SYNSTORIES

- Chiral Monodentate Phosphines and Carboxylic Acids: Cooperative Effects in Palladium-Catalyzed Enantioselective C(sp³)–H Functionalization
  P137, Poster Presented at the ISACS-7 Conference, Edinburgh (UK), June 12–15, 2012

- B(OCH₂CF₃)₃-Mediated Amidation and Transamidation Reactions
  P48, Poster Presented at the ISACS-7 Conference, Edinburgh (UK), June 12–15, 2012

- Young Career Focus: Professor Filip Bureš (University of Pardubice, Czech Republic)

CONTACT

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

This issue of SYNFORM is mostly dedicated to the ISACS-7 (International Symposia on Advancing the Chemical Sciences) Conference – Challenges in Organic Chemistry and Chemical Biology, which was organized under the auspices of the Royal Society of Chemistry in Edinburgh (Scotland, UK) from June 12–15, 2012. The conference, which was co-sponsored by Thieme Chemistry, was a massive success with an impressive list of speakers including the 2010 Nobel Laureates Akira Suzuki (Hokkaido University, Japan) and Ei-ichi Negishi (Purdue University, USA), and a number of other top chemists such as Jonathan Ellman (Yale University, USA), Alois Fürstner (Max-Planck-Institut für Kohlenforschung, Germany), Tom Muir (Princeton University, USA), Tobias Ritter (Harvard University, USA), Jonathan Clayden (Manchester University, UK), and many more. The conference was sold out and it was very refreshing to see a number of young chemists attending the meeting, discussing with the giants of chemistry and presenting posters. Two of them, among the best presented at ISACS-7, have been selected for SYNFORM. In the first SYNSTORY, S. Lemouzy, T. Saget and Professor N. Cramer from the EPF Lausanne (Switzerland) presented a new Pd-catalyzed strategy for C(sp)–H bond functionalization. In the second SYNSTORY, R. Lanigan and Dr. T. Sheppard from the University College London (UK) described a B(OCH2CF3)3-mediated amidation and transamidation process. The issue is completed by a Young Career Focus featuring Professor Filip Bureš (Czech Republic).

Enjoy your reading!

Matteo Zanda
Editor of SYNFORM
Chiral Monodentate Phosphines and Carboxylic Acids: Cooperative Effects in Palladium-Catalyzed Enantioselective C(sp³)–H Functionalization

P137, Poster Presented at the ISACS-7 Conference, Edinburgh (UK), June 12–15, 2012

Advances in transition-metal catalysis are closely linked to the development of new ligands enabling previously impossible transformations to occur. In palladium catalysis, pioneering work by the group of Buchwald and Fu allowed the use of aryl chlorides in many palladium-catalyzed cross-coupling reactions by using bulky electron-rich monodentate phosphines as ligands. Recently, it was found that those ligands are also useful in palladium-catalyzed C–H activation processes. To render such processes enantioselective, one would need chiral versions of these monodentate phosphines. However, most of the chiral phosphines reported to date are bidentate and there is clearly a lack of chiral monodentate phosphines mimicking the stereoelectronic properties of trialkyl or biaryl-dialkyl phosphines.

Professor Nicolai Cramer from the Laboratory of Asymmetric Catalysis and Synthesis at the École Polytechnique Fédérale de Lausanne (Switzerland) said: “Our group previously achieved successful palladium-catalyzed enantioselective C(sp³)–H activations of aryl groups (Angew. Chem. Int. Ed. 2009, 48, 9139) and we then decided to raise the bar to the more challenging C(sp³)–H alkyl bonds.” He continued, “When we started this project there was just one example of palladium(II)-catalyzed asymmetric C–H functionalization with only modest yield and selectivity (38% yield, 37% ee) reported by the group of Yu (Angew. Chem. Int. Ed. 2008, 47, 4882).”

“Our previously optimized protocol failed for this project, as did the other classes of chiral monodentate phosphines,” recalled Professor Cramer, “and so we had to go the hard way and design a new class of ligands. We discovered that the combination of the biaryl scaffold found in the Buchwald-type ligands in combination with a C₂-symmetric phospholane...
moiety used for the bidentate Duphos-type ligands, which has been a workhorse for asymmetric hydrogenations, gave promising results.”

