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(REVIEW ARTICLE)

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Review for metal and organocatalysis of heterocyclic C-H functionalization

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Abstract

Over the last few decades, significant efforts have been put forth towards the C–H bond group functionalization by transition-metalcatalysis and organocatalysis. Several efficient strategies to convert C-H bond to other groups C-C, C-N, C-O bonds have been implemented. The most attractive C-H bond functionalization was the C-H heterocyclic compounds activation that is practical method in organic synthesis. The new C–C, C–N and C–O bond as formed from the C-H bond activation by two diverse ways metal catalysis and/or organocatalysis. The most important is the synthesis of new bioactive heterocyclic compounds by easy and less expensive materials. In this review, we will cover most of the syntheses of heterocyclic derivatives by the functionalization of C-H bond in metal and organocatalytic reagents.

Keywords: Heterocyclic; C-H activation; Metal catalysis; C-H activation; C-H activation organocatalysis.

1. Introduction

Direct C–H bond transformation of saturated alkanes or hydrocarbons sp3 hybridized has become a challenging goal in modern synthetic organic chemistry. This functionalization draws the attention of chemists for almost a century [1-3]. C-H activation was one of the importance's in synthetic organic chemistry in either academic or industry in the last few decades [1-8]. Several methods exist for synthesis and formation of C–C, C–N and C–O bonds possessing functionalization of sp3 C-H bond. The functionalization of inactive C-H bond sp3 hybridized start by the C-H free radical activation of methane to methanol using high temperature and expensive material [7]. The reaction of benzene with mercury (II) acetate was report as the first metal catalyst of the C–H activation by Otto Dimroth in 1902 [4]. The activation of C–H bond to synthesis new of heterocyclic compounds containing nitrogen atoms is important in many pharmaceutical and biologically active compounds. However, the organic synthetic researchers have new strategy in the synthetic rout of organic compounds from the functionalization of C-H bond. Most reports focus on the sp^3, sp^2 C–H bond activation, by using quantities of transition metal activation or transition metal-catalysis and organocatalysis reagents. In the past few decades, many methods have been developed to directly functionalize C–H bonds, often involving the late transition metals or noble metals [9-22]. C–H activation mainly achieve through four metal-mediated pathways: oxidative addition, electrophilic substitution, σ–bond metathesis and metal-associat ccurre/nitrene/oxo insertion [23-26]. The modern methods focus on the organocatalytic reagents (Metal free-catalysis) in the C–H bond activation [27-35]. Moreover, the organocatalytic methods are most important, because methods involving such metal-catalysts are often expensive, another advantage must be the requirement to purify the organic compounds from metallic impurities from the products could be avoided; an important issue in the synthesis of pharmaceutical compounds (Figure 1). Furthermore, the C–H functionalization of sp3 C-H hybridized by organic complexes under visible light activation has a powerful tool in redox reaction chemistry (Figure 2) [36-46].

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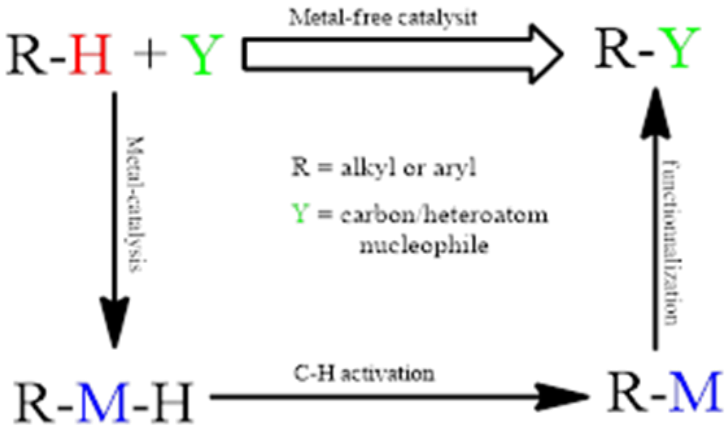


Figure 1 Metal and organocatalytic activation

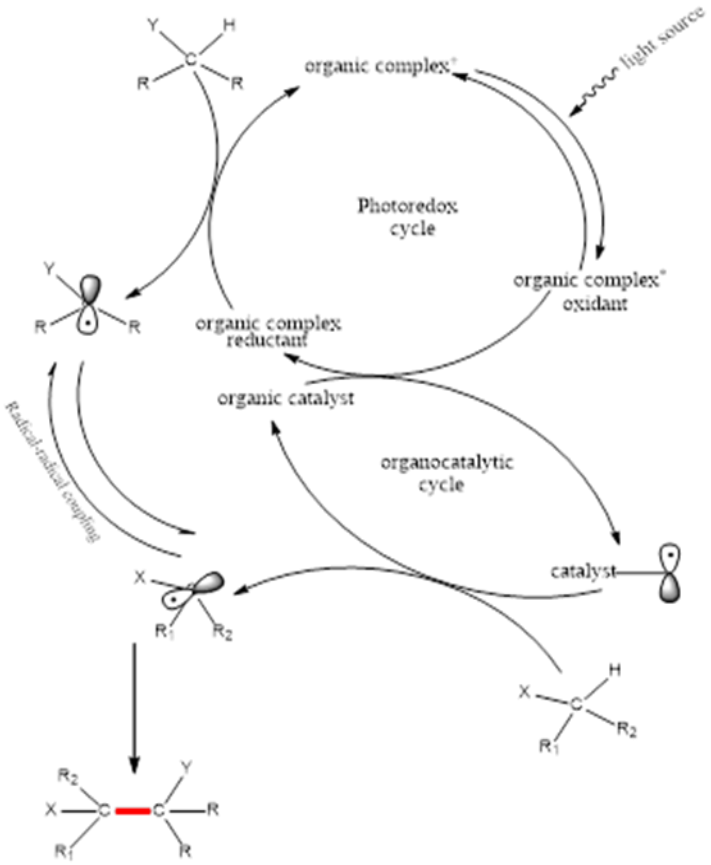
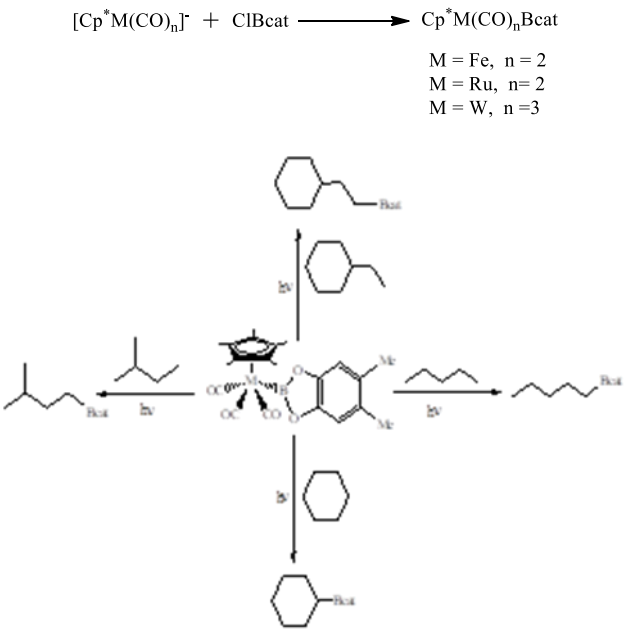


Figure 2 Visible Light Activation Mechanism

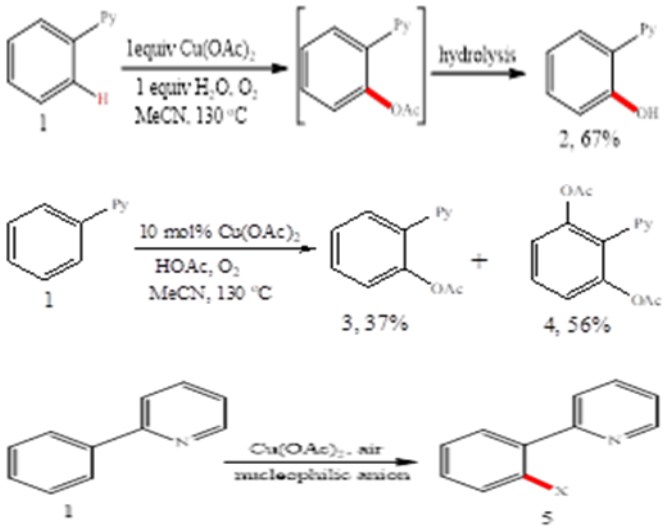
2. Direct c-h bond functionalization by means of transition metal-catalysis

