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Intermolecular Radical C–H Bond Activation: A Powerful Tool for Late Stage Functionalization

Fabrice Dénès*

Abstract: The synthesis of complex molecules *via* radical reactions involving carbon–carbon and carbon–heteroatom bonds has become a very successful approach. Radical chemistry has long been dominated by the use of tin-based reagents. Those strongly contributed to the development of the field, allowing one to achieve spectacular transformations, most of which being difficult or impossible to achieve under ionic conditions, and giving access to invaluable kinetics data that paved the way for the development of improved protocols and the design of new synthetic strategies. However, tin reagents and tin byproducts are often toxic and they proved to make purification steps sometimes tedious. In this context, tin-free methods have progressively gained in interest. This short review aims at providing the reader with alternative methods employing C–H bonds in place of the classical alkyl halides to generate, *via* an intermolecular hydrogen atom transfer (HAT), the radical species. Examples of carbon–carbon and carbon–heteroatom bond formation using this type of C–H bond activation approach will be provided, from early reports to the more recent developments.

Keywords: C–C bond formation · C–H bond activation · HAT · Radical · Radical chain reactions

Dr. Fabrice Dénès was born in Paris (France). He completed his undergraduate and postgraduate studies at the University Pierre et Marie Curie (Paris, France) and received his PhD in 2002 under the supervision of Prof. J.-F. Normant and F. Chemla. He then joined Prof. P. Renaud at the University of Bern (Switzerland) as a postdoctoral associate. In 2005, he moved to the University of Nantes (France) where he was appointed assistant professor in the group of Prof. J. Lebreton. His research interests include the development of synthetic methods based on organometallic or radical reactions.

1. Introduction and Scope of the Review

The formation of carbon–carbon and carbon–heteroatom bonds *via* radical reactions has become a very successful approach to complex molecules, principally due to the mildness of the reaction conditions and the possibility to achieve multiple bond formation *via* cascade processes. Radical chemistry has long been dominated by the use of tin-based reagents[1] to mediate these transformations using alkyl (vinyl and aryl) halides and chalocogenides, or xanthates as radical precursors. Among others, decarboxylative processes and reduction of diazonium salts have also proved very attractive for the generation of radical species. Beside these routes to carbon-centered radicals, the abstraction of a simple hydrogen atom from a C–H bond can be regarded as a more environmentally friendly and atom-economical approach to access carbon-centred radicals.[2] The latter can then engage in carbon–carbon and carbon–heteroatom bond formation, either under classical radical conditions, or with the help of transition metals. Although extremely appealing at first glance in the context of late stage functionalization,[3] the activation of an 'unreactive' C–H bond clearly represents a significant challenge for organic chemists, in particular in terms of regioselectivity of the hydrogen atom abstraction in complex molecular systems. This short review aims at providing the reader with an overview of the processes that make this transformation possible and the types of functionalizations that have been achieved so far. The scope of the review will be limited to processes in which both the C–H activation and the subsequent functionalization involve radical elementary steps. Moreover, alternative processes (*e.g.* homolytic aromatic substitution[4] and the formation of alpha-amino carbon-centred radicals *via* an oxidation-deprotonation process[5,6]) in which a hydrogen atom has been eventually replaced but which differ fundamentally from a direct radical C–H bond activation will not be discussed. The scope of this review will be limited to intermolecular processes. The reader interested in the field of intramolecular hydrogen atom abstraction is directed to previous reviews. More information concerning intermolecular hydrogen atom transfer can be found in various reviews.[2]

2. Mechanistic Considerations

The abstraction of a hydrogen atom from a C–H bond is responsible for damages caused to biomolecules and polymers (*e.g.* lipid peroxidation)[7] but it is also a crucial step in some biological processes of considerable importance such as, among many others, the arachidonic acid cascade leading ultimately to a variety of prostaglandins. The abstraction of the hydrogen atom is governed by different factors, each of them either contributing to increase, or alternatively, to decrease the overall (regio)selectivity of the process. In order to translate biological processes into useful C–H bond functionalization procedures for synthetic chemists, it is important to keep in mind several aspects that will influence the efficiency of the hydrogen abstraction step. Compared to enzyme-catalyzed reactions for which the conformation of the molecule in the active site of the enzyme will have a significant influence on the regio- and sometimes stereoselectivity of the C–H bond

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activation steps, non-enzymatic reactions are governed by different factors, such as: (a) the bond strength of the C–H bonds, (b) electronic effects, (c) conformational, torsional, steric and stereoelectronic effects,[8] as well as medium effects (this list is non-exhaustive).[2b,8g]

To some extent, the nature of the radical species used to abstract the 'unreactive' C–H bond will also play a role and fine-tuning of the reagent may help to improve the innate selectivity of the abstraction process.[9] Typical radical species allowing intermolecular hydrogen atom abstraction from aliphatic C–H bonds include alkoxy radicals and related oxygen-centred radical species, nitrogen-centred radicals (*e.g.* aminyl and iminyl radicals, as well as more electrophilic aminyl radical cations, azidyl radicals), chlorine and bromine radicals, and radical species derived from hypervalent iodine reagents. A variety of photocatalysts such as aromatic ketones, inorganic clusters (polyoxometalate (POMs) anions) and dioxiranes have also proved efficient at abstracting hydrogen atoms from C–H bonds.

When several factors act in a synergistic manner, high to excellent regiocontrol can be obtained, making this approach a powerful tool for late-stage functionalization strategies.[3,10] Not surprisingly, in the case of aliphatic side chains, tertiary C–H bonds are usually more reactive than secondary and primary C–H bonds, as a result of lower bond dissociation energies. However, as mentioned before, steric and electronic factors also play a role and the selectivity for a specific site is not only dictated by the strength of the C–H bonds. In most cases, the electrophilic nature of the radical species used to abstract the hydrogen atom (low-lying SOMO radical species) from aliphatic C–H bonds makes the hydrogen abstraction faster at electron-rich bonds. With heteroatom-substituted substrates, such as alcohols, ethers and amines, the most reactive C–H bond is located alpha to the heteroatom. It is worthy of note that, in the case of amines, the regioselectivity of the hydrogen atom abstraction can be controlled through different mechanisms with either the direct hydrogen atom transfer (HAT) as previously described or, alternatively, the oxidation into the aminyl radical cation followed by deprotonation.

