Exploring Cp*Co-catalysed ligand-directed C–H trifluoromethylthiolation reaction:

from bibliographic research to an action plan

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FINAL DEGREE THESIS
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ABBREVIATIONS AND ACRONYMS

Ar–SCF_3	*Aromatic compound-trifluoromethylthio bond*
BrettPhos	*2-(dicyclohexylphosphino)3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl*
CD_2Cl_2	*Deuterated dichloromethane*
COD	*1,5-cyclooctadiene*
Cp*	*1,2,3,4,5-pentamethylcyclopentadienyl*
C–H bond	*Carbon-Hydrogen bond*
C–Het	*Carbon-Heteroatom bond*
C–C	*Carbon-Carbon bond*
C–M	*Carbon-Metal bond*
C–SCF_3	*Carbon-Trifluoromethylthio bond*
C–X	*Carbon-nucleophile bond*
DCM-d_2	*Deuterated dichloromethane*
DCM	*Dichloromethane*
DCE	*1,2-dichloroethane*
DFT	*Density functional theory*
DG	*Directing group*
DMF	*Dimethylformamide*
equiv.	*Equivalent*
Et_2O	*Diethyl ether*
FG	*Functional group*
h	*Hours*
HFIP	*1,1,1,3,3,3-hexafluoroisopropanol*
KBB	*Knowledge building block*
L_n	*Undetermined ligand(s)*
MeCN	*Acetonitrile*
min	*Minutes*
NCMe	*Acetonitrile*
NMR	*Nuclear Magnetic Resonance*
OAc	*Acetate*
OEt	*Ethoxy*
OPiv	*Pivalate*
OTFA	*Trifluoroacetate*
OTf	*Triflate or trifluoromethanesulfonate*
Ph	*Phenyl*
phen	*Phenanthroline*
2-PPy	*2-phenylpyridine*
rt	*Room temperature*
^tBu	*Tert-butyl group*

THF	*Tetrahydrofuran*
TFE	*2,2,2-trifluoroethanol*
TM	*Transition Metal*
TMS	*Trimethylsilane*
UV	*Ultraviolet*
VTMS	*Vinyltrimethylsilane*

1. Abstract

Over the past decades, the synthetic community has developed new methodologies for expanding the scope of reactions that can be used for constructing molecules. Among them, ligand-directed C–H functionalization has emerged as an alternative to traditional cross-coupling reactions, becoming a cornerstone in modern synthetic chemistry. This field has been dominated by the employment of noble metals, such as Pd, Rh or Ir. However, in the past five years, first-row transition metals, such as cobalt, have demonstrated that they ca not only emulate the same reactivity patterns of precious metals, but also exhibit a unique reactivity. Herein, we present a brief overview of C–H functionalization reactions, paying special attention to the introduction of the SCF_3 moiety in organic scaffolds. We will cover from metal-free synthetic methods to oxidatively induced reductive elimination mechanistic scenario using silver (I) salts as terminal oxidant. Finally, an experimental methodology studying different parameters related to the Cp*Co-catalyzed C–SCF_3 bond-formation would be carried out.

Durant les últimes dècades, la comunitat científica ha desenvolupat noves metodologies per ampliar l'abast de reaccions útils per a la construcció de molècules. La funcionalització dirigida per lligands de l'enllaç C–H ha aparegut com una alternativa a les reaccions tradicionals d'acoblament creuat, convertint-se en una reacció pionera en la química sintètica moderna sent dominada per l'ús de metalls nobles com Pd, Rh i Ir. No obstant això, en els darrers cinc anys, els metalls de la primera sèrie de transició, com el cobalt, han demostrat que no només emulen els mateixos patrons de reactivitat dels metalls preciosos, sinó que presenten una reactivitat única. A continuació, es presenta una breu visió general de les reaccions de funcionalització C–H, posant especial atenció en la introducció del grup SCF_3 en molècules orgàniques. S'abasta des de mètodes sintètics lliures de metalls fins a escenaris mecanístics d'eliminació reductiva induïda per oxidació utilitzant sals de plata (I). Finalment, es duria a terme una metodologia experimental relacionada amb la formació de C–SCF_3 mitjançant Cp*Co.

2. Objectives

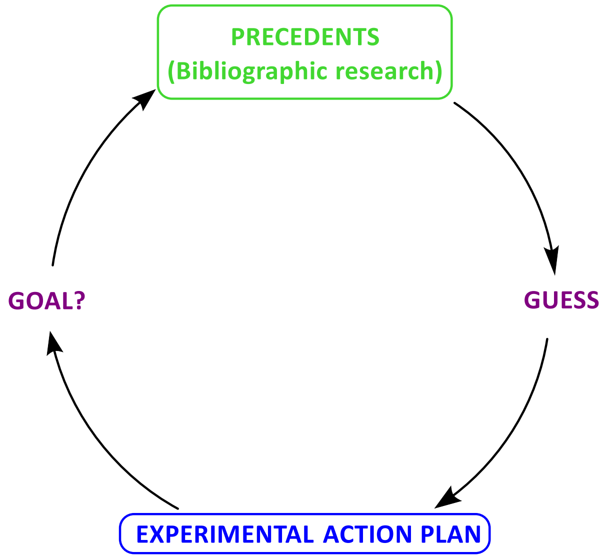
The main goal of this Final Degree Thesis is the study of Cp*Co-catalysed C–SCF_3 bond-forming reactions using a ligand-directed C–H activation approach. To achieve this goal, the following points of view have been investigated:

- Bibliographic research: To provide a more comprehensive picture of the formation of C–SCF_3 bonds using different methodologies and Cp*Co-catalysed C–H functionalization reactions, the following objectives are proposed:
    a) Timeline study of introduction of SCF_3 group.
    b) Description of the ligand-directed C–H activation and its mode of action.
    c) Evaluation of the reactivity of cobalt complexes including Cp*Co systems.
    d) Investigation of oxidatively induced reductive elimination scenario for transition metals-catalysis.
    e) Mechanistic understanding scenario of ligand-directed Cp*Co-catalysed C–H functionalization reaction.
- Experimental research: Optimization conditions for the trifluoromethylthiolation reaction were investigated:
    a) Reactivity studies of different parameters related to the C–SCF_3 bond-forming such as temperature, time, set-up, aerobic conditions, catalysts, solvents, oxidant, trifluoromethylthiolation reagents and base additives.
    b) Development of a new catalytic method using electricity instead of chemical oxidants.

3. Introduction

The main purpose of this Final Degree Thesis has been to introduce the vision of sustainability in organometallic catalysis in order to develop new chemical transformations. To promote this philosophy, the focus of this work has been the use of first-row transition metals, in particular cobalt, as a cost-effective alternative to noble transition metals. The work described has been performed during the exceptional situation of a global pandemic caused by Covid-19, returning to a bibliographic research and experimental action plan tutorized by Dra. Anna Maria Clotet Romeu and supervised by Dra. Mónica H. Pérez Temprano and Dra. Sara Martínez de Salinas Uzquiza.

In order to implement a rational design, the understanding of the underlying steps in a catalytic cycle is the most important goal to improve and develop sustainable approaches. The workflow should start with a bibliographic research to investigate the presented reactivity of Cp*Co complexes in relevant chemical transformations including the minor examples that provided the understanding of the mechanistic scenario (*Scheme 0*). After studying the precedents, a workplan is developed to study and improve a targeted reaction, the ligand-directed Cp*Co-catalysed trifluoromethylthiolation reaction. The last objective of the project would be the implementation of electrochemical conditions instead of the use of chemical oxidants.

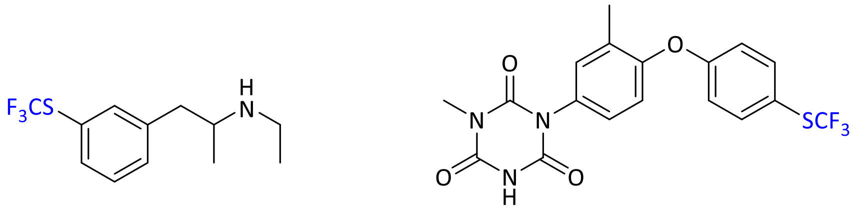


Scheme 0. Workflow of this Final Degree Thesis.

4. Bibliographic research

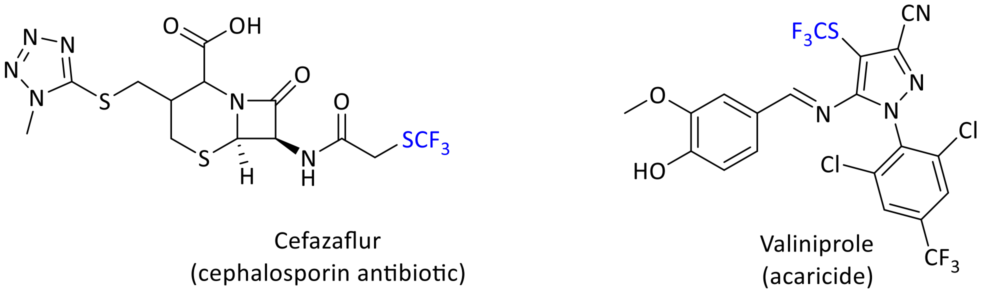
One of the main objectives of a chemist is the synthesis and functionalization of interesting molecules in order to create new benefits to improve our world. In this context, researchers are currently focused on introducing valuable functional groups, increasing the molecular complexity. Because of that, the chemical community has been interested in developing easier and sustainable alternatives for creating new advanced materials and medicines.[1]

In particular, in the last few years, the incorporation of the SCF_3 group onto organic scaffolds has received special attention from the synthetic community. The introduction of the trifluoromethylthio group ($–SCF_3$) is important in the agrochemical and pharmaceutical sector. It is found in aromatic compounds ($Ar–SCF_3$) of pesticides and drugs due to its high lipophilicity properties. Lipophilicity is a key parameter that governs the bioavailability allowing molecules to cross the lipid membranes due to the greatest Hansch constant $\pi = 1.44$ that measures hydrophobicity.[2,3,4] *Figure 1* shows selected examples of relevant bioactive trifluoromethylthiolated derivatives.[5]



Tiflorex
(treatment of anorexia)

Toltrazuril
(coccidiostatic agent)



Cefazaflur
(cephalosporin antibiotic)

Valiniprole
(acaricide)

Figure 1. Trifluoromethylthio derivatives.

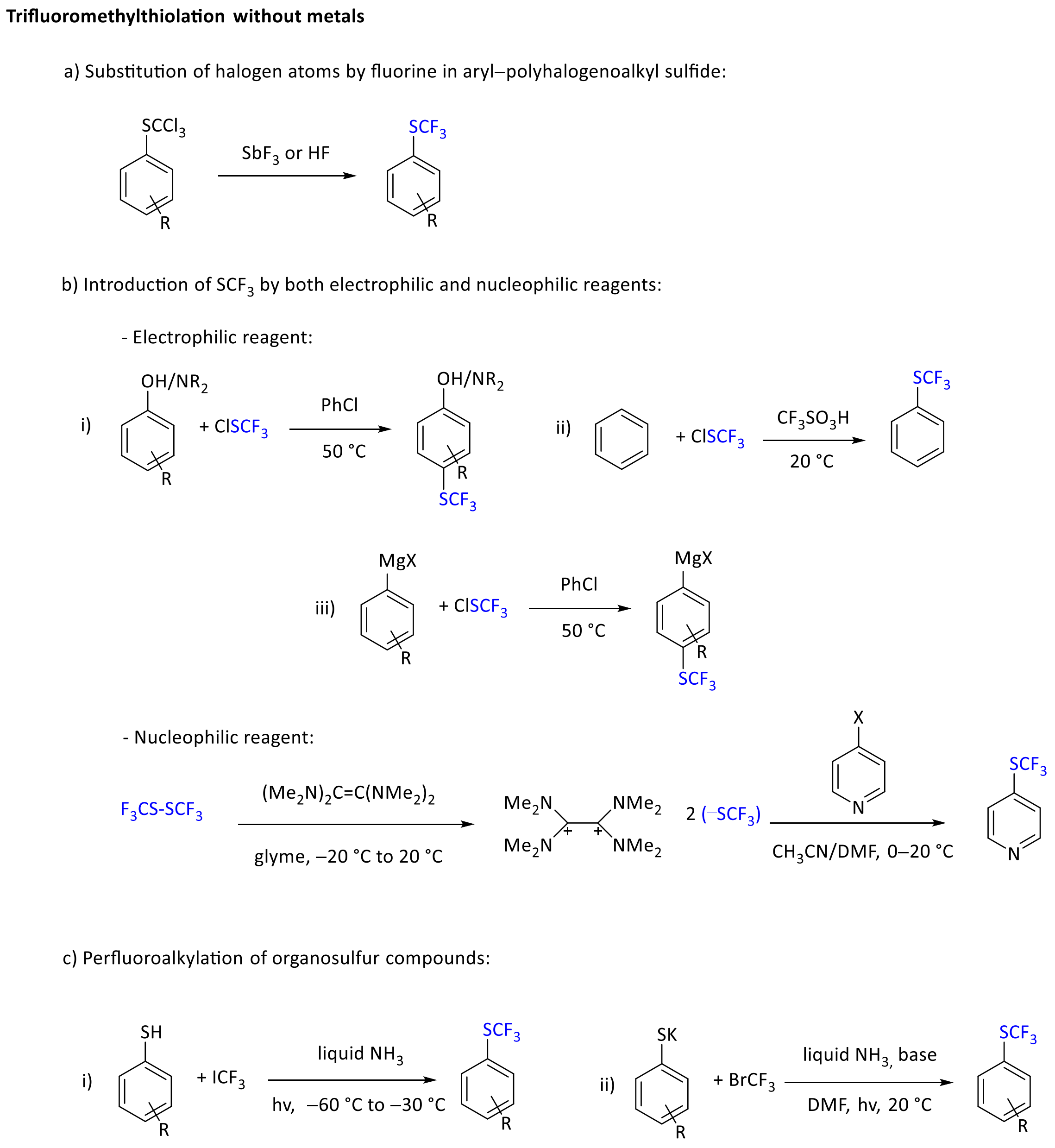
4.1. Introduction of the SCF_3 group without transition metals

Traditionally the aromatic compounds with the trifluoromethylthio group have been synthesized without metals where harsh conditions and prepared preactivated starting reagents had been required, thus limiting the accessibility of different products.

Firstly, halogenation and subsequent substitution of the halogen atoms by fluorine in aryl compounds is the oldest method of trifluoromethylthiolation.[5] The reaction runs by heating a mixture of an excess of antimony trifluoride and aryl trichloromethyl sulfide. In addition, dry hydrogen fluoride is used instead of SbF_3 in industrial processes (*Scheme 1a*).

Employing electrophilic and nucleophilic reagents is also an alternative to introduce the SCF_3 group into aryl compounds. Perfluoroalkyl sulfenyl chloride is an electrophilic reagent which reacts with electron rich aromatic compounds such as phenols and anilines forming *p*-hydroxyaryl trifluoromethyl sulfides or *p*-aminoaryl trifluoromethyl sulfides (*Scheme 1b(i)*). Benzene can also form the resultant trifluoromethyl sulfide in contact with perfluoroalkyl sulfenyl chloride and trifluoromethanesulfonic acid as a catalyst at 20°C (*Scheme 1b(ii)*). Reactions of CF_3SCl with aryl magnesium substrates at low temperatures cause poor yields (*Scheme 1b(iii)*).[2] Thus, the reaction with perfluoroalkyl sulfenyl chloride offers an effective method when electron-donating substituents are present on the ring while electron deficient aromatic compounds are more problematic due to competing secondary reactions such as halogenation and isomerization. On the other hand, tetrakis(dimethylamino)ethylene di-cation trifluoromethyl thiolate is a nucleophilic reagent produced by the reduction of bis(perfluoroalkyl)disulfides by tetrakis(dimethylamino)ethylene and reacts with aryl halides to form the desired product in high yields.

