doi: 10.31674/book.2025ccbsse017

A Brief Review on Recent Developments in C(Sp^2)-H and C(Sp^3)-H Activation Protocols through Cobalt-catalysis

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Abstract

Cobalt (Co) is presently of greater interest to researchers exploring C-H functionalisation than noble metals like Pd, Rh, and Ir due to its accessibility, cost, and low toxicity. In this way, during the past few decades, the number of instances of co-catalysed functionalisation has grown dramatically. This review work focuses on the latest advancements in C(sp^2)–H and C(sp^3)–H co-catalysed functionalisations, including some recent applications on enantioselective transformations.

Keywords: *Alkynes; Allenes; Arene; C-H Activation; Cobalt-Catalysis*

Introduction

Chemistry has always had a significant influence on how we see the world and is frequently regarded as the foundational science. From comprehending the complex mechanistic pathways of biological processes to building new, novel materials with unparalleled functions, chemical science is one of the most vital topics in scientific research and technological advancement. This brief overview article will look at the latest advancements and state-of-the-art techniques in organometallic chemistry by using Co-catalysis to activate carbon chains in quinolone and pyridine-based nitrogen heterocycles using a range of C-H activation techniques. Direct functionalisation of a C-H bond is made possible by transition metal catalysis, which is beneficial because it does not require the traditional functional group manipulation technique. Because it enables the direct functionalisation of a C-H bond without depending on the traditional manipulation of the functional group approach, research on Co-catalysed C-H activation has expanded in the field of organic chemistry during the past few decades (Baccalini *et al*., 2019).

A number of important, bioactive, and naturally occurring chemicals could be synthesised atom-by-atom and step-efficiently by identifying and functionalising a specific carbon-hydrogen bond inside a given molecule. Palladium, rhodium, ruthenium, and iridium were the 4d and 5d transition metals that dominated the area early in the history of C-H activation chemistry. As an alternative, creative techniques using inexpensive, widely available 3D metals have gained more popularity lately. They enable distinct patterns of selectivity and reactivity, which makes this idea intriguing from an environmental and financial standpoint. This notion is significant not only because of their peculiar electrical characteristics. Notwithstanding these advantages, there is still much to discover about novel first-row transition metal-based C–H activation techniques.

Recent Developments

I. Catalytic activity for Hydrosilylation of aldehyde

$$\text{PhCHO} + \text{(EtO)}_3\text{SiH} \xrightarrow{C_6D_6} \text{(PhCH}_2\text{O)Si(OEt)}_3$$

Figure 1: Catalytic Activity for Hydrosilylation of Aldehyde

A more detailed examination of the open-system reaction at 50°C revealed that the hydrosilylation process (Figure 1) was completed in just 10 hours. The same conditions for substituting $PhSiH_3$ for $(EtO)_3SiH$ resulted in a somewhat quicker catalytic reaction, converting PhCHO into several $PhCH_2O$-containing products in 8 hours. Despite the 24-hour duration of the hydrosilylation reaction, Ph_2SiH_2 was shown to be a successful silane for reducing PhCHO. However, with Et_3SiH, no hydrosilylation product was observed even after 48 hours (Li, Krause & Guan, 2018).

Proposed Reaction Mechanism

$$\text{(EtO)}_3\text{SiH} + \text{1b (1 mol\%)} \xrightarrow[\text{24 hr}]{C_6D_6} \xrightarrow[\text{8-10 hr}]{\text{PhCHO (1 eqv.)}} \text{(PhCH}_2\text{O)Si(OEt)}_3$$

$$\text{PhCHO (1 eqv.)} + \text{1b (1 mol\%)} \xrightarrow[\text{24 hr}]{C_6D_6} \xrightarrow[\text{2 hr}]{\text{(EtO)}_3\text{SiH}} \text{(PhCH}_2\text{O)Si(OEt)}_3$$

Figure 2: Mechanistic Considerations

To find out which reactant-initiated catalyst activation, the author mixed 1b (cobalt POCOP pincer complex) with one reactant first (Figure 2) and let the mixture "age" for 24 hours under catalytic conditions before adding the second reactant. The time required to totally eradicate PhCHO was shown to be influenced by the additional sequence. The silane-first process took 8–10 hours to finish, which is comparable to the standard methodology that first mixes PhCHO and $(EtO)_3SiH$ with catalyst 1b.

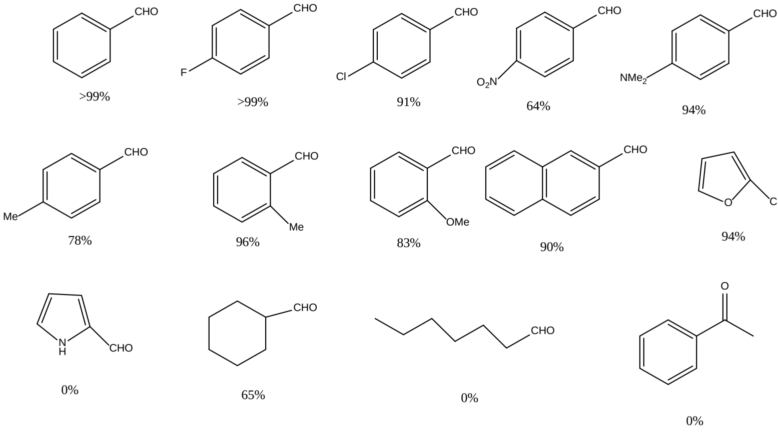


Figure 3: Substrate Scope

In comparison, the aldehyde-first technique shortened the reaction time to two hours. By preactivating the catalyst, PhCHO preserved catalytic efficiency while enabling the hydrosilylation step to be finished in a closed system. Furthermore, we found that it only took two hours to fully decrease PhCHO and that refilling PhCHO and $(EtO)_3SiH$ restarted the catalytic activity after the hydrosilylation reaction was completed. After repeating this process, the conversion rate rose to over 99% in less than two hours, yielding a 300 total turnover figure.

