Expeditious Diastereoselective Synthesis of Elaborated Ketones via Remote Csp³–H Functionalization

Highlighted article by W. Shu, A. Lorente, E. Gómez-Bengoa, C. Nevado
Dear Readers,

In this brief editorial I would like to anticipate that the next issue of SYNFORM is going to be a VERY special one. Guess why. It is a secret for now, I am not going to give any running commentary of our plans for the moment, but our most loyal readers may have already understood. Just a tip: it is an anniversary. Could it be my wedding anniversary? Or maybe when our beloved cat Zorro joined the Zanda family? Or perhaps my 25th birthday? Naaahhh... something more important, way more important... bear with me for another month and you will find out! For the moment, let me just introduce this April issue of SYNFORM. The first story covers a new hypervalent iodine-promoted process – developed by M. Fujita (Japan) – that produces fused cyclic ethers and amines in enantioselective manner from alkenes. The second article is a Young Career Focus interview with T. Noël (The Netherlands) who tells us about his scientific interest and research plans. The third contribution leads us to the novel radical reaction for synthesizing arylboronates developed by L. Jiao (P. R. of China). And the closing article takes us to the nearly uncharted territory of stereo-controlled remote Csp³–H functionalization producing structurally elaborated ketones developed by C. Nevado (Switzerland). Once you have read this one, look out for the next SYNFORM issue!

Enjoy your reading!

Martino Zanda
Metal-Free Enantioselective Oxidative Arylation of Alkenes: Hypervalent-Iodine-Promoted Oxidative C–C Bond Formation

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The oxidative 1,2-difunctionalization of alkenes with carbon nucleophiles represents a great challenge in synthetic organic chemistry and the development of metal-free reactions capable of efficiently producing complex and functionalized molecules is the object of significant research efforts worldwide.

The group of Professor Morifumi Fujita from the University of Hyogo (Japan) has recently been working on this problem. “In this type of functionalization, the alkene is initially oxidized and then receives nucleophilic attacks,” said Professor Fujita. He continued: “Oxidation of the carbon nucleophile needs to be avoided; however, more reactive carbon nucleophiles are more easily oxidized. Thus, the reactivity of both alkene and carbon nucleophile must be tuned. To enhance the reactivity of the alkene towards oxidation, we focused our attention on achieving nucleophilic assistance in the oxidation.”

“Our extensive screening of reaction substrates and conditions allowed us to find that 6-phenyl-1-silyloxy-hex-3-ene 1 was the most suitable alkene substrate for the oxidative carbon–carbon bond formation (Scheme 1),” explained Professor Fujita, continuing: “It is remarkable that the silyloxy group does not act as a protection group; however, it preferentially promotes the nucleophilic oxycyclization to yield 2. The nucleophilic assistance of the silyloxy group was also observed in the oxycyclization of ortho-(4-silyloxybut-1-enyl)benzoate with a hypervalent iodine reagent.”

The oxidative arylation first proceeds through enantioface-differentiating electrophilic addition of lactate-based chiral hypervalent iodine reagent 3 to the alkene (Scheme 1). The following oxycyclization may be accelerated owing to inductive electron-donation of the silyl group. Nucleophilic attack of the phenyl group completes the double cyclization yielding 2.

Professor Fujita said: “The lactate-based chiral hypervalent iodine reagent has been used for several types of highly enantioselective oxidations since our research group first reported it in 2007.2 Electrospray ionization mass spectrometry measurements indicate interaction of the lactate moiety with the electron-deficient iodine atom of 3. We postulate that the interaction may induce pseudo chirality at the iodine center leading to high enantioselectivity.”

Thanks to the concise preparation of 3 and easy derivatization of the lactate side chain, the reagent design allowed the authors to achieve further development of the enantioselective oxidation with hypervalent iodine.

