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Sustainable C(sp^3)–H Bond Functionalization

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Preface

Hydrocarbons are the main feedstock for the chemical industry from oil and natural gas. Generally, carbon–hydrogen (C–H) bond is not considered as a functional group due to its low reactivity and high thermodynamic stability. In recent years, the catalytic functionalization of inert C–H bonds has become an atom-economical and sustainable way to construct new chemical bonds, avoiding the preparation of coupling precursors. The ubiquitous nature of C–H bonds in organic compounds offers us an exciting platform to create new chemistry. The "International Symposium on C–H Activation" is held every 2 years (first in Beijing in 2012; second in Rennes in 2014), and over 200 scholars from about 30 countries participated in the first and second conferences. The third symposium will be held in Montreal in May 2016. The group of "C–H activation" is still growing fast. It becomes a dynamic research project in the disciplines of synthetic chemistry and sustainable chemistry.

C–H bond functionalization is in transition from its infancy to adolescence. In the past decade, a great number of achievements were accomplished in C–H bond functionalization. Chemists have created a series of new methodologies and new strategies to make the chemical reactions more sustainable: from one C–H bond to two C–H bonds coupling, from noble metal catalysis to cheap metal catalysis, and even to metal-free process. However, how to selectively cleave and functionalize $C(sp^3)$-H bond still remains a great challenge owing to its weakest reactivity in organic chemistry. In this book, we mainly discuss the recent advancement of sustainable $C(sp^3)$-H bond functionalization strategies, providing one powerful route to direct construction of carbon–carbon and carbon–heteroatom bonds.

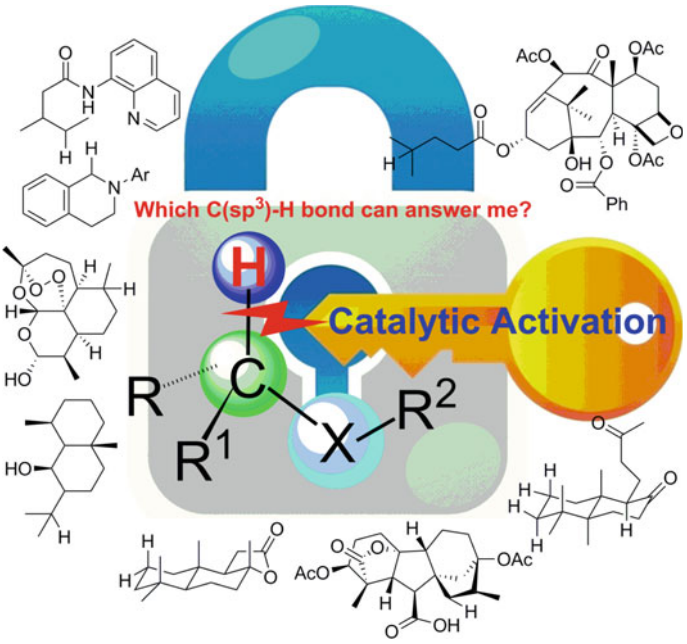
Most references in the book have been published in the recent 5 years. They will bring us a new chance to review the relevant progress of $C(sp^3)$-H bond functionalization and also offer a new research direction. In Chap. 1, we introduce the transition-metal-catalyzed unactivated $C(sp^3)$-H bond functionalization using different directing functional groups. Enantioselective functionalization of unactivated $C(sp^3)$-H bond is very exciting, and the seminal work of J.-Q. Yu is highlighted. In Chap. 2, we mainly focus on the nondirected $C(sp^3)$-H bond functionalization in the

presence/absence of transition metal catalysts. Depending on the electronic, steric, and stereoelectronic properties of the substrate, catalytic oxidative functionalization of α-C(sp^3)-H bond adjacent to heteroatoms, oxidative functionalization of allylic, benzylic C–H bonds, and unactivated C(sp^3)-H bonds are discussed. The transition-metal-catalyzed redox-neutral C(sp^3)-H bond functionalization is also briefly introduced in Chap. 2. As an emerging sustainable synthetic strategy, visible-light-promoted C(sp^3)-H bond functionalization is summarized in Chap. 3.

Each chapter is concluded with a perspective of the C(sp^3)-H bond functionalization methods. We hope this book will be interesting to a wide readership in organic, organometallic, and green chemistry.

October 2015

Jin Xie
Chengjian Zhu



GOLDEN KEYS TO CREATE MOLECULAR ART

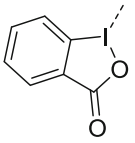
Contents

About the Authors

Dr. Jin Xie was born in Chongqing, China, in 1985. He received his bachelor's degree from Northeast Forestry University in 2008, and Ph.D. in 2013 from Nanjing University under the direction of Prof. Chengjian Zhu. He is now working as a postdoctoral research associate in the group of Prof. A.S.K. Hashmi at the Heidelberg University. His current interests are gold-catalyzed C–H bond functionalization and photoredox catalysis with gold complexes.

Prof. Chengjian Zhu was born in Henan, China, in 1966. He obtained his Ph.D. from Shanghai Institute of Organic Chemistry (CAS) in 1996 under the supervision of Prof. Changtao Qian. Then he worked as a postdoctoral fellow successively in Universite de Bourgogne, University of Oklahoma, and then University of Houston from 1997 to 2000. He joined Nanjing University as associate professor in 2000. Since 2003, he has been a professor at Nanjing University. He has contributed more than 100 publications to a number of prestigious journals, including *Chem. Soc. Rev.*, *J. Am. Chem. Soc.*, *Angew. Chem. Int. Ed.* and *Chem. Sci.*, etc. His present research interests lie in organometallic chemistry and asymmetric catalysis.

Abbreviations

2-chloranil	Tetrachloro-1,2-benzoquinone
AQN	Anthraquinone
BDE	Bond dissociation energy
bdpbz	1,2-Bis(diphenylphosphino)benzene
Boc-	*t*-Butyloxy carbonyl
BPM	bipyrimidine
BPO	Benzoyl peroxide
BQ	1,4-Benzoquinone
Cbz-	Carbobenzyloxy
CDC	Cross-dehydrogenative coupling
Cp*	1,2,3,4,5-Pentamethylcyclopentadiene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCA	9,10-dicyanoanthracene
DCE	Dichloroethane
DCM	Dichloromethane
DCN	1,4-Dicyanonaphthalene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DFT	Density functional theory
DMA	*N,N*-Dimethylacetamide
DMF	*N,N*-Dimethylformamide
DMPO	5,5-Dimethyl-1-pyrroline *N*-oxide
DMSO	Dimethyl sulfoxide
dppb	1,4-Bis(diphenylphosphino)butane
DTBP	Di-*tert*-butyl peroxide
EBX	
EPR	Electron paramagnetic resonance
HAT	Hydrogen atom transfer

HFIP	Hexafluoroisopropanol
MS	Molecular sieves
NBS	*N*-Bromosuccinimide
NHC	*N*-Heterocyclic carbenes
NHPI	*N*-Hydroxyphthalimide
NMP	1-Methyl-2-pyrrolidinone
PIFA	(Bis(trifluoroacetoxy)iodo)benzene
PivOH	Pivalic acid
SCE	Saturated calomel electrode
SCS	Spin center shift
SET	Single electron transfer
t-AmylOH	2-Methyl-2-butanol
TBADT	Tetrabutylammonium decatungstate
TBHP	*tert*-Butylhydroperoxide
TBP	*tert*-Butyl peroxybenzoate
TBPB	*tert*-Butyl peroxybenzoate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

Chapter 1
Transition Metal-Catalyzed, Directing Group-Assisted C(sp^3)–H Bond Functionalization

Abstract Highly regioselective C(sp^3)–H bond functionalization is a very important and attractive research topic as organic compounds usually contain several different kinds of C–H bonds (sp, sp^2, and sp^3). The introduction of a directing group has become one of the most efficient strategies to achieve this target. In this chapter, we discuss the latest advances in metal-catalyzed arylation, allenylation, amidation, and alkylation of inactivated C(sp^3)–H bonds enabled by the directing group strategy.

Keywords C(sp^3)–H activation · Oxidative coupling · Atom economy · Directing group · Palladium catalysis

1.1 Introduction

The pursuit of sustainable synthetic procedures accelerates the innovations of synthetic methods. Transition metal-catalyzed coupling reactions are fundamental tools for the construction of complex molecules, but the prefunctionalization of one or both coupling partners is required. Conceptually, the direct use of C–H bonds for coupling reactions is the most fascinating protocol, since it can avoid prefunctionalization of substrates, shorten the reaction time and improve the atom- and step economy. Therefore, it has been attracting increasing interest from both academia and industry.

Compared to C(sp^2)–H and C(sp)–H bonds, the C(sp^3)–H bond possesses the lowest reactivity and high thermodynamic stability, which makes its functionalization much more challenging yet attractive. In the past decade, we witnessed an explosive development of C(sp^3)–H bond functionalization; the directing group-assisted C(sp^3)–H bond functionalization became one of the most powerful tools to tackle stereo-, regio- and chemoselectivity of one specific C(sp^3)–H bond (Fig. 1.1).

With profuse efforts, a great number of new directing groups were developed to perform the highly selective C–H bond functionalization. As shown in Fig. 1.1, the

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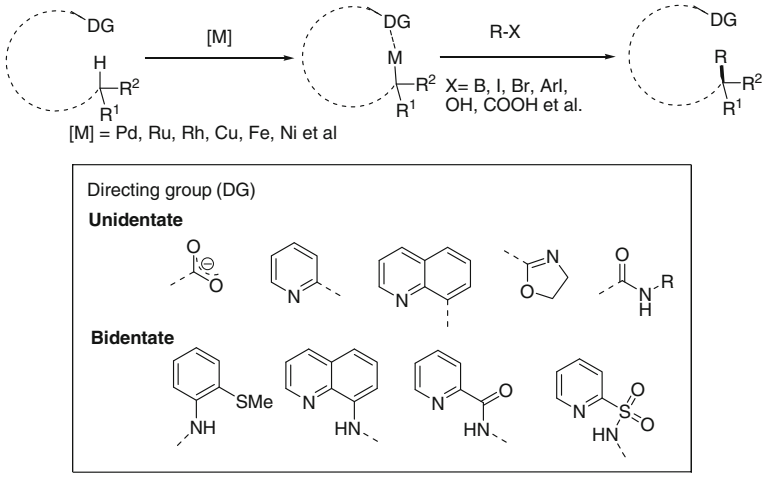
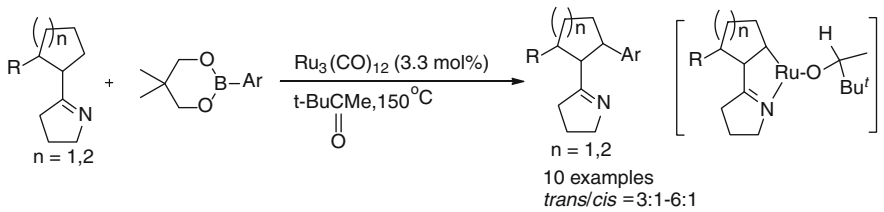


Fig. 1.1 The metal-catalyzed, directing group-assisted C(sp^3)–H bond functionalization

introduction of heteroatom-containing auxiliaries (unidentate and bidentate), is the key to success. The introduced heteroatom in the directing group is prone to coordinate to the metal center and then form a thermodynamically stable five or six-membered metalacyclic organic intermediate with a proximal C(sp^3)–H bond. Herein, the transition metal with rich coordination ability to a heteroatom is crucial for a successful C–H transformation. In general, the prime requirement for directing groups is that they should be easy to upload and readily removal under mild reaction conditions. It is not surprising that the transition metals currently used in C(sp^3)–H bond functionalization are mainly noble metals. The next generation catalytic system with cheaper metals (Fe, Ni, Co, Cu) is of great importance, and has attracted increasing attention in the past 3 years.

1.2 Directed C(sp^3)–H Arylation

Heteroatom-directed C(sp^3)–H bond functionalization with stoichiometric transition metals was first disclosed in 1984 [1]. In 2002, Sames and coworkers developed an efficient route to construct the teleocidin B4 core via the activation of C(sp^3)–H bond to prepare two diastereomeric palladacycle key intermediates [2]. As a follow-up work, $Ru_3(CO)_{12}$-catalyzed arylation of various C(sp^3)–H bonds with arylboronate esters using pyridine, pyrimidine, and amidine as directing groups was reported (Scheme 1.1) [3]. The use of ketones as solvent was necessary for a successful arylation, mainly due to the trapping effect of the ruthenium hydride species. Despite of its efficiency, this transformation needs elevated temperatures (150 °C). Further, pyridine-directed α–C(sp^3)–H arylation of piperidines with arylboronate esters was developed with alcohols as solvent [4].

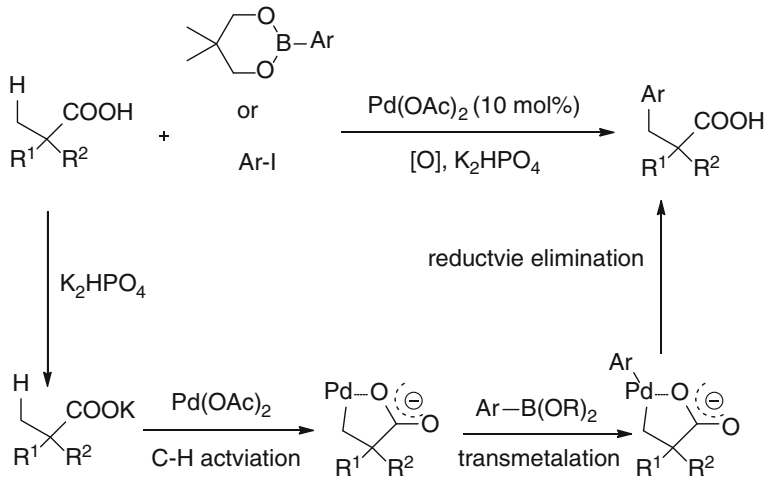


Scheme 1.1 Ru-catalyzed C(sp^3)–H arylation with arylboronate esters [3]

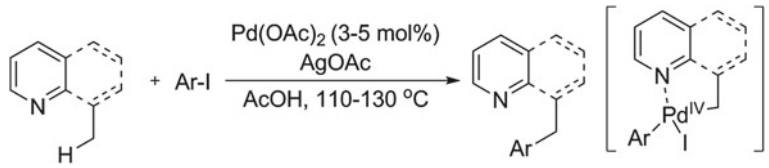
With commercially available boronate esters as aryl coupling partners, the first Pd(II)-catalyzed β–C(sp^3)–arylation of simple carboxylic acids was reported (Scheme 1.2) [5]. The reaction presumably relied on the binding of carboxylate directing group to Pd(II) center, triggering a C–H activation/transmetalation/reductive elimination sequence. The β-arylated carboxylic acids can be obtained in satisfactory yields. It represents an important step forward in arylation of C(sp^3)–H bonds.

Given the abundance of aryl halides, in 2005, $Pd(OAc)_2$-catalyzed, 8-methylquinoline- and 2-ethylpyridine-directed C(sp^3)–H arylation was reported by Daugulis and coworkers using low-cost aryl iodides (Scheme 1.3) [6]. An extension of β–C(sp^3) arylation of carboxylic acids with aryl iodides was then achieved by Yu and coworkers (Scheme 1.2) [5].

From these early achievements, it was found that the heteroatom in the directing group could saturate the coordination site on metal center facilitating the formation of a metallacyclic intermediate, which is able to proceed transmetalation with organometallic reagents (M^n/M^{n-2} catalytic cycle) or oxidative addition with



Scheme 1.2 The Pd(II)-catalyzed β–C(sp^3)–H arylation of aliphatic carboxylic acids [5]



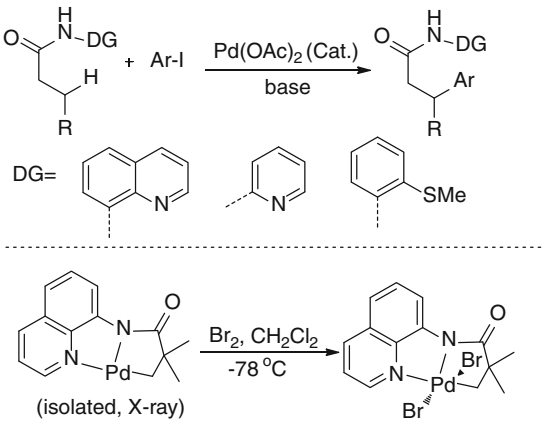
Scheme 1.3 Pd(II)-catalyzed C(sp^3)–H arylation with Ar–I [6]

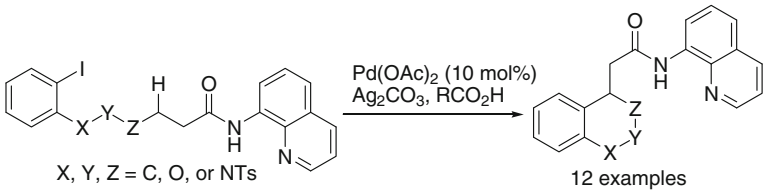
electrophiles (M^n/M^{n+2} catalytic cycle). Accordingly, the improvement of reaction selectivity and efficiency became a core topic in this area during the past decade. Considerable efforts were dedicated to developing new auxiliaries and design new reactions under these basic principles [7–9]. It opens up a new stimulating and promising avenue in the field of synthetic chemistry and green chemistry.

In 2005, Daugulis and coworkers documented a new and efficient two coordination site auxiliary (Scheme 1.4) [10, 11]. The removable directing group, pyridine, quinolone or methyl sulfide, was connected to alkyl chain through an amide linker, affording a powerful platform for remote C(sp^3)–H bond functionalization. The employment of bidentate directing group enabled facile arylation of C(sp^3)–H bond in the presence of silver acetate (Scheme 1.4). Furthermore, the active organopalladium intermediate was isolated and crystallographically characterized, which can undergo oxidation addition to produce Pd(IV) species in the presence of electrophiles (Br_2 or Ar–I). This finding is tentatively indicative of a novel Pd(II)/Pd(IV) mechanism. With Sanford's insistent efforts, the Pd(II)/Pd(IV) catalytic cycle pathway is now accepted by more and more organometallic chemists [12–15].

With a suitable directing group, selective arylation of remote β- and γ–C(sp^3)–H bonds was reported by Corey et al. in 2006. Using quinolone auxiliary, Pd(II)-catalyzed mono- and bis-arylation of β- and γ–C(sp^3)–H bonds of phthalimide-protected amino acids was achieved [16]. Later, β–C(sp^3)–H monoarylation of phthalimide-protected amino acids and simple aliphatic amides were developed

Scheme 1.4 Aliphatic C–H arylation with bidentate directing groups [10]





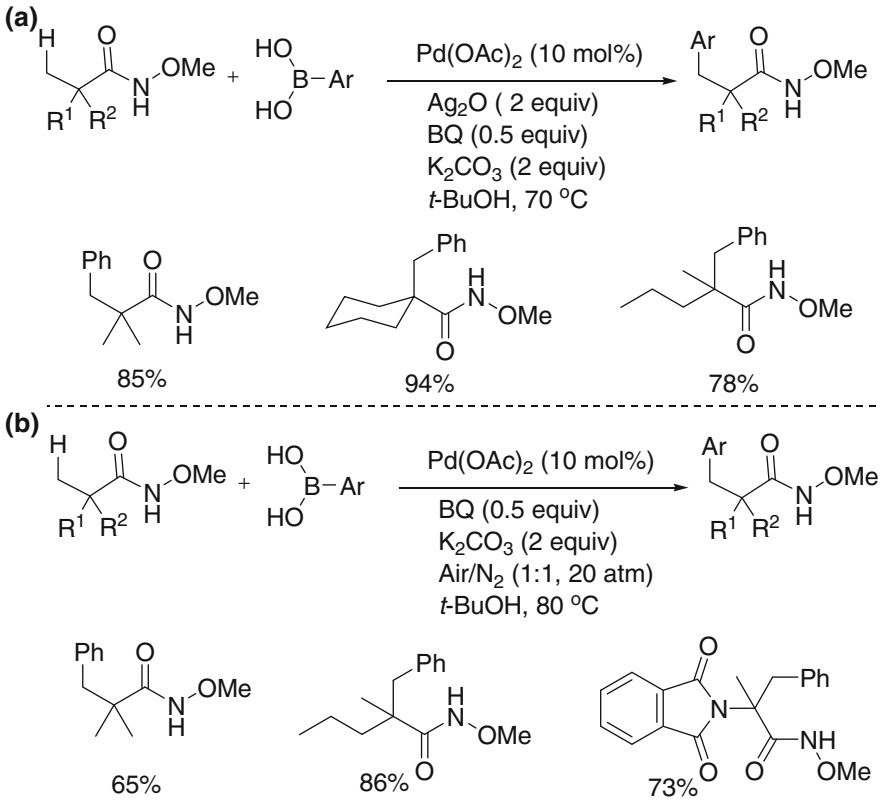
Scheme 1.5 Pd(II)-catalyzed intramolecular C(sp^3)–H arylation [20]

[17, 18]. Importantly, this class of C(sp^3)–H arylation protocol was applied as a key step for the total synthesis of challenging celogentin C by Chen and coworkers. [19] Subsequently, authors from the same group reported an intramolecular C(sp^3)–H arylation using quinolone as the directing group (Scheme 1.5) [20]. They assumed that the addition of carboxylic acids was beneficial to the concerted palladation/deprotonation C–H activation process [21, 22]. To date, the bidentate quinolone auxiliary is still one of the most useful and efficient directing groups for C–H bond functionalization [7].

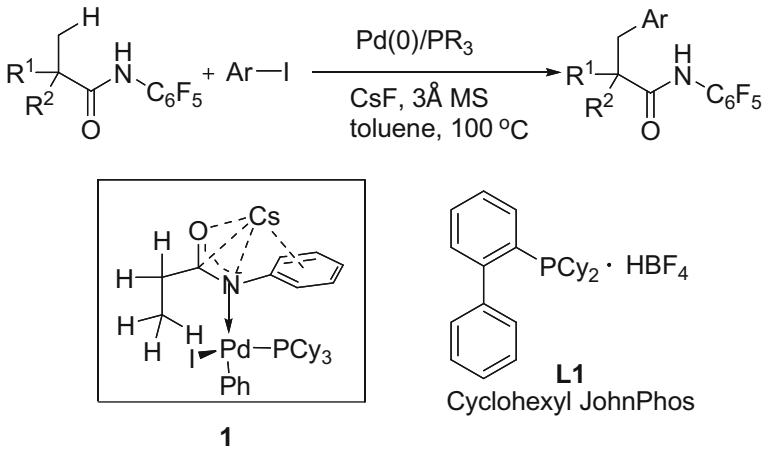
As a follow-up work, Yu et al. succeeded to develop O-methyl hydroxamic acids-directed β–C(sp^3)–H arylation with aryl boronic acids under mild reaction conditions in 2008 (Scheme 1.6) [23]. Remarkably, they identified that air could be employed as a sustainable external oxidant to replace silver salts (Scheme 1.6b). Since the O-methyl hydroxamic acids are readily to undergo a series of organic transformations, this protocol provides a facile access to a class of bioactive target molecules.