Tanguy Saget and Sebastien Lemouzy are members of Professor Cramer’s group. Tanguy Saget added, “Around the same time, we observed that the carboxylate, which is required for the reaction to occur, had a strong influence on the selectivity. On the one hand, this made things far more complicated because it increased tremendously the number of possible condition combinations to test. On the other hand, we felt it was also a great opportunity to discover a cooperative effect between acid and phosphine, achieving high selectivities for our desired transformation.” Out of the initial approximately 20 acids and 10 phosphines they screened, they were pleased to find an effective combination giving selectivities in the range of 90–95% ee. “There are almost endless chiral or achiral carboxylic acids available and probably some would perform even better than 9H-xanthene-9-carboxylic acid, but this one has proved quite general and robust for most of the reactions we have tried so far,” said Tanguy Saget.

With the optimized conditions in hand, the group then studied the scope of the reaction. “The scope is quite broad because we can activate both methyl and methylene C–H bonds to access the indoline scaffold with high ee,” explained Professor Cramer. “We were able to create up to three new stereocenters in a single step with complete diastereoselectivity and excellent enantioselectivity, which showcases the power of this methodology.”

Professor Cramer concluded, “We now use this new class of ligands for other transformations and expect that its use will be widespread, filling a gap in asymmetric catalysis as many processes require monodentate ligands to operate.”

Matteo Zanda
About the authors

Sebastien Lemouzy studied chemistry at I. U. T. Paul Sabatier (Castras, France). After a research stage with Professor Lautens at the University of Toronto (Canada), he moved to the ENSC Montpellier (France) and graduated in 2011 under the guidance of Professor Campagne working on metal-catalyzed π-activation reactions. He then joined the Cramer group. His PhD research focuses on asymmetric rhodium and palladium catalysis.

Tanguy Saget graduated from the ENSC Montpellier (France) in 2009 under the guidance of Professor Campagne. During his studies he performed a six-month internship at EPF Lausanne (Switzerland) in the group of Professor Waser working on cationic cyclizations. In 2009, he began his PhD studies on palladium-catalyzed asymmetric C–H functionalization under the supervision of Professor Cramer, first at the ETH Zürich (Switzerland) and since 2011 at the EPF Lausanne.

Nicolai Cramer completed his PhD at the University of Stuttgart (Germany) in 2005 with Professor Laschat. After post-doctoral studies with Professor Trost at Stanford University (USA), he started his independent career as Habilitant under the guidance of Professor Carreira at the ETH Zürich in 2007. At the end of 2010, he took up his current position as Assistant Professor at the EPF Lausanne. His research interests encompass asymmetric catalysis, C–H and C–C bond activations and the synthesis of bioactive natural products.
The amidation reaction is one of the most common transformations used in the synthesis of pharmaceuticals and there is considerable industrial interest in the development of new clean and efficient approaches (Org. Biomol. Chem. 2006, 4, 2337). Typically, amides are synthesized via amidation of carboxylic acids, which usually requires the use of expensive coupling reagents or a separate preactivation step. Dr. Tom Sheppard from the Department of Chemistry at University College London (UK) said, “We have recently developed tris(2,2,2-trifluoroethyl)borate as a highly effective coupling reagent for the direct amidation of carboxylic acids without any pre-activation (Org. Biomol. Chem. 2011, 9, 1320).

After completion of the reaction the pure amide product can be isolated via simple work-up procedures without the need for chromatography.”

A wide range of acids and amines are tolerated under the reaction conditions including more challenging systems such as benzoic acids and anilines, and carboxylic acids bearing adjacent chiral centers undergo coupling with low rates of epimerization. Both secondary and tertiary amides can be prepared in good yield from readily available primary and secondary amines and a wide range of functional groups are compatible with the reaction conditions, as demonstrated by the work carried out by postgraduate student Rachel Lanigan.

Dr. Sheppard added “The reagent is also effective for transamidation reactions, providing an alternative approach to the synthesis of useful amide products” (Scheme 2).

Dr. Sheppard explained that tris(2,2,2-trifluoroethyl)borate can easily be synthesized from 2,2,2-trifluoroethanol and boron tribromide or the cheap and readily available B₂O₃ (Scheme 3). This latter route is experimentally straightforward and readily scalable.

“We are currently studying the mechanism of these reactions to provide greater understanding of how the reagent is able to activate the reactants,” he said. “It is anticipated that this will enable further improvements to be made via the development of other novel reagents and catalysts for clean amidation reactions.”

Matteo Zanda

Scheme 1 Direct amidation of carboxylic acids with B(OCH₂CF₃)₃

Scheme 2 Transamidation reactions with B(OCH₂CF₃)₃

Scheme 3 Synthesis of B(OCH₂CF₃)₃
About the authors

Rachel Lanigan was born in Edinburgh (UK). She received her \textit{MChem} from the University of Edinburgh in 2010, carrying out her \textit{MChem} research project under the supervision of Professor Hamish McNab working on radical cyclizations of substituted pyrroles by flash vacuum pyrolysis. She is currently pursuing a PhD in organic chemistry under the guidance of Dr. Tom Sheppard at University College London with a focus on the development of $\text{B(OCH}_2\text{CF}_3)_3$-mediated amidation reactions.

