Remote C–H Functionalization

International Edition: DOI: 10.1002/anie.201611463
German Edition: DOI: 10.1002/ange.201611463

Controllable Remote C–H Bond Functionalization by Visible-Light Photocatalysis

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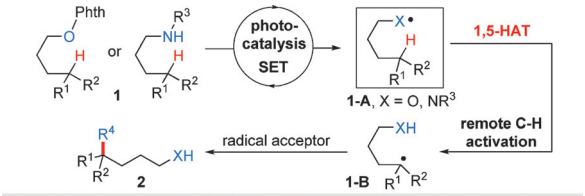
alkylation · C–H functionalization · hydrogen atom transfer · photoredox catalysis · radicals

The direct functionalization of C(sp^3)–H bonds in hydrocarbons constitutes a powerful and atom-economic approach for the construction of various carbon–carbon or carbon–heteroatom bonds owing to their omnipresence in organic molecules.[1] Consequently, over the past few decades, numerous methods have been established for the activation and selective functionalization of such unactivated C–H bonds, such as transition-metal-catalyzed C–H activation and oxidation with the assistance of a directing group.[2] However, the additional steps required for the installation and removal of such directing groups limit their application in synthetic chemistry to some extent. Because of their high bond strength, some challenges are still associated with the activation of remote inert C(sp^3)–H bonds, particularly with respect to the reaction conditions, functional group tolerance, and selectivity control. Therefore, the development of mild processes that enable the controlled activation and functionalization of remote C–H bonds is still a research area of great interest.

Radical translocation processes mediated by heteroatom radicals, especially O- and N-centered radicals, such as 1,5-hydrogen atom transfer (1,5-HAT), provide a potential platform for the controlled functionalization of remote inert C(sp^3)–H bonds owing to the highly reactive nature and unique reactivity of such radicals, as demonstrated by the well-known Hoffmann–Löffler–Freytag and Barton reactions.[3] Compared with various transformations of carbon radicals, however, O and N radical species have remain largely unexplored owing to the lack of convenient strategies for their generation. Currently used methods usually require high-energy UV irradiation, high temperatures, or stoichiometric oxidants, which have always resulted in unsatisfactory regioselectivity or restricted substrate scope. In recent years, visible-light photoredox catalysis has emerged as a powerful technique for the efficient generation of various O and N radicals under mild conditions, and thus provides an attractive approach for the controlled and selective functionalization of remote inert C(sp^3)–H bonds.[4] Several notable advancements with alkoxyl- and amidyl-radical-mediated remote C(sp^3)–H bond functionalization have recently been described (Scheme 1). In these reactions, the activation of typically non-reactive C–H bonds was easily achieved with photogenerated O or N radicals in a 1,5-HAT process as it led to the reformation of strong O–H or N–H bonds; the resultant carbon radicals could be coupled with various radical acceptors to form new C–C bonds in a controllable and selective fashion.



Scheme 1. O- and N-radical-mediated functionalization of remote C(sp^3)–H bonds. Phth = phthaloyl.

In 2015, Chen and co-workers developed the first example of alkoxyl-radical-mediated selective allylation and alkenylation of unactivated C(sp^3)–H bonds by visible-light photocatalysis. This transformation provided the corresponding adducts in moderate to good yields with excellent chemo- and regioselectivity (Scheme 2a),[5] and features mild reaction conditions and a broad substrate scope. It was postulated that the reaction is initiated by visible-light photocatalytic reductive cleavage of the N–O bond of *N*-alkoxy phthalimide **3** to form the key alkoxyl radical **3-A** with Hantzsch ester as the sacrificial reductant. Then, the O radical species activates a remote C(sp^3)–H bond through a 1,5-HAT process in a selective manner to generate the carbon radical **3-B**. Final intermolecular trapping of the newly formed radical **3-B** by allyl sulfone **4** followed by rapid elimination of a sulfinyl radical (**4-A**) furnished the desired product **5**. This work represents a fundamental breakthrough in the field of visible-

