COBALT CATALYZED (sp^2) C-H ACTIVATION REACTIONS WITH MULTI-UNSATURATED SUBSTRATES FOR FIVE- AND SIX-MEMBERED NITROGEN HETEROCYCLE SYNTHESIS

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Subban Kathiravan*, Ian A. Nicholls*

Department of Chemistry and Biomedical Sciences, Linnaeus University Centre for Biomaterials Chemistry, Linnaeus University, Kalmar, Sweden

(e-mail: suppan.kathiravan@lnu.se, ian.nicholls@lnu.se)

Abstract. *Cobalt catalysis has become a powerful strategy for the synthesis of biologically important heterocyclic targets. Due to its ready availability and low cost, the use of this transition metal for heterocycles synthesis has been of special interest as witnessed by its use in a growing number of elegant synthesis studies. Herein we summarize recent developments in the synthesis of heterocycles using cobalt oxidative catalysis.*

Contents

1. Introduction

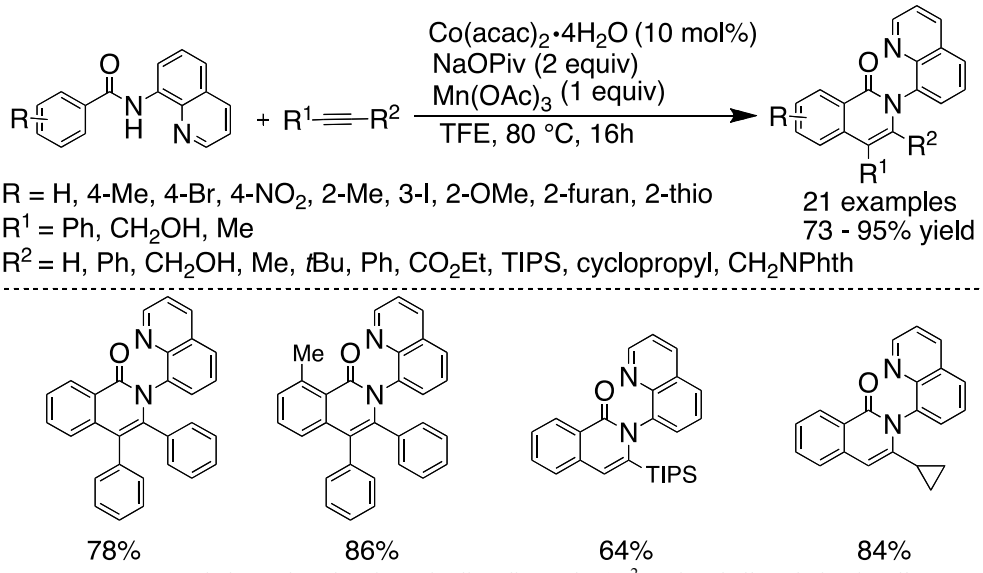
Transition metal catalyzed C-H activation reactions have become one of the most attractive and atom economical methods for the synthesis of heterocycles.[1] In particular, oxidative C-H activation reactions have been identified as a powerful tool for the late stage diversification of organic compounds.[2] Although the use of noble metals including Pd, Rh, Ru, and Ir, has dominated the field of C-H activation,[3] on account of the relatively high cost of these noble metals, the development of inexpensive earth-abundant first row-transition metals as alternative catalysts is attracting increased attention.[4] In this respect, cobalt-catalyzed C-H activation reactions have received significant attention because cobalt is the earth abundant and less expensive than noble metals.[5] Moreover, owing to its unique reactivity and functional group tolerance, the use of cobalt catalysts for C-H activation provides a complementary method to noble metal catalysis.[6]

Kanai *et al.* presented high valent cobalt catalyzed C-H activations for use in the preparation of annulated heterocycles, amongst other types of C-H activation reaction.[7] Later, Daugulis *et al.* established the user of directing group-aided low valent cobalt catalyzed C-H activation reactions.[8] In this review, our focus is on low valent cobalt catalyzed C-H activations with unsaturated substrates. For other related reports the reader advised to read the reviews by Ackermann,[5c] Yoshikai,[4c] and others.[5]

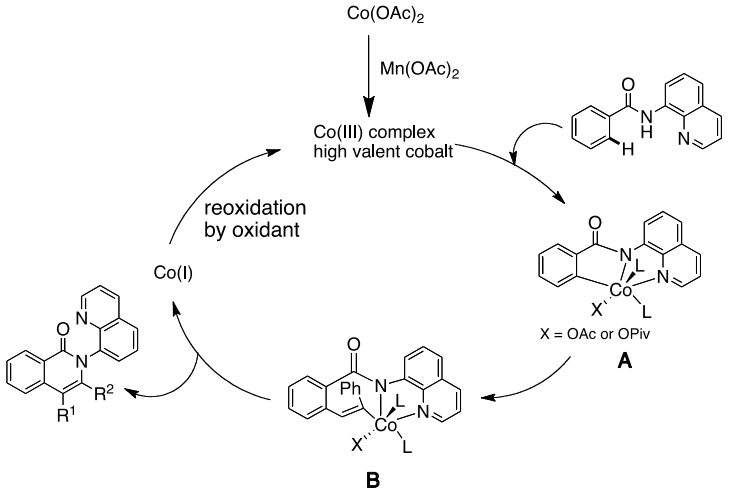
2. C-H activation with carboxamides

In 2014 Daugulis reported a method for cobalt catalyzed aminoquinoline and picolinamide directed C(sp^2)-H bond alkenylation using alkynes.[8] This method showed excellent functional group tolerance with both internal and terminal alkynes. The reaction was performed with $Co(OAc)_2.4H_2O$ as catalyst and $Mn(OAc)_2$ as oxidant (Scheme 1). This was found to be successful with both electron rich and electron poor aminoquinoline amides and various functionalities such as bromo-, nitro- and iodo- groups were tolerated. They even demonstrated the use of the picolinamide directing group in this transformation in order to functionalize benzyl and naphthylamine derivatives.

The reaction is proposed to proceed via the cobalt (III) intermediate which is formed by oxidation of $Co(OAc)_2$ in the presence of aminoquinoline amide ligand.[8] Insertion of the alkyne into the cobalt-aryl bond of **A** would provide complex **B** (Scheme 2). The cobalt acetylide intermediate was ruled out since the terminal alkynes are more reactive than internal alkynes and the authors found that the formation of complex products when they used. The reductive elimination directly produces the product.



Scheme 1. Cobalt-catalyzed aminoquinoline directed C(sp^2)-H bond alkenylation by alkynes.

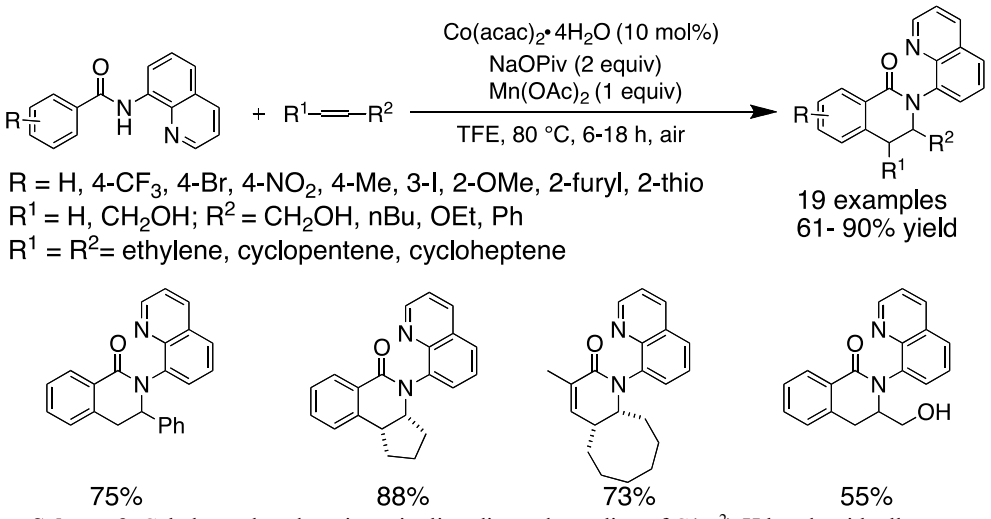


Scheme 2. Proposed mechanism.

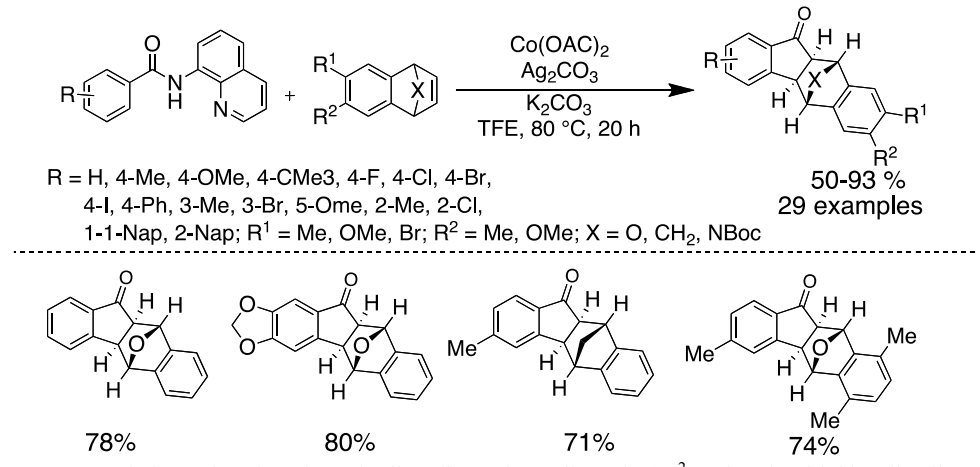
Daugulis even reported a method for cobalt-catalyzed aminoquinoline directed *ortho*-functionalization of sp^2 C-H bonds with alkenes (Scheme 3).[9] The reaction proceeds at room temperature in trifluoroethanol in the presence of the co-catalyst, $Mn(OAc)_2$, and using oxygen from air as an co-oxidant. Various amide derivatives derived from benzoic, heteroaromatic, and acrylic acids react with ethylene as well as mono- and di-substituted alkenes to afford products in good yields. An excellent functional group tolerance was also observed with the aminoquinoline amides substituted with either halogen, nitro, ether or unprotected hydroxyl functionalities.