Tom Sheppard was born in Lancashire (UK). He obtained his MSc degree from the University of Cambridge (UK) in 1999. After a year working in the pharmaceutical industry at GlaxoWellcome, he went on to obtain his PhD from the University of Cambridge in 2004, working under the supervision of Professor Steven Ley on the development of butane-2,3-diacetal desymmetrized glycolic acid. He then carried out postdoctoral research with Professor William Motherwell at University College London, working on new methods for cyclopropane synthesis and novel multicomponent reactions. In 2007, he was awarded an EPSRC Advanced Research Fellowship and appointed to a lectureship at University College London where his research is focused on the development and application of novel organocatalytic and metal-catalyzed reactions.
**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 Professor Filip Bureš, University of Pardubice, Czech Republic.

**BIOGRAPHICAL SKETCH**

Filip Bureš was born in Poprad (Slovakia) in 1979. He graduated from the University of Pardubice (Czech Republic) in 2002, where he also received his PhD in organic chemistry in 2005. Since his doctoral studies, he has been interested in optically active organic compounds and their application as transition-metal-chelating ligands. After his postdoctoral studies at the ETH Zürich (Switzerland) under the guidance of Professor F. Diederich in 2005–2006, he returned to the University of Pardubice, where he was habilitated in 2010. Since the collaborative work with Professor P. Knochel (LMU, München, Germany) in 2003 and Professor F. Diederich, his other research interests involve organometallics, cross-coupling reactions, and materials chemistry with the focus on novel π-conjugated push–pull systems and their applications in organic optoelectronics.

**INTERVIEW**

**SYNFORM |** What is the focus of your current research activity?

**Professor Bureš |** The current activity in my group can be divided into two research streams. The first topic includes the design, synthesis, and further application of chiral derivatives in asymmetric catalysis. Inspired by the structure of the essential α-amino acid histidine, we have focused mainly on optically active derivatives of imidazole. A variety of α-amino acids, terpenes, and amines were utilized as starting chiral precursors for the synthesis of the desired compounds. Target imidazol(in)es were primarily used as chiral nitrogen ligands for the asymmetric version of the Cu(II)-catalyzed Henry reaction.

Since my postdoctoral studies with Professor F. Diederich, I am also interested in the synthesis of π-conjugated push–pull systems with linear as well as nonlinear optical (NLO) properties. Such molecules have been heavily investigated as active components of optoelectronic devices such as OLEDs, OPVCs, switches, and data storage devices. This material-oriented research involves finding a suitable organic material with improved and tunable properties, while its synthesis is very straightforward and utilizes modern organometallics and cross-coupling reactions.

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

**Professor Bureš |** Organic synthesis has charmed my life since my studies at high school. In contrast to other branches of chemistry, I felt that organic chemistry possesses “very simple and general principles”. Thanks to my high school teacher, I am still fascinated by the generality of the electrophilicity(+)/nucleophilicity(−) principle along with the diversity of disconnections in which the construction of a molecule may be carried out. Moreover, as I like to cook, the lab work gives me similar pleasure to see my target compound growing before my eyes.

During my doctoral studies I became acquainted with the condensation methods and classical organic conversions leading to optically active heterocyclic compounds, whereas...
the postdoctoral studies opened my eyes to the transition-metal-mediated C–C and C–X bond formations. In my current research, I am attempting to combine both “old and new” strategies.

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

Professor Bureš | After getting a deeper insight, I realized that organic synthesis is not just a tool but rather an art. Just try to open an issue of SYNTHESIS or SYNELETT and you will be immediately convinced! As I am primarily focusing on a target compound itself rather than on the way to obtain it, I feel fascinated by the modern organic synthesis tools that allow me to make my visions come true. From my point of view, the decade from 1970 to 1980, in which the early cross-coupling reactions were published, can be considered as a breakthrough in modern organic chemistry. I could not imagine my current work without these reactions.

SYNFORM | Your research group is active at the frontiers of asymmetric organic synthesis and materials science. Could you tell us more about your research and its aims?