As shown in Scheme 2, a wide range of both electron-rich and electron-deficient arenes were found to participate in the oxidative arylation. “Although the electron-deficient aryl group has lower reactivity as a carbon nucleophile, even the CF3 substrate yielded the oxidative arylation product 2f,” said Professor Fujita. “Desymmetrization in the oxidative arylation was also achieved to yield 2h as the single diastereomer. Aminoarylation also proceeded to yield methanesulfonyl...”

Scheme 1 Plausible mechanism for enantioselective oxyarylation
(Ms) amide 2k and (2-nitrophenyl)sulfonyl (Ns) amide 2l. The enantioselective aminoarylation provided optically active hexahydrobenz[e]indoles, which are candidate agonists/antagonists for dopamine and serotonin receptors.

Professor Fujita concluded: “The oxidative arylation provides a single-step construction of the polycyclic skeleton with functional groups in an enantioselective manner. This approach also involves a unique utilization of the silyloxy group. We hope that this concept will find further applications in other reactions.”

Scheme 2 Selected scope of the enantioselective oxidative arylation

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About the authors

Mio Shimogaki was born in Hyogo (Japan) in 1989. She completed her B.Sc. at the University of Hyogo (Japan) in 2012. Since April 2012 she has been carrying out her graduate studies on the development of novel oxidation reactions with hypervalent iodine and application to asymmetric syntheses of bioactive natural products at the same university. In March 2017 she will complete her doctoral thesis on oxidative cyclization of alkene using chiral hypervalent iodine(III). Her research interest focuses on the development of new strategies for oxidation with hypervalent iodine.

Morifumi Fujita studied chemistry at Osaka University (Japan) and received his B.E. in 1991. He continued his graduate work on photo-induced electron transfer chemistry under the supervision of Dr. Shunichi Fukuzumi. After completing his M.E. in 1993, he joined the group of Professor Setsuo Takamuku at the same university to carry out his Ph.D. studies as a research fellow of the Japan Society for the Promotion of Science. In 1995, he joined the group of Professor Akira Tai at the Himeji Institute of Technology (Hyogo, Japan) as a research associate. After receiving his doctoral degree from Osaka University in 1997, he carried out postdoctoral work with Professor Steven V. Ley at University of Cambridge (UK) for one year. He returned to the Institute of Technology and began the work on hypervalent iodine chemistry with Professor Tadashi Okuyama. In 2006, he was promoted to Associate Professor at the University of Hyogo. His current research interests focus on the chemistry of reactive intermediates and hypervalent iodine, which are applied to stereoselective reactions and total synthesis.

Takashi Sugimura graduated from Osaka University (Japan) in 1979 and received his Ph.D. in 1984 under the guidance of Professor Ichiro Murata. After working as a postdoctoral fellow at Ohio State University (USA) for two years, he moved to the Himeji Institute of Technology (Japan) in 1986. He became an Associate Professor in 1994. He has been a Full Professor at the University of Hyogo (Japan) since 2006. He has been studying in the fields of both organic synthesis and asymmetric hydrogenation catalysis. In 1995, he received the award for Excellent Young Scientists from The Society of Organic Synthetic Chemistry, Japan. In the field of asymmetric hydrogenation, he is known as a record maker of heterogeneous asymmetric catalysis.
Young Career Focus: Professor Timothy Noël (Eindhoven University of Technology, The Netherlands)

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 Professor Timothy Noël (Eindhoven University of Technology, The Netherlands).

INTERVIEW

SYNFORM What is the focus of your current research activity?

Prof. T. Noël The Noël group is interested in the development of new enabling tools which assist chemists in their daily job and allow them to carry out hazardous manipulations without compromising personal and environmental safety. Key in our strategy is the use of continuous-flow technology. Continuous-flow reactors have been increasingly used in synthetic organic chemistry to facilitate chemistries which are otherwise difficult to carry out. This includes gas-liquid reactions, photochemical transformations, chemistry utilizing hazardous compounds, extreme reaction conditions and multistep reaction sequences. Underlying all these advances are chemical engineering principles that enable chemical processes to be carried out under perfectly controlled reaction conditions.

