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Recent advance in direct sp³ carbon-hydrogen bond functionalizations

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REVIEW INFORMATION

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C-heteroatom bond formation
Csp3-H bond functionalization

ABSTRACT

Direct and selective carbon-hydrogen bond functionalization has attracted enormous attention because it provides more efficient strategies for preparing valuable functional molecules from easily available substrates. Significant and exciting developments in functionalization of un-activation Csp³-H bonds have continuously been made over the past few decades. This review mainly summarizes recent advances on direct Csp³-H bond functionalization for the formation of C-C and C-heteroatom bond under transition-metal-catalysed and metal-free conditions.

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1. Introduction

In the past several decades, the direct C-H functionalizations have attained continuous interest because it provides efficient and straightforward approaches for the construction of complex chemical molecules in atom-economical manners [1-13]. For example, the activation of Csp²-H bond has gradually become more convenient and efficient strategies for the synthesis of numerous available aromatic compounds. However, functionalizations of inert Csp³-H bond are a tremendous challenge owing to their high bond-dissociation energy and low polarity. The inactive Csp³-H bonds are very difficult to functionalize and the transformation Csp³-H bonds to available functional molecules has become the center of attention in theoretical and experimental researches and exhibits significant role in the field of modern synthesis [14-24]. Compared with traditional organohalide electrophiles or organometallic reagents, the Csp³-H bond activation reactions demonstrated wide availability, sustainability and high atom-economy. Great progress has been achieved in the development of inert Csp³-H bond functionalization reactions through oxidative coupling and radical reactions in recent decades. Below this review will primarily provide a perspective on Csp³-H bond functionalization from C-C and C-heteroatom bond forming reactions under transition-metal-catalyzed and metal-free conditions.

2. Transition-metal-catalyzed Csp³-H functionalization

Transition metal catalyzed Csp³-H functionalization has become a significant and useful synthetic approach for preparation of various practical organic molecules. Increased attention has been focused on development of Csp³-H functionalization because these reactions can be performed reasonably mild conditions with remarkably high selectivity and atom- and step-efficiency.

2.1. Formation of C-C bond via Csp³-H functionalizations

The direct functionalization of Csp³-H bonds is an emerging strategy for the construction of C-C bond in view of C-C bonds are the most basic constituent part in organic molecules. Many efforts have focused on the formation Csp³-Csp¹, Csp³-Csp² and Csp³-Csp³ bonds through functionalization of Csp³-H bond employing transition-metal as catalysts in the past twenty years.

2.1.1. Reaction between Csp¹ and Csp³-H bond

In 2013, Vachhani *et al.* [25] reported a simple and efficient gold-catalyzed functionalization of Csp³-H for the preparation of cyclopentapyridinones and spirocyclopenta pyridinones (Scheme 1).

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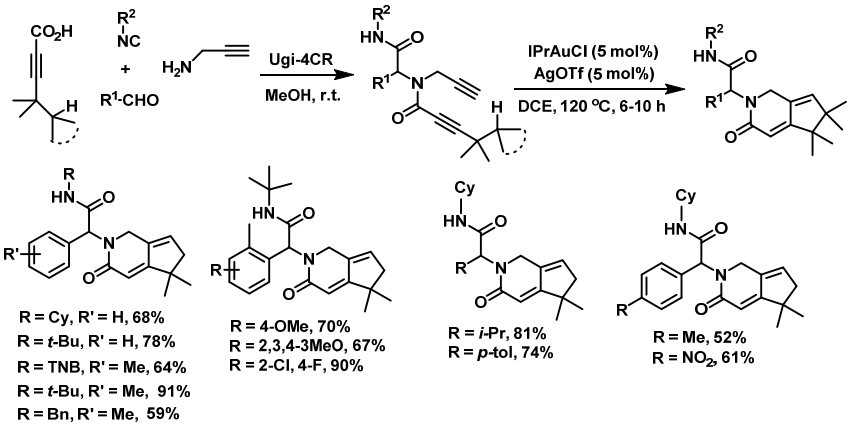
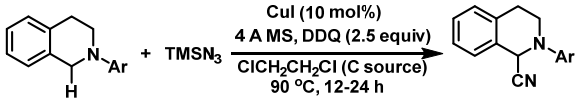
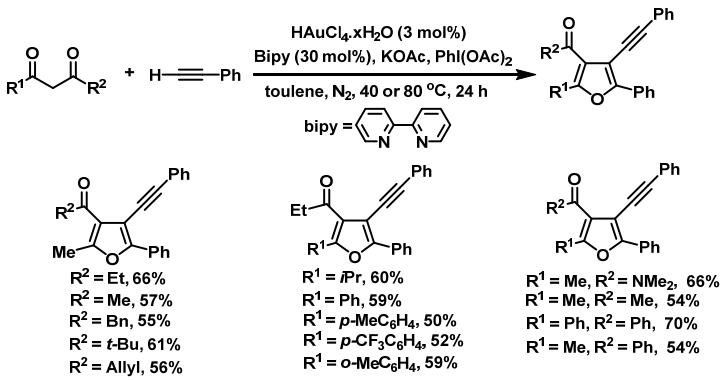


Scheme 1



Ar	Yield (%)	Ar	Yield (%)
4-MeOC$_6$H$_4$	85	4-FC$_6$H$_4$	83
4-ClC$_6$H$_4$	77	4-BrC$_6$H$_4$	62
4-MeC$_6$H$_4$	81	4-*t*BuC$_6$H$_4$	76
4-CF$_3$OC$_6$H$_4$	82	3-MeOC$_6$H$_4$	84
3-ClC$_6$H$_4$	71	3-MeC$_6$H$_4$	95
2-MeOC$_6$H$_4$	66	2-FC$_6$H$_4$	78
2-ClC$_6$H$_4$	58	C$_6$H$_5$	88
3-MeO-4-ClC$_6$H$_4$	76		

Scheme 2

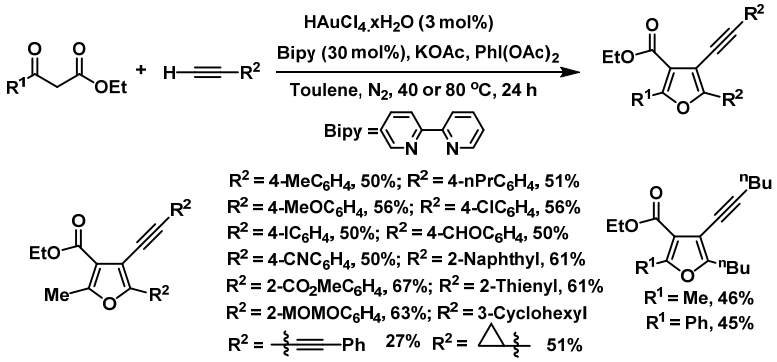


Scheme 3

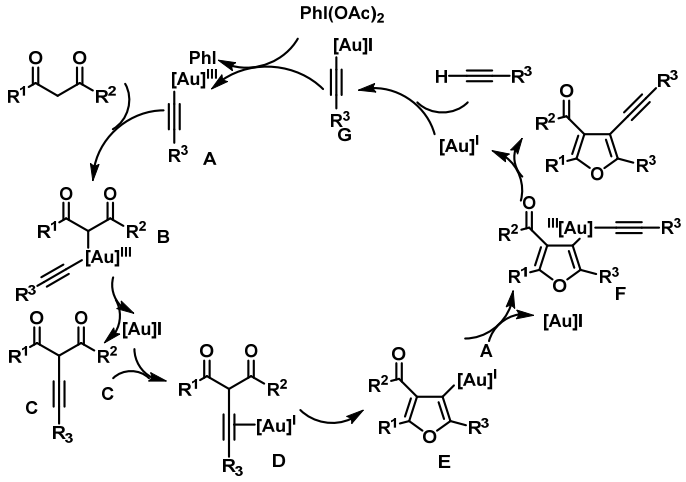
The approach was the Ugi-4CR of regioselective tandem cyclization of *N*-propynylbutynamide giving the corresponding cyclopentapyridinones with moderate to good yields. In 2014, Wang *et al.* [26] described a copper-catalyzed oxidative cyanation of α-C-H tertiary amines employing "CN" source from trimethylsilyl azide (Scheme 2). The reaction smoothly proceeded and afforded the C_1-cyanation of tetrahydroisoquinolines with 58-93% yields under environmentally friendly conditions.

Song and coworkers [27] developed a convenient and efficient strategy for the formation of 3-alkynyl polysubstituted furans from easily available starting substrates through gold-catalyzed oxidative Csp^3-H/Csp-H cross-coupling of between 1,3-dicarbonyl compounds and terminal alkynes (Scheme 3 and 4). The reaction involved a cascade process including cyclization and in situ oxidative alkynylation and tolerated a variety of terminal alkynes as substrates giving the corresponding poly-substituted furans with moderate yields under mild reaction condition. A proposed mechanism for cross-coupling reaction was exhibited in Scheme 5.

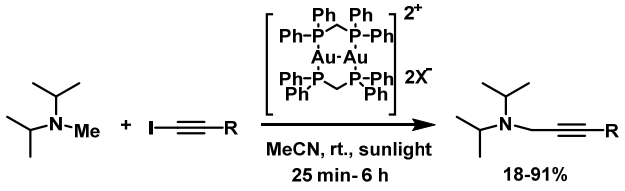
In 2015, Hashmi and coworkers [28] developed a highly efficient radical Csp^3-H alkynylation of tertiary aliphatic amines catalyzed by $[Au_2(m\text{-}dppm)_2]^{2+}$ employing sunlight as a green and sustainable energy source under mild reaction conditions (Scheme 6 and 7). The Csp^3-H alkynylation reaction exhibited higher region selectivities and tolerated to additional functional groups. Mechanistic studies proposed the Csp^3-Csp bond formation was a radical coupling between an α-aminoalkyl and an alkynyl.



