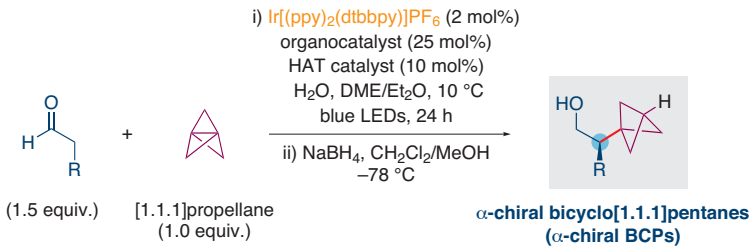
Synform

People, Trends and Views in Chemical Synthesis

2021/08

Direct Catalytic Asymmetric Synthesis of α-Chiral Bicyclo[1.1.1]pentanes

Highlighted article by M. L. J. Wong, A. J. Sterling, J. J. Mousseau, F. Duarte, E. A. Anderson



Contact
Your opinion about Synform is welcome, please correspond if you like:
marketing@thieme-chemistry.com

Thieme

Dear Readers,

The 2020 Journal Impact Factors – which track 2020 citations for articles published in 2018 and 2019 – have just been released by Clarivate and there is a lot to celebrate this year for Thieme Chemistry, as the impact factor of **SYNTHESIS has increased to 3.157** (which is an 18% increase, highest ever) whereas the impact factor of **SYNLETT has reached 2.454** (namely, an outstanding 22% increase). We all know that a high impact factor does not equate to recognition, reputation, prestige, or respect of a journal within the scientific community, which I believe have always been high for SYNTHESIS and SYNLETT, mainly thanks to the rigorous review process at our journals. Nonetheless, a high impact factor can be a powerful magnet for more submissions and in general – despite all of its controversial aspects and implications – it is undeniable that impact factors are directly or indirectly used by some governments, universities and agencies for evaluating the performance of researchers and institutions. For these reasons it would be hypocritical to claim that impact factors are unimportant, so this year's increase for both our flagship journals is a really important and very welcome achievement, besides being testament to the great job done by our Editorial Boards and Offices worldwide. Kudos to them! And what a better way to celebrate than going in full immersion with another exciting issue of SYNFORM!! The first article deals with the fascinating reactions of [1.1.1]propellane with aldehydes to give α-stereogenic bicyclo[1.1.1] pentanes, as described in a recent *Nat. Commun.* paper by F. Duarte and E. A. Anderson (UK). The second article covers a recent Science paper by Y.-F. Wang (P. R. of China) and K. N. Houk (USA) describing the chemoselective sequential C–F bond functionalizations of trifluoroacetamides and trifluoroacetates via ground-breaking radical chemistry. The third article is a Young Career Focus interview with the up-and-coming researcher A. Sukhorukov (Russian Federation), who talks with us about his broad research interests in organic chemistry. Last but not least, a Literature Coverage article focussed on the exciting combination of photoredox and N-heterocyclic carbene (NHC) catalysis developed by A. Studer (Germany) for achieving benzylic C–H acylation.

Enjoy your reading!!

In this issue

Contact
If you have any questions or wish to send feedback, please write to Matteo Zanda at: synform@outlook.com

 Synform **2021/08**, A125 • Published online: July 20, 2021 • DOI: 10.1055/s-0040-1720533

Direct Catalytic Asymmetric Synthesis of α-Chiral Bicyclo[1.1.1]pentanes

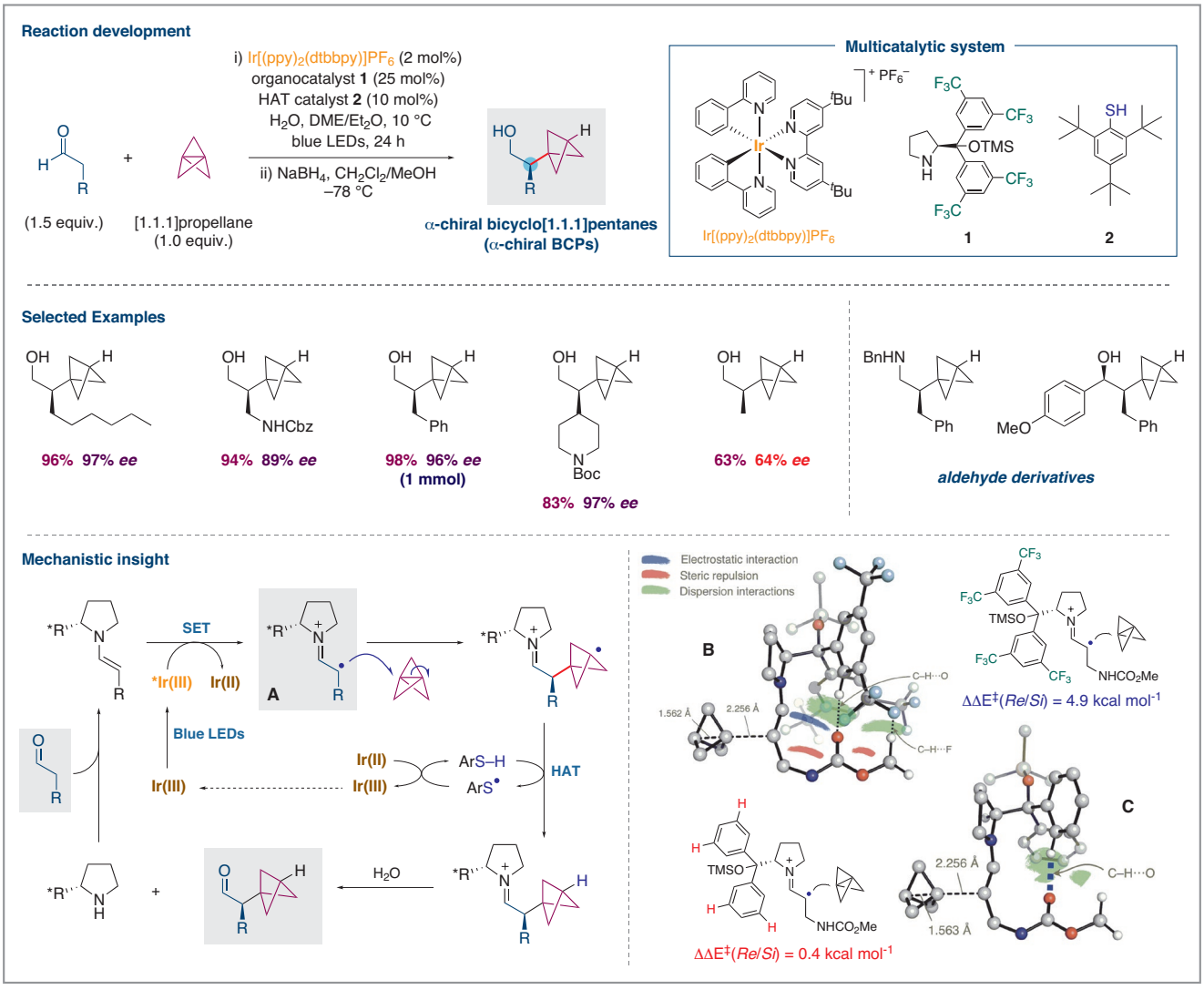
Nat. Commun. **2021**, *12*, 1644; https://doi.org/10.1038/s41467-021-21936-4