In few past decades, the transition metal complexes were used in the activation of alkanes C–H bond in C–H oxidative addition [47], electrophilic cleavage of C–H bonds, and oxidation [48-49]. **John F. H.** and coworkers explained the transition metal complex reactions in the activation of C–H alkanes by using of simple transition-metal complexes of Cp*M(CO), BR, [Cp* = C(CH)] containing an electrophilic, covalently bound main-group ligand react with alkanes. The reactions produce alkylboronate esters, which are common reagents in organic synthesis [11]. (Scheme 1)

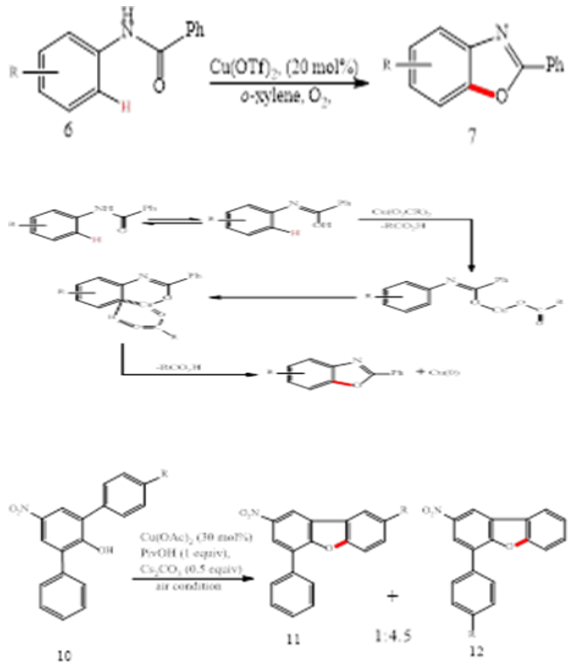


2.1. C-H bond oxidation

Cu, Pd0, PdII, PdIV, Ru and Ir were the famous metal catalysis. This metal catalysis used in the C-H bond activation [50-52]. The oxidation of C-H bond was used Cu (II) - catalyzed under air O_2 condition. The activation of C–H bond using Cu $(OAc)_2$ in presence of H_2O and O_2 could be direct oxidation of aryl C–H bond 6 which direct into ortho-position 7. Furthermore, the initial use of other copper sources, CuX_2, or a combination of Cu $(OAc)_2$ and nucleophilic anions could be equally effective [50-52]. (Scheme 2)

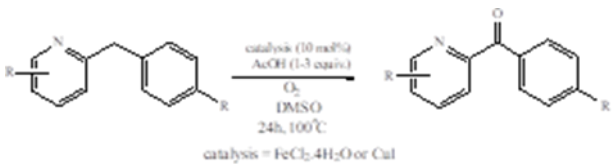


The low-temperature oxidation of methane, ethane, and butane are used in the high catalytic bimetallic system copper chloride and metallic palladium to have methanol [54,55]. The intermolecular oxidation of C–H bond by using copper-catalysis, Hideko and coworkers were explained the aryl intermolecular oxidation of C–H bond by using of $Cu(Otf)_2$ (20 mol%) at 140 xylene under an atmosphere of O_2. The oxidation of N–phenylbenzamide derivatives 6 by using $Cu(Otf)_2$ under oxygen condition to have benzooxazole 12 derivatives in high yield [53]. On the other hand, the intermolecular oxidation also can be done by the $CuBr_2$ is carried out in presence of Cs_2CO_3 and PivOH are employed as additives under an air atmosphere [54,55]. (Scheme 3)

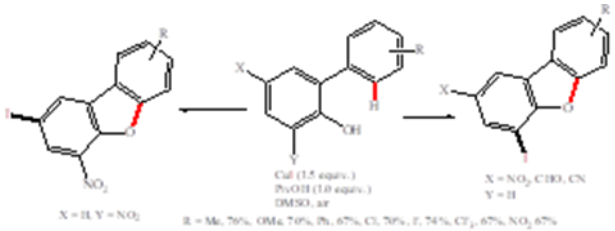


(Scheme 3)

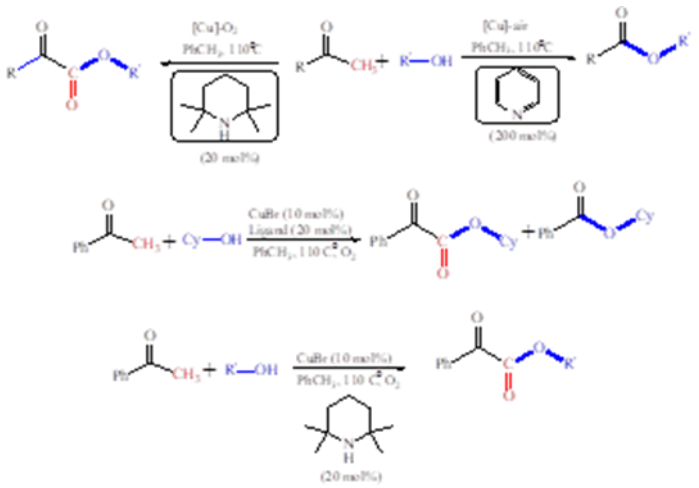
Most oxidation of the inactive Sp^3 C–H such as alcohols, ketones, aldehydes and carboxylic acids was created by quantities of oxyanions of toxic metals like Mn(VII) and Cr(VI), [56,57], the amount of the toxic waste of these oxidants products and limitations on their use by new legislation [58] has prompted scientists to search for more sustainable oxidation methods. In the early article Bert U. W. and co-workers used Cu and Fe catalysis (CuI and $FeCl_2{\cdot}4H_2O$) as oxidant the regioisomeric 4-benzylpyridines using $FeCl_2{\cdot}4H_2O$ as the catalyst. Under the standard conditions previously were developed for 2-benzylpyridines these substrates smoothly oxidized give the corresponding ketones in moderate to good yields [59].



Qiang Zhu and coworkers used the copper iodide in synthesis of 2- or 4-iododibenzofurans in the presence of oxygen at 140 °C 24h; and PivOH in good to moderate yields [60].

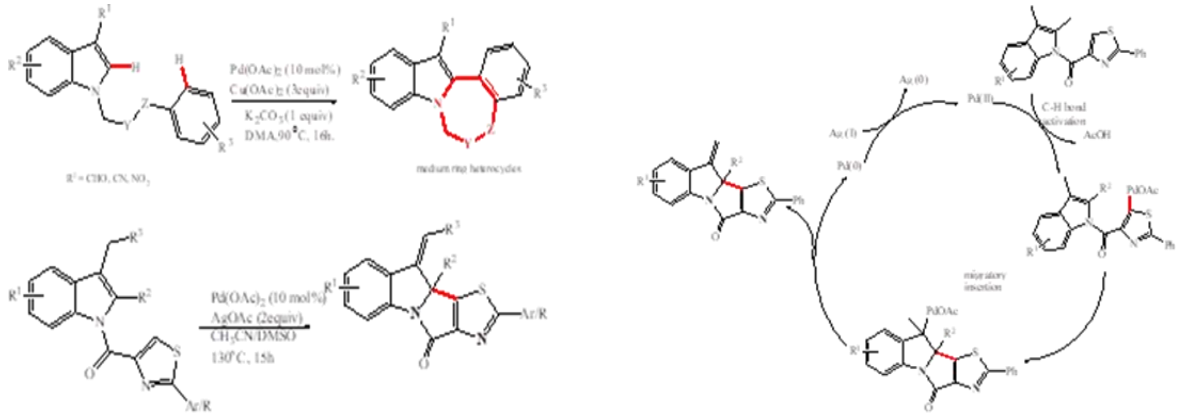


Ning Jiao and coworker's explained Chemo selective oxidative coupling of methyl ketones by using TEMP and copper cocatalyzed with alcohol, the oxidation of methyl ketones by using copper catalyst in the presence of oxygen to have expected products [61,62]. (Scheme 4)



(Scheme 4)

The intermolecular oxidation of C-H coupling of indole derivatives and heteroarenes for medium-ring was reported by **Greaney** and coworkers [63-66]. Intermolecular oxidation by using palladium (II) metal catalysis was explained by **Aijun Lin** and coworkers [67]. (Scheme 5)



(Scheme 5)

