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

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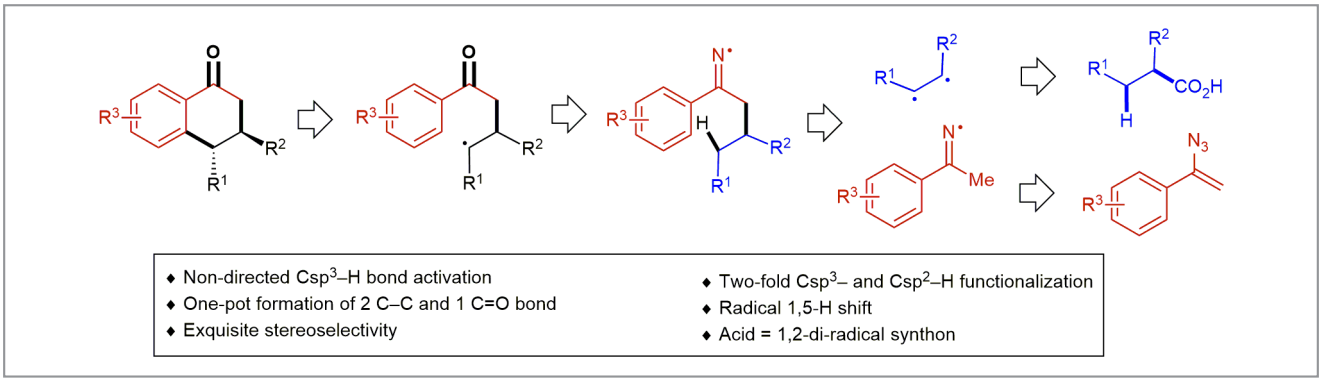
Selective C–H functionalization reactions offer new strategic opportunities for the rapid assembly of molecular complexity. However, and despite substantial efforts particularly in the field of transition-metal catalysis, examples of non-directed, remote Csp³–H activation to forge complex carbon frameworks remain scarce due to the kinetic stability and thus intrinsic challenge associated with the chemo-, 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 synthons 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-dihydronaphthalen-1(2*H*)-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)

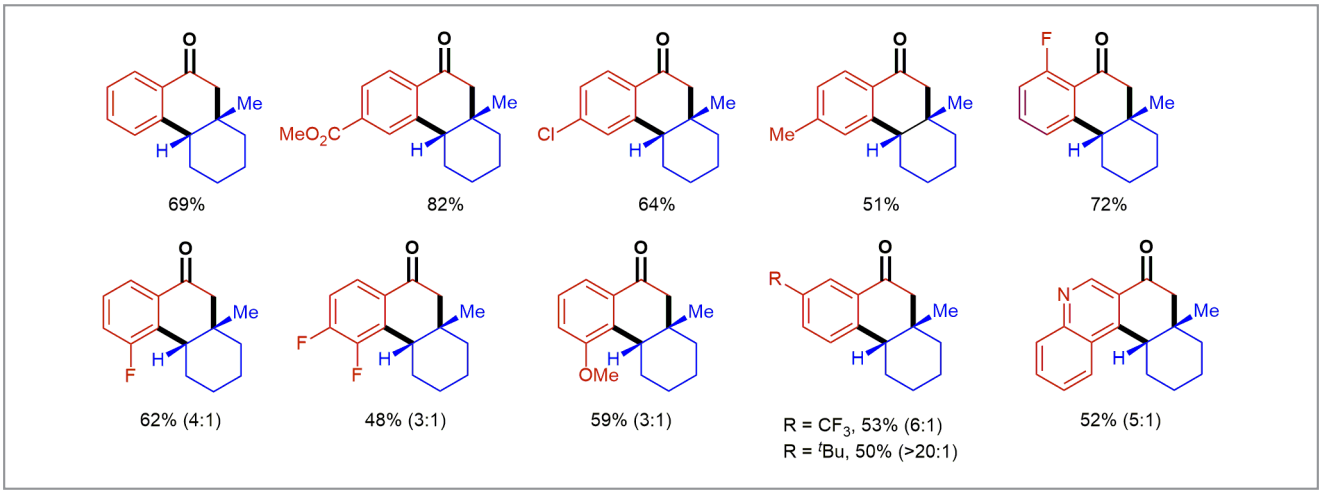


Figure 1 Selected examples for vinyl azides; standard reaction conditions involve: vinyl azide (1.5 equiv), carboxylic acid (1.0 equiv), Ag_2CO_3 (0.3 equiv) and $K_2S_2O_8$ (2.0 equiv) in MeCN–acetone–H_2O (2.5:1:7.5 ratio), 50 °C, 10 h.