The authors also studied the substrate scope and obtained different yields in various products, which are shown in Figure 3.

II. C-H Activation by Insoluble Cationic (Bisphosphin) Cobalt (iii) mealocyle

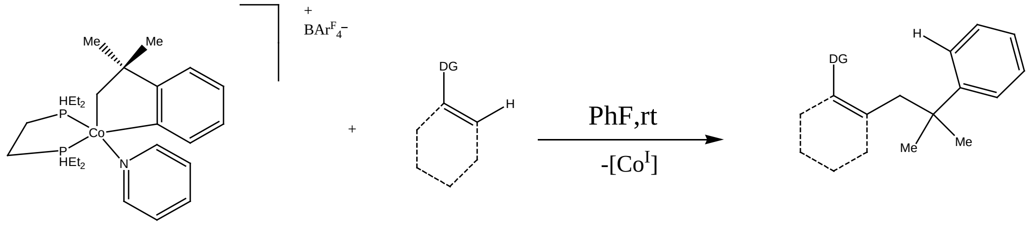


Figure 4: *C-H Activation by Insoluble Cationic (Bisphosphin) Cobalt (iii) mealocyle*

A variety of substrates with distinct coordinating groups and substitution patterns were used in the study (Figure 4) to investigate metallacycle-mediated C-H activation. Significant directed C(sp^2)−H alkylation was typically the outcome of the reactions, which were carried out in fluorobenzene at room temperature. While 2′-bromoacetophenone demonstrated chemo selectivity favouring ortho-C−H over ortho-bromide, a ketone group quantitatively produced ortho-alkylated compounds.

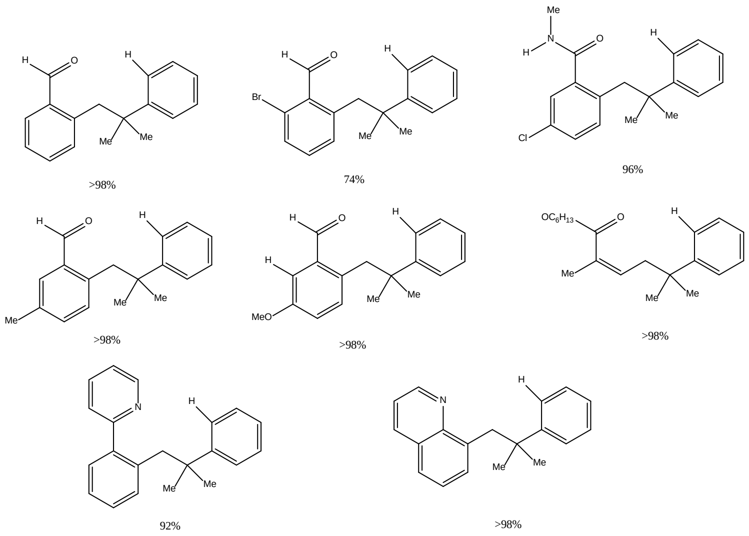


Figure 5: *Substrate Scopes*

Steric issues regulated the site-selectivity of 3-chloro-N-methylbenzamide and 3-chloro-methylacetophenone, favouring less hindered sites. The 6-position was where 3′-Methoxyacetophenone interacted most frequently, with just slight activation at the 2-position. Z-selective compounds were generated in great yield by hexyl methacrylate, which was consistent with known catalytic characteristics. Quinoline functionalised at the 8-position, suggesting compatibility with smaller chelate rings, and N-heterocycle-directed activation with 2-phenylpyridine and quinoline also showed efficacy. (Whitehurst *et al.*, 2022). Additionally, the authors examined the range of substrates and produced a variety of products with varying yields, as illustrated in Figure 5.

III. Regeoselective C(sp^3)- H Alkenylation of Thiamides

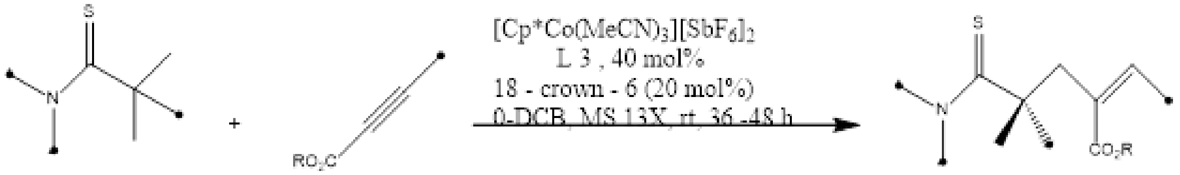


Figure 6: Regeoselective C(sp^3)- H Alkenylation of Thiamides

Under cobalt catalysis, the author investigated various coupling partners for C(sp3)-H activation (Figure 6) and discovered that methyl but-2-ynoate interacted well with thioamide 1a. Benzoic acid helped this reaction create alkenylated thioamide in a 63% yield with remarkable regioselectivity. We tested Fmoc-protected amino acids, such as alanine and trityl-protected asparagine, to achieve enantioselectivity, and the findings were encouraging, albeit small. Enantioselectivity was enhanced by subsequent testing using several amino acid derivatives, particularly L-alanine and L-tert-leucine-based catalysts; the most successful of these was L-tert-leucine derivative. The goal of additional optimisation was to improve these outcomes (Staronova *et al.,* 2023). Further, Figure 7 displays the various yields that the authors achieved from their investigation of the substrate scope.

