

Chapter 2

Recent Advances in Non-directed C(sp³)-H Bond Functionalization

Abstract Selective functionalization of one specific C(sp³)-H bond in a complex molecule without the assistance of a directing group represents the state of the art in organic synthesis and will be a dynamic topic in future. In the past decade, many excellent methods have been developed to accomplish this goal with transition-metal catalysts and even under metal-free conditions. In this chapter, we summarize the recent achievements in this realm during the past 5 years, including oxidative functionalization of α -C(sp³)-H bonds adjacent to heteroatoms, allylic, benzylic, and unactivated aliphatic C(sp³)-H bonds. The total redox-neutral C(sp³)-H bond functionalization is also briefly introduced.

Keywords C-H activation • Tertiary amines • Ethers • Alcohols • sp³ C-H bond • C-H oxidation • C-C coupling • C-H amidation • Metal-free C-H activation • Redox-neutral

2.1 Introduction

Hydrocarbons are main feedstock for chemical industry from oil and natural gas. Generally, a C(sp³)-H bond is not considered as a functional group due to its low reactivity and high thermodynamic stability. The development of mild and efficient methodologies to directly convert C(sp³)-H bonds into other important functionalities would be of meaningful importance in fundamental research and industrial production. Compared with directing group-assisted C-H bond functionalization (Chap. 1) the introduction and subsequent removal of directing groups is not necessary, rendering this chemistry even more attractive and sustainable.

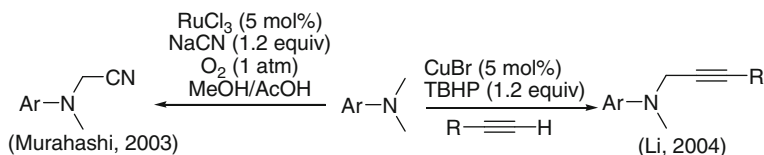
Depending on the substrate structures, especially in the case of radical C(sp³)-H bond functionalization, the bond dissociation energy (BDE) dominates the regioselectivity of the transformation. This field experienced a big boom in the last decade (Fig. 2.1a). However, for complex molecules, the site selectivity of one orientable C(sp³)-H bond from different kinds of C(sp³)-H bonds becomes a tractable obstacle. Allegorically, the C-H bonds in one complex molecule could be



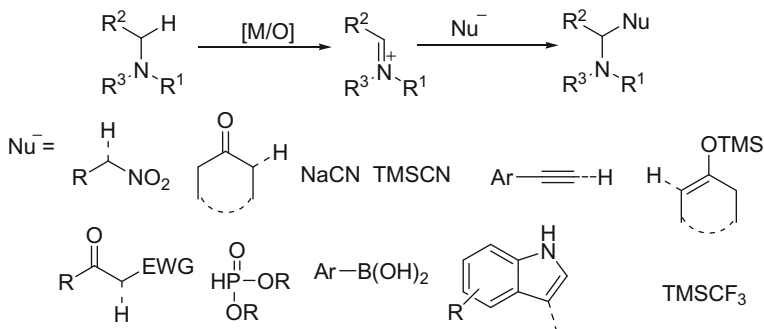
regarded as lots of naughty children. If we can completely know everyone (like every C–H bond in one molecule), it is easy for us to distinguish the slight differences. With profuse efforts, the reactivities of different C(sp³)–H bonds in some natural products turned out to be accessible by electronic, steric and stereoelectronic effects (Fig. 2.1b), leading to correct prediction of chemo- and regioselectivity. This new direction is mainly underdeveloped and should attract considerable future attention.

2.2 Oxidative Functionalization of α -C(sp³)-H Bond Adjacent to Nitrogen Atoms

Murahashi et al. [1] reported Ru(III)-catalyzed aerobic oxidative cyanation of *N,N*-dimethylanilines with NaCN in 2003, and the next year Li and co-workers developed an efficient Cu(I)-catalyzed alkynylation of tertiary amines with TBHP



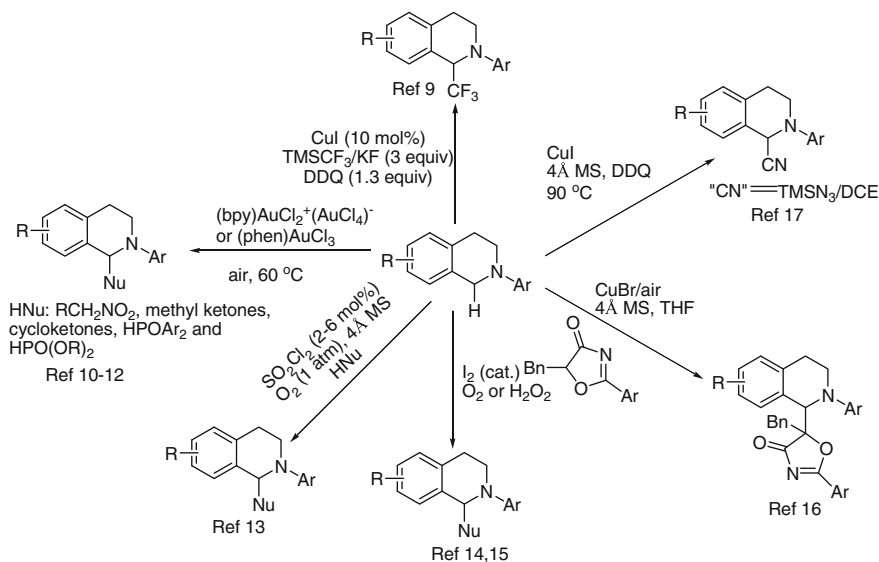
Scheme 2.1 Pioneering work for the oxidative functionalization of tertiary amines [1, 2]



Scheme 2.2 The previous works on oxidative functionalization of tertiary amines

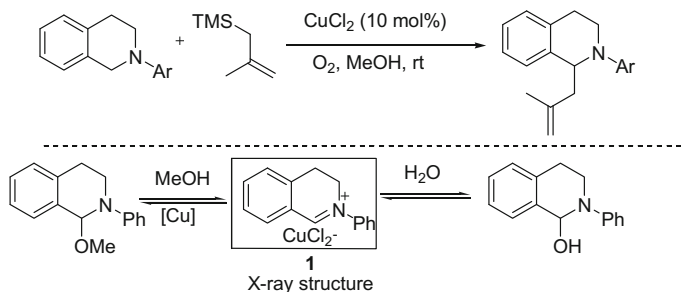
as oxidant (Scheme 2.1) [2]. Both pioneering works stimulated a fast development of oxidative functionalization of tertiary amines. The broad scope and good functional group compatibility enabled various nucleophiles for C–C and C–X bond formation (Scheme 2.2). Several important reviews have highlighted the achievements from 2003 to 2010 [3–7].

The incorporation of fluorine-containing motifs into organic molecules can bring substantial improvement on its bioactivity, chemical and physical properties. Using difluoroenol silyl ethers as nucleophile, the difluoromethylation of *N*-Aryl tetrahydroisoquinoline derivatives was reported in 2009 [8]. Later, copper-catalyzed oxidative C(sp³)-H bond trifluoromethylation of *N*-Aryl tetrahydroisoquinolines with Ruppert-Prakash reagent was developed (Scheme 2.3) [9]. In 2012, Zhu et al. reported on a highly efficient gold(III)-complex catalyzed cross-dehydrogenative coupling (CDC) reaction of *N*-Aryl tetrahydroisoquinolines with various nucleophiles (Scheme 2.3) [10–12]. The most remarkable advantage of Zhu's work is the replacement of an external synthetic oxidant with air, contributing a sustainable gold-catalyzed aerobic oxidative coupling to the community. Subsequently, metal-free, oxidative CDC couplings of *N*-Aryl tetrahydroisoquinolines with various nucleophiles in the catalysis of SO₂Cl₂ [13] and I₂ [14, 15] were disclosed. Interestingly, the 5*H*-oxazol-4-ones were also an efficient coupling partner under copper catalysis or metal-free reaction conditions. [16] More recently, an unprecedented copper-catalyzed cyanation of α -C–H of tertiary amines was reported by employing the combination of TMSN₃ and DCE as novel “CN” source [17].



Scheme 2.3 Recent works on oxidative functionalization of *N*-Aryl tetrahydroisoquinolines [9–17]

Although the copper-catalyzed oxidative functionalization of tertiary amines was well studied, the corresponding mechanistic studies remained elusive. In 2011, Klussmann et al. disclosed the first detailed mechanism of this type of aerobic oxidative Mannich reactions through NMR analysis [18, 19]. The key active intermediate, iminium dichlorocuprate complex **1** was structurally characterized by X-ray crystallography (Scheme 2.4). The solvent plays an important role in the reaction process. It would be a stable reservoir to form hemiaminal methyl ethers, avoiding the decomposition of active iminium ions. The group of Doyle also verified the real role of transition metals in the oxidative Mannich reactions [20]. They assumed that the general role of $\text{Rh}_2(\text{cap})_4$, $\text{RuCl}_2(\text{PPh}_3)_3$, CuBr , FeCl_3 , or

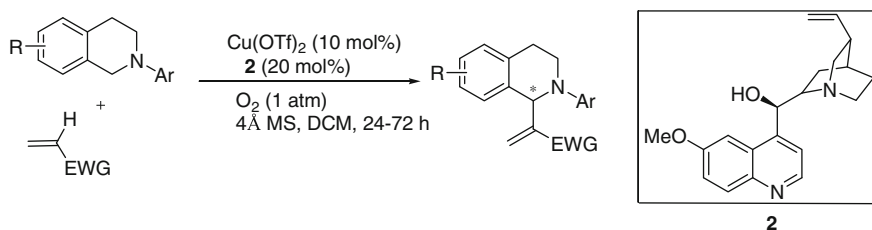


Scheme 2.4 Cu-catalyzed aerobic oxidative allylation of tertiary amines and mechanistic studies [18]

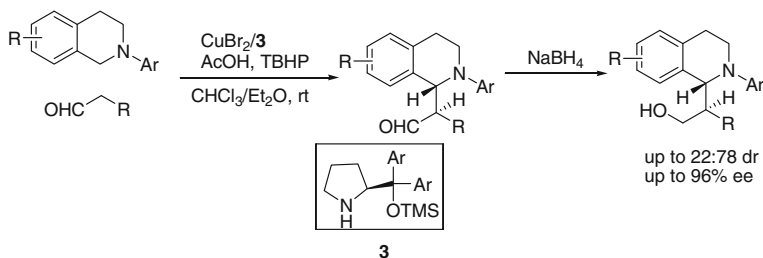
Co(OAc)₂ was to initiate the formation of *tert*-butylperoxy radical (*t*BuOO $\cdot$) from TBHP, and the *tert*-butylperoxy radical mediates the single electron transfer (SET) instead of the transition metals, as previously proposed. Recent findings further demonstrated that use of alternative oxidants could efficiently achieve oxidative coupling in the absence of metals [15, 21–28].

