that can be hydrosilylated selectively to afford chiral α-hydroxy β-amino acid derivatives.”

Professor Zhang revealed that this project was started about three years ago. “The idea was simple and clear, however, it was not so easy to realize,” she said. “The first challenge was the synthesis of the special substrates because it is very difficult for the α-acetoxy β-keto esters to react with amines to form enamines. The second was the search of novel and efficient catalysts,” continued Professor Zhang. “We are very lucky that we now have established a very simple and highly efficient catalytic system. In fact, these novel chiral Lewis base catalysts were readily prepared from a very cheap chiral starting material,” she said. Professor Zhang explained that a simple cyclization made the catalysts rigid and thus highly selective. “It is also gratifying that the reaction gave not only good enantioselectivities but also good diastereoselectivities,” she said. “The good diastereoselectivity might result from dynamic kinetic resolution during the isomerization of the substrate from enamine tautomer to imine tautomer. However, the mechanism has not been investigated thoroughly yet.” According to Professor Zhang, this is an important task in the future research program of her group.

“Dr. Yan Jiang is a very committed researcher in my group,” said Professor Zhang. “She spent much time and effort on this project. First, she tried many methods to settle the synthesis of the substrates. Then she screened the reaction conditions systematically. Having established the methodology, she finally demonstrated its successful application in the construction of the paclitaxel C13 side chain and an oxazolidinone which is a potent hypcholesterolemic agent. The other co-authors also made important contributions to this work,” she acknowledged.

“In the future, this methodology will be extended to other α-substituted β-enamino esters. Hence, more α-substituted β-amino acid derivatives can be prepared. It will be a big challenge to obtain good enantioselectivities as well as diastereoselectivities. This is exactly what we are currently trying to achieve,” concluded Professor Zhang.

Matteo Zanda
About the authors

From left: Dr. Y. Zheng, Dr. C. Shu, Prof. X. Zhang, Dr. Y. Jiang, Dr. X. Chen
(not pictured: Dr. Z. Xue, Prof. W. Yuan)
Young Career Focus: 
Dr. Tanja Gaich (Leibniz University of Hannover, Germany)

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. Tanja Gaich, Leibniz University of Hannover, Germany.

INTERVIEW

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

Dr. Gaich | Our group is dedicated to the total syntheses of natural products with a unique and complex molecular architecture. Owing to the elegance of assembling these intricate structures, Nature serves as a constant source of inspiration in our synthetic planning and execution. To us, in synthetic terms “elegance” is mostly represented by a domino reaction sequence. Thereby we aim to trigger an avalanche of bond-forming events starting from a rather simple molecular intermediate. This results in the assembly of a highly complex molecular architecture – ideally the natural product itself.

SYNFORM | When did you get interested in synthesis?

Dr. Gaich | Originally I got interested in synthesis when I was a student in molecular biology, where I was fascinated by the capability of Nature to assemble complex molecular scaffolds, and the biosynthetic machinery it uses for this purpose. After switching to chemistry, the crucial point that got me into synthesis was the advanced organic chemistry lecture of Professor Mulzer at the University of Vienna.

BIOGRAPHICAL SKETCH

Tanja Gaich was born in Salzburg (Austria), in 1980. She received her Diploma (2005) and her doctoral degree (2009) from the University of Vienna, under the supervision of Professor Johann Mulzer. In 2010, after a postdoctoral stay with Professor Phil S. Baran at the Scripps Research Institute (La Jolla, USA), where she worked on the total synthesis of palau’amine, she started her independent career at the Leibniz University of Hannover in Germany in the research group of Professor Markus Kalesse. Currently, she is funded by a “Liebigstipendium” from the funds of the German chemical industries. Awards: Thieme Chemistry Journal Award 2011, Laudamaxima Award, Erwin-Schrödinger Fellowship, “Wege in die Forschung” Grant, Award of Excellence 2009.

Dr. T. Gaich
SYNFORM | Your research group is active at the frontier of organic synthesis and biomimetic total synthesis. Could you tell us more about your research and its aims?

Dr. Gaich | We think that the capability of understanding and imitating Nature’s pathways is of highest priority for an organic chemist. It enables the development of new reactions and methodologies, which shorten a synthetic route and make it elegant and therefore practical. One way of probing a postulated biosynthetic route is by looking into the chemical feasibility of an in vivo key step or a cascade reaction, and delineating a biomimetic synthesis thereof. In most cases this brings about the advantage that not only an individual molecule, but the whole natural product family is accessed via a single synthetic route.

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

Dr. Gaich | To me, my most important achievement to date is the total synthesis of the penifulvin family.1,2 The synthesis is concise – five steps from commercially available material for the racemic sequence and eight steps for the enantioselective route. The endgame confirms our biosynthetic proposal, which relates the sesquiterpene silphinenes to the penifulvin family via a cascade reaction.

REFERENCES


Matteo Zanda
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In the next issues:

SYNSTORIES

■ Di-tert-butylisobutylsilyl, Another Useful Protecting Group
(Focus on an article from the current literature)

■ Metal-Free, Aerobic Dioxygenation of Alkenes Using Simple Hydroxamic Acid Derivatives
(Focus on an article from the current literature)

■ Professor André Charette
(Focus on a SYNTHESIS/SYNLETT Advisory Board member)

FURTHER HIGHLIGHTS

SYNTHESIS
Review on: Transition-Metal-Catalyzed Rearrangements of Small Cycloalkanes: Regioselectivity Trends of β-Carbon Elimination Reactions
(by C. Assa)

SYNLETT
Account on: Development of Highly Selective Ligands for Separations of Actinides from Lanthanides in the Nuclear Fuel Cycle
(by L. M. Harwood et al.)

SYNFACS
Synfact of the Month in category “Metal-Catalyzed Asymmetric Synthesis and Stereoselective Reactions”:
Gold-Catalyzed Enantioselective Protonation

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