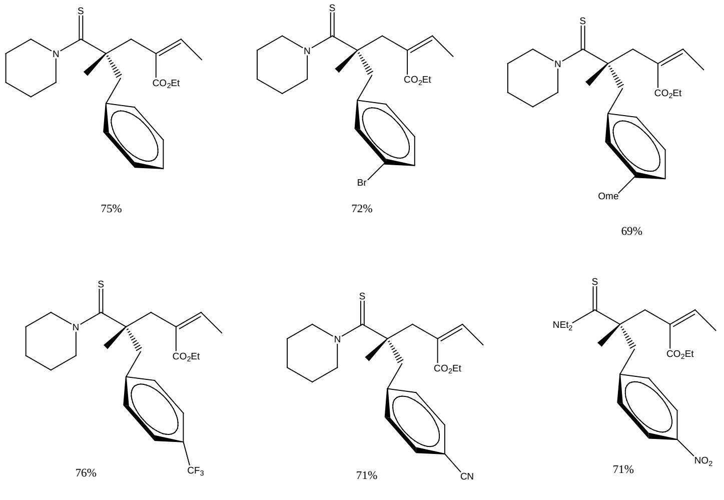


Figure 7: Substrate Scopes

IV. Selective Benzylic C-H Borylation by Tandem Cobalt Catalysis:

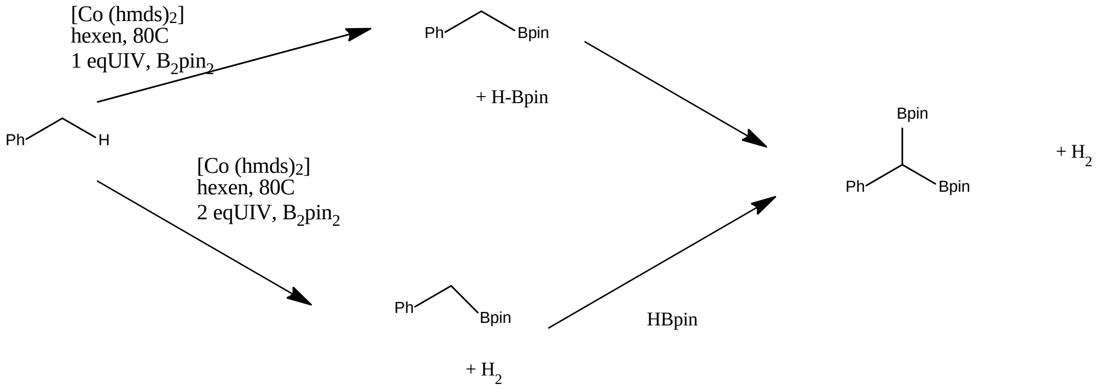


Figure 8: Selective Benzylic C-H Borylation by Tandem Cobalt Catalysis

The author used 5 mol% Co(hmds)$_2$ to evaluate the reaction (Figure 8) between toluene and bis(pinacolato)diboron (B$_2$pin$_2$). This produced benzyl diboronate in n-hexane at 80°C with good conversion and great specificity for benzylic CH-borylation. Cobalt catalysts without the hmds ligand were inactive, and Fe(hmds)$_2$ produced results that were mild. Without the catalyst, no goods were produced (Ghosh *et al.,* 2021). Additionally, the different yields that the authors obtained from their examination of the substrate scope are shown in figure 9.