During the past 5 years, it is our pleasure to witness the development of enantioselective C(sp³)-H functionalization of amines. An early asymmetric CDC reaction of *N*-Aryl tetrahydroisoquinolines with α,β -unsaturated aldehydes and ketones was accomplished in 2012 by Wang's group on using organocatalyst/metal cooperative catalysis (Scheme 2.5) [29]. Moderate to good yields and good enantioselectivities were obtained in the presence of oxygen atmosphere. Unfortunately, the reaction scope is limited to reactive *N*-Aryl tetrahydroisoquinolines. It constitutes an impressive example in the enantioselective C(sp³)-H bond functionalization. As a follow-up work, they successively finished organocatalytic asymmetric CDC coupling of *N*-Aryl tetrahydroisoquinolines with cycloketones [30].

In the same year, Chi et al. developed an enantioselective oxidative coupling of tertiary amines with aliphatic aldehydes by combination of copper catalysis and aminocatalysis (Scheme 2.6) [31]. Both *N*-Aryl tetrahydroisoquinolines and simple *N*-Aryl tertiary amines can undergo this enantioselective alkylation reaction. Soon afterwards, organocatalytic enantioselective CDC reaction of ethers with aliphatic aldehydes [32] and Cu-catalyzed asymmetric CDC reaction of *N*-carbamoyl tetrahydroisoquinolines with terminal alkynes [33] were reported.



Scheme 2.5 Cu-catalyzed aerobic oxidative asymmetric olefination of tertiary amines [29]

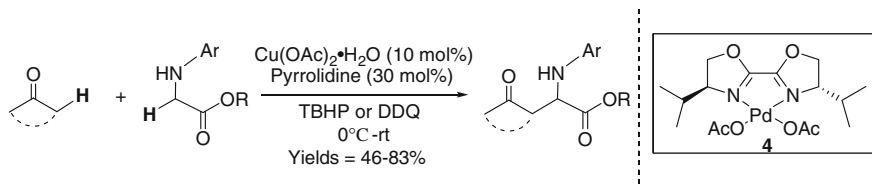


Scheme 2.6 Cu/organocatalyst co-catalyzed enantioselective α -C(sp³)-H alkylation of tertiary amines [31]

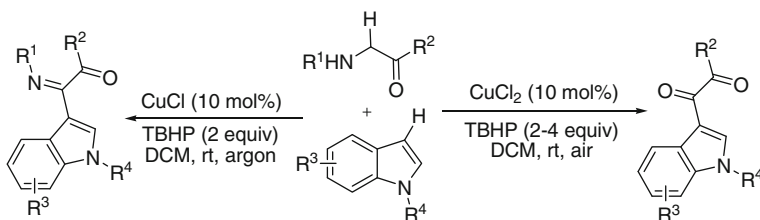
With copper/aminocatalyst relay catalysis, the first oxidative cross-coupling of *N*-Aryl glycine ester and ketones was achieved in the presence of TBHP or DDQ (Scheme 2.7) [34]. Interestingly, different oxidants determine the coupling partner leading to different products. TBHP favors the coupling of methyl ketones and DDQ prefers the coupling of cycloketones. The preliminary enantioselective version was explored by testing different chiral aminocatalysts (up to 15 % ee). Inspired by this work, a highly enantioselective CDC reaction of *N*-Aryl glycine esters and 1,3-diketones was developed [35]. In early 2015, enantioselective C(sp³)-H arylation of *N*-Aryl glycine esters and amides with aromatic boronic acids was accomplished in the presence of chiral Pd(II)-complex **4** (Scheme 2.7) [36]. Besides, Cu-catalyzed aerobic oxidative couplings of glycine esters, amides, and short peptides with indoles were also reported [37]. The mild reaction conditions enable the reaction to be scaled up to 10 g.

An intriguing oxidative coupling of indoles with α -amino ketones can selectively afford α -aryl α -imino and α -aryl α -oxo carbonyl compounds under argon and air atmosphere, respectively (Scheme 2.8) [38]. The mechanistic studies demonstrated that stronger oxidizing conditions favored the hydrolysis process, and the traditional acidification hydrolysis is unlikely. Later, oxidative phosphorylation and alkylation of α -amino ketones with diarylphosphine [39] and ethers [40] were reported.

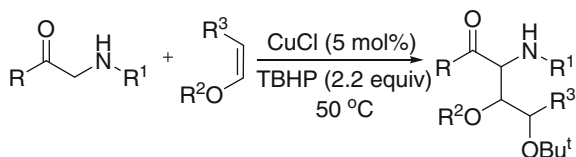
Li's copper-catalyzed oxidative difunctionalization of enol ethers with α -amino carbonyl compounds was recently reported (Scheme 2.9) [41]. This protocol allows rapid synthesis of 2-amino-3,4-dioxy carbonyl products. Significantly, metal-free, DTBP-mediated direct alkylation of α -amino carbonyl compounds with C-H bond of simple alkanes was developed by Cheng and co-workers [42].



Scheme 2.7 Cu/amine synergetic catalysis for CDC of ketones and *N*-Aryl glycine ester [34]

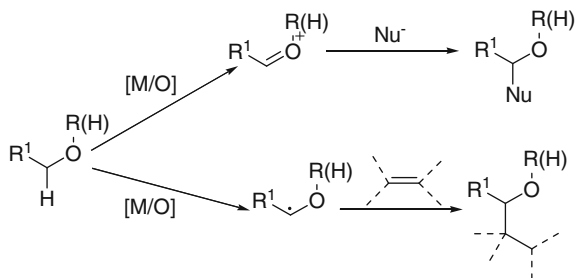
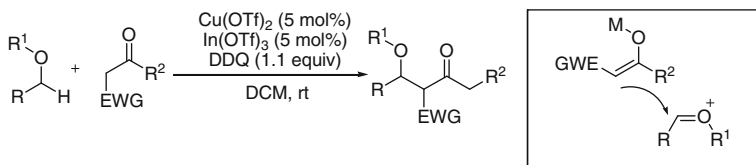


Scheme 2.8 Cu-catalyzed oxidative coupling of α -amino ketones with indoles [38]

**Scheme 2.9** Cu-catalyzed tandem C-C and C-O coupling of enol ethers [41]

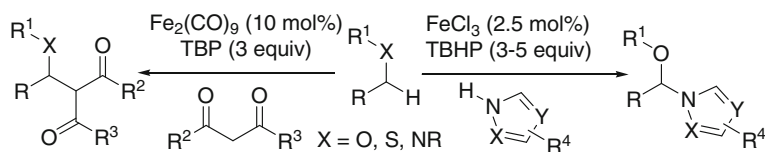
2.3 Oxidative Functionalization of α -C(sp³)-H Bond Adjacent to Oxygen Atom

Ethers and alcohols are important chemical stocks. The chemical modification of these chemicals should be of great interest (Scheme 2.10). In 2006, the group of Li introduced the first example of oxidative CDC reaction of cyclic ethers with malonates and meldrum's acids under a bimetallic catalytic system of Cu(OTf)₂/In(OTf)₃ (Scheme 2.11) [43]. Increasing the reaction temperature from room temperature to 100 °C, allows for a metal- and solvent-free CDC reaction of ketones with isochromanes [44]. The authors reasoned that the generated 2,3-dicyano-4,5-dichlorohydroquinone anions in situ during oxidation of ethers would facilitate the enolization of ketones. As a follow-up work, the same group developed a sustainable aerobic CDC reaction of ethers and carbonyl compounds with catalytic amount of NHPI (*N*-hydroxyphthalimide), Cu(OTf)₂ and In(OTf)₃ [45]. In 2014, metal-free α -C(sp³)-H functionalization of ethers with a diverse range of

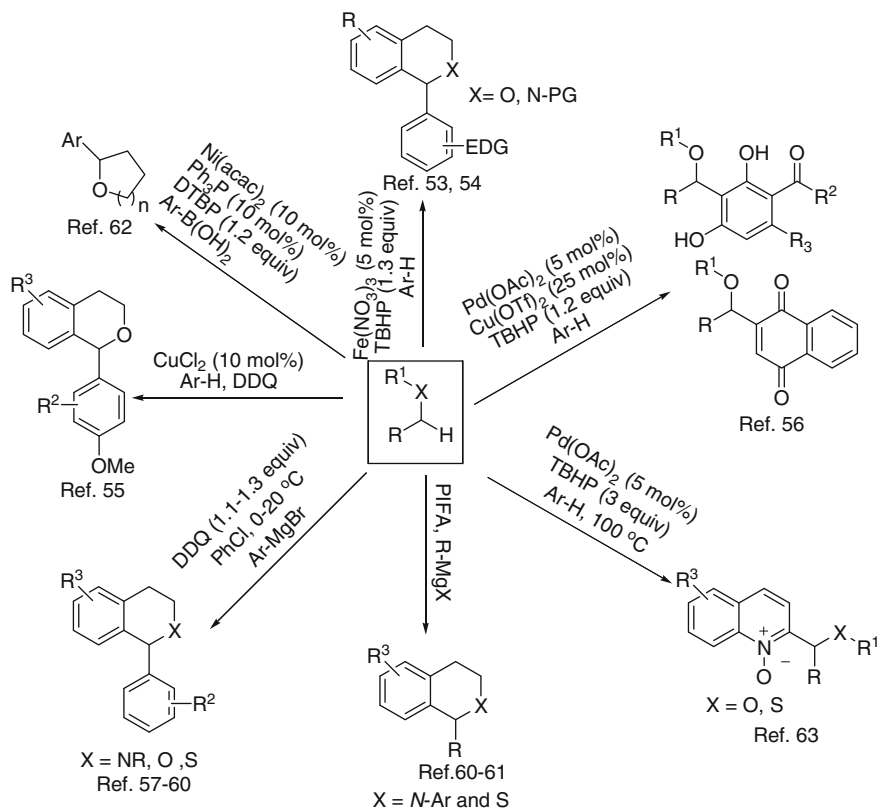
**Scheme 2.10** Two pathways of oxidative C(sp³)-H functionalization of ethers and alcohols**Scheme 2.11** The first CDC reaction of ethers with active methylene nucleophiles [43]

With $\text{Fe}_2(\text{CO})_9$ as catalyst, the CDC reaction of saturated heterocycles with 1,3-diketones was accomplished using TBP as an efficient oxidant (Scheme 2.12) [48]. This protocol shows good compatibility to cyclic and acyclic ethers, thioethers, and tertiary amines. Gratifyingly, besides $\text{C}(\text{sp}^3)\text{--}\text{C}(\text{sp}^3)$ coupling, the oxidative C–N coupling of ethers with azoles also works well (Scheme 2.12) [49]. As a update, with 2-chloranil (tetrachloro-1,2-benzoquinone) as oxidant, benzyl thioethers can be employed as substrates under metal-free conditions [50]. Notably, 2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoro borate is also an effective oxidant for metal-free CDC reaction of isochromanes and carbonyl compounds [51, 52].