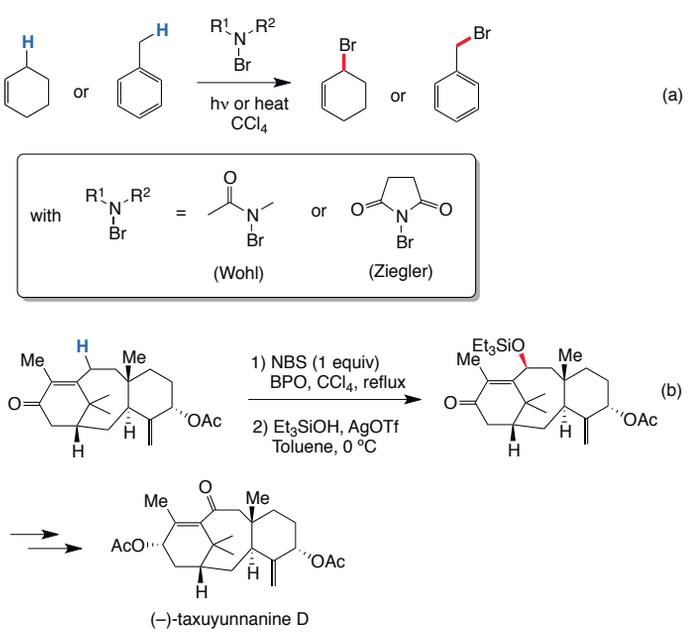
3. Formation of Carbon-Heteroatom Bonds

The generation of a carbon-centered radical from simple C–H bonds allows for the introduction of a variety of functional groups. As previously mentioned the scope of this mini-review is limited to processes involving the formation of carbon–heteroatom bonds *via* radical pathways, and processes involving the oxidation of the radical species into carbocations and their trapping with nucleophiles have not been included. Since the early development of radical chemistry, it has been shown that the replacement of a hydrogen atom by halides could be easily achieved, even though the site selectivity was often an issue. Numerous hydroxylation reactions have been found to involve radical intermediates in biological pathways, and such transformation has also been extensively studied for synthetic purposes. The formation of C–N and C–S bonds can also be achieved from C–H bonds. All these transformations can now be done under much milder reaction conditions than those described in the seminal reports, and continuous efforts have been made to improve the selectivity of these processes. This paragraph will discuss some of the pioneering work in the field, as well as more recent development.

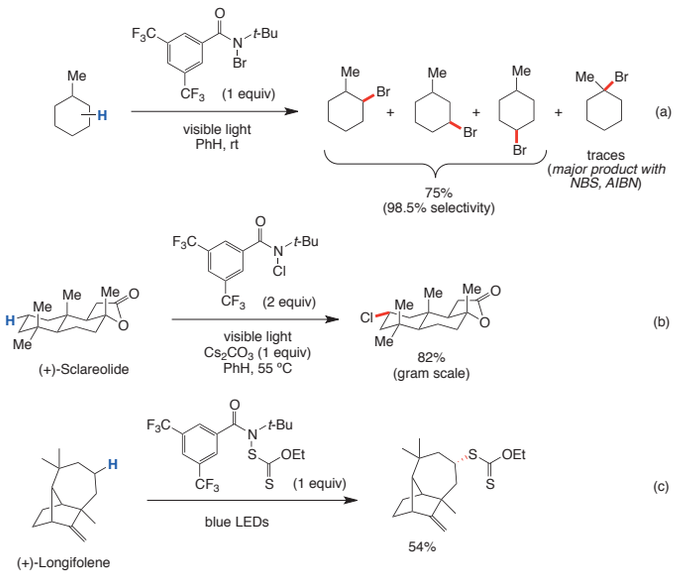
3.1 *Halogenation (Chlorination, Bromination and Fluorination) and Related Processes*

Halogenation of alkanes can be achieved using X_2 (X = Br, Cl, F) upon irradiation or thermal initiation. As the result of an endothermic step for the C–H bond abstraction by the bromine radical, bromination is usually far more site-selective than chlorination or fluorination. In the case of halogenation, important solvent effects have been noticed in the chlorination of short chain alkanes.[11] Chlorination of alkanes can be achieved upon irradiation with molecular chlorine[12] or with sulfuryl chloride (SO_2Cl_2).[13] One of the issues, beside the problem of regioselectivity, is polychlorination. Molar ratio, light power and reaction times need to be controlled to favor mono-chlorination and the process was found to be relatively clean in the case of cycloalkanes when conducting the chlorination with sulfuryl chloride under microflow conditions.[14] Radical bromination using *N*-bromosuccinimide (Wohl–Ziegler reaction)[15,16] was found to be initiated by light irradiation or upon heating, usually in the presence of a radical initiator (Scheme 1, Equation a). In the original papers, CCl_4 was used as a solvent, but alternatives, such as the use of the less toxic solvent trifluorobenzene, can also be used.[17] Examples of highly site-selective allylic bromination reactions have been reported. For instance, Baran used a one-pot sequence to introduce in a stereoselective manner the C10-hydroxyl group in the skeleton of (−)-taxuyunnanine D using a highly regioselective Wohl-Ziegler allylic bromination, followed by the displacement of the bromine atom by triethylsilanol in the presence of AgOTf. Overall, the synthesis of (−)-taxuyunnanine D was accomplished in only five steps from (+)-taxadiene (Scheme 1, Equation b).[18]

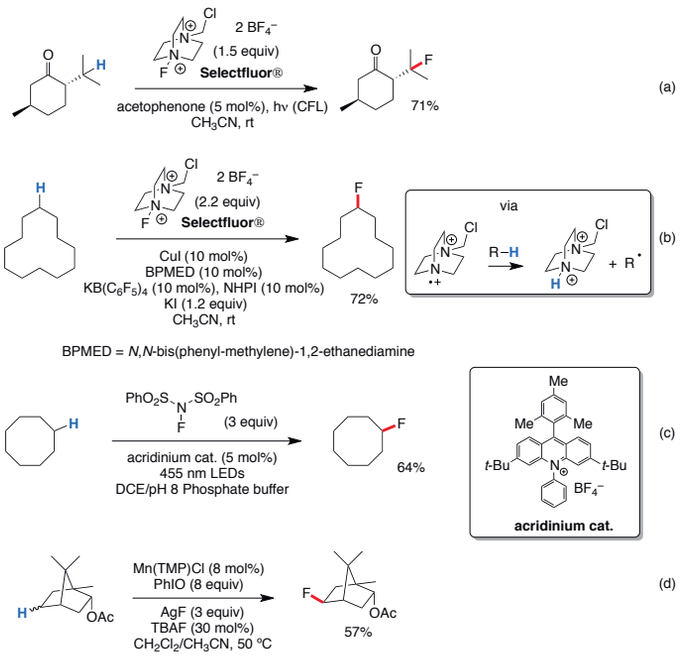
Two different mechanisms have been postulated, namely the Bloomfield mechanism[19] that involves the formation of a nitrogen-centered radical to trigger the C–H activation, or that proposed by Goldfinger,[20] in which NBS would serve as a source of molecular Br_2. In this case, the bromine radical Br would be the hydrogen atom abstracting species. Even though the Bloomfield mechanism sounded extremely appealing as it would offer an opportunity to fine tune the structure of the nitrogen-centered radical and thus improve the selectivity, strong evidence has been provided in the 1970s that the Goldfinger mechanism is more likely (for instance, changes in the structure of the *N*-bromoamide had no effect on the selectivity in allylic bromination).[16b] Nevertheless, more recently Alexanian and co-workers reinvestigated the bromination of alkanes using aromatic *N*–bromoamides as reagent (Scheme 2).[21] Excellent results were obtained with modified *N*-bromoamides for the bromination of aliphatic C–H bonds. Interestingly, the site-selectivity observed in the bromination of methylcyclohexane using these new *N*-bromoamides differed to the one observed using *N*-bromosuccinimide (NBS, AIBN, 60 ºC, neat conditions). In this case, bromination with



Scheme 1. (a) Radical bromination of allylic and benzylic CH bonds with *N*-bromoamide and *N*-bromosuccinimide (Wohl-Ziegler reaction) and (b) application in total synthesis (P. S. Baran and coworkers[18])