A highly diastereoselective method for the synthesis of dihydroepxybenzofluorenone derivatives from aromatic/vinylic amides and bicyclic alkenes was described by Gandeepan and co-workers (Scheme 4).[10] This new transformation was found to take place through a cobalt catalyzed C-H activation and

intramolecular nucleophilic addition to the amide functional group. The reaction proceeds under mild reaction conditions and tolerates a wide variety of functional groups. Mechanistic studies indicated that the C-H bond cleavage may be the rate-limiting step.



Scheme 3. Cobalt-catalyzed, aminoquinoline-directed coupling of C(sp^2)-H bonds with alkenes.

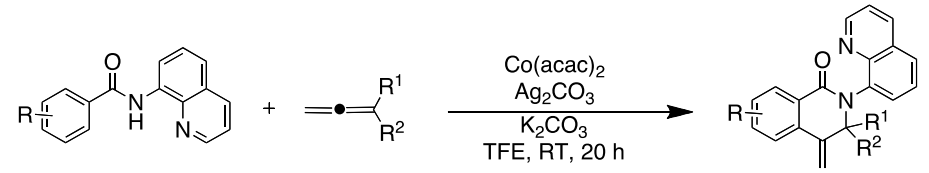


Scheme 4. Cobalt-catalyzed, aminoquinoline-directed coupling of C(sp^2)-H bonds with bicyclic alkenes.

Thrimurtulu and co-workers explored the reactivity of allenes in cobalt catalyzed sp^2 C-H activation reactions for the synthesis of dihydroisoquinolin-1(2*H*)-one (Scheme 5).[11] While 2-substituted amides were tolerated well, producing the expected products in good yield, the *meta*-substituted amides resulted in complicated mixtures of regioisomers. They noted that variation of the electronic properties of the allene has the potential to change allene reactivity. Interestingly, when an electron deficient allene is used instead of an aryl allene they found the formation of either isoquinolone or pyridone derivatives as the major product.

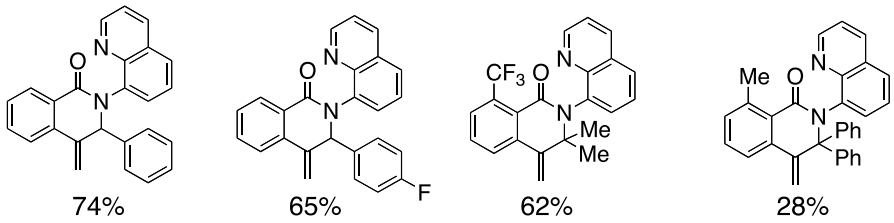
A $Co(OAc)_2$ catalyzed alkyne annulation via C-H/N-H functionalization was described by Ackermann *et al.* where molecular oxygen was used as the sole oxidant (Scheme 6).[12] The user-friendly oxidase strategy proved viable with various internal and terminal alkynes through C-H cobaltation. This methodology

provided step-economical access to the topoisomerase-1 inhibitor 21,22-dimethoxyrosettacin used as an anti-cancer agent. Furthermore, the authors performed DFT calculations that suggested that electronic effects control the regioselectivity of the alkyne insertion step. This cobalt oxidase catalysis was not restricted to terminal alkynes and even internal alkynes were found to undergo chemoselective annulation with benzamides.

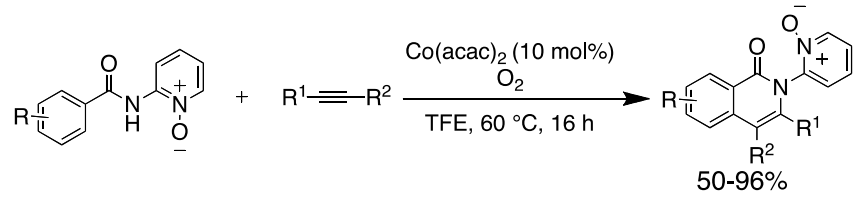


R = H, 2-Me, 4-Me, 2-OMe, 2-F, 2-Cl, 4-Br, 2-Me, 2-Ph, 1-Nap, thio, 2-CF_3; R^1 = H, Ph, 4-FPh, 4-ClPh, Me
R^2 = H, Ph, Me

29-75%
22 examples

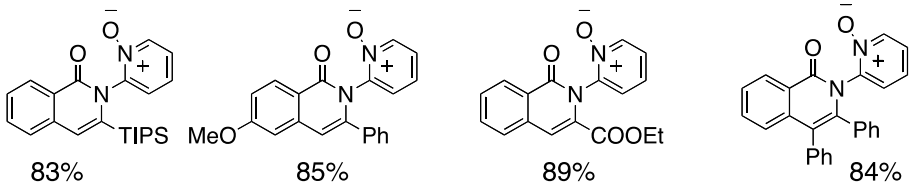


Scheme 5. Cobalt-catalyzed, aminoquinoline-directed coupling of C(sp^2)-H bonds with allenes.



50-96%
26 examples

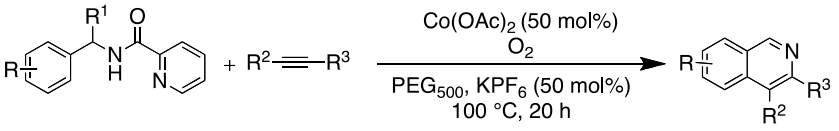
R = H, 4-Me, 4-CF_3, 4-OMe, 4-Br, 3,5-diMe, 3-Me, 4-F, 2-Me
R^1 = *n*-Hex, *n*-Pent, *p*-Tol, CH_2NPhth, TIPS, CO_2Et, CH_2CH_2OCOPh, $(CH_2)_7$-COOH, Ph, 4-FPh, C_2H_5
R^2 = Ph, 4-FPh, C_2H_5, *n*-Pent, Me



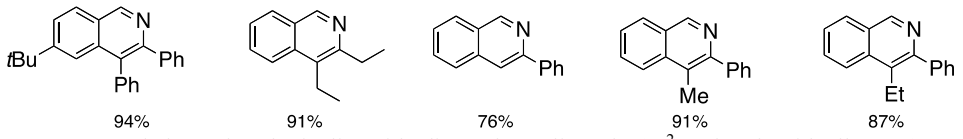
Scheme 6. Cobalt-catalyzed, pyridine-*N*-oxide-directed coupling of C(sp^2)-H bonds with alkynes.

In 2017, Cui and co-workers reported a cobalt catalyzed selective synthesis of isoquinolines using picolinamide as a traceless directing group (Scheme 7).[13] This traceless directing group strategy employed in the cobalt catalyzed oxidative annulation of benzylamides with alkynes to synthesis isoquinolines through C-H/N-H bond activation. Oxygen is used as a terminal oxidant and this protocol exhibits good functional

group tolerance and excellent regioselectivity. Both the terminal and internal alkynes can be efficiently applied to this catalytic system as substrates.

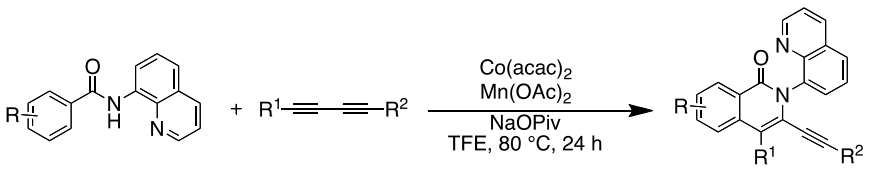


R = 4-Me, 4-OMe, 4-*t*Bu, 4-F, 4-Cl, 4-Br, 4-OCF_3, 4-CF_3, 4-OH
2-Me, 2-OCH_3, 2-F, 2-Cl, 2-Br, 3-Me, 3-OMe, 3-F, 1-Nap
R^1 = Me, Ph
R^2 = Ph, 4-Me, 4-OMe, 4-F, 4-Cl, 4-CF_3, 4-COOEt, 3-Me, 3-OMe, 3-F, 3-Cl, *n*-Prop, *n*-Et, H, Me, *n*-Bu, 4-NO_2
R^3 = Ph, 4-Me, 4-OMe, 4-F, 4-Cl, 4-CF_3, 4-COOEt, 3-Me, 3-OMe, 3-F, 3-Cl, *n*-Prop, *n*-Et, H, 4-NO_2

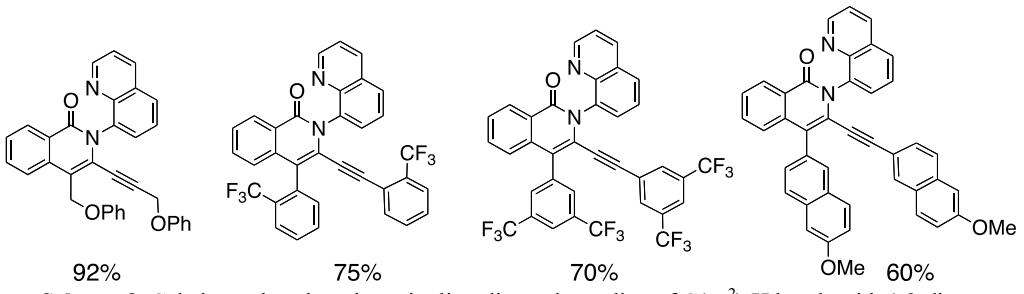


Scheme 7. Cobalt-catalyzed, picolinamide-directed coupling of C(sp^2)-H bonds with alkynes (*n*-Et, *n*-Prop).