Unfortunately, in some cases, the CO*NH*OMe motif can undergo Buchwald–Hartwig amination with Ar–I, affording the C–N coupling by-product [24]. To solve this inherent limitation, Yu and coworkers screened different kinds of amide substituents and finally verified –CONHC$_6$F$_5$ as the optimal directing group. With it, Pd(0)-catalyzed highly selective β–C(sp^3)–H arylation of amides could occur smoothly in the presence of Buchwald's Cyclohexyl JohnPhos ligand **L1** (Scheme 1.7) [24]. In addition, the inorganic base CsF is crucial for a successful arylation. This interesting result spurred them to get an insight into the detailed mechanism. A recent concerted metalation–deprotonation pathway was documented. The key intermediate **1** was proposed by DFT calculations, which could undergo "Cs$_2$–I–F cluster" assisted β–C(sp^3)–H bond activation [25].

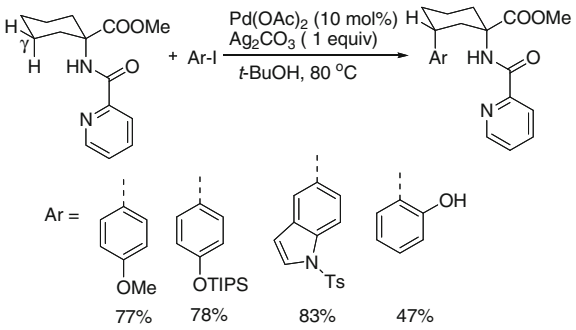
By employing picolinic acid as the directing group, γ–C(sp^3)–H arylation was developed by Chen and coworkers (Scheme 1.8) [26]. A variety of electron-rich and electron-poor aryl iodides were good coupling partners. The selectivity was related to the relative conformation of the C(sp^3)–H bond with regard to the directing group. The use of linear substrates led to decreased yields. However, a limitation of this strategy is that the removal of standard picolinamine auxiliary requires harsh conditions, which compromised its potential in the late-stage modification of complex molecules. To address it, Chen et al. found that the picolinamide



Scheme 1.6 Pd(II)-catalyzed oxidative β–C(sp^3)–H arylation with aryl boronic acids [23]



Scheme 1.7 Pd(0)-catalyzed intermolecular β–C(sp^3)–H arylation of aliphatic amides [24, 25]

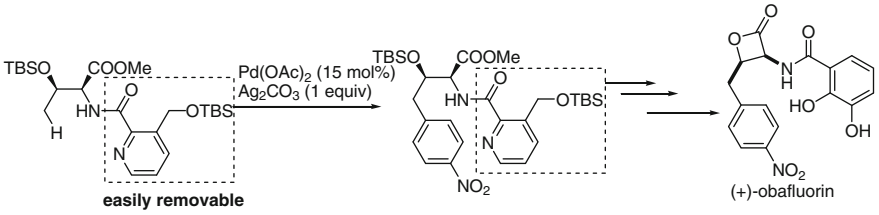


Scheme 1.8 Pd(II)-catalyzed γ–C(sp^3)–H arylation [26]

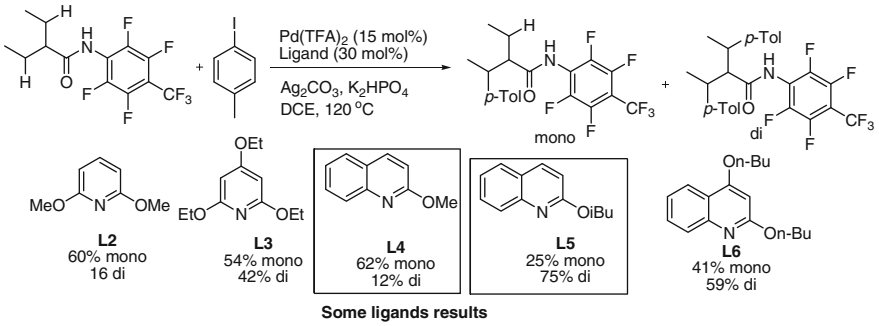
derivative was much more easily removable under mild conditions (Scheme 1.9) [26]. As a consequence, it allowed for the total synthesis of (+)-obafluorin.

In recent years, the choice of ligand accelerated or tuned C–H bond functionalization strategy was esteemed as one important synthetic tool since it could enable different selectivities with different ligands [27–29]. If one reaction is feasible in theory, screening a great number of ligands is indeed useful to discover a new transformation. With this in consideration, in 2012, Pd(II)-catalyzed, ligand-enabled arylation of methylene C(sp^3)–H bond was developed after screening 13 ligands (Scheme 1.10) [30]. The 2-iso-butoxyquinoline **L5** was the best choice for β–C(sp^3)–H arylation (100 % conversion).

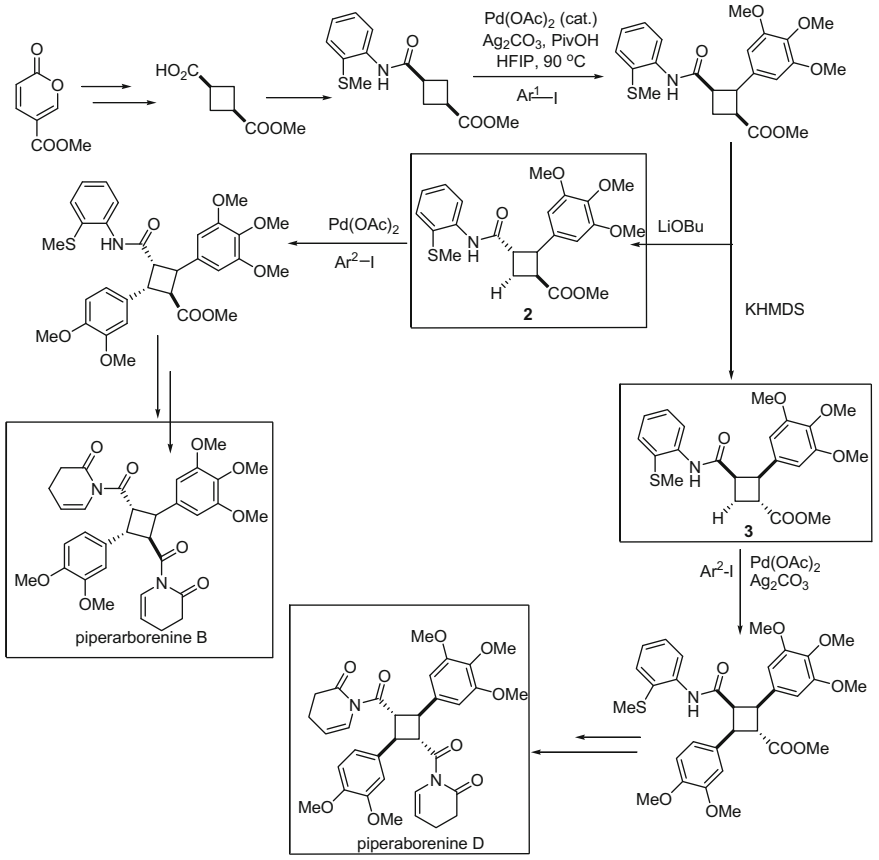
Although C(sp^3)–H arylation protocols gained increasing attention, their applications for total synthesis of complex natural products remain challenging. In 2011, Baran's group developed Pd(II)-catalyzed, directing group-assisted C(sp^3)–H arylation of cyclobutanes. It constitutes a rare example of total synthesis of piperaborenine B and piperaborenine D by sequential C(sp^3)–H arylation tactic (Scheme 1.11) [31]. Both synthetic pathways allow to prepare piperaborenine B and piperaborenine D from commercially available feedstock methyl coumalate in satisfactory yield and regioselectivity (piperaborenine B, 7 steps, 7 % overall yield; piperaborenine D, 6 steps, 12 % overall yield). The key step is the epimerization of the ester and amide moieties under different bases to generate intermediates **2** and **3**,



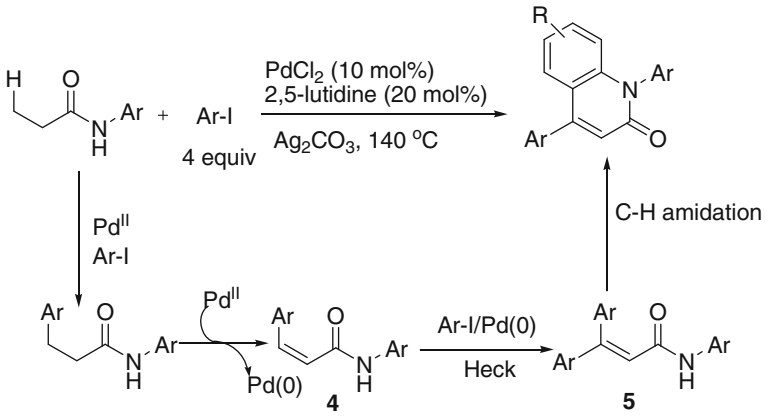
Scheme 1.9 Application of Pd(II)-catalyzed γ–C(sp^3)–H arylation for the synthesis of obafluorin [26]



Scheme 1.10 Ligand-controlled β-arylation of amide derivatives [30]



Scheme 1.11 Sequential C(sp^3)–H arylation for the total synthesis of piperaborenine B and piperaborenine D [31]

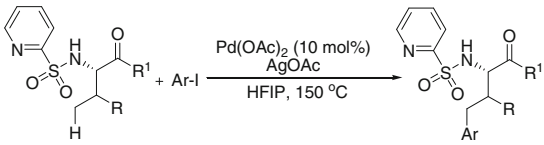


Scheme 1.12 Pd-catalyzed tandem arylation/amidation of several C–H bonds [33]

followed by the second C(sp^3)–H arylation with aryl iodides. Intriguingly, this strategy was also practical for the total synthesis of pipercyclobutanamide through sequential C(sp^3)–H arylation and vinylation [32].

The tandem reactions are of particular importance in organic synthesis owing to their remarkable advantages in consecutive formation of chemical bonds in one operation. Arguably, consecutive C–H bond functionalization can contribute a facile access to complex molecules from simple starting materials. In this context, Yu et al. reported a tandem cyclization sequence by Pd(II)-initiated β–C(sp^3)–H arylation with propionamides (Scheme 1.12) [33]. It affords one economical, highly efficient route to diverse 4-aryl-2-quinolinones from propionic acids. From the mechanistic picture, cleavage of five C–H bonds and formation of three new C–C and one new C–N bonds are involved. As shown in Scheme 1.12, a possible reaction pathway starts from β–C(sp^3)–H arylation of propionamides under palladium catalysis, followed by dehydrogenation via Pd insertion. The resulting Pd(0) species triggers a Heck coupling of *N*–Ar acrylamide intermediate **4** with aryl iodide to form 3,3-darylacrylamide **5**. Finally, intramolecular amidation of sp^2 C–H bond furnishes the desired quinolinone products.

In 2011, Carreetero et al. verified that *N*-(2-pyridyl)sulfony was an easily introduced and removable directing group; preliminary results on C(sp^2)–H bond functionalization was disclosed using this new auxiliary [34]. As their follow-up work, they later reported *N*-(2-pyridyl)sulfonyl-directed γ–C(sp^3)–H arylation [35]. A series of simple amino acid methyl esters and amides were able to deliver highly selective γ-arylated products under optimal conditions (Scheme 1.13). The



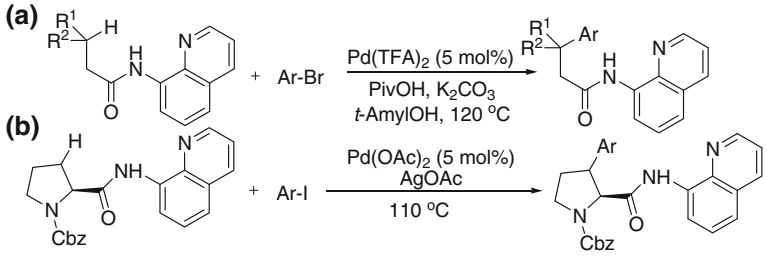
Scheme 1.13 Pd-catalyzed, *N*-(2-pyridyl)sulfonyl-directed γ–C(sp^3)–H arylation [35]

N-(2-pyridyl)sulfonyl could be removed under very mild conditions (Zn powder at 60 °C in THF/aqueous NH_4Cl), affording free primary amines in good yields. The *N*-(2-pyridyl)sulfony auxiliary would render a good choice for late-stage modification of complex molecular architectures.

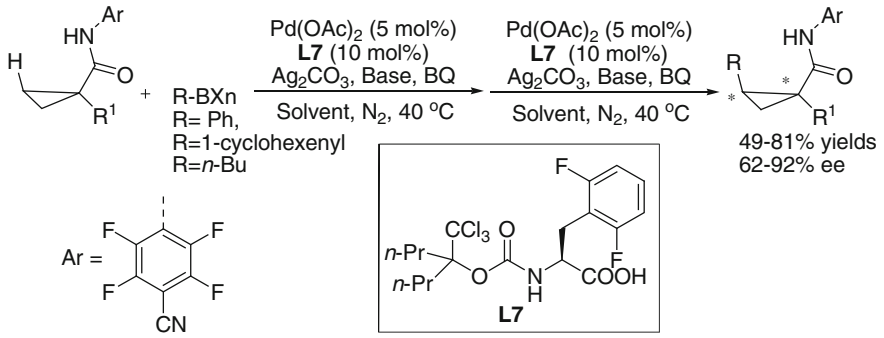
Besides aryl iodides, less reactive aryl bromides were also effective coupling partners in the Pd(II)-catalyzed C(sp^3)–H bond arylations (Scheme 1.14a) [36]. The good functional group compatibility and broad substrate scope enabled it attractive for concise synthesis of cardioselective β-blocker drug molecule Esmolol. Later, Shi et al. developed a Pd(II)-catalyzed monoarylation of β-methyl C(sp^3)–H of alanine derivatives with aryl iodides using 8-aminoquinoline auxiliary [37]. Almost at the same time, a similar organic transformation was accomplished, with aryl iodides and bromides as aryl donors in the catalysis of $Ni(OTf)_2$ [38]. One recent report demonstrated that the unactivated 3-position of proline derivatives could also be arylated with 8-aminoquinoline auxiliary (Scheme 1.14b) [39].

The regio-, chemo- and stereoselectivity was the main scientific issues in transition metal C(sp^3)–H arylation. The regio- and chemoselectivity become controllable with suitable directing groups. However, the control of stereoselectivity in C(sp^3)–H bond functionalization represents a new challenge. In 2011, the Yu's group introduced the first Pd(II)-catalyzed, enantioslective C(sp^3)–H functionalization of cyclopropanes through screening a variety of chiral mono *N*-protected amino acids ligands (Scheme 1.15) [40]. Under the optimized reaction conditions, aryl-, vinyl- and alkylboron reagents can directly couple with the C(sp^3)–H bond of cyclopropanes using amide directing group. To get a better enantioselectivity, all the reagents should be added in two batches, but it does not compromise its synthetic values. This protocol arguably provides a novel route to *cis*-substituted chiral cyclopropanecarboxylic acid derivatives.

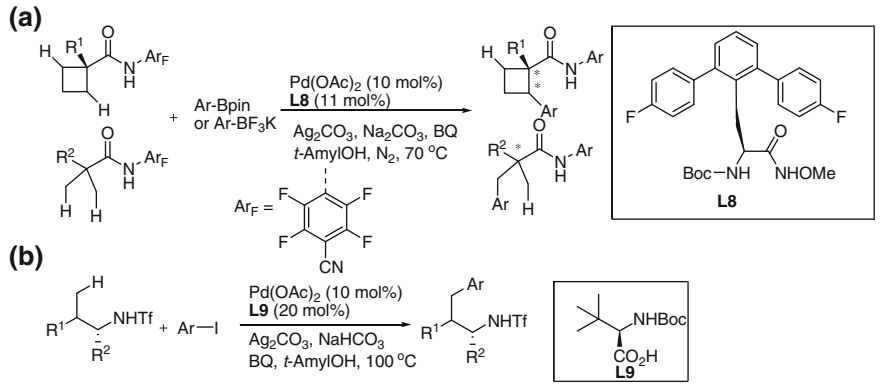
More recently, the ligand-enabled enantioselective C(sp^3)–H bond arylation to cyclobutanecarboxylic acid derivatives with aryboron reagents was accomplished by Yu's group. [41] After screening a great number of chiral amino acids, they found that **L8** was the most effective chiral ligand for enantioselective arylation of methylene C(sp^3)–H bonds. It furnished the desired cyclobutanecarboxylates in good to excellent enantioselectivities (Scheme 1.16a). With the ligand screening tactic, Pd(II)-catalyzed γ–C(sp^3)–H arylation of a variety of alkyl amines was later



Scheme 1.14 8-Aminoquinoline-directed monoarylation [36, 39]



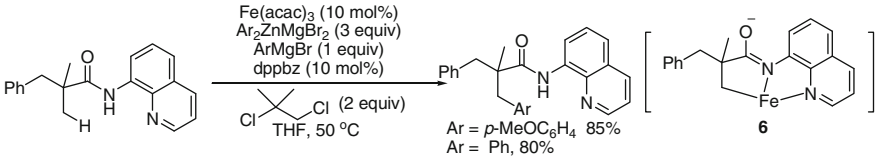
Scheme 1.15 Pd(II)-catalyzed enantioselective C(sp^3)–H arylation of cyclopropanes [40]



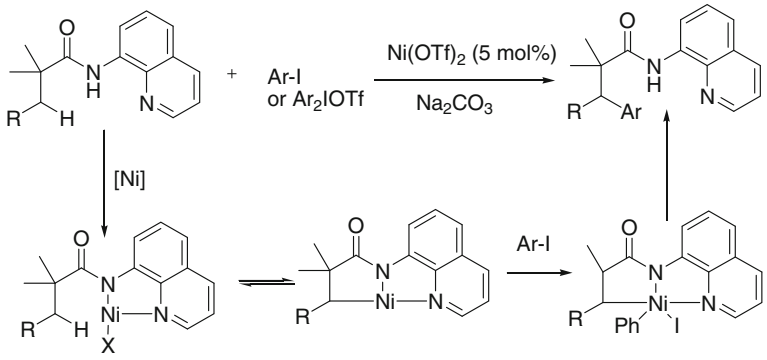
Scheme 1.16 Pd(II)-catalyzed, chiral amino acid-tuned enantioselective C(sp^3)–H arylation [41, 43]

documented with chiral amino acid ligand [42]. Remarkably, chiral amino acid derivatives can readily undergo the γ-arylation reaction and keep the chiral center intact. In early 2015, authors from the same group expanded the reaction scope to *N*–Tf cyclopropylmethylamines and aryl iodides instead of cycloalkanes and boronic acids with chiral Boc-*L*-Val-OH ligand (Scheme 1.16b) [43]. From the mechanism viewpoint, both Pd(II)/Pd(IV) and Pd(II)/Pd(0) catalytic cycles are possible. The corresponding mechanistic study would be of particular interest to chemical community.

It seems that transition metal-catalyzed C(sp^3)–H functionalization is partial to noble palladium catalysts. Virtually, in 2013, Nakamura and coworkers developed a Fe(III)-catalyzed, 8-aminoquinolinyl auxiliary-assisted β–C(sp^3)–H arylation with organozinc reagent in the presence of organic halides as oxidant using (Scheme 1.17) [44]. The preliminary mechanistic study suggests an organoiron intermediate **6**. In 2014, Gu and Ackerman developed Fe(acac)$_3$-catalyzed



Scheme 1.17 Fe(III)-catalyzed β–C(sp^3)–H arylation [44]



Scheme 1.18 Ni(II)-catalyzed, 8-aminoquinoline-directed β–C–H arylation [46, 47]

C–H arylation reaction with a triazole-based directing group [45]. Although the substrate scope is relatively narrow than that with palladium catalyst, it would be helpful to explore and understand the catalytic specialty of iron. Future work will focus on the design of an efficient iron catalytic system to avoid the use of sensitive reagents enabling the reaction applicable.

Using bidentate 8-aminoquinoline directing group, Ni(II)-catalyzed arylation of methyl and methylene C(sp^3)–H bond with aryl iodides [46] and diaryliodonium salts [47] were successively achieved (Scheme 1.18). The mechanistic study clearly indicates that C–H bond cleavage step is reversible and not the rate-determining step. A possible Ni(II)/Ni(IV) catalytic pathway was proposed. More recently, Glorius's group introduced the Cp*Rh(III)-catalyzed arylation of unactivated C(sp^3)–H bond with triarylboroxines using pyridine and quinoline as directing groups [48].

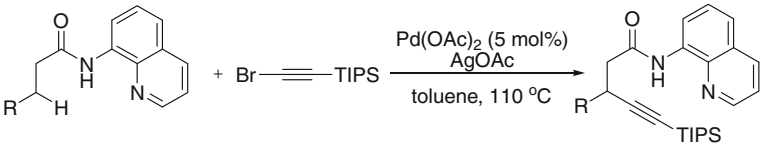
1.3 Directed C(sp^3)–H Alkynylation, Alkenylation, and Alkylation

The alkyne moieties are versatile building blocks and important structural motives in organic materials and biologically active molecules. Sonogashira coupling provides a very powerful protocol for the formation of C(sp^2)–C(sp) bond, but the

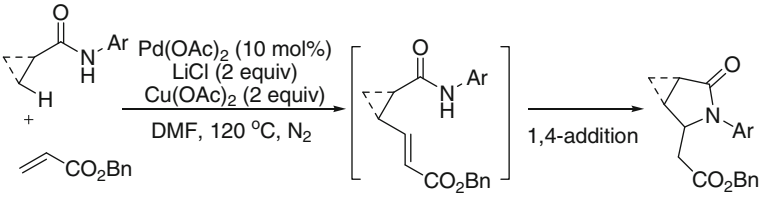
chemospecific construction of C(sp^3)–C(sp) bond from C(sp^3)–H bonds remains a great challenge [49]. The use of terminal alkynes usually leads to the homo-coupling by-products under the oxidative C–H bond functionalization reaction conditions. The first Pd(II)-catalyzed alkynylation of unactivated C(sp^3)–H bond was developed in 2011 with electrophilic 1-bromoalkynes as alkynyl donors (Scheme 1.19) [50]. Screening different directing groups revealed that bidentate 8-aminoquinoline auxiliary was the optimal choice. The substrates bearing methylene groups deliver better yields than methyl groups. The mechanism involves a Pd(II)/Pd(IV) catalytic cycle. Later, Pd(0)/L (L = NHC or PR_3) catalyzed alkynylation of β–C(sp^3)–H bond of aliphatic amides was disclosed [51]. A mechanistically distinct Pd(0)/Pd(II) catalytic system was proposed. Also, Chatani et al. recently found that palladium nanoparticles were efficient for the same alkynylation protocol [52]. These C(sp^3)–H alkynylations provide straightforward routes to introduce the ethynyl group into aliphatic acid derivatives.

In 2010, Yu et al. developed the first Pd(II)-catalyzed alkenylation of C(sp^3)–H bond using *N*-arylamide as directing group in the presence of $Cu(OAc)_2$ (Scheme 1.20) [53]. Various aliphatic amides are readily to furnish the β–C(sp^3)–H alkenylated product, which prefer to form γ-lactams via a 1,4-Michael addition under standard conditions. Intriguingly, this protocol can be applied to the direct olefination of methylene C–H bond. Vinyl boronic acids [40] and vinyl halides [26] are certainly good coupling partners for C(sp^3)–H alkenylations.