Scheme 2. Bromination, chlorination and xanthylation of aliphatic C–H bonds (E. J. Alexanian and coworkers[22–24,26])



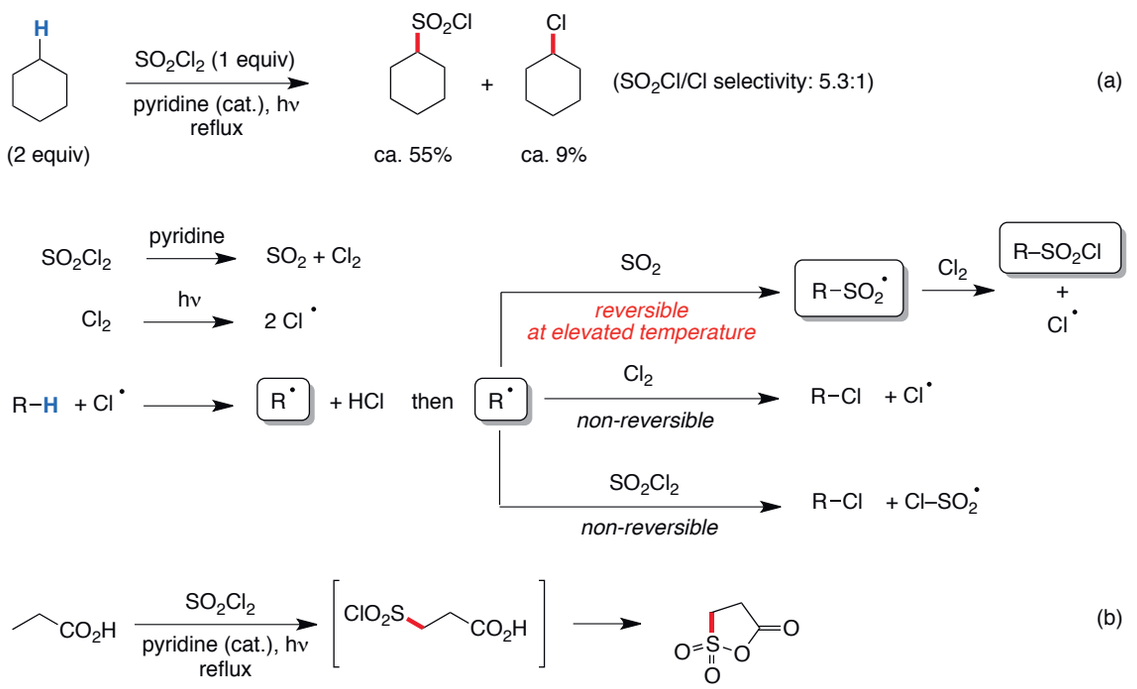
Scheme 3. Examples of radical fluorination based on a C–H activation step

NBS led to a mixture of compounds with a marked preference for the activation of the weaker tertiary C–H bond (*ca.* 62% selectivity for the tertiary position), whereas the Alexanian procedure gave almost exclusively products resulting from the activation of the stronger secondary C–H bonds. To account for their results, the author proposed a Bloomfield mechanism in which the weak *N*–Br bond is homolytically cleaved upon irradiation with visible light, leading to a bromine radical and an amidyl radical. The latter abstracts hydrogen atoms from C–H bonds and bromine transfer from the *N*–Br reagent allows for the introduction of the bromine atom with concomitant formation of an amidyl radical that sustains the radical chain (Scheme 2, Equation a). Bromination has also been achieved through a hydrogen atom abstraction promoted by an oxygen-centered radical generated from a phosphate anion and photoexcited acrydinium ion, followed by the trapping of the carbon-centered radical with diethyl bromomalonate as the bromine atom source.[22] Similarly, chlorination (Scheme 2, Equation b)[9b,23] and the introduction of a xanthate functionality (Scheme 2, Equation c)[24] have been achieved using the corresponding *N*-chloro and *N*-xanthylamide reagents. The resulting xanthates can then be used for further functionalization under radical conditions using the fantastic versatility of xanthates.[25] A similar approach has been used to perform hydrogen atom abstraction followed by a new carbon–carbon bond formation (*vide infra*).[26]

Radical fluorinations of aliphatic C–H bonds have been recently achieved using photo-excited ketones (typically benzophenone or acetophenone) as the H-abstracting species and Selectfluor® as the source of the fluorine atom (Scheme 3, Equation a).[27] The reduction of Selectfluor® with a copper(I) catalyst enables the formation of the corresponding aminyl radical cation. The latter, a strongly electrophilic species, abstracts a hydrogen from a C–H bond to generate a nucleophilic carbon-centered radical which reacts with Selectfluor® to ultimately deliver fluorinated alkanes with concomitant formation of a new aminyl radical cation that sustains the radical chain (Scheme 3, Equation b).[28] The Alexanian and Nicewicz laboratories also reported a fluorination reaction of alkanes based upon a catalytic photoredox approach. The latter requires the use of an acridinium ion/phosphate system to generate the oxygen-centered species, which abstracts the hydrogen atom from the aliphatic C–H bond, and *N*-fluorobenzenesulfonimide (NFSI) to trap the resulting carbon-centered radical (Scheme 3, Equation c).[22] Baran reported recently an electrochemical approach to radical C–H bond fluorination, in which Selectfluor® serves as the source of fluorine and sodium nitrate (20 mol%) is used as an additive to produce, upon oxidation, the radical NO_3• responsible for the initiation of the radical chain reaction (primary C–H bond activation). The aminyl radical cation generated in the fluorine atom transfer step from Selectfluor® propagates the radical chain, as described previously.[29] Finally, Groves and co-workers developed the fluorination of aliphatic and benzylic C–H bonds with manganese-oxo complexes in the presence of a source of fluoride and iodosobenzene to generate a manganese(IV) fluoride porphyrin catalyst (Scheme 3, Equation d).[30] The same group also reported the extension of this approach to the challenging preparation of ^{18}F labeling compounds for applications in positron emission tomography (PET).[31]

3.2 *Chlorosulfonylation (Reed Reaction)*

Upon exposure to SO_2 and Cl_2, alkanes were found to produce alkane sulfonyl chlorides. This reaction, known as the Reed reaction (or Reed process) was first reported by Reed in 1936.[32] The desired monosulfonyl chlorides can be obtained preferentially over, among others, the mono- and polychlorinated compounds, the polysulfonylchlorides, and various other chloroalkyl sulfonyl chlorides, with a strict control of the reaction conditions (ratio of SO_2/Cl_2, temperature, light intensity...).[33] This industrial process involves C–H bond abstraction from aliphatic positions by the chlorine radical and the trapping of the resulting carbon-centered radical with SO_2 to give an alkanesulfonyl radical (a reversible process at high temperature),[34] which ultimately delivers the corresponding sulfonyl chloride (Scheme 4, Equation a).[35] The mechanism of this reaction has been studied by Kharasch who demonstrated that sulfuryl chloride (SO_2Cl_2) can be used in the presence of a catalyst (*e.g.* pyridines, quinolines), the role of which is to decompose the reagent into Cl_2 and SO_2. The mechanism proposed by Kharasch explains why chloroalkanes (instead of alkane sulfonyl chlorides) are formed exclusively by using Cl_2 and SO_2 in the presence of a peroxide, both in the dark or upon irradiation.[13] Under these reaction conditions, the sulfonation of alkanes delivered the corresponding alkane sulfonyl chlorides,[35] whereas the use of carboxylic acid of low molecular weight led, under strictly anhydrous conditions, to sulfo-anhydride (Scheme 4, Equation b).[36]