Bicyclo[1.1.1]pentanes (BCPs) have become highly attractive bioisosteres for *para*-substituted arenes and *tert*-butyl groups in medicinal chemistry, due to their advantageous pharmacokinetic properties.[1] However, the synthesis of BCPs featuring adjacent stereocentres has remained a significant challenge – these motifs would correspond to α-stereogenic benzyl groups, which are again of high importance in drug design. The group of Professor Edward A. Anderson at the University of Oxford (UK) has been studying this area for some time. "At the starting point of our work, just two catalytic methods[2,3] had been reported to install an α-stereocentre on a pre-formed BCP," said Professor Anderson. The group realised that an alternative and very attractive approach to this problem would be the direct formation of a stereogenic centre upon ring-opening of [1.1.1]propellane, the smallest tricyclic hydrocarbon and the ubiquitous precursor to BCPs. "Despite decades of work on ring-opening reactions of [1.1.1]propellane, no such direct asymmetric addition process had been described. The symmetry of this fascinating cage molecule renders an asymmetric ring opening all the more challenging," explained Professor Anderson. He went on: "From our previous work, we knew that radical-based additions proceed in high yields and under mild conditions;[4,5] however, the field of catalytic asymmetric radical reactions as a whole is rather underdeveloped and in early studies, PhD student Marie Wong indeed found that previous asymmetric radical chemistries failed when faced with [1.1.1]propellane. Nonetheless, we were aware of the pioneering work of the MacMillan group on asymmetric alkylations of aldehydes with styrenes as radical acceptors,[6] which used a three-component catalytic system comprising an organocatalyst (typically a Hayashi–Jørgensen diarylprolinol derivative), a photoredox catalyst (an iridium complex), and a hydrogen-atom-transfer catalyst (HAT catalyst, typically a thiol). The key question for Marie," continued Professor Anderson, "was whether these three catalysts could successfully operate on [1.1.1]propellane, as a number of side reactions could be envisaged, such as polymerization of the propellane, or its direct reaction with the thiol HAT catalyst."

Marie undertook a comprehensive screen of reaction conditions, including variations of all three catalysts, reactant equivalents, solvent and concentration, temperature and reaction time, and even LED lamp. Professor Anderson revealed that Marie made some curious discoveries: the enantioselectivity of the reaction appeared critically dependent not only on the nature of the chiral organocatalyst, but also, surprisingly, on the photocatalyst and the HAT catalyst. "As we initially believed the latter two would not be directly involved in the enantiodetermining step – namely, the ring opening of [1.1.1]propellane – we were intrigued to understand more about the origin (or origins) of stereoinduction," Professor Anderson remarked. He went on: "Irrespective of this, we were delighted to find that the reaction could be applied to a wide range of aldehydes, tolerating many functional groups and significant steric hindrance adjacent to the alkylation site. These products are easily transformed into other useful BCP-containing building blocks."

Working with Professor Fernanda Duarte (University of Oxford, UK), PhD student Alistair Sterling had already been establishing a theoretical reaction pathway for this asymmetric bicyclopentylation chemistry, and now took on the challenge to explain these phenomena. Professor Fernanda Duarte explained: "Alistair uncovered several key findings: firstly, that the enantioselectivity of the reaction derives not only from steric blocking of one face of the intermediate iminyl radical cation **A** (see Scheme 1) by the organocatalyst sidechain, but also from stabilizing non-covalent interactions between its trifluoromethyl groups and the aldehyde sidechain (**B**). This explained the importance of the organocatalyst substituents (**C**); and secondly, that the interconversion of the *E* and *Z* iminyl radical cations **A**, formed from oxidation of the corresponding enamines, had a higher energy barrier than their addition to propellane. Therefore, the population of these diastereomeric radical cations could also influence enantioselectivity. As this population is decided by the relative rates of oxidation of the enamine precursors, this explains why the photoredox catalyst could influence enantioselectivity, as the enamine stereoisomers could certainly possess different oxidation potentials."

Professor Anderson concluded: "Overall, this chemistry should provide an efficient and general way to synthesize valuable α-chiral bicyclopentanes for medicinal chemistry research. Our groups are keen to continue exploring both the experimental and theoretical consequences of the concepts we have developed, which we hope should extend beyond BCPs."



Scheme 1 Multicatalytic synthesis of α-chiral bicyclo[1.1.1]pentanes by asymmetric addition of aldehydes to [1.1.1]propellane

REFERENCES

(1) F. Stepan, C. Subramanyam, I. V. Efremov, J. K. Dutra, T. J. O'Sullivan, K. J. DiRico, W. S. McDonald, A. Won, P. H. Dorff, C. E. Nolan, S. L. Becker, L. R. Pustilnik, D. R. Riddell, G. W. Kauffman, B. L. Kormos, L. Zhang, Y. Lu, S. H. Capetta, M. E. Green, K. Karki, E. Sibley, K. P. Atchison, A. J. Hallgren, C. E. Oborski, A. E. Robshaw, B. Sneed, C. J. O'Donnell *J. Med. Chem.* **2012**, *55*, 3414–3424.

(2) Z. J. Garlets, J. N. Sanders, H. Malik, C. Gampe, K. N. Houk, H. M. L. Davies *Nat. Catal.* **2020**, *3*, 351–357.

(3) S. Yu, C. Jing, A. Noble, V. K. Aggarwal *Org. Lett.* **2020**, *22*, 5650–5655.

(4) D. F. J. Caputo, C. Arroniz, A. B. Dürr, J. J. Mousseau, A. F. Stepan, S. J. Mansfield, E. A. Anderson *Chem. Sci.* **2018**, *9*, 5295–5300.

(5) J. Nugent, C. Arroniz, B. R. Shire, A. J. Sterling, H. D. Pickford, M. L. J. Wong, S. J. Mansfield, D. F. J. Caputo, B. Owen, J. J. Mousseau, F. Duarte, E. A. Anderson *ACS Catal.* **2019**, *9*, 9568–9574.

(6) A. G. Capacci, J. T. Malinowski, N. J. McAlpine, J. Kuhne, D. W. C. MacMillan *Nat. Chem.* **2017**, *9*, 1073–1077.

 Synform **2021/08**, A126–A128 • Published online: July 20, 2021 • DOI: 10.1055/s-0040-1720531

About the authors

Dr. M. L. J. Wong

Marie Wong is from Cameron Highlands, Malaysia, and received her MChem degree from the University of Oxford (UK) in 2016. During this time, she conducted research with Prof. Edward Anderson (University of Oxford), Prof. John Hartwig (UC Berkeley, USA) and Prof. Scott Miller (Yale University, USA). She then joined the EPSRC Synthesis for Biology and Medicine Centre for Doctoral Training (SBM CDT) at the University of Oxford. She completed her PhD studies in 2021 on the synthesis and functionalization of α-chiral bicyclo[1.1.1]pentanes under the supervision of Prof. Edward Anderson.

A. J. Sterling

Alistair Sterling received his MChem degree in 2017 from the University of Oxford (UK). During his studies, he spent a semester in the group of Prof. Erick Carreira (ETH Zürich, Switzerland), before returning to Oxford to study total synthesis under the supervision of Prof. Edward Anderson. He subsequently received an Oxford-Radcliffe scholarship to undertake doctoral studies at the University of Oxford, and after briefly working on carbon-rich nanoring synthesis under Prof. Harry Anderson, he joined the groups of Profs. Fernanda Duarte and Edward Anderson. His doctoral research focuses on the development of physical organic models to explain the reactivity of strained organic molecules, using computational techniques to aid the development of new reactions.

