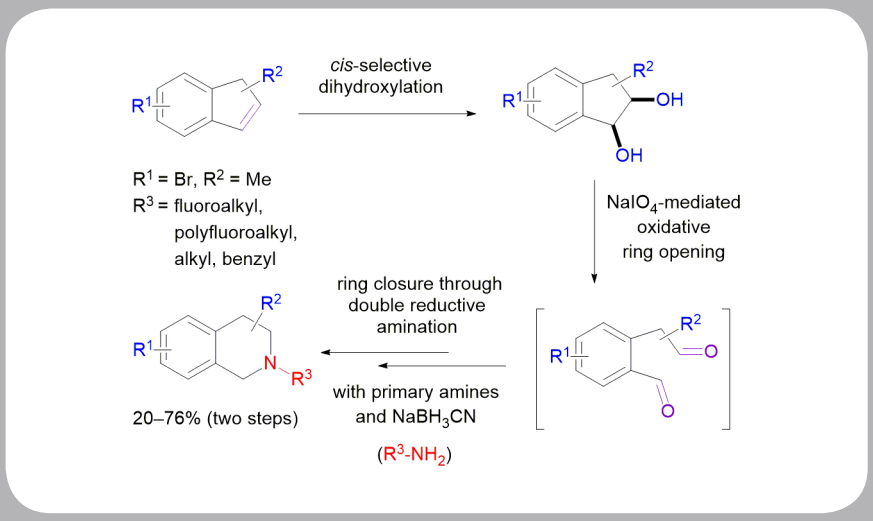
Synform

People, Trends and Views in Chemical Synthesis

2018/11

A *de novo* Synthetic Route to 1,2,3,4-Tetrahydroisoquinoline Derivatives

Highlighted article by R. A. Ábrahámi, S. Fustero, F. Fülöp, L. Kiss



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Thieme

Dear Readers,

In this November issue we welcome a new member of the Thieme Chemistry editorial family: Professor Shuli You, who is Director of the State Key Laboratory of Organometallic Chemistry of the Shanghai Institute of Organic Chemistry (P. R. of China) and joined the Editorial Board of Science of Synthesis in January 2018. In the Editorial Board Focus interview, Professor You tells us about his feelings and plans in the new role, his point of view on modern organic chemistry and his research. Welcome and congratulations Shuli! And this is not the only welcome of this issue: we have also the inaugural "Emerging Technologies" article! This new feature of Synform will cover new technological applications of organic chemistry, whose importance and scope have been already demonstrated by a cluster of publications on the subject over a period of – typically – three to five years. This first article deals with the "click and release of drugs" developed by Dr. Marc Robillard and colleagues at TagWorks (The Netherlands), which is a highly promising tool for releasing "on demand" potent cytotoxic drugs in targeted cancer therapy. The issue is completed by two Literature Coverage articles: in the first, I. Larrosa (United Kingdom) describes the late-stage Ru-catalyzed directed arylation of pharmaceuticals recently published in *Nat. Chem.* In the second, L. Kiss (Hungary) takes us through the work recently published in Synlett on a novel method to access 1,2,3,4-tetrahydroisoquinoline derivatives.

Enjoy your reading!!

In this issue

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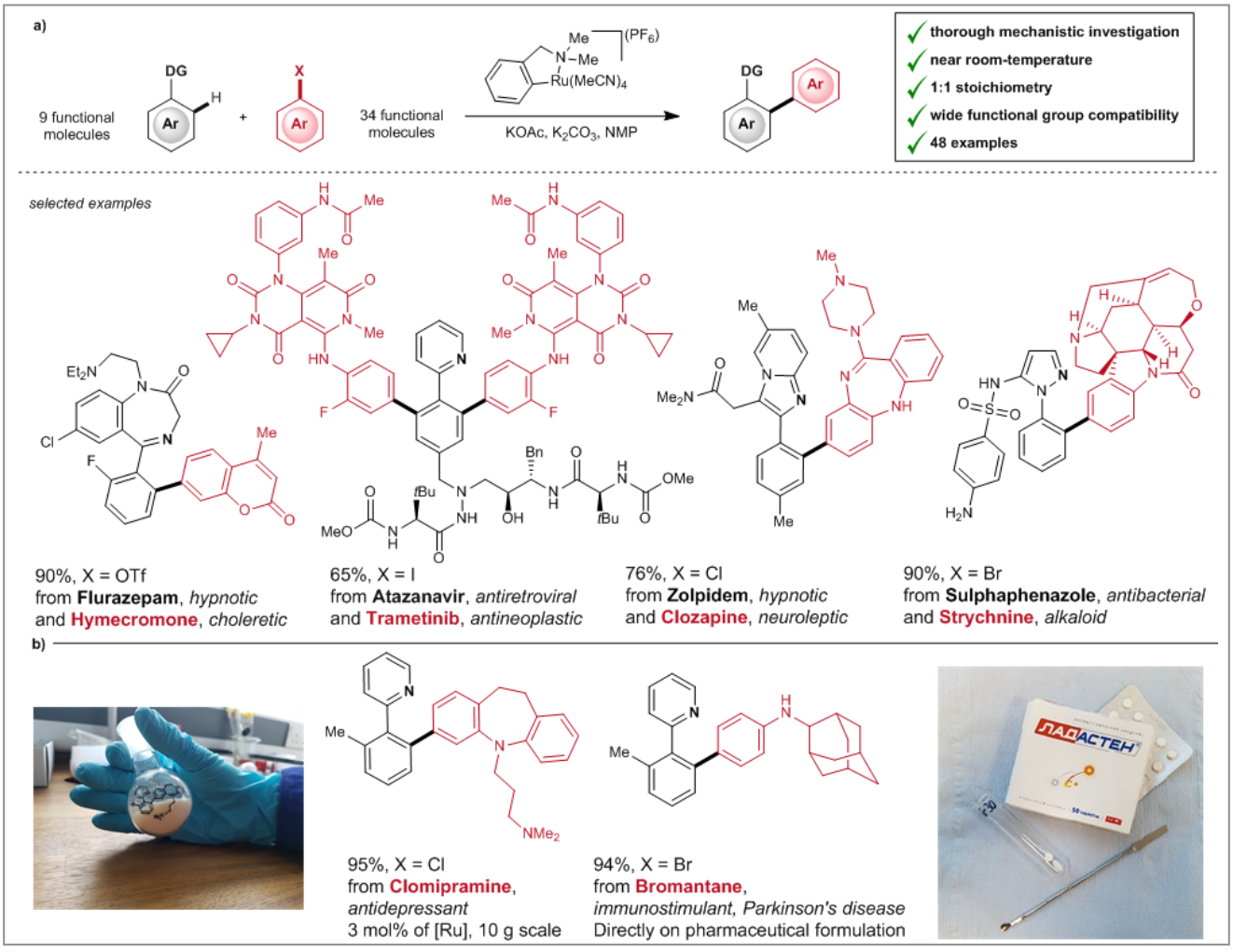
Cyclometallated Ruthenium Catalyst Enables Late-Stage Directed Arylation of Pharmaceuticals