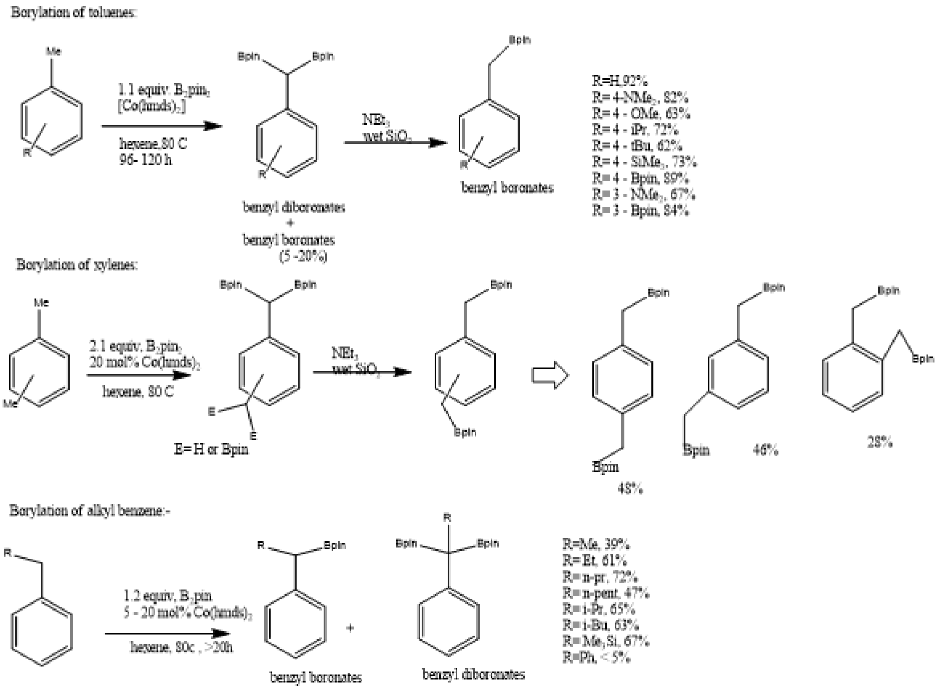


Figure 9: Substrate Scopes

V. Cobalt Catalysed C-H Alkoxylation:

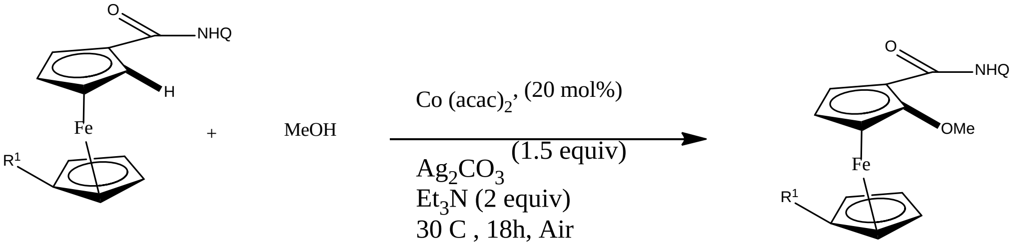


Figure 10: Cobalt Catalysed C-H Alkoxylation

With N-(quinolin-8-yl)ferrocene-1-carboxamide and MeOH, the reaction conditions (Figure 10) are optimised by employing $Co(acac)_2$ as a catalyst, Ag_2O as an oxidant, and $NaHCO_3$ as a base in MeOH at 40°C. The yield from this original configuration was sixteen percent. After testing various bases, Et_3N turned out to be the most effective, raising the yield to 39%. After screening for several oxidants, Ag_2CO_3 increased the yield to 60%. The result was further enhanced to 66% by the use of methenamine. Et_3N was replaced by methenamine, which produced a 44% yield, suggesting that it might also be used as a base. The yield increased to 75% when the temperature was lowered to 30°C. Other catalysts such as $Ni(OAc)_2$, $Cu(OAc)_2$, $Co(PPh_3)Cl$, and $Co(OAc)_2{\cdot}4H_2O$ did not work. Under these circumstances, other bidentate coordinating groups were unable to produce the intended results (Zhang *et al.,* 2021).

Proposed Reaction Mechanism

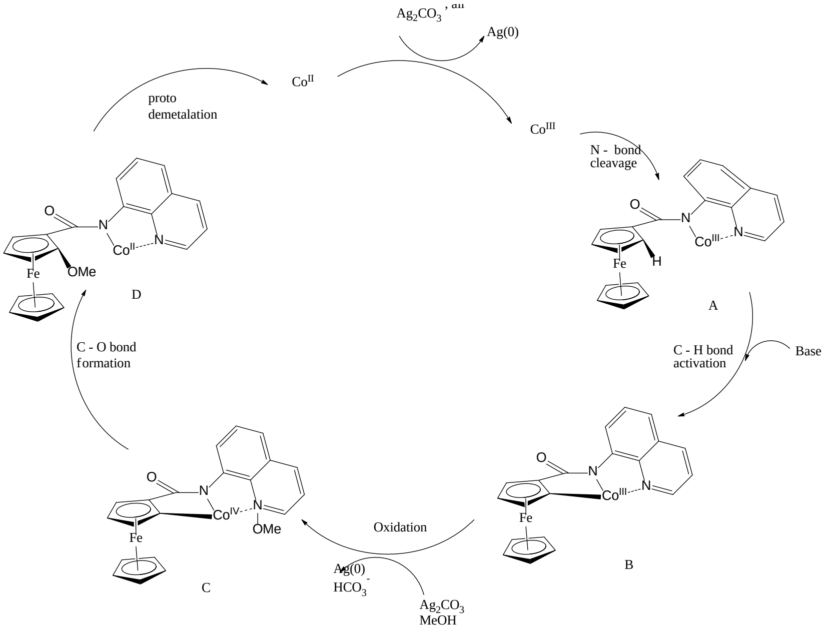


Figure 11: Mechanistic Constitutions

A Co(III)/Co(IV)/Co(II) mechanism for cobalt-catalysed C-H alkoxylation has been proposed by researchers (Figure 11). Ag_2CO_3 first oxidises Co(II) to Co(III), which subsequently interacts with ferrocene to activate the C-H bond via an irreversible CMD route, generating intermediate B. With the help of Ag_2CO_3, an alkyloxygen radical attacks Co(III), producing intermediate C. Following this, protodemetalation and the creation of C-O bonds result in the product formation and the regeneration of Co(II). Selective C-H alkoxylation of ferrocenes is made possible by the technique, which tolerates a variety of functional groups. According to mechanistic studies, the rate-limiting step is C-H bond activation, which most likely involves a Co(III)/Co(IV)/Co(II) cycle (Zhang *et al.,* 2021).

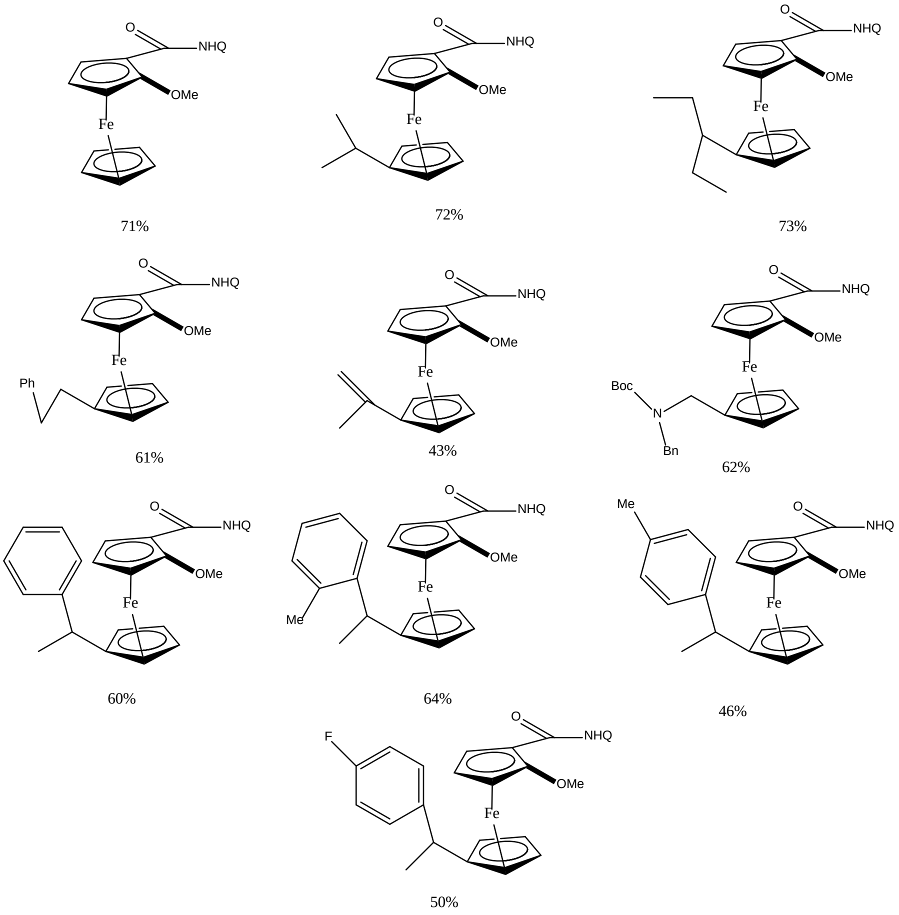


Figure 12: Substrates Scopes

Furthermore, figure 12 displays the various yields that the scientists were able to derive from their analysis of the substrate scope.