Recently, our group presented a report describing a cobalt catalyzed regioselective C(sp^2)-H activation of amides with 1,3-diynes (Scheme 8).[14] This method was developed to efficiently synthesize isoquinones, a structural motif present in a number of biologically active substances. The method was subsequently extended to synthesize bis-heterocyclic derivatives.



R = H, 2-Me, 3-Me, 4-Me, 2-OMe, 3-OMe, 4-OMe, 2-F, 3-F, 4-F, 3-Cl, 4-Cl, 2-Br, 3-Br, 4-Br, 2-I, 3-CF_3, 3,5-CF_3, 4-NO_2 -2-Thio, 2-Furan, 1-Nap, 2-Nap,
R^1 & R^2 = *n*-Bu, *n*-Pent, CH_2CH_2OH, Cypropyl, Cypentyl, COOEt, Me, OMe, 3,5-CF_3, 4-tBu, 2-CF_3, 2-Py, 3-Cl, H

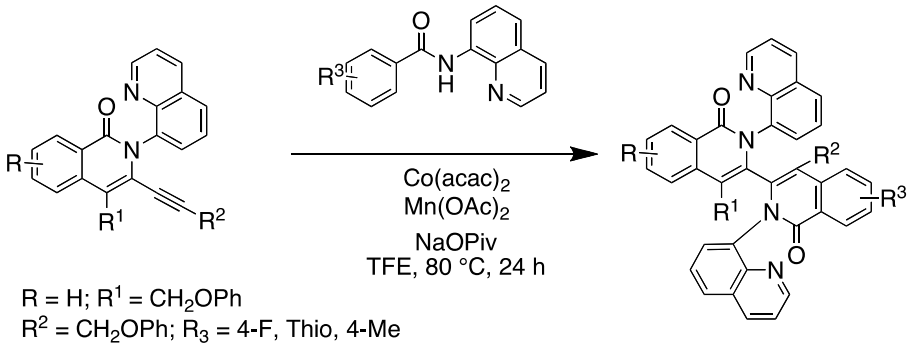


Scheme 8. Cobalt-catalyzed, aminoquinoline-directed coupling of C(sp^2)-H bonds with 1,3-diynes.

On account of the reaction's high degree of functional group-tolerance we then explored the synthesis of bis-heterocycles through tandem double C-H activation of 1,3-diynes (Scheme 9).

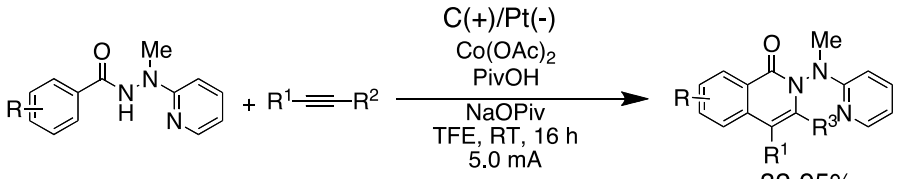
Ackermann and co-workers demonstrated electrochemical oxidative C-H/N-H activation for [4+2]-annulations using internal alkynes (Scheme 10).[15] This electrooxidative C-H activation strategy was

deployed using an undivided cell-setup under exceedingly mild reaction conditions at room temperature using earth-abundant cobalt catalysts. This C-H activation avoids the use of external chemical oxidants in the catalytic cycle and H_2 is the only by-product making this reaction very advantageous from a green chemistry perspective. The authors also illustrated the power of electrochemistry through the electrooxidative removal of the hydrazide directing group for the synthesis of isoquinolones.

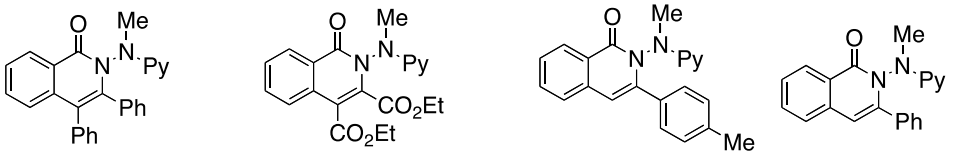


R = H; R^1 = CH_2OPh
R^2 = CH_2OPh; R_3 = 4-F, Thio, 4-Me

Scheme 9. Cobalt-catalyzed, aminoquinoline-directed synthesis of bis-heterocycles.



R = 4-Me, 4-Ph, 4-OMe, 4-OBn, 3-Me, 3-CF_3, 3,5-diMe, 2-F, 3-CN, 4-Cl, 4-Br, 4-I
R^1 = Ph, CO_2Et, Me, n-Bu, 3,4,5-triF, 3,5-diF, H
R^2 = Ph, CO_2Et, *n*-Pr, *n*-Bu, *n*-Hex, *n*-Oct, *t*Bu, thio, 2-CF_3Ph, 3-MePh, 2-FPh, 4-MePh, 4-*n*-PrPh, 4-*t*BuPh, 4-*n*-PentPh, 4-OMePh, 4-CF_3Ph, 4-Br

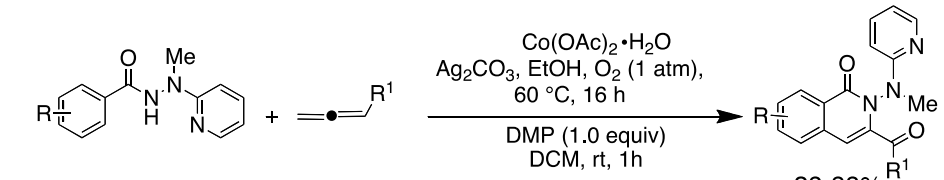


Scheme 10. Cobalt-catalyzed, hydrazide-directed coupling of $C(sp^2)$-H bonds with alkynes.

A strategy for the cobalt catalyzed trifunctionalization of allenes to deliver 3-acylquinolines has recently been developed by Zhai and co-workers (Scheme 11).[16] The reaction proceeds in the presence of molecular oxygen in moderate to good yield with high regioselectivity. The reaction was found to have broad functional group tolerance with respect to both allenes and hydrazides. The authors deployed 2-(1'-methylhydrazinyl)pyridine (MHP) as a directing group for the stabilization of the higher oxidation states of cobalt in the catalytic cycle.

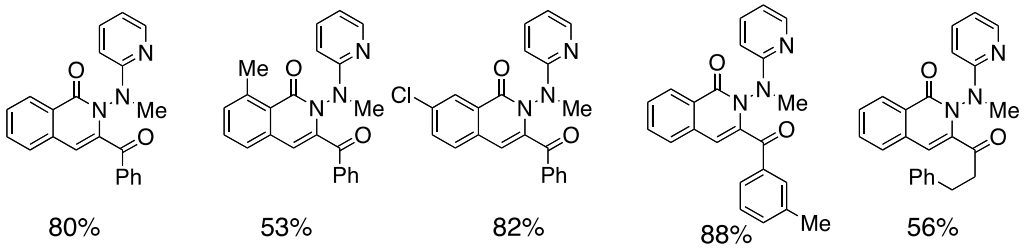
A versatile cobalt catalysis enabled electrochemical C-H activation with allenes was presented by Meyer *et al.* (Scheme 12). Allene annulations were accomplished through tandem C-H/N-H functionalizations with excellent levels of chemoselectivity, site selectivity, and regioselectivity under exceedingly mild conditions. The authors also presented detailed mechanistic studies, including reactions with isotopically labelled compounds, kinetic investigations, and in-operando infrared spectroscopic studies.

Computational studies were supported the presence of a non-rate-determining C-H cleavage in the reaction mechanism and gave key insights into the regioselectivity of the allene annulations. The practical utility of this user-friendly approach was further highlighted through its use in gram scale electrocatalysis.[17]

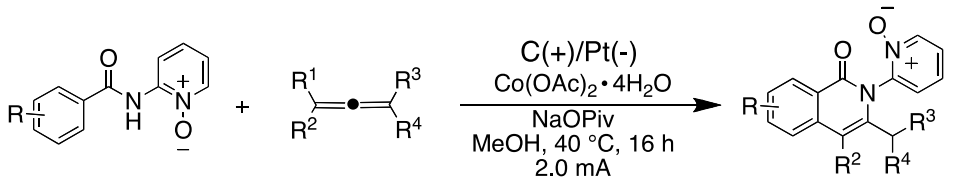


R = H, 4-Me, 4-tBu, 4-OMe, 4-Ph, 4-OPh, 4-SMe, 4-NMe_2, 4-OCF_3, 4-F, 4-Cl, 4-Br, 4-I, 4-CF_3, 4-Ac, 4-CO_2Me, 3-Me, 3-OMe, 3-Cl, 2-Me, 2-OMe, 3,5-diMe, 3,4-diOMe, furan

R^1 = 4-MePh, 3-MePh, 2-MePh, 4-tBuPh, 4-OMePh, 2-Nap, 3-ClPh, 2-ClPh, 3-BrPh, 4-BrPh, $PhCH_2CH_2$



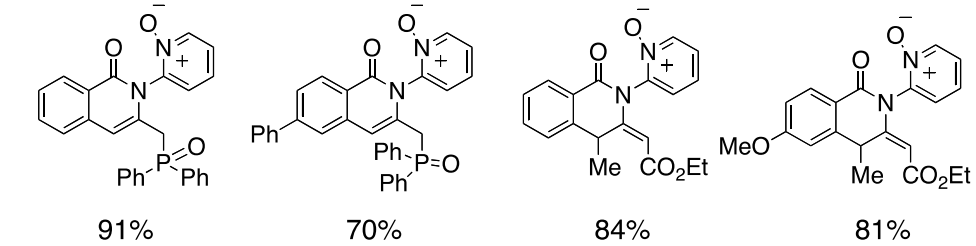
Scheme 11. Cobalt-catalyzed, hydrazide-directed coupling of C(sp^2)-H bonds with allenes.