Scheme 4. Chlorosulfonylation of alkanes (a) and carboxylic acids (b) (M. S. Kharasch and coworkers[35,36])

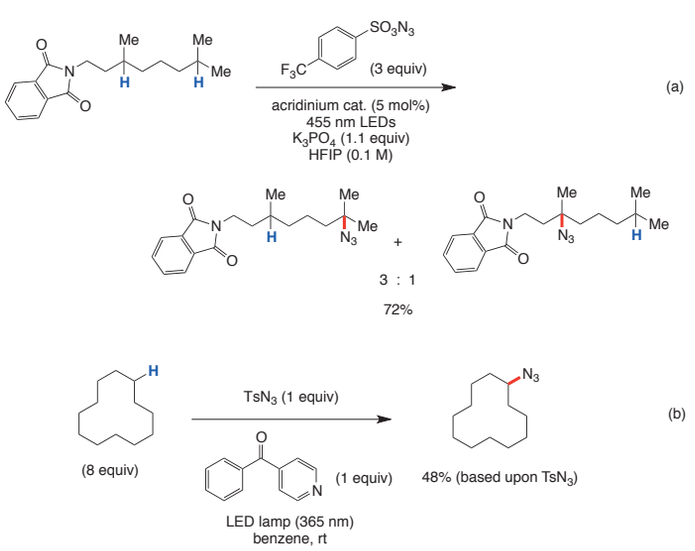
3.3 *Azidation*

The Nicewicz and Alexanian groups reported the use of acridinium catalysts, in combination with a phosphate base (*e.g.* K_3PO_4), to achieve radical C–H activation. The resulting carbon-centered radical could be utilized for a plethora of functionalizations, such as fluorination (*vide supra*), C–C bond formation (*vide infra*), or azidation reaction. In this case, trifluorobenzene sulfonylazide was used as a radical trap (Scheme 5, Equation a)[22] Similarly, C–H activation by photoexcited arylketones has been successfully achieved and the resulting nucleophilic radical trapped with tosylazide (Scheme 5, Equation b).[37]

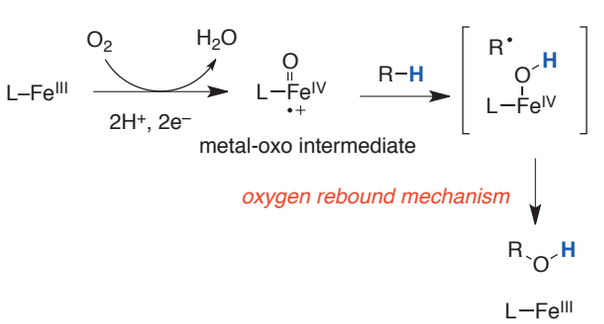
3.4 *Oxidation*

Despite its high oxidation potential, molecular oxygen in its triplet ground state is relatively inefficient to perform oxidation of organic compounds. To achieve C–H bond hydroxylation, as well as other oxidative transformations in biological processes, triplet oxygen can be activated by a range of enzyme cofactors, most of which contain transition metals (iron, copper, or manganese). Oxygen is ultimately reduced to a high-valent metal-oxo intermediate (an oxo-iron(IV) porphyrin radical cation in the case of cytochrome P450), which is responsible for the C–H bond activation. The trapping of the carbon-centered radical generated in the hydrogen atom abstraction is realized by the hydroxoiron(IV) species formed in the previous step in a mechanism now commonly accepted as the 'oxygen rebound mechanism' (Scheme 6).[38,39]

The overall process is of considerable interest as a highly efficient vehicle for the delivery of alcohols (or the corresponding carbonyl compounds upon subsequent oxidation) from simple alkanes. Therefore, considerable efforts have been made to mimic this process and develop green oxidation procedures.[8b,39] The metal center offers unique opportunity to tune the reactivity and control the regioselectivity of the hydrogen atom abstraction, ideally, regardless of the structure of the substrate and the innate reactivity of the different C–H bonds. Many other approaches have been employed to perform the oxidation of the C–H bond into the corresponding C–OH or C=O bonds and a variety of reagent leading to oxygen-centered radicals have been tested for this purpose (*e.g.* TEMPO, *N*-hydroxyphthtalimide (NHPI)). Baran developed an electrochemical oxidation of aliphatic C–H bonds based upon the use of quinuclidine as a precursor for the corresponding aminyl radical cation, which is responsible for the hydrogen atom abstraction. Trapping of the carbon-centered radical with O_2 leads to a peroxyl radical, which, under the electrochemical conditions employed, eventually delivers the corresponding alcohols (for tertiary C–H bonds) or ketones (for secondary C–H bonds). The efficiency of the process has been illustrated by the oxidation of sclareolide on a 50 g scale (Scheme 7, Equation a).[40]

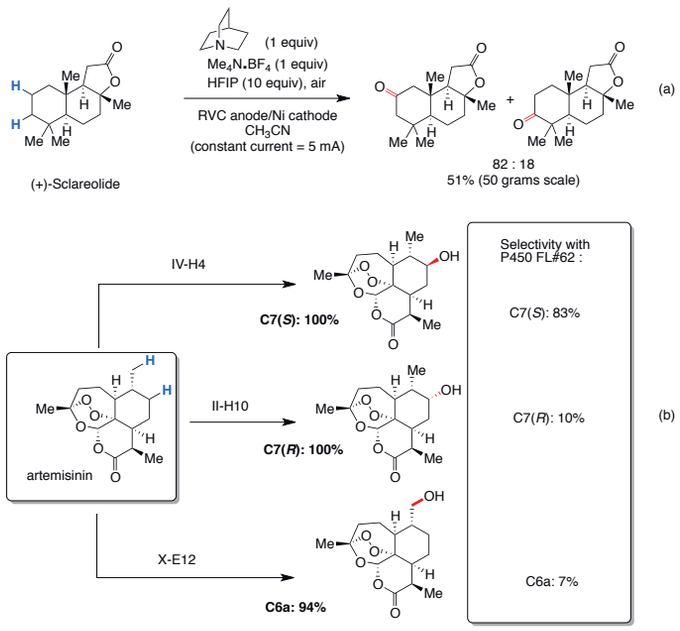


Scheme 5. Examples of radical azidation *via* direct C–H activation



Scheme 6. Hydroxylation with cytochrome P450 (the rebound mechanism)

In a completely different approach, rational design has been used to modify the active site of enzymes and thus, alter the site-selectivity and the stereoselectivity of the oxidation process. A striking example is the work of Fasan and co-workers, presented in Scheme 7, Equation b, in which they were able to direct the mono-hydroxylation of artemisinin by using modified enzymes, in combination with a NADPH cofactor regeneration system. Starting from FL#62, an engineered variant of the fatty acid monooxygenase P-450$_{BM3}$ from *Bacillus megaterium*, they were able to improve its promising activity for the oxidation of artemisinin and ultimately access three different monohydroxylated regio- and stereoisomers. Interestingly, not only were the authors able to improve the original FL#62 selectivity of the mono-hydroxylation of artemisinin with enzymes IV-H4, but they could also reverse the stereoselectivity (with enzymes II-H10) or even access other analogues (with enzymes X-E12). The modified P450 enzymes led to the hydroxylated derivatives in high yields (0.4 g scale), with excellent regiocontrol and stereoselectivity for the oxidation of artemisinin, while the parent monooxygenase P-450$_{BM3}$ showed no activity at all (Scheme 7, Equation b).[9a,41,42]