Muramatsu and Li et al. finished a novel metal-free, DDQ-mediated arylation of isochromans and tetrahydroisoquinolines with commercially available Grignard reagents as aryl donors in 2013 (Scheme 2.13) [57–60]. It constitutes an important step-forward on arylation of $\alpha\text{-C}(\text{sp}^3)\text{-H}$ of ethers, possessing a broad substrate scope toward aromatic Grignard reagents bearing electron-withdrawing and -donating groups. Furthermore, this protocol allows access to mild alkylation and amidation if alkyl Grignard reagents were implemented. Subsequently, the group of Muramatsu explored this strategy to $\text{PhI}(\text{OOCF}_3)_2$ -mediated arylation, alkylation, and even amidation of $\alpha\text{-C}(\text{sp}^3)\text{-H}$ functionalization of isothiochromans (Scheme 2.13) [61]. With commercially available arylboronic acids as aryl donors, an attractive Ni-catalyzed arylation of cyclic ethers was developed by Lei and co-workers (Scheme 2.13) [62]. With quinoline *N*-oxides as heteroaromatic coupling partner, the corresponding CDC reaction with acyclic ethers was accomplished. (Scheme 2.13) [63]. A variety of quinolone-based heterocyclic compounds



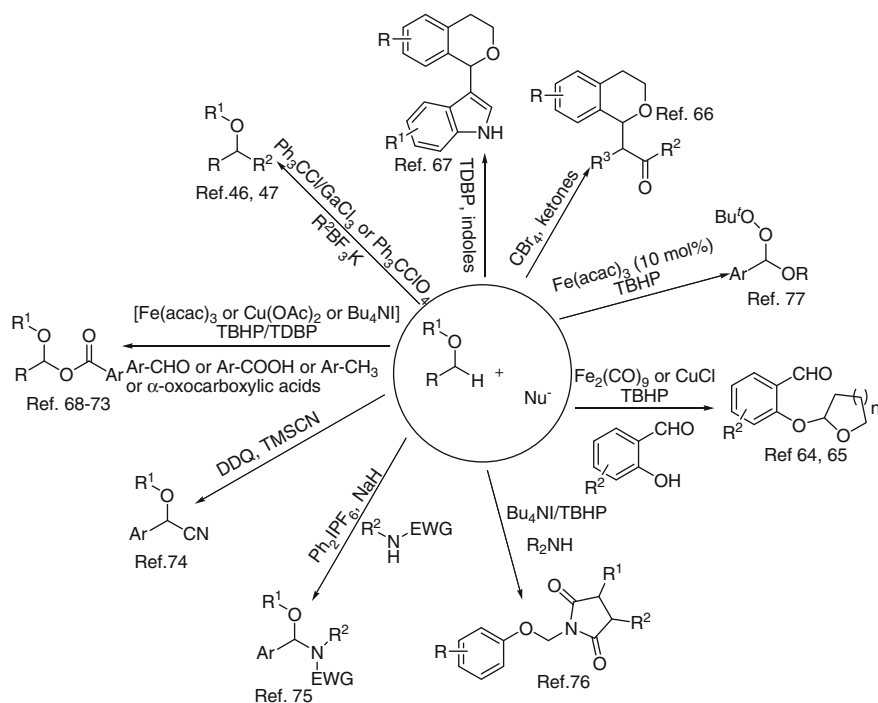
Scheme 2.12 Fe-catalyzed alkylation and amination of C(sp³)-H adjacent to heteroatom [48, 49]



Scheme 2.13 The recent progress of oxidative C(sp³)-H bond functionalization (1) [53–63]

were obtained in moderate to good yields with Pd(OAc)₂ as catalyst and TBHP as oxidant.

Owing to the abundance of ethers in natural compounds and drug leads, this study drawn great attention in a short period. Besides arylation of ethers, various nucleophiles were tested (Scheme 2.14). Notably, although the total reaction process seems to be a nucleophilic attack pathway, some reactions are typical radical reactions. Chang et al. developed an efficient Fe₂(CO)₉- or CuCl-catalyzed oxidative coupling of salicylaldehydes with cyclic ethers, delivering acetal products in good yields keeping the aldehyde functionality untouched (Scheme 2.14) [64, 65]. In the presence of catalytic amounts of CBr₄ (metal-free mediator), Huo et al. [66] developed an amazing CDC reaction of isochromans and ketones (Scheme 2.14). Very recently, TDBP-mediated CDC reaction of *N*-unprotected indole derivatives with isochromans was accomplished (Scheme 2.14) [67]. Using a trityl ion strategy, Liu and co-workers developed a novel C–C coupling reaction, allowing to couple various oragnoboranes with oxygen-containing substrates (Scheme 2.14) [46, 47]. Its broad substrate scope and mild conditions offers a promising protocol for

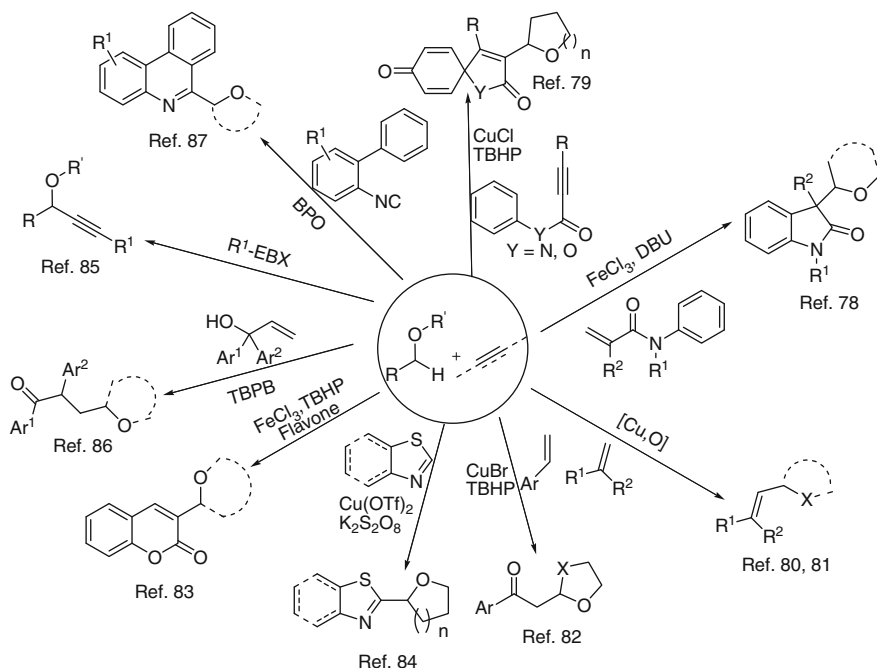


Scheme 2.14 The recent progress of oxidative C(sp³)-H bond functionalization (2) [64–77]

efficient modification of ethers. Very interestingly, different starting materials (carboxylic acids, aldehydes, and even toluene derivatives) coupled with ethers, but similar α -acyloxy ether products were obtained in moderate to excellent yields (Scheme 2.14) [68–73]. Also the cyanation [74], amination [75, 76], and peroxylation [77] of α -C(sp³)-H of ethers have been proved viable (Scheme 2.14).

In principle, generation of α -oxoalkyl radical from ether is highly operative by H-abstraction. The application of α -oxoalkyl radical in synthetic chemistry gained much interest. In 2013, Li et al. reported the first FeCl₃/DBU catalytic system for selective 1,2-alkylarylation of activated alkenes with ethers, providing a new strategy for the construction of oxindoles (Scheme 2.15) [78]. A follow-up work from the same group allows for tandem synthesis of 3-etherified azaspiro [4.5] trienones (Scheme 2.15) [79]. Recently, Lei et al. found that direct radical coupling of ethers or thioethers with alkenes could generate Heck-like alkenylated products (Scheme 2.15) [80, 81]. Other electrophiles, such as styrene [82], falvone [83], thiazole [84], ethynylbenziodoxolone [85], α,α -diaryl allylic alcohol [86], and isocyanides [87] are also good reaction partners to couple with α -oxoalkyl radicals (Scheme 2.15). These works highlight the richness of α -oxoalkyl radical chemistry.

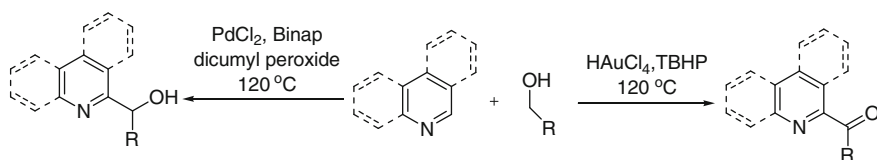
Compared with ethers, the direct selective activation of alcohols is mainly underdeveloped [88]. Although the transfer hydrogenative protocol of alcohols with



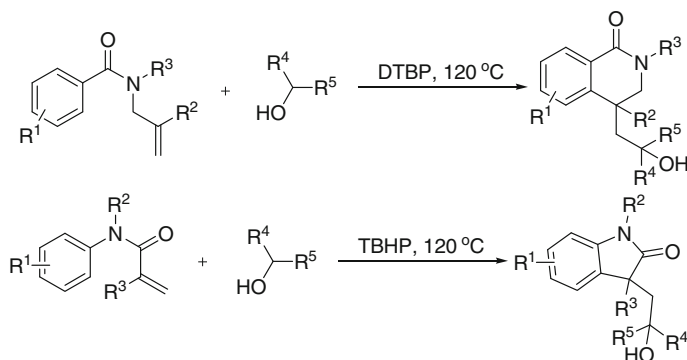
Scheme 2.15 The recent progress of oxidative C(sp³)-H bond functionalization (3)

alkenes and alkynes provides a good platform for C(sp³)-H functionalization of alcohols [89, 90], selective oxidation α -C(sp³)-H of alcohols still remains a great challenge. In the presence of TBHP, the coupling of electron-rich alkynes with aliphatic alcohols could occur readily to produce allylic alcohols [91]. Then Li et al. reported a Pd-catalyzed CDC reaction of heterocycles with α -C(sp³)-H bond of simple alcohols (Scheme 2.16) [92]. Remarkably, a stoichiometric amount of acid is not required for the Pd-catalyzed Minisci process, which in turn leads to a good functional group tolerance. In 2012, Zhu and co-workers expanded this transformation, and they found the use of AuCl₃/TBHP catalytic system, would enable the formation of ketones instead of secondary alcohols (Scheme 2.16) [93].