Next, perfluoroalkylation of organosulfur compounds includes various methods of cationic, anionic, radical and ion-radical processes. One example of ion-radical perfluoroalkylation is the interaction of thiophenol with perfluoroalkyl iodide under UV irradiation in contact with liquid NH_3 at -60°C to -30°C.[2] Moreover, perfluoroalkyl bromides under the same conditions with thiophenoxides containing electron-donating groups result in the formation of the trifluoromethylthio derivatives (*Scheme 1c*).



Scheme 1. Introduction of the SCF₃ group without transition metals.

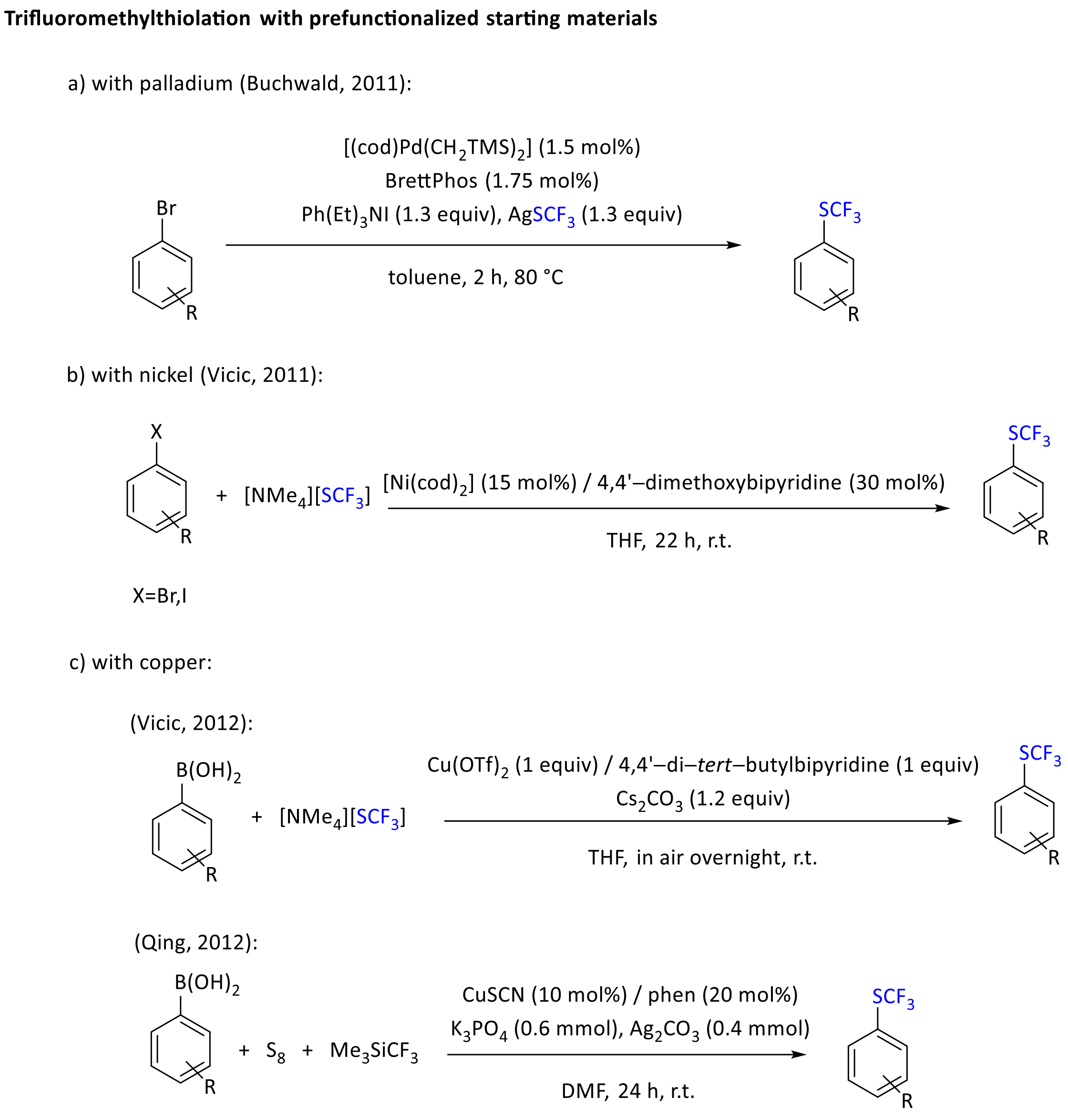
4.2. Transition metal-catalysed trifluoromethylthiolation with prefunctionalized starting materials

For the construction of Ar–SCF_3, metal-free conventional methods often require specific conditions and the formation of by-products as previously mentioned. To overcome this limitation, the chemical community has been developing efficient methods under mild protocols with prefunctionalized starting materials such as aryl boronic acids, aryl bromides and aryl iodides using transition metals.

In 2011, the first study of trifluoromethylthiolation using metals was reported by Buchwald and co-workers in which a Pd-catalysed Ar–SCF_3 bond-forming trifluoromethylthiolation with aryl bromides and $AgSCF_3$ was developed (*Scheme 2a*). The authors demonstrated the utility of their method due to the synthesis of a wide range of trifluoromethylthio derivatives that were obtained under mild conditions for 2 hours with the addition of a soluble quaternary ammonium salt ($Ph(Et)_3NI$).[6] However, this method is unattractive for commercial use due to the combination of expensive reagents and additives that are required.

On the other hand, inexpensive earth-abundant Ni-bipyridine complexes were reported by Vicic and co-workers for the trifluoromethylthiolation of aryl iodides, aryl bromides and aryl boronic acids at room temperature. In the first work, the authors used $[NMe_4][SCF_3]$ as the nucleophilic SCF_3 reagent and they showed that the system works better with aryl iodides than aryl bromides due to their electron-richness.[7] Inspiring by these results, the authors realized that none of these reactions worked with aryl chlorides because of their electron-deficiency. With these precedents, soon after, Vicic and co–workers[8] were able to successfully-trifluoromethylthiolated aryl chlorides previously catalytically converted to aryl boronic acids using a Cu-catalysed oxidative trifluoromethylthiolation reaction under air as the oxidant (*Scheme 2b*).

Similarly to Vicic's work, Qing and co-workers also studied the use of copper oxidative trifluoromethylthiolation reaction with (trifluoromethyl)trimethylsilane ($TMSSCF_3$) and elemental sulphur (S_8) (*Scheme 2c*).[9]



Scheme 2. Trifluoromethylthiolation with prefunctionalized starting materials.

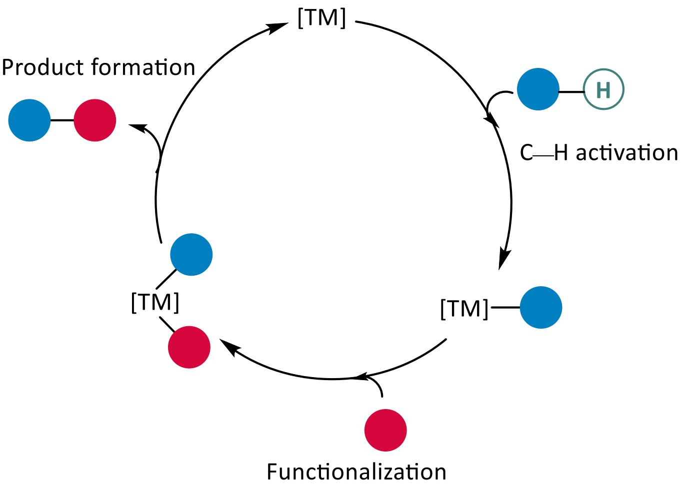
4.3. A new strategy: C–H functionalization with transition metals

Trifluoromethylthiolation with prefunctionalized starting materials required a specific starting structure where the activating group such as halides must be in the targeted position to insert the SCF_3 group. However, having the activating group in the desired position is difficult being these synthetic methods less practical. Therefore, researchers began to study C–H activation as a more ideal approach without the preparation of aryl halides or organometallic reagents.

Regarding the C–H activation, over the past decades, the chemical community has exploited the ability of transition metals due to activate C–H bonds and subsequently transformed them into C–C and C–Het bonds.[10]

These catalytic cycles usually involve three elementary steps (*Scheme 3*). The first step is the C–H activation which promotes the formation of alkyl/aryl–TM intermediate.

Next, the alkyl/aryl–TM intermediate react with the putative reactive species and finally the desired product is formed while the active catalyst is regenerating, subsequently closing the catalytic cycle.



Scheme 3. General mechanism for C–H functionalization.[1]

4.3.1. Mechanistic considerations of C–H activation

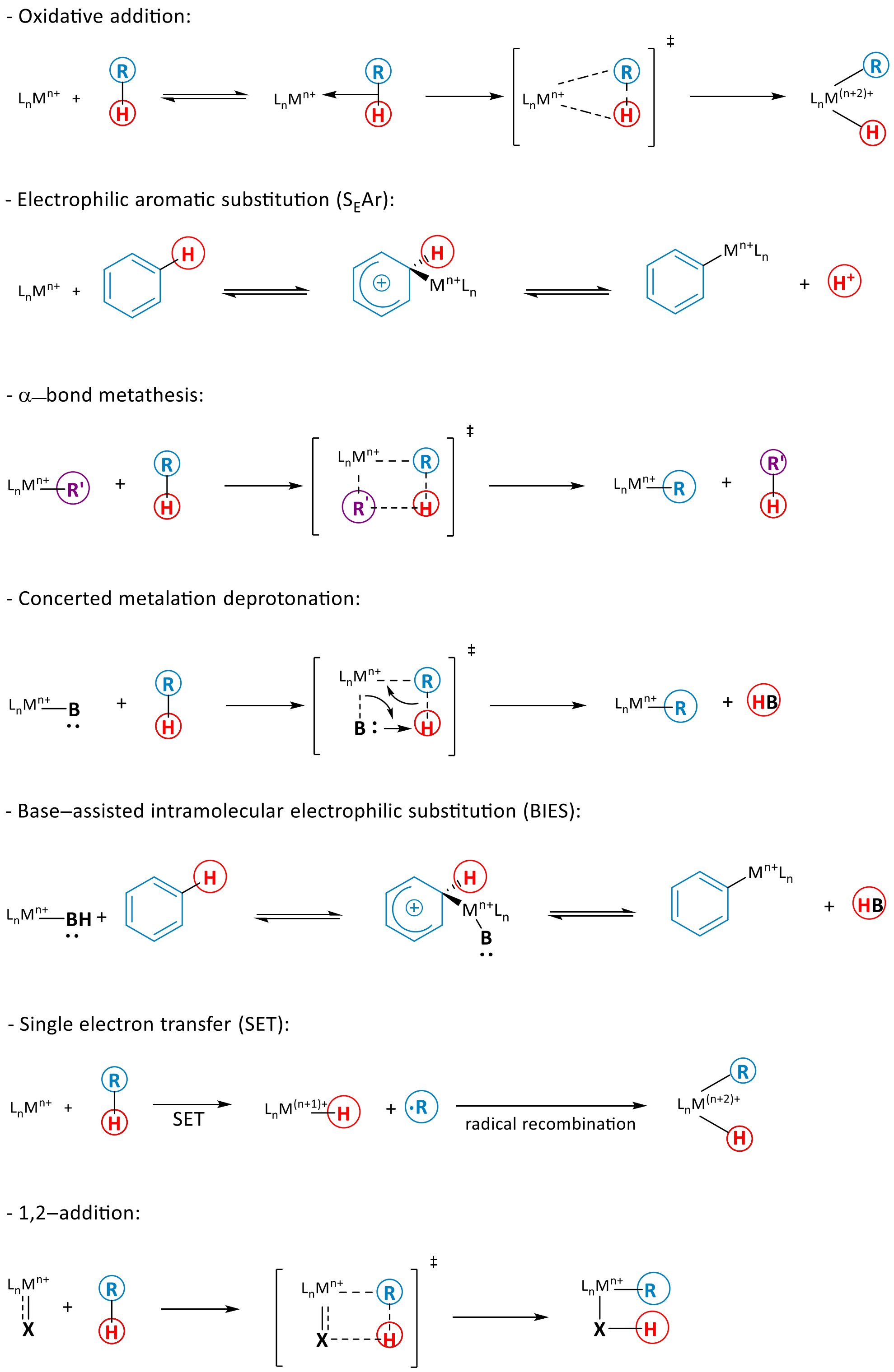
C–H activation is the elementary step where a C–H bond is activated by a transition metal. During the last decade, the chemistry community has devoted their efforts in the study of this step to understand the different mechanism of this common bottleneck in TM-catalyzed C–H functionalization. This step has evolved from electrophilic or radical reactions until the discovery of transition metals that can promote these reactions with great regioselectivity.

Herein, there is a description of well-established mechanisms and others that have been recently introduced in the organometallic field (*Scheme 4*):

- Oxidative addition: Metal center is reversible coordinated with the C–H bond increasing by two units of the oxidation state of the metal and electron count (16 to 18) changing the geometry of the complex due to new α-bonds. This commonly happens because π-backdonation of an electron-rich metal center.[11]
- Electrophilic aromatic substitution (S_EAr): The π-electronic cloud of the substrate interacts with an electrophilic metal center forming metal-carbon bond without changing the oxidation state. The acidity of the proton is enhanced, and it is prone to be abstracted by an external base, recovering the aromaticity of the substrate.[12]
- σ-bond metathesis: It is based in a [2+2] cycloaddition where there is an exchange of a metal-ligand bond with one C–H bond of the substrate via four-membered metallacycle transition state and finally forming new C–M and C–H bond without change of the metal oxidation state.[12]

- Concerted metalation deprotonation (CMD): This mechanism involves the formation of a C–M bond simultaneously than the abstraction of a proton by the coordinate base from the metal complex. This mechanism is proposed when using carboxylate bases.[12]
- Base-assisted intramolecular electrophilic substitution (BIES): The mechanism is a combination of concerted metalation deprotonation and electrophilic aromatic substitution. By the action of a base that is in the coordination sphere of the metal, the vicinal C–H bond is lost according to electrophilic aromatic substitution.[12]
- Single electron transfer (SET): This strategy involves two elementary steps forming two-electron process that creates a carbon-centered radical which react with the metal-hydride specie obtaining the recombination reaction.[12]
- 1,2–addition: In a [2+2]-type reaction, a TM=X double bond (X = CR_2, CR, NR_2, NR, OR) which are the coupling partners are inserted into a C–H bond.[13]

C-H activation modes



- Oxidative addition:
- Electrophilic aromatic substitution (S_EAr):
- α–bond metathesis:
- Concerted metalation deprotonation:
- Base–assisted intramolecular electrophilic substitution (BIES):
- Single electron transfer (SET):
- 1,2–addition:

Scheme 4. C–H activation modes.

4.3.2. Directing group-assisted C–H functionalization

Discrimination of multiple C–H bonds in a complex organic molecule is one of the major challenges for the selective C–H activation. Directing groups (DG) strategy is the most successful solution to control the site-selectivity of the C–H bond-cleavage.

The chelating moiety is commonly a Lewis base that acts as a σ-donor labile or semi-labile ligand providing *o*-functionalization of aromatic compounds using monodentate of bidentate directing groups. There are a wide variety of directing groups which can be divided in two different patterns: strong directing groups and weakly directing groups (*Figure 2*).

