Cobalt Mediated C-H Bond Functionalizations: Emerging Tools for Organic Synthesis

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Cobalt Mediated C-H Bond Functionalization: Emerging Tools for Organic Synthesis

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This review provides a perspective on C-H bond functionalization mediated by cobalt complexes used either in stoichiometric or catalytic amounts without the contribution of any other transition metal, for organic synthesis applications. The competitive cost, availability and lower toxicity of cobalt compared to precious transition metals constitute valuable advantages of the methods.

1 Introduction

The quest for techniques enabling selective functionalization of C-H bonds is attracting substantial interest in recent years, such synthetic tools are step and atom economical reactions allowing for the rapid construction of complex molecules from simple precursors without need for pre-activation.[1] Promoting C-H bond functionalization by use of first row transition metals is an attractive approach[2-5] as most of those metals are naturally abundant, easily available, cheap, with low toxicities in comparison with precious transition metals. Also, the exploration of new reagent systems might lead to new reactivity and selectivity.

Among first row transition metals, cobalt mediated C-H bond functionalization met with recent success.[6] Several reviews tackled the applications of cobalt in organic synthesis for cross coupling reactions,[7] Pauson Khand,[8] hydroformylation,[9] cycloaddition,[10] and other cobalt catalysed C-C bond formations.[11] This review aims at giving a general perspective on C-H bond functionalization mediated by cobalt complexes used either in stoichiometric or catalytic amounts, without contribution of any other transition metal, for application in organic synthesis. First, C-H bond functionalization to form new C-C bonds is reviewed. Second, an overview of cobalt promoted C-H bond functionalization to form new carbon- heteroatom bonds is provided. Throughout the review, reactions are organised by types (e.g. cycloisomerization, cross couplings…), transformations promoted by low-valent cobalt complexes are discussed before reactions promoted by higher-valent cobalt complexes within the different paragraphs.

2 C-H bond functionalization forming new C-C bonds

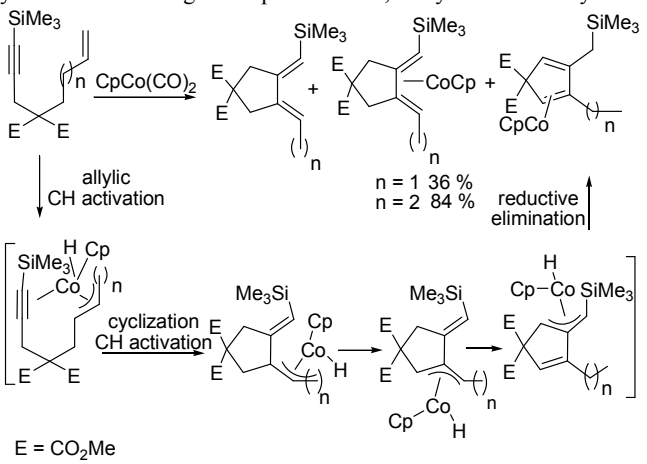
2.1 Intramolecular hydrogen migration

2.1.1 Cycloisomerizations

Cycloisomerizations are powerful tools to rapidly access in one step to (poly)cyclic structures of synthetic interest.

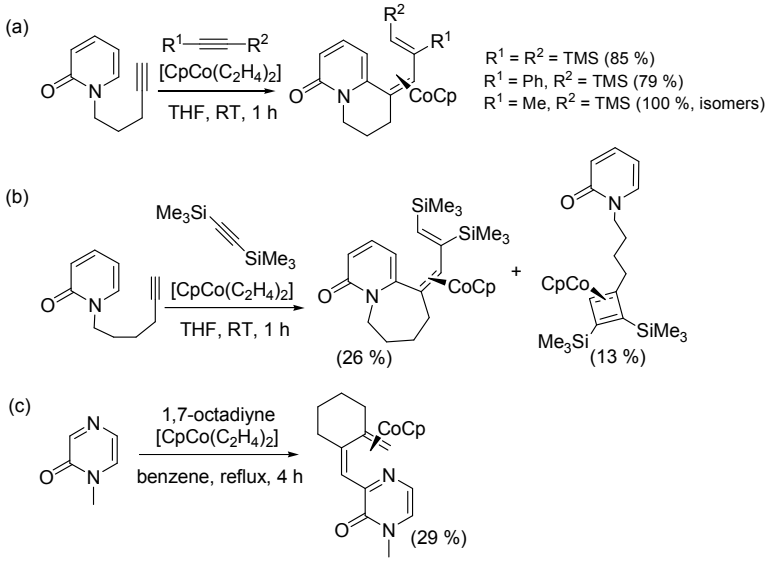
Cycloisomerizations of enynes involving an allylic C-H activation step by use of low-valent cobalt reagents were reported from 1996 onwards. Malacria and coworkers developed cycloisomerizations of some 1,7- and 1,8-enynes in presence

of an equivalent of $CpCo(CO)_2$ in xylenes at reflux under light irradiation leading to five-membered carbocycles (scheme 1).[12] Selective cobalt allylic C-H activation was followed by insertion and migration processes. 1,6-enyne failed to cyclize.



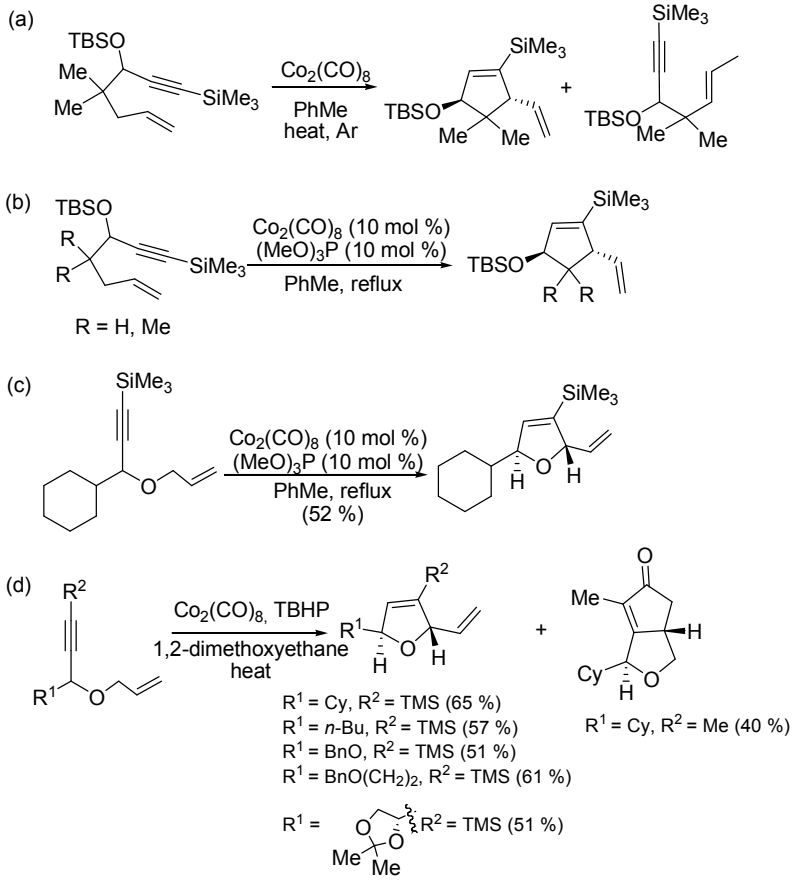
Scheme 1 Cycloisomerizations of 1,7- and 1,8-enynes (Malacria, 1996)

In 2007, Malacria and Vollhardt reported some intermolecular reactions between 3-pentynylpyridone and few alkynes mediated by stoichiometric $[(Cp)Co(C_2H_4)_2]$, generating fused dienylpyridones with good yields. The transformation involved regioselective C-H activation of the heterocycle, intramolecular insertion and migration processes (scheme 2a,b).[13] Homologation of the tether gave a seven membered ring in addition to a cyclobutadiene species. Also, *N*-methylpyrazinone and 1,7-octadiyne when treated with $[CpCo(C_2H_4)_2]$ resulted in the product of C-H activation at position 3 (scheme 2c).



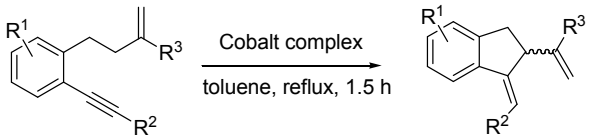
Scheme 2 Intramolecular C-H activation-cycloisomerization (Malacria, Vollhardt, 2007)

From 2001, Gleason published cycloisomerizations of a range of 1,6-enynes and allyl propargyl ethers promoted by $Co(CO)_8$, forming vinyl cyclopentenes and dihydrofurans respectively in moderate yields.[14] The process required stoichiometric quantities of $Co(CO)_8$ (scheme 3a) unless $(MeO)_3P$ additive was present (scheme 3b,c). The formal 5-endo-*dig* cyclization was proposed to proceed via allylic C-H oxidative insertion to form an allylcobalt hydride intermediate followed by sequential C-C and C-H reductive eliminations. When $Co(CO)_8$ was premixed with *tert*-butyl hydroperoxide (TBHP) (scheme 3d), cycloisomerizations of some allyl propargyl ethers afforded 2*H*,5*H*-dihydrofurans with good yields, excellent diastereoselectivities and functional- group tolerance.[15] The reaction could be performed in an iterative fashion, producing bis-THF units with excellent diastereoselectivites. Such cyclization could also be rendered catalytic in metal by use of $(MeO)_3P$ additive.



Scheme 3 Cycloisomerizations of 1,6-enynes and allyl propargyl ethers (Gleason)

More recently, a high yielding cycloisomerization of various arylene 1,7- enynes affording 2,3-dihydroindenes was reported by Jiang, using $Co_2(CO)_8$ as catalyst and ligands (10 mol %) (Ph_3P, *rac*-Binap, sulfone, sulfide, amine) (scheme 4).[16]

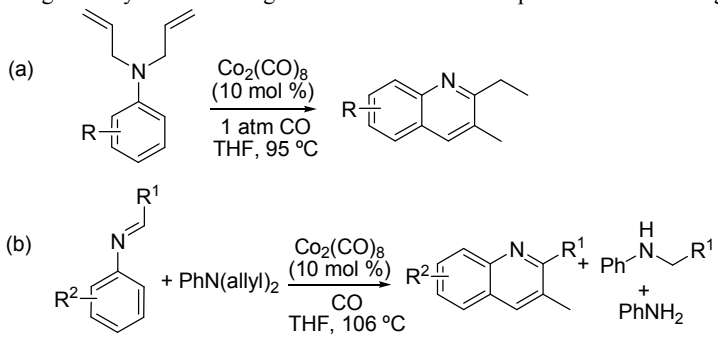


Stoechiometric conditions: $Co_2(CO)_8$ (1.1 eq.)

Catalytic conditions (R_1 = H, R_2 = *t*-Bu, R_3 = Me): $Co_2(CO)_8$ (10 mol %), ligand (10 mol%) (ligand: Ph_3P, *rac*-Binap, BuSMe,$CyNH_2$)

Scheme 4 Cycloisomerization of 1,7-enynes to 2,3-dihydroindenes (Jiang, 2013)

Apart from enyne reactants, several cycloisomerizations of diallylanilines and arylimines catalysed by $Co_2(CO)_8$ in THF under an atmosphere of CO were developed by Jones in 2003, forming 2,3-substituted quinolines in moderate yields (scheme 5a,b). The reactions involved both allylic C-H activation and C-N activation.[17] Electron withdrawing substituents at the aryl ring of diallylanilines inhibited the reaction whereas electron-donating groups seemed to favor it, by weakening the C-N bond by stabilizing the imine intermediate that formed and also by making the C-H activation step faster. Steric bulk at the arene *ortho* positions of nitrogen depleted the yields and altered the regioselectivity Mechanism studies indicated an *ortho* aryl C-H cleavage as one of the first steps in the reaction sequence, such cleavage might be assisted by coordination of a $Co_2(CO)_7$ fragment to the nitrogen. Allyl C-N cleavage did not seem to occur prior to C-H cleavage.