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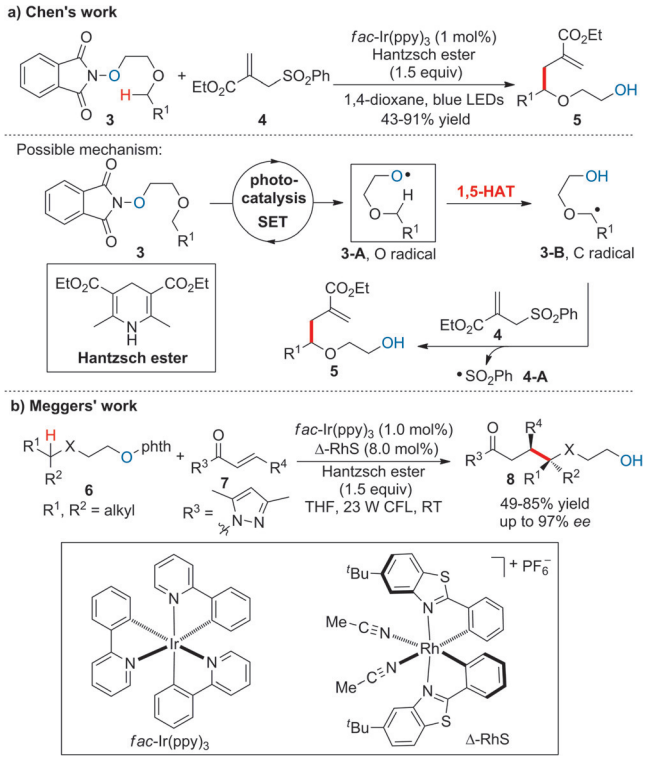
http://dx.doi.org/10.1002/anie.201611463.



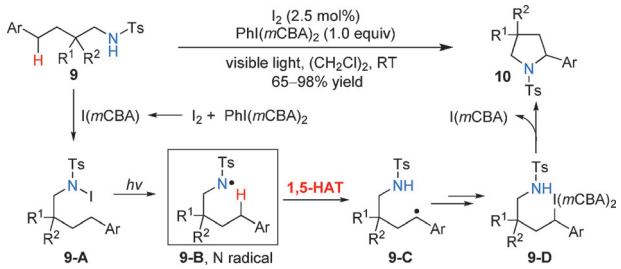
Scheme 2. Controllable functionalization of remote inert C(sp^3)–H bonds through an O-radical-mediated 1,5-HAT process. ppy = 2-phenylpyridine.

light-induced and O-radical-mediated remote C(sp^3)–H bond activation.

Shortly after, Meggers and co-workers also achieved an asymmetric alkylation of remote C(sp^3)–H bonds in *N*-alkoxy phthalimides **6** with α,β-unsaturated *N*-acyl pyrazoles **7** by combining their previously developed chiral rhodium-based Lewis acid catalyst (Δ-RhS) with the photocatalyst *fac*-Ir(ppy)$_3$ under visible-light irradiation (Scheme 2b).[6] Remarkably, in this reaction, the two catalysts proved to be well compatible with each other and enabled the formation of the desired adducts in generally good yields and excellent enantioselectivities.

