COBALT-CATALYZED PICOLINAMIDE-DIRECTED SYNTHESIS OF HETEROCYCLES

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Abstract. *Transition metal catalyzed C-H activation and functionalization methodology has made tremendous advancement in the past few decades. Significant progress for C-H bond functionalization has been achieved using second row transition metal catalysts. In the past decade, C-H functionalization using cobalt catalysts have emerged as an attractive alternative due to its low cost and environmentally friendly properties. The replacement of expensive noble metal catalysts with readily available alternatives is beneficial to achieve more sustainable C-H functionalization methods with the application in the synthesis and in the production of relevant chemical compounds. Herein we describe the developed cobalt-catalyzed, picolinamide-directed methods for the synthesis of heterocyclic compounds.*

Contents

1. Introduction

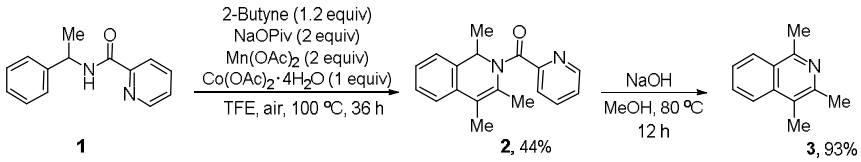
In the past few decades, transition metal catalyzed direct functionalization of ubiquitous C-H bonds has experienced outstanding progress. Developed C-H bond functionalization methodology has emerged as an important tool that allows simplification of synthetic schemes, thereby making synthetic pathway more economical and environmentally beneficial.[1] Most of the discovered methods are based on directed C-H activation to achieve regioselective transformation. The directing group used for C-H activation contains a functional group that can coordinate metal centre in the close proximity to the desired C-H bond thus providing highly selective C-H activation. Among the various directing groups used, bidentate directing groups have been demonstrated as one of the most efficient tools for the selective C-H functionalization.[2] The efficiency of bidentate directing groups in C-H activation and functionalization reactions can be explained by the ability to stabilize high-valent transition-metal intermediates. The quinolinamide and picolinamide directing groups were introduced in 2005 by Daugulis group.[3] Later, in 2014, Daugulis group demonstrated that Co(II) salts in combination with bidentate directing group assistance can be exploited as a high valent Co(III) precursors for the C-H activation and functionalization.[4] Cobalt is a highly desirable alternative to noble metals due to its low cost and environmentally friendly properties; therefore, the discovery of the bidentate directing group-assisted high valent cobalt-catalyzed C-H functionalization inspired researchers from other groups to contribute to this area.[5] Using this approach, a number of methods have been developed for the synthesis of diverse relevant heterocyclic targets, e.g. sultams,[6a-c] saccharines,[6d] phthalimides,[6e,f] isoquinolines,[6g] isoquinolones,[6h, i] phosphaquinolones[6j,k] *etc*.

Since the pioneering work by Daugulis,[3] picolinamide directing group has extensively been used for a large diversity of C-H bond functionalization reactions catalyzed by various transition metals.[7] The wide application of the picolinamide directing group is due to the provided *ortho*-selectivity of C-H activation step. Furthermore, picolinoyl group is easy to introduce on an amine-type substrate, as well as after reaction it is easy to remove from the products.[8]

Herein we summarize the developed C-H functionalization methodology for the synthesis of various heterocycles under cobalt-catalysis using picolinamide as directing group.

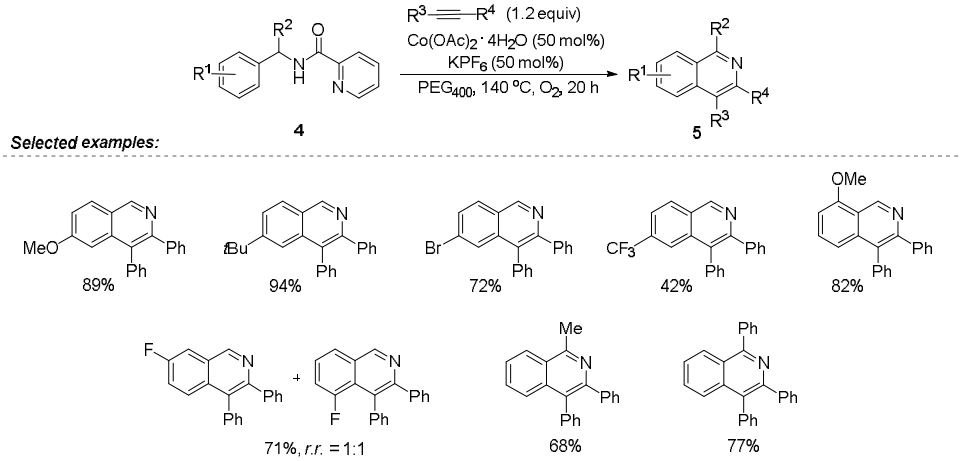
2. C-H functionalization with alkynes

In 2014, Daugulis and Grigorjeva reported the first example of cobalt-catalyzed, picolinamide-directed C-H activation and functionalization (Scheme 1).[4] Although the focus of their research was on the use of 8-aminoquinoline for C-H functionalization of benzamides with alkynes, they additionally demonstrated that picolinamide can be successfully used as a bidentate directing group to achieve selective C-H activation. They showed that 1-methylbenzylamine derived picolinamide **1** in the presence of readily available $Co(OAc)_2 \cdot 4H_2O$ catalyst, NaOPiv additive and $Mn(OAc)_2$ oxidant, can be annulated with 2-butyne to yield 1,2-dihydroisoquinoline derivative **2**. The authors demonstrated that the picolinamide directing group could be easily removed under base hydrolysis conditions to afford isoquinoline **3**.



Scheme 1. The first example of cobalt-catalyzed picolinamide-directed C-H functionalization.

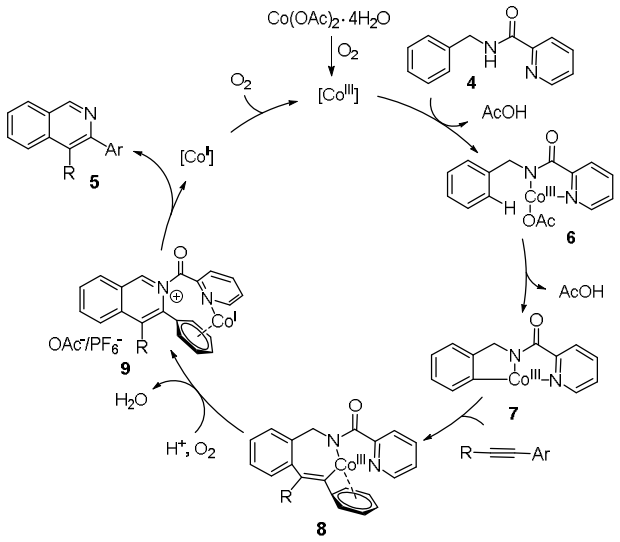
Cui and co-workers later, in 2017 expanded the utility of this method and published an extended study for the synthesis of isoquinoline derivatives **5** from benzylamines **4** and terminal or internal alkynes (Scheme 2).[9] In their report $Co(OAc)_2 \cdot 4H_2O$ catalyst in combination with KPF_6 additive in PEG_{400} were found to be the best catalytic system for successful annulation reaction. Interestingly, the demonstrated methodology displayed picolinamide as a traceless directing group for the first time and gave the reaction products **5**, where the directing group was eliminated in situ. A diverse substitution pattern of benzene ring moiety was tolerated well under the reaction conditions, providing products in moderate to very good yields. In the case of *meta*-substituted benzylamine derivatives **4**, the reaction was generally unselective and yielded isoquinolines **5** as a regioisomer mixtures (ranging from 1:1 to 8:1). Alkyne scope study revealed good compatibility and regioselectivity with both diaryl- and dialkyl-acetylenes as well as terminal alkynes.



Scheme 2. Annulation reaction of benzylamine derivatives **4** with alkynes.