Nat. Chem. **2018**, *10*, 724–731

While the C–H activation field has moved forward dramatically over the last two decades, a recurrent problem lies in the difficulty of activating C–H bonds in the presence of potentially much more reactive functional groups, and to do so under conditions where delicate functionalities can survive. Often, new methodologies developed will be applicable to only a small range of simple substrates and fail when facing 'real world' molecules bearing a range of functional groups. This is particularly the case for many drug-like molecules, which often contain several polar functionalities, and are therefore not only delicate, but also able to coordinate and poison catalysts. However, being able to directly functionalize C–H bonds of complex molecules (i.e., late-stage functionalization) is one of the major targets in the field. Late-stage functionalization allows fast access to new molecules and the exploration of new chemical space while avoiding costly *de novo* syntheses.



Scheme 1 The new methodology and its scope

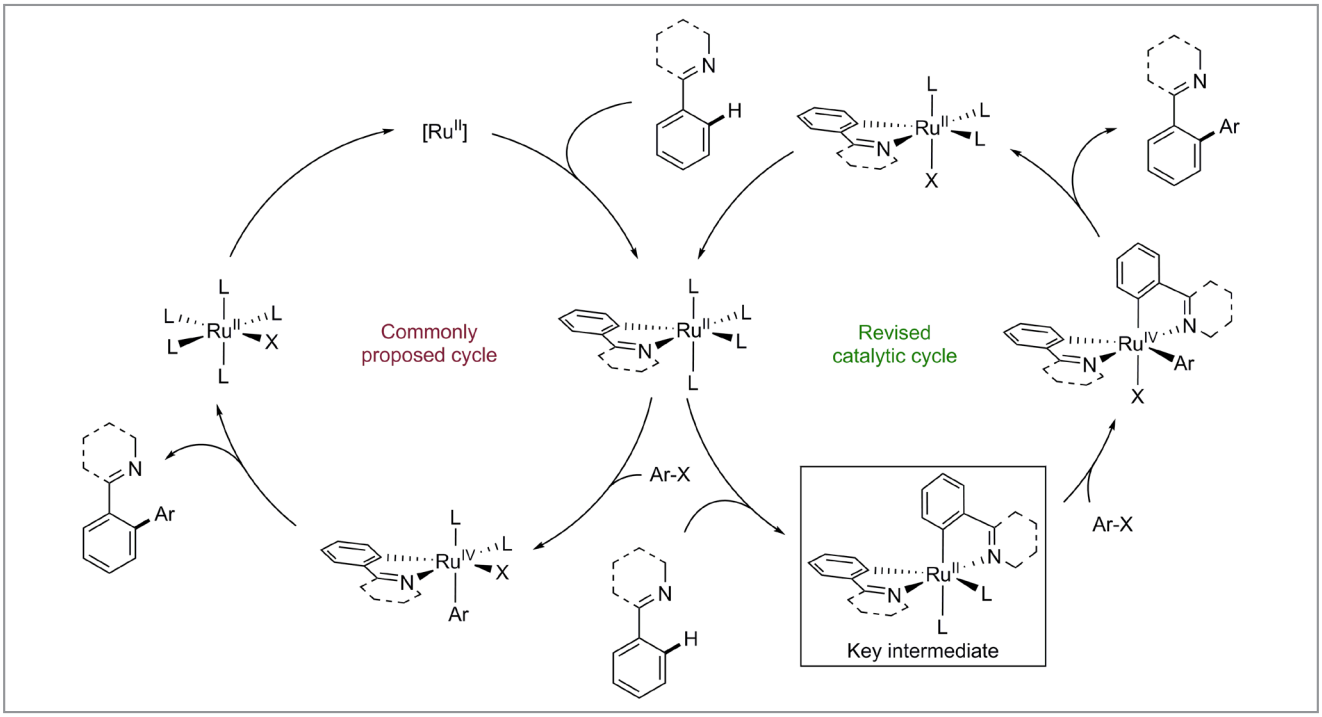
Developing milder and more functional-group-tolerant C–H arylation methodologies, such as that shown in Scheme 1, has been a target of Professor Igor Larrosa's group at the University of Manchester (UK) from day one.

"While investigating the use of ruthenium catalysts on the C–H arylation of electron-deficient aromatics, we made a few observations that did not seem to fit with accepted mechanisms on how ruthenium catalysts are operating (Scheme 2)," said Professor Larrosa. He continued: "That led us into a fully fledged mechanistic investigation on the arylations of phenylpyridines with aryl halides, by means of kinetic analysis, stoichiometric reactions, and isolation of organometallic intermediates. We were very excited when we discovered that a key catalytic intermediate had been missed out until now in these processes: the usually proposed cyclometallated intermediate is not able to undergo oxidative addition with the aryl halide. Instead, a second cyclometallation takes place to form a bis-cyclometallated intermediate, which is the real species capable of oxidative addition. More importantly, we found that the generally employed catalysts were not catalytic intermediates but off-cycle species."

