Privileged strategies for direct transformations of inert aliphatic C–H bonds

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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, is highly appealing. The importance and challenges of this field make it one of the ‘Holy Grails’ of chemistry [1,2].

In the last few decades, direct C(sp³)–H activation of (hetero)arenes and some alkenes has been extensively investigated. 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. Also, the lack of a \( \pi \)-system adjacent to a \( C(\text{sp}^3) \)--H bond makes their interactions with reagents weak. As a result of the efforts of several generations of chemists, significant progress has been made in the direct transformation of inert aliphatic C–H bonds. This perspective summarizes effective strategies for achieving this goal, with some representative examples.

**RADICAL PROCESSES**

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–Loeffler–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, as shown in Scheme 1 [3].

Fenton and Gif chemistry is a powerful and much-used process in both synthetic chemistry and wastewater treatment. White and co-workers made significant contributions to organic synthesis in the oxidation of aliphatic C–H bonds with Fe\(^{2+}\) catalysts on nitrogen-containing ligand supports. High regioselectivity was obtained in complex molecular syntheses (Scheme 2) [4]. Yang [5] and Baran [6] showed the oxidation of independent aliphatic C–H bonds, using various peroxides as the oxidant.

Cross-dehydrogenative coupling is another good example in green chemistry of the construction of C–C bonds from two C–H bonds. Usually, a transition-metal catalyst and a peroxide are used to perform such transformations, mainly through radical processes [7]. Recent advances in the promotion of such transformations under metal-free conditions
have made them more environmentally benign [8].

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 AND NITRENE INSERTIONS

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 [9,10]. Since the first report of this type of reaction by Meerwein in 1942, carbene and metallocarbenoid chemistry has developed rapidly. In 1982, Wenkert’s and Taber’s groups both reported that Rh₂(OAc)₄ is an effective catalyst for C–H insertion reactions. Since then, Doyle, Davies and others have made significant contributions, especially in enantioselective control, using well-designed chiral ligands.

The properties of nitrenes and metal-nitrenoids are similar to those of carbenes and metallocarbenoids, and C–N bonds can be constructed through C–H insertion. In 1968, Breslow and Solan first reported the insertion of a nitrene into cyclohexane by heating a mixture of dichloroamine-T and Zn in cyclohexane. Later, many groups became involved in nitrene chemistry, and it was found that carbamate/sulfamate esters combined with I⁺ are the best nitrogen sources. Both inter- and intra-molecular C–N bond formation can be achieved, even enantioselectively. Such insertions have also been used in the total synthesis of natural products such as tetrodotoxin (Scheme 3) [11], showing the potential of this method for future applications.

TRANSITION-METAL-MEDIATED C–H CLEAVAGE

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, σ-bond metathesis and transition-metal-promoted homolysis are the four major pathways.

Electrophilic metalation

Shilov and co-workers developed a method for the conversion of methane to methanol, using a high-valent metal catalyst, thus is known as the Shilov system. The key intermediate, Me–Pt, is formed by electrophilic substitution of a C–H bond with a Pt⁴⁺ catalyst, and is then oxidized to C–O bonds in the presence of appropriate oxidants. It was later found that many other metals can also be used in this transformation, for example, Pd, Hg, Cu and Au [14].

In the late 1990s, this chemistry was extended to the independent aliphatic C–H bonds of functionalized molecules. Pt plays a valuable role in the oxidative lactonization of amino acids (Scheme 5) [15]. Recently, Pd was shown to be useful in this field. Remote aliphatic C–H bonds can be catalytically transformed to C–C, C–O and C–N bonds, using directing groups or intramolecular initiators. Most importantly, various chiral ligands can be used to achieve asymmetric transformations, leading to a new area of Pd chemistry (Scheme 4) [12,13]. However, σ-bond metathesis is also a possible pathway in catalytic transformations. This chemistry potentially provides a green method for the direct functionalization of hydrocarbons to valuable chemicals. The regulation of the distribution of mixed alkanes to produce valuable petroleum products is another useful application of this method.

Scheme 4. Borylation and silylation via C–H activation.
chemistry, other than cross coupling. The characteristics of this transformation suggest that it takes place via a concerted proton abstraction pathway, known as CMD (concerted metalation–deprotonation).

**σ-Bond metathesis**

Compared with the two above-mentioned pathways, σ-bond metathesis has been well studied theoretically, but it has not been widely used in organic synthesis. Only one successful example has been reported, by Tilley and co-workers, showing the direct hydromethanation of isobutene. However, this reaction is still little studied because the turnover number of the transformation is too low for the reaction to be useful. We believe that it could provide a potential strategy for transforming unfunctionalized molecules into valuable chemicals, and therefore should be paid increased attention.

**Transition-metal-promoted homolysis**

The transition-metal-promoted homolysis of aliphatic C–H bonds is, in principle, possible, and this has been proved experimentally. However, no examples supporting its use in organic synthesis have been reported. This process is complicated, because two metal centers are needed to cleave one C–H bond, and C–M and H–M intermediates are both formed; it therefore needs to be further developed.

**CONCLUSION AND OUTLOOK**

Direct C(sp^3)–H functionalization is undoubtedly one of the most challenging and promising areas of organic synthesis. Much research continues to be devoted to achieving this goal, and many significant contributions have been made in this field. It is important to note that 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. For example, more reliable, cheaper and more efficient processes for potential applications are desirable [16]. The development of efficient asymmetric catalytic systems is also challenging [17].

Developing new strategies for functionalizing independent aliphatic C–H bonds is highly desirable, and there are many challenges and opportunities in this area for chemists. We believe that the efforts of several generations of chemists will lead to exciting developments, making organic synthesis greener and more environmentally benign.

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