To gain insight into the reaction mechanism, mechanistic investigations were performed. The KIE (KH/KD) from two parallel reactions was found to be 1.1, indicating that C-H bond activation might not be involved as the rate-determining step. Subsequently, radical scavenger addition to the reaction mixture under standard reaction conditions did not inhibit the reaction, revealing that the radical processes are not involved

in the reaction mechanism. Considering the mechanistic investigations and literature precedents, authors proposed the plausible catalytic cycle (Scheme 3).[9] According the proposed mechanism, the reaction is initiated by the oxidation of Co(II) to Co(III), followed by coordination and ligand exchange with substrate **4** giving cobalt complex **6**. Then C-H bond activation *via* CMD mechanism takes place and intermediate **7** is formed. Subsequent coordination and migratory insertion of alkyne into Co-C bond furnishes complex **8**, which undergoes reductive elimination to give isoquinolinium salt **9**. Next, C-N bond cleavage gives isoquinoline product **5** and Co(I) species which is reoxidized by O_2 and returned into the catalytic cycle.



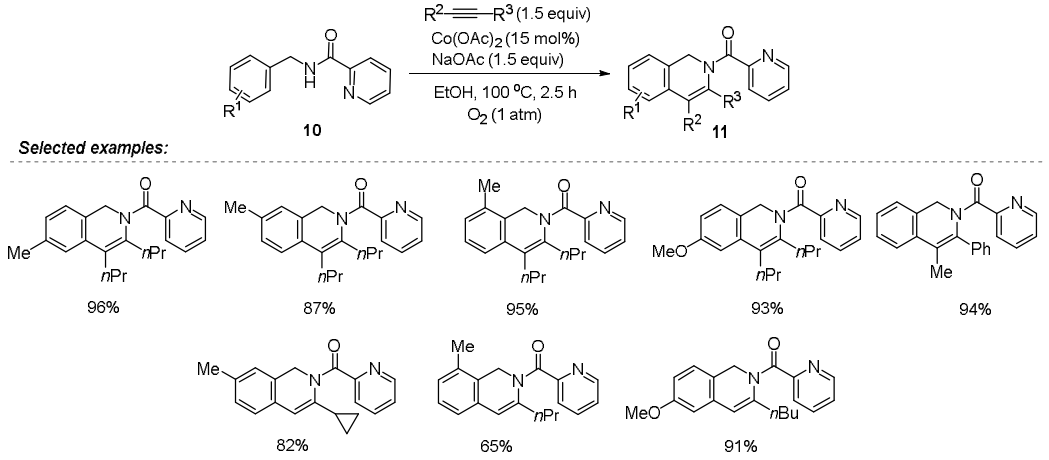
Scheme 3. Plausible reaction mechanism for the synthesis of isoquinolines **5**.

Shortly after, Carretero and co-workers published an approach towards the synthesis of 1,2-dihydroisoquinolines **11** (Scheme 4).[10] In contrast to the method reported by Cui and co-workers, this methodology allowed obtaining 1,2-dihydroisoquinolines **11** in non-traceless fashion, thus avoiding the dehydrogenation of benzylic position. During the optimization studies, authors determined that $Co(OAc)_2$ catalyst, NaOAc additive in ethanol was the best catalytic system where oxygen is used as the sole oxidant. The reaction conditions were mild, and tolerated a large scope of substituents at the benzene moiety. No significant sensitivity to *para*-substituent electronic effects were found, whereas electron-withdrawing substituents at *ortho*-position were less reactive. In the case of *meta*-substituted benzylamine derivatives **10**, activation and functionalization occurred at the more sterically accessible *ortho*-C-H bond, yielding products **11** with excellent regioselectivity. The alkyne scope study showed that reaction was not compatible with diarylacetylenes. Unsymmetrical dialkylacetylenes gave corresponding products **11** with poor regioselectivity. On the other hand, terminal alkyl- and aryl-alkynes displayed excellent regioselectivity and reactivity.

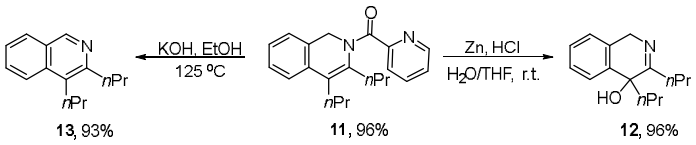
Furthermore, authors demonstrated that the removal of picolinamide directing group was done efficiently without aromatization of heterocyclic ring under reductive acidic conditions (Scheme 5).[10] The resulting unprotected amine undergoes oxidation by atmospheric O_2 to furnish dihydroisoquinoline derivative **12** in excellent yield. The utility of the procedure was demonstrated by subjecting crude reaction product after C-H functionalization to Zn/HCl system to afford products in one pot manner in good and very good yields. On the other hand, commonly used base hydrolysis was also feasible and provided isoquinoline **13** in excellent yield.

Based on mechanistic experiments and literature precedents, authors proposed a simplified plausible catalytic cycle (Scheme 6).[10] Initially, $Co(OAc)_2$ coordination with substrate **10** and concomitant oxidation

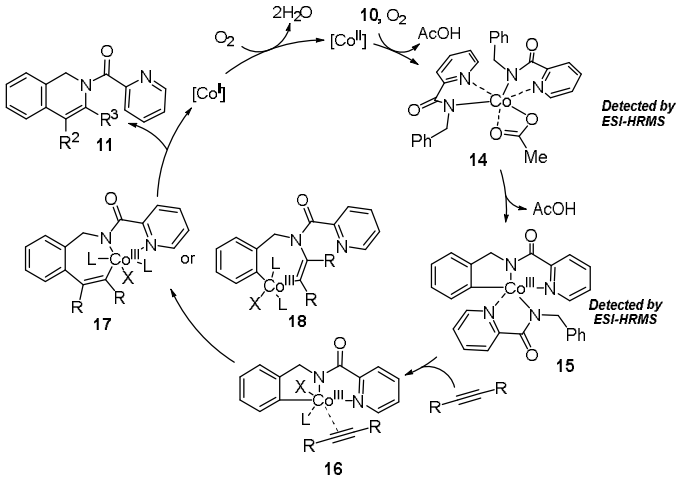
by O_2 forms cobalt complex **14**. Next, C-H bond cobaltation gives five membered cobaltacycle **15**, followed by alkyne coordination in complex **16** and migratory insertion in Co-C bond affording intermediates **17** or **18**. Finally, after reductive elimination 1,2-dihydroisoquinoline **11** is formed, and Co(I) is reoxidized and returned to the catalytic cycle.



Scheme 4. Synthesis of 1,2-dihydroisoquinolines **11** *via* C-H bond functionalization with alkynes.



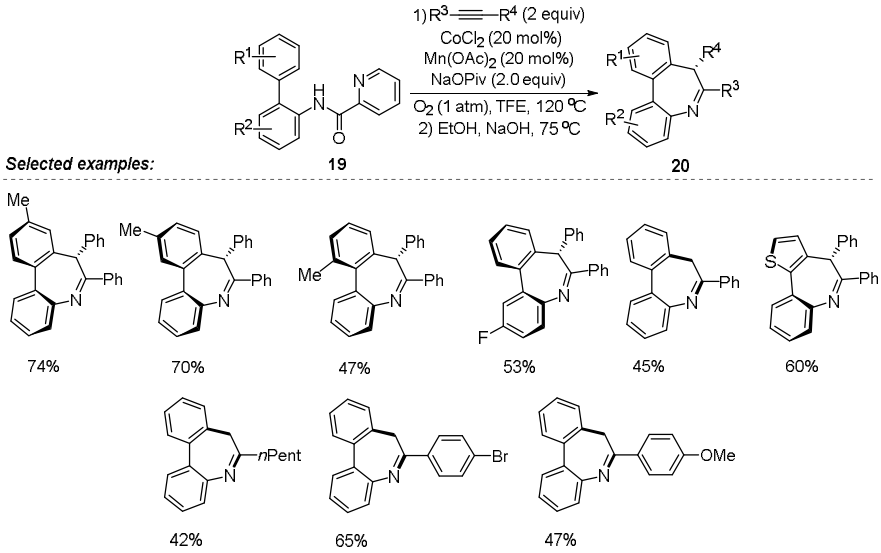
Scheme 5. The cleavage of picolinamide directing group.



Scheme 6. The plausible reaction mechanism for the formation of isoquinolines **11**.