Scheme 5 Conversion of diallylanilines and arylimines to 2,3-substituted quinolines via C-H activation (Jones, 2003)

2.1.2 Intramolecular hydrogen migrations other than cycloisomerization

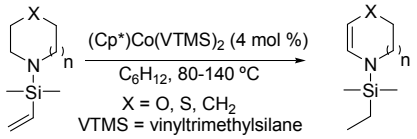
In 2006, Galland developed a method to promote the isomerization of 2-methyl-3-butenenitrile to 2-methyl-2-butenenitrile at 100-150 °C via allylic C-H bond activation, by use of either $Co_2(CO)_8$ alone or in the presence of pyridine or $P(OPh)_3$, $[(Ph_2PCH_2CH_2PPh_2)_2Co]^+[NTf_2]^-$, $[(Ph_2PCH\ CHPPh_2)_2Co]^+[NTf_2]^-$, $NaCo(CO)_4$.[18]

The first example of Co(I)-catalysed selective C(sp3)−H bond activation was reported by Brookhart in 2007 (scheme 6a).[19] Saturated cyclic amines bearing vinylsilane *N*-substituent reacted with $[(Cp^*)Co(CH_2CHTMS)_2]$, selective activation of a C(sp3)-H bonds α from an heteroatom (O, S) in the cyclic amines occurred via formation of a 16 e- intermediate [(Cp*)Co(monoolefin)] followed by oxidative

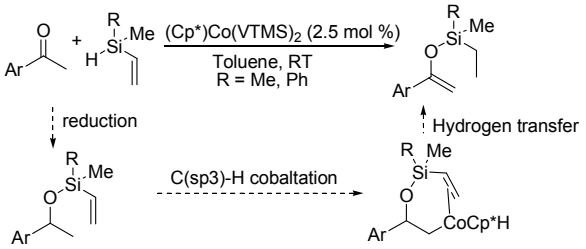
addition of the C(sp3)-H bond to the cobalt(I) centre. Migratory insertion of the vinyl silane into the cobalt hydride followed by β-hydride elimination (from the 3-position of the amine) and reductive elimination led to an enamine product. The catalyst exhibited high reactivity under mild conditions as well as chemo-, regio-, diastereo-, and intramolecular hydrogen transfer selectivities. The catalyst could also efficiently promote tandem hydrosilylation-hydrogen transfer to produce silyl enol ethers from substituted acetophenones and vinyl silanes (scheme 6b).[20] The transformation likely proceeded by reduction of the ketone by vinylsilane hydride to form a vinylsilyl protected alcohol, a C(sp3)-H bond cobaltation then occured followed by hydrogen transfer.

In 2012, Bradley achieved an analogous intramolecular hydrogen transfer on *N*-vinylsilane protected cyclic amines by using a bridging arene complex [(Cp*Co)$_2$-μ-(η4: η4-arene)] as catalyst, allowing for C(sp3)–H bond activation under mild conditions (scheme 6c).[21] A mechanism involving arene sandwich dissociation, generation of a 16 electron species and α to nitrogen C-H bond activation was proposed.

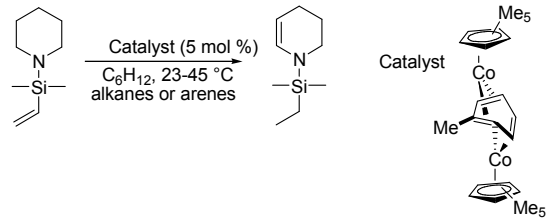
(a) Co(I) catalysed selective C(sp3)-H activation-hydrogen transfer (Brookhart, 2007)



(b) Tandem hydrosilylation-Co(I) catalysed C(sp3)-H activation-hydrogen transfer (Brookhart, 2013)



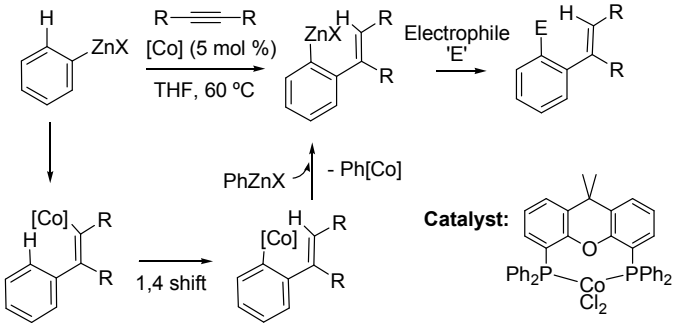
(c) Co(I) catalysed C(sp3)-H activation-hydrogen transfer (Bradley, **2012**)



Scheme 6 C(sp3)−H bond activations with hydrogen transfers forming enamines (Brookhart, Bradley)

During the addition of arylzinc reagents on internal alkynes catalysed by cobalt/XantPhos, a vinyl to arylcobalt 1,4-migration through C(sp2)-H bond activation was observed by Yoshikai forming the more stable *ortho* alkenylarylcobalt species.[22] Such cobalt shift from 2-aryl-1-alkenylcobalt to 2-alkenylarylcobalt intermediate is similar to the rhodium 1,4-migration observed during rhodium(I)-catalysed hydroarylation of alkynes with arylboronic acids.[23]

Subsequent zinc transmetallation afforded *ortho*-alkenylarylzinc species that could be trapped with external electrophiles to access a variety of 1-alkenyl-arenes functionalized in the 2-position in moderate to good yields (scheme 7). Cobalt 1,4-shift was feasible for alkynes such as dialkyl-, arylalkyl-, and silylalkylalkynes. The reaction was accompanied by a substantial degree of E/Z isomerization. Terminal alkynes and sterically hindered alkynes did not participate in the reaction.



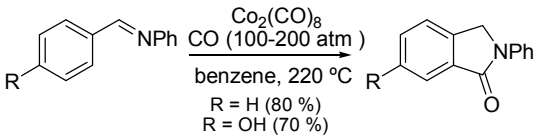
Scheme 7 Addition of arylzinc reagents on internal alkynes (Yoshikai, 2012)

2.2 Cyclocobaltations

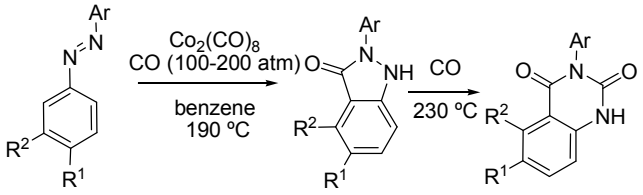
Cyclometalation[24] is often presented as a potential elementary step for catalysed C-H bond functionalization at *ortho* positions from directing groups.[25] Cyclometalations via C-H bond cobaltations were performed on molecules bearing chelating substituents by reaction with stoichiometric cobalt reagents. Although some of the cyclocobaltates discussed in this part were not reacted towards C-H bond functionalization, their possible involvements in catalytic processes make their discussion relevant. Cyclocobaltations of pure coordination chemistry interest only are not discussed here.

In 1955, Murahashi investigated the reactions of dicobalt octacarbonyl $Co_2(CO)_8$ with aromatic aldimines under pressure of carbon monoxide at high temperatures,[26] forming isoindolinones (scheme 8a). Sen later used $[Co(CH_3C(O))(CO)_3(P(o\text{-tol})_3)]$ to catalyse the transformation.[27] The reaction could occur by regioselective activation of the aromatic C-H bond at position *ortho* from the imine, migratory insertion of the hydride species into the benzaldimine functionality, CO coordination, and insertion into the Co-C bond, followed by reductive elimination of the *N*-alkylphthalimidine and regeneration of the starting Co species. C-H bond functionalization at *ortho* positions of azobenzenes by use of $Co(CO)_8$ was also studied by Murahashi, it formed indazolones at 190 ºC while quinazolinediones formed at 230ºC.[28] Heating indazolone in the presence of $Co(CO)_4$ under pressure of carbon monoxide formed quinazolinedione (scheme 8b).

(a) Formation of isoindolinones via cyclometalations

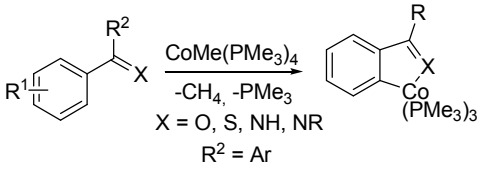


(b) Formation of indazolones and quinazolinediones via cyclometalations



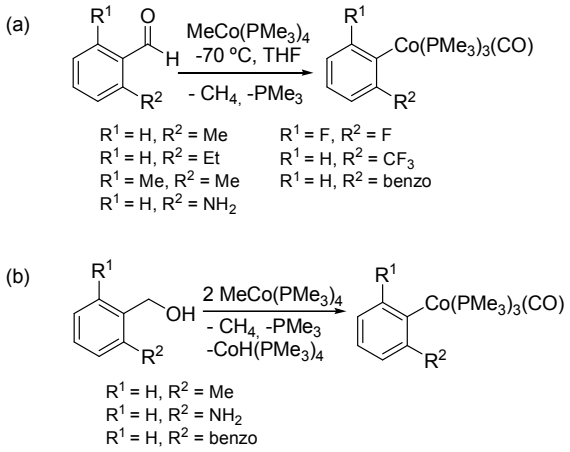
Scheme 8 Cyclometalation of aromatic aldimines and azobenzenes with $Co_2(CO)_8$ (Murahashi)

Seminal work by Klein and coworkers showed that electron rich cobalt(I) species at low temperatures (-70 ºC) can promote cyclometalation of arenes bearing directing groups. Using $CoMe(PMe_3)_4$ as precursor, efficient *ortho* C-H metalations of benzophenone imines, benzaldimines,[29] *N*-naphthyl ferrocenylideneamine[30] arylketones[29b,c] and thiobenzophenone derivatives[31] occurred along with methane formation (scheme 9). To note, Sun and Li reported that the pyridine moiety of 2-vinylpyridine could also serve as a directing group to activate *ortho* vinylic C-H bond towards cyclometalation under the same conditions.[29a,32]



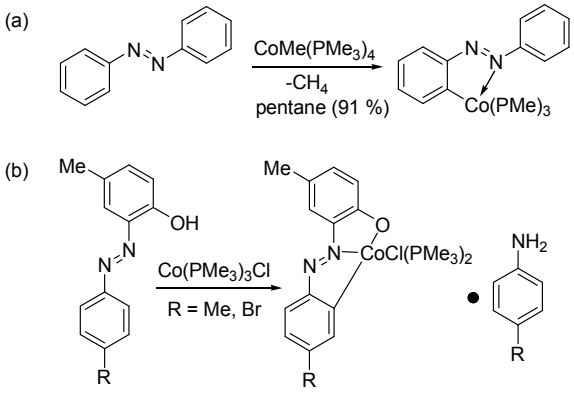
Scheme 9 Cyclometalation of aromatic imines, arylketones and thiobenzophenone with $CoMe(PMe_3)_4$

On the other hand, various *ortho*-substituted aromatic aldehydes (scheme 10a) and related benzylic alcohols (scheme 10b) reacted with $CoMe(PMe_3)_4$ via tandem aldehydic or alcoholic C-H activation/carbonyl migratory deinsertion to give trimethylphosphine stabilized aryl-monocarbonyl complexes of cobalt.[33]



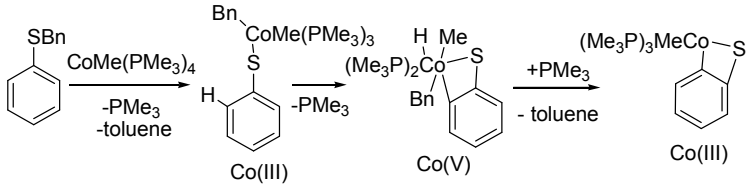
Scheme 10 C-H activation/carbonyl migration from *ortho*-substituted aromatic aldehydes and benzylic alcohols (Klein, 2009)

$CoMe(PMe_3)_4$[34,25a] and $CoCl(PMe_3)_3$ promoted the cyclometalation of azobenzene and 2-(4'-R-phenylazo)-4-methylphenols (R= Me or Br)[25b] respectively (scheme 11). In the latter case, organocobalt(III) complexes were formed via C-H activation,[21] one sacrificial equivalent of 2-(4'-R-phenylazo)-4-methylphenol was cleaved into two aniline portions in order to scavenge the equivalent of H_2 formally produced upon O-H and C-H bond activation.