2.2. Heterocyclic C-N bonds formation

Heterocyclic compounds are highly important because of their abundance in numerous natural products such as vitamins [68] and alkaloids [69] as well as pharmaceuticals of biological activity [70] and electroactive materials [71]. From this point the synthesis of C–N or C–O by the activation of C–H bond is very important. Xin W. and co-worker [72] synthesis new heterocyclic by the amination of five member heterocyclic ring with Metal or organocatalysis. To optimize the reaction of 2-Acetylfuran **10** (0.5 mmol) and saccharin (2.0 equiv) as substrates, under atmospheric conditions in the presence of CuCl (10 mol%) and select Fluor (2.0 equiv) at 120 °C for 6 h with nitro methane (CH_3NO_2) as the solvent, the desired imidation product 1-(5-aminofuran-2-yl)ethanone **11** was obtained in 55 % yield (Table 1, entry 1). The yield of **11** could be increased to 71 % by employing $Cu(OAc)_2$ as the catalyst (Table 1, entry 4). No reaction was observed in the absence of copper salts (Table 1, entry 5). Other oxidants such as $Ce(SO_4)_2$,$K_2S_2O_8$ Based, and $PhI(OAc)_2$ did not perform well (Table 1). After detailed screening, tert-butyl-hydroperoxide (TBHP) was found to be the best oxidant and the desired 2-imidation product **35**. When the Copper salt catalyst was substituted with organocatalytic nBuNI; satisfactorily, the b-imidation product **36** could be obtained in 89 % yield (Table 1). The use of nBu_4NBr, KI, and I_2 instead of nBuNI decreased the yields of **35** to 42 %, 69 %, and 0 %, respectively (Table 1)

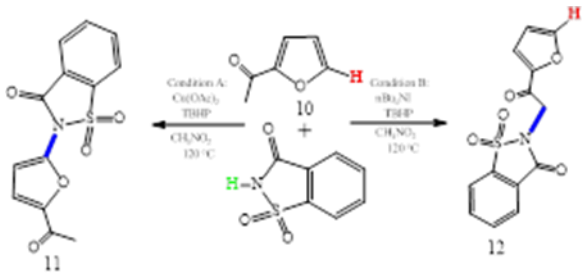
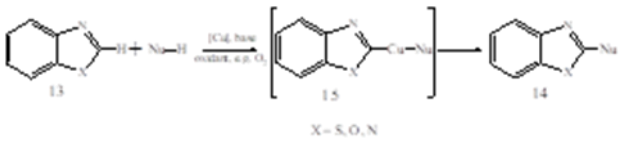


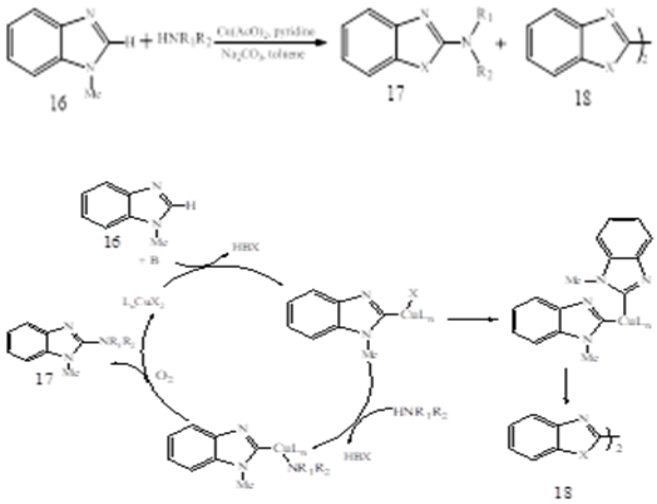
Table 1 Optimization of the reaction conditions

Entry	Catalyst	Oxidant	Yield 11	Yield 12
1	CuCl	Selectfluor	55	0
2	CuBr	Selectfluor	47	0
3	$Cu(Otf)_2$	Selectfluor	61	0
4	$Cu(Oac)_2$	Selectfluor	71	0
5	No	Selectfluor	0	0
6	$Cu(Oac)_2$	$Ce(SO_4)_2$	0	0
7	$Cu(Oac)_2$	$K_2S_2O_8$	0	0
8	$Cu(Oac)_2$	$PhI(Oac)_2$	23	0
9	$Cu(Oac)_2$	TBHP	91	0
10	nBu_4NI	TBHP	0	89
11	nBu_4NBr	TBHP	0	42
12	KI	TBHP	0	69
13	I_2	TBHP	0	0
14	nBu_4NI	DTBP	0	83

Direct heterocyclic C-H bond amination was carried using aerobic oxidation in presence of metal-catalysis. The copper catalysis in aerobic condition was used in the amination of heterocyclic inactive sp^3 C–H in presence of K_2CO_3. The aerobic cross-coupling of heterocyclic (**13**) with nucleophiles would lead to the 2-amido-substituted heterocyclic (**14**) through the organocopper intermediate (**15**) in analogy to the Chan-Lam oxidative coupling of arylboronic acids and nucleophiles [73-83].



The oxidation reaction of N-methylbenzimidazole (**16**) to obtain pyrrolidinone (**17**) was carried out in the presence of catalytic copper salts and less than 1 atom of O_2. In the initial screening of Cu sources, BrØnsted bases, and solvents, optimal results were observed with 0.2 equiv of $Cu(OAc)_2$ and 2 equi of Na_2CO_3 with pyridine as additive in toluene [88]. (Scheme 6)



(Scheme 6)

In the other way the intermolecular amination was obtained by using copper salt catalysis. The Cu–catalyzed sp^3 C–H aminativecyclization of 2-alkyl-N-arylbenzamides has been developed by using di-tert-butyl peroxide, and various substituted substrates were found to be suitable for the reaction. This process provides a powerful approach to synthesize N-aryl-isoindolinones (table 2) [89].

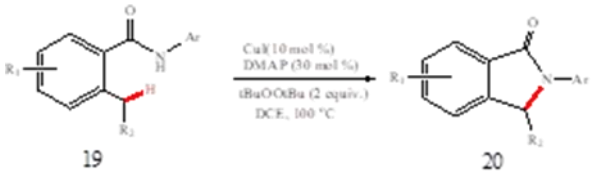
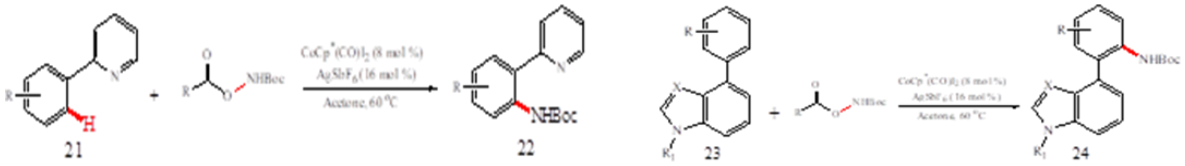


Table 2 reaction conditions with the yield

Entry	Cu (mol %)	Ligand (mol %)	Solvent	Yield (%)
1	CuI (20)	none	benzen	trace
2	CuI (20)	Phen (40)	benzen	15
3	CuI (20)	bipy (40)	benzen	13
4	CuI (20)	pyridine (40)	benzen	17
5	CuI (20)	pyridine (40)	toluene	22
6	CuI (20)	pyridine (40)	DMSO	trace
7	CuI (20)	pyridine (40)	DCE	57
8	$Cu(Oac)_2$ (20)	pyridine (40)	DCE	26
9	CuBr (20)	pyridine (40)	DCE	46
10	CuBr (20)	pyridine (40)	DCE	47
11	CuI (20)	4-MeO-Py (40)	DCE	65
12	CuI (20)	DMAP (40)	DCE	86
13	CuI (10)	DMAP (3)	DCE	85

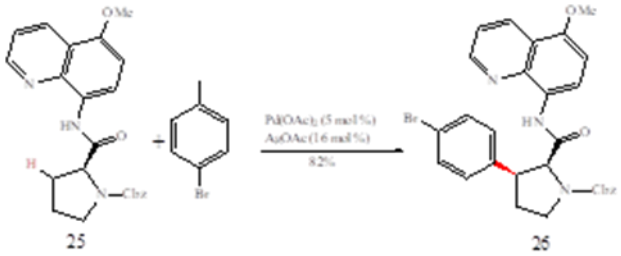
The direct C-H amination of arenes was carried out by cobalt (III)-catalysis and O-acylcarbamates as a convenient amino source as imino source. The reaction of 2-phenylpyridine **24** was reacted with aroyloxy carbamate as an amidating

reagent when CoCp*(CO)I_2 (8 mol %) employed as a catalyst in the presence of $AgSbF_6$ (16 mol %) was in acetone at 60 °C. Direct C–H Amidation of 6-Arylpurine Derivatives was obtained by using N-Boc moiety and the cobalt (III)-catalysis [90-92]. (Scheme 7)