In 2019, Zhong and co-workers developed a novel *o*-arylaniline **19** C-H bond functionalization protocol to obtain dibenzoazepines **20** (Scheme 7).[11] The optimized reaction conditions included $CoCl_2$ as

catalyst, NaOPiv additive, $Mn(OAc)_2$ co-oxidant and O_2 as the terminal oxidant. Authors devised a one-pot procedure and treated the crude reaction mixture from C-H bond functionalization step with NaOH in ethanol to cleave the picolinamide directing group. The reaction substrate scope studies revealed that benzene rings with electron rich substituents (Me, SMe, OMe) gave products **20** in better yields than electron poor ones (CF_3, F). Regarding the alkyne scope, electronic effect was reversed: electron poor alkynes gave products **20** in better yields than electron rich ones, although the majority of products were obtained in moderate yields. Interestingly, the unsymmetrical diaryl alkynes gave regioisomer mixtures in 1.2:1 ratio. An exception was the alkyne with strongly electron-biased substituents at *para*-position of the arenes (OMe and CF_3), providing the product in highly regioselective manner (>20:1). Unfortunately, dialkyl- or alkylaryl-alkynes were unreactive, whereas terminal alkynes turned out to be compatible coupling components and yielded products **20** predominately in moderate yields, albeit with excellent regioselectivity.

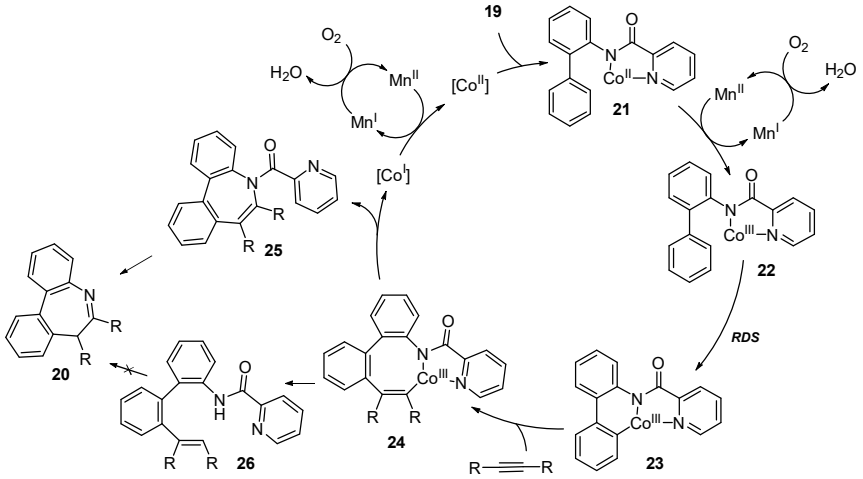


Scheme 7. Synthesis of dibenzoazepines **20** *via* C-H bond functionalization of *o*-arylanilines **19**.

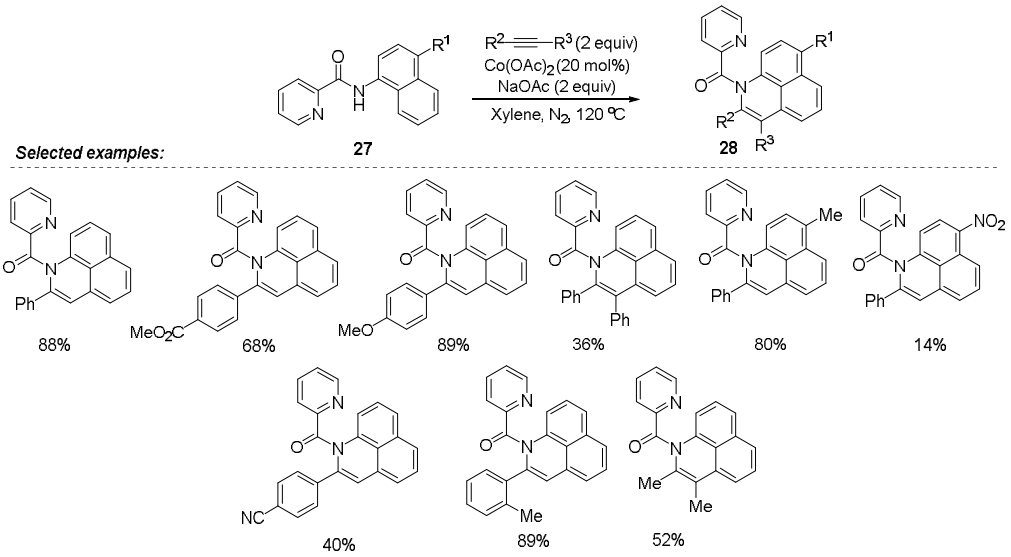
The proposed catalytic cycle (Scheme 8)[11] is based on experimental data and the literature precedents. The reaction is initiated by the coordination of Co(II) to the substrate, yielding Co(II) complex **21**, followed by oxidation with $Mn(OAc)_2/O_2$ oxidant system to generate Co(III) complex **22**. Next, cobalt complex **23** forms by C-H cobaltation of **22**, which as suggested by intermolecular KIE experiment is probably the rate-determining step. Besides, the increase of product **20** yield using electron rich substrates also implies that a base-assisted intramolecular electrophilic substitution-type mechanism could be operative within the C-H metalation. Subsequently, alkyne coordination and migratory insertion into Co-C bond gives intermediate **24**, which undergoes reductive elimination to give product **25**. Finally, hydrolysis and tautomerization of the double bond leads to more stable imine form **20**. Alternative pathway from complex **24** to open chain product **26** *via* protodemetalation mechanism followed by cyclization to form **20** was omitted, because the control experiment where **26** was subjected to standard reaction conditions gave no traces of product whatsoever.

Yang and co-workers in 2020 developed an efficient method for the synthesis of benzoquinolines **28** by cobalt catalyzed, picolinamide-directed naphthylamine **27** C-H bond functionalization with alkynes (Scheme 9).[12] The optimized reaction conditions required $Co(OAc)_2$ catalyst, NaOAc additive in xylene at 120 °C for successful transformation. Similarly, to other literature reports, in this transformation no additional external oxidant was necessary, as the atmospheric oxygen was capable to oxidize the cobalt catalyst. The majority of the alkyne scope was demonstrated using terminal alkynes, only two examples with

internal alkynes were shown. The authors found that electron-poor alkynes performed worse than electron-rich, and gave products in low and moderate yields. Influence of the naphthalene substituents showed that electron-donating group (Me) is compatible with the reaction conditions, on the other hand, naphthalene **27** substituted with electron-withdrawing group (NO_2) yielded product **28** in only 14% yield.



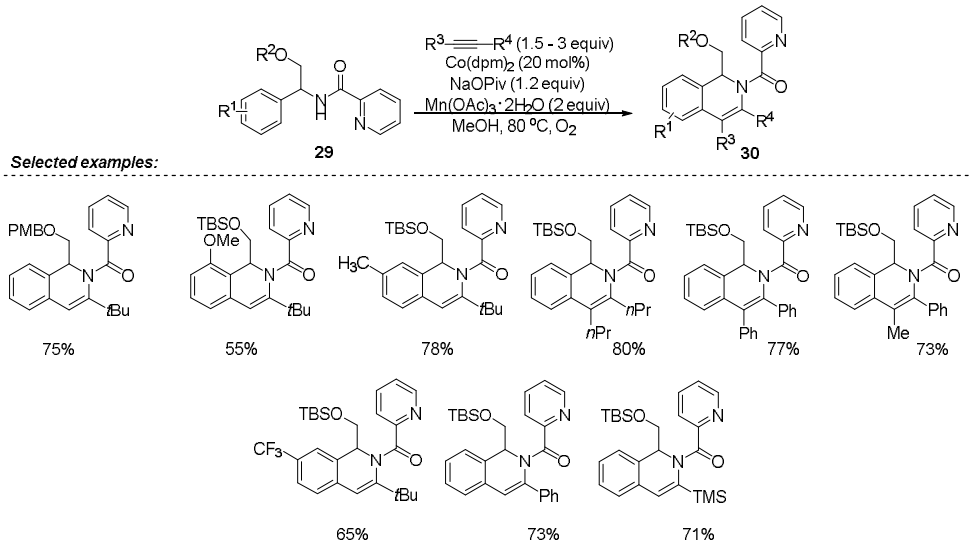
Scheme 8. Plausible reaction mechanism for the synthesis of dibenzoazepines **20**.