These mechanistic insights led the group to the design of a new class of ruthenium catalysts: species that already contain a cyclometallating unit. "In particular, we found that a benzylamine cyclometallating unit was able to impart greatly enhanced reactivity to the ruthenium catalyst, when compared to previous catalysts, so that high reactivity was achieved at close to room temperature," explained Professor Larrosa.

"The most important feature of this new catalyst is that, due to its extremely high reactivity, it is able to carry out late-stage arylation on a broad spectrum of highly functionalized molecules, presenting superb compatibility with delicate functional groups and with the presence of several of those functional groups in the same molecule," remarked Professor Larrosa. He continued: "Furthermore, because of the high reactivity, only stoichiometric amounts of the coupling partner are needed, instead of the typical need for an excess (sometimes even 2- or 3-fold excess) of one of them."

Professor Larrosa concluded: "We believe this class of catalysts will become very useful not only for late-stage arylation but also for other types of late-stage functionalization."



Scheme 2 The commonly proposed and revised mechanisms

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About the authors

Dr. M. Simonetti

Marco Simonetti received his MSc in 2010 from the University of Insubria (Italy) under the supervision of Prof. Andrea Penoni. In 2011, he joined the group of Prof. Antonio Papagni at the University of Milano-Bicocca (Italy). Later, he joined Prof. Igor Larrosa's group at Queen Mary University of London (UK) where he obtained his PhD in 2015. He continued working with Prof. Larrosa at the University of Manchester (UK) on the development of Ru-catalyzed C–H functionalization reactions, until January 2018. In March 2018, he joined Dr Daniele Leonori's group at the University of Manchester (UK) where is currently developing photocatalytic transformations.

D. M. Cannas

Diego M. Cannas graduated in medicinal chemistry and technology at The University of Urbino "Carlo Bo" (Italy) in 2015 under the supervision of Prof. Giovanni Piersanti. In the same year, he moved to the UK to join the group of Prof. Igor Larrosa at The University of Manchester as a PhD student. His research interests focus on transition-metal-catalyzed C–H functionalization and reaction mechanism elucidation.

Professor I. Larrosa

Igor Larrosa graduated in chemistry from the University of Barcelona (Spain) in 1999, where he also completed MChem (2000) and PhD (2004) degrees with Profs. Felix Urpi and Pere Romea. After a research period in Prof. Erick M. Carreira's laboratories at ETH (Zurich), Igor moved as a postdoctoral researcher to Imperial College London (UK) to work in Prof. Anthony G. M. Barrett's group. In September 2007 he started his independent career as a Lecturer at Queen Mary University of London (UK). In 2011, Igor was awarded a European Research Council starting grant. Since 2014, Igor has held a Chair in Organic Chemistry at the University of Manchester. Igor's research interests lie in transition-metal catalysis, with particular emphasis on the development of novel methodologies for C–H and C–C activation.

Synform SYNLETT Highlight

A *de novo* Synthetic Route to 1,2,3,4-Tetrahydroisoquinoline Derivatives

Synlett **2018**, *29*, 2066

The group of Professor Loránd Kiss at the Institute of Pharmaceutical Chemistry, University of Szeged (Hungary) has a profound interest in the development of selective methods for the synthetic access to highly functionalized fluorinated saturated heterocycles and β-amino acid derivatives.[1] Organofluorine chemistry is an expanding research field, having led to various applications of fluorine-containing compounds in organic synthesis, materials science, medicinal chemistry and drug discovery.[2]

Because of the high biological relevance of compounds possessing the 1,2,3,4-tetrahydroisoquinoline framework, a large number of synthetic approaches towards the creation of an isoquinoline or 1,2,3,4-tetrahydroisoquinoline core are presently known.[3] However, synthetic routes to tetrahydroisoquinoline derivatives containing fluorine atom(s) in their structure are not particularly abundant.[4] The aim of the team from the laboratory of Professor Kiss was to fill this gap and develop effective synthetic methodologies to access varied fluorinated 1,2,3,4-tetrahydroisoquinoline derivatives. The two procedures used most frequently for the incorporation of fluorine atoms into the skeleton of an organic scaffold are:

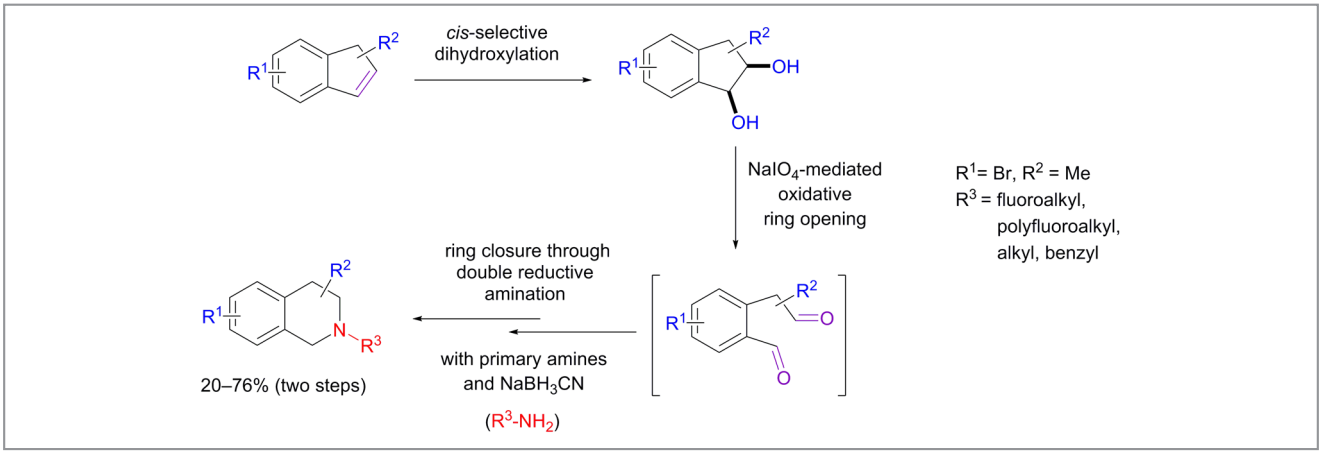
a) late-stage fluorination protocols using either nucleophilic or electrophilic fluorinating reagents, and

b) the application of various fluorine-containing building elements in a certain stage of the synthesis.