Scheme 11 Cyclometalation of azobenzenes with $CoCl(PMe_3)_3$ and $CoMe(PMe_3)_4$

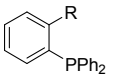
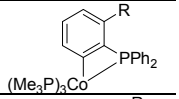
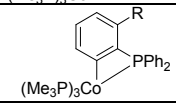
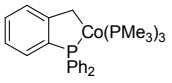
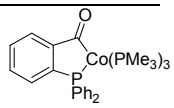
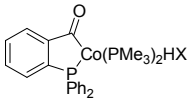
Reacting benzylsulfide reactants with $CoMe(PMe_3)_4$ led to oxidative addition of the S-C benzyl bond (scheme 12).[35] Four- and five-membered cobaltacycles with a thiophenolato anchoring group were formed through C–H activation. Toluene eliminated from a cobalt(V) intermediate by reductive elimination. The reactive methyl group remained attached to the cobalt atom during cyclometalation.

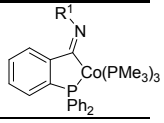
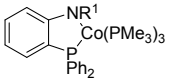
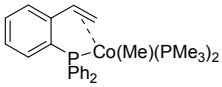


Scheme 12 Cyclometalation of benzylsulfides via benzyl-sulfide C-S bond cleavage (Klein, 2008)

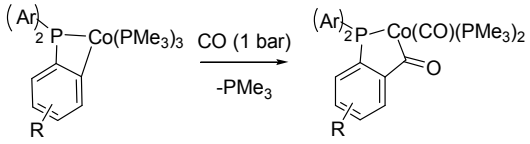
Cyclocobaltations were extended to arylphosphines.[36] Triarylphosphines bearing a substituent at one of the six *ortho* phenyl positions reacted with [$CoMe(PMe_3)_4$] or $CoCl(PMe_3)_3$/MeLi forming four, five- or six-membered cobaltocycles with C,P-chelating ligands and concommitent methane formation (table 1); four-membered cobaltacycles originated from an *ortho* metalation process (entries 1-2) while activation of C(sp2)-H or C(sp3)-H bonds in the side chain produced five- or six-membered cobaltacycles (entries 3-8). Electronic effects brought by substituents at positions *ortho* from phosphine groups were small while steric hindrance did affect the reaction course. Thus, 2-(diphenylphosphinyl)alkyliminobenzaldehydes reacted with $CoMe(PMe_3)_4$ to form five membered metalacycles by reaction with CH-N group (entry 6).[37] Bulky alkyl substituent (CMe_3) on the imine prevented a close approach of the CH-N group to the cobalt, the cyclometalation switched to the *ortho* position where the four *ortho* positions of the PPh_2 group are not involved (entry 1). Methylcobalt complexes activated the aldehyde function of 2-diphenylphosphinobenzaldehyde to afford five-membered chelate rings $Co(Ph_2PC{=}O)(PMe_3)_3$ (entry 4),[38] cobalt halides $CoX(PMe_3)_3$ oxidatively added the aldehyde function to produce octahedral compounds *mer*-$CoH(X)(Ph_2PC{=}O)(PMe_3)_2(X)$ (X = I, Br, Cl) (entry 5). Reaction of benzylphenylphosphines with $CoMe(PMe_3)_4$ gave *ortho*-metalated cobalt(I) complexes through *ortho* C-H bond activation of a benzyl group (entry 3).[39]

Table 1 Cyclometalation of triarylphosphines

Entry	Reactant	R	Conditions	Product
1		H, NMe_2, CH_2NMe_2, Et, *i*-Pr, Ph, CN, ethylacetal, CH=NtBu	$CoMe(PMe_3)_4$	
2	-	H	$CoCl(PMe_3)_3$, MeLi	
3	-	Me	$CoMe(PMe_3)_4$	
4	-	CHO	$CoMe(PMe_3)_4$	
5	-	CHO	$CoXPMe_3$ X = Cl, Br, I	

6	-	$CH=NR_1$ R_1 = Et, *i*-Pr, Cy	$CoMe(PMe_3)_4$	
7	-	NH_2, NHMe	$CoMe(PMe_3)_4$	
8		vinyl	$CoMe(PMe_3)_4$	

Four-membered metalacycles could generally insert CO into the Co-C bond under 1 bar CO whereas ring expansion did not occur for five- and six-membered analogues, for which CO substituted one of the PMe_3 ligands of cobalt without further insertion into Co-C bond (scheme 13).[36e]



Scheme 13 Insertion of CO into metalacycles (Klein, 2009)

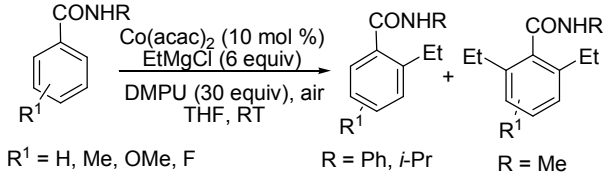
2.3 Cross couplings with organometallic reagents RM+ArH

Cross couplings between C(sp2)-H bonds and organometallics catalysed by first row transition metals are developing as efficient strategies to promote regioselective C-C bond formations. Mixing inorganic salts of Co (or Mg, Mn, Fe, Cu, Zn, Cd) with a polar organometallic compounds RM (M=alkali or alkaline earth metal) form organobimetallic combinations that can exhibit reactivities that are different from the reactivites of the corresponding monometal reagents, either because they form together new structures, as observed with Turbo reagents or 'ate complexes, or because they act in a complementary way.[40] Bimetallic combinations (mixed aggregAtes) served for example for dehalogenative metalations,[41] deprotonative metalations,[40] radical processes.[43] Various mechanisms have been proposed depending on the ligands and metals: steps involving one-electron transfer from a metal, two-electron transfer from a metal, ligand transfer have been suggested. Few studies aiming at the identification of the active bimetallic species were reported. An example is the excellent report by Mulvey aiming at elucidation of the structures of active organozinc and cadmium 'ate species *in solution*.[44] Another example is the excellent work by Fürstner investigating on the structures and reactivities of some organoiron 'ate species formed by mixing FeX_n salts with organolithium or magnesium reagents.[45]

Recent reports use bimetallic combinations as catalysts for direct C-H bond functionalizations.[2-5] The nature of the mixed reagents operating in polar solvents, the exact role of the metals within such mixtures and the role of the additives employed remain generally unknown, reaction conditions are mainly empirical. Organobimetallic combinations are generally treated as a black box mixture. Formation of 'ate complexes depends (among other parameters) on reaction

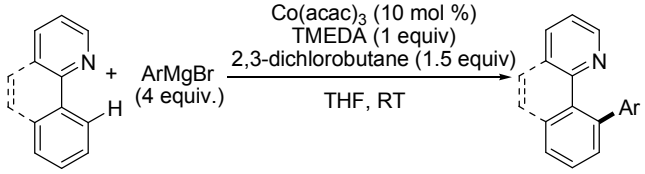
temperatures, cobalt bimetallic combinations generally fail to promote C-H bond functionalization at moderate and high temperatures. Bimetallic mixtures of cobalt used as catalysts for C-H bond functionalization are reviewed throughout the following paragraphs.

In 2011, Nakamura managed to introduce regioselectively a primary alkyl group at *ortho* C(sp2)-H positions of aromatic secondary carboxamides via oxidative cross couplings by mixing EtMgCl with catalytic amounts of cobalt salt in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) and dry air as sole oxidant (scheme 14).[46] Cobalt(0)ates formed *in situ* were proposed as intermediates. DMPU was a key to control the reactivity, maybe to stabilize alkylcobalt intermediates. Tertiary amides did not react: amides anions might act as ligands of the metal to favor the reaction. *Ortho* dialkylated product was selectively obtained with *N*-methylcarboxamide reactant whereas *N*-phenyl- or *N*-isopropylcarboxamide gave the monoalkylated products only. Using 2-phenylpyridine as reactant, monoalkylated products were obtained mainly. The reaction is rather limited in scope, as organomagnesiums other than EtMgCl gave poor yields. By-products were typically those produced by the homocoupling and β-hydride elimination of the organometallic reagent.



Scheme 14 *Ortho* alkylation of aromatics bearing DMG with ArMgBr (Nakamura, 2011)

The same year, Shi published some regioselective *ortho* arylations of 2-arylpyridines by oxidative cross coupling, combining ArMgBr with a cobalt salt (10 mol %) and TMEDA (1 equiv). Cobalt(0)ates formed *in situ* were also proposed as intermediates. Moderate to excellent yields of *ortho* arylated products were obtained at room temperature using 2,3-dichlorobutane as oxidant (scheme 15).[47] A large quantity of preformed arylmetal (3-4 equiv) was needed as 1 equiv of the reagent is used for the removal of the *ortho*-hydrogen atom and another 1 equiv for the arylation. The use of alkyl Grignard reagents possessing a β-hydrogen, as well as Grignard reagents with high steric hindrance gave modest to poor results. The substrate scope was limited by the high reactivity of Grignard reagents. Mechanistic studies indicated that the C-H cleavage was not the rate determining step.



Scheme 15 *Ortho* arylation of 2-arylpyridine with ArMgBr (Shi, 2011)

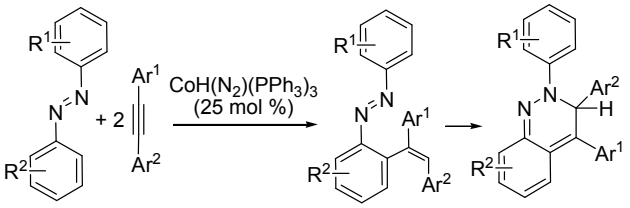
2.4 Direct C(sp2)-H bonds cobaltation - insertions of unsaturated bonds

Additions of unsaturated bonds into C(sp2)-H bonds are atom-economical reactions allowing for the rapid formation of substituted structures.

2.4.1 Insertion of alkynes into C-H bonds

Rhodium and ruthenium catalysed chelation-assisted hydroarylation of alkynes and alkenes were pioneered by Murai, Jun, Bergman and Ellman.[48] Cobalt can promote such reactions.

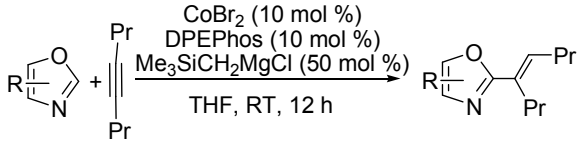
A series of anti-additions of internal alkynes (diarylacetylenes) into *ortho* C-H bonds of azobenzenes catalysed by $CoH(N_2)(PPh_3)_3$ or $CoH_3(PPh_3)_3$ were reported by Kisch in 1994 (scheme 16),[49] thermal electrocyclic ring closures of adducts provided 2,3-dihydrocinnolines except when a methyl- or chloro- substituent was present at the 3-position. Coordination of diarylacetylenes and insertion into the catalyst cobalt-hydride bond would be followed by substitution of a phosphine ligand by azobenzene; subsequent arene *ortho*metalation would afford adducts. The reaction had limited scope.