Scheme 9. Cobalt-catalyzed naphthylamine **27** annulation with alkynes.

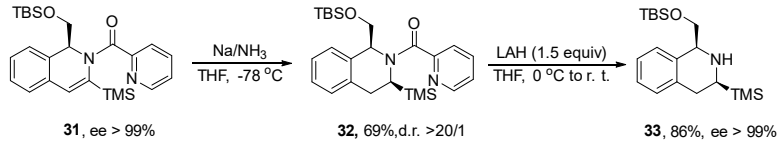
In the same year, our group reported a cobalt-catalyzed, picolinamide-directed C-H functionalization of phenylglycinols **29** with alkynes to afford 1,2-dihydroisoquinolines **30** (Scheme 10).[13] We found that $Co(dpm)_2$ catalyst, NaOPiv base and $Mn(OAc)_3{\cdot}2H_2O/O_2$ oxidant system in methanol at 80 °C is the most appropriate catalytic system for this transformation. Several different alcohol-protecting groups (MOM, PMB and TBS) were viable and gave reaction products smoothly. In contrast, unprotected alcohol did not

result in product formation, most likely due to possible cobalt coordination to oxygen atom thereby deactivating the cobalt catalyst. The reaction conditions are mild, tolerated wide variety of benzene substituents: electron-donor and electron-acceptor groups as well as halogen atoms, giving products mostly in very good yields and with complete regioselectivity towards less hindered *ortho*-C-H bond if *meta*-substituted substrates were used. Alkyne scope studies revealed that both terminal and symmetrical/unsymmetrical internal alkynes with diverse electronic properties were applicable and resulted in corresponding products with predominantly very good yields and excellent regioselectivity. An additional advantage of the developed methodology was the complete retention of original stereochemistry at α-position of substrate that allowed obtaining enantiopure products.



Scheme 10. Cobalt-catalyzed C-H annulation of phenylglycinols **29** with alkynes.

The synthetic utility of this transformation was demonstrated by accessing tetrahydroisoquinoline **33**. The reduction of 1,2-dihydroisoquinoline **31** in presence of Na/NH_3 led to the formation of **32** in highly diastereoselective manner. Subsequent directing group cleavage with $LiAlH_4$ gave tetrahydroisoquinoline **33** in very good yield and without enantiopurity loss (Scheme 11).[13]

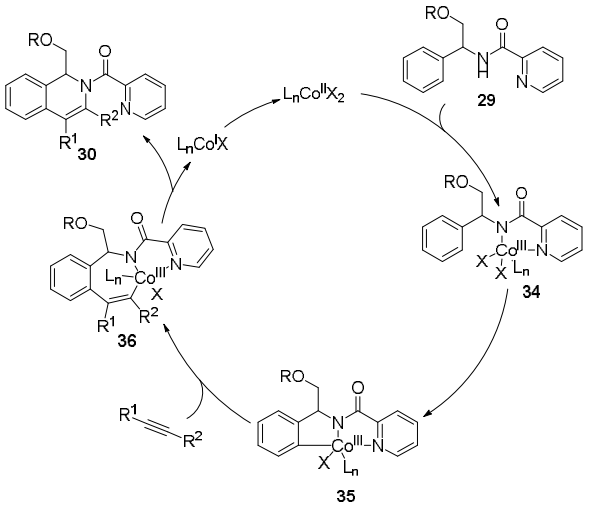


Scheme 11. 1,2-Dihydroquinoline **31** reduction and removal of the picolinamide directing group.

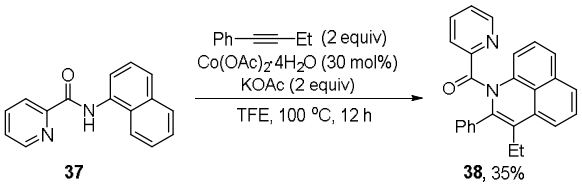
Based on experimental observations and literature precedents, we proposed a plausible catalytic cycle (Scheme 12).[14] Initially, oxidation of the Co(II) catalyst in the presence of phenylglycinol **29** generates Co(III) complex **34**. Subsequent C-H activation step forms cobaltacycle **35**. Next, alkyne coordination and insertion into Co-Ar bond gives intermediate **36**. Finally, reductive elimination step would give reaction product **30** and Co(I) species that after oxidation with $Mn(III)/O_2$ system returns to the catalytic cycle.

In 2020, Qi and co-workers reported the cobalt-catalyzed, picolinamide-directed hydroarylation of naphthylamines **37** with internal alkynes and diynes. Their catalytic system consisted of $Co(OAc)_2·4H_2O$ catalyst, KOAc base in TFE at 100 °C under air. This work was mainly focused on open-chain

hydroarylation products, however a single example of C-H annulation product **38** was also presented, albeit in a low yield (Scheme 13).[14]

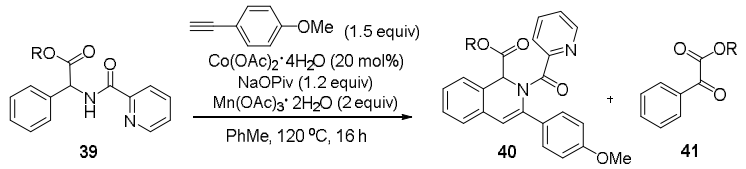


Scheme 12. Plausible mechanism for the annulation of phenylglycinols **29** with alkynes.



Scheme 13. Annulation of naphthylamine derivative **37**.

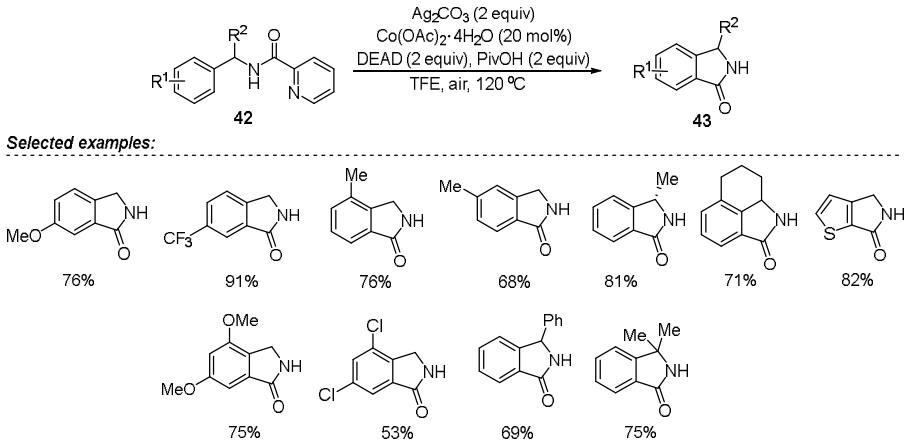
Our group continued investigations on cobalt-catalyzed, picolinamide-directed C-H bond functionalization methodology, and in 2021, we reported a study on phenylglycine **39** C-H bond functionalization.[15] Our previous results showed that phenylglycinols **29** were compatible substrates for the annulation reaction with alkynes. We set our goal to transfer the methodology to more challenging substrates: amino acids as a continuation of our research. The optimization studies showed that phenylglycine derivatives **39** are difficult substrates for C-H functionalization, mainly due to their instability under typical reaction conditions and tendency to form ketoesters **41** *via* oxidative cleavage (Scheme 14).[15] We managed to optimize phenylglycine **39** C-H bond annulation with *para*-methoxyphenylacetylene obtaining annulation product **40** up to 36% yield.



Scheme 14. Cobalt-catalyzed C-H bond annulation of glycine esters **39** with alkynes.

3. C-H functionalization with CO or CO surrogates

In 2017, Zhong and co-workers reported the first example of cobalt-catalyzed, picolinamide-directed carbonylation C(sp^2)-H bond (Scheme 15).[16] Under cobalt catalysis, using picolinamide directing group, benzylamines **42** were transformed into isoindolinone derivatives **43** in a traceless fashion. The developed catalytic system consisted of $Co(OAc)_2 \cdot 4H_2O$ catalyst, Ag_2CO_3 oxidant, PivOH additive and diethyl azodicarboxylate (DEAD) as the carbon monoxide surrogate. These mild reaction conditions provided good compatibility with alkyl, aryl, halogen and alkoxy substituents giving products in good to very good yields and excellent regioselectivity in the case of *meta*-substituted benzylamine derivatives **42**. Additionally, the authors found that developed carbonylation method was scalable up to 2 g. Besides, no loss of enantiopurity was observed when chiral starting materials were used.