R = H, 4-Me, 4-OMe, 4-tBu, 4-F, 4-Ph, 3,4-diMe, 1-Nap, 1-Flu, 4-I, 3-OMe, 3,4-OCH_2O, 3-F, 4-Ac, 4-CO_2Me,4-SMe, 3-benzothio, 2,3-vinyl

R^2 = H, Me, nPr; R^3 = Me, H, CO_2Et;

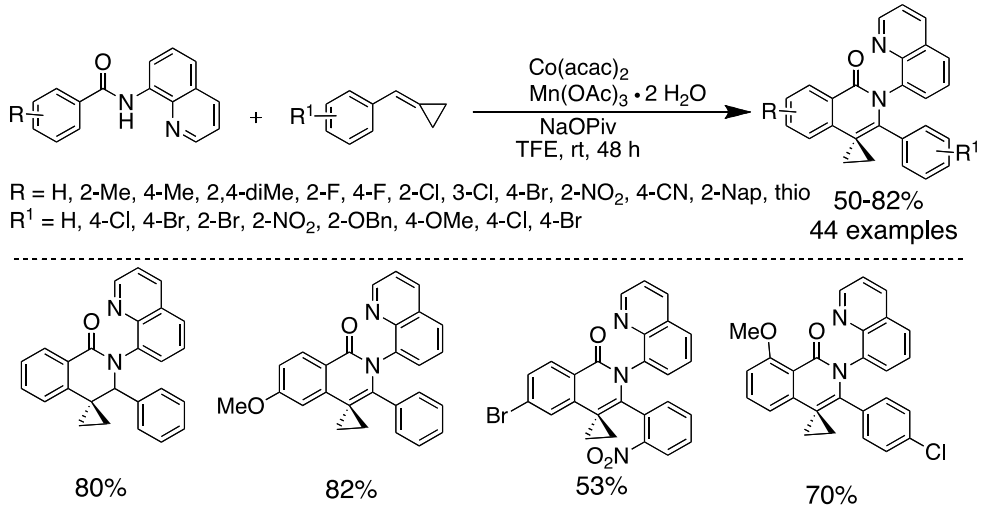
R^4 = $P(O)Ph_2$, P(O)(p-TolPh)$_2$



Scheme 12. Cobalt-catalyzed, pyridine-*N*-oxide-directed coupling of C(sp^2)-H bonds with allenes.

A bidendate chelation assisted C-(sp^2)-H activation and annulation of benzamides and alkylidene cyclopropanes (ACPs) was developed by Volla and co-workers (Scheme 13). The authors observed a unique

reactivity of the organocobalt species that led to a selective migratory insertion across the more electron rich C-C double bond of the ACP. This was followed by a faster reductive elimination from the seven membered cobaltacycle to furnish the corresponding spiro-dihydroisoquinoline derivatives with conservation of the cyclopropyl group. This cobalt catalyzed C-H activation was realized at room temperature with both aryl and heteroaryl amides. This methodology was extended to include the use of dipheyphosphinamides and, interestingly, the authors even observed the formation of homocoupling products when they conducted the reaction without methylenecyclopropane.[18]



Scheme 13. Cobalt-catalyzed, aminoquinoline-directed coupling of C(sp^2)-H bonds with allylidenecyclopropanes.

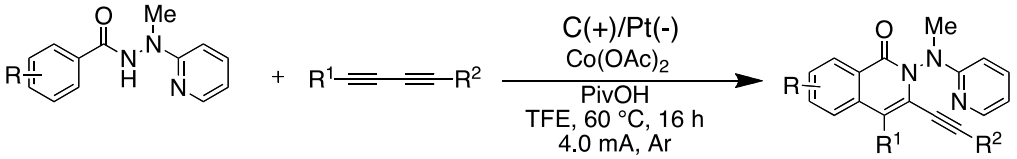
An efficient electro-oxidative C-H/N-H activation with 1,3-diynes has been described by Mei and co-workers that uses earth abundant cobalt catalysis (Scheme 14). The pyridinyl hydrazine was used as a robust directing group and provided the alkynylated isoquinolinone in very good yield under mild reaction conditions. To further illustrate the synthetic utility of their protocol, a 5.0 mmol scale reaction was performed that resulted in an 82% isolated yield.[19]

Many groups have focused on the use of *N,N*-bidendate chelation assistance for cobalt catalyzed C-H activation reactions. The Song group devised a novel strategy with *N,O*-bidendate directing group to access isoquinolines (Scheme 15). [20] The weakly coordinating nature of the carboxylic acid was employed for the preparation of isoquinolines. An interesting feature is the use of the *N-O* bond of the α-imino-oxy acid as an internal oxidant. With this strategy in hand, the authors have deployed it for terminal as well as internal alkynes. This operationally simple reaching is amenable to use with a broad substrate scope and provides products in good yield.

Lei and co-workers developed an efficient methodology for reactions with ethylene and acetylene (Scheme 16). These two-carbon building blocks participate in the cobalt catalyzed dehydrogenative C-H/N-H [4+2]-annulation of aryl/vinyl amides in an electrochemical reaction protocol.[21] Significantly, this work provides an example of the use of an electrochemical recycling of the cobalt catalyst in these oxidative C-H functionalization reactions, thus avoiding the use of external chemical oxidants and co-oxidants. High reaction efficiency and good functional group tolerance are observed under divided cell electrolytic conditions.

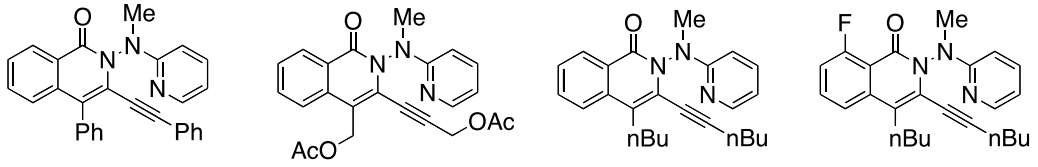
An 8-aminoquinolyl auxiliary-assisted cobalt catalyzed *ortho*-C-H functionalization annulation of arenes and alkenes with alkynylsilanes has been recently reported by Lin and Shen (Scheme 17). [22] The alkynylsilanes were coupling partners with a broad range of benzamides and acrylamides, affording the

corresponding isoquinolone and pyridine derivatives in moderate to high yields. It is worth noting that the silyl group in the final products can be retained or removed by switching the reaction conditions.



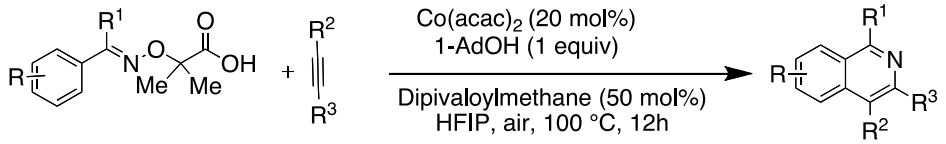
R = H, 4-Me, 4-OMe, 4-OBn, 4-Ph, 4-NMe_2, 4-Cl, 4-Br, 4-I, 3-Me, 3-Ac, 3-CN, 3-CF_3, 3,4-diMe, 2-F, 2-Me, 2-Nap, Cy, Furan, Thio
R^1 = *n*-Bu, Ph, Me, *n*-Pr, *n*-Hex, TMS, CH_2OAc, $(CH_2)_4$-OH
R^2 = *n*-Bu, Ph, Me, *n*-Pr, *n*-Hex, TMS, CH_2OAc, $(CH_2)_4$-OH, Ph

32 examples
57 - 92% yield



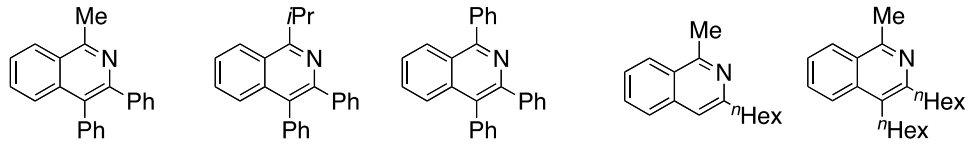
73% 57% 77% 84%

Scheme 14. Cobalt-catalyzed, hydrazide-directed coupling of C(sp^2)-H bonds with 1,3-diynes.