Scheme 16 Anti-addition of alkynes to azobenzenes (Kisch, 1994)

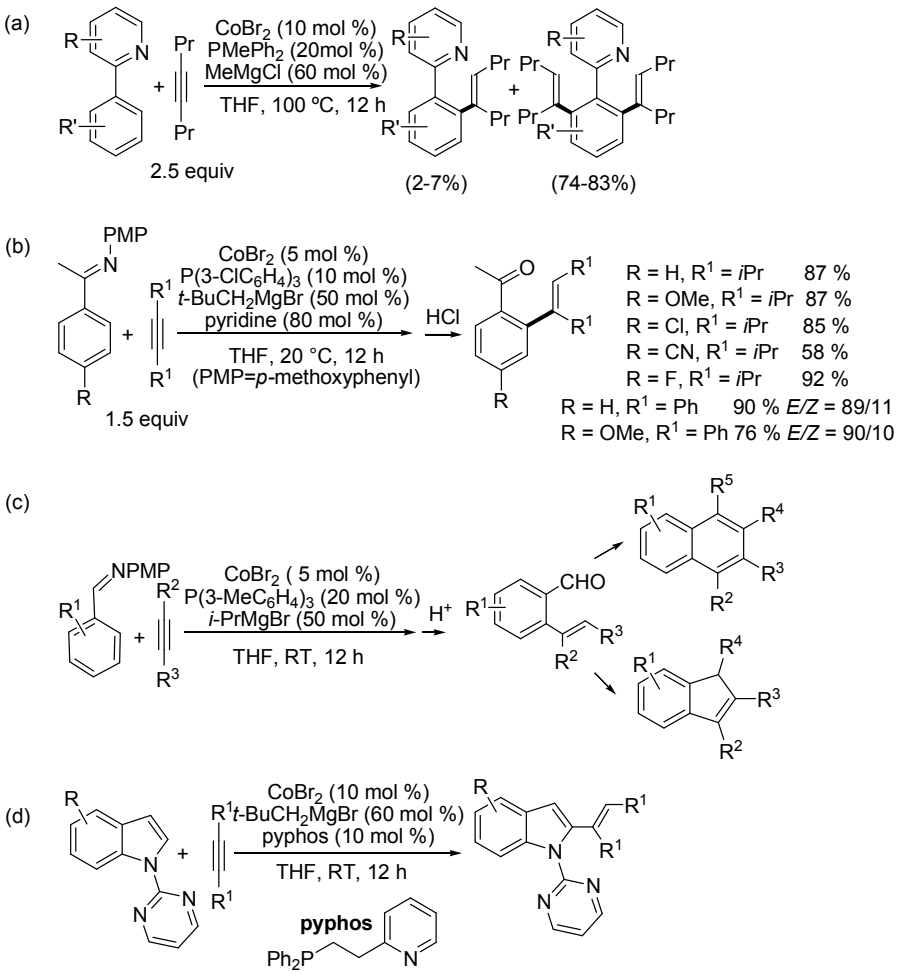
From 2010 onwards, bimetallic systems of cobalt salts, organomagnesium and ligands were used to catalyse C(sp2)-H bond activations and *syn* additions of alkynes. Analogous reactions catalysed by Ru, Pd, Rh were already described.[50] C-C bond formation at the less hindered acetylenic carbon was usually observed likely due to the preference of the cobalt centre to avoid steric repulsion during the alkyne insertion step. Each substrate required fine tuning of reaction conditions, the choices of ligand, organomagnesium, temperature *were critical* for the catalytic activity and regioselectivity. The active catalyst structures remain elusive at this stage, the organomagnesium likely acts as a reducing agent for the cobalt precatalyst, and experimental data suggest that organomagnesium plays an important role in the active catalytic species (likely an organocobalt(0)species).

Thus, systems composed of {$CoBr_2$ (10 mol %), organomagnesium (50 mol %), diphosphines (10 mol %)} catalysed alkenylations at position 2 of substituted oxazoles and benzothiazoles with high regio-, chemo- and stereoselectivity and good yields under mild conditions by *syn* additions of a C(sp2)-H bond on symmetrical internal alkynes (scheme 17).[51] A proposed mechanism involves an oxidative addition of the C(sp2)-H bond of oxazole on cobalt followed with insertion of alkyne into the Co-H bond and reductive elimination of the alkenyl(oxazolyl)cobalt species. Nickel(0) monophosphine catalysts show broader scope of heteroarenes for similar hydroheteroarylations.[52]



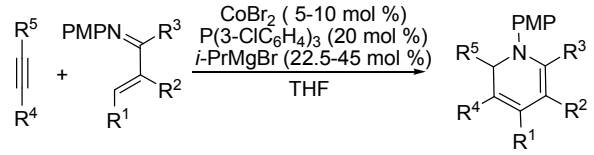
Scheme 17 Alkenylation of oxazoles (Yoshikai, 2010)

Bimetallic systems composed of $CoBr_2$, phosphine ligands, organomagnesium catalysed chelation assisted *ortho* C(sp2)-H bond cleavages on arenes and heteroarenes bearing directing groups such as 2-pyridyl, imines, pyrazolyl, pyrimidyl;[53] subsequent *syn*-insertion of non-activated internal alkynes into the Co-H bond and reductive elimination afforded hydroarylation products (scheme 18). Whenever those bimetallic systems catalysed the transformations at much lower temperatures than rhodium(I),[54] cobalt bimetallic systems were inefficient at moderate and high temperatures unlike rhodium (I), likely due to a putative 'ate active catalyst structure (formation of 'ate complexes depends on reaction temperature). Steric and electronic factors in the reactants played important roles in the insertion step. Thus, on 2-phenylpyridine (scheme 18a), *ortho* dialkenylations were obtained with moderate to good yields while monoalkenylations were possible when a methyl group was present at position 3 on the pyridine ring. Terminal alkynes did not participate in the reaction. For acetophenone imines (scheme 18b) *syn* monoalkenylations occured with symmetrical internal alkynes under mild conditions, the regioselectivities of hydroarylations were modest with non-symmetrical alkynes, and some E/Z isomerization of the imine moiety was observed. The acetophenone imine reactants bearing *m*-methyl and *m*-trifluoromethyl groups were selectively alkenylated at the less hindered *ortho* C(sp2)-H position whereas the presence of *m*-methoxy, *m*-fluoro, *m*-chloro, *m*-cyano substituents acting as secondary directing groups for the cobalt catalyst led to selective addition of the alkyne onto the more hindered *ortho* C(sp2)-H positions. *Ortho* alkenylations were also achieved on aromatic aldimines (scheme 18c). *Syn* alkenylation at C2 position on indoles bearing *N*-pyrimidyl groups was performed with a variety of internal alkynes (scheme 18d), good regioselectivities were obtained with non-symmetrical alkynes, the scope of alkynes was complementary to rhodium(III) catalysed hydroarylations of indoles.[55]



Scheme 18 Alkenylation of substituted aromatics (Yoshikai, 2010-12)

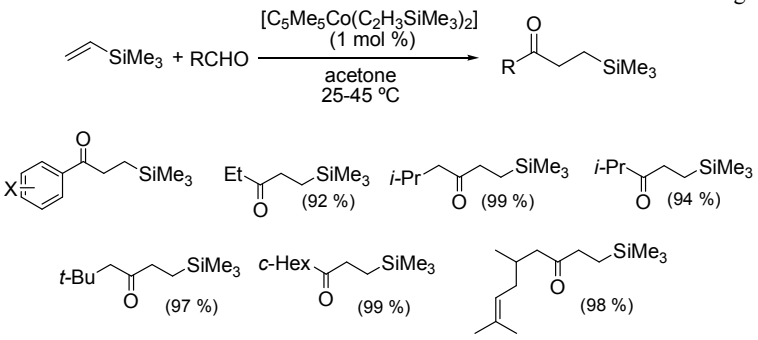
Olefinic C-H alkenylation of various α,β-unsaturated imines with internal alkynes were catalysed by {$CoBr_2$, Ar_3P, organomagnesium}; subsequent 6π-electrocyclization of the resulting azatriene derivatives afforded dihydropyridine derivatives in good yields under mild conditions (scheme 19).[56] Chloro, bromo, and cyano groups were tolerated as imine substituents. The use of unsymmetrical alkynes gave poor regioselectivities. A low-valent cobalt species was proposed to react *via* nitrogen assisted oxidative addition with the olefinic C-H bond of the imine, subsequent alkyne insertion and reductive elimination then cyclization would afford the product. The effect of the quantity of each component of the catalytic system on the overall catalytic activity was investigated, the organomagnesium likely reduces cobalt(II) to cobalt(0) and forms an organocobalt(0)ate as active catalytic species : the alkyl group of the organomagnesium significantly affects the catalytic activity. The active species likely bears phosphine ligand.



Scheme 19 Alkenylation of α,β-unsaturated imines (Yoshikai, 2013)

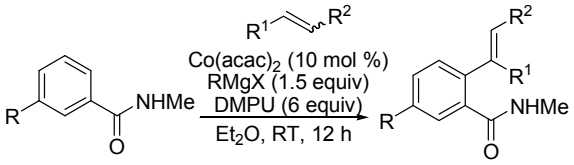
2.4.2 Insertion of alkenes into C-H bonds

From 1997 onwards, Brookhart published some activations of aldehydic C-H bonds by oxidative addition using low-valent $[(C_5Me_5)Co(C_2H_3SiMe_3)_2]$ precatalyst. Both *intra*- and *inter*molecular hydroacylation of vinyltrimethylsilane were achieved using a series of electron rich aromatic or aliphatic aldehydes, affording ketones with exclusive anti-Markovnikov selectivity (scheme 20).[57] Other silanes were less effective. Detailed kinetic and spectroscopic mechanistic investigations suggested the reductive elimination to form the new C-C bond to be the turnover limiting step.



Scheme 20 *Inter*molecular hydroacylation of vinyltrimethylsilane using electron rich aromatic or aliphatic aldehydes forming ketones (Brookhart)

In 2011, Nakamura achieved some regioselective *ortho* alkylations of substituted secondary benzamides catalysed by bimetallic combinations of $Co(acac)_2$ (10 mol %), organomagnesium (CyMgCl or MeMgCl, 1.5 equiv), DMPU (6 equiv). A mechanism was suggested: the first equivalent of organomagnesium likely deprotonates the amide NH bond, the rest of organomagnesium likely reduces Co(II) and forms *in situ* the active 'ate catalytic species; chelation-assisted *ortho* C(sp2)-H activation at room temperature would then occur followed by insertion of various olefins into the Co-H bond (scheme 21).[58] A variety of olefins, including a wide variety of terminal and internal alkenes as well as styrene and 1-phenyl-1-propene could insert, reaction occurred predominantely at the terminal position of the alkene. Tendency to dialkylation was observed, however steric hindrance at one *ortho* position by the presence of a *meta* substituent allowed for selective monoalkylation at the less hindered position. Tolerance to functional groups (halogens, olefins, esters, amides) was observed.

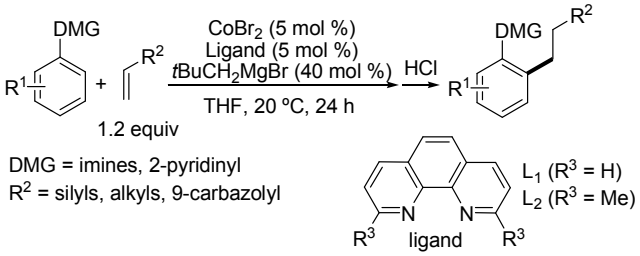


Scheme 21 *Ortho*-alkylation of benzamides (Nakamura, 2011)

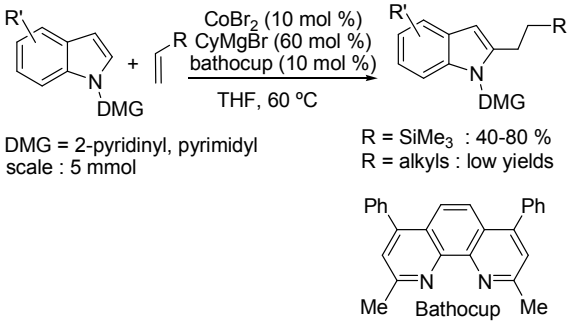
An analogous bimetallic system with phenanthrene ligand catalysed some regioselective *ortho* monoalkylations of arenes and heteroarenes bearing pyridine and imines directing groups under mild conditions[59] by insertion of terminal olefins into *ortho* C(sp2)-H bonds (scheme 22a,b). Several organomagnesium compounds allowed for the transformation, yet the method was sensitive to the structure and the quantity of organomagnesium used: 40 mol % of *t*$BuCH_2MgBr$ offered the best results. The alkylation occured at the less hindered or more acidic C(sp2)-H position on the reactant.

Hydroarylation of styrenes occurred with a variety of acetophenone imines, aromatic aldimines and aryl-2-pyridines, using a catalytic bimetallic system composed of $CoBr_2$ (10 mol %), Me_3SiCH_2MgCl or *t*$BuCH_2MgBr$ (80-100 mol %), PCy_3 (10 mol %) (or P(*o*-Tol)$_3$ for aldimines reactants). The scope was limited to styrenes. Experimental data indicate the involvement of organomagnesium in the active catalytic species (organocobalt(0)ate). Interestingly, 1,1-(branched) diarylethane products were formed preferentially (scheme 22c) which is a difference with ruthenium and rhodium catalysts that provide linear selectivities.[48] Dialkylation was obtained depending on substrates: with aryl aldimine, disubstitutions were often observed as main products with good yields when no substituents were present at *ortho* positions of arene reactant, whereas with phenylpyridine, dialkylation product was not obtained. Branched and linear product formations were competitive, the regioselectivities of hydroarylations depended on the structure of the ligand, on the electronic nature of the reactant, and on the organomagnesium structure.[60] Changing the ligand to IMes.HCl (10 mol %), the hydroarylation of styrenes with 2-arylpyridines or acetophenone imines switched to 1,2-(linear) diarylethane products with good regioselectivities (scheme 22c) but moderate yields.[61] A mechanism for the hydroarylation of styrenes with 2-arylpyridine was proposed : reversible cleavage of C-H bond *via* chelation assisted oxidative addition of C-H on the Co centre would be followed by insertion of styrenes into the Co-H bond then reductive elimination as rate and regioselectivity determining step.