VI. Annulation with Allenes

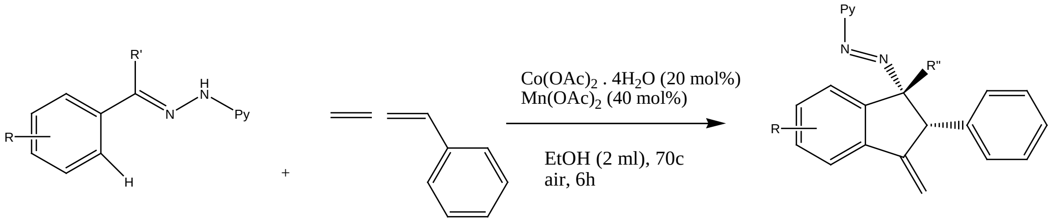


Figure 13: Annulation with Allenes

Proposed Reaction Mechanism

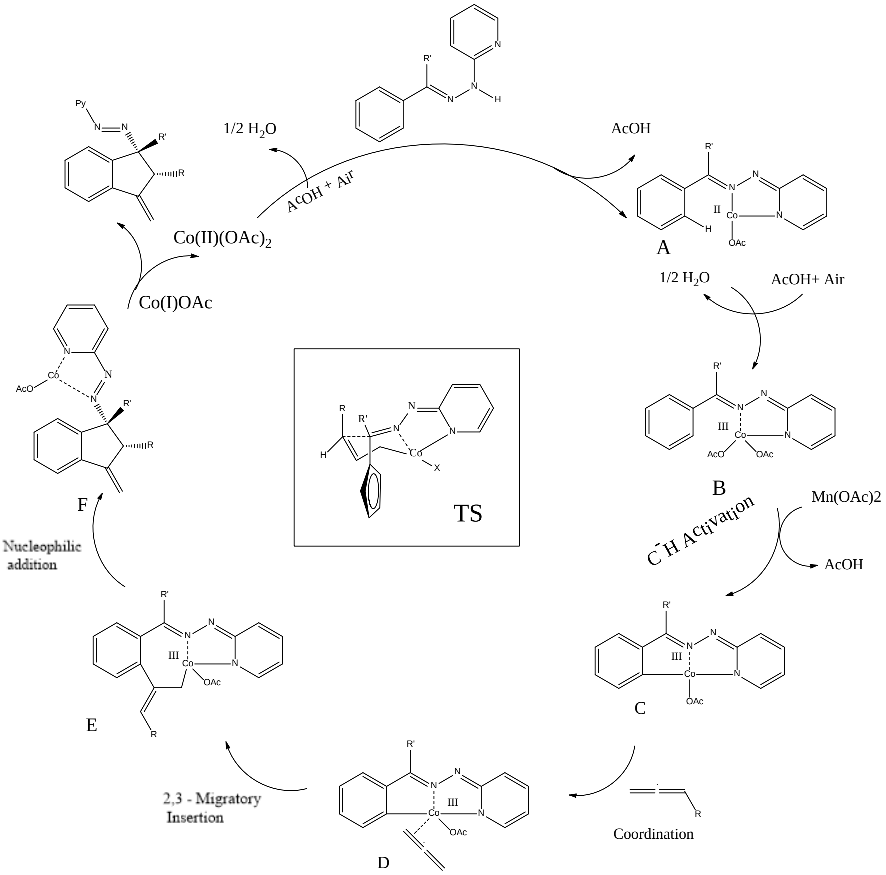


Figure 14: Mechanistic Constitutions

The authors (Dey & Volla, 2021) screened the process by reacting phenyl allene with several substituted hydrazones (Figure 13). Consequently, indane derivatives with moderate to good yields were produced. The hydrazone derivative combines with a Co(II) catalyst to generate intermediate A, which initiates the suggested pathway (Figure 14).

Complex C is the product of oxidation and a coordinated metalation deprotonation (CMD) process aided by Mn(OAc)$_2$. The allyl cobalt intermediate E, a σ-allyl complex, is produced by coordination with the allene and selective 2,3-migratory insertion of the less-substituted double bond. Using a six-membered cyclic transition state, this intermediate is intramolecularly nucleophilically added to the imine carbon to form intermediate F. Decomplexation yields the end product, and the catalytic cycle is completed by oxidising the Co(I) produced back to Co(II).

