Carbon-carbon bond formation at selective aliphatic carbon sites

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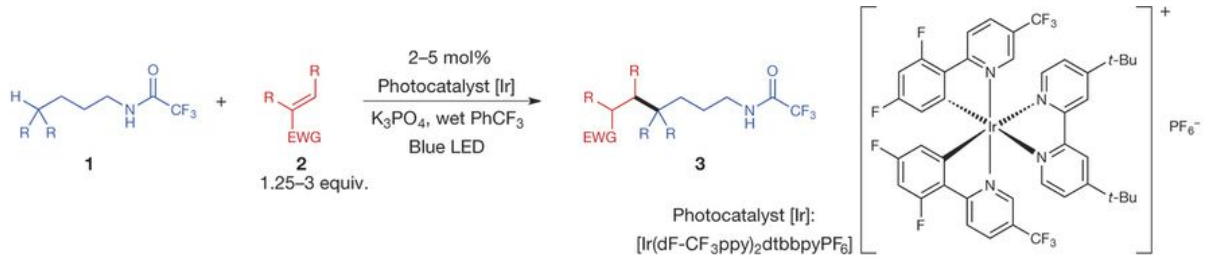

Trifluoroacetamide as the directing group for C–H functionalization. Credit: *Nature*, DOI: 10.1038/nature19810

(Phys.org)—John C. K. Chu and Tomislav Rovis of Colorado State University and Columbia University have devised a strategy for C-C bond formation at inert tertiary C-H bonds of amides. This reaction involves cleavage of the C-H bond and subsequent coupling with an alkene. Their reaction works with a variety of amides and alkenes and is selective for a particular C-H among all seemingly indistinguishable C-H bonds. Their report appears in *Nature*.

"We were motivated to develop chemistry that would be broadly used," Dr. Rovis told *Phys.org*. "Alkyl sidechains are ubiquitous. Functionalizing a single one in the presence of all these others, we felt, would be embraced by the end-users in industry and academia."

In organic chemistry, the saturated carbon (sp^3 hybridized carbon)forms the backbone of organic molecules. Often chemists wish to form C-C bonds from simple molecules, but strategies to form a C-C bond at an inert C-H site are limited due to the high bond strength of the C-H bond and the difficulty with targeting a particular C-H bond. However, these difficulties also means that forming a C-C bond at C-H sites obviate the need for a functional group at the reaction site which presents an opportunity to derivatize the molecule of interest in ways that traditional methods do not allow.

Chu and Rovis' protocol features a 1,5 hydrogen atom transfer whose relatively low-energy six-membered transition state accounts for the observed selectivity. The protocol involves using an iridium photocatalyst that oxidizes the amide to form a nitrogen radical. A hydrogen atom is then transferred from the carbon four atoms away from the amide to the nitrogen radical (i.e., 1,5 hydrogen atom transfer). The resulting carbon radical then couples to an alkene to form a C-C bond.

With the use of different alkenes, an array of products can be formed from an amide. This feature is highly desirable especially in the field of medicinal chemistry, which demands access to a large number of molecules for structure-activity relationship studies and optimization of drug candidates. A wide variety of amides are competent substrates. The reaction proceeds smoothly regardless of the steric environment at the C-H bonds or the presence of other functional groups in the amide.

They successfully formed C-C bonds with acrylate esters, acrylamides, and vinyl ketones. Substituents (e.g., methyl and dimethyl) at the carbon next to the activated amine did not hinder the reaction either. Protecting groups on other substituents still led to C-C bond formation, as well as oxygen atoms next to the target C-H bond. Notably, certain reactions required more catalyst (e.g., methyl vinyl ketone) to eliminate the

competing reactions, and others required that the alkene concentration was increased.

It is noteworthy that for molecules with multiple tertiary C-H bonds, only the one at the fourth carbon away from the amide is selectively cleaved for C-C bond formation. Chu and Rovis also found that 1,5 hydrogen atom transfer is always favored over 1,6 hydrogen atom transfer. In one instance, the product from 1,5 hydrogen atom transfer was isolated and re-subjected to a different alkene, yielding a product incorporating two different alkenes via the formation of two C-C bonds.

Finally, this newly developed strategy can be applied to medicinally-valuable molecules. For instance, an analogue of Pregabalin, a drug for the treatment of nerve and muscle pain, can be obtained through selective C-C bond formation of a particular C-H bond. This underscores the potential of Chu and Rovis' protocol for the derivatization of biologically active molecules, which is a strategy extensively used for improving pharmacological properties of drug candidates.

More information: John C. K. Chu and Tomislav Rovis "Amide-directed photoredox-catalyzed C-C bond formation at unactivated SP3 C-H bonds" *Nature*, DOI: 10.1038/nature19810

Abstract
Carbon–carbon (C–C) bond formation is paramount in the synthesis of biologically relevant molecules, modern synthetic materials and commodity chemicals such as fuels and lubricants. Traditionally, the presence of a functional group is required at the site of C–C bond formation. Strategies that allow C–C bond formation at inert carbon–hydrogen (C–H) bonds enable access to molecules that would otherwise be inaccessible and the development of more efficient syntheses of complex molecules1, 2. Here we report a method for the

formation of C–C bonds by directed cleavage of traditionally non-reactive C–H bonds and their subsequent coupling with readily available alkenes. Our methodology allows for amide-directed selective C–C bond formation at unactivated sp3 C–H bonds in molecules that contain many such bonds that are seemingly indistinguishable. Selectivity arises through a relayed photoredox-catalysed oxidation of a nitrogen–hydrogen bond. We anticipate that our findings will serve as a starting point for functionalization at inert C–H bonds through a strategy involving hydrogen-atom transfer.

Further reading:

Catalytic Alkylation of Remote C–H Bonds Enabled by Proton-Coupled Electron Transfer. Choi, G. J.; Zhu, Q.; Miller, D. C.; Gu, C. J.; Knowles, R. R. Nature 2016, Accepted DOI: 10.1038/nature19811