Traditionally strong DGs are σ-donors and/or π-acceptors motifs such as pyridine, oxazoline, sulfide and phosphine that have the ability of giving cyclometallated intermediates which can be thermodynamically stable. This could cause limitations on the range of nucleophiles and electrophiles able to react with them.[14] In addition, this strategy presents another disadvantage: these directing groups are synthetically restrictive, either because they have to be installed or removed or because they are a permanent part of the molecule. Therefore, over the past years, the synthetic community has developed new methodologies based on the employment of prevalent functional groups, such as ketone, aldehyde, ester or amides, as weakly coordinating moieties. However, the isolation and characterization of these metallacycles containing this type of organic scaffolds is more challenging.

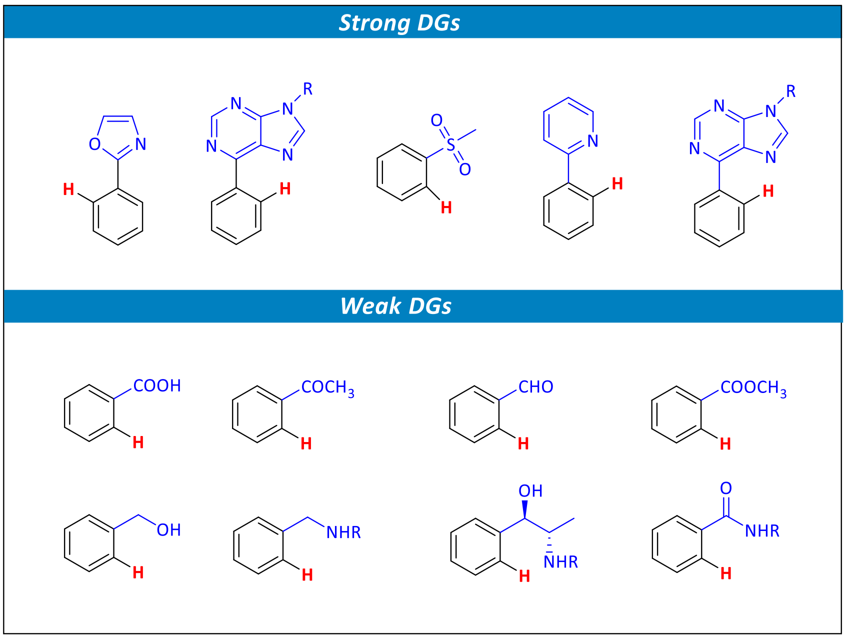


Figure 2. Examples of strong and weak directing groups.

4.3.2.1. *C–H activation with noble transition metals*

Over the past two decades, C–H functionalization was achieved employing noble transition-metals such as ruthenium[15], rhodium[16], palladium[17] and iridium[18]. These metals are also called precious metals due to the economic value and rare occurrence in Earth.

Catalytic systems required noble metals for the efficient construction of organic molecules because they can exhibit robustness in different reactions which previously had been thought inaccessible[12] such as structural rearrangements and dehydrogenation of aliphatic hydrocarbons.[19]

Owing to the common interest in the catalyst mode of action, many research groups have studied the mechanistic intricacies of precious metal-catalyzed C–H functionalization reactions, in particular palladium, rhodium, ruthenium and iridium. However, first-row transition metals, that are a practical greener alternative, have been comparatively underutilized. This is surprising due to their unique reactivity profiles.

Indeed, first-row transition-metals have a unique and versatile reactivity presented due to its low electronegativity, small radius and facile access to multiple oxidation states through 1 or 2 electron processes.[20] As a result of its small radius, the coordination number tend to be lower than for the second and third transition metal series.[21]

4.3.2.1.1. Cobalt-catalyzed C–H functionalization

An ideal platform for implementing the C–H functionalization strategy is using cobalt complexes for several reasons: it is abundant in Earth and has a low cost compared to rhodium and iridium. However, the most important feature of cobalt is the potential rich manifold of reactivity patterns involved in homogeneous catalysis and the formation of more nucleophilic cobalt intermediates that can react with less electrophilic moieties.

Cobalt-catalyzed C–H functionalization can be divided into two approaches (*Figure 3*): low-valent reactions where the active catalyst is typically Co(0) or Co(I) and the high-valent reactions where the active cobalt catalyst is typically Co(III).

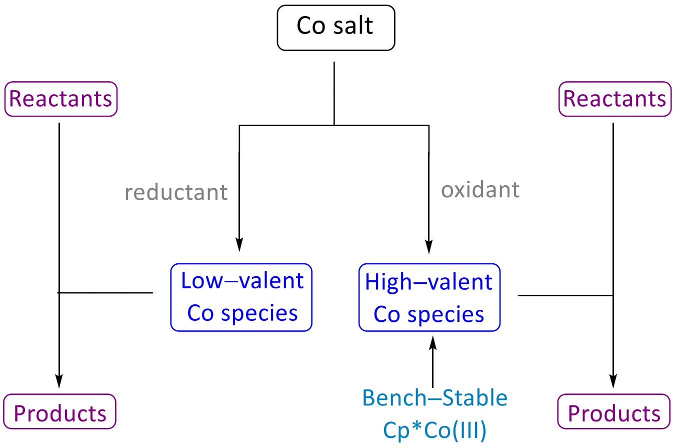
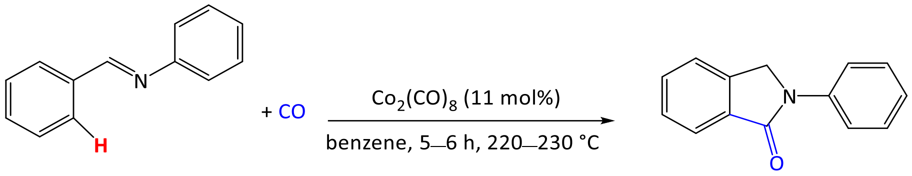


Figure 3. Low-valent and high-valent Co-catalysis.

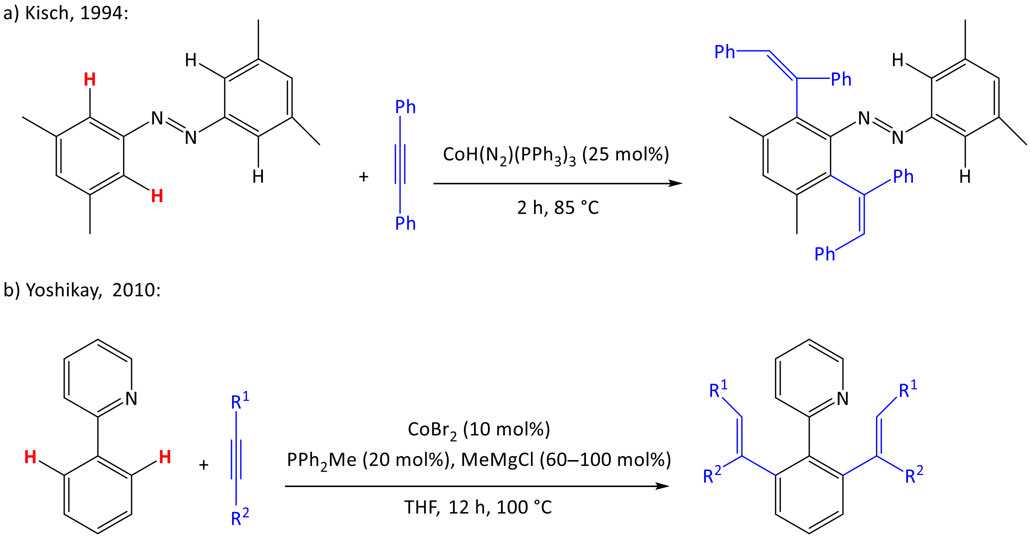
4.3.2.1.2. Low-valent Co-catalyzed C–H functionalization

The first-time cobalt was used in the laboratory was in 1941 when Kharasch and Fields applied a cobalt salt for the homocoupling reactions of aryl Grignard reagents and organic halides providing the first example of C–C coupling using cobalt.[22] In 1955, Murahashi and co-workers reported the first catalytic example of low-valent Co-catalyzed C–H functionalization reaction where 2-phenylphthalimine was synthesized using dicobalt octacarbonyl ($[Co_2(CO)_8]$).[23] The reaction runs under very harsh conditions (100–200 atm CO at 220–230 °C), allowing the introduction of CO in an aromatic imine by Co-catalyzed chelation-assisted *o*-carbonylation (*Scheme 5*).



Scheme 5. Murahashi's Co-catalyzed C–H functionalization.

Sixty years later, subsequent to these pioneering findings, Co-catalyzed directed C–H functionalization reactions has turned into one of the most promising and effective catalysis. Early examples used low-valent cobalt complexes such as Co^0 and Co^I as active catalysts. Kisch and co-workers reported the first low-valent hydroarylation of alkynes with azobenzenes synthesizing dialkenated products using unstable $CoH(N_2)(PPh_3)_3$ as a catalyst.[24] Fifteen years later, low-valent C–H functionalization hydroarylation reaction using 2-aryl pyridines with alkynes was developed by Yoshikay and co-workers in order to improve the preformed examples: lower reaction temperatures and stable and commercially available catalyst precursors.[25] They used a stable $CoBr_2$, a phosphine ligand and a Grignard reagent which allows the in-situ formation of the active low-valent cobalt complex by reduction. This groundbreaking discovery was followed by a series of reports of low-valent cobalt-catalyzed C–H bond functionalization reactions (*Scheme 6*).

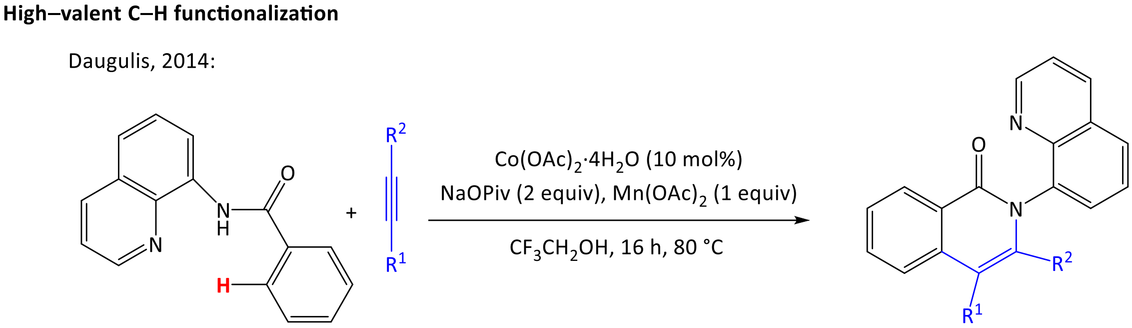


Scheme 6. Low-valent Co-catalyzed C–H functionalization.

Low-valent cobalt catalyzed reactions need Grignard reagents which acts as bases and reductants for generating active cobalt species from precatalysts. However, it is necessary to develop other novel cobalt-catalyzed reactions without Grignard reagents for allowing compatibility with a wide range of functional groups.

4.3.2.1.3. High-valent Co-catalyzed C–H functionalization

The first example of Co-catalyzed directed C–H functionalizations using inexpensive and bench stable cobalt(II) salts such as $Co^{II}(OAc)_2{\cdot}4H_2O$, in combination with an external oxidant, was reported by Daugulis in 2014.[26] The authors, inspired by their previous work on palladium catalysis, employed 8-aminoquinoline or picolinamide as directing group for the oxidative annulation with alkynes to furnish isoquinolones (*Scheme 7*). They envisioned that, in the absence of ligands such as Cp*, this type of bidentate DGs could not only stabilize highly reactive cobalt intermediates formed during the reaction, but also facilitate the C–H activation step. Since this pioneering work, Maiti[27], Ackermann[28], Zhang[29] and Song[30] have demonstrated the efficiency of these systems not only to promote C–C and C–Heteroatom bond formation using electrophiles as coupling partners, but also with nucleophiles.



Scheme 7. High-valent Co-catalyzed C–H functionalization.

Inspired by this methodology, the chemical community has been used cobalt salts as precatalysts to form C–C and C–heteroatom bonds. However, these previously mentioned high-valent Co-catalyzed C–H functionalization reactions have limitations due to the use of oxidants that are not compatible with some functional groups. For this reason, other alternative high-valent Cp^*Co^{III} approaches, which have advantages in terms of reactivity have been studied.

4.3.2.1.4. High-valent Cp*Co^{III}-catalyzed C–H functionalization

Bench-stable [Cp*M(III)] systems (M= Co, Rh and Ir) are stabilized due to the ligand Cp* which has a strong electron-donating effect due to the methyl groups and steric hindrance. However, changing the metal center attached to this common ligand system often offers distinctive results even in the same organic transformation.[20,31]

The employment of [Cp*Co^{III}] complexes has represented a tremendous advance in cobalt catalysis in recent years. The initial breakthrough was reported by Kanai and Matsunaga in 2013.[32] Since then, the same group along with Ackermann[37], Glorius[35], and Ellman[46] among others, have demonstrated the potential of [Cp*Co^{III}] complexes to catalyze C–H functionalization processes of substrates containing traditional monodentate directing groups (DGs) such as pyridines, pyrimidines or imines. These [Cp*Co^{III}] catalysts can not only emulate the same reaction patterns of analogous Rh-based systems, but also exhibit a unique reactivity: since cobalt is less electronegative than rhodium, the Cp*Co^{III}–C bond in the putative cobaltacycle is more polarized than that of the Cp*Rh^{III}–C species. The higher nucleophilicity of these organometallic Cp*Co(III) intermediates allow them to react with less electrophilic moieties.[33]

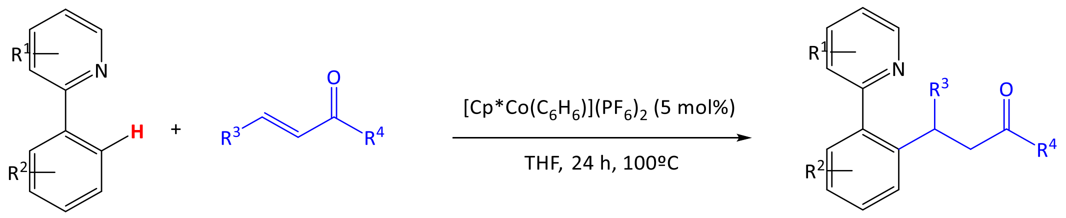
Despite the growth of the employment of this systems, these cobalt systems are still unexplored in terms of knowledge and present some significant synthetic limitations when compared to analogous noble metal systems:

- There is minimal precedent for Csp^3–H functionalization and the employment of nucleophiles as coupling partners.
- There is an important lack of fundamental understanding on the mechanisms of these transformations.

In 2013, Matsunaga, Kanai and co-workers disclosed the first example of high-valent Cp*Co^{III}-catalyzed C–H functionalization employing a Cp*Co(III) as a catalyst core imitating expensive Cp*Rh(III) catalysis.[32] The [Cp*Co^{III}(C$_6$H$_6$)](PF$_6$)$_2$ complex was the most suitable catalyst for directed C–H bond functionalization of 2-aryl pyridines using polar electrophiles such as enones and *N*-sulfonylimines at 100 °C for 24 h (*Scheme 8*).

Cp*Co(III)‒catalyzed C‒H functionalization

Matsunaga and Kanai, 2013:



Scheme 8. First Cp*Co-catalyzed C–H functionalization.