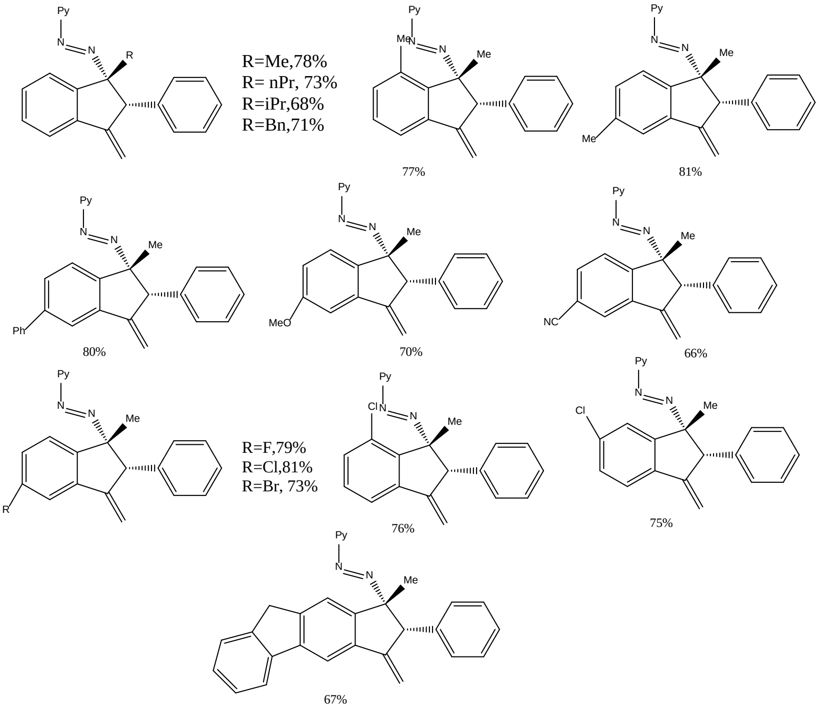


Figure 15: Substrates Scope

The authors experimented with the substrate shown in Figure 15 and obtained a range of yields.

VII. High Valent Cobalt Catalysed C-H Functionalisation

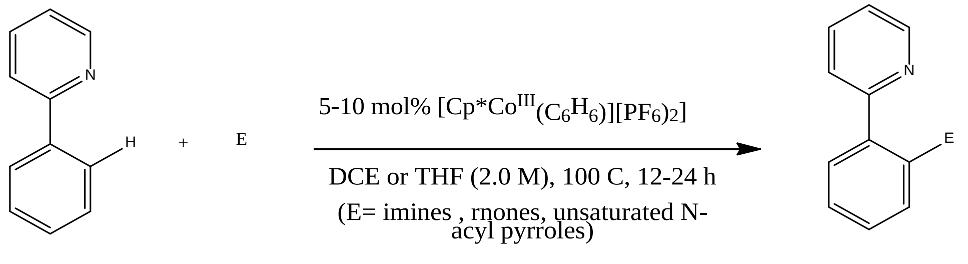
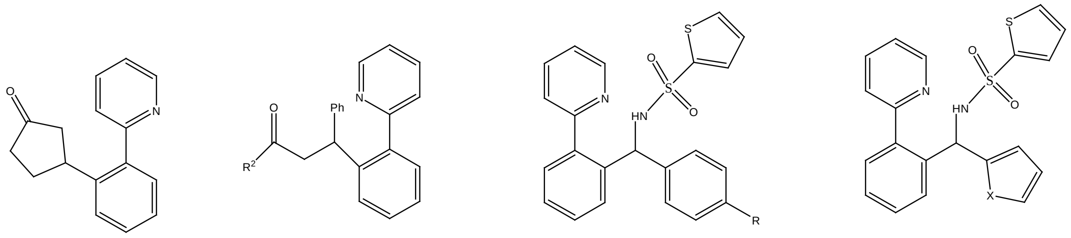


Figure 16: High Valent Cobalt Catalysed C-H Functionalisation

Cobalt-Catalyzed C(sp²)-H and C(sp³)-H Activation

In 2013, scientists (Yoshino *et al.,* 2013) discovered a cationic compound, [Cp*CoIII(C_6H_6)](PF_6)$_2$ (Figure 16). With the help of this combination, 2-arylpyridines can be added nucleophilically to N-sulfonylimines and enones as polar electrophiles without the use of extraneous chemicals. Other Co(III) complexes with less packed or sterically more hindered groups on the cyclopentadiene ring were found to be less effective.



90%

R^2 = Ph, 80%

R^2 = m-MEO-C_6H_4, 76%

R^2 = Me, 78%

R= H, 80%

R= CF_3, 64%

R = OMe, 57%

x= S, 69%

x= O, 66%

Figure 17: Substrates Scopes

Under the ideal circumstances, moderate to high yields were attained with good compatibility across functional groups, such as ether, amino, acetyl, and halogen groups. Additionally, α, *β*-unsaturated N-acyl pyrroles were used as ester and amide surrogates to generate Michael adducts. The C-H functionalisation is most likely to take place by electrophilic aromatic substitution or a CMD process in order to create the Cp*Co(III) intermediate. Electrophile coordination and insertion lead to protodemetalation, which regenerates cyclo-metalated Co(III) and produces the equivalent product (Yoshino *et al.,* 2013). The authors experimented with the substrate shown in Figure 17 and obtained a range of yields.

VIII. Asymmetric C-H Amidation of Ferrocenes

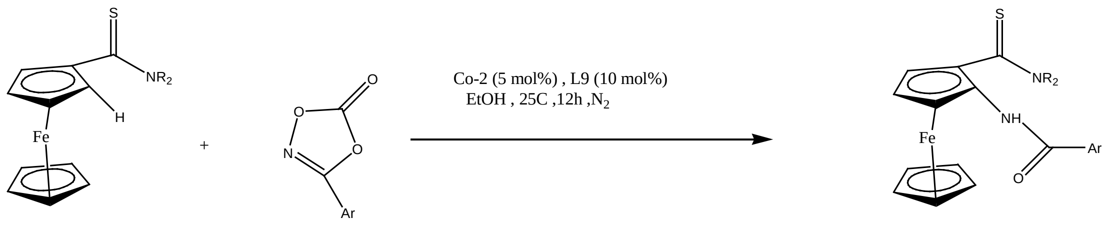


Figure 18: ***Asymmetric C-H Amidation of Ferrocenes***

Planarly chiral ferrocene derivatives have been preferred as ligands or catalysts in asymmetric catalysis (Figure 18). In 2019, the Shi group created a new chiral monoprotected amino acid (MPAA) ligand to achieve the asymmetric amine modification of ferrocene thioamides with dioxazolones. The planar chiral amidated compounds showed moderate enantioselectivity (36%–55% ee) and good yields (48%–97%). Additionally, the enantiomeric purity could be raised to >99% ee with a single crystallisation (Zheng *et al.,* 2022).