Scheme 4



Scheme 5

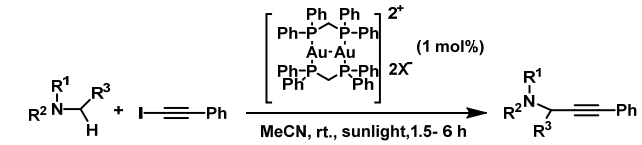


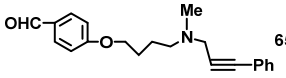
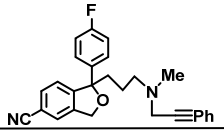
Scheme 6

2.1.2. Reaction between Csp² and Csp³-H bond

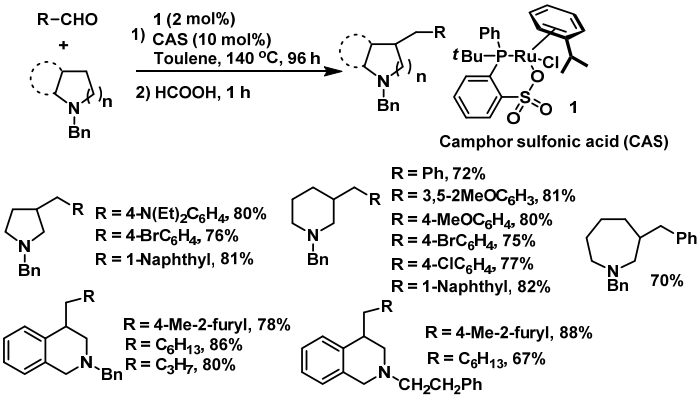
In 2011, Sundararaju *et al.* [29] developed a highly regioselective C(3)-alkylation reaction promoted by ruthenium(II) complexes via functionalization of Csp^3-H bond of saturated cyclic amines (Scheme 8). The catalytic reaction involved activation of Csp^3-H bond through initial dehydrogenation of cyclic amines and hydrogen auto transfer processes and provided the resulting products with moderate to good yields. In 2012, Piou *et al.* [30] reported an efficient palladium(0)-catalyzed domino carbopalladation for one-pot synthesis of spirooxindoles through functionalization of Csp^3-H bond with reaction of aldehyde (Scheme 9). This reaction provided a novel and useful approach for the elaboration of domino reactions using Csp^3-Csp^3 bond forming reactions as an elementary step.

Li and coworakers [31] described a $CuCl_2$-catalyzed base-switched methylenation and formylation employing tetramethylethylenediamine (TMEDA) as a carbon source and atmospheric oxygen as an oxidant under mild conditions (Scheme 10 and 11). The electronic properties of the *N*-protecting groups and substituents including substituted pattern played important roles in the reactivity of methylenation and formylation reactions. The reaction smoothly proceeded and gave the corresponding product *bis*-indolylmethanes, diphenylmethanes and 3-formylindoles with good yields and high regioselectivities.

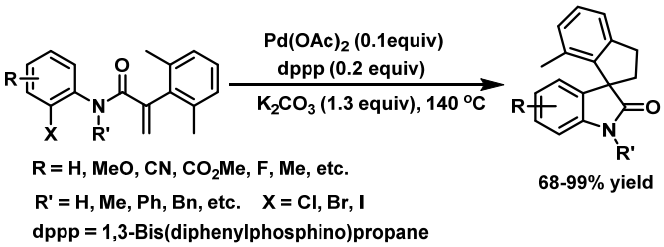


R^1	R^2	R^3	Yield (%)	R^1	R^2	R^3	Yield (%)
i-Pr	*i*-Pr	H	81	*i*-Pr	*i*-Pr	Me	62
Et	Et	Me	70	Pr	Pr	Pr	56
Cy	Cy	H	63	Cy	Me	H	84
Me	$(Me)_2NCH_2CH_2$	H	50	Me	Bu	H	80
Cy	*i*-$PrCH_2CH_2$	H	78	Me	$HO(CH_2)_2O(CH_2)_2$	H	67
Me	$(EtO)_2CH(CH_2)_3$	H	71	Me	$EtN(Boc)(CH_2)_3$	H	78
Me	$PhCH_2$	H	50				
			65				62

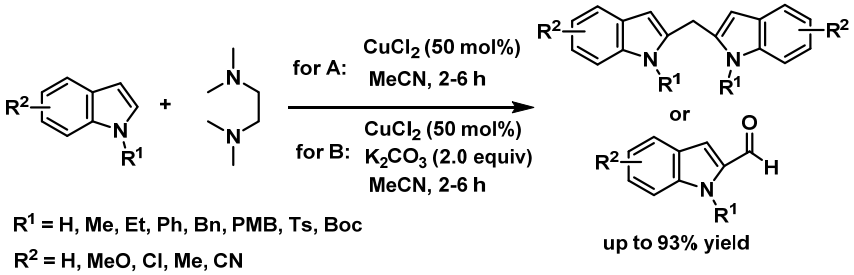
Scheme 7



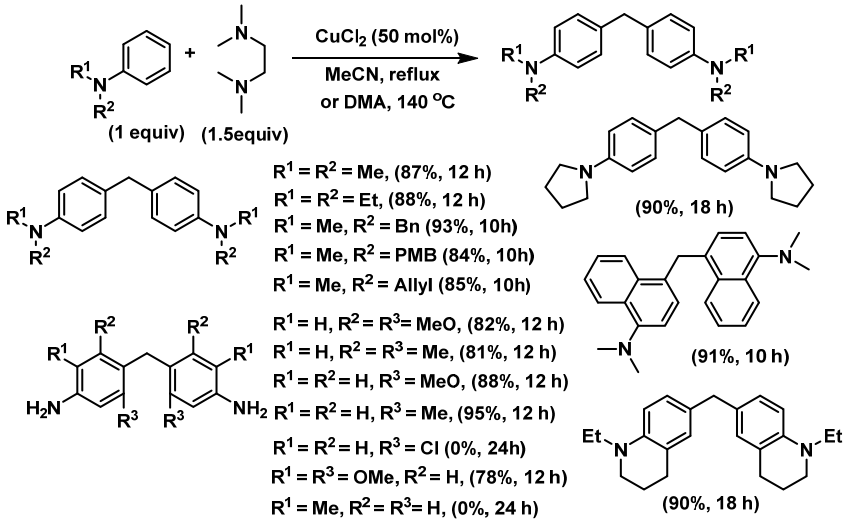
Scheme 8



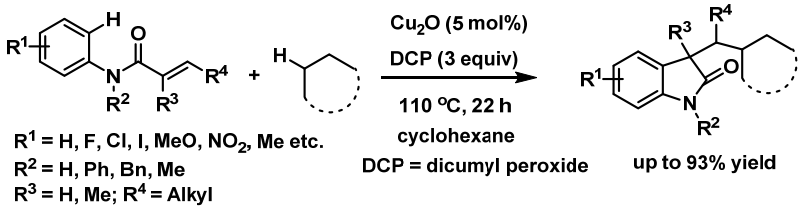
Scheme 9



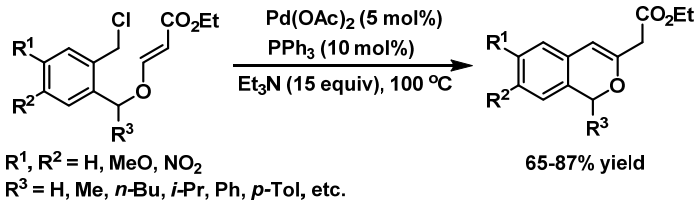
Scheme 10



Scheme 11



Scheme 12

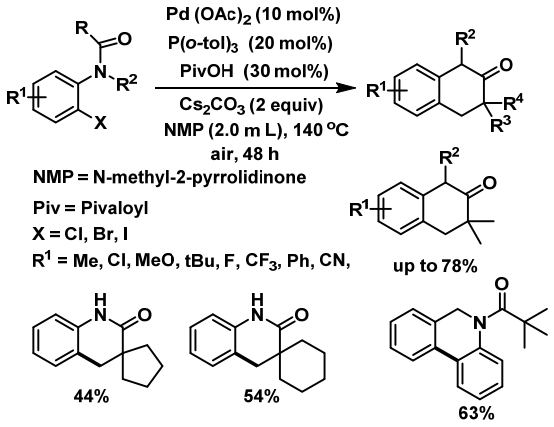


Scheme 13

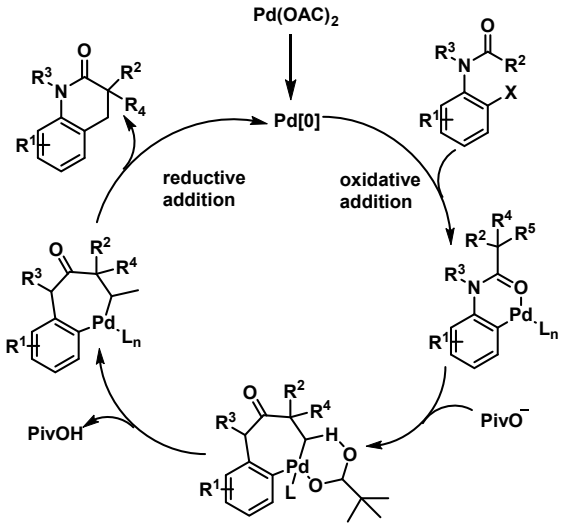
In 2014, Liu and coworkers [32] described a highly efficient strategy for the preparation of alkyl-substituted oxindoles with up to 93% yields via Cu-catalyzed oxidative alkylarylation of acrylamides with simple alkanes (Scheme 12). The reaction was a free-radical cascade process through selective activation of unactivated Csp^3-H functionalization/C-C bond formation. Gharpure and coworkers [33] developed a simple and efficient synthesis of isochromene derivatives via an intramolecular, benzylic Csp^3-Csp^2 bond forming Heck reaction on vinylogous carbonates (or β-alkoxyacrylates) (Scheme 13). The competitive Heck reaction between a normal olefin and a vinylogous carbonate moiety resulted in corresponding dihydronaphthalene products through coupling with olefin exclusively. The protocol was widely used in the synthesis of a core of natural products *cis*-dihydrokalafungin and monocerolide.

Shi and coworkers [34] developed palladium-catalyzed activation of an inert Csp^3-H bond for the preparation of 3,3-disubstituted 3,4-dihydroquinolinone derivatives 3,4-dihydro quinolinones from simple *ortho*-halogenated acetilide derivatives under mild conditions (Scheme 14). A plausible mechanism proposed that the reaction involved infrequent key intermediate seven-membered palladacycle in the catalytic cycle (Scheme 15). Another group described [35] a direct and novel $Pd(OAc)_2$-promoted arylation of methylene Csp^3-H bonds in aliphatic amides with PIP directing group (Scheme 16 and 17). The protocol showed good structural versatility and high functional group tolerance in both aryl halides and aliphatic amides and providing the corresponding β-arylated carboxylic acid derivatives with up to 78% yields.

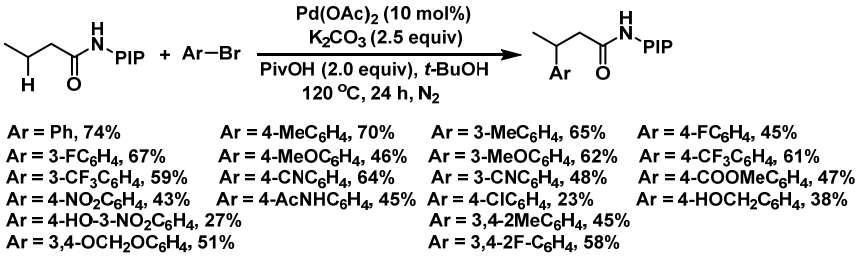
Maes and coworkers [36] developed a novel method for α-alkylation of piperidines with dioxolane protected alkenones using a ruthenium catalytic system (Scheme 18 and 19). The process was effectively proved on the α-alkylation of various piperidines with a pyridin-2-yl directing group and provided the corresponding monoalkylated and bisalkylated products with moderate to good yields from readily accessible substrates. Mao and coworkers [37] developed a copper-catalyzed oxidative coupling reaction of *N*,*N*-substituted amides with olefins or cinnamic acids for the synthesis of *N*-(3-oxo-3-phenylpropyl)-acetamide and N-cinnamylacetamide derivatives through oxyalkylation of vinylarenes and decarboxylative alkenylation of Csp^3-H (Scheme 20). The simple and practical protocol could provide the resulting products as potential precursors for the preparation of β-amino carbonyls and cinnamyl amines through further hydrolysis.