(Scheme 7)

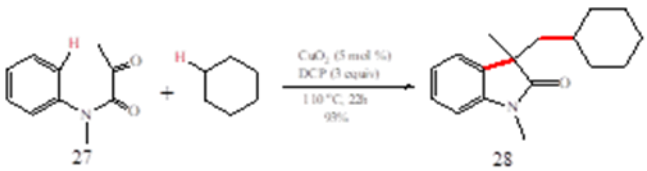
Recently, the Heterocyclic sp^3 C–H bond functionalization was obtained with the palladium catalyst. The reaction of pyrrolidine derivative **25** with *p*-substituted toluene to have C–C bond 3-arylated pyrrolidine **26** by using $Pd(Oac)_2$ (5 mol %) [91-92]. (Scheme 8)



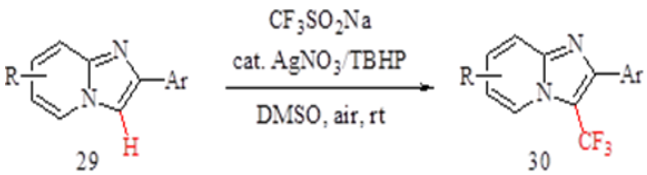
(Scheme 8)

2.3. C-C bond formation

The heterocyclic C-C bond formation by the sp^3 C–H activation using metal catalysis was obtained by **Liu** and co-workers, [93] by the C–H bond functionalization of the alkylarylation of alkenes with simple alkanes in the presence of dicumyl peroxide and a copper salt as a catalyst, the unsaturated benzamide **27** reacts with alkanes, to form the oxindole [94]. The oxy radical abstracts a hydrogen from the alkane and the resulting alkyl radical adds to the unsaturated amide to generate a new radical that reacts intramolecularly with the benzene ring to ultimately form **28**.

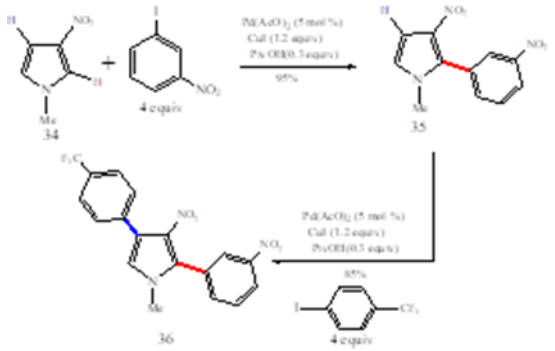


The oxidation of the imidazopyridine 29 was carried out by using of Langlois reagent and a silver-catalyzed oxidative trifluoromethylation to obtain the trifluoromethyl derivative 30 [95]. tert-butyl hydrogen peroxide (TBHP) was used as the oxidant and the silver catalyst was used as the radical abstract from the trifluoromethyl radical.



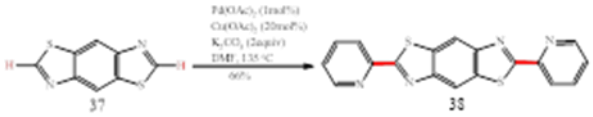
(Scheme 9)

For more reactions of regioselective of heterocyclic C-H bond activation Yamaguchi and co-workers used the palladium and/or copper salts as catalyst, [96] the regioselective functionalization of 4-nitropyrazoles, Palladium- or nickel-catalyzed conditions were curried for the selective arylation at C–5, as illustrated for the conversion of the imidazole 34 to 35 (Scheme 8). Under more activation conditions with palladium or copper catalysis, a second arylation was obtained to generate the triaryl derivative 36 [97].

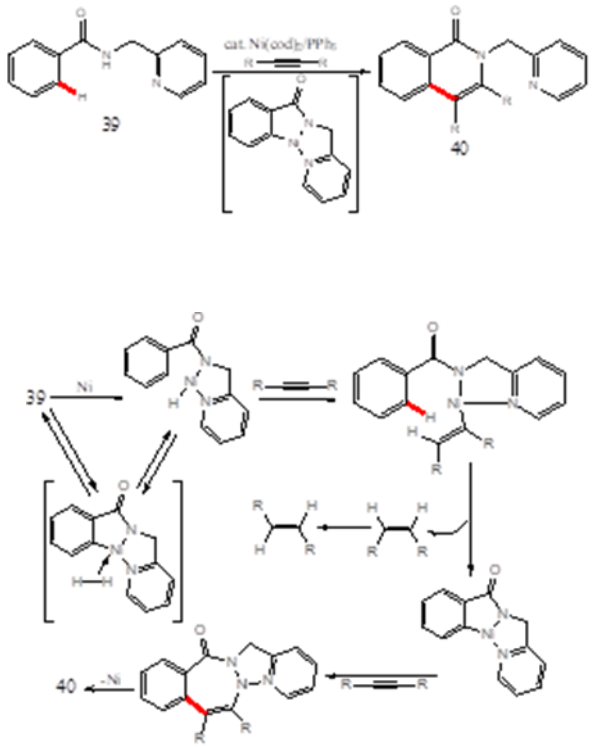


(Scheme 9)

Thus, the heterocyclic C–H functionalization was directed to synthesize bioactive and pharmaceutical compounds. The arylation of of benzobisthiazole derivatives 37 converted to the 38 by using palladium and copper salts catalysis. This result is useful in building blocks of bioactive heterocyclic compounds [98].



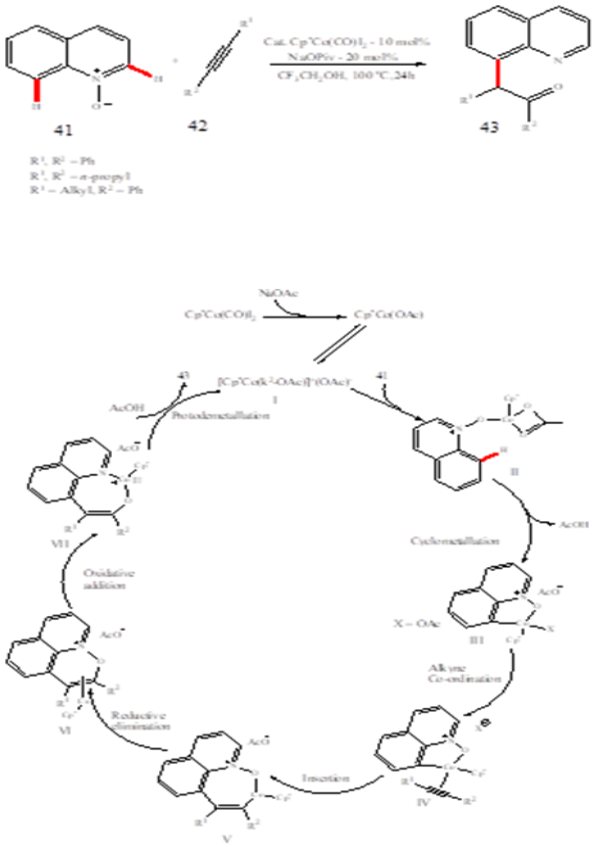
The aromatic C-H activation by using nickel complex [99] was recently reported by Naoto Chatani [100]. Naoto Chatani used Ni catalyzed transformation of ortho C-H bonds utilizing, such as oxidative cycloaddition of aromatic amides with alkynes, has been achieved. The Ni-catalyzed transformation of such ortho C-H bonds utilizing chelation assistance (Scheme 9). The reaction of amide 39 with 4-octyne in the presence of Ni(cod)2/PPh3 as the catalyst in toluene at 130 °C for 18 h gave isoquinolone derivative 40 in 28% yield as a single product longer reaction time (3 days) resulted in an increase in the product yield to 66%.



(Scheme 10)

Coupling of quinoline N-oxide with internal alkynes via C-H activation was reported by Nagaraju B; by using Cp*Co(III) catalyzed. Quinoline-N-oxide 41 as a model substrate and diphenylacetylene 42 in the presence of Cp*Co(CO)I2 (10

mol%) and NaOAc (20 mol%) in TFE (Trifluoroethanol) at 100°C for 24h give the expected product 43 [101]. (Scheme 11)



(Scheme 11)

3. Organocatalysis (metal free) activation of C-H bond

Most of the reported C–H bond functionalization was restricted to the metal-mediated approaches. Recently, Most scientists direct to replace the rare and toxic metal catalysis with organocatalysis such as BrØnsted acids, thiourea derivatives catalysts, tetra-alkylammonium iodide catalysts, etc., (Chen, et al., 2011). Thus, these organocatalysis can be synthesized from cheap materials, and direct to chiral compounds with high efficient and removed from the products easily than the metal catalysis.