Taking advantage of these tools, our ambition is to develop new catalytic strategies for chemical synthesis that engage novel reactivity concepts which facilitate the rapid generation of biologically active molecules. By combining these tools and new reactivity concepts, we strive in the long run to develop an automated and chemo-catalytic equivalent to Nature’s biosynthetic machinery that will build essentially any molecule on demand.

Our approach is unique in the sense that we position ourselves at the interface of organic synthetic chemistry and chemical engineering. I have an M.Sc. in chemical engineering and I obtained my Ph.D. in organic synthetic chemistry. My group consists of both synthetic chemists and chemical engineers. Consequently, we are able to rapidly recognize those synthetic problems which would benefit from microreactor technology and to tackle the problem from a different angle than was done traditionally.
SYNFORM  When did you get interested in synthesis?

Prof. T. Noël I got interested in organic synthesis in high school. In my final year, we got a basic introduction to organic chemistry and I immediately realized that this was a topic that seemed natural to me. After the examinations, the teacher came to me and said that I had talent for organic chemistry and that I should do something with it. I never forgot those encouraging remarks and every time I needed to make a decision about my career, I chose the more synthetic career path.

Next, I started my academic education and I enrolled in a chemical engineering program. The reason I chose chemical engineering is because of the large breadth of different topics it provides. It not only offers chemistry subjects but also courses on mathematics, mechanics, automation, electricity, etc. Also, we got some basic organic chemistry courses and again I was deeply interested in the subject. I decided in my final year that I should do something with it and, consequently, I performed my M.Sc. final thesis in the group of Johan Van der Eycken on the synthesis of a fluorescent label for labelling a peptidic inhibitor of HIV. I liked this synthetic experience so much that I decided to stay in that group and perform Ph.D. studies in organic synthesis. In 2009, I obtained my Ph.D. and, subsequently, I went to the USA to do a postdoc at MIT in the group of Stephen L. Buchwald. There, I started for the first time in my life to work with flow microreactors. Immediately, I realized that all the pieces fell into place and I deeply enjoyed the project. This was the ideal subject for me as knowledge about both organic synthesis and chemical engineering was required to come to a satisfactory result.

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

Prof. T. Noël Organic synthesis is an indispensable part of many related disciplines, for example chemical biology, materials science, medicinal chemistry, nanotechnology, molecular motors, etc. Without organic synthesis, these disciplines would simply not be possible. It is therefore crucial that we keep training future student generations in this important discipline.

I believe personally that more and more synthetic processes will be automated in the future. If you read the recent reports on this subject, then you will learn that a combination of smart programming and flow reactors allows computers to optimize chemical reactions. This type of work remains a time-consuming undertaking for the chemist but can now be done overnight with great success. Moreover, it also avoids exposure to hazardous chemicals and is therefore perfectly suitable for carrying out those optimizations which pose a high risk to the practitioner (e.g. working with oxygen gas under high pressure, working with HCN, or other toxic substances). This does not mean that chemists will be entirely replaced. Chemists will still be required to monitor the processes, to provide input and to make a final selection in what is worth pursuing and what is not. Nevertheless, there is still a lot of work on the plate to really make these automated optimization robots widely applicable and fail-proof.

Another important role for organic synthesis is the development of milder transformations which are driven by sustainable activation modes, for example photoredox catalysis, electrochemistry, and other room-temperature catalysis modes. Currently, thermochemical activation is one of the most-used ways to drive chemical reactions forward. Strikingly, industrial process heating operations account for 70% of the total energy use. The development of new synthetic methods and processes driven by renewable energy sources, for example solar and wind energy, would be a tremendous improvement. Here as well, continuous-flow chemistry can help to maximize the energy efficiency of these transformations, for example by overcoming the Bouguer–Lambert–Beer limitation of photochemistry.

SYNFORM  Your research group is active in the area of photoredox catalysis and C–H activation. Could you tell us more about your research and its aims?