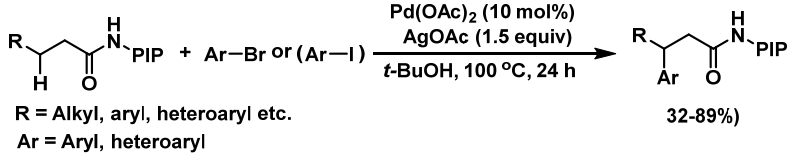
Scheme 14



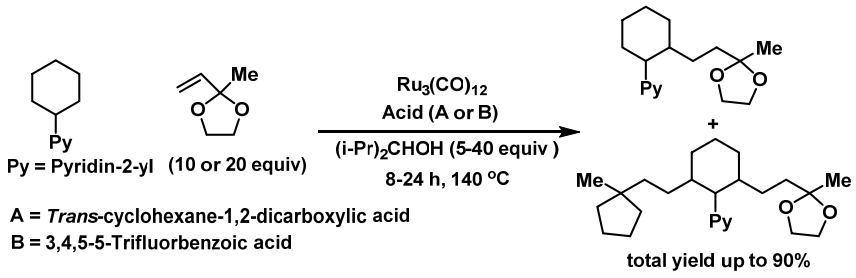
Scheme 15



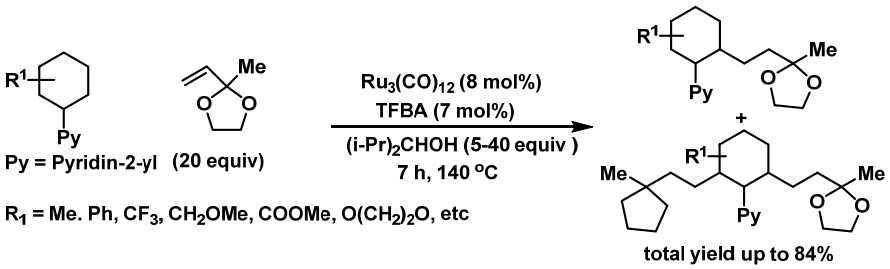
Scheme 16



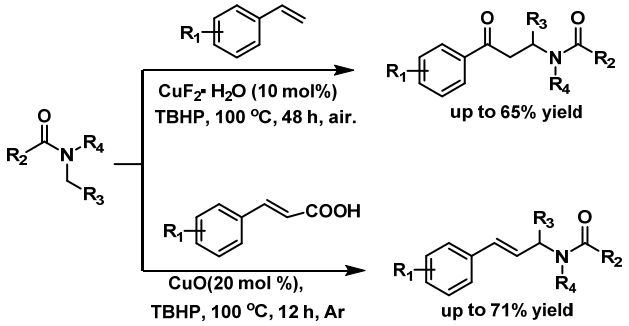
Scheme 17



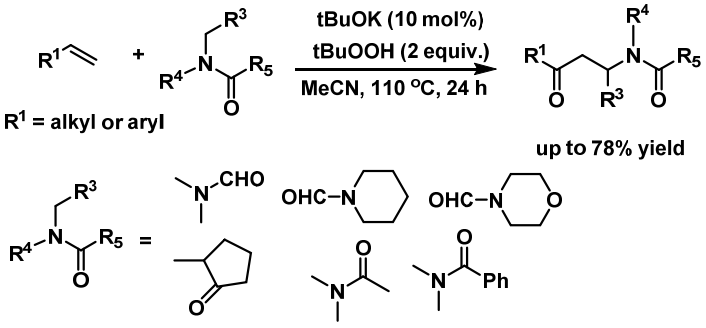
Scheme 18



Scheme 19



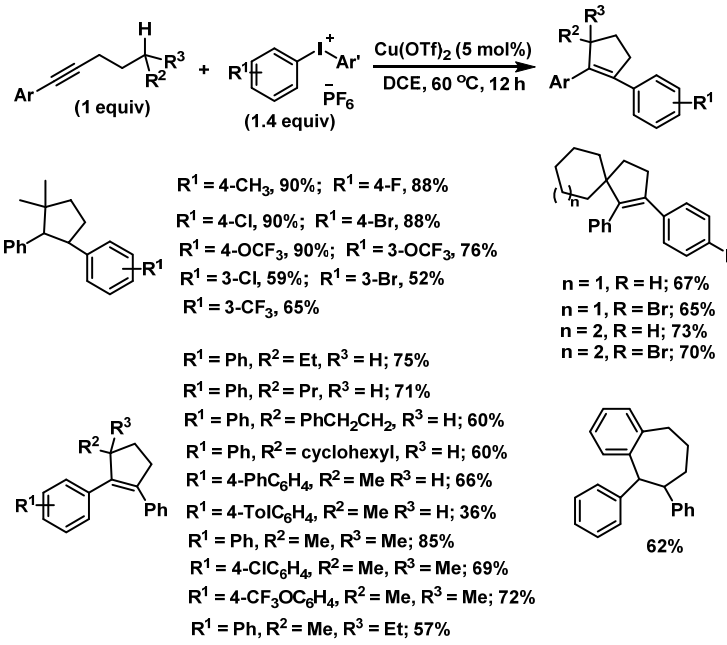
Scheme 20



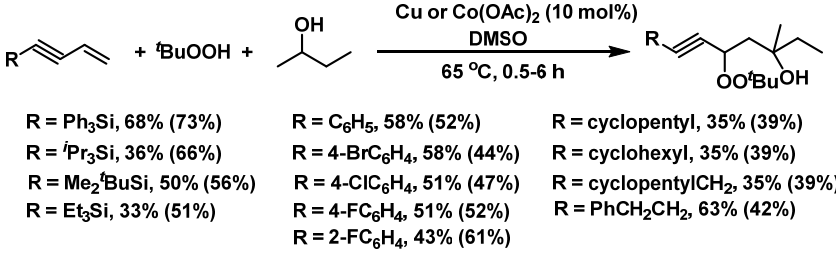
Scheme 21

Li and coworker [38] developed a selective synthesis of β-amino ketones and α,β-unsaturated amides via oxidative coupling of unactivated terminal alkenes with amides employing peroxides as oxidant (Scheme 21). This reaction proceeded through an oxidative radical pathway involved selective functionalization of the amide Csp^3-H bonds of versus Csp^2-H functionalization of the carbonyl with a broad substrate scope and excellent chemselectivities. Chen and coworkers [39] achieved an economical and efficient copper-catalyzed arylcarbocyclization reaction of alkynes for the formation of C-C bond via activation of inert Csp^3-H bond (Scheme 22). This method was promoted diaryliodonium salts and providing the resulting products carbocycles with moderate to good yields.

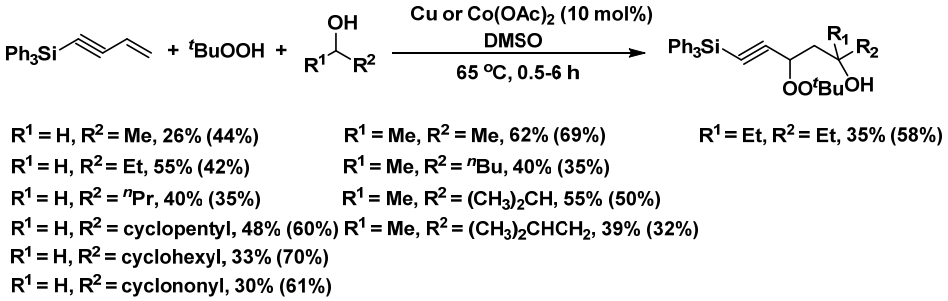
In 2015, Cheng and Loh [40] developed a copper- and cobalt catalyzed direct three-component oxidative coupling of olefins and alcohols through α-C-H activation of alcohols empolying hydroperoxides as radical initiator (Scheme 23 and 24).