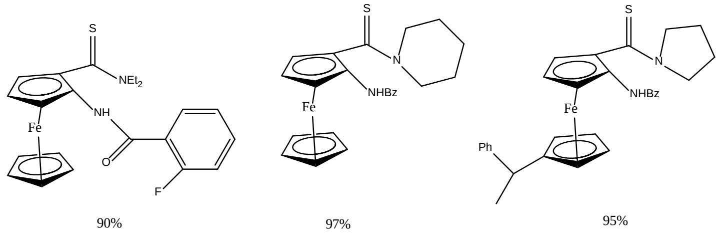


Figure 19: Substrate Scopes

Using different substrates, the authors experimented and got a variety of products with high yields, as depicted in Figure 19.

IX. Chiral Carboxylic Acid Assisted Enantioselective C-H Activation

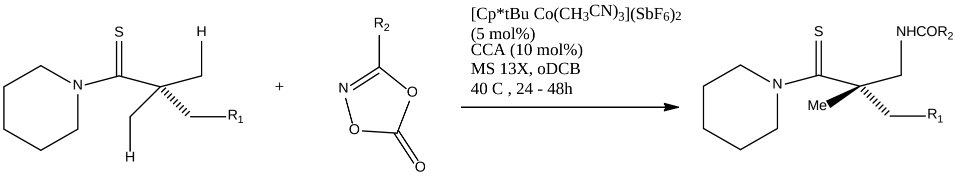


Figure 20: Chiral Carboxylic Acid Assisted Enantioselective C-H Activation

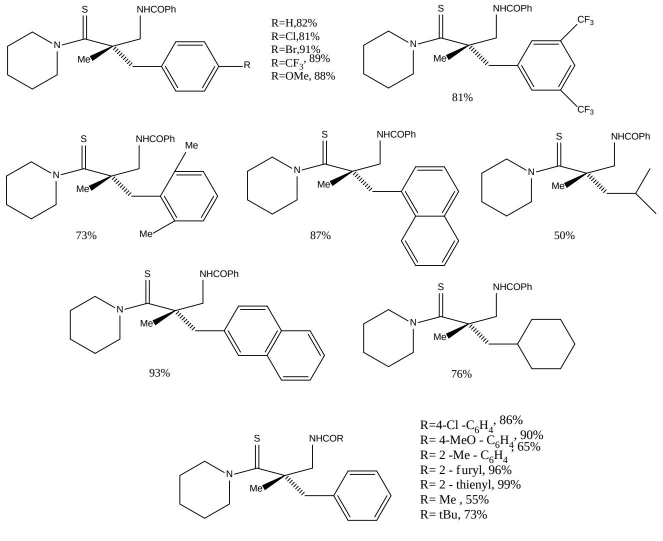


Figure 21: Substrate Scopes

An enantioselective C(sp^3)−H amidation of thioamides is described (Figure 20) using the Cp*^{t}Bu-Co(III) catalyst and amino acid ligands. Imide-protected α-amino acids were chosen because they are simple to synthesise and function well as ligands for transition-metal catalysts. The enantioselectivity was greatly enhanced by the sterically hindered imide moiety, which provided steric bulk without connecting to the metal centre. The optimal choice was determined to be C, with a maximum chiral ligand ratio of 94:6. By producing amines, amides, and aldehydes from their byproducts, gram-scale reactions demonstrated potential for practical synthetic uses (Yoshino & Matsunaga, 2021). The authors also studied many substrates as described in the above substrate scope (Figure 21) and obtained the products with decent yields.

X. Cobalt (III) Catalysed C-H Activation

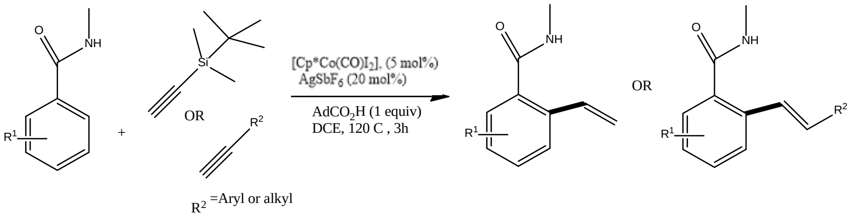


Figure 22: Cobalt (III) Catalysed C-H Activation

In 2018, Muniraj and Prabhu synthesised vinylated products from various 4-Me, 3-Me, and 4-OMe substituted N-methyl benzamides by reacting benzamides with alkynes and silyl-alkynes (Figure 22). Vinylation only occurred at the ortho position for 3-Me-substituted benzamide. Additionally, three compounds (with yields ranging from 50% to 56%) were extracted from halogenated N-methylbenzamides. Additionally, a 53% yield of N-methyl-4-vinyl benzamide was generated. Ortho-substituted benzamide produced a trace amount of product due to steric hindrance. Additionally, the yields of the amide made from thiophene were low (36%). Unreacted N-methyl benzamide was recovered in every instance. Even terminal alkynes, such as 1-pentyne and phenylacetylene, produced alkenylated compounds with yields of 60% to 68% (Muniraj & Prabhu, 2018).