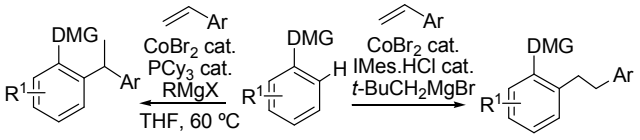
(a) Alkylations of arenes bearing DMGs with terminal alkenes



(b) C2-alkylations of indoles with alkenes



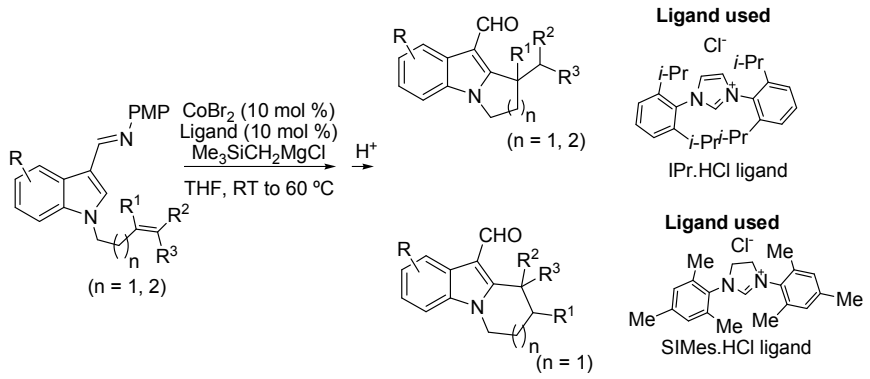
(c) Regioselectivity switchable hydroarylation of styrenes



DMG = -C(Me)(NPMP), 2-pyridinyl
RMgX = *t*-$BuCH_2MgBr$, Me_3SiCH_2MgCl

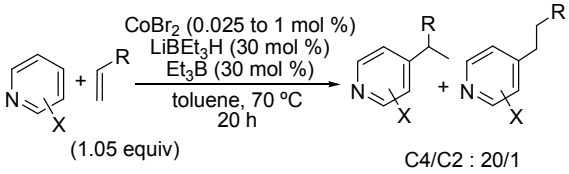
Scheme 22 *Ortho* alkylation of substituted aromatics (Yoshikai, 2011-13)

Intramolecular olefin hydroarylations of indoles bearing *N*-homoallyl or bishomoallyl tethers and a C3 aldimine directing group were catalysed by {$CoBr_2$ (10 mol %), Me_3SiCH_2MgCl (100 mol %), *N*-heterocyclic carbene (10 mol %)} under mild conditions: regiodivergent 5-exo-, 6-endo-, and 6-exo-type cyclizations afforded a series of dihydropyrroloindole and tetrahydropyridoindole derivatives (scheme 23).[62] The regioselectivity of cyclization depended on the structure of the olefin tether, and was also controllable by the steric nature of the NHC ligand when the tether was a parent homoallyl group. An example of formation of a quaternary carbon centre through chelation assisted C-H activation was also described.



Scheme 23 Intramolecular hydroarylations of indole derivatives (Yoshikai, 2013)

Kanai showed that $CoBr_2$ combined to $LiBEt_3H$ catalysed the direct alkylations of pyridines with 1-alkenes with good C4/C2 selectivity (scheme 24).[63] Styrene derivatives gave branched products preferentially, aliphatic alkenes gave linear products. The presence of catalytic Et_3B was a key to improving the C4-selectivity. The mechanism could go through a hydrometalation of alkenes with cobalt hydride to form an alkyl–metal species, its nucleophilic addition to pyridine would form a dihydropyridine intermediate that would re-aromatize without need of oxidants.

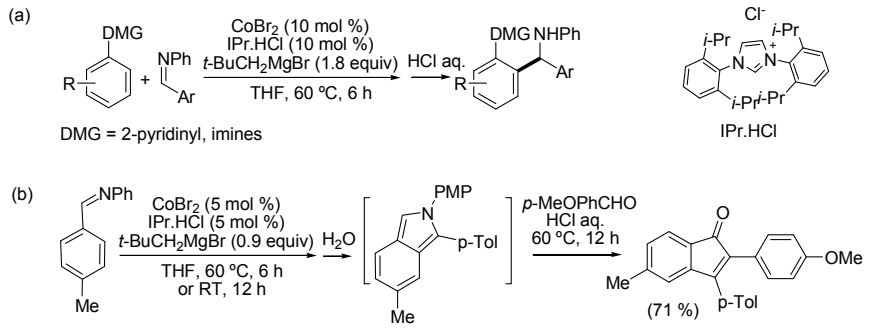


Scheme 24 Alkylation of pyridines (Kanai, 2013)

2.4.3 Addition to polar unsaturated C-Heteroatom bonds

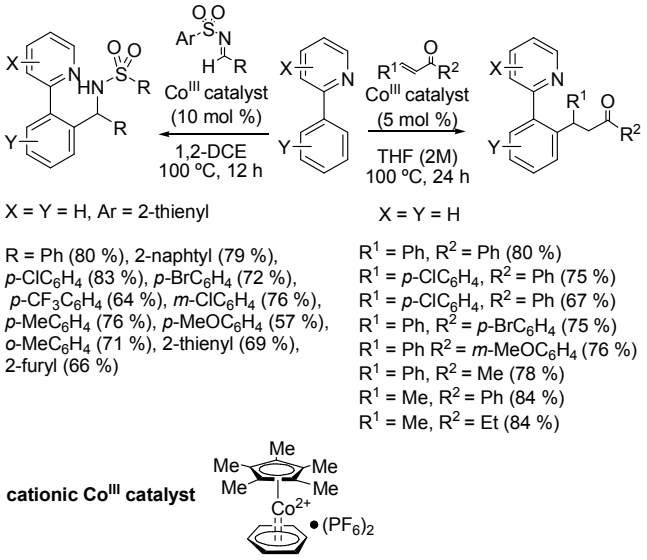
Examples of transition metal catalysed direct additions of aromatic C-H bonds to polar unsaturated C-heteroatom bond are scarce.

Using low-valent cobalt complexes, Murahashi and Sen described insertions of carbon monoxide to C-H bonds after cyclocobaltation (paragraph 2.2). Polar C=N bonds also served as reaction partners: arylcobalt species were formed by regioselective *ortho* C(sp2)-H bond activations of 2-arylpyridines, 2-arylpyrazoles and 2-(hetero)arylimines using a bimetallic system composed of {$CoBr_2$ (cat.), IPr.HCl (cat.), *t*$BuCH_2MgBr$ (1.8 equiv)}, the arylcobalt species acted as nucleophiles on aromatic aldimines.[64] Moderate yields of addition product were obtained (scheme 25a).[65] A putative mechanism involves the formation of a low-valent alkylcobalt catalytic species reacting with the aromatic reactant via chelation assisted C–H oxidative addition to give a cobaltacycle species. The intermediate would do nucleophilic attack on the aldimine, followed by transmetalation with the Grignard reagent to afford the addition product and regenerate the species. Self-coupling of arylaldimide was also observed, forming isoindole derivatives (scheme 25b).



Scheme 25 *Ortho* addition of polar CN bonds to substituted aromatics (Yoshikai, 2012)

A high-valent cationic [Cp*CoIII(arene)]$(PF_6)_2$] complex was reported by Kanai in 2013 to catalyse additions of 2-arylpyridines *ortho* C-H bonds to polar electrophiles (scheme 26).[66] Aryl imines with either an electron-donating or an electron withdrawing substituent at the *para* or *meta* position were good electrophiles, the reaction also proceeded with sterically hindered *ortho*-substituted imine and heteroaryl imines. Additions to enones afforded Michael adducts with good yields, β-substituted (aryl, alkyl)-α,β-unsaturated esters and amides did not afford the desired Michael adducts, but α,β-unsaturated *N*-acyl pyrroles could be used as surrogates. The C-H activation likely proceeds through electrophilic aromatic substitution or concerted metalation–deprotonation mechanism to form a cyclometalated intermediate.



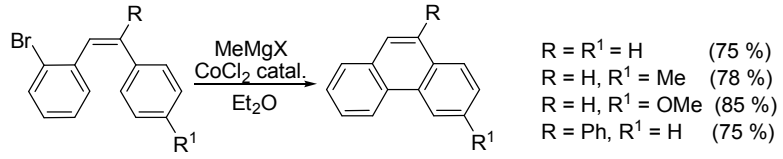
Scheme 26 *Ortho* additions of polar bonds to aromatics bearing DMG (Kanai, 2013)

2.5 Cross couplings reactions RX+ArH

Cross coupling reactions between arenes and RX (X = departing group) are efficient ways to promote new C-C bond formations.

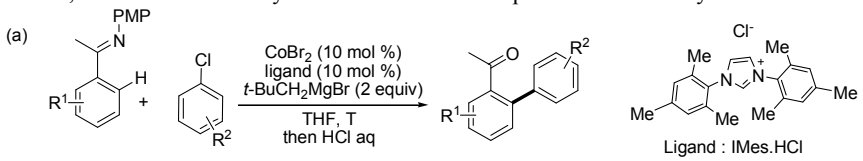
2.5.1 Cross couplings reactions RX+ArH using low-valent cobalt complex

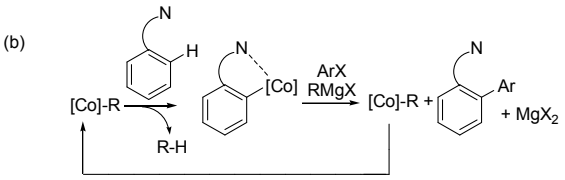
The first examples of arylations of C-H bonds were reported from 1965, when Tiecco published an intramolecular radical mediated aryl-aryl coupling using a bimetallic combination of MeMgBr and catalytic amounts of $CoCl_2$ (scheme 27).[67]



Scheme 27 Intramolecular reductive cyclisation of arenes (Tiecco, 1965)

Aryl chlorides are attractive electrophilic coupling partners since they are cost effective and widely available.[68] In 2012, Yoshikai achieved regioselective *ortho*-arylations of acetophenone imines by cross coupling with aryl chlorides, using a combination of $CoBr_2$ (10 mol %), neopentylmagnesium bromide (2 equiv) and IMes or PEt_3 at room temperature (scheme 28a).[69] The reaction was limited to less reactive aryl halides as the cross-couplings of tBuCH$_2$MgBr with reactive arylhalides such as an aryl bromide override the desired direct arylation. The activation of *ortho* C(sp2)-H bonds could be favored by coordination with the DMG, formation of a cobaltacycle was suggested (scheme 28b). The regioselectivity had some dependence to acidity and steric hindrance of the reactant. A higher reactivity of electron-poor aryl chlorides was observed, average to good yields of biaryls were obtained with substituted chlorobenzenes. The Co-IMes system tolerated aryl chlorides bearing electronically different *para*-substituents (dimethylamino, siloxy, fluoro) but did not promote the reaction with highly electron poor *p*-chlorobenzotrifluoride. The Co-PEt_3 system complemented the limitations of the former, as it enabled the arylation with this electrophile in moderate yield.