R = H, 4-Me, 4-OMe, 4-Et, 4-*t*Bu, 4-F, 4-Cl, 4-Br, 4-CF_3, 3-Me, 3-OMe, 3-Cl, 2-F, thio, Nap
R^2 = H, Ph, 4-BrPh, Me, *n*-Pr, *n*-Hex, CH_2CH_2Ph, *t*Bu, TIPS
R^3 = *n*-Hex, CH_2CH_2Ph, *t*Bu, TIPS

28 examples
33 - 97% yield



91% 77% 69% 47% 74%

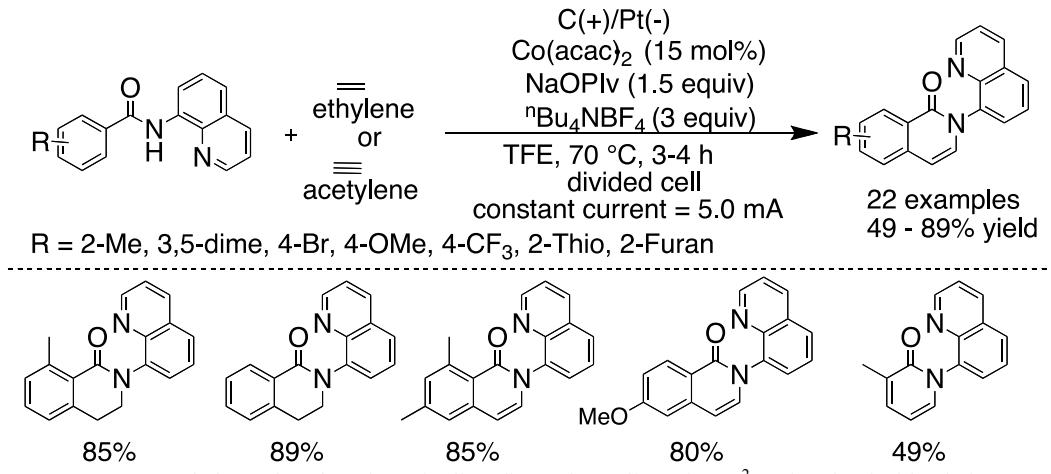
Scheme 15. Cobalt-catalyzed, *N*,*O*-bidendate-directed coupling of C(sp^2)-H bonds with alkynes.

We recently demonstrated the use of benzothiophene-[*b*]-1,1-dioxide in C(sp^2)-H activation with aminoquinoline amides by using cobalt catalyst in the presence of oxidant (Scheme 18).[23] A broad range of annulated benzothiophene derivatives was obtained in good to very good yield. The synthetic utility of this method was highlighted by its use in a gram scale reaction. Mechanistic studies showed the possibility of a double C-H activation via an aza-Michael pathway.

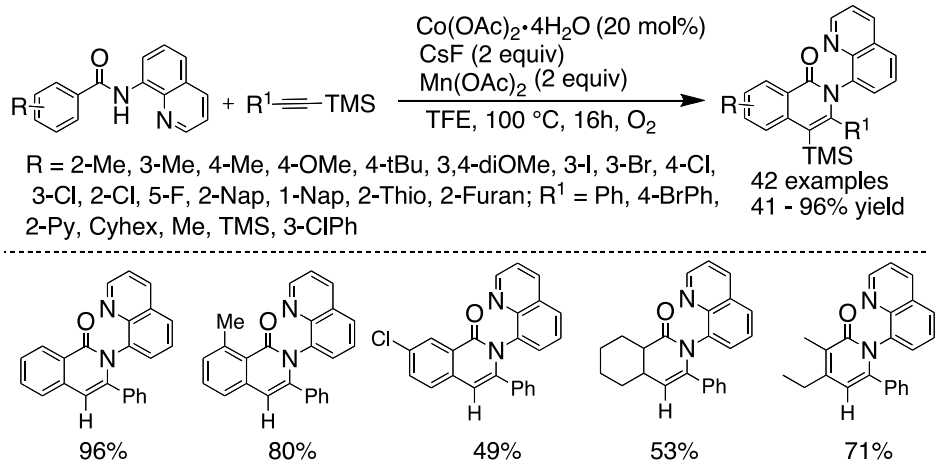
3. C-H activation with phosphinamides

Heterocyclic organophosphorous compounds have found extensive use as ligands in transition metal-driven catalysis.[24] New approaches for their synthesis are therefore of interest. Using transition metal

catalyzed C-H activation reactions for generating this interesting heterocyclic class in an atom economical fashion has shown promise. Recently, the groups of Lee, Miura, Kim and others have described the use of phosphorous derived functionalities as directing groups for *ortho*-C-H activations in conjunction with expensive second row transition metals,[25] through the use of earth abundant metal catalyst for this purpose is highly desirable.



Scheme 16. Cobalt-catalyzed, aminoquinoline-directed coupling of C(sp^2)-H bonds of with ethylene and acetylene.

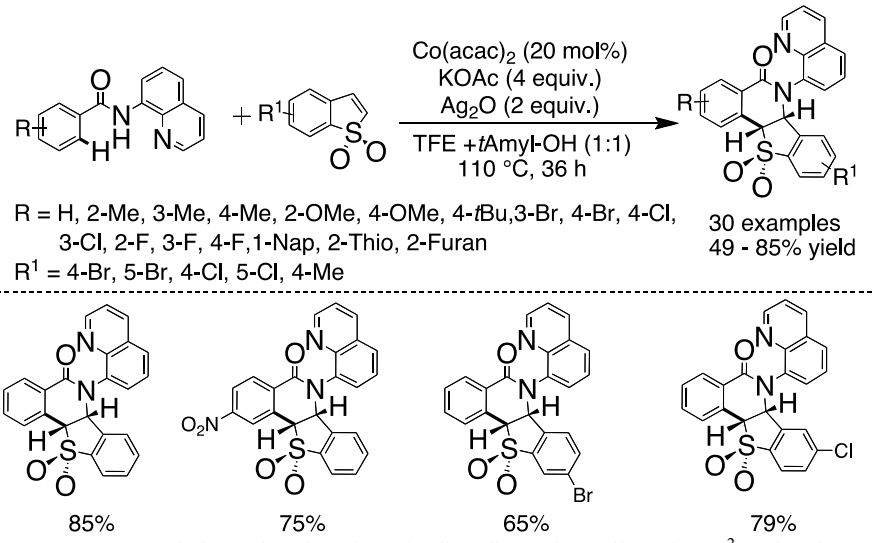


Scheme 17. Cobalt-catalyzed, aminoquinoline-directed coupling of C(sp^2)-H bonds of with trimethylsilylacetylene.

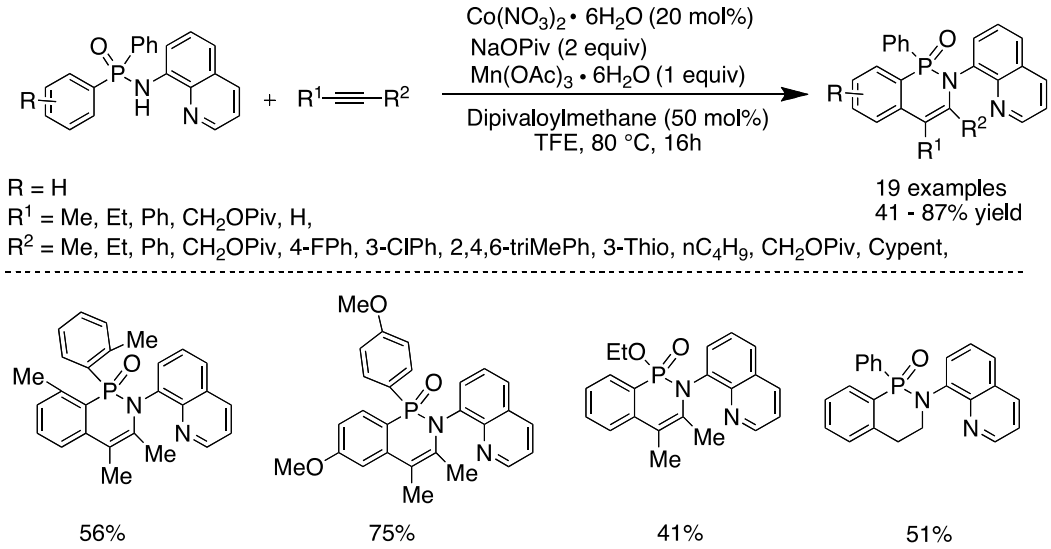
In this respect, the Daugulis group has described the use of arylphosphinic amides for the aryl sp^2 C-H bonds with alkynes, alkenes, and allyl pivalate.[26] The reactions were efficiently catalyzed by $Co(NO_3)_2$ hydrate in ethanol or mixed dioxane/*t*BuOH solvent in the presence of $Mn(OAc)_3.2H_2O$ additive, sodium pivalate, or acetate base and used air-derived oxygen as an oxidant. The authors even demonstrated the removal of the directing group to afford the *ortho*-functionalized *P*,*P*-diarylphosphinic acids (Scheme 19).

After the initial discovery by Daugulis of the use of the phosphorous directing group in cobalt catalyzed C-H activation reactions, Volla and co-workers extended this methodology through the use of

heterobicyclic alkenes for the effective synthesis of polyaryl cyclic phosphinamides at room temperature through ring opening/aromatization sequence, with the reaction demonstrating a high levels of diasteroselectivity (Scheme 20).[27]

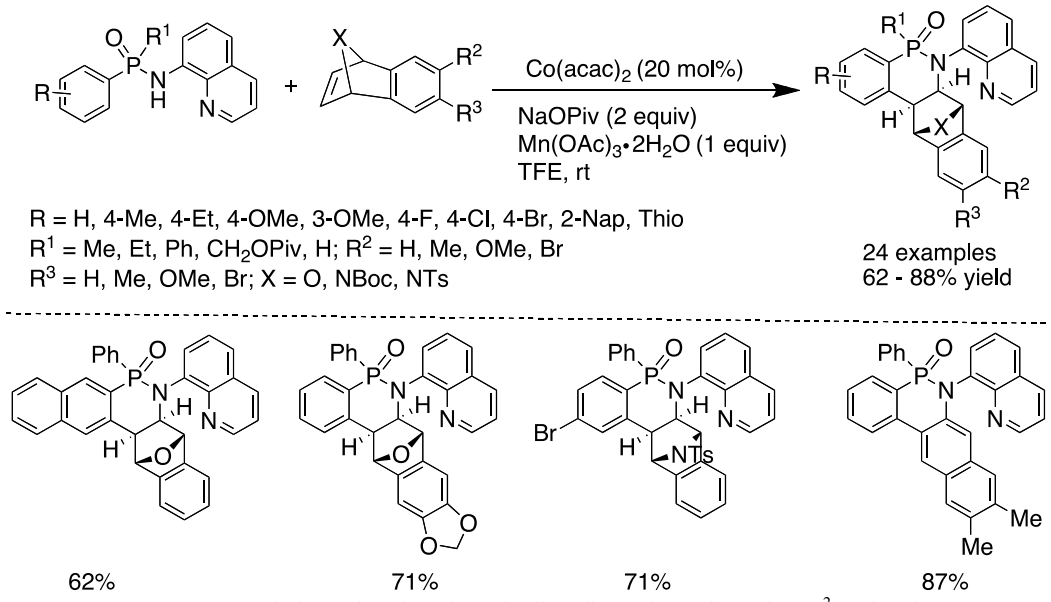


Scheme 18. Cobalt-catalyzed, aminoquinoline-directed coupling of C(sp^2)-H bonds of with benzothiophene-[*b*]-1,1-dioxide.