Prof. T. Noël Since the start of my independent academic career in 2012, my group has been intrigued by visible light photoredox catalysis. Photoredox catalysis provides neat solutions for previously elusive organic transformations (broad scope, high functional group tolerance, mild reaction conditions). We have developed a number of different photocatalytic transformations over the years, including the Stadler–Ziegler reaction, trifluoromethylation reactions, oxidation chemistry and disulfide formation. Typically, we select those transformations which have a gaseous reagent. Such gas-liquid reaction mixtures can be handled in flow very well and mass transfer limitations are minimized. However, one of the biggest hurdles of photoredox chemistry was its scalability and we have worked on continuous-flow microreactor solutions to overcome these challenges. We have also studied the engineering aspects concerned with photocatalytic gas–liquid reactions in flow. This includes the potential (i) to extract kinetics efficiently, (ii) to increase the energy efficiency of the photomicroreactor and (iii) to scale the chemistry up with a numbering-up strategy.
Similarly, we have selected C–H activation chemistry as a notable field where continuous-flow processing can make a difference. Again, we try to select reactions with a gaseous reagent, for example oxygen. These transformations are very hard to carry out in standard batch labware. Due to improved gas–liquid characteristics and excellent heat transfer, we were able to reduce the reaction times from hours to the minute range.

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

**Prof. T. Noël** This is a hard question as I like each publication we have published. However, our recent discovery on Luminescent Solar Concentrator based photomicroreactors is definitely something special (D. Cambié, F. Zhao, V. Hessel, M. G. Debije, T. Noël 'A leaf-inspired luminescent solar concentrator for energy-efficient continuous-flow photochemistry' *Angew. Chem Int. Ed.* 2017, 56, 1050). Previously, solar photochemistry was done by placing the reaction flask outside in the sun. Reaction times were typically in the range of several hours to days depending on the amount of light. So, almost nobody uses solar energy to power their reactions due to the low solar intensity at higher latitudes. However, our novel leaf-inspired photomicroreactor (see Figure 1) allows efficient harvesting of solar energy by using a luminescent solar concentrator. The reactor is fabricated from PDMS polymer which contains fluorescent dyes that can capture solar light and, due to internal reflection, the re-emitted light is guided towards the reaction channels. Moreover, the emission profile of the embedded dye was matched with the absorption spectrum of the photocatalyst which flows in the reaction channels. Due to this spectral overlap, the reaction mixture flowing in the channels experiences an amplified photon flux that is wavelength-concentrated to an energy window where the reaction occurs optimally. Interestingly, our device works particularly well in those regions where sunlight is not abundant. The device can capture diffuse light and still direct this light efficiently to the reaction channels. The ability to concentrate energy aids in enhancing the chemical reactivity in the reaction channels and makes solar energy a viable activation mode in organic synthesis.

![Figure 1 Luminescent solar concentrator based photomicroreactors which allow for increased harvesting of solar light for application in organic synthetic photochemistry](image)
Arylboronates are widely used in organic chemistry, and methods that could produce arylboronates from easily available starting materials in a transition-metal-free manner are in high demand. Although there are several precedents in the literature, problems such as the expense of the boron source, low reactivity, and operational inconvenience remain to be solved.

The group of Professor Lei Jiao at Tsinghua University (Beijing, P. R. of China) studied the mechanism of carbon–halogen bond activation of haloarenes by small organic molecules, which is a key step in base-promoted homolytic aromatic substitution (BHAS) reactions (J. Am. Chem. Soc. 2016, 138, 7151; Chem. Eur. J. 2017, 23, 65). Professor Jiao said: “As a consequence, we were interested in utilizing the aryl radical generated in this process to synthesize more useful molecules, rather than merely producing biaryl compounds. Therefore, we hoped to synthesize arylboronates from haloarenes using this carbon–halogen bond activation strategy.”