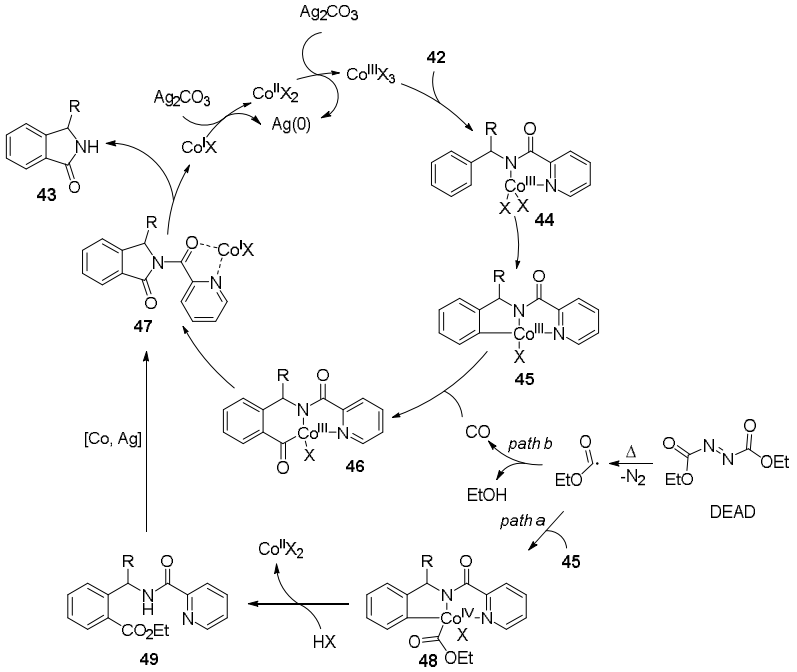
Scheme 15. Benzylamine **42** C(sp^2)-H bond carbonylation.

The plausible catalytic cycle for the carbonylation reaction is provided by the authors and is depicted in Scheme 16.[16] The reaction is initiated by the oxidation of Co(II) to Co(III) species and coordination to the substrate **42** to form complex **44**. Next, C-H cobaltation takes place and forms cobalt complex **45**. According to *path a*, the esteric radical, that is generated in situ from DEAD *via* thermolysis, attack to complex **45**, forming Co(IV) intermediate **48**. Subsequently, reductive elimination and intramolecular cyclization with successive directing group hydrolysis would give product **43** and Co(II) species. According to *path b*, esteric radical generates CO gas, which coordinates and migratory inserts into Co-C bond to give complex **46**. The reductive elimination furnishes complex **47** and directing group cleavage steps would yield the product **43** and Co(I) species, that after oxidation with Ag_2CO_3 would be released back to the catalytic cycle. The mechanistic studies showed that only 10% of product was obtained if intermediate **49** was subjected to the reaction conditions, suggesting that *path a* is not the major reaction pathway.

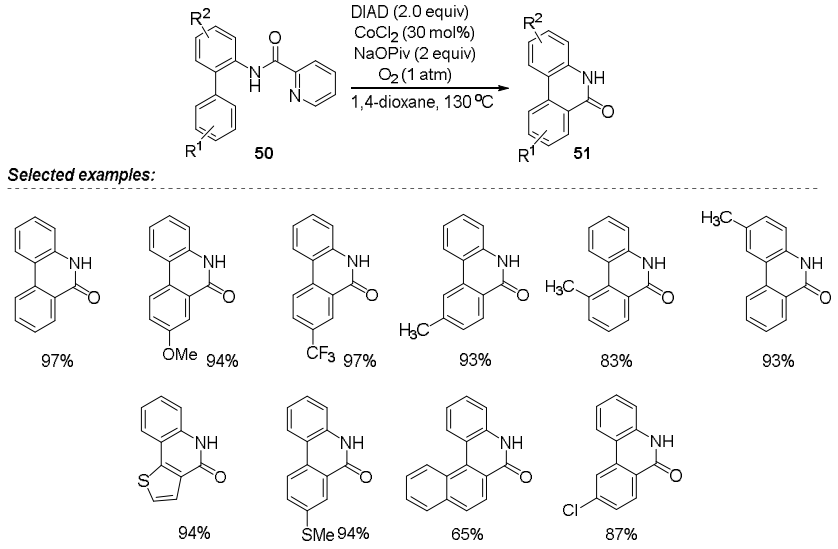
Next year, Zhong and co-workers published a new methodology for the synthesis of *N*-unprotected phenanthridinones **51** from arylanilines **50** (Scheme 17).[17] In their study authors employed a traceless picolinamide directing group in combination with $CoCl_2$ catalyst, NaOPiv base and DIAD as a CO source. The use of external oxidants was unnecessary as the O_2 was sufficient to maintain the reaction. The developed reaction conditions were mild; therefore, authors offered a broad substrate scope and the majority of selected substrates tolerated reaction conditions extremely well, giving products predominantly in excellent yields and highly regioselective manner. Interestingly, besides benzene, thiophene was also compatible with the reaction conditions and gave product in very high yield.

Based on the control experiments and previous literature data, authors proposed the plausible reaction mechanism, which is depicted in Scheme 18.[17] First, the carbonylation reaction is initiated by the coordination of Co(II) salt with arylaniline **50** to form intermediate **52**. Next, oxidation of complex **52** to Co(III) complex **53** takes place, followed by the C-H activation step to generate cyclic intermediate **54**. The

coordination and migratory insertion of CO, which is released by thermal decomposition of DIAD, results in a cyclic Co(III) intermediate **55**. The reductive elimination results in complex **56**, which contains Co(I) species and is formed *via N,O*-coordination. Further hydrolysis of **56** gives phenanthridinone **51** and releases Co(I) which is oxidized to Co(II) and is returned to catalytic cycle.

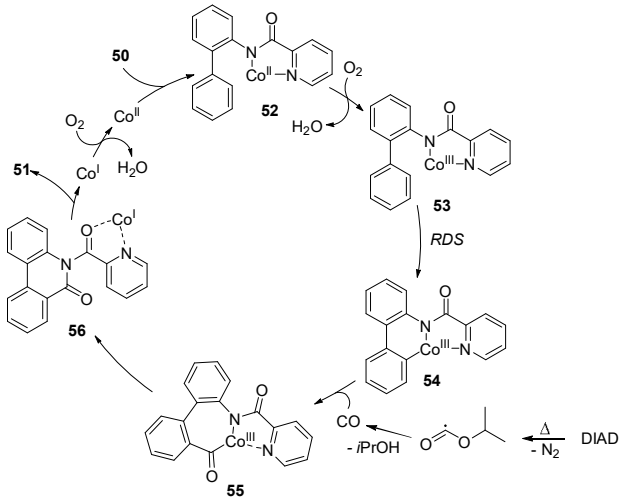


Scheme 16. Proposed mechanism for the cobalt-catalyzed carbonylation of benzylamine **42** C-H bond.



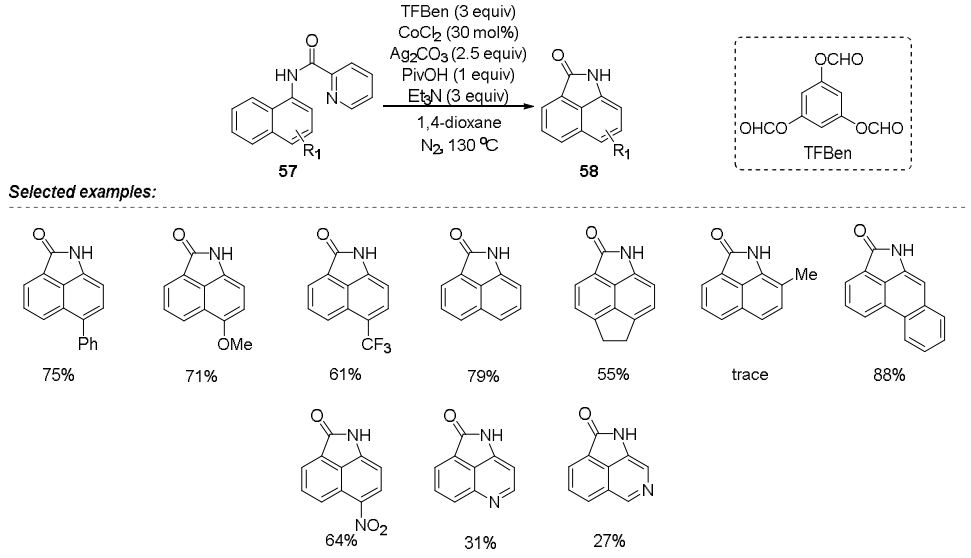
Scheme 17. Cobalt-catalyzed C-H carbonylation of phenanthridinones **50**.