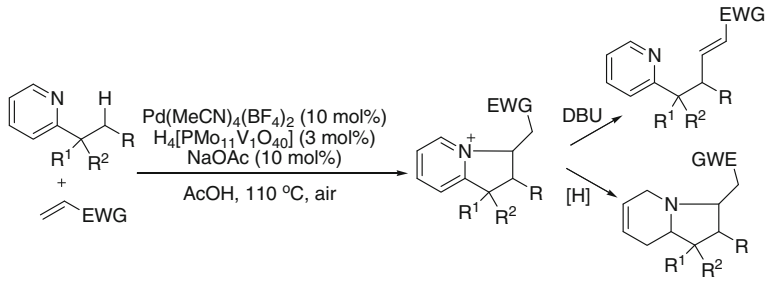
In 2011, Sanford et al. developed an elegant Pd(II)-catalyzed, pyridine-directed aerobic olefination of C(sp^3)–H bonds. The use of air as an external oxidant renders this protocol very promising. It constitutes an extremely rare example of Pd(II)-catalyzed aerobic C(sp^3)–H bond functionalization in the absence of copper salts additives. The resulting cyclic pyridinium salt can easily afford 6,5-*N*-fused bicyclic framework or alkene product under reductive conditions or organic base,



Scheme 1.19 Pd(II)-catalyzed electrophilic β–C(sp^3)–H alkynylation [50, 52]



Scheme 1.20 Pd(II)-catalyzed β–C(sp^3)–H alkenylation [53]

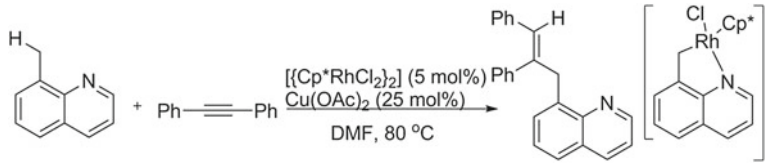


Scheme 1.21 Pd(II)-catalyzed aerobic olefination of unactivated C(sp^3)–H bonds for cyclic pyridinium product [54]

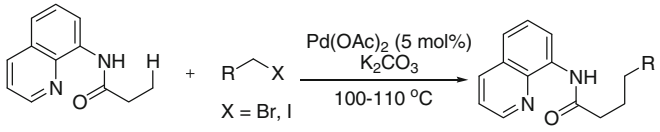
respectively (Scheme 1.21) [54]. However, the reaction scope was limited to activated alkenes, due to the low reactivity of unactivated olefins in the intramolecular Michael addition step.

Interestingly, a Rh(III)-catalyzed alkenylation of benzylic C(sp^3)–H bond was successfully developed (Scheme 1.22) [55]. Insertion of alkynes into the generated five-membered rhodacycle intermediate can produce 8-allylquinolines in good to excellent yields with high stereoselectivity. This represents the first example of an efficient incorporation of an unactivated alkene moiety to an sp^3-hybridized C–H bond.

We highlight the recent advance of C(sp^3)–C(sp^2) and C(sp^3)–C(sp) coupling from C(sp^3)–H bond in the above content. Another challenging is efficient C(sp^3)–C(sp^3) cross couplings because the alkyl–alkyl reductive elimination from a metal center is usually very slow and thus the reactive organometallic intermediate is susceptible to side reactions. In 2010, Daugulis et al. developed catalytic alkylation of remote C(sp^3)–H bond with alkyl halides (Scheme 1.23) [11, 56]. Although only



Scheme 1.22 Rh(III)-catalyzed mild benzylic C(sp^3)–H olefination [55]

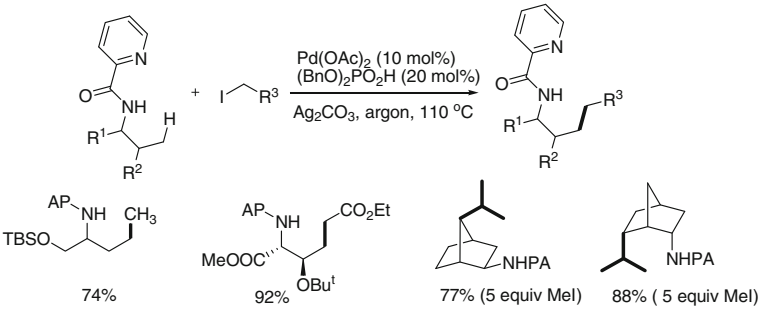


Scheme 1.23 Pd(II)-catalyzed C(sp^3)–C(sp^3) coupling with C–H bond and alkyl halides [11, 56]

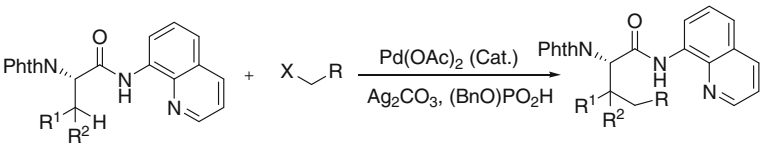
a few examples were disclosed, it brings chemists a new direction of highly attractive C(sp^3)–C(sp^3) cross-coupling and therefore complements the existing C(sp^3)–H bond alkylation strategies. Although alkyl boronic acids or boronic esters have been successfully employed as efficient alkylation reagents [23, 57], alkyl halides are much more challenging and desirable since they are low-cost and feedstock chemicals.

In the light of Daugulis's creative work [11], the subclass of C(sp^3)–H alkylation is booming rapidly in the past 5 years. In 2013, a Pd(II)-catalyzed primary alkylation of remote C(sp^3)–H of picolinamide-protected aliphatic amines was developed by Chen and coworkers (Scheme 1.24) [58]. It was found that both Ag_2CO_3 and dibenzyl phosphates were critical additives. A diverse range of primary alkyl iodides uniformly gave the desired products in moderate to good yields. Moreover, sequential C(sp^3)–H alkylation offers a convenient access to several highly valuable nitro-containing compounds.

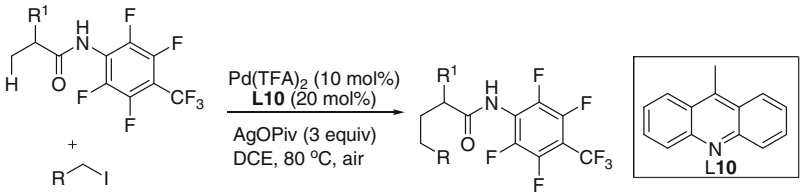
Subsequently, using 8-aminoquinoline auxiliary, Chen [59] and Shi [60] simultaneously reported on a Pd(II)-catalyzed alkylation of primary and secondary C(sp^3)–H bonds with various alkyl halides (Scheme 1.25). Both publications require the addition of Ag_2CO_3 and dibenzyl phosphate as promoters. Chen and coworkers suspected that $(BnO)_2PO_2H$ and Ag_2CO_3 could result in the formation of a soluble complex and $(BnO)_2PO_2H$ could act as a ligand to accelerate the turnover of catalyst. In 2014, Shi et al. further updated this method [61]. A similar organic transformation occurred while NaOCN and 4–Cl–$C_6H_4SO_2NH_2$ were employed instead of $(BnO)_2PO_2H$. The use of new promoters led to a significantly broader



Scheme 1.24 Pd(II)-catalyzed, picolinamide-directed remote alkylation of C(sp^3)–H bond [58]



Scheme 1.25 Pd(II)-catalyzed β–C(sp^3)–H alkylation of aliphatic amides [59, 60]



Scheme 1.26 Pd(II)-catalyzed selective β-alkylation of C(sp^3)–H bond [63]

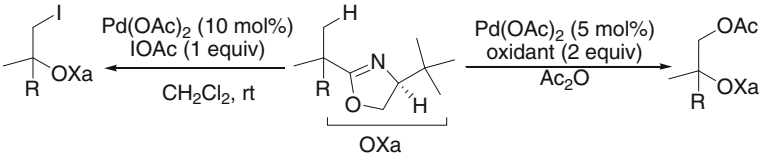
substrate scope. Very interestingly, the 8-aminoquinoline-directed, Ni(II)-catalyzed alkylation of C(sp^3)–H bonds of aliphatic amides with alkyl halides is also reported [62].

In the same year, based on their success of arylation of β–C(sp^3)–H bond with *N*-arylamide directing group [30], the corresponding alkylation protocol was developed with alkyl iodides (Scheme 1.26) [63]. One notable feature is that this protocol can be finished under atmospheric pressure, although a stoichiometric amount of AgOAc is necessary.

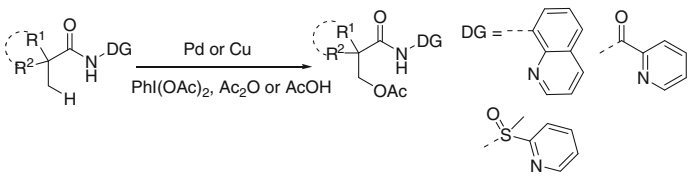
1.4 Directed C–X Bond Forming from C(sp^3)–H Bond

The first desymmetric iodination of unactivated C(sp^3)–H bond was accomplished in 2005 by using removable chelating oxazoline (OXa) as directing group (Scheme 1.27) [64]. The $Pd(OAc)_2$-catalyzed direct iodination reactions are compatible for methyl and cyclopropyl C(sp^3)–H bonds. All the examined substrates gave monoiodination products in good yields. Moreover, it is easy to recycle the palladium catalyst after the reaction finished owing to the precipitation of PdI_2 species. Later, an extension of this strategy was applied for concise synthesis of 1,3-diiodide derivatives, which would rapidly cyclize to 2-(1-alkylcylcloprpyl) dimethyloxazolines [65]. Satisfyingly, with the chiral oxazoline auxiliary, Pd(II)-catalyzed diastereoselective acyloxylation of prochiral C(sp^3)–H bond was reported (Scheme 1.27) [66].

The site-selective acyloxylation of aliphatic amides was developed on employing different bidentate directing groups (Scheme 1.28). With 8-aminoquinoline auxiliary, Corey and coworkers reported Pd(II)-catalyzed diastereoselective acyloxylation



Scheme 1.27 $Pd(OAc)_2$-catalyzed C(sp^3)–H iodination and acyloxylation [64, 66]



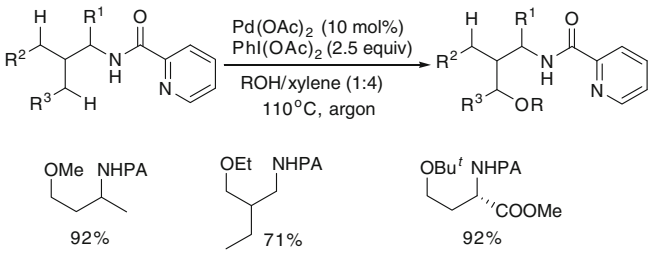
Scheme 1.28 Metal-catalyzed β–C(sp^3)–H acyloxylation of aliphatic amides [16, 67–72]

of C(sp^3)–H bond of β–hydroxy-α-amino acids in the presence of oxone, Ac_2O and $Mn(OAc)_2$ [16]. With $PhI(OAc)_2$ as external oxidant and also acetoxylating reagent, a much more straightforward procedure was reported [67–69]. The recent works focused on the direct use of carboxylic acids as effective coupling partners for direct acyloxylation of β–C(sp^3)–H bond [70, 71]. The bromination and chlorination of primary β–C(sp^3)–H bond was in parallel disclosed using reusable *S*-methyl-*S*-pyridyl-sulfoximine auxiliary (MPyS) [72].

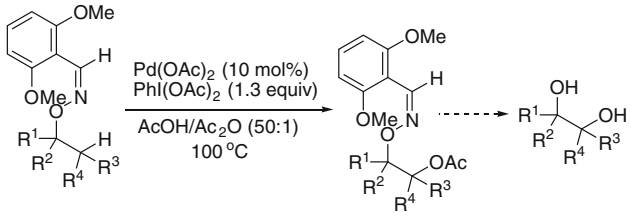
Alkyl ethers are an important subclass of compounds in natural products. The direct construction of alkyl ethers from C(sp^3)–H bonds is a challenging but promising access and thus is being actively pursued. Chen et al. first addressed this unsolved difficulty. They developed a Pd(II)-catalyzed, picolinamide-assisted functionalization of γ–C(sp^3)–H bond with primary, secondary, and even bulky tertiary alcohols (Scheme 1.29) [73]. The perfect compatibility of simple alcohols was one of the most striking features. Furthermore, under the optimized reaction conditions, functionalization of unreactive primary C(sp^3)–H bond ispreferential even in the presence of secondary C(sp^3)–H bond. Besides C–O bond coupling, picolinamide-assisted Pd(II)-catalyzed tandem arylation and oxidation of benzylic C–H bond can dexterously construct unsymmetric diaryl ketones [74].

Another imposing example of Pd(II)-catalyzed acetoxylation of inert C(sp^3)–H bonds was reported by Dong and coworkers with oxime as a new readily removable directing group (Scheme 1.30) [75]. The substrate scope is very broad. The C–H bonds of methyl, methylene, and methine groups can be successfully acetoxylated. This protocol provides a flexible route to a wide range of 1,2-diols.

The amidation of unactivated C(sp^3)–H bond is arguably an atom-economic and attractive strategy for C–N bond formation. In 2012, both Daugulis's [76] and



Scheme 1.29 Pd(II)-catalyzed oxidative C–O coupling of γ–C(sp^3)–H with alcohols [73]

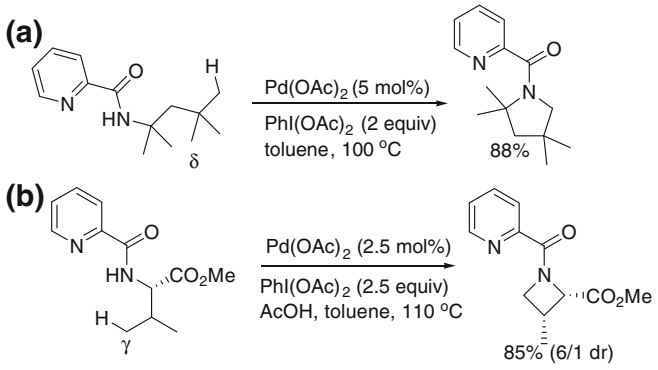


Scheme 1.30 Pd-catalyzed intramolecular acetoxylation for the synthesis of 1,2-diols [75]

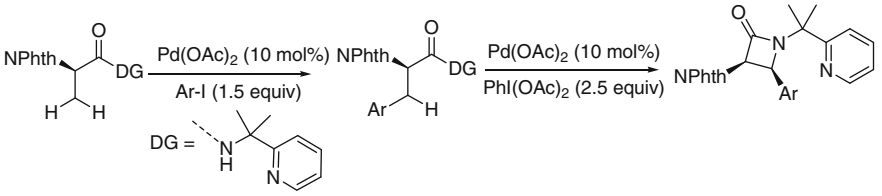
Chen's group [77] developed a Pd(II)-catalyzed intramolecular amidation with picolinamide directing group (Scheme 1.31). In Daugulis's case, to from a relatively stable organopalladium transition state, activating of δ–C(sp^3)–H bond is regioselectively manipulated. It allows for construction of five-membered heterocycles (Scheme 1.31a). Differently, Chen et al. dedicated to functionalizing α-amino acid derivatives, and $Pd(OAc)_2$-catalyzed intramolecular amination of γ–C(sp^3)–H bond were realized (Scheme 1.31b). As a consequence, it affords an efficient route to construct four-membered azetidines.

An analogous C–H amidation was reported by Shi and coworkers when they tried to optimize the reaction conditions of the monoarylation protocol (Scheme 1.32) [17]. First aylation of the β–C(sp^3)–H bond of the methyl group and subsequent intramolecular amidation at the same position delivered chiral α-amino-β-lactams in moderate to high yields with good diastereoselectivities. Noteworthy, during optimization of reaction conditions, the authors verified a competitive C(sp^3)–H acetoxylation process along with amidation.

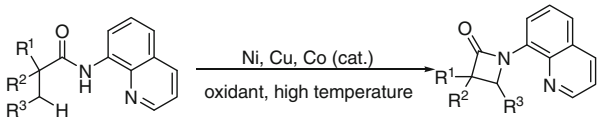
To avoid the formation of acetoxylated by-products, the best choice is to use other oxidants instead of $PhI(OAc)_2$. Ge and coworkers developed several efficient intramolecular amidation protocols of β–C(sp^3)–H bonds catalyzed by nickel, [78] copper [79] and cobalt [80] (Scheme 1.33). The use of cheap transition metals



Scheme 1.31 Pd(II)-catalyzed intramolecular amidation of remote unactivated C(sp^3)–H bond [76, 77]



Scheme 1.32 Pd(II)-catalyzed sequential arylation/amidation of C(sp^3)–H bonds [17]



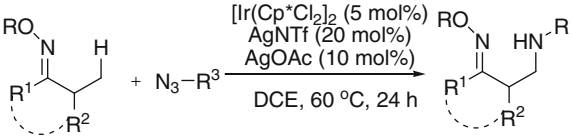
Scheme 1.33 Metal-catalyzed intramolecular amidation of β–C(sp^3)–H bond [78–80]

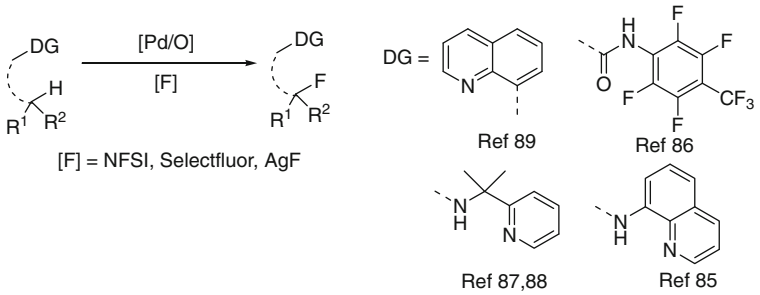
instead of noble palladium catalysts for unactivaed C(sp^3)–H functionalization is mainly underdeveloped and will undoubtedly be highly pursued in the future.

With sulfonyl and acyl azides as nitrogen precursors, Ir(III)-catalyzed methyl C–H amination reaction occurred smoothly under mild reaction conditions with oxime as directing group (Scheme 1.34) [81]. Much to our surprise, the authors pointed out that other efficient noble catalysts, such as $[RhCp^*Cl_2]_2$, $[Ru(p\text{-cymene})Cl_2]_2$ and Pd $(OAc)_2$ failed to achieve the identical transformation. Owing to the high functional group tolerance, this C(sp^3)–H amination protocol was applied to the synthesis of a series of complex compounds. Intriguingly, You and coworkers recently disclosed a Cp*Rh(III)-catalyzed intermolecular amination of C(sp^3)–H bond with sulfonamide on using pyridyl moiety auxiliary [82].

In early 2015, using bidentate 8-aminoquinoline as directing group, Zhang [83] and Shi [84] almost simultaneously reported Ni(II)-catalyzed β-thioetherification of unactivated C(sp^3)–H bonds of propionamides. Due to the intrinsic properties of the fluorine atom, fluorination of C(sp^3)–H bonds is meaningful both to synthetic chemistry and drug discovery. In recent years, several groups have made important contributions in this area. With the assistance of different kinds of directing groups, Pd-catalyzed C(sp^3)–H fluorination protocols were successively developed with electrophilic fluorine reagents (NFSI [85] and Selectfluor [86–88]) and nucleophilic AgF [89] (Scheme 1.35). Notably, unnatural enantiopure β-fluoro-α-amino acid derivatives were obtained with this protocol. In mechanism, the reductive elimination on the palladium center to form a C(sp^3)–F bond instead of the typical β-hydride elimination is rather priceless.

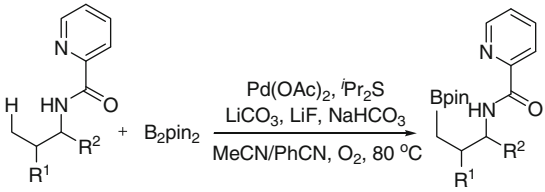
Scheme 1.34 Ir–catalyzed intermolecular amination of C(sp^3)–H bonds [81]





Scheme 1.35 Pd(II)-catalyzed fluorination of unactivated C(sp^3)–H bonds [85–89]

Scheme 1.36 Pd(II)-catalyzed aerobic oxidative borylation of γ–C(sp^3)–H bond [90]



Organoborane compounds are one of the most commonly used coupling partners for C–C couplings. In 2014, Shi et al. achieved a Pd(II)-catalyzed selective borylation of methyl C–H bond with O_2 as a benign oxidant (Scheme 1.36) [90]. Unambiguously, the produced C–B coupling products possess low reactivity in the presence of palladium catalyst. The direct borylation of unactivated γ–C(sp^3)–H bond also contribute an efficient access to alcohols, amines, and various functionalized molecules.

1.5 Conclusions

In summary, we have witnessed a rapid development of transition metal-catalyzed, directing group-assisted unactivated C(sp^3)–H bond functionalization. It has become a competent tool for a sustainable construction of chemical bonds. Deep understanding of the mechanistic pathway and design of chiral ligands for enantioselective functionalization of general C(sp^3)–H bonds will gain considerable attention in near future. The exploitation of new catalytic system with cheap metals and sustainable conditions (external oxidant: O_2; solvent: H_2O) will be of particular interest both to academia study and industry development.

Notwithstanding the advance attained, directing group-assisted C(sp^3)–H bond functionalization have to deal with the appended auxiliary: first introduction then final removal process. The recent contributions on bifunctional ligand-assisted

C–H bond functionalization strategy [91, 92] open a new consideration of directing group chemistry and would be more attractive in future. It can perfectly orient the regioselectivity but avoid extra steps for auxiliary.

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Chapter 2
Recent Advances in Non-directed C(sp^3)–H Bond Functionalization

Abstract Selective functionalization of one specific C(sp^3)–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(sp^3)–H bonds adjacent to heteroatoms, allylic, benzylic, and unactivated aliphatic C(sp^3)–H bonds. The total redox-neutral C(sp^3)–H bond functionalization is also briefly introduced.