Inspiring by these results, the group of Matsunaga and Kanai described in 2014 an alkenylation/annulation reaction with indoles and alkynes showing the different behavior of Cp*Co(III) and Cp*Rh(III) complexes.[33]

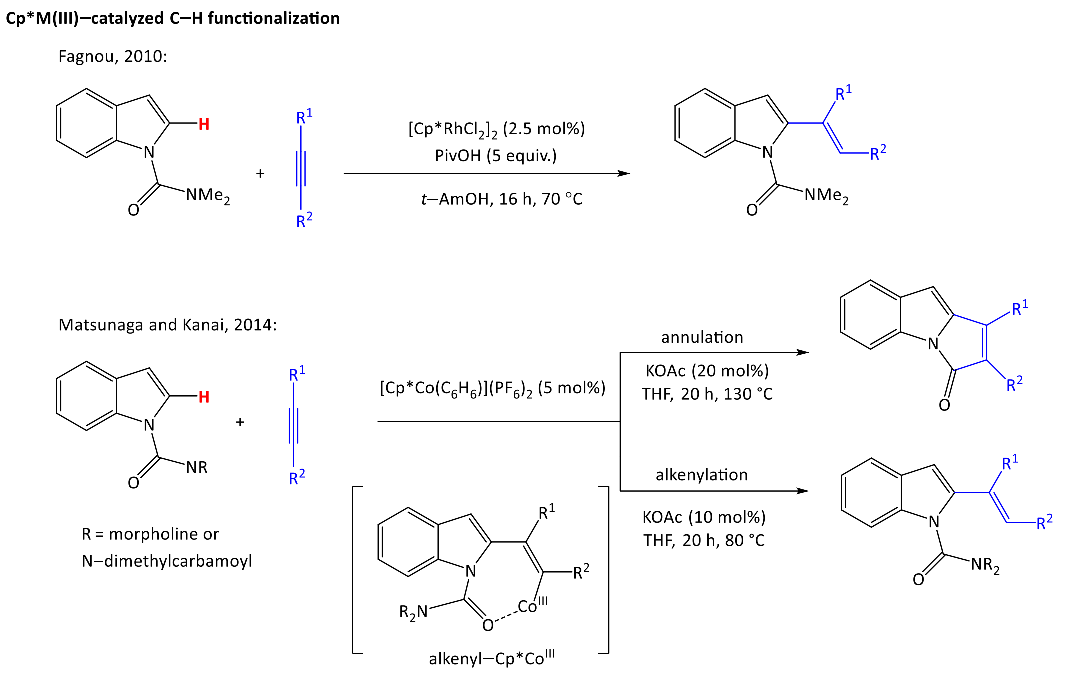
On the one hand, Cp*Rh-catalyzed alkenylation using alkynes was reported by Fagnou and co-workers in 2010[34] when two products were obtained: an annulation product (indoles) and an hydroarylation product that was the undesired product in their synthesis of indoles. During the optimization of their method to construct indoles, the group reported a formation of a side product when they removed the oxidant and they used a carboxylic acid allowing a highly acidic medium ($pK_a > 1$). Additionally, this annulation product was not an intermediate from the catalytic cycle to the desired indole according to different mechanistic studies. Leading to improve the yield of indoles producs, Fagnou and co-workers created new conditions avoiding the alkenylation products.

With these precedents, soon after, Matsunaga and Kanai used Fagnou's optimized conditions for studying the alkenylation/annulation sequence to observe the difference activity using $[Cp^*Co^{III}(C_6H_6)](PF_6)_2$ (*Scheme 9*). The results showed that Cp*Co have a good compatibility with a wide range of functional groups and allow the formation of the alkenylated products and annulated products by adjusting the reaction conditions.

To promote the annulation reaction, it is necessary bearing a morpholine unit as a leaving group with 20 mol% of KOAc at 130 °C for 20 h giving pyrroloindolones. On the other hand, alkenylation reaction was also suitable with Cp*Co catalyst and it tends to be successful with terminal alkynes. In this case the leaving group for obtaining the alkenylated products is *N*-dimethylcarbamoyl indole using 10 mol% KOAc at 80 °C for 20 h.

This dual behavior is due to alkenyl-Cp^*Co^{III} intermediate species. The C–M bond of the alkenyl-Cp^*Co^{III} species are more polarized than C–M bond of the Cp*Rh species and it causes that Cp*Co can react with poorly electrophilic *N*-carbamoyl directing group due to more nucleophilic character giving different products depending on the conditions.

The Cp*Rh catalysis is not compatible with the annulation product probably due to the lower nucleophilicity of the organorhodium intermediate.



Scheme 9. Orthogonal reactivity of Cp*Rh and Cp*Co.

In summary, the chemical community have proved the potential of Co-catalyzed C–H functionalization reactions enabling the activation of C(sp^2)–H and C(sp^3)–H bonds of substrates leading to the formation of C–C and C–Heteroatom bonds, using electrophiles as coupling partners. C(sp^3)–H functionalization is underdeveloped if compared to its C(sp^2)–H functionalization and still needs to be deeply explored.

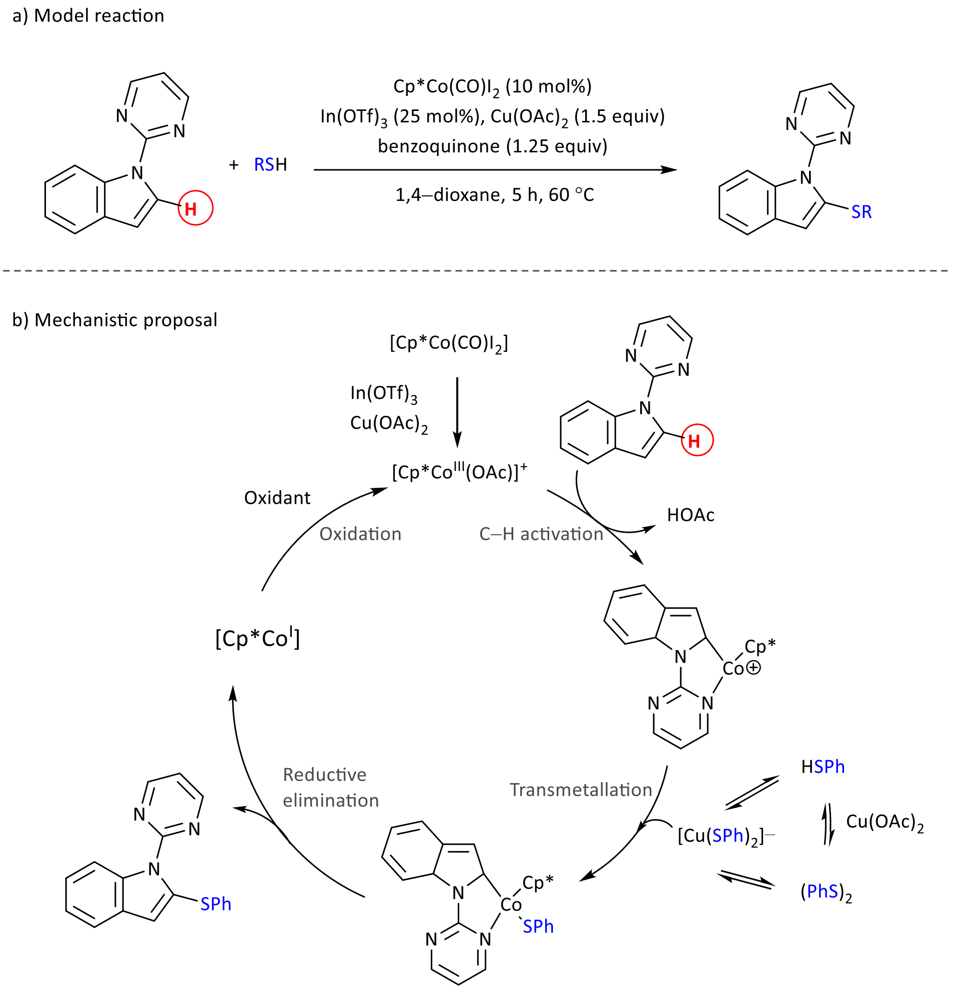
4.3.3. Cp*Co C–H functionalization reactions using nucleophiles as coupling partners

Only three examples have been reported of Cp*Co-catalyzed C–H functionalization reactions using nucleophilic coupling partners creating new C–S bonds in a simple and modular way.

In 2016, Glorius and co-workers reported the unexplored Cp*Co-catalyzed dehydrogenative C–H thiolation using Cp*Co(III) catalyst giving thiolated indoles with high functional-group tolerance.[35]

The group explored two difficulties: catalyst deactivation due to sulfur compounds and challenges to achieve that the active catalyst closes the cycle. Gratifyingly, the use of different additives such as $In(OTf)_3$ and copper additives seems to solve these problems.

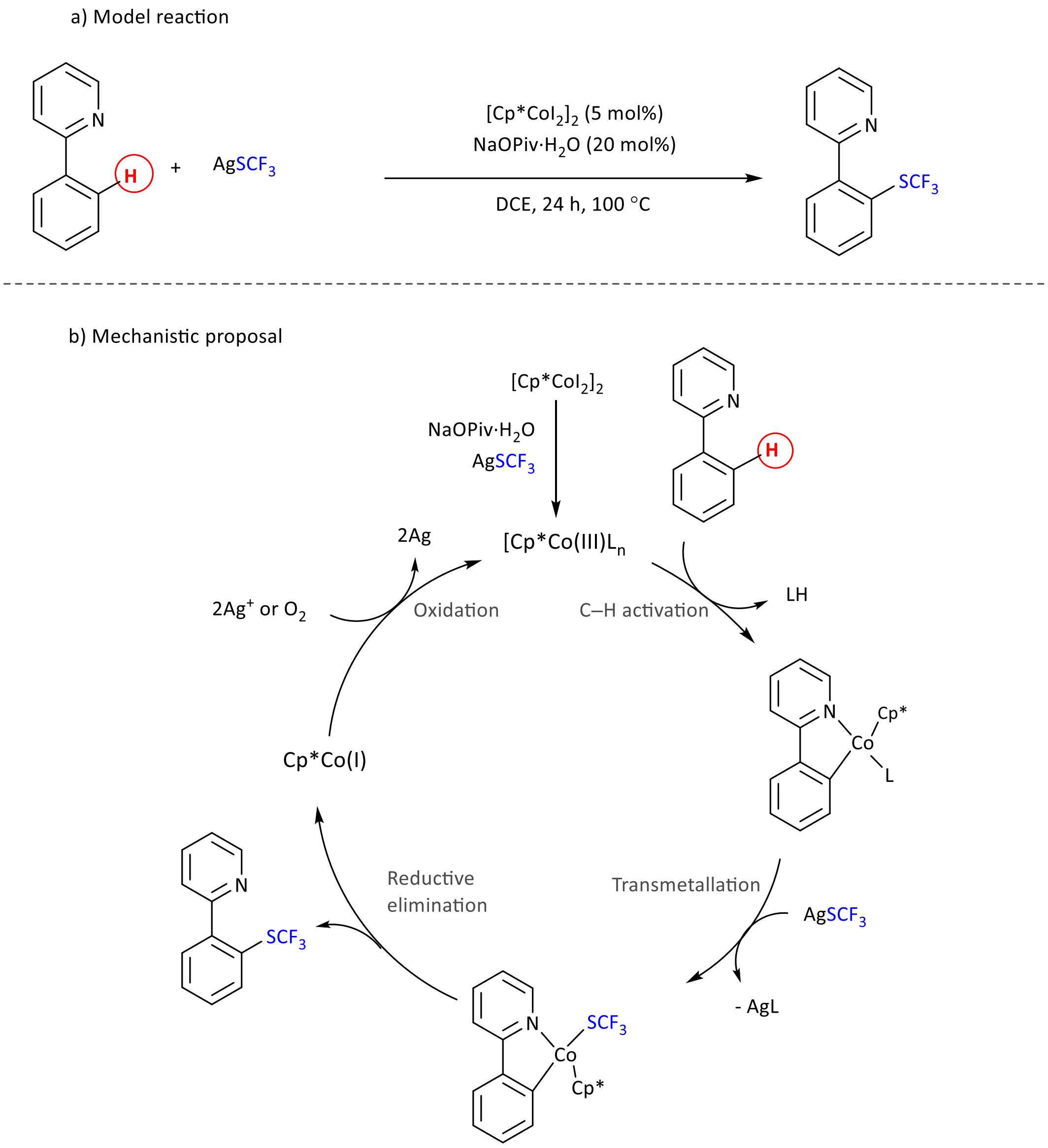
They proposed a tentative reaction mechanism based of different experiments (*Scheme 10*). First of all, the active catalyst $[Cp^*Co^{III}(OAc)]^+$ is formed by iodide abstraction with $In(OTf)_3$ which should aid in the coordination of thiolates avoiding the formation of complexes with other metals such copper and other metals. Next, the C–H activation occurs generating cobaltacycle that after a transmetallation step with $[Cu(SPh)_2]^-$ form a cobalt(III) thiolate intermediate. In that step copper plays an important role due to the formation of anionic Cu^{I} complexes that is the active specie. Finally, C–S bond-forming reductive elimination releases the desired product and cobalt(I) is re-oxidized by copper or benzoquinone to form the active catalyst.



Scheme 10. Cp*Co-catalyzed C–H thiolation by Glorius and co-workers.

In this context, Wang and co-workers also reported directed C–H trifluoromethylthiolation under other optimized conditions.[36] The group demonstrated the role of AgSCF$_3$ under oxidative reaction conditions: the active trifluoromethylthiolation is AgSCF$_3$ that may activate the Co(III) catalyst or CF$_3$SSCF$_3$. Indeed, mechanistic studies show that CF$_3$SSCF$_3$ is not an intermediate specie for this reaction.

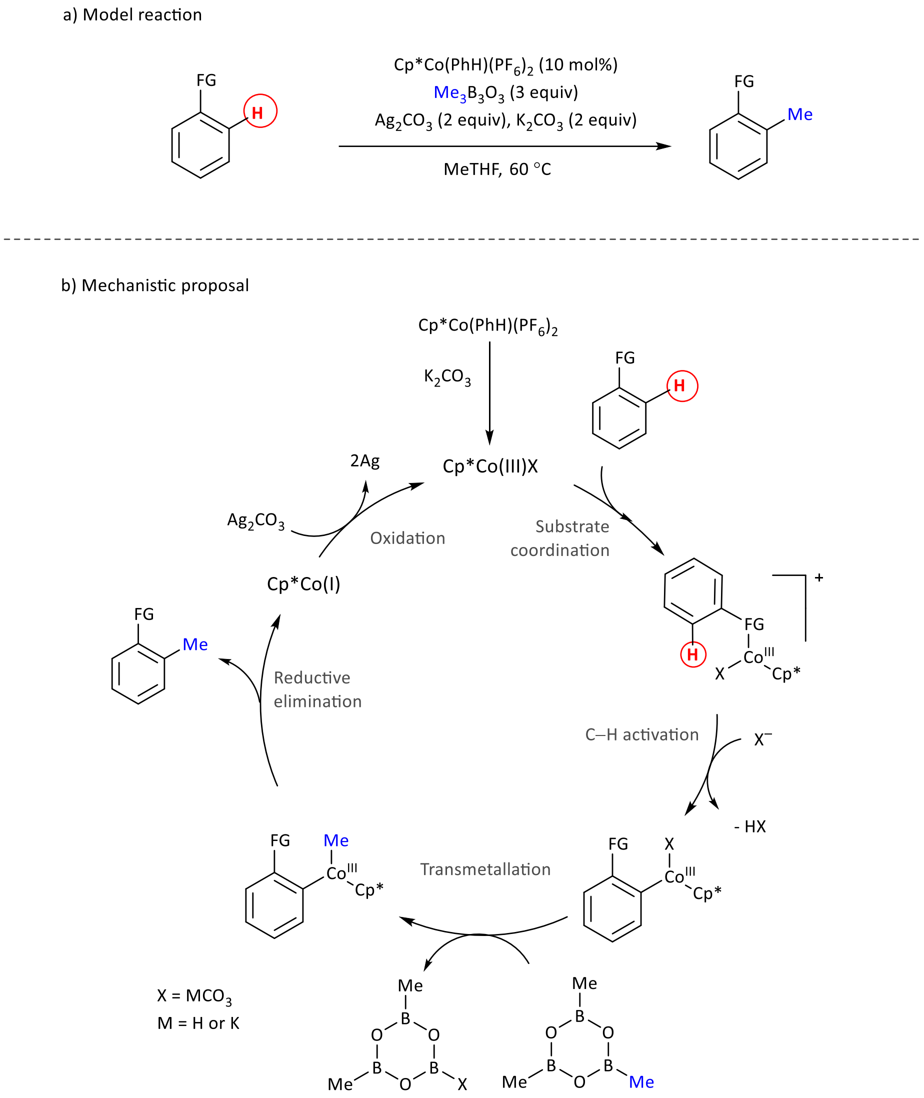
The authors proposed a Co$^{I/III}$ catalytic cycle that involves a reversible C–H activation obtaining Cp*Co(III) intermediate, a transmetallation step with AgSCF$_3$ forming Co(III) thiolate intermediate, followed by a C–SCF$_3$ bond forming reductive elimination step which forms the desired product and the Cp*Co(I), which is oxidized by Ag$^+$ or O$_2$ to regenerate the active catalyst Cp*Co(III)L$_n$ (*Scheme 11*).