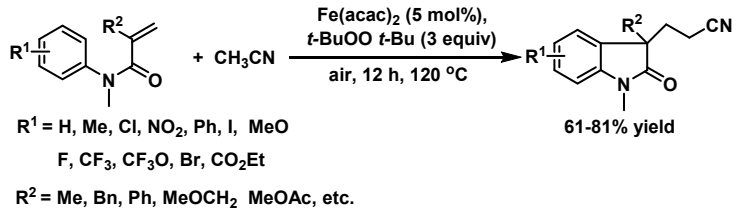
Scheme 22



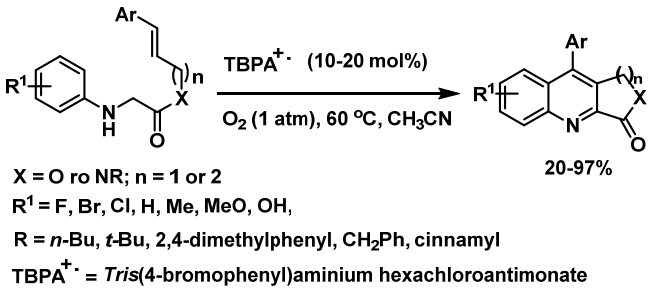
Scheme 23



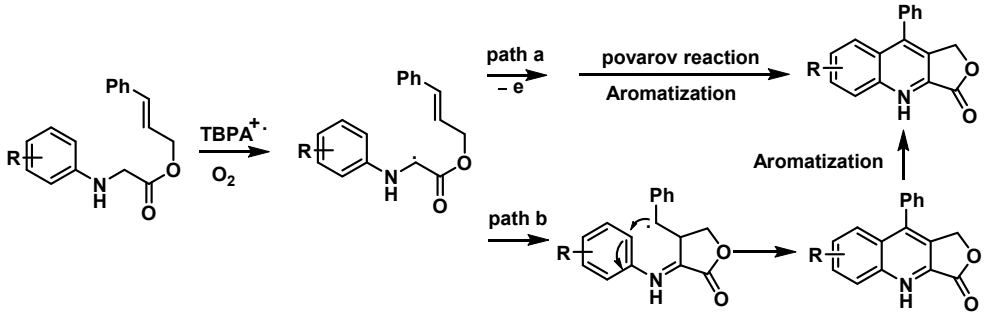
Scheme 24



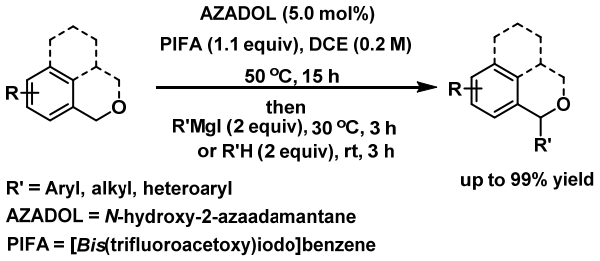
Scheme 25



Scheme 26



Scheme 27



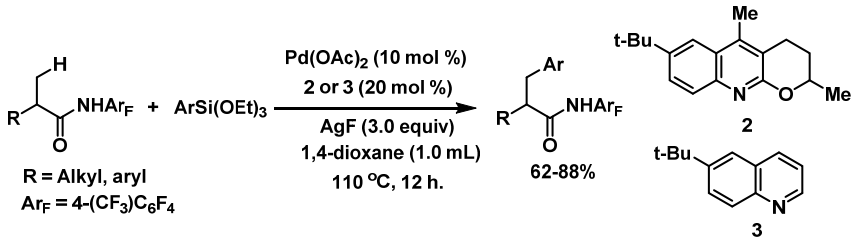
Scheme 28

Alkylation-peroxidation of various aliphatic, silylated, and aryl 1,3-enynes gave β-peroxy alcohols and β-hydroxyketones with extreme functional group tolerance, and the corresponding products β-peroxy alcohols further transformed to propargylic 1,3-diols and β-hydroxyynones. Later, Pan *et al.* [41] described an efficient strategy for the synthesis of oxindoles through radical cyanomethylation/arylation of arylacrylamides using $Fe(acac)_2$ as catalyst and acetonitrile as the radical precursor (Scheme 25). This reaction mainly involved dual C-H bond functionalization of Csp^3-H of acetonitrile and C sp^2-H of the phenyl group. The process showed excellent functional groups compatibility and transformed to the corresponding products in higher yields.

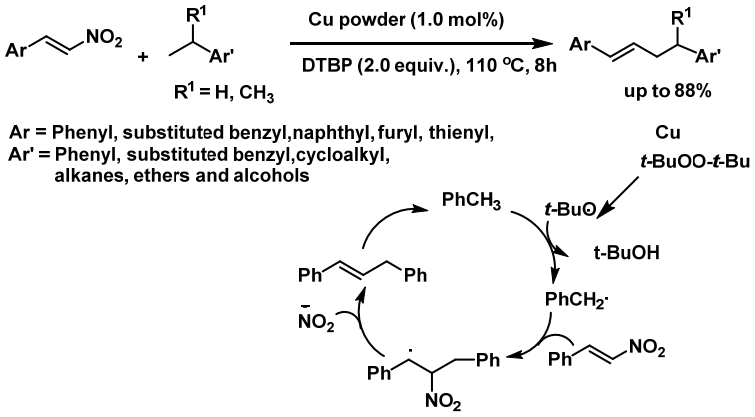
Jia and coworker [42] achieved a novel synthesis of quinoline-fused lactones and lactams from readily accessible starting materials via Csp^3-H bond oxidation of *N*-aryl glycine esters and amides under catalytic radical cation salt-induced conditions (Scheme 26). This reaction involved intramolecular annulation catalytic Csp^3-H oxidation two new C-C bond and two new hetercyclolic ring. The approach exhibited some advatanges including mild reaction conditions, high level compatibility with a variety of functional groups and high efficiency in the construction of polycyclic products. Plausible mechanism of radical-cation-prompted intramolecular annulation was showed in Scheme 27.

Muramatsu and Nakano [43] developed a practical Csp^3-H bond functionalization employing safe and green oxidants and 5.0 mol % of AZADOL as catalyst under wild condition (Scheme 28). The catalytic reaction smoothly proceeded with a broad range of substrates and nucleophiles tolerance and transformed to the corresponding products with up to 99% yields. Yu and coworkers [44] reported Pd(II)-catalyzed cross-coupling of Csp^3-H bonds carboxylic acid derivatives with arylsilanes in moderate to good yields (Scheme 29). The potential utility of quinoline-based ligands was essential for the key to catalytic coupling reaction.

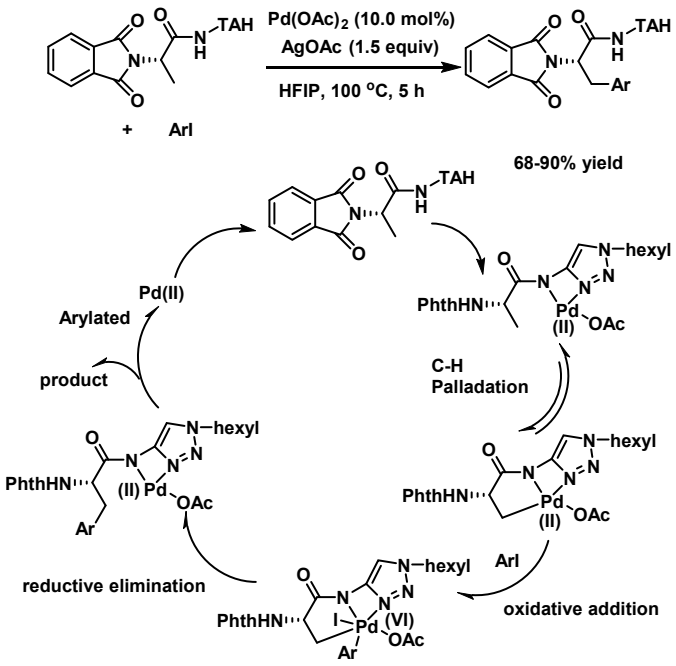
The direct oxidative Csp^3-H functionalization through radical pathway formed C-heteroatom (C, O, S) bonds has attracted extensive attentions in recent years. Yuan and coworkers [45] demonstrated Cu-promoted the addition of a benzyl or alkyl radical to β-nitrostyrenes with up to 88% yields employing di-*tert*-butyl peroxide (DTBP) as the oxidant. The reaction exhibited highly tolerant to additional functional groups, various substituted β-nitrostyrenes could be successfully to proceed and converted to the corresponding (*E*)-β-alkylstyrene derivatives via the radical addition and denitro-elimination mechanism. A proposed mechanism was shown in Scheme 30. Firstly, DTBP decomposes to produce the *tert*-butoxyl radical in the presence of copper. Next, *tert*-butoxyl radical acts on C-H bond of methyl in toluene and resulting in the benzyl radical.



Scheme 29



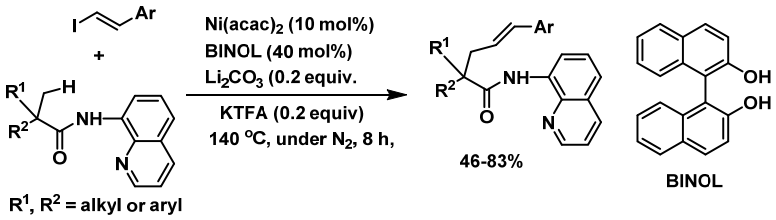
Scheme 30



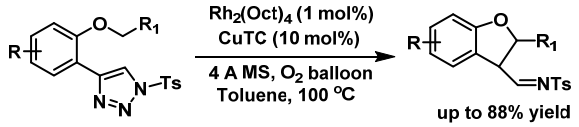
Scheme 31

Then addition of the benzyl radical to the β-position of the C-C double bond in β-nitrostyrenes gemerated an intermediate radical. Finally, the intermediate radical converted to the product through elimination of the NO_2 free radical.

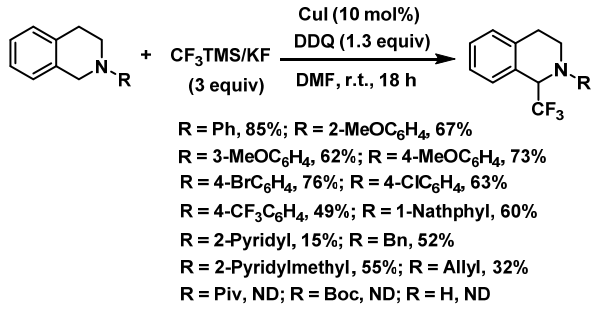
Ding and co-worker [46] achieved palladium-catalyzed Csp^3-H arylation of amino acid derivatives with various aryl iodides using click-triazoles as conveniently approachable and easily removable directing group. The protocol provided a practical strategy for the synthesis of both natural and synthetic amino acids with moderate to good yields and exhibited high level functional group tolerance and wide applications. Proposed reaction mechanism was exhibited in Scheme 31.



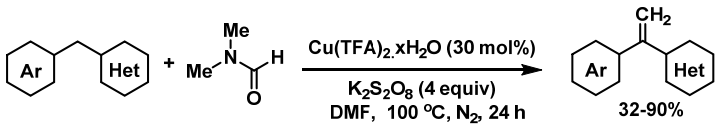
Scheme 32



Scheme 33



Scheme 34



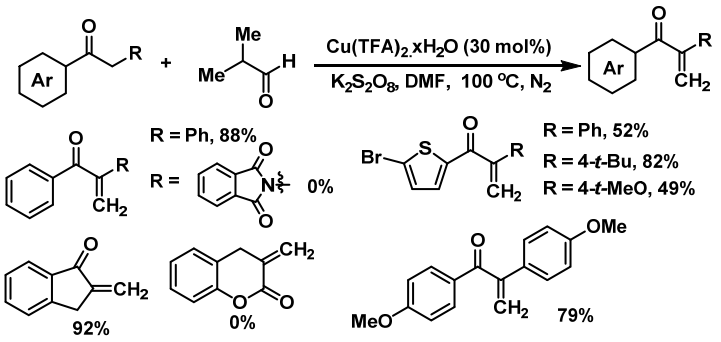
Scheme 35

Shi and coworkers [47] described a highly efficient for alkenylation of unactivated Csp³-H bonds with vinyl iodides employing catalytic system including Ni(acac)₂ as the catalyst and BINOL as the ligand (Scheme 32). The reaction smoothly accomplished with a wide variety of functional groups tolerance and transformed the resulting products functionalized carboxamides bearing α-quaternary carbon centers.