Professor Kiss said: "In order to reach the current goal we have used the second protocol to create fluorinated tetrahydroisoquinoline derivatives. The novel synthetic route we have developed is based on an oxidative ring opening/ring closing with reductive amination protocol.[5] The synthesis starts from indene and some substituted indene derivatives and, as key steps, it involved olefin bond cleavage through dihydroxylation/$NaIO_4$-mediated oxidation followed by cyclization with primary amines under reductive amination conditions."

The diols, derived from OsO_4-catalyzed dihydroxylation of indene derivatives, were subjected to oxidative ring cleavage with NaIO4. The formed unstable diformyl intermediates, after work-up with extraction without isolation, were further transformed with commercially available fluorine-containing primary amines to give the target tetrahydroisoquinoline compounds in two steps (Scheme 1).

"The two-step protocol consists of reductive amination of diformyl intermediates with difluoroethylamine, trifluoroethylamine, fluoroethylamine or perfluorinated amines in the presence of $NaBH_3CN$, through cyclization with ring expansion, and leads to the corresponding tetrahydroisoquinoline derivatives **1**–**7** in moderate to good yields (Figure 1)," explained Professor Kiss. He continued: "The synthetic procedure was further extended by using indene derivatives substituted



Scheme 1 Synthetic strategy

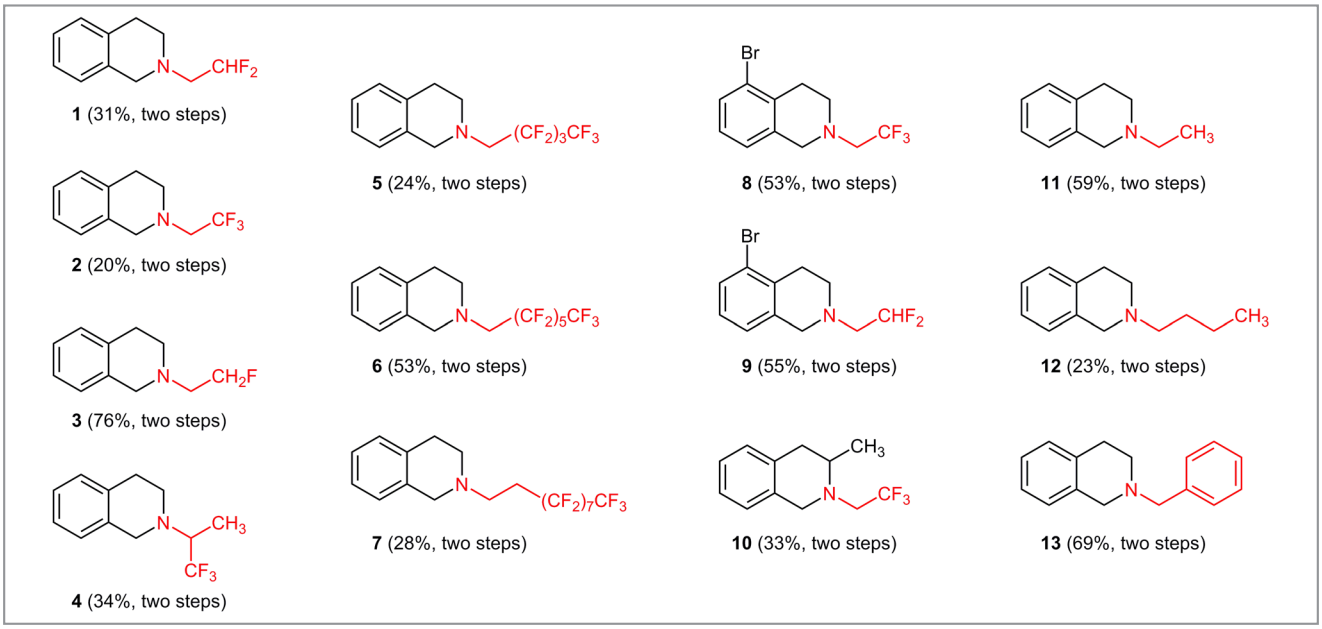


Figure 1 Reaction scope

either on the benzene or on the five-membered ring. Accordingly, 7-bromo-1*H*-indene and 2-methyl-1*H*-indene were selected as model starting compounds to furnish the corresponding isoquinoline derivatives **8**–**10** through the oxidative ring opening/reductive ring closing technique (Figure 1)."

Finally, the group also explored the applicability of the developed method towards various non-fluorinated substances. Professor Kiss remarked: "The generalization of this procedure was demonstrated by using three different primary amines: ethylamine, butylamine, and benzylamine. Cyclization of the diformyl intermediate in the reaction with these amines produced the corresponding N-substituted tetrahydroisoquinoline derivatives **11**–**13** in moderate yields (Figure 1)."

"In summary, we developed a relatively simple and efficient procedure for the construction of 1,2,3,4-tetrahydroisoquinoline systems possessing various fluorine-containing or non-fluorinated substituents," said Professor Kiss. He concluded: "This method, based on oxidative ring cleavage of the olefinic bond of indene or indene derivatives followed by reductive ring closure through double reductive amination of diformyl intermediates using fluorinated amines, might be further extended towards other tetrahydroisoquinoline derivatives. We are currently investigating other applications of the method."