Scheme 11. Cp*Co-catalyzed directed C–H trifluoromethylthiolation by Wang and co-workers.

In June 2020, Ackermann and co-workers reported a Cp*Co-catalysed C–H methylation[37] for the late-stage derivatization of advanced drugs molecules allowing the modulation of its properties. The group used Cp*Co(PhH)$(PF_6)_2$ as a catalyst which provided an efficient methylation with a high level of functional group tolerance using common boron-based methyl source with the presence of K_2CO_3 additive base and Ag_2CO_3 as the oxidant at 60 °C in MeTHF.

The authors proposed a $Co^{I/III}$ catalytic cycle where the substrate coordination via an appropriate functional group was the first step, followed by C–H activation affording the Cp*Co(III) intermediate complex. Next, transmetallation step provided the formation of methyl-coordinated cobalt(III) complex by the presence of $Me_3B_3O_3$. Finally, Me–Ar(FG) bond forming reductive elimination was afforded which forms the desired product and Cp*Co(I) that is oxidized by Ag_2CO_3 regenerating the active catalyst (*Scheme 12*).



Scheme 12. Cp*Co-catalyzed C–H methylation by Ackermann and co-workers.

Despite these examples, the employment of nucleophilic coupling partners in Cp*Co-catalyzed transformations have not been explored in detail. Moreover, the reactivity of the Cp*Co^{III} metallacycle species with organometallic nucleophiles to elucidate if these cobalt(III) complexes can participate in C–C or C–X coupling reactions have not been investigated experimentally. This can be explained due to the lack of a synthetic method for accessing [Cp*Co^{III}L$_n$X] complexes (X = nucleophile).

4.4. Oxidatively induced reductive elimination for Cp*M–catalysis

Recently, Chang and co-workers have demonstrated the enormous potential of high-valent transition metal catalysis involving the group 9 metals, Ir and Rh. They showed that an oxidative induced reductive elimination, from an assumed high valent rhodium or iridium intermediate, can facilitate the direct arylation of C–H bonds when using silanes or boranes as nucleophilic reagents in the presence of oxidants.

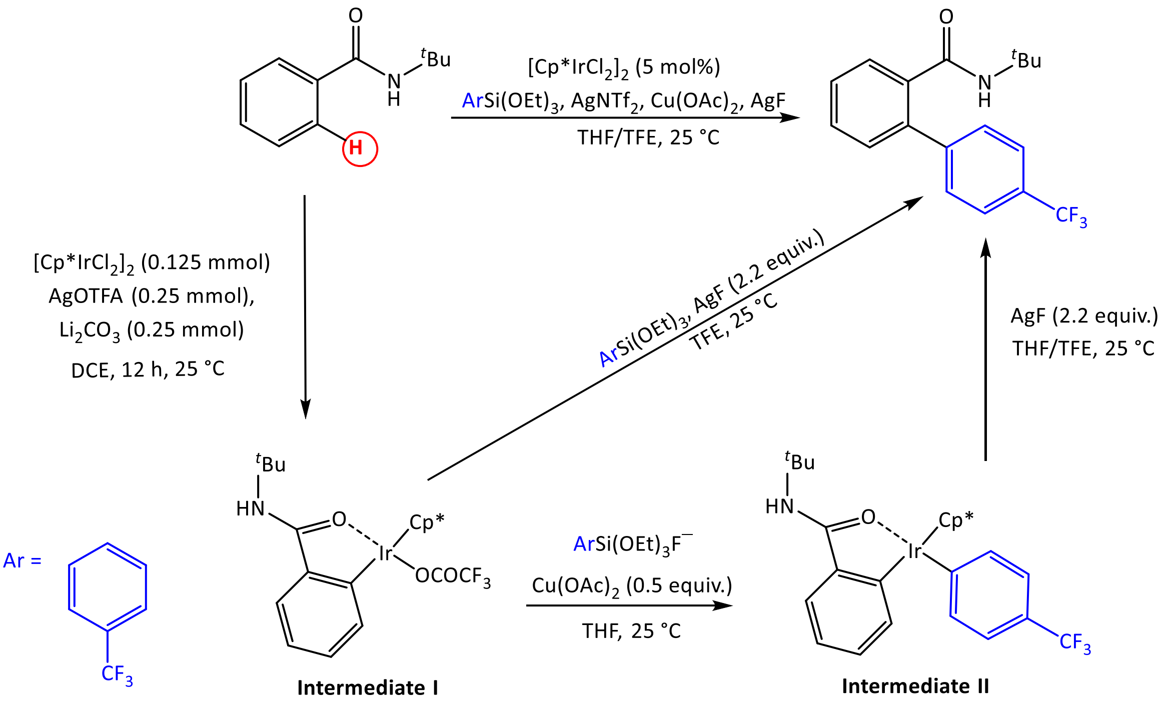
In 2018, when developing a Cp*Ir^{III}-catalyzed C–H arylation protocol by using arylsilanes as coupling partners, Chang and co-workers[38] identified the reductive elimination step as the bottleneck of the process for traditional Ir(I/III) catalytic cycles. They observed that the iridacycle intermediate **II**, formed through a transmetalation step with in-situ generated coinage metal-aryl species, did not undergo the desired C–C bond formation (*Scheme 13*). To overcome this limitation, they proposed the modulation of the electronics of the post-transmetallation Cp*Ir^{III} intermediate, through selective oxidation, to facilitate the challenging C–C bond-forming reaction from a high-valent Ir^{IV} or Ir^{V} species.

They were able to oxidatively induce the reductive elimination process in the presence of different silver oxidants and to develop a catalytic version under similar reaction conditions. The reaction between the post-transmetallation Cp*Ir^{III} intermediate **II** and AgF in THF/TFE co-solvent at room temperature furnished the formation of the C–aryl bond, giving the arylated product while without silver oxidant the product was not formed, even at elevated temperature (120 °C).

In order to link all these understanding advances, they validated their work with density functional theory (DFT) calculations. According to the Hammond postulate, when the oxidation state of the metal is increased the energy barrier decreases ($\Delta G_{RE}^{\ddagger}$) and the transition state becomes more reactant-like and less energetic increasing the distance between two *ipso* carbons C(sp^2)–C(aryl), leading to a facile reductive elimination and allowing an inaccessible product. The results of calculated transition-state Gibbs free energies decrease, and these results suggest that the theoretical acceleration of the reductive elimination rate decrease by ~14 and ~22 orders of magnitude for the oxidation of Ir(III) to Ir(IV) and Ir(V) accessing species, respectively.

In addition, the authors also demonstrated the formation of the targeted organic product when applying electric current to the post-transmetallation intermediate. This experimental result supported the formation of high-valent iridium species.

Oxidatively induced reduction elimination: stoichiometric reactions.

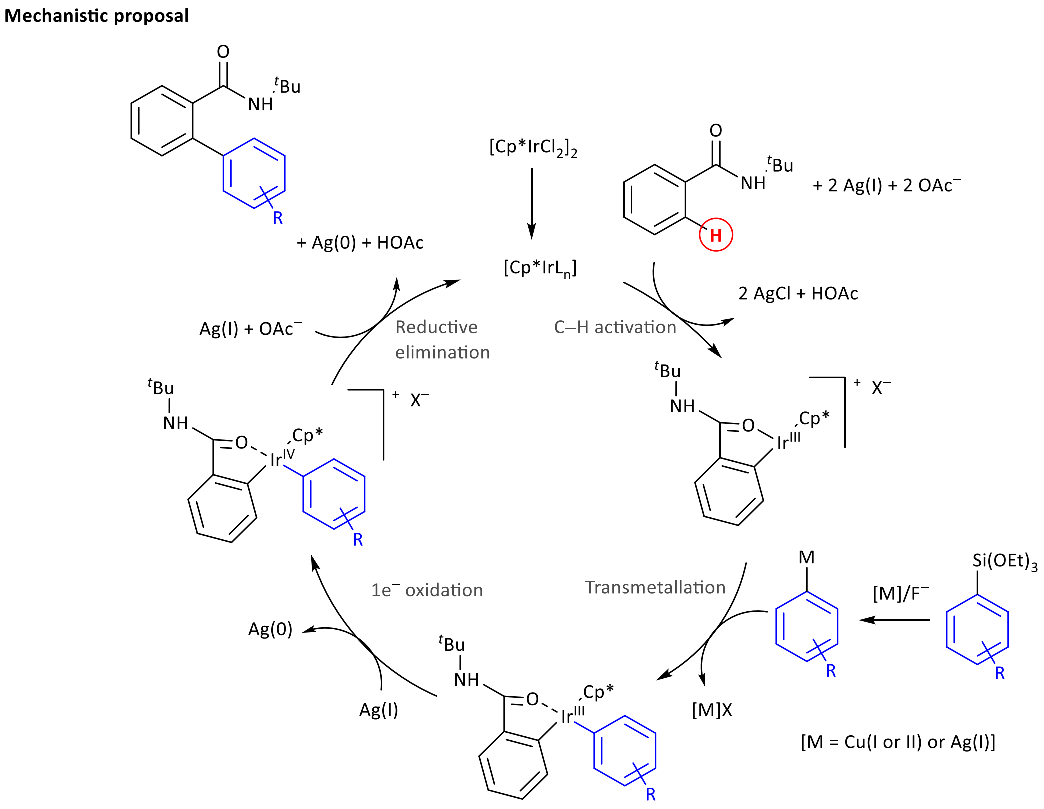


Scheme 13. Catalysis reaction and stoichiometric reactions.

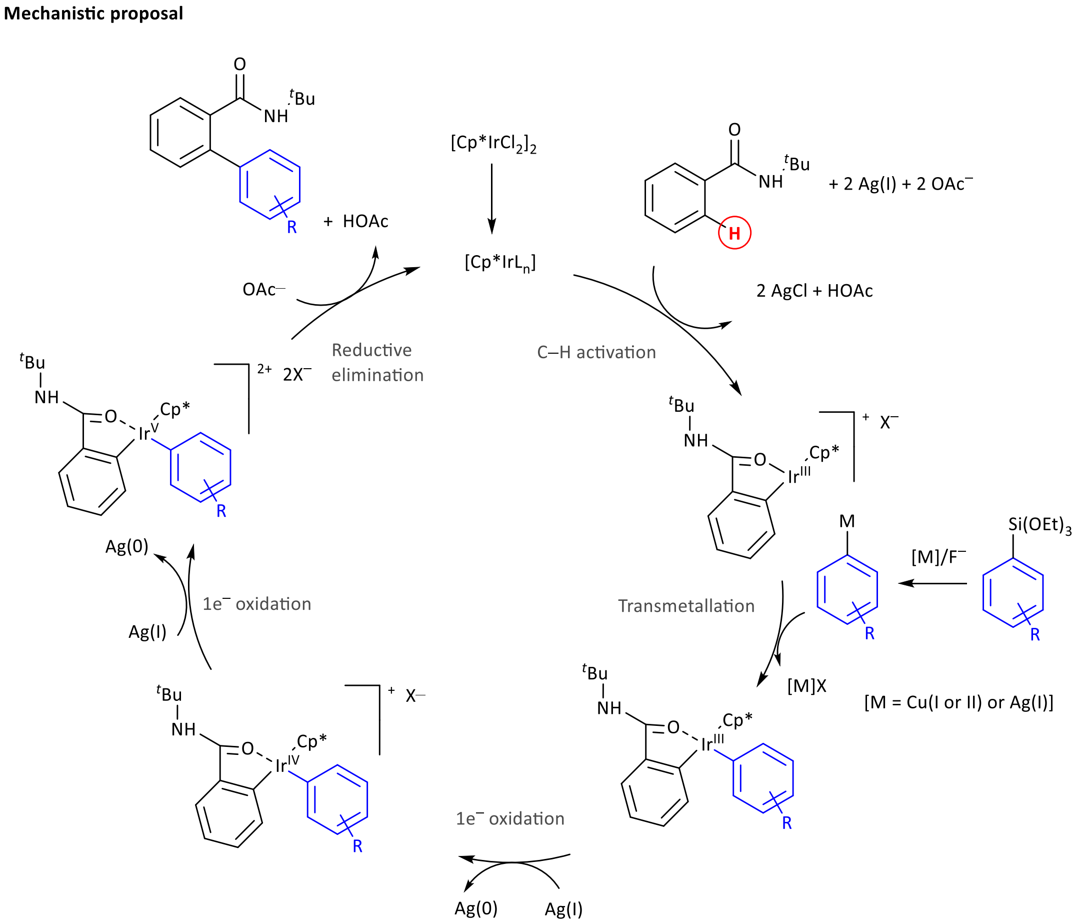
With all this information a plausible catalytic cycle was proposed by Chang and co-workers (*Scheme 14*). First of all, the active catalyst is formed by chloride abstraction and reacts with Ag(I) or copper acetate allowing the formation of a cyclometallated Ir(III) intermediate. Next, the transmetallation steps occurs through the aryl copper or silver reagent, giving the post-transmetallation intermediate **II**.

Secondly, Ag(I) specie oxidizes the post-transmetallation intermediate to form high-valent Ir(IV)–aryl intermediate that proceeds to afford oxidatively induced reductive elimination reaction obtaining the desired arylated product. In order to close the catalytic cycle, another Ag(I) oxidant specie may oxidized the intermediate **III** to regenerate the Ir (III) active catalyst.

An alternative catalytic cycle was proposed by Chang and co-workers with the presence of Ir(V)–aryl intermediate than cannot be discarded (*Scheme 15*).



Scheme 14. Mechanistic proposal by Chang and co-workers.

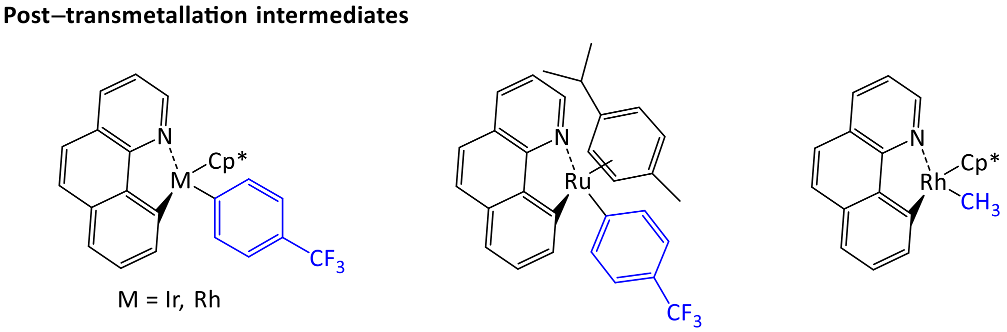


Scheme 15. An alternative catalytic cycle.