3.1. C-H bond oxidation

Most reports in the C-H bond oxidation were used rare or toxic metal catalysis such as CuI, Fe_2SO_4, $K_2S_2O_8$, AgOTf, $Cu(OAc)_2$, $K_3Fe(CN)_6$, Fe(acac)3, PdIV, Ru, Ir ……etc., [104-112]. The first report in the C (sp3)-H functionalization with metal free catalyst in the direct transformation of hydrocarbons and N-hydroxyphthalimide (NHPI) to alkyloxyamines by using n-Bu_4NI catalyst was reported by Yunhe Lv [113-115]. The reaction of hydrocarbons with NHPI in the presence of n-Bu4NI (0.2 equiv.) as catalyst and tert-butyl hydroperoxide (TBHP, 2 equiv.) as oxidant exhibited excellent catalytic activity and gave the desired product in good yield table 3.

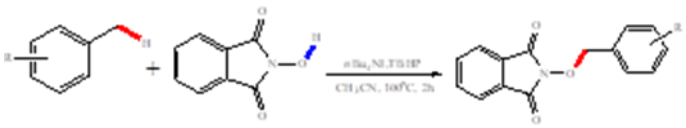


Table 3 reaction conditions with the yield

Entry	Oxidant	Catalyst	Solvent	T (°C)	Yieldc (%)
1	TBHP	n-Bu_4NI	CH_3CN 130	85	85
2	TBHP	n-Bu_4NI	EtOAc	130	73
3	TBHP	n-Bu_4NI	DCM	130	55
4	TBHP	KI	CH_3CN	130	25
5	TBHP	NH_4I	CH_3CN	130	28
6	TBHP	I_2	CH_3CN	130	0
7	TBHP	NIS	CH_3CN	13	Trace
8	$Na_2S_2O_8$	n-Bu_4NI	CH_3CN	130	0
9	TBHP	n-Bu_4NI	CH_3CN	130	Trace
10	H_2O_2	n-Bu_4NI	CH_3CN	130	0
11	-	n-Bu_4NI	CH_3CN	130	Trace
12	TBHP	-	CH_3CN	130	Trace
13	TBHP	n-Bu_4NI	CH_3CN	100	92
14	TBHP	n-Bu_4NI	CH_3CN	90	81
15	TBHP	n-Bu_4NI	CH3CN	70	52

The formation of C-O, C-N and C=N via the C(sp3)-H activation by means of organocatalytic (metal free) reagents was reported by Chengjian Zhu and coauthors [116-119]., by the reaction of active methylene compounds and benzyl amine derivatives in the presence of n-Bu4NI as an organocatalyst and TBHP as an oxidant could initiate the reaction at room temperature. The reaction of ethyl acetoacetate 43 with benzylamine 44 in the presence of n-Bu4NI catalyst (20 mol%), and an oxidant (4.0 equiv.) to have the product 45 with good yield as explained in table 4

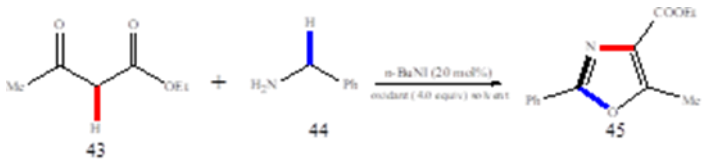
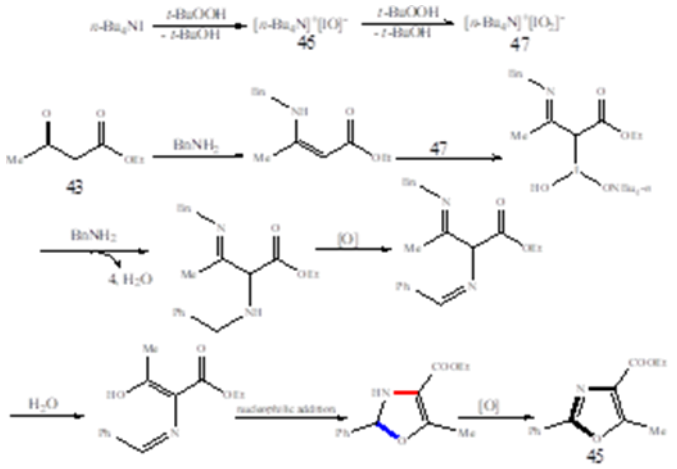


Table 4 reaction conditions with the yield

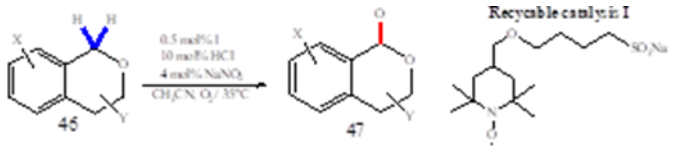
Entry	Catalyst	Solvent	Oxidant	Time/h	Yieldc(%)
1	n-Bu_4NI	EtOAc	TBHP	10	67
2	n-Bu_4NCl	EtOAc	TBHP	24	0
3	n-Bu_4NBr	EtOAc	TBHP	24	0
4	NaI	EtOAc	TBHP	10	45
5	I_2	EtOAc	TBHP	10	36
6	-	EtOAc	TBHP	24	0
7	n-Bu_4NI	EtOAc	T-HYDRO	8	70
8	n-Bu_4NI	EtOAc	T-HYDRO	8	32
9	n-Bu_4NI	EtOAc	T-HYDRO	6	Nd
10	n-Bu_4NI	EtOAc	T-HYDRO	6	61
11	n-Bu_4NI	EtOAc	T-HYDRO	8	38
12	n-Bu_4NI	DMF	T-HYDRO	8	10
13	n-Bu_4NI	MeCN	T-HYDRO	8	27

The mechanism of the cascade reaction [120] was explained by Ishihara and co-workers, [121] suggested that the active iodine species ammonium hypoiodite ([n-Bu_4N]+[IO]-) or iodite (n-[Bu_4N]+[IO2]-) plays an important role in the cascade sp3 C–H activation reaction as in the (scheme 12)



(Scheme 12)

The aerobic C-H oxidation of C(sp3)-H activation by organocatalytic (metal free) recyclable catalyst TEMPO. TEMPO one of the most choice in industry [122] and has been widely used for the oxidation of alcohols to carbonyls, [123,124], and it use in the oxidative functionalization of other functionalities represents an important challenge and the examples are very limited [125-131]. Recently, **Wei Wang** and coworkers was reported the oxidation of benzylic C(sp^3)-H by using TEMPO catalyst. The oxidation of benzylic C-H by means of recyclable TEMPO derived sulfonate organocatalysts in presence of $NaNO_2$ and HCl aqueous solution as the co-catalyst [132-138] and O_2 as the oxidant for large-scale [139-142]. The aerobic oxidation of isochroman derivatives 46 was treated with 2 mol % TEMPO catalyst I, 4 mol % NaNO2 (solid), and 10 mol % concn HCl (12.0 M) aq solution with an O2 balloon in 3 mL of CH3CN at rt to afford ketone 17 (Scheme 13)

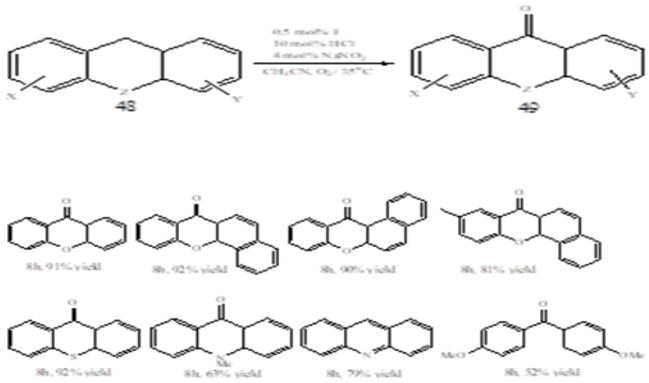


(Scheme 13)