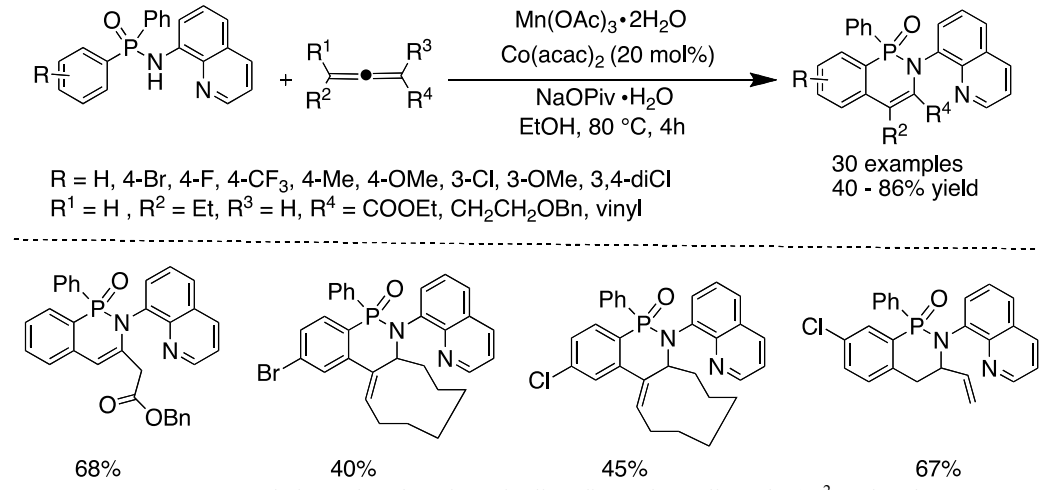


Scheme 19. Cobalt-catalyzed, aminoquinoline-directed coupling of C(sp^2)-H bonds of phosphinic amides with alkynes.

Later, Rao's group utilized phosphinamides with allenes for the synthesis of phosphaisoquinolin-1-one by annulation through a cobalt promoted C-H activation (Scheme 21).[28]



Scheme 20. Cobalt-catalyzed, aminoquinoline-directed coupling of C(sp^2)-H bonds of phosphinic amides with bicyclic alkenes.



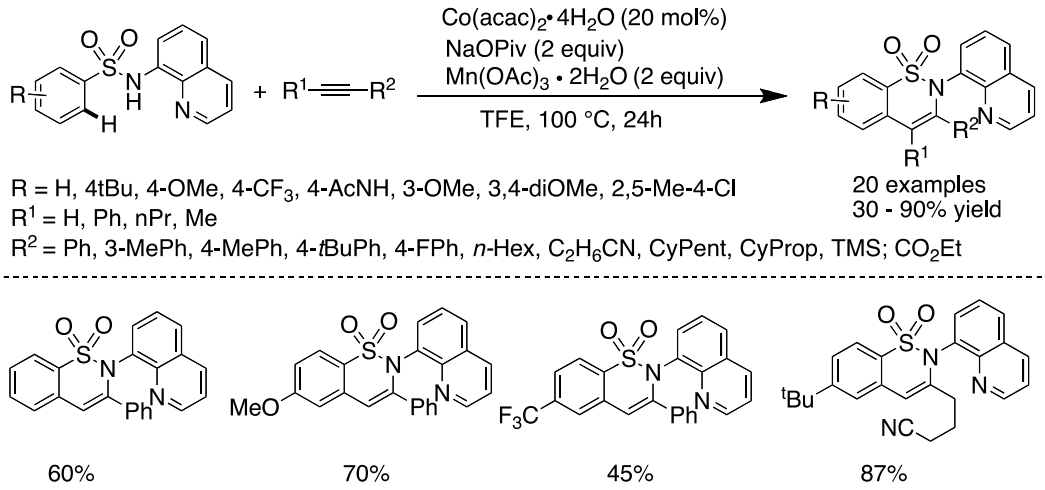
Scheme 21. Cobalt-catalyzed, aminoquinoline-directed coupling of C(sp^2)-H bonds of phosphinic amides with allenes.

4. C-H activation with sulfonamides

The sulfonamide and, to a lesser extent, sultam moieties can be found in a range of biologically active substances, some of which are used in pharmaceuticals.[29-30] Straightforward methods for their synthesis are relatively rare. Noble metals such as Pd, Rh and Ru have been utilized for the preparation of sultam derivatives using sulfonamide as a directing group.[31]

The introduction of cobalt catalyzed C-H functionalization of aminoquinolinamides and their derivatives by the group of Sundarraju involved an elegant method for the annulation of sulfonamide with

internal and terminal alkynes (Scheme 22).[32] Unlike the noble metal catalysis with sulfonamides this non-noble metal catalysis takes advantage of the reactivity with the terminal alkynes which is a different mode of reactivity to that of noble metal catalysis. The method was developed using commercially available cobalt catalysts and manganese salts as oxidants. The role of substituent on the amide was found to be crucial as the authors observed significant reductions in yield when substituted with CF_3 group (40%). At the same time the group of Yang reported sodium chlorate as a viable sub-stoichiometric oxidant for cobalt-catalyzed oxidative annulation of aryl sulfonamides with alkyens.[33] Additionally, the group of Sundarraju and Riba[34] demonstrated the use of $Mn(OAc)_3 \bullet 2H_2O$ as an oxidant for regeneration of the active catalyst.



Scheme 22. Cobalt-catalyzed, aminoquinoline-directed coupling of C(sp^2)-H bonds of sulfonamides with internal alkynes.

The use of sulphonamides for the synthesis of sultams through cobalt catalyzed C-H activation was simultaneously reported by the independent studies from the groups of Rao and Volla (Scheme 23).[35-36] Both the groups have described the use of aryl and heteroaryl sulphonamides for the intermolecular heteroannulation with allenes. The methodology accommodated a wide range of electron-poor and electron-rich allenes.

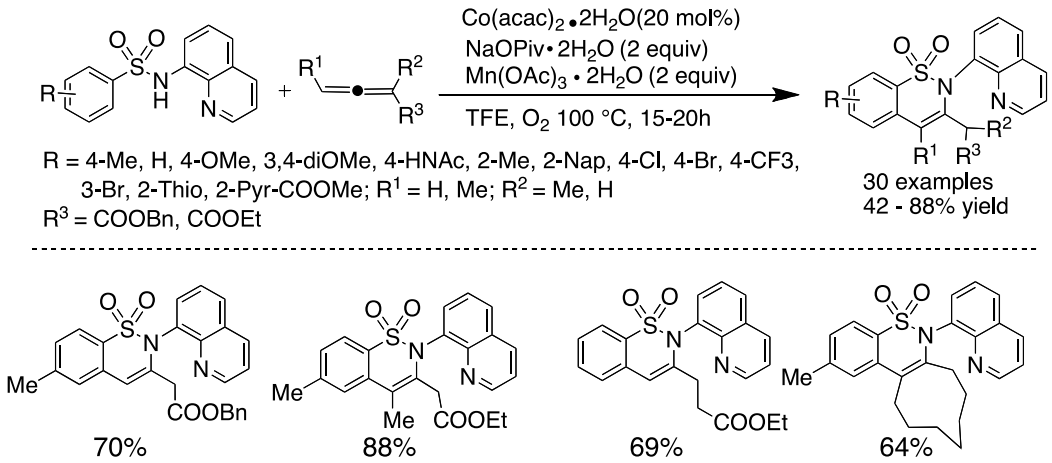
5. C-H activation for five memberered heterocycles

The use of inexpensive cobalt catalysts has also been reported in the synthesis of five membered heterocycles. In this category the researchers mainly used carbonylation, isocyanide insertion, decarboxylative procedures. In this section we will describe the methods used for the synthesis of five membered heterocycles using cobalt catalysis.