It is clear that α -oxoalkyl radicals have the potential to add to unsaturated chemical bonds. Thus, metal-free, peroxide-mediated radical coupling reactions of



Scheme 2.16 The oxidative coupling of simple alcohols with heterocycles [92, 93]

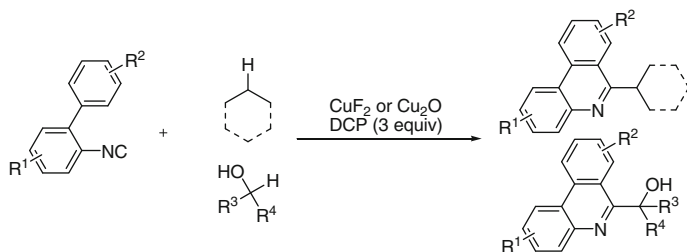


Scheme 2.17 The metal-free, oxidant-mediated alkylarylation of alkenes with alcohols [94, 95]

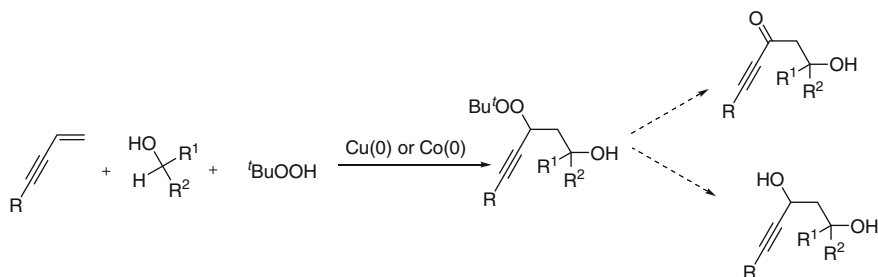
simple alcohols with suitable alkenes would be controllable. With radical initiators DTBP or TBHP, sustainable alkylarylation protocols of C=C double bond were developed by Han [94] and Duan [95] (Scheme 2.17). The continual work of Han achieved an excellent access to α,ω -amino alcohols by radical addition of α -oxoalkyl radical to olefins [96]. Oxidative coupling of α -C(sp³)-H of alcohols with H-phosphonates produces a new route to α -hydroxy phosphonates [97].

The group of Liu developed a copper-catalyzed radical tandem cyclization process of isocyanides with simple alkanes or alcohols (Scheme 2.18) [98]. The impressive substrate scope provides a convenient access to various alkylated phenanthridines.

In early 2015, Loh and co-workers achieved an elegant Cu(0)- or Co(0)- catalyzed three component oxidative coupling of 1,3-enynes (or styrenes), simple alcohols, and TBHP (Scheme 2.19) [99]. The resulting β -peroxy alcohols and β -hydroxyketones are important building blocks. They can further be transformed into β -hydroxyynones and propargylic 1,3-diols.



Scheme 2.18 Cu-catalyzed isocyanides insertion into C(sp³)-H bond of alkanes and alcohols [98]



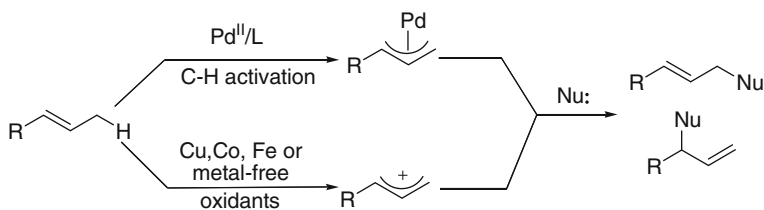
Scheme 2.19 Cu(0) or Co(0)-catalyzed three component oxidative coupling of 1,3-enynes, TBHP and alcohols [99]

2.4 Oxidative Functionalization of Allylic and Benzylic C(sp³)-H Bond

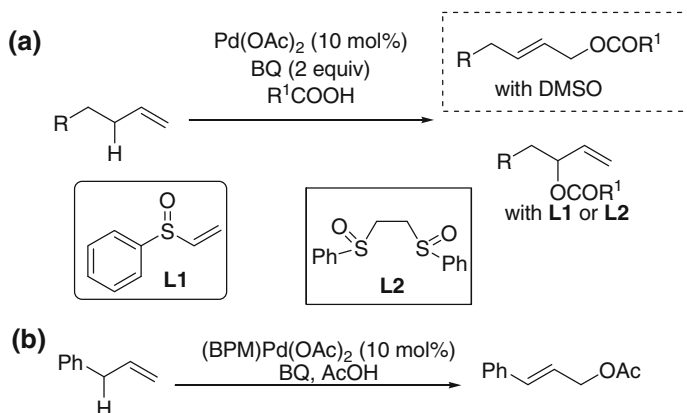
Selective cleavage and functionalization of allylic C(sp³)-H bonds is a synthetically attractive strategy (Scheme 2.20). The pioneering work has illustrated the possibility of allylic C-H bond using electrophilic π -allylpalladium intermediates. In recent years, the transition-metal-catalyzed selective allylic and benzylic C-H bond functionalization gained particular interests.

For a long time, the Pd-mediated (non-catalytic process) intermolecular allylic C-H acetoxylation was limited to cycloalkenes [100]. In 2004, the group of White overcame this limitation by adding sulfur-containing ligands or solvents to the Pd (II)/BQ system (Scheme 2.21a) [101–103]. Generally, this finding dramatically switches the selectivity and efficiency of open-chain terminal alkenes. The DMSO can suppress Wacker oxidation *via* sulfoxide ligation to palladium catalyst, and finally delivered linear (*E*)-allylic acetates as products, whereas, ligand **L1**, or **L2** leads to branched allylic acetates. Later, Bercaw et al. found that bipyrimidine (BPM) was also an efficient ligand to improve the selectivity of Pd(II)-catalyzed allylic acetoxylation in acetic acid solution (Scheme 2.21b) [104].

With TBHP as external oxidant, CuBr and CoCl₂ co-catalyzed allylic C(sp³)-H alkylation of methylenic C(sp³)-H bond was first reported in 2006 [105]. Two years later, Pd(II)-catalyzed intra- or intermolecular allylic C(sp³)-H alkylation with active



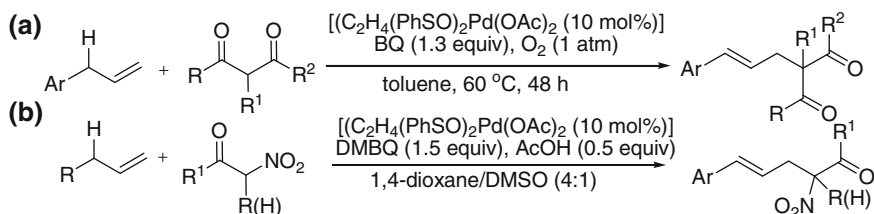
Scheme 2.20 The general strategies for allylic C(sp³)-H bond functionalization



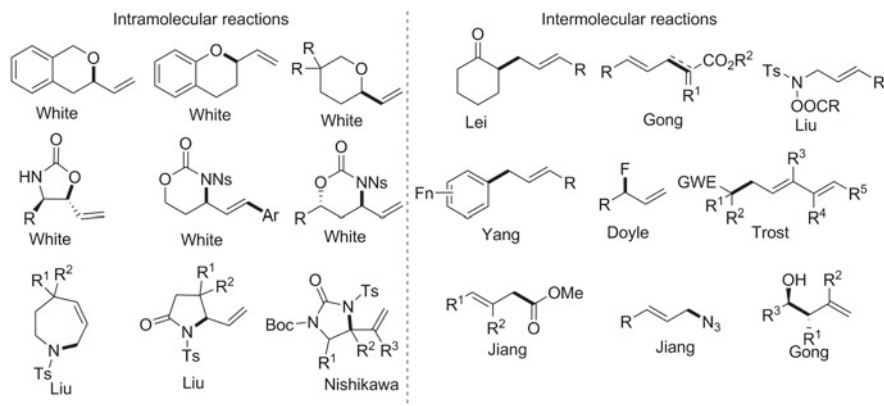
Scheme 2.21 Pd-catalyzed acetoxylation of allylic C(sp³)-H bond [101–104]

1,3-dicarbonyl nucleophiles was developed (Scheme 2.22a) [106]. The employment of a sulfur-containing ligand is a key factor to its success. Simultaneously, the group of White reported a similar allylic C–H alkylation protocol with methyl nitroacetate instead of 1,3-dicarbonyl compounds (Scheme 2.22b) [107]. The follow-up study from White's group applied this novel strategy to highly challenging tertiary nucleophiles [108] and inactivated α -olefines [109]. These protocols strongly broadened the application of Tsuji–Trost alkylation.

Arguably, the Pd(II)-catalyzed allylic C(sp³)-H bond functionalization became one exciting topic in the realm of C–H bond functionalization. A great number of potential applications for the synthesis of complex molecules were also developed (Scheme 2.23). One of the most active groups, the White's group successively accomplished a series of important transformations with regard to allylic C(sp³)-H bonds, including the late-stage allylic C–H alkylation of natural products (Scheme 2.23) [110–117]. A mechanistic study from Fristrup's group brought insights into the Pd(II)/bis-sulfoxide-catalyzed allylic C–H bond functionalization [118]. Very interestingly, the sulfoxide ligands free, Pd(II)-catalyzed intermolecular allylic C–H alkylation of substituted 1,4-dienes and *N*-allyl imines were disclosed by Trost and Hansmann (Scheme 2.23) [119, 120].



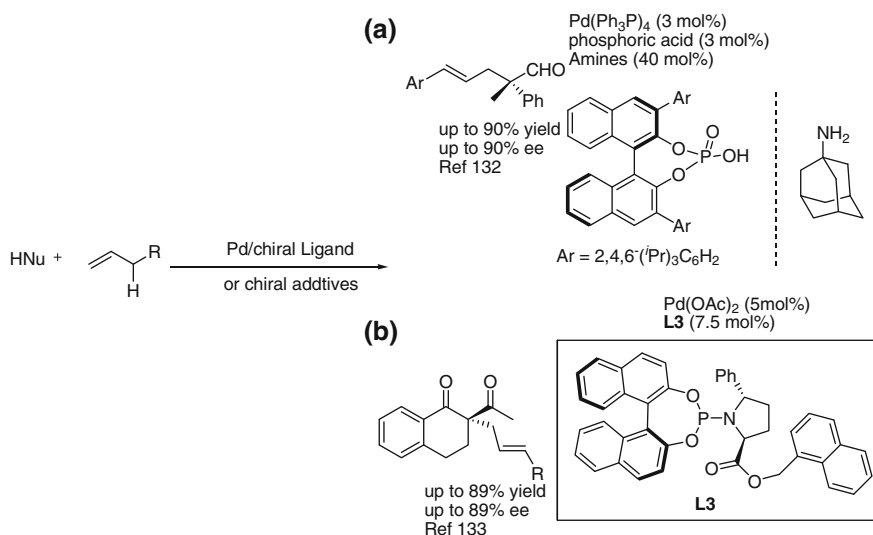
Scheme 2.22 Pd-catalyzed oxidative intermolecular allylic C(sp³)-H alkylation with active C–H nucleophiles [106, 107]



Scheme 2.23 Selected examples of allylic C(sp³)-H bond functionalization [110–131]

In 2009, Liu et al. reported Pd(OAc)₂-catalyzed intra- and intermolecular aerobic oxidative C–N coupling of allylic C–H bond with saccharin derivatives (Scheme 2.23) [121, 122]. The main innovation of Liu's work is the novel catalytic system (Pd(OAc)₂ without sulfoxide) and practical reaction conditions (O₂ as the external oxidant without other co-catalysts). A similar C–N bond formation reaction was recently reported by Nishikawa and co-workers using Pd(TFA)₂/bis-sulfoxide catalytic system (Scheme 2.23) [123]. As Liu's follow-up work, the employment of stronger oxidant PhI(OPiv)₂ allows oxidative amination of unactivated alkyl olefins in excellent regioselectivity [124]. During the mechanistic study, they found naphthoquinone played an important role in the step of carbon–carbon double bond coordination to palladium catalyst center. In 2013, the group of Doyle developed an attractive strategy for direct incorporation of fluorine into the allylic C(sp³)–H bond [125]. The combination of Pd(II)/Cr(III) dual catalysis enables monofluorination of a diverse range of allylic C–H bond with cheap Et₃N·3HF in satisfactory branched selectivity (Scheme 2.23). It constitutes an rare example of mild fluorination of C(sp³)–H bond. The Pd(II)-catalyzed oxidative carbonylation of allylic C–H bond with CO provides an attractive route to β-enoic acid esters (Scheme 2.23) [126]. In early 2015, Gong and co-workers reported a highly diastereoselective allylic C–H Aldol-type reaction (Scheme 2.23) [127]. More recently, other coupling partners, ketones [128], α-diazo esters [129], sodium azide [130], and electron-deficient arenes [131], were tested (Scheme 2.23).