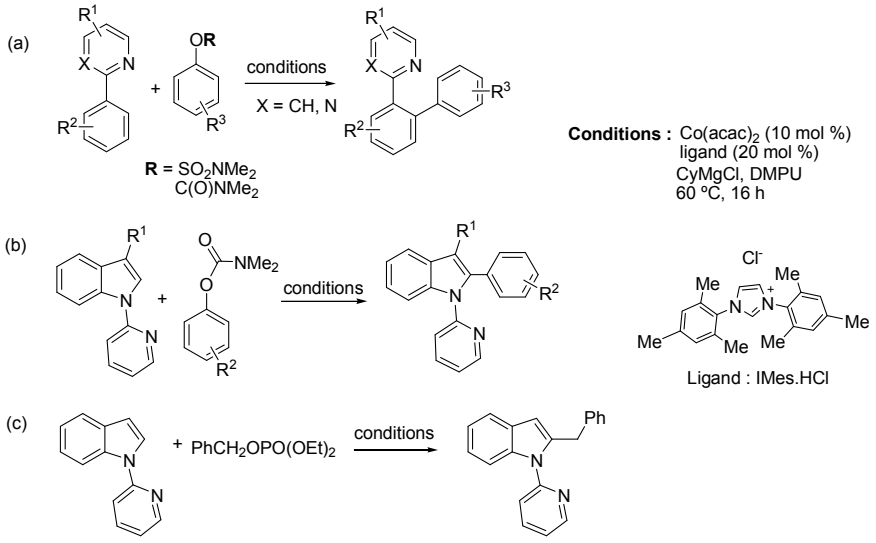




Scheme 28 *Ortho* arylation of acetophenone imines with arylchlorides (Yoshikai, 2012)

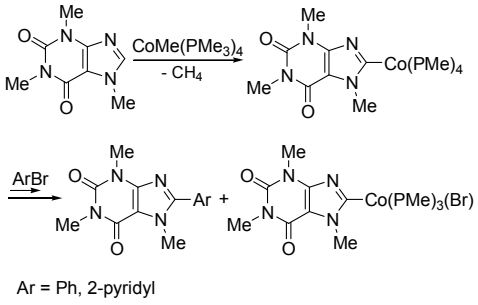
Instead of using halide derivatives, Ackermann developed chelation-assisted direct arylations or benzylations of arenes and heteroarenes under mild conditions with phenol-derived electrophiles (sulfamates, carbamates, phosphates) using a bimetallic catalytic system of $Co(acac)_2$ (10 mol %), IMes.HCl (20 mol %), CyMgCl (2 equiv) in DMPU (scheme 29).[70] Electron-rich aryl sulfamates, and both electron-rich and functionalized electron-deficient aryl carbamates were efficient electrophilic partners for arylations even when bearing sterically hindered *ortho*

substituents (scheme 29a). Various pyridyl-substituted arenes and heteroarenes bearing electron-donating or electron-withdrawing substituents provided the desired mono-arylated products (scheme 29b). *N*-substituted indoles were selectively arylated at the C2 position and one example of direct benzylation on indoles with benzyl phosphate was described (scheme 29c). The reactivity of the arene seemed to be governed by C-H bond acidities, mechanistic studies indicated a non-radical reaction mechanism.



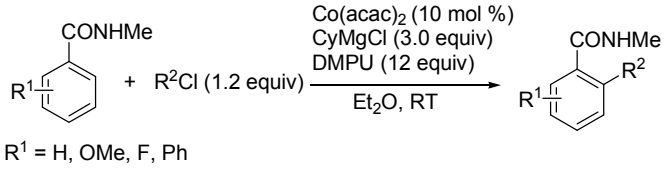
Scheme 29 Direct arylation or benzylation of arenes and heteroarenes with phenol-derived electrophiles (Ackermann, 2012)

A method for C-H bond arylation at position C8 of caffeine using stoichiometric quantities of $CoMe(PMe_3)_4$ and ArBr (Ar = Ph, 2-Pyridyl) was reported by Li in 2013 (scheme 30).[71] Based on the isolated intermediates, a mechanism was proposed: a single electron oxidative addition of $CoMe(PMe_3)_4$ at the C8 C-H bond of caffeine would form a Co(III) species, a reductive elimination would then form methane and a 8-caffeinyl cobalt(I) complex (C8-caffeinyl)$Co(PMe_3)_4$. Reaction of the latter with aryl bromides would afford a cobalt (II) complex C8-(caffeinyl)$Co(PMe_3)_3Br$ and a coupling product 8-aryl caffeine.



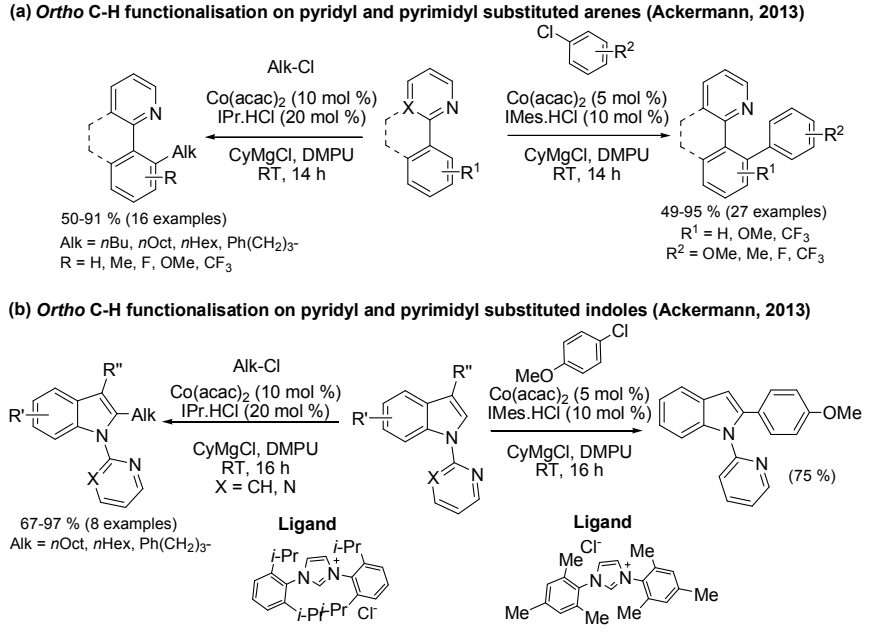
Scheme 30 C-H bond activation of caffeine by $CoMe(PMe_3)_4$ –coupling (Li, 2013)

Alkylations of arenes at *ortho* positions from DMG catalysed by bimetallic combinations were also reported. Thus, in 2011 Nakamura achieved *ortho* alkylations of few *N*-methylbenzamides by alkyl chlorides (included primary) at room temperature, catalysed by $Co(acac)_2$ (10 mol %) mixed with CyMgCl (3 equiv) (scheme 31).[72] More than 2 equiv. of organomagnesium are formally required, to deprotonate the amide nitrogen and remove the *ortho* hydrogen and to reduce Co(II) catalyst. The scope of the reaction was scarce; the deprotonated amide seemed to act as a directing group. A radical like activation of the alkyl chloride was suggested.



Scheme 31 *Ortho* arylation of benzamides with alkylchlorides (Nakamura, 2011)

In 2013, Ackermann published a series of *ortho* C-H bond functionalization on heteroaryl-substituted arenes by reaction with alkyl and aryl chlorides, forming sterically hindered *ortho* substituted biaryls at ambient temperature (scheme 32a,b).[73] The reaction was catalysed by $Co(acac)_2$ (5 mol %), CyMgCl, IMes.HCl or IPr.HCl, DMPU. Direct alkylations with β-H containing primary or secondary alkyl chlorides on pyridyl and pyrimidyl substituted arenes and heteroarenes were reported. *Ortho* alkylations of acetophenone imines with various primary and secondary alkyl halides (Cl, Br) are also feasible with moderate efficiencies (Yoshikai, scheme 32c). A mechanism was proposed, via single-electron transfer from a cobalt species to the alkyl halide to generate the corresponding alkyl radical.[74]

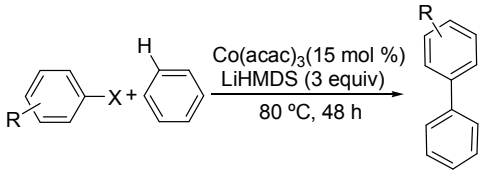


Scheme 32 Direct arylation of heteroaryl-substituted arenes with aryl/alkyl chlorides

2.5.2 Cross couplings reactions RX+ArH using high-valent cobalt complex

In 2011, Lei achieved some intermolecular direct arylations of non-activated benzenes or naphtalene with haloaryl electrophiles catalysed by $Co(acac)_3$ and LiHMDS (3 equiv) at 80 ºC (scheme 33). A radical mechanism was proposed.[75] The direct arylation of benzene with a wide range of electron-rich aryl bromides afforded biaryl products in good yields while electron poor aryl bromides afforded biaryls with moderate yields. The presence of *ortho* substituents on the electrophile led to sluggish reactions. Aryl iodides also afforded good yields of coupling products. Direct arylation of benzene by chloroarenes catalysed by $CoBr_2$ (30 mol %), DMEDA (60 mol %), LiHMDS (3 equiv) afforded average yields of biaryl products. The direct arylation of naphtalene was not regioselective. Few intramolecular direct arylations were also performed under similar conditions. Kappe studied the influence of each of the reaction parameters (metal catalyst, catalyst loading, temperature, pressure) to improve the efficiency of the direct arylation of benzene with aryl bromides.[76] It revealed that several metals (in particular Co complexes) are able to catalyse this arylation in the absence of ligand. Significant reduction of catalyst and base loading and increase of catalyst turnover was achieved: full

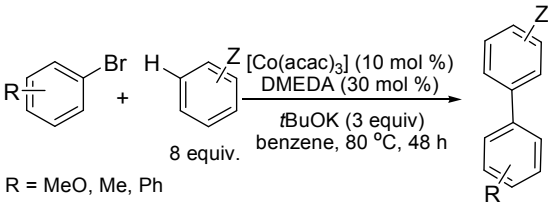
conversion could be achieved within 5 min at 200 ºC, while retaining high selectivity. The scope of the reaction was evaluated with various substituted aryl bromides.



X = Br, R = *p*-MeO (85 %), *p*-EtO (82 %), *p*-Me (80 %),
p-*t*Bu (82 %), *p*-Cl (89 %), *p*-Ph (79 %),
p-CF_3 (55 %), H (86 %), *m*-MeO (86 %),
m-Cl (92 %), *o*-Cl (82 %), *o*-MeO (<5 %),
o-F (77 %), *o*-Me (10 % at 80 °C, 62 % at 120 °C)
X = I, R = *p*-MeO (86 %), *p*-Cl (94 %), H (72 %),
m-Cl (87 %), *o*-Cl (80 %)

Scheme 33 Direct arylation of arenes with arylhalides (Lei, 2011)

The same year, Shi reported some direct arylations of substituted non activated benzenes with substituted aryl bromides using a catalytic system of $Co(acac)_3$, DMEDA and *t*BuOK (scheme 34).[77] Mechanism studies indicated that a radical intermediate rather than the cleavage of the C-H bond is the rate-determining step. Electron-donating substituents such as methoxy and methyl groups on the aryl bromide ring promoted the cross-couplings; the desired products were isolated in moderate to good yields regardless of the position of those groups. Steric hindrance at the arene ring highly affected the efficiency of the reaction. The electronic properties of the arene unit also affected the efficiency of the reaction: low to moderate yields were obtained with electron-rich arenes. An enhancement of the acidity of the C-H bonds dramatically increased the yields of biaryl products. Regioselectivity issues are a limiting factor of those methods.