Keywords C–H activation · Tertiary amines · Ethers · Alcohols · sp^3 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(sp^3)–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(sp^3)–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(sp^3)–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(sp^3)–H bond from different kinds of C(sp^3)–H bonds becomes a tractable obstacle. Allegorically, the C–H bonds in one complex molecule could be

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DOI 10.1007/978-3-662-49496-7_2

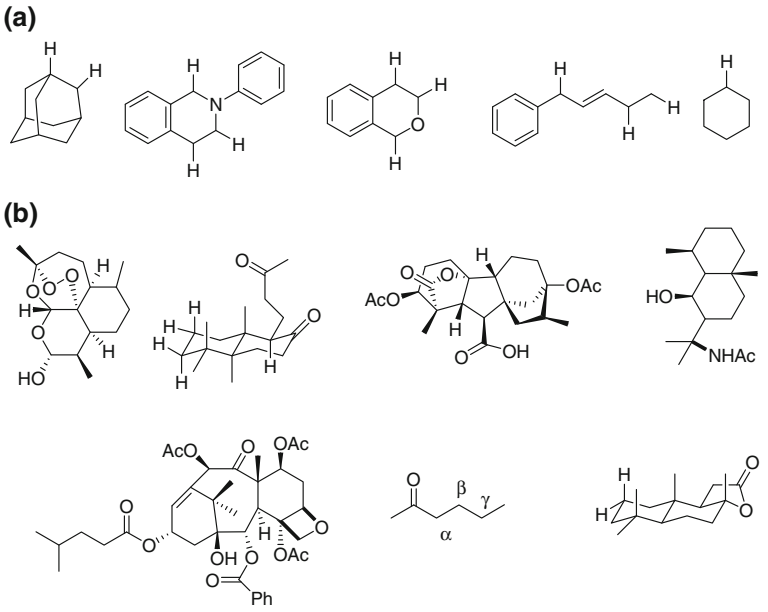


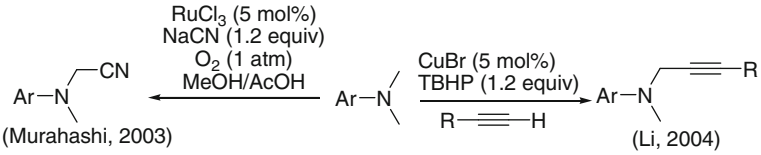
Fig. 2.1 Which C–H bond can talk to me? **a** Simple hydrocarbons (BDE controls the regioselectivity). **b** Complex molecules: which C–H bond can answer me?

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(sp^3)–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.

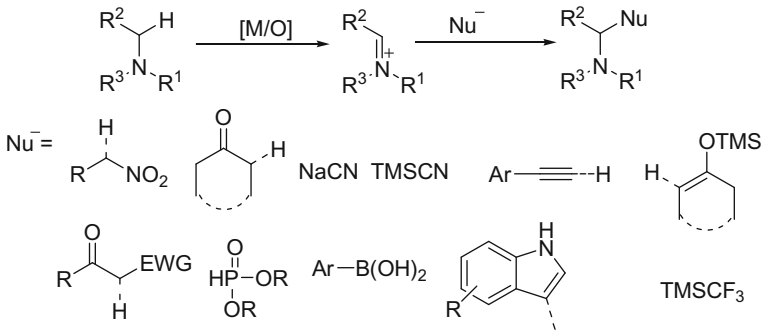
2.2 Oxidative Functionalization of α-C(sp^3)–H Bond Adjacent to Nitrogen Atoms

Nitrogen-containing compounds are highly important targets for organic synthesis. The development of efficient methods to modify nitrogen-containing molecules is highly desirable. Oxidative functionalization of α-C(sp^3)–H bonds of tertiary amines is one emerging topic.

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



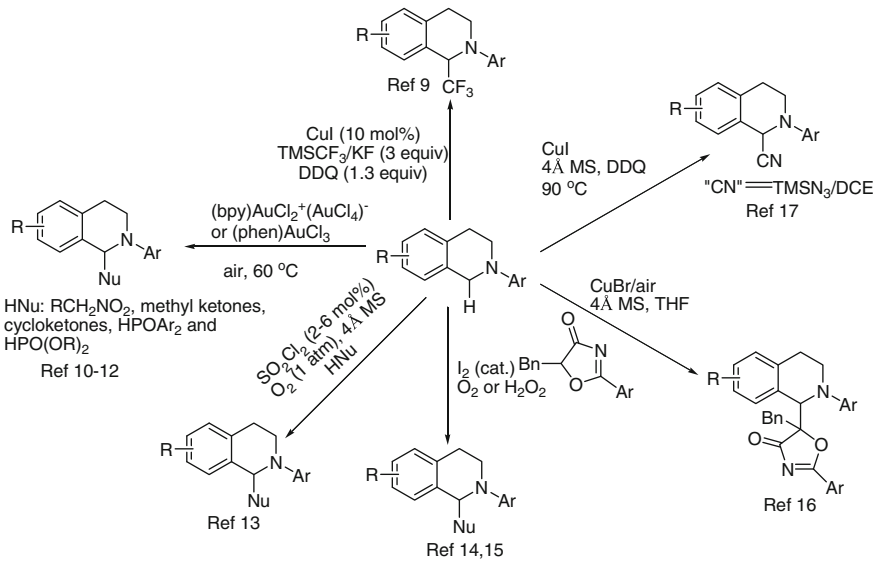
Scheme 2.1 Pioneering work for the oxidative functionalization of tertiary amines [1, 2]



Scheme 2.2 The previous works on oxidative functionalization of tertiary amines

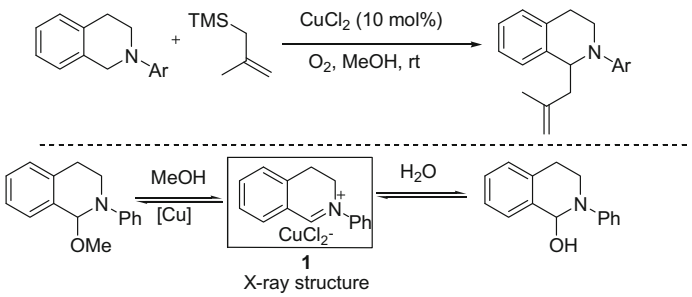
as oxidant (Scheme 2.1) [2]. Both pioneering works stimulated a fast development of oxidative functionalization of tertiary amines. The broad scope and good functional group compatibility enabled various nucleophiles for C–C and C–X bond formation (Scheme 2.2). Several important reviews have highlighted 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(sp^3)–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 SO_2Cl_2 [13] and I_2 [14, 15] were disclosed. Interestingly, the 5*H*-oxazol-4-ones was 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 $TMSN_3$ 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 $Rh_2(cap)_4$, $RuCl_2(PPh_3)_3$, CuBr, $FeCl_3$, or

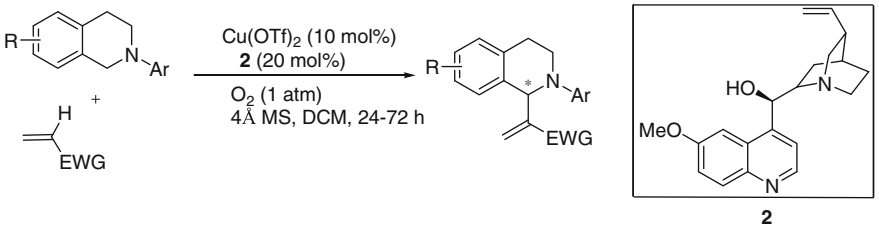


Scheme 2.4 Cu-catalyzed aerobic oxidative allylation of tertiary amines and mechanistic studies [18]

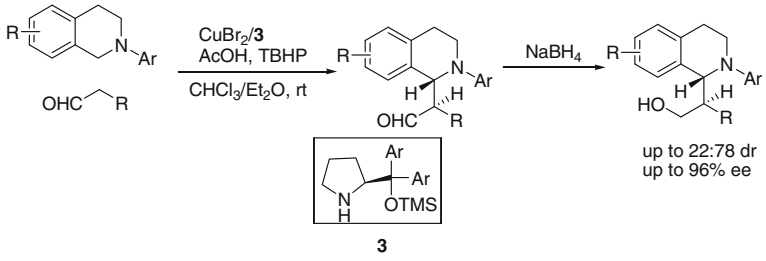
$Co(OAc)_2$ was to initiate the formation of *tert*-butylperoxy radical ($^tBuOO\cdot$) from TBHP, and the *tert*-butylperoxy radical mediates the single electron transfer (SET) instead of the transition metals, as previously proposed. Recent findings further demonstrated that use of alternative oxidants 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(sp^3)–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 tetrohydroisoquinolines. It constitutes an impressive example in the enantioselective C(sp^3)–H bond functionalization. As a follow-up work, they successively finished organocatalytic asymmetric CDC coupling of *N*-Aryl tetrahydroisoquinolines with cyclcoketones [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 tetrohydroisoquinolines 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]

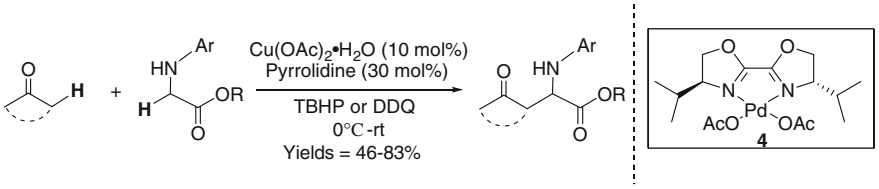


Scheme 2.6 Cu/organocatalyst co-catalyzed enantioselective α-C(sp^3)–H alkylation of tertiary amines [31]

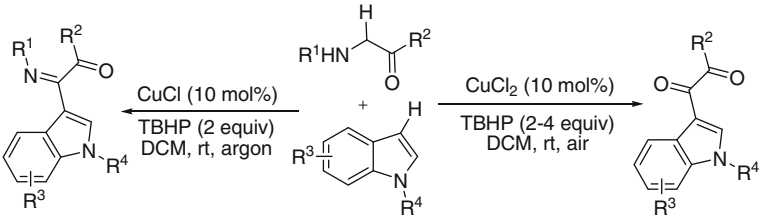
With copper/aminocatalyst relay catalysis, the first oxidative cross-coupling of *N*-Aryl glycine ester and ketones was achieved in the presence of TBHP or DDQ (Scheme 2.7) [34]. Interestingly, different oxidants determine the coupling partner leading to different products. TBHP favors the coupling of 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(sp^3)–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 phosphonation and alkylation of α-amino ketones with diarylphosphine [39] and ethers [40] were reported.

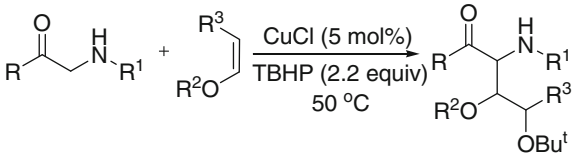
Li's copper-catalyzed oxidative difunctionalization of enol ethers with α-amino carbonyl compounds was recently reported (Scheme 2.9) [41]. This protocol allows rapid synthesis of 2-amino-3,4-dioxy carbonyl products. Significantly, metal-free, DTBP-mediated direct alkylation of α-amino carbonyl compounds 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]



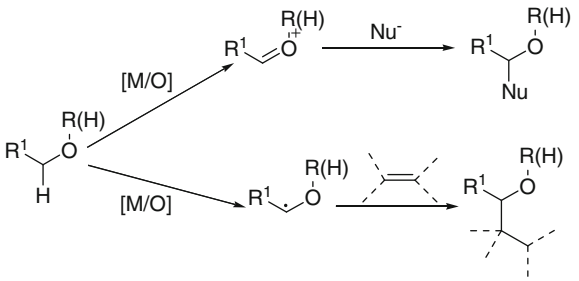
Scheme 2.8 Cu-catalyzed oxidative coupling of α-amino ketones with indoles [38]



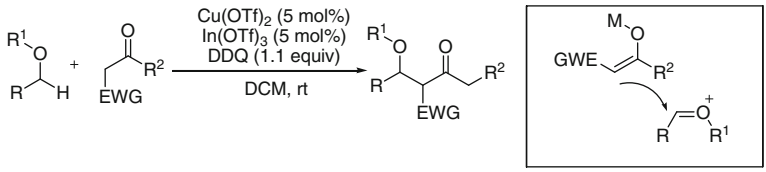
Scheme 2.9 Cu-catalyzed tandem C–C and C–O coupling of enol ethers [41]

2.3 Oxidative Functionalization of α-C(sp^3)–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(sp^3)–H functionalization of ethers with a diverse range of



Scheme 2.10 Two pathways of oxidative C(sp^3)–H functionalization of ethers and alcohols



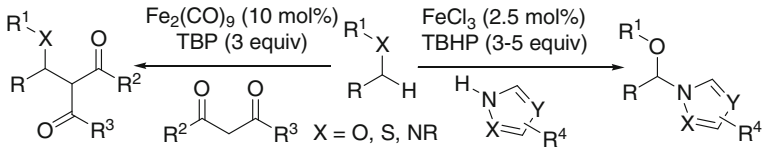
Scheme 2.11 The first CDC reaction of ethers with active methylene nucleophiles [43]

nucleophiles (organoboranes, ketones, aromatic rings, etc.) was disclosed [46, 47]. It substantially expanded the substrate scope with regard to nucleophiles.

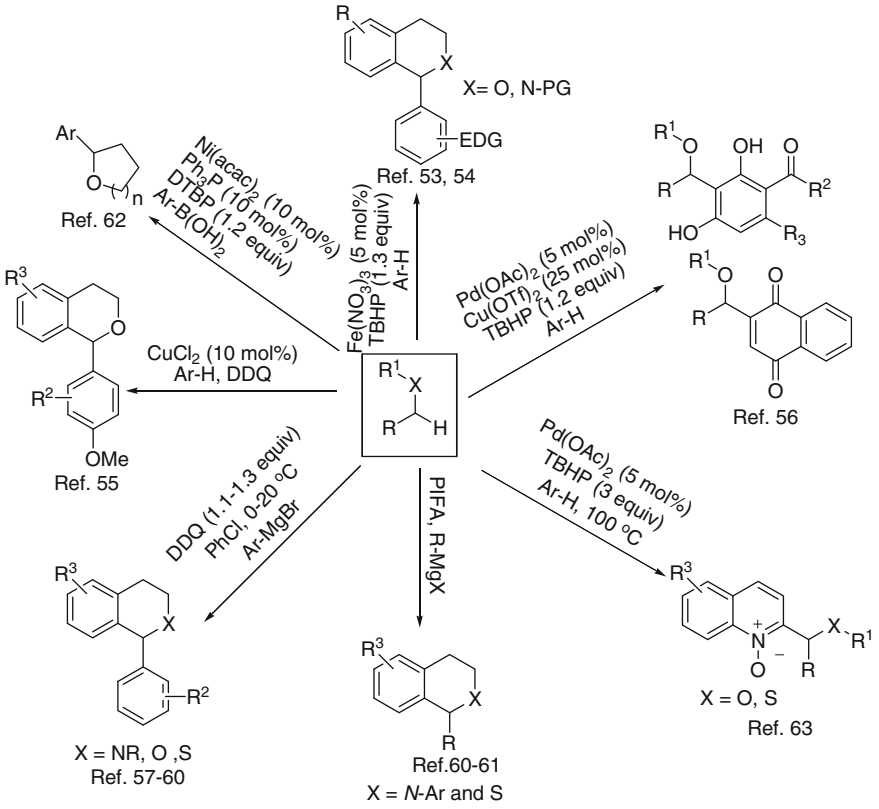
With $Fe_2(CO)_9$ as catalyst, the CDC reaction of saturated heterocycles with 1,3-diketones was accomplished using TBP as an efficient oxidant (Scheme 2.12) [48]. This protocol shows good compatibility to cyclic and acyclic ethers, thioethers, and tertiary amines. Gratifyingly, besides C(sp^3)–C(sp^3) 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].

After these pioneering works in the functionalization of ethers, a great number of new methodologies emerged soon (Schemes 2.13, 2.14 and 2.15). In 2010, the group of Schnürch developed Fe(III)-catalyzed arylation of tetrahydroisoquinolines and isochromans with oxidant TBHP (Scheme 2.13) [53, 54]. A series of *N*-Boc protected tetrahydroisoquinolines are good coupling partners. In 2012, copper(II)-catalyzed oxidative coupling of isochromans with electron-rich anisoles was achieved (Scheme 2.13) [55]. The Pd-catalyzed oxidative coupling of protecting-group free phenols with α-C(sp^3)–H of ethers and alcohols was also disclosed in 2014 (Scheme 2.13) [56]. However, the scope of the above methods was limited to electron-donating aromatic groups.

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 α-C(sp^3)–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 $PhI(OOCF_3)_2$-mediated arylation, alkylation, and even amidation of α-C(sp^3)–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



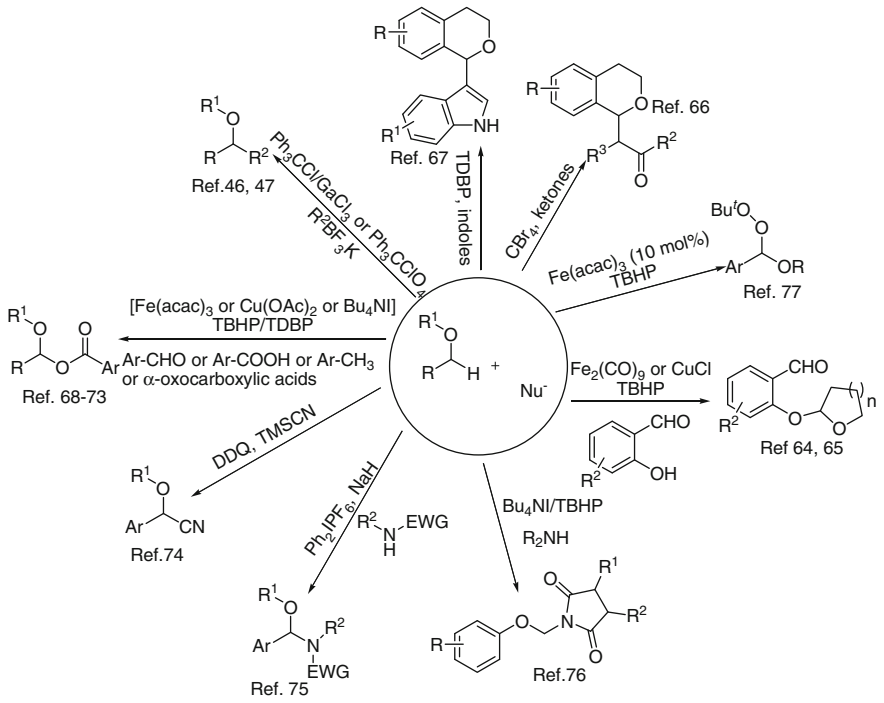
Scheme 2.12 Fe-catalyzed alkylation and amination of C(sp^3)–H adjacent to heteroatom [48, 49]



Scheme 2.13 The recent progress of oxidative C(sp^3)–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 $Fe_2(CO)_9$- 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 CBr_4 (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 isochramans 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

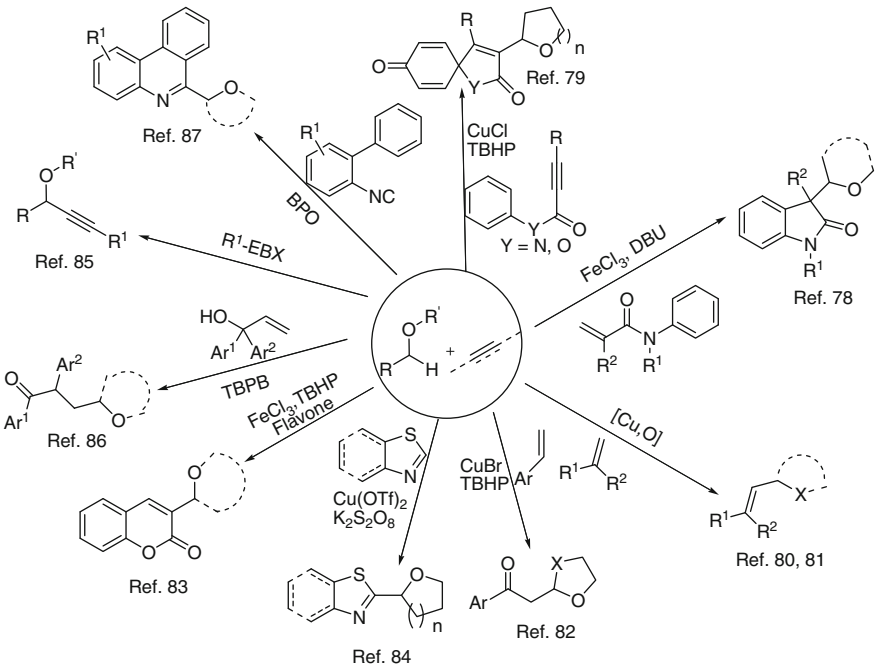


Scheme 2.14 The recent progress of oxidative C(sp^3)–H bond functionalization (2) [64–77]

efficient modification of ethers. Very interestingly, different starting materials (carboxylic acids, aldehydes, and even toluene derivatives) coupled with ethers, but similar α-acylocy 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(sp^3)–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 $FeCl_3$/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 azaspriro [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.