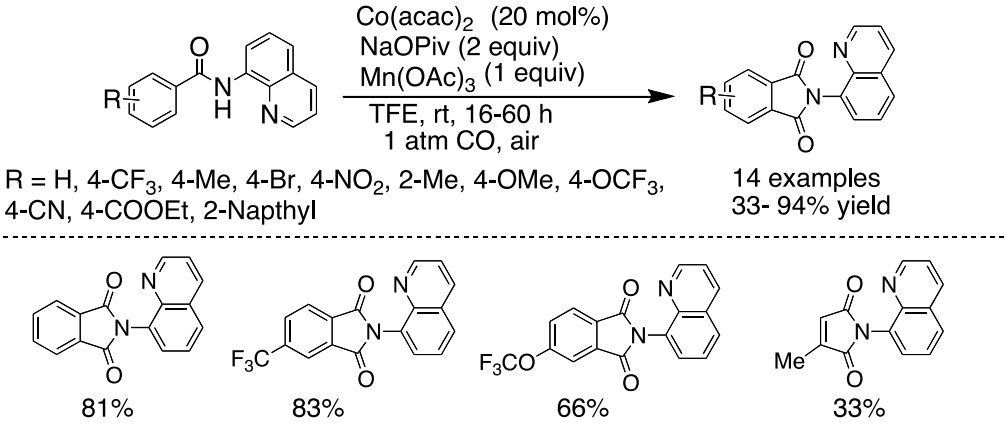
The Daugulis group expanded upon their seminal studies on the use of cobalt catalyzed C(sp^2)-H activation for the synthesis of heterocycles through a number of avenues, including through the development of a method for direct carbonylation of aminoquinoline benzamides at room temperature using carbon monoxide as a C1 building block (Scheme 24). [37] The reactions proceeded under mild conditions and they even adopted the same reaction conditions for the coupling of aminoquinolinamides with alkenes[8] and alkynes[9]. Finally, they have showed the method for the directing group can be removed under mild conditions affording phthalimides.

Zhang and co-workers reported a novel and efficient approach for the C(sp^2)-H bond carbonylation of benzamides has been developed using stable and inexpensive $Co(OAc)_2 \bullet 4H_2O$ as the catalyst and the commercially available and easily handled azodicarboxylates as the non-toxic carbonyl source (Scheme

25).[38] A broad range of substrates bearing diverse functional groups was tolerated. This study provided the first example of the use of azidocarboxylates as carbonylation source.



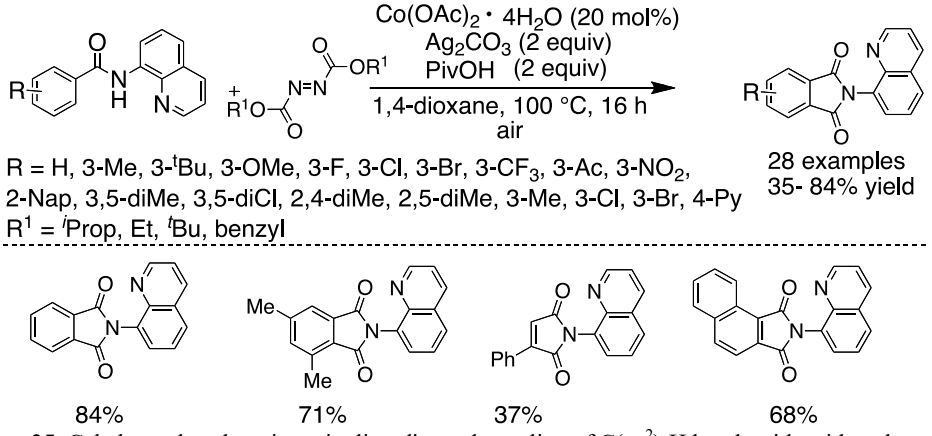
Scheme 23. Cobalt-catalyzed, aminoquinoline-directed coupling of C(sp^2)-H bonds of sulfonamides with allenes.



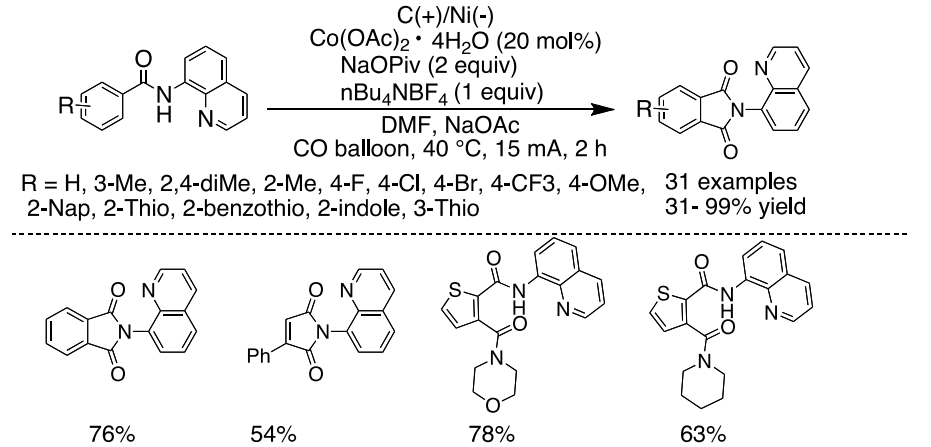
Scheme 24. Cobalt-catalyzed, aminoquinoline-directed coupling of C(sp^2)-H bonds with carbonmonoxide.

Recently, a cobalt catalyzed electrochemical oxidative C-H/N-H carbonylation that doesn't require external oxidants was developed by the Lei group (Scheme 26).[39] These reactions proceed smoothly under anodic oxidation conditions using a divided cell, and H_2 was generated at the cathode. They also presented an amidation reaction with carbon monoxide under slightly modified conditions. This cobalt catalysis showed good selectivity for inter- and intra-molecular carbonylation reactions of amides. A $Co^{II}/Co^{III}/Co^{I}$ catalytic cycle was proposed based on XANES and CV studies.

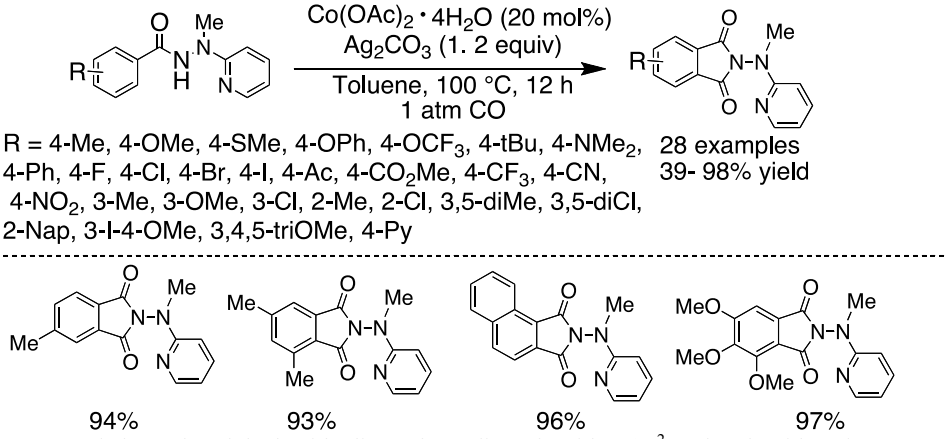
Zhai and coworkers used carbon monoxide as a C1 source in the synthesis of phthalimides with benzoyl hydrazides as the bidendate directing group (Scheme 27).[40] The protocol has generated a broad range of phthalimide derivatives in good to excellent yields. Through hydrogenolysis the directing group can be removed after the C-H activation completed.



Scheme 25. Cobalt-catalyzed, aminoquinoline-directed coupling of C(sp^2)-H bonds with azidocarboxylate.

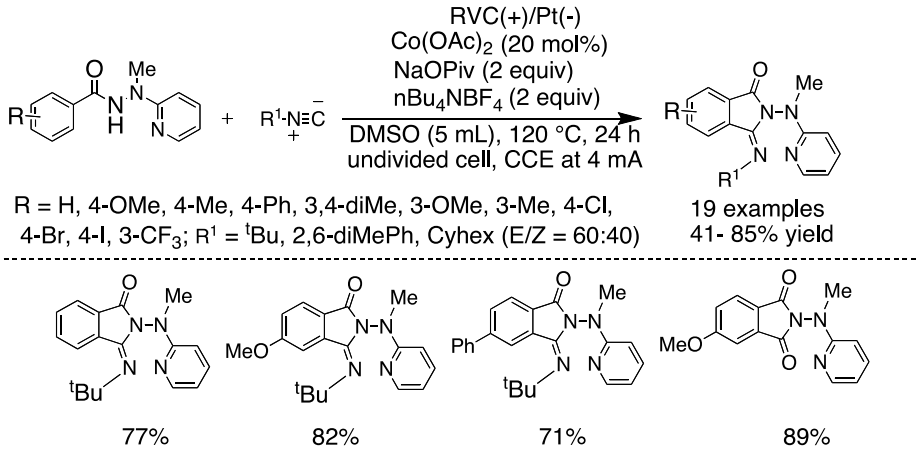


Scheme 26. Cobalt-catalyzed, aminoquinoline-directed coupling of electrooxidative C(sp^2)-H bonds with carbonmonoxide.



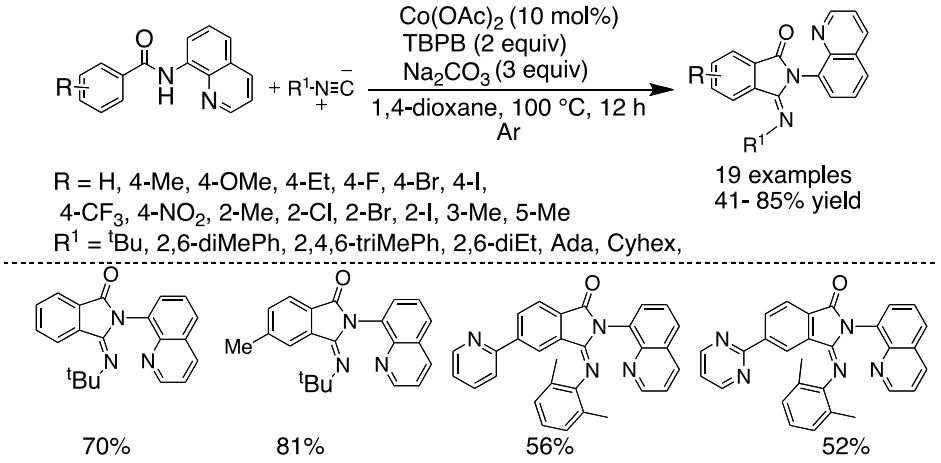
Scheme 27. Cobalt-catalyzed, hydrazide-directed coupling of amide C(sp^2)-H bonds with carbon monoxide.

