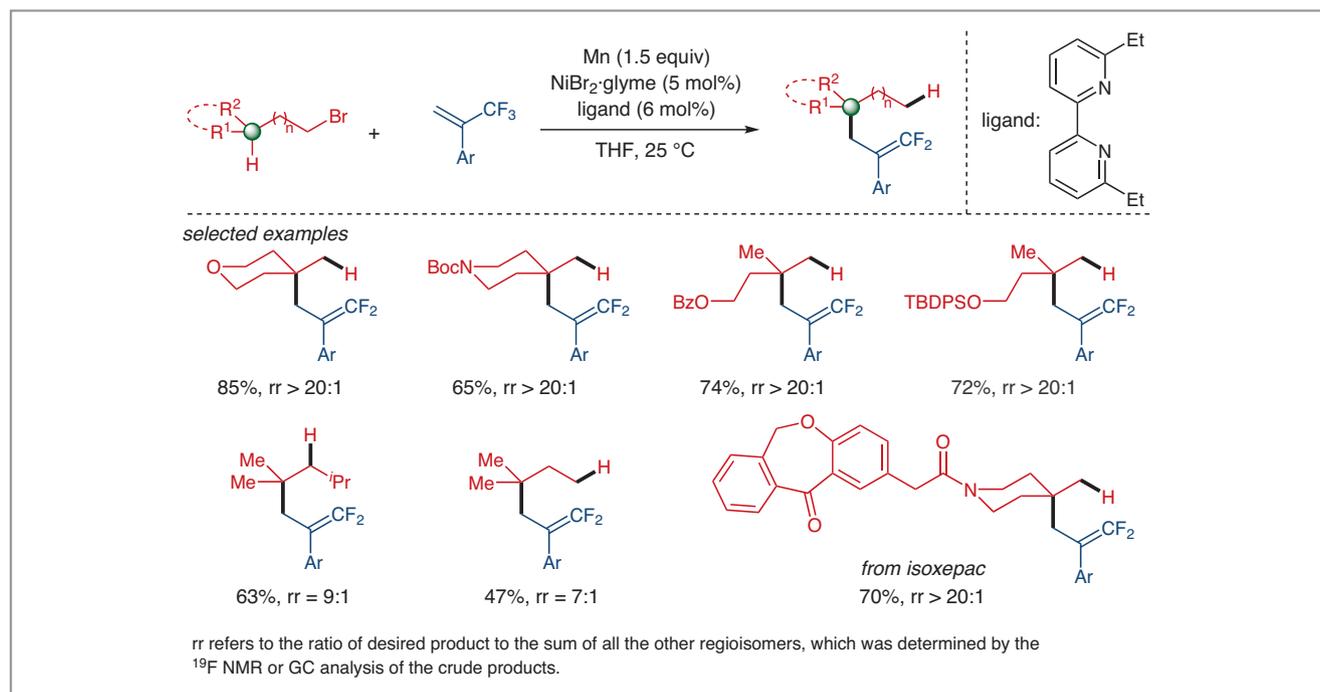


Migratory Functionalization of Unactivated Alkyl Bromides for Construction of All-Carbon Quaternary Centers via Transposed *tert*-C-Radicals

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All-carbon quaternary centers are ubiquitous in natural products and pharmaceuticals, as well as functional materials. “Conceptually, tertiary-C–C cross-coupling constitutes one of the most concise and straightforward approaches to access structures with spherical groups,” explained Professor Chao Feng (Nanjing Tech University, P. R. of China). He continued: “However, the apparent steric repulsion and potential β -hydride elimination severely impede the development of this strategy. Established protocols have focused mainly on functionalization of tertiary alkyl nucleophiles (alkyl-Mg, Zn and B), or electrophiles (alkyl halides/pseudohalides), but limited functional groups or coupling partners can typically be used. Furthermore, the unwanted regioisomers deriving from isomerization of the metallic *tert*-alkyl intermediate were often obtained, together with the target product. Therefore, developing general methods for novel types of C–C bond formation at the sterically demanding tertiary carbons

from easily available starting materials is highly appealing.” Recently, a collaborative effort between the group of Professor Feng and that of Professor Patrick J. Walsh (University of Pennsylvania, USA) uncovered a way of constructing all-carbon quaternary-center-embedded frameworks from unactivated primary/secondary alkyl bromides via a Ni–H-engaged chain-walking event (Scheme 1). “This transformation provides a mechanistically distinct and efficient entry to the three-dimensional structures with good regioselectivity, thus complementing the existing catalytic accesses,” said Prof. Feng, who continued: “Moreover, this finding advances the boundary of chain-walking-associated remote functionalization. By exploiting the usually undesired β -H elimination and reinsertion of metal hydrides, transition-metal catalysts (Pd, Ni, Co, Rh, etc.) are able to move to a remote position relative to the initial metalation site, thus enabling migratory functionalization.”



Scheme 1 Construction of all-carbon quaternary centers via migratory functionalization

“As demonstrated by Martin (ICIQ, Spain), Zhu (Nanjing University, P. R. of China), and others,¹⁻⁴ the viable remote sites include C(sp³) centers positioned α to aromatics, boron, carbonyls, and primary C(sp³), which offer more stabilized carbon–metal bonds throughout the carbon chain,” added Professor Feng. “In contrast, the method proposed in this paper takes advantage of the less stabilized positions, which could furnish the C-centered radicals and undergo subsequent functionalization, thus allowing unprecedented migratory functionalization.” Prof. Feng explained: “In this perspective, a formal radical rearrangement is achieved through a chain-walking process, which is usually observed only with carbocations. The 3,3-difluoroallyl represents a new functionality that could be accommodated in Ni–H-engaged catalytic systems.”

As demonstrated in prior work by the Feng group, the strongly electron-withdrawing fluorine substituents render the C=C bond resistant to the electrophilic Ni–H complex. “In addition, the successful expansion to Giese-type reaction with other electron-deficient olefins, such as acrylate, enone and acrylonitrile, emphasizes the versatility of this protocol,” said Professor Feng, who concluded: “This is just the first episode of this unique chain-walking-enabled functionalization at tertiary carbons, and some even more elegant techniques to precisely distinguish between inherently similar tertiary, secondary, and primary carbons are expected based on this strategy.”

Mattes Fenchel

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Prof. P. J. Walsh

Patrick J. Walsh received his B.A. from University of California San Diego and his Ph.D. at University of California Berkeley (USA) with Prof. Robert G. Bergman (1991). He was a postdoctoral researcher with Prof. K. B. Sharpless at Scripps (USA, 1994–1999) and a professor at Centro de Graduados e Investigación, Instituto Tecnológico de Tijuana (Mexico, 1996–1999). In 1999 he moved to the University of Pennsylvania (USA). Prof. Walsh has held honorary positions in China, including Nanjing Tech University (P. R. of China).



Prof. C. Feng

Chao Feng studied chemistry at Nanjing University of Science and Technology (P. R. of China) and received his MSc degree in 2007 under the supervision of Prof. Chun-Xu Lv. Then he moved to Nanyang Technological University (Singapore) and obtained his PhD under the supervision of Prof. Teck-Peng Loh in 2012. After four years of postdoctoral research in Prof. Loh's group, he started his independent work and became a full professor at Nanjing Tech University (P. R. of China) from 2016. In 2017, he was granted the Thieme Chemistry Journals Award. His research interests include fluorine chemistry and photoredox catalysis.