Dr. J. J. Mousseau

James J. Mousseau was born in Montréal, Quebec, Canada. Upon completing his B.Sc. in Honors Biochemistry in 2004 at Concordia University (Canada), he continued his M.Sc. studies at Concordia under the supervision of Professor Louis Cuccia and was involved in the synthesis of novel crescent-shaped urea-linked heterocyclic foldamers. In 2011 he completed his Ph.D. studies under Professor André Charette at Université de Montréal (Canada) studying arene direct functionalization processes. After completing an NSERC Postdoctoral Fellowship at the Massachusetts Institute of Technology (USA) under Professor Tim Jamison, he joined Pfizer in 2013 in Groton, CT (USA) as a medicinal chemist working in the area of inflammation and immunology. He is a co-author on ~40 publications and recent synthetic interest has been around developing new methodologies to provide chemists with tools to 'escape the flatland'.

Professor F. Duarte

Fernanda Duarte is an Associate Professor in Chemistry at the University of Oxford (UK). Her current position commenced in 2018, following appointments at the University of Edinburgh (UK; Chancellor's Fellow), the University of Oxford (Newton Fellow) and Uppsala University (Sweden; PDRA). She leads a diverse team of researchers working at the interface of organic chemistry, supramolecular catalysis, and computational chemistry. Her main research interests centre on the prediction of chemical reactivity in the condensed phase, combining classical, quantum and machine-learning approaches. Her group has also developed a series of computational software to facilitate molecular design and reaction mechanism exploration. She has published over 50 peer-reviewed scientific publications and received several awards, including most recently the 2020 MGMS Frank Blaney Award from the Molecular Graphics and Modelling Society.

Professor E. A. Anderson

Edward A. Anderson is Professor of Organic Chemistry at the University of Oxford (UK). He began his independent career as an EPSRC Advanced Research Fellow in 2007, during which he was appointed as Associate Professor at Jesus College, Oxford in 2009, and then as Professor in 2016. His research interests encompass a wide range of synthetic organic chemistry, including natural product total synthesis, transition-metal catalysis and mechanistic study, bicyclo[1.1.1]pentanes and related small rings, antiparasitic natural products, the chemistry of ynamides and yndiamides, and EPR spectroscopy in nucleic acids. He is a recent recipient of the Novartis Chemistry Lectureship (2018), and RSC Bader Award (2020).

 Synform **2021/08**, A126–A128 • Published online: July 20, 2021 • DOI: 10.1055/s-0040-1720531

Sequential C–F Bond Functionalizations of Trifluoroacetamides and Acetates via Spin-Center Shifts

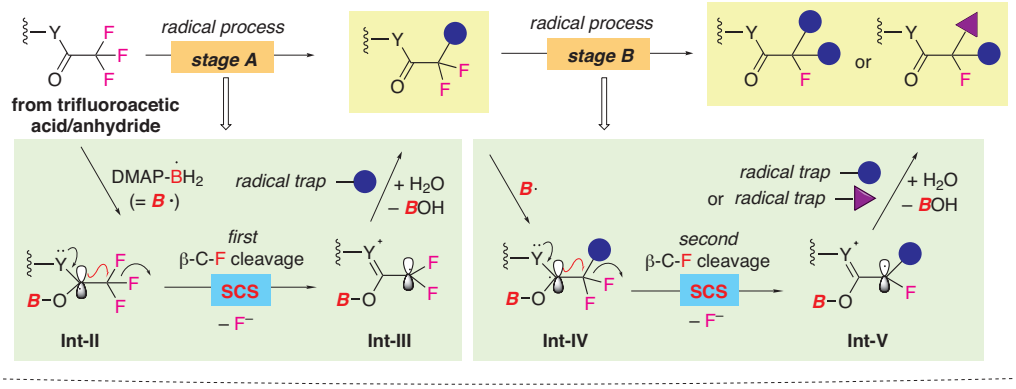
Science **2021**, *371*, 1232–1240

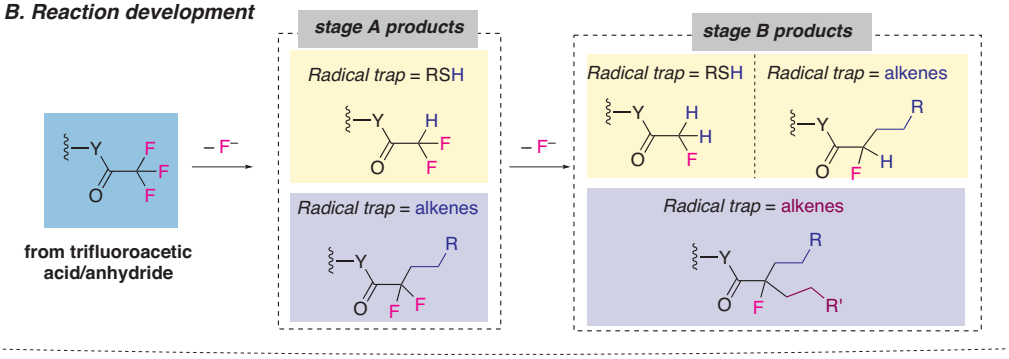
Monofluoro- and difluoro-substituted organic molecules have properties that make them valuable in many applications. New methods to synthesize these molecules attract wide interest. Among various methods reported for accessing fluorinated compounds, introduction of trifluoromethyl groups has been an effective and economical pathway, since many trifluoromethyl sources are inexpensive and readily available. Thus, a large number of defluorination approaches have been developed to produce mono and difluoro compounds. However, selectively producing either difluoro or monofluoro compounds from trifluoro is exceedingly challenging, because when the first C–F bond is broken, the remaining two get weaker, thus often resulting in exhaustive defluorination. Therefore, "strategies that selectively snip off one or two C–F bonds would be very valuable in synthetic and medicinal chemistry," said Professor Yi-Feng Wang, from the University of Science and Technology of China (Hefei, P. R. of China), whose research program is focused on discovery of new chemical reactivity and synthetic applications of Lewis base–boryl radicals. "During our studies, we had developed a Lewis base–boryl radical enabled desulfurizative reduction of thioamides to organic amines (*Org. Lett.* **2018**, *20*, 24–27)," continued Professor Wang, who added: "Encouraged by these findings, we next conceived an analogous radical reduction reaction of amides. Surprisingly, when a trifluoroacetamide was treated with 4-dimethylaminopyridine (DMAP)-BH_2·, hydrodefluorination reactions occurred instead, giving a mixture of di- and monofluoromethyl products, albeit with moderate chemoselectivity. After optimization of reaction conditions, we successfully improved both the chemoselectivity and yields, leading to selective formation of mono- and dihydrodefluorination products." Preliminary mechanistic studies suggested that α-fluorocarbonyl radical intermediates were generated during the defluorination process. The group was intrigued by this finding, because C–F bonds are supposed to be inert, with a very high bond dissociation energy that constrains homolytic cleavage. The authors thought that clarification of this defluorinative radical generation mechanism would be of great interest. "After checking literature precedents and especially discussing with Prof. S. Z. Zard (École Polytechnique, Paris, France), when he visited us in November 2018, we were drawn to consider a spin-center shift (SCS) mechanism that involves 1,2-radical delocalization and leaving-group elimination," explained Professor Wang. He continued: "We surmised that the defluorination reaction would likely proceed through the attack of DMAP-BH_2· to the carbonyl oxygen atom, followed by an SCS process to eliminate a fluoride ion. More importantly, the repeat of this process to the resulting product would enable the second C–F bond cleavage. On this basis, we hypothesized a two-stage process with each stage involving an SCS for the C–F bond cleavage of trifluoroacetic acid derivatives (Scheme 1A)." According to Professor Wang, in **stage A**, the first SCS of the transient **Int-II** – generated through the attack of the carbonyl oxygen atom by DMAP-BH_2· – takes place, triggering the cleavage of a single β-C–F bond. "The resulting α,α-difluorocarbonyl radical, **Int-III**, can be subsequently captured by a radical trap to provide an α,α-difluoroacetyl product and complete the monodefluorinative transformation," continued Professor Wang. "In **stage B**, if the DMAP-BH_2· is continuously present, the **stage A** product participates in a second SCS to generate the radical **Int-V**, which is then trapped by a second component to furnish monofluorinated products. The use of different traps in **stages A** and **B** should enable rapid and efficient synthesis of densely functionalized monofluoro products."