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-dihydronaphthalen-1(2*H*)-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

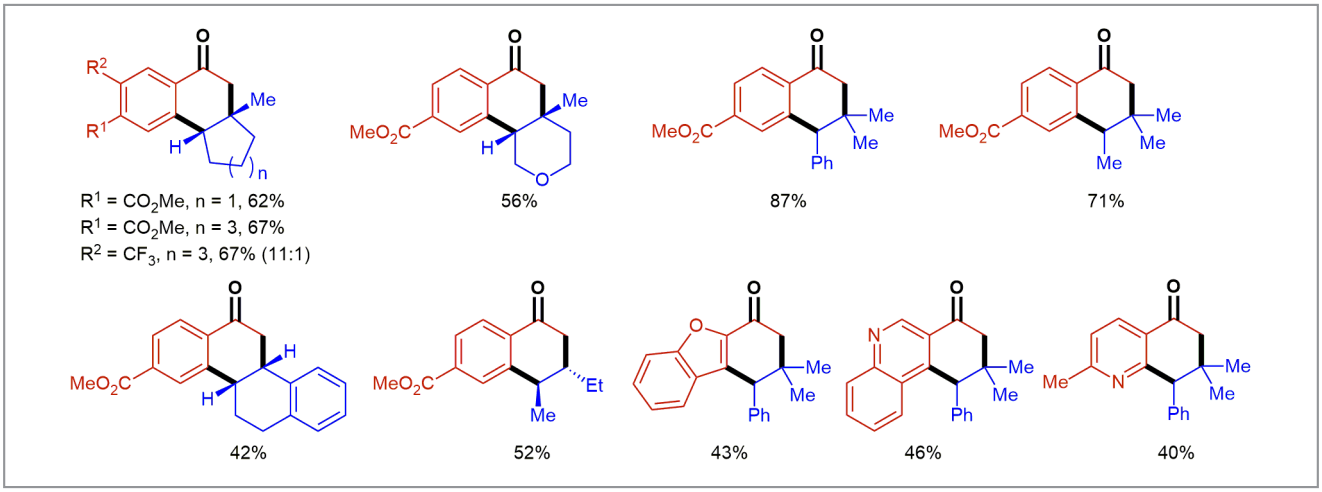
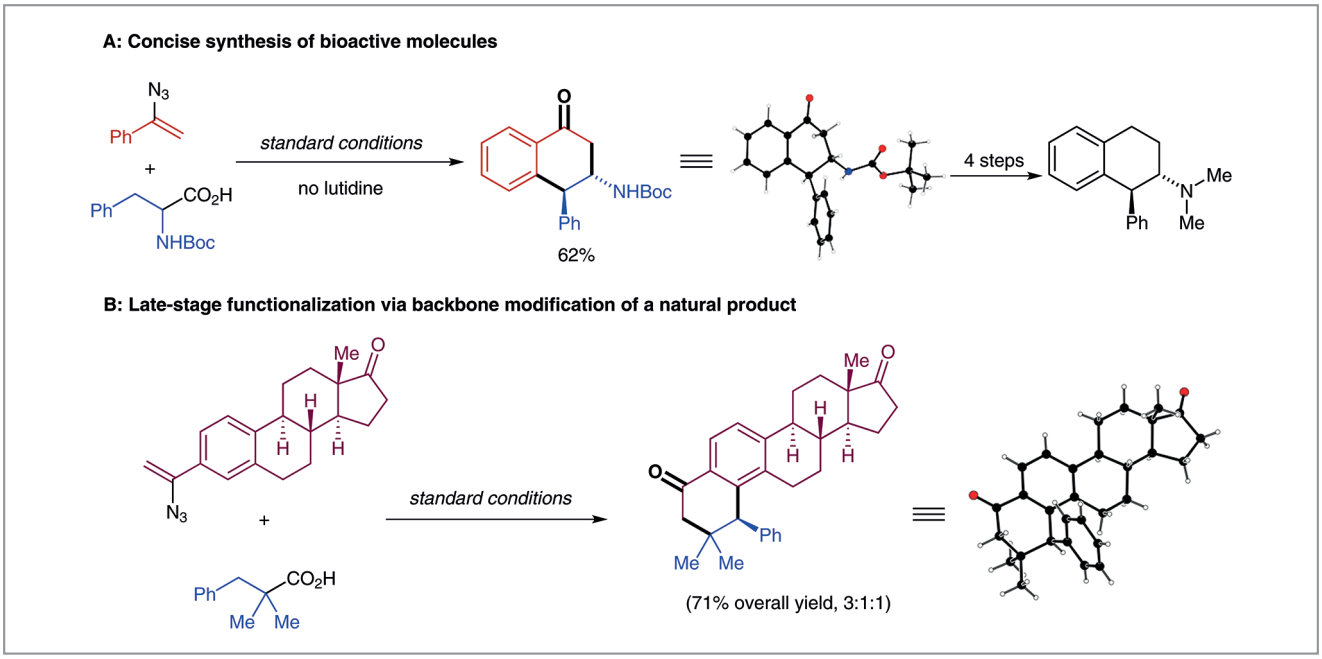


Figure 2 Selected examples for aliphatic carboxylic acids

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 Csp^3–H activation, followed by a Csp^2–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**) Ag^2Co^3 (30 mol%), acetone (0.2 mL), MeCN (0.5 mL); (**B**) like **A**, 2,6-lutidine (1.2 equiv)]

About the authors

Prof. C. Nevado

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. W. Shu

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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