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About the authors

Prof. L. Kiss

Loránd Kiss completed his Ph.D. in 2002 in the Department of Organic Chemistry at the Faculty of Sciences, Debrecen University (Debrecen, Hungary) under the supervision of Prof. Sándor Antus. In 2003, he joined the research team of Professor Ferenc Fülöp at the Institute of Pharmaceutical Chemistry, University of Szeged (Szeged, Hungary), where he started to work in the area of cyclic β-amino acid chemistry. He undertook postdoctoral research in the laboratories of Prof. Norbert De Kimpe at Ghent University (Ghent, Belgium), and Prof. Santos Fustero at the Department of Organic Chemistry, University of Valencia (Valencia, Spain). He has published 90 scientific papers in reputable journals. He is currently professor and department head at the Institute of Pharmaceutical Chemistry, University of Szeged. His scientific interest is directed towards the selective functionalization of β-amino acid derivatives and the synthesis of highly functionalized fluorinated building blocks.

Prof. F. Fülöp

Ferenc Fülöp was born in Szank, Hungary in 1952. He received his MSc degree in chemistry in 1975 and his Ph.D. in 1979 from József Attila University (Szeged, Hungary). At the beginning of his career he worked in Chinoin Pharmaceuticals (Budapest, Hungary) for six years. In 1991, he was appointed as a full professor at the Institute of Pharmaceutical Chemistry, University of Szeged, and between 1998 and 2017 he was the head of the institute. He is a member of the Hungarian Academy of Sciences and has a wide range of research interests in synthetic organic chemistry. His recent activities have focused on the use of amino alcohols and β-amino acids in enzymatic transformations, various asymmetric syntheses, foldamer construction, and flow chemistry, in view of the development of pharmacologically active derivatives.

R. A. Ábrahámi

Renáta A. Ábrahámi graduated as a pharmacist in 2015 from the University of Szeged (Hungary). She has been working at the Institute of Pharmaceutical Chemistry, University of Szeged since 2011. In 2015 she started her Ph.D. under the supervision of Loránd Kiss and Ferenc Fülöp. Her recent research topic focuses on the synthesis of varied functionalized six- or seven-membered saturated N-heterocycles and on the preparation of highly substituted fluorinated building blocks.

Prof. S. Fustero

Santos Fustero was born in Aínsa (Spain) in 1949. He studied chemistry at the University of Zaragoza (Spain), where he received his B.Sc. degree in 1972. He obtained his Ph.D. in organic chemistry in 1975 from the same university, working in the area of heterocyclic chemistry under the supervision of Professor J. Barluenga and Professor V. Gotor. He spent two years as a postdoctoral research associate at Professor H. Lehmkuhl's laboratory at the Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr (Germany), researching organometallic chemistry. In1983, he became an associate professor at the University of Oviedo (Spain) and, in 1990, he was promoted to full professor in organic chemistry at the University of Valencia (Spain). In 2005, he became research group leader at Centro de Investigación 'Príncipe Felipe' (CIPF) in Valencia. His research interests include organofluorine and medicinal chemistry, organocatalysis, and new reaction methodologies.

Editorial Board Focus: Professor Shuli You (Shanghai Institute of Organic Chemistry, P. R. of China)

Background and Purpose. From time to time, SYNFORM portraits Thieme Chemistry Editorial Board or Editorial 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. This Editorial Board Focus presents Professor Shuli You (Shanghai Institute of Organic Chemistry, P. R. of China) who joined the Editorial Board of Science of Synthesis in January 2018.

Biographical Sketch

Prof. S. You

Shuli You was born in Henan (P. R. of China) and received his BSc in chemistry from Nankai University (P. R. of China) in 1996. He obtained his PhD from Shanghai Institute of Organic Chemistry (SIOC, P. R. of China) in 2001 under the supervision of Prof. Lixin Dai before doing postdoctoral studies with Prof. Jeffery Kelly at The Scripps Research Institute (USA). From 2004, he worked at the Genomics Institute of the Novartis Research Foundation (USA) as a principal investigator before returning to SIOC as a professor in 2006. He is currently appointed as the director of the State Key Laboratory of Organometallic Chemistry of SIOC. His research interests mainly focus on asymmetric C–H functionalization and catalytic asymmetric dearomatization (CADA) reactions. He is the recipient of AstraZeneca Excellence in Chemistry Award (2011), RSC Merck Award (2015) and Ho Leung Ho Lee Foundation Prize for Scientific and Technological Innovation (2016).

INTERVIEW

SYNFORM *Please comment on your role as a member of the Editorial Board of Science of Synthesis.*

Prof. S. You It is such a great honor for me to join the Editorial Board of Science of Synthesis. This unique reference work covers all methods of organic synthesis offering full-text descriptions of organic transformations together with validated experimental procedures. Other notable features include that the entire content is available online, and is entirely searchable based on the structures, substructures and reaction types. I am very excited about my new role and look forward to contributing to the growth of Science of Synthesis.

SYNFORM *How do you describe the value of a product such as Science of Synthesis to the chemistry community?*

Prof. S. You Comprehensive. Extracted, validated, reliable references.

SYNFORM *What do you think about the modern role and prospects of synthetic chemistry, in particular its importance in and for the pharmaceutical industry?*

Prof. S. You Synthetic chemistry continues to grow and warrant the successful development of pharmaceutical industry. The new ways for disconnecting chemical bonds and forming new ones will provide better synthetic routes with shorter time and less waste. The access to novel molecular scaffolds and chemical structures enabled by the development of synthetic chemistry will expand the chemical space for the pharmaceutical industry as well.

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SYNFORM *What is the focus of your current research activities?*

Prof. S. You My current research mainly focuses on the development of novel strategies and methods for asymmetric catalysis. These include enantioselective C–H bond direct functionalization processes and catalytic asymmetric dearomatization (CADA) reactions. Catalytic reactions featuring high efficiency (in terms of yield, selectivity, atom economy, etc.) are the ultimate goal of this laboratory, with the hope to provide useful methods for the total synthesis of natural products and other functional molecules.