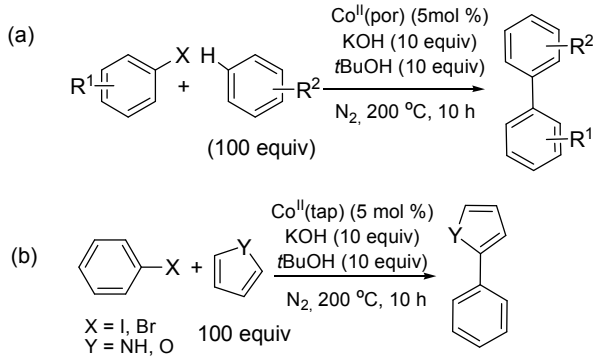


R = MeO, Me, Ph

Scheme 34 Direct arylation of unactivated arenes with arylbromides (Shi, 2011)

Chan used cobalt(II) porphyrin to catalyse the direct C-H arylation of non-activated arenes[78] (100 equiv) with electron rich or poor arylhalides (I or Br, 1 equiv) at 200 ºC (scheme 35a). For substituted non-activated arenes reactants, regioselectivities were low; the electronic effect of substituent on the arene ring did not affect the regioselectivity of arylation much but decreased the yield. Substituents at *ortho* position of bromoarenes decreased the yields of biaryl formation; while reactions with aryl iodides and CoII(t4-OMepp) catalyst afforded good yields of biaryls. Kinetic studies indicated the C–H bond cleavage was not rate-determining: the mechanism likely goes through a radical pathway with the formal iodine atom abstraction being rate-determining. The rate of direct C–H arylation of benzene increased with the electron-richness of cobalt(II)–porphyrins complexes, the

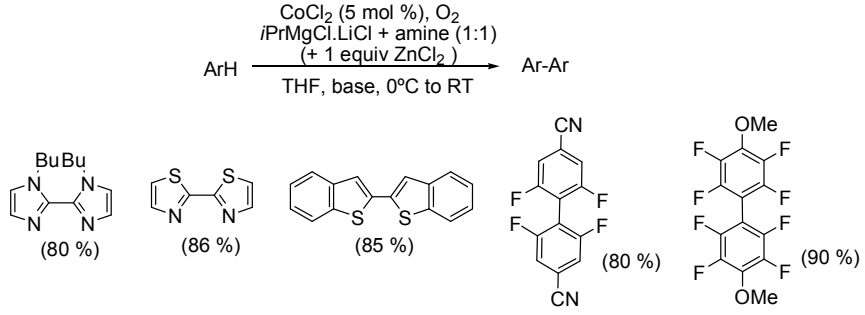
nucleophilic radical nature of CoII(por) is enhanced by electron-donating porphyrin ligands to facilitate the Ar–I bond cleavage. Changing reactants to heterocycles such as non-activated pyrroles and furans[79] (100 equiv) (scheme 35b) led to the formation of 2-arylheteroaromatics products exclusively with moderate to good yields. Slower reaction rate and lower yields were obtained with arylbromide electrophiles. Reactions were not regioselective for thiophenes and pyridines series. A mechanism via homolytic aromatic substitution was proposed.



Scheme 35 Direct arylation of unactivated arenes with arylhalides using porphyrin Co (Chan)

2.6 Base assisted aromatic C(sp2)-H bond cobaltations- functionalisations

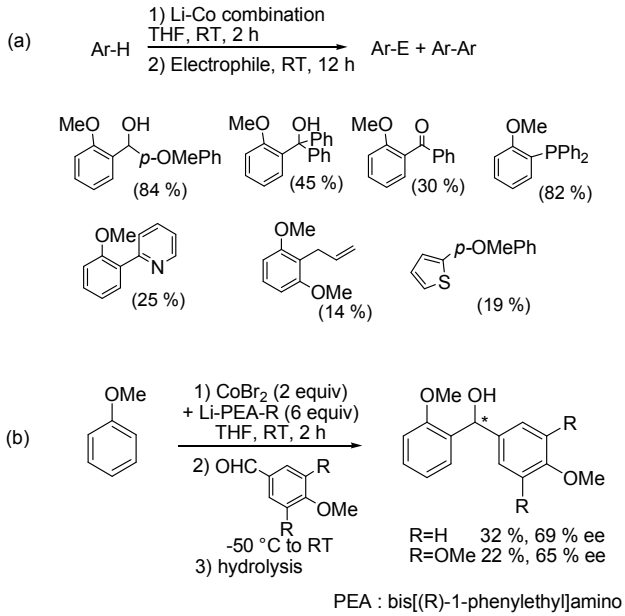
Daugulis developed efficient cobalt catalysed deprotonative dimerizations of acidic arenes such as thiazole, *N*-butylimidazole, benzothiophene as well as electron-poor arenes such as tetrafluoroanisole and difluorobenzonitrile, using oxygen as terminal oxidant (scheme 36).[80] The bases used for the process were formed by combination of *i*PrMgCl.LiCl, amine (tetramethylpiperidine or dicyclohexylamine) and $ZnCl_2$ when needed (for higher substrate stability as well as enhanced functional group tolerance). For sensitive substrates, Mg bases were used and lower yields were obtained.



Scheme 36 Deprotonative dimerization of acidic arene (Daugulis, 2010)

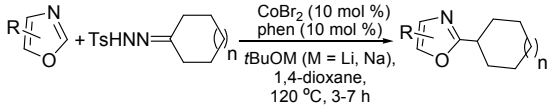
Mongin reported a series of regioselective deprotometalations of substituted arenes and heteroarenes by use of homo- or heteroleptic mixed lithium-cobalt(II) combinations containing amido and alkyl ligands that were prepared by premixing stoichiometric amounts $CoBr_2$ and organolithium reagents (scheme 37).[81] The resulting arylcobalt species reacted with various electrophiles affording substituted

arenes. Using bis[(*R*)-1-phenylethyl]amino (PEA) ligand, some degree of stereoselectivity was obtained during the reaction of arylcobalt species with benzaldehydes.

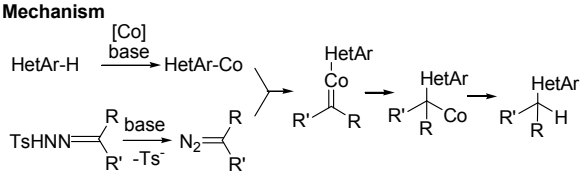


Scheme 37 Deprotometalations by homo- and heteroleptic mixed lithium-cobalt combinations-electrophile quench (Mongin)

Miura established some direct alkylations of benzothiazoles, 5-aryloxazoles and unsubstituted oxazole with *N*-tosylhydrazones (cyclopentane, cyclohexane and cycloheptane *N*-tosylhydrazones) catalysed by $CoBr_2$/phen in the presence of substoichiometric *t*BuOM (M = Li, Na) (scheme 38).[82] A base assisted direct cobaltation at the most acidic C(sp2)-H bond of the azole provided a heteroaryl cobalt species. In the same pot, *N*-tosylhydrazone was converted *in situ* to the corresponding diazo compound with concomitant elimination of the Ts group by the action of a base. Subsequent reaction of the diazo compound with the heteroarylcobalt species and 1,2 migration of the heteroaryl group from Co to the carbon centre afforded an alkyl cobalt intermediate. Protonation or ligand exchange with the C-H bond of the starting heteroarene afforded the desired heterocycles bearing a secondary alkyl side chain.



Mechanism



Scheme 38 Direct alkylation of heteroarenes with tolylhydrazones (Miura, 2012)

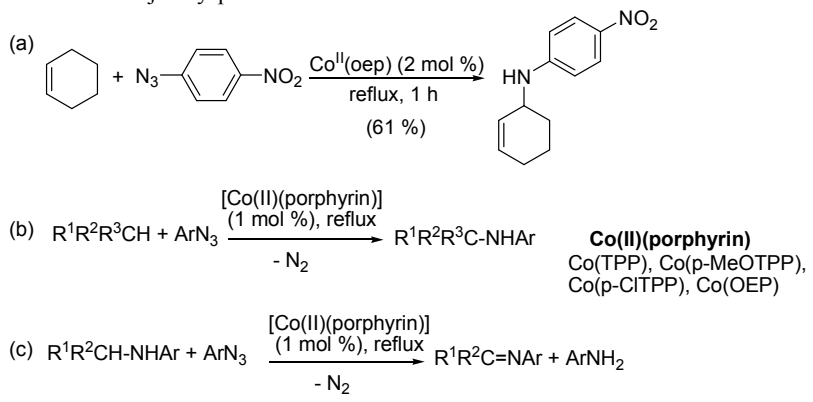
3 C-H bond functionalization forming new C-Heteroatom bonds

3.1 Direct C-N bond formations under non oxidative conditions

Direct C-H bond aminations at activated C-H allylic or benzylic positions under non oxidative conditions were reported by use of cobalt-porphyrin catalysts and formation of cobalt-nitrene intermediates.

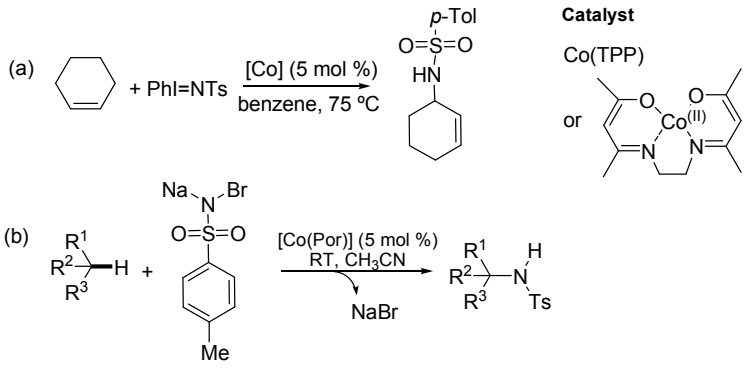
3.1.1 Intermolecular direct aminations of activated C-H bonds via formation of cobalt nitrene species

Cenini and coworkers established from 1999 that a variety of cobalt(II) porphyrins could catalyse nitrogen-atom insertions of aromatic azides into allylic or benzylic C-H bonds. For example, unsubstituted cyclohexene or benzylic C-H bonds could be aminated by *p*-nitrophenylazide using Co(II)(oep) catalyst (scheme 39a).[83] According to the nature of the reactant, an amine or an imine could be obtained with moderate yields (scheme 39b,c). Changing the hydrocarbon reactants required a screening of porphyrin ligands to achieve high yield. The product distribution was affected by the electronic nature of the aryl azide: when an electron-rich azide was used (*e.g.* *p*-methoxyphenylazide), the yield of allylic C–H bond amination was reduced. The major by-product was reduction of the azide.



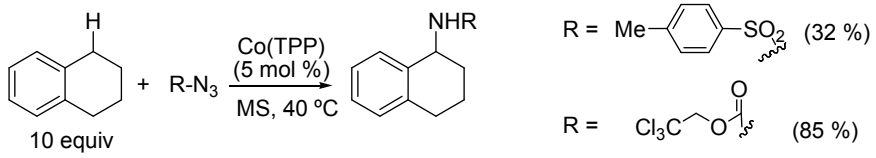
Scheme 39 Amination of allylic C-H bonds arylazides (Cenini)

The source of nitrogen could be varied. Using PhI=NTs, porphyrin complexes of cobalt(II) could catalyse aminations of C–H bonds of unfunctionalized cyclic or terminal alkenes and C–H bond of toluene, allylic amines were obtained in moderate to good isolated yields (scheme 40a).[84] With bromamine-T as the nitrene source (scheme 40b), cobalt porphyrin complexes of electron-deficient sterically demanding TDClPP ligands catalysed the intermolecular amination of a range of benzylic C–H bonds forming tosyl protected amines.[85]



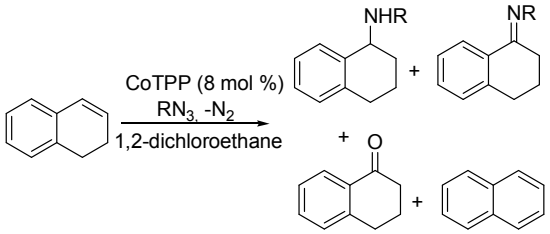
Scheme 40 Amination of alkenes by PhI=NTs or bromamine-T

Zhang extended the scope of cobalt(II) tetraphenylporphyrin catalysed intermolecular benzylic C–H bond aminations. Tetrahydronaphtalene reacted with 2,2-trichloroethoxycarbonyl azide ($TrocN_3$) or tosyl-azide to form protected amines in moderate to high yields (scheme 41).[86] The reaction was sensitive to the electronic- and steric nature of the azide, significantly higher yields were obtained with Troc-azide. Benzylic C-H bond aminations of ethylbenzene, toluene and 1,2,3,4-tetrahydronaphthalene were also achieved using $N_3C(O)OMe$, N_3SO_2Ph, $N_3C(O)Ph$, and $N_3P(O)(OMe)_2$. Mechanisms were studied by density functional theory (DFT) calculations and electron paramagnetic resonance (EPR) spectroscopy.[87] A stepwise radical process was proposed involving coordination of the azide to the cobalt centre followed by elimination of nitrogen to produce cobalt(III)-nitrene radical anion intermediates. Those readily abstract a hydrogen atom from a benzylic position of the organic substrate.