Table 5 reaction conditions with the yield

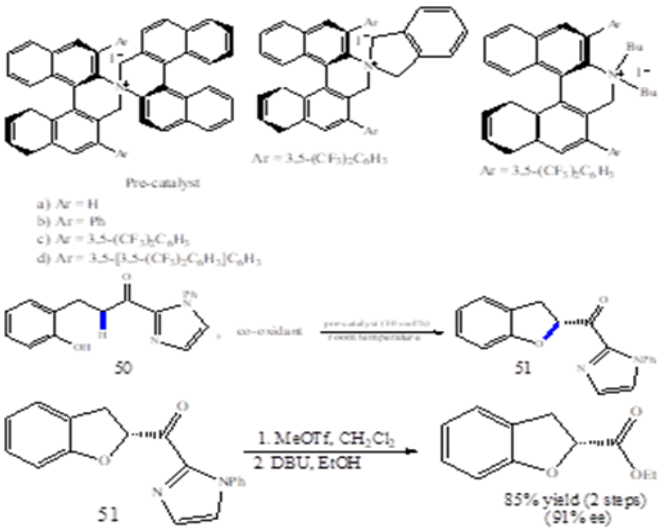
Entry	Catalyst	I (mol %)	Oxidant	Time/h	Yieldc(%)
1	CH_3CN	2	TBHP	12	59
2	CH_3CN	2	TBHP	8	83
3	CH_3CN	1	TBHP	8	77
4	CH_3CN	0.5	TBHP	8	80
5	CH_3CN	0.3	TBHP	12	67
6	$ClCH_2CH_2Cl$	0.5	TBHP	8	57
7	THF	0.5	T-HYDRO	8	34
8	DMF	0.5	T-HYDRO	8	51
9	H_2O	0.5	T-HYDRO	8	21
10	CH_3CN	0.5	T-HYDRO	8	14

The aerobic oxidation of xanthones 48 into ketones 49 without touch the substituted S, N, and/or O atoms with good yield in the presence of TEMPO recyclable catalysis was also studied (Scheme 14)



(Scheme 14)

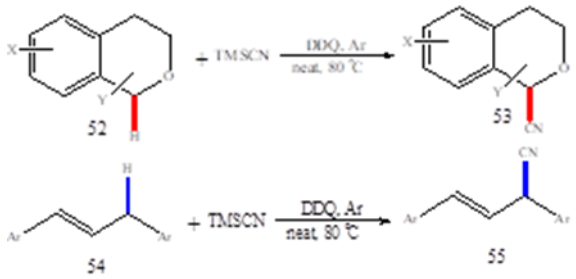
Kazuaki I. and couther's was reported chiral hypervalent iodine compounds for enantioselective oxidative coupling to proven a particular challenge in asymmetric catalysis [143,144]. The oxidation of compound 50 was carried out with aryl-λ3-iodanes as pre-catalyst in the presence of co-oxidant hydrogen peroxide or TBHP to have 51 (Scheme 15)



(Scheme 15)

3.2. C-C bond formation

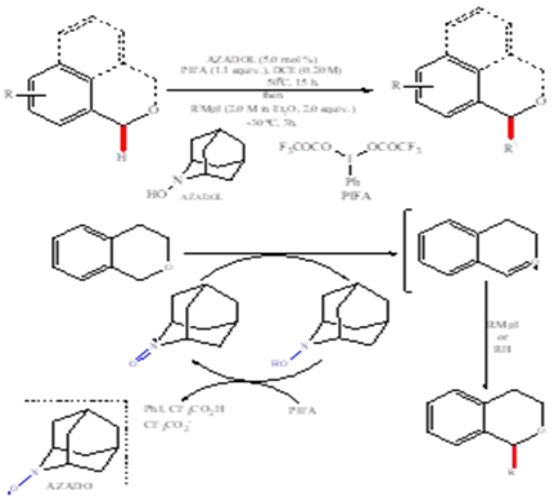
One of the most important C-H bond functionalization is C-C bond formation. Recently, there are many reports studied the development of methods for the functionalization of C-H bonds using metals catalysis or other oxidative reagents to afford C-C bonds [145-154]. The cynation of tetrahydroquinoline derivatives 52 and 1,3-diarylpropenes 54 using TMSCN in presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as a catalyst under air condition to have the cyano compounds 53, 55 was reported by Min Wang and coworkers, [155-157] the reaction of 0.5 mmol of tetrahydroqinoline derivatives and 1.5 mmol of TMSCN in presence of 0.6 mmol of DDQ as a catalyst under air to have the cyano compound 53. (Scheme 16)



Entry	54, Ar	Yield[%]
1	54a, Ph	55a, 74
2	54b, 4-F-C_6H_4	55b, 57
3	54c,4-Cl-C_6H_4	55c, 62
4	54d,4-Br-C_6H_4	55d, 58
5	54e,4-Me-C_6H_4	55e, 50
6	54f,4-tBu-C_6H_4	55f, 68

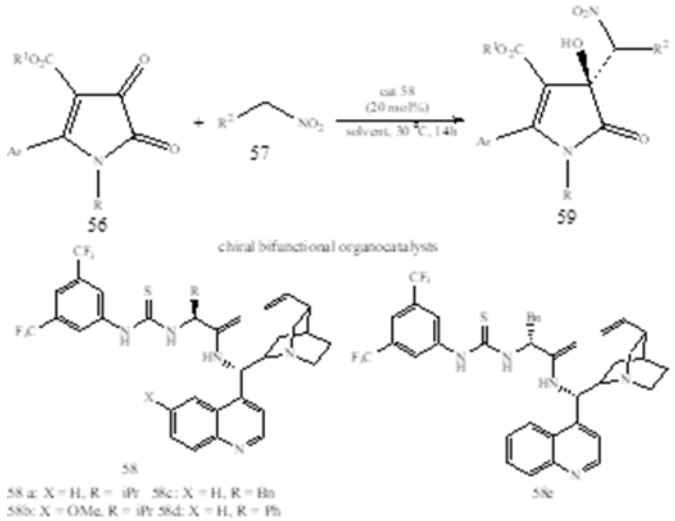
(Scheme 16)

Cross-dehydrogenative coupling (CDC) reactions are one of the most commonly used as atom-economic methods [158-165]. Rare, expensive metals and stoichiometric amounts of peroxides and harsh reaction conditions have used on most of CDC reactions. Recently, the catalytic methods for C(sp3)–H bond arylation at the C(1) position of isochroman are still limited [165]. The activation of C(sp3)-H of isochromine by the combination of N-hydroxy-2-azaadamantane (AZADOL) and PIFA to introduce the aryl and various functional groups into the position 1 was reported by Wataru Muramatsu and Kimihiro Nakano.91 Isochomine derivatives was initiated by AZADOL (5.0 mol%) and PIFA (1.1 equv.) in 1,2-dichloroethane (DCE), followed by nucleophilic addition using R\MgI/Et2O (2.0 equiv.) [166-169]. (Scheme 17)



(Scheme 17)

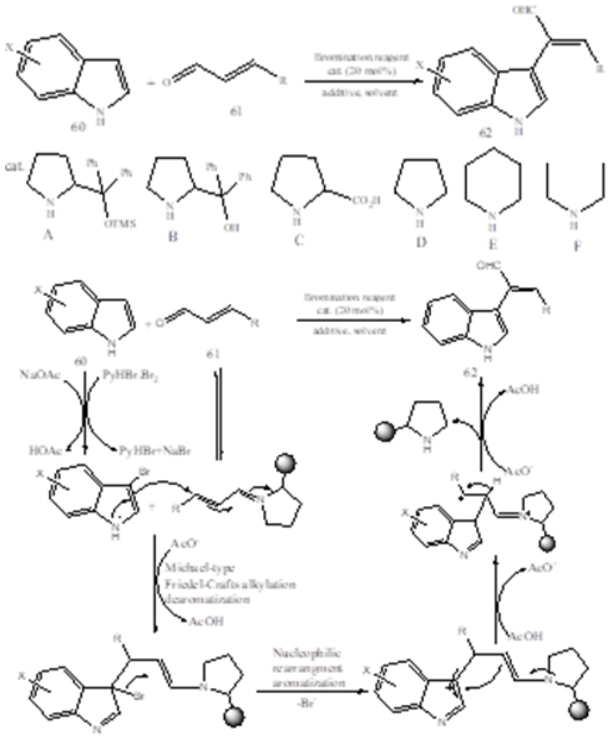
Asymmetric catalyst plays an important role in the C–H bond functionalization and numerous catalytic asymmetric reactions have been developed with various activation modes [170-175]. Using of chiral bifunctional thioureas bearing multiple hydrogen-bond donors successfully used as chiral organocatalysts for the asymmetric Michael addition and Mannich reactions [176]. However, Henry reaction is one of the most important carbon–carbon bond-forming reactions that provide straightforward access to β-nitroalcohols compounds [177-179]. The reaction of pyrrole derivatives 56 and nitro derivatives 57 in the presence of various chiral bifunctional organocatalysts 58 in dichloromethane to synthesized chiral pyrrole derivatives 59 [180-182]. (Scheme 18)