Meanwhile, the enantioselective allylic C(sp³)–H bond functionalization was also explored. In 2014, the first enantioselective α -allylation of aldehydes was achieved by combination of asymmetric counter anion catalysis with Pd(II)-catalyzed allylic C(sp³)–H bond activation. The resulting allylated aldehyde products were obtained in good to excellent yields and high enantioselectivities (Scheme 2.24a) [132]. After screening of many chiral ligands, Trost et al. [133] verified a new class of non-C2-symmetric phosphoramidite ligand **L3**, which is the best chiral ligand for allylation of 1,3-diketones (Scheme 2.24b). Although good to



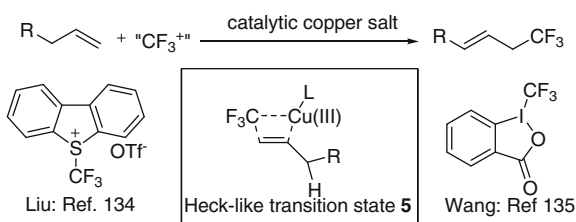
Scheme 2.24 Enantioselective linear alkylation of allylic C(sp³)-H bond [132, 133]

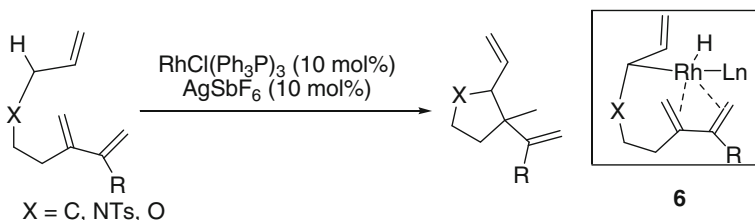
excellent enantioselectivities were observed, its substrate scope with respect to olefins was very limited. To solve this, cinnamyl acetate was used as an alternative coupling partner.

Besides palladium catalysis, other transition-metal catalysts are also efficient for allylic C-H activation. In 2011, Liu [134] and Wang [135] reported Cu(I)-catalyzed trifluoromethylation of allylic C(sp³)-H bond, respectively (Scheme 2.25). Various unactivated alkenes could tolerate the reaction condition well, delivering the sp³-sp³ C-C coupling products in moderate to good yields. Liu et al. proposed that the trifluoromethylation occurred *via* a Heck-like four membered-ring transition state **5** (Scheme 2.25). In the same year, In(OTf)₃-catalyzed allylic C-H oxidation of cycloalkenes for subsequent C-O and C-N bond formation was developed. In the presence of *N*-propylthiosuccinimide reagents, different kinds of nucleophiles (alcohol, carboxylic acid and sulfonamide) works well affording allyl ethers, esters and sulfonamides [136].

An impressive example of Rh(I)-catalyzed, diene-assisted allylic C(sp³)-H bond activation was disclosed by Yu and co-workers in 2010. The unprecedented

Scheme 2.25 Cu-catalyzed trifluoromethylation of allylic C(sp³)-H bond [134, 135]





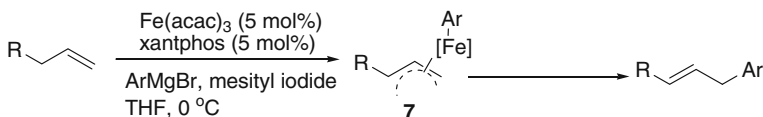
Scheme 2.26 Rh-catalyzed, diene-assisted allylic C(sp³)-H bond functionalization [137]

protocol starts with allylic C-H activation to form intermediate **6**, followed by insertion into alkenes. The resulting polysubstituted tetrahydropyrroles, tetrahydrofurans, and cyclopentanes are valuable chemicals (Scheme 2.26) [137]. Its notable features are excellent regio- and stereoselectivity without the need of an external oxidant. Another Rh(III)-catalyzed oxidative allylic C(sp³)-H activation of enamines for concise synthesis of substituted pyrroles was reported by Glorius et al. [138]. Both works provide novel routes to biologically important heterocyclic compounds.

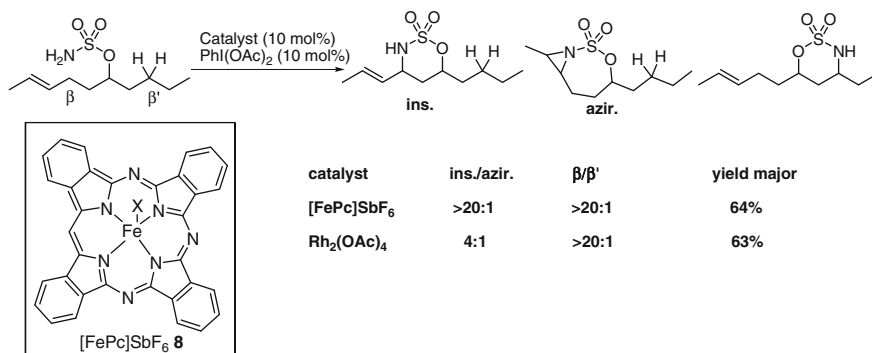
Iron catalysis is an emerging branch in metal-catalyzed coupling strategies. In 2010, Jiao et al. accomplished the first Fe(II)-catalyzed allylic C-H oxidation to alkenyl nitriles with TMSN₃ as nitrogen source and DDQ as external oxidant [139]. As a follow-up work, the same group developed FeCl₂-catalyzed oxidative, dehydrogenative C-O coupling of propargyl azides with carboxylic acids in the presence of DDQ [140]. The authors envisioned that azido moiety would be an assisting group for specific allylic C-H bond activation.

It is noteworthy that the first Fe(acac)₃-catalyzed non-oxidative allylic C-H arylation with commercially available aryl Grignard reagents was achieved by Nakamura et al. in 2013 (Scheme 2.27). [141] The mechanistic study indicates allylic C(sp³)-H bond activation to form an allyliron species **7** is the rate-determining step during the reaction process. The future efforts will focus on detailed mechanism studies.

Remarkably, in year 2012 White et al. achieved an elegant Fe(III)-catalyzed highly regioselective intramolecular amination of allylic C(sp³)-H bond (Scheme 2.28) [142]. After screening a variety of substrates that containing assorted C(sp³)-H bonds (3°, 2° aliphatic, ethereal, and benzylic C-H bond), they found that [FePc]⁺ **8** preferably reacts with the allylic C-H bond rather than other C(sp³)-H bonds. In sharp contrast, when Rh₂(OAc)₄ was employed under the same conditions, low regio- and site selectivity was observed. This work highlights the striking



Scheme 2.27 Fe-catalyzed redox-neutral allylic C(sp³)-H arylation [141]

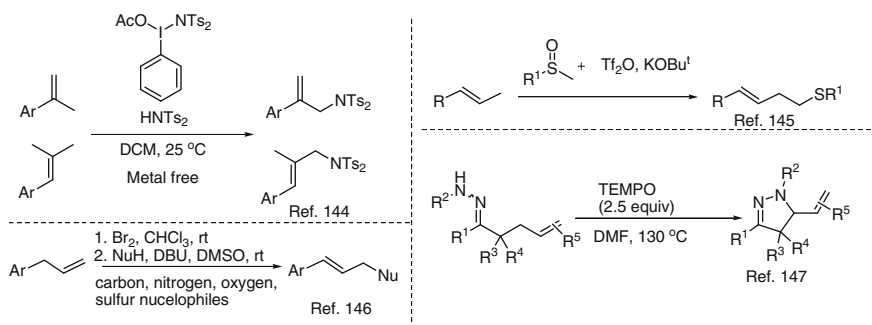


Scheme 2.28 [FePc]⁺-catalyzed regio- and site-selective allylic C(sp³)-H bond amination [142]

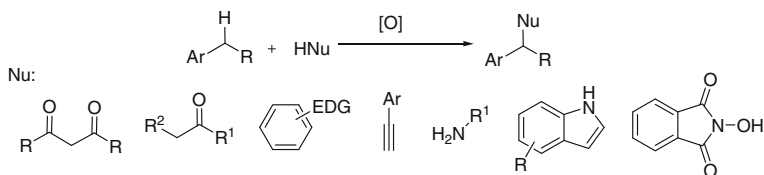
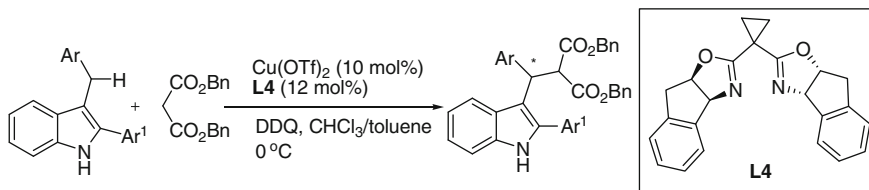
features of cheap and nontoxic iron-based catalyst. The next year, ligand-tuned, silver-catalyzed highly chemoselective allylic C-H amination was also reported [143]. By manipulating the coordination geometry of silver complex, selective aziridination and allylic C(sp³)-H insertion can be achieved.

In addition, beyond the transition-metal catalysts, much more recent works focused on the metal-free allylic C(sp³)-H bond functionalization (Scheme 2.29) [144–147]. For example, Muñiz et al. reported a metal-free, I(III)-mediated intermolecular amination of allylic C-H bonds [144]. The hypervalent iodine(III) reagent acted as the oxidant, while bistosylimide was the real nitrogen source.