Scheme 7. (a) Electrochemical oxidation of aliphatic C–H bonds (P. S. Baran and coworkers[40]); (b) Directed C–H bond hydroxylation with three modified P450 enzymes (IV-H4, II-H10 and X-E12)

4. Carbon–Carbon Bond Formation

4.1 *Hydrogen Atom Transfer (and Related Processes)*

Two slightly different mechanisms will be discussed in this section, namely the direct hydrogen atom transfer, with hydrogen atom abstraction from the precursor by the radical adduct resulting from the C–C bond formation (Scheme 8, Equation a), and indirect hydrogen atom transfers, which requires the intervention of a mediator in the radical chain process (Scheme 8, Equation b).

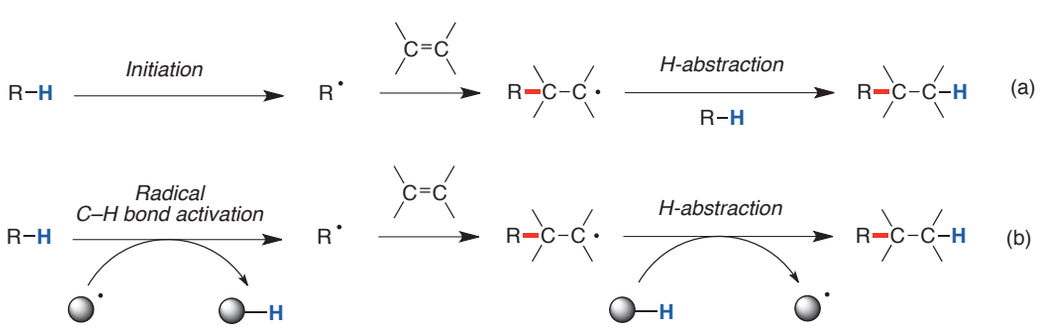
Kharasch reported in the 1950s that, in the presence of a radical initiator such as acetyl peroxide or upon visible light irradiation, aldehydes added to olefins to give ketones.[43] A radical chain mechanism involving the generation of an acyl radical through hydrogen atom abstraction from the aldehyde, followed by addition onto the alkene and the abstraction of the aldehydic C–H bond by the resulting carbon-centered radical was proposed to account for the formation of the adducts (Scheme 9).

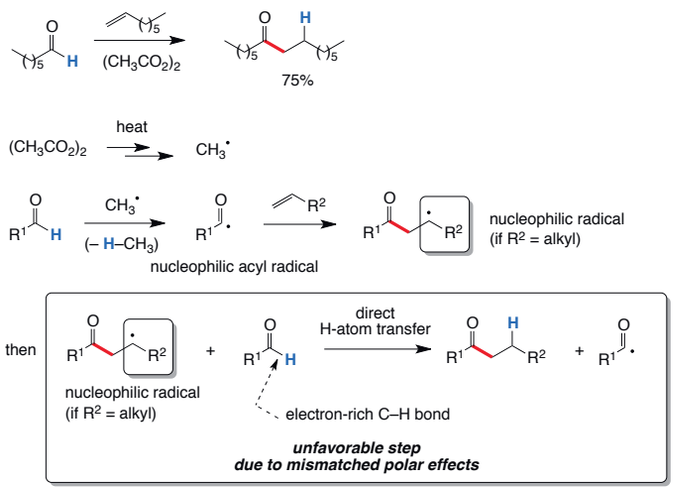
The poor efficiency of this process is attributed to the lack of efficiency of the C–H bond abstraction by nucleophilic carbon-centered radicals. Roberts and co-workers showed later that the process could be significantly improved by using substoichiometric amounts of a thiol (Scheme 10, Equation a).[44] Thiols are excellent hydrogen atom donors and the corresponding thiyl radicals are electrophilic, which makes them more suitable than carbon-centered radicals to abstract hydrogen atoms from electron-rich C–H bonds.[45] In this approach the inefficient step of direct hydrogen atom abstraction by the carbon-centered radical is advantageously replaced by two more efficient steps: hydrogen atom abstraction from a good hydrogen atom donor (the thiol), and hydrogen atom abstraction from the aldehyde by the electrophilic species (the thiyl radical) generated in the previous step (concept of polarity reversal catalysis).[46] This approach was successfully applied in its intramolecular version to the synthesis of (–)-cyanthiwigin F, a marine polycyclic compound isolated from the marine sponge *Myrmekiodermastyx* (Scheme 10, Equation b).[47]

Photoexcited aryl ketones have been found to abstract hydrogen atoms from electron-rich C–H bonds, including those located alpha to oxygen and nitrogen atoms.[48] The excited triplet state (unpaired electron with the same spin) of aryl ketones has for instance been used to initiate radical chain reactions in which a hydrogen atom transfer takes place. The hydrogen atom is initially abstracted from a C–H bond to generate a nucleophilic alpha-oxyalkyl radical (from alcohols, acetals, or aldehydes), which then adds to electron-poor alkenes such as vinylketones. The resulting electrophilic carbon-centered radical abstracts a hydrogen from an electron-rich C–H bond in the precursor, delivering the desired adduct and generating a new radical species thereby propagating the chain (Scheme 11, Equation a).[49] In order to circumvent the problems of purification on large scale posed by the presence of starting benzophenone and benzopinacol resulting from the dimerization of the hydroxydiphenylmethyl radical intermediate, Fraser-Reid and co-workers showed that this method of initiation could be advantageously replaced with the use of di-*tert*-butyl-hyponitrite (DTBHN) as a source of alkoxy radicals,[50] allowing the isolation of the adducts in high yields (Scheme 11, Equation b).[51]

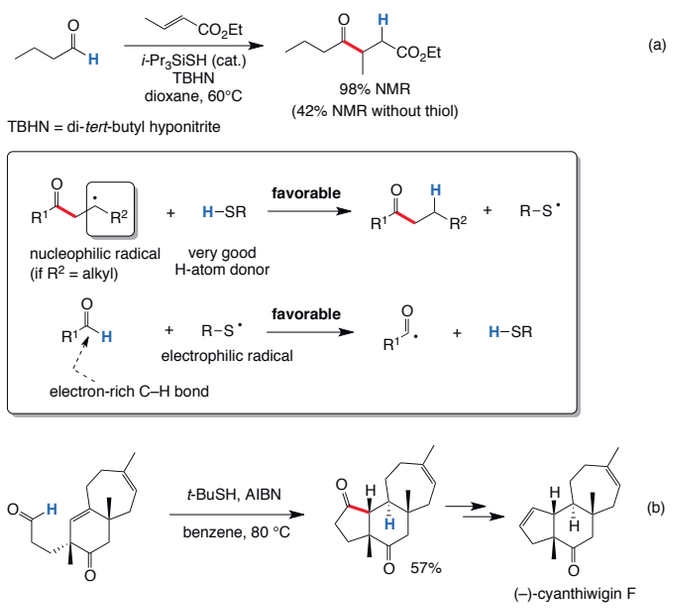
Polyoxometalates (POMs) such as the tetrabutylammonium salt of the decatungstate $[W_{10}O_{32}]^{4-}$ anion (TBADT) are a class of photocatalysts which can be regarded as mimics of alkoxyl radicals as they are characterized by the presence of highly electrophilic oxygen centers with partial radical character. As such, they can react either *via* single electron transfers or by direct hydrogen atom transfer (HAT). Accordingly, they were found to be