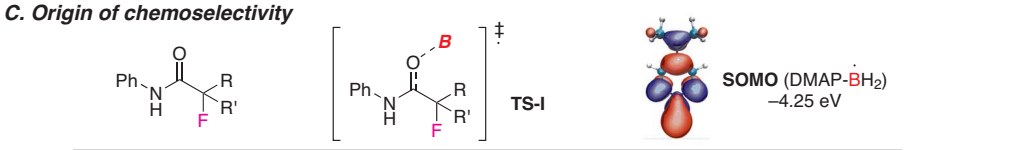
To the group's delight, this two-stage process showed broad substrate scope and good chemoselectivity (Scheme 1B). "For example, reduction of intermediates in **stages A** and **B**, wherein RSH was used as the polarity reversal catalyst, could afford di- and mono-fluoromethyl products selectively, and only minor over-reduction products were observed in the formation of difluoro products," remarked Professor Wang, continuing: "Notably, no trihydrodefluorination product was detected in either case. Alkenes could be used as the radical trap in both **stages A** and **B**, leading to diverse defluorinative coupling products. Interestingly, when two different alkenes were employed in **stages A** and **B**, products containing a monofluorinated tertiary stereogenic center were constructed."

To gain deeper insight into the SCS process, as well as to figure out the effect responsible for controlling the chemoselectivity, the group carried out detailed computational studies in collaboration with Prof. K. N. Houk (University of California, Los Angeles, USA). "This collaboration started when we met at a lecture that Prof. Houk gave at Nankai University," explained Professor Wang. He continued: "We then worked on it together for around one and a half years. The results showed

  • Published online: July 20, 2021 • DOI: 10.1055/s-0040-1720531







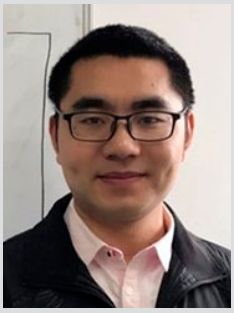
Substrate	TS-I	ΔG‡ (kcal/mol)	ΔG (kcal/mol)	SOMO/LUMO gap	
1a R = R' = F	**TS-I-1a**	7.9	–13.0	DMAP-$\dot{B}H_2$/**1a**	4.03 eV
2a R = F, R' =H	**TS-I-2a**	9.2	–11.0	DMAP-$\dot{B}H_2$/**2a**	4.14 eV
3a R = R' = H	**TS-I-3a**	11.1	–5.8	DMAP-$\dot{B}H_2$/**3a**	4.45 eV

Scheme 1 Sequential C–F bond functionalizations of trifluoroacetamides and trifluoroacetates via spin-center shifts (SCSs)

that the SCS process proceeded with a surmountable energy barrier for N–H amide, while a Na salt is essential to assist the cleavage of a C–F bond in tertiary amides and esters. These theoretical results are consistent with experimental ones. Further DFT calculations revealed that the chemoselectivity is determined by the declining reactivity of DMAP-BH_2• towards the addition to defluorinated products (Scheme 1C). This trend is attributed to the increasing singly occupied molecular orbital (SOMO)/lowest unoccupied molecular orbital (LUMO) gaps between DMAP-BH_2· and the substrates. Therefore, once the first C–F is removed, the resulting carbonyl group is less attractive to the DMAP-BH_2·, thus ensuring exquisite chemoselectivity during defluorination."

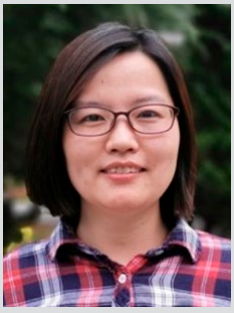
Professor Wang concluded: "We believe that the SCS strategy reported in this work will be applicable to other carbon–heteroatom bonds (i.e., C–O, C–N, and C–Cl, among others) and we are now exploring these transformations."

About the authors



Y.-J. Yu

You-Jie Yu received his B.S. degree from the Department of Chemistry, Nanjing Agricultural University (P. R. China) in 2015. Currently he is pursuing his Ph.D. under the supervision of Prof. Y.-F. Wang at the University of Science and Technology of China (USTC, P. R. of China). His main research interests lie in the areas of free radical chemistry and fluorine chemistry.

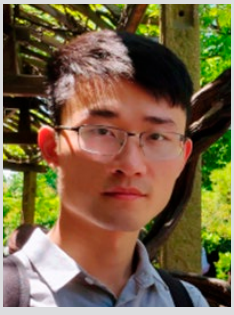


F.-L. Zhang

Feng-Lian Zhang received her B.Sc. from Nankai University (P. R. of China) in 2011 and obtained her Ph.D. from Nanyang Technological University Singapore under the supervision of Prof. Shunsuke Chiba in 2016. After that she worked as a postdoctoral researcher at USTC (2016–2019), where she is now a research associate professor. Her current focus is organoboron chemistry, including methodology development and mechanistic investigation through computational studies.

T.-Y. Peng

Tian-Yu Peng received his B.Sc. in chemistry from Central China Normal University (P. R. of China) in 2015. Currently he is pursuing his Ph.D. under the supervision of Prof. Y.-F. Wang at USTC. His research interest is the development of new synthetic methodology enabled by Lewis base–boryl radicals.



C.-L. Wang

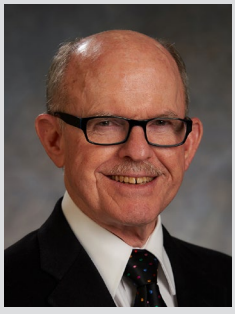
Chang-Ling Wang received his B.Sc. (2018) from the Department of Chemistry at the Anhui University of China (P. R. of China). He is now a Master's student in the group of Prof. Y.-F. Wang at USTC. He is currently working on NHC–boryl radical chemistry.

J. Cheng

Jie Cheng obtained his B.Sc. (2018) from USTC in organic chemistry under the supervision of Prof. Y.-F. Wang. Now he is a Master's student at the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (P. R. of China) under the supervision of Prof. Yinlong Guo. He is now focusing on the study on mass spectrometry-oriented carbon–carbon double-bond isotopic labeling reagents.

C. Chen

Chen Chen received her B.S. (2018) in organic chemistry at USTC. She learned skills of synthesis in the Wang lab and did her undergraduate thesis under the supervision of Prof. Y.-F. Wang. She is now a Ph.D. candidate at Department of Materials Science and Engineering at the University of Illinois, Urbana-Champaign (USA).



Prof. K. N. Houk

K. N. Houk received his Ph.D. at Harvard (USA), working with R. B. Woodward on experimental tests of orbital symmetry selection rules. He has taught at Louisiana State University (USA), the University of Pittsburgh (USA), and UCLA (USA) since 1986. He is the Saul Winstein Research Chair in Organic Chemistry. His research group develops rules to understand reactivity and builds computational models of complex organic reactions. He collaborates prodigiously with chemists all over the world, publishing over 1320 articles in refereed journals to date.