Compared with allylic C-H bond, benzylic C-H bond has similar BDE. Under the oxidative conditions, it is still susceptible to undergo SET to form a benzyl radical or carbocation, which would like to be trapped by a series of C(sp³)-H nucleophiles or electron-rich aromatic rings (Scheme 2.30). For example, active methylenic 1,3-dicarbonyl compounds [148–153], nitrogen nucleophiles (amines or amides or almidine), [154–158] *N*-hydroxyamides [159], ketones [160, 161], aldehydes [162], electron-rich alkenes [163], aromatic rings [164, 165], and terminal alkynes [166] are good coupling partners in the oxidative benzylic C-H bond



Scheme 2.29 Metal-free, allylic C(sp³)-H bond functionalization [144–147]

**Scheme 2.30** Benzylic C(sp³)–H bond functionalization [148–166]**Scheme 2.31** Cu-catalyzed enantioselective alkylation of benzylic C(sp³)–H bond [169]

functionalization with metals or even under metal-free conditions. In addition, Lectka et al. introduced an efficient Fe(acac)₃-catalyzed monofluorination of benzylic C–H bond with Selectfluor reagent [167, 168].

One representative example in enantioselective alkylation of benzylic C–H bond was disclosed by Gong and co-workers in 2010. Highly enantioselective alkylation of 3-arylmethylindoles with dibenzyl malonate was achieved in the presence of catalytic amounts of chiral copper complex **L4** (Scheme 2.31) [169]. This protocol provides an excellent enantioselective route to natural product skeleton of 2,3,4,4a,9,9a-hexahydro-1H-pyrido[2,3-b]indoles.

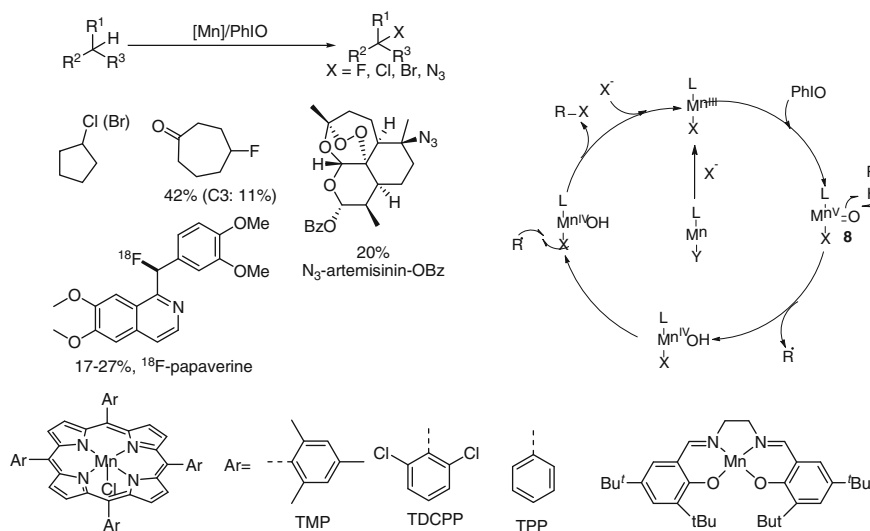
2.5 Oxidative Functionalization of General C(sp³)–H Bond

In contrast to the above cases, direct functionalization of unactivated, general C(sp³)–H bonds arguably represents a great challenge owing to the strong BDE and poor regioselectivity [170]. This difficulty was suitably addressed by chemists in recent years. In this regard, a great number of new catalytic systems and new catalytic methodologies are extremely booming [171, 172]. Based on the electronics, sterics and stereoelectronics of substrates, predictable regioselectivity was accomplished in the last 5 years. Some works represent the state of the art in the C(sp³)–H bond functionalization.

The group of Groves recently reported a series of Mn-catalyzed, highly selective halogenation [173–176] and azidation [177] of aliphatic C(sp³)–H bonds (Scheme 2.32). In general, the regioselectivity depends on the BDE of aliphatic

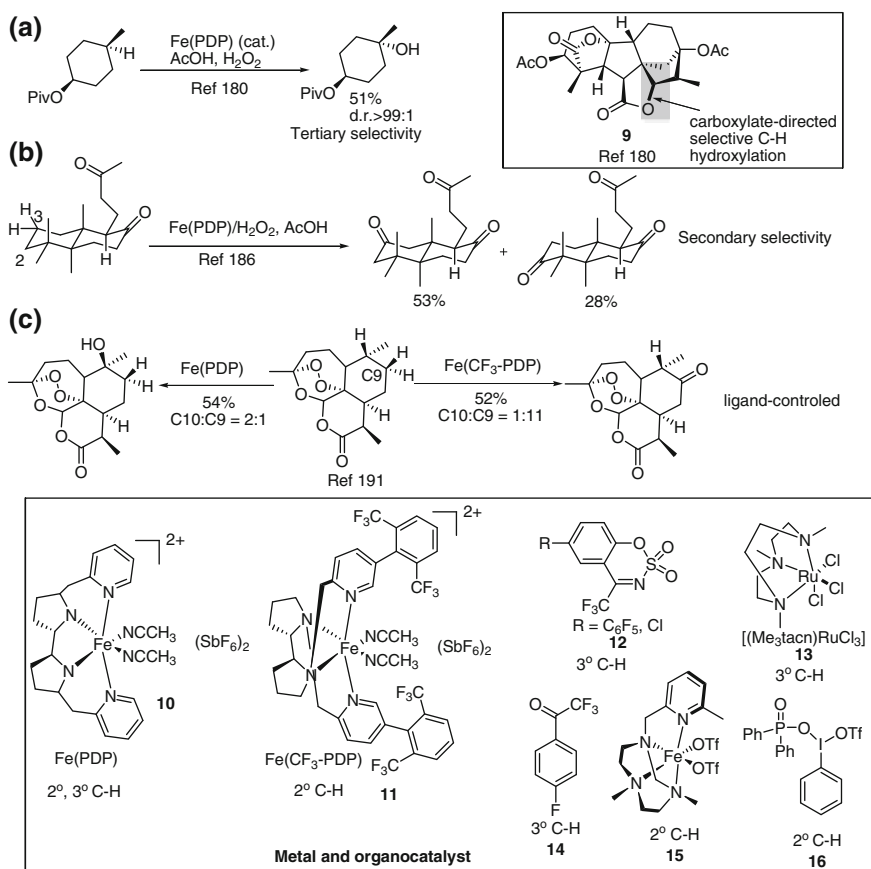
C-H bond. If active benzylic C-H bond was involved in the substrates, the halogenation site was usually in that position. This is consistent with their proposed mechanism in Scheme 2.32. The oxomanganese(V) species **8** is prone to abstract a hydrogen atom from C(sp³)-H bond with a relatively weak BDE, and the resulting substrate-derived carbon-centered radical is highly reactive for further transformation. The mild reaction conditions and good selectivity have showcased the possibility of late-stage functionalization of complex natural products and bioactive molecules.

The enzymatic oxidation of C(sp³)-H bond is an important and fundamental transformation in biological systems. Therefore, the development of a practical catalytic method with broad scope, predictable selectivity to streamline C(sp³)-H bond oxidation is highly exciting [178]. To demonstrate the practicability of a creative protocol, its late-stage application to complex molecules cannot be circumvented any more. One can image, selective oxidation of one specific C(sp³)-H bond from a complex molecule is very difficult because usually it cannot be predicted which C-H bond could be addressed [179]. In 2007, the White's group started to address these unresolved difficulties with Fe(PDP) complex (Scheme 2.33a) [180]. Selective hydroxylation of tertiary C(sp³)-H bond was achieved under very mild reaction conditions, and gratifying yields (>50 % yield) were obtained for a series of complex molecules. For example, owing to the electronic effect of carboxyl group, diastereoselective hydroxylation of secondary C-H bond in tetrahydrogibberellic acid analog leads to lactonization product **9** in good yield. Later, Bois and Hilinski successively developed several novel strategies for selective hydroxylation of unactivated tertiary C-H bonds by employing organocatalyst **12** [181], **14** [182], [(Me₃tacn)RuCl₃] **13** [183, 184] and RuCl₃ [185].



Scheme 2.32 Mn-catalyzed radical C(sp³)-H bond transformations [173–177]

As a continuity, in 2010, the group of White introduced an efficient methylene C-H oxidation method with Fe(PDP) as catalyst and H₂O₂ as environmentally benign oxidant (Scheme 2.33b) [186]. After testing about 30 substrates, the authors found the chemical environment of substrates enabled selective secondary C-H bond oxidation. The most important issue is that the selectivity can indeed be predicted using fundamental concepts of electronics, sterics, and stereoelectronics. Very recently, Fe(II)-complex **15** and hyperiodine (III) **16** were found to be good catalysts to enhance the methylenic C-H selectivity [187–190]. One interesting finding from White's group demonstrated that the regioselective oxidation of secondary and tertiary C-H bond could be tuned by employing different ligands (Scheme 2.33c) [191]. The indelible achievements from Sherman's group illustrated enzymatic selective hydroxylation of unactivated secondary and tertiary C-H bond was guided by molecular dynamics simulations [192, 193]. Furthermore, a recent publication from Baran's group introduced a systematic study using both chemical and

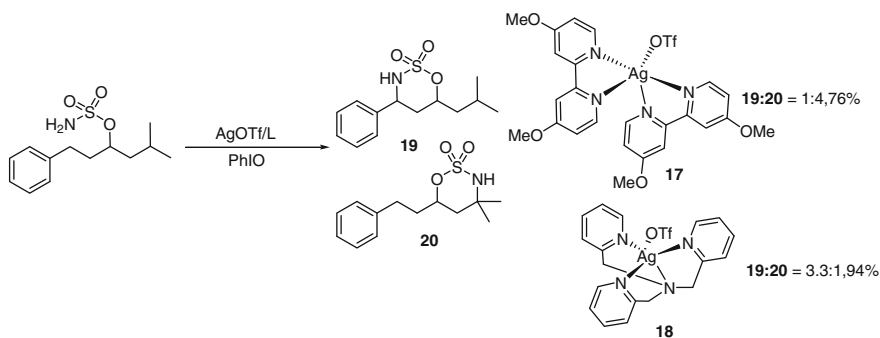


Scheme 2.33 The recent progress of selective oxidation of aliphatic C(sp³)-H bond

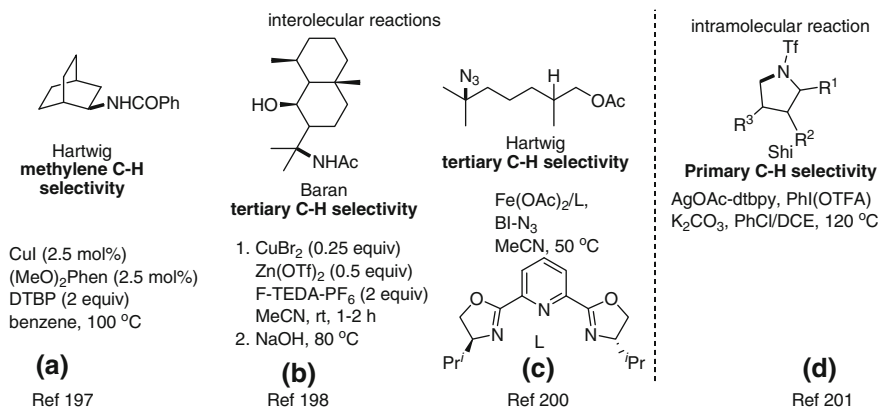
enzymatic methods for aliphatic C-H oxidation, which showcased different regioselectivities [194].