Scheme 41 Intermolecular benzylic C-H bond amination by azides (Zhang, 2010)

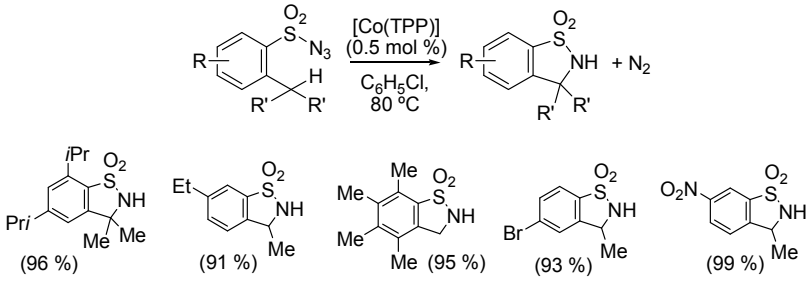
In 2012, Gallo described reactions of dihydronaphthalene with aryl azides catalysed by Co(porphyrin) complexes (scheme 42), benzylic amines of tetrahydronaphthalene were obtained with moderate yields.[88] The amination occured with a concomitant reduction of the dihydronaphthalene double bond. The best catalyst/solvent combination was Co(TMOP)/1,2-dichloroethane. The electronics of the catalyst had little influence on reaction yields.



Scheme 42 C-H amination of dihydronaphtalene with arylazides (Gallo, 2012)

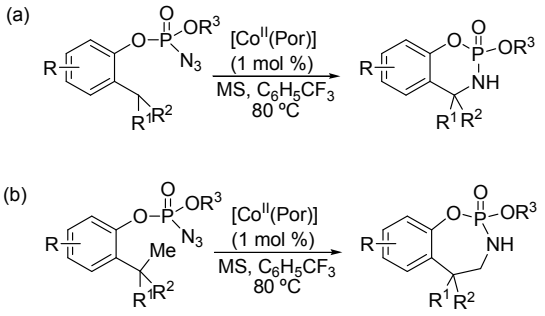
3.1.2 Intramolecular direct C-H bonds aminations via formation of cobalt nitrene species

Intramolecular aminations of benzylic C-H bonds catalysed by cobalt porphyrin complexes with arylsulfonyl azides as nitrogen source were reported by Zhang in 2007, leading to cyclization to five-membered ring benzosultams (scheme 43).[89] An increase in porphyrin ligand steric hindrance and/or electron deficiency resulted in poor catalytic activity. An increase in substitution on the aromatic ring led to higher-yielding formation of the amination products suggesting a positive buttressing effect of *meta* and *para* groups on the nitrene insertion of *ortho* C-H bonds.



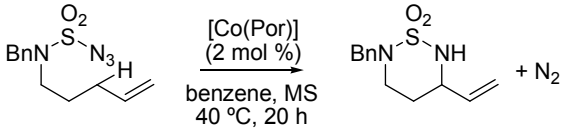
Scheme 43 Intramolecular amination of benzylic C-H bonds by arylsulfonylazides (Zhang, 2007)

Arylphosphoryl azides formed cyclized cyclophosphoramidates in high yield via intramolecular 1,6- or 1,7-C-H nitrene insertions (scheme 44).[90] When the benzylic position was fully substituted, seven-membered ring formation readily occurred without increasing the catalyst loading or reaction temperature.



Scheme 44 Intramolecular 1,6- or 1,7-C-H nitrene insertion into benzylic C–H bonds (Zhang, 2010)

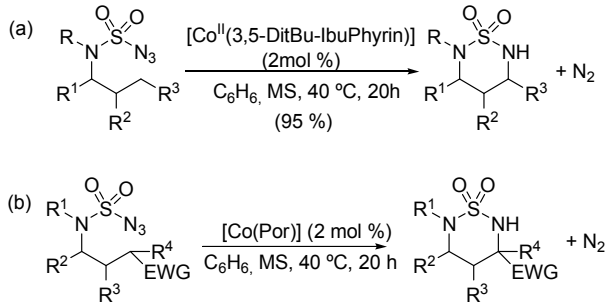
Allylic C-H bond aminations were also possible: several Cobalt(II) porphyrins catalysed intramolecular 1,6-*allylic* C-H aminations to access allylic 1,3-diamines from *N*-bishomoallylic and *N*-allylic sulfamoyl azides (scheme 45).[91] Allylic C-H bonds with various substitution patterns could be functionalized to produce *N*-heterocycles. Conditions were tolerant to alkyl-, bromo- and nitro-substituents. A ''nitrene radical'' intermediate was proposed during the reaction with a preferred stepwise H-atom abstraction–homolytic substitution pathway. The metal complex is involved in the C–N bond-forming step.



[Co(3,5-di*t*Bu-IbuPhyrin)] : 99 %
[Co(TPP)] : 43 %

Scheme 45 Intramolecular 1,6-allylic amination with azide derivatives (Zhang, 2011)

Few reports described intramolecular 1,6-C-H aminations at non allylic/benzylic C-H bonds. Using cobalt(II) [3,5-DitBu-IbuPhyrin], a range of sulfamoyl azides furnished six-membered cyclic sulfamides with excellent regio-, diastereoselectivity and stereospecificity (scheme 46a).[92a] Stereoselective intramolecular 1,6-C-H amination of electron-deficient C-H bonds, including those adjacent to electron-withdrawing CO_2R, $C(O)NR_2$, C(O)R, and CN groups was possible in excellent yields with high regio- and stereoselectivity (scheme 46b), thus providing a direct method for the synthesis of α-amino acid derivatives from the corresponding carboxylate precursors.[92b]



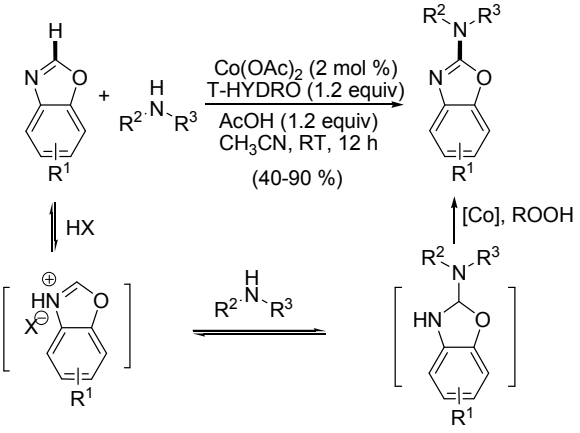
Scheme 46 Intramolecular 1,6- C-H amination of non allylic non benzylic C-H bonds with sulfamoyl azides (Zhang, 2010-2012)

3.2 Direct oxidative C-H aminations

Using amines as nitrogen source for C-H bond aminations is an attractive approach. Few examples of cobalt catalysed oxidative aminations of activated C-H bonds were reported so far, those are intermolecular processes.

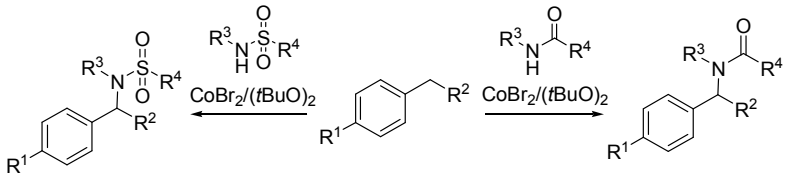
In 2010, Chang reported direct oxidative C-H aminations of a range of benzoxazole derivatives (substituents at position 5- or 4-) with several secondary amines (1.2 equiv) catalysed by cobalt(II) acetate in combination with aqueous *t*butyl hydroperoxide as oxidant (1.2 equiv) and acetic acid (1.2 equiv), affording high yields of 2-aminated products at room temperature (scheme 47).[93] The choices

of oxidants and acid additives were crucial for the reaction efficiency. Amination using cyclic amines (morpholinyl, piperidinyl, piperazinyl) as well as acyclic secondary amines (diallyl amine, benzylmethyl amine, methyl propargylamine, diethylamine…) afforded good yields of aminated azoles, but primary amines or ammonia did not afford aminated products. Functional groups such as *N*-Boc were tolerated. The acid additive might initially protonate the heteroarene to provide a salt which is more sensitive to the subsequent nucleophilic attack of amine; a cobalt catalysed rearomatization of the putative 2-aminobenzoxazolidine intermediate would then produce 2-aminobenzoxazole.



Scheme 47 Oxidative C-H amination of benzoxazoles with secondary amines (Chang, 2010)

A year later, Yu published intermolecular benzylic C-H aminations catalysed by $CoBr_2/(t\text{BuO})_2$ using primary and secondary amides such as sulfonamides, carboxamides, carbamates via dehydrogenative-coupling (scheme 48).[94] The benzyl substrates with electron-donating groups gave good yield while an electron-withdrawing group retarded the reaction. The mechanism could involve benzylic radicals which are further oxidized to form the benzylic cation through a single-electron transfer process. The subsequent nucleophilic addition of an amide then proton abstraction would deliver the coupling product and regenerate the catalyst.

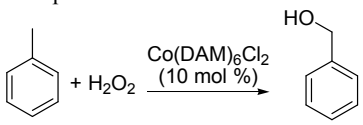


Scheme 48 Intermolecular amination of benzylic C-H bonds by amides (Yu, 2011)

3.3 C-H bond oxidations to C-O bonds

Few examples of direct benzylic C-H bond oxidations to C-O bonds catalysed by cobalt complexes were published. In 2000, Baruah reported a direct benzylic C-H bond oxidation of toluene to benzyl alcohol mainly, along with benzaldehyde and trace amount of *p*-cresol and *o*-cresol catalysed by a diacetylmonoxime Co(II) chloride complex with hydrogen peroxide as oxidant (scheme 49).[95] A mechanism

via formation of a hydroxy radical was suggested causing hydroxylation at the benzylic position. Such catalytic system also caused oligomerisation of activated aromatic compounds such as phenols and anilines at 60 ºC.



Scheme 49 Direct benzylic C-H bond oxidation of toluene to benzyl alcohol (Baruah, 2000)

Few methods for oxidation of non-activated C-H bonds were also reported. In 2000, Sen achieved the oxidation of primary C-H bonds of alkanes (ethane, propane, cyclohexane) to mixtures of aldehyde, alcohol, carboxylic acid by dioxygen (100 psi) catalysed by Co(II) porphyrin complexes at 85 °C in presence of H_2O; CF_3COOH; CO (200 psi); N_2 (800 psi).[96] The perfluorinated metalloporphyrin Co(TPP-F20) was a more efficient catalyst than its non-fluorinated analogue. Carbon monoxide was a coreductant essential for the alkane oxidation and in the process was converted to carbon dioxide. Primary C-H bonds were more reactive than the weaker secondary C-H bonds or C-H bonds α to an alcohol functionality. The rate determining step did not involve C-H bond cleavage. A high-valent cobalt-oxo species was proposed as the species breaking strong C-H bonds. The turnover rates are too slow to be of practical utility.

In 2013, Zhang showed that Co(III) complex $[Co(tfb)(bpy)_2](NO_3)\cdot 3H_2O]$ (Htfb = tetrafluorobenzoic acid, bpy = 2,2'-bipyridine) promoted the oxidation of cyclohexane in the presence of *t*-butyl hydroperoxide as the oxidant; cyclohexanol and cyclohexanone were the only observed products.[97]

5 Conclusions and perspective

The last decade saw a rapid development of C-H bonds functionalization. Cobalt can sometimes replace precious metals to promote such reactions under milder conditions. For cobalt catalysis to become a credible alternative to costly rare transition metals for greener processes, the scope of cobalt catalysed transformations needs to be expanded with less substrate dependent reaction conditions, with good regiocontrol of functionalization using removable or exploitable directing groups unlike pyridine.

Cobalt mediated C-H bond functionalization using bimetallic combinations lack of mechanistic insight; the active catalytic species remain elusive at this stage. Many reports suggest low-valent organocobalt(0)ate species as active catalytic species, the reactivities of such species remain essentially unexplored. Understanding the cooperation between metals should pave the way to new reactivities, greener processes involving first row transition metals, should allow for the rational design of more efficient bimetallic combinations towards highly selective atom economical synthetic organic processes.

Considering the recent achievements in term of chemo- and regioselectivity under mild conditions using cobalt complexes, new catalytic systems of cobalt for C-H bond functionalizations (e.g. dehydrogenative couplings) might rapidly develop as a viable economical alternative that avoid heavy transition metal remaining.

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