Prof. Y.-F. Wang

Yi-Feng Wang received his Ph.D. in 2011 at the Nanyang Technological University, Singapore under the supervision of Profs. Koichi Narasaka and Shunsuke Chiba. He continued to work with Prof. Chiba as a research fellow (2011–2015) and was appointed as a Lee Kuan Yew Postdoctoral Fellow during 2012–2014. In 2015, he started his independent research work at USTC as a full professor. His research interests include radical chemistry, organoboron chemistry, and the synthesis of bioactive molecules.

 Synform **2021/08**, A129–A131 • Published online: July 20, 2021 • DOI: 10.1055/s-0040-1720531

Young Career Focus: Prof. Dr. Alexey Sukhorukov (N. D. Zelinsky Institute of Organic Chemistry, and D. Mendeleev University of Chemical Technology, Russian Federation)

Background and Purpose. SYNFORM regularly meets 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 Young Career Focus presents Prof. Dr. Alexey Sukhorukov (N. D. Zelinsky Institute of Organic Chemistry, and D. Mendeleev University of Chemical Technology, Russian Federation).

Biographical Sketch

Prof. Dr. A. Sukhorukov

Alexey Sukhorukov received his M.Sc. from D. Mendeleev University of Chemical Technology (Russian Federation) in 2007 and his Ph.D. from the N. D. Zelinsky Institute of Organic Chemistry (Russian Federation) in 2009 with Professor Sema Ioffe. After working as a research associate and senior scientist, he defended his habilitation thesis on the CH-functionalization of nitronates in 2018. In 2020, he was promoted to a head of a newly created department (Laboratory of organic and metal-organic nitrogen-oxygen systems) at the same institute. He also holds the position of Full Professor at the Organic Chemistry Department of D. Mendeleev University of Chemical Technology (Russian Federation). Prof. Sukhorukov has been a recipient of several awards, including the Thieme Chemistry Journals Award (2021), The Moscow Government Award for Young Scientists (2019), and the Gold Medal of the Russian Academy of Sciences (2010). His research interests cover the chemistry of nitrogen–oxygen compounds, stereoselective synthesis of pharmaceutically relevant molecules, reaction mechanisms, and chemistry of diamondoid molecules.

INTERVIEW

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

Prof. Dr. A. Sukhorukov My research activity is primarily focused on the chemistry of compounds having nitrogen–oxygen bonds (NO-compounds). I believe that the role of these compounds is underestimated, especially in organic synthesis, medicinal and coordination chemistry. Indeed, the history of chemistry gives us amazing examples, wherein NO-compounds have made a tremendous impact on the development of some critical spheres of human activity. I shall give two examples not from the military sphere to justify this. One is the introduction of synthetic fertilizers based on nitrates (produced via nitrogen fixation), the event that brought the agricultural industry to a substantially new level. Another example is the discovery of the role of nitric oxide as a signaling molecule in many physiological and pathological processes (Nobel Prize for Physiology and Medicine, 1998). This led to the development of nitric oxide donors as new-generation pharmaceuticals for the treatment of cardiovascular disorders.

Being incorporated into the organic framework, the nitrogen–oxygen linkage provides unique reactivity. The ease of the cleavage of the N–O bond can be exploited to construct more stable carbon–carbon and carbon–heteroatom bonds via umpolung and redox-neutral processes. This concept has been recognized only recently, and its synthetic potential is being actively explored.[1,2] Our group is very much involved in the development of N–O cleavage-driven synthetic transformations, C–H functionalization processes in particular.[3,4]

Another aspect of my interest in NO-compounds is their underestimated potential for medicinal chemistry. Until recently, heterocycles having exocyclic nitrogen–oxygen bonds were considered as rather exotic among natural products.

 Synform **2021/08**, A132–A135 • Published online: July 20, 2021 • DOI: 10.1055/s-0040-1720531

The situation changed in the early 2000s when numerous marine metabolites and alkaloids possessing an isoxazoline and 1,2-oxazine ring (five- and six-membered heterocycles with an exocyclic N–O bond) were isolated and shown to have promising physiological properties, in particular, anti-cancer and anti-inflammatory activities.[5,6] This greatly stimulated research on the medicinal chemistry of NO-heterocycles. In the near future, the emergence of new scaffolds based on NO-heterocycles can be anticipated. I am proud that our team, together with our collaborators, is contributing to this field.

While my students are doing experiments, I spend time writing review articles, book chapters and highlights on topics related to our research. This helps me to expand my knowledge in chemistry, find synthetic challenges and get new ideas.

SYNFORM *When did you get interested in synthesis?*

Prof. Dr. A. Sukhorukov As a kid, I used to mix things at home pretending to be a chemist. During school times, I had a small chemistry lab at home. I got a book called "*Experiments without Explosions*", which contained many exciting experiments to be done safely at home. While my friends were playing football, I used to wash test-tubes, preparing for the next experiment. When studying in high school at Moscow Chemical Lyceum, I got a strong interest in organic chemistry intrigued by the ability of artificial organic synthesis to create complex molecules derived from nature. At university I used to read "*Classics in Total Synthesis*" by Professor K. C. Nicolaou,[7] the book which strengthened my desire to become an organic chemist. At that time, I didn't realize how difficult it is to do target-oriented multistep synthesis, especially when you do it with your own hands. So difficult, but so exciting!

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

Prof. Dr. A. Sukhorukov The primary role of organic synthesis is to prepare molecules of the target structure in the most efficient and least time-consuming manner. In this sense, I always considered organic chemists as a sort of molecular architect. However, the way we assemble molecules is far from what I would call ideal. We do multi-step synthetic sequences, produce lots of side- and by-products, and waste litres of toxic organic solvents for compound isolation/purification, to end up with only a few milligrams of target compound from 10 grams of starting material. In comparison, Nature assembles molecules much more efficiently through biocatalysis and self-assembly routes. That is why catalytic cascade reactions, click chemistry and bioinspired syntheses are the key topics for the future development of organic synthesis.

Looking towards the future, I believe scientists will create a sort of a molecular 3D printer, a machine, which will do the job for synthetic chemists. Although some attempts are being made in this direction,[8] automated organic synthesis in a general sense is still science fiction. But even if such a machine is created, this does not mean that there will be nothing more to investigate in organic chemistry.

Thus, I anticipate that the way we do organic synthesis will dramatically change in the future. And I wish our research will contribute to the development of practical syntheses.

SYNFORM *Could you tell us more about your group's areas of research and your aims?*

Prof. Dr. A. Sukhorukov Our laboratory has broad research interests that focus on the chemistry of nitrogen–oxygen compounds (major research topics are shown in Figure 1). We are particularly keen on studying the reactivity of NO-compounds (nitro derivatives, oximes, NO-heterocycles, etc.), development of new synthetic methods, total synthesis of bioactive molecules, and finding new applications for NO-compounds in the fields of medicinal chemistry, click reactions, domino-transformations and coordination chemistry. Our team is also interested in studying reaction mechanisms using combined techniques including detection/isolation of chemical intermediates, DFT calculations and *operando* spectroscopy.

In the last ten years, we have developed a set of methods for the umpolung C–H functionalization of nitronates based on pericyclic processes, transition-metal-promoted reactions and nitrosoalkene chemistry (Figure 1, a). The driving force of these reactions is the cleavage of the weak N–O linkage, which provokes the formation of new carbon–heteroatom bonds. This methodology was efficiently applied as a key stage in the asymmetric total synthesis of several natural products and drug candidates (Figure 1, b). Moreover, our synthetic approach provides access to libraries of polysubstituted NO-heterocycles (1,2-oxazines, isoxazolines, isoxazoles), among which some compounds with promising pharmaceutical profiles were identified (Figure 1, c).