Professor Bureš | Whereas the first topic deals with optically active heterocyclic derivatives, the second one involves organic π-conjugated systems. Although it seems that these topics are not related, they possess joint features. Whereas in my older research interest, the imidazole serves as an N-chelating auxiliary, the second topic utilizes this heterocycle as an aromatic system. Starting from a chiral pool, we are attempting to develop inexpensive, chiral, and active ligands for asymmetric catalysis. We have prepared several families of α-amino acid-, terpene-, amine-, and tartrate-derived imidazoles, imidazolines, and dicationic imidazoliophanes (Figure 1). These optically active compounds, featuring either N=C–C=N(X) binding pockets similar to bipy or C2-symmetric backbones, were further investigated as Cu(II)-chelating ligands, catalysts of asymmetric reactions, and biologically active substances.

In a π-conjugated system end-capped with electron donors and acceptors, an intramolecular charge-transfer (ICT) occurs. This feature makes these molecules highly polarized and results in their very interesting optical properties and manifold applications. Depending on the character of the π-conjugated system, we have investigated three classes of push–pull compounds: i) systems of multiple bonds (CEEs); ii) aromatic systems (TCAQs); and iii) heteroaromatic systems (Scheme 2). The development of a novel π-conjugated system with improved nonlinearity and absorption, emission, solvatochromic, electrochemical, and switchable properties targeting optoelectronic devices is our primary aim. In this respect, incorporation of a heteroaromatome into the chromophore backbone, as in biimidazole and pyrazine derivatives, brings higher thermal and chemical robustness required by fabrication processes. On the other hand, cyanoethynylethene (CEE) has recently been recognized as a molecule with exceptionally large second-order hyperpolarizability.

Figure 1 Representative optically active derivatives
SYNFORM | What is your most important scientific achievement to date and why?

Professor Bureš | I would not evaluate the state of my own research. I think that the scientific community can do this much better and more objectively. I feel that our contributions to both aforementioned fields of organic chemistry were already appreciated by the scientists and recently also by Thieme Chemistry. It is difficult to point out one molecule or reaction; I believe that our contribution is complex. In the near future, we will to focus on the synthesis of new α-amino acid derived imidazol(in)es as very promising optically active ligands, while several new and significantly improved organic materials are also on the way.

Matteo Zanda
COMING SOON COMING SOON

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In the next issues:

SYNSTORIES

- Fluoroform-Derived CuCF\(_3\) for Low-Cost, Simple, Efficient, and Safe Trifluoromethylation of Arylboronic Acids in Air (Focus on an article from the current literature)
- Ion-Paired Chiral Ligands for Asymmetric Palladium Catalysis (Focus on an article from the current literature)

FURTHER HIGHLIGHTS

SYNTHESIS
Review on: 1,6-Conjugate Addition of Nucleophiles to \(\alpha,\beta,\gamma,\delta\)-Diunsaturated Systems
(by E. M. P. Silva, A. M. S. Silva)

SYNLETT
Synfacts on: Synthesis of Naphthylamines and Anthrylamines via \(\eta^1\)-Benzylpalladium Intermediates
(by S. Zhang, M. Bao)

SYNFACTS
Synfact of the Month in category “Synthesis of Materials and Unnatural Products”: Use of Acetylene Gas as Dienophile in a Diels–Alder Reaction

CONTACT
Matteo Zanda,
NRP Chair in Medical Technologies
Institute of Medical Sciences
University of Aberdeen
Foresterhill, Aberdeen, AB25 2ZD, UK
and
C.N.R. – Istituto di Chimica del Riconoscimento Molecolare
Via Mancinelli, 7, 20131 Milano, Italy,
E-mail: Synform@chem.polimi.it, fax: +39 02 23993080

Editor
Matteo Zanda, NRP Chair in Medical Technologies, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, AB25 2ZD, UK and
C.N.R. – Istituto di Chimica del Riconoscimento Molecolare
Via Mancinelli, 7, 20131 Milano, Italy

Editorial Assistant: Alison M. Sage
synform@chem.polimi.it; fax: +39 02 23993080

Editorial Office
Managing Editor: Susanne Haak, susanne_haak@thieme.de, phone: +49 711 8931 786
Scientific Editor: Selena Boothroyd, selena.boothevy@thieme.de
Scientific Editor: Stefanie Baumann, stefanie.baumann@thieme.de, phone: +49 711 8931 776
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Production Editor: Thorsten Schön, thorsten.schoen@thieme.de, phone: +49 711 8931 781
Editorial Assistant: Sabine Heller, sabine.heller@thieme.de, phone: +49 711 8931 744
Marketing Manager: Julia Stützner, julia.stuetzner@thieme.de, phone: +49 711 8931 771
Postal Address: SYNTHESIS/SYNLETT/SYNFACTS, Editorial Office, Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, phone: +49 711 8931 744, fax: +49 711 8931 777
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