Proposed Reaction Mechanism

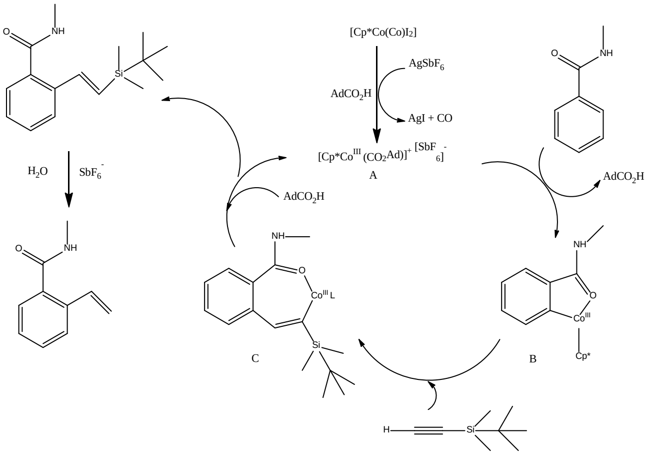


Figure 23: Mechanistic Constitutions

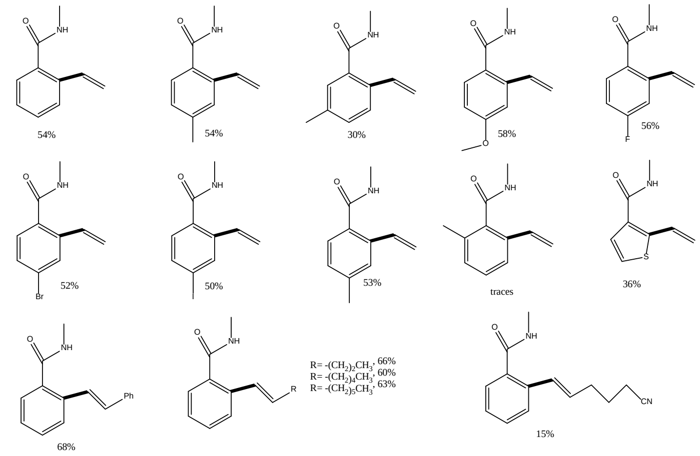


Figure 24: Substrate Scopes

Based on previous studies and control trials, a proposed procedure (Figure 23) is depicted for the production of catalytically active species-A. A interacts with the amide to form cobaltacycle-B. After that, intermediate C is created by inserting the alkyne. $AdCO_2H$ promoted the protodemetallization of C, which yielded vinylsilane and regenerated catalyst A. When SbF_6 is present, desilylation eventually yielded the final product. The authors' research yielded varied results using the substrate shown in Figure 24.

XI. Functionalisation Catalysed by Simple, Low Valent Co Complex

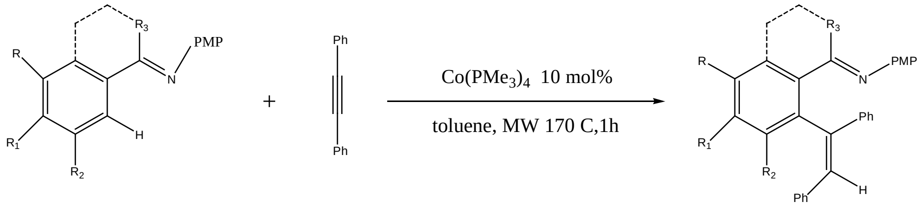


Figure 25: Functionalisation Catalysed by Simple, Low Valent Co Complex

Fallon and coworkers (2015) investigated the hydroarylation process using diphenylacetylene and a variety of imines in this work (Figure 25). With para-substituted imines, the reaction demonstrated high yields while tolerating neutral, electron-withdrawing, and electron-donating (like OMe) groups. Standard yields were replicated by gram-scale synthesis. Because of a secondary directing effect seen in cobalt, ruthenium, and iridium catalysis, substrates with methoxy, fluoro, and cyano groups favoured the more hindered ortho position, whereas substrates with meta-methyl substitutions selected the less hindered ortho position. Notably, imines made from tetralone, propiophenone, and 2-acetonaphthone also successfully produced the required molecules (Fallon *et al.,* 2015).

For both catalysts, the catalytic cycle shown in Figure 26 entails ligand exchange to create intermediate (I), which is then followed by a hydrogen transfer to create intermediate (II). Intermediate (III) is formed by subsequent reductive elimination, and the observed antiselectivity is explained by isomerisation. The importance of cobalt in double bond isomerisation is demonstrated by the reported iridium-catalysed ketone addition, which results in 55% isomerisation to the anti-product. However, because ketones have weaker anchoring effects than imines, this process is less effective.

Proposed Reaction Mechanism

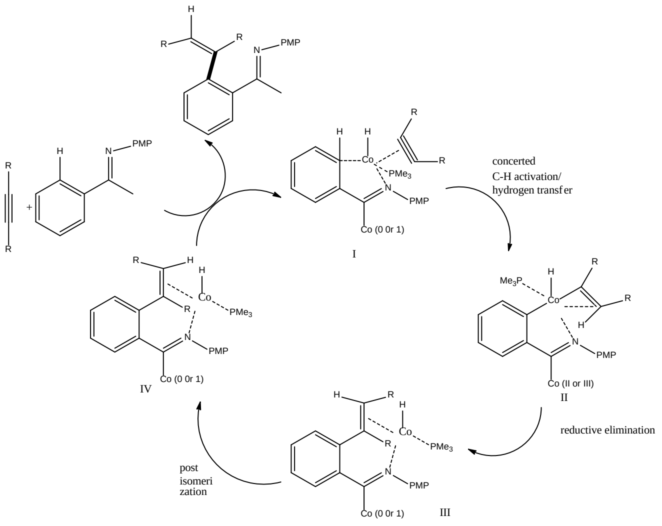


Figure 26: Mechanistic Constitutions

Conclusion

By emphasising the transformative impacts of co-catalysis on society and its numerous applications in C-H bond activation processes, this book chapter provides an insight into the most recent advancements in organometallic chemistry. These results may undoubtedly be applied to other heterocycle derivatives to promote further investigation and collaboration, which will deepen our grasp of the myriad possibilities in cobalt chemistry. This might be accomplished by looking at the developments of the past decade as well as the future paths of a number of sub-disciplines.

Acknowledgment

The teacher-in-charge of Maharaja Manindra Chandra College, who provided office space and internet access, is acknowledged by the author. The author also thanks his coworkers in the Maharaja Manindra Chandra College Chemistry Department for their unwavering support.

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