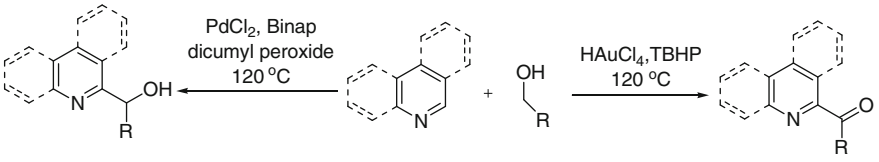
Compared with ethers, the direct selective activation of alcohols is mainly underdeveloped [88]. Although the transfer hydrogenative protocol of alcohols with



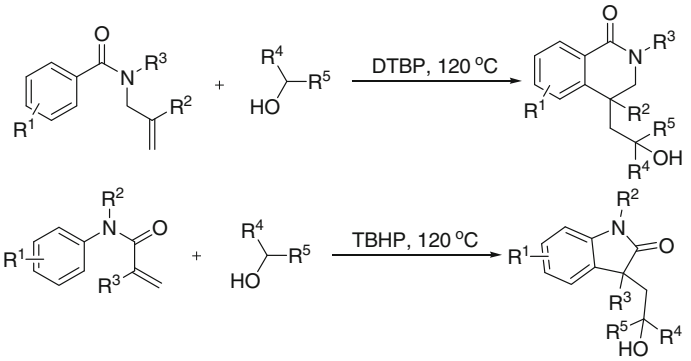
Scheme 2.15 The recent progress of oxidative C(sp^3)–H bond functionalization (3)

alkenes and alkynes provides a good platform for C(sp^3)–H functionalization of alcohols [89, 90], selective oxidation α-C(sp^3)–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(sp^3)–H bond of simple alcohols (Scheme 2.16) [92]. Remarkably, a stoichiometric amount of acid is not required for the Pd-catalyzed Minisic 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 $AuCl_3$/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]

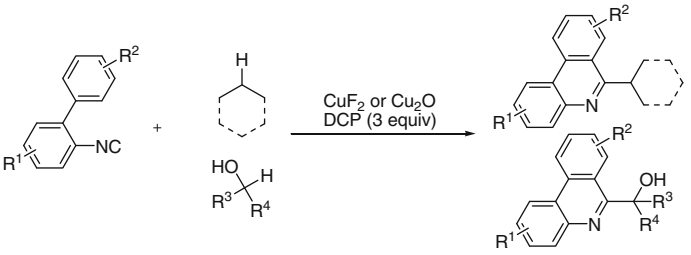


Scheme 2.17 The metal-free, oxidant-mediated alkylarylation of alkenes with alcohols [94, 95]

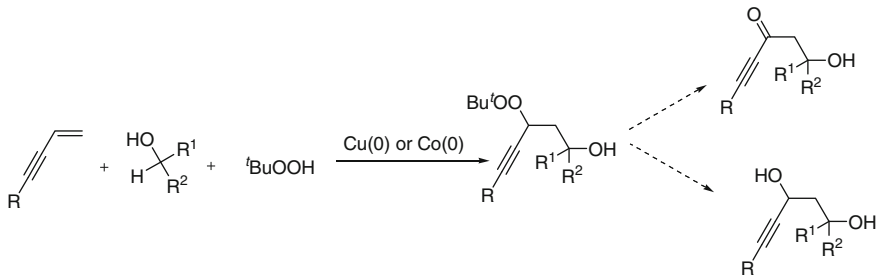
simple alcohols with suitable alkenes would be controllable. With radical initiators DTBP or TBHP, sustainable alkylarylation protocols of C=C double bond were developed by Han [94] and Duan [95] (Scheme 2.17). The continual work of Han achieved an excellent access to α,ω-amino alcohols by radical addition of α-oxoalkyl radical to olefins [96]. Oxidative coupling of α-C(sp^3)–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(sp^3)–H bond of alkanes and alcohols [98]



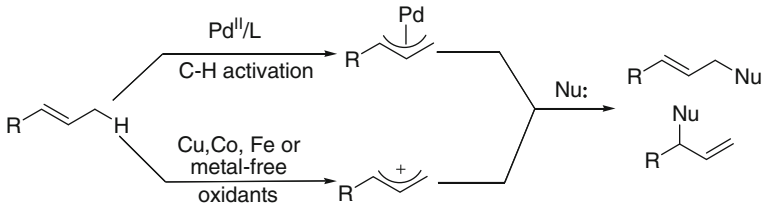
Scheme 2.19 Cu(0) or Co(0)-catalyzed three component oxidative coupling of 1,3-enynes, TBHP and alcohols [99]

2.4 Oxidative Functionalization of Allylic and Benzylic C(sp^3)–H Bond

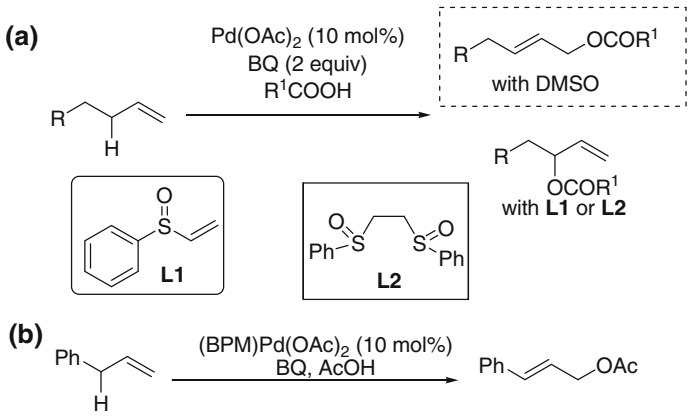
Selective cleavage and functionalization of allylic C(sp^3)–H bonds is a synthetically attractive strategy (Scheme 2.20). The pioneering work has illustrated the possibility of allylic C–H bond using electrophilic π-allylpalladium intermediates. In recent years, the transition-metal-catalyzed selective 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 $CoCl_2$ co-catalyzed allylic C(sp^3)-H alkylation of methylenic C(sp^3)–H bond was first reported in 2006 [105]. Two years later, Pd(II)-catalyzed intra- or intermolecular allylic C(sp^3)–H alkylation with active



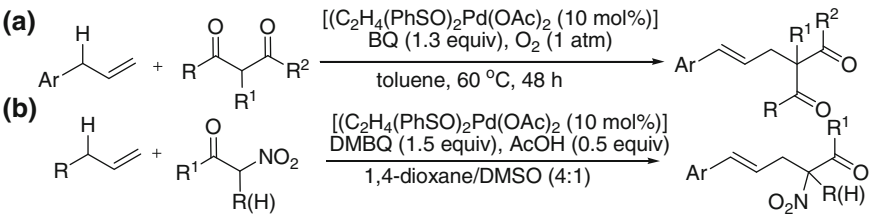
Scheme 2.20 The general strategies for allylic C(sp^3)–H bond functionalization



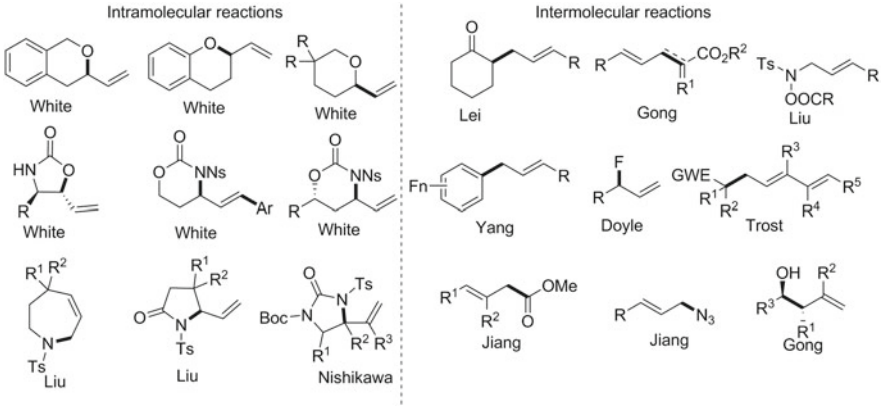
Scheme 2.21 Pd-catalyzed acetoxylation of allylic C(sp^3)–H bond [101–104]

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(sp^3)–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(sp^3)–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*-ally imines were disclosed by Trost and Hansmann (Scheme 2.23) [119, 120].



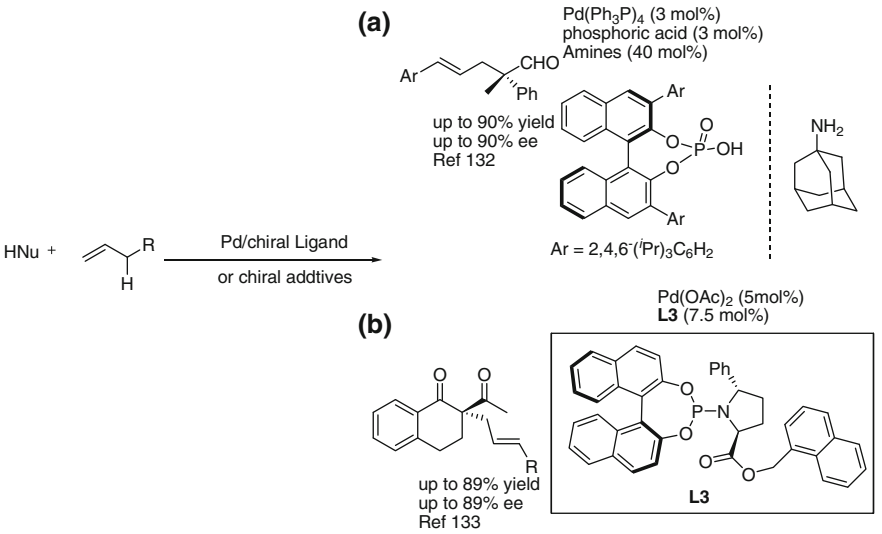
Scheme 2.22 Pd-catalyzed oxidative intermolecular allylic C(sp^3)–H alkylation with active C–H nucleophiles [106, 107]



Scheme 2.23 Selected examples of allylic C(sp^3)–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 (O_2 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(sp^3)–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 $Et_3N{\cdot}3HF$ in satisfactory branched selectivity (Scheme 2.23). It constitutes an rare example of mild fluorination of C(sp^3)–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(sp^3)–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(sp^3)–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



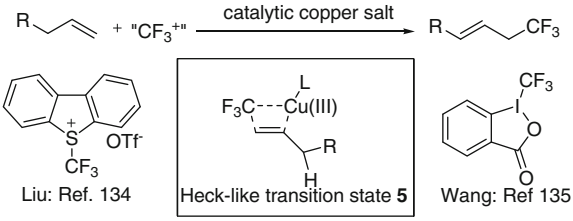
Scheme 2.24 Enantioselective linear alkylation of allylic C(sp^3)–H bond [132, 133]

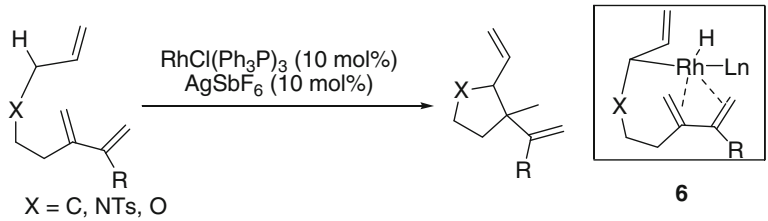
excellent enantioselectivities were observed, its substrate scope with respect to olefins was very limited. To solve this, cinnamyl acetate was used as an alternative coupling partner.

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(sp^3)–H bond, respectively (Scheme 2.25). Various unactivated alkenes could tolerate the reaction condition well, delivering the sp^3-sp^3 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*-propythiosuccinimide 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(sp^3)–H bond activation was disclosed by Yu and co-workers in 2010. The unprecedented

Scheme 2.25 Cu-catalyzed trifluoromethylation of allylic C(sp^3)–H bond [134, 135]





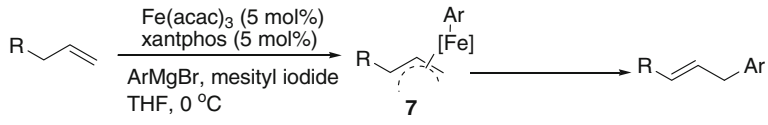
Scheme 2.26 Rh-catalyzed, diene-assisted allylic C(sp^3)–H bond functionalization [137]

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(sp^3)–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.

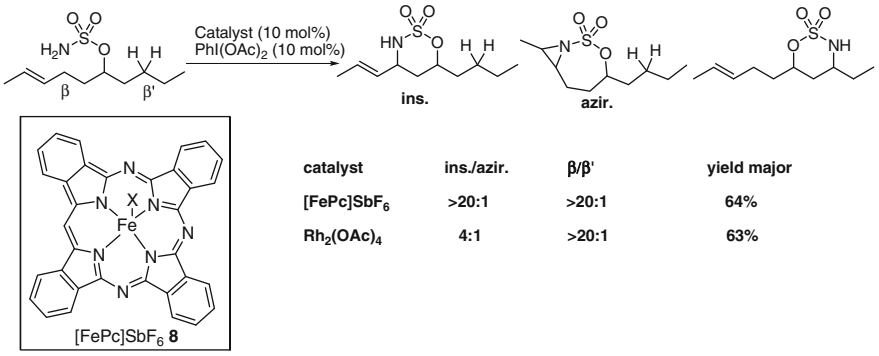
Iron catalysis is an emerging branch in metal-catalyzed coupling strategies. In 2010, Jiao et al. accomplished the first Fe(II)-catalyzed allylic C–H oxidation to alkenyl nitriles with $TMSN_3$ as nitrogen source and DDQ as external oxidant [139]. As a follow-up work, the same group developed $FeCl_2$-catalyzed 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(sp^3)–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(sp^3)–H bond (Scheme 2.28) [142]. After screening a variety of substrates that containing assorted C(sp^3)–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(sp^3)–H bonds. In sharp contrast, when $Rh_2(OAc)_4$ 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(sp^3)–H arylation [141]



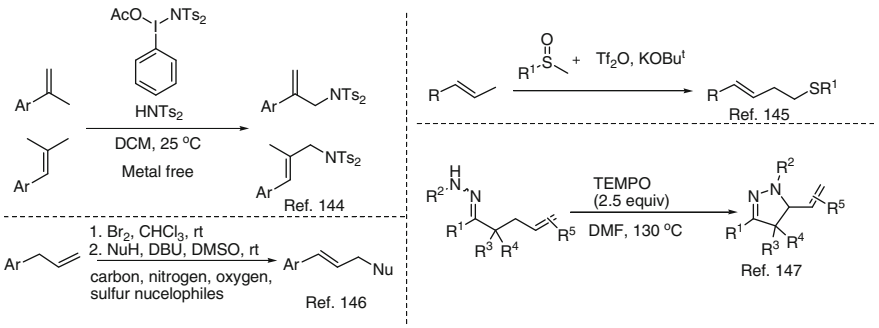
catalyst	ins./azir.	β/β'	yield major
[FePc]SbF$_6$	>20:1	>20:1	64%
Rh$_2$(OAc)$_4$	4:1	>20:1	63%

Scheme 2.28 [FePc]$^+$-catalyzed regio- and site-selective allylic C(sp^3)–H bond amination [142]

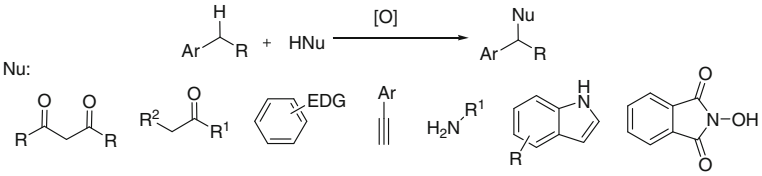
features of cheap and nontoxic iron-based catalyst. The next year, ligand-tuned, silver-catalyzed highly chemoselective allylic C–H amination was also reported [143]. By manipulating the coordination geometry of silver complex, selective aziridination and allylic C(sp^3)–H insertion can be achieved.

In addition, beyond the transition-metal catalysts, much more recent works focused on the metal-free allylic C(sp^3)–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.

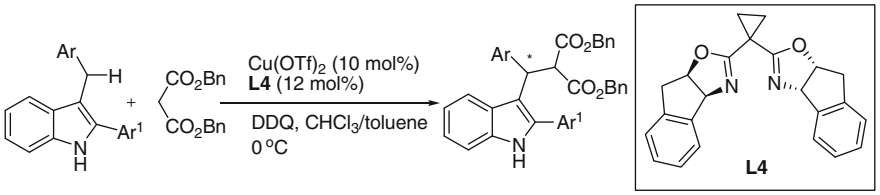
Compared with allylic C–H bond, benzylic C–H bond has similar BDE. Under the oxidative conditions, it is still susceptible to undergo SET to form a benzyl radical or carbocation, which would like to be trapped by a series of C(sp^3)–H nucleophiles or electron-rich aromatic rings (Scheme 2.30). For example, 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(sp^3)–H bond functionalization [144–147]



Scheme 2.30 Benzylic C(sp^3)–H bond functionalization [148–166]



Scheme 2.31 Cu-catalyzed enantioselective alkylation of benzylic C(sp^3)–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.

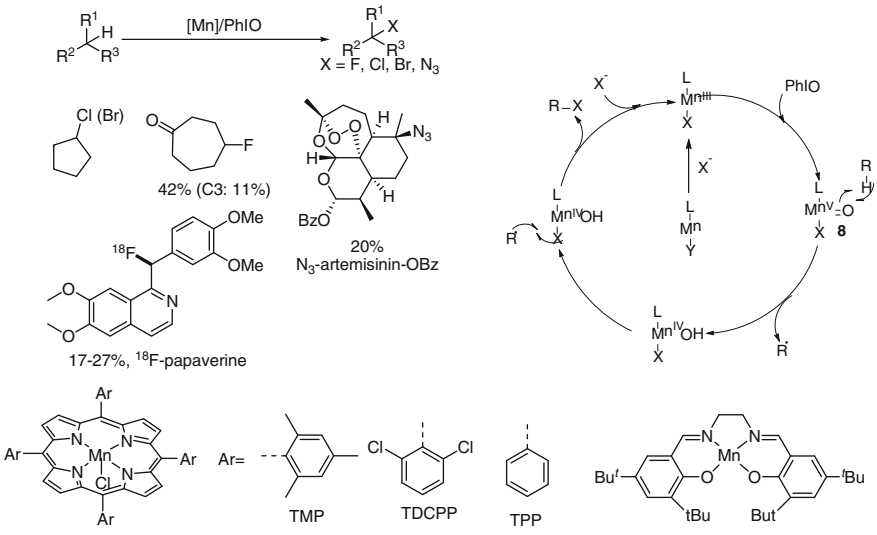
2.5 Oxidative Functionalization of General C(sp^3)–H Bond

In contrast to the above cases, direct functionalization of unactivated, general C(sp^3)–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(sp^3)–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(sp^3)–H bonds (Scheme 2.32). In general, the regioselectivity depends on the BDE of aliphatic

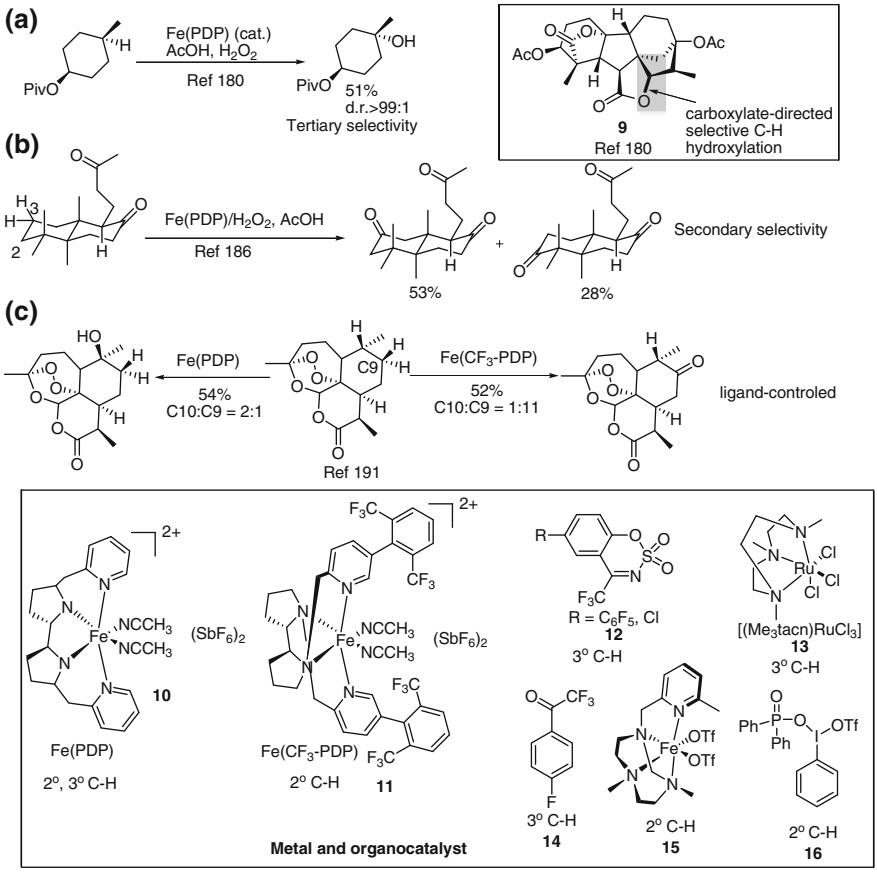
C–H bond. If active benzylic C–H bond was involved in the substrates, the halogenation site was usually in that position. This is consistent with their proposed mechanism in Scheme 2.32. The oxomanganese(V) species **8** is prone to abstract a hydrogen atom from C(sp^3)–H bond with a relatively weak 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(sp^3)–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(sp^3)–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(sp^3)–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(sp^3)–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], [(Me$_3$tacn)RuCl$_3$] **13** [183, 184] and RuCl$_3$ [185].



Scheme 2.32 Mn-catalyzed radical C(sp^3)–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 H_2O_2 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

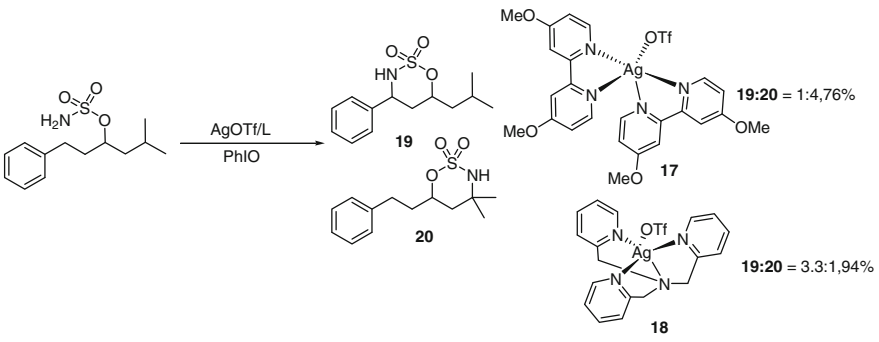


Scheme 2.33 The recent progress of selective oxidation of aliphatic C(sp^3)–H bond

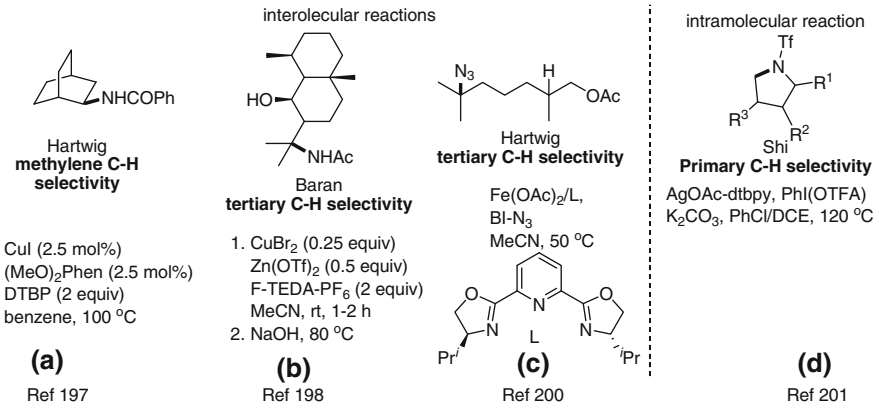
enzymatic methods for aliphatic C–H oxidation, which showcased different regioselectivities [194].

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(sp^3)–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(sp^3)–H bond proved applicable even though electron-rich tertiary C–H bond was present. In contrast, with Selectfluor as strong oxidant, $CuBr_2$-catalyzed intermolecular oxidative C–N coupling is practical to tertiary C(sp^3)–H bond selectivity over secondary and primary C–H bond (Scheme 2.35b) [198]. With 3° > 2° > 1° C(sp^3)–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(sp^3)–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(sp^3)–H bond represents a new challenge. Using AgOAc as catalyst, intramolecular C–N bond coupling with primary C(sp^3)–H selectivity was accomplished by Shi and co-workers in 2014.