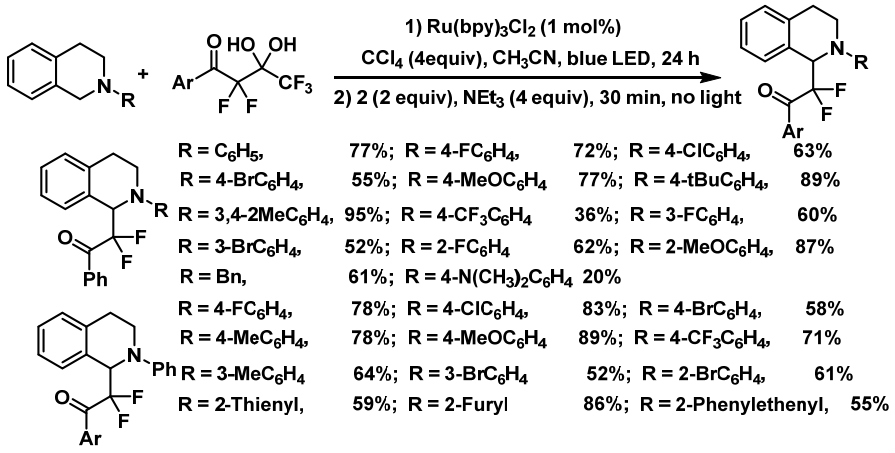
Kang and coworkers [48] developed an efficient cascade reaction for the synthesis of benzofuran derivatives from 1-sulfonyl-1,2,3-triazoles with up to 88% yields through rhodium-catalyzed Csp³-H insertion and copper-catalyzed aerobic oxidation (Scheme 33). The cascade reaction provided more convenient approach for one-pot synthesis of benzofuran starting from terminal alkyne via copper-catalyzed alkyne-azide cycloaddition and dehydrogenation cascade reaction.

2.1.3. Reaction between Csp³ and Csp³-H bond

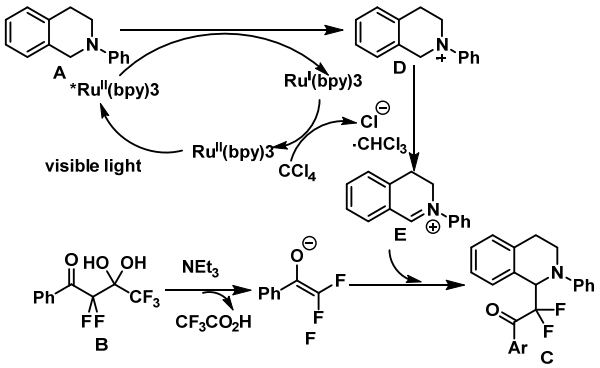
In 2011, Mitsudera and Li [49] achieved a novel protocol for the synthesis of trifluoromethylated products through oxidative Csp³-H activation of various tetrahydroisoquinoline derivatives at the α-position of nitrogen employing DDQ and Ruppert-Prakash reagent (Scheme 34). The approach could successfully generate the corresponding trifluoromethylated products using various amines as substrates in 15-90% yields under mild conditions. Lei and coworkers [50] reported a simple and useful method for the synthesis arylvinylketones and arylvinylpyridines from arylketones and 1-aryl-1-pyridinemethanes through a direct copper-catalysed oxidative Csp³-H methylenation to terminal olefins using DMF as one carbon source (Scheme 35 and 36). The reaction showed high level of functional group tolerace and giving the corresponding products with potential biological activities and pharmaceutical applications.



Scheme 36



Scheme 37

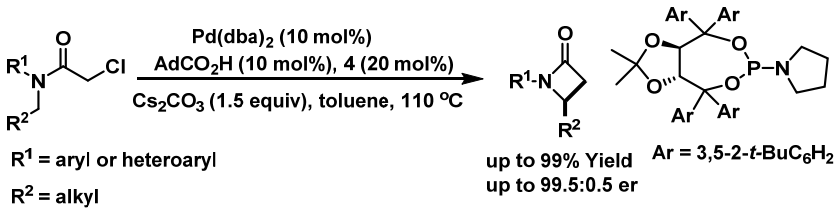


Scheme 38

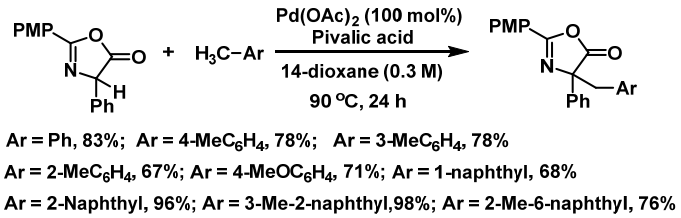
Li *et al.* [51] developed a convenient and effective protocol for the preparation of C_1-difluoro- methylated tetrahydroiso quinoline derivatives through C-H functionalization of tertiary amines employing visible-light photoredox catalysis (Scheme 37). This method used stable, easily obtained α,α-difluorinated gem-diol as the CF_3 source and resulting in the corresponding products with moderate to high yields at ambient temperature. A possible mechanism for direct Csp^3-H difluromethylation was shown in Scheme 38.

Four-membered heterocycles like β-lactams were important structural motifs owing to their rich biological activities as well as their high propensity of ring-opening in organic reactions. In 2014, Cramer and coworkers [52] reported a stereoselective strategy for the synthesis of wide valuable β-lactams via functionalization of Csp^3-H from readily accessible chloroacetamide substrates employing aldol phosphoramidite ligand in combination with adamantyl carboxylic acid as cocatalyst (Scheme 39). The reaction provided an economical and efficient process for functionalization of four-membered heterocycles with excellent yields and enantio selectivities.

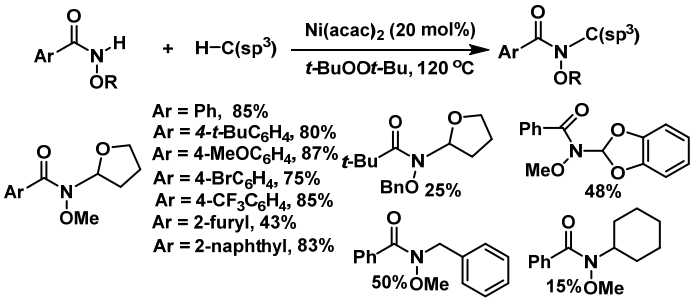
In 2015, Curto and Kozlowski [53] described a novel selective coupling of a carbon nucleophile with methyl, ethyl, propyl, and butyl arenes without directing group using a simple system consisting of $Pd(OAc)_2$ and pivalic acid (Scheme 40).



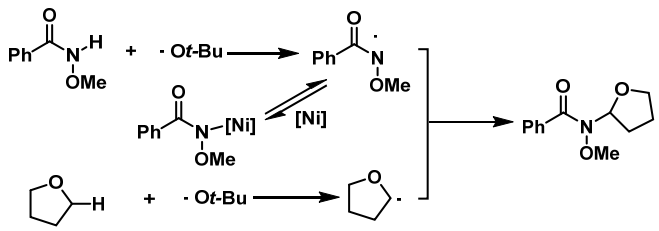
Scheme 39



Scheme 40



Scheme 41



Scheme 42

These double C-H activation showed desirable selectivity for at the terminal methyl sites of alkyl arenes substitite for arene Csp^2 -H activation more commonly observed. Mechanistic studies indicated the resultant azlactone products obtained through a radical process for oxidation with $Pd(OAc)_2$ and consistent with a Pd-catalyzed C-H activation. The process provided alkylarene derivatives which can readily transform to α-amino acid with moderate to good yield under wild conditions.

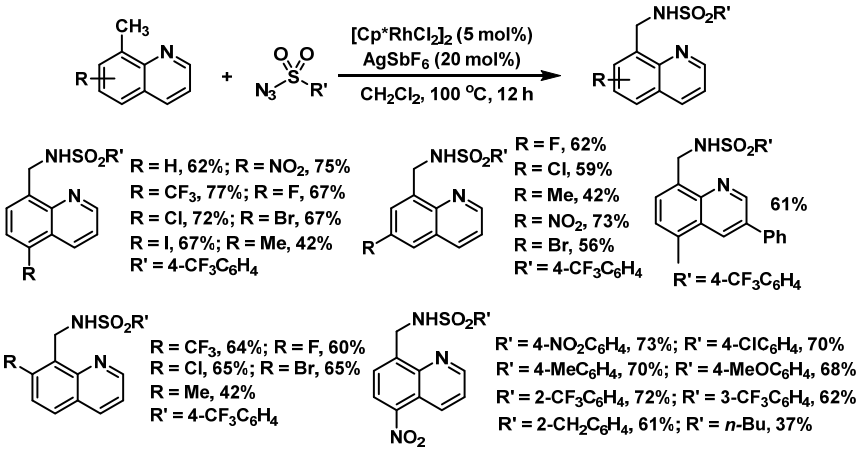
2.2. Formations C-Heteroatom bond via Csp^3-H functionalizations

Over the past decades, the construct of C-heteroatom bond (C-O, C-N, C-S, etc.) via the direct functionalizations C-H bond has attracted extensive attention. In particular, remarkable success has been achieved with respect to the functionalization of unactive Csp^3-H bonds.

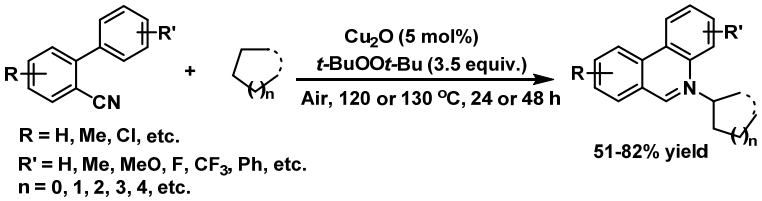
2.2.1. C-N bond formations

The C-N bond was one of the most substantial part in the construction of many natural products and complicated organic molecules. In 2014, Zhou *et al.* [54] reported an oxidative Csp^3-H/N-H cross-coupling reaction of N-alkoxy-amides with aliphatic hydrocarbons employing $Ni(acac)_2$ as catalyst and di-*tert*-butyl peroxide as oxidant (Scheme 41). Experiments and DFT calculations disclosed that the reaction involved transition-metal-assisted radical/radical cross-coupling with the transient sp^3 carbon radical to form Csp^3-N bonds. A plausible mechanism based on these assumptions and experimental results was exhibited in Scheme 42.

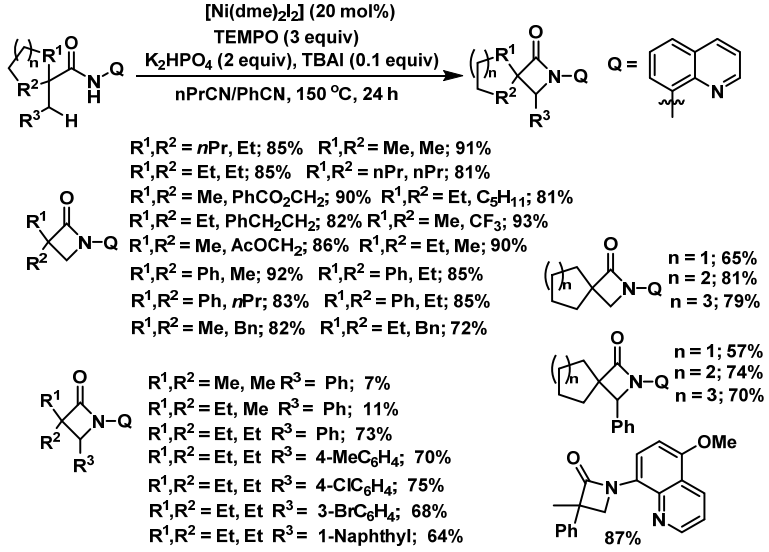
Wang *et al.* [55] achieved an efficient protocol for the preparation of quinolin-8-ylmethanamine derivatives via the amidation reactions of cationic 8-methylquinolines with azides using rhodium(III) complex as catalyst (Scheme 43).