If the ligand-tuned regioselectivity is mentioned in this realm, the works of Schomaker's group attract much attention. In 2014, they reported Ag(I)-catalyzed selective intramolecular amination of aliphatic C-H bonds (benzylic versus tertiary C-H bond) [195]. The main regioselectivity proved controllable using different ligands. Interestingly, AgOTf-bipy complex **17** prefers amination of the most electron-rich tertiary C-H bond, while AgOTf-tpa catalyst **18** is inclined to the less hindered benzylic C-H bond (Scheme 2.34). However, selective intermolecular amination of C(sp³)-H bond is more taxing, and recent observations revealed that the substrate structure of amine source was an important factor to benzylic versus tertiary C-H selectivity [196].

In early 2014, an elegant CuI-catalyzed intermolecular amidation of cyclic and linear aliphatic alkanes with simple amides, sulfonamides, and imides was reported using external oxidant DTBP (Scheme 2.35a) [197]. The choice of ligand phenanthroline is a definitive item for excellent regioselectivity. Attractively, selective amidation of secondary C(sp³)-H bond proved applicable even though electron-rich tertiary C-H bond was present. In contrast, with Selectfluor as strong oxidant, CuBr₂-catalyzed intermolecular oxidative C-N coupling is practical to tertiary C(sp³)-H bond selectivity over secondary and primary C-H bond (Scheme 2.35b) [198]. With 3° > 2° > 1° C(sp³)-H site selectivity, a three component coupling of unactivated alkane C-H bond, isocyanate, and DTBP were developed [199]. The relatively weak BDE of tertiary C-H bond renders radical cleavage of this kind of C-H bond enthalpically favorable. With this consideration in mind, in early 2015, Hartwig's group developed Fe(II)-catalyzed late-stage azidation protocol of remote tertiary C(sp³)-H bond (Scheme 2.35c) [200]. The mechanistic studies revealed that radical C-H cleavage process is the turnover-limiting step. Compared with these works on secondary and tertiary C-H bonds, selective functionalization of primary C(sp³)-H bond represents a new challenge. Using AgOAc as catalyst, intramolecular C-N bond coupling with primary C(sp³)-H selectivity was accomplished by Shi and co-workers in 2014.



Scheme 2.34 Ligand-controlled, Ag-catalyzed regioselective amination of C(sp³)-H bond [195]

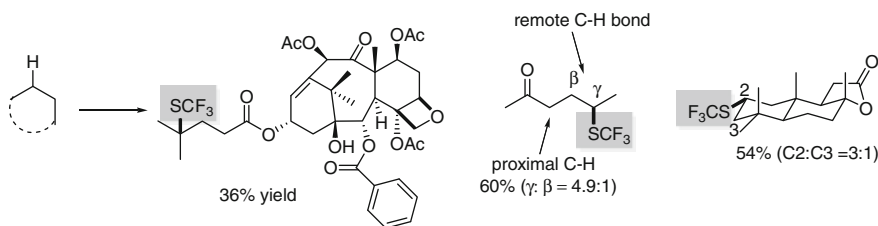


Scheme 2.35 Highly selective amination of aliphatic C(sp³)-H bond [197–201]

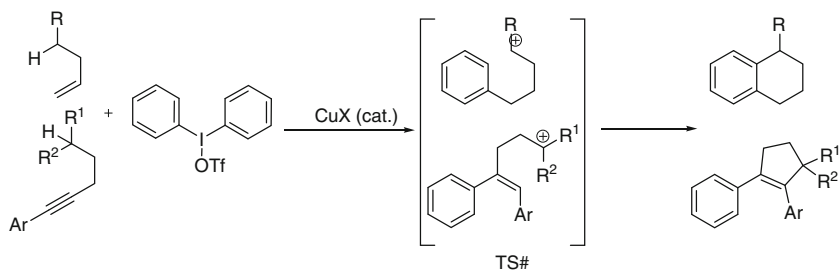
(Scheme 2.35d) [201]. The authors thought the generated hyperelectrophilic Ag(III) species in situ would account for the less sterically hindered primary C–H bond selectivity. Furthermore, the use of chiral dirhodium carbene is viable for enantioselective primary C–H bond insertion, and it allows for selective late-stage functionalization of steroids [202].

The introduction of fluoroalkyl groups into important scaffolds is an efficient route to improve their chemical and physical properties. In 2015, Tang [203] and Chen [204] independently reported AgSCF₃-mediated trifluoromethylthiolation of unactivated C(sp³)-H bond in the presence of persulfate salts (Scheme 2.36). In general, this radical trifluoromethylthiolation protocol shows a broad scope and excellent site selectivity with preference for methine over methylene C–H bond. Dominated by the electronic effects, selectivity of trifluoromethylthiolation occurred at remote C(sp³)-H bond from electron-withdrawing groups. Both works show great potential for mild incorporation of trifluoromethylthiol group into complex molecules. Besides, a novel direct fluorination of unactivated aliphatic C–H bond was also presented by Lectka and co-workers [205].

As in their profuse efforts in electrophilic Cu(III) chemistry, an excellent Cu(I)-catalyzed cascade arylcarbocyclization sequence with alkenes and alkynes was



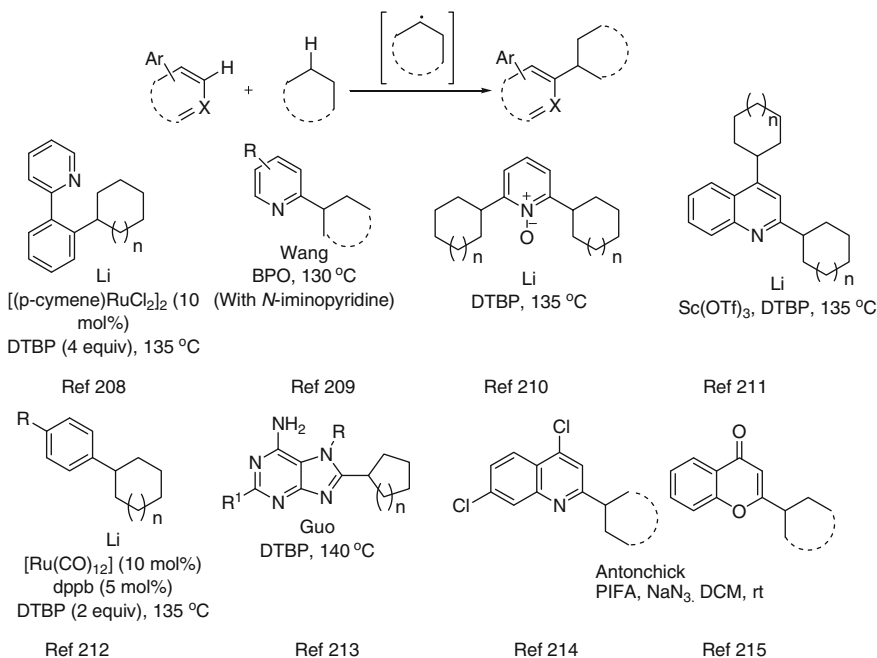
Scheme 2.36 Radical trifluoromethylthiolation of unactivated C(sp³)-H bond [203, 204]



Scheme 2.37 Cu-catalyzed cascade arycarbocyclization sequence involving C(sp³)-H bond functionalization [206]

disclosed by the group of Gaunt. It involved the cleavage of unactivated C(sp³)-H bond for the formation of one key carbocation intermediate (Scheme 2.37) [206]. Simultaneously, Chen et al. reported the identical arycarbocyclization reaction with alkynes [207].

It is well known that simple alkanes are ready to undergo hydrogen abstraction to form carbon-centered radicals in the presence of radical initiators (TBHP, DTBP, K₂S₂O₈, etc), and the resulting nucleophilic alkyl radicals are able to attack unsaturated chemical bonds, such as alkenes, alkynes, aromatic rings, and isocyanides (Scheme 2.38). In 2008, Li et al. introduced a novel [Ru(*p*-cymene)Cl₂]₂-catalyzed,



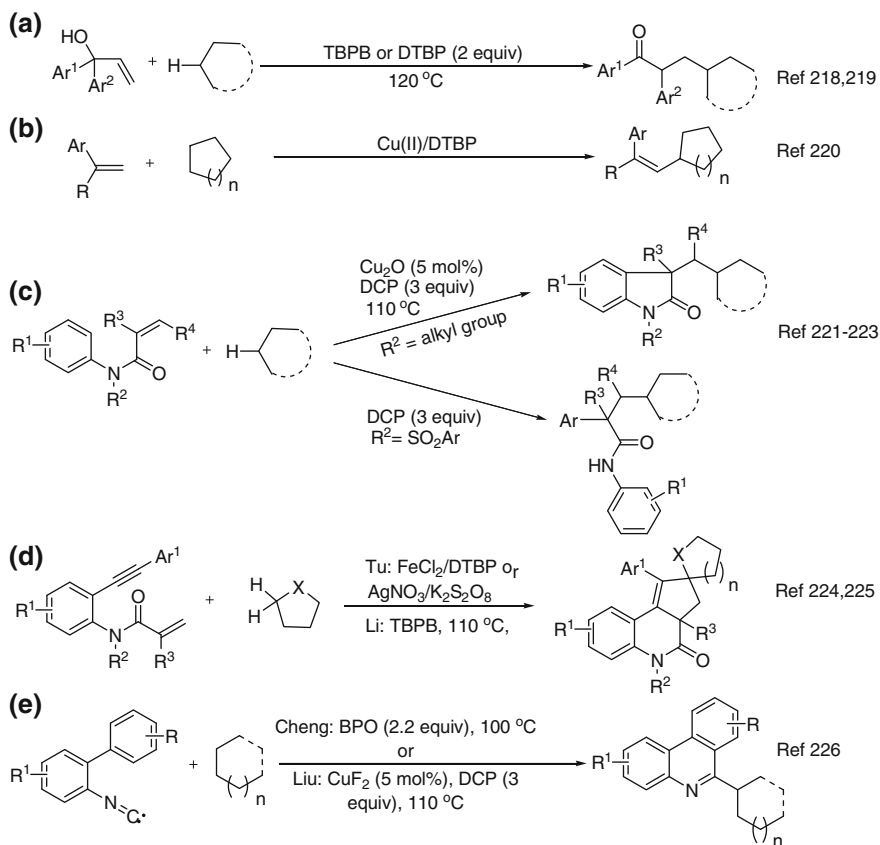
Scheme 2.38 Recent achievements of arylation of simple alkanes [208–215]

pyridine-directed alkylation of arenes [208]. Although good regioselectivity was observed, mono- and bis-alkylation products cannot be controlled. To solve this, Wang et al. documented radical alkylation of *N*-iminopyridine ylides with simple alkanes, and the desired mono-alkylated heteroarenes were obtained in good yields [209].