Scheme 2.34 Ligand-controlled, Ag-catalyzed regioselective amination of C(sp^3)–H bond [195]

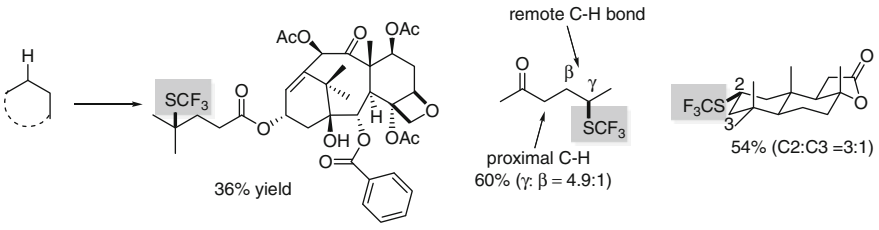


Scheme 2.35 Highly selective amination of aliphatic C(sp^3)–H bond [197–201]

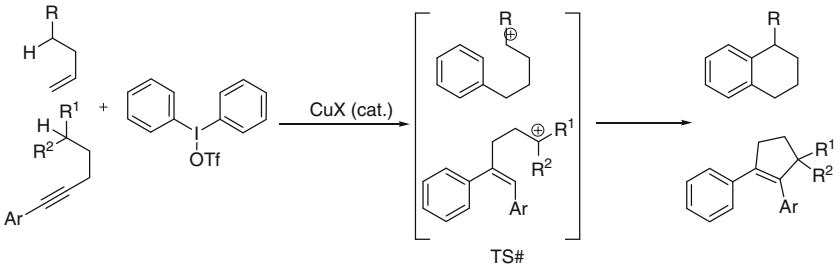
(Scheme 2.35d) [201]. The authors thought the generated hyperelectrophilic Ag(III) species in situ would account for the less steric hindered primary C–H bond selectivity. Furthermore, the use of chiral dirhodium carbene is viable for enantioselective primary C–H bond insertion, and it allows for selective 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 $AgSCF_3$-mediated trifluoromethylthiolation of unactivated C(sp^3)–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 trifluomethylthiolation occurred at remote C(sp^3)–H bond from electron-withdrawing groups. Both works show great potential for mild incorporation of trifluoromethylthioly 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 arycarbocyclization sequence with alkenes and alkynes was



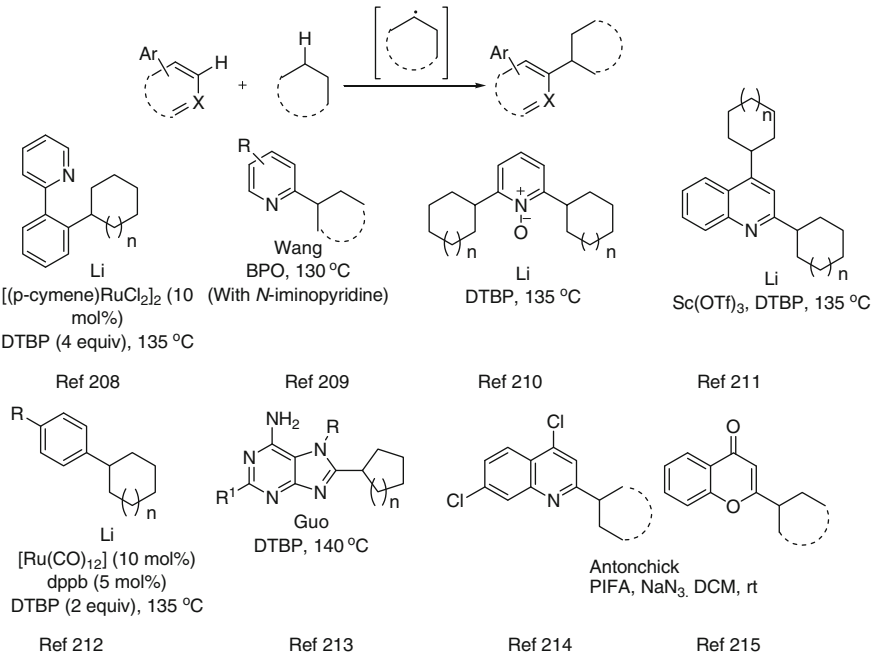
Scheme 2.36 Radical trifluomethylthiolation of unactivated C(sp^3)–H bond [203, 204]



Scheme 2.37 Cu-catalyzed cascade arycarbocyclization sequence involving C(sp^3)–H bond functionalization [206]

disclosed by the group of Gaunt. It involved the cleavage of unactived C(sp^3)–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, $K_2S_2O_8$, 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)Cl_2]$_2$-catalyzed,



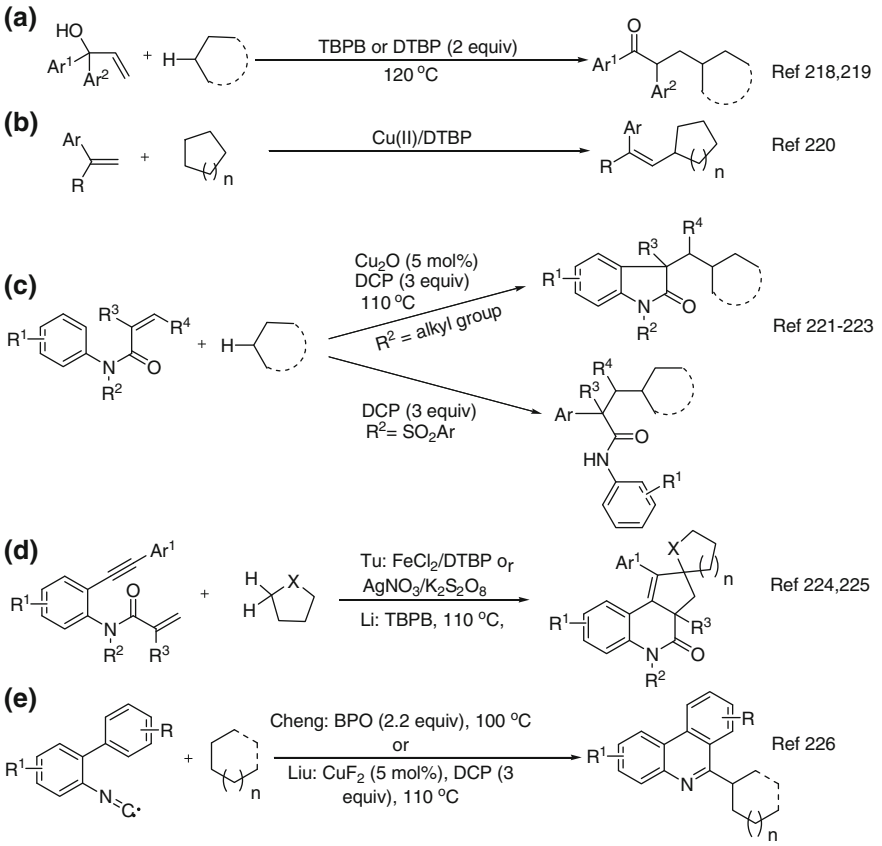
Scheme 2.38 Recent achievements of arylation of simple alkanes [208–215]

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].

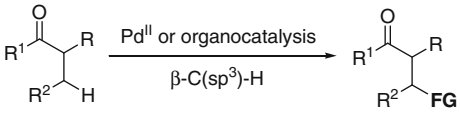
Li's group later developed several aliphatic C–H arylation protocols following the principle of radical chemistry [210–212]. DTBP-mediated highly selective alkylation of important ladenosines was reported in the absence of transition-metal catalysts [213]. Antonchick et al. reported $PhI(OTFA)_2$/NaN_3-mediated 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(sp^3)–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(sp^3)–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(sp^3)–H functionalization of carbonyl compounds is a well-known tool in organic synthesis, but functionalization of remote β-C(sp^3)–H bond remains unusual (Scheme 2.40). For example, Pihko and co-workers developed Pd(II)-catalyzed oxidative β-C(sp^3)–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(sp^3)–H bond functionalization with a wide range of nucleophiles [237–239]. Two important independent reports on organocatalytic (aminocatalysis and NHC catalysis) β-C(sp^3)–H bond of aliphatic aldehydes were also achieved by Wang [240] and Chi [241].



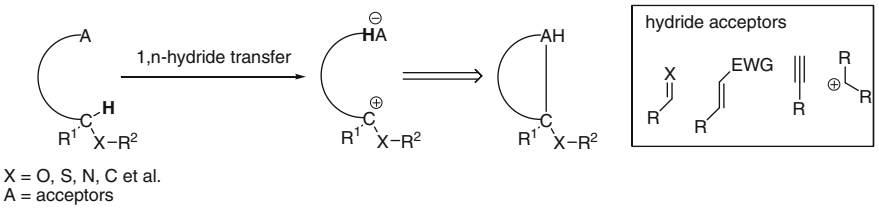
Scheme 2.39 Radical addition of alkyl radicals to unsaturated chemical bond [218–226]



Scheme 2.40 Recent progress of β-C(sp^3)–H functionalization of carbonyl compounds [233–241]

2.6 Redox-Neutral C(sp^3)–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(sp^3)–H bond functionalization.



Scheme 2.41 The intramolecular H-shift for C(sp^3)–H bond functionalization [243]

2.6.1 1,n–H Shift-Induced C(sp^3)–H Bond Functionalization

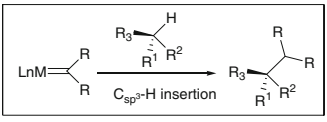
As shown in Scheme 2.41, the linkage of an sp^3 hydride donor and a hydride acceptor in one molecule is the general and necessary condition for H-shift-type C(sp^3)–H bond functionalization. In the presence of transition metals or Lewis acids, the hydride-shift can readily occur to construct new chemical bonds. In recent years, this kind of C(sp^3)–H bond functionalization gained much attention. Remarkably, the hydride-shift C–H bond functionalization mode usually requires the substrates possesses 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(sp^3)–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(sp^3)–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(sp^3)–H bond insertion

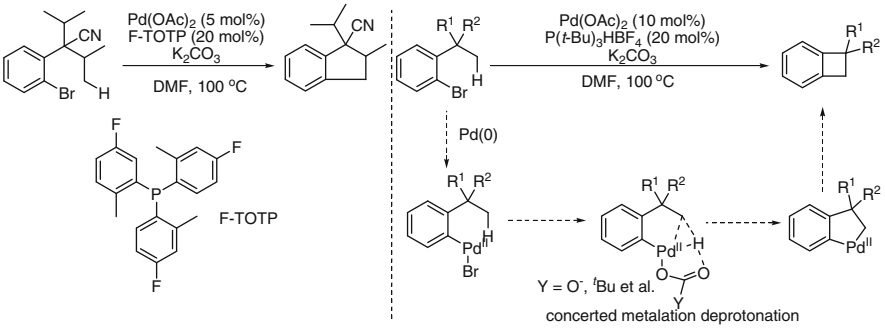
^{26}Fe ^{27}Co ^{28}Ni ^{29}Cu
^{44}Ru ^{45}Rh ^{46}Pd ^{47}Ag
^{76}Os ^{77}Ir ^{78}Pt ^{79}Au



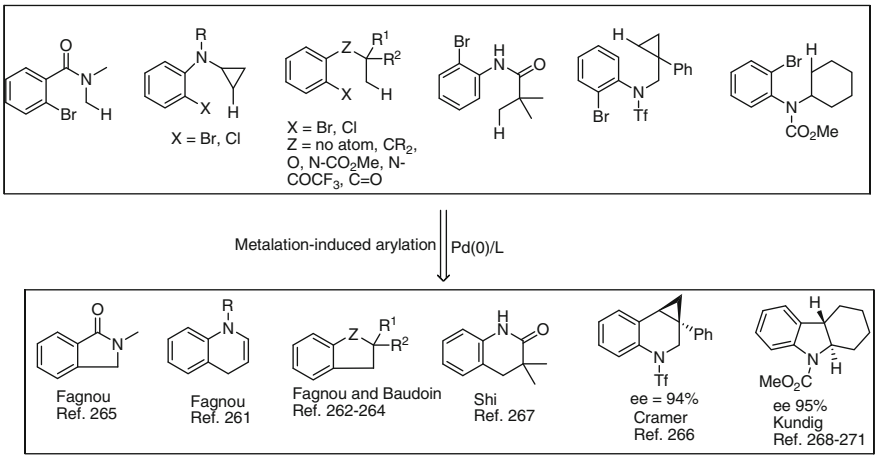
2.6.3 *Metalation-Induced Arylation of C(sp^3)–H Bond*

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(sp^3)–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(sp^3)–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(sp^3)–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(sp^3)–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(sp^3)–H arylation products were obtained in good enantioselectivities [268–271]. Furthermore, this metalation strategy can also be compatible to intermolecular remote C(sp^3)–H arylation of carbonyl compounds without the help of directing groups [272–274].



Scheme 2.43 Pd-catalyzed redox-neutral intramolecular arylation of C(sp^3)–H bond [259, 260]



Scheme 2.44 Representative examples for intramolecular arylation of C(sp^3)–H bond [261–271]

2.7 Conclusions

In conclusion, the recent work on the functionalization of aliphatic C(sp^3)–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(sp^3)–H bond. It represents the state of the art in organic synthesis. Future efforts should be dedicated to developing sustainable and practical enantioselective C(sp^3)–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.

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Chapter 3
Functionalization of C(sp^3)–H Bond by Visible-Light Photoredox Catalysis

Abstract Solar energy is a unique and renewable resource in nature. Visible-light-induced organic reactions are featured as energy saving and environmentally benign. It becomes one ideal protocol for chemists to deal with radical chemistry. In the past five years, we witnessed a rapid development of visible-light-induced organic transformations. In this chapter, we highlight the recent achievements of visible-light-promoted C(sp^3)–H bond functionalization.

Keywords Visible-light photoredox catalysis · C(sp^3)–H bond functionalization · Sustainable chemistry · C–C coupling

3.1 Introduction

In last century, some pioneers have dedicated to converting solar energy into chemical energy for chemical transformations [1–5]. However, organic molecules generally cannot absorb visible light (λ = 400–760 nm) efficiently, thereby, visible-light-induced organic reactions are still tractable obstacles to chemists. The use of suitable photosensitizers is considered as a good choice to achieve this target in the range of visible light.

In 2008, MacMillan [6] and Yoon [7] independently reported the pioneering works on asymmetric alkylation of aldehydes and [2 + 2] cycloaddition by visible light photoredox catalysis. Both publications represent an important milestone for application of visible light in contemporary organic synthesis. Generally, irradiation of photocatalyst with visible light enables efficient metal-to-ligand charge transfer (MLCT), and the generated excited-state photocatalyst can either donate one electron to electron acceptors (Ar–NO_2, $S_2O_8^{2-}$, Fe^{3+}) or accept one electron from electron donors (tertiary amines, xanthate, ascorbate, etc.) (Fig. 3.1a). Taking $Ru(bpy)_3Cl_2$, for example, as shown in Fig. 3.1b, the structure of excited-state $^*Ru(bpy)_3Cl_2$ makes it feasible to act as either an oxidant or a reductant in one quenching cycle.

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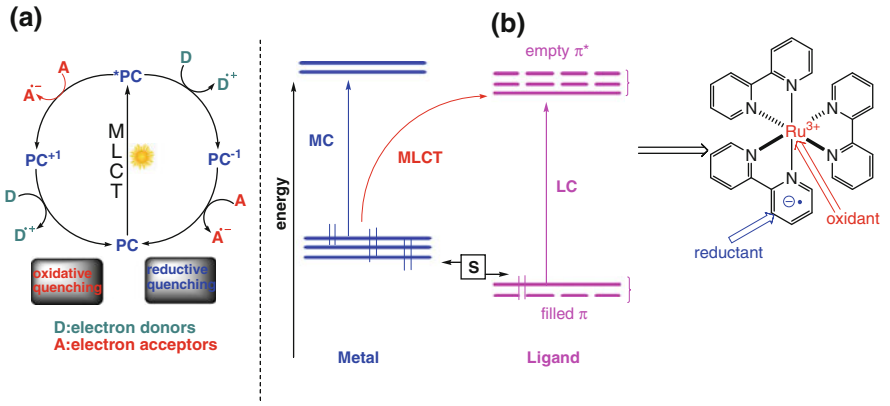
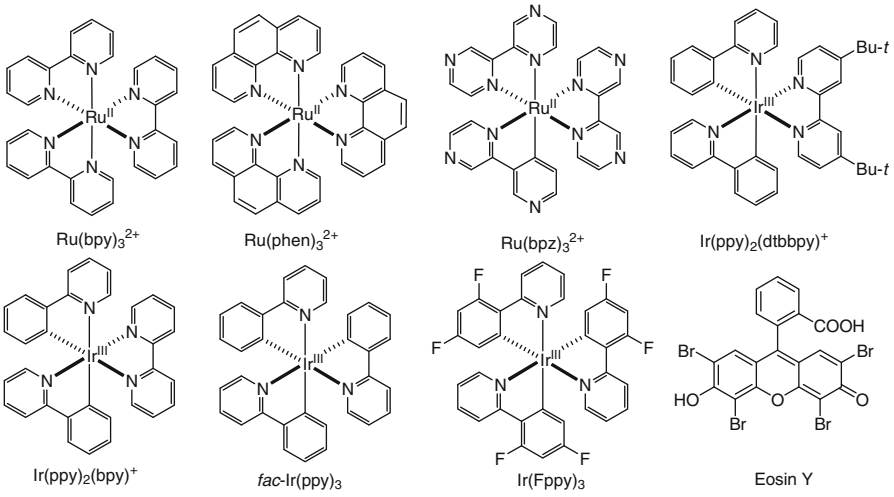


Fig. 3.1 **a** Photoredox catalysis mechanistic pathway [9]. **b** Orbital paradigm of metal-centered, metal-to-ligand, and ligand-centered charge transfer (MC, MLCT, and LC) [8, 13]

Its notable features on simple operation, rapid new reaction discovery, and energy saving have drawn great enthusiasm of organic chemists. Up to date, several important reviews have summarized fundamental organic transformations [9–14]. In this chapter, we highlight the recent achievements of visible-light photocatalytic C(sp^3)–H bond functionalization with different photosensitizers as illustrated in Scheme 3.1.



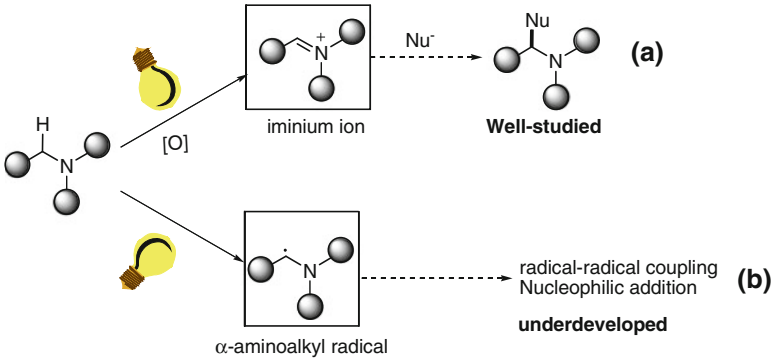
Scheme 3.1 Representative photocatalysts. Reprinted with the permission from Ref. [14]. Copyright 2014 Elsevier

3.2 α-C(sp^3)–H Bond Functionalization of Amines

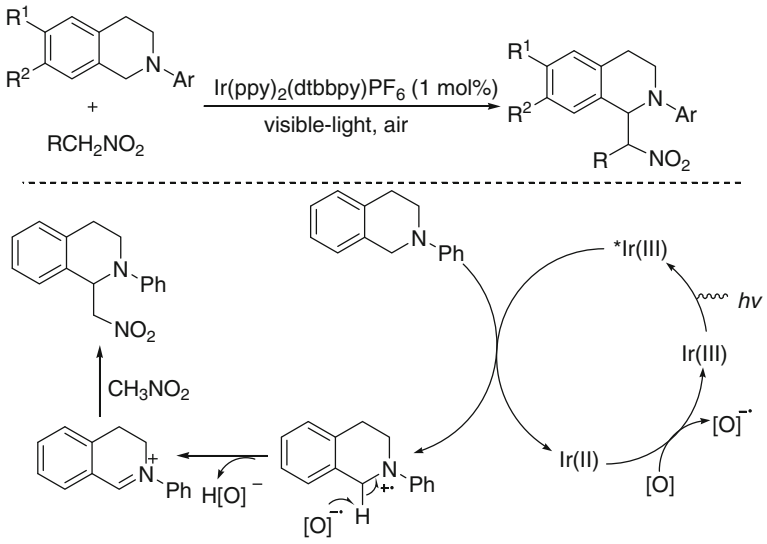
The tertiary amine motifs are widely found in natural products and bioactive compounds. In principle, double electron oxidation of tertiary amines can produce iminium intermediate, which is able to be trapped by a diverse range of nucleophiles (Scheme 3.2a). Alternatively, single-electron oxidation of tertiary amines would form α-aminoalkyl radical (Scheme 3.2b). The further organic transformations of α-aminoalkyl radical have become one new trend for modification of tertiary amines. The exploitation of α-aminoalkyl radical chemistry constitutes an important complement to the well-studied oxidative iminium ion chemistry.

One representative work on photocatalytic iminium ion chemistry was developed in 2010 by Stephenson and co-workers (Scheme 3.3) [15]. Intriguingly, the aza-Henry reaction occurs smoothly by visible-light photoredox catalysis in the absence of any synthetic oxidants (such as TBHP, H_2O_2). Unreactive nonbenzylic amines in the CuBr-catalyzed oxidative aza-Henry reaction [16] appear to be good substrates. The control experiments indicate that both light and photocatalyst are essential. A possible mechanism is outlined in Scheme 3.3. Single-electron transfer (SET) of tertiary amine to long-lived excited-state *Ir(ppy)$_2$(dtbbpy)PF$_6$ leads to produce tertiary amine radical cation, followed by H-abstraction to generate iminium intermediate, which would be rapidly trapped by nucleophilic nitroalkane to give aza-Henry product. Meanwhile, oxidizing Ir(II) to ground state Ir(III) with CH_3NO_2 or O_2 completes the photocatalytic cycle.

The Stephenson's work undoubtedly stimulates a rapid development of visible-light-driven C(sp^3)–H bond functionalization of tertiary amines. Soon afterward, numerous nucleophiles were employed under the principle of iminium ions chemistry by visible-light photoredox catalysis (Scheme 3.4). The oxidative Mannich reaction of *N*-Aryl tetrahydroisoquinolines with ketones [17] and enol silanes [18] were developed by Rueping and Xia, respectively. As a follow-up work, Rueping et al. [19] reported an efficient alkynylation of α-C(sp^3)–H bond



Scheme 3.2 Two possible pathways for α-C(sp^3)–H bond functionalization of tertiary amines by photoredox catalysis

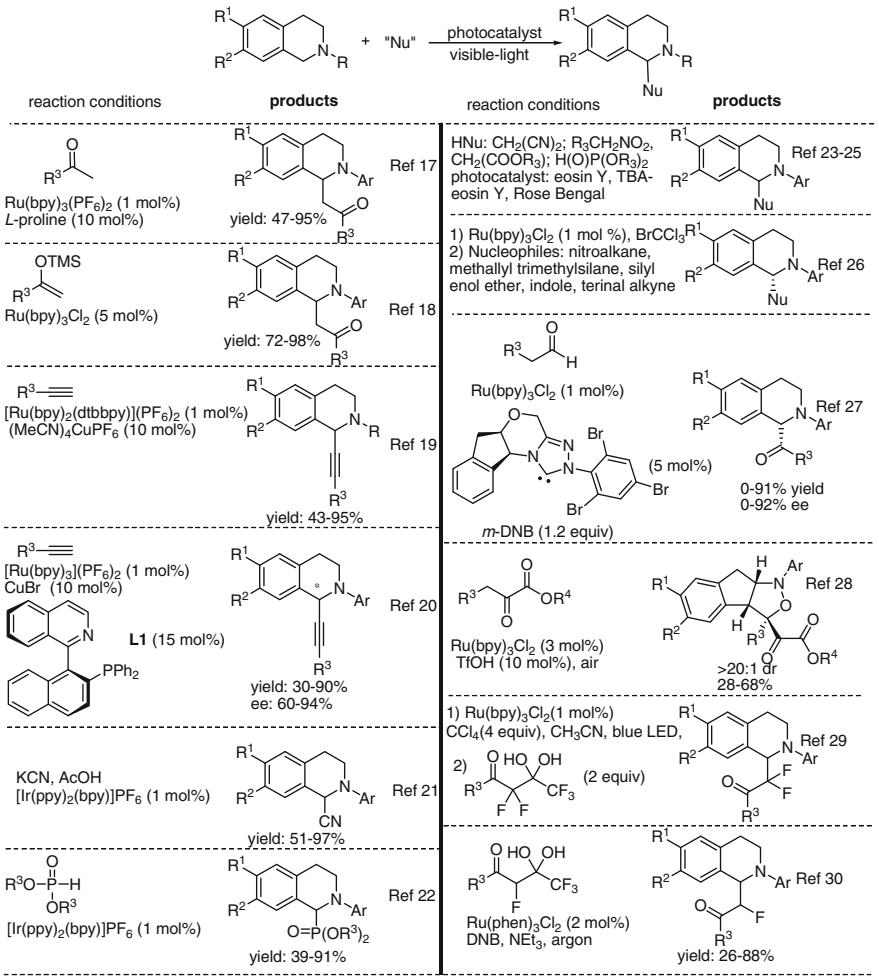


Scheme 3.3 Visible-light-mediated oxidative aza-Henry reaction [15]

with terminal alkynes by combination of photoredox catalysis and copper catalysis. With suitable chiral copper catalyst, an asymmetric alkynylation is practicable [20]. Moreover, α-cyanation [21] and α-phosphonation [22] of tertiary amines were also achieved. Besides transition metal photocatalysts, organic dyes were employed as efficient photosensitizers [23–25]. Using $BrCCl_3$ as an external oxidant, mechanistic insight into the iminium ions chemistry was reported [26]. Interestingly, it was found that deprotonation and C–H atom abstraction process of amine radical cation were two competitive pathways for the formation of iminium ion intermediate.