Another topic of our research is the chemistry of diamondoid molecules, in particular adamantanes and diamantanes doped with multiple heteroatoms (Figure 1, d). Despite their chemical beauty, these highly symmetrical structures are of interest from both fundamental and practical perspectives. Adamantane-like structures are usually expected to be very stable. However, this is not always true, and for reasons that are not completely understood, not all combinations of heteroatoms in the adamantane cage result in stable structures. Moreover, the synthesis of new heteroadamantanes is always tricky. From my experience, a reasonable route

 Synform **2021/08**, A132–A135 • Published online: July 20, 2021 • DOI: 10.1055/s-0040-1720531

suggested on the basis of a retrosynthetic analysis would definitely not work here. But if you are lucky, you'll find a self-assembly synthesis, which is absolutely unexpected from the first glance. In our lab, we design such self-assembly approaches to heteroadamantanes of hitherto unknown types, study their structure using experimental and computational methods, and try to find useful applications for these molecules in cooperation with our collaborators.

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

Prof. Dr. A. Sukhorukov Probably, my most significant achievement to date is the synthesis of 1,4,6,10-tetraazaadamantane ('isourotropin' or TAAD).[9] This highly symmetrical diamondoid molecule is the first isomer of hexamine (urotropin) synthesized since the discovery of the latter by the Russian chemist Alexander Butlerov in 1859.[10] Hexamine is a unique molecule both from structural and application points of view. I can mention that it is the oldest applied synthetic pharmaceutical, and the first organic compound for which X-ray diffraction analysis was performed. I believe 'isourotropin' and its derivatives will also find interesting applications in chemistry and related fields. Thus, we have shown that the incorporation of the 'isourotropin' motif into lipophilic biomolecules enhances their water solubility. We also developed a controllable click–declick methodology based on the coupling of boronic acids with quaternary derivatives of 'isourotropin'.[11] This technique is already being used by other researchers to construct click conjugates.[12] Coordination

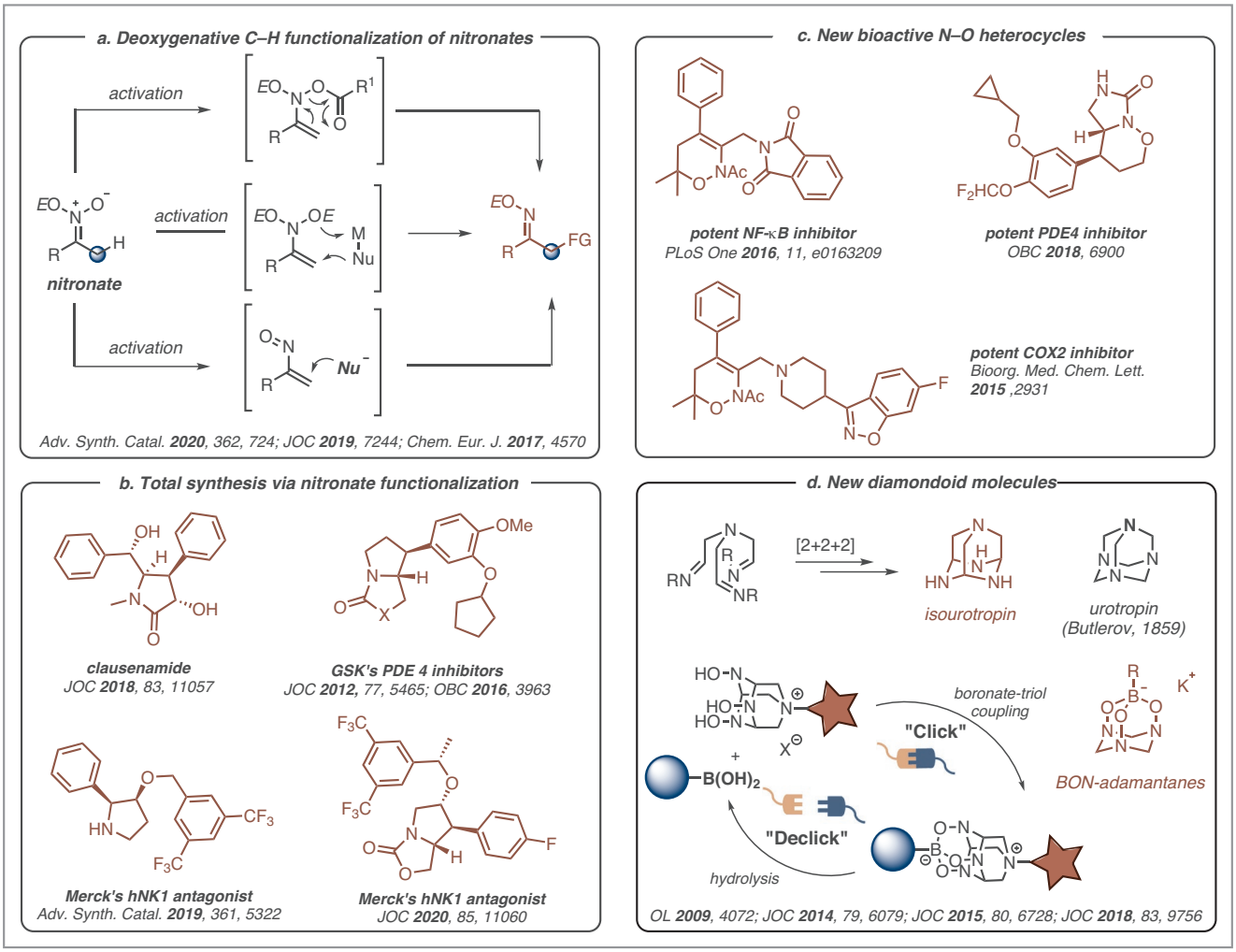


Figure 1 Overview of research areas pursued in the Sukhorukov lab

chemistry of 'isourotropin' derivatives is actively explored by inorganic chemists from the University of Idaho and the University of Marburg.[13] Finally, our colleagues recently have shown that 1,4,6,10-tetraazaadamantane derivatives enhance the thermal and photochemical stability of perovskite films.[14] I am sure we will see other examples in near future.

REFERENCES

(1) D. Kaiser, C. J. Teskey, P. Adler, N. Maulide *J. Am. Chem. Soc.* **2017**, *139*, 16040–16043.
(2) Z. Xu, H. Chen, Z. Wang, A. Ying, L. Zhang *J. Am. Chem. Soc.* **2016**, *138*, 5515–5518.
(3) A. Y. Sukhorukov *Adv. Synth. Catal.* **2020**, *362*, 724–754.
(4) A. Y. Sukhorukov *Synlett* **2020**, *31*, 439–449.
(5) E. Garo, C. M. Starks, P. R. Jensen, W. Fenical, E. Lobkovsky, J. Clardy *J. Nat. Prod.* **2003**, *66*, 423–426.
(6) K. Kaur, V. Kumar, A. K. Sharma, G. K. Gupta *Eur. J. Med. Chem.* **2014**, *77*, 121–133.
(7) K. C. Nicolaou, E. J. Sorensen *Classics in Total Synthesis: Targets, Strategies, Methods* (1st ed.); Wiley: New York, **1996**.
(8) M. Trobe, M. D. Burke *Angew. Chem. Int. Ed.* **2018**, *57*, 4192–4214.
(9) A. N. Semakin, A. Y. Sukhorukov, Y. V. Nelyubina, Y. A. Khomutova, S. L. Ioffe, V. A. Tartakovsky *J. Org. Chem.* **2014**, *79*, 6079–6086.
(10) A. Butlerow *Ann. Chem. Pharm.* **1859**, *111*, 242–252.
(11) I. S. Golovanov, G. S. Mazeina, Y. V. Nelyubina, R. A. Novikov, A. S. Mazur, S. N. Britvin, V. A. Tartakovsky, S. L. Ioffe, A. Y. Sukhorukov *J. Org. Chem.* **2018**, *83*, 9756–9773.
(12) R. H. de Vries, J. H. Viel, O. P. Kuipers, G. Roelfes *Angew. Chem. Int. Ed.* **2021**, *60*, 3946–3950.
(13) D. Premužić, M. Hołyńska, A. Ozarowski, C. Pietzonka, A. Roseborough, S. A. Stoian *Inorg. Chem.* **2020**, *59*, 10768–10784.
(14) V. V. Ozerova, I. S. Zhidkov, A. Boldyreva, N. N. Dremova, N. A. Emelianov, G. V. Shilov, L. A. Frolova, E. Z. Kurmaev, A. Y. Sukhorukov, S. M. Aldoshin, P. A. Troshin *Energies* **2021**, *14*, 669.