With this idea in mind, the group first tried to capture the aryl radical directly by using bis(pinacolato)diboron (B$_2$pin$_2$). “We simply added B$_2$pin$_2$ to a BHAS reaction system (ArI/DMEDA/t-BuOK in benzene),” said Professor Jiao. “However, only the biaryl product (ArPh) was found and no borylation product could be observed. It seemed that the aryl radical reacted with B$_2$pin$_2$ in a low efficiency, as shown in several literature reports.” Professor Jiao’s group stopped attempting this reaction for months, until Li Zhang – a PhD student – found a new publication that reported the formation of pyridine-stabilized boryl radical by the reaction between 4-cyanopyridine and B$_2$pin$_2$ (Angew. Chem. Int. Ed. 2016, 55, 5985). “An idea soon came to his mind that the pyridine-stabilized boryl radical might trap the aryl radical more easily than B$_2$pin$_2$.

![Scheme 1](image-url)
itself to generate arylboronate, thanks to the persistent radical effect,” said Professor Jiao. “We discussed this new idea and agreed that it was worth trying.”

He continued: “Indeed when we added a catalytic amount of 4-cyanopyridine to the reaction system, the arylboronate product was observed. After optimization of the reaction conditions, the designed borylation reaction for aryl iodides was realized in good yields. However, aryl bromides were found to be less suitable substrates using the conditions above. We therefore sought to boost their reactivity by tuning the electronic nature of the pyridine catalyst, but failed. Fortunately, we finally solved the problem by replacing the para-cyano group in the pyridine catalyst by a para-phenyl group, which was thought to further stabilize the boryl radical.”

The optimized conditions of the borylation reaction were at that point very simple: just mixing each reaction component and the solvent in a vessel and heating in an oil bath was sufficient. “The reaction is best performed under inert atmosphere, but it is not very sensitive to air – reaction under air produced the desired borylation product with slightly decreased yield,” explained Professor Jiao. “The reaction is scalable if performed in a flask, producing arylboronates on >1 g scale in one batch. The scope of the borylation reaction is broad, including aryl iodides, aryl bromides, activated aryl chlorides, and alkenyl iodides (Scheme 1).” These features make this method rather attractive for diverse synthetic applications. In particular, for the borylation of aryl iodides, inexpensive pyridine could be used as the catalyst instead of 4-phenylpyridine, making the synthesis more cost-effective. “We believe that this reaction could serve as a good complement to the present synthetic methods for producing arylboronates,” said Professor Jiao.

The mechanism of the reaction is also intriguing. Although experimental results supported the intermediacy of the aryl radical in the borylation process, another question still remained: whether the aryl radical reacts with the pyridine-stabilized boryl radical (the designed radical coupling pathway) or with the ate complex formed by B₂pin₂ and MeOK (the Sₘᵣ₁ pathway). “To solve this problem, we designed a series of competition experiments and found that the preference for borylation compared with a hydrogen atom transfer probe was favored by increasing the amount of the pyridine catalyst,” said Professor Jiao. He concluded: “This piece of evidence strongly supported the C–B bond formation through the interaction between an aryl radical and a pyridine-related boryl species, rather than the ate complex or B₂pin₂.”

Li Zhang obtained his B.Sc. degree in chemistry from China Agricultural University (P. R. of China) in 2015. In the same year, he joined Professor Jiao’s group at Tsinghua University (P. R. of China) as a Ph.D. candidate. His research interest is the mechanism of radical-based cross-coupling reactions.