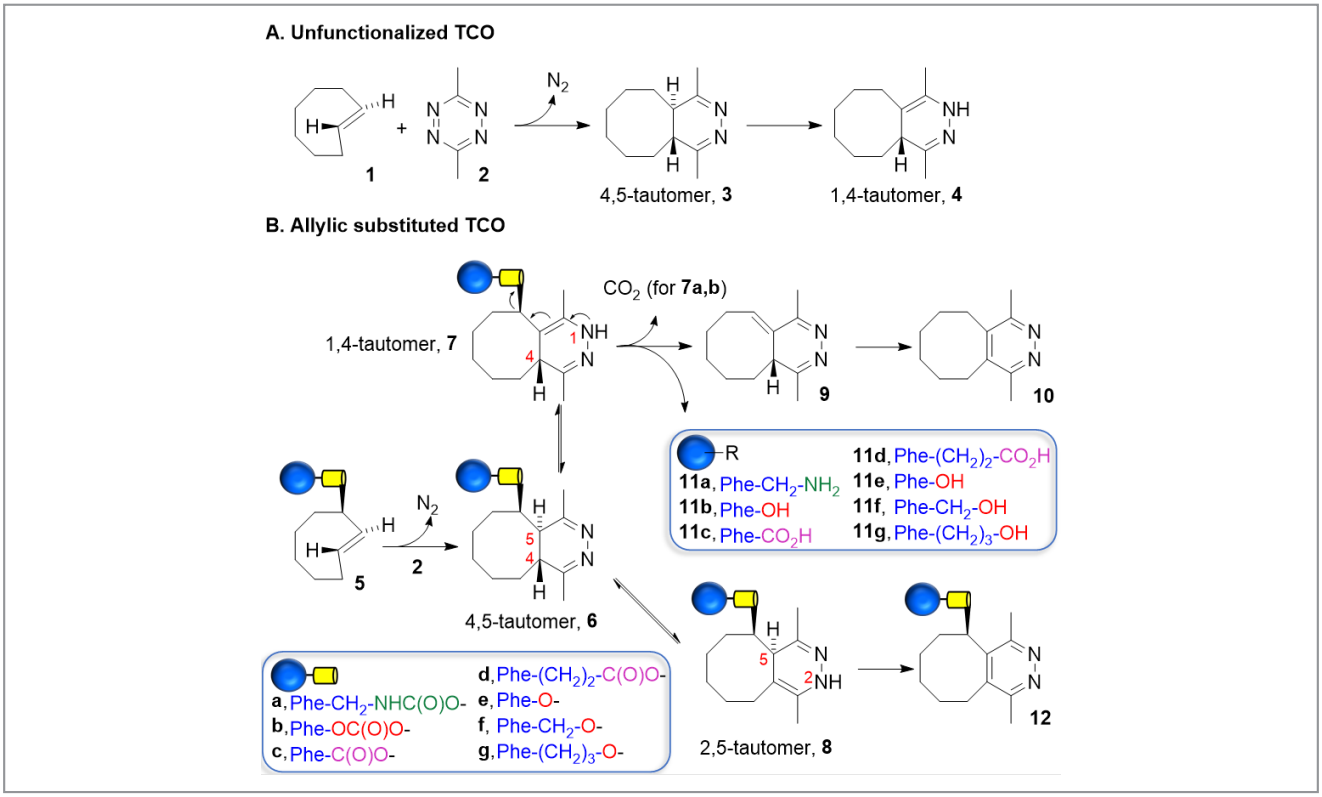
SYNFORM *You are a leading researcher with regard to green chemistry. Could you tell us more about how important you perceive this particular topic to be?*

Prof. S. You There is no doubt that green chemistry is becoming a more and more important consideration for synthetic organic chemists. As organic chemists, while we are aiming to develop methodologies that could expand our synthetic ability for delivering novel functional molecules, we are also considering the principals to make the new methods and syntheses greener. When we develop new synthetic methods, we pay particular attention to the utilization of readily available substrates and non-toxic reagents, the development of highly efficient catalysts and mild conditions, and obtaining high yields in combination with high selectivity and atom-economy.

Chemically Cleavable Antibody–Drug Conjugates: Drug Release in One Click

Since the introduction of the Staudinger ligation, the field of bioorthogonal chemistry has grown rapidly, and today's bioorthogonal toolbox includes a plethora of reactions that are highly selective and function in aqueous and complex media at physiological pH. Among these, the inverse-electron-demand Diels–Alder (IEDDA) cycloaddition between strained alkenes and tetrazines (TZs) has proven to be an extraordinary tool due to exceptional speed allowing very low reagent concentrations, potentially enabling in vivo click chemistry for medical applications. This reaction has already been applied in a range of fields, such as materials chemistry, chemical biology (protein modification in vivo, study of dynamic processes in living cells, and high-resolution imaging, among others) and nuclear medicine (radiolabeling of sensitive molecules, and pretargeted radioimmunoimaging and therapy). At first, the IEDDA reaction was viewed only as a powerful ligation tool. Until a few years ago.

In 2013 Dr. Marc Robillard from Tagworks Pharmaceuticals (The Netherlands) and co-workers developed a bioorthogonal bond cleavage reaction, the IEDDA pyridazine elimination, to enable selective elimination chemistry in living systems (*Angew. Chem. Int. Ed.* **2013**, *52*, 14112–14116). "In this modification of the IEDDA cycloaddition, the strained alkene is a *trans*-cyclooctene (TCO) modified at the allylic position with a suitable leaving group, which in our first design was an amine linked to the TCO as a carbamate (Scheme 1)," said Dr. Robillard. He continued: "We hypothesised that, upon TCO reaction with a TZ and release of N_2, the 4,5-dihydropyridazine



Scheme 1 A) IEDDA conjugation B) IEDDA pyridazine elimination of the axial isomers of TCO carbamate, carbonate, esters, and ethers. R. M. Versteegen et al. Click-to-Release from *trans*-Cyclooctenes: Mechanistic Insights and Expansion of Scope from Established Carbamate to Remarkable Ether Cleavage *Angew. Chem. Int. Ed.* **2018**, 57, 10494–10499 © Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.