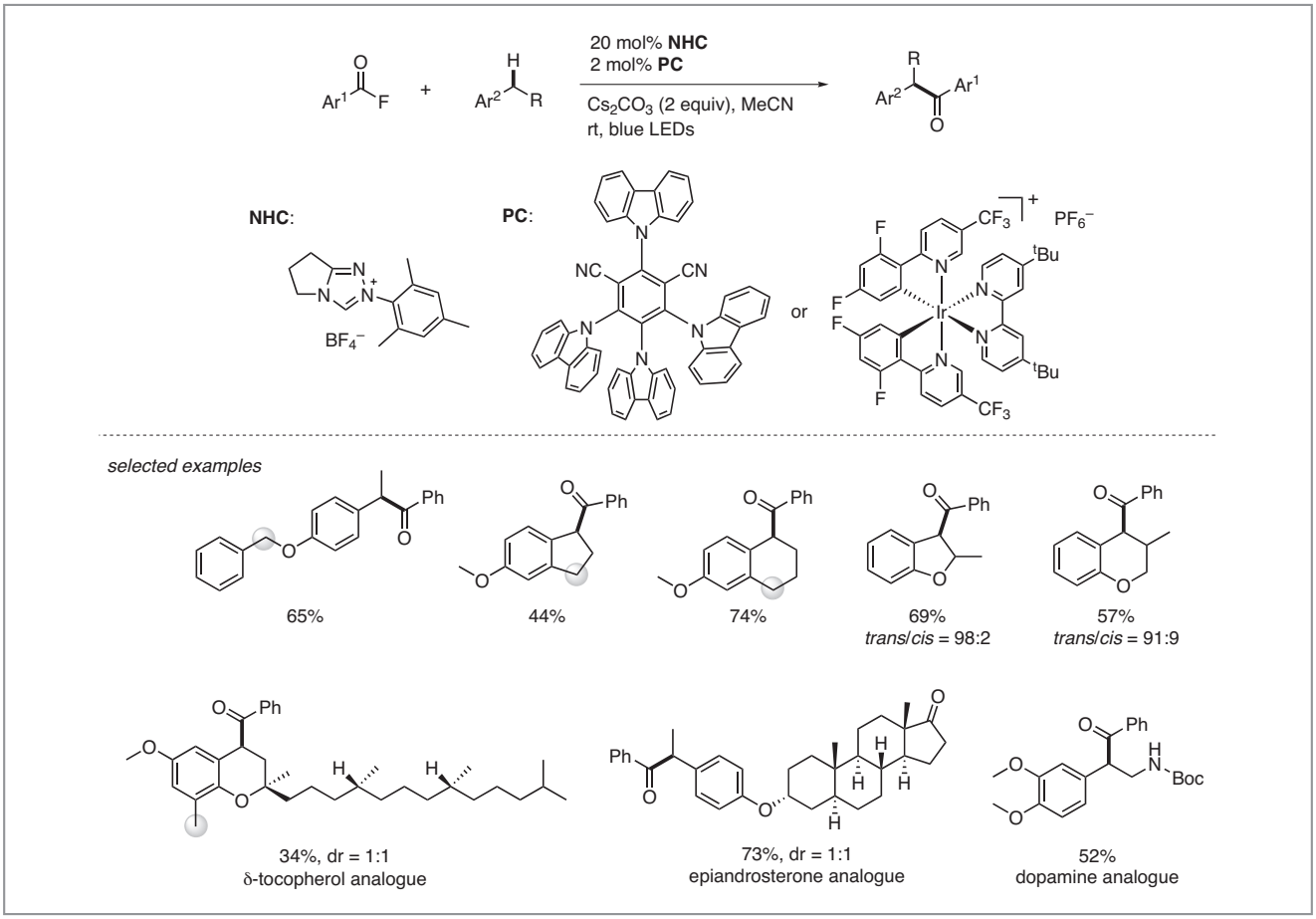
  • Published online: July 20, 2021 • DOI: 10.1055/s-0040-1720531

Benzylic C–H Acylation by Cooperative NHC and Photoredox Catalysis

Nat. Commun. **2021**, *12*, 2068; DOI: 10.1038/s41467-021-22292-z

The acylation of a C–H bond is a powerful and straightforward approach for the synthesis of ketones. "Acylation of arene sp^2 C–H bonds, as shown in classical Friedel–Crafts reactions, is very well developed, while less progress has been achieved for sp^3 C–H bond acylation," said Professor Armido Studer of the Westfälische Wilhelms-University Münster (Germany). He further argued: "Considering that many bioactive compounds contain benzylic C–H bonds in their skeletons, acylation of such sites would be highly interesting and useful, particularly if site-selective functionalization can be achieved for substrates bearing more than one benzylic C–H bond. That approach would ideally also allow for late-stage acylation of complex compounds, e.g. natural products, drugs or drug candidates."

Professor Studer's group has a long-standing interest in N-heterocyclic carbene (NHC) catalyzed radical transformations, which could offer a potential solution to the challenging issue posed by site-selective late C–H acylation. "Cross-coupling of benzylic radicals with NHC-stabilized ketyl-type radicals generated *in situ* is feasible, as realized in our recently disclosed radical alkene acyltrifluoromethylation,[1]" said Professor Studer, explaining that: "A key consideration in achieving



Scheme 1 Cooperative photoredox/NHC catalysis for site-selective acylation of benzylic C–H bonds

acylation of benzylic C–H bonds is to find an efficient way to generate benzylic radicals with concomitant single electron transfer (SET) reduction of acylazolium ions. Such acylazolium ions should be generated *in situ* by reaction of an acyl donor with the carbene catalyst, in a process that must be compatible with C-radical generation. Moreover, to close a redox catalysis chain, generation of the benzylic radical should be achieved via an SET-oxidation process, rendering the whole cascade a redox-neutral process."

Following this approach, the Münster group recently demonstrated the feasibility of the acylation of benzylic C–H bonds using cooperative NHC- and photocatalysis. The generation of the benzylic radical occurs by SET-oxidation of the arene and subsequent deprotonation. "It is notable that excellent site selectivity was observed, even for systems bearing two benzylic sites. Interestingly, the bond dissociation energy of the benzylic C–H bond is not the regiochemistry-determining factor, it is the deprotonation of the arene radical cation," said Professor Studer. He continued: "Apparently, the deprotonation approach offers an advantage over intermolecular C–H abstraction for the site-selective generation of benzylic radicals." In order to demonstrate the potential of their strategy, late-stage benzoylation of three biologically active compounds was carried out with high regioselectivities.