Scheme 8. Hydrogen atom transfer radical chain reaction (with or without relay)





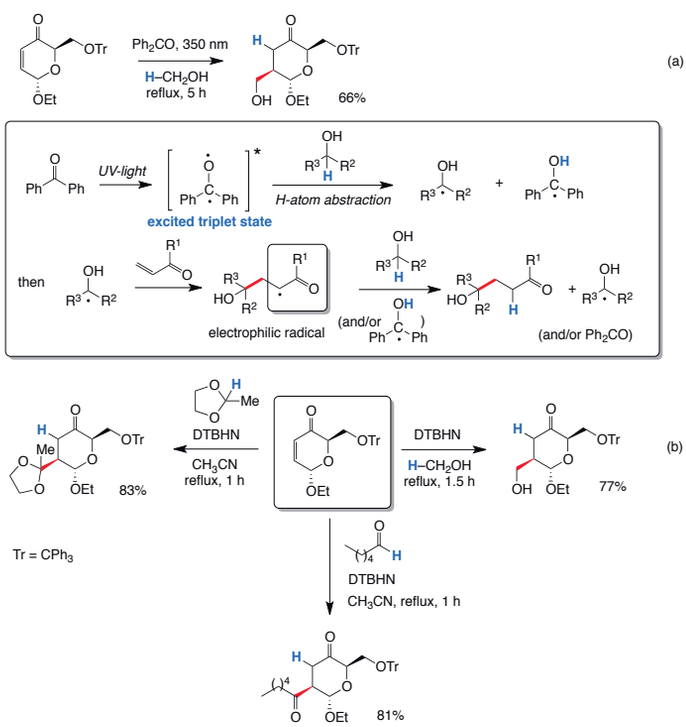
Scheme 9. Non-catalyzed addition of aldehydes to alkenes initiated by peroxides (M. S. Kharasch *et al*.[43])



Scheme 10. (a) Inter- and intramolecular addition of aldehydes to alkenes using the concept of polarity reversal catalysis (B. P. Roberts[46]); (b) Application in total synthesis (B. M. Stoltz[47])

excellent reagents to abstract, upon irradiation, a hydrogen atom from electron-rich C–H bonds, such as those located alpha to an oxygen atom. These include alcohols, dialkylethers and aldehydes (Scheme 12, Equation a).[52] However, their field of application is not limited to the generation of alpha-oxyalkyl radicals and efficient processes involving the abstraction of a hydrogen atom from benzylic[53] or even aliphatic C–H bonds[8e,54] have been reported.[55] Interestingly, due to the electrophilic character of the photoexcited polyoxometalate anion, a high regioselectivity for the more electron-rich C–H bond is usually observed with ketones and nitriles as the precursors (Scheme 12, Equation b).[56,57] Acyl radicals generated from the corresponding aldehydes in the presence of TBADT were added to electron-alkenes leading to dissymmetrical ketones.[52c]

The Nicewicz and Alexanian groups reported carbon–carbon bond formation reactions using an acridinium catalyst and a phosphate base to achieve the initial radical C–H activation.[22] The acridinium ion is a highly oxidizing photo-redox catalyst ($E_{1/2}$(cat*/cat·) = +2.08 V vs SCE), which could generate oxygen-centered radicals upon irradiation with visible light (450 nm LEDs) *via* single electron transfer (SET) with the phosphate anion. The resulting phosphate-derived oxygen-centered radical can then abstract a hydrogen atom from a variety of C–H bonds to give the corresponding carbon-centered radicals. The latter could then react with a range of classical radical trap to achieve C–heteroatom (*e.g.* bromination, chlorination, fluorination, trifluoromethylthiolation, azidation), or C–C bond formation (Scheme 12, Equation c), provided that in this case a more reducing acridinium catalyst is used (the role of which is likely to reduce the radical resulting from the addition to the electron-poor acceptor to the corresponding carbanion).



Scheme 11. Addition of alcohols, ethers and aldehydes to alkenes promoted by photo-excited aryl-ketones or initiated by di-*tert*-butylhyponitrite (DTBHN) (B. Fraser-Reid and coworkers[51])

By combining the developments issued from the Knowles and Alexanian laboratories, the two groups have recently developed a C–H alkylation reaction involving a multisite-proton-coupled electron transfer (MS-PCET).[26] A noncovalent complex formed between an iridium(III) photocatalyst and a monobasic phosphate was suggested to be the active species that abstracts the hydrogen atom at C–H bonds, including from aliphatic side chains. The resulting radical species was efficiently trapped with electron-poor alkenes such as the 1,1-bis-(phenylsulfonyl)ethylene (Scheme 12, Equation d).

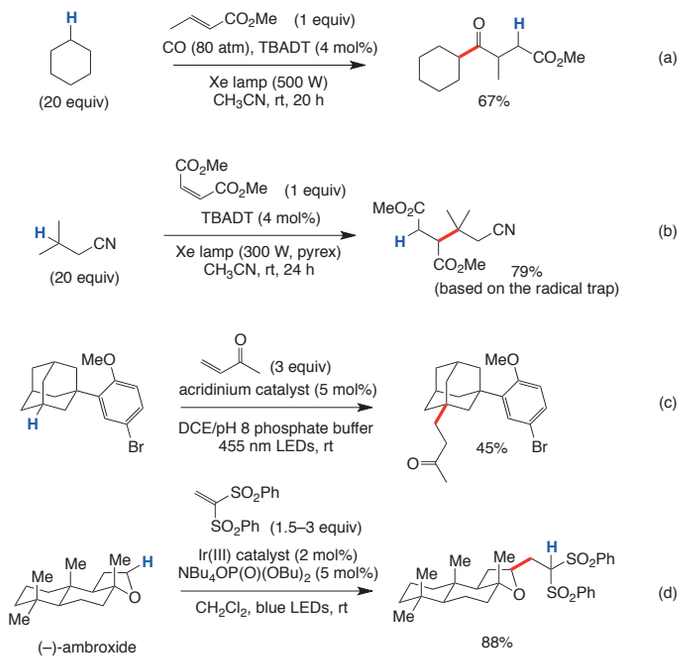
4.2 *Homolytic Aromatic Substitution: Minisci-type Reactions*

The replacement of a hydrogen atom in the heteroarene is the result of a homolytic aromatic substitution process and not a radical C–H bond activation. The discussion below has been limited to methods that involve a C–H bond activation to generate the radical species that adds to the heteroaromatic compound.