In 2019, Chang and co-workers[39] extended their approach to understand Ir(III)-, Rh(III)- and Ru(II)-catalyzed C–C bond-formation reactions using arylboronic esters as prefunctionalized starting material under mild conditions. The group synthesized the pre-transmetallation and post-transmetallation intermediates using different synthetic procedures (*Scheme 16*).

The later intermediates were characterized by single-crystal X-ray diffraction and cyclic voltammetry studies. Experimental studies showed that silver(I) salts promote the reductive elimination step by single-electron oxidations at room temperature. In sharp contrast, the C–C bond-forming reaction did not occur under oxidant-free conditions.

Next, encouraged by these results, they investigated the development of Cp*Rh^{III}-catalyzed C–H methylation reaction using methyl boronic ester as coupling partner. As previously, the reductive elimination proceeds via a single-electron oxidation from Rh^{IV}–Me species.



Scheme 16. Post-transmetallation intermediates.

In conclusion, they demonstrated the enormous potential of high-valent metal species to facilitate C–C bond-forming reaction. They developed a method to couple different nucleophiles –by oxidizing the isolable post-transmetallation intermediate using chemical oxidants or electro-chemical conditions at room temperature.

4.5. Mechanistic understanding of cobalt catalysis

Since Cp*Co^{III}-catalyzed C–H functionalization has emerged as efficient strategy being an alternative to second and third-row transition metals, researchers have found an unexploited field for promoting different transformations. However, there are still important fundamental questions to address in cobalt catalysis at molecular level and also in terms of reactivity patterns.

From a mechanistic point of view, these transformations are generally proposed to proceed through 'hypothetical' catalytic cycles based on other noble metal mechanisms. However, due to the unknown nature of the key intermediates, the vast majority of these mechanistic proposals are essentially speculative. The proposed reversibility of the C–H activation by Cp*Co^{III} species along with the high reactivity of many of the recognized cobalt reactive species within the catalytic cycle have prevented the isolation and in most cases the detection of these intermediates.

This lack of fundamental knowledge limits the election of the most efficient experimental conditions (e.g. additives, solvent, etc.) for promoting the desired transformations.

To overcome this unambiguity, a synergistic cooperation between computational and experimental approaches will be crucial for enabling the rational design and development of Cp*Co transformations by the collaboration of Maseras Research Group.[1] In this context, the Pérez-Temprano Group has implemented a philosophy to understand organometallic processes trapping reactive TM intermediates (*Figure 4*). The group uses this transient species as knowledge building blocks (KBBs) for uncovering the factors that determine the success or failure of the elementary steps involved in these cobalt transformations.

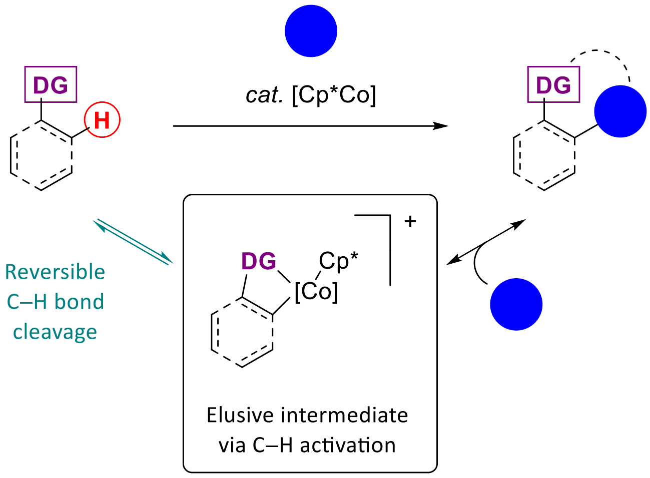


Figure 4. A representative scheme of Cp*Co-catalyzed C–H functionalization reactions.

The group has followed two different approaches for accessing these elusive intermediates. In 2017, the group accessed one of the most widely invoked cobaltacycles using an oxidative addition route, follow by a halide abstraction. They took advantage of the ability of MeCN to act as stabilizing ligand to synthesize otherwise highly reactive cobalt species.[40]

Inspired by these results, in 2018, the group took advantage of the unique stabilizing capability of MeCN to overcome the reversible nature of the C–H activation step and access two of the most widely invoked cationic cobaltacycles or KBBs which have been proposed in the literature as reactive intermediates after the C–H metalation step. Using these metallacyclic intermediates as starting point, the group detected and fully characterized a wide variety of post-insertion Cp*Co metallacyclic intermediates obtained from migratory insertions with alkynes and alkenes.[41] Recently, the group has applied their oxidative addition route for isolating Cp*Co(III) metallacyclic intermediates containing weakly functional groups.[42]

Figure 5 shows the catalytically relevant Cp*Co^{III} species collected by the Pérez-Temprano group along with other intermediates obtained by the groups of Kanai[33], Zhu[43], Sundararaju[44,45] and Ellman[46].

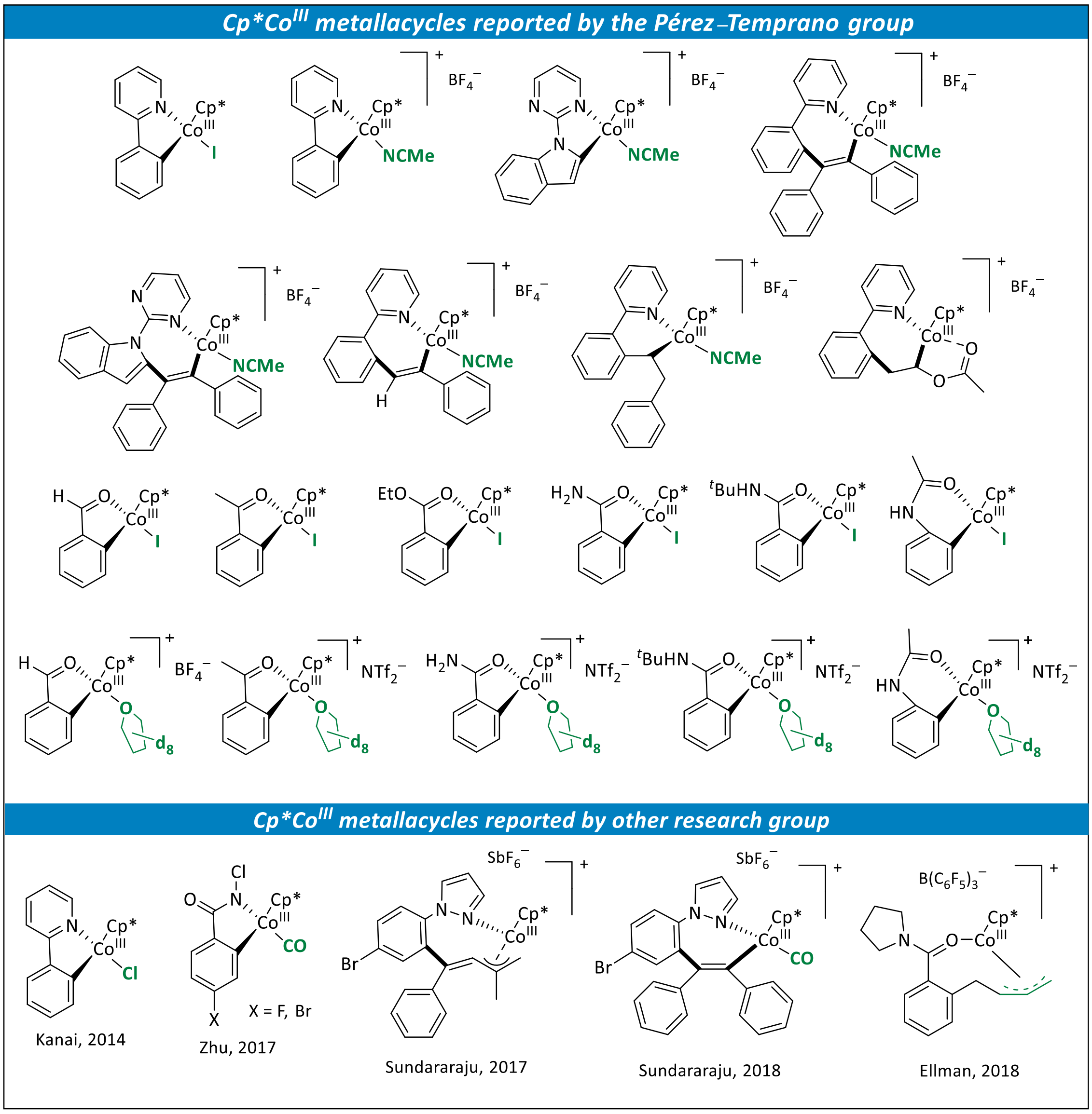


Figure 5. Reported Cp*Co(III) metallacycles.

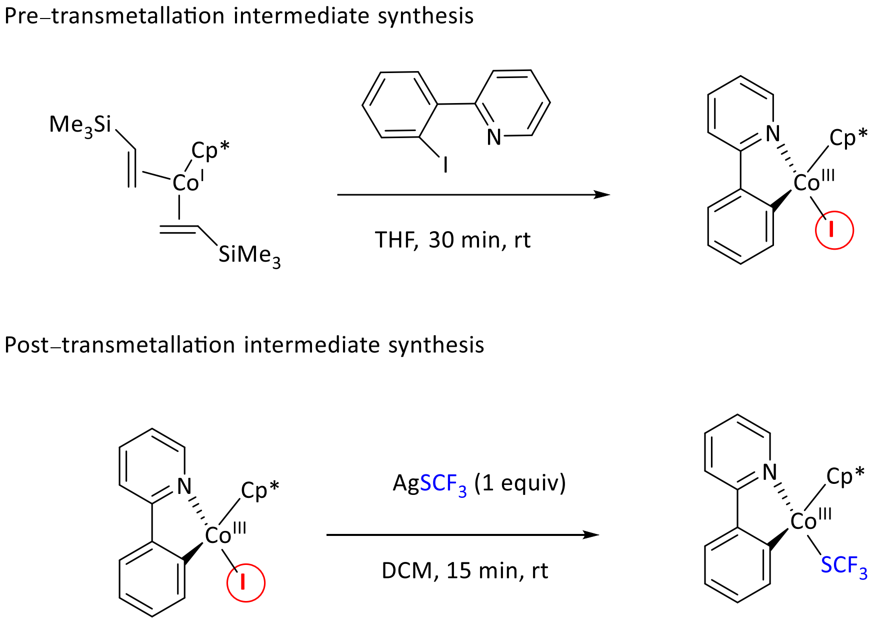
For the future of Cp*Co transformations, the mechanistic information is crucial. The isolation of these knowledge building blocks (KBBs) will contribute not only to rely on extensive screenings and serendipitous discoveries but also to improve reactions using mechanistic knowledge.

4.6. Study of Cp*Co-catalyzed trifluoromethylthiolation by Pérez and co-workers

As mentioned before, one of the main interests of the Pérez-Temprano group is to uncover the mechanistic “blackbox” of Cp*Co^{III}-based systems. In this context, currently, the group is investigating the mechanism of C–H functionalization reactions using nucleophiles as coupling partners. In particular, they have targeted the study of C–SCF_3 bond-forming reactions using $AgSCF_3$ as sulfur source.

In this context, the group has stablished three main objectives: (i) the synthesis of a representative Cp*Co post–transmetallation intermediate, (ii) the investigation of the participation of high-valent cobalt species in reductive elimination events and (iii) uncovering the ability of silver species to oxidize Cp*Co^{III} complexes.

The group has isolated the desired post-transmetallation intermediate, using as starting point a [Cp*Co(2-PPy)I]. This pre-transmetallation intermediate is afforded by an oxidative reaction, between 2-(2-iodophenyl)pyridine and [Cp*Co^{I}(VTMS)$_2$] in THF at room temperature for 30 min.[40] Next, the post-transmetallation intermediate was obtained by the subsequent treatment with one equivalent of $AgSCF_3$ at room temperature for 15 min (*Scheme 17*).


Pre–transmetallation intermediate synthesis

Post–transmetallation intermediate synthesis

Scheme 17. Synthesis of pre-transmetallation and post-transmetallation intermediates.

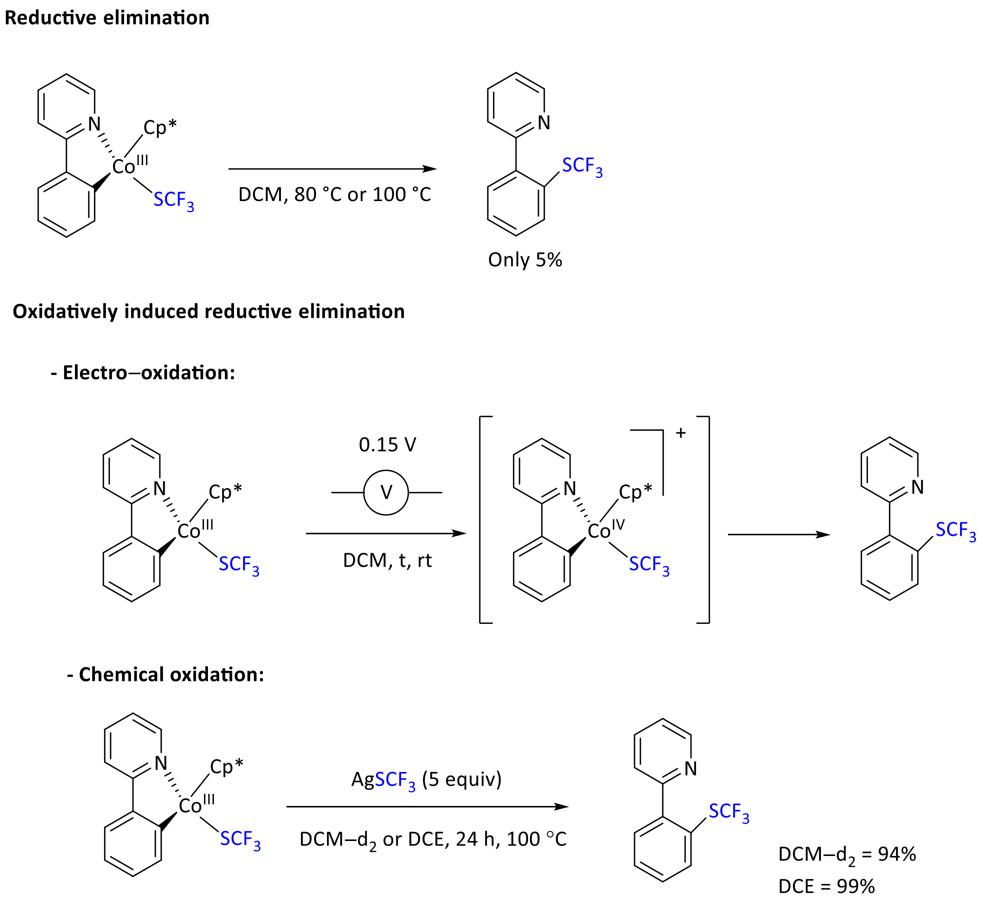
The [Cp*Co(2-PPy)(SCF_3)] complex was characterized by NMR spectroscopy and single crystal X-ray diffraction studies being the first example of Cp*Co derivatives transmetallated species that could be isolated. In addition, the complex was stable under air for at least two months.

Having in hand a reliable synthesis for the desired cobaltacycle, they explored the mechanism of the reductive elimination step for promoting the formation of the C–SCF$_3$ bond paying special attention on the potential participation of high-valent cobalt intermediates complexes. To study how the formation of the product occurs, a few hypotheses were taken into account: (i) a reductive elimination step that forms the desired product under thermal conditions or (ii) an oxidatively induced reductive elimination reaction which requires an oxidant for the formation of the C–SCF$_3$ bond.