Scheme 43



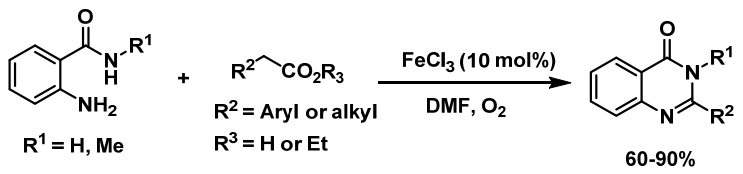
Scheme 44



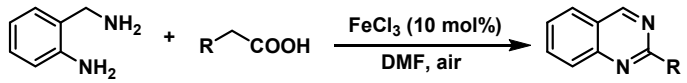
Scheme 45

The reaction smoothly proceeded and gave the corresponding products with various 8-methylquinolines external oxidants or basesin higher yields. Huang and coworkers [56] developed an convenient strategy for the preparation of 6-alkyl phenanthridines through a cascade alkylarylation reaction of 2-isocyanobiphenyls with simple alkanes (Scheme 44). The synthetic process was mainly based on dual Csp^3-H/Csp^2-H functionalizations via both copper-catalyzed and DTBP promoted pathways, and demonstrated some advantages including higher yields, high level compatibility of functional groups and mild reaction conditions.

Ge and coworkers [57] reported a nickel-mediated functionalization of unactivated Csp^3-H bond for the highly selective preparation of 2,2-disubstituted propionamides through intramolecular dehydrogenative cyclization of aliphatic amides (Scheme 45). The aliphatic amides with the assistance of a bidentate directing group could transform to the cyclization of aliphatic amides with high functional-group tolerance.

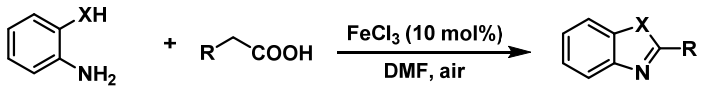


Scheme 46



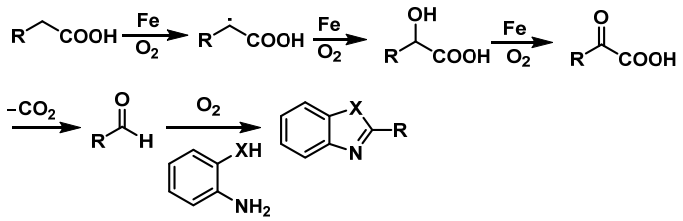
R = C_6H_5, 90%; R = 4-$MeOC_6H_4$, 80%; R = 4-HOC_6H_4, 79%
R = 4-$NH_2C_6H_4$, 75%; R = 4-$NO_2C_6H_4$, 90% ; R = 4-BrC_6H_4, 83%
R = 3-ClC_6H_4, 83%; R = Naphthyl, 78%; R = Thienyl, 81%

Scheme 47

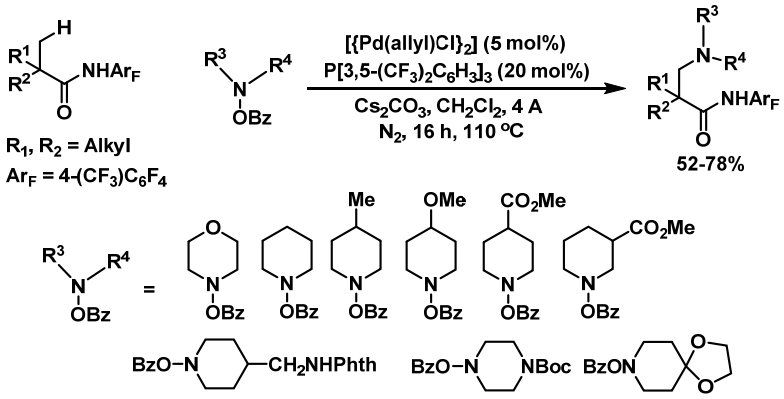


X = S, R = 4-$MeOC_6H_4$, 78%; X = S, R = 4-BrC_6H_4, 90%
X = S, R = 4-$NO_2C_6H_4$, 91%; X = S, R = Naphthyl, 82%
X = NH, R = 4-$MeOC_6H_4$, 80%; X = NH, R = 3-Pyridyl, 81%

Scheme 48



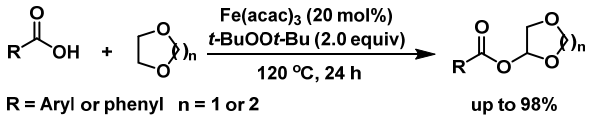
Scheme 49



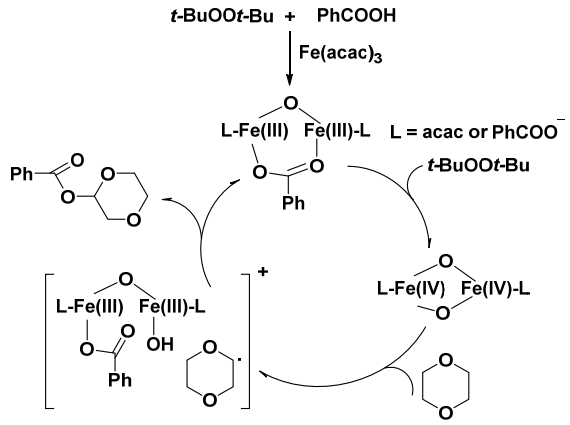
Scheme 50

Moreover, Csp^3-H bond functionalization of β-methyl groups was favored over the aromatic Csp^2-H bonds this reaction. Chen *et al.* [58] reported a green protocol for the construction of N-heterocycles from carboxylic acid derivatives and *o*-substituted anilines through aerobic oxidative functionalization of Csp^3-H bonds using iron as a catalyst and molecular oxygen or air as oxidant (Scheme 46-48). These processes mainly involved three steps including aerobic oxidation of Csp^3-H bond, decarboxylation and subsequent oxidation cyclization. A plausible reaction mechanism for iron-catalyzed aerobic oxidative functionalization of Csp^3-H bonds was described in Scheme 49.

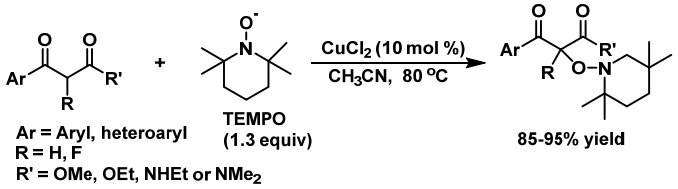
Yu and coworker [59] developed a novel and efficient intermolecular Csp^3-H amination reaction using a Pd0/PdII catalytic cycle and an electron-deficient triarylphosphine ligand (Scheme 50).



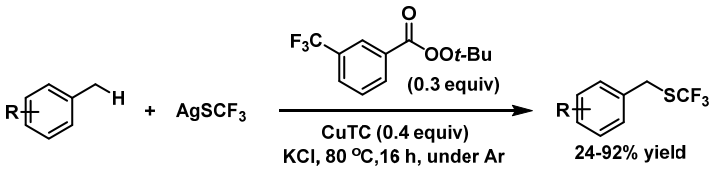
Scheme 51



Scheme 52



Scheme 53



Scheme 54

The catalytic reaction cycle underwent oxidative addition of R_2N-OBz to a Pd0/PAr_3 catalyst and then Pd-NR_2 intermediate was produced by cleavage of a Csp^3-H bond. The reaction smoothly proceeded and generated synthetic precursors for novel β-amino acids in 52-78% yields without external oxidants. The electron-deficient triaryl-phosphine was significant for the realization of Csp^3-H amination reaction.

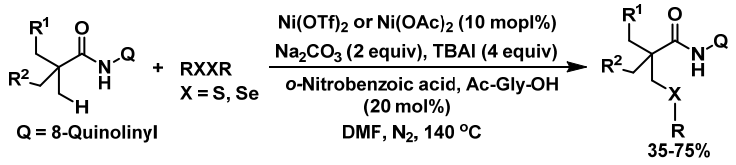
2.2.2. C-O bond formations

In 2014, Zhao *et al.* [60] developed a useful strategy for the synthesis of α-acyloxy ethers through iron-catalyzed cross-dehydrogenative coupling esterification of unactive Csp^3-H bonds with carboxylic acids employing di-*tert*-butyl peroxide (DTBP) as the oxidant (Scheme 51). The protocol tolerated various cyclic ether substrates to react with aromatic acids, and resulting in the corresponding products α-acyloxy ethers with up to 98% yields. A proposed mechanism from an intermolecular competing kinetic isotope effect (KIE) experiment was exhibited in Scheme 52.

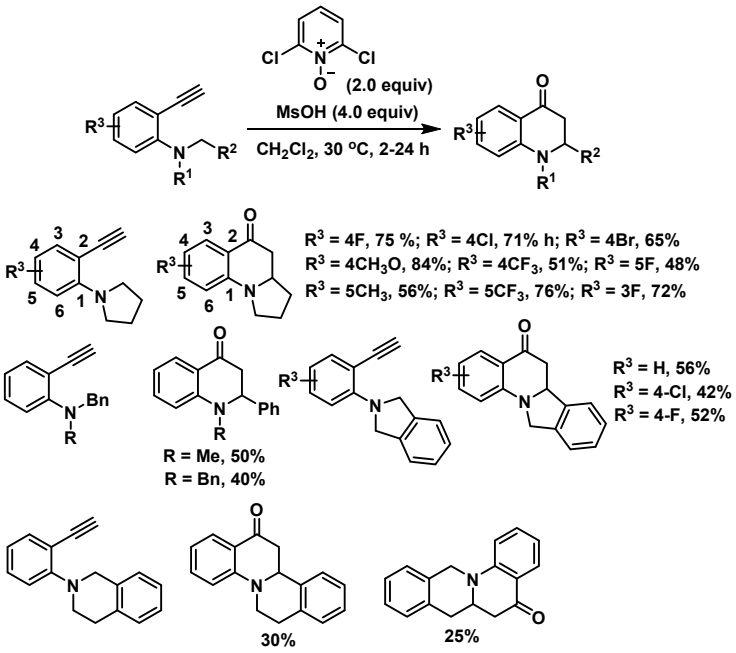
Luo *et al.* [61] achieved a simple method for the direct construction of alkoxyamine derivatives from easily available 1,3-dicarbonyl with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and its derivatives through copper-catalyzed oxidative activation of Csp^3-H bond compounds (Scheme 53). This protocol provided a practical green and useful approach for the one-pot synthesis of alkoxyamines with 75-95% yields which was properly applied to the preparation of quaternary α-hydroxy acid derivatives.