Lei Jiao studied at Peking University (Beijing, P. R. of China) where he received his B.Sc. (2005) and Ph.D. degrees (2010) in chemistry. After postdoctoral research with Professor Thorsten Bach at Technische Universität München (Germany) from 2010 to 2013, he started his independent career as a principle investigator in the Center of Basic Molecular Science at Tsinghua University (P. R. of China) in January 2014. His research group focuses on mechanistic studies of organic reactions, mechanism-based design and development of new catalytic systems, and their application in natural product synthesis. He has received the Thieme Chemistry Journals Award (2014) and Qiu Shi Outstanding Young Scholar Award (2015).
Selective C–H functionalization reactions offer new strategic opportunities for the rapid assembly of molecular complexity. However, and despite substantial efforts particularly in the field of transition-metal catalysis, examples of non-directed, remote Csp³–H activation to forge complex carbon frameworks remain scarce due to the kinetic stability and thus intrinsic challenge associated with the chemi-, regio- and stereoselective functionalization of aliphatic C–H bonds. Professor Cristina Nevado at the University of Zurich (Switzerland) is interested in exploring new research avenues in the area of selective C–H bond activation. She said: “Radical-centered C–H functionalizations represent a distinct option to activate isolated, aliphatic C–H bonds via an H-atom abstraction mechanism as seminally exemplified by the Hofmann–Löffler–Freytag (HLF) reaction. Typically, Csp³–H functionalizations using 1,n-H-transfer rely on pre-formed radical precursors such as Csp²–halide bonds, azides, amidines, etc. Due to the highly reactive nature of the free-radical species involved, reaction control in terms of stereo- and site-selectivity remains challenging and thus only a few applications in complex settings have been reported thus far.” On the other hand, alkyl carboxylic acids are ubiquitous in nature and can be readily found in both natural products as well as in commercial chemical supplier catalogues. “The carboxylic group is typically stable and eminently diversifiable owing to the field of combinatorial chemistry, in which carboxylic acids are the ‘workhorse’ building block,” said Professor Nevado. She continued: “Recently, our group has described a radical-mediated, directing-group-free regioselective 1,5-hydrogen transfer of unactivated Csp³–H bonds followed by a second Csp²–H functionalization utilizing alkyl carboxylic acids and vinyl azides as starting materials to produce a variety of elaborated fused ketones with exquisite stereoselectivity (Scheme 1). This study demonstrates that aliphatic acids can be strategically harnessed as 1,2-diradical synths and that secondary aliphatic C–H bonds can be engaged in stereoselective C–C bond-forming reactions, highlighting the potential of this protocol for target-oriented natural product and pharmaceutical synthesis.”

“The presence of electron-withdrawing groups (ester, fluoro, chloro or bromo) in the para-position of the aryl vinyl azide moiety proved to be amenable to the standard reaction conditions,” said Professor Nevado. She added: “Synthetically useful yields were also obtained with substrates bearing electron-donating groups at the para position. 2-Fluorobenzene vinyl azide could be efficiently engaged in this reaction. 3-Fluoro-, 3,4-difluoro-, 3-methyl- and 3-methoxy-substituted substrates produced 3,4-dihyronaphthalen-1(2H)-ones in good yields with moderate ortho-regioselectivities. In contrast, 3-trifluoromethyl- and 3-tert-butyl-substituted substrates favored the para-cyclized adducts in 6:1 and >20:1 ratio, respectively. These results clearly indicate that the regioselectivity is dictated by both the steric and electronic nature of the meta-substituents in the starting material. Heteroaromatics could also be selectively incorporated as demonstrated by the successful reaction of a quinoline derivative. It is important

**Scheme 1** Synthesis of elaborated ketone scaffolds enabled by remote Csp³–H functionalization (new bonds highlighted in bold)
to point out that only syn-diastereoisomers are observed in these transformations (Figure 1)."

Different aliphatic acids were also studied (Figure 2). "Five- and seven-membered tertiary carboxylic acids could be easily incorporated in this reaction, representing a straightforward route to the core structure of the hamigerans A and B, secondary metabolites with promising cytotoxic as well as potent antiviral activities," explained Professor Nevado. She continued: "Acyclic substrates were also highly efficient partners in these transformations so that fully aliphatic as well as homobenzylic carboxylic acids bearing both electron-donating and electron-withdrawing groups could be efficiently coupled under the reported conditions. Secondary carboxylic acids were also evaluated. A 2-tetrahydronaphthyl derivative produced the desired hexahydrochrysene-based ketone in synthetically useful yield whereas β,γ-disubstituted 3,4-dihydropyrrthalen-1(2H)-ones could be isolated in moderate to good yields as single diastereoisomers. The reaction protocol is also compatible with amino acids so that phenylalanine derivatives could be used in this reaction. Both benzofuran and quinoline derivatives proved to be amenable to the standard reaction conditions in the presence of 2,2-dimethyl-3-phenylpropanoic acid, delivering tricyclic adducts, respectively. X-ray diffraction analysis confirmed the structural assignment..."
of the reaction products and the trans-relative configuration of the only diastereoisomer observed in the reaction of secondary acyclic substrates.”