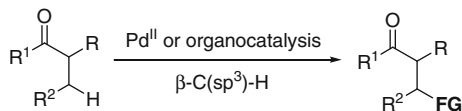
Li's group later developed several aliphatic C-H arylation protocols following the principle of radical chemistry [210–212]. DTBP-mediated highly selective alkylation of important lidenosines was reported in the absence of transition-metal catalysts [213]. Antonchick et al. reported PhI(OTFA)₂/NaN₃-mediated CDC reaction of heteroarenes (chromones) with simple alkanes [214, 215]. These protocols enable metal-free aliphatic C-H heteroarylation under mild reaction conditions. Interestingly, different from Antonchick's work [215], the radical addition of simple alkyl radicals to chromones proved viable to afford 2-alkylchromanones in good yields [216]. The group of Lei recently developed Ni(acac)₂-catalyzed radical cross-coupling of alkyl radicals and aryl radicals, yet enabling direct arylation of unactivated C(sp³)-H with arylborates [217].

The radical additions of carbon-centered radicals to alkenes are fundamental C-C forming reactions. Ji [218] and Han [219] independently reported a metal-free, oxidative alkylation-initiated radical 1,2-aryl migration of α,α -diaryl allylic alcohols using DTBP or TBPB as radical initiators (Scheme 2.39a). Similarly, the oxidative Heck-like coupling of styrenes with cyclic alkanes was reported (Scheme 2.39b) [220]. It affords an atom economical route as alternative to the conventional Heck coupling. The radical addition of simple alkanes to benzene-linked alkenes (Scheme 2.39c) [221–223], 1,6-enynes (Scheme 2.39d) [224, 225] and isocyanides (Scheme 2.39e) [98, 226] has created great potential to construct important heterocyclic skeletons with metal or under metal-free conditions. Two similar reports from Li's group [225] and Tu's group [224] simultaneously revealed the unfrequented dual 1,1-C(sp³)-H functionalization, which allows for cascade construction of spirocyclopenta[c]quinolines. Besides, with suitable H-abstraction reagents (TBHP, TDBP, DCP etc), the alkyl radicals of simple alkanes can be directly coupled with 1,3-dicarbonyl compounds [227], disulfide [228], aryl isothiocyanates [229], sulfoximines [230, 231] and aromatic aldehydes [232].

The α -C(sp³)-H functionalization of carbonyl compounds is a well-known tool in organic synthesis, but functionalization of remote β -C(sp³)-H bond remains unusual (Scheme 2.40). For example, Pihko and co-workers developed Pd(II)-catalyzed oxidative β -C(sp³)-H arylation of β -keto esters with electron-rich arenes [233–236]. The Pd(II)-catalyzed dehydrogenative transformation of ketones to α,β -unsaturated ketones allows divergent β -C(sp³)-H bond functionalization with a wide range of nucleophiles [237–239]. Two important independent reports on organocatalytic (aminocatalysis and NHC catalysis) β -C(sp³)-H bond of aliphatic aldehydes were also achieved by Wang [240] and Chi [241].



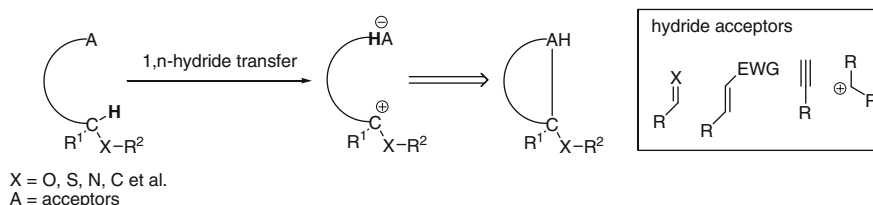
Scheme 2.39 Radical addition of alkyl radicals to unsaturated chemical bond [218–226]



Scheme 2.40 Recent progress of β -C(sp³)-H functionalization of carbonyl compounds [233–241]

2.6 Redox-Neutral C(sp³)-H Bond Functionalization

Different from the above discussion, redox-neutral means the reactions totally do not require external oxidants or reductants. In this part, we would like to briefly introduce the redox-neutral C(sp³)-H bond functionalization.



Scheme 2.41 The intramolecular H-shift for C(sp³)-H bond functionalization [243]

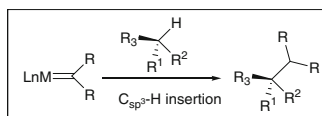
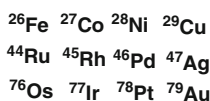
2.6.1 1,n-H Shift-Induced C(sp³)-H Bond Functionalization

As shown in Scheme 2.41, the linkage of an sp³ hydride donor and a hydride acceptor in one molecule is the general and necessary condition for H-shift-type C(sp³)-H bond functionalization. In the presence of transition metals or Lewis acids, the hydride-shift can readily occur to construct new chemical bonds. In recent years, this kind of C(sp³)-H bond functionalization gained much attention. Remarkably, the hydride-shift C-H bond functionalization mode usually requires the substrates possess a migrating hydrogen with a relatively high hydridic character, such as benzylic hydrogen or hydrogen adjacent to heteroatoms. Owing to the page limit, herein we do not discuss their achievements. If the readers are interested in this field, please read recent reviews on this topic [242–244].

2.6.2 Metal-Carbenoid-Induced C(sp³)-H Bond Functionalization

The metal-carbenoid intermediate has been widely applied in organic synthesis for cycloaddition, cyclopropanation, and selective C-H bond insertion [245, 246]. The traditional methods to prepare metal carbenoids are from diazo compounds, and the recent reports have shown the feasibility to generate metal carbenes or carbenoids in situ from some precursors, such as alkynes [247] and cyclopropenes [248]. With great efforts, the metal-carbenoid chemistry was esteemed as one efficient redox-neutral C(sp³)-H bond functionalization protocol (Scheme 2.42). Herein, we list several key reviews in this topic to readers for extending reading [249–254].

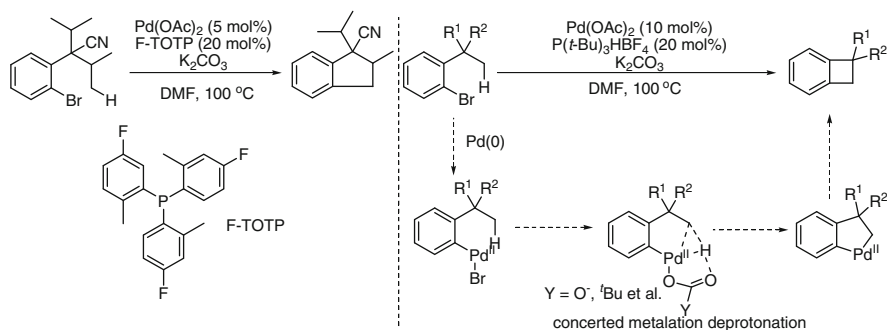
Scheme 2.42 The metal-carbenoid-induced C(sp³)-H bond insertion



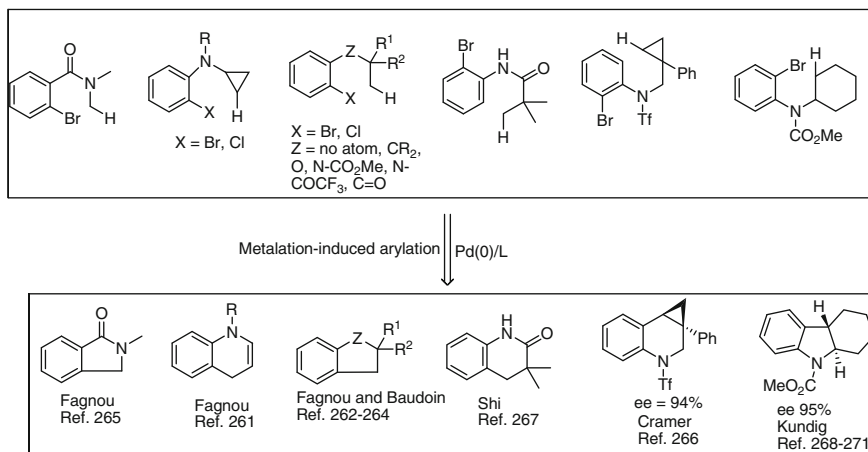
2.6.3 Metalation-Induced Arylation of C(sp³)-H Bond

In early 1990, Dyker and co-workers have demonstrated the possibility of Pd(II)-catalyzed C-H activation from aryl iodides to the synthesis of polycyclic compounds [255, 256]. But unfortunately it is another “black swan event” in organic synthesis [257] because this strategy was paid little attention as long as thirteen years. In 2003, during the study of Pd(II)-catalyzed C(sp³)-H activation of benzylic gem-dialkyl group on bromobenzene, Baudoin et al. [258] observed a significant amount byproduct benzocyclobutene. This interesting finding spurred them to optimize the reaction conditions. After screening several palladium catalysts and ligands, Pd(0)-catalyzed intramolecular C(sp³)-H arylation protocol was developed for concise synthesis of five- [259] and four- [260] membered carbocycles (Scheme 2.43). This strategy is distinguished by predictable arylation of unactivated aliphatic C-H bond without directing groups and external oxidants, and thus complement the current oxidative C(sp³)-H bond functionalization.

Valued carbocycles and heterocycles were elegantly constructed with this strategy (Scheme 2.44) [261–266]. Interestingly, although four- and five-membered rings were normally obtained, the Shi's group recently proved the possibility for the synthesis of six-membered heterocycles [267]. Using chiral phosphine/palladium complex as catalyst, enantioselective arylation of C(sp³)-H bond can be achieved producing the desired products in good to excellent enantioselectivity under elevated temperature [266]. The group of Kündig applied chiral NHC ligands in this transformation, and a diverse range of C(sp³)-H arylation products were obtained in good enantioselectivities [268–271]. Furthermore, this metalation strategy can also be compatible to intermolecular remote C(sp³)-H arylation of carbonyl compounds without the help of directing groups [272–274].



Scheme 2.43 Pd-catalyzed redox-neutral intramolecular arylation of C(sp³)-H bond [259, 260]



Scheme 2.44 Representative examples for intramolecular arylation of C(sp³)–H bond [261–271]

2.7 Conclusions

In conclusion, the recent work on the functionalization of aliphatic C(sp³)–H bond has shown great potential to construct carbon–carbon and carbon–heteroatom bonds without the assistance of directing groups. Based on the substrate structure, sterics, and electron effects, chemists have developed substantial tools to selective functionalize one special C(sp³)–H bond. It represents the state of the art in organic synthesis. Future efforts should be dedicated to developing sustainable and practical enantioselective C(sp³)–H bond functionalization in the absence of directing groups. The use of cheap yet nontoxic transition metals (Fe, Cu, Zn et al) will be actively pursued. Let us showcase the chemists' wisdom on this challenging chemistry.

Acknowledgments The National Natural Science Foundation of China (No. 21372114, 21172106), and the Research Fund for the Doctoral Program of Higher Education of China (20120091110010) and the Brand Major Project of Jiangsu Province are kindly acknowledged.

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2016, XII, 81 p. 117 illus., 112 illus. in color., Softcover

ISBN: 978-3-662-49494-3