The performed intermolecular competition experiment gave KIE value of k_H/k_D=1.72, while obtained KIE value from two parallel reaction was k_H/k_D=2.24. These KIE experiments indicated that C-H bond cleavage might occur in a rate-determining step. Besides, from experiments with a radical scavenger addition, authors found, that the esteric radical species, generated from DIAD, most likely are not the active carbonylation species, as addition of TEMPO showed only a slight influence on the reaction yield.



Scheme 18. Plausible reaction mechanism for the C-H bond carbonylation in arylanilines **50**.

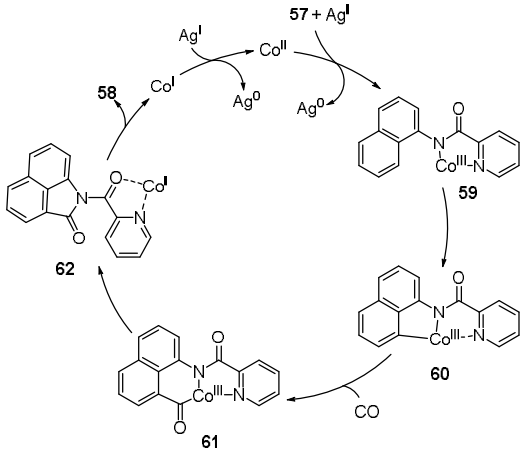
In 2019, Wu and co-workers developed a methodology for the synthesis of benzoindolones **58** *via* C-H bond carbonylation of the naphthylamine derivatives **57** (Scheme 19).[18]



Scheme 19. Cobalt-catalyzed naphthylamine **57** C-H bond carbonylation.

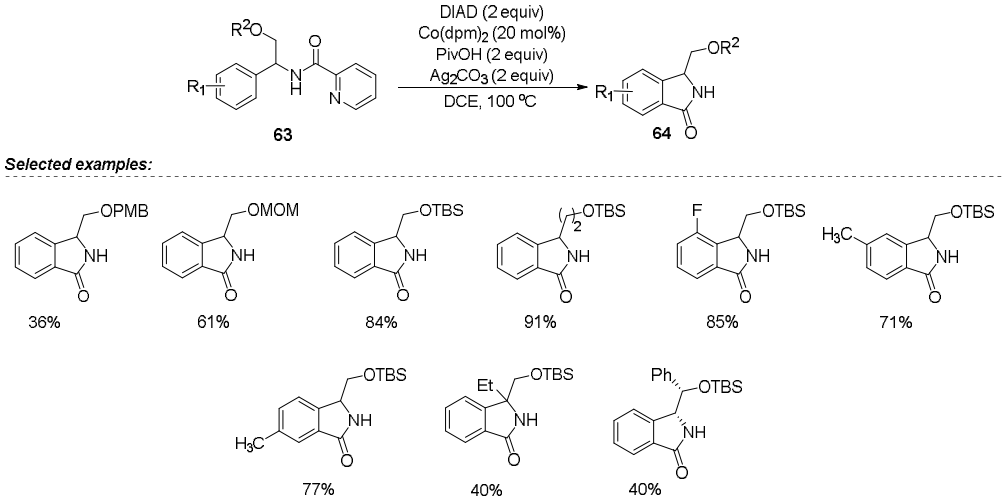
Similarly to other C-H carbonylation reports, in this case picolinamide directing group was used in traceless fashion and was cleaved in situ under the reaction conditions. Benzene-1,3,5-triyl triformate (TFBen) was used as an efficient and solid CO gas surrogate. The authors demonstrated that the substitution pattern at C4 position is rather flexible. A large variety of functional groups: alkyl, aryl, heteroaryl, alkynyl, halogen, esters were well tolerated and gave products in yields ranging from low to very good. The only significant limitation was the lack of substitution at C2 position, in such case, only trace amount of product was detected. This result suggests that the steric effect play a very important role in a substrate design. This methodology is also scalable and can be realized up to 4 mmol of **57**, although 19% drop in yield was observed (Scheme 19).

The proposed plausible catalytic cycle was based on the experimental data and literature precedents (Scheme 20).[18] The catalytic cycle is initiated with the coordination of Co(II) to the substrate **57** followed by an oxidation with Ag(I) to afford complex **59**. Subsequently, C-H activation step forms cobaltacycle **60**. The CO gas, which is generated in situ from TFBen coordinates and inserts into Co-C bond to give acyl cobalt species **61**. Next, the reductive elimination takes place, followed by the hydrolysis of the directing group in intermediate **62** yielding benzoindolone **58** and returning Co(I) to the catalytic cycle, where it is reoxidized to Co(II). The addition of TEMPO as the radical scavenger under the standard conditions did not affect the product yield, thereby excluding the radical process. Performed KIE experiments indicated that the C-H bond cleavage was not involved in the rate-determining step.



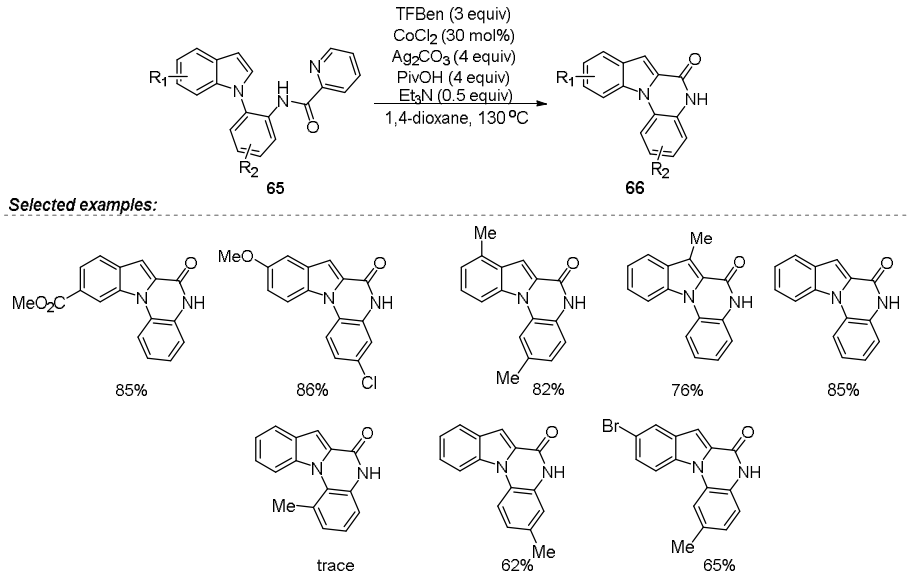
Scheme 20. Plausible catalytic cycle for the C-H bond carbonylation of naphthylamines **57**.

In 2020, we explored C-H bond carbonylation possibilities of amino alcohol derivatives **63**. This substrate design had proven to be effective for C-H bond annulation with alkynes, which we had reported earlier that year. In our work, we developed a catalytic system for the C-H bond carbonylation reaction using picolinamide as a traceless directing group to obtain isoindolinones **64** (Scheme 21).[19] From the perspective of alcohol protecting groups, we found similar reactivity pattern as previously.[13] Thus, TBS, PMB, MOM protecting groups could be used, although TBS group was superior over the others and gave product in higher yield. Unfortunately, unprotected amino alcohol derivatives did not gave corresponding carbonylation product **64**, that we attributed to excessive chelation and deactivation of the cobalt catalyst by an oxygen atom. Reactions using various *ortho*-, *meta*- and *para*-substituents were successful and in majority of cases products were obtained in good and very good yields with excellent regioselectivity in the case of *meta*-substituted amino alcohols **63**. We demonstrated that the reaction conditions are mild and no loss of enantiopurity of product **64** was detected under the reaction conditions. Furthermore, this methodology was transferred to more challenging quaternary and sterically hindered substrates, reactions yielded products in moderate yields, and higher catalyst loading and longer reaction times were required.