Despite Glorius and Wang have proposed Co$^{I/III}$ manifolds for the reported C–S bond formations,[35,36] the Pérez-Temprano group hast observed that the reaction of the post-transmetallation intermediate under thermal conditions at 80 °C or 100 °C, only provides traces of the reductive elimination product (*Scheme 18*).

Inspired by the literature precedents by Chang and co-workers, the group has investigated the involvement of an oxidatively induced reductive elimination step. Cyclic voltammetry analysis and DFT studies were carried out to show the redox activity of the post-transmetallation intermediate by Pérez-Temprano group. Moreover, theoretical studies support an endergonic reductive elimination reaction from Cp*Co(III) specie. In addition, chronoamperometry experiments (CA) shows the formation of the organic product when promoting the formation of Cp*Co(IV) species.

The ability of AgSCF$_3$ to oxidize [Cp*Co(2-PPy)(SCF$_3$)] can be probed by carrying out stoichiometric experiments using AgSCF$_3$ as the only oxidant presents in the reaction (*Scheme 18*). The reaction of the post-transmetallation intermediate with 5 equivalents of AgSCF$_3$ at 100 °C during 1 hour in DCM or DCE led to the almost quantitative formation of the organic product (94% in DCM-d$_2$ and 99% in DCE), suggesting an oxidatively induced reductive elimination scenario.



Scheme 18. Experimental information of the mechanistic scenario.

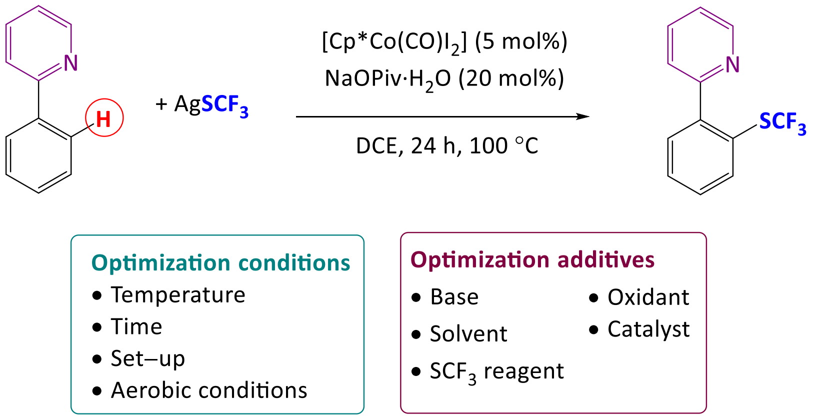
In conclusion, these studies suggest a (Co^{III}-Co^{IV}-Co^{II}) oxidatively induced reductive elimination reaction by the ability of $AgSCF_3$ to oxidize the [Cp^*Co^{III}(2-PPy)(SCF_3)] post-transmetallation intermediate complex to [Cp^*Co^{IV}(2-PPy)(SCF_3)][X] intermediate complex allowing the formation of the desired 2-(2-((trifluoromethyl)thio)phenyl)pyridine.

5. Proposed draft

The understanding of the Cp*Co-catalysed trifluoromethylthiolation catalytic cycle and the subsequent optimization for developing a new catalytic method using electricity instead of chemical oxidants and other trifluoromethylthiolation reagents are the main goals of this Final Degree Thesis (*Scheme 19*).

At this point, the optimization conditions for achieving high yields of the trifluoromethylthiolated product can be investigated initiating our studies by proposing the following objectives:

- Synthesis and characterization of catalysts and starting compounds.
- Calibrated curves between internal standard and targeted molecules.
- Repetition of the catalysis by Wang and co-workers.
- Reactivity studies using different conditions such as temperature, time, set-up and aerobic conditions.
- Reactivity studies using different additives such as catalyst, base, oxidant, solvent and SCF_3 reagent within the catalytic cycle.
- Use of electrochemical conditions: study of different parameters.



Scheme 19. Optimization of proposed catalysis.

This proposed draft was designed to be carried out at Pérez-Temprano research group of Institute of Chemical Research of Catalonia (ICIQ).

5.1. Synthesis and characterization of catalysts and starting compounds

First of all, the synthesis and characterization of all starting products must be carried out in order to ensure the purity of the initial compounds within the catalysis. The starting compounds that have to be synthesized are the catalysts $[Cp^*Co(CO)I_2]$ and $[Cp^*Co(NCMe)_3][SbF_6]$ along with NMe_4SCF_3, the targeted trifluoromethylthiolating reagent.

5.1.1. Synthesis and characterization of [Cp*Co(CO)I_2] catalyst

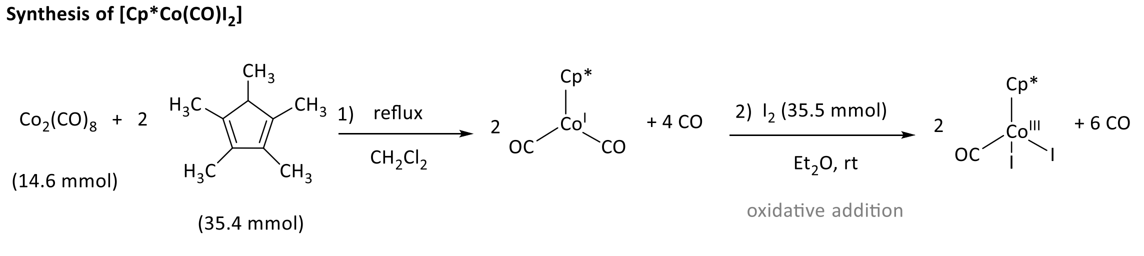
[Cp*Co(CO)I_2] is a really versatile catalyst that provides a wide range of useful bond-forming reactions.[47]

The preparation of air-stable carbonyl(pentamethylcyclopentadienyl)cobalt diiodide catalyst complex was reported by Roe and Maitlis in 1971.[48] The group used the commercially available $Co_2(CO)_8$, pentamethylcyclopentadiene and iodine in just one-pot (*Scheme 20*).

The first step consists in refluxing under argon $Co_2(CO)_8$ and pentamethylcyclopentadiene in CH_2Cl_2. To a well-dried 500 mL Schlenk flask would be added $Co_2(CO)_8$ (5.0 g, 14.6 mmol), previously degassed CH_2Cl_2 (100 mL) and pentamethylcyclopentadiene (5.55 mL, 35.4 mmol) under argon. Secondly, the reaction mixture would be refluxed constantly stirred under argon at 50 °C for 6 h, and then would be cooled to ambient temperature. In that point, the suspension must be a brown coffee mixture. Next, the CH_2Cl_2 would be removed under vacuum giving rise the desired brown crystals. However, a small amount of non-desired green crystals may form relating to Co^{II} species due to an oxidation reaction.

The second step is an oxidative addition reaction in order to oxidize the Co(I) to Co(III) due to the addition of two iodides in the final structure. On the one hand, to a second Schlenk flask would be added I_2 (9.0 g, 35.5 mmol) with previously degassed Et_2O (50 mL). The residue of brown and green crystals would be dissolved in degassed Et_2O (50 mL) and then the solution of iodine would be added dropwise with constantly stirring under low temperature. During this exothermic addition, it can be observed the release of carbon monoxide gas. After the addition, the dark mixture would be stirred for 1 h at room temperature forming a dark solid. Next, the Et_2O would be removed under vacuum and the resulting residue would be re-dissolved in hexane and filtrated for removing the iodine impurities. In order to isolate the catalyst, the residue would be re-dissolved in CH_2Cl_2 where the catalyst is soluble, and the green impurities are not soluble. Finally, the solvent would be evaporated to afford the dark [Cp*Co(CO)I_2] solid. The yield obtained by Maitlis was 75%.

In order to characterize the catalyst, a ^1H –NMR experiment can be carried out. The ^1H –NMR spectrum must show a peak at 2.21 ppm relating to the protons of pentamethylcyclopentadienyl moiety and also the $CDCl_3$ solvent peak. The described synthesis and characterization can be done in two days.



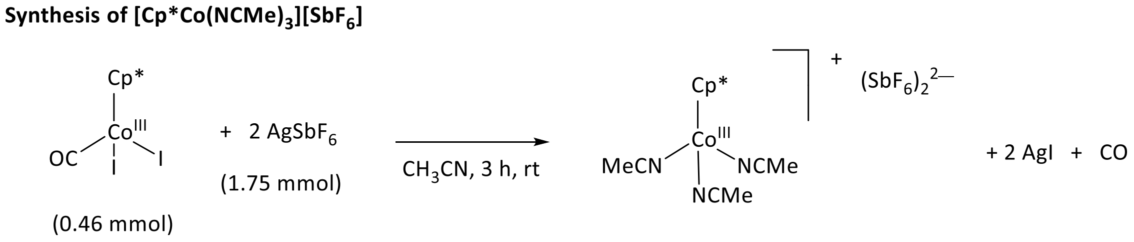
Scheme 20. Synthesis of [Cp*Co(CO)I_2] catalyst.

5.1.2. Synthesis and characterization of [Cp*Co(NCMe)$_3$][SbF$_6$]$_2$ catalyst

Glorius and co-workers[49] reported the modified procedure for the synthesis of [Cp*Co(NCMe)$_3$][SbF$_6$]$_2$ catalyst from Shi and co-workers.[50] The group of Glorius used [Cp*Co(CO)I$_2$] precursor catalyst with a solution of commercially available AgSbF$_6$ in CH$_3$CN (*Scheme 21*).

First of all, a solution of AgSbF$_6$ (600 mg, 1.75 mmol) in dried CH$_3$CN (4.6 mL) would be added to a suspension of [Cp*Co(CO)I$_2$] (220 mg, 0.46 mmol) in dried CH$_3$CN (3.6 mL), precipitating AgI precipitate immediately. Secondly, the mixture reaction would be stirred for 3 h at room temperature. After three hours, the residue would be filtered through celite and washed with 3 x 20 mL of CH$_3$CN. The solvent would be removed under vacuum to 15 mL, and then Et$_2$O (50 mL) would be added dropwise to precipitate a purple solid. Finally, the purple precipitated would be filtrated, washed with Et$_2$O (50 mL) and dried under vacuum. The yield obtained by Glorious and co-workers was 90%.

The characterization of this catalyst can be also done with an ^{1}H –NMR. In this case, the spectrum can should show three peaks: one singlet peak at 1.44 ppm relating to the protons of Cp*, one singlet peak relating to the protons of the CH$_3$CN ligand (2.55 ppm) and another CDCl$_3$ solvent peak. In addition, we could characterize by ^{19}F –NMR or ^{13}C –NMR. [Cp*Co(NCMe)$_3$][SbF$_6$]$_2$ can be synthesized in three days involving the previously preparation of [Cp*Co(CO)I$_2$].



Scheme 21. Synthesis of [Cp*Co(NCMe)$_3$][SbF$_6$]$_2$ catalyst.

5.1.3. Synthesis and characterization of [NMe$_4$]SCF$_3$ trifluoromethylthiolation reagent

Tyrra[51] and co-workers reported the preparation of [NMe$_4$]SCF$_3$ from Me$_3$SiCF$_3$, elemental sulfur and the corresponding fluorides in glyme or THF. After thirteen years, Schoenebeck[52] and co-workers reported a slightly modified synthesis (*Scheme 22*).

Under inert atmosphere, elemental sulfur (343 mg, 10.7 mmol) would be dissolved in THF (80 mL) at room temperature. Next, trifluoromethyltrimethylsilane (1.83 g, 12.9 mmol) would be added in the mixture followed by the cooling to -60 °C and the subsequent addition of tetramethylammonium fluoride (1 g, 10.7 mmol) under nitrogen flow to the mixture constantly stirred for 13 h. After 13 h, the reaction mixture would be warmed to room temperature.

An off-white-orange residue would be filtered under inert atmosphere and subsequently washed with THF/diethyl ether giving the solid which would be dissolved in a small amount of acetonitrile. The resulted solution would be filtered and using an excess of THF the product precipitated. The white $[NMe_4]SCF_3$ solid would be filtered again and washed with THF/diethyl ether and dried under vacuum. The yield obtained by Schoenebeck's group was 89%.

Synthesis of $[NMe_4]SCF_3$

$$\underset{(12.9\ \text{mmol})}{8\ \mathrm{Me_3SiCF_3}} \;+\; \underset{(10.7\ \text{mmol})}{\mathrm{S_8}} \;+\; \underset{(10.7\ \text{mmol})}{8\ [\mathrm{NMe_4}]\mathrm{F}} \xrightarrow[\text{THF, 13 h, –60 °C to rt}]{\qquad\qquad} 8\ [\mathrm{NMe_4}]\mathrm{SCF_3} \;+\; 8\ \mathrm{Me_3SiF}$$

Scheme 22. Synthesis of $[NMe_4]SCF_3$ trifluoromethylthiolation reagent.

$[NMe_4]SCF_3$ could be characterized by ^1H and ^{19}F –NMR spectroscopy. The ^1H –NMR spectrum should show a signal relating to nine protons at 3.14 ppm in CD_3CN, and the ^{19}F –NMR spectrum should exhibit a peak relating the SCF_3 moiety at -8.0 ppm. The preparation of this trifluoromethylthiolation reagent can be done in two days.

5.2. Calibrated curves between internal standard and targeted molecules

An internal standard is a well-defined molecule that have a similar structure and behaviour as the compounds that we want to characterize. This substance is added in a known amount to the solution of the sample and presents signals that can be distinguished from the targeted compounds by the instrument. In addition, the internal standard must be inert with the molecules that we want to characterize.[53]

In that case, the technique that would be used for measuring the concentration of the compounds of the catalysis is Nuclear Magnetic Resonance. This application of this technique enables the elucidation and identification of compound structures.

In our project, the targeted molecules are 2-phenylpyridine and 2-(2-((trifluoromethyl)thio)phenyl)pyridine. These two compounds have distinctive protons and fluorides in their structure being acceptable compounds for NMR concentration measurements. It would be desirable to use an internal standard with protons and fluorides to calculate the yield of the catalytic reactions without any additional work-up. This means a fast and straightforward analysis of the catalytic protocol. In fact, 4,4-difluorodiphenyl is a desirable internal standard because it contains two fluorides (multiplet peak at -115.7 ppm) and eight protons (multiplet peak at 7.13 ppm and multiplet peak at 7.50 ppm). In addition, 1,3,5-trimethoxybenzene can also be a good internal standard to measure the compounds concentrations by ^1H –NMR spectroscopy because their signals do not usually overlap with the aromatic zone signals due to electron-donating properties of the methoxy group. A singlet signal at 6.08 ppm and a singlet signal at 3.08 ppm can be show in ^1H –NMR spectroscopy. Relating to a good internal standard which contains fluorides, trifluorotoluene contains three fluorides which provides a well-defined signal at -62.6 ppm by ^{19}F –NMR spectroscopy.

The purpose of the internal standard is giving a method to know the concentration of the targeted compounds. To obtain an internal standard calibration curve, a sequence of known concentration of 2-phenylpyridine and 4,4-difluorodiphenyl in $CDCl_3$ creating different proportions are measured by ^{1}H –NMR spectroscopy. For example, a relation of 1:1 (PPy:IS), 1:2 (PPy:IS), 2:1 (PPy:IS) and 1:4 (PPy:IS).

First, the peaks from 2-phenylpyridine by ^{1}H –NMR spectroscopy must be distinguished between the internal standard signals. As diagnostic signals, we would choose doublet signal at 8.10 ppm relating to two protons of 2-phenylpyridine and other signal relating to four protons of 4,4-difluorodiphenyl at 7.15 ppm.

In order to create the internal standard calibration curve, the real concentration of the two compounds must be known according to the number of protons relating to the peak in each relation. Secondly, the concentration ratio is afforded dividing the concentration of protons relating to 2-phenylpyridine with the concentration of protons relating to 4,4-difluorodiphenyl.