(**6**) tautomerises to the 1,4 analogue (**7**) which then undergoes an electron cascade resulting in elimination of CO_2 and free amine. We set out to apply this new elimination reaction in the chemically triggered release of drugs from tumour-bound antibody–drug conjugates (ADCs) to expand the scope of amenable ADC targets from internalizing cancer receptors to those that do not internalise, and to targets in the tumour stroma. Current ADCs are designed to release their drug inside the cancer cell by means of proteases, pH-induced linker hydrolysis, or disulfide-to-thiol reduction promoted by reductases, and therefore can only be used with internalizing cancer receptors. The IEDDA pyridazine elimination has been used in other applications as well, including local prodrug activation for cancer therapy (*ACS Cent. Sci.* **2016**, *2*, 476-482), T-cell activation (*ACS Chem. Biol.* **2018**, *13*, 1569–1576), and protein profiling and uncaging in living cells (*ACS Cent. Sci.* **2016**, *2*, 325–331; *Chem. Commun.* **2017**, *53*, 8443–8446), amongst others."

In a recent article (*Angew. Chem. Int. Ed.* **2018**, *57*, 10494–10499) the group further expanded the scope of the IEDDA pyridazine elimination by demonstrating that, besides carbamate-derived amines, other chemical functionalities can also be liberated following the reaction between an allylic-substituted TCO and a TZ. "In this work, we synthesised TCOs comprising a range of allylic substituents (Scheme 1): aromatic carbonate (**5b**), aromatic and aliphatic esters (**5c**,**d**), and aromatic, benzylic and aliphatic ethers (**5e–g**)," explained Dr. Robillard. With these TCO derivatives the group carried out a thorough evaluation on the formation and disappearance of the dihydropyridazine tautomers and elimination products formed after IEDDA reaction with TZs. The relatively slow tautomerisation in $CDCl_3$ allowed them to study closely the release reaction using ^1H NMR and GCMS before moving to more relevant buffered aqueous solutions. "We were able to further support our original hypothesis, namely that the 1,4-dihydropyridazine tautomer is the species producing fast release," remarked Dr. Robillard. He continued: "We also found that the non-releasing 2,5-tautomer can convert slowly into the 1,4-tautomer, thereby contributing to the release and leading to a biphasic release profile. Furthermore, we were particularly pleased to find that ethers, even aliphatic ethers, could also be cleaved in a high yield with this strategy, given the stability

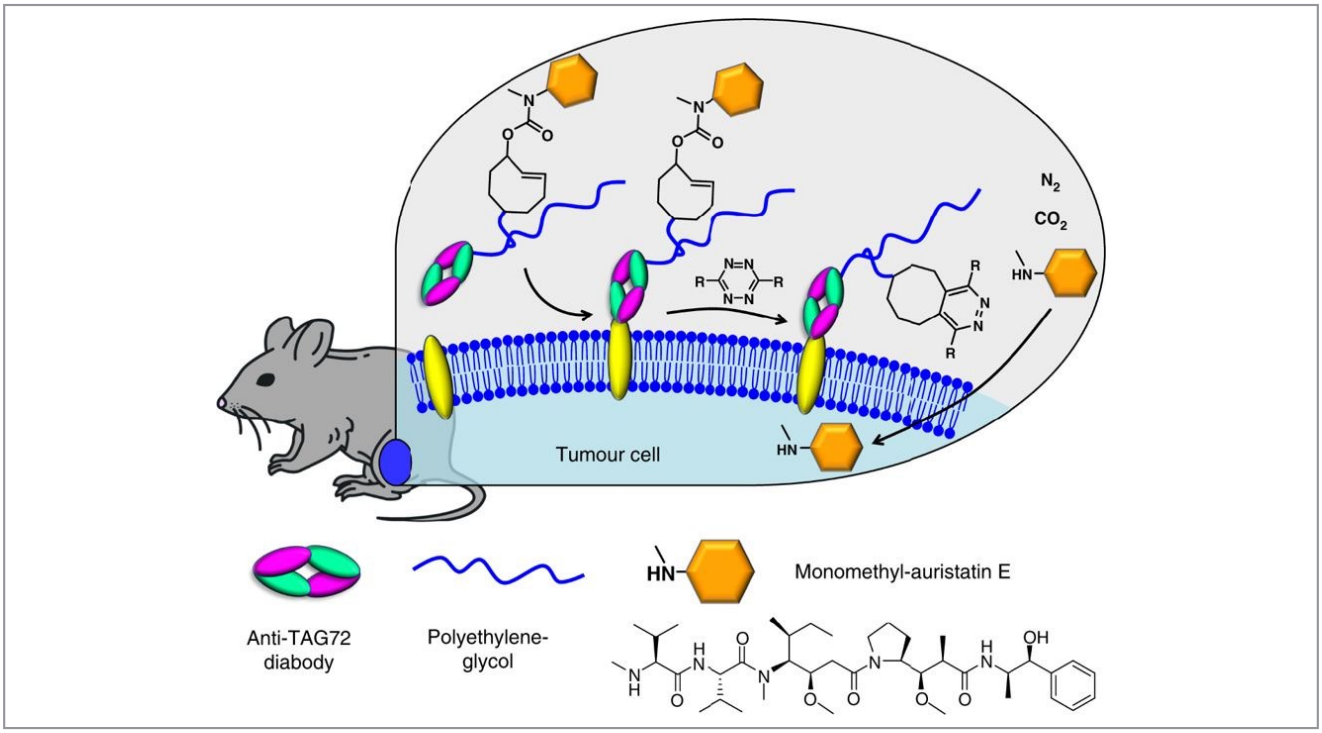


Figure 1 Triggered drug release using "click-to-release" chemistry in vivo: on-tumour liberation of a cell-permeable drug (monomethylauristatin E; MMAE) from a TCO-linked ADC following systemic administration of a TZ activator. Reprinted from R. Rossin et al. *Nat. Commun.* **2018**, *9*, 1484 (Creative Commons Attribution 4.0 International license http://creativecommons.org/licenses/by/4.0/).

of the ether bond and the poor leaving group nature of alkoxides." This indicated that the elimination is mainly governed by the formation of the rapidly eliminating 1,4-dihydropyridazine tautomer, and less by the nature of the leaving group. According to Dr. Robillard, expanding the scope of this cleavage reaction will allow the use of drugs lacking amenable amines, such as duocarmycins. Furthermore, it expands the scope of chemical functionalities that can be unmasked in the context of chemical biology and synthetic chemistry.