Entry	R/R¹/Ar	R²	Time	Yield %	ee%
1	iPr/Me/Ph	H	14	55	65
2	iPr/n-Bu/Ph	H	70	52	70
3	iPr/Et/2-ClC_6H_4	H	62	53	73[d]
4	iPr/Et/3-$MeOC_6H_4$	H	62	73	71
5	iPr/Et/3-ClC_6H_4	H	120	47	71
6	iPr/Et/3-BrC_6H_4	H	120	44	70
7	iPr/Et/4-$MeOC_6H_4$	H	62	61	72
8	iPr/Et/4-MeC_6H_4	H	48	64	69
9	iPr/Et/4-FC_6H_4	H	62	73	70
10	iPr/Et/2-thienyl	H	120	51	71
11	iPr/Et/1-naphthyl	H	120	75	51[e]
12	H/Me/Ph	H	120	41	48
13	Ph/Et/Ph	H	120	42	29
14	iPr/Et/Ph	Me	24	23	22[f]
15	iPr/Me/4-$MeOC_6H_4$	H	84	51	69
16	iPr/Me/3-$MeOC_6H_4$	H	120	71	58

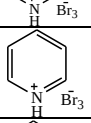
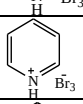
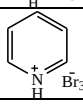
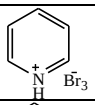
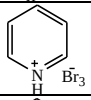
(Scheme 18)

Direct β-indolylation of enals, the investigation of an efficient metal-free organocatalysed C–H α-arylation reaction of enals remains highly challenging [183-187]. There is very few reports about the metal free approach for the direct C(sp2)–C(sp2) cross-coupling α-indolylation of enals from unfunctionalized indoles and enals. Xinhong Yu and coworkers was reported the one-pot operation, the perquisite 3-bromoindoles could be in situ produced from an electrophilic bromination reaction of indoles with pyridine hydrobromide perbromide, thereby creating an ambiphilic nucleophilic/electrophilic center for the subsequent Michael addition initial cascade process. The reaction of indole derivatives 60, with trans-cinnamaldehyde derivatives 61 in the presence of pyridine hydrobromide perbromide, racemic diphenylprolinol trimethylsilyl ether (A, 20 mol%) and base NaOAc were carried out in toluene (Tol) [188,189] to obtain the desired product 62. (Scheme 19, table 6)



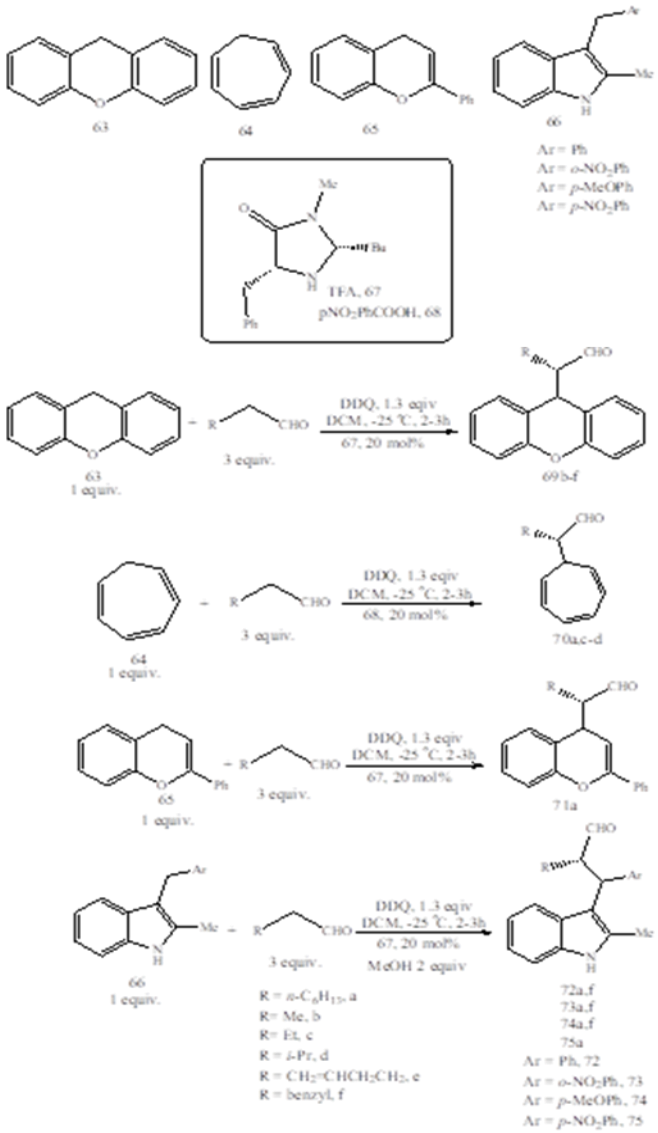
(Scheme 18)

Table 6 reaction conditions with the yield.

Entry	Cat.	Bromination reagent	Solvent	Additive	Yield (%)
1	A		Toluene	NaOAc	32
2	A		MeCN	NaOAc	35
3	A		$CHCl_3$	NaOAc	30
4	A		Tol: $CHCl_3$ (1:1)	NaOAc	62
5	A		Tol: $CHCl_3$ (1:1)	TEA	42
6	A	NBS	Tol: $CHCl_3$ (1:1)	NaOAc	50
7	B		Tol: $CHCl_3$ (1:1)	NaOAc	-
8	C		Tol: $CHCl_3$ (1:1)	NaOAc	-
9	D		Tol: $CHCl_3$ (1:1)	NaOAc	-
10	E		Tol: $CHCl_3$ (1:1)	NaOAc	10
11	F		Tol: $CHCl_3$ (1:1)	NaOAc	-

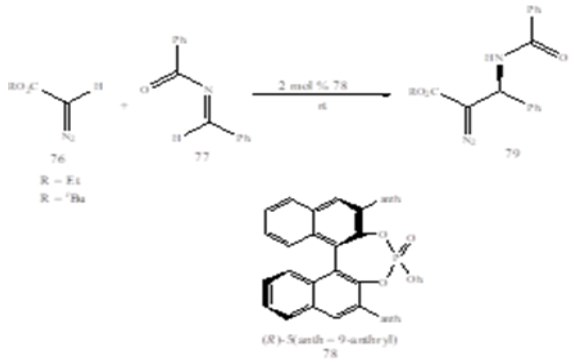
The organocatalysis is possibile to use in the SN1-type reactions [190-192]. Pier Giorgio Cozzi and coworkers used stabilized carbocations generated by benzylic alcohols in situ for the enantioselective a-alkylation of aldehydes [193-195]. However, the activation of C–H bonds of alkanes could be coupled with a direct stereo selective organocatalytic reaction [196-198]. This methodology has enormous potential, as all concepts developed in organocatalytic reactions can be used in the direct functionalization of C–H bonds, with all the advantages of simple reaction conditions, and absence of metal catalysts.

