

## Privileged strategies for direct transformations of inert aliphatic carbonhydrogen bonds

July 31 2014



This graphics shows the total synthesis of tetrodotoxin via C-H activation. Credit: Science China Press

Functional group transformations are central to organic synthesis. Traditionally, the functionalities used in such transformations are highly active organic groups such as halogens, ester groups and hydroxyl groups. Carbon–hydrogen bonds are ubiquitous structural motifs in organic compounds, but they are not considered to be functional groups because (1) in general, the bond dissociation energy of a C–H bond is high, and therefore, such bonds are thermodynamically hard to break;



and (2) the selective activation of one C–H bond among many similar and different C–H bonds in one organic molecule is difficult. However, direct C–H transformations, which could be used to perform synthetic chemistry in a greener and more atom-economical way, are highly appealing. The importance and challenges of this field make it one of the 'Holy Grails' of chemistry.

Guihua Chen and Zhang-Jie Shi, scientists at the College of Chemistry and Molecular Engineering, at Peking University in the Chinese capital, account progress and challenges in this area, "Privileged strategies for direct transformations of inert aliphatic C–H bonds," published in the Beijing-based journal *National Science Review*.

"In the last few decades, direct C(sp2)–H activation of (hetero)arenes and some alkenes has been extensively investigated," they state in the study. "Many examples and applications of such activations in organic synthesis have been reported. Some progress has also been made in achieving the direct transformation of relatively active benzylic and allylic C–H bonds. In contrast, less effort has been devoted to the activation of 'inert' aliphatic C–H bonds of alkyl groups, because the challenge is greater. The acidity of an alkyl C(sp3)–H bond is lower than those of other C–H bonds, making the cleavage of such bonds much more difficult."

Several generations of chemists conducting research have collectively made significant progress in the direct transformation of inert aliphatic C–H bonds.

The new study presented by Guihua Chen and Zhangjie Shi summarizes effective strategies for advances in this area, with some representative examples.

Compared to the well-developed arene/alkene C-H activation, the



functionalization of inert aliphatic C–H bonds of alkyl groups is still under investigation.

In general, there are three methods for the functionalization of aliphatic C-H bonds: the radical process, carbene/nitrene insertion and transitionmetal mediated/catalyzed reactions.

As a result of the development of petroleum chemistry and traditional organic transformations, the photo- and thermo-induced direct halogenation of aliphatic C–H bonds via radical pathways is well known. Unfortunately, this is not an ideal organic reaction and has not been widely used in organic synthesis because of its poor selectivity. Significant efforts have been made to overcome this problem. An improved radical process, the Hoffmann–Loffler–Freytag (HLF) reaction, is probably the best-known radical reaction for constructing C–N bonds in organic synthesis. It is usually used for the synthesis of nitrogen-containing cycles and has even been successfully used in natural product chemistry.

Other strategies include Fenton and Gif chemistry and crossdehydrogenative coupling (CDC). Radical processes are still the most powerful strategy for functionalizing aliphatic C–H bonds. The development of new techniques and new systems will make such strategies more controllable and useful in the near future.

Carbene/nitrene insertion in aliphatic C–H bonds is another well-studied and reliable method for direct conversion of C–H to C–C and C–N bonds. Over the course of decades of progress, this is the most reliable and well-developed method for aliphatic C-H activation; even an asymmetric variant has developed well.

Transition-metal-mediated C–H cleavage and further stoichiometric and catalytic transformations represent another powerful method for direct



C–H bond transformations. Because the formation of C–M intermediates is key to the reaction, the process is referred to as C–H activation rather than C–H transformation. In this strategy, oxidative addition, electrophilic substitution,  $\sigma$ -bond metathesis and transition-metal-promoted homolysis are the four major pathways.

Direct C(sp3)–H functionalization is undoubtedly one of the most challenging and promising areas of organic synthesis. Several successful and elegant strategies have been developed and used in organic synthesis. However, compared with traditional organic transformations, this area is still less well studied, and much research is still needed.

More reliable, cheaper and more efficient processes for potential applications are needed. The development of efficient asymmetric catalytic systems is also challenging.

Developing new strategies for functionalizing independent aliphatic C–H bonds will present many challenges and opportunities for chemists. The collective efforts of several generations of chemists will lead to exciting developments, making <u>organic synthesis</u> greener and more environmentally benign.

Provided by Science China Press

Citation: Privileged strategies for direct transformations of inert aliphatic carbon-hydrogen bonds (2014, July 31) retrieved 1 May 2024 from <u>https://phys.org/news/2014-07-privileged-strategies-inert-aliphatic-carbon-hydrogen.html</u>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.