"In parallel with the abovementioned mechanistic studies, we conducted the first therapeutic evaluation of chemically cleavable ADCs in mouse models of human cancer, which recently appeared in *Nature Communications* (*Nat. Commun.* **2018**, *9*, 1484)," said Dr. Robillard. This was a collaborative project between Tagworks and several other companies (SyMO-Chem, Avipep, Levena, Syncom) and was carried out at the laboratories of the Radboud University Medical Center and Radboud University, in The Netherlands. "The ADC used in this study is based on a diabody targeting TAG72, a non-internalizing pan-carcinoma target widely expressed in a range of epithelial-derived human adenocarcinomas such as ovarian, colorectal and breast cancers. The ADC carries four bifunctional TCOs linked via a carbamate to monomethylauristatin E (MMAE), a potent and cell-permeable antimitotic agent (Figure 1)," explained Dr. Robillard.

This click-cleavable ADC (tc-ADC) was tested in two mouse models of colon and ovarian carcinomas, in a side-by-side comparison with an analogous ADC containing the protease-sensitive valine–citrulline linker (vc-ADC), designed for intracellular release and used in the marketed ADC Adcetris. "At first, however, we dedicated considerable effort to developing a suitable TZ-based activator, capable of effective on-tumour reaction with the TCO and efficient MMAE release from the ADC," said Dr. Robillard. He continued: "After our first proof-of-concept study on chemically triggered drug release in vivo (*Bioconjugate Chem.* **2016**, *27*, 1697–1706), we realised that sustained circulation of the activator is the key for success. The 3,6-bisalkyl TZs that give high release have a relatively low reactivity and, as small molecules, they clear from circulation too quickly, precluding quantitative on-tumour reaction. Therefore, in our recent study we designed a 3,6-bisalkyl TZ activator containing a PEG_{11}-DOTA (DOTA = 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) moiety that showed a 12 minute half-life in blood and low retention in non-target tissues. Sequential administration of the tc-ADC and activator pair was shown to lead to high ADC uptake in tumours and complete on-tumour IEDDA reaction, producing high tumour levels of free MMAE one and three days post-ADC activation. The presence of a DOTA chelator in the activator structure presented the opportunity to add a gamma-emitting radiometal (indium-111) and to demonstrate by SPECT-CT imaging that ADC activation took place throughout the tumour." The group's subsequent efficacy studies demonstrated a potent therapeutic effect for the chemically cleavable tc-ADC, with a markedly delayed tumour growth in the human colorectal cancer model (LS174T) and pronounced and durable tumour regression for at least four months (the duration of the study) in the ovarian cancer tumour model (OVCAR-3; Figure 2). On the contrary, the gold standard (enzymatically cleavable) vc-ADC failed to control tumour growth in both models. The limited therapeutic effect observed in the ovarian model for vc-ADC was most likely due to extracellular protease-based MMAE release.

"Overall, the IEDDA pyridazine elimination has already proven to be a very versatile reaction with diverse applications in medicine, chemical biology and synthetic chemistry

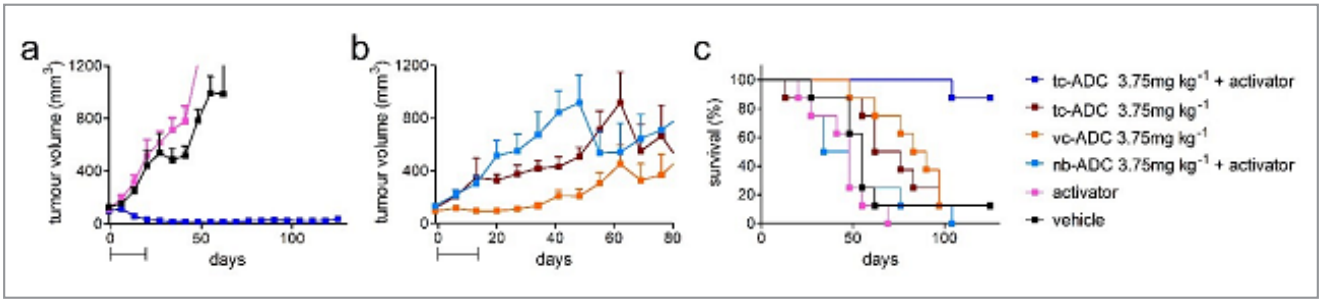


Figure 2 Mean OVCAR-3 tumour volumes (with SEM) in mice that within two weeks received i.v. (a) four cycles of the combination of tc-ADC with activator, activator alone, or vehicle, in comparison to mice that received i.v. four cycles of (b) tc-ADC alone, vc-ADC alone, or the combination of non-binding nb-ADC with activator. (c) Survival curves. The bars below the x axis indicate the treatment periods. Adapted from R. Rossin et al. *Nat. Commun.* **2018**, *9*, 1484 (Creative Commons Attribution 4.0 International license http://creativecommons.org/licenses/by/4.0/).

and we expect the number of applications to continue to grow," said Dr. Robillard. He concluded: "We believe that extracellular click-to-release is one of the key applications for this powerful technology, as it expands the scope of current ADC therapy and it allows other therapeutic targets to be addressed. The therapeutic proof of concept shown in *Nature Communications* is an important step towards the use of such click-to-release approaches in the clinic."

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