With a relay NHC catalysis and photocatalysis, enantioselective α-acylation of *N*-Aryl tetrahydroisoquinolines with aliphatic aldehydes was developed [27]. Strong oxidants such as $BrCCl_3$ resulted in the decomposition of NHC catalyst, and *m*-DNB (1,3-dinitrobenzene) was used herein. In early 2013, Zhu and co-workers reported a visible-light-mediated tandem C–H and C–N cleavage sequence to rationally construct bicyclic isoxazolidine skeletons in only one step [28]. Although the isoxazolidine was obtained in moderate yields, this protocol is attractive with respect to the stereoselectivity and step economy compared with the known synthetic routes. Given the importance of fluoroalkyl group in medical chemistry and synthetic chemistry, visible-light-mediated difluoroalkylation and monofluoroalkylation of *N*-Aryl tetrahydroisoquinolines were successively developed [29, 30].

On the other hand, novel photosensitizers were synthesized and applied in the visible-light-mediated oxidative functionalization of *N*-Aryl tetrahydroisoquinolines. A promising organogold complex was developed for aerobic oxidative C(sp^3)–H functionalization of secondary and tertiary amines (Scheme 3.5) [31]. Another feature of this novel gold complex was underlined by production of



Scheme 3.4 Visible-light-mediated oxidative functionalization of tetrahydroisoquinoline derivatives with nucleophiles [17–30]

hydrogen from water and acetonitrile mixture. Also with a gold photosensitizer, aerobic oxidative Mannich reaction was achieved [32]. In addition, a robust Pd complex [33] and Pt complex [34] were verified as promising photocatalysts. For instance, visible-light-induced cross-dehydrogenative coupling reaction of *N*-Aryl tetrahydroisoquinolines with indoles is workable using Pt complex (Scheme 3.6) [34]. The mechanism study with electron paramagnetic resonance (EPR) experiment is indicative of a superoxide radical anion (O_2^{-}) during the reaction process.

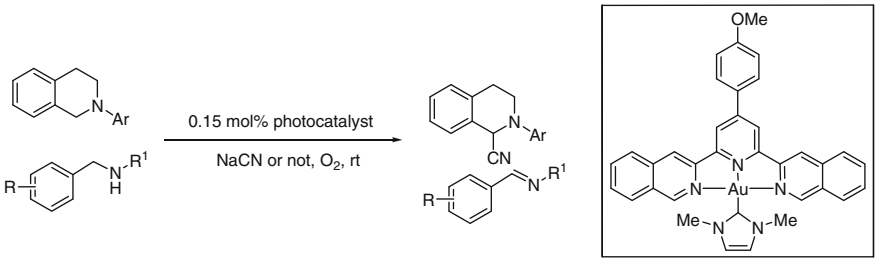
One important visible-light-induced C–H oxidation/[3 + 2] cycloaddition/oxidative aromatization tandem sequence was developed by Xiao and co-workers in 2011, allowing for concise synthesis of pyrrolo[2,1-a]isoquinolines (Scheme 3.7) [35].

Simultaneously, a similar [3 + 2] cycloaddition reaction furnishes the cycloadduct products in exo/endo diastereomers in the absence of NBS [36]. By means of photoredox catalysis, some important heterocyclic scaffolds of isoquino[2,1-*a*] [1, 3] oxazine and isoquino[2,1-*a*]pyrimidine can be elegantly constructed [37].

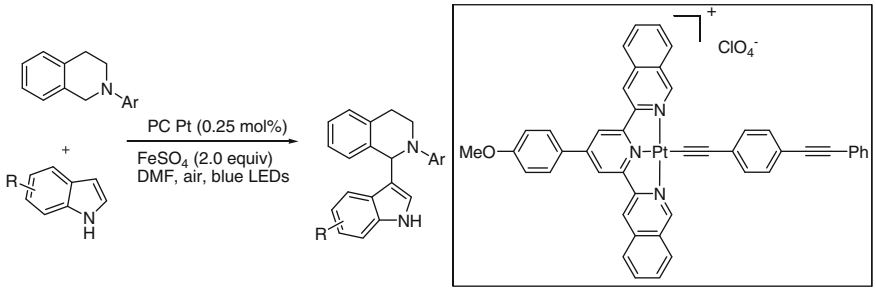
Despite these great accomplishments, the scope with regard to tertiary amines is generally limited to *N*-substituted tetrahydroisoquinolines. Therefore, the exploitation of new nitrogen-containing substrate is highly desirable. As a consequence, Xiao and co-workers designed a new benzylamine substrate and thus an intramolecular C–N bond coupling was developed (Scheme 3.8) [38]. It offers a new route for the construction of highly substituted tetrahydroimidazole derivatives. Owing to the steric repulsion, the *Re* face is much more favorable than the *Si* face. In the light of Li's [39] and Huang's [40] previous works, highly efficient α-indolation of *N*-Aryl glycine peptides and esters [41] and α-amino carbonyl compounds [42] were reported (Scheme 3.9).

With a strong oxidant [$(NH_4)_2S_2O_8$], visible-light-driven Friedel–Crafts amidoalkylation of dialkylamides was reported via oxidation of C(sp^3)–H bond adjacent to amide nitrogen atom (Scheme 3.10) [43]. Alternatively, Stephenson and co-workers found that mild heating of amides with persulfate salts could also work for the Friedel–Crafts amidoalkylation reaction.

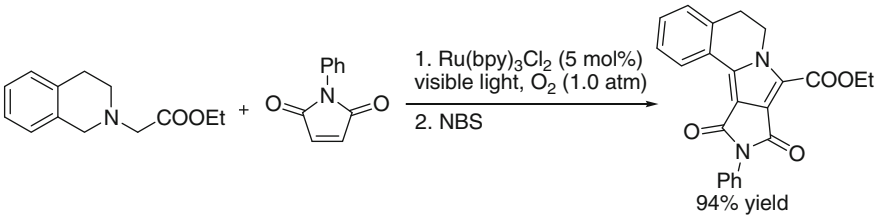
Compared with homogeneous catalysis, the heterogeneous photoredox catalysis is mainly underdeveloped. The CdS, TiO_2, mesoporous graphitic carbon nitride,



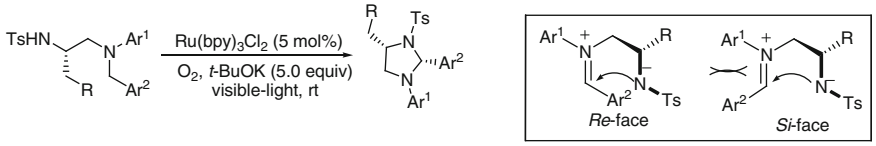
Scheme 3.5 Visible-light photoredox catalysis with gold complex [31]



Scheme 3.6 Platinum-catalyzed α-C(sp^3)–H indolation of tertiary amines by visible light [34]



Scheme 3.7 Visible-light-induced C–H oxidation/[3 + 2] cycloaddition/oxidative aromatization sequence [35]

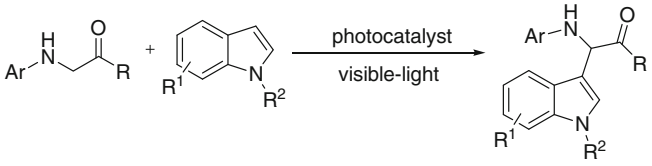


Scheme 3.8 Visible-light-mediated intramolecular C–N coupling [38]

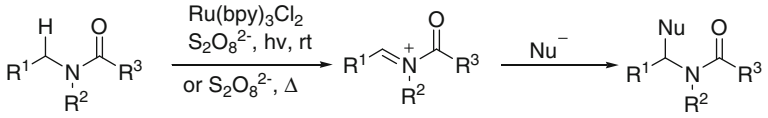
and photosensitive polymers were recently examined [44–47]. The promising microphotochemistry has been applied in organic transformations [48, 49].

Single-electron oxidation of tertiary amines is controllable by photoredox catalysis delivering nucleophilic α-aminoalkyl radicals (Scheme 3.11). The recent findings in this area illuminate a nice addition to the above iminium ion chemistry.

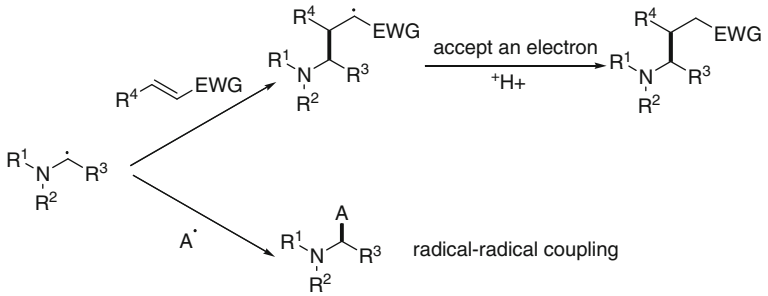
Due to the nucleophilicity of α-aminoalkyl radical, it is supposed to add to electron-deficient alkenes. This assumption was first achieved by Nishibayashi [50] and Reiser [51] in early 2012 (Scheme 3.12). They reported visible-light-mediated addition of α-aminoalkyl radicals derived from tertiary amines to Michael acceptors (unsaturated esters and vinyl ketones). Also, radical addition to acrylate derivatives was later accomplished (Scheme 3.12) [52]. As a follow-up work, Nishibayashi et al. developed visible-light-promoted radical C(sp^3)–H amination of benzocyclic tertiary amines using di-*tert*-butyl azodicarboxylate as nitrogen source (Scheme 3.12) [53]. In 2013, Yu et al. found that *N*,*N*-dimethylaniline derivatives could react with *N*-aryl- and *N*-benzylmaleimides to give tetrahydroquinoline products with air as oxidant (Scheme 3.12) [54]. Unfortunately, the other olefins, such as furan-2,5-dione, diethyl maleate, methyl acrylate, and 1-phenylprop-2-en-1-one, fail to undergo this transformation. The mechanistic



Scheme 3.9 Visible-light-mediated indolation of glycine derivatives [41]

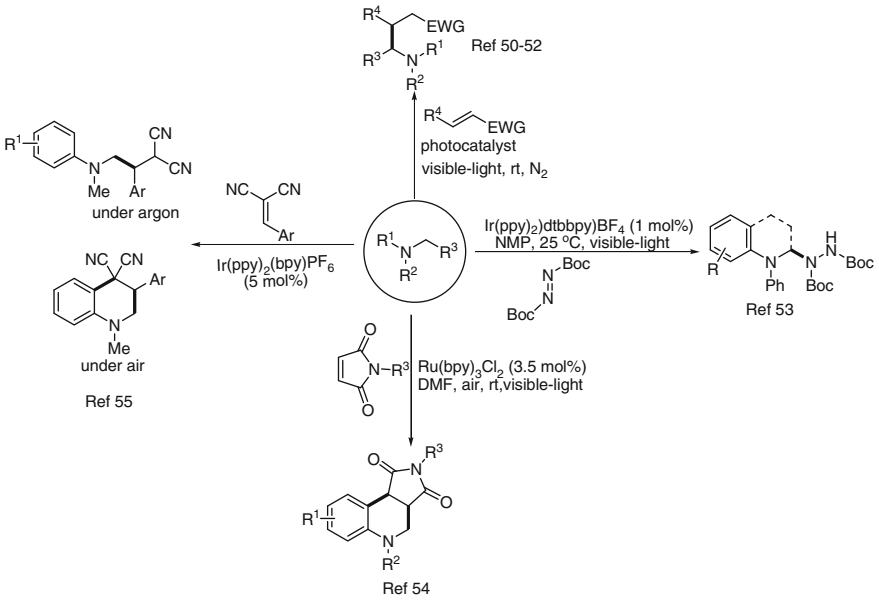


Scheme 3.10 Visible-light-induced Friedel–Crafts amidoalkylation [43]



Scheme 3.11 The useful organic transformation of α-aminoalkyl radical

studies indicate that electron/proton transfer process and hydrogen atom transfer (HAT) are two competitive pathways for the formation of α-aminoalkyl radical. Interestingly, Rueping and co-workers pointed out that radical addition or radical



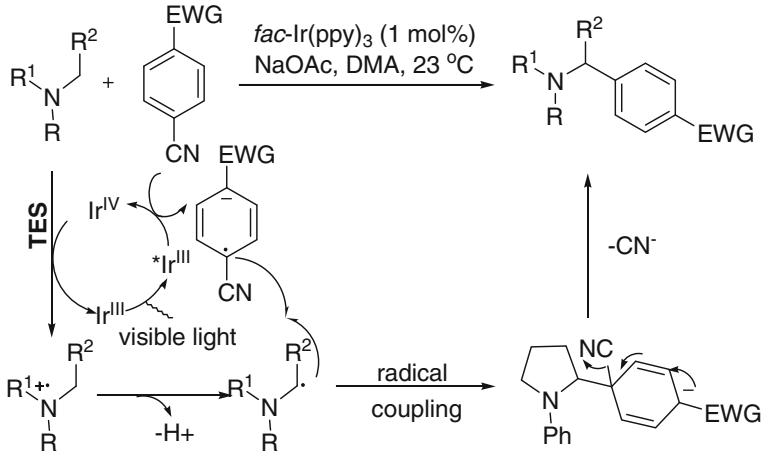
Scheme 3.12 Radical additions of α-aminoalkyl radicals [50–55]

addition/cyclization of α-aminoalkyl radical with Michael acceptors could be tuned (Scheme 3.12) [55]. Under nitrogen atmosphere, radical addition process was preferential; switching to oxygen atmosphere, an unexpected radical addition/cyclization sequence was observed.

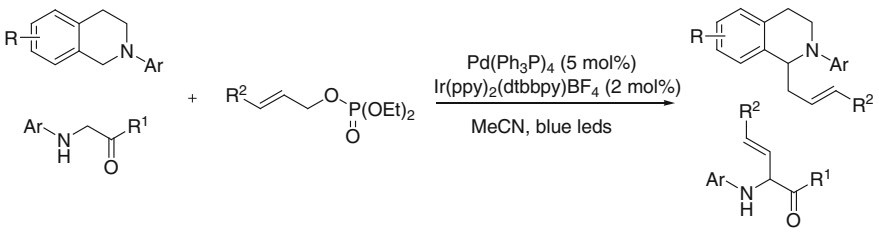
The long-lived α-aminoalkyl radicals render the feasibility to couple α-aminoalkyl radicals with other radicals. The first visible-light-mediated radical–radical cross-coupling of α-aminoalkyl radical with another radical was reported by MacMillan and co-workers (Scheme 3.13) [56]. A novel α-C(sp^3)–H arylation reaction was developed. The possible mechanism starts from oxidative quenching of excited-state *Ir(ppy)$_3$ with electron-poor cyanobenzene, generating a strong oxidant Ir(IV) species [$E_{1/2}$(IV/III) = +0.77 V vs. SCE] and a cyanobenzene radical anion. A thermodynamic favorable SET from tertiary mines to Ir(IV) species can finally lead to α-aminoalkyl radical, which is ready to undergo radical–radical heterocoupling with electron-poor cyanobenzene radical anion. Expulsion of a cyanide group delivers the desired α-arylated tertiary amines in satisfactory yields.

Later, visible-light-mediated α-C(sp^3)–H heteroarylation of aromatic and aliphatic tertiary amines with chloroheteroarenes was reported [57, 58]. Remarkably, direct coupling of *N*-methyl tertiary amines with unfunctionalized pyridazine derivatives allows a new access to JAK2 inhibitor LY2784544 [59].

In early 2015, Xiao and co-workers developed a redox-neutral radical–radical cross-coupling protocol, allowing for direct α-allylation of amines by dual visible light and palladium catalysis (Scheme 3.14) [60]. Both tertiary amines and secondary amines could undergo the allylation reaction smoothly. It renders a rapid and elegant access to 8-oxoprotoberberine derivatives. To get mechanistic insights, EPR spin trapping experiment with DMPO was carried out and the proposed α-aminoalkyl radical was determined.



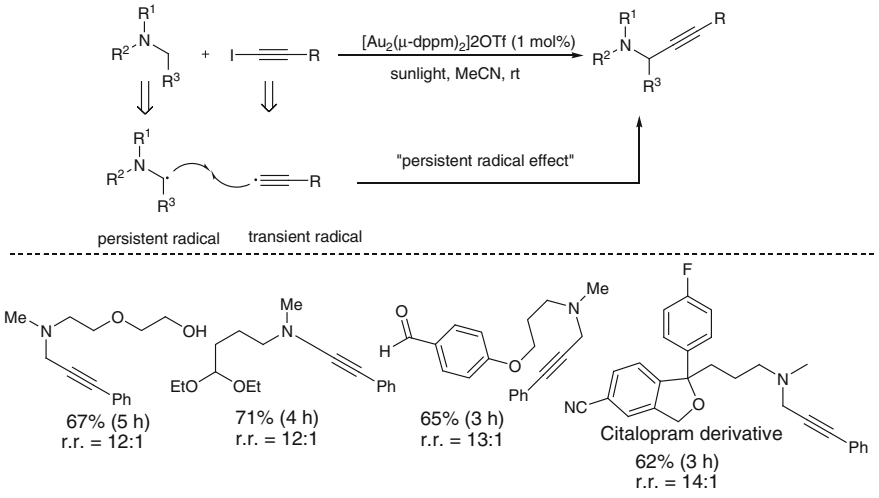
Scheme 3.13 The cross-coupling of α-aminoalkyl radical with aryl radical anion [56]



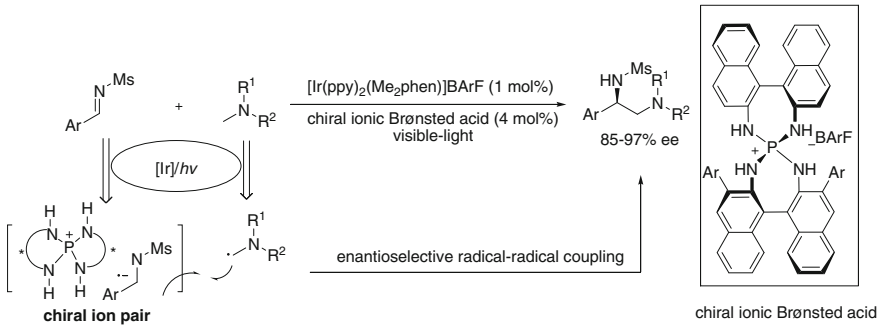
Scheme 3.14 The cross-coupling of α-aminoalkyl radical with an ally radical [60]

Almost at the same time, the Hashmi group developed a gold-catalyzed, photoredox radical–radical coupling of α-aminoalkyl radicals with alkynyl radicals (Scheme 3.15) [61]. The protocol is distinguished by its high efficiency, excellent functional group compatibility, and good regioselectivity. Under the irradiation of sunlight, selective radical alkynylation of α-C(sp^3)–H bond of aliphatic tertiary amines was achieved. Some challenging propargylic amines with A3 coupling strategy become applicable with this radical coupling access. The authors clarified that the persistent radical effect [62] would account for its good selectivity while recombination of two radicals.

Very recently, Ooi's group reported the first enantioselective radical–radical cross-coupling of α-aminoalkyl radical with *N*-sulfonyl aldimine radical anion using a synergistic ionic Brønsted acid catalysis and photocatalysis (Scheme 3.16) [63]. Under visible-light irradiation, reductive quenching of excited-state photocatalyst first generates α-aminoalkyl radical via deprotonating of tertiary cation radical and the generated strong reductant Ir(II) species would like to take place



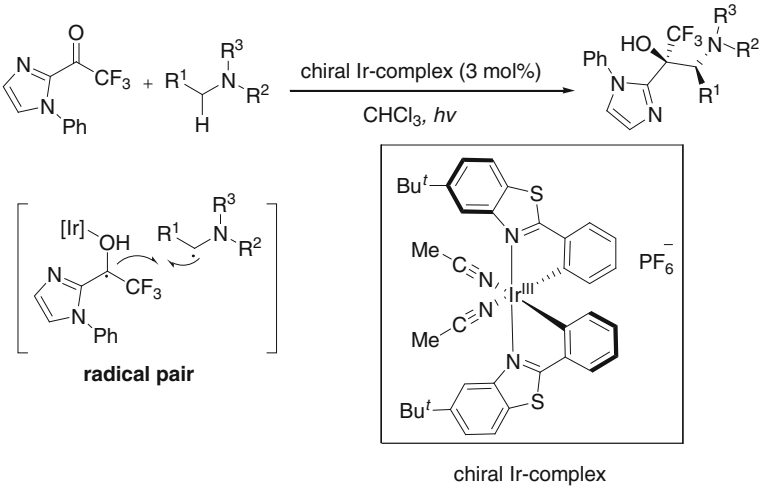
Scheme 3.15 The cross-coupling of α-aminoalkyl radical with alkynyl radical [61]



Scheme 3.16 The asymmetric cross-coupling of α-aminoalkyl radical with imine anion radical [63]

SET with *N*-sulfonyl aldimine to form imine radical anion. In the presence of chiral ionic Brønsted acid catalyst, the resulting *N*-sulfonyl aldimine radical anion prefers to form a chiral ion pair. The radical–radical heterocoupling of α-aminoalkyl radical with chiral ion pair-based anion radical affords 1,2-diamine derivatives in high enantioselectivties.