4.2.1 *H-Abstraction alpha to an Oxygen Atom*

Following their pioneering work in the field,[58] Minisci and coworkers also used C–H bond activation at the alpha position of the oxygen atom in alcohols, ethers and formamides to achieve functionalization of pyridines and related heteroarenes (*via* their activated protonated form). The reaction required the use of a peroxide (as a source of oxygen-centered radical) and a Brønsted acid for the activation of the heteroarene as the corresponding protonated ions.[59]

Elad showed that, upon irradiation with ultraviolet light (λ > 260 nm) or, alternatively upon irradiation in the presence of a

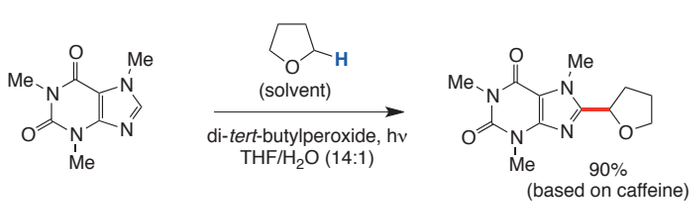


Scheme 12. C–C Bond formation *via* C–H bond activation and with alkenes as the radical trap.

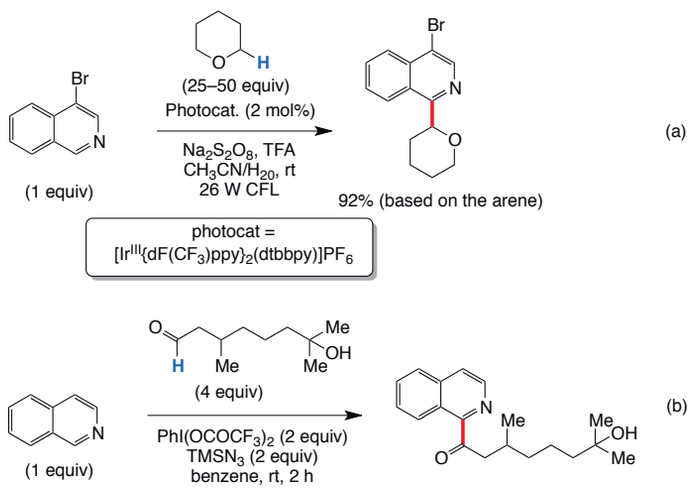
peroxide such as di-tertbutylperoxide or dicumylperoxide (λ > 290 nm), alpha-oxoalkyl radicals could be efficiently generated from ethers and acetals and condensed with purine derivatives such as caffeine, adenine or guanosine, selectively at position 8 (Scheme 13).[60] It was proposed that the hydrogen atom abstraction is achieved by alkoxy radicals (generated by decomposition of the peroxide upon irradiation) whereas, in the absence of peroxide, the excited purine system would be the hydrogen atom abstracting species.

Due to the importance of this type of structural motif, extensive work has been conducted in this field to increase the scope of the reaction and develop milder reaction conditions to achieve the functionalization of heteroarenes. In this context, substantial advances have been made in the past ten years.[61] For instance, efforts have been made to achieve this transformation in the absence of a protic source. The reaction has been found to proceed with alcohols in the presence of dicumyl peroxide and substoichiometric amounts of $PdCl_2$ in place of the strong Brønsted acid.[62] Similarly, ethers were condensed with heteroarenes in the presence of di-tert-butylperoxide and a substoichiometric amount of scandium triflate ($Sn(OTf)_3$).[63]

Hydrogen atom abstraction alpha to the oxygen atom of ethers has also been achieved thanks to a persulfate salt in combination with the use of a photocatalyst and the resulting alpha-oxyalkyl radical trapped with a variety of heteroarenes under mild conditions (Scheme 14, Equation a).[64] Antonchick and coworkers reported a Minisci-type coupling reaction between aldehydes and heteroarenes promoted by (bis(trifluoroacetoxy)iodo)benzene ($PhI(OCOCF_3)_2$ or PIFA) and $TMSN_3$ or NaN_3. In this case, the C–H bond activation in the starting aldehyde is posited to be



Scheme 13. UV-light induced C–H bond functionalization with cyclic ethers (D. Elad[60])



Scheme 14. Heteroarene functionalization with alpha-oxyalkyl radicals generated via a radical C–H bond activation: (a) Addition of cyclic ethers (Z. Z. Huang and coworkers[63]); (b) Acylation reaction (A. P. Antonchick and coworkers[65])

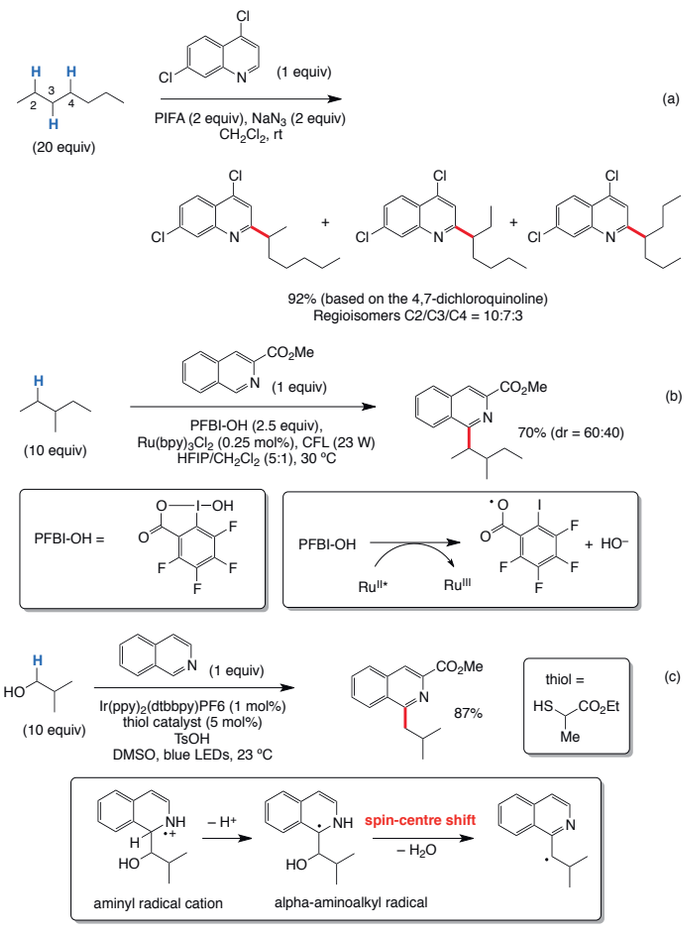
achieved by the azide radical (N_3•) resulting from the homolytic cleavage of the iodine-nitrogen bond in the $PhI(OCOCF_3)(N_3)$ species intermediate (Scheme 14, Equation b).[65]