Scheme 21. Cobalt-catalyzed C-H bond carbonylation of amino alcohols **63**.

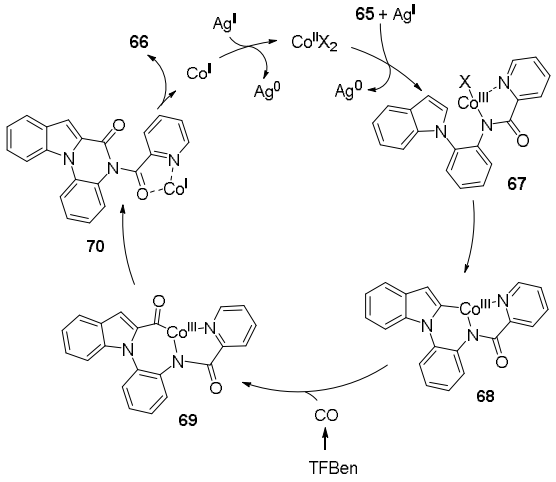
In 2021, Wu and co-workers reported an approach for the synthesis of free indoloquinoxalinones **66**. Their work involved the use of picolinamide as a traceless directing group for indolylaniline **65** C-H bond carbonylation employing TFBen as CO surrogate (Scheme 22).[20] The optimized reaction conditions tolerated several alkyl, alkoxy, halogen and ester functional groups, and gave corresponding products in moderate to good yields. Introduction of a substituent on the aniline moiety had negative impact on the reaction efficiency, as all of the products were obtained in lower yields and in some cases reaction required higher temperature or prolonged reaction time compared to substrates with non-substituted aniline.



Scheme 22. Cobalt-catalyzed indolylaniline **65** C-H bond carbonylation.

If methyl substituent was introduced at the C6 position of the aniline, only product traces were obtained. The authors suggest that the steric effect of *ortho*-methyl group might interfere with the indole and aniline position in different plane that caused difficulty to form C-N bond. However, a series of indole-substituted substrates **65** were tested for C-H bond carbonylation, providing good reactivity (Scheme 22).

The proposed catalytic cycle for the cobalt-catalyzed synthesis of indoloquinoxalinones **66** is depicted in Scheme 23,[20] and is similar to C-H bond carbonylation of naphthylamines **57**. Initially, the Co(II) catalyst is coordinated to the substrate **65** and oxidized to Co(III) complex **67** by Ag(I) salt. Next, C-H bond activation takes place and forms complex **68**. Further, coordination and migratory insertion of CO, which is generated from TFBen, lead to acyl cobalt complex **69**. After the reductive elimination step, intermediate **70** is formed which then is hydrolysed to give product **66**. The released Co(I) species are reoxidized by Ag(I) and are returned to the catalytic cycle.

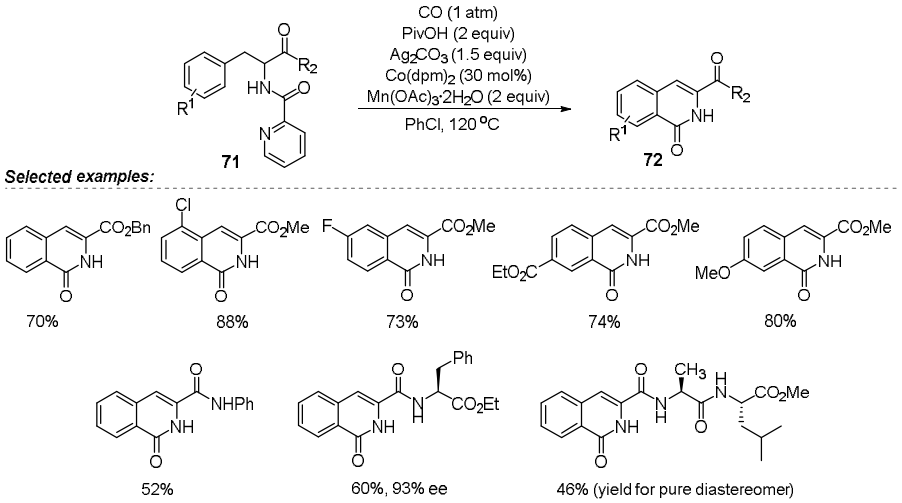


Scheme 23. Plausible mechanism for the C-H bond carbonylation of indolylanilines **65**.

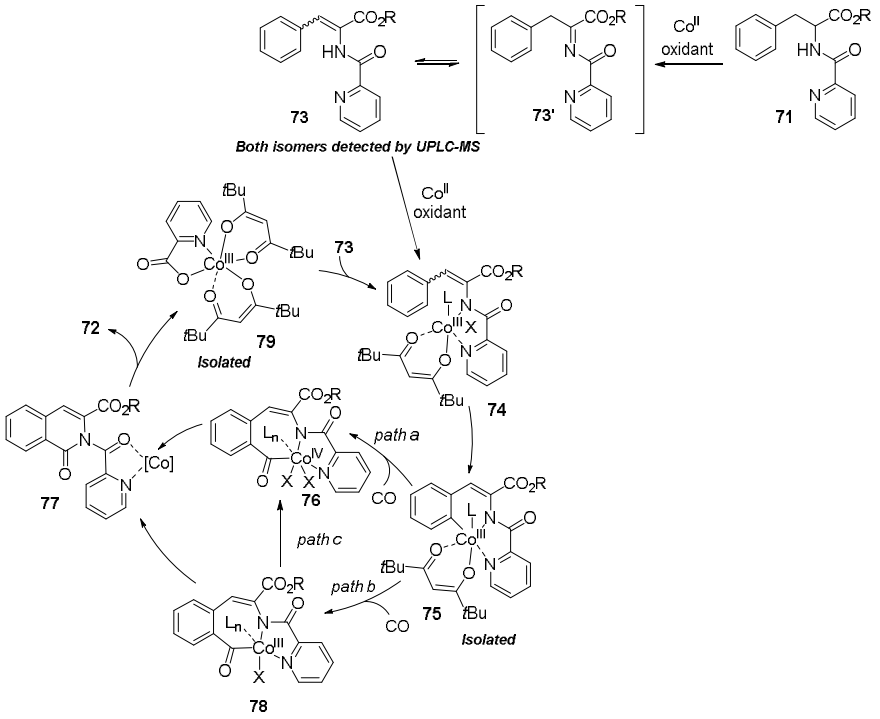
Recently, our group demonstrated a novel method for the synthesis of 1,2-dihydroisoquinolinones **72** *via* C-H bond carbonylation of phenylalanine derivatives **71** (Scheme 24).[21] Developed catalytic system included $Co(dpm)_2$ catalyst, PivOH additive and $Ag_2CO_3/Mn(OAc)_3 \cdot 2H_2O$ oxidant system in chlorobenzene. Diverse functional groups were compatible with the reaction conditions and gave products mostly in good yields. The substrate scope studies showed that both electron-donating and electron-withdrawing substituents at *ortho*-, *meta*- and *para*-positions of the benzene were tolerated well. In the case of *meta*-substituted amino acid derivatives **71**, we obtained products arising from the functionalization of the less hindered C-H bond, even in the case of *meta*-fluoro substituent. Additionally, we demonstrated that our developed catalytic system were successful for the late stage functionalization of short dipeptides and tripeptides, and gave corresponding carbonylation products in acceptable to good yields. Unfortunately, under the reaction conditions partial racemization occurred.