2.2.3. C-S bond formations

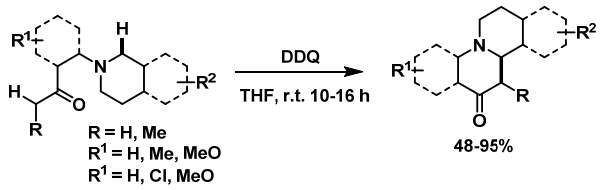
In 2014, Chen *et al.* [62] developed a copper-catalyzed trifluoromethylthiolation of benzylic Csp^3-H bonds through indirected oxidative C-H activation employing t-BuOOBz(3-CF_3) as the oxidant and $AgSCF_3$/KCl as the active trifluoromethylthio source (Scheme 54). The process gave a simple and efficient method for the synthesis of various benzyl trifluoromethyl sulfides with 24-92 yields.



Scheme 55



Scheme 56



Scheme 57

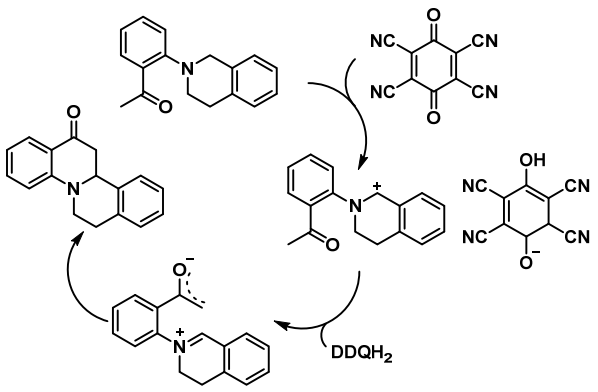
In 2015, Zhang and coworkers [63] developed an efficient process for nickel-catalyzed β-thioetherification of unactivated Csp^3-H bond of propionamides with the assistance of 8-aminoquinoline produced the β-thio carboxylic acid derivatives in 35-75% yields (Scheme 55). The thioetherification reaction exhibited high regioselectivity and functional-group compatibility, resulting in the successful construction of C-S bonds via the direct coupling of disulfide with unactivated Csp^3-H bonds.

3. Metal-free Csp^3-H functionalizations

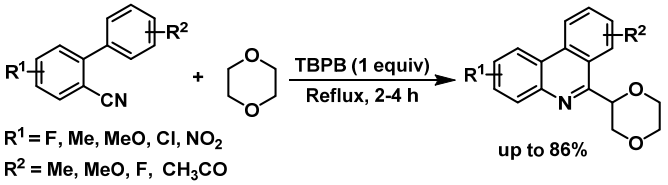
Although transitional metal-catalyzed Csp^3-H bond functionalization have made considerable advances in the past several decades, More and more interests have been attracted in the development of environmental friendly and efficient non-metallic oxidative system for functionalization Csp^3-H bond.

3.1. C-C bond formations

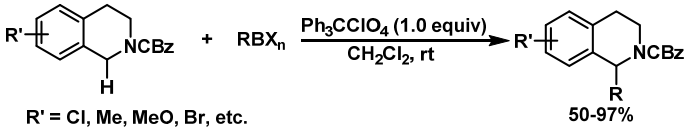
In 2012, Chen *et al.* [64] achieved a direct and practical pyridine-*N*-oxide-mediated ring-closing reaction via Csp^3-H functionalization of inertial aryl alkynes under metal-free condition (Scheme 56). In this reaction, the Brösted acid MsOH could efficiently promoted the intramolecularly cyclization reaction producing the resulting products with 25-84% yields. Zhang *et al.* [65] developed an original and practical strategy for the formation of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)-mediated Csp^3-Csp^3 bonds via intramolecular oxidative cross-coupling reaction under mild conditions (Scheme 57). The economical approach mediated by (DDQ) provided the various tetrahydroquinoline derivatives with 48-95% yields. A proposed mechanism for intramolecular oxidative coupling reaction under metal-free conditions was exhibited in Scheme 58.



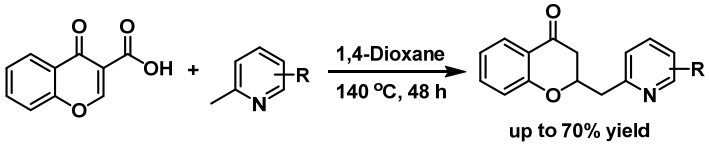
Scheme 58



Scheme 59



Scheme 60



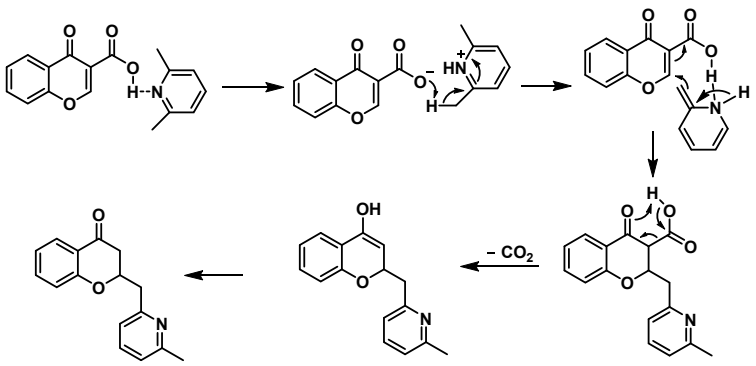
Scheme 61

In 2014, Cao *et al.* [66] developed a pratical approach for the formation of 6-alkyl phenanthridines via the 2-isocyanobiaryl insertion with 1,4-dioxane mediated by *tert*-butyl peroxybenzoate (Scheme 59). The process formed two new C-C bonds through a sequential functionalization of Csp^3-H/ Csp^2-H bond giving the corresponding products in up to 86% yield under metal-free conditions. Liu and coworkers [67] reported an efficient Ph_3CClO_4-promoted Csp^3-H functionalization for the construction of various α-substituted *N*-benzyl and *N*-allyl carbamates under ambient temperature and metal-free condition (Scheme 60). The approach showed excellent functional-group tolerance with respect to both *N*-carbamates and nucleophile partners offering the resulting products with moderate to excellent yields.

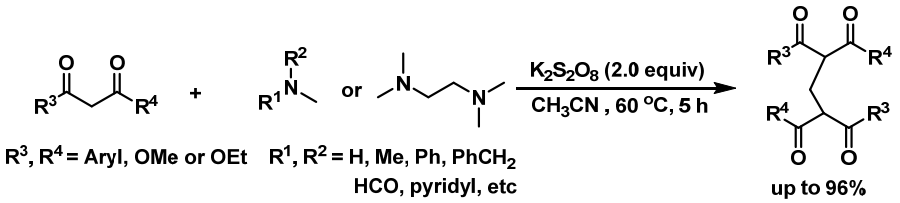
Xiao and coworkers [68] developed an efficient and innovative strategy for the synthesis of biologically significant azaarene 2-substituted chromanones via tandem Csp^3-H functionalization/ decarboxylation of 4-oxo-4*H*-chromene-3-carboxylic acid with 2-alkylazaarenes (Scheme 61). The reaction tolerated a variety of electronically and sterically diverse azaarenes and transformed to coupled products with moderate to good yields. A proposed mechanism was exhibited in Scheme 62.

Yuan and coworkers [69] developed a novel methylenation reaction for synthesis of methylene-bridged bis-1,3-dicarbonyl compounds through oxidative Csp^3-H activation and C-N cleavage of *N*-methyl amines under transition-metal-free (Scheme 63). The process exhibited outstanding advantages including employing cheap oxidant and methylene source, convenient operational, wild reaction conditions and avoiding the use of transition metal catalyst. Long and coworkers [70] developed a economical and green intramolecular oxidative Csp^3-H/Csp^3-H coupling reaction for the construction of 2-arylquinolin-4(1*H*)-ones under metal-free condition (Scheme 64). The oxidative Mannich reaction directly produced a variety of 2-arylquinolin-4(1*H*)-ones with up to 98% yield from simple readily available *N*-arylmethyl-2-aminophenyl ketone using TEMPO as the oxidant and KO*t*Bu as the base.

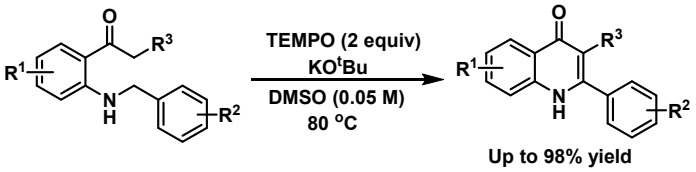
Han and coworker [71] described a radical alkylation reaction of α,α-diaryl allylic alcohols with simple alkanes through oxidative Csp^3-H bond functionalization of alkanes and alkylation using di-*tert*-butyl peroxide as the oxidant (Scheme 65). The reaction smoothly proceeded with a wide range of simple alkane substrates and α,α-diaryl allylic alcohols and generated the resulting products α-aryl-β-alkylated carbonyl ketones in up to 93% yield.



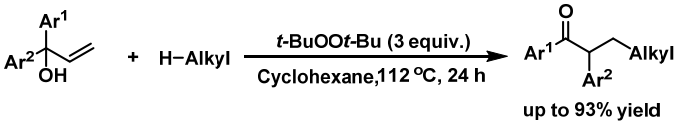
Scheme 62



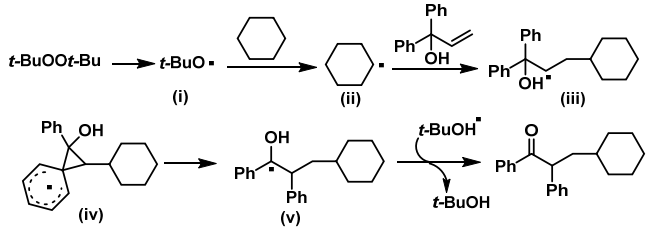
Scheme 63



Scheme 64



Scheme 65

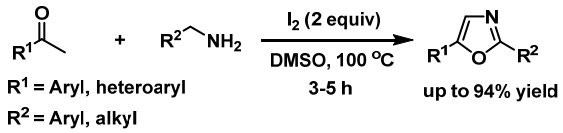


Scheme 66

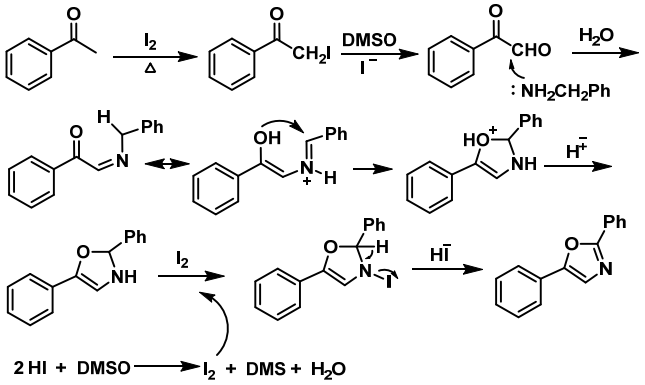
The reaction still involved the formation of new C(Ar)-Csp^3 and Csp^3-Csp^3 bond in one step through functionalization of Csp^3-H bond and cascade process of 1,2-aryl migration. A proposed catalytic cycle for the rearrangement is showed in Scheme 66. Initially, *tert*-butoxy radical intermediate (i) was generated by homolysis of DTBP. Secondly, the reaction of intermediate (i) and cyclohexane produced a cyclohexane radical intermediate (ii) which reacted with allylic alcohol to afford radical (iii). Next, migration of the aryl group through spiro[2,5]octadienyl radical (iv) formed radical intermediate (v). Finally, the intermediate E reacted with tert-butoxy radical intermediate A resulting in the goal product and *t*-BuOH.