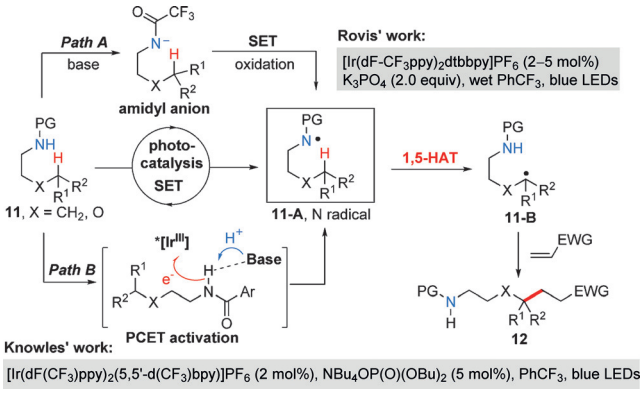
In analogy to O radicals, N radicals are also able to abstract a hydrogen atom through an intramolecular 1,5-HAT process in a selective manner.[3] Given the ubiquity of N–H bonds in organic compounds, the development of mild catalytic strategies that enable the direct conversion of N–H bonds into N radicals could provide an economical approach for remote C–H activation.[3] In 2015, Muñiz and Martínez developed an iodine-catalyzed visible-light-initiated amination of remote C(sp^3)–H bonds (Scheme 3).[7] It was postulated that the key steps involve visible-light-induced homolysis of the in situ formed N–I bond for the formation of N radical **9-B**, 1,5-HAT of **9-B** for the generation of C radical **9-C**, and nucleophilic amination to give the final product.

Very recently, the groups of Rovis[8] and Knowles[9] independently reported on the photoredox-catalyzed direct generation of amidyl radicals from amide precursors and their successful application in the selective alkylation of remote



Scheme 3. Iodine-catalyzed amination of remote C(sp^3)–H bonds enabled by an N-radical-mediated 1,5-HAT process. *m*CBA = 3-chlorobenzoate, Ts = *para*-toluenesulfonyl.

C(sp^3)–H bonds. Rovis and co-workers found that the pK_a value of the N–H bond was critical for the desired reaction, and the readily removable trifluoroacetyl moiety was identified to be the most efficient activating group (Scheme 4, path A). The optimal reaction conditions involved the use of K_3PO_4 as the base and [Ir(dF-CF_3ppy)$_2$dtbbpy]PF_6



Scheme 4. Photoredox-catalyzed selective alkylation of remote C(sp^3)–H bonds in an N-radical-mediated 1,5-HAT process. dF-CF_3ppy = 2-(2,4-difluorophenyl)-5-trifluoromethylpyridine, dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine, EWG = electron-withdrawing group, PG = protecting group.

as the photocatalyst, and this process had a broad substrate scope and high functional group tolerance with respect to amides and acrylate esters. This mild procedure could also be successfully applied for the late-stage modification of biologically active molecules. Mechanistic studies by cyclic voltammetry and Stern–Volmer assays suggest that a stepwise deprotonation/single electron transfer (SET) oxidation should be operative during N-radical generation. In the meantime, Knowles[9] and co-workers developed a similar N-radical-mediated selective alkylation of remote C(sp^3)–H bonds in *N*-alkyl amides by combining photoredox-catalyzed proton-coupled electron transfer (PCET) and 1,5-HAT (Scheme 4, path B). Under the optimal reaction conditions, which include an iridium photocatalyst and a phosphate base, a wide range of amides with various degrees of steric bulk adjacent to the amidyl nitrogen atom as well as alkyl and aryl enones were well tolerated to give the corresponding products in good yields and excellent regioselectivities. Remarkably,

this activation approach could also be rendered intermolecular. In contrast to Rovis' work, here, the key amidyl radical was postulated to be formed by concerted PCET activation of the N–H bond, which should explain why a variety of structurally and electronic diverse amides can be functionalized in this process.

In summary, we have highlighted some elegant advances in the use of visible-light photocatalysis for the functionalization of remote inert C(sp^3)–H bonds under mild reaction conditions. These site-selective transformations are based on 1,5-HAT processes of photogenerated O and N radicals, and open new opportunities for reaction design and the development of catalytic asymmetric variants.

Acknowledgements

We thank the National Science Foundation of China (21272087, 21232003, 21472058, and 21622201) for funding.

Conflict of interest

The authors declare no conflict of interest.

How to cite: *Angew. Chem. Int. Ed.* **2017**, *56*, 1960–1962
Angew. Chem. **2017**, *129*, 1988–1990

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Manuscript received: November 23, 2016
Final Article published: January 20, 2017