DDQ is a well-known oxidizing reagent for organic synthesis, [199] and the coupling reaction between nucleophiles and benzylic substrates mediated [196-203]. The reaction was promoted by the MacMillan-type of catalyst [196,-204], while chiral diphenylprolinol TBS ether catalyst [205], did not prove effective in this transformation. α-Alkylation of compounds xanthene 63, 1,3,5-cycloheptatriene 64, 65, and 66 was reacted with aldehydes by using organocatalysis 67, 68 [206-208]. (Scheme 19)



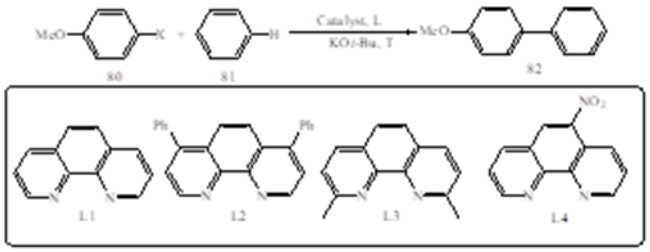
(Scheme 19)

Addition reaction to carbonyl, imine, and α,β-unsaturated carbonyl compounds, such as Friedel-Crafts alkylations, using catalytic asymmetric sp2 C-H bond, is one of a powerful challenging organic transformation [207,208]. When (76) reacted with an acyl imine 77 was attempted at room temperature in chloroform-d1 under the influence of 2 mol % of achiral phosphoric acid (78). Starting imine (77) to the direct alkylation product (79) was observed within 1 h, and the product was isolated in 70% yield [209-215]. (Scheme 20)



(Scheme 20)

Cross-coupling reactions of arenes to construct biaryls, [216-218], Such reactions have been deemed to be among the most 'aspirational' reactions as yet underdeveloped in the 'key green chemistry research areas' favoured by the pharmaceutical industry. Recently, cross-coupling of aromatic C-H bond was carried out by the combination of Co(acac)3 and 1,10-phenanthroline (L1, L2, L3, L4) in the presence of KOt-Bu (as a base) as most efficient conversion of 80 occurred, and product 82 could be isolated in 71% yield [219,220]. (Scheme 21)

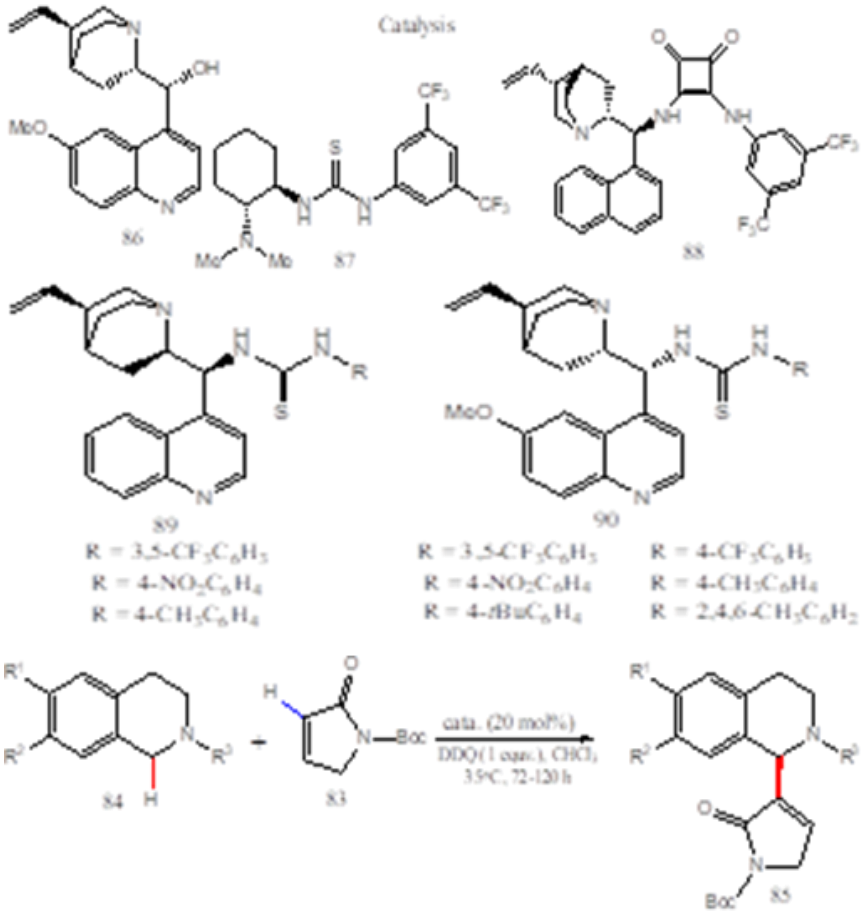


Entry	X	Co (10 mol %)	L (mol%)	T (°C)	Yiled %
1	I	$Co(acac)_3$	DMEDA (40)	80	69
2	I	$Co(acac)_3$	**L1** (40)	80	71
3	Br	$Co(acac)_3$	**L1**(40)	80	70
4	I	-	**L1** (40)	80	62
5	Br	-	**L1** (40)	80	5
6	I	-	**L1** (20)	100	83
7	Br	-	**L1** (20)	100	48
8	Br	-	**L1** (40)	100	87
9	Br	-	DMEDA (40)	100	0
10	Br	-	**L2** (40)	100	92
11	Br	-	**L3** (40)	100	59
12	Br	-	**L4** (40)	100	0
13	I	-	**L1** (5)	100 (48h)	80

(Scheme 21)

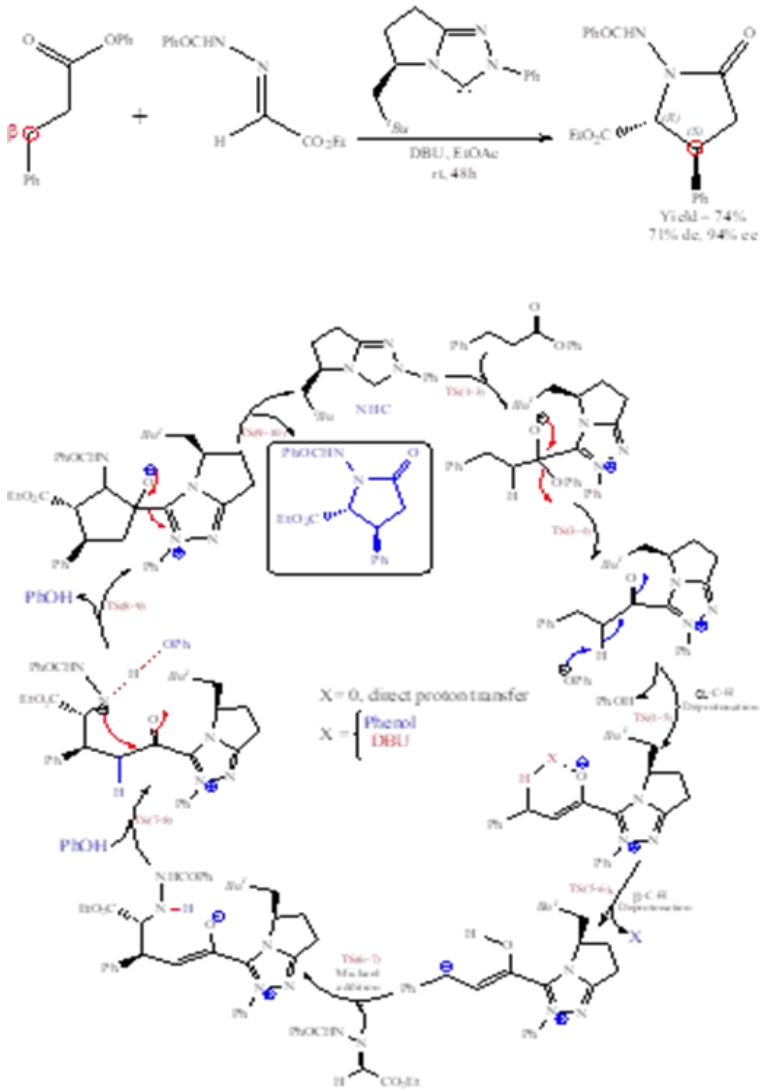
Shibasaki's group used the dinuclear nickel catalytic system for the efficient asymmetric vinylogous Mannich reaction and Michael reaction in 2010, [221], many studies have investigated the reaction of α,β-unsaturated γ-butyrolactam and various electrophiles. Most of the reactions occurred at the γ-position of α,β-unsaturated γ-butyrolactam [221-223]. Recently, α,β-unsaturated γ-butyrolactam 83 could react smoothly with various aromatic-substituted

tetrahydroisoquinolines 84 in the presence of numerous of organocatalysis compounds (metal free) to generate the desired products in good yields and good to excellent enantioselectivities [224-226]. (Scheme 22)



(Scheme 22)

There are some reports in the computational studies focusing on homoenolate as well as umpolung type NHC catalysis, [227-229], no reports have been available on the mechanism of this new form of NHC reactivity leading to β-C-H functionalization. **Raghavan** group have some reports in the mechanistic insights into NHC-catalyzed reactions [230,231]. Asymmetric NHC-catalyzed β-C-H functionalization was reported by **Raghavan B. Sunoj** and co-worker to investigate the reaction mechanism by using density functional theory computational methods [232]. The mechanism involved in NHC-catalyzed direct β-C-H activation of saturated carboxylic esters leading to the formation of γ-lactams (Scheme 23). The description focused on the most preferred pathway identified on the basis of the computed Gibbs free energies at the SMDEtOAc/B3LYP-D2/6-31G** level of theory.



(Scheme 23)

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this paper

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