3.2. C-Heteroatom bond formations

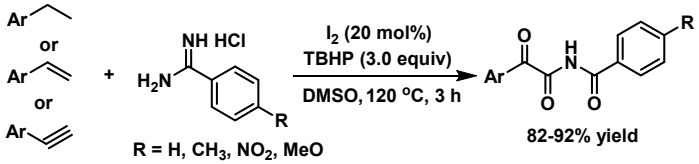
In 2013, Gao *et al.* [72] developed an efficient strategy for the synthesis of 2,5-disubstituted oxazoles via Csp^3-H functionalization promoted by I_2 from easily available methyl ketones and benzylamines under metal free and peroxide-free conditions (Scheme 67).



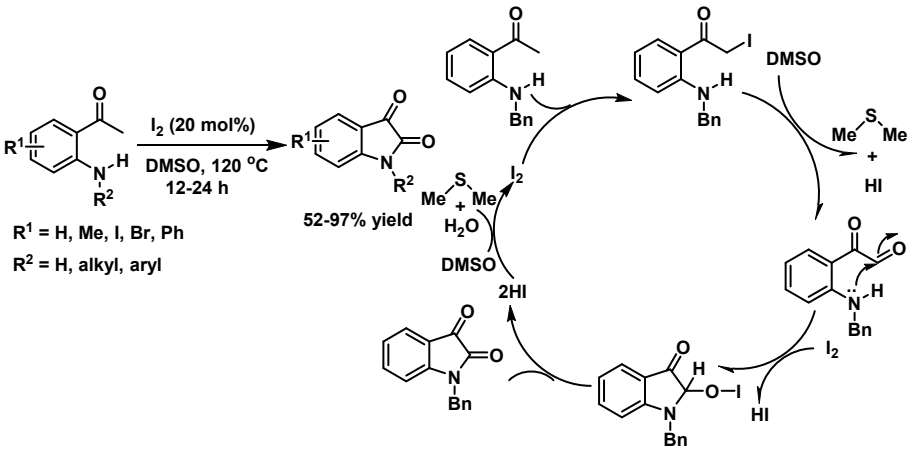
Scheme 67



Scheme 68



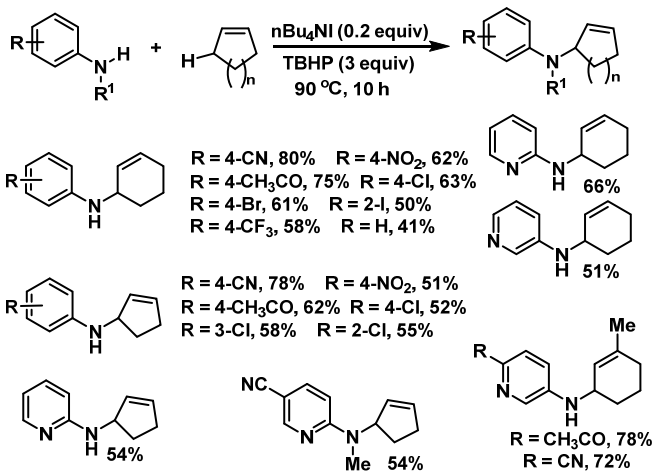
Scheme 69



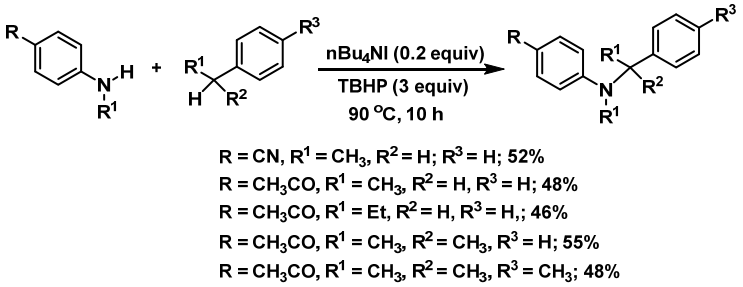
Scheme 70

The reaction involved dual functionalization of α-Csp^3-H of carbonyl and α-Csp^3-H of nitrogen atom and produced the corresponding oxazole derivatives with up to 94% yield. A plausible mechanism for I_2-promoted dual Csp^3-H functionalization of acetophenone and benzylamine was proposed in Scheme 68.

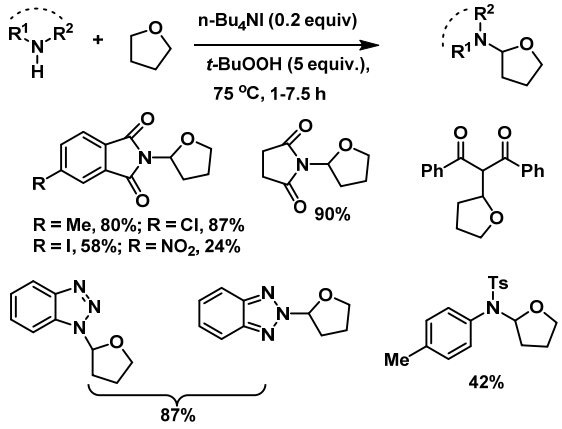
Chaskar and coworkers [73] developed a simple synthetic protocol for iodine-catalyzed synthesis α-ketoimide from diverse substrates via sp^3, sp^2 and sp C-H functionalization subsequent oxidative cross coupling with benzamidines hydrochloride under metal-free conditions (Scheme 69). This process showed eminent advantages, such as, good functional group tolerance, inexpensive catalyst, operational simplicity and good to excellent yields of the products. Rajeshkumar *et al.* [74] described a highly applicant molecular iodine-catalyzed Csp^3-H oxidation and intramolecular C-N bond formation of 2'-aminoacetophenones for the synthesis of isatins under metal and peroxide free reaction conditions. The reaction provided corresponding products isatins in excellent yields with tolerance to a range of substrates. The proposed mechanism was exhibited in Scheme 70.



Scheme 71



Scheme 72

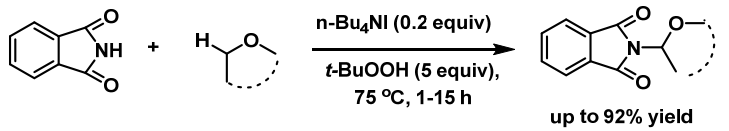


Scheme 73

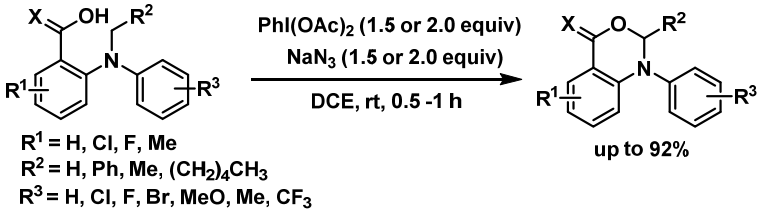
Zhang *et al.* [75] described a practical and direct amination of allylic and benzylic Csp^3-H with anilines mediated by n-Bu_4NI/TBHP for the formation of *N*-substituted anilines under metal-free conditions (Scheme 71 and 72). The novel approach provided a straightforward efficient pathway for the synthesis various *N*-substituted anilines for easily available substrates.

Du and coworkers [76] developed a direct amination of various alkyl ethers with different amines for constructing hemiaminal ether skeletons promoted by *n*-Bu_4NI/*t*-BuOOH (Scheme 73 and 74). The organocatalytic amination of alkyl ethers involved intermolecular oxidative Csp^3-N bond formation employing *t*-BuOOH as oxidant and *n*-Bu_4NI as catalyst under metal-free and wild reaction conditions.

Du and coworkers [77] described an intramolecular Csp^3-O bond formation through intramolecularly functionalizing Csp^3-H bonds adjacent to the nitrogen in *N*,*N*-diaryl tertiary amines mediated by $PhI(OAc)_2/NaN_3$ (Scheme 75). The protocol provided a convenient path for the direct synthesis of a series of 1,2-dihydro-(4*H*)-3,1-benzoxazin-4-one and 1,2-dihydro-(4*H*)-3,1-benzoxazine derivatives in up to 92% yield under mild reaction conditions.



Scheme 74



Scheme 75

Although considerable advances in the field of Csp³-H functionalization under metal-free conditions have been achieved in recent years, the development of more efficient and versatile strategies for functionalization Csp³-H bond is a more challenging task and represents an significant trends in synthetic chemistry. In particular, more efforts should be paid in the exploring novel catalytic oxidative systems and further studies on reaction mechanism.

4. Conclusions

Functionalization Csp³-H bond represents one of the most powerful approaches for the direct and selective transformation of ubiquitous C-H bonds into various functional groups in the field of organic synthesis. Most of Csp³-H bond functionalizations are mainly based on the applications of transition metal compounds and radical systems as initiators. Great efforts have been made in the development of direct Csp³-H bond functionalizations through oxidative coupling and radical reactions in recent decades. Although Csp³-H bond functionalization has steadily acquired a great deal of inspiring acheivements in recent years, new challenges and opportunities arise along with these researches. For example, the most common strategies for the transformations need to be expanded less substrate-dependent and utilization of a directing group. Most proposed reaction mechanisms are only preliminary speculations without further experimental and theoretical evidences. The highly region-selective and enantioselective Csp³-H functionalization may still remain significant challenges for impeding widespread application of the reactions. An increasing demand for green, metal-free and highly region- or enantio-selective Csp³-H functionalization will represent current directions in the field. We believe the ideal Csp³-H functionalization is only just beginning to be realized and will undoubtedly continue to acquire more satifactory achievements in the near future.

Acknowledgements

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