"Compared with other protocols for acylation of benzylic C–H bonds that proceed via metal-catalyzed or ionic pathways,[2–5] our method provides a mechanistically distinct process featuring radical–radical cross-coupling," remarked Professor Studer. He concluded: "This work opens new avenues in the area of direct C–H bond acylation and asymmetric transformations are expected."

REFERENCES

(1) Q.-Y. Meng, N. Döben, A. Studer *Angew. Chem. Int. Ed.* **2020**, *59*, 19956–19960.
(2) S. Yu, Y. Li, L. Kong, X. Zhou, G. Tang, Y. Lan, X. Li *ACS Catal.* **2016**, *6*, 7744–7748.
(3) D. A. DiRocco, T. Rovis *J. Am. Chem. Soc.* **2012**, *134*, 8094–8097.
(4) C. L. Joe, A. G. Doyle *Angew. Chem. Int. Ed.* **2016**, *55*, 4040–4043.
(5) T. Kawasaki, N. Ishida, M. Murakami *J. Am. Chem. Soc.* **2020**, *142*, 3366–3370.

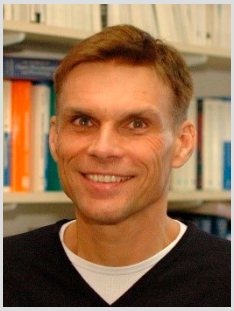
About the authors

Dr. Q.-Y. Meng

Qing-Yuan Meng received his PhD in 2013 at the Technical Institute of Physics and Chemistry, CAS (P. R. of China) under the supervision of Prof. Li-Zhu Wu and Prof. Chen-Ho Tung. He worked as an assistant professor in the same group (2013–2016) before he went to Regensburg (Germany), working with Prof. Burkhard König as a postdoctoral researcher (2016–2019). Currently, he is doing a second postdoctoral research stay with Prof. Armido Studer at the Westfälische Wilhelms-Universität Münster (Germany). His current research interests include NHC catalysis and photoredox catalysis..

L. Lezius

Lena Lezius completed her BSc in chemistry at the Westfälische Wilhelms-Universität Münster (Germany) in 2019. She has been working on her MSc in chemistry since 2019 at the same university, and is currently working on her Master's thesis under the supervision of Prof. Armido Studer. Her research interests are focused on radical reactions enabled by cooperative NHC/photoredox catalysis.



Prof. A. Studer

Armido Studer received a B.S. degree and a PhD in chemistry from ETH Zürich (Switzerland, with Prof. Dieter Seebach) in 1991 and 1995, respectively, and conducted postdoctoral research at the University of Pittsburgh (USA, with Prof. Dennis Curran) before he obtained his Habilitation at ETH Zürich in 1996. Then he moved to the Philipps-Universität Marburg (Germany), working as an associate professor (2000–2004). He has been a full professor of organic chemistry at the Westfälische Wilhelms-Universität Münster (Germany) since 2004. He is the recipient of several awards including the ERC Advanced Grant (2016) and the Pedler Award of the Royal Society of Chemistry (2019), and is an elected member of the German National Academy of Sciences 'Leopoldina' (2020).

© 2021. Thieme. All rights reserved. Synform **2021/08**, A136–A137 • Published online: July 20, 2021 • DOI: 10.1055/s-0040-1720531

Coming soon

Literature Coverage

Illuminating the Dark Conformational Space of Macrocycles Using Dominant Rotors

Literature Coverage

Regioselective Activation of Benzocyclobutenones and Dienamides Lead to Anti-Bredt Bridged-Ring Systems by a [4+4] Cycloaddition

Literature Coverage

Diastereodivergent Intermolecular 1,2-Diamination of Unactivated Alkenes Enabled by Iodine Catalysis

Further highlights

Synthesis **Review: Applications of the Horner–Wadsworth–Emmons Olefination in Modern Natural Product Synthesis**
(by C. Beemelmanns and co-workers)

Synlett **Account: Perrhenate Esters as Intermediates in Molecular Complexity-Increasing Reactions**
(by P. E. Floreancig)

Synfacts **Synfact of the Month in category "Synthesis of Natural Products and Potential Drugs": Total Synthesis of (+)-Talassimidine and (+)-Talassamine**

For current SYNFORM articles, please visit www.thieme-chemistry.com
SYNFORM issue 2021/09 is available from August 18, 2021
at www.thieme-connect.com/ejournals

Impressum

Editor
Matteo Zanda
C.N.R. – Istituto di Scienze e Tecnologie Chimiche (SCITEC)
Via Mancinelli, 7, 20131 Milano, Italy
Editorial Assistant: Alison M. Sage, synform@outlook.com

Editorial Office
Senior Director:
Susanne Haak, susanne.haak@thieme.de
Scientific Editors:
Stefanie Baumann, stefanie.baumann@thieme.de
Selena Boothroyd, selena.boothroyd@thieme.de
Michael Binanzer, michael.binanzer@thieme.de
Giuliana Rubulotta, giuliana.rubulotta@thieme.de
Kathrin Ulbrich, kathrin.ulbrich@thieme.de
Acquisition Editor:
Juan Zhang, juan.zhang@thieme.com
Senior Production Manager:
Thorsten Schön, thorsten.schoen@thieme.de
Senior Production Editor:
Thomas Loop, thomas.loop@thieme.de
Production Assistant:
Tobias Brenner, Tobias.brenner@thieme.de
Editorial Assistant:
Sabine Heller, sabine.heller@thieme.de
Marketing Director:
Julia Stötzner, julia.stoetzner@thieme.de
Postal Address: Chemistry Journals, Editorial Office, Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany.
Homepage: www.thieme-chemistry.com

Publication Information
Synform will be published 12 times in 2021 by Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, and is an additional online service for Synthesis, Synlett and Synfacts.

Product Names
Product names which are in fact registered trademarks may not have been specifically designated as such in every case. Thus, in those cases where a product has been referred to by its registered trademark it cannot be concluded that the name used is public domain. The same applies to labels, names or other signs.

Ordering Information for Synthesis, Synlett and Synfacts
The Americas: Thieme New York, 333 Seventh Avenue, New York, NY 10001, USA.
Via e-mail: customerservice@thieme.com
Via website: www.thieme-chemistry.com
Phone: +1 212 760 0888; Fax: +1 212 947 0108
Order toll-free within the USA: +1 800 782 3488

Europe, Africa, Asia, and Australia: Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany.
Via e-mail: customerservice@thieme.de
Via website: www.thieme-chemistry.com
Phone: +49 711 8931 421; Fax: +49 711 8931 410

Current list prices are available through www.thieme-chemistry.com.

Online Licensing Information
The online versions of Synform as well Synthesis, Synlett, Synfacts and SynOpen are available through www.thieme-connect.com/products/ejournals/journals) where it is also possible to register for a free trial account. For information on multi-site licenses and pricing for corporate customers, as well as backfiles, please contact our regional offices:

The Americas: esales@thieme.com, phone: +1 212 584 4695
Europe, Africa, Asia (ex. India), and Australia: eproducts@thieme.de, phone: +49 711 8931 407
India: eproducts@thieme.in, phone +91 120 45 56 600

Manuscript Submission to Synthesis, Synlett, and SynOpen
Manuscript submissions will be processed exclusively online via http://mc.manuscriptcentral.com/synthesis, http://mc.manuscriptcentral.com/synlett and http://mc.manuscriptcentral.com/synopen, respectively. Please consult the Instructions for Authors before compiling a new manuscript. The current version and the Word template for manuscript preparation are available for download at www.thieme-chemistry.com.