The first electrocatalytic C-H activation with isocyanides by cobalt salts has been recently developed by Sau *et al*. (Scheme 28).[41] The broadly applicable cobalt catalysts likewise set the stage for efficient electrooxidative C-H functionalizations of benzhydrazides with inexpensive carbon monoxide (5 examples) in the absence of chemical oxidants at room temperature.



Scheme 28. Cobalt-catalyzed, hydrazide-directed coupling of amide C(sp^2)-H bonds with isocyanide.

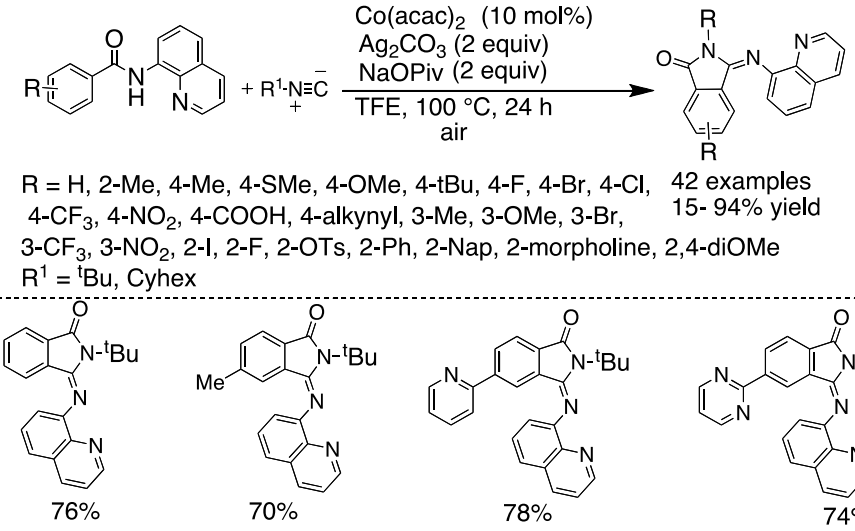
A cobalt catalyzed (4+1) cycloaddition of easily accessible amides with isocyanides has been used by Gu *et al.* for the high yield synthesis of 3-iminoisoindolinone derivatives under mild conditions (Scheme 29).[42] The reaction proceeds via intramolecular C(sp^2)-H activation and isocyanide insertion. Strongly coordinating N-heterocyclic directing groups such as pyridine, pyrimidine, and even pyrazole were fully tolerated in this cobalt catalyzed C-H activation. The group of Hao independently presented the same type of reaction.[41]



Scheme 29. Cobalt-catalyzed, aminoquinoline-directed coupling of amide C(sp^2)-H bonds with isocyanide.

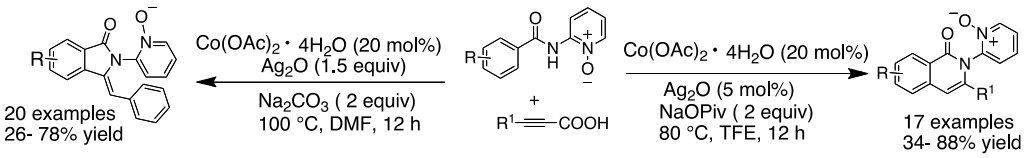
Sundararaju and co-workers have reported a cobalt catalyzed isonitrile insertion/acyl group migration between C-H and N-H bonds of arylamides through intramolecular *trans*-amidation (Scheme 30).[43] They

have also explored the impact on reactivity of the directing group by having strongly coordinating functional groups on the reacting substrates.



Scheme 30. Cobalt-catalyzed, aminoquinoline-directed coupling of amide C(sp^2)-H bonds with isocyanide through trans-amidation.

A cobalt(II) catalyzed decarboxylative C-H activation/annulation cascade reaction was described by Song and co-workers (Scheme 31).[44] The reaction provides ready access to isoquinolones and isoindolones in good yields. The role of oxidant is very crucial and controls the outcome of the catalytic activity enabling a switch from isoquinolones to isoindolinones with excellent selectivity.

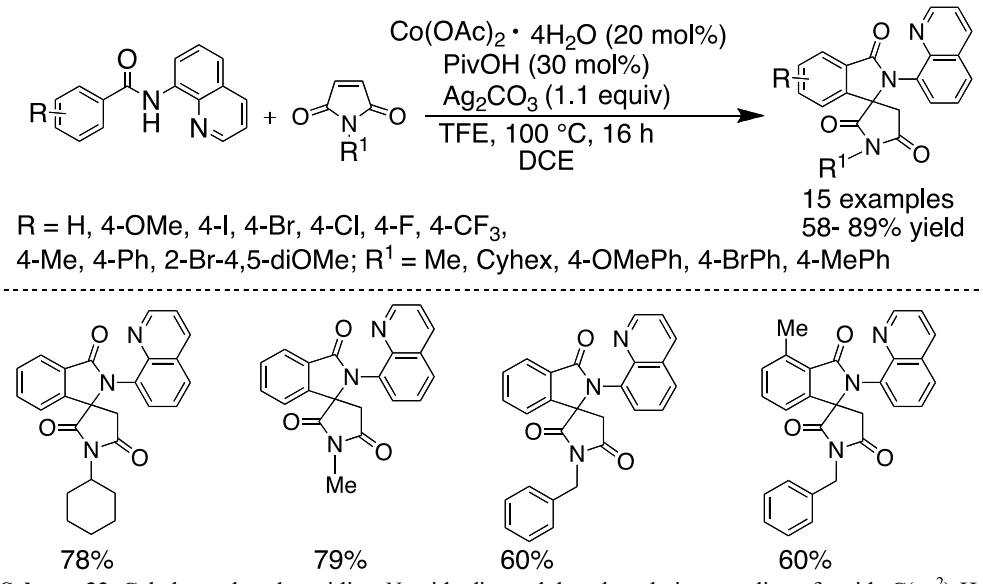


Scheme 31. Cobalt-catalyzed, pyridine-*N*-oxide directed decarboxylative coupling of amide C(sp^2)-H bonds with alkynes.

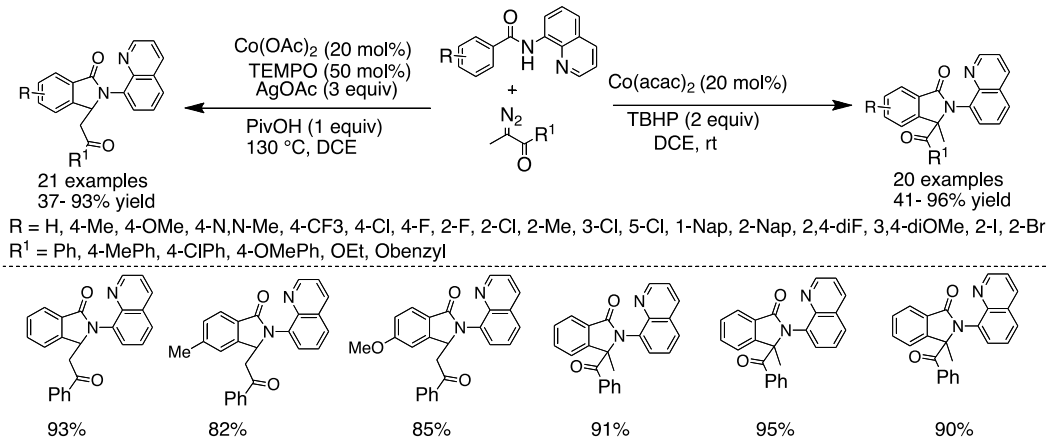
Cobalt(II) catalyzed oxidative cyclization of benzamides with maleimides was used by Jeganmohan and co-workers in 2017 for the synthesis of isoindolones (Scheme 32).[45] The cyclization reaction was compatible with an array of substituted benzamides and maleimides.

Li and Wang reported a regioselective synthesis of isoindolones using a controllable α- or β-functionalization in a cobalt catalyzed C(sp^2)-H activation of aromatic amides with α-diazokentones. In

the presence of $Co(acac)_2$/TBHP, the authors achieved α-functionalization and, interestingly, when switched to $Co(OAc)_2$/AgOAc β-functionalization was obtained (Scheme 33).[46]



Scheme 32. Cobalt-catalyzed, pyridine-*N*-oxide directed decarboxylative coupling of amide $C(sp^2)$-H bonds with alkynes.



Scheme 33. Cobalt-catalyzed, aminoquinoline directed coupling of amide $C(sp^2)$-H bonds with α-diazoketones.

6. Conclusion

In this review we have illustrated the power of easily accessible, inexpensive, and comparatively non-toxic cobalt catalysts for the synthesis of five and six membered heterocycles through $C(sp^2)$-H bond functionalization as reflected in the literature in this rapidly developing area. These versatile catalytic systems have been explored in many different coupling reactions and their utility has been well demonstrated and often supported through mechanistic studies. In the case of the six-membered heterocycles a major focus has been the coupling of unsaturated substrates, *e.g.* alkynes, alkenes, 1,3-diynes, and allenes,

for the synthesis of isoquinolones and dihydroisoquinolones. The synthesis of five membered heterocycles using cobalt catalysts has been achieved using either carbon monoxide or isonitrile as a C1 building block to yield isoindolone heterocycles. On account of the wide range of catalytic transformations accessible through relatively cheap cobalt-based catalysis and the generally broad scope of substrates amenable and good yields obtained, together motivate increased interest in exploring new cobalt-based catalysis strategies.

Acknowledgements

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