Next, the peak area ratio of internal standard and 2-phenylpyridine from ^{1}H –NMR spectrum is measured with the division of the 2-phenylpyridine area peak and 4,4-difluorodiphenyl area peak. First, the value of internal standard area peak is previously normalized. Taking together, the ratio concentration versus the peak area ratio afford the internal standard calibration curve which allows the comparison of the instrumental responses from the targeted compounds to the responses of the added internal standard.

In addition, an internal calibration curve obtained with different proportions of 2-(2-((trifluoromethyl)thio)phenyl)pyridine and 4,4-difluorodiphenyl can also be obtained. In that case, the internal calibration curve by ^{1}H –NMR spectroscopy would be the relation of the singlet peak relating to 4 protons of internal standard with a double doublet peak at 7.32 ppm relating to one proton of the product. According to the ^{19}F –NMR spectrum, it is possible to create an internal calibration curve with the relation of the peaks of internal standard and product: the singlet peak at -41.8 ppm corresponds to the three fluorides of the product and the singlet peak at -151.7 ppm shows the two internal standard fluorides.

The quantification of the 2-(2-((trifluoromethyl)thio)phenyl)pyridine yield is really straightforward thanks to internal standard calibration curve: once the NMR spectra are recorded, we would identify the peaks of internal standard and the targeted molecule and we have to integrate in order to know the value of the targeted compounds area peak normalizing and the value of the internal standard area peak.

Next, in order to know the yield based on product, the relation of the value of the targeted compound area peak with the concentration ratio between [IS] and predicted [product] from the limiting reagent (in that case, 2-phenylpyridine) provides the yield of the reaction.

5.3. Repetition of the catalysis by Wang and co-workers

Wang and co-workers reported directed C–H trifluoromethylthiolation reaction under optimized conditions showed in *Scheme 11*. To study the reproducibility of the proposed catalysis, three repetitions of Wang's catalytic reaction procedure would be carried out.

The optimization conditions and used additives are summarized in *Table 1*. The only change of Wang's conditions would be the use of [$Cp^*Co(CO)I_2$] as catalyst instead of [Cp^*CoI_2]$_2$ due to its easier synthesis and higher activity in previously reported catalytic procedures.

Table 1. Conditions of trifluoromethylthiolation reaction by Wang and co-workers.

Reaction	Trifluoromethylthiolation of 2–phenylpyridine					**SOLVENT**
	Substrates		**Additives**			
Substance	2-phenylpyridine	$AgSCF_3$	Catalyst [$Cp^*Co(CO)I_2$]	Base $NaOPiv.H_2O$	Oxidant (same as substrate)	DCE, 100 °C, 24h
MM (g/mol)	155.20 ρ=1.086 mg/μL	208.94	476.99	142.13		
Amount	14.29 μL	41.79 mg	4.77 mg	2.84 mg		0.5 mL
Mmol	0.1 mmol	0.2 mmol	0.01 mmol	0.02 mmol	x	
Equiv.	1	2	10 mol%	20 mol%		

The methodology of catalytic reaction procedure is explained below:

A capped vial is charged with $NaOPiv{\cdot}H_2O$ (2.84 mg, 0.02 mmol), [$Cp^*Co(CO)I_2$] (4.77 mg, 0.01 mmol) and $AgSCF_3$ (41.79 mg, 0.2 mmol) with a magnetic stir bar. The vial is crimped under argon atmosphere and subsequently 0.5 mL of DCE and 2-phenylpyridine (14.29 µL, 0.1 mmol) are added. To prevent the possible evaporation of the solvent, Teflon and Parafilm are incorporated into the joins of the crimped vial. The mixture was heated at 100 °C for 24 h with constantly stirring.

After 24 hours and cooling down to room temperature, the resulted brown mixture is filtered using a cotton-silica-celite filter and washed with petroleum ether/diethyl acetate 20:1. The resulted solution was evaporated under vacuum. Next, a known concentration of internal standard (in that case, 4,4-difluorodiphenyl) is added with 0.5 mL of $CDCl_3$ to transfer the mixture at NMR tube for the characterization process.

The yield obtained by the group of Wang was 65%. Next, we would try to improve the resulted yield understanding the roles of each parameter within the catalytic cycle. On the one hand, different conditions such as temperature, time and set-up can be modified. On the other hand, different additives such as base, trifluoromethylthiolation reagent and solvent can also be altered.

5.4. Reactivity studies using different conditions such as temperature, time, set-up and aerobic conditions

Temperature, time, set-up and aerobic conditions are parameters that can modify the outcome of the reaction:

- Temperature: The temperature reported by Wang and co-workers was 100 °C. To control the reaction temperature, a sand bath on the hot plate apparatus with an internal temperature control would be used.

  We would study the targeted catalysis by Wang and co-workers with three experiments at lower temperatures that could allow an optimized range of the reaction temperature. For example, 40 °C, 60 °C and 80 °C are proposed temperatures.

  If the three experiments achieve similar results of Wang's catalysis, we demonstrate that the reaction can be carried out under milder conditions.

- Time: In order to study this parameter, three experiments with 6 hours, 12 hours and 18 hours would be performed and analysed.

- Set-up: Wang and co-workers used a crimped vial as a set-up for the proposed catalysis. The crimped vial is designed to allow a stable atmosphere into a small space reacting easier the different compounds. To find out if the set-up modifies the outcome of the reaction, we would change the use of crimped vial to a young sample flask.

- Aerobic conditions: The optimized conditions of Wang and co-workers involve inert atmosphere. To study the outcome of the reaction under aerobic conditions, we would carry out the proposed catalysis under air.

5.5. Reactivity studies using different additives such as catalyst, base, oxidant, solvent and SCF_3 reagent within the catalytic cycle

Having in hand the best conditions for temperature, time, set-up and aerobic conditions, the influence of the additives would be studied. In our case, the involved additives within the catalytic cycle are the catalyst, base, oxidant, trifluoromethylthiolation reagent and solvent.

- Catalyst: $[Cp^{*}Co(NCMe)_3][SbF_6]_2$ complex could be an alternative catalyst to the proposed catalysis. The main benefit of this compound is relating to the lability of the acetonitrile ligands forming the active specie without using a silver salt decreasing the used equivalents for the catalytic cycle.

In addition, a catalyst loading experiment with 5 mol% equivalents of $[Cp^*Co(CO)I_2]$ catalyst (2.38 mg, 0.005 mmol) and 10 mol% equivalents of $NaOPiv\cdot H_2O$ (1.42 mg, 0.01 mmol) would afford a conclusion in terms of sustainability.

- Base: $NaOPiv\cdot H_2O$ is the base additive in the catalysis by Wang and co-workers. The role of this base could be studied with two experiments of 1 equivalent of $NaOPiv\cdot H_2O$ (14.21 mg, 0.1 mmol) and without any base. In addition, a screening of bases can be investigated to obtain a better performance. The bases that would study are summarized in *Scheme 23*.

Cation and anion change

- CsOAc
- KOAc
- Cs_2CO_3

Cation change

- CsOPiv

Anion change

- NaOAc
- Na_2CO_3

Scheme 23. Screening of bases.

- Oxidant: The experiment that we would carry out is the proposed catalysis with 2 equivalents of 1-fluoro-2,4,6-trimethylpyridinium triflate (57.85 mg, 0.2 mmol) to try to promote the oxidation of Co(III) to Co(IV) and the regeneration of the active cobalt specie from Co(II) to Co(III). If the reaction yield is lower, the problem could be in the last oxidation step to regenerate the active catalyst.

- Trifluoromethylthiolation reagent: $AgSCF_3$ is the trifluoromethylthiolation reagent and the oxidant of the proposed catalysis of Wang and co-workers. However, there are other trifluoromethylthiolated compounds such as $[NMe_4]SCF_3$ that can also be used as nucleophilic SCF_3 transfer reagents.[5]

  In that point, we propose the initial catalysis using only 1 equivalent of $AgSCF_3$ (20.89 mg, 0.1 mmol) to promote the regenerating step of the catalyst. On the other hand, a catalysis with 1 equivalent of $[NMe_4]SCF_3$ (17.52 mg, 0.1 mmol) in place of $AgSCF_3$ with 1 equivalent of an oxidant (28.93 mg, 0.1 mmol) can also be an experiment to know the efficiency of $[NMe_4]SCF_3$. Other experiments to know the ideal trifluoromethylthiolation reagent with the effect of the catalyst and oxidant are summarized in *Table 2*.

Table 2. Different experiments to understand the relation of each compound.

Entry	Change in conditions
0	Reported conditions
1.1	Using $[Cp^*Co(CO)I_2]$
1.2	**Entry 1.1** & 1 equiv $AgSCF_3$
1.3	**Entry 1.1** & 1 equiv $AgSCF_3$ & 1 equiv oxidant
1.4	**Entry 1.1** & 1 equiv $[NMe_4]SCF_3$ & 1 equiv oxidant
2.1	Using $[Cp^*Co(NCMe)_3][SbF_6]_2$ & DCE:HFIP, 80 ºC
2.2	**Entry 2.1** & 2 equiv $AgSCF_3$
2.3	**Entry 2.1** & 1 equiv $AgSCF_3$ & 1 equiv oxidant
2.4	**Entry 2.1** & 1 equiv $[NMe_4]SCF_3$ & 1 equiv oxidant
3.1	Using $[Cp^*Co(NCMe)_3][SbF_6]_2$ & HFIP, 80 ºC
3.2	**Entry 3.1** & 2 equiv $AgSCF_3$
3.3	**Entry 3.1** & 1 equiv $AgSCF_3$ & 1 equiv oxidant
3.4	**Entry 3.1** & 1 equiv $[NMe_4]SCF_3$ & 1 equiv oxidant

- Solvent: The direct role of solvents in reactions must be studied because the solvents interact directly with the catalyst, the substrates and products increasing or decreasing the rate of the reaction.
  1,2-dichloroethane is the used solvent by the group of Wang. The group of Pérez-Temprano has recently reported the beneficial effect of hexafluoroisopropanol in Cp*Co-catalyzed C–H functionalization reactions.[41]

  We would investigate the effect of this solvent and cosolvents DCE:HFIP using $[Cp^*Co(CO)I_2]$ and $[Cp^*Co(NCMe)_3][SbF_6]_2$ at 80 °C. Acetonitrile can also be used as a reaction solvent due to the solubility of each compound within the catalysis.

5.6. Use of electrochemical conditions: study of different parameters

In order to explore the possibility to achieve the 2-(2-((trifluoromethyl)thio)phenyl)pyridine without chemical oxidants, electrochemical experiments would be carried out.

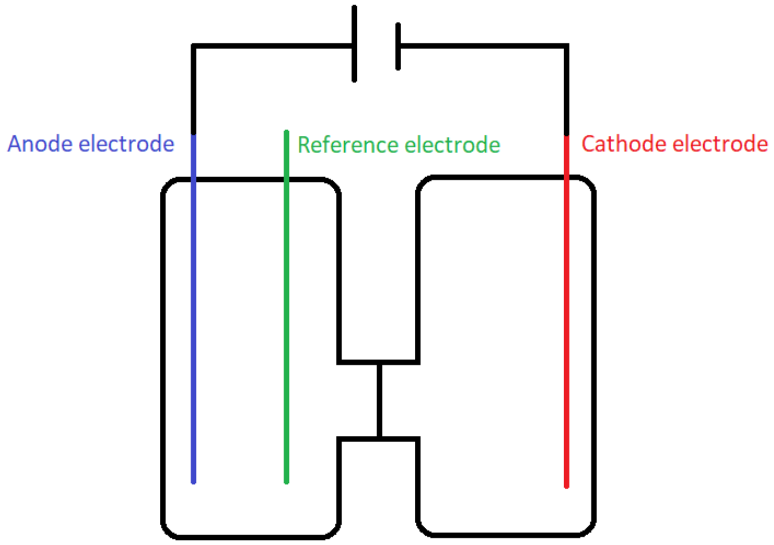
The Pérez-Temprano group proposed that $AgSCF_3$ can act as one-electron oxidant in two different steps: for accessing to high-valent Co(IV) species and for regenerating the active species after the C–SCF_3 reductive elimination step. Electrochemical reaction conditions can also promote this electron transfer, being a more sustainable system for Cp*Co-catalyzed C–H functionalization reactions.

Electrochemical divided cell is composed of anodic chamber where the anode electrode is presented and cathodic chamber having the cathode electrode, being separated by a permeable membrane[54] (*Scheme 24*). The driving force of redox processes is the potential that is usually described as voltage and it is measured by an external power source connected to the electrochemical cell controlling potential between working electrode and reference electrode.

The different parameters that have a significant impact of the reaction are the constitution, surface area and reusability of electrodes because the electron transfer reaction takes place on the surface area of the anode electrode being the working electrode which allows the desired oxidative reaction.

Electrolytes additives, which are charged species, can improve conductivity due to the neutralization of the charge cell. Ammonium and alkali metal-based salts are the most common electrolytes additives. On the other hand, an ideal solvent would have the capacity of dissolve electrolytes, substrate and reactants. DCM would be a good solvent for the first experiments under electrochemical conditions.

Taking together, a divided cell with glassy carbon electrodes and silver-silver chloride reference electrode charged with saturated solution of potassium chloride (KCl) electrolyte additive in DCM would be the first electrochemical conditions that would be carried out with the proposed equivalents of Wang's additives. In this experiment, $AgSCF_3$ is no longer required as an oxidant additive. However, the reaction needs a trifluoromethylthiolation reagent that can be $AgSCF_3$ or $[NMe_4]SCF_3$. If the desired product is not formed, the first step is to increase the current and voltage to force the trifluoromethylthiolation reaction.



Scheme 24. Electrochemical divided cell.

6. Conclusions

From this Final Degree Thesis, we can conclude that the proposed objectives aiming to investigate the Cp*Co-catalysed directed C–H trifluoromethylthiolation reaction have been achieved.

- We have described the most relevant trifluoromethylthiolation experiments over the past decades, including the use of starting products without transition metals under harsh required conditions.
- We have illustrated the new strategies regarding the C–H functionalization with transition metals. First, we have defined the general mechanism for the C–H activation step. In addition, we have presented the directing groups strategy to control the site-selectivity of the C–H bond-cleavage.
- We have outlined the blooming of cobalt in ligand-directed C–H functionalization including low and high-valent cobalt complexes. Moreover, the use of bench-stable Cp*Co complexes have been highlighted.
- The creation of the C–S bond has been explored by Cp*Co^{III}-catalyzed C–H functionalization reactions using nucleophiles as coupling partners where only three examples have been reported.
- We have detailed the oxidatively induced reductive elimination scenario described for transition metals catalysis where the use of oxidants allowed the formation of high-valent intermediates which facilitates the formation of the desired molecules.
- We have described the mechanism scenarios of cobalt catalysis to understand organometallic processes. The importance of this investigation with the isolation of relevant cobaltacycle intermediates allowed to be known the reactivity of putative cobalt intermediates.
- The synthesis of [Cp*Co^{III}(PPy)(SCF$_3$)] post-transmetallation intermediate enabled us to understand the mechanism by which the C–SCF$_3$ coupling occurs. Finally, different studies suggest a (Co^{III}-Co^{IV}-Co^{II}) oxidatively induced reductive elimination reaction where AgSCF$_3$ oxidizes the post–transmetallation intermediate complex facilitating the reductive elimination step.
- From an experimental point of view, we have designed an action plan to develop an improved catalytic system for the synthesis of the trifluoromethylthiolated product (2-(2-((trifluoromethyl)thio)phenyl)pyridine). In particular, we have prepared a timeline with all the experiments that we would carry out in order to study the different parameters and understand their effect in the formation of C–SCF$_3$ bond.

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