To gain some insights into the reaction mechanism, we performed several control experiments, based on obtained results as well as literature precedents we proposed a plausible reaction mechanism (Scheme 25).[21] According to proposed catalytic cycle, initially phenylalanine **71** is converted to imine **73'** under oxidative conditions in the presence of Co(II) catalyst, which then tautomerizes to corresponding enamine **73**. The control experiments, where the addition of radical scavenger TEMPO significantly suppressed the carbonylation reaction of phenylalanine **71**, but only slightly affected the carbonylation if enamine **73** was used as the starting substrate, indicate that the radical pathway may be involved for the generation of enamine **73**. Next, enamine **73** coordinates to Co(II) and is oxidized to Co(III) complex **74**, followed by the C-H cobaltation to form complex **75**. Further, three possible pathways could be envisioned. According to

path a, Co(III) complex **75** is oxidized to Co(IV), followed by CO coordination and insertion, to give intermediate **76**, that after the reductive elimination step forms **77**.



Scheme 24. Cobalt-catalyzed C-H bond carbonylation of phenylalanines **71**.

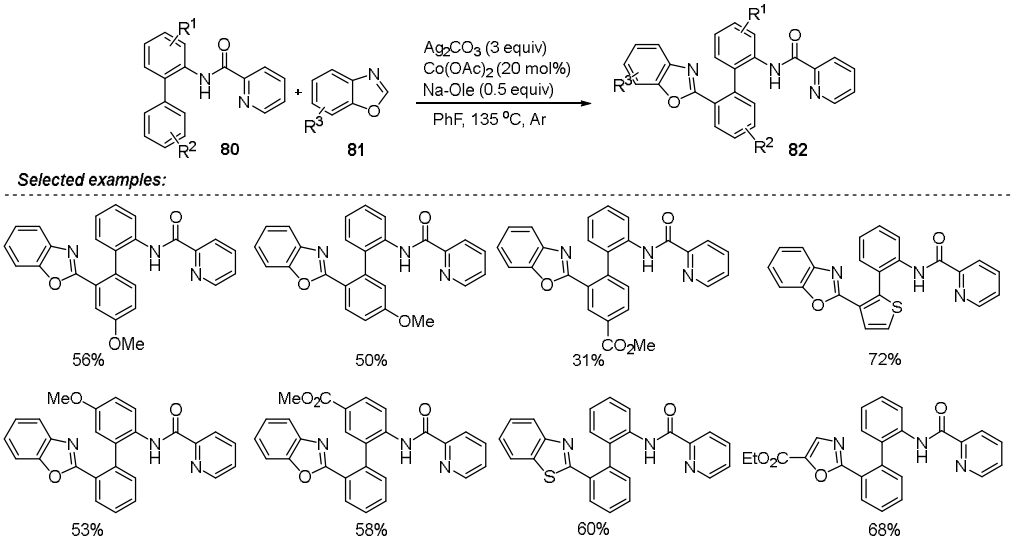


Scheme 25. Plausible mechanism for the C-H bond carbonylation of phenylalanines **71**.

Alternatively, formation of the cobalt intermediate **77** could occur *via* coordination and migratory insertion of CO in complex **75**, followed by the reductive elimination step (*path b*). Similarly, *path c* could also be possible according to which, CO coordination and migratory insertion in complex **75** takes place to furnish Co(III) intermediate **78**, followed by oxidation to Co(IV) complex **76**. Finally, after the hydrolysis of complex **77**, product **72** is formed and cobalt is reoxidized to Co(III) complex **79**, which *via* ligand exchange restarts the catalytic cycle. The performed control experiment, where C-H activation intermediate **75** was transformed into the carbonylation product in absence of external oxidant under CO atmosphere indicated that *path b* might be more favourable over the other pathways (Scheme 25).

4. C-H functionalization with heteroarenes

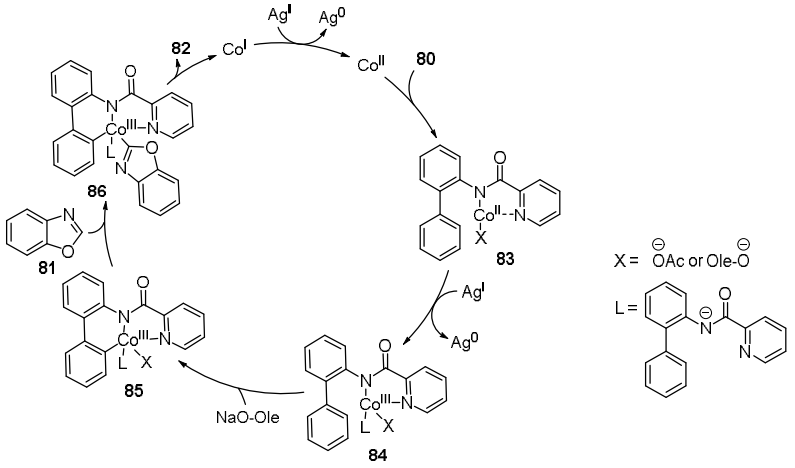
Wang and co-workers in 2020 reported the only example known so far of cobalt-catalyzed, picolinamide-directed arylaniline **80** C-H bond heteroarylation with heteroarenes **81** (Scheme 26).[22] The presented work provided an efficient access to 2-(2-arylphenyl)azole **82** motifs, which are known to possess antifungal and anti-inflammatory properties. The reported catalytic system consisted of $Co(OAc)_2$ catalyst, Ag_2CO_3 oxidant and sodium oleate base. The authors examined the generality of the method by testing several substitution patterns in both of arylaniline **80** aromatic moieties as well as substrate scope with the respect to azoles **81**. They found that R^1 substituent at aniline had only a slight effect on the product yield. Regardless of the substituent position or electronic pattern, the majority of products were obtained in moderate yields. However, R^2 substituent at the *ortho*-aryl ring had a greater influence on the substrate **80** reactivity. The use of substrates containing weak electron-withdrawing groups such as 4-F and 4-Cl slightly decreased the product **82** yield compared to unsubstituted substrates, whereas strong electron-withdrawing groups ($-CF_3$, $-CO_2Me$) displayed even poorer reactivity and gave corresponding products **82** in low yields. The less potent substrate reactivity was attributed to the decreased efficiency of the C-H bond activation step. The examination of the azole **81** substituent influence on the reaction yield showed that similarly to R^1 substituents, no significant change in reactivity was observed neither for the position nor for the electronic properties of the functional group. Additionally, the authors showed that benzothiazoles and oxazoles are also competent arylaniline **80** C-H bond functionalization counterparts.



Scheme 26. Cobalt-catalyzed arylaniline **80** C-H bond functionalization with heteroarenes **81**.

On the basis of the conducted control experiments and literature data, authors proposed plausible mechanism for arylaniline **80** C-H bond functionalization with heteroarenes **81** (Scheme 27).[22] According to the proposal, first, Co(II) catalyst coordinates to the substrate, providing complex **83**, which is oxidized by

Ag_2CO_3 to Co(III) complex **84**. Next, irreversible C-H bond cobaltation takes place *via* base-assisted concerted metalation-deprotonation (CMD) mechanism to obtain cyclic C-H activation intermediate **85**. Subsequently azole **81** is coordinated to the cobalt centre to form intermediate **86**, followed by the reductive elimination to give the desired product **82** and Co(I) species, which are oxidized by Ag_2CO_3 to Co(II) and returned back to the catalytic cycle.



Scheme 27. Plausible mechanism for the arylaniline **80** C-H bond functionalization with heteroarenes **81**.

5. Conclusions

In this chapter, we have summarized the cobalt-catalyzed, picolinamide-directed C-H functionalization methodologies for the synthesis of various heterocyclic targets, which substructures are the key fragments in various natural products or pharmaceutically active compounds. We have compiled the published methods for C-H functionalization with alkynes yielding isoquinolines, 1,2-dihydroisoquinolines, dibenzoazepines and benzoquinolines, as well as C-H bond carbonylation methods to access isoindolinones, phenanthridinones, benzoindolones, indoloquinoxalinones and 1,2-dihydroisoquinolinones, and one C-H bond heteroarylation method, which allowed to obtain 2-(2-arylphenyl)azole derivatives. Results described in this review demonstrate that the bidentate directing group assisted cobalt-catalyzed C-H bond functionalization is a powerful tool for the construction of different types of heterocyclic compounds with the potential application in medicinal chemistry. One of the greatest advantage of the picolinamide directing group is the ability to act in a traceless fashion. Besides the developed methods described, this is still highly active field and many new discoveries might be expected in the nearest future.

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