By coincidence, using a bifunctional chiral Ir(III)-complex catalyst (photosensitizer and Lewis acid), Megger and Wang developed an elegant visible-light-induced stereocontrolled radical–radical heterocoupling of α-aminoalkyl radical with α-oxoalkyl radical derived from trifluoromethyl ketones (Scheme 3.17) [64]. Specially, except the chiral Ir complex, other available photocatalysts such as [Ru(bpy)$_3$]2Cl and [Ir(ppy)$_2$(dtbbpy)]PF$_6$ failed this transformation. It highlights the advantages of this new bifunctional Ir-complex. The authors presumed that the



Scheme 3.17 The asymmetric cross-coupling of α-aminoalkyl radical and α-oxoalkyl radical [64]

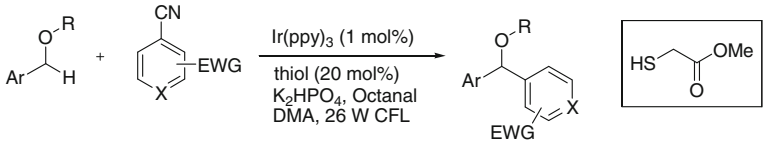
formation of a radical pair was crucial for asymmetric induction. Under the optimized conditions, 14 enantioenriched 1,2-amino alcohols were obtained from ketones and tertiary amines. While the reaction scope was very limited, the novel asymmetric catalytic C–C coupling mode will draw numerous interests in the stereocontrolled radical–radical recombination.

3.3 α-C(sp^3)–H Functionalization of Ethers and Alcohols

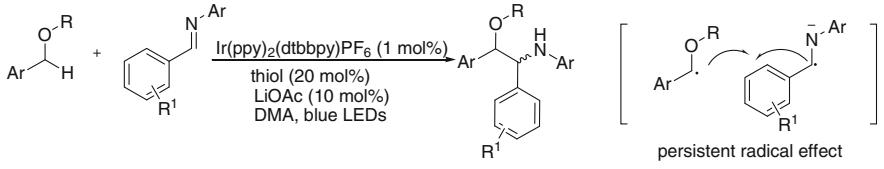
Although the oxygen atom is relatively difficult to donate one electron to photocatalyst, the α-C(sp^3)–H bond of ethers has weak bond dissociation energy (BDE). Consequently, in 2014, MacMillan and co-workers combined organocatalyst (thiol) and photocatalyst ($Ir(ppy)_3$) to develop radical arylation of C(sp^3)–H bond of benzyl ethers (Scheme 3.18) [65]. Interestingly, addition of octanal can substantially improve the reaction efficiency because it presumably sequestered the generated cyanide anion. Also, this catalytic combination is suitable for arylation of allylic C–H bond [66]. As a follow-up work, the authors from the same group applied this novel dual catalysis strategy to radical coupling of benzylic ethers with Schiff bases (Scheme 3.19) [67]. The recombination of two radicals was governed by persistent radical effect [62].

With the continuous efforts of MacMillan and co-workers, a direct α-arylation of cyclic and acyclic ethers with heteroarenes was reported via a Minisci-type pathway (Scheme 3.20) [68]. However, cleavage of α-C(sp^3)–H bond of ethers requires a strong hydrogen atom transfer reagent ($Na_2S_2O_8$).

One impressive strategy for α-C(sp^3)–H functionalization of alcohols was developed in 2015 still from MacMillan's group. Indeed, instead of expected α-C–H heteroarylation of alcohols, unprecedented alkylation of heteroarenes was



Scheme 3.18 Visible-light-induced α-C(sp^3)–H bond arylation of ethers [65]

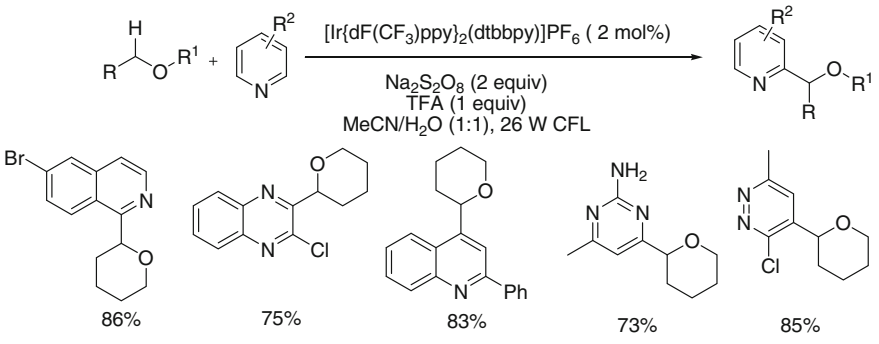


Scheme 3.19 Visible-light-induced cross-coupling of two radicals [67]

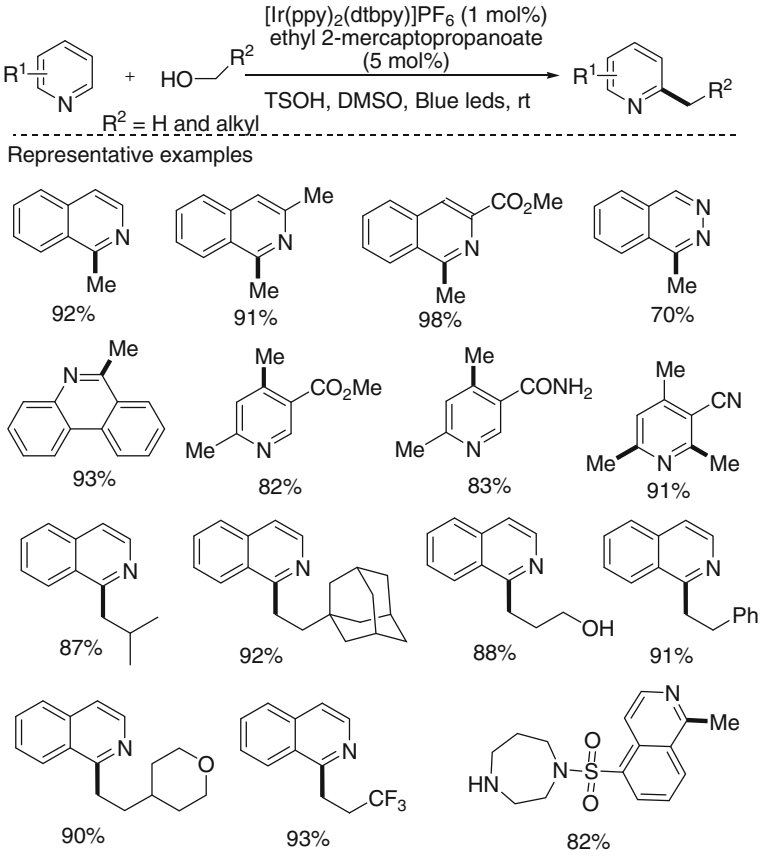
achieved via spin center shift (SCS) pathway (Scheme 3.21) [69]. This protocol is highly promising and attractive, since the simple and abundant unactivated alcohols can be used as alkylating reagents. It was also featured by methylation of a wide range of heteroarenes with methanol. It will gain considerable attention in the drug development and discovery in the future owing to the privilege of methyl group in medicinal agents [70]. This protocol complements the existing Minisci alkylation reactions [71]. As shown in Scheme 3.20, the substrate scopes with regard both to heteroarenes and unactivated alcohols are very attractive. Selective methylation of medicinally relevant molecules (fasudil and milrinone) was explored.

To get the mechanistic insights, the authors performed careful mechanistic studies to support the proposed spin-center shift (SCS) pathway. While the concept of spin-center shift is strange to organic chemists, it is actually a well-known process in biochemical transformation [72]. A plausible mechanism starts from SET of excited-state Ir(III) species to protonated heteroarenes, affording an strong oxidant Ir(IV) species. This ambiguous event just initiates a dual catalytic cycle. After initiation, as outlined in Scheme 3.22, single-electron oxidation of thiol catalyst and subsequent deprotonation could produce thiyl radical. Notably, the polar-effect-assisted HAT from alcohol to thiyl radical can perfectly furnish α-oxoalkyl radical, which rapidly adds to the protonated heteroarenes to give aminyl radical cation. Deprotonating of aminyl radical cation and followed by SCS would generate the benzylic radical. Another SET event of benzylic radical with excited-state Ir(III) species delivers the alkylated heteroarenes and regenerates a new dual catalytic cycle.

Subsequently, MacMillan and co-workers focused their attention on the development of general and mild methods to cope with the regioselectivity of highly functionalized alcohols. Generally, selective functionalization of a strong α-C(sp^3)–H bond of alcohol in the presence of weaker C(sp^3)–H bonds is arguably an intractable difficulty. To address this unsolved problem, MacMillan et al. had a careful literature study, and concluded that the HAT process depends not only on the BDE of C–H bond but also on the polar effect in the transition state [73]. The hydrogen-bond-type



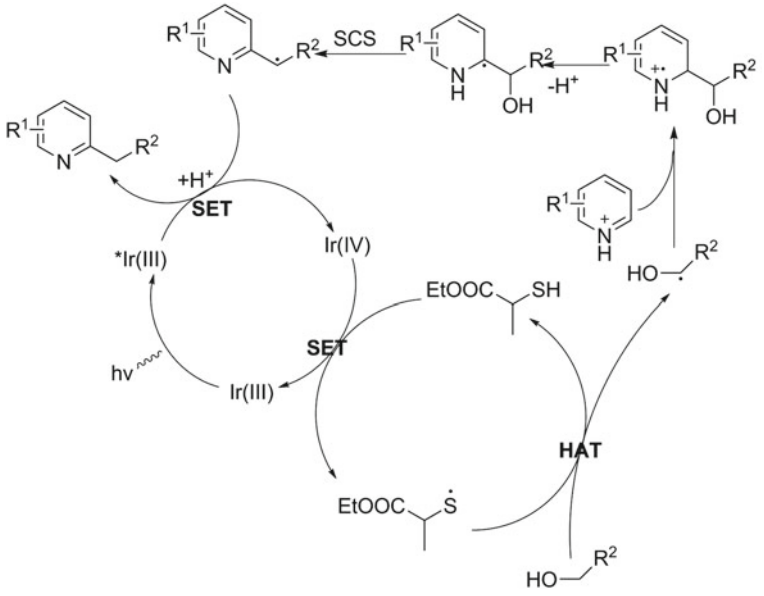
Scheme 3.20 Visible-light-mediated heteroarylation of C(sp^3)–H bond of ether [68]



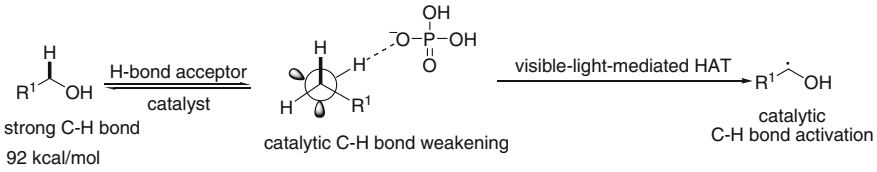
Scheme 3.21 Visible-light-mediated alkylation of heteroarenes with alcohols [69]

catalyst should interact with the hydroxyl group, and thus enabled α-C–H of alcohol more liable to undergo HAT process (Scheme 3.23).

With this consideration in mind, a visible-light-mediated, selective alkylation of α-C(sp^3)–H bond of densely functionalized alcohols was achieved (Scheme 3.24) [73]. Herein, $Bu_4NPO_4H_2$ was employed as a hydrogen bond acceptor and quinuclidine was the first time to be verified as a HAT catalyst in photoredox catalysis. Remarkably, under the optimized reaction conditions, exclusively selective hydrogen abstraction of α-C(sp^3)–H bonds adjacent to hydroxyl groups was accomplished even though diverse weaker C(sp^3)–H bonds were involved in the molecules (such as the C–H bond of ether, allylic, benzylic, etc.). The resulting nucleophilic α-oxoalkyl radical then attacks Michael acceptor (methyl acrylate), followed by single-electron reduction and cyclization to produce lactones.



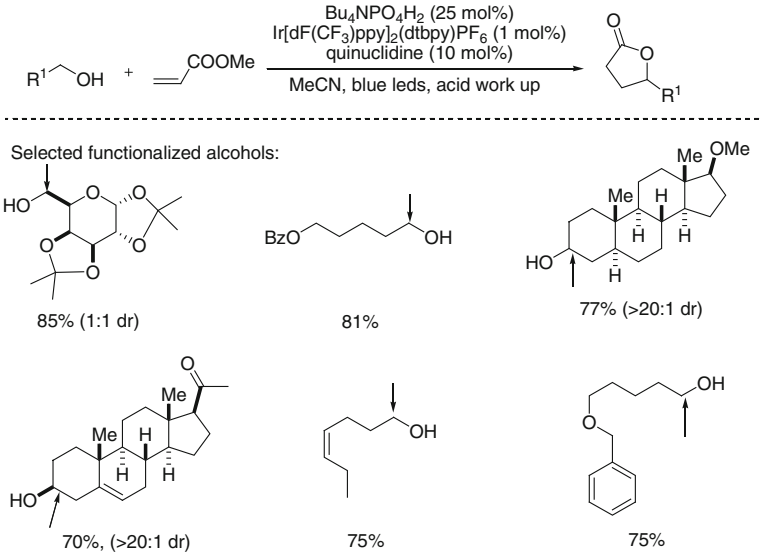
Scheme 3.22 Possible mechanism [69]



Scheme 3.23 Hydrogen-bond-assisted α-C–H activation of alcohol [73]

3.4 Selective Functionalization of Unactivated C(sp^3)–H Bond

Aldehydes and ketones are useful building blocks in organic synthesis. The direct α-C–H substitutions of carbonyl compounds are well known. However, selective β-C(sp^3)–H functionalization remains rare. The MacMillan group introduced 5πe$^-$ activation model by dual aminocatalysis and photocatalysis, opening up a practical synthetic route to β-substituted aldehydes and ketones (Scheme 3.25). With this novel strategy, radical–radical coupling of enaminyl radical with electron-poor cyanobenzene radical anion can elegantly produce β-arylated aldehydes and ketones [74]. A recombination of enaminyl radical with imine anion radical was also developed [75]. In the presence of Michael acceptors, radical addition of enaminyl radical to electron-deficient alkenes affords β-alkylated aldehydes [76].



Scheme 3.24 Hydrogen-bond-assisted α-C–H alkylation of alcohol [73]

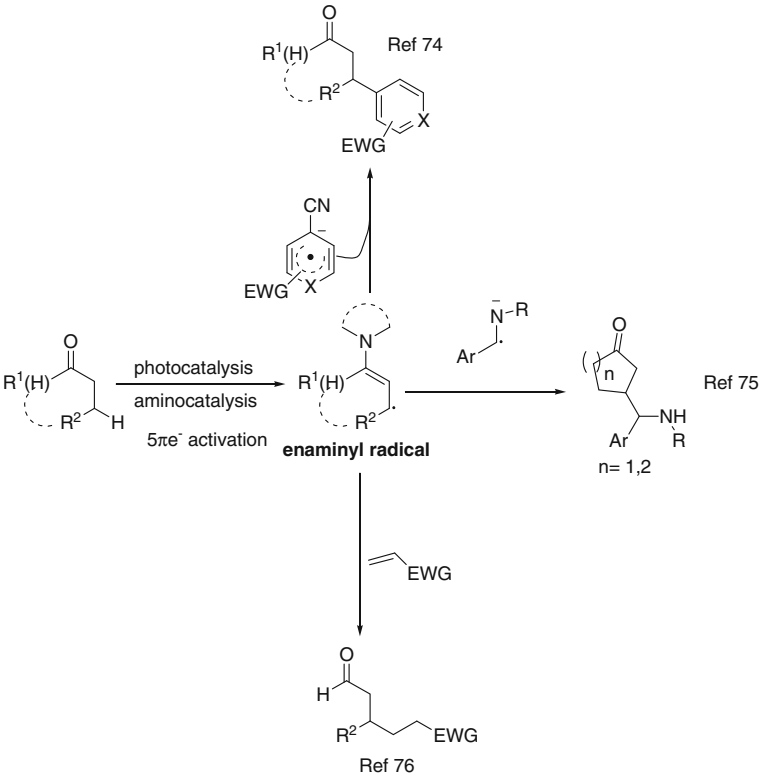
These protocols represent important step forward in β-C(sp^3)–H bond functionalization of carbonyl compounds and hopefully provide potential application in the future.

In the same year, Fagnoni and co-workers developed a sunlight-induced β-alkylation and acylation of cyclopentanones using tetrabutylammonium decatungstate (TBADT) as the photocatalyst (Scheme 3.26) [77]. The authors rationalized that the polar radical transition state was a key point for its regioselectivity.

In 2013, Chen et al. developed a direct and economical fluorination of benzylic C–H bond (Scheme 3.27) [78]. Using diaryl ketones as photosensitizers, visible-light-induced fluorination of various benzylic C–H bonds was accomplished with Selectfluor as fluorine source. Selective mono- and difluorination can be controlled with different photosensitizers. 9-Fluorenone catalyzes the monofluorination, while xanthone favors benzylic C–H difluorination. Also, in the same year, light-induced pyridination of benzylic C–H bond was developed [79].

Using benzophenone as photosensitizer, radical alkenylation of unactivated C(sp^3)–H bond was developed with 1,2-bis(phenylsulfonyl)ethylene as coupling partner (Scheme 3.28) [80]. A variety of substrates were compatible, including amides, ethers, alcohols, and cycloalkanes. Moreover, the obtained sulfonylalkenes are useful building blocks for the construction of prenyl and pyrrole derivatives.

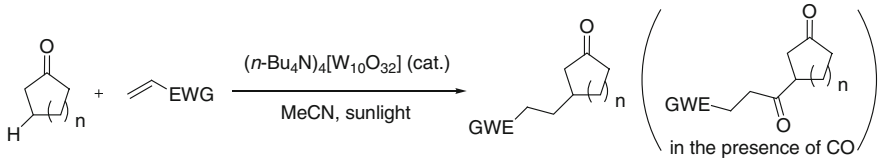
Activation of 1,4-dicyanonaphthalene (DCN) under light enabled an efficient intra- and intermolecular C–O bond formation with benzylic C(sp^3)–H bonds (Scheme 3.29) [81]. Furthermore, benzylic C(sp^3)–H bonds can be oxidized into ketones in the presence of water. Very recently, a visible-light-driven DCA



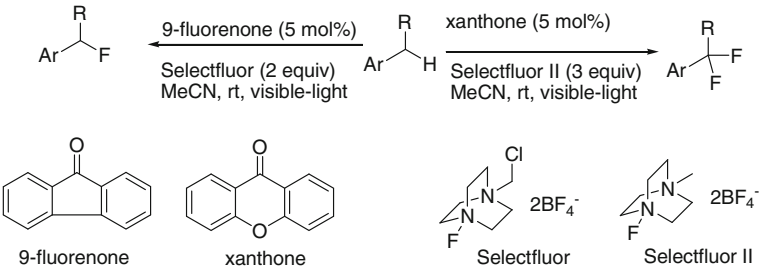
Scheme 3.25 Photocatalytic β-C(sp^3)–H arylation of aliphatic aldehydes and ketones [74–76]

(9,10-dicyanoanthracene)-catalyzed intermolecular amination of benzylic C–H bond was reported [82].

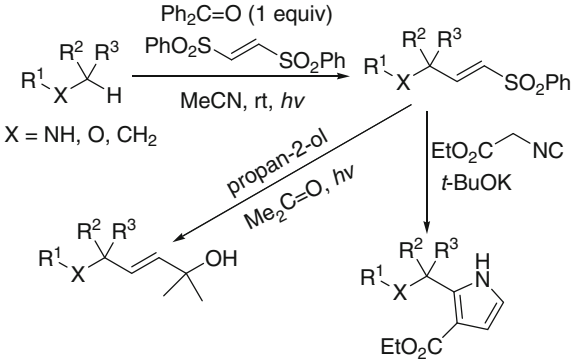
Compared to benzylic C–H bond, selective functionalization of aliphatic C(sp^3)–H bond is much more difficult. Using anthraquinone (AQN) [83] or TBADT [84] as photosensitizers, the challenging monofluorination of unactivated C(sp^3)–H bonds was achieved, rendering excellent regioselectivity (Scheme 3.30). The authors rationalized that triplet–triplet energy transfer of AQN to Selectfluor generates cationic *N*-radical, which could abstract one hydrogen atom from the electron-rich C (sp^3)–H bond.



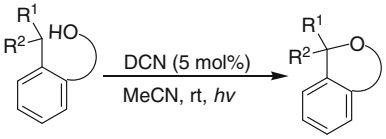
Scheme 3.26 Sunlight-mediated β-(sp^3)–H alkylation of cycloketons [77]



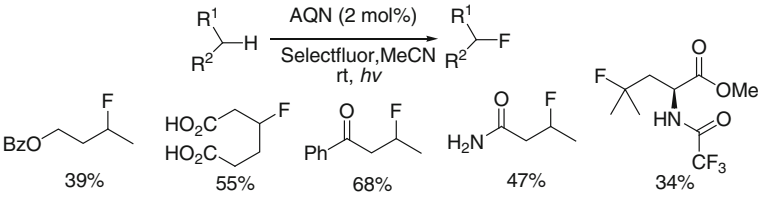
Scheme 3.27 Photocatalytic mono- and difluorination of benzylic C–H bonds [78]



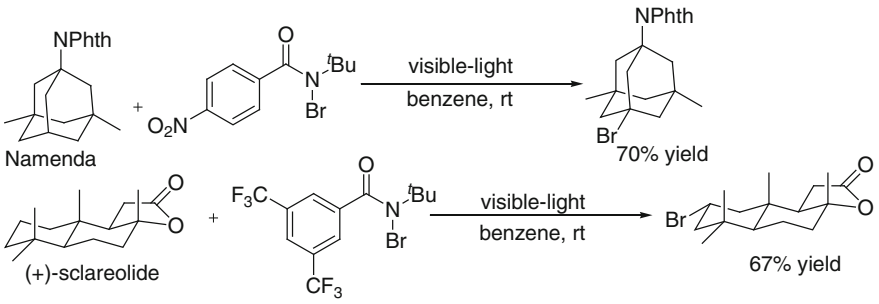
Scheme 28 Light-induced alkenylation of C(sp^3)–H bond [80]



Scheme 3.29 Metal-free, DCN-catalyzed C(sp^3)–H cleavage for C–O coupling [81]



Scheme 3.30 Light-induced radical fluorination of unactivated C(sp^3)–H bond [83]



Scheme 3.31 Visible-light-mediated highly selective bromination of unactivated C(sp^3)–H bond [85]

More recently, Alexanian and co-workers introduced a new method for selective bromination of aliphatic C(sp^3)–H bonds, streamlining complex molecule synthesis. Under visible-light irradiation, photocatalyst-free bromination of unactivated C(sp^3)–H bond was achieved using *N*-bromoamides as bromine source (Scheme 3.31) [85]. Significantly, 2° and 3° C(sp^3)–H selectivity can be controlled with different *N*-bromoamide reagents. Later, intramolecular amidation and chlorination of aliphatic C(sp^3)–H bonds was accomplished by means of visible-light photocatalysis [86]. This strategy is an important update to the Hofmann–Löffler–Freytag reaction.

3.5 Conclusions

In the past five years, we have witnessed a rapid development of visible-light photoredox catalysis in organic synthesis. A great number of excellent C(sp^3)–H bond functionalization protocols were reported. Visible-light-driven C–H bond functionalization is distinguished by its notable features in mild reaction conditions, good functionality compatibility, and easy operation as well as the overall sustainability. The application of this new chemistry in industry manipulating process is currently underdeveloped. Certainly, visible-light-mediated C(sp^3)–H bond functionalization will become one important branch in green chemistry. In the future, photoredox catalysis will become an emerging platform for enantioselective radical reactions.

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