4.2.2. *H-Abstraction at Aliphatic Positions*

The system developed by Antonchick and co-workers (PIFA/NaN_3) also allowed for the C–H bond activation of simple alkanes.[66] Simple cyclic alkanes give the Minisci-type adducts in good to high yields. As expected, linear alkanes lead to a mixture of regioisomers as the result of a lack of selectivity in the hydrogen atom abstraction step, with a preference for the activation of tertiary C–H bonds (Scheme 15, Equation a). Contrary to these observations, Chen, He and coworkers reported recently a photoredox-mediated alkylation of heteroarenes with a high selectivity for the C–H bond activation at methylene sites (Scheme 15, Equation b).[67] In this case, the radical species that abstracts the hydrogen atom from the C–H bond was proposed to be a carboxyl radical resulting from the reduction of a hypervalent iodine derivative, a perfluoro analogue of hydroxyl benziodoxole (PFBI-OH) by the photoexcited state of a ruthenium(II) catalyst ($Ru(bpy)_3Cl_2$) generated upon irradiation with visible light (23 W compact fluorescent lamp (CLF)). The authors showed that the presence of the fluoro substituent on the aromatic ring *ortho* to the carboxyl group was crucial to achieve high selectivity for the methylene C–H bonds, even though the reason for this preference remained unclear. To circumvent the regioselectivity issues observed with simple alkanes, MacMillan developed an elegant approach, drawing inspiration from the biosynthesis of DNA, which invoques a spin-center shift (SCS) process leading to a new carbon-centered radical with concomitant elimination of water. In this approach, alcohols serve as a source of oxyalkyl radicals and the corresponding primary adducts (aminyl radical cation) evolve by loss of a proton to give the corresponding alpha-aminoalkyl radical, which undergoes a spin-center shift to eventually deliver the corresponding deoxygenated adduct (Scheme 15, Equation c).[68] The hydrogen atom abstraction from the C–H bond alpha to the hydroxyl group is achieved by a thiyl radical. Overall, this approach allows for a formal C–H bond activation of primary and secondary position, with a high regioselectivity.

4.3 *Fragmentation Methods*

The C–H bond activation promoted by photoexcited aromatic ketones can be coupled with the formation of carbon–carbon bonds.[48] Cyanation, allylation, vinylation and alkynylation have been successfully achieved using the fragmentation method with sulfone-based radical traps with a wide range of



Scheme 15. (a) and (b) Generation of alkyl radicals *via* C–H bond activation at aliphatic positions (groups of A. P. Antonchick[66] and G. Chen[67]); (c) Regioselective C–H bond activation from alcohols and spin-centre shift (SCS) process (D. W. C. MacMillan[68])

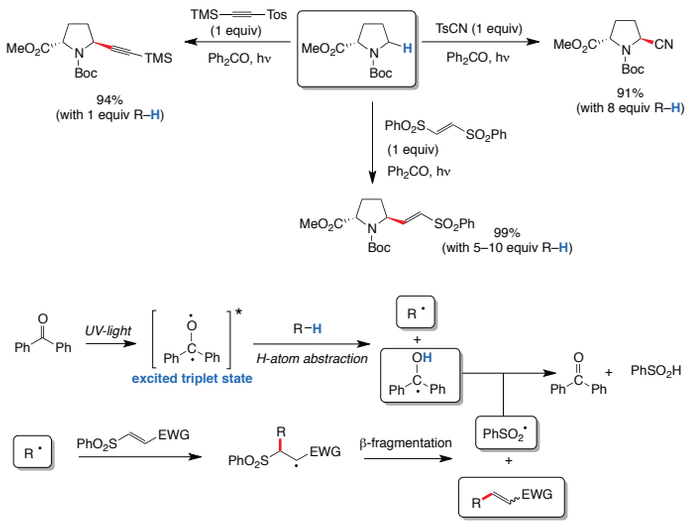
substrates, including cyclic amines (Scheme 16) and ethers, alcohols, and molecules presenting unactivated aliphatic C–H bonds. Single electron transfer (SET) between the sulfonyl radical released in the fragmentation step and the hydroxydiphenylmethyl radical intermediate allows for the regeneration of benzophenone.

4.4 *Carbon–Carbon Bond Forming Reaction via Radical C–H Bond Activation and Transition Metal-catalyzed Cross-coupling Reaction*

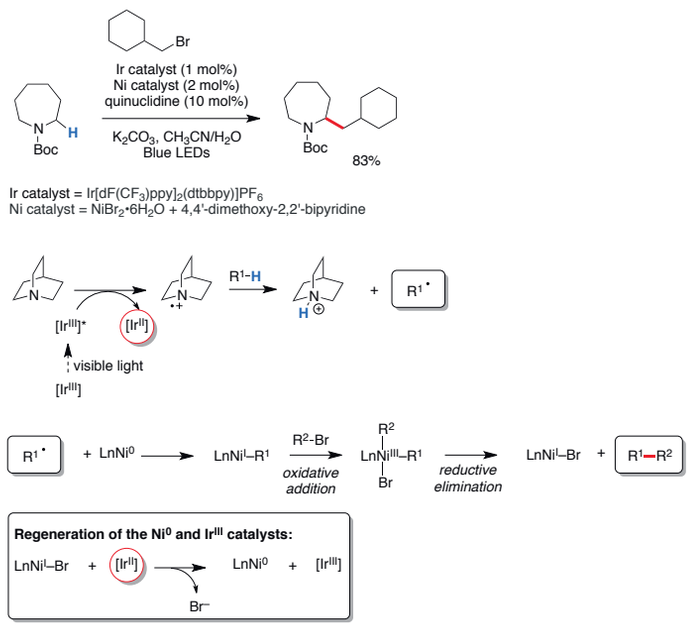
MacMillan and co-workers developed a triple catalytic combination, which allows for the C–H bond functionalization alpha to a nitrogen,[69] oxygen or sulfur atom using a catalytic systems comprised of an iridium(III) photocatalyst and a quinuclidine derivative to achieve the C–H bond abstraction (*via* the formation of the quinuclidine aminyl radical cation), an alkyl bromide, and a nickel(II) catalyst for the subsequent cross-coupling reaction (Scheme 17).[70,71]

5. Conclusion

In the past ten years, intermolecular hydrogen atom transfer (HAT) has gained considerable interest as a new approach for the generation of carbon-centered radicals. Since the early observations that C–H bonds could be cleaved by radical species (the decomposition of chloroform to give phosgene and HCl under air atmosphere is known since the nineteenth century), considerable progress has been made to extend the scope of transformations that can be achieved, sometimes with high regioselectivity. The development of mild reaction conditions, together with a growing understanding of the factors that govern the site-selectivity



Scheme 16. UV-light induced C–H bond functionalization with cyclic ethers (S. Kamijo[48])



Scheme 17. Generation of carbon-centred radical *via* intermolecular C–H bond activation and subsequent nickel-catalysed cross-coupling reaction with alkyl bromides (D. W. C. MacMillan and coworkers[70])

of these processes, has led to spectacular examples of 'late stage functionalizations (LSFs)',[3,8b,10b] an extremely appealing approach for many applications, and especially for the diversification of drug leads. Indeed, by generating analogs rapidly from advanced intermediates, the late stage functionalization approach delivers oxidized metalolites (C–H oxidation reactions), or analogs *via* new carbon–carbon or carbon–heteroatom bonds formation. Nevertheless, important issues still need to be solved, as illustrated by the functionalization of 'unreactive' alkanes, for which large excesses of the substrate are often required to get high yields. Moreover, with these types of precursors, the regioselectivity of the C–H bond activation is rarely controlled, thus leading to a mixture of functionalized products (except with symmetrical, cyclic systems where all C–H bonds are identical). In principle, these disadvantages could also be turned into a more concise strategy, as one single reaction could deliver several analogues. The lack of selectivity can then become an asset, as long as analytical methods to analyze complex mixture are available,[72] and purification techniques capable of delivering pure, fully characterized compounds.

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