The synthetic utility of these transformations was further demonstrated by the efficient conversion of (tert-butoxycarbonyl)phenylalanine into a tetralone precursor which, after four steps, can be transformed into trans-1-phenyl-2-(dimethylamino)tetralin, which was previously reported to be an efficient ligand for human histamine H1 receptors with the potential to treat neurodegenerative and neuropsychiatric disorders (Scheme 2A). “We also sought to explore the possibility of applying this reaction in the context of a structure-diversification natural product synthesis setting,” explained Professor Nevado. She continued: “To this end, we were pleased to observe the successful conversion of estrone-derived vinyl azide with 2,2-dimethyl-3-phenylpropanoic acid into the corresponding pentacyclic adduct (Scheme 2B). These transformations highlight the potential of this methodology to broaden the structural diversity of highly complex biologically relevant blueprints and to impact SAR optimization in medicinal chemistry campaigns.”

“In summary, a straightforward route to a variety of elaborated fused ketones is presented here based on a radical-mediated stereoselective C–H functionalization relay strategy,” said Professor Nevado. The reaction proceeds through a 1,5-H transfer enabled by a directing-group-free remote Csp3–H activation, followed by a Csp2–H functionalization in an intricate radical cascade. The use of vinyl azides and aliphatic acids circumvents the traditional multi-step synthesis of a pre-functionalized H-radical transfer precursor. Notably, aliphatic acids serve as 1,2-diradical equivalents in these transformations in which two C–C bonds and one C=O bond are formed in a single synthetic operation. Professor Nevado said: “While further experiments will be needed to unravel the full mechanistic scenario underlying these transformations, preliminary studies suggest that the 1,5-H transfer is connected to the reaction rate-determining step. The synthetic utility of this methodology was successfully demonstrated by the efficient synthesis of bioactive molecules and late-stage functionalization of natural products.” She concluded: “We believe this work showcases the potential of hydrogen shifts as a useful synthetic tool for undirected inert aliphatic C–H activation in the context of both pharmaceutical and natural product synthesis.”

Scheme 2 Synthetic applications [standard conditions: (A) Ag2Co3 (30 mol%), acetone (0.2 mL), MeCN (0.5 mL); (B) like A, 2,6-lutidine (1.2 equiv)]
**About the authors**

**Cristina Nevado** received her Ph.D. from the Autonoma University of Madrid (Spain) working with Professor Antonio M. Echavarren. After a postdoctoral stay in the group of Professor Alois Fürstner at the Max-Planck-Institut für Kohlenforschung (Germany), she started her independent career as an Assistant Professor at the University of Zurich (Switzerland) in 2007, being promoted directly to Full Professor in 2013. Cristina has been awarded the Chemical Society Reviews Emerging Investigator Award and the Thieme Chemistry Journals Award in recognition of her contributions in the field of synthetic organic chemistry in 2011 and the Werner Prize of the Swiss Chemical Society in 2013. In 2012, she received an ERC Junior Investigator grant. Rooted in the wide area of organic chemistry, her group is interested in the development and fundamental mechanistic understanding of new organometallic reactions and their application in complex chemical synthesis.

**Dr. Wei Shu** received his B.S. at Nankai University (P. R. of China) and Ph.D. at Shanghai Institute of Organic Chemistry (SIOC, P. R. of China) under the supervision of Professors Shengming Ma and Guochen Jia. After a postdoctoral stay in the research group of Professor Stephen L. Buchwald at MIT (USA), he joined Professor Cristina Nevado’s group at the University of Zurich (Switzerland) in 2015 as a postdoctoral associate. His research interests focus on the development of remote C–H functionalization reactions.
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